THE FRIEDEL-CRAFTS ISOPROPYLATION OF 2-SUBSTITUTED PYRROLE DERIVATIVES

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THE FRIEDEL-CRAFTS ISOPROPYLATION OF 2-SUBSTITUTED PYRROLE DERIVATIVES

A Thesis

by

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ABSTRACT[*]

The Friedel-Crafts isopropylations of methyl 2-pyrrolecarboxylate, 2-acetylpyrrole, and 2-pyrrolecarboxaldehyde have been investigated. Various Lewis acids were employed as catalysts and solvents included carbon disulfide, ethylene chloride, and nitromethane. The changes in product distribution and reaction rate with variations in substrate, solvent, catalyst and conditions of reaction are discussed.

Under normal reaction conditions (carbon disulfide solvent, aluminum chloride catalyst, 50°C.), the alkylation of methyl 2-pyrrolecarboxylate gave the 4-isopropyl, 5-isopropyl, and 4,5-diisopropyl-2-esters, all of which have been isolated and identified. It was found that while the 4-isopropyl-2-ester rearranged to the 5-isopropyl-2-ester under the reaction conditions, neither the latter nor the 4,5-diisopropyl-2-ester underwent any change. The behaviour of 2-acetylpyrrole under Friedel-Crafts conditions was similar to that of the ester but alkylation was more complete and occurred predominantly at the 4-position giving much less of the other products. Also, the 4-isopropyl group did not rearrange as readily as that of the ester. In marked contrast to the other substrates, 2-pyrrolecarboxaldehyde underwent reaction very rapidly to give only the 4-isopropyl-2-carboxaldehyde which was shown not to rearrange.

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[*] Some of the present work dealing with the isopropylation of methyl 2-pyrrolecarboxylate has been published recently (1).

Ultraviolet, infrared, and nuclear magnetic resonance spectra of the various pyrrole derivatives are discussed. N. m. r. studies indicate that substantial changes in the electron density pattern of the pyrrole ring are brought about by donor-acceptor complexing between the Lewis acid and the carbonyl oxygen of the substrate molecules. The relative strength of complexing along the series: aldehyde > ketone > ester, is considered to provide a partial explanation of the product distributions observed in Friedel-Crafts isopropylation.

Molecular orbital calculations of localization energies for electrophilic attack on 2-pyrrolecarboxaldehyde have been found to account satisfactorily for the results which have been observed in nitration. As well, in agreement with experiment, the calculations indicate that complexing of the carbonyl oxygen with Lewis acids, as in the Friedel-Crafts reaction, should greatly favor substitution at the 4-position.

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1. INTRODUCTION

In 1877 Charles Friedel and James Mason Crafts produced amylbenzene from a reaction between amyl chloride and benzene in the presence of anhydrous aluminum chloride (2). The generality of the reaction and its usefulness as a synthetic method rapidly became apparent and the interest accorded it by chemists is reflected in the voluminous literature covering innumerable aspects of the theory and application of the Friedel-Crafts reaction.

The term "Friedel-Crafts reaction" is generally taken to mean the alkylation or acylation of an aromatic hydrocarbon and in this thesis, unless otherwise specified, will refer to the former. However, as Olah has pointed out (3), broadly speaking, reactions of the Friedel-Crafts type include acid catalyzed polymerization, halogenation, nitration, dealkylation, disproportionation, and migration and internal rearrangement of alkyl groups among others.

Electrophilic substitution is the most characteristic chemical reaction of aromatic compounds. Since the Friedel-Crafts reaction is typical of reactions of this class, there will follow an outline of the nature of aromaticity and the theory of electrophilic substitution with particular reference to heteroaromatic reactivity.

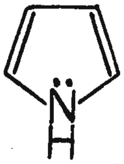
2. ELECTROPHILIC SUBSTITUTION IN HETEROAROMATIC COMPOUNDS

(i) Aromaticity:

Historically, a number of physical and chemical properties have been associated with aromatic character. These have included such vague generalities as the fragrant odours of many natural products derivable from benzene and its homologues and the smoky flame observed when these compounds are burned. As well there have been the more important, but no more definitive, observations that aromatic compounds in general, while often resistant to many reagents which will normally attack points of unsaturation, are fairly readily substituted by electrophiles, and that many condensed polycyclic aromatics possess carcinogenic activity. Perhaps the most valuable criterion of aromatic character lies in the so-called ring current effect (4), which arises in the presence of a magnetic field and which manifests itself in the low field chemical shifts observed in the proton magnetic resonance spectra of aromatic molecules, including the heterocycles discussed in this thesis.

The earliest important contribution to the problem of bonding in aromatic systems was that of Kekulé (5) in whose dynamic model lay the first explanation of the equivalence of the six positions of benzene. Later, the electronic theory of valence, the formulation of quantum mechanics, and the development of the molecular orbital (m.o.) and valence bond (v.b.) theories led to the well known Hückel representation (6). From the m. o. theory has arisen what is called the "4n+2 rule" which states, in effect, that cyclic, fully conjugated systems will have aromatic character if they possess 4n +2 π-electrons. This, of course, is directly connected with the idea of the "aromatic sextet" and Streitwieser (7) has discussed the matter in considerable detail.

Among the aromatic systems possessing six π-electrons are the five membered heterocycles, pyrrole (I), furan (II), and thiophene (III), which are isoelectronic with the cyclopentadienide ion (IV). In each case the aromatic sextet is made up of contributions of one p-electron each from the carbon atoms and two p-electrons from the heteroatom. Attention will be focussed mainly on pyrrole and its derivatives with an electron withdrawing group in the 2-position.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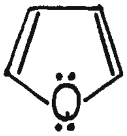
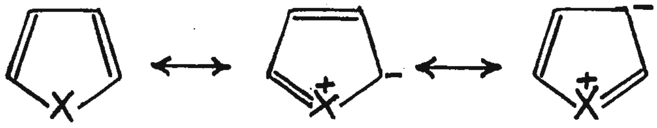

II


III


IV

(ii) <u>Heteroaromatic reactivity:</u>

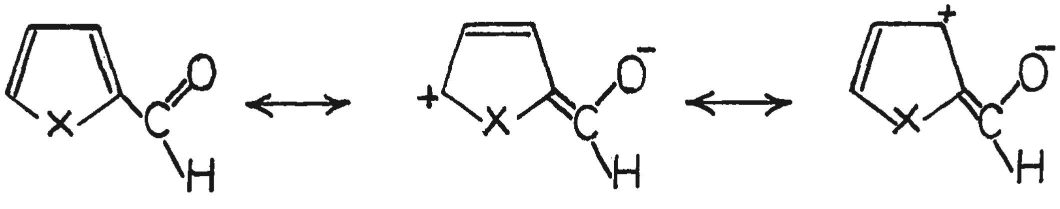
The simple five-membered heteroaromatics may be represented as resonance hybrids of structures V, VIa and VIb


V VIa VIb

X=NH,O,S.

where V is the major contributor. Of the other two structures, VIais the more important as it involves a smaller charge separation and hence lower energy than VIb. This simple representation suggests that the π-electrons of the heteroatom are partially delocalized into the ring, thereby increasing the electron density at the carbon atoms and, in particular, making the α-positions the more susceptible to electrophilic attack. This is borne out by experiment, as for example, the protonation (8), nitration (9, 10) and acylation (11) of pyrrole; the acylation of furan (12); and the sulphonation, nitration and acylation of thiophene (ref.12, page 108), all occur predominantly or exclusively at the 2-position.

