A STUDY OF REACTIONS OF 4-CHLOROMETHYL 1,4-DIHYDROPYRIDINES WITH NUCLEOPHILES

M. THOMAS THOMAS

A STUDY OF REACTIONS OF 4-CHLOROMETHYL 1,4-DIHYDROPYRIDINES WITH NUCLEOPHILES

By

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ABSTRACT

Reactions of 4-chloromethyl 1,4-dihydropyridines with some nucleophiles have been studied. It was found that the nature of the reacting nucleophile determines the ring size of the product. Reaction with thiocyanate, selenocyanate, and thiourea give dihydropyridine derivatives while ring expansion was effected by reaction with sulphite.

A study of kinetics of reactions with thiocyanate and cyanide under identical conditions was attempted. Results indicate that thiocyanate reaction is S_N2 type. Reproducible results were not obtained for the reaction with cyanide.

A method for the determination of thiocyanate in the presence of chloride suitable for the kinetics experiments was developed.

An interesting rearrangement of the 4-chloromethyl 1,4-dihydropyridine on reaction with urea was studied and from available evidence a pyrazolopyridone structure has been suggested for the product.

INTRODUCTION

Molecular orbital treatment of benzene by Huckel resulted in the rule that "monocyclic coplanar systems of trigonally hybridized atoms which contain (4n+2) π-electrons will possess relative electronic stability". This rule predicted non-benzenoid aromatic systems like the cycloheptatrienylium cation (1) which was unknown then. However for about a decade no attempt was made to test these predictions.

Organic chemists began to show interest in structures based on the cycloheptatrienylium cation only after 1945 when Dewar[1] postulated the tropolone ring system for stipitatic acid to account for its aromatic properties. Attempts to develop synthetic methods for these compounds followed and as a result, a variety of methods is available now.

One of the general methods of synthesis involves expansion of a six-membered ring to a seven-membered ring. This has been achieved by the use of aliphatic diazo compounds such as diazomethane[2,3] and diazoacetic ester[4,5,6] on benzene derivatives. Dihalocarbenes[7,8] also have been reported to bring about ring expansion.

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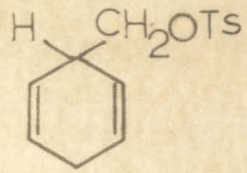

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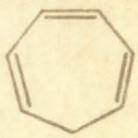

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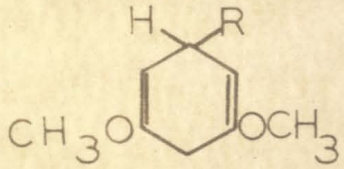
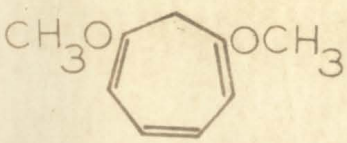


(4)

a R = COOH
b R = CH_2OTs



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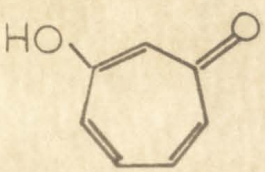

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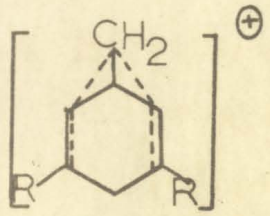
Solvolytic ring expansion of 1,4-dihydrobenzyl tosylates initially investigated by Nelson, Fassancht and Piper[9] and later modified by Chapman and Fitton[10] has proved to be a convenient synthetic route to the troponoid system The ready availability of 1,4-dihydrobenzoic acids by metal-ammonia[11] reduction of the aromatic acids is a factor which is greatly in favour of these methods.

Essential steps in the synthesis were lithium-aluminium hydride reduction of 1,4-dihydrobenzoic acid to the benzyl alcohols, conversion to the corresponding tosylates and solvolysis of the tosylates (2) in acetic acid in the presence of a buffer, sodium dihydrogen phosphate monohydrate. Nelson[9] and coworkers obtained cycloheptatriene (3) as one of the products.

Chapman and Fitton prepared 3,5-dimethoxy 1,4-dihydrobenzoic acid (4a) by Birch reduction of 3,4,5-trimethoxybenzoic acid and applying the above method obtained a mixture of 1,3-dimethoxy cycloheptatrienes (5). Solvolysis of the tosylate (4b) was conducted in pyridine. The cycloheptatriene mixture on oxidation with bromine gave β-tropolone (6) in 28% overall yield. α-Tropolone, γ-tropolone and tropone were also prepared by similar methods.

Ionization of 1,4-dihydrobenzyl tosylate (4b) could involve assistance by both double bonds (7) or assistance principally by one double bond (8). By a comparison of the rates of solvolysis of 3-substituted-1,4-dihydrobenzyl tosylates with the 3,5-disubstituted and unsubstituted tosylates they showed that "primary assistance to ionization comes from one, not both, double bonds".



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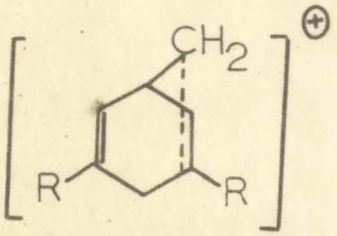

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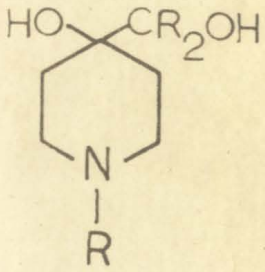

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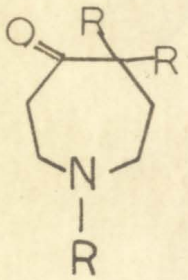

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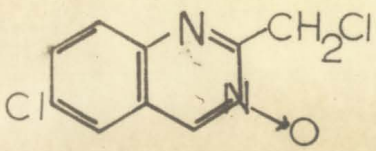

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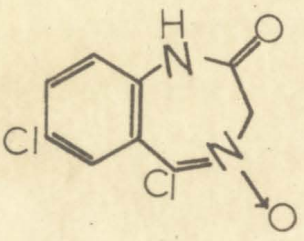


(12)

Rapid progress in the development of synthetic methods for various cycloheptatriene compounds and a better understanding of their properties naturally stimulated interest in seven-membered heterocyclic compounds, especially those containing nitrogen. Introduction of heteroatoms into the tropylium ion π-lattice has been predicted to lower the energy of the resulting species and render it highly susceptible to oxidation[12]. Despite this, much work continued to be directed to the synthesis of azepines.

As in the case of the homocyclic compounds, various synthetic methods have been employed to prepare seven-membered heterocyclic rings. Most of these methods are not of general applicability; they are only suitable for preparing particular compounds.

Synthetic methods involving ring expansion employed for the cycloheptatriene compounds could also be suitable for synthesis of seven-membered heterocycles. Piperidine carbinol (9) has been reported to give the hexahydroazepinone (10) on treatment with concentrated sulphuric acid[13]. A Wagner-Meerwein type rearrangement of the carbonium ion is presumed to result in the formation of the product.

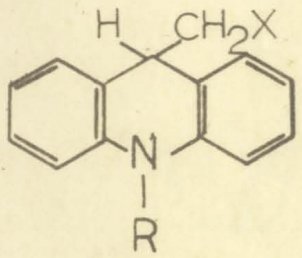
Derivatives of azepines have been prepared by ring expansion of benzenes with nitrogenous entities. Paquette[14] obtained 3,5,7-trimethyl-1,3-dihydro-2H-azepin-2-one by adding a cold ethereal chloramine solution to a solution of sodio-2,4,6-trimethyl phenoxide in excess 2,4,6-trimethyl phenol. Benzene has been converted into 1-ethoxycarbonyl-1H-azepine by reaction with ethyl azidoformate, $N_3.CO_2Et$, under photolytic conditions[15]. 1-Cyano-1H-azepine has also been prepared by a

similar method[16]. Cyanonitrene formed by the thermolysis of cyanogen azide reacted with aromatic compounds to give 1-cyanoazepines.

There are several examples of expansion of a heterocyclic ring fused to a benzene ring. The action of alcoholic sodium hydroxide on the chloromethyl derivative (11) caused ring expansion to the dihydroazepinone oxide (12) which was then reduced to the corresponding dihydroazepinone[17].

Bergmann and Rabinovitz[18] have described the ring expansion of dihydroacridine derivatives. Dibenzazepine was obtained by the action of polyphosphoric acid on the carbinol (13; R=H, X=OH). Craig and collaborators[19] got the same rearrangement using phosphorus pentoxide in xylene. This reaction is similar to the rearrangement of 9,10-dihydroanthracene-9-methanol to dibenzocycloheptatriene as reported by Rigaudy and Tardieu[20]. The N-methyl derivative of the dibenzazepine was formed by the action of silver perchlorate[21] on the iodomethyl compound (13; R=CH_3, X=I) in ether.

A reaction involving ring expansion of a dihydropyridine similar to the solvolytic ring expansion of 1,4-dihydrobenzyl tosylates has been reported recently[22]. Gregory[23] reinvestigated the work of Benary[24] on diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (14; R=CO_2Et, R^1=CH_2Cl). This compound on reaction with hot ethanolic potassium cyanide gave two products. Benary assigned the cyanomethyl 1,4-dihydropyridine structure to one (14; R=CO_2Et, R^1=CH_2CN) and the pyrrole structure to the other (15; R=CH_2CN).



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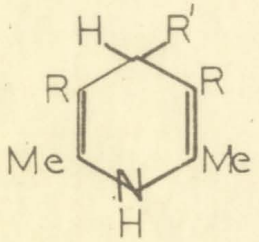

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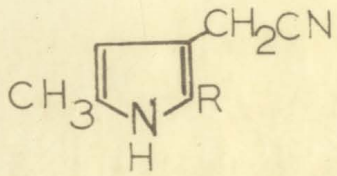

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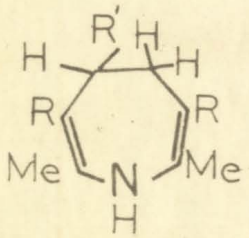

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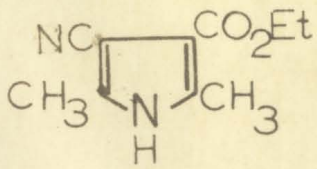

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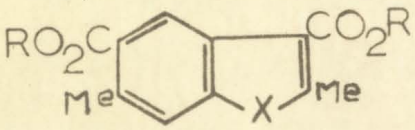


(18)

Gregory[23] concluded after a thorough study of the spectral characteristics and the properties of Benary's 'cyanomethyl dihydropyridine' that it was, in fact, a dihydroazepine compound (16; R=CO_2Et, R'=CN). This was confirmed by an unambiguous synthesis of 4-cyanomethyl-1,4-dihydropyridine (14; R=CO_2Et, R'=CH_2CN) which turned out to be different from the compound obtained by Benary's reaction. It was also shown that the pyrrole was actually (17), and that the cyanoazepine compound (16; R=CO_2Et, R^1=CN) was a specific intermediate in the formation of the pyrrole. Pyrrole formation was completely avoided by conducting the reaction at room temperature.

The dihydropyridine (14; R=CO_2Et; R^1=CH_2Cl) is easily obtained by reaction between ethyl 2-aminocrotonate and 1,2-dichloroethyl ethyl ether. This fact combined with the interesting ring enlargement and the unusual reverse process happening under different conditions gave a **fillip to** further work on this dihydropyridine system.

The dihydroazepine compound (16; R=CO_2Et, R^1=CN) was found to undergo some rearrangements giving bicyclic compounds[23,25]. Reaction with nitrous acid gave the furopyridine (18; X=O, R=Et) while silver nitrate produced the furopyridine as well as an azaindene (18; X=NH, R=Et).

