

THE CHEMISTRY OF SOME DIHYDROPYRIDINE DERIVATIVES

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THE CHEMISTRY OF SOME DIHYDROPYRIDINE  
DERIVATIVES

by



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## ABSTRACT

Reactions of 4-chloromethyl-1,4-dihydropyridine and 4-(1-chloroethyl)-1,4-dihydropyridine derivatives with enolate ions from  $\beta$ -dicarbonyl compounds have been studied, and shown to give the corresponding 4-substituted-4,5-dihydroazepines under mild conditions. Under vigorous conditions intramolecular Michael addition takes place (provided the dicarbonyl substituent possesses an acidic hydrogen atom) giving 2-azabicyclo[3.2.1]oct-3-enes; the stereochemistry of this reaction is considered. The reactions of some simpler nucleophiles with these chloro-compounds were also investigated.

Rearrangements of 4-cyano-4,5-dihydroazepines in both acidic and basic conditions were reinvestigated. The isolation of a ring-opened intermediate and a substituted dihydro-2-pyridone from the acid-catalysed rearrangement provide support for a postulated mechanism.

The competitive reactions of chloroalkyl and bromoalkyl substituted 1,4-dihydropyridines with different bases were studied in both concentrated and dilute solution and a mechanism for the ring expansion reaction was postulated.

Methyl 5-acetyl-2,6-dimethylnicotinate and its dihydro-compound were synthesized, particularly for mass spectral correlations. Mass spectra of some 1,4-dihydropyridines, 4H-azepines, 4,5-dihydroazepines, 2-azabicyclo[3.2.1]oct-3-enes, furo[2,3-b]pyridines, pyrrolo[2,3-b]pyridines, and  $\beta$ -(3-methoxycarbonyl-2-methyl-1-pyrrolyl)-crotonic acid are reported and discussed.

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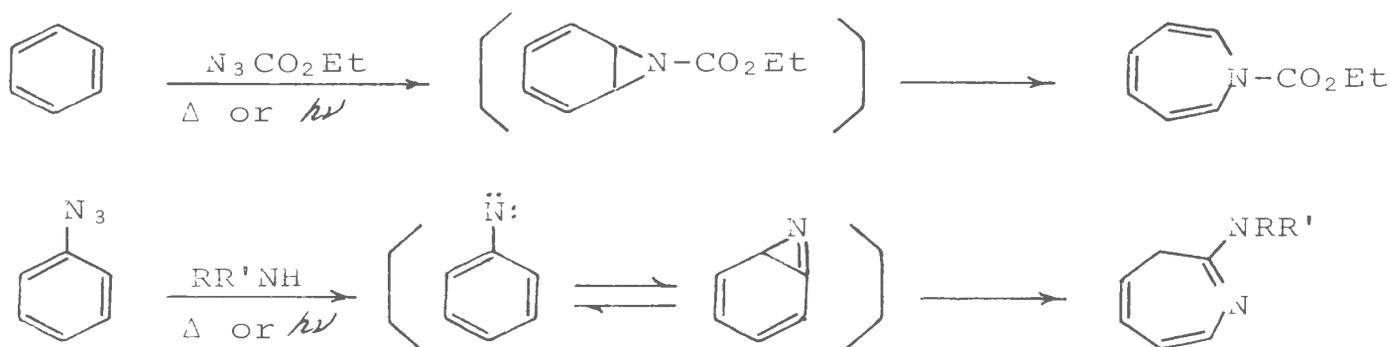
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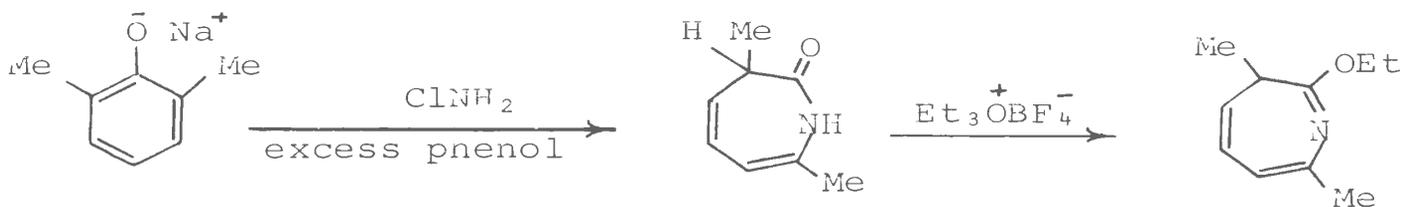
## INTRODUCTION

The ring expansion of six-membered ring carbocyclic compounds to give products containing seven-membered carbocyclic rings is well documented<sup>1</sup> and has recently been extended to the preparation of derivatives of azepine. In this latter case, the nitrogen atom has been introduced using (A) a nitrene insertion reaction<sup>2</sup>, (B) the reaction of chloramine with phenols<sup>3</sup>, (C) the addition of iodine isocyanate to 1,4-dihydrobenzene derivatives, followed by an internal nucleophilic displacement<sup>4</sup>, and (D) the photorearrangement of anthranils<sup>5</sup>.

A.



B.

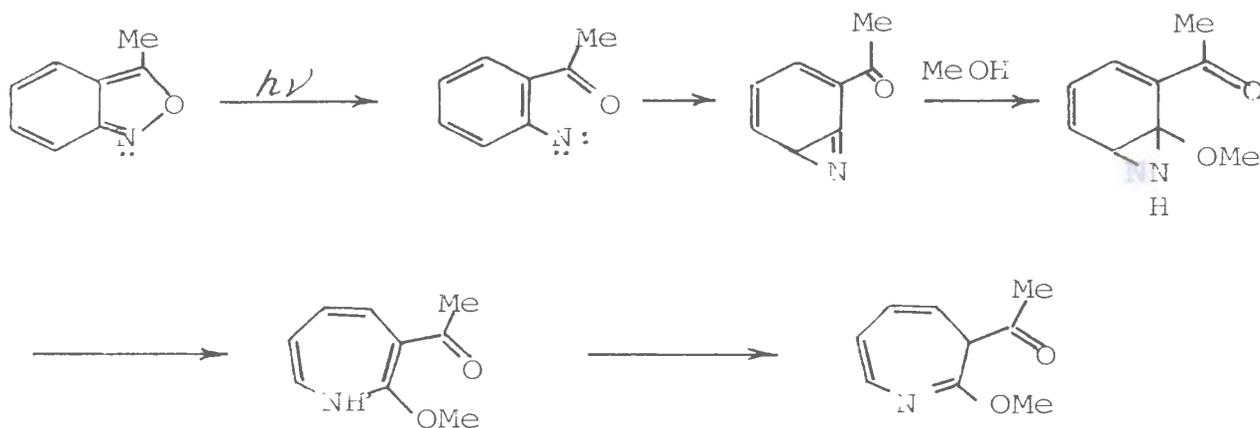


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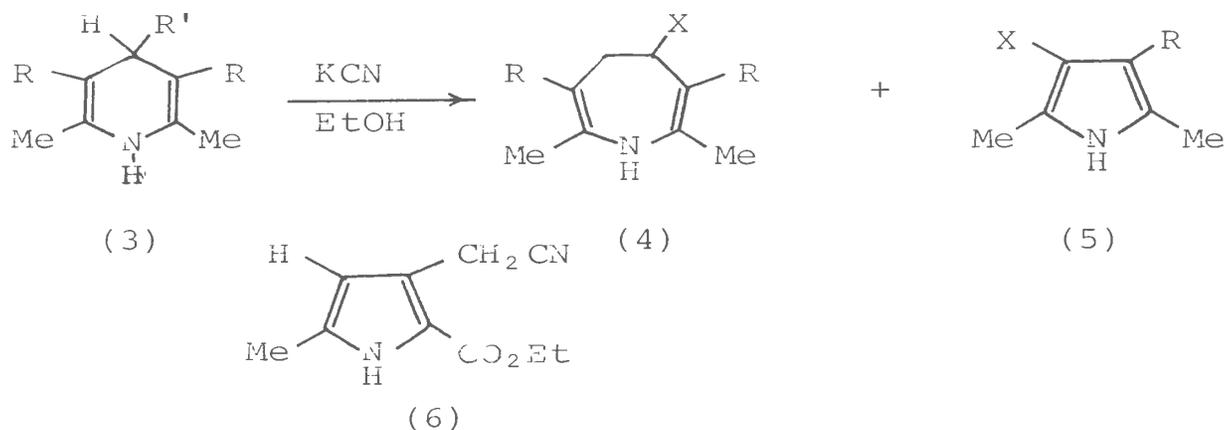
An alternative approach to the synthesis of azepine derivatives would be to start with a six-membered nitrogen heterocyclic ring and expand by one carbon atom. Thus the dibenzoazepine (2, R=H) and its N-methyl derivative (2, R=Me) have been obtained by the action of polyphosphoric acid<sup>6</sup> or phosphorus pentoxide<sup>7</sup> on the dihydroacridine (1, R=H, X=OH) or silver perchlorate<sup>8</sup> in ether on the iodomethyl compound (1, R=Me, X=I) respectively.



In 1962, the first ring expansion of a dihydropyridine to an azepine derivative was reported<sup>9</sup>. Recent work in this

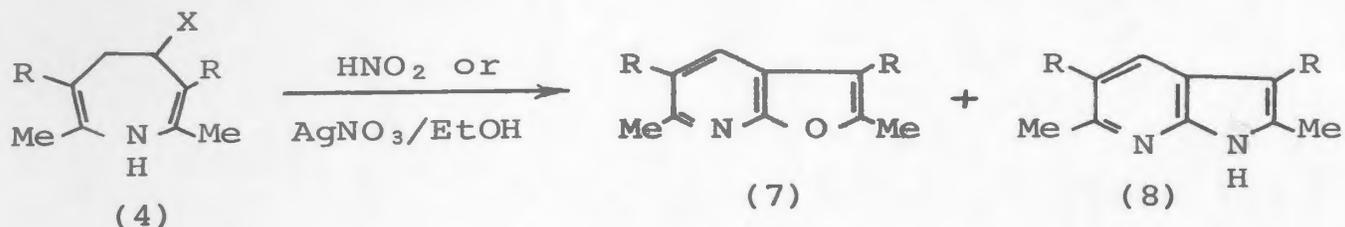
area has resulted in the synthesis of derivatives of several different ring systems and the discovery of some interesting rearrangements which will herein be reviewed.

The reaction of the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Et, R'=CH<sub>2</sub>Cl) with potassium cyanide in refluxing ethanol gave two products, to which Benary assigned the 4-cyanomethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Et, R'=CH<sub>2</sub>CN) and the cyanomethyl-pyrrole (6) structures<sup>10</sup>. This reaction was re-examined by Johnson and co-workers<sup>9</sup> who showed, on the basis of chemical and spectroscopic properties, that the two products were the 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub>Et, X=CN), and the pyrrole (5, R=CO<sub>2</sub>Et, X=CN). Further the pyrrole (5, R=CO<sub>2</sub>Et, X=CN) was shown to be formed from the 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub>Et, X=CN) by base catalysis, the other product being ethyl acrylate. The 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub>Et, X=CN) was synthesized by a rational route and shown to be different from any of the products of the cyanide reaction.



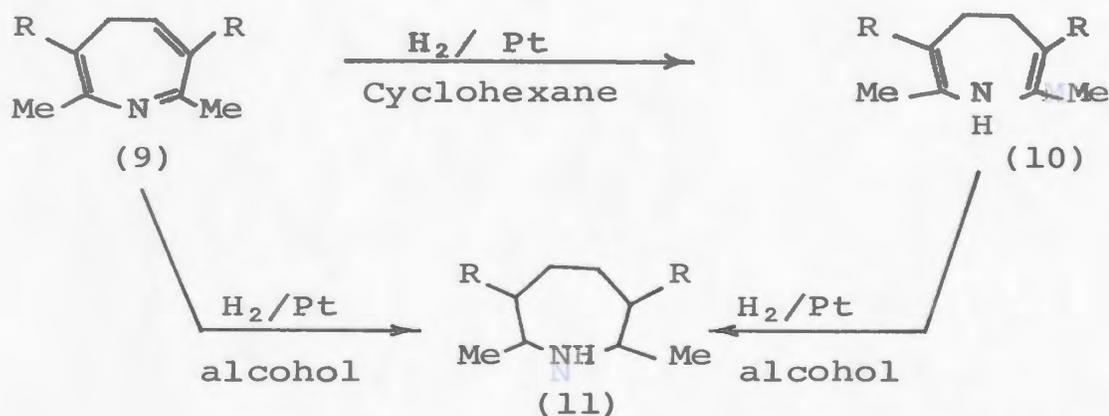
Attempts to oxidize the 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub>Et, X=CN) using nitrous acid or silver nitrate<sup>11</sup> gave mainly the furo [2,3-b] pyridine (7, R=CO<sub>2</sub>Et) along with a small

amount of the pyrrolo [2,3-b] pyridine (8, R=CO<sub>2</sub> Et).



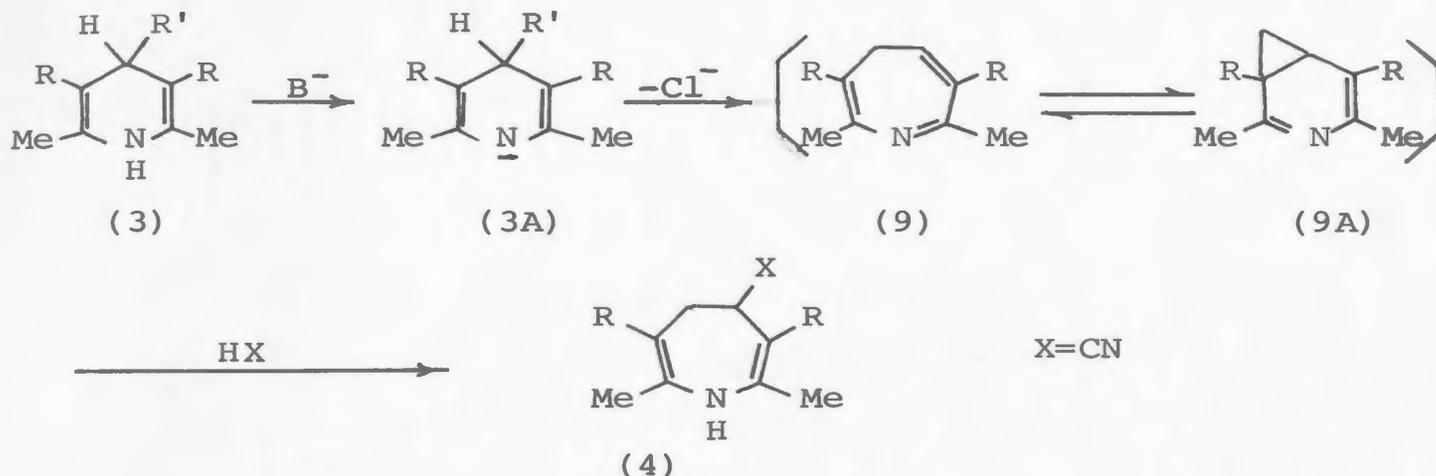
When treated with sodium ethoxide in cold ethanol solution, the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub> Et, R'=CH<sub>2</sub>Cl) gave the 4-ethoxy-4,5-dihydroazepine<sup>12</sup> (4, R=CO<sub>2</sub> Et, X=OEt) which on gentle warming eliminated ethanol to form the 4H-azepine (9, R=CO<sub>2</sub> Et). 4H-Azepines were also obtained by pyrolysis of the 4-methoxy-4,5-dihydroazepine (4, R=CO<sub>2</sub> Me, X=OMe) at 100°<sup>13</sup> or the 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub> Et, X=CN) at 265°<sup>12</sup>.

Hydrogenation of 4H-azepine<sup>12</sup> (9, R=CO<sub>2</sub> Me) with Adams catalyst in a non-polar solvent, eg. cyclohexane, gave 4,5-dihydro-1H-azepine (10, R=CO<sub>2</sub> Me) and both will give perhydroazepine (11, R=CO<sub>2</sub> Me) in alcoholic solution.



The kinetics of the ring expansion reaction with cyanide ion have been studied by Brignell and his co-workers<sup>14</sup>, and the mechanism was postulated to involve the formation of

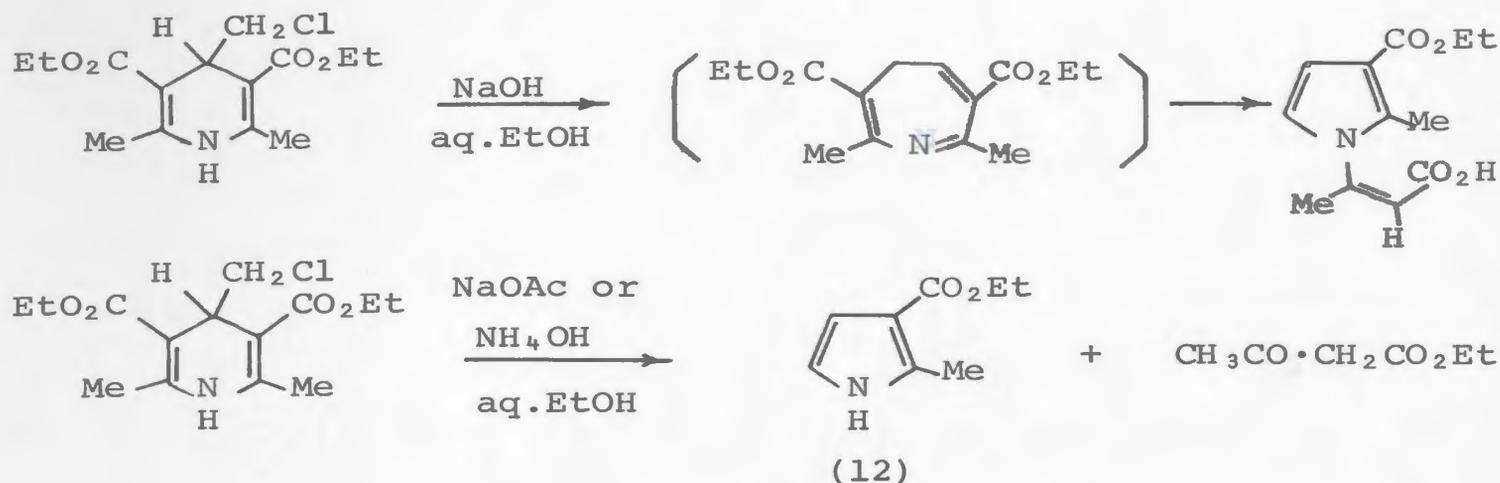
dihydropyridine anion (3A) by a base-catalysed rate-determining step, followed by subsequent fast rearrangement with elimination of chloride ion to form the 4H-azepine (9, R=CO<sub>2</sub>Me) or its valence isomer, the 3-azanorcaradiene (9A), and finally the addition of hydrogen cyanide to this 4H-azepine (9, R=CO<sub>2</sub>Me).



However, the solvolysis of the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Me, R'=CH<sub>2</sub>Cl) in methanol containing triethylamine gave the 4-methoxy-4,5-dihydroazepine (4, R=CO<sub>2</sub>Me, X=OMe), and the reaction rate was independent of the concentration of triethylamine. This result strongly suggested a mechanism involving homoallylic participation<sup>15</sup>. (see below-page 9).

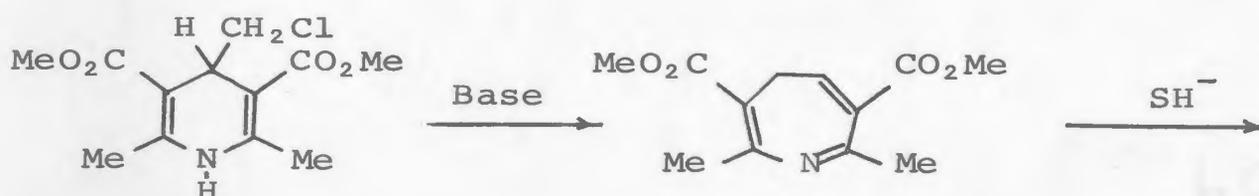
When either the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Et, R'=CH<sub>2</sub>Cl) or the 4H-azepine (9, R=CO<sub>2</sub>Et) was treated with aqueous ethanolic sodium hydroxide, the  $\beta$ -(3-ethoxycarbonyl-2-methyl-1-pyrrolyl)crotonic acid<sup>12</sup>, rather than the expected 4-hydroxy-4,5-dihydroazepine (4, R=CO<sub>2</sub>Et, X=OH), was obtained. With hot aqueous ethanolic sodium acetate or ammonium hydroxide at room temperature, the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Et, R'=CH<sub>2</sub>Cl) and the 4H-azepine (9, R=CO<sub>2</sub>Et) both eliminated

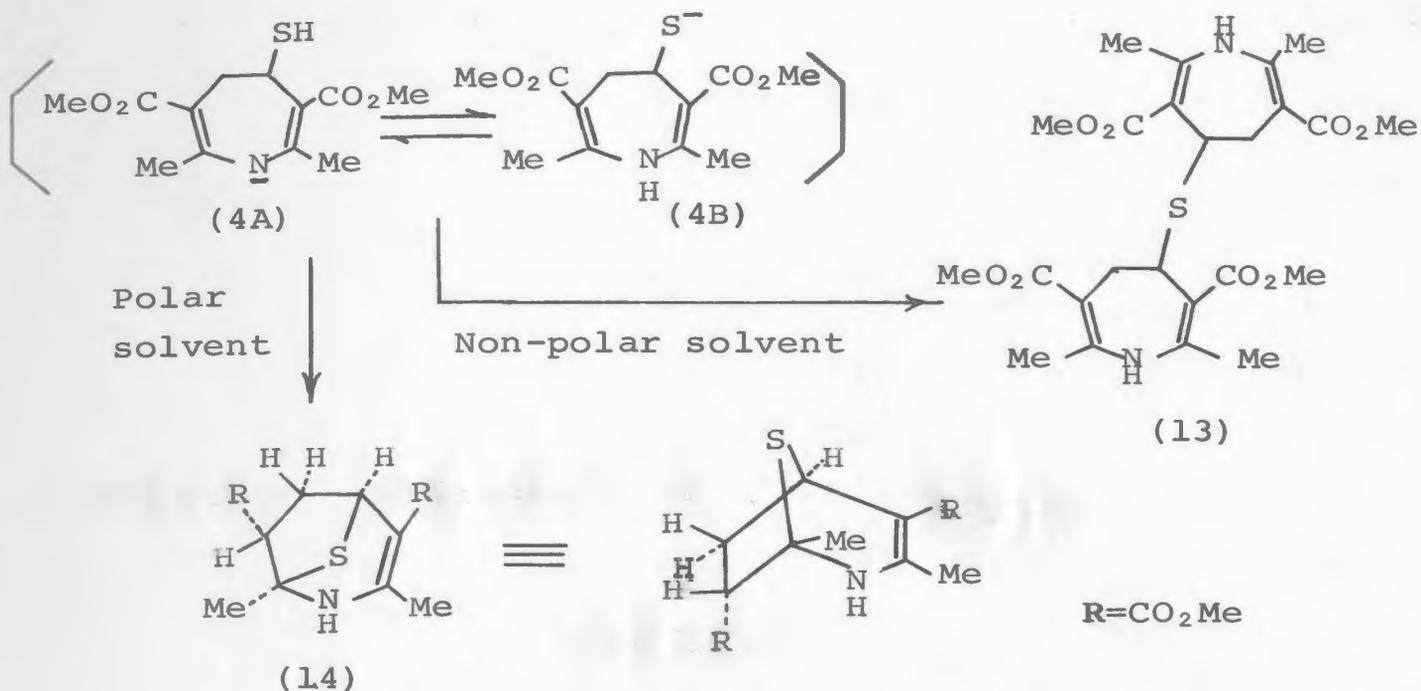
ethyl acetoacetate to give the pyrrole (12)<sup>12</sup>.



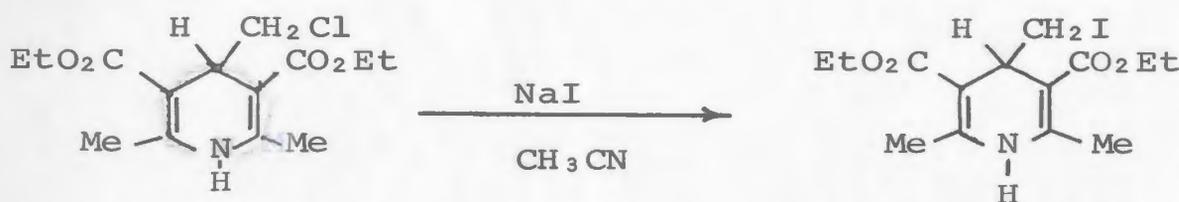
When treated with potassium hydrogen sulfide in non-polar solvent, the 4H-azepine (9, R=CO<sub>2</sub>Me) gave bis-(2,7-dimethyl-3,6-dimethoxycarbonyl-4,5-dihydro-4-azepinyl) sulfide (13). In polar solvent, both the 4-chloromethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Me or CO<sub>2</sub>Et, R'=CH<sub>2</sub>Cl) and the 4H-azepine (9, R=CO<sub>2</sub>Me) gave dimethyl 1,3-dimethyl-8-thia-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate (14, R=CO<sub>2</sub>Me or CO<sub>2</sub>Et)<sup>16</sup>. The mechanism of the formation of the bis-azepinyl sulfide (13) and the sulfur bridged azabicyclic compound (14) was postulated to proceed via the conjugate base (3A) which rearranges to the intermediate 4H-azepine (9) followed by attack of hydrosulfide ion on the 5-position. The resulting tautomeric ion (4B) then attacks another molecule of 4H-azepine to form bis-azepinyl sulfide (13) in non-polar solvent, but in a polar solvent, the 4,5-dihydroazepinyl sulfide ion (4B) undergoes an internal Michael addition to give the sulfur bridged azabicyclic compound (14). The structure of the bis-azepinyl sulfide (13) was based on spectral data, eg. ultraviolet absorption and n.m.r.

spectrum similar to that of the 4-cyano- (4, R=CO<sub>2</sub> Me, X=CN) and the 4-methoxy-4,5-dihydroazepine (4, R=CO<sub>2</sub> Me, X=OMe) and the observations that it was converted to the 4,5-dihydro-1H-azepine (10, R=CO<sub>2</sub> Me) by desulfurization with Raney Ni, to the 4-cyano-4,5-dihydroazepine (4, R=CO<sub>2</sub> Me, X=CN) by potassium cyanide, and to the sulfur bridged azabicyclic compound (14, R=CO<sub>2</sub> Me) by potassium hydrogen sulfide. The structure of the sulfur bridged azabicyclic compound (14, R=CO<sub>2</sub> Me) was supported by spectral measurements, eg. the ultraviolet absorption showed presence of 3-aminocrotonate chromophore<sup>17</sup>; the infrared spectrum showed free and hydrogen bonded NH stretching, a saturated and an unsaturated ester carbonyl stretching; nuclear magnetic resonance showed 5-H at τ 5.29 (broad doublet with J=5.5 and 1.0 Hz), 7<sub>exo</sub>-H at τ 6.92 (double doublet with J=11.5 and 3.5 Hz), 6<sub>endo</sub>-H at τ 7.24 (broad double doublet with J=12.5, 3.5, and 1.0 Hz), 6<sub>exo</sub>-H centred at τ 7.58 multiplet coupling with three other protons, and the stereochemistry was confirmed by X-ray diffraction analysis<sup>16b</sup>. The endo configuration of the 7-methoxycarbonyl group was presumed to be due to the steric interaction between the 7-methoxycarbonyl and 1-methyl group. Potassium hydrogen selenide and primary amines, such as methylamine or benzylamine, also gave the corresponding bicyclic compounds<sup>13</sup>.





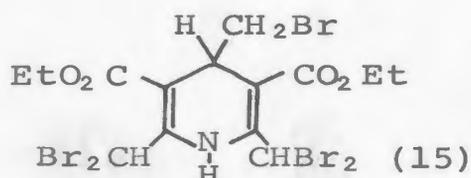
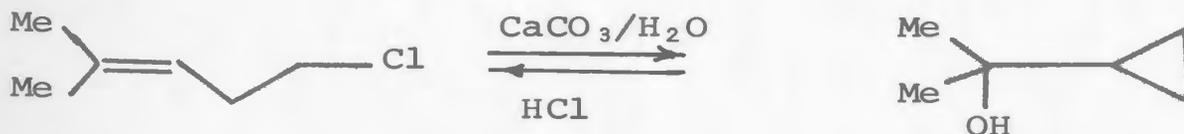
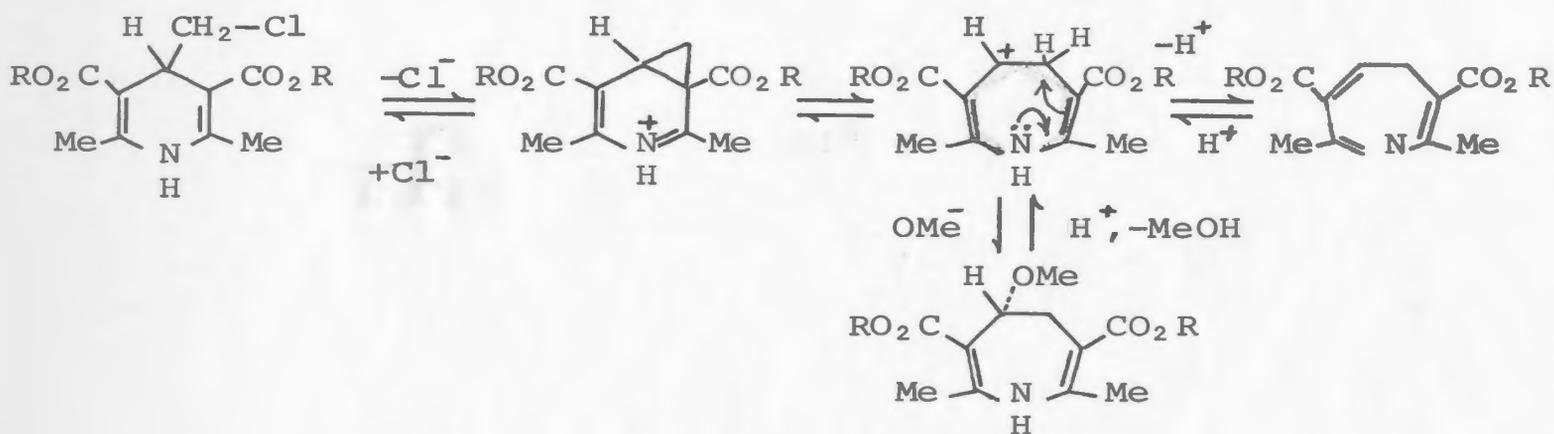
Several other basic nucleophiles, such as p-tolythio<sup>13</sup>, azide<sup>9a</sup>, borohydride<sup>12,16a</sup> etc. also brought about ring expansion of the dihydropyridine ring. However, in the case of iodide<sup>14</sup>, thiocyanate<sup>18</sup>, or selenocyanate ion<sup>18</sup>, substitution without ring expansion occurred.



Both the 4H-azepine (9, R=CO<sub>2</sub>Me) and the 4-ethoxy-4,5-dihydroazepine (4, R=CO<sub>2</sub>Me, X=OEt) have been shown to undergo ring contraction to regenerate the 1,4-dihydropyridine system in acidic conditions<sup>12</sup>, e.g. with hydrochloric acid or hydrobromic acid in ether solution, the corresponding 4-halogenomethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub>Me, R'=CH<sub>2</sub>Cl or CH<sub>2</sub>Br) is the only product, but in methanol solution, the 4-methoxymethyl-1,4-

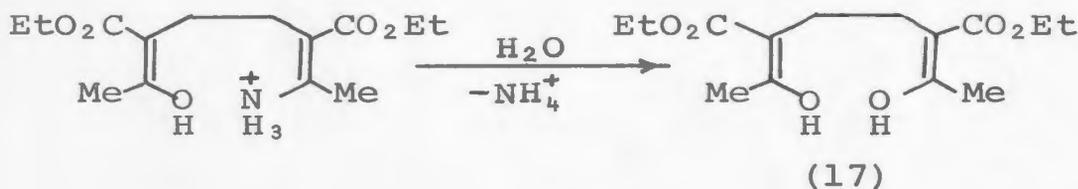
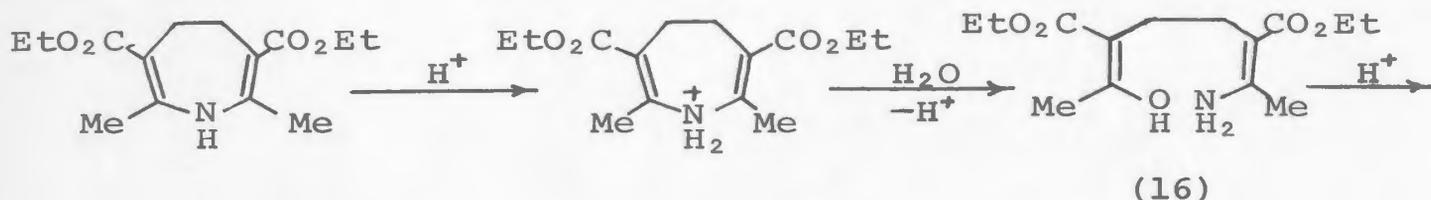
dihydropyridine (3, R=CO<sub>2</sub> Me, R'=CH<sub>2</sub> OMe) is produced along with the 4-halogenomethyl-1,4-dihydropyridine (3, R=CO<sub>2</sub> Me, R'=CH<sub>2</sub> Cl or CH<sub>2</sub> Br)<sup>15</sup>. Also bromination of the 4H-azepine (9, R=CO<sub>2</sub> Et) with bromine in carbon tetrachloride, gave not an azepine but a pentabromo-derivative of 1,4-dihydropyridine (15)<sup>12</sup>.

These results have been interpreted by postulating an equilibrating set of carbonium ions (or a non-classical ion) formed by homoallylic participation and electron release from the nitrogen<sup>15</sup>. The formation of dihydropyridines in acid solution but azepine derivatives in non-acidic solution is then similar to other homoallylic systems<sup>19,20</sup> where the homoallyl system is preferred in acidic conditions, but the cyclopropyl carbinyl system is preferred in non-acidic conditions.

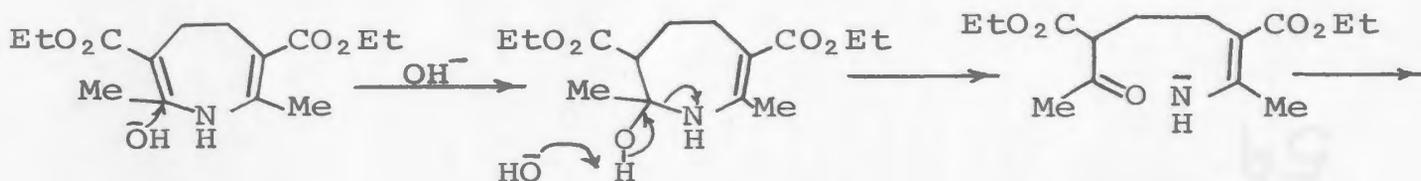


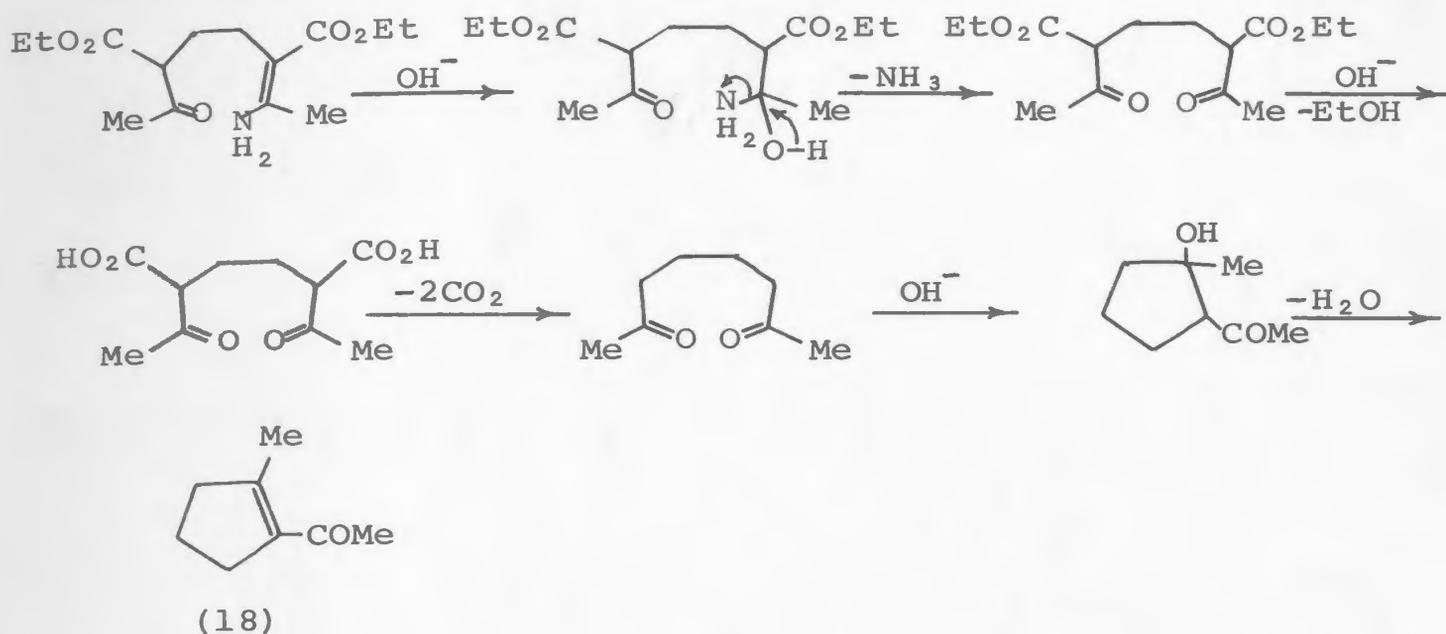
The 4,5-dihydro-1H-azepine (10, R=CO<sub>2</sub>Et) was quite reactive to both acids and bases. Thus with dilute hydrochloric acid and the 4,5-dihydroazepine (10, R=CO<sub>2</sub>Et) ring opening occurred to form the enamine ester (16) which rapidly hydrolyzed to 2,5-diacetyl adipic ester (17)<sup>1,2</sup>. The reaction with aqueous ethanolic potassium hydroxide was thought to involve nucleophilic attack by two hydroxide ions on the iminobis-(β-crotonic ester) system, followed by ester hydrolysis, decarboxylation, then internal aldol condensation of octa-2,7-dione to form 1-acetyl-2-methylcyclopentene-1 (18)<sup>1,2</sup>.

Acid Hydrolysis :

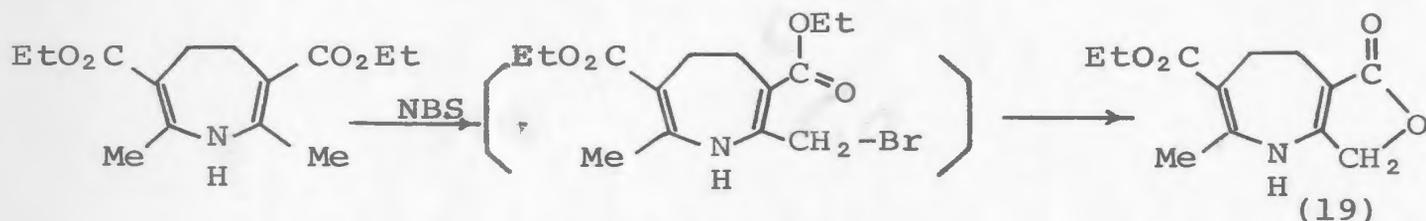


Base Hydrolysis :

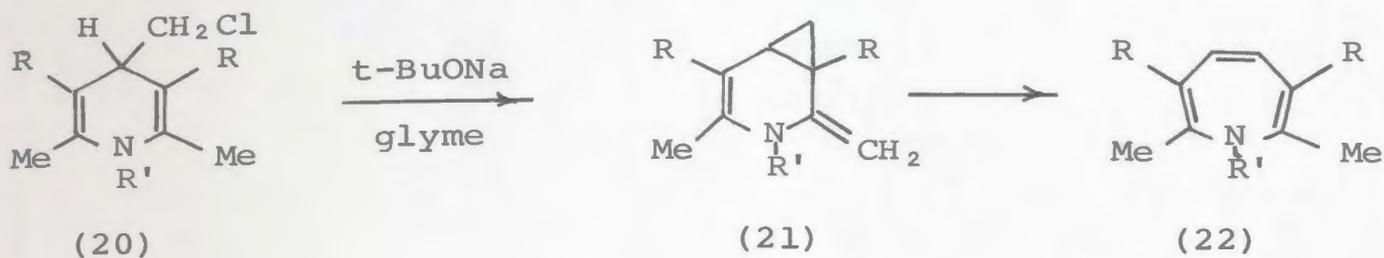




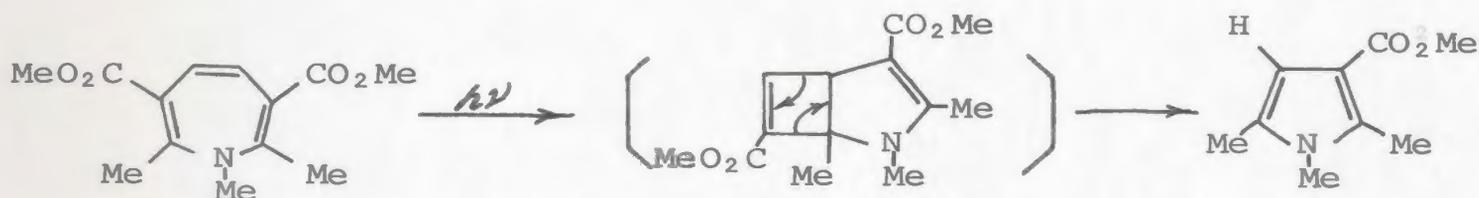
An attempt to brominate the 4,5-dihydro-1H-azepine (10, R=CO<sub>2</sub>Et) with N-bromosuccinimide in carbon tetrachloride solution only led to the formation of the 4,5-dihydroazepine lactone (19)<sup>21</sup>.