Pyrrole, furan, and thiophene derivatives having an electron withdrawing (-R) group in the 2-position are still fairly reactive to electrophilic attack. In terms of simple resonance theory, the orientation in such systems is expected to be influenced mainly by (a) the α-directing influence of the heteroatom, and by (b) the "meta" or 4-directing influence of the 2-substituent through deactivation of the 3- and 5- positions as illustrated by the v.b. structures VII ,VIII and IX for the 2-carboxaldehyde. It is to be expected that the product distribution, reflecting the relative importance of these effects, will favour 4-substitution for a strong -R group but give greater amounts of the 5-substituted product as weaker -R groups



VII VIII IX

X=NH, O,S.

are used. This general trend has been observed by Tirouflet and Fournari (10) in the nitration of several 2-substituted pyrroles and thiophenes. Bromination of 2-pyrrolecarboxaldehyde and methyl 2-pyrrolecarboxylate has been shown to give predominantly the 4-bromo derivative (13, 14) while the less selective chlorination of methyl 2-pyrrolecarboxylate gave approximately equal amounts of the 4- and 5-chloro-2-esters (14). However bromination of 2-thiophenecarboxaldehyde has been reported by Gronowitz (15) to give almost exclusively the 5-monobromo product. He has attributed this result to the over-riding α-directing influence of the heteroatom and suggested that in the nitration reaction, 4-substitution may have been brought about by an enhanced -R effect of the aldehyde group caused by protonation of the carbonyl oxygen.

TABLE I (10)

Nitration of 2-substituted heterocycles

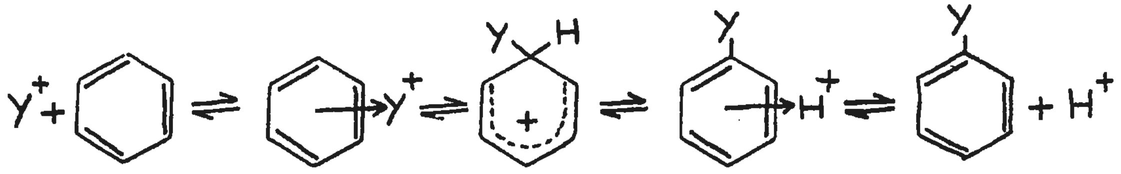
	% 4-nitration	
2-substituent	thiophene series	pyrrole series
NO_2	80	67
CHO	75	59
$CHCH_3$	52	57
CN	43	42
COOH	31	55
$CH(OCOCH_3)_2$	14	-
H	5	9

Various theoretical treatments corroborate the simple resonance picture for the unsubstituted five-membered heterocycles. For example, m. o. calculations by Longuet-Higgins and Coulson (16) on pyrrole show the π-electron density to be higher at the α- than at the β-positions, while localization energies calculated by Brown (17, 18) predict the predominance of α-substitution in electrophilic attack on pyrrole. However, the literature records no previous application of the Huckel m. o. method to 2-substituted pyrroles.

(iii) <u>Electrophilic substitution:</u>

The present outline of the theory of electrophilic substitution is concerned mainly with nitration; modifications will be introduced later when the mechanism of the Friedel-Crafts reaction is discussed in detail.

Electrophilic substitution is considered to involve two steps:* first, formation of the electrophile, Y^+, and second, reaction of Y^+ with the aromatic substrate to form the products. The second step which probably involves σ- and π-complex intermediates is often represented by an analogous reaction scheme and free energy profile to that shown here for benzene.



X XI XII

π-complex σ-complex π-complex

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[*] For a discussion of the kinetics of electrophilic substitution reactions see ref. (19).

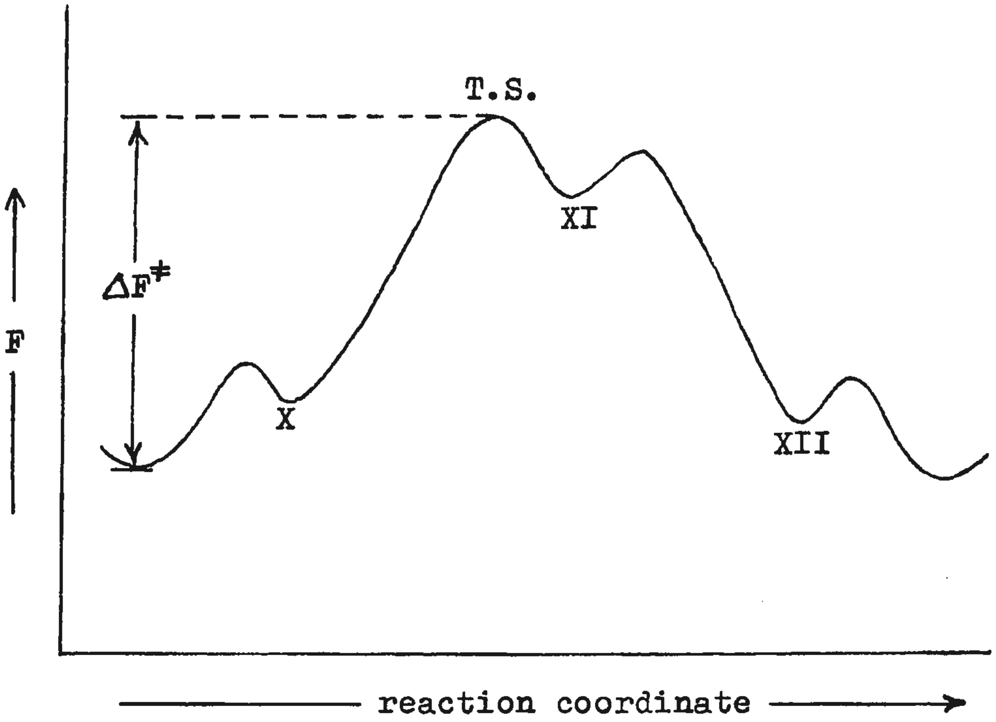
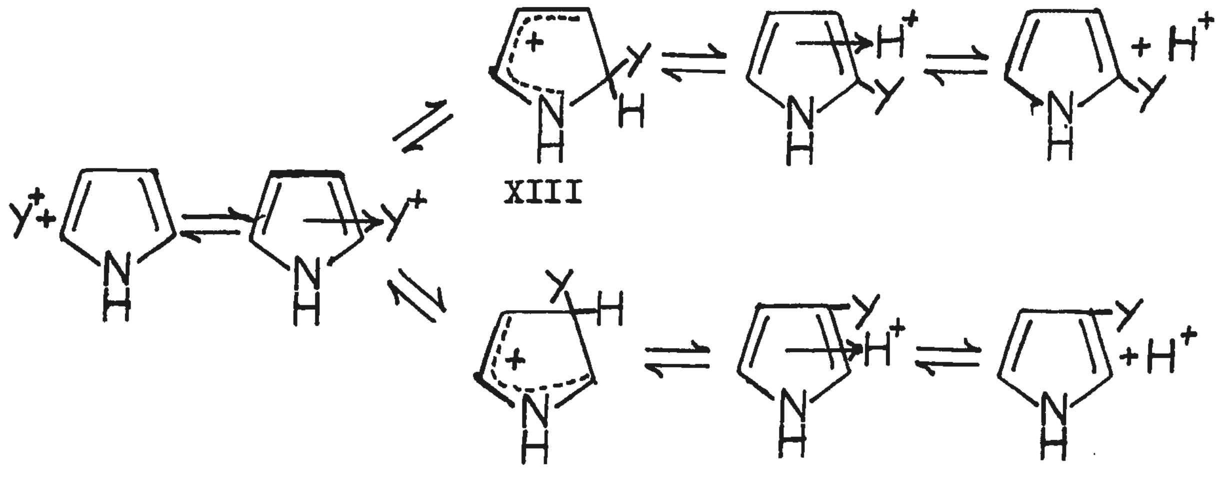


Figure 1. Free energy profile for aromatic substitution (ref. 6, page 321).

It is evident that for such a molecule as pyrrole where there are two different positions available for substitution, there will be two rate determining transition states (T. S.) of different energies and that the relative amounts of the two possible products will depend on the relative rates of reaction at the two positions, i.e. on the relative free energies of activation, $\Delta F^{\ddagger}$. By Hammond's postulate (20), the σ-complex or Wheland intermediate, XI, should resemble the T. S. in energy and is, therefore, chosen as a model for the T. S. In effect, one carbon atom is assumed to take on a tetrahedral configuration, thereby being taken out of conjugation with the π-electron system.

By analogy with the foregoing discussion for benzene, electrophilic attack on pyrrole may be represented as follows:



XIII

XIV

π-complex σ-complexes π-complexes

Thus a computation of the relative free energies of activation for α- and β- attack involves an evaluation of the differences in energy between pyrrole and the σ-complexes XIII and XIV respectively.