Anderson and Johnson[26] studied the reaction of the chloromethyl 1,4-dihydropyridines (14; R=CO_2Et, R^1=CH_2Cl and R=CO_2Me, R^1=CH_2Cl) with other nucleophiles. Reaction with sodium ethoxide produced 4-ethoxy dihydroazepine (16; R=CO_2Et), R^1=OC_2H_5) which readily eliminated ethanol to form the 4-H azepine (19). Reaction with sodium acetate in dimethyl sul-

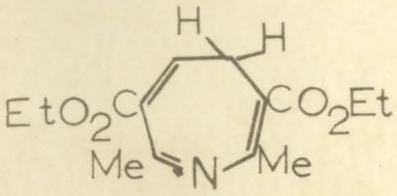
phoxide produced 3-H-azepine (20). The proposed structures for the azepines were based partly on observed chemical reactions and partly on interpretation of n.m.r. spectra.

It was shown that 3-H-azepine was the more stable isomer and that the rearrangement of the 4-chloromethyl 1,4-dihydropyridine (14; R=CO_2Et,R'=CH_2Cl) to 4-H-azepine (19) was reversible.

Childs, Johnson and Grigg[27] studied the reactions of analogous N-methyl dihydropyridine (21) prepared by condensation of 1,2-dichloroethyl ethyl ether with methyl 3-methylaminocrotonate. The reaction of (21) with potassium cyanide did not yield the expected cyanoazepine; three products which could be explained as the rearrangement products of the cyanoazepine were obtained. They were 2-amino-3-methylterephthalate(22), 2,6-dimethylfuro-[2,3,b] -pyridine-3,5-dicarboxylate (18;X=0,R=Me) and a third one which was identified as dimethyl 2-cyano-2,3,4-trimethyl-3-azabicyclo-[4,1,0]-hept-4-ene-1,5-dicarboxylate(23) on the basis of its spectral properties.

The initial step in the reaction was proposed as ionization of the chloride aided by the lone pair of electrons on nitrogen. The resulting species (24) then reacted with cyanide in the form of its resonance hybrids.

The N-methyl dihydropyridine compound (21) on treatment with t-butoxide in 1,2-dimethoxyethane gave two isomeric products, an azepine (25) and a bicyclic compound (26).



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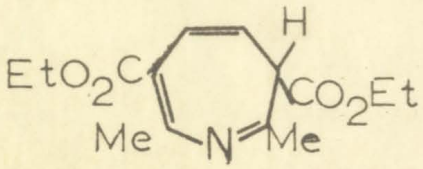

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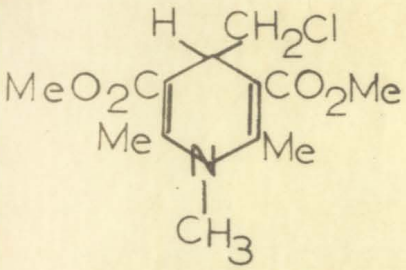

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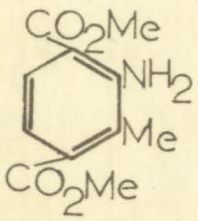

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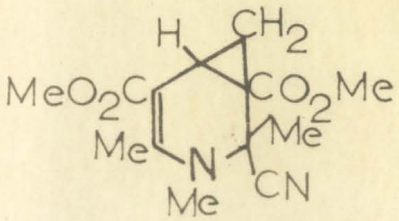

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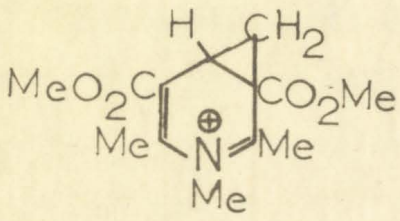


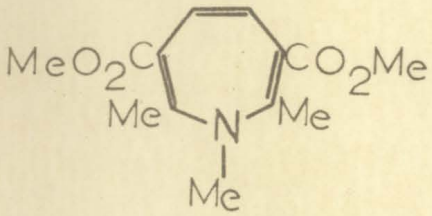
(24)

Brignell and collaborators undertook a kinetic study of the rearrangement of 4-chloromethyl-1,4-dihydropyridine (14; R=CO_2Et, R'=CH_2Cl) with potassium cyanide in aqueous ethanol at room temperature. The observation that only basic nucleophiles bring about rearrangement to dihydroazepine led them to discard a 1,2-shift mechanism for the rearrangement. They showed that the reaction is second order base-catalysed. The initial step in the reaction was suggested to be the formation of a dihydropyridine anion (27).

$$RNH \xrightarrow[\text{slow}]{\text{base}} R\bar{N} \longrightarrow \text{Products}$$

The subsequent stages were postulated as loss of chloride and rapid rearrangement to azepine (28) followed by rapid 1,4-addition of hydrogen cyanide to yield the 4-cyanodihydroazepine (16; R=CO_2Et, R'=CN). In support of this mechanism it was shown that the powerfully nucleophilic, but nonbasic iodide ion did not react in alcohol or acetone; however, simple replacement of the chlorine by iodide took place in boiling acetonitrile. 4-H-azepine which was suggested as a steady state intermediate was shown to add hydrogen cyanide to give the 4-cyanodihydroazepine (16) in 85% yield.

Gregory and Bullock[29] studied the kinetics of solvolysis of 4-chloromethyl-1,4-dihydropyridines (14; R=CO_2Et, R'=CH_2Cl and R=CO_2Me, R'=CH_2Cl)in absolute ethanol and methanol. They found that the main product of methano-



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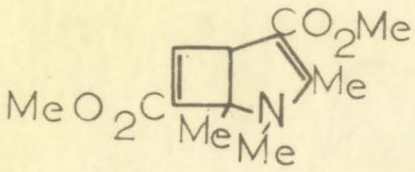

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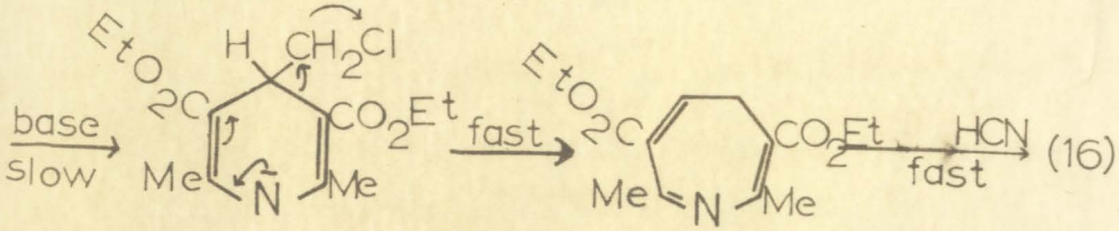

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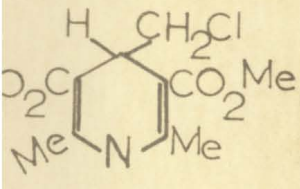

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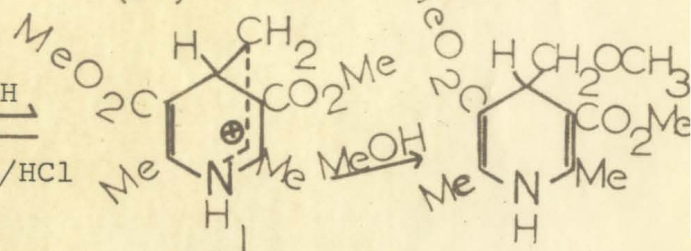

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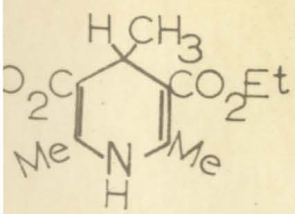

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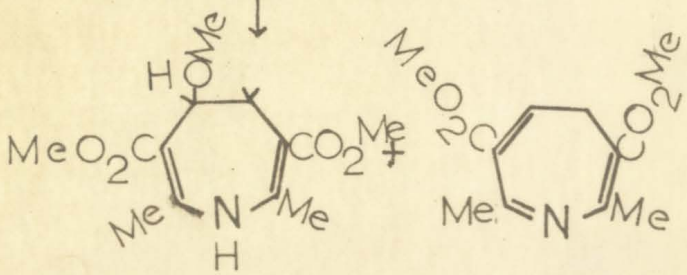


lysis was 4-methoxymethyl-dihydropyridine (14; R=CO_2Me, R'=CH_2OMe). Methanolysis in the presence of excess triethylamine resulted in ring expansion forming 4-methoxydihydroazepine (16; R=CO_2Me; R'=OMe) as the main product.

On the basis of their observations and the kinetic results, a reaction mechanism involving a transition state with a potential seven-membered ring (29) was proposed.

The reaction mechanism suggested by Brignell et al[28] involving proton removal from NH- group as the first step was examined and was shown to be disputable. An alternative suggestion that the nature of the nucleophile reacting with (14a) in a way determines the ring size of the product has been put forward.

From a study of the work on dihydropyridines described above, it is apparent that reaction with certain nucleophiles result in ring expansion while reaction with some others give products with retention of the ring structure of the reactant. Moreover, Gregory's[29] work seems to show that control of reaction at $-CH_2Cl$ to produce six or seven-membered ring product is possible by varying the conditions of the reaction. These and other observations raise some pertinent questions about the reactions of the dihydropyridine system.

(i) Does the nucleophilic substitution with retention of ring structure differ kinetically from the reaction involving ring expansion?

(ii) What property of the reacting nucleophile causes ring expansion? Can we say that basicity decides the ring structure of the product?

(iii) Can we find a single nucleophile which will effect retention or expansion of the ring under controlled conditions?

It was, therefore, decided to make a modest attempt to get some more information about this intriguing system.

DISCUSSION

Swain and Scott[30], in an attempt to give quantitative meaning to the term "nucleophilicity", suggested a linear free energy relationship between nucleophilicity of the attacking nucleophile and the thermodynamic properties of the reactants.

$$\log \frac{K}{K_o} = Sn$$

In this equation K is the second-order rate constant for a nucleophilic displacement by a reagent whose nucleophilicity is n on a substrate whose sensitivity to change in nucleophilicity is S and K_o is the second order rate constant for nucleophilic attack by water, the standard nucleophile. Nucleophilicity constants for various nucleophiles have been calculated using the equation. An examination of these constants reveals that feebly basic anions like iodide and thiocyanate have high nucleophilic reactivity. This was presumed to be due to the polarizability of the valency electrons of the elements in the ions.

Nucleophile	Nucleophilicity Constant.
SCN^-	4.77
I^-	5.04
CN^-	5.10
$S\bar{O}\bar{3}$	5.10

Edwards and Pearson[31] in a discussion of factors determining nucleophilic reactivity mention three properties; basicity, polarizability and unshared pairs of electrons on an atom bonded to the attacking atom. Solvent effects, significance of ion pairs and steric effects were excluded from the discussion.

Thiocyanogen is often classified as a pseudo-halogen and it is known that thiocyanogen is similar to iodine in its chemical reactivity, but is slightly less electronegative.

E^{o}, SCN^{o}, SCN^{-} = 0.769

E^{o}, I^{o}, I^{-} = 0.54

Since the effect of action of iodide on 4-chloromethyl dihydropyridine (14; R=CO_2Et, R^1=CH_2Cl) is known[28], reaction with thiocyanate was attempted.

The dihydropyridine compound reacted with ammonium thiocyanate on refluxing in ethanol forming a colourless compound. A comparison of it's ultraviolet and nuclear magnetic spectra with those of the chloromethyl compound (14) revealed that it is a 1,4-dihydropyridine compound. Thiocyanate product has λ_{max}(ethanol) 231, 353; Σ_{max}19,420, 6,970 4-chloromethyl dihydropyridine (14)[23] λ_{max}231, 349; Σ_{max} 19,400, 7,650.

The n.m.r. spectrum also was very similar to that of the parent compound except for the doublet corresponding to the methylene carrying the thiocyanate group. This doublet appeared at τ=6.93; in the chloro compound it is at τ = 6.48.

Infrared spectrum showed a sharp band at 2155 cm^{-1} corresponding to the nitrile stretching vibration in organic thiocyanates.[32,33] Isothiocyanates exhibit broad and strong bands centered around 2100 cm^{-1} and at lower concentrations they show finer resolution.

The thiocyanate structure was confirmed by the easy elimination of the -SCN group on reaction with Raney Nickel and formation of (30). The product of thiocyanate reaction is therefore diethyl 4-thiocyanatomethyl-1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxylate (14; R= CO_2Et, $R'=CH_2SCN$).