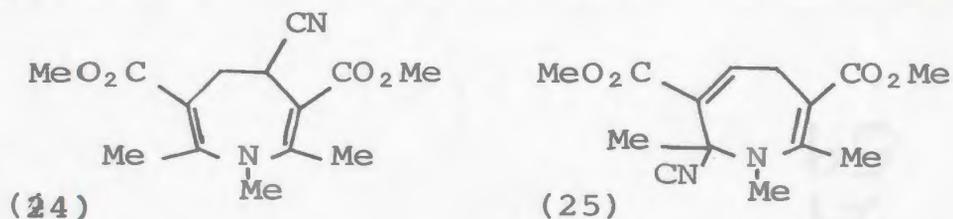
The N-substituted dihydropyridines, such as N-methyl- (20, R=CO<sub>2</sub>Me or CN, R'=Me) or N-phenyl-4-chloromethyl-1,4-dihydropyridine (20, R=CO<sub>2</sub>Me or CN, R'=Aryl) also appear to undergo ring expansion, e.g. Dihydropyridine (20, R=CO<sub>2</sub>Me, R'=Me) gave the aza-norcarene derivative (21, R=CO<sub>2</sub>Me, R'=Me) which isomerized to the more stable N-methyl-1H-azepine (22, R=CO<sub>2</sub>Me, R'=Me) on heating<sup>2,2,3,2,4</sup>. The N-methyl-1H-azepine (22, R=CO<sub>2</sub>Me, R'=Me) was shown to undergo thermal rearrangement to the 6-methylaminofulvene (23)<sup>2,4,2,5</sup>.



The N-methyl-1H-azepine (22, R=CO<sub>2</sub>Me, R'=Me) was irradiated in cyclohexane to give methyl 1,2,5-trimethylpyrrole-3-carboxylate.<sup>22</sup>



On treatment of the N-methyl-4-chloromethyl-1,4-dihydropyridine (20, R=CO<sub>2</sub>Me, R'=Me) with potassium cyanide, four compounds (7, 26, 27, 28) were obtained after column chromatography<sup>22</sup>. These compounds were thought to be the hydrolysis products of the intermediate cyanodihydroazepines (24, 25) by ring opening and recyclization and the proportion of the products varied with the amount of potassium cyanide used. (see Table 1 -page 13).



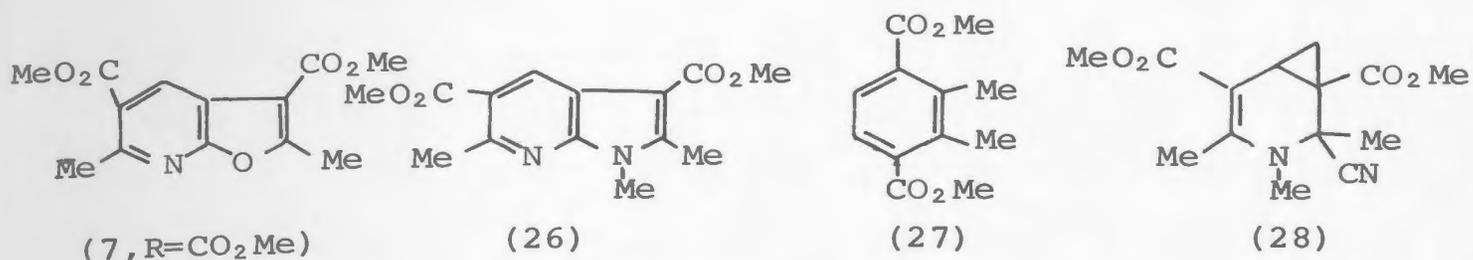
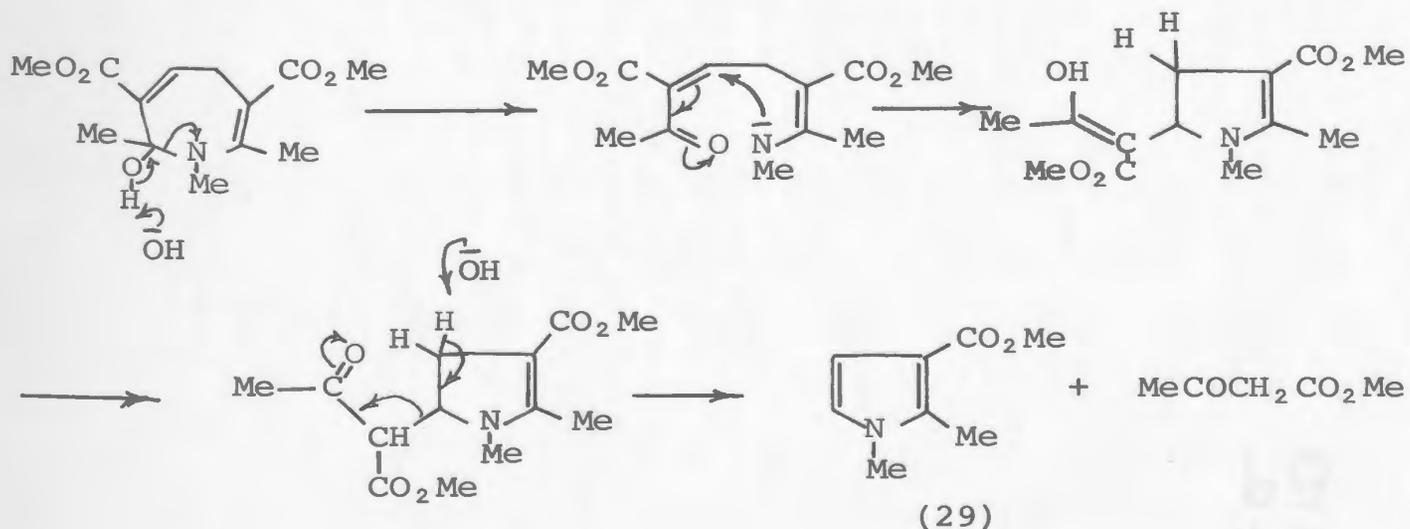


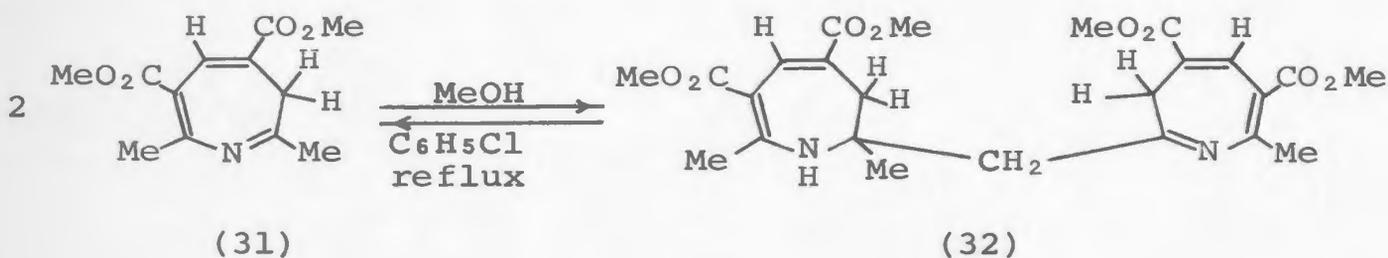
Table 1 : Products of the Reaction of the N-methyl-4-chloro-methyl-1,4-dihydropyridine (20, R=CO<sub>2</sub>Me, R'=Me) with KCN.

Reagents (mole)		Products ( % )			
Dihydropyridine	KCN	(7)	(26)	(27)	(28)
1	4.4	10	1	10	5
1	1	trace	trace	25	10

On refluxing the N-methyl-4-chloromethyl-1,4-dihydropyridine (20, R=CO<sub>2</sub>Me, R'=Me) with aqueous methanolic potassium hydroxide, ring contraction took place with elimination of methyl acetoacetate and produced the N-methylpyrrole derivative (29)<sup>22</sup>. The reaction mechanism was proposed as follows:

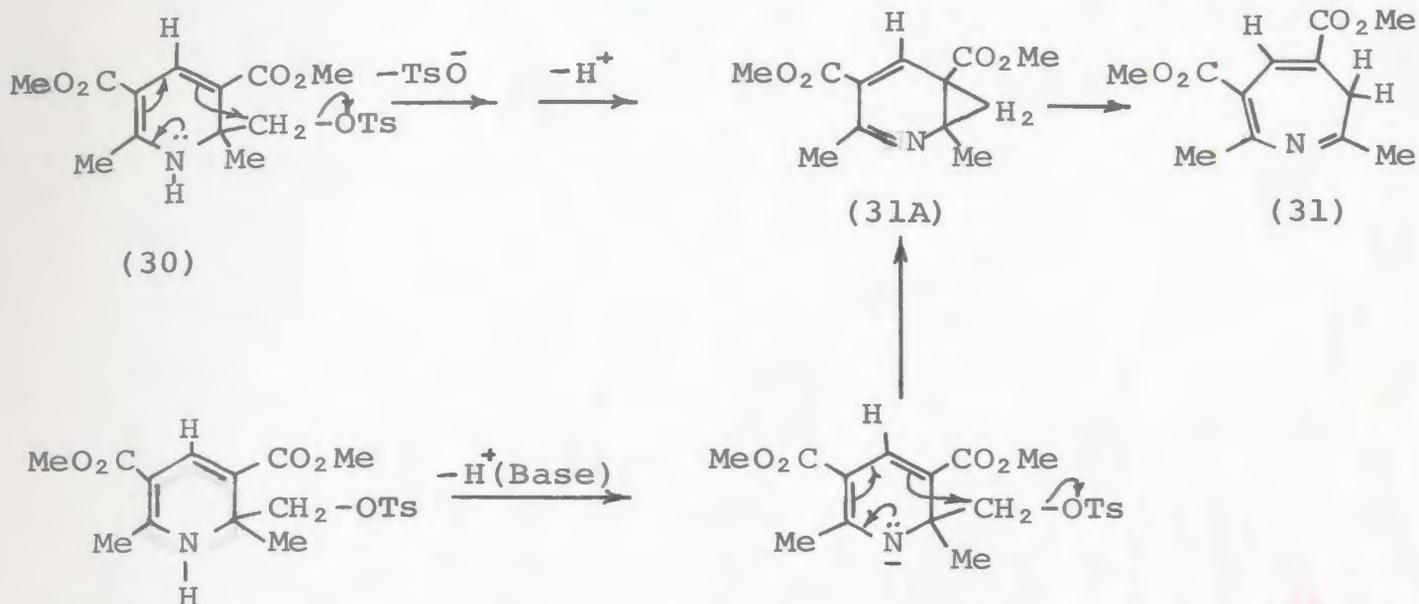


More recently Bergen and Kellogg<sup>26</sup> found a similar ring expansion of a 1,2-dihydropyridine. On heating the 3,5-dimethoxycarbonyl-2,6-dimethyl-2-tosyloxymethyl-1,2-dihydropyridine ( 30 ) at 100° in pyridine, elimination of p-toluenesulfonic acid occurred, resulting in formation of the 3H-azepine ester ( 31 ) and its dimer ( 32 ). The structure of these products were based on the ultraviolet and variable-temperature nuclear magnetic resonance spectra and on the selective hydrogenation of the imino portion. The formation of the dimer ( 32 ) was thought to involve the nucleophilic 1,2-addition of the 3H-azepine ( 31 ) to a second molecule of 3H-azepine ( 31 ) resembling the dimerization of the 1,2,5,6-tetramethyl-3,4-diazanorcaradiene<sup>27</sup>. This is in contrast to other azepine derivatives which dimerize by Diels-Alder-like cycloadditions<sup>28</sup>. The dimerization was promoted by hydroxylic solvents and retrogression to the monomer was observed on refluxing in chlorobenzene.



The mechanism of the formation of the 3H-azepine ester ( 31 ) was postulated to involve as first step either the elimination of tosylate anion by a unimolecular process, or base-catalysed removal of proton from the nitrogen atom. Both routes result in migration of the vinyl group, rather than nitrogen ( cf. formation of aziridine intermediates from  $\beta$ -aminoethyl

chlorides ) <sup>29</sup> .

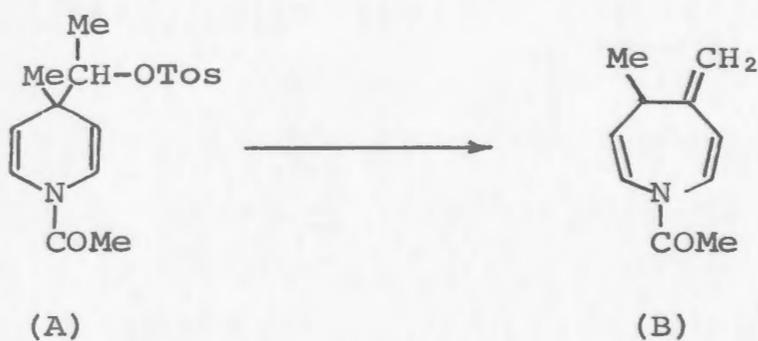


It is apparent from the foregoing discussion that a variety of interesting products is available from 4-chloromethyl-1,4-dihydropyridines ( 3 ) although there is little evidence for the mechanism of their formation.

The object of the present work is to discover new reactions of these interesting compounds and try to obtain mechanistic evidence for some of the rearrangements involved.

In view of Chapman's work on the ring expansion of dihydrobenzyl tosylates <sup>20</sup> , it would seem that the methyl groups at C-2,6 and the electron-withdrawing groups at C-3,5 are not essential for the ring expansion to occur. However, no attempt has been made to prove this, since electron-withdrawing groups at C-3,5 are important for stabilisation of 1,4-dihydropyridines, and the synthesis of relatively unsubstituted dihydropyridines bearing appropriate groups in the 4-position has been

unsuccessful to date. After submission of this thesis, it has been reported that solvolysis of the tosylate A, lacking substituents at C-2,3,5,6, gave the azepine derivative B. [P.M. Atlante, J.F. Biellmann and J. Moron, *Tetrahedron*, 29, 391, 1973.]



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## DISCUSSION

### Nucleophilic Reactions of 4-Chloroalkyl-1,4-dihydropyridines.

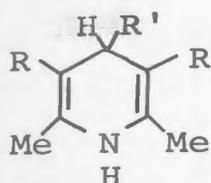
At the outset of this work, it was noticeable that no attempts had been made to examine the action of carbanionoid nucleophiles, e.g. enolate ions of  $\beta$ -dicarbonyl compounds, on the 4-chloromethyl-1,4-dihydropyridines ( 3 ). If such reactions followed the normal course, then the initial product would be a substituted dihydroazepine, e.g. dimethyl 4-(diacetylmethyl)-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (4d) and if the  $\beta$ -dicarbonyl group has an acidic proton remaining, then intramolecular Michael addition may take place to give an 2-azabicyclo[3.2.1]oct-3-ene, e.g. dimethyl 8,8-diacetyl-1,3-dimethyl-2-azabicyclo[3.2.1]oct-3-ene-4,7-dicarboxylate ( 36a ) . The reaction of hydrosulfide ion with the 4-chloromethyl-1,4-dihydropyridine ( 3a ) has been reported<sup>16a</sup> to give a similar bicyclic compound, 2-aza-8-thiabicyclo[3.2.1]oct-3-ene ( 14a ) and such a compound would be an appropriate model for studying the stereochemistry of the enolate products using the ring proton coupling constants.

#### (a.) With Hydrosulfide Ion.

The reaction of sodium hydrosulfide and the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) in ethanol at 65° afforded two crystalline products. The main product,  $C_{13}H_{19}NO_4S$ , white prisms, (m.p. 163-164° , Rf=0.53 ), showed ultraviolet absorption at  $\lambda_{max}$  231 and 291nm ( $\epsilon$  2,850 and 12,900), indicating

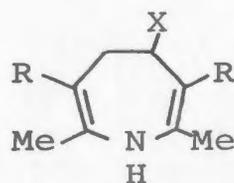
the possibility of 3-aminocrotonate chromophore<sup>17</sup>. The infrared spectrum revealed the presence of N-H stretching ( 3408 and 3307  $\text{cm}^{-1}$ ), saturated ester carbonyl (1737  $\text{cm}^{-1}$ ), and unsaturated ester carbonyl ( 1689  $\text{cm}^{-1}$ ) bands. From the foregoing evidence the 1,4-dihydropyridine and 4,5-dihydroazepine systems can be excluded. The n.m.r. spectrum showed the presence of two methyl esters (  $\tau$  6.26, singlet ), two C-methyl groups (  $\tau$  7.70 and 8.23, singlets ), a C-methyl group (  $\tau$  8.94, doublet,  $J=7.0$  Hz ), a single proton absorption at  $\tau$  5.01 (broad singlet) for NH, whose chemical shift was concentration dependent, two protons at  $\tau$  5.32 ( doublet,  $J=4.8$  Hz ) and 7.45 ( doublet,  $J=7.4$  Hz ), and a proton at  $\tau$  6.96 ( multiplet ). From the coupling constants of above three protons and the doublet methyl group, the product has a  $-\overset{!}{\text{C}}\text{H}-\text{CH}(\text{Me})-\text{CH}(\text{CO}_2\text{Me})-$  system. The mass spectrum of this compound showed parent peak at  $m/e$  285, and a base peak at  $m/e$  185, which can be interpreted as loss of methyl crotonate from the molecular ion. This spectral data is in good agreement with the 2-aza-8-thiabicyclo [3.2.1] oct-3-ene structure ( 14a ). The stereochemistry may be established by n.m.r. ( see later-page 19 ). From the re-examination of the reaction of the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and potassium hydrosulfide in aqueous ethanol, Ashby and Eisner<sup>16a</sup> proposed the 2-aza-8-thiabicyclo 3.2.1 oct-3-ene ( 14a ) structure for the product which Benary had earlier claimed<sup>30</sup> to be the 1,4-dihydropyridine ( 3,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{R}'=\text{CH}_2\text{SH}$  ). The structural assignment was mainly based on spectral data and was discussed in the previous section. With the similarity of the

ultraviolet, infrared, and mass spectra of our compound and that of Ashby and Eisner, they should both have the same cyclic system.



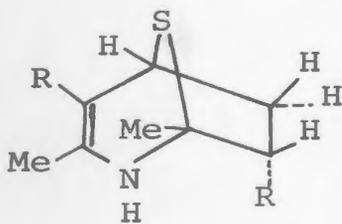
(3)

- a, R=CO<sub>2</sub>Me, R'=CH<sub>2</sub>Cl
- b, R=CO<sub>2</sub>Me, R'=CH<sub>2</sub>Br,
- c, R=CO<sub>2</sub>Me, R'=CH<sub>2</sub>OMe
- d, R=CO<sub>2</sub>Et, R'=CH<sub>2</sub>Cl
- e, R=CO<sub>2</sub>Me, R'=CHMeCl
- f, R=CO<sub>2</sub>Me, R'=CHMeBr
- g, R=CO<sub>2</sub>Me, R'=CHMeOMe
- h, R=CO<sub>2</sub>Me, R'=CHMeSCN



(4)

- a, R=CO<sub>2</sub>Me, X=OMe
- b, R=CO<sub>2</sub>Me, X=N<sub>2</sub> $\begin{matrix} \text{CO}-\text{CH}_2 \\ \text{CO}-\text{CH}_2 \end{matrix}$
- c, R=CO<sub>2</sub>Me, X=CN
- d, R=CO<sub>2</sub>Me, X=CH(COMe)<sub>2</sub>
- e, R=CO<sub>2</sub>Me, X=CH(COMe)CO<sub>2</sub>Me
- f, R=CO<sub>2</sub>Me, X=CH(CO<sub>2</sub>Et)<sub>2</sub>
- g, R=CO<sub>2</sub>Et, X=OEt
- h, R=CO<sub>2</sub>Et, X=CN



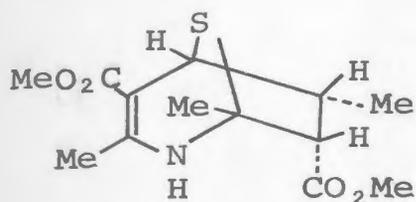
(14)

- a, R=CO<sub>2</sub>Me
- b, R=CO<sub>2</sub>Et

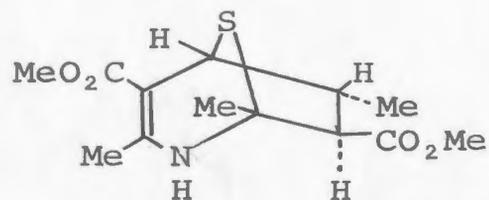
Assignment of the conformations of the C-6 methyl and C-7 methoxycarbonyl groups in the major product was based on the coupling constants among three ring protons. The multiplet at  $\tau$  6.96 is assigned to the proton at C-6 which is coupled to the protons at C-5 and C-7 and the methyl protons at C-6. The low field doublet is assigned to the proton at C-5 whose chemical shift is lowered by the sulfur atom and adjacent unsaturation. This proton is coupled to the proton at C-6 and the coupling constant 4.8 Hz is consistent only with the C-6 proton occupying an exo configuration ( the 6-endo H forms a dihedral angle of almost  $90^\circ$  with 5-H in the Dreiding model and the coupling constant should be very close to zero ). The other doublet at  $\tau$  7.45 is then the proton at C-7. Since the proton at C-6 is exo, the proton at C-7 must be exo for the dihedral angles of C-6 exo - C-7 exo and C-6 exo - C-7 endo are approximately  $0^\circ$  and  $120^\circ$  respectively. The former is in better agreement with the observed coupling constant  $J=7.4$  Hz. The complete structure of the main product is thus given as 1,3-dimethyl-4-methoxycarbonyl-6-endomethyl-7-endomethoxycarbonyl-2-aza-8-thiabicyclo 3.2.1 oct-3-ene ( 33a ). The ultraviolet absorption at  $231\text{nm}(\epsilon 2,850)$  might be explained as due to the interaction between lone pair electrons on nitrogen and the 7-endomethoxycarbonyl group<sup>31</sup>.

The other product,  $C_{13}H_{19}NO_4S$ , white needles, ( m.p.  $144-146^\circ$ ,  $R_f=0.51$  ), showed ultraviolet absorption at  $\lambda_{\text{max}} 293.5\text{nm}(\epsilon 13,550)$ , indicating the possibility of 3-aminocrotonate chromophore<sup>17</sup>. The infrared spectrum showed a N-H stretching

( 3423 and 3322  $\text{cm}^{-1}$  ), saturated ester carbonyl ( 1734  $\text{cm}^{-1}$  ), and unsaturated ester carbonyl ( 1687  $\text{cm}^{-1}$  ). The mass spectrum showed parent peak at m/e 285 and a base peak at m/e 185. With the great similarity of these data, this compound should have the same ring system as main product. The n.m.r. spectrum suggested the presence of two methyl esters ( $\tau$ 6.30, singlet), two C-methyl groups ( $\tau$ 7.69 and 8.17, singlets ), a C-methyl group ( $\tau$ 9.01, doublet,  $J=6.5$  Hz ), a NH proton ( $\tau$ 4.91, broad singlet, signal concentration dependent ), two single protons ( $\tau$ 5.23 and 6.84, doublets,  $J=4.7$  and 3.0 Hz respectively ), and a proton giving a multiplet at  $\tau$  6.91. The low field doublet with coupling constant 4.7 Hz was assigned to proton at C-5 which only has one adjacent proton and whose chemical shift was influenced by the sulfur atom and adjacent unsaturation. The coupling constant again suggests the exo configuration for H at C-6 in this compound. The other doublet with coupling constant 3.0 Hz therefore comes from 6-exo H and 7-endo H coupling ( dihedral angle close to  $120^\circ$  ). The conformations of the 6-methyl and 7-methoxycarbonyl groups were therefore assigned as endo- and exo- respectively in this compound, and the compound ( 33b ) was the C-7 epimer of the main product ( 33a ). The proton absorption of the 7-endo H in compound ( 33b ) was 0.61 ppm to lower field than the 7-exo H in compound ( 33a ). The compound ( 33b ) with 7-exo methoxycarbonyl group was easily epimerized to the stable compound ( 33a ) with 7-endo methoxycarbonyl group by base treatment. The reason for the greater stability of the endo-methoxycarbonyl compound is not apparent.

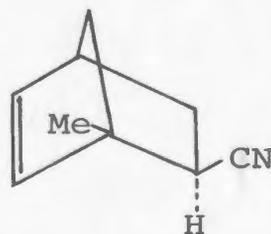
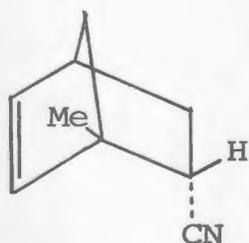


(33a)



(33b)

In this connection, it is interesting that in the case of the structurally related bicyclo[2.2.1] heptenes, the endo-cyano-compound is only 0.39K cal/mole more stable than the exo isomer<sup>37</sup>.



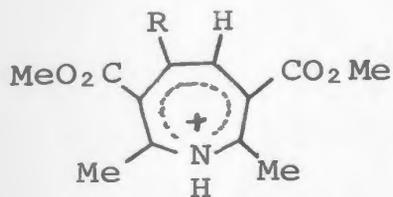
(b.) With Acetylacetonate Enolate Ion.

Reaction of the 4-chloromethyl-1,4-dihydropyridine (3a) with sodium acetylacetonate in dimethylformamide at low temperature yielded a white crystalline product A, C<sub>17</sub>H<sub>23</sub>NO<sub>6</sub>, (m.p. 147-148.5°) and which showed ultraviolet absorption at λ<sub>max</sub> 231 and 329nm (ε 12,100 and 12,250) in 95% EtOH indicating a 4,5-dihydroazepine ring system. The ultraviolet absorption

further indicated that C- rather than O-alkylation had taken place since the product of O-alkylation ( 35 ) would show an additional band at 250nm due to the  $-O-C=C-COMe$  chromophore\* . The spectrum slowly changes to  $\lambda_{max}$  234, 297, and 326 nm ( $\epsilon_{11,900}$ , 26,300 and 12,100 ) in 0.01N ethanolic sodium hydroxide, which we believe is due to hydroxide ion catalysed ring-opening to give a bisketoester and formation of an enolate ion. It is not understood why a rapid initial shift and intensification does not take place on addition of base, as would be expected by the presence of the acetylacetyl side chain. The infrared spectrum showed N-H stretching ( $3414\text{ cm}^{-1}$ ), unsaturated ester carbonyl and acetyl group ( overlap at  $1703$  and  $1700\text{ cm}^{-1}$ ). The n.m.r. spectrum showed absorptions as follows : broad singlet at  $\tau$  4.32 for NH, two methyl esters at  $\tau$  6.32 and 6.35(singlets), two C-methyl groups at  $\tau$  7.67 and 7.75(singlets), two acetyl  $CH_3$  groups at  $\tau$  7.90 and 7.92 (singlets), a doublet at  $\tau$  6.29(  $J=11.0\text{ Hz}$ ), a proton at  $\tau$ 5.71 (multiplet), a proton at  $\tau$  6.85(double doublet,  $J=14.0$  and  $5.6\text{ Hz}$  ), a proton at  $\tau$  7.80(partially obscured by four methyl signals ). The mass spectrum showed a very weak parent peak at  $m/e$  337 and a strong peak at  $m/e$  237(probably the azepine cation ( 34a ) by loss of acetylacetone, possibly via McLafferty rearrangement, but not necessarily so since dihydroazepines

\* Dimedone enol ethyl ether showed ultraviolet absorption at 250 nm(  $\epsilon_{19,200}^{32}$  ) .

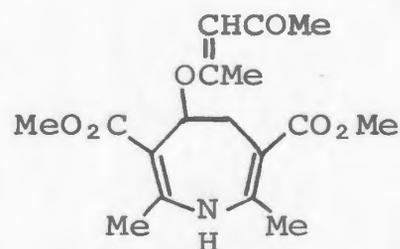
having less complex substituents also show a peak corresponding to the azepine ; see section on mass spectra at the end of the discussion ). On the basis of the spectral data the product was thus assigned the structure ( 4d ).



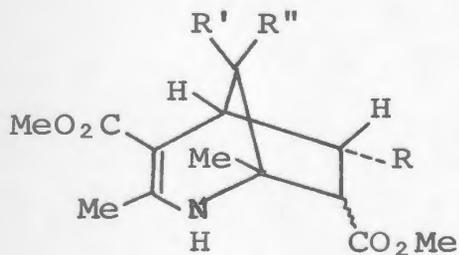
(34)

a, R=H

b, R=Me



(35)



(36)

a, R=H, R'=COMe, R''=COMe

b, R=H, R'=COMe, R''=CO<sub>2</sub>Me

or ( R'=CO<sub>2</sub>Me, R''=COMe )

c, R=H, R'=COMe, R''=CO<sub>2</sub>Et

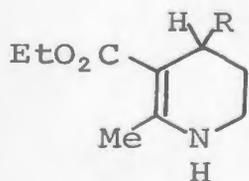
or ( R'=CO<sub>2</sub>Et, R''=COMe )

d, R=Me, R'=COMe, R''=COMe

e, R=Me, R'=COMe, R''=CO<sub>2</sub>Me

or ( R'=CO<sub>2</sub>Me, R''=COMe )

When the reaction was carried out at a higher temperature, instead of the 4,5-dihydroazepine ( 4d ) an isomeric compound B,  $C_{17}H_{23}NO_6$ , (m.p.192.5-193.5<sup>0</sup>), was obtained. This compound was also obtained by treatment of the 4,5-dihydroazepine ( 4d ) with sodium acetylacetonate in the same conditions. The ultraviolet absorption of this compound showed  $\lambda_{max}$  289nm ( $\epsilon$ 13,600) which thus eliminates either a dihydropyridine or dihydroazepine chromophore, but which is in good agreement with a 3-aminocrotonate chromophore in a 6-membered ring, e.g. the tetrahydropyridines ( 37, R=H and 37, R=Me ) have  $\lambda_{max}$  290nm ( $\epsilon$ 14,500) and 285nm ( $\epsilon$ 17,800) respectively<sup>3 3</sup>. The infrared spectrum showed a N-H stretching (3418  $cm^{-1}$ ), saturated ester carbonyl (1736  $cm^{-1}$ ), unsaturated ester carbonyl (1694  $cm^{-1}$ ), and acetyl (1721  $cm^{-1}$ ). The n.m.r. spectrum contained a broad singlet at  $\tau$  5.83 for NH, two methyl esters at  $\tau$  6.32 (singlet), two methyl groups at  $\tau$  7.73 and 8.21 (singlets), two acetyl groups at  $\tau$  7.86 and 7.97 (singlets). The remaining four protons in the range of  $\tau$  6.1-8.6 are partially obscured by the four methyl resonances which appear in this region, thus making detailed analysis impossible.

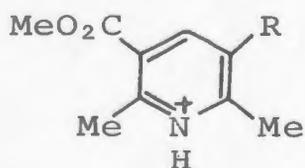


(37)

a, R=H

b, R=Me

The mass spectrum showed parent peak at m/e 337 and a base peak at m/e 208, probably the pyridinium ion ( 38a ) by loss of methyl acrylate and acetyl radical from the molecular ion (see mass spectra section). This fragmentation is very similar to that for the 2-aza-8-thiabicyclo [3.2.1] oct-3-ene system, suggesting that the compound B must have a similar bicyclic system. All the spectroscopic data support a gross structure containing a 2-azabicyclo [3.2.1] oct-3-ene ring system ( 36a). However, because of the complexity of the n.m.r. spectrum, the stereochemistry of the methoxycarbonyl group could not be assigned unambiguously in this compound. For the complete stereochemical studies, the reaction product of the 4-chloromethyl-1,4-dihydropyridine ( 3a ) or 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) with cyclopentadienyl anion was more convenient and will be discussed later.



(38)

- a, R=COME
- b, R=CO<sub>2</sub>Me
- c, R=CO<sub>2</sub>Et

The formation of the 4,5-dihydroazepine ( 4d ) from the acetylacetone reaction was considered to involve elimination of hydrogen chloride by base to give the 4H-azepine ( 9a ), followed by Michael addition of the enolate ion and protonation on nitrogen to give the product ( 4d ). The O-alkylation product ( 35 ) was considered to be thermally unstable since

there is precedent for elimination of the addend to give the original 4H-azepine ( 9 ), ( cf. the compounds ( 4a,g ) will easily eliminate the 4-substituents in solution, such as carbon tetrachloride<sup>1 2,1 3</sup>, or in warm basic conditions<sup>1 2</sup> ). On the other hand, the C-alkylation product ( 4d ) was quite stable to heat and could be purified by sublimation under vacuum without decomposition. Therefore the C-alkylation product ( 4d ) was isolated. When the 4-substituent has a sufficiently acidic proton, examination of molecular models shows that the corresponding carbanion centre can approach sufficiently close to C-7 of the dihydroazepine to effect an intramolecular Michael addition to give the 2-azabicyclo [3.2.1] oct-3-ene ( 36a ). ( see Scheme 1 ). The bicyclic compound ( 36a ) was formed from the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and sodium acetylacetonate or from the 4-(diacetylmethyl)-4,5-dihydroazepine ( 4d ) under more vigorous conditions.

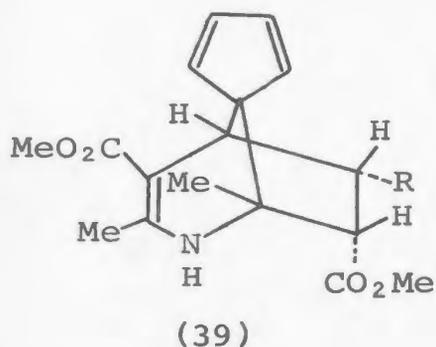


(c.) With Cyclopentadienyl Anion.

In the reaction of cyclopentadienyl anion and the 4-chloromethyl-1,4-dihydropyridine ( 3a ), a product,  $C_{17}H_{21}NO_4$ , ( m.p.195-196.5<sup>0</sup> ) was obtained and which showed ultraviolet absorption at  $\lambda_{max}$  295nm ( $\epsilon$ 16,200) which is characteristic of a 3-aminocrotonate chromophore in a six-membered ring<sup>3 3</sup>. The expected absorption at about 250nm for dialkylcyclopentadiene<sup>3 4</sup> was not distinguishable in the spectrum of this compound, but was quite apparent in the spectrum of the analogous product ( 39b ) from the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ), ( see later ). The infrared spectrum showed N-H stretching ( 3427  $cm^{-1}$  ), saturated ester carbonyl ( 1739  $cm^{-1}$  ), and unsaturated ester carbonyl ( 1681  $cm^{-1}$  ). The n.m.r. spectrum contained a broad singlet at  $\tau$  5.72 for NH, whose chemical shift was concentration dependent, four olefinic protons at  $\tau$  3.69 ( multiplet ) corresponding to the cyclopentadienyl olefinic protons, two methyl esters at  $\tau$  6.29 and 6.38 ( singlets ), two methyl groups at  $\tau$  7.82 and 8.79 ( singlets ), and four protons at  $\tau$  6.81 ( double doublet,  $J=4.9$  and 11.8 Hz ), 7.02 ( broad doublet,  $J=5.8$  and 1.0 Hz ), 7.36 ( broad double doublet,  $J=4.9, 14.0$  and 1.0 Hz ), and 7.62 ( multiplet,  $J=5.8, 11.8,$  and 14.0 Hz ). ( see Fig. 1 ). These signals, especially the latter four proton absorptions are in good agreement with the proposed structure ( 39a ).

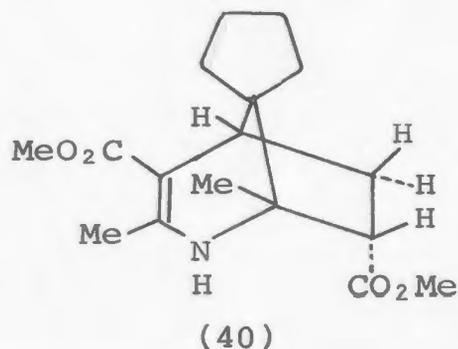
From Dreiding models, the dihedral angles between the 5-H and 6-exo H and the 5-H and 6-endo H were 30<sup>0</sup> and almost 90<sup>0</sup> respectively and should show coupling constants  $\sim 6$  and  $\sim 0.5$ Hz,

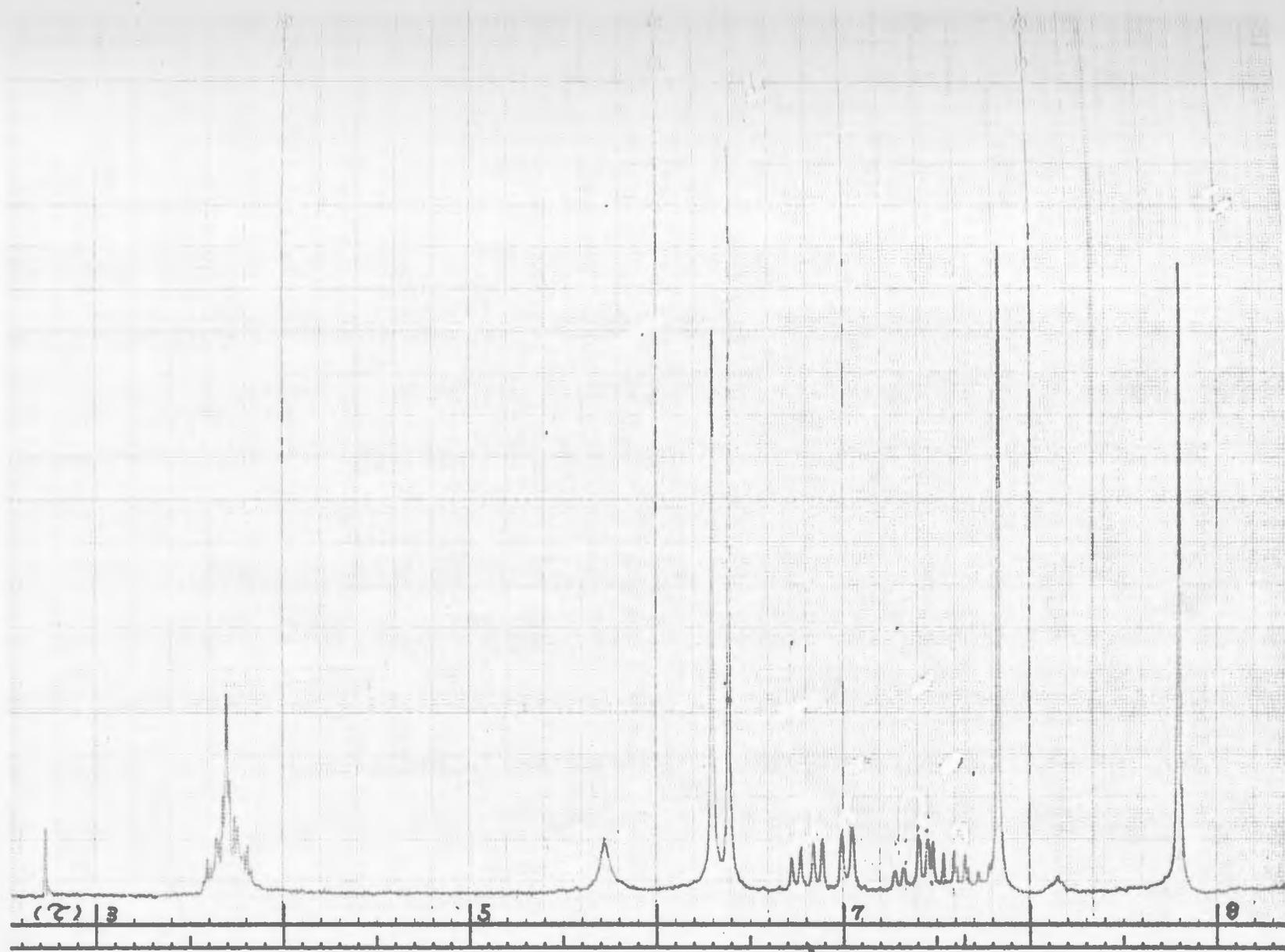
while the dihedral angles between the 7-exo H and 6-exo H and the 7-exo H and 6-endo H were  $0^{\circ}$  and  $120^{\circ}$  respectively and should show coupling constants  $\sim 10$  and  $\sim 5$  Hz. The very weak coupling between protons at C-5 and C-6 endo causes the proton at C-5 to appear as a broad doublet and the broad doublet at  $\tau$  7.02 with coupling constants 5.8 and about 1.0 Hz was thus assigned to the proton at C-5. The multiplet at  $\tau$  7.62 which contained a coupling constant of 5.8 Hz was consequently the exo proton at C-6. The double doublet signal at  $\tau$  6.81 with coupling constants 11.8 and 4.9 Hz was assigned to the 7-exo H, and the broad double doublet at  $\tau$  7.36 was assigned to the 6-endo H using arguments based on the observed coupling constants and measured dihedral angles. Again the conformation of the 7-methoxycarbonyl group was assigned an endo configuration. The mass spectrum showed a strong parent peak at  $m/e$  303 and strong peaks at  $m/e$  217 and 158 corresponding to loss of methyl acrylate and subsequent loss of methoxycarbonyl radical. These fragmentations strongly supported the assigned 2-azabicyclo-[3.2.1] oct-3-ene structure ( 39a ).



a, R=H

b, R=Me





(Fig. 1) The n.m.r. spectrum of dimethyl 1,3-dimethyl-2-azabicyclo[3.2.1]-  
oct-3-ene-4,7-dicarboxylate-8-spiro-cyclopentadiene ( 39a ).

From the reaction of the 4-(1-chloroethyl)-1,4-dihydropyridine (3e) and cyclopentadienyl anion, an analogous compound (39b) with ultraviolet absorption at  $\lambda_{\max}$  241 and 297 nm ( $\epsilon$  3,100 and 15,400), and infrared spectrum similar to compound (39a) was obtained. The extra methyl group was assigned to the 6-endo configuration by a study of coupling constants between protons attached to C-5, C-6, C-7 and the methyl group at C-6. The n.m.r. spectrum showed three protons as a doublet at  $\tau$  7.03 ( $J=5.2$  Hz), another doublet at  $\tau$  7.27 ( $J=8.2$  Hz), and a multiplet centered at  $\tau$  6.92 ( $J=5.2, 8.2$  and  $6.5$  Hz). The methyl group appeared as a doublet at  $\tau$  8.93 with coupling constant 6.5 Hz collapsing to a singlet when decoupled by irradiation at 308 Hz.

The C-1 methyl proton signals at  $\tau$  8.79 and 9.02 in the cyclopentadiene spiro-compounds 39a and 39b respectively are at higher field compared with the C-1 methyl groups in the other bicyclic compounds (36 and 41). The question arises as to whether the C-1 methyl protons are shielded by the diene system in the cyclopentadiene compounds (39a,b) or deshielded by the C-8 carbonyl and alkoxy carbonyl groups in compounds (36 and 41). To solve this problem, cyclopentadiene system in the spiro compound 39a was reduced by catalytic hydrogenation.