From the postulates of absolute rate theory (20), the rate constant, k_r, for a reaction is given by the expression

$$k_r = \kappa \frac{kT}{h} e^{-\Delta F^{\ddagger}/RT} \qquad ..(1)$$

where the transmission coefficient, κ , is taken as unity and k, T, h, R, and $\Delta F^{\ddagger}$ have their usual significance. If $k_r(\alpha -)$ and $k_r(\beta -)$ refer to the rate constants for electrophilic substitution at the α- and β- positions of pyrrole respectively, then the relative rates of reaction are given by equation (2).

$$\log\left(\frac{k_r(\alpha-)}{k_r(\beta-)}\right) = \frac{\Delta F^{\ddagger}(\beta-) - \Delta F^{\ddagger}(\alpha-)}{2.303\ RT} \qquad ..(2)$$

And if the product distribution is kinetically controlled, the relative percentages of products may be substituted for the rate constants giving equation (3).

$$\log\left(\frac{\%\alpha-}{\%\beta-}\right) = \frac{\Delta F^{\ddagger}(\beta-) - \Delta F^{\ddagger}(\alpha-)}{2.303\ RT} \qquad ..(3)$$

Since

$$\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad ..(4)$$

therefore $\log\left(\frac{\%\alpha-}{\%\beta-}\right) = \frac{\Delta H^{\ddagger}(\beta-) - \Delta H^{\ddagger}(\alpha-)}{2.303\ RT}$ ..(5)

$$+ \frac{\Delta S^{\ddagger}(\alpha-) - \Delta S^{\ddagger}(\beta-)}{2.303\ RT}$$

It is now assumed that the entropy of activation is independent of the nature of the substrate thus making the last term in equation (5) vanish, and that the enthalpy of activation for reaction at a particular site is equivalent to the difference in π-electron energy between the ground state and the appropriate transition state (i.e. Wheland intermediate).

Equation (5) then becomes

$$\log\left(\frac{\%\alpha-}{\%\beta-}\right) = \frac{\Delta E_{\pi}(\beta-) - \Delta E_{\pi}(\alpha-)}{2.303\ RT} \qquad ..(6)$$

This equation should enable a prediction of the relative amounts of products from a theoretical calculation of localization energies.

The foregoing assumptions, while plausible, cannot be accepted without reservation. For example, it is evident that the method requires a correlation between emperimental results measured at a finite temperature in solution using quantities calculated for a ground state and transition state models at $0^{o}K$ in the gas phase. That is, translations, rotations, and vibrations of the molecules are neglected as well as possible differences in solvation of the two transition states. The main justification for the application of the method in this form lies in the useful correlations between theory and experiment found by several authors (see, for example, ref. (7), Chapter 11). Not too much significance should be attached to small differences.

3. FRIEDEL-CRAFTS ALKYLATION

(i) General considerations:

The Friedel-Crafts reaction is considered to occur by way of a carbonium ion mechanism. Brown (22) has suggested that donor-acceptor complexing between an alkyl halide and a Lewis acid leads to formation of a polarized complex in an equilibrium with the corresponding ion pair which is dependent on the stability of the carbonium ion and the reaction conditions:

$$R\text{-}Cl + AlCl_3 \rightleftharpoons \overset{\delta+}{R}....Cl....\overset{\delta-}{AlCl_3} \rightleftharpoons R^+AlCl_4^-$$

The complex may then be attacked by available nucleophilic positions of the aromatic substrate. Olah (23) has proposed a similar mechanism for isopropylations in nitromethane solution but noted the possibility of simultaneous reaction of the complexed alkyl halide and of the ion pair with the aromatic substrate at different rates and selectivities. These descriptions are consistent with the third order kinetics observed for alkylations, the rate of reaction being proportional to the concentrations of aromatic, alkyl halide and catalyst (22, 24).

Although "anhydrous" conditions are usually specified for Friedel-Crafts reactions, it is recognized that total exclusion of moisture is a virtual impossibility. Indeed it has been found that water, in trace amounts, promotes rather than hinders reactions of the Friedel-Crafts type (e.g. 25, 26, 27,28, 29). Nenitzescu (25) considers the active species in the isomerization of saturated hydrocarbons with water promoted aluminum chloride to be $H(AlCl_3OH)$; however, the precise mode of interaction of such co-catalysts with alkyl halides and aromatic substrates has not been clearly established.

A great many Lewis acids have been employed as Friedel-Crafts catalysts, a general order of catalytic activity for some commonly used reagents being as follows (30):

$$AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > TiCl_4$$

However, the relative effectiveness of the various catalysts is very much dependent on the reaction conditions as discussed by Olah (30). The most common catalyst, aluminum chloride, is not particularly soluble in many organic solvents and thus often gives heterogeneous reaction mixtures. Aluminum bromide, while a stronger acid, is also much more soluble than aluminum chloride and often proves to be a much better catalyst. Nitroalkane solutions are sometimes used, giving milder, and homogeneous, reaction conditions with little isomerization. Carbon disulfide has been claimed to prevent isomerization (31) although quite the contrary has been observed in the present work (c.f. page40). Other solvents are chlorobenzene, ethylene chloride, and methylene chloride, as well as an excess of the aromatic hydrocarbon.

Formation of viscous "red oils" is characteristic of Friedel-Crafts reactions. These are believed to consist of ternary complexes of the form $[ArH_2]^+[AlCl_4]^-$ where the proton is σ- bonded to the ring (32). The complexed aluminum chloride is not catalytically active but the ionic "red oil" can dissolve substantial quantities of uncomplexed catalyst and thus provide a highly polar medium for reaction.

The usual considerations regarding directing effects of substituent groups predict <u>ortho-para</u> attack for alkylation of monoalkylbenzenes. However, in addition to the expected products, large amounts of the <u>meta</u>-isomers have been observed (33). The formation of this product is favoured by vigorous reaction conditions. For example, reactions catalyzed by aluminum chloride (particularly with molar or larger amounts of catalyst) carried out over long reaction times and at high temperatures lead to extensive <u>meta</u>-dialkylation.

Brown (34, 35) has attributed the relatively high proportion of <u>meta</u>-isomer found in the alkylation of monoalkylbenzenes under "non-isomerizing" conditions, to the high reactivity and consequential low (positional and substrate) selectivity of the electrophilic reagent. Olah (23, 36) has criticized the Brown treatment on a number of points. It is well known that isomerization and disproportionation often accompany alkylation reactions leading to increased amounts of the <u>meta</u>-isomer in the final product distribution (37, 38, 39); Olah considers that weakly basic solvents cannot provide non-isomerizing conditions. It is clear that if the product distribution is thermodynamically controlled (as in cases where extensive isomerization and disproportionation occur), selectivity data will be meaningless. Furthermore, it is difficult to understand why a <u>meta</u>-position in toluene should have a partial rate factor less than that for a benzene position by as much as a factor of ten (ref. 30, page 920).

(ii) Mechanism:

The question of the location of the rate determining transition state on the free-energy profile has been discussed by Olah (23) in the light of studies made on the isopropylation of toluene under "non-isomerizing" conditions using as catalyst the aluminum chloride-nitromethane complex. It is considered that for strong electrophiles the rate determining (and substrate selectivity determining) transition state resembles an oriented π-complex (Figure 2), contrary to the usual representation (Figure 3) wherein the substrate selectivity is determined by the rate determining σ-complex type transition state. In both cases the positional selectivity must be determined by a transition state resembling the appropriate Wheland intermediate. Olah considers the representation of Figure 3 to be more appropriate to electrophilic attack by weak reagents, in which case π-complex formation is expected to be a low energy process. No doubt the free energy profile will change with the nature of the reagents, and the precise formulation of the rate determining transition state will be very much a function of the particular reaction. The representation of Figure 2 in which the substrate and positional selectivities are determined separately allows explanation of the observed low substrate but high positional selectivity in the isopropylation (23) and benzylation (35) of toluene under "non-isomerizing" conditions, as well as the low partial rate factor for a toluene <u>meta</u>-position.