Potassium and barium thiocyanates gave the same product; reaction with barium thiocyanate took place even at room temperature as shown by the appearance of barium chloride precipitate.

In order to test the influence of substituents at positions 3 and 5 on the reaction, preparation of thiocyanates from the following dihydropyridines was attempted.

a. 14; R=CO_2Me, $R'=CH_2Cl$

b. 14; R=COMe, $R'=CH_2Cl$

c. 14; R=CN, $R'=CH_2Cl$

Compounds a and b gave the corresponding 4-thiocyanatomethyl dihydropyridines; c did not react under any condition.

The reaction was repeated with the N-methyl compound (21) to study the effect of a substituent on nitrogen and the thiocyanate product was obtained without difficulty. All the compounds showed the characteristic u.v. spectrum of the dihydropyridine chromophore. A comparison of the spectral characteristics of the parent compounds and the thiocyanate products is given in Table I.

Now, we have two different reactions of the dihydropyridine, one reaction with a basic nucleophile resulting in expansion of the ring and another with a nonbasic nucleophile in which the product retains the ring structure of the reactant. A study of the kinetics of these two reactions would be helpful in understanding the mechanisms.

Preliminary experiments showed that the thiocyanate reaction at 55°C with equimolecular amounts of the reactants was 75%complete in 10 hours. Since this reaction does not take place in aqueous ethanol and proceeds at a convenient rate only at 55°C it was decided to study both reactions at the same temperature in absolute ethanol.

Progress of reaction with thiocyanate was followed by analysing the reaction mixture at definite intervals for the unreacted thiocyanate by standardised volumetric procedure described in the section on 'Analytical Methods'.

In a reaction of this type there is the possibility of a reaction between the chlorocompound and the solvent.

$$RCH_2Cl + C_2H_5OH \rightarrow RCH_2OC_2H_5 + \overset{+}{H} + Cl^-$$

TABLE I

Comparison of Ultraviolet Spectra of Thiocyanatomethyl and Chloromethyl-1,4-dihydropyridines

Compound	$R^1 = CH_2Cl$		$R^1 = CH_2SCN$	
	λ_{max} mm.	Σ_{max} mm.	$\lambda_{max.}$ mm	$\Sigma_{max.}$
14; R=CO_2Et	231; 349	19,400, 7,650	233; 353	19,420,7,000
R=CO_2Me	232; 349	18,000; 7,360	232; 352	18,900;6,700
R=COMe	252; 370	17,800; 8,300	251; 375	18,600;7,300
21; CO_2Me	231; 252;340	16,710;10,320;7,840	235; 255; 345	17,500; 9,600; 7,040

The fact that the Volhard titration for inorganic thiocyanate and chloride in the mixture remained unchanged during the kinetic run shows that no additional chloride ions were produced by solvolysis. Moreover, product analysis has shown that the thiocyanate compound is formed in 90% yield. Gregory[29] has shown that the 4-methoxymethyl dihydropyridine does not produce the chlorocompound by reaction with methanolic hydrogen chloride. An equilibrium due to the solvolysis and reverse reaction simultaneous with the thiocyanate reaction is therefore highly improbable.

A second order plot of $\log \frac{A}{B}$[34] for different initial concentrations of the reactants against time gave a good straight line up to 50% completion of the reaction. Rate constant values showed gradual increase after the first half-life. Such drift in the value of rate constant has been observed for nucleophilic reactions with alkyl halides[35] and has been attributed to changes in ionic strength. Plots of $\frac{1}{C}$ against time for equal initial concentrations of reactants also showed the same drift. Slopes of the lines representing 50% of reaction were taken and the rate constants calculated. Table II shows some of the results obtained.

TABLE II

Reaction between 4-chloromethyl 1,4 dihydropyridine and ammonium thiocyanate at 55°C.

Conc. of chloro compound, moles / litre. (EtOH)	Conc. of thiocyanate moles/litre.	K x 10^3 l $mole^{-1}$ sec^{-1}
0.03	0.03	1.25
0.03	0.03	1.21
0.05	0.05	1.10
0.015	0.030	1.13
0.015	0.030	1.22

Rate constants obtained for reactions with potassium and barium thiocyanates are given in Table III.

TABLE III

Rate constants for reaction of 4-chloromethyl 1,4-dihydropyridine with different thiocyanates in EtOH.

Thiocyanate used	Number of runs	Rate constant X 10^3 l. $mole^{-1}$ sec^{-1}
Ammonium	7	1.18
Potassium	2	1.28
Barium	2	2.71

Plots for kinetic run with barium thiocyanate gave good straight line for more than 75% completion of reaction. A kinetic run with lithium chloride in the reaction mixture gave K X 10^3 = 1.12 1. $mole^{-1}$ sec^{-1} for ammonium thiocyanate which is not significantly different from the other value.

Reaction between 4-chloromethyl 1,4-dihydropyridine and potassium cyanide at 55°C was fast and was complete within 30 minutes. A specially designed vapour-free reaction vessel used by Moelwyn-Hughes[36] for kinetic studies was found to be convenient for this reaction. The reaction was followed by analysing for unreacted cyanide at various times during the run by titration with silver nitrate.

It was found that the second order rate constant varied with initial concentration of the dihydropyridine compound.

TABLE IV

Reaction of chloromethyl dihydropyridine with potassium cyanide at 55°C.

Conc. of chloro compound mol/l.	Conc. of pot. cyanide mol/l.	K x 10^2 l $mole^{-1}sec^{-1}$
0.0227	0.006	3.80
0.0106	0.017	7.88

Brignell[28] also has reported that consistent results could not be obtained for the rate constant in spite of careful control of conditions.

The purpose of the present investigation has been to compare the reactivities of the two nucleophiles, thiocyanate and cyanide, towards the dihydropyridine compound under the same conditions. No attempt was therefore made to trace the cause of the variation, due to time limitations.

Comparison of the rate constants for thiocyanate and cyanide reactions with similar concentrations of the chlorocompound has shown that the cyanide reaction is about 30 times faster than the other. This difference is much more than predicted by the order of nucleophilicities from Swain and Scott's equation. These nucleophilic constants were calculated from $\frac{K}{K_o}$ values determined for reactions in aqueous solvents. It is presumed that the order of nucleophilicity is valid when applied to reactions in ethanol, another hydroxylic solvent, especially because both reactions have the same substrate.

Moelwyn-Hughes has studied the rates of reaction of methyl iodide with potassium thiocyanate[37] and potassium cyanide[38] in water.

Kinetic constants for the reactions

$CH_3I + X^-$ $CH_3X + I^-$ in aqueous solution at 298°K

X^-	K(l. mole^{-1} sec^{-1})	Ea(cal/mole)
CN^-	5.76×10^{-4}	20, 470 ± 120
SCN^-	3.58×10^{-4}	19, 950 ± 400

As the results show, the cyanide reaction was only 1.6 times faster than the thiocyanate under the same experimental conditions.

No kinetic data for reaction of primary alkyl chloride with thiocyanate in absolute alcohol is available; Crowell[39] studied the rates of reaction of alkyl bromides with sodium thiocyanate in 95% ethanol and reported K=1.67 X 10^{-5} 1. $mole^{-1}$ sec^{-1} for ethyl bromide at 25°C. A comparison of this value and the rate constant for thiocyanate reaction with chloromethyl dihydropyridine at 55°C is difficult. However, considering the difference in temperatures it is probably right to conclude that the thiocyanate reaction with chloromethyl dihydropyridine is not much faster than reaction with primary alkyl halide. This is different from the results of Gregory's[29] study of methanolysis of chloromethyl dihydropyridine. It was observed that the rate obtained was about 10^3 times the methanolysis rate for a normal primary halide at comparable temperatures. This increased reactivity has been explained by assuming carbonium ion stabilisation by the homoallylic system in the molecule.

Solvolysis in the presence of base has been shown to effect ring expansion; but, thiocyanate reaction conducted in the presence of triethylamine still gave the dihydropyridine product with reduced yield. This is because thiocyanate compound is unstable in the presence of base and part of the product decomposed during the reaction.

Mechanism suggested by Brignell[28] and collaborators implies that basic nucleophiles or anions of weak acids will cause ring expansion. Reaction with thiocyanate seems to support this suggestion. It is known from observed pH values that thiocyanic acid is as strong as perchloric acid[40].

To test whether the above inference is really correct, action of selenocyanate ion on the chloromethyl dihydropyridine was tried. Selenocyanate is similar to thiocyanate in most of its reactions except that selenocyanic acid is a weak acid as shown by the pH of a solution of potassium selenocyanate in water. No reference to pK_a value of selenocyanic acid could be found. pH of a 0.1M solution of potassium selenocyanate was found to be about 10.4 at 25°C. From the relationship $K_h = \frac{K_W}{K_a}$, pK_a for selenocyanic acid was calculated to be 7.8, while the pK_a of hydrocyanic acid is 9.31[41].

Reaction of chloromethyl dihydropyridine (14; R=CO_2Et, R^1=CH_2Cl) with potassium selenocyanate in acetonitrile gave a product which showed all the spectral characteristics of the thiocyanate compound (14; R=CO_2Et, R^1=CH_2SCN). The compound is evidently a dihydropyridine derivative (14; R=CO_2Et, R^1=CH_2SeCN).

There is a small difference in the pK_a values of hydrocyanic acid and selenocynic acid. It was necessary to test whether this had any effect on the reaction of their anions. Sulphite was chosen as the nucleophile to test this because pK_a for the second dissociation of sulphurous acid is 6.9.

Anhydrous sodium sulphite reacted with the chloromethyl dihydropyridine in hot absolute ethanol easily. U.v. spectrum taken using the alcoholic solution after reaction (λ_{max} 230, 326; Σ_{max} 1:1) had all the characteristics of the spectrum of 4-substituted, 4-H-azepine derivative (e.g. 16 $\lambda_{max.}$ 229, 326; $\Sigma_{max.}$ 15, 100, 15,400). It was evident that ring expansion occurred during reaction with sulphite. Attempts to isolate a pure product failed, since the compound seems to be very hygroscopic.

4-H-azepine (19), the suggested intermediate in the cyanide reaction, was prepared by the method of Anderson and Johnson. Reactions with potassium selenocyanate and sodium sulphite were tried; unlike potassium cyanide, they did not react in aqueous ethanol. When the azepine was refluxed with ammonium thiocyanate in ethanol for several hours, 4-thiocyanatomethyl-1,4-dihydropyridine (14; R=CO_2Et, R^1=CH_2SCN) was formed. However, there is no possibility of the azepine being an intermediate in the thiocyanate reaction because reaction between chloromethyl dihydropyridine and ammonium thiocyanate is complete within one hour.

Before further discussion it is necessary to give a summary of the effect of reaction of various nucleophiles with 4-chloromethyl 1,4-dihydropyridine (Table on page 27).

Two features of the nucleophiles which react with retention of ring structure have to be noted. (i) The atom in the nucleophile which forms the bond with carbon is an element below the first row of the periodic table and has several nonbonding electrons in the outer orbitals.

Reaction of 4-chloromethyl 1,4-dihydropyridine (14; R=CO_2Et, R'=CH_2Cl) with Nucleophiles

Nucleophile	Solvent	Reaction Condition	Effect on Ring	Main Product	Ref.
$C\bar{N}$	Ethanol or DMSO	Room temperature	Ring expansion	4-cyanodihydroazepine	22
CH_3O	Methanol	45°C	No expansion	4-methoxymethyl dihydropyridine	29
$CH_3\bar{O}$	"	45°C In the presence of excess triethylamine	Ring expansion	4-methoxydihydroazepine	29
$CN\bar{O}$	Ethanol	Refluxed	Ring expansion	4-H azepine	26
I^-	Acetonitrile	Refluxed	No expansion	4-Iodomethyl 1,4-dihydropyridine	28
$SC\bar{N}$	Ethanol	Refluxed	No expansion	4-Thiocyanatomethyl 1,4-dihydropyridine	This work
$SeC\bar{N}$	Acetonitrile	Refluxed	No expansion	4-Selenocyano methyl 1,4-dihydropyridine	This work
$SO_3\bar{N}a$	Ethanol	Refluxed	Ring expansion	Dihydroazepine compound. Product not isolated.	This work

(ii) They have empty d orbitals which are of relatively low energy and can be used to accommodate some electrons. The significance of these two features is discussed below.