The hydrogenation product,  $C_{17}H_{25}NO_4$ , (m.p. 212-213.5 $^{\circ}$ ), showed ultraviolet absorption  $\lambda_{\max}$  296 nm ( $\epsilon$  16,900) and infrared spectrum  $\nu_{\max}$  3427  $cm^{-1}$  for N-H stretching, saturated ester carbonyl, 1730  $cm^{-1}$ , unsaturated ester carbonyl, 1664  $cm^{-1}$ , indicating no change in the heterocyclic ring. The

n.m.r. spectrum contained eight cyclopentane ring protons at  $\tau$  8.38, indicating the cyclopentadiene was hydrogenated, the four protons at  $\tau$  7.06 ( double doublet,  $J=11.0$  and  $5.0$  Hz ), 7.30 ( broad doublet,  $J=5.5$  and  $0.5$  Hz ), 7.65 ( broad double doublet,  $J=5.0$ ,  $12.5$  and  $0.5$  Hz ), and 7.86 ( octet,  $J=5.5$ ,  $11.0$ , and  $12.5$  Hz ) indicating same hetero ring system and same 7-endo methoxycarbonyl configuration in the tetrahydro-compound ( 40 ). The C-1 methyl protons absorption at  $\tau$  8.71 showed only 0.08 ppm shift to low field. Therefore the C-1 methyl protons in compounds ( 36 and 41 ) were largely deshielded by adjacent carbonyl and alkoxy carbonyl groups at C-8.

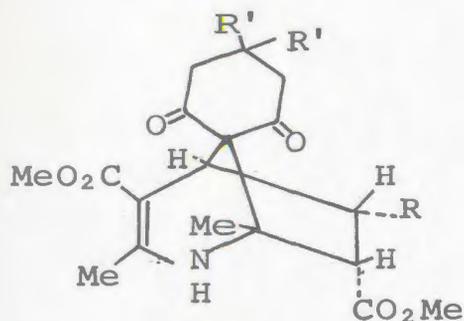
(d.) With Other Enolate Ions.

Several other enolate ions were reacted with the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ), and the corresponding 4-substituted 4,5-dihydroazepines ( 4,42 ) and 2-azabicyclo[3.2.1]-oct-3-enes ( 36 ) were formed under different conditions. (see Table 2 ).

The reaction of the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) with methyl acetoacetate or ethyl acetoacetate, each gave only a single 2-azabicyclo[3.2.1] oct-3-ene ( 36 ) for which we can not assign the configuration of 8-acetyl and 8-methoxycarbonyl or 8-ethoxycarbonyl groups unambiguously. Evidence supporting the single compound nature of the product were sharp melting point, one spot on t.l.c., and clear signals of acetyl  $\text{CH}_3$  and

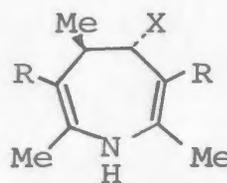
methyl ester  $\text{CH}_3$  or ethyl ester  $\text{CH}_3$  in the n.m.r. spectra. This stereospecificity was unexpected and the complete stereochemistry of the products might be determined by X-ray diffraction analysis. The reason for the stereospecificity is not clear, although it may have its origin in steric considerations, since no bicyclo compound has been isolated from the reaction of diethyl sodiomalonate. Thus it may not be possible to accommodate an ester grouping on one side of C-8.

Also of particular interest are the spiro compounds obtained by using cyclic 1,3-diketones, e.g. dimedone gave compound 41b and 41d.



(41)

- a,  $\text{R}=\text{H}$ ,  $\text{R}'=\text{H}$
- b,  $\text{R}=\text{H}$ ,  $\text{R}'=\text{Me}$
- c,  $\text{R}=\text{Me}$ ,  $\text{R}'=\text{H}$
- d,  $\text{R}=\text{Me}$ ,  $\text{R}'=\text{Me}$



(42)

- a,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{OMe}$
- b,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{N} \begin{array}{l} \text{CO}-\text{CH}_2 \\ | \\ \text{CO}-\text{CH}_2 \end{array}$
- c,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{CN}$
- d,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{CH}(\text{COMe})_2$
- e,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{CH}(\text{COMe})\text{CO}_2\text{Me}$
- f,  $\text{R}=\text{CO}_2\text{Me}$ ,  $\text{X}=\text{CH}(\text{CO}_2\text{Et})_2$

The 4-(1-methoxycarbonyl-2-oxopropyl)-5-methyl-4,5-dihydroazepine (42e) from the reaction of methyl sodioacetate and the 4-(1-chloroethyl)-1,4-dihydropyridine (3e) was shown by the n.m.r. spectrum to contain two components even after removal of the bicyclic compound (36e). However,

separation either by crystallization or chromatography, was unsuccessful and thin layer chromatography revealed only one spot. This product probably is a simple compound which could show two different forms in the n.m.r. spectrum. e.g. A.) keto-enol equilibrium; B.) mixture of cis and trans 4,5-disubstituted compounds; C.) two isomers due to restriction of rotation of the 4-(1-methoxycarbonyl-2-oxopropyl) group by adjacent methyl group at C-5 and methoxycarbonyl group at C-3. The n.m.r. spectrum suggested the two components were present in approximately 1:1 ratio and since the ultraviolet spectrum of this product is similar to other members of the series, a 50% enol content seems unlikely. All 4,5-disubstituted compounds isolated thus far have had trans stereochemistry about C-4 and C-5. This interpretation of the n.m.r. spectrum therefore seems unlikely. The third possibility based on restricted rotation is believed to be the correct explanation of the n.m.r. results. The product then would be a mixture of two components, one having methoxycarbonyl group cis to the 5-methyl group and one with acetyl group cis to the 5-methyl group. If this explanation is correct then a compound having two equivalent groups instead of methoxycarbonyl and acetyl should exist in one form only; the n.m.r. spectrum of the compound ( 42d ) derived from acetylacetone showed only one component. In addition, the product ( 4e ), in which rotation cannot be restricted since the 5-methyl group is absent, showed only one component.

Table 2 : Reactions of 4-Chloromethyl-1,4-dihydropyridine( 3a ) and 4-(1 -Chloro-ethyl)-1,4-dihydropyridine( 3e ) with Enolate Ions.

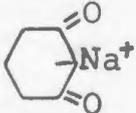
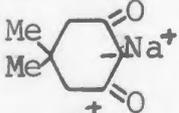
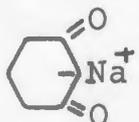
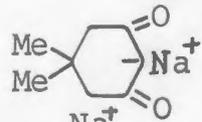
Dihydropyridine	Reagent	Solvent	Temp. (°C)	Products
3a	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Me}$	DMF	0-5	Dihydroazepine( 4e )
3a	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Me}$	DMF	90	2-Azabicyclo(3.2.1)oct-3-ene( 36b )
3a	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Et}$	DMF	90	2-Azabicyclo(3.2.1)oct-3-ene( 36c )
3a	$\text{EtO}_2\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Et}$	THF	40	Dihydroazepine( 4f )
3a	$\text{EtO}_2\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Et}$	DMF	120	Dihydroazepine( 4f )
3a		DMF	70	2-Azabicyclo(3.2.1)oct-3-ene( 41a )
3a		DMF	65	2-Azabicyclo(3.2.1)oct-3-ene( 41b )
3e	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Me}$	DMF	R.T.	Dihydroazepine( 42e )
3e	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Me}$	DMF	100	2-Azabicyclo(3.2.1)oct-3-ene( 36e )

Table 2 : (continued)

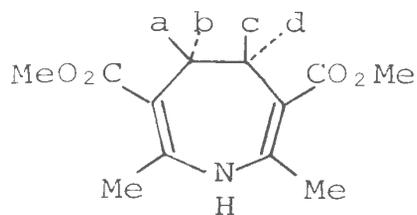
Dihydropyridine	Reagent	Solvent	Temp. (°C)	Products
3e	$\text{EtO}_2\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Et}$	THF	40	Dihydroazepine ( 42f )
3e	$\text{EtO}_2\overset{\text{Na}^+}{\text{C}}\text{HCO}_2\text{Et}$	DMF	120	Dihydroazepine ( 42f )
3e		DMF	90	2-Azabicyclo[3.2.1]oct-3-ene ( 41c )
3e		DMF	90	2-Azabicyclo[3.2.1]oct-3-ene ( 41d )
3e	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCOMe}$	DMF	R.T.	Dihydroazepine ( 42d ) and 2-Azabicyclo[3.2.1]oct-3-ene ( 36d )
3e	$\text{MeCO}\overset{\text{Na}^+}{\text{C}}\text{HCOMe}$	DMF	100	2-Azabicyclo[3.2.1]oct-3-ene ( 36d )

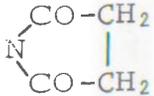
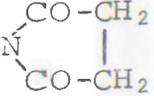
(e.) With Other Nucleophiles.

The simple basic nucleophiles, such as sodium cyanide, potassium succinimide, methanolic triethylamine, with the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) or potassium succinimide with the 4-chloromethyl-1,4-dihydropyridine ( 3a ) gave the corresponding 4-substituted 4,5-dihydroazepines ( 4 and 42 ) which showed characteristic 4,5-dihydroazepine ultraviolet absorption. The products from the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) showed doublet saturated methyl signals with coupling constants around 6.8-7.2 Hz in the n.m.r. spectra, indicating the new substituent is not attached to the same carbon atom which carries the saturated methyl group. The conformation of the new substituents and the saturated methyl group were assigned as trans based on the coupling constants of the two ring protons ( see Table 3 ) and the configuration of the C-6 methyl groups in the bicyclic compounds ( 33 and 39b ). For the importance of this see later.

The reaction of the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) with potassium thiocyanate only gave the simple replacement product ( 3h ) which showed same ultraviolet absorption as starting material ( 3e ).

Table 3 : The Coupling Constants of the Ring Protons of the 4-Substituted 4,5-dihydroazepines ( 4a,b,c and 42a,b,c ).

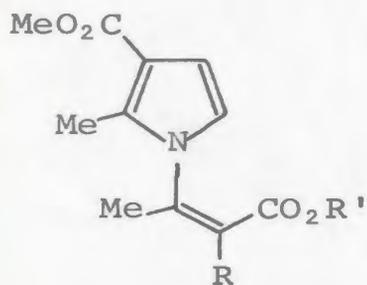


Compound	Substituents				Coupling Constants ( Hz )
	a	b	c	d	
4a	H	H	H	OMe	$J_{ab}=15.0, J_{bc}=7.0, J_{ac} \approx 1$
4b	H	H	H		$J_{ab}=14.0, J_{bc}=6.5, J_{ac}=1.0$
4c	H	H	H	CN	$J_{ab}=15.0, J_{bc}=6.2, J_{ac}=1.5$
42a	Me	H	H	OMe	$J_{bc}=6.6$
42b	Me	H	H		$J_{bc}=6.0$
42c	Me	H	H	CN	$J_{bc}=6.2$

(f.) With Hydroxide Ion.

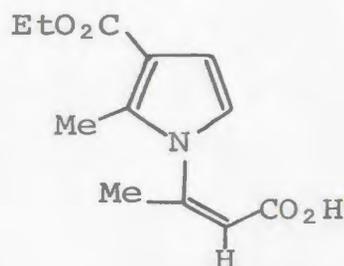
From the reaction of the 4-chloromethyl-1,4-dihydropyridine ( 3d ) with dilute ethanolic sodium hydroxide, a crystalline product,  $C_{12}H_{15}NO_4$ , was isolated. This was subsequently shown to be the  $\beta$ -(3-ethoxycarbonyl-2-methyl-1-pyrrolyl)crotonic acid ( 44 ) by Johnson and Anderson<sup>12</sup>, who suggested that the product was formed via the 4H-azepine ( 9b ) and showed that the latter compound did indeed give the pyrrolyl crotonic acid ( 44 ) under similar conditions.

In an attempt to learn more about the mechanism of this interesting rearrangement, the reaction has been reinvestigated . It is noteworthy that although the starting material has two ester groupings, only one, invariably that attached to the 3-position of the pyrrole ring, is found in the product while the other one undergoes hydrolysis to the acid. This observation poses the question as to whether this is due to some unconsidered aspect of the mechanism or whether it is simply a reflection of the relative rates of hydrolysis of the two ester groupings in the diester ( 43b ). It is well known that pyrrole-2-esters are more easily hydrolysed by base than pyrrole-3-esters<sup>35,36</sup>.



(43)

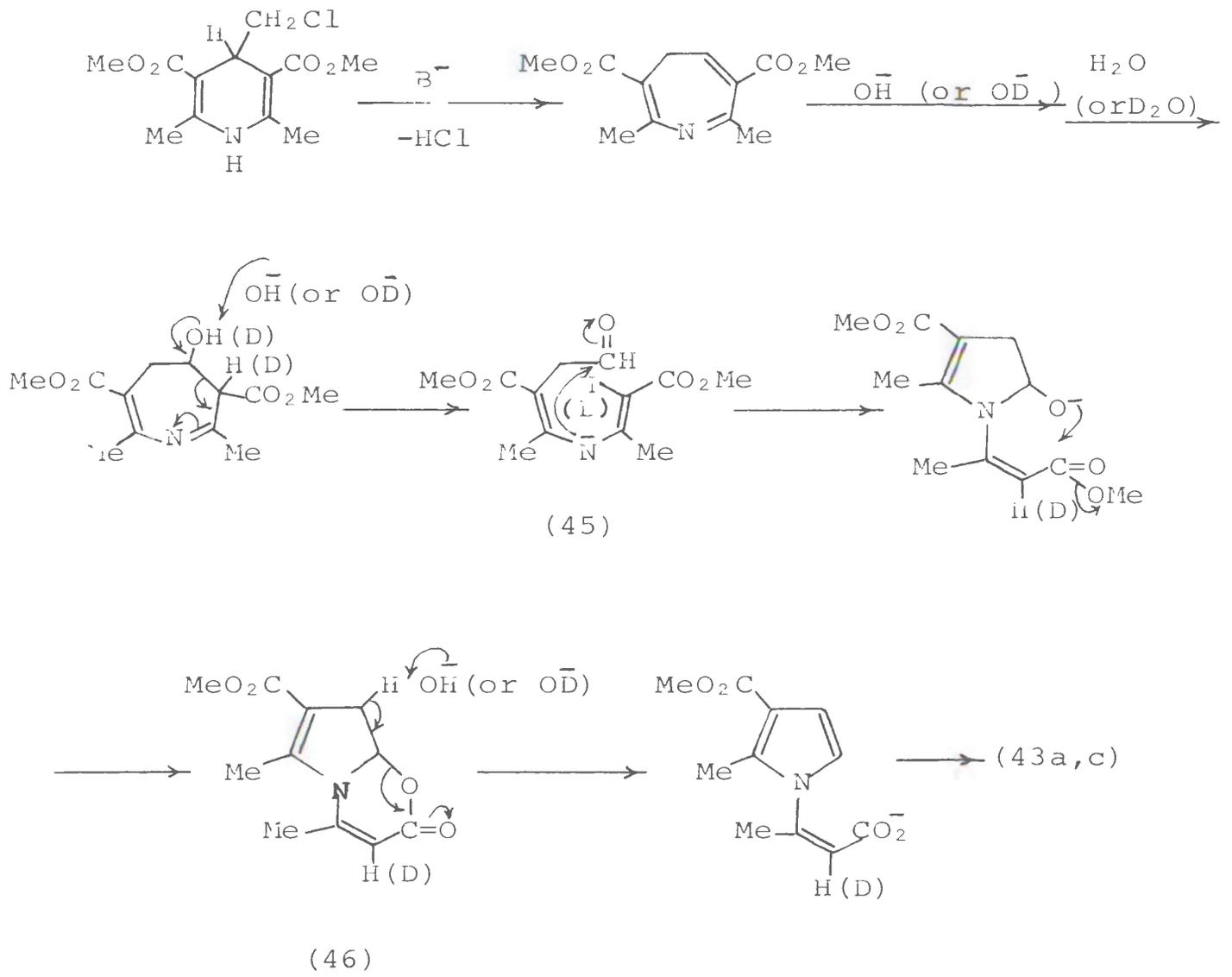
- a, R=H, R'=H
- b, R=H, R'=Me
- c, R=D, R'=H



(44)

The  $\beta$ -pyrrolyl-crotonic acid ( 43a ) and the  $\beta$ -pyrrolyl- $\alpha$ -deuteriocrotonic acid ( 43c ) were obtained in good yield from the reaction of the 4-chloromethyl-1,4-dihydropyridine ( 3a ) with potassium carbonate in aqueous dimethyl sulfoxide and in hexadeuteriodimethyl sulfoxide-deuterium oxide. The methyl  $\beta$ -pyrrolylcrotonate ( 43b ) was prepared from the acid ( 43a ) and showed to not undergo selective hydrolysis on the crotonic ester group in the rearrangement reaction condition. The  $\alpha$ -hydrogen of the  $\beta$ -pyrrolylcrotonic acid did not show isotopic exchange in the above reaction condition. Obviously the deuterium atom was introduced in the earlier step of the reaction and the formation of the  $\beta$ -pyrrolylcrotonic acid ( 43a ) was thought to involve hydration of the 4H-azepine ( 9 ) to form 4-hydroxy-4,5-dihydroazepine by 1,2-addition or 1,4-addition and tautomerization,<sup>3 8</sup> and following basic catalysed retro-Claisen ring opening to give an enaminealdehyde ( 45 ) which undergoes cyclization and lactonization to form lactone ( 46 ). The lactone ( 46 ) was then hydrolysed and finally aromatization by base gave the  $\beta$ -pyrrolylcrotonic acid (43a,c). The same basic treatment of the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) did not give the corresponding  $\beta$ -pyrrolylcrotonic acid but yielded the 4H-azepine ( 47 ) even after stirring for one month. These different results are probably due to the steric effect of the C-5 methyl group in the hydration step.

( Scheme 2 )



(g.) Preparation of the 4-Methyl-4H-azepine ( 47 ).

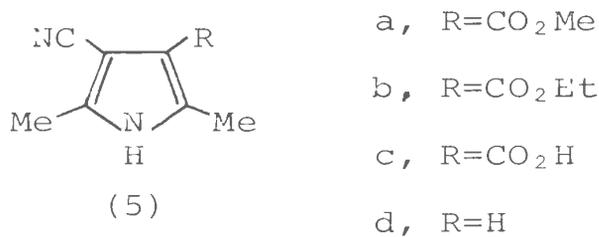
The 4-methyl-4H-azepine ( 47 ) was prepared following Johnson's method by the reaction of the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) and sodium ethoxide in absolute ether, and by pyrolysis of the 4-methoxy-5-methyl-4,5-dihydroazepine ( 42a ) . The product was distilled under reduced pressure as pale yellow oil which showed ultraviolet absorption at  $\lambda_{\max}$  213 and 295nm ( $\epsilon$ 8,200 and 7150 ). The corresponding 4H-azepine(9a) showed  $\lambda_{\max}$  216, 275 and 388nm ( $\epsilon$ 20,700; 3,600; 2,900 ). The infrared spectrum showed unsaturated ester carbonyls ( 1723 and 1702  $\text{cm}^{-1}$  ). The n.m.r. spectrum in carbon tetrachloride at room temperature showed two methyl esters at  $\tau$  6.22 and 6.25 (singlets), a methyl group at  $\tau$  7.60(singlet), a methyl group at  $\tau$  7.77(broad singlet), and a methyl group at  $\tau$  9.14 ( very broad ). At 80<sup>0</sup> , the n.m.r. spectrum showed two methyl esters at  $\tau$  6.24 and 6.27 (singlets), two methyl groups at  $\tau$  7.62 and 7.80 (singlets), a methyl group at  $\tau$  9.12 (doublet, J=7.0 Hz), and a olefinic proton at  $\tau$  4.77 (doublet, J=9.0 Hz). This indicated a slow ring inversion on this compound at room temperature.<sup>26,39</sup> The mass spectrum showed a strong parent peak at m/e 251, and base peak at m/e 192 corresponding to the elimination of CO<sub>2</sub>Me radical.

This compound was also obtained from the reaction of the 4-(1-chloroethyl)-1,4-dihydropyridine( 3e ) with potassium carbonate in dimethyl sulfoxide and by the pyrolysis of the 5-methyl-4-succinimino-4,5-dihydroazepine ( 42b ).

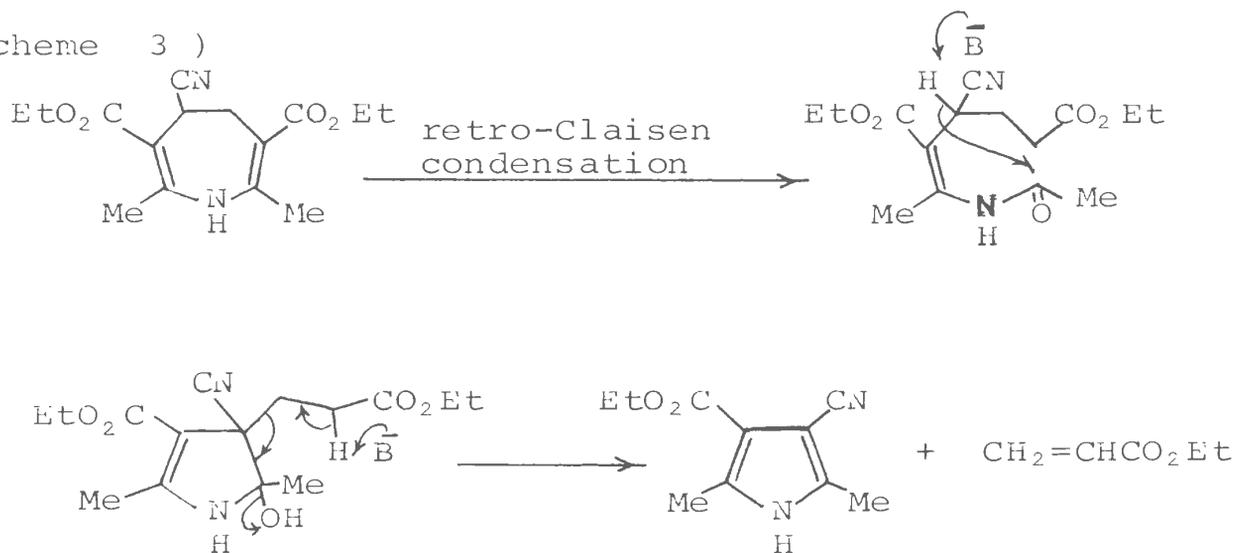
Rearrangements of 4-Cyano-4,5-dihydroazepines.

(a.) Base-catalysed Rearrangement.

From the reaction of chloro-compound ( 3d ) and potassium cyanide, the pyrrole ( 5b ) was isolated along with the 4-cyano-4,5-dihydroazepine ( 4h ), especially when heated. The formation of pyrrole was thought to involve base-catalysed ring contraction of the 4-cyano-4,5-dihydroazepine ( 4h ), since treatment of the 4-cyano-4,5-dihydroazepine ( 4h ) with alcoholic potassium hydroxide gave pyrrole ( 5b ) and ethyl acrylate. The mechanism was originally postulated to occur via a retro-Claisen condensation, followed by base-catalysed cyclization and elimination of ethyl acrylate, as outlined in the following scheme ( scheme 3 ).

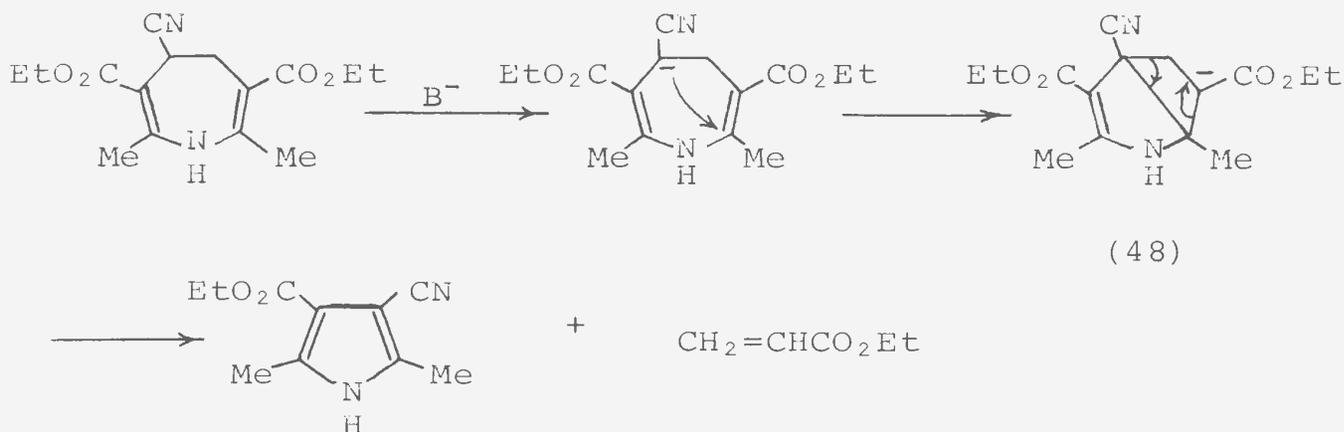


( Scheme 3 )



Later on Johnson and Anderson found that the simpler 4,5-dihydroazepine ( 10 ) with aqueous potassium hydroxide, eliminated ammonia and produced 1-acetyl-2-methylcyclopentene (18), (see introduction section, page 10 ). With cyano substituent, the reaction follows a different course. Johnson and Anderson<sup>12</sup> therefore suggested a transannular interaction mechanism involving formation of carbanion at C-4, followed by nucleophilic attack on the C-7 position, and aromatisation by elimination of ethyl acrylate from the bicyclic compound ( 48 ). (see Scheme 4 ).

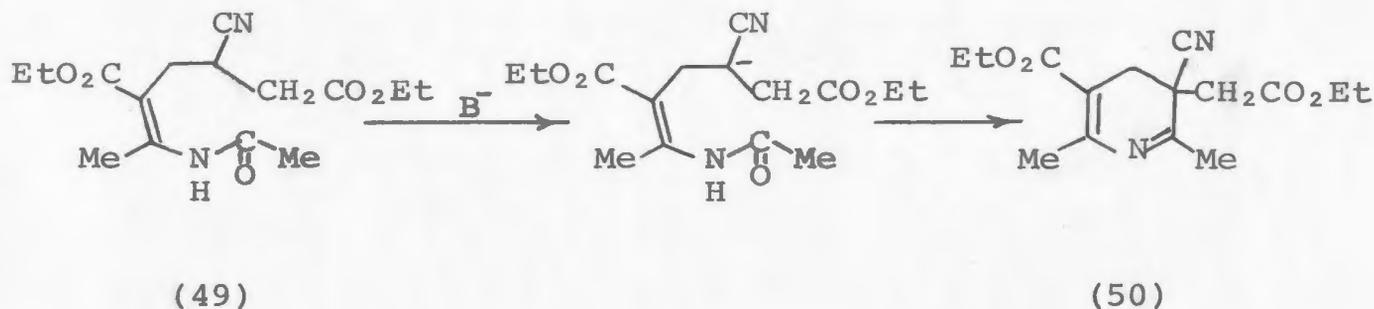
( Scheme 4 )



From the reaction of the 4-cyano-4,5-dihydroazepine ( 4c ) in boiling methanolic potassium hydroxide, we obtained ethyl acrylate and a small amount of its ammonia addition product, methyl 3-aminopropionate which were detected and separated from the distillate by gas liquid chromatography, and were confirmed by mass spectrometry. The pyrrole ( 5a ) was isolated from the residue in good yield, and was identified by the spectral data and also by the conversion of the methyl

ester to the corresponding ethyl ester by transesterification. From the 4-cyano-5-methyl-4,5-dihydroazepine ( 42c ), the same pyrrole ( 5a ) was produced and the corresponding volatile compounds, methyl crotonate and methyl 3-aminobutyrate were detected and separated by gas liquid chromatography.

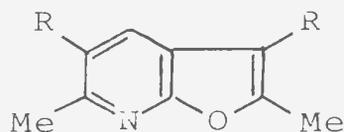
If ring contraction involved the retro-Claisen condensation, ring opening should be possible on the alternative double bond giving the acyclic intermediate ( 49 ) which could not cyclize to the pyrrole but instead might cyclize to give the 3,4-dihydropyridine ( 50 ). No trace of such a product was detected. Although no intermediate of the type 48 has been isolated to date, the mechanism suggested by Anderson and Johnson remains the most likely possibility.



(b.) Acid-catalysed Rearrangement.

During studies of the oxidation of the 4-cyano-4,5-dihydroazepine ( 4h ), Bullock, Gregory and Johnson<sup>9b, 11</sup> found that a small amount of the furo [2,3-b] pyridine ( 7b ) was formed from the action of sodium nitrite in glacial acetic acid. The yield was improved by the action of aqueous ethanolic silver nitrate, and along with the furo [2,3-b] pyridine ( 7b ) a small amount of the pyrrolo [2,3-b] pyridine ( 8b ) was formed. The structures of these rearrangement products were based on spectral data, and chemical properties (e.g. aromaticity, basicity ), and degradation to 6-methyl-3-n-propyl-2-pyridone by hydrolysis, decarboxylation and hydrogenolysis.

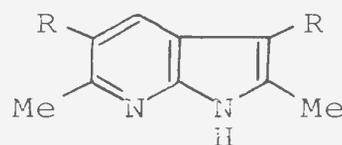
The mechanism of the formation of the furo [2,3-b] - pyridine ( 7b ) and the pyrrolo [2,3-b] pyridine ( 8b ) was postulated to involve protonation of the vinylamine system, followed by hydrolysis to the acyclic intermediate ( 51 ) which could be further converted to (52) by acid. A double cyclization and oxidation then leads to the furo [2,3-b]pyridine( 7b). Double cyclization of (51) and oxidation of (53) will lead to the pyrrolo [2,3-b]pyridine( 8b ). No further investigation and intermediate isolation has been reported. ( see page 48-scheme 5).



(7)

a, R=CO<sub>2</sub>Me

b, R=CO<sub>2</sub>Et

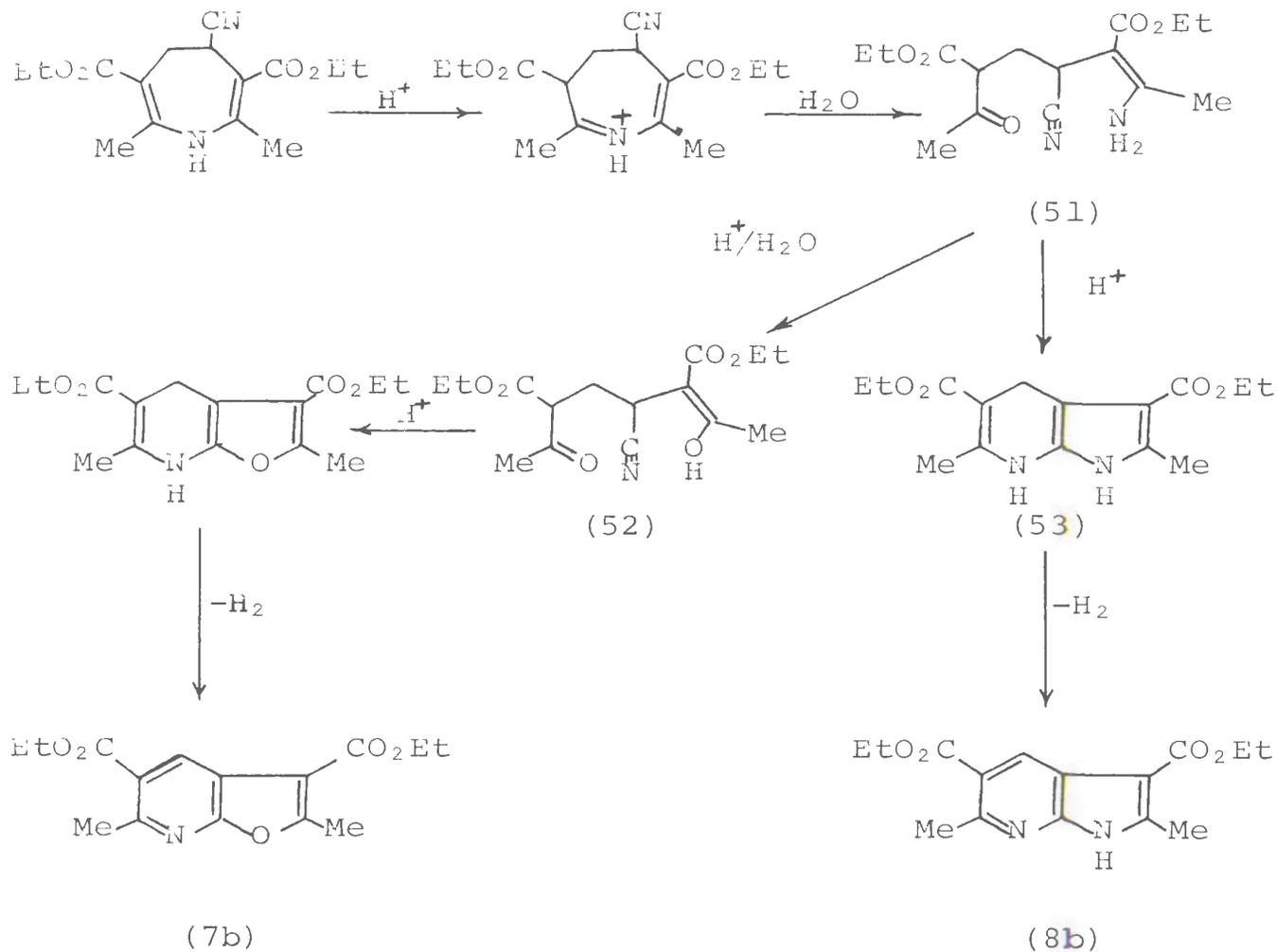


(8)

a, R=CO<sub>2</sub>Me

b, R=CO<sub>2</sub>Et

( Scheme 5 )



We have reinvestigated this reaction in the hope that evidence could be obtained which would support or reject the above mechanism. If the mechanism is correct, the 4-cyano-5-methyl-4,5-dihydroazepine ( 42c ) should give a furo[2,3-b]-pyridine with the extra methyl group in the 4-position. The 4-cyano-5-methyl-4,5-dihydroazepine ( 42c ) was synthesized and reacted with aqueous methanolic silver nitrate, to give three compounds A (  $C_{14}H_{15}NO_5$  ), B (  $C_{14}H_{19}NO_6$  ), and C (  $C_{14}H_{16}N_2O_4$  ).

Compound A showed ultraviolet absorption at  $\lambda_{\max}$  218, 251, and 287nm ( $\epsilon$  23,800, 9,150; 8,500 ) with shoulder at  $\lambda_{\max}$  260.5nm ( $\epsilon$  8,000) and infrared spectrum  $\nu_{\max}$  at 1727  $\text{cm}^{-1}$ , corresponding to the ester carbonyl. The n.m.r. spectrum showed two methyl esters at  $\tau$  6.03 and 6.09 (singlets), and three methyl groups at  $\tau$  7.29, 7.36 and 7.45 (singlets) shifted to low field compared with starting material indicating the strong ring current and hence the aromatic nature of the compound. The compound C showed ultraviolet absorption at  $\lambda_{\max}$  228 and 294nm ( $\epsilon$  24,900; 11,000) with shoulder at  $\lambda_{\max}$  250nm ( $\epsilon$  15,500), and infrared spectrum  $\nu_{\max}$  at 3435, 3205, 1727, and 1709  $\text{cm}^{-1}$  corresponding to the N-H and ester carbonyl stretchings. The n.m.r. spectrum showed a proton at  $\tau$  -2.05 for NH, two methyl esters at  $\tau$  6.03 and 6.11 (singlets), and three methyl groups at  $\tau$  7.32, 7.35, and 7.42 (singlets), which were again shifted to low field compared with starting material, indicating aromaticity. The very similar spectra suggested that the two compounds possessed similar ring systems differing only in the replacement of the oxygen atom of A by NH function in compound C.

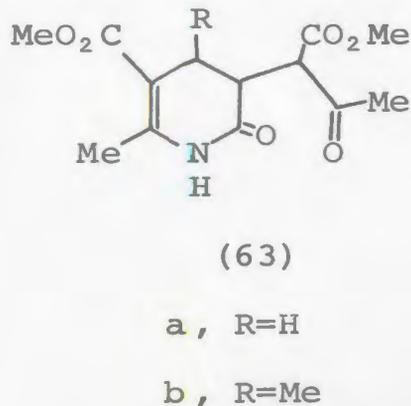
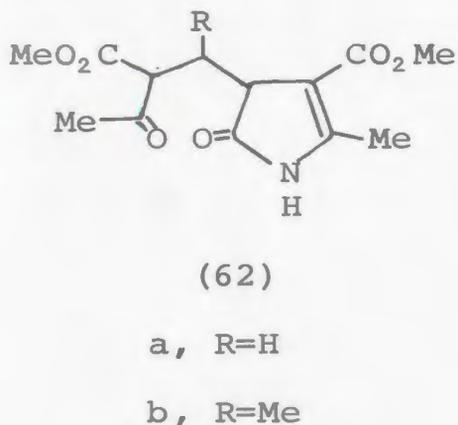
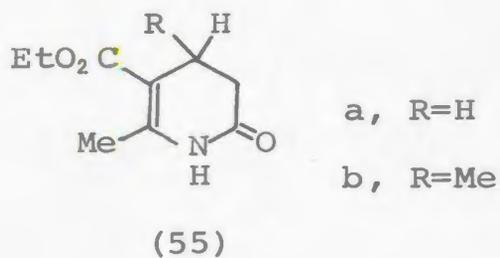
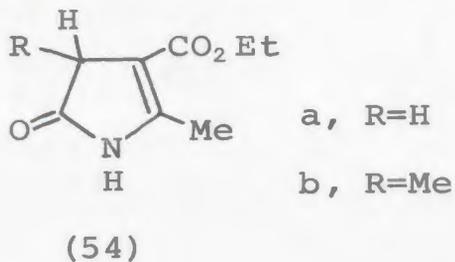
From the 4-cyano-4,5-dihydroazepine ( 4c ) only two compounds D (  $\text{C}_{13}\text{H}_{13}\text{NO}_5$  ) and E (  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$  ) were obtained. Compound D was identical with the furo [2,3-b] pyridine ( 7a ) from the reaction of the N-methyl-4-chloromethyl-1,4-dihydropyridine ( 20,  $\text{R}=\text{CO}_2\text{Me}$  ) and potassium cyanide<sup>22</sup>. The ultraviolet and infrared spectra of compound D and E were almost identical with the furo [2,3-b] pyridine ( 7b ) and the pyrrolo-[2,3-b] pyridine ( 8b ), and again similar to the compound A

and C from the reaction of the 4-cyano-5-methyl-4,5-dihydroazepine (42c). There was no compound corresponding to compound B formed in this reaction. From above simple relationship, the compound A was assigned as furo [2,3-b] pyridine ring system, and the compounds C and E as pyrrolo [2,3-b] pyridine ring system. Mass spectra of these four compounds A, C, D, and E, all showed strong parent peaks ( as base peaks ) and similar fragmentation patterns corresponding to the elimination of MeO, MeOH, and CO<sub>2</sub>Me species. ( see mass spectra section). This is again a good support of the stable ring structures.

Compound B showed ultraviolet absorption at  $\lambda_{max}$  214 and 279.5nm ( $\epsilon$  3,200 and 11,500) in 95% EtOH, indicating the 3-acetamidocrotonate chromophore possibly the  $\beta$ -unsaturated- $\gamma$ -lactam or the  $\gamma$ -unsaturated- $\delta$ -lactam, ( e.g. the  $\gamma$ -lactams 54a, 54b give ultraviolet absorption at  $\lambda_{max}$  218, 280nm ( $\epsilon$  3,240 and 11,180) and 218, 280nm ( $\epsilon$  4,250 and 12,000); the  $\delta$ -lactams 55a, 55b give ultraviolet absorption at  $\lambda_{max}$  212, 279nm ( $\epsilon$  2,435 and 11,740) and 214, 279nm ( $\epsilon$  2,915 and 12,270<sup>40</sup> ). The infrared spectrum showed N-H stretching ( 3400 and 3224  $cm^{-1}$  ), saturated ester carbonyl ( 1750  $cm^{-1}$  ), unsaturated ester carbonyl and ketone carbonyl ( overlap at 1720-1695  $cm^{-1}$  ), amide carbonyl ( 1640  $cm^{-1}$  ), support the 3-acetamido-crotonate and methyl acetoacetate systems. Mass spectrum showed parent peak at m/e 297 and base peak at m/e 181 corresponding to loss of methyl acetoacetate by McLafferty rearrangement. From the evidence of the foregoing spectra the two possible structures 62b and 63b were postulated, and the n.m.r. spectrum is in agreement with 63b.

Three protons at  $\tau$  5.99 ( d, J=11.4 Hz ), 6.34 ( d.d,

$J=11.4$  and  $5.5$  Hz), and  $6.91$  (m,  $J=7.0$  and  $5.5$  Hz) were in good agreement of the structure 63b . In the structure 62b, three protons should give doublet, doublet, and multiplet pattern. The remaining signals at  $\tau$  6.19 and 6.22 (singlets) were assigned to non-equivalent ester methyls,  $\tau$  7.55 and 7.72 (singlets) for ring methyl and acetyl, and a doublet at  $\tau$  9.06 ( $J=7.0$  Hz) for the remaining methyl group which has one adjacent proton. The ultraviolet spectra of 62b and 63b should be very similar for there is not much difference between the ultraviolet spectra of unsaturated five-membered lactam and six-membered lactam, but the amide carbonyl and the unsaturated ester carbonyl stretching frequencies of the product B were in good agreement with the  $\gamma$ -unsaturated- $\delta$ -lactam<sup>40</sup> . This product could be converted to the furo [2,3-b] pyridine ( 67b ) in cold conc. sulfuric acid.



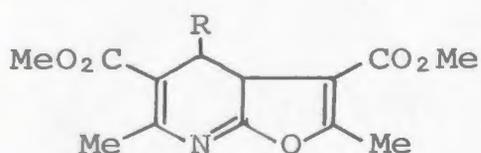
Reaction of the 4-cyano-5-methyl-4,5-dihydroazepine ( 42c ) in aqueous methanolic hydrochloric acid, mainly yield compound B and along with small amount of A and C.

Treatment of the 4-cyano-4,5-dihydroazepine ( 4c ) with strong acidic resin, Dowex 50W-X8 in aqueous methanol mainly produced a colorless oil F, and small amount of the furo [2,3-b] pyridine ( 67a ) and the pyrrolo [2,3-b] pyridine ( 68a ). The product F,  $C_{13}H_{17}NO_6$ , gave positive ferric chloride test and showed ultraviolet absorption at  $\lambda_{max}$  260nm (  $\epsilon$ 1,700 ) in 95% EtOH, and  $\lambda_{max}$  275nm (  $\epsilon$ 27,000 ) in 0.01N methanolic sodium hydroxide, indicating the methyl acetoacetate chromophore . Infrared spectrum showed saturated ester carbonyl (  $1752\text{ cm}^{-1}$  ), ketone carbonyl (  $1729\text{ cm}^{-1}$  ) and cyano group (  $2252\text{ cm}^{-1}$  ) again indicating the presence of the  $\beta$ -keto-ester system. ( cf. Dimethy  $\alpha,\alpha'$  -diacetyladipeate showed ester carbonyl at  $1752\text{ cm}^{-1}$  and ketone carbonyl at  $1724\text{ cm}^{-1}$  ).

Compound F was shown to undergo cyclization and oxidation to give the furo [2,3-b] pyridine ( 67a ) on long exposure to air in solution containing a trace of acid. This compound also cyclized to form compound G on heating without acid catalyst, and the compound G was oxidized by air or nitrous acid to give furo [2,3-b] pyridine ( 67a ).