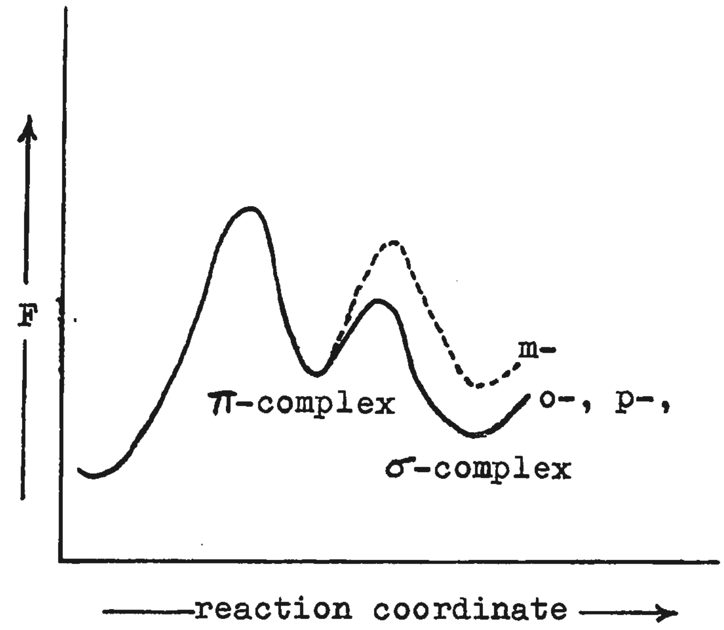


Figure 2. Free energy profile for aromatic substitution with strong electrophiles- π-complex type T. S. rate determining (23).

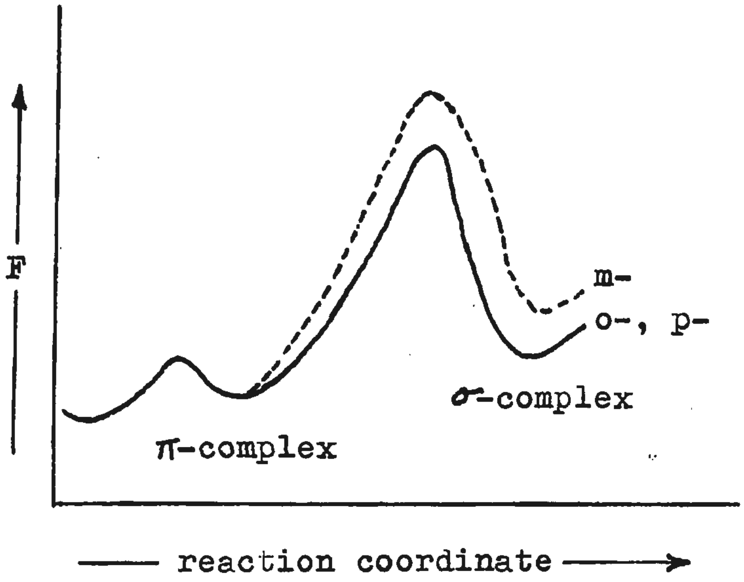


Figure 3. Free energy profile for aromatic substitution with weak electrophiles- σ-complex type T. S. rate determining (23).

Olah (23) has discussed Brown's views regarding the nature of the transition state and orientation in the products of alkylation. Brown considers that the migration of a σ-complexed group prior to deprotonation should not be regarded as an isomerization of products. However, Olah points out that even in such a case the migration is still thermodynamically influenced. Kinetically controlled alkylation may occur as well, but the relative quantities of meta-isomer formed through direct alkylation and through isomerization cannot be accurately estimated.

It should be noted that migration prior to deprotonation is essentially the same process as the isomerization which may occur in the presence of aluminum chloride and hydrogen chloride. In the latter case protonation at the ring carbon bearing the alkyl group gives the same σ-complex as formed by alkylation. Xylenes have been shown to isomerize by an intramolecular 1,2-shift mechanism with no disproportionation (40). Allen *et al.* have found that for ethyl and isopropyl groups intermolecular migration is of some importance (41, 42), while for t-butyl groups the intermolecular process is dominant (43). Studies by Olah *et al.* on the rearrangement of the diethylbenzenes (28), diisopropylbenzenes (29), and t-butyltoluenes (27) in nitromethane with water-promoted aluminum chloride as catalyst indicate that the ethyl and isopropyl groups isomerize *via* the intramolecular 1,2-shift mechanism, the t-butyl group *via* detachment as a carbonium ion, or more likely, *via* a π-type intermediate.

In the donor solvent, nitromethane, complex formation with the catalyst and conjugate acid is considered to deactivate the latter for ring protonation (σ-complex formation) thus precluding isomerization. Olah has demonstrated this point by means of an attempted isomerization of a synthetic mixture of alkyl benzenes (23). However, a question might well be raised regarding the possibility of isomerization <u>before</u> deprotonation even under "non-isomerizing" conditions. This possibility is just as applicable to Olah's systems as to Brown's. Although Olah has shown alkylations in nitromethane to be more selective than reactions in non-basic solvents, the extent of thermodynamically controlled isomerization occurring before deprotonation cannot be estimated and such isomerization cannot be distinguished from kinetically controlled direct <u>meta</u> substitution. Thus, the positional selectivity of the Friedel-Crafts reaction may be, in fact, much higher than present results seem to indicate, but how much higher has not yet been determined.

(iii) <u>Alkylation of deactivated substrates:</u>

Campbell and Spaeth (44) have investigated the isopropylation of acetophenone, methyl benzoate and benzoic acid, observing that although the yields were low, the products were largely or entirely composed of the <u>meta</u>-isomer. The selectivity shown in these cases is much greater than in the nitration of such compounds where from 10 - 30 % of the <u>ortho-</u> plus <u>para-</u> isomers is usually produced (45). This has been attributed to complexing of the carbonyl oxygen by the catalyst thereby greatly enhancing the electron withdrawing character of the substituent group. Such complexing of carbonyl compounds with Lewis acids is well established (46, 47).

Several thiophene and furan derivatives possessing a -R group in the 2-position have been alkylated in fair to good yield (48, 49, 50, 51) with alkyl halides and aluminum chloride, but there has been no previous study of the alkylation of pyrrole or any of its simple derivatives. Isopropylation of methyl 2-furoate and similar compounds was found by Gilman and Calloway (48) to produce only the 5-isomer while in the isopropylation of furfural the only product isolated was the 4-isomer in low yield (53). Spaeth and Germain (51) observed in the isopropylation of methyl 2-thienyl ketone that more than 90% of the product was the 4-isopropyl derivative in contrast to nitration (10) where approximately equal amounts of the 4- and 5-isomers were obtained.

Some of the foregoing results agree with the predictions of simple resonance theory: that in five-membered heterocycles the -R effect of the 2-substituent enhanced by complexing with the catalyst should lead to attack at the 4-position; but the results of Gilman _et al._ on the furan systems wherein alkylation gave only the 5-isomer are clearly anomalous.

4. MOLECULAR ORBITAL CALCULATIONS

(i) General theory:

In the molecular orbital (m.o.) method* the aromatic π-electrons are assumed to occupy polycentric m.o.'s, each m.o. being represented as a linear combination of atomic orbitals (a.o.'s):

$$\psi_j = \sum_{r=1}^{n} c_{jr}\varphi_r \qquad ..(7)$$

where ψ_j is the jth m.o., φ_r is the carbon 2p a.o., and c_{rj} is the coefficient of the rth a.o. in the jth m.o. The energy of each m.o. is found by applying the usual variation treatment to the Schrodinger equation in the form

$$H\psi = E\psi \qquad ..(8)$$

where H is the Hamiltonian operator and E is the energy of the m.o. Since for a conjugated system of n atoms there will be n a.o.'s and since the energy of the system is minimized with respect to each coefficient, there will result from the variation treatment, n secular equations of the form

$$\sum_{r} c_r(H_{rs}-ES_{rs})=0 \qquad ..(9)$$

where $H_{rs} = \varphi_r H \varphi_s d$

and $S_{rs} = \varphi_r H \varphi_s d$

These equations have a non-trivial solution only if the corresponding secular determinant equals zero, i.e.