From the experimental evidence given so far, it can be concluded that the mechanism suggested by Brignell et al[28] is not applicable to all the reactions involving ring expansion, it is probably correct for the particular cyanide reaction. It is also true that basicity of the nucleophile is not the only factor which determines the course of the reaction and the nature of product. This is confirmed by the result of an attempted reaction between the chloromethyl dihydropyridine and the strongly basic sulphide ion. The chloro compound was stirred with sodium sulphide in ethanol for 24 hours. No change in the u.v. spectrum corresponding to the formation of dihydroazepine product was observed.

The intermediate (29) with a potential seven-membered ring has been suggested[29] in an attempt to explain the expansion and retention of ring observed under different conditions of solvolysis. However, it is doubtful whether such intermediate can be assumed for the thiocyanate reaction which always gives the same product irrespective of the presence and absence of base.

It appears that a transition state for an SN^2 reaction is more appropriate for the reaction between chloromethyl dihydropyridine and thiocyanate. Polarizability of the ion enables it to rearrange its electron distribution in such a way as to reduce repulsions of its non-

bonded electrons in the transition state. This is achieved by polarizing unshared pairs away from the electrons in the bonds of the substrate. It is here that the empty d orbitals become useful.

No assistance by N-H bond breaking is envisaged in the above transition state. The fact that N-methyl compound (21) also reacts with thiocyanate easily producing the dihydropyridine compound shows that the assumption is valid.

The reaction of a polarizable nucleophile with non-bonding electrons on the attacking atom was tested by reaction between the chlorocompound (14; R=CH_2Cl) and thiourea. Iso-thiuronium compounds were formed by the dihydropyridines (14a, 14b, and 21) but not the one with cyano groups at 3 and 5 positions (14c). The compounds were prepared as the picrates. U.v. spectra of the solutions were taken before adding picric acid. The dihydropyridine spectrum with peaks at λ231 and 350 mμ was obtained showing that no ring expansion took place. This was confirmed by the n.m.r. spectra which showed all the absorptions, except one, of the parent compound without much change. The doublet corresponding to the CH_2 attached to sulphur of iso-thiuronium group was shifted to τ= 7.0.

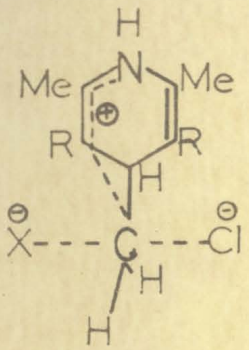
The isothiuronium picrate on reaction with lithium hydroxide in ethanol gave a product which still retained the dihydropyridine ring as shown by the u.v. spectrum.

The absence of reaction between chloromethyl dihydropyridine with 3,5-dicyano substituents and thiocyanate has to be considered. Chloro compounds with either carbethoxy or acetyl substituents at positions 3 and 5 react easily. It is known from Hammett σ values that cyano group is a stronger electron withdrawing group than carbethoxy or acetyl.

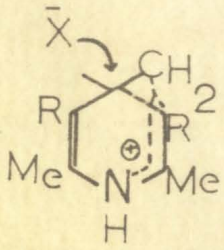
Substituent	σ (Meta)
CN	+ 0.56
$CO_2C_2H_5$	+ 0.37
CO_2CH_3	+ 0.321
$COCH_3$	+ 0.376

The transition state (31a) suggested is possible by delocalisation of the positive charge through the homoallylic system in which either 3 or 5 position is included. Presence of strong electron-withdrawing group at position 3 will inhibit the effect of homoallylic system and thereby delocalisation of the charge. The reaction therefore fails to take place. The 3,5-dicyanodihydropyridine compound reacts with potassium cyanide[22] giving the corresponding cyanodihydroazepine product. This is obviously because the mechanism of ring expansion is different from the other reaction.

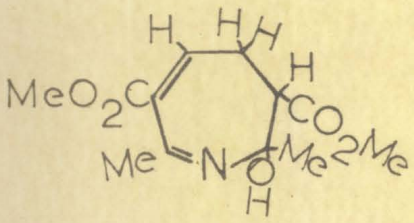
For ring expansion a transition state of the type (31b) suggested by Gregory[29] with attack by nucleophile at carbon 4 of the ring is possible. Nucleophiles like thiocyanate, iodide and thiourea can not approach the ring close enough for bond formation because of the repulsion between the non-



(31a)



(31b)



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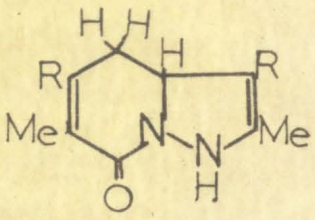


(33)

(a) R = CO_2Et.

(b) R = CO_2Me.

(c) R = COMe.

bonded electrons of the nucleophile and the electrons in the bonds of the ring. Assuming that the repulsion is reduced by polarizing the non bonded electrons away from the nucleophile-substrate region, the result is a decrease in basicity and consequently nucleophilic reactivity. In the transition state (31a) suggested for thiocyanate reaction, the X...C...Cl bonds are longer than normal valency bonds and so, close approach is not necessary. Cyanide ion has no nonbonded electron pairs and therefore attack at carbon 4 of the transition state is not obstructed. Moreover, the strong basicity also is helpful in the reaction. The inability of strongly basic sulphide ion to react under the conditions of the cyanide reaction can be attributed to the nonbonded electron pairs on the sulphur.

Admittedly, the explanation given for the two types of reactions suffers from a defect which is shared by the other suggested mechanisms it is too simple for a complicated system. One important lapse is that the part played by solvent in the reaction has not been discussed.

It has been mentioned earlier that the product of reaction between the chloromethyl 1,4-dihydropyridine (14; R=CO_2Et; R'=CH_2Cl) and potassium cyanate is 4-H-azepine (19). The first step in the reaction is probably formation of 4-cyanatodihydroazepine compound which then eliminates cyanic acid forming the 4-H-azepine. This is similar to the formation of 4-H-azepine from the chloro compound by reaction with sodium ethoxide in boiling ether. The 4-methoxydihydroazepine was shown to form 4-H-azepine easily by elimination of ethanol. It was decided to study

the effect, if any, on the reaction when ammonium cyanate is used.

It is known that ammonium cyanate isomerises into urea in ethanol when heated; but, it is possible that some cyanate ions will exist in solution in equilibrium at room temperature. The reaction of the chloro compound with urea in ethanol was therefore, tried. An interesting reaction was found to take place between the two.

When the chloro compound in ethanol was stirred with excess urea at room temperature, change in the ultra-violet spectrum showed the occurrence of a reaction. The characteristic peaks at λ_{max} 231 and 349 mμ of the dihydro-pyridine gradually decreased and the new peak formed at λ_{max} 263. The spectrum did not change after six days and it was presumed that the reaction was complete.

Two products were isolated from the solution. Product A was obtained by removing part of the solvent by vacuum evaporation and precipitation by adding excess water; product B was obtained from the aqueous alcoholic filtrate by ether extraction and was identified as ethyl 2-methyl pyrrole-3-carboxylate. The same pyrrole is produced from 4-chloromethyl 1,4-dihydropyridine by reaction with ammonia.

The main product A, obtained in good yield was found to be a single compound; no other component was separated by chromatography. On crystallisation from cyclo-hexane it formed a "woolly" crystalline mass.

The same product was obtained when the chloro compound and urea were heated in ethanol under reflux and the reaction was complete in 2 hours. The reaction was re-

peated with the other dihydropyridines, (14; R=CO_2Me, R' = CH_2Cl and R=COMe and R' =CH_2Cl), and similar products were obtained without difficulty. The 3,5-dicyano compound (14; R=CN,R' =CH_2Cl) did not react even when refluxed for several days. One surprising result was obtained when the reaction was tried on the N-methyl compound (21). The product obtained was the same as the one from the corresponding N-H compound. This was confirmed by mixed melting point and spectra.

Ultraviolet and nuclear magnetic resonance spectral data of the product A differed from the reported data for all the other compounds from 4-chloromethyl 1,4-dihydropyridine. U.v. showed two peaks λ_{max}263; 310; ϵ_{max} 26,200, 7,150).

The n.m.r. spectrum in $CDCl_3$ showed two non-equivalent ester groups, two methyl groups, and a set of complex resonances between τ5 and 5.6 and τ6.3 and 7.5. The low field absorptions were superimposed on the quartet of the ethyl ester. The simpler spectrum of the product from the dimethyl ester (14; R=CO_2Me, R' =CH_2Cl) was analysed and the following features were noted (solvent $CDCl_3$ with one drop of trifluoroacetic acid).

One sharp signal, slightly split (J=1.5 c/sec) of intensity 3 τ= 7.69 (C-CH_3). Singlet, intensity 3,τ = 7.34 (C-CH_3). Singlet, intensity 6,τ = 6.20 (CO_2CH_3). Quartets τ= 5.25, 6.87 and 7.22. Singlet, broad τ= 1.36 (NH). The quartets were broad and appeared to show multiple splitting. Part of the high field quartet was superimposed on the base of the singlet at τ= 7.34. The possible inference is that

the quartets represent an ABX system such as $CH-CH_2$ which is present in some of the products from the chloro compound.

One interesting feature of the spectrum is the difference in the chemical shifts of the two methyl groups which are equivalent in the parent compound (singlet, τ= 7.64). No other product from 14(R=CO_2Me or Et, R'=CH_2Cl) reported until recently showed a difference of 0.35 p.p.m. However, very recently a compound with the unconfirmed structure (32) has been reported to be showing the two CH_3's at τ=7.88 and 8.26. The position of -NH determined in a solution without adding trifluoroacetic acid was still at low field τ=1.4 showing that it is either attached to an electron withdrawing group or is part of an aromatic ring. The fact that the ultraviolet spectrum shifted from λ_{max} 263 to 293 and 310 to 360 when one drop of sodium hydroxide solution was added to an alcoholic solution of the compound suggested a -CONH- group in the compound.

Empirical formula was found to be $C_{15}H_{20}N_2O_5$ corresponding to loss of chlorine and addition of CNO^- to the parent compound; but the spectra did not correspond with the simple substitution products.

In order to elucidate the structure of the compound some chemical reactions were attempted on the compound. Reaction with bromine in acetic acid gave a product which was unstable in solution and decomposed quickly. Purification and characterisation were unsuccessful.

As a result of the study of reactions of urea it was at first suggested that the compound contains a lactam ring. Hydrolysis of the proposed lactam was attempted without any success. When mild conditions were employed, the compound was recovered unchanged; under stronger hydrolytic conditions it decomposed completely.

Absence of a band above 1710 cm^{-1} in the infrared spectrum indicated that there is no fused lactam ring. The band at 1710 cm^{-1} was present in the parent compound also. In fact, the spectrum between 1600 and 1800 cm^{-1} was very similar to the spectrum of the chloro compound.

Reaction of the compound with nitrous acid gave a product in low yield which had empirical formula $C_{15}H_{17}N_3O_7$. The n.m.r. spectrum of the nitrosated compound showed two nonequivalent ester groups, two methyl groups and an -NH. The retention of the -NH shows that it is most probably part of a ring.

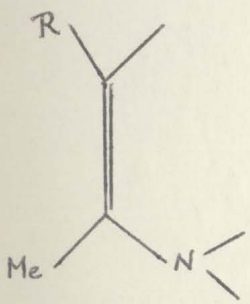
A clue to the mechanism of the reaction and thereby the structure of the compound was sought by studying the numerous rearrangements of the chloromethyl dihydropyridines and their compounds. Two features of this reaction were given emphasis.

(i) The N-H and N-Me compounds, both give the same product. Some reaction probably occurs at the dihydropyridine nitrogen. But, the formation of furopyridine compound[27] (18;X=O) from the N-Me compound by the action of cyanide shows that this is not an essential step. The suggested mechanism included a ring opening and then cyclisation.