Compound G,  $C_{13}H_{15}NO_5$  , showed ultraviolet absorption at  $\lambda_{max}$  223 and 347 nm (  $\epsilon$ 9,400 and 8,550 ) in 95% EtOH. Infrared spectrum showed N-H stretching (  $3297\text{ cm}^{-1}$  ), unsaturated ester carbonyls (  $1720$  and  $1686\text{ cm}^{-1}$  ). The n.m.r. spectrum showed a broad singlet at  $\tau$  0.52 assigned for NH, two methyl

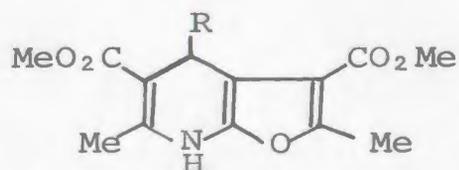
esters at  $\tau$  6.22 and 6.35 ( singlets ), a methyl group at  $\tau$  7.53 (singlet), another methyl group at  $\tau$  7.80 (triplet,  $J=0.5$  Hz ) which showed long range coupling with ring protons which appear as a quartet at  $\tau$  6.40 (  $J=0.5$  Hz ). From this spectroscopic data, especially the NH signal, a possible structure 60a was excluded, and the structure 61a was in good agreement with the above spectral data and chemical evidence. The mass spectrum showed parent peak at  $m/e$  265 and peaks corresponding to M-1 and M-2, probably the furo-pyridinium ion ( 69 ) and the furo-[2,3-b] pyridine ( 67a ) by dehydrogenation.



(60)

a, R=H

b, R=Me



(61)

a, R=H

b, R=Me

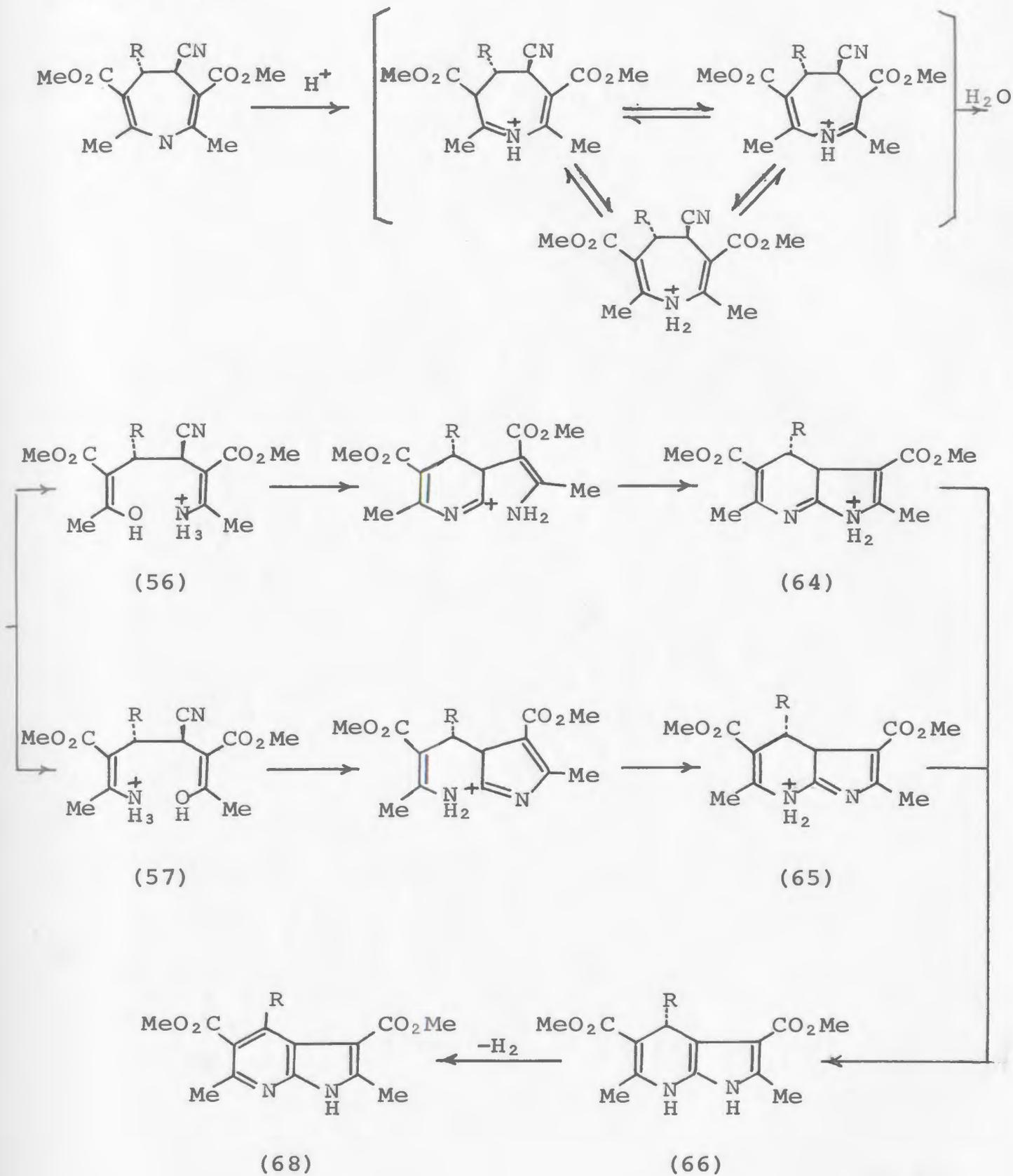
Isolation of the ring-opened intermediate, the cyano-diketodiester ( 58a ) from the acidic reaction of the 4-cyano-4,5-dihydroazepine ( 4c ), and the strong tendency of this compound to undergo acid-catalysed cyclization, support a mechanism for the formation of the furo [2,3-b] pyridine ( 67 ) involving initial protonation of the 4-cyano-4,5-dihydroazepine ( 4c, 42c ) on the dienamine function, followed by hydrolysis to form ring-opened ketoiminoester ( 56, 57 ) and further hydrolysis to form the cyanodiketodiester ( 58 ). This compound

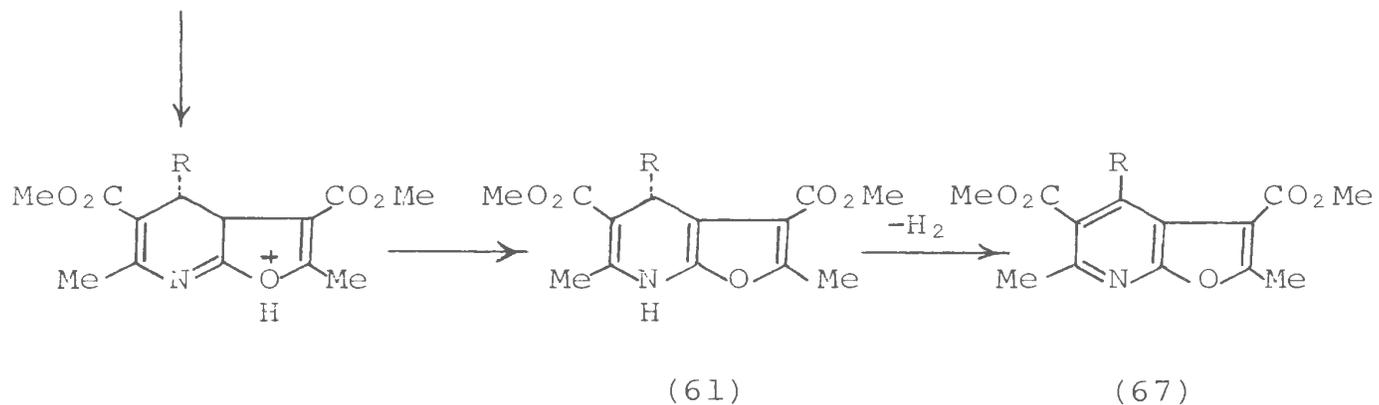
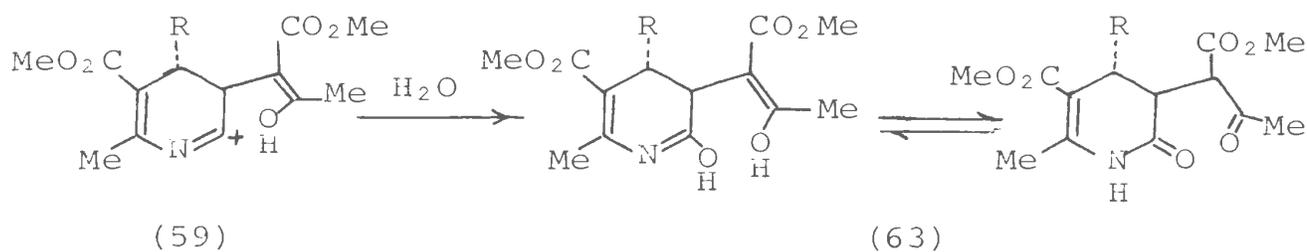
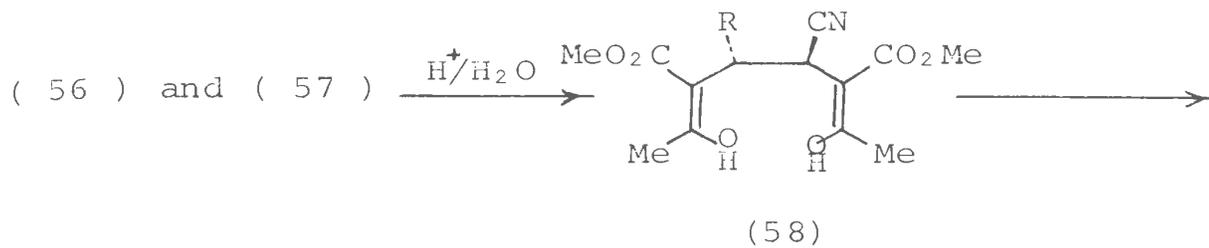
cyclized to form the six-membered ring intermediate ( 59 ) by acid-catalysed reaction of cyano group and keto group. The intermediate ( 59 ) may then form either the furopyridine system or the lactam ( 63 ) by competitive nucleophilic attack by the acetoacetate side chain or a water molecule\* .( cf. Many 5-oxonitriles have been cyclized to form lactams by acid-catalysed reaction<sup>41</sup> ). In the case of the 4-cyano-5-methyl-4,5-dihydroazepine ( 42c ), the cyclization was slightly hindered by the methyl group and the competitive reaction favored the hydration and gave more lactam, especially in the strong acidic conditions.

The furo [2,3-b]-1,4-dihydropyridine ( 61a ) which converted from the acyclic compound ( 58a ) was shown to undergo oxidation to form furo [2,3-b] pyridine ( 67a ), by air or by nitrous acid. The pyrrolo [2,3-b] pyridines ( 68 ) were formed by a similar cyclization from the ketoiminoesters ( 56, 57 ).

\* The mechanism for the cyclization of the acyclic nitrile follows that of Meyers and Sircar, although it is appreciated that this suffers from the disadvantages of the large distance between the N of the cyanide and the C of the carbonyl group, and the formation of high-energy cations. [A.I. Meyers and J. C. Sircar in "The Chemistry of the Cyano group" edited Z. Rappoport. Interscience London 1970. page 341.] This may mean that attack by water or the enolic hydroxyl on the nitrile carbon atom and by the N on the carbonyl carbon is concerted.

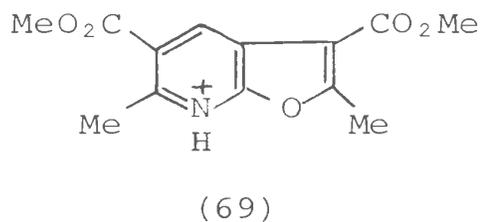
( Scheme 6 )





a, R= H

b, R=Me



The Mechanism of the Ring Expansion of 4-Halogenoalkyl-1,4-dihydropyridines.

A wide range of products such as derivatives of pyrrole, dihydroazepine, azepine, fulvene, furo [2,3-b]pyridine, pyrrolo [2,3-b] pyridine, and 2-azabicyclo [3.2.1] oct-3-ene had been reported from the reaction of the 4-chloromethyl-1,4-dihydropyridine ( 3 ) with various nucleophiles (see introduction section ). The rearrangement products largely depend on the basic character of the nucleophiles and the N-substitution, and these products occasionally undergo further base-catalysed rearrangements but almost invariably a ring expansion reaction appears to be necessary as initial step.

In order to study the ring expansion reaction and related rearrangements, the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) was prepared by condensation of 1,2-dichloropropyl ethyl ether and methyl 3-aminocrotonate in benzene. The product showed characteristic 1,4-dihydropyridine ultraviolet absorption<sup>+2</sup>, and the structure was confirmed by elemental analysis and other spectral characteristics ( see Experimental section ). This compound possesses a methyl group on the carbon atom where the chlorine is located and will act as label in the rearrangements. The corresponding bromo-compound ( 3f ) was prepared by the treatment of the 4-methoxy-5-methyl-4,5-dihydroazepine ( 42a ) with conc. hydrobromic acid in ether. The spectral data of the bromo-compound ( 3f ) were similar to its chlorine analogue ( see Experimental section ). For the comparison of

the reactions with some nucleophiles, the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and the 4-bromomethyl-1,4-dihydropyridine ( 3b ) were also prepared by Johnson's method.<sup>12</sup>

From a kinetic study of the rearrangement of the 4-chloromethyl-1,4-dihydropyridine ( 3d ) with potassium cyanide in aqueous ethanol at room temperature, Brignell and collaborators<sup>14</sup> postulated a general base-catalysed second order reaction, in which the removal of the hydrogen from NH is the rate-determining step. In support of this mechanism it was shown that the N-methyl 4-chloromethyl 1,4-dihydropyridine ( 20, R=CO<sub>2</sub>Me ) reacts much slower, and the powerfully nucleophilic, but non-basic iodide ion did not react in alcohol or acetone. However, simple replacement of the chloride by iodide took place in boiling acetonitrile .

From a study of the solvolysis of the 4-chloromethyl-1,4-dihydropyridine ( 3a ), Gregory and Bullock<sup>15</sup> found that methanolysis without adding triethylamine gave the 4-methoxymethyl-1,4-dihydropyridine ( 3c ) as major product. But in the presence of triethylamine the main product was the 4-methoxy-4,5-dihydroazepine ( 4a ) and the reaction rate in the latter case was independent of the amount of triethylamine added. On the basis of these observation and kinetic results, and the ability of the 4H-azepine ( 9a ) or 4-methoxy-4,5-dihydroazepine ( 4a ) to react with acid to regenerate dihydropyridines, a reaction mechanism involving a non-classical carbonium ion or an equilibrating set of classical carbonium ions formed by homoallylic participation and electron release from the nitro-

gen was proposed.

If the rate-determining step was the removal of proton from NH, and then followed by very rapid rearrangement and elimination of halide ion, the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and the 4-bromomethyl-1,4-dihydropyridine ( 3b ) should react at the same rate. However, it has been found that in the competitive reaction of equimolar quantities of the 4-chloromethyl-1,4-dihydropyridine ( 3a ) and the 4-bromomethyl-1,4-dihydropyridine ( 3b ) with potassium carbonate in dimethyl sulfoxide- $d_6$ , the bromo-compound ( 3b ) was used up within 30 minutes while at this time more than 70% of the chloro-compound ( 3a ) remains from the n.m.r. measurement. Assuming that the acidities of the NH groupings are approximately the same in the two compounds, then the reaction rate seems to depend on the nature of the leaving group. The competitive reaction of the 4-(1-chloroethyl)-1,4-dihydropyridine ( 3e ) and the 4-(1-bromoethyl)-1,4-dihydropyridine ( 3f ) also showed a similar result. (see Experimental section). In order to eliminate the solubility factor involved in the reaction, the competitive reaction was carried out in very dilute solution with excess reagent and at constant temperature (  $26^{\circ}$  ). The reactions were followed by measurement of the ultraviolet absorption spectra ( see Experimental section and Fig. 2 ).

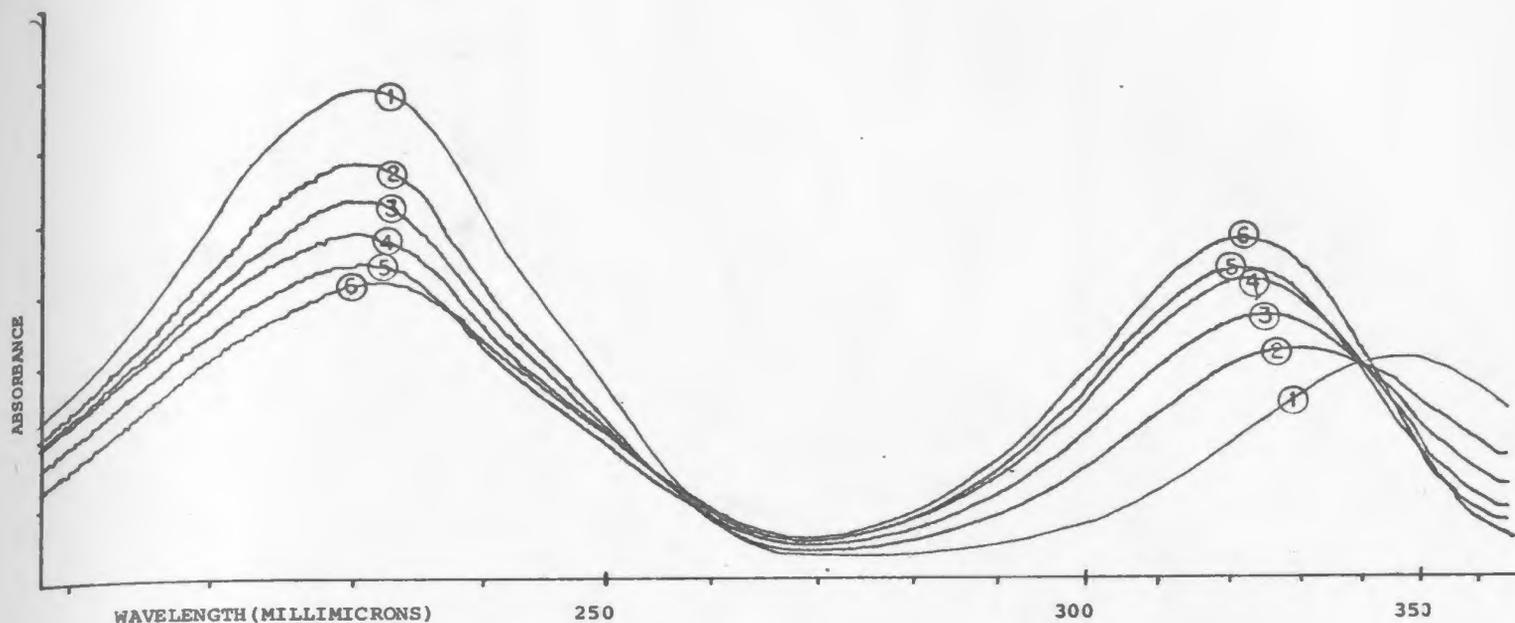
From the results, it is clear that the bromo-compound ( 3b ) reacts faster than the chloro-compound ( 3a ) either in the presence of strongly basic or weakly basic conditions, and both compounds react in strongly basic conditions much faster

than in weakly basic conditions. Thus the reaction is dependent on the nature of leaving groups and also dependent on the base strength. This suggests that both a modified Brignell's mechanism, and Gregory and Bullock's mechanism probably are equally possible.

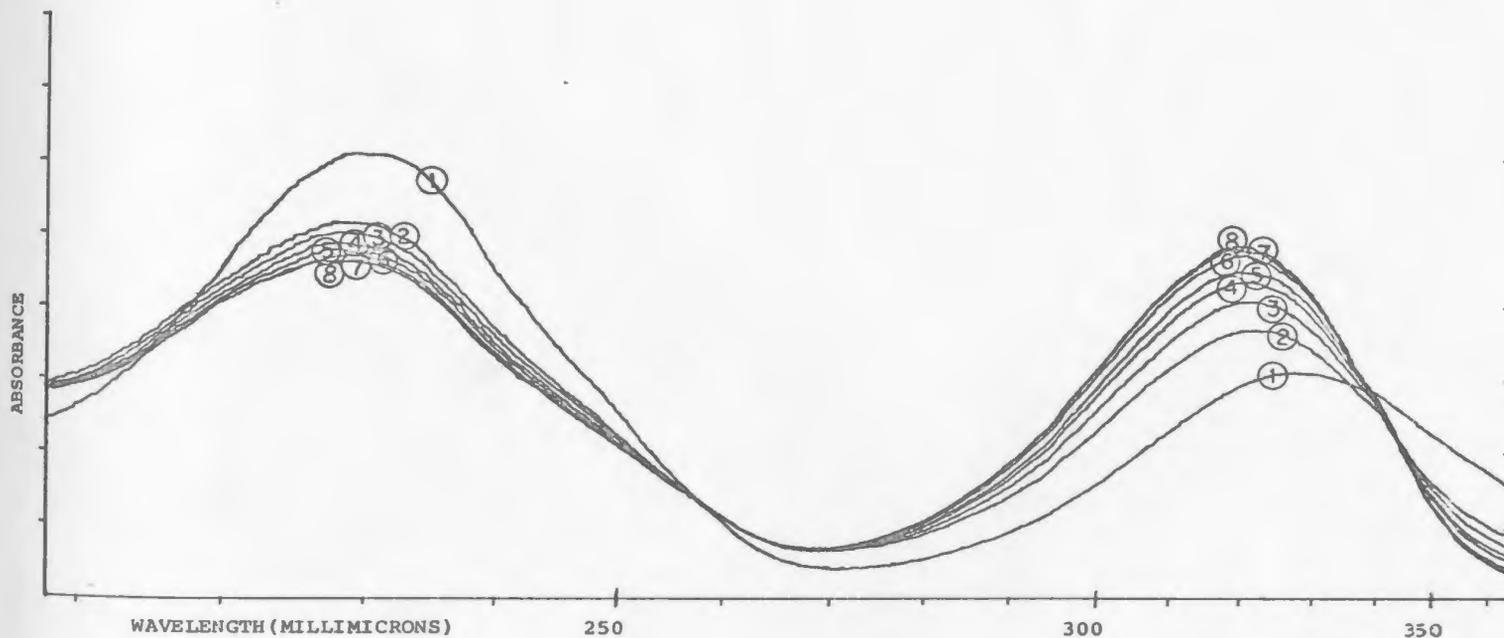
In strongly basic conditions, removal of proton from nitrogen atom take place very rapidly and is followed by elimination of halide ion which is the rate-determining step. In weakly basic conditions, homoallylically assisted ionization of halide ion may occur as a rate-determining first step to give an equilibrating set of carbonium ions or a non-classical carbonium ion which may then react with nucleophile to give 4-substituted 4,5-dihydroazepine ( 4 ) or lose a proton to give the 4H-azepine ( 9 ). The equilibrium concentration of the N-deprotonated species ( 3A ) would be much lower in weakly basic media and therefore a small fraction of the reaction, if any, would proceed by the modified Brignell route.

The formation of product may occur by attack of nucleophile on the carbonium ion, or by addition to the 4H-azepine ( 9 ) or its valence isomer, the azanorcaradiene ( 9A ). The addition to the 4H-azepine is a type of Michael reaction because the 4H-azepine ( 9 ) has  $C=C(C=N)-CO_2R$  system which showed two electron withdrawing groups on the C-5 and C-6 double bond. ( cf. the system  $C=C-C=N$  behaves like the  $C=C-C=O$  in the Michael reaction, and quinone imides <sup>4 3</sup>, 2-vinylpyridines, and 4-vinylpyridines <sup>4 4</sup> are good acceptors in the Michael reaction towards the reactive methylene compounds ).

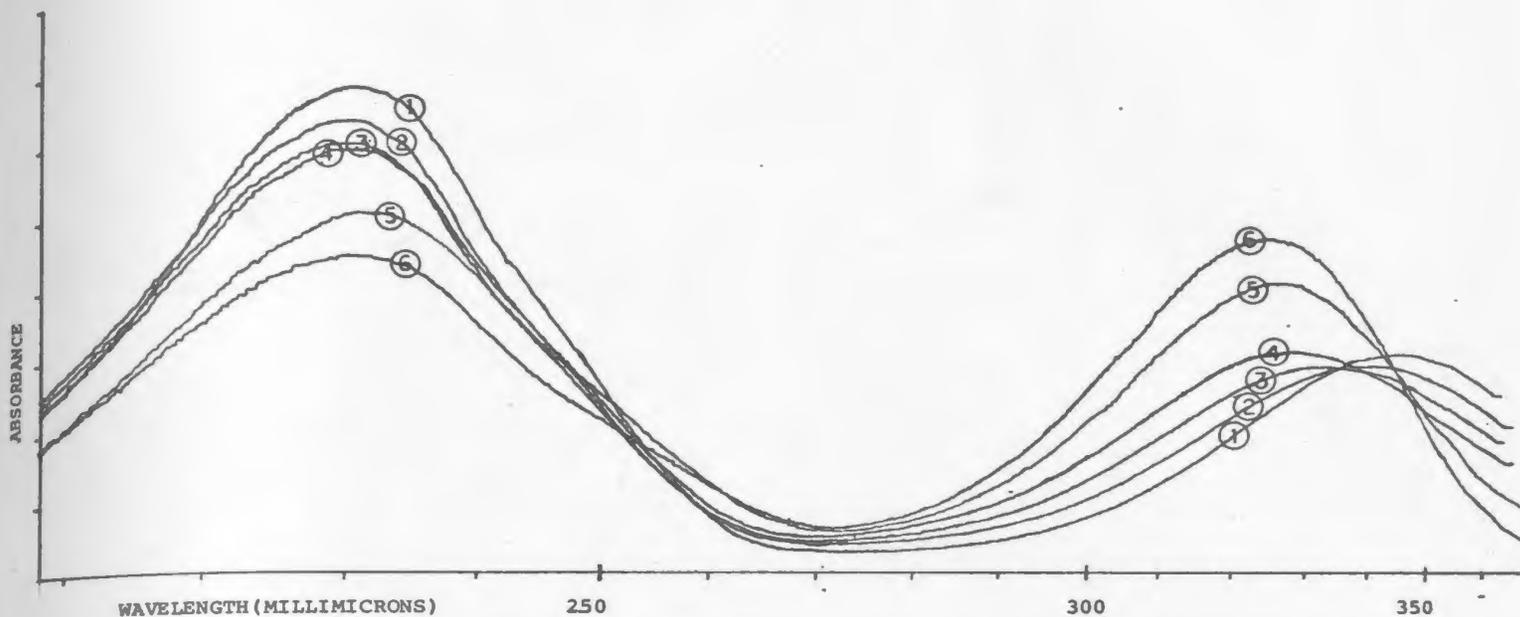




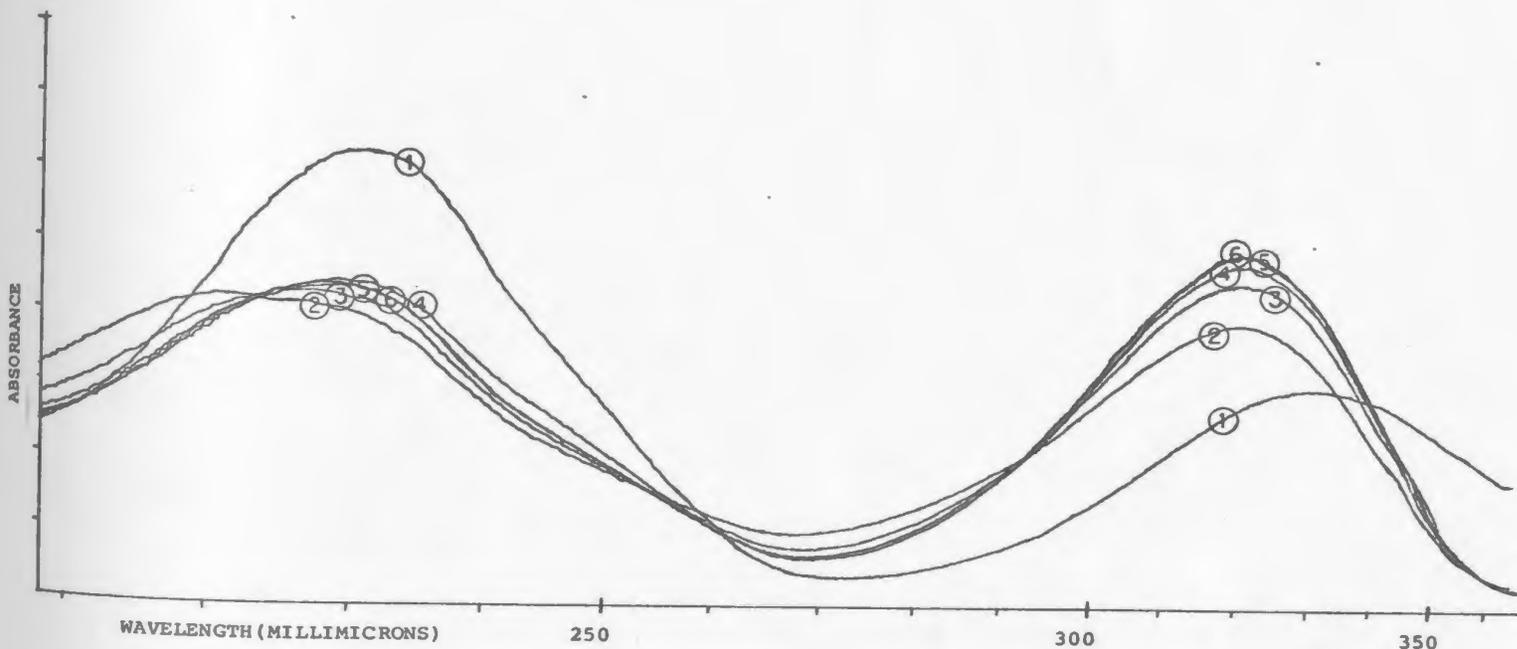
(Fig. 2a) Reaction of the 4-chloromethyl-1,4-dihydropyridine (3a) with sodium methoxide in methanol : 1, 0 h; 2, 12 h; 3, 25 h; 4, 38.5 h; 5, 49.5 h; 6, 86.5 h.



(Fig. 2b) Reaction of the 4-bromomethyl-1,4-dihydropyridine (3b) with sodium methoxide in methanol : 1, 0 min.; 2, 5 min.; 3, 10 min.; 4, 15 min.; 5, 20 min.; 6, 30 min.; 7, 40 min.; 8, 50 min.



(Fig. 2c) Reaction of the 4-chloromethyl-1,4-dihydropyridine (3a) with triethylamine in methanol : 1, 0 h; 2, 11 h; 3, 22 h; 4, 35 h; 5, 96 h; 6, 192 h.



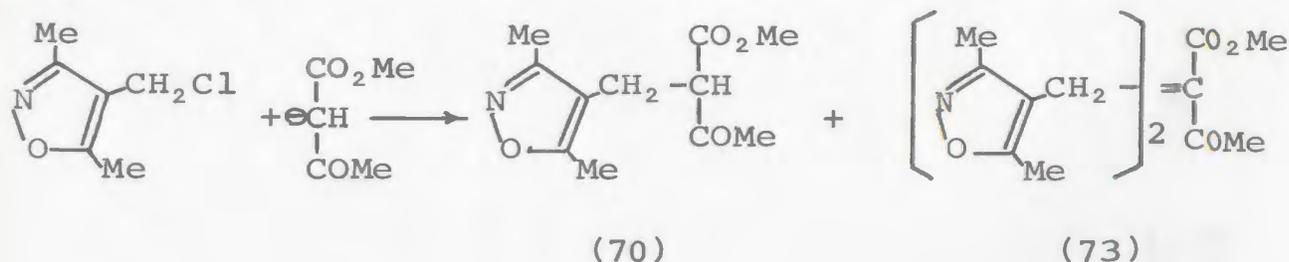
(Fig. 2d) Reaction of the 4-bromomethyl-1,4-dihydropyridine (3b) with triethylamine in methanol : 1, 0 h; 2, 11 h; 3, 22 h; 4, 35 h; 5, 48.5 h; 6, 59.5 h.

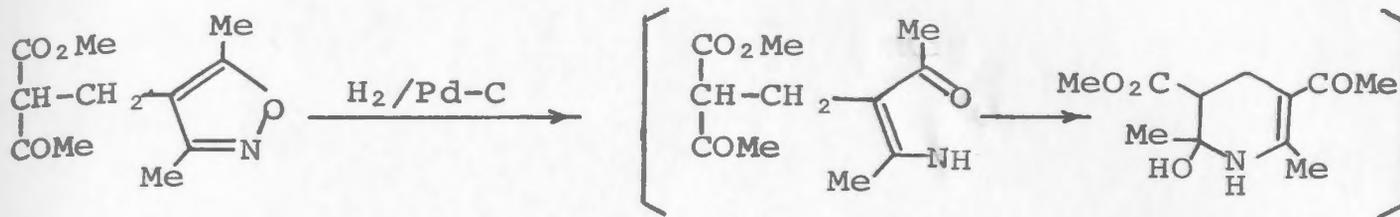
Preparation of Methyl 5-acetyl-2,6-dimethyl-1,4-dihydronicotinate and the corresponding Nicotinic Acid Methyl Ester.

For the comparison of the peaks which were found in the mass spectra of the 8,8-diacetyl-2-azabicyclo[3.2.1]oct-3-ene ( 36a,d ) and the 8-acetyl-8-alkoxycarbonyl-2-azabicyclo[3.2.1]oct-3-ene ( 36b,c,e ), the methyl 5-acetyl-2,6-dimethyl-1,4-dihydronicotinate ( 71 ) and the corresponding nicotinate ( 72 ) were synthesized according to the Stork's method.<sup>4 5</sup>

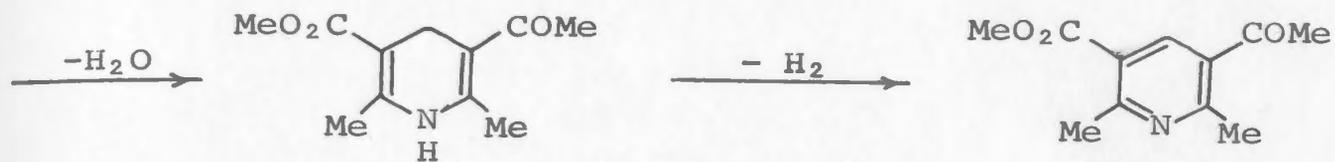
Transformation of methyl  $\alpha$ -(3,5-dimethyl-4-isoxazolylmethyl)-acetoacetate ( 70 ) by catalytic hydrogenolysis in methanol with the presence of triethylamine and palladium on charcoal to give methyl 5-acetyl-2,6-dimethyl-1,4-dihydronicotinate ( 71 ), which undergoes air oxidation or nitrous acid oxidation to form methyl 5-acetyl-2,6-dimethylnicotinate ( 72 ). The methyl  $\alpha$ -(3,5-dimethyl-4-isoxazolylmethyl) acetoacetate ( 70 ) was obtained by alkylation of the methyl acetoacetate with sodium hydride and 4-chloromethyl-3,5-dimethylisoxazole in dimethylformamide, and was purified by distillation ( dialkylation product remains as residue ). ( see Scheme 8 ).

( Scheme 8 )





(70)



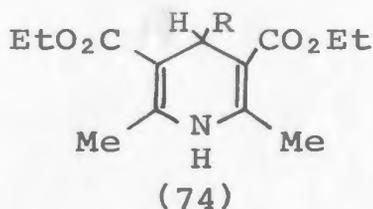
(71)

(72)

Mass Spectra.

(a.) 1,4-Dihydropyridines.

The relative simple mass spectra of 1,4-dihydropyridines have been reported to be result of well-defined fragmentation processes, the most important of which is the formation of the aromatic pyridinium ion which may take place either by loss of a hydrogen atom or by loss of radical R $\cdot$  from the 4-position <sup>4 6,4 7</sup>.



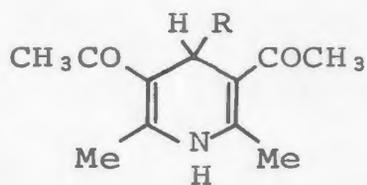
- a. R=H
- b. R=Me
- c. R=CHMe<sub>2</sub>

In the 3,5-diethoxycarbonyl-1,4-dihydropyridines (74), three main fragmentation processes were established by high resolution mass measurements and metastable peaks <sup>4 7</sup>. The expulsion of the radical from 4-position led to the stable pyridinium ion and this tendency increased as the size of group R increased ( e.g., the molecular ion in compound(74c) was absent whereas the compounds ( 74a and 74b ) gave molecular ions 22% and 3% respectively). The subsequent fragmentations of the pyridinium ion involved either elimination of EtOH between ethoxycarbonyl and a nearby methyl group by McLafferty rearrangement, or elimination of ethylene from ethoxycarbonyl group followed by carbon dioxide elimination.

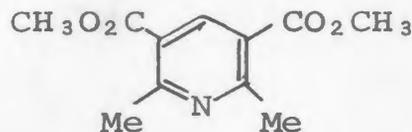
The mass spectra of the 4-substituted dimethyl 2,6-

dimethyl-1,4-dihydropyridine-3,5-dicarboxylates ( 3 ) did not show molecular peaks except 3g which gave only a very weak peak at m/e 283(0.0006%). All of these compounds gave a very strong peak at m/e 224, due to the corresponding pyridinium ion by elimination of 4-substituents. (see Table 4 ). A fairly strong peak at m/e 251, probably the azepine cation radical (34b) generated by loss of hydrogen halide, methanol, or thiocyanic acid depending on the 4-substituent from the molecular ion. The peaks at m/e 192, 164, 160, 132, 91 and the peaks at m/e 236, 220, 219, 204, 192, 191, 176 were then the fragmentations due to the methoxycarbonyl groups and methyl groups from the pyridinium ion ( 38b ) and azepine ion ( 34b ) respectively, and were supported by the observation of the corresponding metastable peaks at m/e 176.4, 166.6, 164.7, 140.2, 133.3, and 108.9. ( see scheme 9 ).

The mass spectra of the 3,5-diacetyl-1,4-dihydropyridines ( 75 ) are dominated by the M-R ions and the fragmentation, by loss of CH<sub>3</sub> radical is more favored than loss of CH<sub>3</sub>CO radical from the molecular ions<sup>47</sup>.



(75)



(76)

The 5-acetyl-1,4-dihydronicotinate ( 71 ) showed a strong parent peak at m/e 209 and a strong aromatic pyridinium ion at m/e 208 formed by expelling a hydrogen atom from 4-position. The elimination of CH<sub>3</sub> radical from the molecular ion

is the base peak and was supported by the observation of the corresponding metastable peak at m/e 180.3 ( see scheme 10 ).

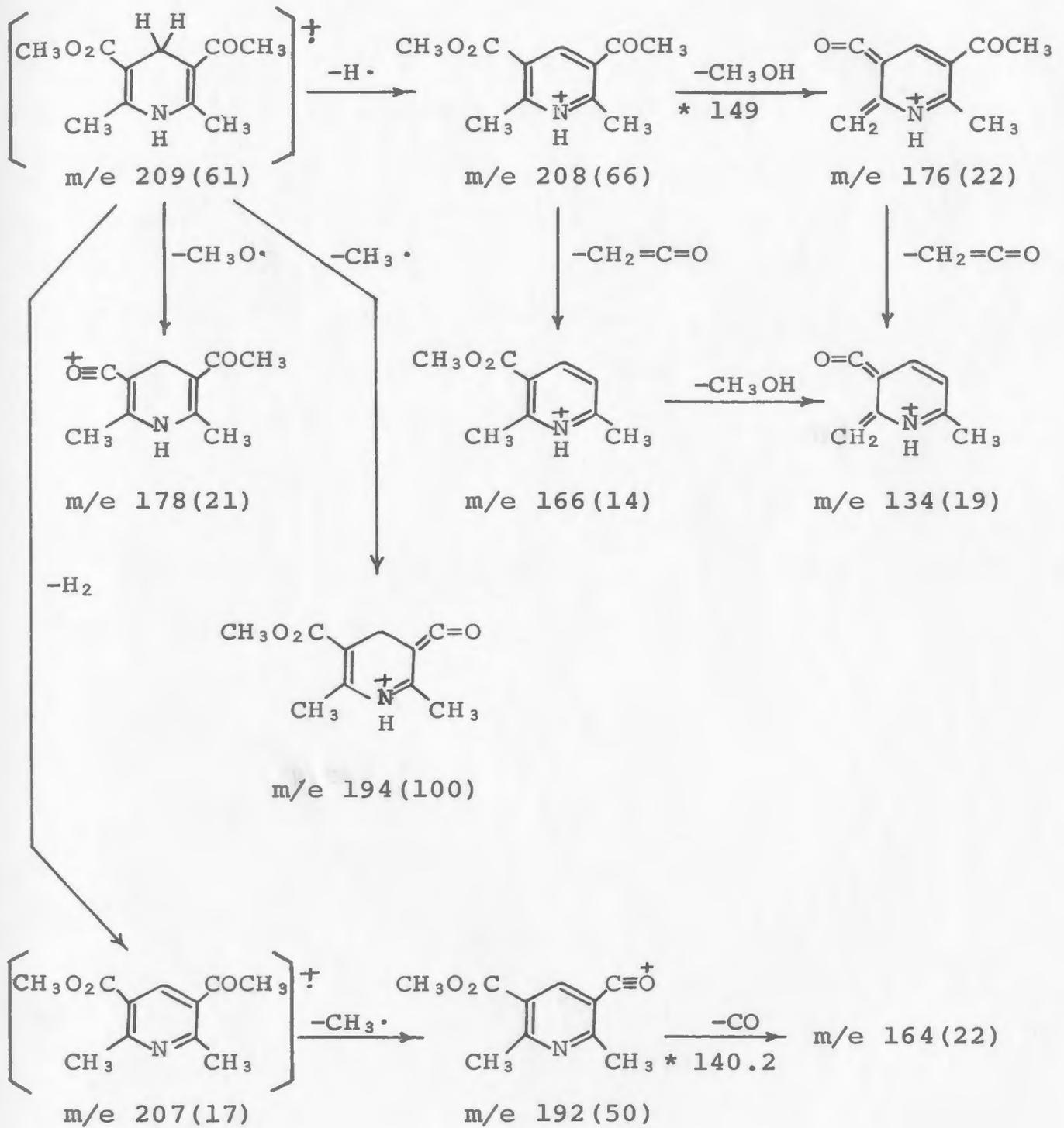
Table 4 : Peak intensities in spectra of 4-substituted-1,4-dihydropyridines ( 3 ).