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* Extensive treatments of the m.o. method are available in the literature; see, for example, references (7) and (54).

$$\begin{vmatrix} H_{11} - ES_{11} & H_{12} - ES_{12} & \cdots & H_{1n} - ES_{1n} \\ H_{21} - ES_{21} & H_{22} - ES_{22} & \cdots & H_{2n} - ES_{2n} \\ \cdots & \cdots & \cdots & \cdots \\ H_{n1} - ES_{n1} & H_{n2} - ES_{n2} & \cdots & H_{nn} - ES_{nn} \end{vmatrix} = 0 \qquad ..(10)$$

The Coulomb integral, $\alpha = H_{rr}$, gives the energy of an electron in a carbon 2p orbital, while the resonance integral, $\beta = H_{rs} = H_{sr}$, is a measure of the interaction energy between two atomic orbitals; β is usually taken to be zero for nonadjacent orbitals. From the definition of the overlap integral, S_{rs}, it is evident that for separately normalized a.o.'s, $S_{rr} = S_{ss} = 1$. Also, the assumption is usually made that $S_{rs} = 0$ for $r \neq s$, which while not strictly correct greatly simplifies the problem.

The foregoing substitutions are made and then the determinant is further simplified by dividing through by β and putting

$$x = \frac{\alpha - E}{\beta} \qquad ..(11)$$

Corresponding to this determinant is an nth degree polynomial having n real roots, x_j, whence the energies of the m.o.'s are given by

$$E_j = \alpha - x_j \beta \qquad ..(12)$$

The m.o.'s are represented as energy levels displaced above and below α as an arbitrary zero of energy as shown in Figure 4 for pyrrole.

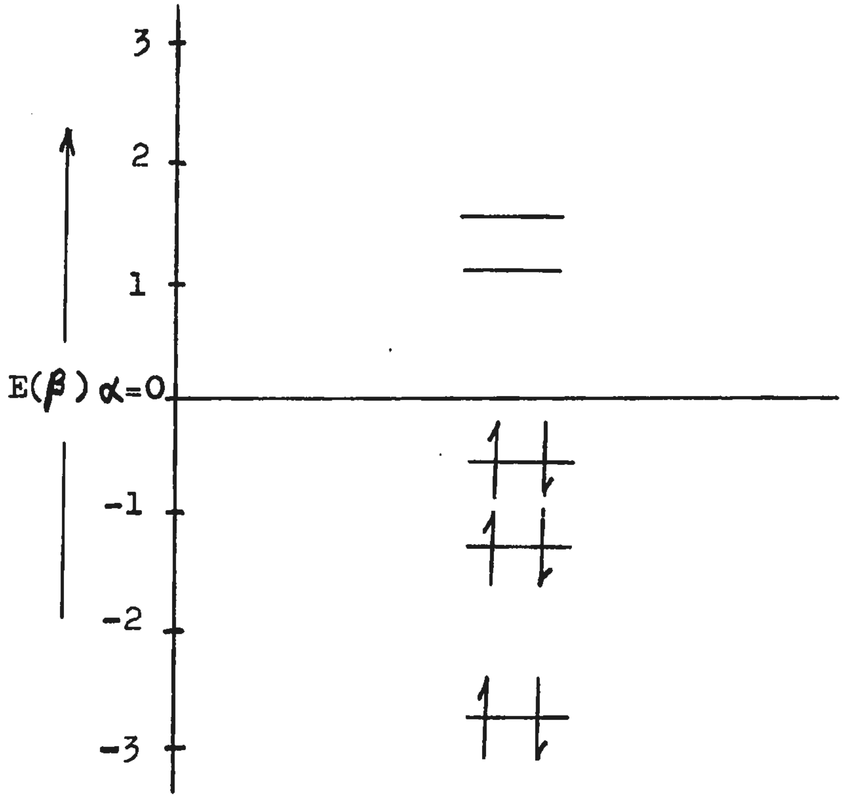

Figure 4: Molecular orbitals of pyrrole (h=2.0, h'=0.0).

Since β is negative, negative values of the roots give energy levels displaced below the energy zero, i.e. the bonding m.o.'s, while the positive roots give energy levels corresponding to the antibonding m.o.'s. The total π-energy of the system is taken as the sum of the energies of the electrons occupying m.o.'s.

It should be emphasized that α and β are empirical parameters in the theory. The integrals they represent are not usually evaluated although a value might be assigned depending on the particular application.

In setting up the secular determinant for pyrrole the same general method is employed but modifications are made to compensate for the presence of the nitrogen atom. Since nitrogen is more electronegative than carbon the appropriate Coulomb integral is made more negative by expressing it in the form

$$\alpha_N = \alpha + h \qquad ..(13)$$

where the inductive parameter, h, is usually assigned values in the range 0 to 2. Also, the carbon atoms adjacent to the nitrogen are considered to be more electronegative than the carbon atoms in benzene, so the appropriate Coulomb integral is written

$$\alpha_{C'} = \alpha + h' \qquad ..(14)$$

where h', the auxiliary inductive parameter, is given values in the range 0 to 0.25. In 2-pyrrolecarboxaldehyde the inductive parameters l and l' are used to modify the Coulomb integrals for the oxygen and its adjacent carbon atom by analogy with h and h'. The resonance integrals for the CN and CO bonds, β_{CN} and β_{CO}, are considered to be unchanged relative to β_{CC}.

(ii) <u>Application to electrophilic substitution in pyrrole:</u>

The best approach to the problem of orientation in substitution reactions would be to carry out an exact quantum mechanical calculation of the energy differences between the ground state and the various transition states. An exact calculation is not possible, but approximate methods have been used with much success. By choosing the appropriate Wheland intermediate as a model for the transition state and applying the m.o. theory as outlined in the previous section, one can readily calculate the difference in π-energy between the ground state and the transition state, i.e. the localization energy.

The simple m.o. treatment has been applied to pyrrole by Brown (17,18) in order to calculate π-electron densities and localization energies for electrophilic, radical and nucleophilic substitution. Brown (17) found that the localization energies, but not the π-electron densities, predicted the orientation observed experimentally. It was later found that using the values h=2, h'=0.19 would bring the π-electron densities into line with the localization energies and the observed orientation (18).

In the present work Brown's original calculation of localization energies was repeated using the parameters h'=0.00 and a range of h from -1.0 to +2.0*. The localization energies are plotted as a function of h in Figure 5.

Further plots of localization energies vs h for electrophilic substitution are given in Figures 6, 7 and 8 for h' equal to 0.00, 0.20, and 0.25 respectively wherein h is varied from 0.0 to 2.0 in intervals of 0.2. For h'=0.00 α-substitution is predicted over the whole range of h, while for h'=0.20 or 0.25 β-substitution is favoured for values of h up to 1.53 and 1.78 respectively, at which points the α- and β- curves cross. In the last two cases much larger values of h are required to bring about agreement with experiment than where no auxillary inductive parameter is used. For the present purposes only Figure 6 is considered.

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* All secular determinants, corresponding polynomial equations, roots, E_π values, and localization energies are given in Appendix 2. The roots of the polynomials were evaluated on an I. B. M. 1620 computer using programs prepared by Dr. M. Lal of the Mathematics Department of Memorial University.