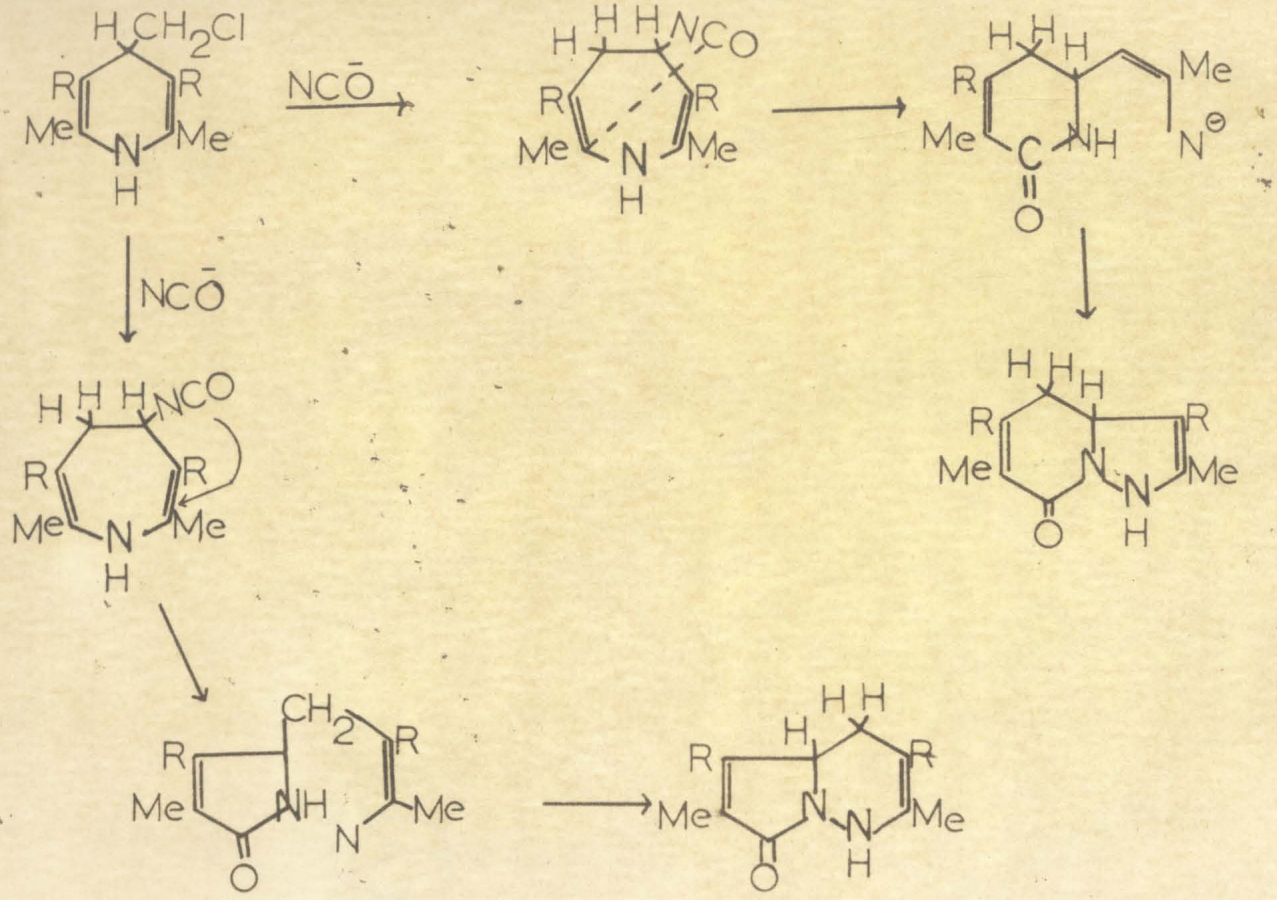
(ii) Since the reaction takes place easily under relatively mild conditions it is possible that a ring opening followed by cyclisation takes place. This will be similar to the reaction between the chloro compound and potassium cyanide[22] when shaken in ethanol at room temperature for six days forming the furopyridine compound (18; X=O).

On the basis of its methodof formation, spectral characteristics, and its reactions, a bicyclic structure (33) is proposed for product A from the reaction of 4-chloromethyl 1,4-dihydropyridines and urea.

The first step in the reaction is replacement of chloride by isocyanate forming the isocyanate of the dihydroazepine. The isocyanate substituent causes ring opening by attack on the 6:7 or 2:3 double bond as shown in the scheme. The system $-\overset{\curvearrowleft}{N} = \overset{\delta+}{C} = \overset{\curvearrowright}{O}$ probably attacks



the group in the seven membered ring in a manner similar to the Michael reaction.[25]



(34)

ANALYTICAL METHODS

Experiments designed to study kinetics of replacement of halogen in an organic compound by thiocyanate usually pose the problem of determining the progress of the reaction. This is mainly an analytical problem because of the similarities in the reactions of halides and thiocyanates.

Moelwyn-Hughes[37] in an attempt to study kinetics of reaction between methyl iodide and thiocyanate ion in aqueous solution tested two volumetric and two gravimetric methods to estimate the concentration of the iodide or the thiocyanate ion in each other's presence and found them unsatisfactory. Finally a conductivity method was adopted taking advantage of the small difference in the ionic mobilities of thiocyanate and iodide ions. This method is of restricted applicability because of an inherent source of error. The increase in conductivity due to the slight hydrolysis of methyl iodide could be a significant fraction of the increase due to the ionic exchange. It is evidently not suitable for the reaction between the chloromethyl dihydropyridine and thiocyanate ion in alcohol.

The reaction between the chlorocompound and ammonium thiocyanate was found to proceed at 55° at a convenient rate suitable for rate measurement by chemical analysis. Moreover, the solubility of thiocyanate salts in alcohol permitted the reaction to be conducted at concentrations required by the analytical methods employed.

Various methods involving oxidation-reduction reactions were tested for estimating thiocyanate in the aqueous extracts from the reaction mixture. Schulek's[43] brominecyanide method is inconvenient because of the vigorous shaking required and the possibility of imcomplete removal of bromine. It gave inconsistent results for recovery tests.

Pagel and Ames[44] estimated thiocyanate by adding known excess of iodine to the thiocyanate solution in the presence of a buffer and titrating the excess iodine with thiosulphate. This method was used by LaMer and Greenspan[45] in their kinetic study of replacement of bromine from brominated fatty acids by thiocyanate ion. This method as well as the potassium bromate titration of Joshi[46] gave unsatisfactory values when used to estimate thiocyanate in the extract from the reaction mixture.

Crowell[39] used Lang's iodine cyanide method for studying the kinetics of reaction between alkyl bromides and sodium thiocyanate in aqueous alcohol. This method with slight modification gave quite satisfactory results. But one serious disadvantage of the method is the formation of a large amount of hydrogen cyanide during the titration. An attempt was, therefore, made to develop a method for estimation of thiocyanate in the presence of chloride, by modifying one of the existing methods.

Thiocyanate has been estimated gravimetrically by oxidation to sulphate and precipitation with barium chloride. Hydrogen peroxide[47] in the presence of alkali has been mentioned as one of the oxidising agents and

although not much detail was given, the method appeared to be promising. Gravimetric methods for kinetic measurements are tedious and time consuming. A volumetric method for estimating the sulphate produced by oxidation would be more convenient.

A very useful reagent in the volumetric estimation of sulphate, as in the estimation of several elements and ions, is EDTA (ethylene diamine tetraacetic acid). Munger[48], Ueno[49], Gwilt[50], Bond[51] and several others have used EDTA for the volumetric determination of sulphate in a variety of materials. The method involves adding measured excess of barium chloride to the sulphate solution and after precipitating the sulphate as barium sulphate, titrating the unreacted barium against EDTA solution using a suitable indicator.

Bond applied the method for estimating milligram amounts of sulphate in soil extracts. He showed that the results were not satisfactory when the method was used for very small amounts of sulphate because of incomplete precipitation and that the error could be avoided by using barium chloride freshly seeded with sulphate.

It was assumed that a combination of the above two methods i.e. oxidation of thiocyanate with hydrogen peroxide and estimation of the resulting sulphate by EDTA titration under proper conditions could form a convenient method for estimation of thiocyanate in the presence of chloride. An investigation of the accuracy of the method and its suitability for the kinetics experiment was undertaken.

Reagents:

Disodium salt of ethylenediamine tetraacetic acid. 0.02N solution. The solution was standardised with standard calcium solution.

Barium chloride solution. 0.02N. The solution was seeded with sulphate by adding one or two drops of dilute sulphuric acid and standardised by titration with the EDTA solution.

Magnesium chloride solution 0.02N.

Buffer solution: A solution of 67.5 gm. of ammonium chloride and 570 ml of concentrated ammonium hydroxide was diluted to one litre. To each 50 ml of sample, 1 ml of buffer solution was added to give a pH of 10.

Indicator: Erichrome Black T in methanol.

Procedure:

The thiocyanate solution is diluted to 30 ml, 2 ml N potassium hydroxide added, then 2 ml 30% hydrogen peroxide and the mixture is gently boiled for 10-15 minutes. N hydrochloric acid is added to the solution until the solution is just acid to dimethyl yellow. The solution is then boiled and by means of a pipette 10 ml of barium chloride solution is added slowly after which boiling is continued for one minute. After cooling and dilution to 50 ml, 1 ml buffer solution, 2 ml magnesium chloride solution and drops of indicator solution are then added and titrated with EDTA. When the indicator colour changed 1 ml more of magnesium chloride solution is added and the titration is completed with additional EDTA. The first end-

point is not used because its accuracy will be poor.

To test the accuracy of the method, solutions of potassium thiocyanate and ammonium thiocyanate were prepared and standardised by silver nitrate titration and also by the above method. There was complete agreement between the values obtained by the two methods within limits of experimental error.

It was necessary to test whether the method could be applied to the determination of inorganic thiocyanate in the reaction mixture from kinetics experiments. The possibility that a small amount of the organic thiocyanate compound formed might get into the aqueous extract and cause high values had to be investigated.

This was tested by preparing solutions containing different amounts of the thiocyanate compound, chlorocompound and ammonium thiocyanate, extracting the ammonium thiocyanate from 1 ml of the solution as in the kinetics procedure and estimating by the procedure described.

Results of Recovery Tests on Estimation of Thiocyanate

	Composition of synthetic reaction mixture gm/100 ml.	Thiocyanate added mg.	Thiocyanate recovered mg.	% recovery
I	Chlorocompound 1.5 g +thiocyanato methyldihydro-pyridine 0.012g	43.5	43.3*	99.5*
II	Chlorocompound 0.15g + thio-cyanatomethyl dihydropyridine 1.5 g.	4.35	4.25*	97.7*

* Average of three different estimations.

I represents the composition of a solution during the initial periods of a kinetic run and II represents concentration towards the end of a reaction.

Results show that recoveries are quite satisfactory.

Various extraction procedures were tried for separating the unreacted inorganic thiocyanate from the organic compounds in the reaction mixture and the method described in the section on rate measurements was found satisfactory. When ordinary grade benzene was used recovery of added thiocyanate was not complete. When pure benzene('99 mol % pure' from Fisher Scientific Co.) was used, recoveries were excellent.

Bond[51] reported an optimum concentration of sodium chloride allowable, above which there was interference with the precipitation of barium sulphate. But it is seen from the satisfactory recovery values that the potassium chloride formed from the potassium hydroxide added does not interfere with the precipitation of barium sulphate under the conditions of the procedure described. Most of the chloride formed during the kinetic run precipitates and not much of it is transferred into the aqueous extract.

Results of one of the kinetic runs are given in Table V.

Good agreement between the values for rate constants obtained by the EDTA method and Lang's iodine cyanide method would be a confirmation of the suitability of this method for this type of kinetics experiments. However, on comparison of the values, it was found that the values by EDTA method were lower than the other by about 10-15%. Further work, possibly a statistical study, of the two methods is required in order to trace cause of the difference.