Compound	3e	3f	3g	3h
Inlet temp. (°C)	135 <sup>0</sup>	100-110 <sup>0</sup>	105 <sup>0</sup>	105-108 <sup>0</sup>
m/e				
M(intensity)	287( 0 )	333( 0 )	283(0.0006)	310( 0 )
224	(100)	( 94)	(100)	( 60)
A* 192	(99.5)	( 93)	(24)	(100)
164	(18)	(11)	( 7)	( 8)
251	(29)	(26)	(0.3)	(37)
236	(15)	(11)	(0.8)	(14)
220	(34)	(27)	( 5)	(31)
219	(41)	(40)	(0.3)	(45)
* 204	(17)	(18)	(0.8)	(16)
B 192	(99.5)	(93)	(24)	(100)
191	(33)	(25)	(1.8)	(30)
176	(25)	(20)	(0.8)	(17)
160	(82)	(82)	(5.7)	(64)
132	(51)	(50)	( 3)	(38)
91	(42)	(32)	(1.2)	(23)

\* The ions of group A arise by the fragmentation pathway involving formation of a pyridinium ion, while those of group B arise from a seven-membered ring. It is clear that in the case of 3g the latter pathway is very minor, probably because the methoxyl group is a poor leaving group. It has not been possible to demonstrate whether the initial step, namely elimination of HX, of the latter pathway is thermal or electron impact induced, in spite of measurement of mass spectra at different temperatures. Thermolysis of 3e, 3f and 3h can be accomplished outside the mass spectrometer but is complicated by the formation of polymer and the pyridine(76), and the volatilisation of starting material in vacuo.



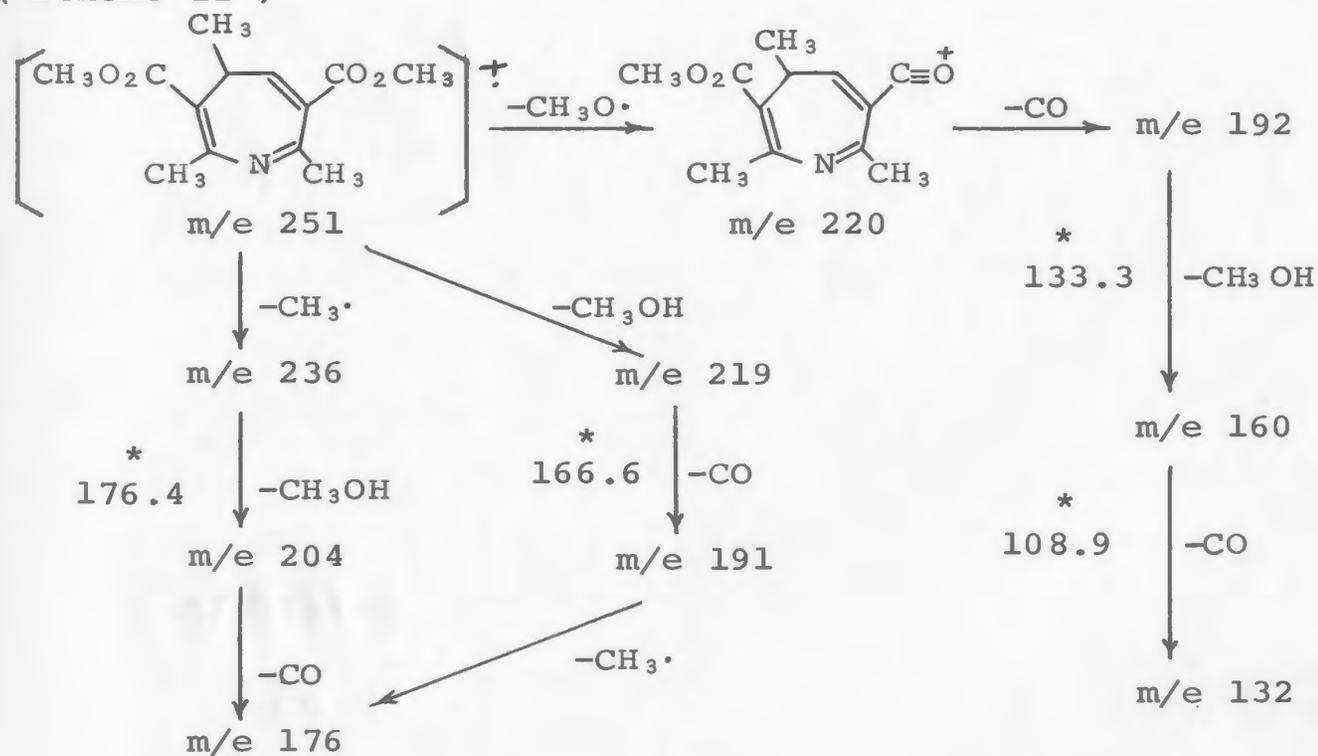
( Scheme 10 )



(b.) 4H-Azepine.

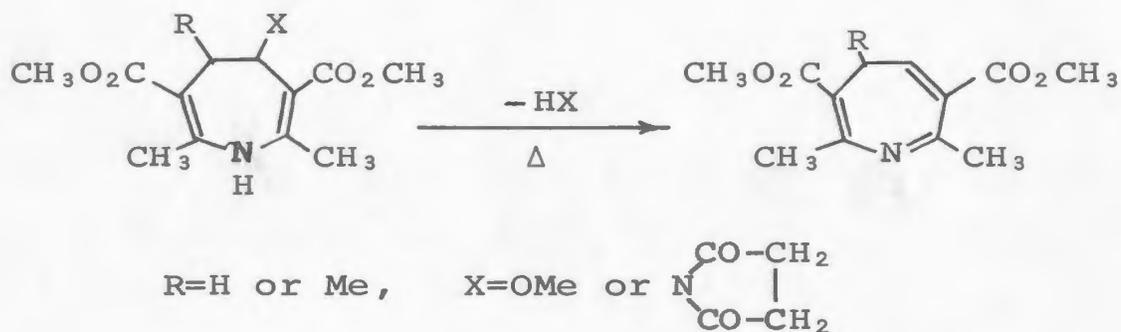
The mass spectrum of the 4H-azepine( 47 ) was almost identical with the spectra of the corresponding 1,4-dihydropyridines( 3 ) except for the pyridinium ion( 38b ), m/e 224, which was found as base peak in the 1,4-dihydropyridine spectra but was almost completely absent from the spectrum of the 4H-azepine( 47 ). (see Table 5 and Scheme 11 ). The 4H-azepine( 47 ) gave quite a strong parent peak at m/e 251 and a peak at m/e 192 as base peak indicating the elimination of methoxycarbonyl residue from the molecular ion. The strong peaks at m/e 160 and 132 were then formed by the same pathway as in the 1,4-dihydropyridines( 3 ) by loss of CH<sub>3</sub>OH and CO from the base peak and was supported by the observation of the corresponding metastable peaks at m/e 133.3 and 108.9.

( Scheme 11 )



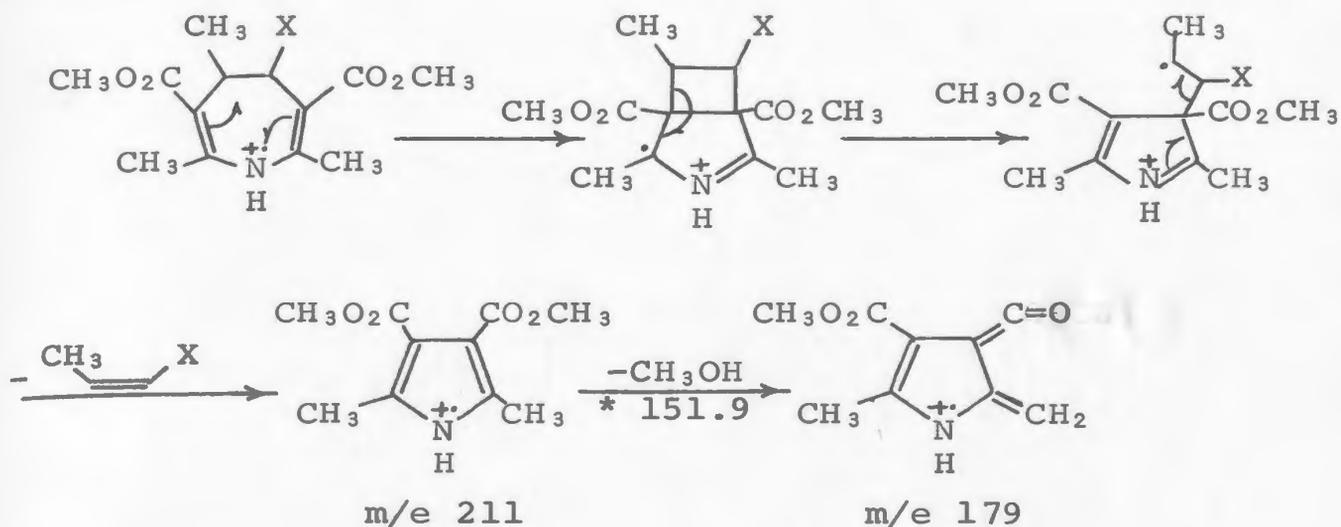
(c.) 4-Substituted 4,5-dihydroazepines.

The 4-methoxy-4,5-dihydroazepine ( 42a ) and the 4-succinimino-4,5-dihydroazepines ( 4b, 42b ) which easily eliminated their 4-substituents showed similar spectra to those of the corresponding 4H-azepines ( 9a, 47 ), (see Table 5 ), and was probably due to the pyrolysis of the compounds in the inlet system. ( cf. the 4-methoxy-4,5-dihydroazepine ( 4a ) was easily pyrolysed at  $100^{\circ}$  <sup>13</sup>, and the 4-succinimino-4,5-dihydroazepine ( 42b ) at  $180^{\circ}$  to give 4H-azepines ( 9a, 47 ) ).



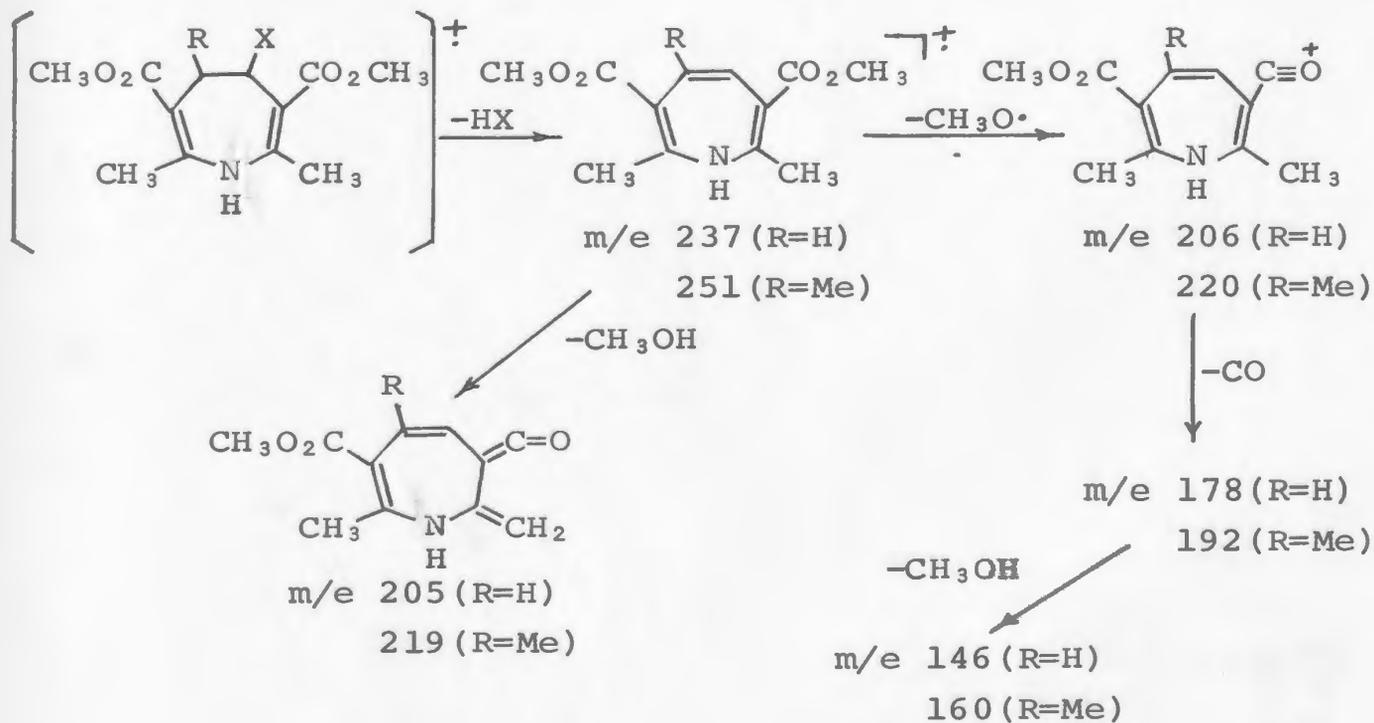
In the case of the other 4-substituted 4,5-dihydroazepines, such as  $\text{X}=\text{CN}$ ,  $\text{CH}(\text{CO}_2\text{Et})_2$ ,  $\text{CH}(\text{COCH}_3)\text{CO}_2\text{Me}$ ,  $\text{CH}(\text{COCH}_3)_2$ , the spectra were more complicated, especially the 4-substituted 5-methyl-4,5-dihydroazepines ( 42c~f ), for which a different fragmentation pathway seems to be possible. The peak at  $m/e$  179 was the base peak in the 4-substituted 5-methyl-4,5-dihydroazepines ( 42c~f ) and was thought to be formed by loss of  $\text{CH}_3\text{OH}$  from  $m/e$  211 ion, which was supported by the observation of the metastable ion at  $m/e$  151.9 . (see Scheme 12 ).

( Scheme 12 )



Both 4-substituted 4,5-dihydroazepines ( 4 ) and 4-substituted 5-methyl-4,5-dihydroazepines ( 42 ) gave strong azepine ions and their fragmentation peaks. The azepine ions could be formed either by McLafferty rearrangement or elimination of the 4-substituents and hydrogen atom separately.

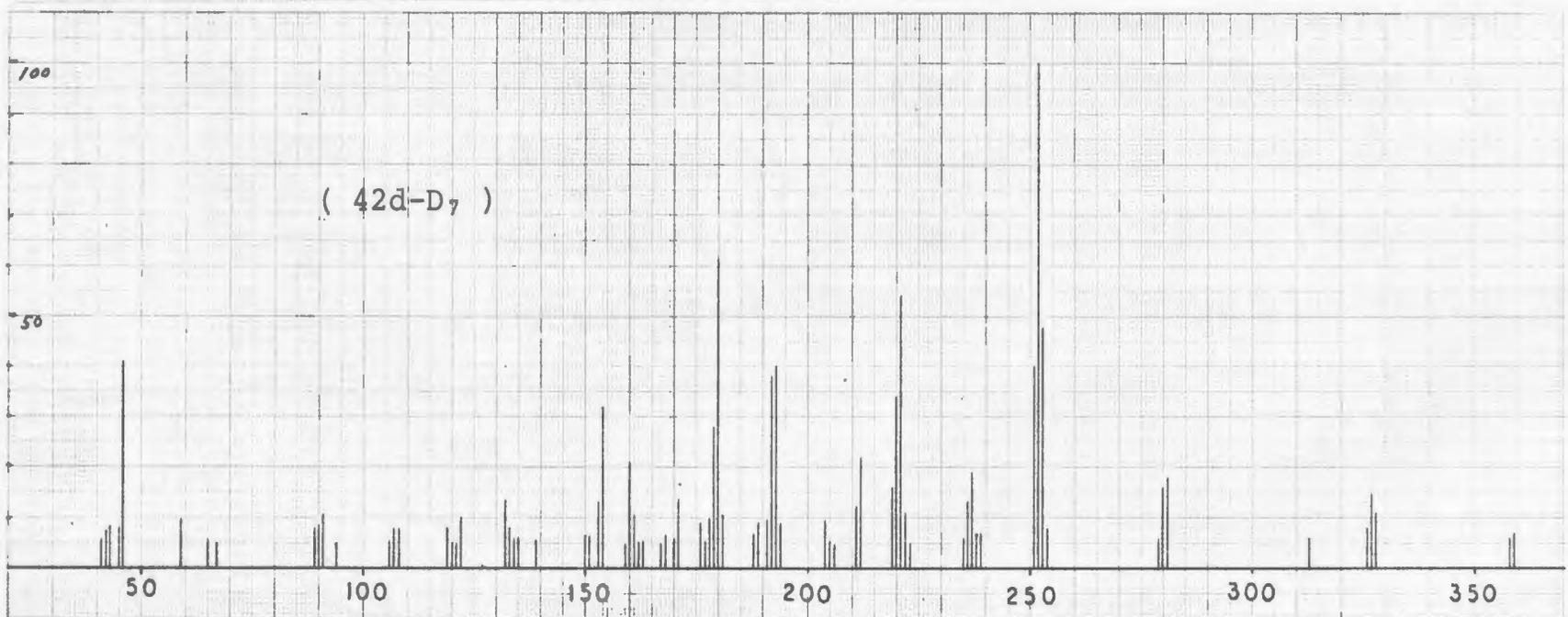
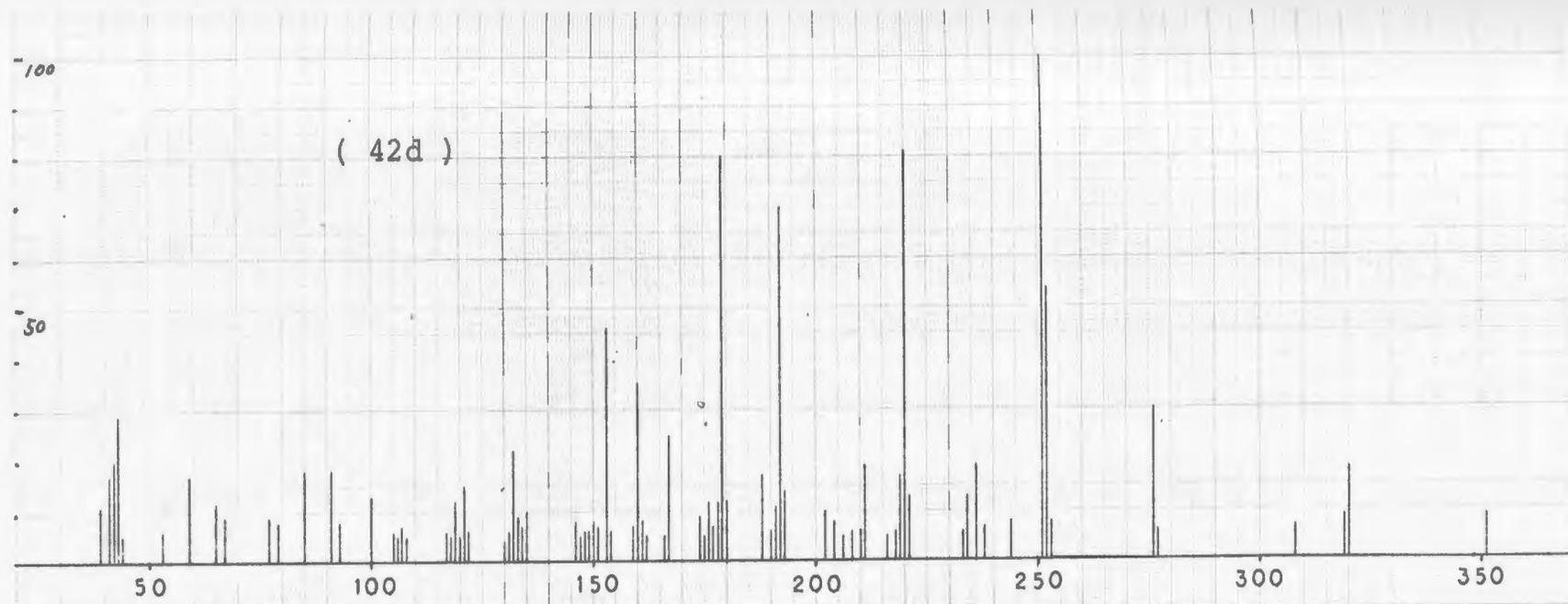
( Scheme 13 )



The above fragmentations were supported by the comparison of the spectra of the 4-(diacetylmethyl)-4,5-dihydroazepine( 42d ) and the deuteriated 4-(diacetylmethyl)-4,5-dihydroazepine ( 42d-D<sub>7</sub> ). (see Fig. 3 ).

Table 5 : Peak intensities in spectra of 4H-azepine( 47 ) and 4,5-dihydroazepines( 42a,b ).

Compound	47	42a	42b
m/e			
M (intensity)	251(34)	283(10 )	350( 5 )
251	(34)	(33 )	(57 )
236	(13)	(23 )	(19 )
224	(1.5)	( 13)	( 4 )
220	(28)	( 35)	(33 )
219	(47)	( 38)	(51 )
211	(1.5)	(2.5)	( 4 )
204	(18)	( 15)	(18 )
192	(100)	(100)	(100)
191	(34)	( 28)	(32 )
179	( 2)	( 13)	(26 )
178	(10)	( 9)	(11 )
176	(24)	(25)	(24 )
164	( 6)	( 9 )	( 6 )
160	(90)	(64)	(79 )
132	(47)	(40)	(49 )
91	(26)	(37)	(38 )

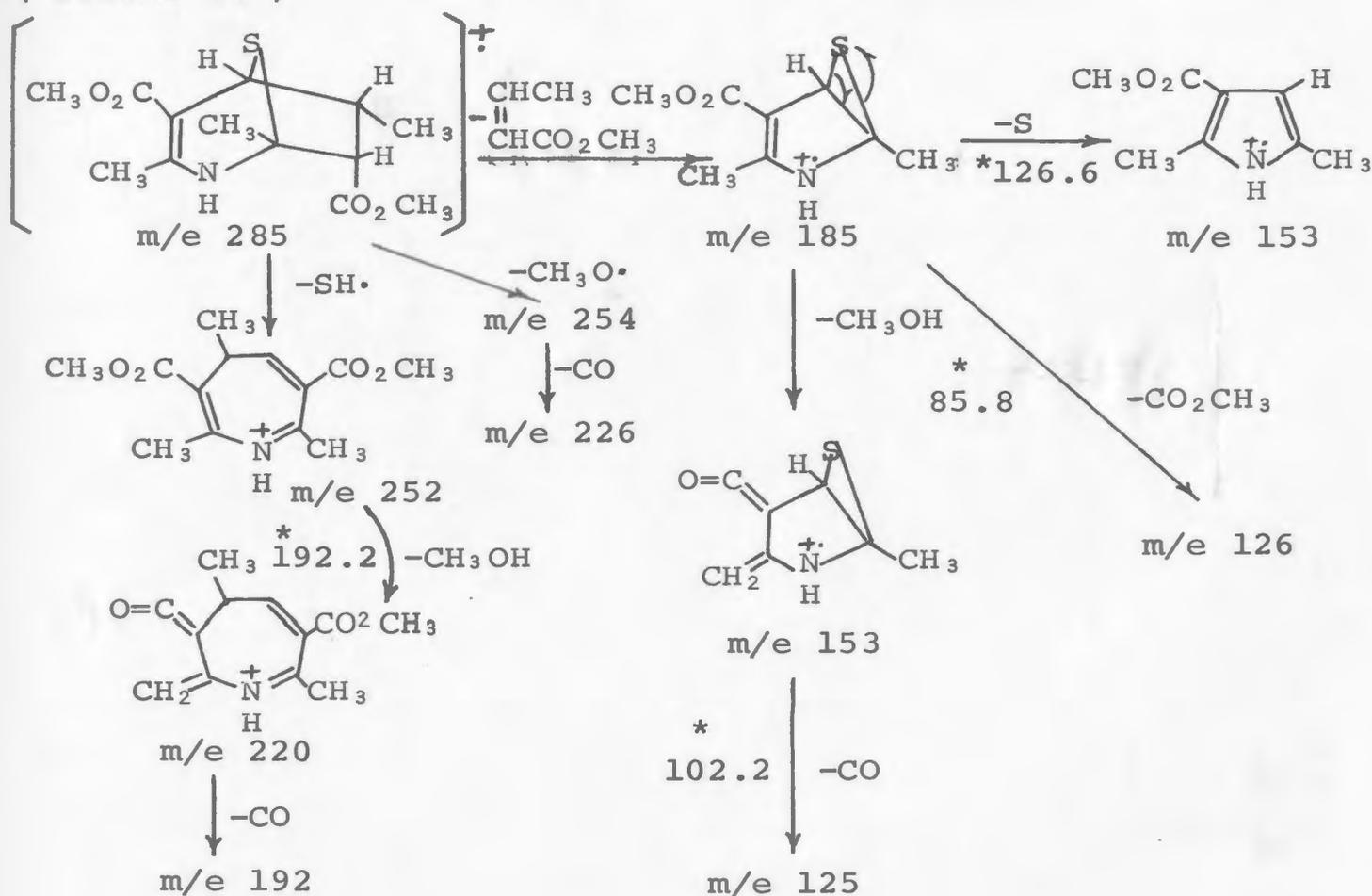


(Fig. 3) The mass spectra of the 4,5-dihydroazepine(42d) and its deuteriated compound (42d-D<sub>7</sub>).

(d.) 2-Aza-8-thiabicyclo[3.2.1] oct-3-enes.

The mass spectra of the 2-aza-8-thiabicyclo[3.2.1]oct-3-ene ( 14a ) showed strong parent peak and a base peak at m/e 185 by loss of methyl acrylate from the molecular ion. The latter stable ion then eliminated 32 mass units to give another strong peak at m/e 153 and was supported by the observation of the corresponding metastable peaks. The two isomers of the methyl analogue, 33a and 33b, both gave a strong parent peak at m/e 285 and a base peak at m/e 185 by elimination of methyl crotonate. The elimination of sulfur or methanol from the base peak is also very strong and gave the corresponding metastable peak. ( see Scheme 14 ).

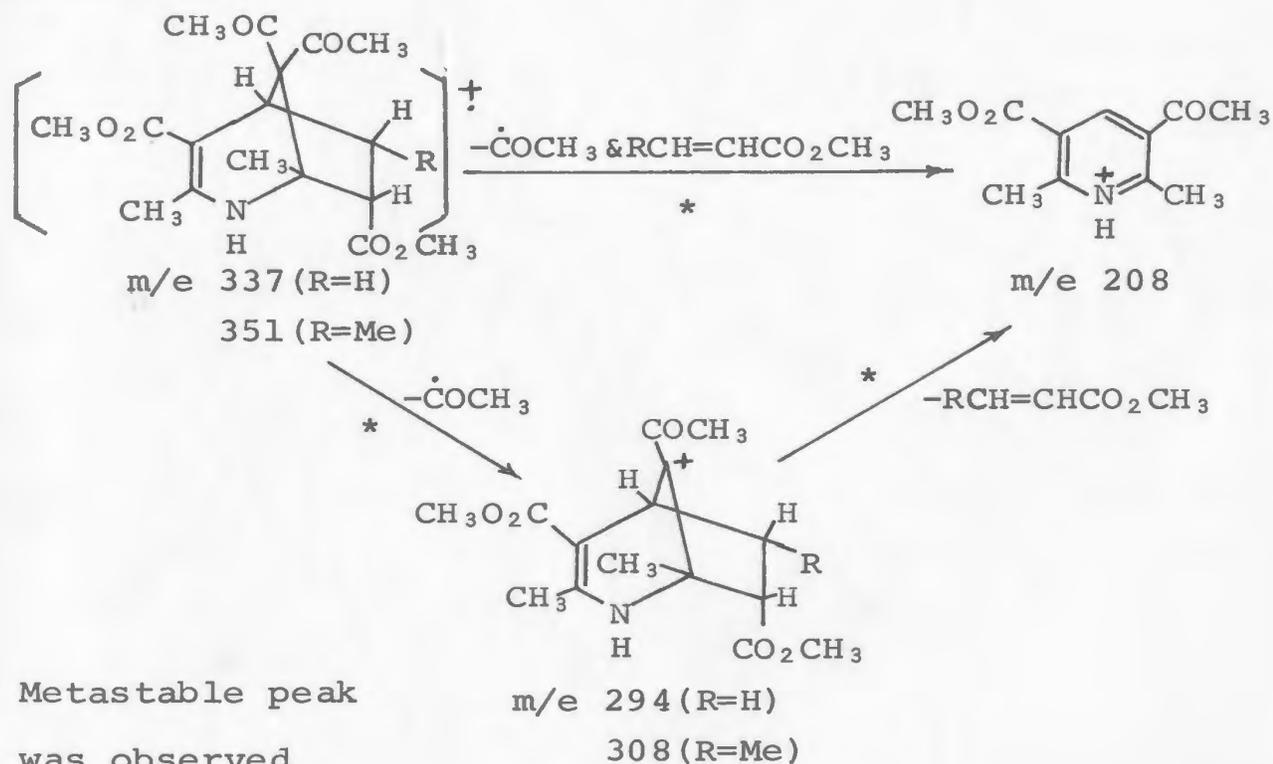
( Scheme 14 )



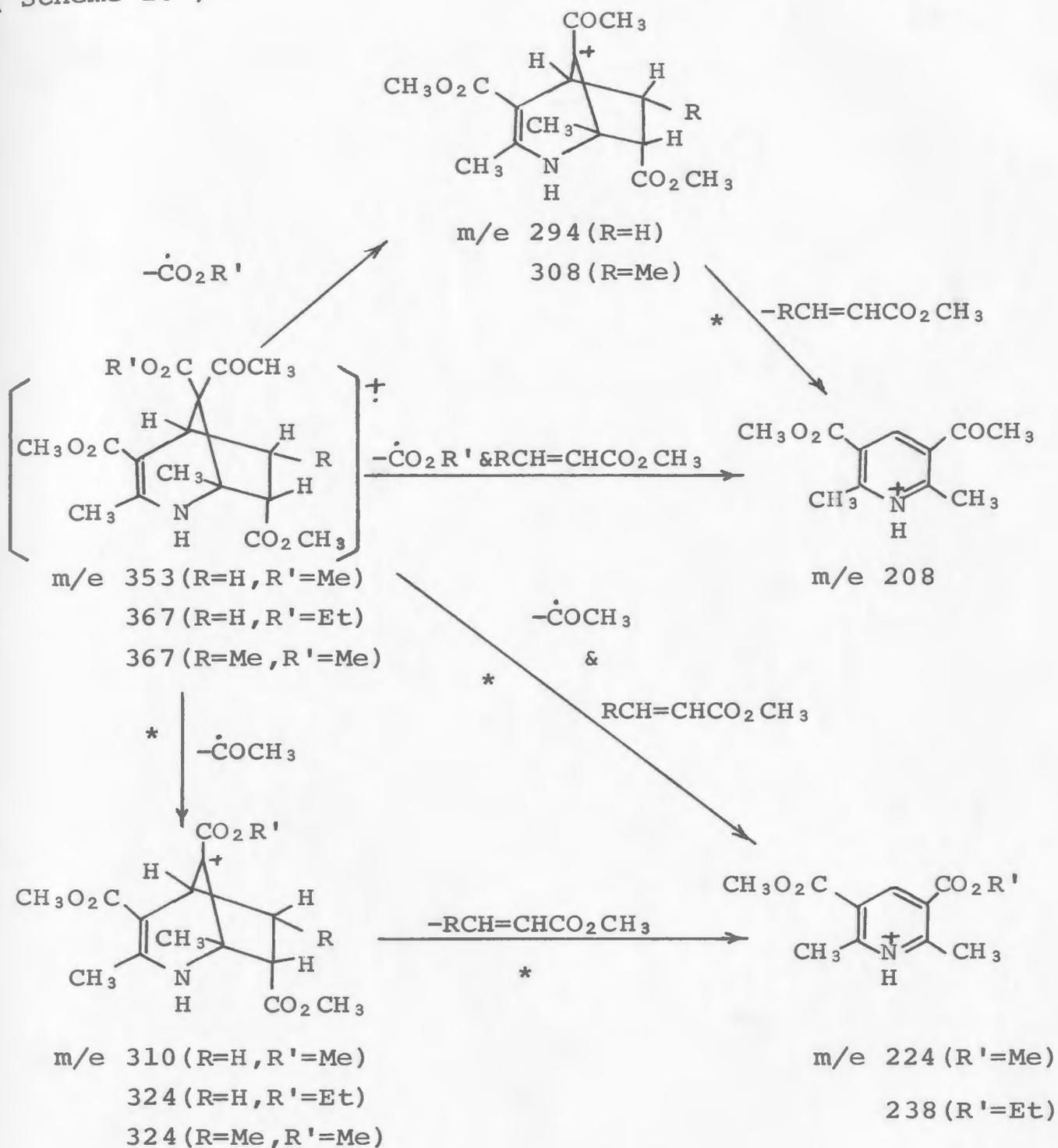
(e.) 2-Azabicyclo[3.2.1]oct-3-enes

The mass spectra of the 2-azabicyclo[3.2.1]oct-3-enes ( 36 ) were quite simple compared with the corresponding 4,5-dihydroazepines( 4, 42 ). The stable pyridinium ions( 38 ) were the base peaks in all cases and might be formed by stepwise loss of acetyl radical and methyl acrylate in compounds( 36a, b) or methyl crotonate in the compounds( 36d,e ) or loss of two fragments at the same time. Both fragmentation pathways were supported by the observation of the corresponding metastable peaks ( see Scheme 15,16 ) and also by comparison of the spectra of dimethyl 8,8-diacetyl-1,3,6-trimethyl-2-azabicyclo[3.2.1] oct-3-ene ( 36d ) and its deuteriated compound ( 36d-D<sub>7</sub> ). ( see Fig. 4 ).

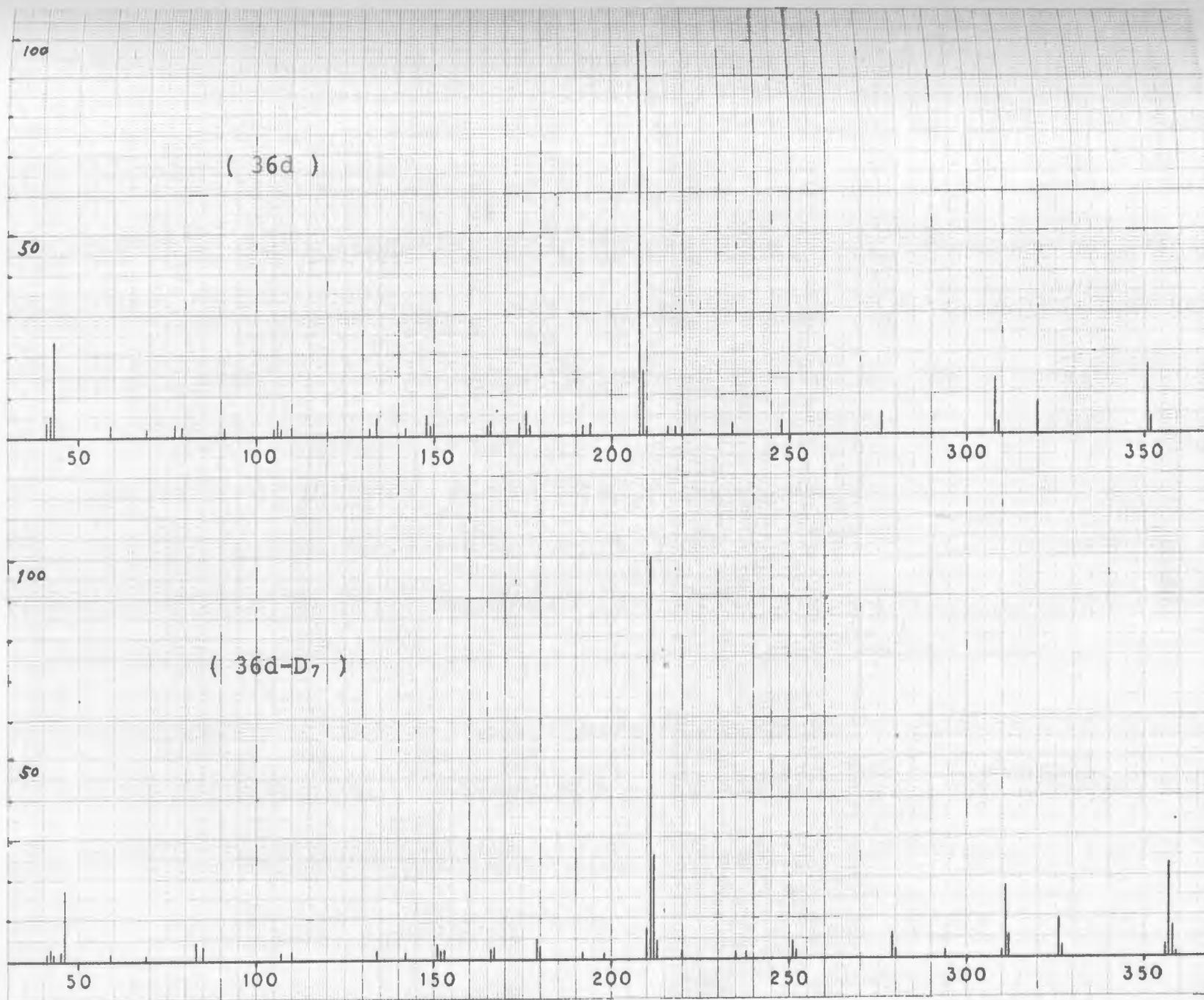
( Scheme 15 )



( Scheme 16 )



\* Metastable peak was observed

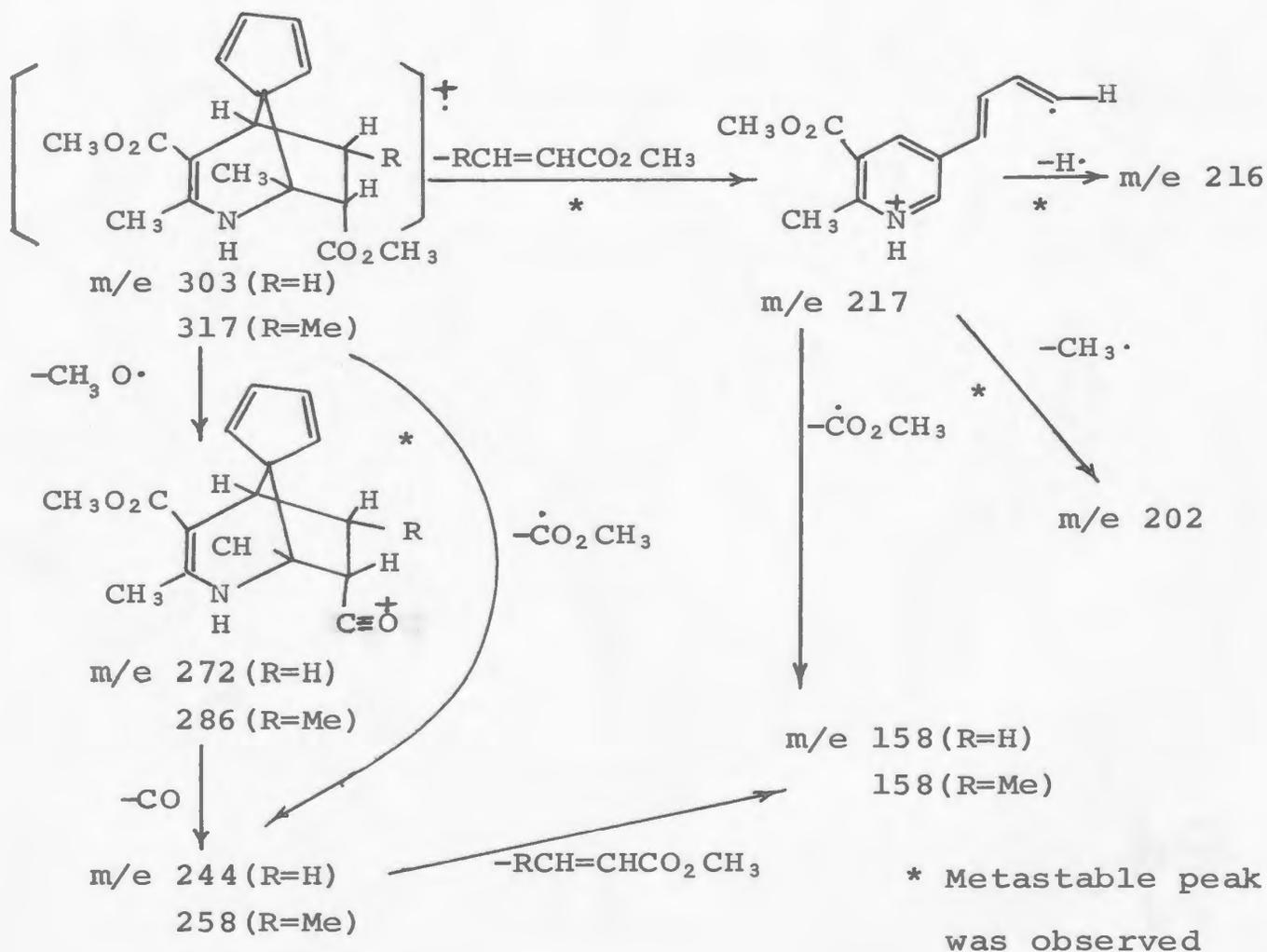


(Fig. 4) The mass spectra of the 2-azabicyclo [3.2.1] oct-3-ene ( 36d ) and its deuteriated compound ( 36d-D<sub>7</sub> ).

(f.) 2-Azabicyclo[3.2.1] oct-3-ene-8-spiro-cyclopentadienes.

The mass spectra of the 2-azabicyclo[3.2.1] oct-3-enes ( 39 ) showed strong parent peaks because the 8-substituents can not be eliminated in one step, and the fragmentation was very similar to that of the above bicyclic compounds ( 36 ). The pyridinium ions again formed by loss of methyl acrylate (or methyl crotonate ) and were supported by the observation of the corresponding metastable peaks. The fragmentation by loss of methoxycarbonyl radical from both molecular ions and the pyridinium ions are also very important. ( see Scheme 17 ).