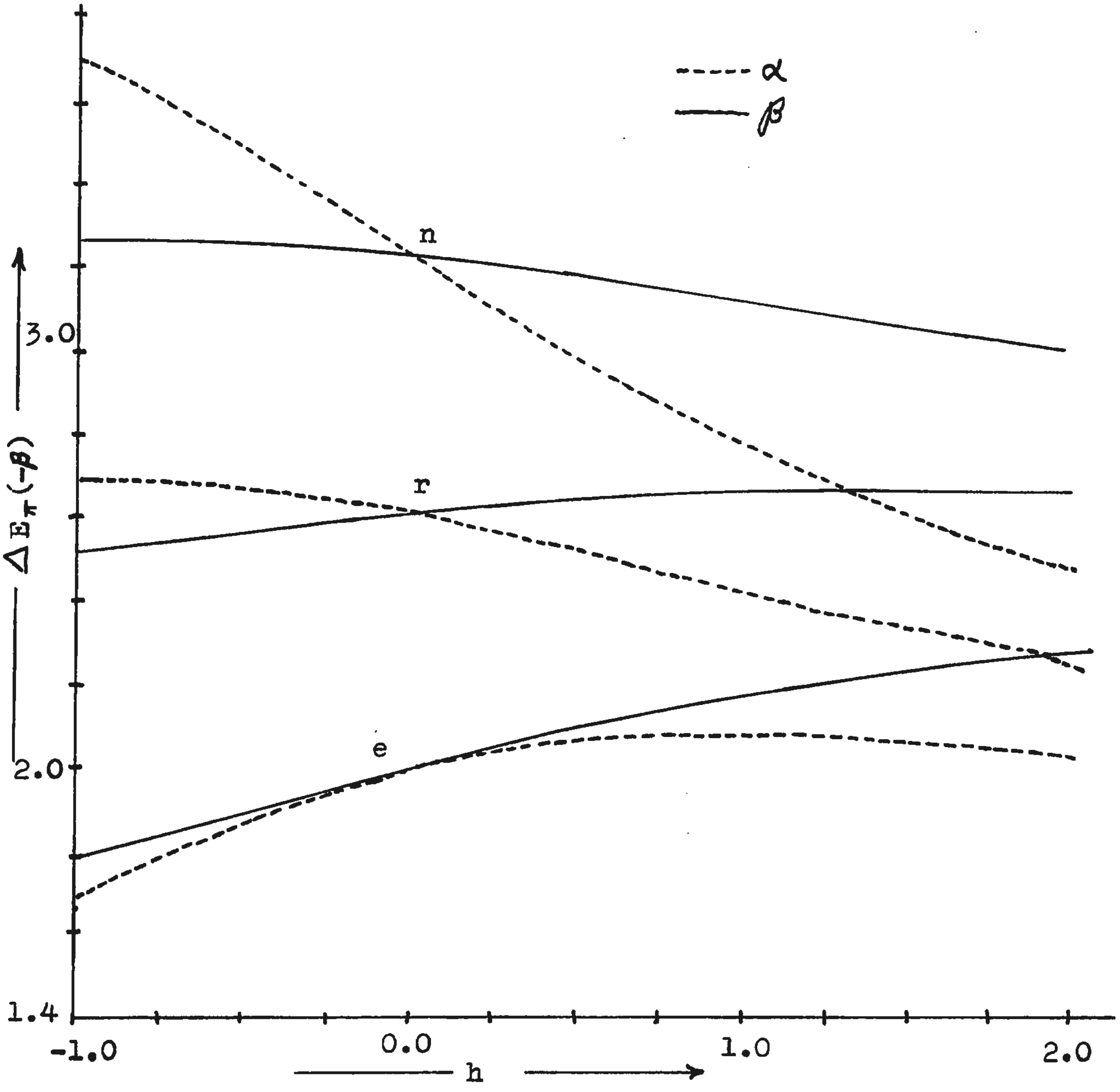

Figure 5. Localization energies (ΔE_{π}) for pyrrole.
e = electrophilic; r = radical; n= nucleophilic.

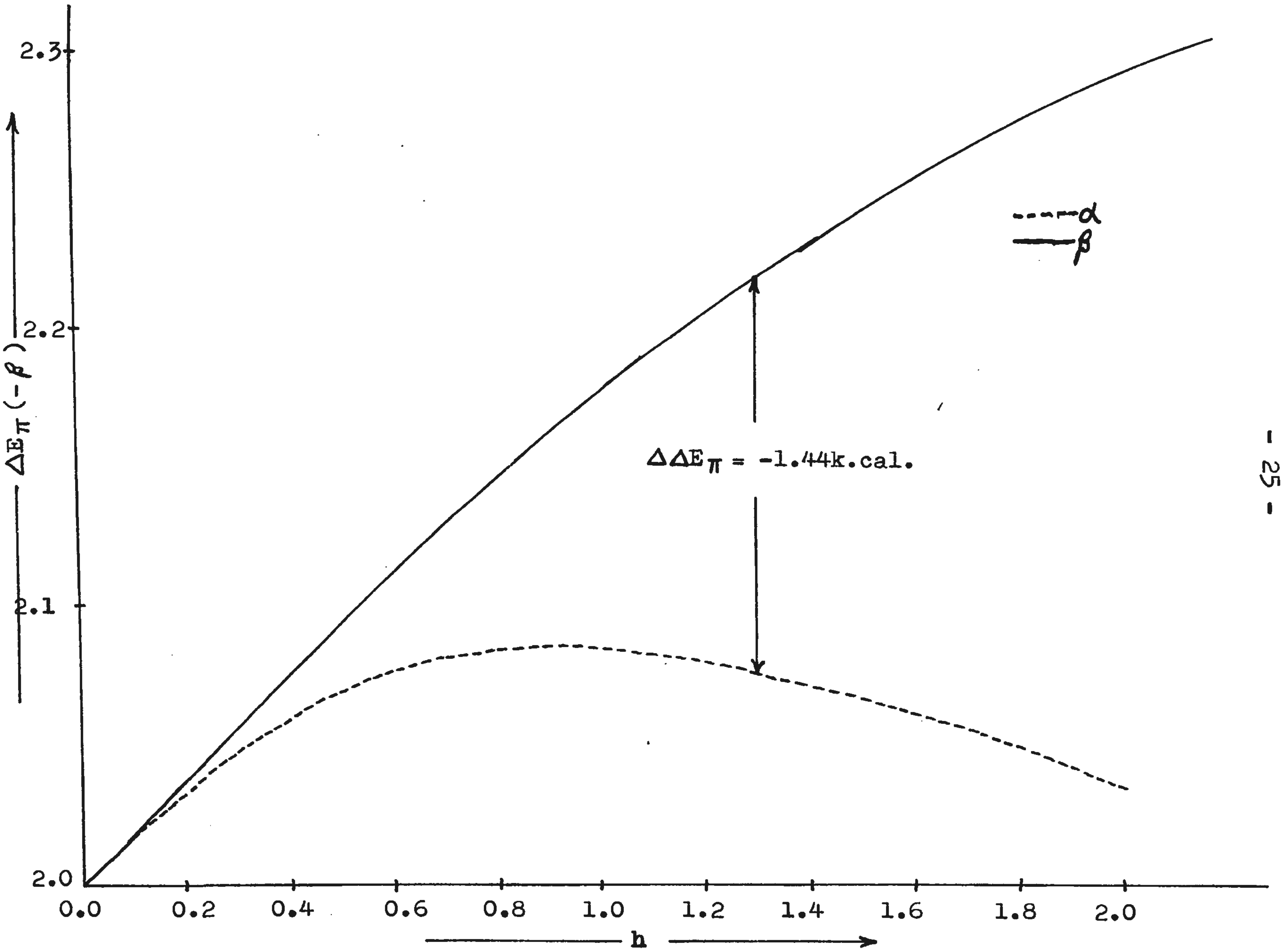

Figure 6. Localization energies for electrophilic substitution in pyrrole. ΔE_{π} vs h for h'=0.