TABLE V

Determination of rate constant by the use of EDTA method for estimating SCN^-

Initial [XCl] = 0.0501 M Initial [SCN^-] = 0.0501 M

1 ml of reaction mixture was taken for estimation of SCN^-.

Time Minutes	Volume of $BaCl_2$ added N = 0.0207	Volume of 0.0214N EDTA required for unreacted $BaCl_2$	Ammonium thiocyanate moles/l X 10^2	$\frac{1}{C}$
0	10 ml	5.02 ml	4.979	20.08
60	"	5.55 "	4.412	22.67
120	"	5.97 "	3.962	25.24
180	5 ml	1.65	3.410	29.33
240	"	2.05	2.982	33.54
300	"	2.30	2.714	36.85
375	"	2.52	2.479	40.34
450	"	2.77	2.211	45.23
510	"	3.00	1.965	50.89
570	"	3.22	1.730	57.80
620	"	3.38	1.559	64.14

$K = 1.03 \times 10^{-3}\ l.mol^{-1}sec^{-1}$

Determination of cyanide in the presence of chloride.

Liebig's method modified by Deniges for the determination of cyanide is well known. Ryan and Culshaw[52] developed a modified Liebig titration method using p-dimethylaminobenzylidene rhodanine as internal indicator and this method was adopted for the determination of cyanide in industrial wastes[53].

Because of the low solubility of potassium cyanide in absolute ethanol the kinetics of reaction between chloromethyl dihydropyridine and cyanide ion were studied with low concentrations of the reactants. An analytical method suitable for estimating milligram amounts of cyanide was therefore necessary. Ryan and Culshaw's method was chosen for the purpose. The limit of sensitivity of this method has been given as 0.1 mg/l CN^-. The method has been shown to be quite reliable when the cyanide concentration is greater than 1 mg/ 1 $C\bar{N}$.

Reagents:

Standard silver nitrate solution 0.005N. Sodium hydroxide solution (10% solution). Indicator 0.02g p-dimethylaminebenzylidene rhodamine dissolved in 100 ml acetone.

Procedure:

The cyanide solution is diluted to 50 ml, 10 ml sodium hydroxide solution and 10 drops of indicator are added and titrated.

For estimating the cyanide in the reaction mixture an extraction procedure was tried; but, the recoveries were low. Several trial titrations were done to study the effect of presence of alcohol, chlorocompound, and the cyanoazepine on the results of titration of solutions containing known amounts of cyanide. It was found that direct titration of 2 ml of reaction mixture gave promising results. Precipitation of a small amount of the organic compounds on dilution with water caused some difficulty in observing the end point and so, 2 ml of pure carbon tetrachloride was added before the titration. This addition of carbon tetrachloride had a very unexpected effect on the titration.

The endpoint of this titration is indicated by the first change in colour from a canary yellow to a salmon hue. It has been mentioned that most analysts[54] find this titration difficult until they become accustomed to the endpoint. In fact, this was found to be the case. When the titration was done after adding 2 ml carbon tetrachloride, at the endpoint the colourless carbon tetrachloride layer turned to a light salmon hue. This change was sharp and could be easily observed. The mixture in the flask must be shaken thoroughly after addition of each drop of silver nitrate near the endpoint.

Recovery tests showed that no free cyanide is produced by the decomposition of cyanoazepine in alkaline solution during the titration.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237B instrument. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 spectrophotometer; ethanol (95%) was used as solvent.

A Varian A-60 spectrometer was used to obtain the nuclear magnetic resonance (n.m.r.) data. Spectra were taken at 60 Mc/s with tetramethylsilane (TMS) as an internal reference. The chemical shifts are given as τ values where $\tau = 10-\delta$, δ being the chemical shift in p.p.m. from the T.M.S. absorption.

Elemental analyses were done by Alfred Bernhardt, Mulheim (Ruhr), Germany.

Kinetics Experiments. Methods and Materials.

Ethanol was purified by the method of Lund and Bjerrum[55]. Oxygen was excluded during the drying and distillation by passing a stream of dry nitrogen. The 'super dry' alcohol was stored under nitrogen and opened only in a drybox which was swept with dry nitrogen. Benzene (Fisher 'Analyzed') was used without further purification.

Ammonium thiocyanate (Analar) was dried and on analysis was found to be 99.5% pure. It was recrystallised from water twice, dried in a vacuum desiccator in the dark for several days and then in an oven at 110°C for 2 hours. Potassium thiocyanate (Analar) was purified by Kolthoff's method. 'Analar' salt was recrystallised from water twice,

dried in a desiccator at room temperature and then in an oven at 120-150°.

Barium thiocyanate sometimes contains ammonium thiocyanate. It was therefore purified by boiling a solution of the thiocyanate with barium hydroxide until no ammonia evolved. The solution was then made faintly alkaline by adding 6N sulphuric acid and the remainder of barium hydroxide neutralised by passing carbon dioxide. The solution was heated to boiling, filtered, the filtrate concentrated and then allowed to cool. The barium thiocyanate was further recrystallised from water, then dried over calcium chloride in a vacuum desiccator, and dried in an oven at 120°C for 2 hours.

Potassium cyanide (Analar) was dried at 120° for 10 hours and kept in a desiccator.

The chloromethyl dihydropyridine (14; R=CO_2Et, R'=CH_2Cl) was prepared by Benary's[56] method. It was recrystallised from benzene 5 times giving colourless crystals.

Reaction with thiocyanate was conducted in sealed ampoules. These ampoules were treated with hot nitric acid, washed, kept in deionised water for 3 days and then dried in an oven. This technique is not suitable for the fast cyanide reaction and therefore, the vapour-free reaction vessel mentioned earlier was used with success.

Rate measurements:

Reaction with thiocyanate.

Required weights of the dihydropyridine compound and ammonium thiocyanate were weighed accurately in weighing bottles and transferred to a drybox through which a stream of dry nitrogen was passed throughout the preparation of the solution. The compounds were dissolved in the specially dried ethanol as quickly as possible, mixed and made up to 100 ml. This method of dissolving both reactants in the same flask was adopted because there is practically no reaction between the two at room temperature. Ampoules were sealed with about 6 mls of the solution in each and then placed in a thermostat at 55°C. Four minutes were allowed for the solution to attain equilibrium and then the first tube was withdrawn from the bath, immediately cooled under the tap and opened. Two mls (1 ml for the EDTA method) were pipetted into a mixture of benzene (25 ml) and deionised water (10 ml) in a separating funnel. The mixture was shaken thirty times and allowed one minute for the separation of the phases. The aqueous phase was then transferred to a titration flask. The tail of the funnel was then washed out with 5 ml of water. Ten ml more of water was then added to the benzene and extracted with 20 shakings. Thiocyanate in the total aqueous layer was determined by one of the methods described in the section, "Analytical methods'. The remaining ampoules were taken from the bath at 30 minute intervals and analysed for thiocyanate.

The temperature of the thermostat was checked against a standard thermometer which was itself calibrated by a platinum resistance thermometer.

Results of a typical kinetic run are given in Table VI.

Reaction with potassium cyanide.

Because of the low solubility of potassium cyanide in absolute ethanol a saturated solution of the cyanide in ethanol was prepared and the concentration determined by titration of an aliquot with silver nitrate by a modified Liebig's method. Approximately 100 ml of the cyanide solution was brought to the temperature of the bath, then a measured volume of a solution containing the required weight of chlorocompound was added to it, thoroughly mixed and poured into the reaction vessel. It was necessary to use the minimum possible amount of chlorocompound solution to prevent the temperature of the mixture from falling too much below the temperature of the bath. A concentrated solution of the chlorocompound had to be used and this also presented some difficulties because of the limited solubility of the chlorocompound in ethanol. This procedure was adopted instead of preheating the chlorocompound solution also before admixture, to avoid solvolysis.

After allowing one minute to reach thermal equilibrium, the first sample was collected in a flask cooled in ice and salt mixture. A portion of this solution (2 ml) was immediately measured into a titration flask containing water (50 ml) and 10 ml of 10% sodium hydroxide solution.

TABLE VI

Reaction between 4-chloromethyl 1,4-dihydropyridine and ammonium thiocyanate (Ethanol at 55°C)

XCl = 14; R = CO_2Et, R' = CH_2Cl. Initial [XCl] = 0.01502M; Initial [$SC\bar{N}$] = 0.03009M

Time Minutes	Volume of 0.06N KIO_3	Instantaneous $[SC\bar{N}]C_A$	Instantaneous $[XCl]C_B$	$\log_{10} \frac{C_A}{C_B}$
0	6.00 ml	0.02978	0.01471	0.3062
60	5.75	0.02853	0.01346	0.3263
120	5.45	0.02705	0.01198	0.3537
180	5.22	0.02590	0.01083	0.3788
240	5.07	0.02516	0.01009	0.3969
300	4.82	0.02410	0.00903	0.4264
390	4.58	0.02288	0.00781	0.4669
450	4.44	0.02219	0.00712	0.4938
510	4.30	0.02150	0.00643	0.5242

$K = 1.09 \times 10^{-3}$ l. $mole^{-1}$ sec^{-1}

TABLE VII

Kinetic run for reaction between 4-chloromethyl 1,4-dihydropyridine (XCl) and potassium cyanide (Ethanol at 55°C)

XCl = 14; R = CO_2Et, R' = CH_2Cl Initial [XCl] = 10.56×10^{-3} moles / l.

Initial $[C\bar{N}]$ = 16.732×10^{-3} moles / l.

Time Seconds	Instantaneous $[CN^-] \times 10^3 = C_A$	Instantaneous $[XCl] \times 10^3 = C_B$	$\log_{10} \frac{C_A}{C_B}$
0	15.203	9.031	0.2261
180	13.821	7.649	0.2569
360	12.669	6.497	0.2900
540	11.379	5.207	0.3395
720	10.366	4.194	0.3931
900	9.444	3.272	0.4603
1080	8.753	2.581	0.5303
1260	8.062	1.890	0.6300

$K = 7.880 \times 10^{-2}$ 1. $mole^{-1}$ sec^{-1}

Carbon tetrachloride (2ml) (specpure) was then added and the mixture titrated against silver nitrate using a micro-burette by the modified Liebig's method. (See Analytical Methods). Further samples were withdrawn at three minute intervals and the unreacted cyanide in each determined. It took only thirty minutes to finish one kinetic run

Results for a typical kinetic run are given in Table VII.

Preparations:

Diethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3, 5-dicarboxylate (14; R=CO_2Et, R'=CH_2Cl) was prepared according to Benary's method[56].

Ethyl β-aminocrotonate[57] (50 g) was melted, cooled until just before crystallisation started then 1,2-dichloroethyl ethyl ether (58.6g) was added. As soon as the first signs of reaction started to appear, ammonia (10% solution, 300 mls) was added. A vigorous exothermic reaction took place and the reaction vessel was cooled under the tap when necessary. After about 30 minutes standing the semisolid mass was filtered under vacuum and a yellow solid was obtained when the oily byproduct was sucked away by a filter pump. The product was washed quickly with a small quantity of cold ethanol, then a small quantity of cold ether. The yellow solid was recrystallised from benzene m.p. 136-137° (lit. 56,22, 133-134°, 134-136°).

Dimethyl 4-chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (14; R=CO_2Me, R'=CH_2Cl).

This compound was prepared from methyl β-aminocrotonate and 1,2-dichloroethyl ethyl ether according to the procedure for the ethyl ester with slight modification, cold water being used instead of ammonium hydroxide. The product was crystallised from benzene. m.p. 158-159° (lit.,[26] 158-159°).

4-Chloromethyl 3,5-diacetyl-1,4-dihydro 2,6-dimethylpyridine (14; R=COMe, R'=CH_2Cl).