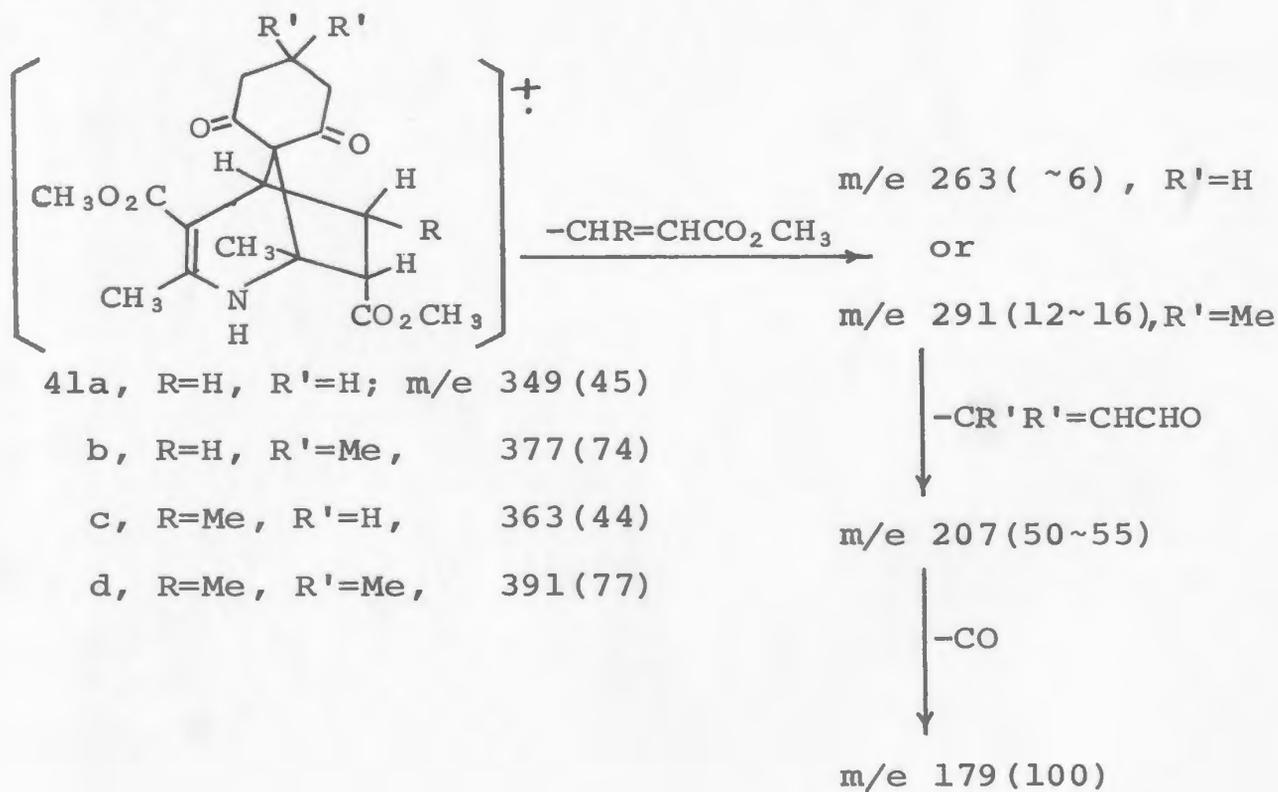
( Scheme 17 )



(g.) 2-Azabicyclo[3.2.1] oct-3-ene-8-spiro-(2',6'-dioxocyclohexane) and 2-azabicyclo[3.2.1] oct-3-ene-8-spiro-(4',4'-dimethyl-2',6'-dioxocyclohexane).

The mass spectra of the 2-azabicyclo[3.2.1] oct-3-ene-8-spiro-(2',6'-dioxocyclohexane) ( 41a,c ) and the 2-azabicyclo[3.2.1] oct-3-ene-8-spiro-(4',4'-dimethyl-2',6'-dioxocyclohexane) ( 41b,d ) showed strong parent peaks and the fragmentations are very complicated compared with the bicyclic compounds ( 36 ). The base peak at m/e 179 was formed by elimination of methyl acrylate ( or methyl crotonate ),  $\text{CH}_2=\text{CH}\cdot\text{CHO}$  ( or  $\text{Me}_2\text{C}=\text{CH}\cdot\text{CHO}$  ) and carbon monoxide. ( see scheme 18 ).

( Scheme 18 )



(h.)  $\beta$ -(3-Methoxycarbonyl-2-methyl-1-pyrrolyl) crotonic Acid and its Methyl Ester.

The mass spectra of the  $\beta$ -(3-methoxycarbonyl-2-methyl-1-pyrrolyl) crotonic acid ( 43a ) and its  $\alpha$ -deuterio compound ( 43c ) showed strong parent peaks as base peak, and the fragmentation is shown in the scheme 19 and table 6 . The methyl  $\beta$ -(3-methoxycarbonyl-2-methyl-1-pyrrolyl) crotonate also gave a strong parent peak and similar fragmentation.

( Scheme 19 )

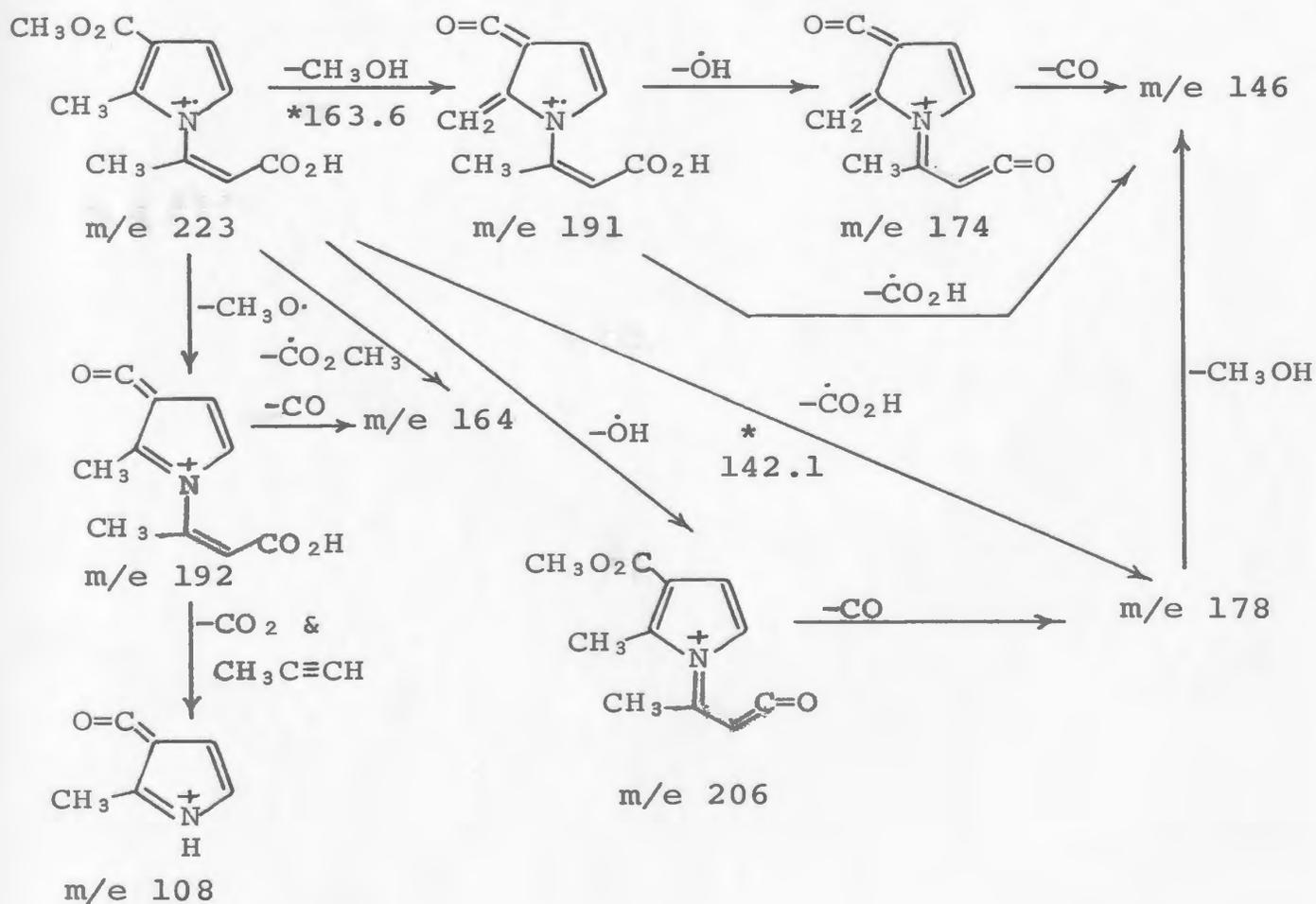
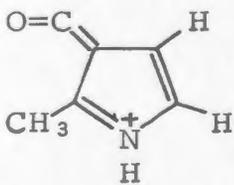


Table 6 : Peak intensities of the  $\beta$ -(3-methoxycarbonyl-2-methyl-1-pyrrolyl) crotonic acid and its  $\alpha$ -deuteriated compound.

Compound	43a ( $\alpha$ -H )		43c ( $\alpha$ -D )	
	m/e	%	m/e	%
M	223	(100)	224 (100), 223	(31)
M-(OMe)	192	(68)	193	(53)
M-(HOMe)	191	(23)	192	(37)
M-(CO <sub>2</sub> H)	178	(54)	179	(45)
M-(HOMe & Me)	176	(19)	177	(16)
M-(CO <sub>2</sub> Me)	164	(22)	165	(16)
M-(HOMe & CO <sub>2</sub> H)	146	(55)	147	(38)
	108	(42)	108	(34)
Metastable Peaks	163.6	(223→191)	164.8	(224→192)
	142.1	(223→178)	143.1	(224→179)

(i.) Furo [ 2,3-b ] pyridines and Pyrrolo [ 2,3-b ] pyridines.

The mass spectra of the furo [ 2,3-b ] pyridines ( 67 ) and the pyrrolo [ 2,3-b ] pyridines ( 68 ) showed parent peaks as base peak, and the fragmentation by loss of methoxide radical, methanol and carbon monoxide are very important. ( see Scheme 20 and Table 7 ).

( Scheme 20 )

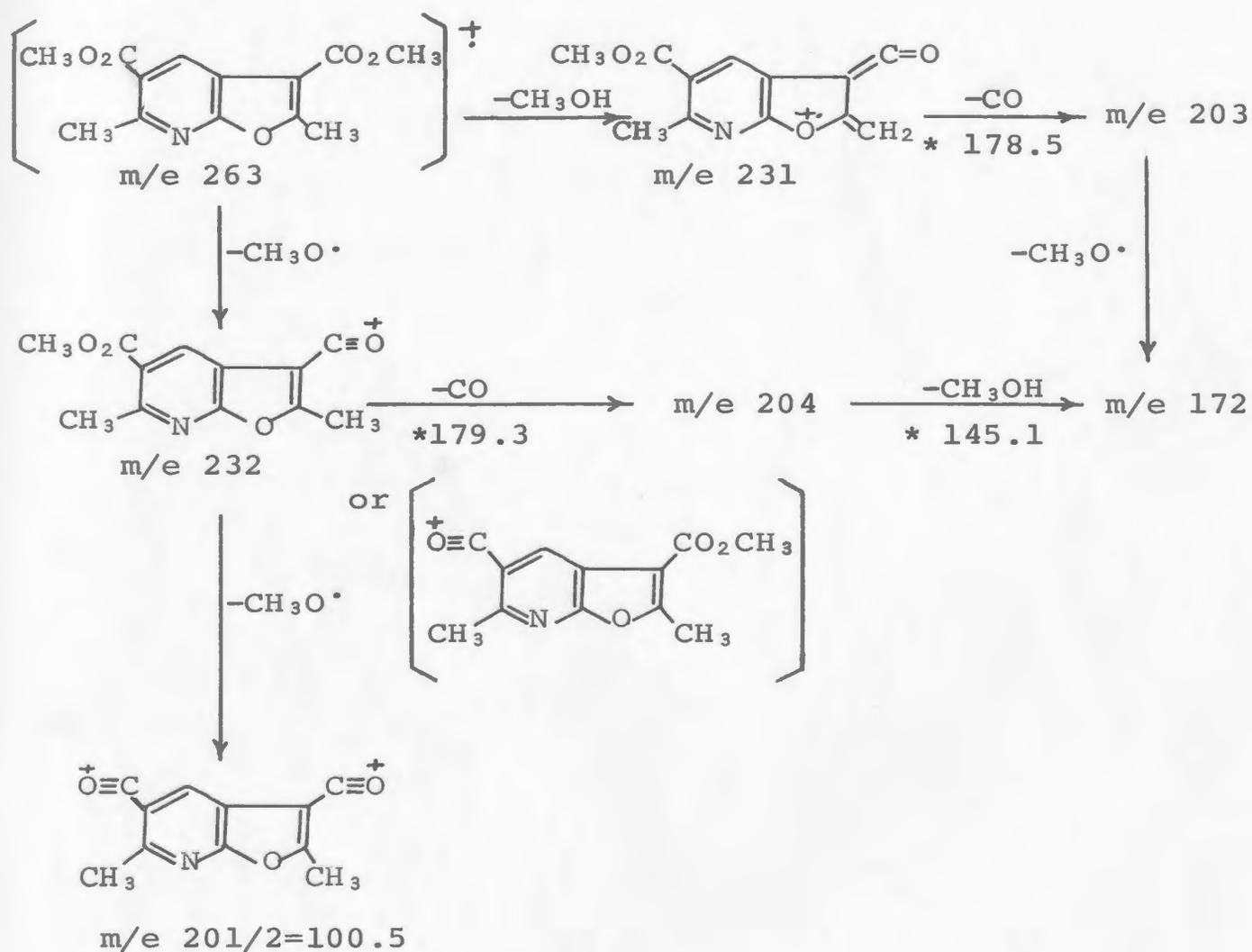


Table 7 : Peak intensities in spectra of Furo(2,3-b)pyridines and Pyrrolo(2,3-b)pyridines.

Compound	67a	67b	68a	68b
M (intensity)	263(100)	277(100)	262(99.7)	276(100)
M-(OMe)	232( 96)	246( 84)	231(100)	245( 83)
M-(HOMe)	231( 70)	245( 63)	230( 43)	244( 35)
M-(OMe&CO)	204( 20)	218( 14)	203( 15)	217( 16)
M-(HOMe&CO)	203( 46)	217( 44)	202( 43)	216( 48)
M-(HOMe,OMe, & CO)	172( 22)	187(13 )	171( 49)	186( 18)
M-(OMe) <sub>2</sub> (double charge ion )	100.5(9)	107.5(16)	100(10)	107(20)

## EXPERIMENTAL

Melting points were determined on the Fisher-Johns melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on a Unicam SP.800 ultraviolet spectrophotometer using 95% ethanol as solvent unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer 237B grating infrared spectrophotometer using chloroform as solvent unless otherwise stated. Infrared band intensities arbitrarily designated s (strong), m (medium), w (weak), and b (broad). Nuclear magnetic resonance spectra were recorded on a Varian A-60 analytical spectrometer and resonance positions were reported on the  $\tau$  scale, using tetramethylsilane as an internal reference and deuteriochloroform as solvent unless otherwise stated. Spin-spin decouplings were measured on a Varian HA-100 spectrometer. Mass spectra were recorded using a Hitachi-Perkin-Elmer RMU-6E mass spectrometer with direct inlet system, and the spectra were normalized. The value in the bracket following the mass number is the relative abundance of the ion compared with the base peak equal to 100%. The variation of total ion current during the spectrum of each compound was less than 6%. Analyses were performed by the Alfred Bernhardt microanalysis laboratory, West Germany. Petroleum ether (boiling range 40-60<sup>o</sup>) was used in all of these experiments.

Dimethyl 4-(1-chloroethyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (3e).

A mixture of 1,2-dichloropropyl ethyl ether<sup>48</sup> (40ml.), and methyl 3-aminocrotonate(48g.) in benzene(50ml.) was stirred at room temperature for 2 days. Water(300ml.) and ether(300ml.) were added and shaken for a few minutes then poured into a separatory funnel. The organic layer was collected and the aqueous layer was extracted with ether(3 x 300ml.). The combined ether solution was washed with water(2 x 50ml.) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from benzene to yield 3e as white crystals (18.2g.; 30%), m.p.167-169<sup>0</sup>. The analytical sample was prepared by recrystallization twice from benzene to give white prisms, m.p.169-170<sup>0</sup>.

Ultraviolet spectrum :  $\lambda_{\max}$  232nm(  $\epsilon$ 16,850), 339nm(  $\epsilon$ 7,300).

Infrared spectrum :  $\nu_{\max}$  3429m(NH), 3318bw(NH), 1697s(C=O), 1649m(C=C), 1621m, 1471s, 1435s, 1383w, 1377w, 1319m, 1308m, 1277m, 1154w, 1126m, 1107s, 1074m, 1012w  $\text{cm}^{-1}$ .

N.M.R. spectrum :  $\tau$ , 3.78(s, NH), 5.59(d, J 5.0 Hz, 4-H), 5.98(m, J 5.0 and 6.6 Hz, 1'-H), 6.22(s, ester Me), 7.62(s, nuclear Me), and 8.66(d, J 6.6 Hz, Me).

Mass spectrum : m/e 287 M (0), 256(5), 252(6), 251(29), 236(15), 225(17), 224(100), 221(5), 220(34), 219(41), 204(17), 193(16), 192(99.5), 191(33), 188(5), 178(9), 177(6), 176(25), 165(11), 164(18), 163(10), 162(7), 160(82), 159(18), 151(9), 150(15), 149(10), 148(7), 144(5), 135(7), 134(8), 133(14), 132(51), 121(6), 120(8), 119(20), 118(8), 117(8), 107(6), 106(7), 105(9), 104(5),

93(6), 92(8), 91(42), 79(12), 78(9), 77(17), 67(8), 66(5), 65(20), 63(7), 59(28), 53(9), 52(9), 51(12), 44(5), 43(11), 42(14), 41(12), 39(17).

Anal. Calcd. for  $C_{13}H_{18}ClNO_4$  : C, 54.26; H, 6.31; N, 4.87; Cl, 12.32. Found : C, 54.44; H, 6.08; N, 4.80; Cl, 12.28.

Dimethyl 1,3,6-trimethyl-8-thia-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate ( 33a,b ).

The chloro-compound(3e, 1.5g.) was added to a solution of sodium hydrosulfide(0.8g.) in ethanol(50ml.) and the mixture was heated to  $65^{\circ}$  on a water bath for 5 h. After cooling, the reaction mixture was poured into cold water(200ml.) containing ammonium chloride(5g.) and the solution was extracted with ether (3 x 200ml.). The ether extract was washed with water(3 x 30ml.) and the solvent removed under reduced pressure. The residue was recrystallized from benzene-petroleum ether to give white prisms( 33a, 0.78g.; 52%), m.p. $163-164^{\circ}$ .

Ultraviolet spectrum :  $\lambda_{max}$  231nm(  $\epsilon$ 2,850), 291nm(  $\epsilon$ 12,900).

Infrared spectrum :  $\nu_{max}$  3408m(NH), 3307bw(NH), 1737s(C=O), 1689s(C=O), 1588s, 1479s, 1450m, 1436m, 1382m, 1362m, 1308m, 1288m, 1255m, 1172s, 1154m, 1142m, 1113m, 1090s, 1069m, 1021m  $cm^{-1}$ .

N.M.R. spectrum :  $\tau$ , 5.01(s, NH), 5.32(d, J 4.8 Hz, 5-H), 6.26(s, ester Me), 6.96(m, J 4.8, 7.0, and 7.4 Hz, 6-H), 7.45(d, J 7.4 Hz, 7-H), 7.70(s, 3-Me), 8.23(s, 1-Me), and 8.94(d, J 7.0 Hz, 6-Me).

Mass spectrum : m/e 286(10), 285(55), 254(14), 253(9), 252(30),

238(6), 226(19), 225(6), 222(6), 221(5), 220(16), 210(9), 195(5), 194(26), 193(6), 192(12), 188(5), 187(6), 186(12), 185(100), 184(10), 183(6), 182(7), 179(6), 178(9), 170(7), 165(5), 166(19), 164(12), 163(6), 162(6), 160(6), 155(13), 154(14), 153(86), 152(16), 151(10), 150(8), 139(5), 138(10), 135(6), 134(11), 132(7), 128(7), 127(20), 126(60), 125(28), 122(11), 121(5), 120(7), 119(7), 115(9), 111(8), 108(8), 107(5), 106(7), 99(6), 95(6), 94(25), 93(8), 92(5), 91(12), 85(10), 84(42), 83(17), 79(8), 77(11), 76(8), 69(10), 68(9), 67(12), 65(10), 59(33), 57(5), 53(11), 52(5), 51(6), 45(10), 43(6), 42(37), 41(20), 39(17).

Anal. Calcd. for  $C_{13}H_{19}NO_4S$  (mol.wt. 285) : C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found (mass spectrum 285) : C, 54.59; H, 6.54; N, 4.78; S, 11.34.

From the mother liquor, the more soluble isomer formed needles and was separated by hand (33b, 0.51g.; 34%), m.p. 144-146° .

Ultraviolet spectrum :  $\lambda$  max 293.5nm(  $\epsilon$  13,550).

Infrared spectrum :  $\nu$ max 3423m(NH), 3322wb(NH), 1734s(C=O), 1687s(C=O), 1669m, 1587m, 1488s, 1454m, 1436m, 1380m, 1347m, 1321m, 1293m, 1169s, 1145m, 1096s, 1070m, 1011m  $cm^{-1}$ .

N.M.R. spectrum :  $\tau$ 4.91(s, NH), 5.23(d, J 4.7 Hz, 5-H), 6.30(s, ester Me), 6.84(d, J 3.0 Hz, 7-H), 6.91(m, J 3.0, 4.7, and 6.5 Hz, 6-H), 7.69(s, 3-Me), 8.17(s, 1-Me), and 9.01(d, J 6.5 Hz, 6-Me).

Mass spectrum : m/e 287(5), 286(12), 285(71), 255(5), 254(26), 253(18), 252(64), 226(14), 225(7), 224(5), 222(11), 221(9), 220(40), 210(5), 194(13), 193(9), 192(27), 188(9), 187(7),

186(12), 185(100), 184(10), 182(8), 180(5), 179(6), 178(9), 167(6), 166(24), 164(5), 162(5), 161(6), 160(18), 155(15), 154(14), 153(98), 152(15), 151(9), 150(8), 149(5), 138(5), 135(5), 134(10), 133(6), 132(12), 128(5), 127(20), 126(55), 125(28), 122(9), 121(6), 120(7), 119(9), 111(6), 108(7), 107(5), 106(7), 95(5), 94(25), 93(8), 92(5), 91(15), 85(6), 84(11), 83(6), 79(8), 77(10), 76(5), 69(6), 68(6), 67(10), 65(10), 59(29), 53(9), 51(5), 45(9), 44(5), 43(6), 42(30), 41(16), 39(14).

Anal. Calcd. for  $C_{13}H_{19}NO_4S$  (mol. wt. 285): C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found (mass spectrum 285): C, 54.60; H, 6.64; N, 5.05; S, 11.09.

The low melting point compound(33b) was converted to the stable epimer (33a) by refluxing with sodium methoxide in dioxane for 5 h.

Dimethyl 4-(diacetylmethyl)-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (4d).

A mixture of chloro-compound( 3a, 300mg.) and sodium acetylacetonate(300mg.) in dry dimethylformamide(15ml.) was stirred for 6 h. at 0-5<sup>0</sup>. The mixture was then poured into cold water(100ml.) containing ammonium chloride(5g.), and extracted with ether(3 x 60ml.). The ether extract was washed with water (3 x 20ml.) and the solvent removed under reduced pressure. The residue was recrystallized from ether-petroleum ether to give white prisms (215mg.; 58%), m.p.147-148.5<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  231nm( $\epsilon$ 12,100), 329nm( $\epsilon$ 12,250). In 0.01N NaOH/95%EtOH,  $\lambda_{max}$ 234nm( $\epsilon$ 11,900), 297nm( $\epsilon$ 26,300), 326nm(

$\epsilon$  12,100).

Infrared spectrum:  $\lambda_{\max}$  3414m(NH), 1703s(C=O), 1700s(C=O), 1632m, 1511s, 1435m, 1385m, 1359m, 1323m, 1257m, 1109m, 1078s  $\text{cm}^{-1}$ .

N.M.R. spectrum:  $\tau$  4.32(s, NH), 5.71(m), 6.29(d, J 11.0 Hz), 6.32 and 6.35(each s, ester Me), 6.85(d.d, J 14.0 and 5.6 Hz), 7.67 and 7.75(each s, nuclear Me), 7.80(obscured by four methyl resonances), 7.90 and 7.92(each s, COMe).

Mass spectrum: m/e 337(1.4), 262(11), 238(16), 237(50), 222(13), 207(5), 206(42), 205(40), 190(6), 179(24), 178(91), 177(18), 174(5), 164(13), 162(12), 149(8), 148(12), 147(14), 146(100), 137(7), 136(7), 134(6), 121(5), 119(9), 118(39), 105(22), 100(54), 93(5), 91(10), 85(60), 79(5), 78(9), 77(32), 72(6), 65(8), 59(31), 58(6), 53(10), 52(10), 51(12), 44(11), 43(44), 42(52), 41(12), 39(50).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{23}\text{NO}_6$  (mol.wt.337): C, 60.52; H, 6.87; N, 4.15. Found(mass spectrum 337): C, 60.36; H, 6.93; N, 4.09.

Dimethyl 8,8-diacetyl-1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate (36a).

(a.) A mixture of chloro-compound (3a, 2.0g.) and sodium acetylacetonate(2.0g.) in dry dimethylformamide(60ml.) was stirred for 10h. at  $60^\circ$ . The mixture was then poured into cold water(300ml.) containing ammonium chloride(20g.) and extracted with ether (3x200ml.). The ether extract was washed with water (3x30ml.) and the solvent removed under reduced pressure to give white needles (2.1g.; 85%), m.p.192.5-193.5 $^\circ$ .

Ultraviolet spectrum :  $\lambda_{\max}$  289nm( $\epsilon$ 13,600).

Infrared spectrum :  $\nu_{\max}$  3418m(NH), 1736s(C=O), 1721s(C=O), 1694s(C=O), 1589m, 1477m, 1451m, 1434m, 1379m, 1357m, 1306m, 1260m, 1173s, 1096s  $\text{cm}^{-1}$ .

N.M.R. spectrum :  $\tau$ , 5.83(s, NH), 6.32(s, ester Me), 7.73(s, 3-Me), 7.86 and 7.97(each s, COMe), 8.21(s, 1-Me). The remaining four protons in the range of 6.1-8.6 are partially obscured by two ester methyl and two acetyl resonances.

Mass spectrum : m/e 338(5), 337(23), 306(10), 294(12), 262(8), 209(16), 208(100), 176(6), 43(21), 42(5).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{23}\text{NO}_6$  (mol. wt. 337): C, 60.52; H, 6.87; N, 4.15. Found (mass spectrum 337): C, 60.52; H, 6.91; N, 4.27.

(b.) A solution of the 4,5-dihydroazepine(4d, 6mg.) and sodium acetylacetonate (3mg.) in dry dimethylformamide (0.3ml.) was stirred at 60-65° for 2 h. then water(4ml.) containing ammonium chloride(10mg.) was added to the reaction mixture. After standing for 1 h. in an ice-water bath white crystals was deposited. Which was collected and washed with water to give the bicyclic-compound( 36a, 4mg.) as white prisms, m.p.192.5-193.5° , and was identical with the authentic sample by mixed melting point and u.v., i.r., mass spectra.

Dimethyl 4-(diacetylmethyl)-4,5-dihydro-2,5,7-trimethylazepine-3,6-dicarboxylate( 42d ).

A mixture of the chloro-compound(3e, 1.0g.) and sodium acetylacetonate (1.0g.) in dry dimethylformamide ( 20 ml.)

was stirred for 24h. at room temperature. The solution was then poured into cold water (100ml.) containing ammonium chloride (5g.) and extracted with ether (3x70ml.). The ether extract was washed with water(2x20ml.) and evaporated under reduced pressure. The residue was dissolved in benzene and chromatographed on silica gel H, using benzene-ethyl acetate for elution. The first fraction was collected and after removal of solvent, the residue crystallized from ether-petroleum ether to give 36d as white prisms(0.16g.; 13%), m.p. 180-181<sup>0</sup> . From the second fraction, the dihydrozepine 42d was obtained after removal of solvent and recrystallization from ether-petroleum ether, white needles, (0.72g.; 60%), m.p. 104-106<sup>0</sup> .

Ultraviolet spectrum:  $\lambda_{\max}$  231nm(  $\epsilon$ 11,100), 328nm(  $\epsilon$ 12,700).

Infrared spectrum:  $\nu_{\max}$  3414m(NH), 1699s(C=O), 1631m, 1510s, 1433s, 1376m, 1359m, 1318m, 1256m, 1153m, 1113m, 1081s,  $\text{cm}^{-1}$ .

N.M.R. spectrum:  $\tau$  4.24(s, NH), 5.93(d,d, J 5.5 and 11.0 Hz, 4-H), 6.30 and 6.33(each s, ester Me), 6.34(d, J 11.0 Hz, Acetylacetone CH), 6.75(m), 7.70 and 7.71 (each s, nuclear Me), 7.90 and 7.92 (each s, COMe), and 9.11(d, J 6.8 Hz, 5-Me).

Mass spectrum: m/e 351(9), 320(18), 319(9), 308(7), 277(6), 276(30), 253(8), 252(54), 251(100), 244(8), 238(7), 236(19), 234(13), 233(6), 221(13), 220(81), 219(17), 218(6), 216(5), 211(19), 210(6), 208(6), 206(5), 204(8), 202(10), 193(14), 192(70), 191(11), 190(6), 188(17), 180(12), 179(80), 178(12), 177(7), 176(12), 175(5), 174(9), 167(25), 166(5), 162(5), 161(8), 160(35), 159(7), 154(6), 153(46), 151(7), 150(8), 149(6), 148(6), 147(5), 146(8), 135(10), 134(7), 133(9), 132(22), 131(6), 130(4),

122(6), 121(15), 120(5), 119(12), 118(5), 117(6), 108(5), 107(7), 106(5), 105(6), 100(13), 93(8), 91(18), 85(18), 79(8), 77(9), 67(9), 65(12), 59(17), 53(6), 44(5), 43(29), 42(20), 41(17), 39(11).

Anal. Calcd. for  $C_{18}H_{25}NO_6$  (mol. wt.351) : C, 61.52; H, 7.17; N, 3.98. Found (mass spectrum 351) : C,61.55; H,7.25; N,3.97.

Deuterium exchange reaction of 42d .

A solution of the 4,5-dihydroazepine( 42d, 150mg.) and small amount of sodium methoxide in dioxane(10ml.) and deuterium oxide(10ml.) was stirred at room temperature for 10h. The solvent was removed under reduced pressure and the residue was recrystallized from ether-petroleum ether to give deuterium exchanged compound 42d-D<sub>7</sub> as white needles,135mg., m.p.104-106 ° . Mass spectrum showed seven hydrogens on the acetyl-acetone were exchanged by deuterium ( see Fig. 3 ).

Dimethyl 8,8-diacetyl-1,3,6-trimethyl-2-azabicyclo{3.2.1}oct-3-ene-4,7-dicarboxylate (36d) .

(a.) A mixture of chloro-compound( 3e, 2.0g.) and sodium acetylacetonate(2.0g.) in dry dimethylformamide(30ml.) was heated on an oil bath for 6 h. at 100° . After cooling, the solution was poured into cold water(100ml.) containing ammonium chloride(10g.) and extracted with chloroform(3 x 100ml.). The chloroform extract was washed with water(3x20ml.) and evaporated in vacuo. The residue was recrystallized from chloroform-ether-petroleum ether to give white prisms( 1.82g.; 74%), m.p.

180-181<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{\max}$  292nm(  $\epsilon$ 13,100) .

Infrared spectrum :  $\nu_{\max}$  3436m(NH), 1733s(C=O), 1695s(C=O), 1668m, 1586m,1493m, 1459m,1435m, 1380m,1358m, 1175s, 1097s  $\text{cm}^{-1}$ .

N.M.R. spectrum : (DMSO- $d_6$ )  $\tau$ ,3.07(s, NH), 6.39 and 6.42(each s, ester Me), 7.73(s, 3-Me), 7.92 and 7.97(each s, COMe), 8.39(s, 1-Me), and 9.16(d, J 6.0 Hz, 6-Me). One ring proton at  $\tau$  6.2-6.4 was partially obscured by ester methyl signals, The other two protons are overlapping between  $\tau$  7.0-7.4.

Mass spectrum : m/e 351(17), 320(8), 308(14), 276(6), 209(16), 208(100), 176(6), 148(6), 134(5), 43(24), 42(6) .

Anal. Calcd. for  $\text{C}_{18}\text{H}_{25}\text{NO}_6$  (mol. wt.351) :C, 61.52; H, 7.17; N, 3.98. Found(mass spectrum 351):C, 61.39;H,7.33; N, 3.89.

(b.) A mixture of the 4,5-dihydroazepine(42d,10mg.) and sodium acetylacetonate(5mg.) in dry dimethylformamide(0.3 ml.) was stirred at 60-65<sup>0</sup> for 2 h. The solution was then worked up as its analogue 4d to yield bicyclic-compound(36d, 7mg.) as white prisms, m.p.181-182<sup>0</sup> . Which was identical with the authentic sample by mixed melting point and spectral data.

(c.) 4H-Azepine(47, 160mg.) and sodium acetylacetonate(100mg.) in dry dimethylformamide(10ml.) was stirred at 90<sup>0</sup> for 6 h. and the reaction mixture was poured into ice water(60ml.). The product was extracted with ether(3 x 30ml.) and the ether extract was washed with water(3 x 10ml.) and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, and the residue was recrystallized from ether-petroleum ether to yield white needles(180mg.; 80%), m.p.180-181<sup>0</sup> . This substance was

identical with the authentic sample by mixed melting point and spectral data.

Deuterium exchange reaction of 36d .

A solution of bicyclic compound(36d, 120mg.) and small amount of sodium methoxide in dioxane(10ml.) and deuterium oxide (10ml.) was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was sublimed at 150<sup>0</sup> under 0.05mm Hg. to give white prisms,100mg., m.p.181-182<sup>0</sup> . Mass spectrum showed all six hydrogens of the two 8-acetyl groups and one hydrogen attached to nitrogen were exchanged by deuterium.

Dimethyl 4-(1-methoxycarbonyl-2-oxopropyl)-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate ( 4e ) .

The chloro-compound( 3a,1.0g.) in dry dimethylformamide(10ml.) was added to a solution of methyl sodioacetoacetate (0.63g.) prepared by adding methyl acetoacetate(0.6g.) to a suspension of sodium hydride(110mg.)in dry dimethylformamide (20ml.) on an ice-water bath. The mixture was stirred for 7 h. at 0-5<sup>0</sup>.and then poured into cold water(200ml.) containing ammonium chloride(10g.). The product was extracted with ether (3 x 100ml.) and the ether extract washed with water(3 x 20ml.). The solvent was evaporated in vacuo and the residue recrystallized from chloroform-ether-petroleum ether to give white prisms(0.84g.; 65%), m.p.142-143<sup>0</sup>. (lit. 138-139<sup>0</sup><sup>13</sup> ). Ultraviolet spectra :  $\lambda_{max}$  231nm( $\epsilon$ 12,000), 330nm( $\epsilon$ 12,950). In 0.01N NaOH/95%EtOH  $\lambda_{max}$  234nm( $\epsilon$ 12,300), 274nm( $\epsilon$ 25,400), 323nm

( 10,800) after 1h.

Mass spectrum: m/e 353(2), 321(6), 278(10), 238(17), 237(34), 222(7), 206(29), 205(24), 179(24), 178(54), 177(11), 174(5), 164(8), 162(7), 149(5), 148(7), 147(9), 146(58), 137(5), 136(5), 119(6), 118(22), 116(14), 105(13), 101(10), 91(6), 88(4), 85(17), 84(7), 78(6), 77(18), 74(10), 69(14), 65(5), 59(28), 53(6), 52(6), 51(6), 51(7), 44(7), 43(100), 42(12), 41(5), 39(7).

Trimethyl 8-acetyl-1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene  
-4,7,8-tricarboxylate ( 36b ).

The chloro-compound ( 3a, 1.0g.) in dry dimethylformamide(10ml.) was added to a solution of methyl sodioacetoacetate (1.06g.) in dry dimethylformamide(20ml.) as above, and the mixture was heated on an oil bath for 6h. at 90°. After cooling, the mixture was poured into cold water(100ml.) containing ammonium chloride(5g.). The product was extracted with chloroform (3x60ml.) and the chloroform extract washed with water (3x20ml.). The solvent was removed under reduced pressure and the residue recrystallised from ether-petroleum ether to give white needles (0.92g, 71%) m.p. 147-148.5°.

Ultraviolet spectrum:  $\lambda_{max}$  290nm(  $\epsilon$  14,550 ).

Infrared spectrum:  $\nu_{max}$  3415m(NH), 1738s(C=O), 1706s(C=O), 1688(C=O), 1598m, 1475m, 1460m, 1454m, 1435s, 1380m, 1356m, 1332m, 1304m, 1265m, 1174m, 1116m, 1096s, 1079r, 998w  $cm^{-1}$ .

N.M.R. spectrum:  $\tau$  , 5.91(s, NH), 6.33(s, two ester Me), 6.77( a.d, J 11. and 5.5Hz, ), 7.72(s, 3-Me), 7.95(s, COMe). and 8.23 (s, 1-Me), One proton at  $\tau$  6.25-6.45, two protons at  $\tau$  7.5-8.2 were partially obscured by ester methyls, methyl and acetyl

signals respectively.

Mass spectrum:  $m/e$  354(5), 353(22), 322(11), 310(7), 290(5), 225(14), 224(100), 208(5), 192(7), 160(5), 43(12), 42(5) .

Anal. Calcd. for  $C_{17}H_{23}NO_7$  (mol. wt. 353): C, 57.78; H, 6.56; N, 3.96. Found (mass spectrum 353): C, 57.70; H, 6.69; N, 4.09.

Dimethyl-8-acetyl-8-ethoxycarbonyl-1,3-dimethyl-2-azabicyclo  
[3,2.1] oct-3-ene-4,7-dicarboxylate (36c) .

The chloro-compound ( 3a, 2.0g.) in dry dimethylformamide(15ml.) was added to a solution of ethyl sodioacetate(2.34g.) in dry dimethylformamide(30ml.) as were its analogs 36a and 36b, and the mixture was heated on an oil bath for 6h. at  $90^{\circ}$ . After cooling, the mixture was poured into cold water(200ml.) containing ammonium chloride(5g.). The product was extracted with chloroform (3 x 60ml.) and the chloroform extract washed with water(3 x 20ml.). The solvent was removed under reduced pressure and the residue recrystallized from ether-petroleum ether to give white needles, (2.1g.; 77%), m.p.  $112.5-113^{\circ}$  .

Ultraviolet spectrum :  $\lambda_{max}$  291.5nm(  $\epsilon$  14,250) .

Infrared spectrum :  $\nu_{max}$  3423m(NH), 1735s(C=O), 1707s(C=O), 1688s(C=O), 1598m, 1476m, 1437m, 1382m, 1357m, 1306m, 1097s  $cm^{-1}$

N. M. R. spectrum :  $\tau$  ,5.83(q, J 7.0 Hz, ethyl ester  $CH_2$ ), 6.28 (s, methyl esters), 6.85(d.d, J 11.2 and 5.8 Hz), 7.68(s, 3-Me), 7.93(s, COMe), 8.20(s, 1-Me), 8.82(t, J 7.0 Hz, ethyl ester  $CH_3$ ) .

Two protons at  $\tau$  5.5-6.2 were obscured by ethyl ester  $CH_2$  signal, and two protons at  $\tau$  7.5-8.2 were partially obscured by methyl and acetyl  $CH_3$  signals.

Mass spectrum : m/e 368(8), 367(38), 336(15), 324(10), 239(17), 238(100), 210(18), 208(7), 43(6).

Anal. Calcd. for  $C_{18}H_{25}NO_7$  (mol. wt. 367): C, 58.84; H, 6.86; N, 3.81. Found (mass spectrum 367): C, 58.82; H, 6.79; N, 3.86.

Dimethyl 4-(1-methoxycarbonyl-2-oxopropyl)-4,5-dihydro-2,5,7-trimethylazepine-3,6-dicarboxylate (42e).

Methyl sodioacetoacetate(0.56g.) in dry dimethylformamide(20ml.) was prepared as above. The chloro-compound(3e, 1.0g.) was added and the mixture stirred for 24h. at room temperature, and then poured into cold water(300ml.) containing ammonium chloride(10g.). The product was extracted with ether (3 x 100ml.) and the ether extract washed with water(3 x 20ml.). The solvent was evaporated in vacuo, and the residue was crystallized from ether-petroleum ether to give white prisms(0.98g.; 76.5%), m.p.98-100°. Although the n.m.r.spectrum(see below) suggested the presence of two isomers, these have not been separated by either recrystallization or chromatography.

Ultraviolet spectrum :  $\lambda_{max}$  232nm(  $\epsilon$ 11,800), 327nm(  $\epsilon$ 14,150).

Infrared spectrum :  $\nu_{max}$  3415m(NH), 1741m(C=O), 1705s(C=O), 1636m, 1513s, 1436s, 1379m, 1359m, 1321m, 1257m, 1161m, 1115m, 1083s  $cm^{-1}$ .

N.M.R. spectrum :  $\tau$ , 4.32(b, NH), 6.29, 6.31, 6.33, and 6.40(each s, ester Me), 7.69, 7.71(each s, nuclear Me), 7.84, 7.86(each s, COMe), 9.09, 9.11(each d, J 7.0 Hz, 5-Me), three protons at  $\tau$ 5.8-7.0.

Mass spectrum : m/e 367(19), 337(5), 336(22), 335(7), 324(6), 304(6), 293(5), 292(23), 278(5), 276(5), 260(5), 253(10), 252(65), 251(100), 250(6), 238(9), 236(9), 234(5), 232(5), 224(10), 221(7), 220(46), 219(8), 212(5), 211(31), 210(5),

204(5), 193(13), 192(47), 191(7), 190(6), 188(7), 180(14), 179(93), 178(8), 176(6), 174(6), 168(16), 167(9), 166(5), 161(5), 160(15), 154(5), 153(28), 151(6), 150(6), 149(6), 146(7), 134(6), 133(7), 132(13), 122(5), 121(12), 119(8), 118(5), 117(5), 116(5), 108(5), 107(5), 106(5), 105(6), 93(10), 92(5), 91(15), 85(5), 79(8), 77(9), 74(5), 69(6), 67(12), 66(5), 65(13), 59(26), 55(5), 53(9), 51(5), 45(6), 44(10), 43(78), 42(31), 41(19), 39(14).

Anal. Calcd. for  $C_{18}H_{25}NO_7$  (mol. wt. 367): C, 58.85; H, 6.86; N, 3.81. Found (mass spectrum 367): C, 58.90; H, 6.96; N, 3.84.

Trimethyl 8-acetyl-1,3,6-trimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7,8-tricarboxylate ( 36e ) .

The chloro-compound( 3e, 400mg.) was added to a solution of methyl sodioacetoacetate(405mg) in dry dimethylformamide (10ml.) as above, and the mixture was heated on an oil bath for 6h. at  $90^{\circ}$  . After cooling, it was poured into cold water (100ml.) containing ammonium chloride(5g.). The product was extracted with ether(3x60ml.), and the ether extract washed with water(3x10ml.) and evaporated in vacuo. The solid residue was crystallised from ether-petroleum ether to yield white prisms (370mg.; 72%), m.p.  $132-133.5^{\circ}$  .