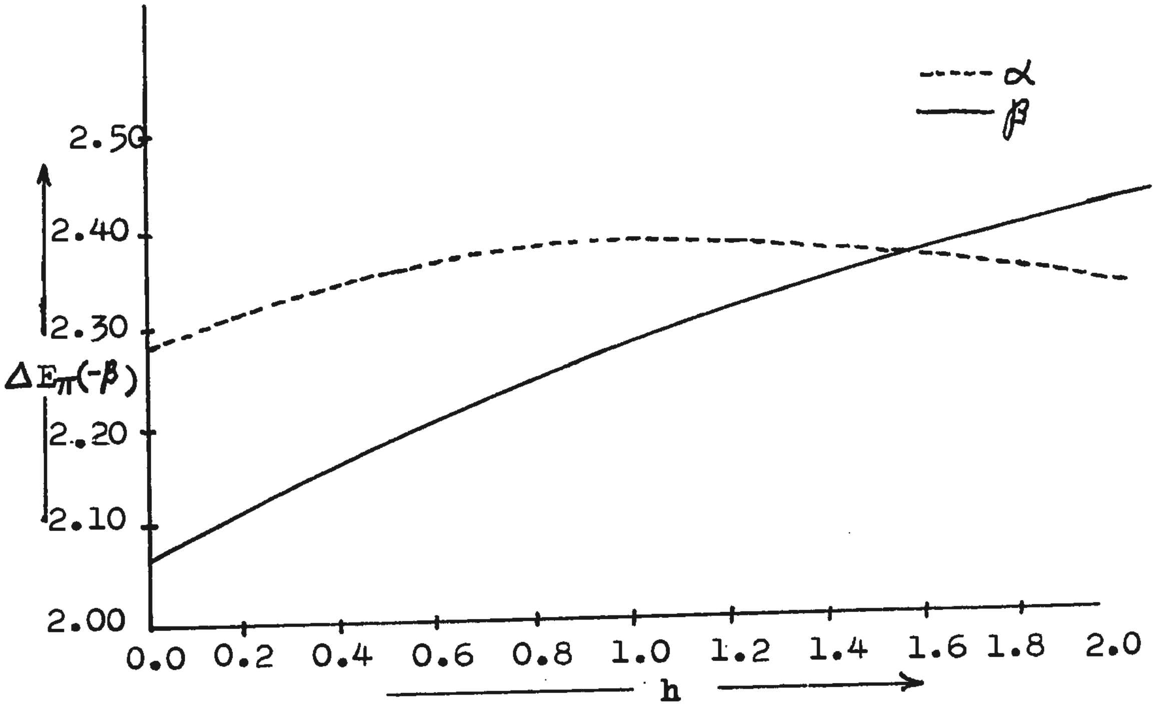

Figure 7. ΔE_π vs h for h'=0.20. Localization energies for electrophilic substitution in pyrrole.

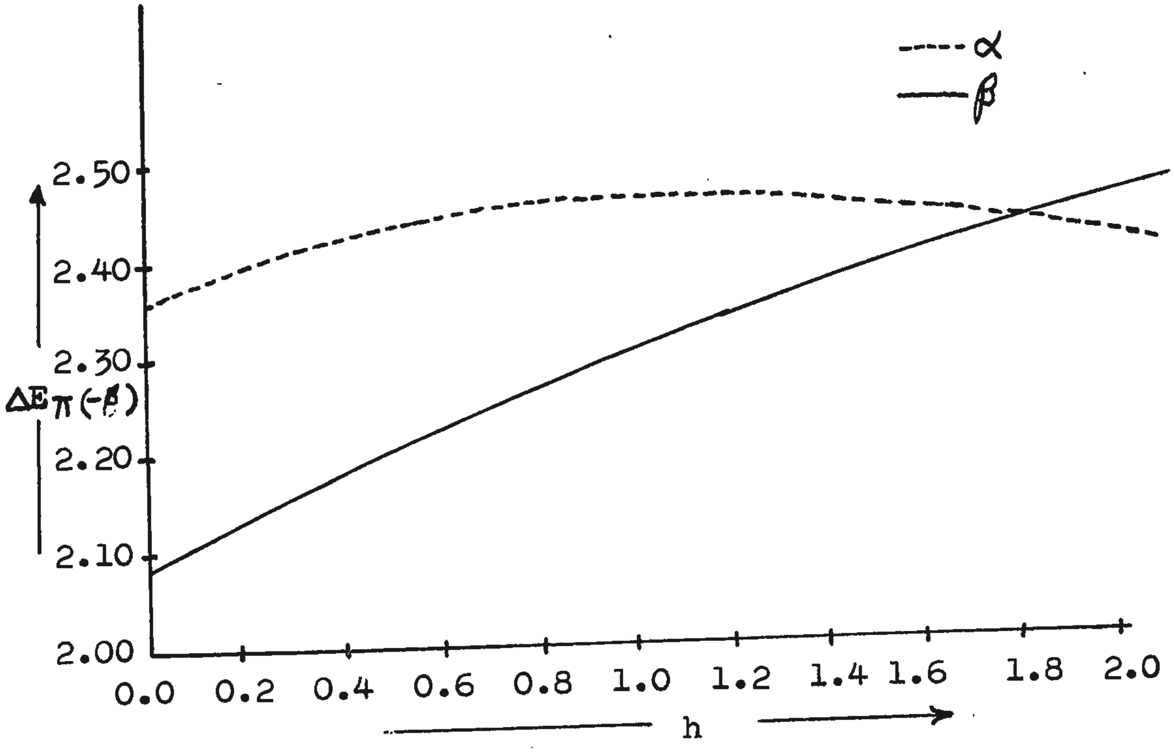

Figure 8. Localization energies for electrophilic substitution in pyrrole. ΔE_π vs h for h'=0.25.

From Equation (6), previously derived from absolute rate theory, it is clear that in the nitration, say, of pyrrole, the product ratio will be determined by the difference in the localization energies (i.e. $\Delta\Delta E_{\pi}$) for substitution at the α- and β- positions. If the product ratio and β are known, $\Delta\Delta E_{\pi}$ is easily determined and from a plot of ΔE_{π} vs h (Figure 6) one can obtain a value of h corresponding to the calculated energy separation, $\Delta\Delta E_{\pi}$.

A value for β was obtained (Appendix 1) from a correlation between partial rate factors for nitration and corresponding localization energies for several aromatic hydrocarbons. The calculated value, $\beta = -9.78$ k.cal./mole, bears no relation to β's calculated by other means; it is used here simply because the present application is the same as the source from which it was derived.

Substituting in Equation (6) the product ratio found by Tirouflet and Fournari (10) in the nitration of pyrrole at 40° gives

$$\Delta\Delta E_{\pi} = \frac{2.303 \times 1.987 \times 313}{1000} \log\left(\frac{9}{91}\right) \text{ k.cal/mole}$$

or $\Delta\Delta E_{\pi} = -1.44$ k. cal/mole

Since $\Delta\Delta E_{\pi} = m\beta$,

therefore $m = \frac{-1.44}{-9.78} = 0.240$

From Figure 6 it is readily found that the energy separation of $0.240\,\beta$ corresponds to $h=1.28$. Thus the choice of the Coulomb inductive parameter has been put on an experimental basis.

If the theory is refined to include a finite auxilliary inductive parameter, one may find further values of h and h' that will give agreement with experiment (i.e. an energy separation 0.240β) from such correlations as shown in Figures 7 and 8. It is evident that in these cases h will be substantially greater than the value derived above.

(iii) Electrophilic substitution in 2-pyrrolecarboxaldehyde

The problem of electrophilic substitution in 2-pyrrolecarboxaldehyde was approached in the same way as the pyrrole problem of the previous section. The secular determinants for 2-pyrrolecarboxaldehyde and the Wheland intermediates corresponding to electrophilic substitution at the 3-, 4-, and 5- positions were set up and solved as shown in Appendix 2. The Coulomb inductive parameters used for the nitrogen were h'=0.00, h=1.28 as determined previously. The auxilliary inductive parameter for the aldehyde carbon, l' was fixed first at 0.00 and then at 0.20 as l, the Coulomb inductive parameter for the oxygen, was varied from 0.00 to 4.0 in intervals of 1.0. The localization energies so determined are plotted as a function of l in Figures 9 and 10.