Acetylacetoneamine ($CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{NH}{\overset{\|}{C}}-CH_3$) (10g) was dissolved in benzene (10 ml) at room temperature. 1,2-dichloroethyl ethyl ether (10 ml) was added and the solution stirred at room temperature. The solution gradually turned deep orange. Water (20 ml) was added and the mixture filtered. The yellow precipitate was collected (3.1g) and crystallised from chloroform. (m.p. 149-150° (decomp.) n.m.r. spectrum ($CDCl_3$) showed resonances at τ=3.17 (singlet, broad)NH; τ=5.67 triplet (J=6.5 c/sec proton at C_4; τ= 6.73, doublet (J=6.5 c/sec) $-CH_2Cl$; τ=7.63 and 7.65, singlets, $COCH_3$ and 2,6-CH_3.

Dimethyl 4-chloromethyl-1,4-dihydro-1,2,6-trimethylpyridine-3,5-dicarboxylate(21).

Methyl β-methylaminocrotonate[58] (51.6g) and 1,2-dichloroethyl ethyl ether (48.4 ml) were dissolved in benzene (130 ml). The temperature rose during

30 minutes and was kept at about 70° by cooling. After two hours the precipitated methylammonium chloride was separated and washed with benzene (2 x 15 ml). The combined organic phase was washed quickly with water (4 x 10 ml) dried over magnesium sulphate; then filtered and concentrated by vacuum evaporation. Petroleum ether (b.p. 40-60°) was added and a crystalline product was formed (27.5g). The product was recrystallised from benzene. m.p.110-111°.

Infrared spectrum ($CHCl_3$) had bands at 1695 cm^{-1} and 1640 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) contained the following bands:

triplet, (J=5.75 c/sec.), τ=5.59 (proton at C_4), singlet τ=6.20 ($COCH_3$), doublet (J=5.75 c/sec.) τ=6.66 (CH_2Cl), singlet τ=6.77 ($N-CH_3$), singlet τ=7.51 (CH_3 at C_2 and C_6).

4-Chloromethyl-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (14; R=CN, $R'=CH_2Cl$).

The modified method according to Bullock and Gregory[59] was employed. β-Aminocrotononitrile (5g) was melted and then cooled almost to crystallisation. 1,2-dichloroethyl ethyl ether (5.04 g) was added followed immediately by water (30 ml). After the reaction had subsided, the mixture was warmed on the steam bath for 5 min, cooled and filtered. The product was crystallised from aqueous ethanol. m.p. 178-179° (lit.[59] 178-180°).

Diethyl 4-thiocyanatomethyl-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylate (14; R=CO_2Et, R'=CH_2SCN).

The chlorocompound (14; R=CO_2Et, R'=CH_2Cl) (6.0g) and ammonium thiocyanate dried in vacuum desiccator (1.54g) were heated with stirring in absolute ethanol (100 ml) under reflux. A precipitate of ammonium chloride appeared after 30 minutes. Refluxing was continued for one hour more and then the mixture was allowed to cool. The ammonium chloride precipitate was filtered off and washed twice with small amounts of ethanol (2 x 10 ml). The filtrate was concentrated to one third its volume by evaporation under vacuum with slight warming, cooled, excess water added and allowed to stand. The precipitate formed was filtered and washed several times with water. The filtrate, on standing overnight deposited another crop of crystals, total yield (5.7g, 88%). The product when recrystalised from hexane-benzene mixture formed colourless needles. m.p. 103-104°. Ultraviolet data given in Table VIII.

Infrared spectrum showed maxima ($CHCl_3$) at 970, 1020, 1045, 1105 (S), 1160, 1175, 1277, 1305 (m), 1330, 1375, 1385, 1470 (s), 1625, 1657 (m), 1690 (s), 2155, 2900, 2924, 2968, 3324 and 3436 cm^{-1}.

Nuclear magnetic resonance spectrum of the compound in chloroform had the following bands:

(1) a singlet, τ= 3.65 (N-H),

(2) a triplet τ= 5.60 (proton at C_4) superimposed on a quartet τ=5.75 (J=7C/sec.) ($-CH_2-$ of ethyl ester).

(3) a doublet, (J=4.5 c./sec) τ=6.93 ($-CH_2SCN$),

(4) a singlet τ=7.65 (methyl groups at C_2 and C_6),

(5) a triplet, (J= 7 c/sec), τ= 8.68 (CH_3 of ethyl ester).

Dimethyl 4-thiocyanatomethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (14; R=CO_2Me; R'=CH_2SCN).

When ammonium thiocyanate was used, reaction was not complete even after refluxing for 4 hours. The preparation was therefore repeated using barium thiocyanate.

Chlorocompound (14; R=CO_2Me, R'=CH_2Cl) (1.3 g) and anhydrous barium thiocyanate (1.4g) were heated under reflux with ethanol (40 ml) for 2 hours with stirring to prevent bumping. Barium chloride precipitated after 15 minutes heating.

After cooling and following the procedure for the diethyl ester, a product (1.3g;93%) was obtained which could be recrystallised from a mixture of benzene and ethanol first and then, from benzene m.p. 175-176°. Infrared spectrum (KBr disc) had bands at 3320, 3222 (NH); 2135 (SCN); 1695 (CO_2Me) and 1655 cm^{-1}. n.m.r. spectrum (d_6DMSO) had signals at τ=0.94 singlet, broad (NH); τ=5.76, triplet, J=4.5 C/sec (4-nuclear proton); τ=6.35, singlet (CO_2CH_3); τ=7.05, doublet, J=4.5 C/sec ($-CH_2SCN$) and τ=7.74, singlet (2 and 6 methyl groups).

4-Thiocyanatomethyl-1,4-dihydro-2,6-dimethyl-3,5-diacetylpyridine (14; R=COMe, $R'=CH_2SCN$).

Modification of the previous method was necessary because the compound reacted with the solvent also when ethanol was used.

Chlorocompound (14; R=COMe, $R'=CH_2Cl$) (0.5g), anhydrous barium thiocyanate (0.5g) and acetonitrile (30 ml) were heated under reflux for 2 hours; after cooling and filtration the precipitate was washed with a small quantity of acetonitrile. The solvent was removed by evaporation under vacuum. Benzene (10 ml) was added to the residue which was heated on a steam bath and then treated with alcohol drop by drop until most of the residue dissolved. The insoluble part was removed by filtration while hot and the filtrate allowed to cool. Yellow needle shaped crystals were formed (0.36 g; 70%). On recrystallisation from benzene-alcohol mixture the product had m.p.169-170°.

Infrared spectrum (KBr disc) contained bands at 3260, 3155 cm^{-1}. (NH); 2140 (SCN); 1665 (COMe) and 1600 cm^{-1}. n.m.r. spectrum showed the following resonances in deuterated dimethyl sulphoxide (DMSO) solution. Singlet τ= 7.71, intensity 12 (3,5-$COCH_3$ and 2,6-CH_3 superimposed on each other), doublet τ= 7.16 (J=6/C/sec.) -CH_2-SCN, triplet τ= 5.71 (J=6 C/Sec.) 4-nuclear proton, singlet (broad) τ= 0.85.

Dimethyl 4-thiocyanatomethyl-1,4-dihydro-1,2-6-trimethyl-pyridine-3,5-dicarboxylate (21-CH_2SCN).

Chlorocompound[21] (1g) and anhydrous barium thiocyanate (1g) were mixed with absolute ethanol (25 ml) and kept in a bath at 55° with stirring. Very soon barium chloride precipitated and the solution turned reddish brown. After 5 hours the mixture was cooled, filtered and the residue washed with a small quantity of ethanol. The solvent was then removed by evaporation under vacuum, (20 ml) water was added and the mixture extracted with ether (3 x 10 ml). The extract was washed once with a small quantity of water, dried with magnesium sulphate, filtered and evaporated when a brown oil was formed which crystallised on standing for a few days. Cyclohexane (20 ml) was added to the residue in the flask, heated in a bath at 55°-60° and benzene was added drop by drop until the crystals dissolved. A small amount of brown viscous matter remained undissolved and the clear solution was decanted off and allowed to cool. The product (0.5g, 46%) when recrystallised from cyclohexane-benzene mixture formed prismatic crystals. m.p. 88-89°. Important bands in infrared spectrum ($CHCl_3$) were 2145 (SCN), 1688 (CO_2Me) cm^{-1}. n.m.r. spectrum ($CDCl_3$) had the following bands: triplet (J=5.5 C/sec) τ=5.6 (nuclear proton); singlet τ= 6.21 (CO_2CH_3), singlet τ= 6.75 (N-CH_3), doublet (J=5.5 C/sec.) τ=7.12 (-CH_2SCN), singlet τ= 7.48 (2 and 6 methyl groups).

Diethyl 4-selenocyanomethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (14; R=CO_2Et, R'=CH_2SeCN).

Chlorocompound (14; R=CO_2Et, R'=CH_2Cl) (1g) and potassium selenocyanate (0.8g) were refluxed in acetonitrile (50 ml) with stirring for 2 hours. The solution was cooled, and filtered. The precipitate was washed with acetonitrile and the bulk organic phase evaporated under vacuum with gentle warming. The oil obtained crystallised on standing overnight. Hexane (20 ml), was added and the mixture was heated on a steam bath. Benzene was added drop by drop until most of the product dissolved. Filtration of the insoluble particles (unreacted potassium selenocyanate) followed by cooling gave colourless needles (0.55 g; 44.7%). Recrystallisation from hexane-benzene mixture gave a product m.p. 100-101°.

Infrared spectrum ($CHCl_3$) had bands at 3420 (NH), 2140 (SeCN) and 1685 cm^{-1} (CO_2Et). The n.m.r. ($CDCl_3$) spectrum was similar to that of the corresponding thiocyanate compound. Singlet (broad) τ=3.95 (NH), triplet (τ=5.66 superimposed on a quartet τ=5.79 (J= 7 C/sec. CH_2 of ethyl ester), doublet τ=6.79 (J=5 C/sec. CH_2-SeCN), singlet τ=7.67 (2 and 6 CH_3), triplet (J= 7 C/sec.) τ= 8.7 (CH_3 of ethyl ester).

Found: C,48.22; H, 5.47; N, 7.44; $C_{15}H_{20}N_2O_4Se$ requires C,48.52; H,5.43; N, 7.55.

Reaction of thiocyanate compound with Raney nickel.

The thiocyanate (14; R=CO_2Et, R'=CH_2SCN) compound (50 mg) and Raney nickel W_2 (0.2g) were refluxed in ethanol (10 ml) for 4 hours. The solution was filtered, treated with water until a turbidity was formed and allowed to stand when white platelets were formed (23 mg). Recrystallisation from aqueous ethanol gave crystals m.p. 128-130 undepressed an admixture with an authentic sample (lit.[60,61] 127-129°, 131°).

The compound showed fluorescence in solution and in the crystalline state.

Preparation of iso-thiuronium picrates of 4-chloromethyl 1,4-dihydropyridines [14; R'=CH_2-S-C(=NH_2)-NH_2 $^{+}_{-}$ $O.C_6H_2(NO_2)_3$]

The chlorocompound (R'=CH_2Cl) (1.5g) and thiourea (1.5g) were heated under reflux in ethanol (25 ml) for 3-4 hours, picric acid (1.5g) was added and the mixture was, warmed until a clear solution was obtained. Crystals deposited on cooling the solution.

The time required for reaction, yield, melting points and elemental analyses are given in Table IX.

n.m.r. spectra of the iso-thiurourum picrates. Solvent d_6DMSO.

Spectra of the dihydropyridine part of the picrates were very similar to those of the parent chlorocompound with slight changes in chemical shifts.

3,5-Diethyl ester compound (14; R=CO_2Et).

τ=0.87 (S, broad; NH), 1.06 (S, broad; NH_2), 1.3 (S; benzene proton), 5.65 (t; superimposed on a quartet; 4-H), 5.8 (quartet; J=7 C/Sec) CH_2 of ethyl ester), 6.93 (d; J=5.5 C/Sec; $-CH_2-S$), 7.72 (S;C-CH_3), 8.67 (t; J=7 C/Sec; ester CH_3).

Dimethyl ester compound (14; R=CO_2CH_3).

τ=0.86 (s,broad; NH), 1.08 (S, broad; NH_2), 1.32 (S; benzene proton), 5.78 (t; J=5.5 C/Sec; 4-H), 6.29 (S; ester CH_3), 6.92 (d; J=5.5 C/Sec; $-CH_2-S$), 7.72 (S, C-CH_3).