Ultraviolet spectrum:  $\lambda_{max}$  293nm( $\epsilon$  15,200).

Infrared spectrum:  $\nu_{max}$  3427m(NH), 1737s(C=O), 1709s(C=O), 1680m(C=O), 1669m, 1596m, 1486m, 1462m, 1436, 1371m, 1358m, 1263m, 1173m, 1096s, 1013w  $cm^{-1}$

N.M.R. spectrum:  $\tau$ , 5.52(s, NH), 6.29, 6.30 and 6.31(each s, ester

Me), 6.70(d, J 12.0 Hz), 7.38(m), 7.69(s, 3-Me), 7.83(s, COMe), 8.34(s, 1-Me), and 9.04(d, J 7.0 Hz, 6-Me). A proton at  $\tau$  6.2-6.3 was obscured by ester methyl signals, and another proton at  $\tau$  7.1-8.0 was partially obscured by methyl signals.

Mass spectrum: m/e 368(6), 367(25), 336(14), 324(13), 304(5), 292(6), 264(5), 225(18), 224(100), 208(10), 192(8), 165(5), 132(5), 59(5), 43(17).

Anal. calcd. for  $C_{18}H_{25}NO_7$  (mol. wt. 367): C, 58.85; H, 6.86; N, 3.81. Found (mass spectrum 367): C, 58.86; H, 6.57; N, 3.75.

Dimethyl 4-(diethoxycarbonylmethyl)-4,5-dihydro-2,7-dimethyl-azepine-3,6-dicarboxylate (4f).

The chloro-compound( 3a, 2.0g.) in dry tetrahydrofuran (10ml.) was added to a solution of diethyl sodiomalonate(2.8g.) prepared by adding diethyl malonate(2.7g.) to a suspension of sodium hydride(370mg.) in dry tetrahydrofuran (20ml.) on an ice-water bath. The mixture was stirred for 15h. at 40° and then poured into cold water(300ml.) containing ammonium chloride(10g.). The product was extracted with ether(3x150ml.) and the ether extract was washed (with water(3x30ml.) and evaporated to dryness. The solid residue was recrystallized from ether-petroleum ether to give white prisms(2.2g.; 75.5%), m.p. 99-100.5° .

Ultraviolet spectrum:  $\lambda_{max}$  230nm(  $\epsilon$  11,850), 329nm( $\epsilon$  13,200).

Infrared spectrum:  $\nu_{max}$  3417m(NH), 1750s(C=O), 1728(C=O), 1705s(C=O), 1633m, 1513s, 1436m, 1386w, 1371m, 1322m, 1255m, 1112m, 1078s, 1020w  $cm^{-1}$ .

N.M.R. spectrum:  $\tau$ , 4.27(s, NH), 5.85 and 5.94(each q, J 7.1 and

7.2 Hz, ester CH<sub>2</sub>), 6.31 and 6.35 (each s, ester Me), 6.69 (d.d, J 15.8 and 6.0 Hz), 6.70 (d, J 11.0 Hz), 7.66 and 7.73 (each s, nuclear Me), 8.76 and 8.81 (each t, ester CH<sub>3</sub>). One proton at  $\tau$  5.85, one proton at  $\tau$  7.6-8.0 were obscured by ethyl ester CH<sub>2</sub> and nuclear Me signals respectively.

Mass spectrum : m/e 397(4), 366(7), 352(5), 320(5), 292(8), 264(5), 252(6), 239(6), 238(40), 237(82), 224(8), 222(12), 211(11), 207(8), 206(51), 205(42), 190(8), 180(8), 179(54), 178(97), 177(17), 174(8), 165(5), 164(13), 163(5), 162(12), 160(5), 153(10), 149(8), 148(12), 147(14), 146(93), 137(8), 136(8), 135(6), 134(10), 133(72), 132(6), 121(8), 120(5), 119(9), 118(34), 117(5), 116(8), 115(100), 109(5), 106(5), 105(27), 93(5), 91(10), 88(28), 87(14), 79(5), 78(8), 77(28), 73(6), 70(7), 69(7), 67(5), 65(7), 61(10), 60(19), 59(30), 55(5), 53(9), 52(9), 51(11), 45(22), 44(13), 43(80), 42(27), 41(10), 39(10).

Anal. Calcd. for C<sub>19</sub>H<sub>27</sub>NO<sub>8</sub> (mol. wt. 397): C, 57.43; H, 6.85; N, 3.53. Found (mass spectrum 397): C, 57.29; H, 6.93; N, 3.43.

Dimethyl 4-(diethoxycarbonylmethyl)-4,5-dihydro-2,5,7-trimethyl-azepine-3,6-dicarboxylate (42f).

The chloro-compound (3e, 1.0g.) in dry tetrahydrofuran (5ml.) was added to a solution of diethyl sodiomalonate (1.29g.) prepared by adding diethyl malonate (1.2g.) to a suspension of sodium hydride (170mg.) in dry tetrahydrofuran (25ml.) cooled in a bath containing ice-water. The mixture was stirred for 20h. at 40° and then poured into cold water (300ml.) containing ammonium chloride (10g.). The product was extracted

with ether(3 x 100ml.), and the bulked ether extract was washed with water(2 x 30ml.) and evaporated to dryness. The solid residue was recrystallized from ether-petroleum ether to give white prisms(0.94g.;66%), m.p. 125.5-127°.

Ultraviolet spectrum :  $\lambda_{\max}$  230nm(  $\epsilon$  11,800), 326nm(  $\epsilon$ 14,900).

Infrared spectrum :  $\nu$  max 3420m(NH), 1749s(C=O), 1727s(c=o), 1701s(C=O), 1631m, 1510s, 1445m, 1433m, 1369m, 1320m, 1304m, 1259s, 1113m, 1080s, 1012w  $\text{cm}^{-1}$ .

N. M. R. spectrum :  $\tau$  4.28(s, NH), 5.86 and 5.94(each q, J 7.3 and 7.2 Hz, ester  $\text{CH}_2$  ), 6.03(d.d, J 6.0 and 11.6 Hz,4-H), 6.30 and 6.34(each s, ester Me), 6.58(m, J 6.8 and 6.0 Hz, 5-H), 6.79(d, J 11.6 Hz, malonic ester CH), 7.68(s, nuclear Me), 8.78 and 8.82(each t, J 7.3 and 7.2 Hz, ester  $\text{CH}_3$  ), and 9.07 (d, J 6.8 Hz, 5-Me).

Mass spectrum : m/e 411(3), 380(11), 366(6), 334(7), 306(13), 278(10), 266(11), 253(8), 252(45), 251(87), 250(6), 238(17), 236(10), 234(6), 220(44), 219(5), 218(6), 211(19), 208(8), 206(6), 193(9), 192(39), 190(6), 188(9), 180(16), 179(100), 178(8), 176(6), 174(6), 168(6), 167(16), 160(16), 153(29), 150(5), 146(6), 133(7), 132(12), 121(13), 119(7), 93(7), 91(10), 79(5), 77(6), 67(6), 65(9), 59(11), 45(6), 44(8), 43(12), 42(16), 41(12), 39(7).

Anal. Calcd. for  $\text{C}_{20}\text{H}_{29}\text{NO}_8$  (mol.wt. 411) : C, 58.37; H, 7.10; N, 3.40. Found(mass spectrum 411) : C, 58.42; H, 7.13; N,3.36.

Dimethyl 1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-(2',6'-dioxocyclohexane) ( 41a ).

The chloro-compound( 3a, 819mg.) in dry dimethyl-

formamide(10ml.) was added to a solution of sodium cyclohexane-1,3-dionate(895mg.) prepared by adding cyclohexane-1,3-dione (840mg.) in dry dimethylformamide(8ml.) to a suspension of sodium hydride(160mg.) in dry dimethylformamide(5ml.) on an ice-water bath. The mixture was heated on a water bath for 10h at 70° with magnetic stirring. After cooling, the mixture was poured into cold water(100ml.) containing ammonium chloride (5g.) and the solution extracted with ether(3 x 100ml.). The ether extract was washed with water(3 x 20ml.) and the solvent removed in vacuo. The residue was crystallized from ether-petroleum ether to give white prisms(940mg.; 90%), m.p. 219.5-220.5° .

Ultraviolet spectrum :  $\lambda_{\max}$  289nm(  $\epsilon$  14,900 ).

Infrared spectrum :  $\nu_{\max}$  3416m(NH), 1725s(C=O), 1692s(C=O), 1659m, 1586m, 1478m, 1452m, 1435m, 1374w, 1351m, 1334m, 1305m, 1279m, 1252w, 1172m, 1119m, 1096s, 1060w  $\text{cm}^{-1}$ .

N. M. R. spectrum :  $\tau$  5.80(s, NH), 6.31 and 6.32(each s, ester Me), 7.96(s, 3-Me), 8.25(s, 1-Me). One proton at  $\tau$  6.2, one proton at  $\tau$  6.5 were partially obscured by ester methyl signal. The other two ring protons and the cyclohexanedione six ring protons were overlapping between  $\tau$  6.7-8.8.

Mass spectrum : m/e 350(10), 349(45), 319(5), 318(24), 293(9), 290(8), 286(9), 266(6), 265(36), 263(7), 262(5), 258(9), 235(6), 234(9), 232(5), 231(20), 230(7), 224(5), 221(6), 220(20), 208(10), 207(55), 206(13), 193(5), 192(27), 180(12), 179(100), 178(6), 176(8), 166(6), 165(22), 164(7), 160(8), 150(7), 149(6), 148(13), 146(5), 134(9), 133(5), 132(7), 120(5), 118(5), 106(7),

105(7), 96.5(12), 91(8), 80.5(15), 79(6), 77(9), 67(6), 65(6), 59(3), 55(20), 53(5), 43(6), 42(20), 41(8), 39(6).

Anal. Calcd. for  $C_{18}H_{23}NO_6$  (mol.wt. 349) : C, 61.88, H, 6.64; N, 4.19. Found (mass spectrum 349) : C, 61.82; H, 6.40, N, 4.19.

Dimethyl 1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-(4',4'-dimethyl-2',6'-dioxocyclohexane)  
( 41b ).

The chloro-compound( 3a, 273mg.) in dry dimethylformamide(5ml.) was added to a solution of 5,5-dimethylcyclohexane-1,3-dione(350mg.) prepared from dimedone(320mg.) and sodium hydride(52mg.) in dry dimethylformamide(10ml.). The mixture was heated on a water bath for 8h at 65° with magnetic stirring. After cooling, the mixture was poured into cold water (100ml.) containing ammonium chloride(5g.) and the solution extracted with ether(3 x 80ml.). The ether extract was washed with water(3 x 20ml.) and the solvent removed in vacuo. The residue was crystallized from chloroform-petroleum ether to give white needles(310mg.; 82%), m.p. 221.5-222.5° .

Ultraviolet spectrum :  $\lambda_{max}$  289nm(  $\epsilon$  14,550 ).

Infrared spectrum :  $\nu_{max}$  3416m(NH), 1727s(C=O), 1697s(C=O), 1662m, 1593m, 1482m, 1467m, 1456m, 1437m, 1376m, 1356m, 1322m, 1308m, 1267m, 1174m, 1112s, 1095m  $cm^{-1}$ .

N. M. R. spectrum :  $\tau$ , 5.84(s, NH), 6.32(s, two ester Me), 7.98(s, 3-Me), 8.27(s, 1-Me), 8.81 and 9.16(each s, dimedone ring Me). Eight protons give complicated signals between  $\tau$  6.1-8.4 and were hard to interpret.

Mass spectrum : m/e 378(17), 377(74), 349(5), 347(6), 346(28), 330(6), 318(11), 314(11), 291(16), 290(7), 286(12), 265(14), 259(34), 258(7), 249(7), 248(17), 235(9), 234(5), 224(10), 221(5), 220(26), 208(13), 207(50), 206(12), 204(19), 192(8), 180(13), 179(100), 178(6), 176(7), 166(8), 165(20), 164(6), 160(7), 150(6), 149(5), 146(5), 134(8), 132(7), 106(6), 105(7), 91(6), 84(5), 83(22), 77(7), 59(7), 54(15), 43(9), 42(14), 41(9), 39(5) .

Anal. Calcd. for  $C_{20}H_{27}NO_6$  (mol. wt. 377): C, 63.64; H, 7.21; N, 3.71. Found (mass spectrum 377); C, 63.70; H, 7.23; N, 3.85.

Dimethyl 1,3,6-trimethyl-2-azabicyclo [3.2.1] -oct-3-ene-4,7-dicarboxylate-8-spiro-(2,6-dioxocyclo-hexane) ( 41c ).

The chloro-compound( 3e, 500mg.) in dry dimethyl-formamide(8ml.) was added to a solution of sodium cyclohexane-1,3-dionate(485mg.) prepared by adding cyclohexane-1,3-dione (430mg.) to a suspension of sodium hydride(87mg.) in dry dimethyl-formamide(10ml.) on an ice-water bath. The mixture was heated on an oil bath for 10h. at  $90^{\circ}$  with magnetic stirring. After cooling, the mixture was poured into cold water(100ml.) containing ammonium chloride(5g.) and the solution extracted with ether(3x60ml.). The ether extract was washed with water(2x20ml.) and the solvent removed in vacuo. The residue was dissolved in benzene and chromatographed on silica gel H, using benzene-ethyl acetate for elution. The middle fraction was collected and after removal of solvent, the residue recrystallized from ether-petroleum ether to give colorless prisms(380mg.; 60%), m.p.  $137-138.5^{\circ}$ .

Ultraviolet spectrum :  $\lambda_{\max}$  292nm(  $\epsilon$ 15,250).

Infrared spectrum :  $\nu_{\max}$  3436m(NH), 1728s(C=O), 1695s(C=O), 1667m, 1652m, 1585m, 1495m, 1458m, 1437m, 1380m, 1360m, 1337w, 1313m, 1282m, 1175m, 1108m, 1098s, 1067m, 1019w, 979w  $\text{cm}^{-1}$ .

N. M. R. spectrum :  $\tau$ , 5.27(s, NH), 6.15(d, J 5.8 Hz, probably 5-H), 6.29 and 6.31(each s, ester Me), 7.86(s, 3-Me), 8.35(s, 1-Me), 9.04(d, J 7.0 Hz, 6-Me). The other two ring protons and six cyclohexanedione protons were overlapping between  $\tau$  6.3-8.8.

Mass spectrum : m/e 364(10), 363(44), 332(21), 307(9), 304(8), 300(6), 280(6), 279(28), 272(9), 264(6), 263(6), 252(5), 248(6), 244(5), 235(6), 234(5), 232(6), 231(8), 221(6), 220(23), 208(10), 207(50), 206(12), 193(6), 192(32), 180(17), 179(100), 178(7), 176(6), 167(11), 166(6), 165(18), 164(7), 160(6), 154(10), 153(6), 150(8), 149(6), 148(9), 134(8), 132(6), 122(5), 106(6), 105(6), 96.5(10), 91(7), 80.5(15), 79(5), 77(7), 69(5), 67(6), 59(6), 55(15), 43(6), 42(14), 41(9), 39(5).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{25}\text{NO}_6$  (mol.wt.363) : C, 62.80; H, 6.93; N, 3.85. Found(mass spectrum 363) : C, 62.65; H, 6.93; N, 3.79.

Dimethyl 1,3,6-trimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-(4',4'-dimethyl-2',6'-dioxocyclohexane)  
( 41d ).

The chloro-compound( 3e, 500mg.) in dry dimethylformamide(8ml.) was added to a solution of sodium 5,5-dimethylcyclohexane-1,3-dionate(593mg.) prepared by adding dimedone (536mg.) in dry dimethylformamide(10ml.) to a suspension of sodium hydride(88mg.) in dry dimethylformamide(2ml.) on an ice-water bath. The mixture was heated on an oil bath for 10h at

90° with magnetic stirring. After cooling, the mixture was poured into cold water(100ml.) containing ammonium chloride(5g.) and the solution extracted with ether(3 x 80ml.). The ether extract was washed with water(3 x 20ml.) and the solvent removed under reduced pressure. The residue was crystallized from ether-petroleum ether to give white prisms(462mg.;68%), m.p. 218.5-219.5° .

Ultraviolet spectrum :  $\lambda_{\max}$  292nm(  $\epsilon$  15,050).

Infrared spectrum :  $\nu_{\max}$  3436m(NH), 1728s(C=O), 1696s(C=O), 1668m(C=O), 1652m, 1585m, 1502m, 1496m, 1464m, 1457m, 1439m, 1376m, 1360m, 1321m, 1304m, 1269m, 1174s, 1100s, 1085m, 1014w  $\text{cm}^{-1}$ .

N. M. R. spectrum :  $\tau$ , 5.49(s, NH), 6.20(d, J 5.8 Hz, probably 5-H), 6.33 and 6.36( each s, ester Me), 7.88(s, 3-Me), 8.37(s, 1-Me), 9.06(d, J 7.0 Hz, 6-Me), 8.80 and 9.16(each s, dimedone ring Me). The other two ring protons and four cyclohexanedione protons were overlapping between  $\tau$  6.3-8.2.

Mass spectrum : m/e 392(20), 391(77), 363(8), 362(6), 361(6), 360(26), 344(5), 332(12), 328(7), 304(6), 300(11), 291(12), 284(5), 279(14), 276(5), 272(6), 264(5), 263(10), 260(7), 259(20), 252(8), 249(7), 248(17), 238(6), 235(11), 234(6), 221(6), 220(32), 218(5), 208(13), 207(50), 206(11), 204(11), 193(5), 192(14), 182(12), 180(21), 179(100), 178(7), 176(7), 174(5), 168(8), 167(18), 166(8), 165(19), 164(7), 160(6), 155(5), 154(6), 153(10), 150(9), 149(8), 148(5), 146(5), 142(7), 135(5), 134(10), 133(5), 132(6), 122(6), 121(5), 120(5), 119(6), 110(6), 108(7), 107(7), 91(7), 84(5), 83(24), 80.5(5), 79(5), 77(7), 69(7), 67(15), 66(8), 65(5), 59(7), 55(13), 53(5), 43(10),

42(14), 41(13), 39(6).

Anal. Calcd. for  $C_{21}H_{29}NO_6$  (mol.wt. 391) : C, 64.43; H, 7.47; N, 3.58. Found (mass spectrum 391) : C, 64.38; H, 7.49; N, 3.39.

Dimethyl 1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-cyclopentadiene (39a).

The chloro-compound (3a, 2.73g.) in dry dimethylformamide (20ml.) was added to a solution of cyclopentadienyl sodium (2.2g.) prepared from freshly distilled cyclopentadiene (3.5ml.) and sodium hydride (600mg.) in dry dimethylformamide (20ml.) on an ice-water bath. The mixture was heated on a water bath for 6h at  $60^{\circ}$  with magnetic stirring. After cooling, the mixture was poured into cold water (300ml.) containing ammonium chloride (20g.) and the solution extracted with ether (3 x 200ml.). The ether extract was washed with water (3 x 30ml.) and the solvent removed under reduced pressure. The residue was crystallized from ether-petroleum ether and aqueous dioxane to give colorless prisms (2.05g.; 67.5%), m.p.  $195-196.5^{\circ}$ .

Ultraviolet spectrum :  $\lambda_{max}$  295nm ( $\epsilon$  16,200).

Infrared spectrum :  $\nu_{max}$  3427m (NH), 1739s (C=O), 1681s (C=O), 1593s, 1479m, 1452m, 1438m, 1380m, 1349m, 1334m, 1303m, 1296m, 1277m, 1171m, 1149m, 1120m, 1094s, 1078m  $cm^{-1}$ .

N. M. R. spectrum : (Varian HA-100)  $\tau$  3.69 (m, cyclopentadiene ring protons), 5.72 (s, NH), 6.29 and 6.38 (each s, ester Me), 6.81 (d.d, J 4.9 and 11.8 Hz, 7-H), 7.02 (b.d, J 5.8 and  $\sim$ 1.0 Hz, 5-H), 7.36 (b.d.d, J 4.9, 14.0 and 1.0 Hz, 6endo H), 7.62 (m, J 5.8, 11.8 and 14.0 Hz, 6exo H), 7.82 (s, 3-Me), 8.79 (s, 1-Me).

Mass spectrum : m/e 304(13), 303(67), 288(13), 273(5), 272(30), 256(6), 245(17), 244(100), 243(9), 240(7), 230(9), 228(8), 218(8), 217(51), 216(59), 213(6), 212(27), 211(8), 202(82), 196(5), 188(5), 185(11), 184(34), 183(6), 182(7), 179(8), 171(6), 170(11), 169(13), 168(11), 159(9), 158(63), 157(14), 156(16), 154(6), 152(6), 144(7), 143(13), 142(12), 141(9), 131(6), 130(9), 129(18), 128(19), 127(6), 116(12), 115(29), 106(6), 103(7), 93(7), 91(14), 89(6), 84(9), 79(6), 78(6), 77(13), 65(10), 59(14), 55(9), 53(6), 51(6), 42(26), 41(6), 39(10).

Anal. Calcd. for  $C_{17}H_{21}NO_4$  (mol. wt. 303): C, 67.31; H, 6.98; N, 4.62. Found (mass spectrum 303): C, 67.57; H, 7.03; N, 4.75.

Dimethyl 1,3-dimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-cyclopentane ( 40 ).

Spiro-compound ( 39a , 250mg.) and platinum oxide (50 mg.) in methanol (20ml.) were stirred under hydrogen at 1 atm. pressure and room temperature. The hydrogen absorption took place in 30min. and stirring was continued for another 30min.. The catalyst was filtered off and the filtrate was evaporated in vacuo. The tetrahydrospiro-compound ( 40 ) was crystallized as white prisms (242mg.; 96%) m.p. 207-210<sup>0</sup>. The analytical sample was recrystallized twice from aqueous methanol to give white prisms, m.p. 212-213.5<sup>0</sup>.

Ultraviolet spectrum:  $\lambda_{max}$  296nm (  $\epsilon$  16,950 ).

Infrared spectrum:  $\nu_{max}$  3427m(NH), 1730s(sat. CO<sub>2</sub>Me), 1664s(unsat. CO<sub>2</sub>Me) 1589s, 1478s, 1453m, 1435s, 1378m, 1352m, 1330m, 1302m, 1277m, 1165m, 1114s, 1081m. cm<sup>-1</sup>.

N.M.R. spectrum: (Varian HA-100)  $\tau$  , 5.96(s, NH), 6.32 and 6.36 (each s, ester Me), 7.06(d.d, J 11.0 and 5.0 Hz, 7-H), 7.30(b.d, J 5.5 and -0.5 Hz, 5-H), 7.65(b.d.d, J 5.0, 12.5 and -0.5 Hz, 6endo H), 7.86(m, J 5.5, 11.0 and 12.5 Hz, 6exo H), 7.90(s, 3-Me), 8.38(b.s, cyclopentane ring H), 8.71(s, 1-Me).

Mass spectrum: m/e 308(10), 307(48), 277(5), 276(27), 248(14), 220(9), 207(20), 206(100), 193(13), 192(37), 180(5), 179(32), 162(5), 134(6.5), 91(5), 42(5) .

Anal. Calcd. for  $C_{17}H_{25}NO_4$  (mol.wt. 307): C, 66.43; H, 8.20; N, 4.59. Found (mass spectrum 307): C, 66.27; H, 8.22; N, 4.69 .

Dimethyl 1,3,6-trimethyl-2-azabicyclo [3.2.1] oct-3-ene-4,7-dicarboxylate-8-spiro-cyclopentadiene(39b) .

The chloro-compound( 3e, 1.0g.) in dry dimethylformamide (10ml.) was added to a solution of cyclo-pentadienyl sodium (767mg.) prepared by adding freshly distilled cyclopentadiene (1.5ml.) to a suspension of sodium hydride(210mg.) in dry dimethylformamide(20ml.) in an ice-water bath . The stirred mixture was heated on a water bath for 10h. at 60° . After cooling, the mixture was poured into cold water(200ml.) containing ammonium chloride(10g.) and the solution extracted with ether(3x150ml.) . The ether extract was washed with water(3x20ml.) and the solvent removed under reduced pressure. The residue was crystallized from ether-petroleum ether and aqueous dioxane to give white prisms(0.42g.; 38%), m.p. 158-159.5° .

Ultraviolet spectrum:  $\lambda_{max}$  241nm(  $\epsilon$ 3,100), 297nm(  $\epsilon$ 15,400)

Infrared spectrum:  $\nu_{max}$  3422m(NH), 1728s(C=O), 1679s(C=O), 1666s, 1586s, 1476m, 1460m, 1449m, 1438m, 1434m, 1377m, 1366m, 1347m,

1314m, 1298m, 1286m, 1266s, 1172m, 1149s, 1122m, 1094s, 1076s, 1017m  $\text{cm}^{-1}$ .

N.M.R. spectrum: (Varian HA-100)  $\tau$ , 3.22, 3.73 and 3.90 (each m, cyclopentadiene ring H), 5.38 (s, NH), 6.32 and 6.38 (each s, ester Me), 6.92 (m, J 5.2, 6.5 and 8.2 Hz, 6-H), 7.03 (d, J 5.2 Hz, 5-H), 7.27 (d, J 8.2 Hz, 7-H), 7.74 (s, 3-Me), 8.93 (d, J 6.5 Hz, 6-Me), and 9.02 (s, 1-Me).

6-Me, doublet becomes singlet when irradiated at 308 Hz.

Mass spectrum: m/e 318(10), 317(46), 302(20), 286(16), 270(18), 259(11), 258(56), 257(13), 254(8), 251(5), 244(5), 242(21), 238(5), 227(5), 226(22), 225(8), 224(5), 220(6), 219(7), 218(14), 217(80), 216(75), 211(7), 210(11), 208(9), 204(7), 203(19), 202(100), 198(18), 192(13), 185(10), 184(17), 183(11), 182(10), 181(9), 180(5), 179(11), 171(7), 170(18), 169(7), 168(8), 167(6), 166(7), 165(5), 160(12), 159(9), 158(25), 157(13), 156(14), 155(5), 154(5), 153(5), 152(7), 149(9), 144(9), 143(20), 142(15), 141(12), 132(10), 131(6), 130(6), 129(10), 128(15), 122(6), 119(7), 117(8), 116(11), 115(24), 108(8), 107(6), 105(7), 103(6), 94(6), 93(10), 92(7), 91(17), 89(5), 84(18), 79(7), 78(8), 77(13), 69(10), 67(7), 66(6), 65(12), 59(15), 53(6), 51(7), 44(50), 43(16), 42(22), 41(22), 40(11), 39(13).

Anal. calcd. for  $\text{C}_{18}\text{H}_{23}\text{NO}_4$  (mol.wt. 317): C, 68.12; H, 7.30; N, 4.41. Found (mass spectrum 317): C, 67.87; H, 7.42; N, 4.34.

Dimethyl 4,5-dihydro-2,7-dimethyl-4-succinimino-azepine-3,6-dicarboxylate (4b).

The chloro-compound (3a, 3.0g.) was added to a stirred solution of potassium succinimide (1.4g.) in absolute ethanol (80ml.). After 48h. the solvent was removed under reduced pre-

ssure, and the residue recrystallized from chloroform-petroleum ether to give white prisms(2.78g.; 75%). m.p. 192.5-193.5° .

Ultraviolet spectrum:  $\lambda_{\max}$  235nm( $\epsilon$  11,800), 330nm( $\epsilon$  13,800) .

Infrared spectrum:  $\nu_{\max}$  3410m(NH), 1775w(C=O), 1705s(C=O), 1622w, 1511m, 1505s, 1435m, 1402m, 1385m, 1358m, 1326m, 1288m, 1134w, 1089s  $\text{cm}^{-1}$  .

N.M.R. spectrum:(Varian HA-100)  $\tau$ , 4.22(s, NH), 4.48(d.d, J 1.0 and 6.5 Hz, 4-H), 6.36 and 6.39(each s, ester Me), 6.78(d.d, J 6.5 and 14.0 Hz, trans 5-H), 7.48(s, succinimino group,  $\text{CH}_2$ ), 7.60(d.d, J 1.0 and 14.0 Hz, 5-H), 7.56 and 7.77(each s, nuclear Me). The trans 5-H, quartet becomes doublet with irradiation at 552 Hz.

Mass spectrum: m/e 336(5.7), 277(5), 251(5), 245(5), 238(11), 237(66), 224(4), 222(16), 219(5), 218(5), 217(5), 207(5), 206(31), 205(35), 192(7), 190(9), 180(6), 179(40), 178(100), 177(21), 165(5), 164(16), 163(7), 162(16), 153(9), 150(5), 149(9), 148(13), 147(15), 146(97), 137(10), 136(11), 135(5), 134(8), 133(6), 121(12), 120(7), 119(11), 118(42), 117(5), 109(7), 108(5), 107(5), 106(7), 105(24), 104(4), 100(5), 99(47), 94(6), 93(9), 92(5), 91(13), 83(5), 79(8), 78(13), 77(37), 67(7), 66(7), 65(11), 59(35), 56(42), 55(14), 53(15), 52(15) 51(19), 50(6), 45(9), 44(13), 43(12), 42(19), 41(11), 39(16) .

Anal. calc'd. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_6$  (mol.wt. 336): C, 57.14; H, 5.99; N, 8.33 . Found (mass spectrum 336): C, 57.05; H, 6.09; N, 8.22 .

Dimethyl 4,5-dimethoxy-2,5,7-trimethyl-4-succinimino-azepine-3,6-dicarboxylate ( 42b ) .

The chloro-compound( 3e, 2.87g.) was added to a stirred

solution of potassium succinimide (1.4g.) in absolute ethanol (60 ml.). After 48h. the solvent was removed under reduced pressure, and the residue recrystallised from chloroform-ether-petroleum ether to give white prisms (2.58g.; 74%), m.p. 180-181°.

Ultraviolet spectrum:  $\lambda_{\max}$  235nm ( $\epsilon$ 10,450), 328nm ( $\epsilon$ 14,650).

Infrared spectrum:  $\nu_{\max}$  3410m(NH), 1772w(C=O), 1701s(C=O), 1623w(C=C), 1509s, 1431m, 1397w, 1373m, 1351m, 1335m, 1254m, 1168w, 1099m, 1075m  $\text{cm}^{-1}$ .

N.M.R. spectrum: (Varian HA-100)  $\tau$ , 4.09(s, NH), 4.69(d, J 6.0 Hz, 4-H), 6.37(s, ester Me), 6.65(m, J 6.0 and 7.2 Hz, 5-H), 7.49(s, succinimino group, CH), 7.54(s, 2-Me), 7.82(s, 7-Me), and 9.03(d, J 7.2 Hz, 5-Me). The 5-H, multiplet becomes doublet on irradiation at 99 Hz. The 4-H, doublet and 5-Me, doublet become singlets on irradiation at 336Hz. The 5-H, multiplet becomes quartet on irradiation at 534Hz.

Mass spectrum: m/e 350(5), 319(5), 291(4), 252(10), 251(57), 236(19), 224(5), 221(6), 220(33), 219(51), 218(5), 211(5), 204(18), 193(15), 192(100), 191(32), 190(5), 179(26), 178(11), 177(7), 176(24), 167(12), 164(6), 163(9), 162(6), 161(12), 160(79), 159(19), 153(15), 151(8), 150(12), 149(7), 148(7), 144(5), 135(8), 134(5), 133(12), 132(49), 121(9), 120(7), 119(21), 118(8), 117(8), 107(6), 105(8), 99(52), 93(7), 92(7), 91(38), 79(9), 77(12), 67(8), 66(6), 65(18), 63(5), 59(21), 56(47), 55(11), 53(8), 52(7), 51(9), 44(11), 43(13), 42(14), 41(13), 39(13).

Anal. calcd. for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_6$  (mol. wt 350): C, 58.27; H, 6.33; N, 8.00. Found (mass spectrum 350): C, 58.05; H, 6.45; N, 7.84.

Dimethyl 4,5-dihydro-4-methoxy-2,5,7-trimethylazepine-3,6-  
dicarboxylate ( 42a ).

The chloro-compound( 3e ,3.1g.) and triethylamine (1.5ml.) in methanol(250ml.)were heated on an oil bath at 50° for 48h. Methanol was removed under reduced pressure, and the residue dissolved in ether. The ether solution was washed with water and the solvent was removed in vacuo. The solid residue was recrystallised from ether-petroleum ether to give colorless crystals( 42a , 2.65g. ; 87%), m.p. 152-155°. The analytical sample was prepared by recrystallisation twice from ether-petroleum ether to give colorless prisms, m.p. 157-159° (rapid heating ).

Ultraviolet spectrum:  $\lambda_{\text{max}}$  231nm(  $\epsilon$ 12,750), 325nm(  $\epsilon$ 15,550).

Infrared spectrum :  $\nu_{\text{max}}$  3418m, (NH), 1701s (C=O), 1634m (C=C), 1513s, 1434s, 1378m, 1323m, 1258s, 1181w, 1117m, 1100s, 1080s, 1054w, 977w  $\text{cm}^{-1}$ .

N.M.R. spectrum : (Varian HA-100)  $\tau$ , 4.32(s, NH), 5.40(d, J 6.6Hz, 4-H), 6.28(s, ester Me), 6.45(m, J 6.6 and 6.8 Hz, 5-H), 6.71(s, OMe), 7.64 (s, 2-Me), 7.71(s, 7-Me), and 9.23(d, J 6.8Hz, 5-Me). Irradiation at 356Hz decouples 4-H doublet and 5-Me doublet to singlets.

Mass spectrum: m/e 283(10), 268(8), 252(15), 251(33), 236(23), 224(14), 221(6), 220(35), 219(38), 208(16), 204(15), 193(16), 192(100), 191(28), 179(13), 178(9), 177(6), 176(25), 167(6), 164(9), 163(8), 162(6), 161(10), 160(64), 159(15), 151(8), 150(12), 148(9), 135(8), 134(7), 133(12), 132(40), 121(7), 120(7), 119(18), 118(8), 117(7), 107(6), 106(5), 105(7), 93(7), 92(8), 91(37), 89(5), 79(11), 77(13), 75(8), 74(10), 67(10), 65(18),

63(5), 59(28), 53(30), 52(8), 51(11), 43(33), 42(14), 41(13), 40(5), 39(16).

Anal. Calc'd. for  $C_{14}H_{21}NO_5$  (mol. wt.283): C, 59.36; H, 7.47; N, 4.94. Found (mass spectrum 283) : C, 59.15; H, 7.60; N, 4.87.

Reaction of Dimethyl 4,5-dihydro-4-methoxy-2,5,7-trimethyl-azepine-3,6-dicarboxylate( 42a ) with Methanolic Hydrogen Chloride.

To the 4-methoxy-4,5-dihydroazepine(42a, 300mg.) in dry methanol(5ml.) was added 0.2N methanolic hydrogen chloride solution(10ml.). The solution was stirred at room temperature for 30 min. The solvent was then removed under reduced pressure and the excess hydrogen chloride was removed by adding dry ether and removing the ether under vacuum 3 times. The residue was then separated by preparative t.l.c.on silica gel G. The higher Rf band gave the dihydropyridine( 3e, 92mg.; 30% ), m.p.165-167° and was identical with the dimethyl 4-(1-chloroethyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ( 3e ).

From the second band, the dihydropyridine ( 3g ) was obtained(175mg.; 58%), m.p.124-127°. The analytical sample was recrystallized from ether-petroleum ether to give colorless prisms, m.p. 127-129°.

Ultraviolet spectrum :  $\lambda_{max}$  233.5nm( $\epsilon$  14,050), 347nm( $\epsilon$  6,700).

Infrared spectrum :  $\nu_{max}$  3430m(NH), 3306b(NH), 1696s(C=O), 1650m(C=C), 1618m, 1472s, 1435m, 1382w, 1309m, 1151m, 1128s, 1102m, 1050w, 1007w  $cm^{-1}$ .

N.M.R. spectrum :  $\tau$ , 3.69(s, NH), 5.66(d, J 5.0 Hz, 4-H), 6.24

(s, ester Me), 6.69(s, OMe), 6.84(m, J 5.0 and 6.5 Hz, CH), 7.69 (s, nuclear Me), and 9.03(d, J 6.5 Hz, Me).

Mass spectrum: m/e 283(0.0006) 252(6), 225(22), 224(100), 220(5), 192(24), 165(5), 164(7), 160(6), 149(5), 59(7) .

Anal. calcd. for  $C_{14}H_{21}NO_5$  (mol.wt. 283): C, 59.36; H, 7.47; N, 4.94. Found (mass spectrum 283): C, 59.32; H, 7.49; N, 5.05.

From the last band, the pyridine (76, 12mg.; 5%) was obtained after extraction with methanol and pass through short basic alumina column, and purified by sublimation, white prisms, m.p. 98-99<sup>0</sup> . (lit. 100-102<sup>0</sup> )<sup>26</sup>.

Dimethyl 4-(1-bromoethyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ( 3f ) .

To the 4-methoxy-4,5-dihydroazepine ( 42a, 200mg.) in ether(50ml.) was added conc. hydrobromic acid (0.5ml.) in a separatory funnel. The mixture was shaken for 5 min. and the ether layer was washed with water(3x5ml.). After removal of ether, the brome-compound 3f was obtained as pale yellow prisms, ( 213mg.; 91%). m.p. 159-162<sup>0</sup> . The analytical sample was purified by recrystalization from benzene-petroleum ether to give white prisms, m.p. 164-165<sup>0</sup> .

Ultraviolet spectrum:  $\lambda_{max}$  233nm(  $\epsilon$ 14.550), 333nm(  $\epsilon$ 7.050)

Infrared spectrum :  $\nu_{max}$  3431m(NH), 3320bw(NH), 1700s(C=O), 1653m, 1620m, 1476s, 1439s, 1387m, 1380m, 1321m, 1312m, 1281m, 1270m, 1183m, 1156m, 1130m, 1110s, 1075m, 1016m  $cm^{-1}$  .

N.M.R. spectrum : 3.91(s, NH), 5.57(d, J 5.2Hz, 4-H), 5.86(m, J 5.2 and 6.8 Hz, CH), 6.23(s, ester Me), 7.62(s, nuclear Me), and 8.46(d, J 6.8 Hz).

Mass spectrum: m/e 332M(O), 252(6), 251(26), 236(11), 225(13), 224(94), 220(27), 219(40), 205(5), 204(18), 193(13), 192(93), 191(25), 178(9), 177(5), 176(20), 165(7), 164(11), 163(7), 162(6), 161(11), 160(82), 159(17), 151(6), 150(13), 149(34), 148(5), 144(6), 141(7), 135(6), 134(5), 133(11), 132(50), 121(5), 120(5), 119(15), 118(6), 117(9), 107(5), 106(5), 105(8), 104(6), 93(6), 92(6), 91(32), 83(5), 82(13), 80(14), 79(16), 78(100), 77(35), 76(9), 74(5), 71(6), 70(7), 69(6), 67(7), 66(5), 65(16), 63(6), 59(20), 57(15), 56(10), 55(12), 53(8), 52(22), 51(21), 50(14), 44(34), 43(23), 42(22), 41(28), 40(27), 39(27).  
Anal. calcd. for  $C_{13}H_{18}NO_4$  Br : C, 47.00; H, 5.46; N, 4.22; Br, 24.05. Found: C, 47.07; H, 5.55; N, 4.37; Br, 24.18.

Dimethyl 4-cyano-4,5-dihydro-2,5,7-trimethylazepine-3,6-dicarboxylate ( 42c ).

(a.) The chloro-compound ( 3e, 4.0g.) was added to a stirred solution of sodium cyanide(1.6g.) in dimethyl sulfoxide (30ml.), and stirring continued for 48h. After addition of water(200ml.) the reaction mixture was extracted with ether (3x200ml.). The ether solution was washed with water(2x30ml.) and the solvent was evaporated under reduced pressure to give a pale yellow solid(3.5g.) which t.l.c. revealed to be two compounds. Recrystallization from ether-petroleum ether, afforded the less soluble cyano-compound( 42c ) as white prisms(2.41g.; 62.5%), m.p. 147-148.5° .

Ultraviolet spectrum:  $\lambda_{max}$  229nm( $\epsilon$  14,400), 326nm( $\epsilon$  16,300).

Infrared spectrum:  $\nu_{max}$  3416m(NH), 2246w(C $\equiv$ N), 1709s(C=O), 1696s(C=O), 1633m(C=C), 1510s, 1434m, 1302m, 1273m, 1248m, 1114m,

1098m, 1075s  $\text{cm}^{-1}$

N.M.R. spectrum: (Varian HA-100)  $\tau$ , 3.83(s, NH), 5.66(d, J 6.2Hz, 4-H), 6.26(s, 3-ester Me), 6.27(s, 6-ester Me), 6.27(m, J 6.2 and 6.8 Hz, 5-H), 7.61(s, 2-Me), 7.66(s, 7-Me), and 9.06(d, J 6.8Hz, 5-Me). The 4-H doublet and the 5-Me doublet become singlets on irradiation at 373 Hz.

Mass spectrum : m/e 278(26), 264(8), 263(47), 248(6), 247(35), 238(12), 231(19), 219(11), 211(17), 204(12), 203(17), 192(6), 188(4), 187(13), 180(15), 179(100), 178(5), 160(12), 159(21), 151(6), 147(6), 146(6), 145(6), 144(5), 143(5), 132(8), 121(21), 119(26), 118(28), 117(5), 116(5), 108(5), 93(10), 91(8), 80(4), 79(5), 78(6), 77(6), 67(9), 66(6), 65(10), 59(13), 53(5), 52(6), 51(7), 43(5), 42(28), 41(14), 39(12).

Anal. calcd. for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4$  (mol.wt. 278): C, 60.42; H, 6.52; N, 10.07. Found (mass spectrum 278): C, 60.31; H, 6.37; N, 9.96.

The more soluble compound( 5a ) was obtained by removal of solvent from the mother liquor and recrystallization from benzene to give white prisms (0.58g.; 23%), m.p. 180.5-181.5°

Ultraviolet spectrum :  $\lambda_{\text{max}}$  211nm(  $\epsilon$ 15,000), 263nm(  $\epsilon$ 8,700).

Infrared spectrum :  $\nu_{\text{max}}$  3435m(NH), 3251b.m(NH), 2233s(C#N), 1710s(C=O), 1596w, 1548m, 1447s, 1414m, 1382w, 1334w, 1277s, 1139s, 1098m  $\text{cm}^{-1}$ .

N.M.R. spectrum:  $\tau$ , 6.20(s, ester Me), 7.53 and 7.65(each s, nuclear Me). NH signal was not observed.

Mass spectrum : m/e 179(8), 178(66), 164(6), 163(53), 148(11), 147(100), 146(47), 145(32), 120(7), 119(23), 118(32), 117(7), 92(9), 91(5), 78(18), 77(9), 76(10), 75(5), 65(7), 52(6), 51(13), 50(7), 42(44), 41(7), 39(5) .

Anal. calc. for  $C_9H_{10}N_2O_2$  (mol. wt. 178): C, 60.67; H, 5.66; N, 15.71. Found (mass spectrum 178): C, 60.75; H, 5.88; N, 15.71.

(b.) 4H-Azepine (47, 310mg.), and potassium cyanide (150mg.) in methanol (25ml.) was stirred for 10h. at room temperature. The mixture was then poured into ice water (100ml.) and extracted with ether (3x60ml). The ether extract was washed with water (3x15ml.) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was recrystallized from ether-petroleum ether to give cyano compound (42c, 85mg.). The mother liquor was evaporated and separated by preparative t.l.c. on silica gel G. to yield cyano compound (42c, 172mg.; total yield 75%) and methoxy compound (42a, 16mg.; 4.6%) and both were identical with the authentic compounds.

Hydrolysis and transesterification of methyl 2,5-dimethyl-4-cyanopyrrole-3-carboxylate (5a).

The pyrrole methyl ester (5a, 1.5g.) was stirred in the solution of 10% sodium hydroxide (100ml.) and methanol (10ml.) at room temperature for 30h. Unreacted ester was then removed by ether extraction and the aqueous solution was neutralized with sulfuric acid, and extracted with ether (3x60ml.). The ether extract was washed with water (3x10ml.) and the solvent evaporated in vacuo to give white crystal 5c (1.23g.; 89%). The pure sample was obtained by sublimation at  $200^{\circ}$  under 0.05mm Hg. to give white prisms, m.p.  $325-333^{\circ}$ . (decomp.).

lit.  $264^{\circ}$  (decomp.)<sup>10</sup>. Some decarboxylated pyrrole 5d deposited

on the upper part of the sublimation tube giving m.p. 87-88.5° .  
lit 87.5-88.5°<sup>9a</sup>, 89°<sup>49</sup>. The pyrrole acid 5c (0.5g.) in  
alcoholic hydrogen chloride (50ml.) was stirred at 40° for 20h.  
After removal of solvent, the residue was extracted and recrysta-  
llized from benzene to yield white prisms (0.28g.; 47.5%), m.p.  
149-150.5°, lit. 149.5-151°<sup>49</sup> and 150-151°<sup>9a</sup> and was identical with  
the authentic sample by mixed melting point and spectral data.  
This ethyl pyrrolecarboxylate 5b was also obtained by trans-  
esterification of methyl pyrrolecarboxylate 5a with sodium  
ethoxide in absolute ethanol at 50° for 1 day.

Dimethyl 2,6-dimethyl-4-(1-thiocyanatoethyl)-1,4-dihydropyridine-  
3,5-dicarboxylate (3h).

A solution of the dihydropyridine (3e, 1.4g.) and  
potassium thiocyanate (0.6g.) in methanol (50ml.) was heated under  
reflux for 2h. The solution was evaporated in vacuo, and the  
residue was dissolved in ether (80ml.). The ether solution was  
washed with water (3 x 10ml.) and dried over anhydrous magnesium  
sulfate. Ether was evaporated until the volume was approximately  
10ml. and an equal amount of petroleum ether was added to yield  
colorless prisms (3h, 1.31g.; 86.5%), m.p. 142-145°. The  
analytical sample was purified by recrystallization twice from  
ether-petroleum ether to give white prisms, m.p. 149-150.5° .  
Ultraviolet spectrum :  $\lambda$  max 233nm ( $\epsilon$  17,350), 341nm ( $\epsilon$  6,700).  
Infrared spectrum :  $\nu$  max 3428m(NH), 3306o.w(NH), 2154m(SCN),  
1699s(C=O), 1645m, 1617m, 1470s, 1434m, 1379m, 1315m, 1303m,  
1277m, 1149m, 1124m, 1106s, 1072m  $\text{cm}^{-1}$  .  
N. M. R. spectrum :  $\tau$ , 3.09(s, NH), 5.58(d, J 5.0 Hz, 4-H), 6.21

(s, ester Me), 6.64(m, J 5.0 and 7.2 Hz, CH ), 7.61(s, nuclear Me), and 8.62(d, J 7.2 Hz, Me).

Mass spectrum : m/e 310 M(0), 252(6), 251(37), 236(14), 225(8), 224(60), 220(31), 219(5), 204(16), 193(13), 192(100), 191(30), 178(8), 176(17), 165(5), 164(8), 163(7), 162(5), 161(9), 160(64), 159(14), 151(6), 150(10), 149(11), 148(5), 141(5), 135(5), 133(10), 132(38), 120(5), 119(14), 118(5), 105(5), 91(23), 79(5), 78(5), 77(8), 65(9), 59(50), 57(5), 51(6), 44(22), 43(7), 42(6), 41(8), 39(8).

Anal. Calcd. for  $C_{14}H_{18}N_2O_4S$  : C, 54.18; H, 5.85; N, 9.03; S, 10.33. Found : C, 54.10; H, 5.81; N, 8.97; S, 10.39.

$\beta$ -(3-Methoxycarbonyl-2-methyl-1-pyrrolyl) crotonic Acid (43a).

(a.) To the dihydropyridine(3a, 500mg.) in dimethyl sulfoxide(5ml.) was added potassium carbonate(1g.) in water(2.5 ml.). The mixture was stirred at room temperature for 2 h and then poured into ice-water(50ml.). Non-acidic products were removed by ether extraction, and the aqueous solution was neutralized with sulfuric acid. The acid 43a was extracted with ether(3 x 20ml.), and the ether extract was washed with water (3 x 5ml.). After removal of the solvent, the residue was sublimed under 0.05 mm Hg. at  $120^{\circ}$  to give white prisms(325mg.; 79.5%), m.p.147-148 $^{\circ}$ .

Ultraviolet spectrum :  $\lambda_{max}$  246.5nm(  $\epsilon$ 10,700).

Infrared spectrum :  $\nu_{max}$  3570-2420 v.b(COOH), 1704s(C=O), 1670m, 1558m, 1497m, 1444s, 1304s, 1158m, 1116m, 1045w, 914w  $cm^{-1}$ .

N.M.R. spectrum :  $\tau$ , 3.34 and 3.46(each d, J 3.2 Hz, ring

H), 3.78(q, J 1.5 Hz, Olefinic H), 6.25(s, ester Me), 7.59(s, ring Me), 7.78(d, J 1.5 Hz, Olefinic Me).

Mass spectrum : m/e 224(14), 223(100), 208(7), 206(6), 193(9), 192(68), 191(23), 190(11), 179(7), 178(54), 176(19), 174(8), 164(22), 163(6), 162(10), 160(10), 150(10), 148(5), 147(10), 146(55), 138(7), 134(7), 124(5), 122(8), 120(19), 119(16), 118(12), 117(7), 109(5), 108(42), 107(6), 106(10), 104(6), 93(6), 91(7), 85(7), 84(8), 80(12), 79(10), 78(7), 77(7), 67(13), 65(6), 63(5), 59(6), 53(16), 52(14), 51(12), 43(11), 42(8), 41(12).  
Anal. Calcd. for  $C_{11}H_{13}NO_4$  (mol.wt.223): C, 59.19; H, 5.87; N, 6.28. Found (mass spectrum 223): C, 59.23; H, 5.81; N, 6.15.

(b.) A mixture of the dihydropyridine(3a, 80mg.) and sodium bicarbonate(200mg.) in glyme(30ml.) and water(10ml.) was stirred for 10 days at room temperature. The reaction mixture was then poured into water(100ml.) and extracted with ether (3 x 20ml.) to remove water insoluble products. Dilute sulfuric acid was added to neutralize the aqueous layer and extracted with ether(3 x 30ml.). The ether extract was worked up as above to give white prisms(38mg.;58%), m.p.148-149<sup>0</sup>. This product was identical with the authentic sample from the above procedure by mixed melting point and spectral data.

The acid (43a, 50mg.) and potassium carbonate(100mg.) in dimethyl sulfoxide-d<sub>6</sub>(1ml.) and deuterium oxide(0.5ml.) were stirred at room temperature for one day. The acid was isolated and purified as above to give white prisms(44mg.), m.p. 148-149<sup>0</sup>. This product showed no deuterium exchange in the n.m.r. spectrum.

Methyl  $\beta$ -(3-methoxycarbonyl-2-methyl-1-pyrrolyl) crotonate (43b).

The methyl ester(43b) was obtained quantitatively by methylation of the acid with diazomethane, and purified by distillation from bulb tube at 120-125<sup>o</sup> (oil bath temperature) under 0.05 mm Hg. It solidified when standing, m.p.41<sup>o</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  249nm(  $\epsilon$ 10,600).

Infrared spectrum :  $\nu_{max}$  1730s(C=O), 1703s(C=O), 1676m, 1557m, 1494m, 1442m, 1392w, 1379w, 1304m, 1244m, 1174m, 1156m,1116m, 1055m, 917w  $cm^{-1}$  .

N.M.R. spectrum :  $\tau$ , 3.47 and 3.62 (each d, J 3.2 Hz, ring H), 3.99(q, J 1.4 Hz, olefinic H), 6.25 and 6.45 (each s, ester Me), 7.64(s, ring Me), 7.84(d, J 1.4 Hz, olefinic Me),

Mass spectrum : m/e 237(100), 222(7), 207(9), 206(64), 205(14), 204(6), 190(12), 179(8), 178(62), 174(19), 173(6), 162(13), 160(7), 147(12), 146(52), 120(6), 119(15), 118(43), 117(5), 108(19), 106(7), 99(6), 91(6), 87.5(7), 79(6), 67(14), 59(16), 58.5(7), 53(8), 52(8), 51(8), 45(9), 39(18).

Anal. Calc'd. for C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub> (mol.wt.237) : C, 60.75; H, 6.37; N, 5.90. Found (mass spectrum 237) : C, 60.78; H, 6.46; N, 6.02.

The methyl ester(43b, 50mg.) and potassium carbonate (50mg.) in dimethyl sulfoxide-d<sub>6</sub> (1ml.) and deuterium oxide (0.5ml.) were stirred for one day, and showed no ester group hydrolysis from the n.m.r. spectrum and t.l.c..

$\beta$  - (3-Methoxycarbonyl-2-methyl-1-pyrrolyl) -  $\alpha$ -deuteriocrotonic  
Acid ( 43c ) .

To the dihydropyridine( 3a, 80mg.) in dimethyl sulf-oxide-d<sub>6</sub> (1ml.) was added potassium carbonate(60mg.) in deuterium oxide(0.5ml.). The mixture was stirred at room temperature for one day, and then worked up as above to give prisms(54mg.; 82%), m.p.149-150<sup>0</sup>.

Ultraviolet spectrum :  $\lambda_{max}$  246.5nm(  $\epsilon$ 10,500 ).

Infrared spectrum :  $\nu_{max}$  3535-2430v.b(COOH), 1704s(C=O), 1659m, 1558m, 1499m, 1443s, 1325m, 1249s, 1158m, 1126m, 1048m cm<sup>-1</sup>.

N.M.R. spectrum :  $\tau$ , -0.65(b.s, COOH), 3.32 and 3.50(each d, J 3.2 Hz, ring H), 6.17(s, ester Me), 7.58(s, ring Me), 7.80(s, olefinic Me).

Mass spectrum : m/e 225(15), 224(100), 223(31), 209(5), 207(6), 194(7), 193(53), 192(37), 191(14), 180(6), 179(45), 178(15), 177(16), 176(6), 175(6), 165(16), 164(8), 163(7), 161(7), 151(7), 150(5), 148(8), 147(38), 146(14), 138(7), 135(5), 124(5), 123(5), 121(10), 120(15), 119(29), 118(15), 109(9), 107(6), 106(9), 105(5), 94(5), 92(5), 85(8), 80(11), 79(7), 78(7), 67(8), 59(7), 53(11), 52(9), 51(7), 43(10), 42(7), 41(6), 40(10), 39(15).

Dimethyl 2,7-dimethyl-4H-azepine-3,6-dicarboxylate ( 9a ).

(a.) Dihydropyridine( 3a, 600mg.) and powdered potassium carbonate(500mg.) in dimethyl sulfoxide(12ml.) was stirred at room temperature for 3.5h . The reaction mixture was poured into cold water(50ml.) and extracted with ether(3x15ml.). The ether extract was washed with water(3x5ml.) and dried over anhydrous magnesium sulfate. After removal of solvent, the residue was distilled from a bulb tube under 0.05 mm Hg. The product was distilled at 110-115<sup>0</sup> (oil bath temperature) as pale yellow oil, ( 9a, 352mg.; 68%) and crystallized on standing, m.p. 67-72<sup>0</sup>. This substance was identical with the authentic 4H-azepine( 9a ) prepared by the method of Anderson and Jonnson<sup>1 2</sup> .

(b.) The 4-succinimino-4,5-dihydroazepine( 4b, 150mg.) was introduced into a sublimation tube, followed by a column of small glass beads(20cm). The tube was preheated at 180-185<sup>0</sup> for 5 min. and then distilled at the same temperature under 0.03mm Hg. A colorless oil and white prisms were condensed on the top cool part of the tube. The oil was dissolved in cyclohexane and, on addition of petroleum ether, yielded white prisms, (73mg.; 69%), m.p. 76-77<sup>0</sup>, and was identical with the samples obtained from pyrolysis of the 4-methoxy-4,5-dihydroazepine( 4a ) and potassium carbonate treatment of the 4-chloromethyl-1,4-dihydropyridine( 3a ) in dimethyl sulfoxide by mixed melting point and spectral data. The white prisms formed on the tube was purified by washing with cyclohexane and recrystallized from

ethanol to give white prisms, (36mg., 81%), m.p.  $125^{\circ}$ , water soluble, and was shown to be identical with succinimide by mixed melting point and i.r., n.m.r., mass spectra.

Dimethyl-2,4,7-trimethyl-4H-azepine-3,6dicarboxylate ( 47 ).

(a.) Dihydropyridine( 3e, 2.5g.) and powdered potassium carbonate (2.0g.) in dimethyl sulfoxide(35ml.) was stirred at room temperature for 5h. and then poured into cold water(120ml.). The product was extracted with ether(3x50ml.) and the ether extract was washed with water(3x20ml.) and dried over anhydrous magnesium sulfate. After removal of solvent, the residue was distilled from a bulb tube under 0.03mm Hg. The product was distilled at  $110-115^{\circ}$  (oil bath temperature) as pale yellow oil, ( 47, 1.8g.; 82% ) .

Ultraviolet spectrum :  $\lambda_{max}$  213nm(  $\epsilon$  8,200 ), 295nm(  $\epsilon$  7,150 ).

Infrared spectrum :  $\nu_{max}$  1723s(C=O), 1702w(C=O), 1620m, 1562w, 1435s, 1374m, 1298m, 1247s, 1209m, 1190w, 1163w, 1112m  $cm^{-1}$ .

N. M. R. spectra : (  $CCl_4$  )

(a.) at R.T.,  $\tau$ , 6.22 and 6.25(each s, ester Me), 7.60(s, nuclear Me), 7.55-7.95(b, centred at  $\tau$  7.75, nuclear Me), and 8.85-9.45 (v.b, centred at  $\tau$  9.15, nuclear Me).

(b.) at  $80^{\circ}$ ,  $\tau$ , 4.77(d, J 9.0 Hz, 5-H), 6.24 and 6.27(each s, ester Me), 7.12(m, 4-H), 7.62 and 7.80 (each s, nuclear Me), and 9.12(a, J 7.0 Hz, 4-Me).

Mass spectrum : m/e 252(6), 251(34), 236(13), 220(28), 219(47), 204(18), 193(14), 192(100), 191(34), 178(10), 177(6), 176(24), 164(6), 163(9), 162(6), 161(13), 160(90), 159(21), 151(7),

150(12), 149(7), 148(6), 144(5), 135(6), 133(10), 132(47), 120(5), 119(16), 118(6), 117(6), 92(5), 91(26), 79(6), 77(8), 65(10), 59(13), 39(5),

Anal. Calc'd. for  $C_{13}H_{17}NO_4$  (mol.wt.251) : C, 62.13; H, 6.82; N, 5.57. Found (mass spectrum 251) : C, 62.08; H, 6.75; N, 5.73.

(b.) The 4H-azepine(47) was obtained with the yield of 76% according to Anderson and Johnson's method by treatment of the dihydropyridine( 3e ) with sodium ethoxide in dry ether. The product was identical with the authentic sample from the dihydropyridine( 3e ) with potassium carbonate by spectroscopy.

(c.) The 5-methyl-4-succinimino-4,5-dihydroazepine ( 42b, 150mg.) was pyrolysed at  $175-180^{\circ}$  using the same technique of sublimation through hot glass beads as its analogue to give colorless oil(82mg.;76%), and was identical with the product obtained from potassium carbonate treatment of the 4-(1-chloroethyl)-1,4-dihydropyridine( 3e ) by spectroscopy.

(d.) The 4-methoxy-5-methyl-4,5-dihydroazepine( 42a, 100mg.) was pyrolysed at  $160^{\circ}$  using the same procedure as succinimino-compound to yield colorless oil( 65mg., 73%), and was identical with the authentic sample by i.r., u.v., n.m.r., mass spectra.

#### Reaction of the 4H-Azepine( 47 ).

(a.) To the 4H-azepine( 47, 450mg.) in ether(50ml.) was added conc. hydrochloric acid(1ml.) in a separatory funnel. The mixture was shaken for 5 min. and then ice water(10ml.) was added to dilute the acid. The ether layer was separated and

washed with water(3 x 5ml.). After removal of ether, the solid dihydropyridine( 3e ) was formed as pale yellow prisms(4.35mg.; 84.5%). The pure compound was obtained by recrystallization twice from benzene to give white prisms, m.p.168-169<sup>0</sup>, and was identical with the product from the dichloroether and methyl 3-aminocrotonate (Mixed melting point and u.v., i.r., n.m.r. spectra.) .

(b.) To the 4H-azepine( 47, 220mg.) in ether(50ml.) was added conc. hydrobromic acid(0.5ml.) in a separatory funnel. The mixture was shaken for 5 min. and worked up in the same way as the chloro-analogue to give the pale brownish dihydropyridine ( 3e, 246mg.; 85% ) , m.p.156-160<sup>0</sup> . The pure compound was obtained by recrystallization from benzene-petroleum ether to give white prisms, m.p.164-165<sup>0</sup>, and was identical with the sample from the reaction of the 4-methoxy-5-methyl-4,5-dihydro-azepine( 42a ) with the conc. hydrobromic acid by mixed melting point and spectral data.

base-catalysed Rearrangement of 4-Cyano-4,5-dihydroazepine (42c).

To the cyano-compound( 42c, 300mg.) in methanol(10ml.) was added potassium hydroxide(65mg.) in methanol(2ml.), and the solution was heated on the steam bath under reflux for 2 h. Most of the methanol was then distilled off slowly, and the rest was distilled under reduced pressure and collected on a dry ice cooling trap. The vapor-phase chromatogram, measured on a Beckman GC-2A gas chromatograph instrument, using column No. 70007(Carbowax 4000 Dioleate on C-22 Firebrick) at 70<sup>0</sup> and 12 lb/sq inch pressure of helium, showed two peaks. The first fraction was identical with methyl crotonate by retention time and its mass spectrum.

The second fraction was collected and the mass spectrum showed a molecular ion seventeen mass units more than for methyl crotonate, and gave no ultraviolet absorption.

Mass spectrum : m/e 117 M(12), 102(13), 101(10), 85(8), 75(29), 69(9), 59(100), 43(51), 41(11), 15(55).

The residue was dissolved in methanol(5ml.) and poured into ice-water(50ml.). The precipitate was collected and recrystallized from benzene to give white prisms, 5a, m.p.180-181<sup>0</sup> and was identical with the methyl 4-cyano-2,5-dimethylpyrrole-3-carboxylate which was obtained as a by-product in the synthesis of the 4-cyano-4,5-dihydroazepine( 42c ).

Acid-catalysed Rearrangement of 4-Cyano-4,5-dihydroazepines .

(a.) Silver Nitrate and the 4-Cyano-4,5-dihydroazepine ( 4c ).

A solution of the cyano-compound ( 4c, 2.0g. ) and silver nitrate(1.4g.) in methanol(30ml.) and water(2ml.) was heated under reflux for 2 days. The deposited silver was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in chloroform and chromatographed on basic alumina using benzene and ethyl acetate as eluent. The first fraction yielded, after removal of solvent, dimethyl 2,6-dimethylfuro [2,3-b] pyridine-3,5-dicarboxylate ( 67a ) as white needles(1.32g.; 66%), m.p.122-123<sup>0</sup> (lit. 122.5-124<sup>0</sup> ). This compound ( 67a ) was confirmed by comparison of the spectra of the authentic sample obtained from the reaction of the N-methyl-4-chloromethyl-1,4-dihydropyridine ( 20, R=CO<sub>2</sub>Me ) with potassium cyanide<sup>22</sup>.

Ultraviolet spectrum :  $\lambda_{\max}$  219nm(  $\epsilon$ 30,800 ), 292.5nm( $\epsilon$ 7,600), infl. 247.5nm(  $\epsilon$ 9,050 ).

Infrared spectrum :  $\nu_{\max}$  1721s(C=O), 1599m, 1460m, 1441m, 1404m, 1322m, 1253s, 1150m, 1093s cm<sup>-1</sup>.

N.M.R. spectrum :  $\tau$ , 1.30(s, ring H), 6.03 and 6.05(each s, ester Me), 7.13 and 7.20(each s, nuclear Me).

Mass spectrum : m/e 264(16), 263(100), 248(13), 233(14), 232(96), 231(70), 216(15), 204(20), 203(46), 188(8), 175(8), 173(5), 172(22), 160(5), 144(9), 116(7), 100.5(9), 89(6), 76(5), 59(8), 50(5), 43(26).

The second fraction yielded dimethyl 2,6-dimethyl-pyrrolo [2,3-b] pyridine-3,5-dicarboxylate ( 68a ) as white fine crystals (0.22g.; 11%), m.p. 250-251<sup>o</sup>.

Ultraviolet spectrum :  $\lambda_{max}$  235.5nm(  $\epsilon$ 35,400 ), 298nm(  $\epsilon$ 8,250 ), infl. 255nm(  $\epsilon$ 16,500 ).

Infrared spectrum :  $\nu_{max}$  3426w(NH), 1709s(C=O), 1615m, 1549m, 1445m, 1415m, 1316m, 1257s, 1171m, 1099s, 1071m  $cm^{-1}$ .

N.M.R. spectrum : ( DMSO- $d_6$  )  $\tau$ , 1.30(s, ring H), 6.12 and 6.16 (each s, ester Me), 7.25 and 7.33(each s, nuclear Me).

Mass spectrum : m/e 263(18), 262(99.5), 247(15), 232(16), 231(100), 230(43), 229(5), 215(10), 204(5), 203(15), 202(43), 199(7), 187(10), 173(5), 172(12), 171(49), 170(7), 159(10), 144(14), 143(13), 131(6), 117(6), 116(10), 115(6), 104(5), 102(7), 100(10), 90(5), 89(7), 86(7), 77(6), 76(8), 75(7), 67(5), 63(5), 51(7), 50(5), 44(12), 42(9).

Anal. Calcd. for  $C_{13}H_{14}N_2O$  (mol.wt.262) : C, 59.54; H, 5.38; N, 10.68. Found (mass spectrum 262): C,59.49; H,5.38; N,10.51.

(b.) Silver Nitrate and the 4-Cyano-4,5-dihydroazepine( 42c ).

A solution of the cyano-compound ( 42c, 2.0g.) and silver nitrate (1.4g.) in methanol(30ml.) and water(2ml.) was heated under reflux for 2 days. The deposited silver was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in benzene and chromatographed on silica gel II using benzene and ethyl acetate as eluent. After removal of solvent, the first fraction yielded dimethyl 2,4,6-trimethyl-

furo [2,3-b] pyridine-3,5-dicarboxylate ( 67b ) as colorless prisms (0.39.; 19.5%), m.p. 95-96<sup>0</sup> . The analytical sample was recrystallized twice from aqueous dioxane to give colorless prisms, m.p. 98-98.5<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  218nm(  $\epsilon$ 23,800), 251nm(  $\epsilon$ 9,150), 287nm(  $\epsilon$ 8,500), infl. 260.5nm(  $\epsilon$ 8,000).

Infrared spectrum :  $\nu_{max}$  1727s(C=O), 1582m, 1441m, 1387m, 1377m, 1334m, 1291m, 1268s, 1176m, 1093s, 1070m, 1002w  $cm^{-1}$  .

N.M.R. spectrum :  $\tau$ , 6.03 and 6.09 (each s, ester Me), 7.29, 7.36 and 7.45 (each s, nuclear Me).

Mass spectrum : m/e 278(18), 277(100), 262(6), 247(13), 246(84), 245(63), 230(9), 218(14), 217(44), 214(7), 189(10), 188(11), 187(13), 159(5), 158(7), 107.5(16), 107(7), 89(6), 77(5), 65(6), 43(25), 39(5),

Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>5</sub> (mol.wt. 277) : C, 60.64; H, 5.45; N, 5.05. Found (mass spectrum 277): C, 60.52; H, 5.58; N, 4.89.

The second fraction yielded white prisms (63b, 0.37g.; 17%), m.p. 141.5-146<sup>0</sup> . The analytical sample was recrystallized four times from benzene to give white prisms, m.p. 151-153<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  214nm(  $\epsilon$ 3,200), 279.5nm(  $\epsilon$ 11,500).

Infrared spectrum :  $\nu_{max}$  3395m(NH), 3218b.w(NH), 1753s(C=O), 1714s(C=O), 1701s(C=O), 1641s, 1458m, 1439s, 1391m, 1381m, 1361m, 1343m, 1305m, 1251s, 1178m, 1162m, 1143m, 1114m, 1092m, 1053m, 985w  $cm^{-1}$  .

N.M.R. spectrum :  $\tau$ , 1.37(s, NH), 5.99(d, J 11.4 Hz, side chain H), 6.19 and 6.22 (each s, ester Me), 6.43(d.d, J 11.4 and 5.5 Hz,

3-H), 6.91(m, J 7.0 and 5.5 Hz, 4-H), 7.55(s, 6-Me), 7.72(s, COMe), 9.06(d, J 7.0 Hz, 4-Me).

Mass spectrum : m/e 297(14), 282(5), 266(13), 255(5), 254(6), 250(15), 234(7), 224(7), 223(11), 222(18), 208(19), 206(6), 194(11), 191(6), 190(5), 183(5), 182(34), 181(100), 180(39), 178(6), 164(14), 163(11), 162(9), 155(6), 151(6), 150(16), 149(13), 148(12), 143(5), 142(56), 136(14), 135(7), 134(5), 122(5), 121(7), 120(5), 114(5), 113(17), 111(5), 110(46), 108(6), 107(5), 106(6), 94(5), 93(8), 92(5), 91(6), 85(7), 82(10), 81(6), 80(5), 79(5), 77(5), 69(13), 68(8), 67(8), 66(7), 65(8), 59(15), 55(9), 54(6), 53(9), 44(6), 43(58), 42(31), 41(15), 39(10).

Anal. Calcd. for C<sub>14</sub> H<sub>19</sub> NO<sub>6</sub> (mol.wt.297) : C, 56.56; H, 6.44; N, 4.71. Found(mass spectrum 297) : C, 56.44; H, 6.47; N, 4.52 .

The third fraction yielded dimethyl 2,4,6-trimethyl-pyrrolo [2,3-b] pyridine-3,5-dicarboxylate( 68b ) as white prisms,(0.82g.; 41%), m.p. 155-157<sup>0</sup> . The analytical sample was recrystallized twice from ether-petroleum ether to give white prisms, m.p. 157.5-159<sup>0</sup> .

Ultraviolet spectrum : λ<sub>max</sub> 228nm( ε24,900), 294nm( ε11,000), infl. 250nm( ε15,500).

Infrared spectrum : ν<sub>max</sub> 3435m(NH), 3205b.w(NH), 1727s(C=O), 1709s(C=O), 1600w, 1572m, 1537m, 1446s, 1416m, 1402m, 1383m, 1327m, 1296m, 1266s, 1175m, 1107s, 1080m, 1066m, 1006w, 818w cm<sup>-1</sup>

N. M. R. spectrum : τ, -2.05(s, NH), 6.03 and 6.11(each s, ester Me), 7.32, 7.35 and 7.42(each s, nuclear Me).

Mass spectrum : m/e 277(18), 276(100), 261(5), 246(13), 245(83), 244(35), 229(9), 217(16), 216(48), 213(16), 202(5), 201(12), 187(9), 186(18), 185(11), 173(6), 158(12), 157(7), 122(7),

107(20), 106.5(8), 93(8), 92(5), 89(6), 78(6), 77(5), 65(5).

Anal. Calcd. for  $C_{14}H_{16}N_4O_4$  (mol.wt.276) : C, 60.86; H, 5.84; N, 10.14. Found(mass spectrum 276) : C, 60.73; H, 5.99; N, 10.10.

Action of conc. Sulfuric Acid on the Compound ( 63b ).

Compound 63b (20mg.) in conc. sulfuric acid(1ml.) was stirred at room temperature for 3h and then poured into ice-water(30ml.). The acidic solution was neutralized with dil. sodium hydroxide solution and extracted with ether( 3x20ml.). The ether extract was washed with water and dried over anhydrous magnesium sulfate. Solvent was evaporated and the residue recrystallized from aqueous methanol to give prisms, (6mg.;32%), m.p. 95-96<sup>0</sup>. This substance was identical with the furopyridine ( 67b ) by mixed melting point and u.v. and mass spectra.

**(c )** Dowex 50W-X8 and the 4-Cyano-4,5-dihydroazepine(4c).

A mixture of the cyano-compound( 4c, 2.0g.) and Dowex 50W-X8(15g.) in methanol(60ml.) and water(10ml.) was stirred at 45 for 4h under a nitrogen atmosphere. After cooling, the resin was filtered off and the solvent was removed under reduced pressure. The residue was transferred to a sublimation apparatus and distilled at 135-140 (oil bath temperature) under 0.02-0.03 mm Hg. to give a viscous colorless oil(58a, 1.74g.;81%).

Ultraviolet spectra  $\lambda_{max}$  218nm(  $\epsilon$ 1,350), 260nm(  $\epsilon$ 1,700).

0.01N NaOH/95%EtOH  $\lambda_{max}$  275nm(  $\epsilon$  27,000).

Infrared spectrum :  $\nu_{max}$  3474b(enol), 2252m(C $\equiv$ N), 1752s(C=O), 1729s(C=O), 1657m, 1616w, 1439m, 1362m, 1253s, 1201m  $cm^{-1}$ .

Mass spectrum : m/e 283(1.5), 263(3), 241(3), 210(9), 168(7), 167(5), 155(22), 129(20), 117(15), 116(12), 112(5), 98(5), 97(20), 87(28), 85(5), 59(5), 55(16), 44(5), 43(100).

Anal. Calc'd. for  $C_{13}H_{17}NO_6$  (mol.wt. 283) : C, 55.12; H, 6.05; N, 4.95. Found (mass spectrum 283) : C, 55.13, H, 6.14; N, 5.13.

Dimethyl 2,6-dimethylfuro [2,3-b] -4,7-dihydropyridine-3,5-dicarboxylate (61a).

The compound (58a, 1.0g.) was sealed under vacuum and the tube was heated at  $160^{\circ}$  for one day. The oil was solidified as pale yellow solid, and was recrystallized twice quickly from chloroform, ether, and petroleum ether to give pale yellow crystals, (61a, 0.54g.; 58%), m.p.  $178-179.5^{\circ}$ .

Ultraviolet spectrum :  $\lambda_{max}$  223nm ( $\epsilon$  9,400), 347nm ( $\epsilon$  8,550).

Infrared spectrum : (KBr)  $\nu_{max}$  3297m(NH), 1720s(C=O), 1686m(C=O), 1654s, 1604s, 1526s, 1510m, 1435s, 1290s, 1264s, 1090  $cm^{-1}$ .

N. H. R. spectrum : (DMSO- $d_6$ )  $\tau$  0.52(s, NH), 6.22 and 6.35 (each s, ester Me), 6.40(q, J 0.5 Hz, dihydropyridine ring H), 7.53(s, furan ring Me), 7.80(d, J 0.5 Hz, dihydropyridine ring Me).

Mass spectrum : m/e 266(8), 265(50), 264(35), 263(15), 251(14), 250(100), 234(24), 233(7), 232(33), 231(16), 218(15), 206(19), 205(14), 204(35), 203(10), 191(5), 190(20), 174(14), 173(7), 172(15), 162(6), 147(5), 146(10), 145(5), 103(7), 100.5(7), 86.5(6), 77(5), 67(6), 59(9), 43(17), 42(5).

Anal. Calc'd. for  $C_{13}H_{15}NO_5$  (mol.wt. 265) : C, 58.84; H, 5.70; N, 5.28. Found (mass spectrum 265) : C, 58.86; H, 5.49; N, 5.05.

This compound (61a) was oxidized to the corresponding furo-

pyridine ( 67a ) when exposed to the air.

Reaction of Dihydropyridines and Potassium Carbonate.

(a.) The dihydropyridine ( 3a, 100mg.) and powdered potassium carbonate ( 80mg.) in dimethyl sulfoxide-d<sub>6</sub> ( 2ml.) was stirred at room temperature in a small test tube. The reaction was followed by taking clear solution from the reaction mixture and measuring the n.m.r. spectra. Results were recorded based on the integration of methyl signals of the dihydropyridine ( 3a ) and the 4H-azepine ( 9a ) as follows :

Time ( min. )	Dihydropyridine ( 3a ) %	4H-Azepine ( 9a ) %
0	100	0
20	80	20
60	35	65
150	0	100

(b.) Dihydropyridine ( 3e, 100mg.) and powdered potassium carbonate ( 80mg.) in dimethyl sulfoxide-d<sub>6</sub> ( 2ml.) was stirred at room temperature in a small test tube and the reaction was followed by n.m.r. spectra as above.

Time ( min. )	Dihydropyridine ( 3e ) %	4H-Azepine ( 47 ) %
0	100	0
5	90	10
25	60	40
62	20	80
122	5	95
225	0	100

(c.) Dihydropyridines 3a ( 91mg., 0.33 m mole ), 3b ( 106mg., 0.33 m mole ), and powdered potassium carbonate ( 152 mg., 1.1 m mole ) in dimethyl sulfoxide-d<sub>6</sub> ( 1.5ml. ) and 2 drops of deuterium oxide were stirred at room temperature in a small test tube and the reaction was followed by n.m.r. spectra as above.

Time ( min. )	Chloro-compound ( 3a ) %	Bromo-compound ( 3b ) %
0	100	100
10	85	15
30	70	0

(d.) Dihydropyridines 3e (96mg., 0.33m mole), 3f (111mg., 0.33m mole), and powdered potassium carbonate (152mg., 1.1m mole) in dimethyl sulfoxide-d<sub>6</sub> (1.5ml.) and 2 drops of deuterium oxide were stirred at room temperature and the reaction was followed by n.m.r. spectra.

Time (min.)	Chloro-compound( 3e ) %	Bromo-compound( 3f ) %
0	100	100
10	90	10
30	75	0
60	60	0

(e.) 10ml. of 0.3 mmoles solutions of the 4-chloro-methyl-1,4-dihydropyridine( 3a ) were reacted separately with 10ml. of 2m moles solution of sodium methoxide and triethylamine at 26<sup>0</sup> in dark. Reactions were followed by ultraviolet spectra. Similar reactions under identical conditions were studied on the 4-bromomethyl-1,4-dihydropyridine( 3b ). (see Fig. 2 at discussion section ).

Methyl  $\alpha$ -(3,5-dimethyl-4-isoxazolylmethyl)acetoacetate ( 70 ).

A solution of 4-chloromethyl-3,5-dimethylisoxazole (14.6g.) in dry dimethylformamide (30ml.) was added to a solution of methyl sodioacetoacetate(13.8g.) prepared by adding methyl acetoacetate(12.5g.) to a suspension of sodium hydride (2.4g.) in dry dimethylformamide(120ml.) cooled in ice-water. The mixture was stirred at room temperature for 6h and then poured into cold water(600ml.). The products were extracted with ether(3x150ml.) and the ether extract was washed with water(3x20ml.) and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, and crystals were formed when standing. The crystal was filtered off and crystallized from chloroform and ether to give white prisms of the dialkylation product, methyl  $\alpha,\alpha$ -bis(3,5-dimethyl-4-isoxazolylmethyl) acetoacetate( 73 ), 4.3g., 13%, m.p.108-109<sup>o</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  221nm(  $\epsilon$  7,850 ).

Infrared spectrum :  $\nu_{max}$  1745s(C=O), 1712s(C=O), 1629m, 1433s, 1358m, 1104m, 984w, 898w  $cm^{-1}$  .

N. H. R. spectrum :  $\tau$  6.30(s, ester Me), 7.07(s, CH<sub>2</sub>), 7.70 and 7.85(each s, isoxazole ring Me), 8.00(s, COMe).

Mass spectrum : m/e 335(5), 334(17), 291(11), 225(14), 224(40), 194(9), 193(4), 192(35), 183(6), 182(12), 178(5), 150(13), 111(18), 110(100), 69(11), 68(99.5), 43(95), 42(48), 41(25), 39(23).

Anal. Calcd. for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub> (mol.wt. 334): C, 61.07; H, 6.63; N, 8.38. Found (mass spectrum 334): C, 61.28; H, 6.78; N, 8.40.

The filtrates were combined and evaporated in vacuo, and the residue was distilled under reduced pressure to yield the monoalkylation product, methyl  $\alpha$ -(3,5-dimethyl-4-isoxazolylmethyl)acetoacetate as viscous oil, (70, 13.4g.; 59%), boiling at 106-110<sup>0</sup> under 0.03 mm Hg.

Ultraviolet spectrum :  $\lambda_{\max}$  221.5nm(  $\epsilon$  4,300).

Infrared spectrum :  $\nu_{\max}$  1752s(C=O), 1724s(C=O), 1640m, 1438m, 1364m, 1150m  $\text{cm}^{-1}$ .

N. M. R. spectrum :  $\tau$ , 6.26(s, ester Me), 6.30(t, J 7.6 Hz, CH), 7.13(d, J 7.6 Hz, CH<sub>2</sub>), 7.67(s, COMe), 7.77(s, isoxazole ring Me).

Mass spectrum : m/e 225(6), 207(7), 183(7), 169(6), 166(13), 152(6), 151(5), 150(39), 148(5), 125(8), 124(15), 111(5), 110(56), 109(15), 108(7), 97(5), 82(8), 69(7), 68(55), 67(9), 55(5), 43(100), 39(8).

Anal. Calcd. for C<sub>11</sub>H<sub>15</sub>N O<sub>4</sub> (mol.wt. 225): C, 58.66; H, 6.71; N, 6.22. Found (mass spectrum 225): C, 58.60; H, 6.63; N, 6.21.

Methyl 5-acetyl-2,6-dimethyl-1,4-dihydropyridin-3(2H)-one (71).

Methyl  $\alpha$ -(3,5-dimethyl-4-isoxazolylmethyl)acetoacetate(70, 5g.), triethylamine(2ml.), and 5% palladium on charcoal(150mg.) in methanol(30ml.) were stirred under hydrogen at 1 atm. and room temperature for 10h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene and chromatographed on alumina(Brockman No. 1) and eluted with benzene-ethyl acetate

(1:1) to give the dihydronicotinate as yellow crystals, ( 71, 3.2g.; 69%), m.p. 158-163<sup>0</sup> . It was easily oxidized to the corresponding pyridine by exposure to air. The analytical sample was purified by rapid recrystallization twice from chloroform and petroleum ether to give yellow prisms, m.p. 173-174<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{\max}$  243.5nm (  $\epsilon$  12,750 ), 395nm(  $\epsilon$ 7,450 ), inf. 264.5nm (  $\epsilon$ 7,000 ) .

Infrared spectrum :  $\nu_{\max}$  3435m(NH), 3315bw(NH), 1701s(C=O), 1679s(C=O), 1593m, 1473s, 1435m, 1383m, 1362m, 1324m, 1310m, 1123s, 1093m, 1010m, 925m.  $\text{cm}^{-1}$ .

N.M.R. spectrum:  $\tau$ , 2.55(s, NH), 6.30(s, ester Me), 6.62(m, J 0.7 Hz, 4-H), 7.79 and 7.83(each d, J 0.7 Hz, nuclear Me), 7.86(s, COMe).

Mass spectrum : m/e 210(8), 209(61), 208(66), 207(7), 195(12), 194(100), 193(6), 192(50), 178(21), 176(22), 166(14), 165(8), 164(22), 162(7), 151(5), 150(15), 149(7), 148(8), 136(13), 134(19), 132(7), 120(11), 108(6), 107(10), 106(21), 105(5), 104(5), 81.5(5), 79(10), 78(5), 77(13), 67(12), 66(6), 65(10), 64(6), 63(8), 59(8), 53(8), 52(6), 51(7), 43(55), 42(27), 41(6), 39(14).

Anal.calcd. for  $\text{C}_{11}\text{H}_{15}\text{NO}_3$  (mol. wt.209 ) :C, 63.14; H, 7.23; N, 6.69. Found (mass spectrum 209): C, 63.05; H, 7.22; N, 6.68.

Methyl 5-acetyl-2,6-dimethylnicotinate ( 72 ).

To the dihydronicotinate ( 71, 0.65g.) in glacial acetic acid ( 6ml.) was added dropwise a solution of sodium nitrite ( 0.3g.) in water ( 1.5ml.). After standing for 30 min. the solution was poured into ice-water ( 50ml.), and the product was extracted with ether ( 3 x 20ml.). The ether extract was washed with water ( 3 x 5ml.) and the solvent was evaporated in vacuo. The residue was distilled under reduced pressure to give an oil boiling at 100-105<sup>0</sup> ( oil bath temperature ) under 0.5 mm Hg. and which solidified on standing, ( 0.48g.; 75% ), m. p. 40.5-41.5<sup>0</sup> .

Ultraviolet spectrum :  $\lambda_{max}$  213nm( $\epsilon$ 25,900), 243nm( $\epsilon$ 10,250), 276nm( $\epsilon$ 4,150), infl. 286nm( $\epsilon$ 3,450).

Infrared spectrum :  $\nu_{max}$  1732s(C=O), 1696s(C=O), 1598m, 1541m, 1435m, 1373m, 1365m, 1359m, 1285s, 1098s, 956m cm<sup>-1</sup>.

N.M.R. spectrum :  $\tau$ , 1.28(s, 4-H), 5.95(s, ester Me), 7.08 and 7.15( each s, nuclear Me), 7.32(s, COMe).

Mass spectrum : m/e 208(6), 207(42), 193(13), 192(100), 176(13), 165(6), 164(46), 160(5), 132(12), 120(15), 106(11), 105(5), 104(7), 79(7), 77(13), 64(6), 63(9), 59(9), 51(6), 43(49), 42(8), 39(7).

Anal. Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub> ( mol. wt. 207 ): C, 63.76; H, 6.32; N, 6.76. Found (mass spectrum 207): C, 63.58; H, 6.31; N, 6.73.

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