N-methyl-3,5-dimethyl ester compound (14; N-CH_3; R=CO_2Me).

τ=1.06 (S, broad; NH_2), 1.32 (S; benzene protons), 5.77 (t; J=6.5 C/Sec, 4-H), 6.29 (S; ester CH_3), 6.61 (S; N-CH_3), 7.06 (d; J=6.5 C/Sec; $-CH_2-S-$), 7.54 (S; C-CH_3).

3,5-Diacetyl compound (14; R=COMe).

τ = 0.72 (S, broad; NH), 1.02 (S, broad; NH_2), 1.31 (S; benzene protons), 5.73 (t; J=6.5 C/Sec; 4-H), 7.10 (d; J=6.5 C/sec; $-CH_2-S-$), 7.67 (S; C-CH_3 and CO. CH_3 superimposed on each other).

Reaction of iso-thiuronium picrate with sodium bicarbonate.

1.0 g of the iso-thiuronium picrate (R=CO_2Et) was suspended in water and heated on a steambath. Ethanol was then added until the compound just dissolved completely and sodium bicarbonate added in small amounts until there

was no more vigorous effervescence and the solution turned orange. On cooling, a very small amount of precipitate was formed.

The product showed the typical ultraviolet spectrum of dihydropyridines λ_{max} 230 and 345 mμ.

n.m.r. spectrum in $CDCl_3$ did not show any thiol proton. τ=4.02 (S, broad; NH), 5.62 (t; superimposed on a quartet; 4-H), 5.76 (q; $-CH_2$ of ethyl ester), 7.25 (d;$-CH_2-$)7.67 (S; $C-CH_3$), 8.73 (t; CH_3 of ethyl ester).

Analysis for elements was not done because of the difficulty in getting a sufficiently pure sample.

Reaction of 4-H azepine (19) with ammonium thiocyanate.

The azepine was prepared by the method of Anderson and Johnson.[26]

A solution of 4-chloromethyl-1,4-dihydropyridine (2.5 g) in ethanol (75 ml) was mixed with potassium cyanate (1.4g) and the mixture heated under reflux for 3 hours on the water bath. After filtering, part of the solvent was removed by evaporation under vacuum. The solution was cooled, diluted with ether (30 ml) treated with water (30 ml) and the ethereal layer separated. The ether extract was washed with a small amount of water, and dried with anhydrous magnesium sulphate. After filtering the solvent was removed under reduced pressure. The golden-coloured oil was then distilled under reduced pressure. The sample gave ultraviolet and n.m.r. spectra as reported.

50 mg of the above oil was mixed with ethanol (10 ml) and ammonium thiocyanate (50 mg) and heated under reflux for 8 hours. The mixture was cooled and diluted with excess water. On standing for sometime colourless needles were formed (35 mg) which were recrystallised from hexane-benzene. The product was shown to be 4-thiocyanatomethyl 1,4-dihydropyridine (14; R=CO_2Et, R'=CH_2SCN) by mixed melting point and comparison of infrared spectra.

The experiment was repeated by keeping the mixture at room temperature, but the ultraviolet spectrum showed no change even after a few days.

Reaction of chloromethyl-1,4-dihydropyridines (14; R'=CH_2Cl) with urea.

The chloromethyl 1,4-dihydropyridine (14; R=CO_2Et, R'=CH_2Cl) (3g) and urea (2g) were mixed with ethanol (60 ml) and heated under reflux. Progress of the reaction was followed by the ultraviolet spectrum. After 2 hours the solution was cooled and concentrated by removing more than half the solvent under vacuum. Excess water (100 ml) was added and the solution allowed to stand. The precipitate formed was filtered and washed with water (2.0g). Recrystallisation from cyclohexane gave a product, m.p. 132-133°.

The alcohol in the filtrate was removed by vacuum distillation with warming. The solution was cooled, neutralised with hydrochloric acid and extracted with ether three times. The combined ether extract was washed once

with water, dried with anhydrous magnesium sulphate and evaporated under vacuum. A pleasant smelling oil (which gave a light red colour with ferric chloride) was formed. On standing for 2 days crystals were formed. The oil was removed by suction and also by pressing between filter papers. The solid was crystallised from aqueous ethanol and then sublimed. m.p. 76-77° (lit. 77-78°). It showed all the spectral features reported for ethyl 2-methyl-pyrrole-3-carboxylate.

Reaction of N-methyl chlorocompound (21) with urea.

The chlorocompound (0.2 g), urea (0.2 g) and ethanol (10 ml) were heated under reflux for 2 hours and the product separated by adding excess water. It was crystallised from cyclohexane. By mixed melting point and comparison of infrared spectra it was shown to be the same compound as that obtained from the N-H compound (14; R=CO_2Et, R'=CH_2Cl).

Dimethyl-2,6-dimethyl-4,4a-H, pyrazolo-[2,3-a] pyrid-7 one 3,5-dicarboxylate.

The same method as for the diethyl ester compound was used. The product was recrystallised from ethanol. m.p. 210-212°.

2,6-dimethyl-3,5-diacetyl-4,4a-H pyrazolo [2,3-a] pyrid-7 one.

1 g of chlorocompound (R=COMe; R'=CH_2Cl) and urea (1g) were heated under reflux with ethanol for 30 minutes, part of the solvent was removed by vacuum evaporation and the product was precipitated by adding excess water, (0.42g). Recrystallisation from aqueous ethanol gave a product m.p. 215-216°.

Infrared ($CHCl_3$) contained bands at 937, 1130, 1310 (m), 1335, 1355, 1375 (m), 1400, 1622, 1700, 3100, 3210, 3405 cm^{-1}.

n.m.r. spectrum ($CDCl_3$) showed resonances at τ = 1.32 (S, broad; NH), 5.25 (q, showing multiple splitting, X of ABX), 6.72 (q,) another set of resonances superimposed on a singlet at 7.32, 7.66 (S; $COCH_3$), 7.78 (S; split; $C-CH_3$).

Ultraviolet spectral data given in Table XI.

Reaction of pyrazolo-pyridone compound with nitrous acid.

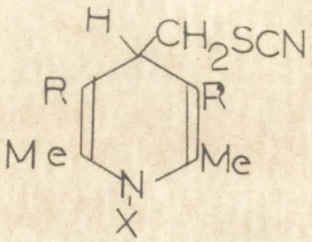
The compound (1g) was dissolved in acetic acid (25 ml) and a saturated solution of sodium nitrite containing 1g was added in small amounts with stirring. After the addition the mixture was stirred for 4 hours and then heated on a water-bath for 15 minutes, cooled, and carefully neutralised with a saturated solution of sodium carbonate. The solution turned dark red and a gum was formed. Products from two such experiments were combined and crystallised from benzene (0.26 g).

The recrystallised product was found to be impure and it was therefore dissolved in benzene-chloroform (1;1) and chromatographed using a neutral alumina column. Eluents used were benzene-chloroform, chloroform and ethanol. No product was eluted by the first two; a yellow compound was eluted by ethanol. This was recrystallised from ethanol when yellow cubes were obtained. m.p. 215-217°. Calculated for $C_{15}H_{17}N_3O_7$, C, 51.28; H, 4.88; N, 11.96; Found, C, 51.36; H, 5.03; N, 11.99. Molecular weight (Rast method) 340.

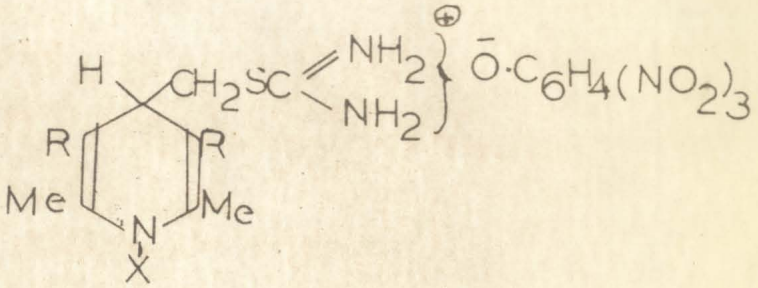
Ultraviolet spectrum (ethanol 95%) had λ_{max} 210, 242 mμ. ε_{max} 23,600, 10,500.

Infrared spectrum (KBr disc) showed bands at 3,200, 1750, 1725 (s), 1685, 1625, 1507, 1435, 1235, 1180 and 1100 cm^{-1}.

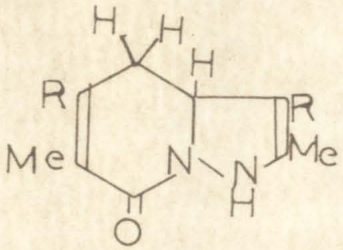
n.m.r. spectrum ($CDCl_3$ and trifluoracetic acid) had absorptions at τ= -0.1 (S, broad; NH), 5.60 (q; CH_2 of ethyl ester), 5.63 (q; CH_2 of ester), 7.16 (S, C-CH_3), 7.56 (S,C-CH_3), 8.65 and 8.67 (two triplets; CH_3 of two nonequivalent ethyl ester groups).



(35)



(36)



(37)

TABLE VIII

Elemental analysis of 4-thiocyanatomethyl-1,4-dihydropyridines[35]

Compound	Molecular Formula	Calculated				Found			
		C	H	N	S	C	H	N	S
R=CO_2Et, X = H	$C_{15}H_{20}N_2O_4S$	55.54	6.22	8.64	9.89	55.44	6.25	8.78	10.00
R=CO_2Me, X=H	$C_{13}H_{16}N_2O_4S$	52.68	5.44	9.46	10.82	52.67	5.36	9.63	10.71
R=COMe, X=H	$C_{13}H_{16}N_2O_2S$	59.06	6.10	10.60	12.13	59.16	6.16	10.63	12.36
R=CO_2Me, X=Me	$C_{14}H_{18}N_2O_4S$	54.17	5.84	9.03	10.33	54.43	5.89	8.98	10.27

TABLE IX

Iso-thiuronium picrates of 4-chloromethyl 1,4-dihydropyridines (36)

yields, melting points and elemental analyses

Compound	Time req'd. for reaction	Yield %	m.p.	Molecular formula	Calculated			
					C	H	N	S
R=CO_2Et, X=H	3 hours	88.6	204-205°	$C_{21}H_{26}N_6O_{11}S$	44.21	4.59	14.73	5.62
R=CO_2Me, X=H	3 "	66.7	218-220°	$C_{19}H_{22}N_6O_{11}S$	42.06	4.09	15.49	5.91
R=COMe, X=H	2 1/2	77.2	222-224° (decomp.)	$C_{19}H_{22}N_6O_9S$	44.70	4.35	16.47	6.28
R=CO_2Me, X=CH_3	8 1/2	71.8	195-197° (decomp.)	$C_{20}H_{24}N_6O_{11}S$	43.16	4.35	15.10	5.76
					Found			
					C	H	N	S
					44.40	4.71	14.70	5.81
					42.23	4.17	15.42	6.10
					44.85	4.55	16.27	6.40
					43.30	4.42	15.03	5.65

TABLE X

Elemental analyses of urea reaction products from chloromethyl 1,4-dihydropyridines (37)

Compound	Molecular formula	Calculated			Found		
		C	H	N	C	H	N
R=CO_2Et	$C_{15}H_{20}N_2O_5$	58.43	6.54	9.09	58.38	6.61	9.11
R=CO_2Me	$C_{13}H_{16}N_2O_5$	55.71	5.75	10.00	55.79	6.07	10.22
R=COMe	$C_{13}H_{16}N_2O_3$	62.88	6.50	11.29	62.78	6.49	11.37

TABLE XI

Ultraviolet spectral data for urea reaction products from chloromethyl-1,4-dihydropyridines (37)

Solvent Ethanol (95%)

Compound	ε_{max} m.μ.	ε_{max}
R=CO_2Et	263, 310	26,200, 7,150
R=CO_2Me	262, 310	25,000, 7,000
R=COMe	283, 330	24,270, 8,700

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