At l=0, l'=0 (Figure 9), where the system corresponds to 2-vinylpyrrole, 5-substitution is greatly favoured over attack at the 3- and 4- positions. However, as l increases, the localization energies for the 3- and 5- positions increase much more rapidly than $\Delta E_{\pi}(4-)$, making the 4-positions the preferred site of attack for all values of l greater than one. Nitration of 2-pyrrolecarboxaldehyde gives 59% of the 4- and 41% of the 5-isomer (10) corres-

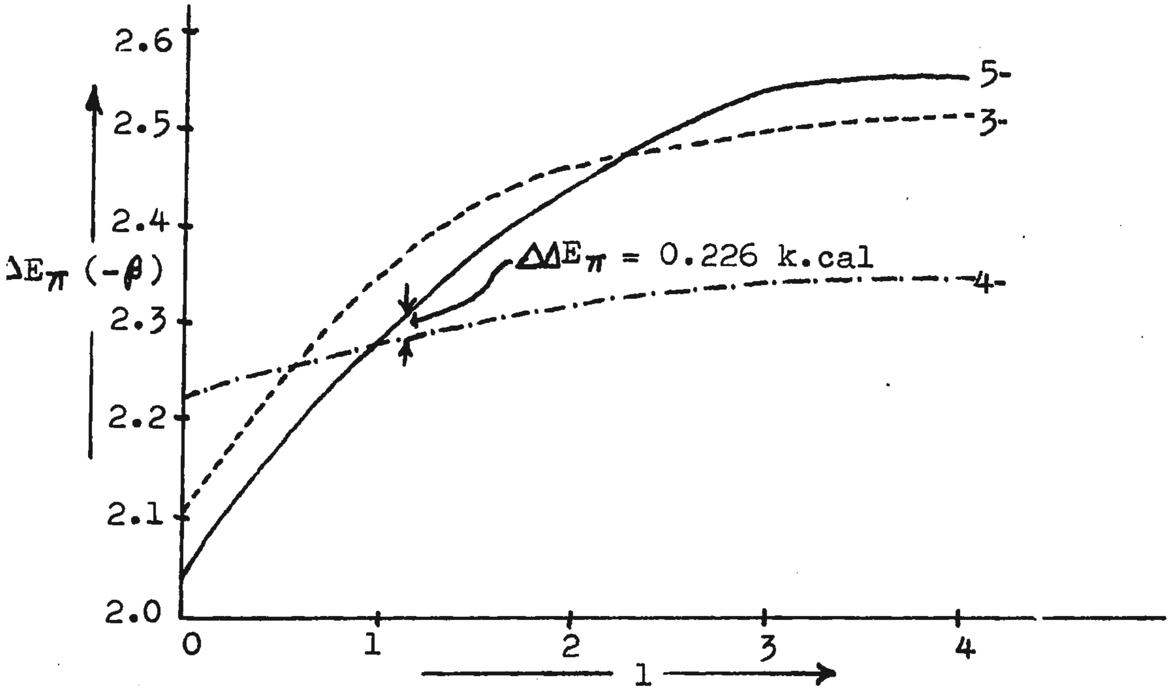

Figure 9. Localization energies for electrophilic substitution in 2-pyrrolecarboxaldehyde. ΔE_{π} vs l for l' = 0.00

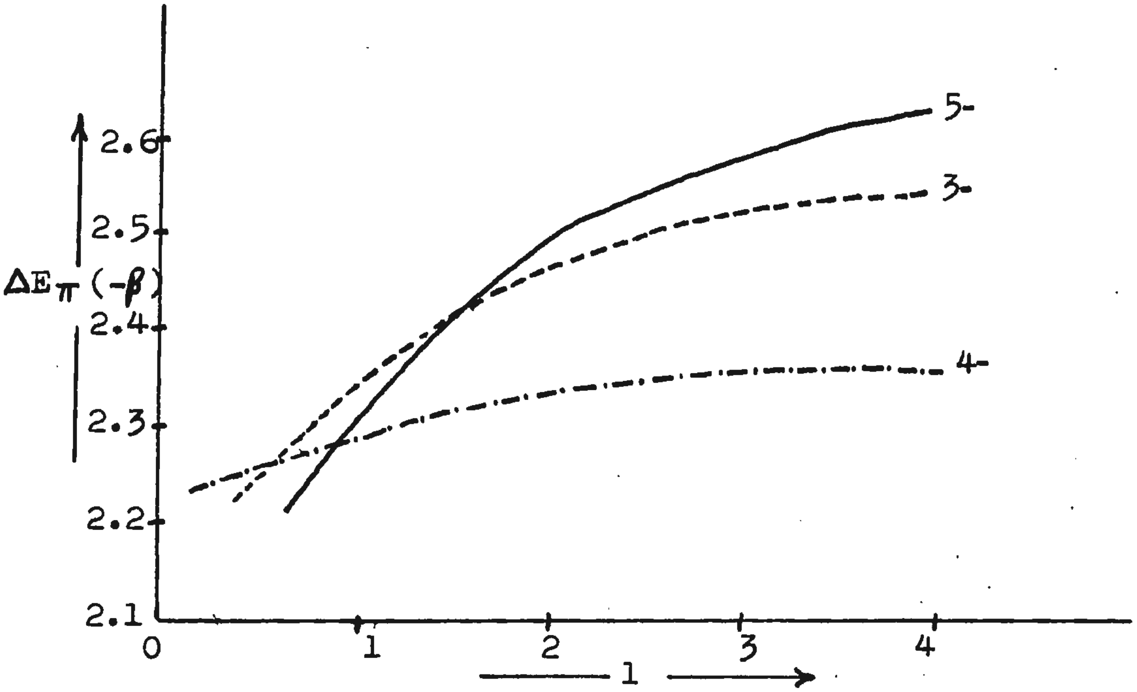

Figure 10. Localization energies for electrophilic substitution in 2-pyrrolecarboxaldehyde. ΔE_{π} vs l for l' = 0.20

ponding to $\Delta\Delta E_{\pi}(4-, 5-) = 0.0231 = 0.226$ k.cal/mole and a Coulomb inductive parameter $l=1.14$ for the carbonyl oxygen.

As l increases further the energy separation rapidly becomes much greater; for example $l=2$ corresponds to a 4-/5- ratio of 12:1. Enhancing the electronegativity of the oxygen by increasing l approximates the situation in the Friedel-Crafts reaction where the carbonyl group is complexed with the Lewis acid catalyst. Thus it is reasonable to expect a greatly increased proportion of the 4-substituted compound from Friedel-Crafts alkylation relative to that found, for example, in nitration where the carbonyl remains uncomplexed*. It is not possible to give quantitative expression to this prediction in the present treatment (e.g. β for the Friedel-Crafts reaction probably differs substantially from the value for nitration) but the trend is obvious and in agreement with predictions from simple resonance theory as well as experiment (page 4; 50). It should be noted that the curve (in Figure 9) for 3-substitution crosses that for 5-substitution at $l=2.2$, but at this point >95% 4-substitution is predicted.

From Figures 9 and 10 it is seen that the localization energies for attack at the 3- and 4- positions are insensitive to the value of l' in contrast to $\Delta E_{\pi}(5-)$. However from both figures the same general conclusions may be drawn.

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* It has not been established whether protonation of the carbonyloxygen occurs under the conditions of nitration (sulfuric acid medium). Nitration in acetic anhydride occurs on the corresponding diacetate (10) giving predominantly 5-substitution.

5. ISOPROPYLATION OF 2-SUBSTITUTED PYRROLE DERIVATIVES.

(i) Preparations, procedures and product identification:

The pyrrole derivatives chosen as substrates for the Friedel-Crafts reactions were methyl 2-pyrrolecarboxylate, 2-pyrrolecarboxaldehyde and 2-acetylpyrrole.

Methyl 2-pyrrolecarboxylate was prepared by the action of methyl chloroformate on pyrrylmagnesium bromide in a modification of the method of Maxim et al. (55). In addition to a small amount of methyl 1-pyrrolecarboxylate (56), two other higher boiling by-products were isolated. One of these was shown by its infrared and nuclear magnetic resonance (n. m. r.) spectra and mixed melting point to be methyl 1,2-pyrroledicarboxylate recently reported by Hodge and Rickards (57). The other was identified as methyl 1,3-pyrroledicarboxylate by mild base hydrolysis and partial decarboxylation to the known 3-pyrrolecarboxylic acid (58). The infrared spectrum of this acid was identical to that of an authentic specimen and the mixed melting point was not depressed. The n. m. r. spectrum of the 1,3-diester was in agreement with the assigned structure; the infrared spectrum had carbonyl adsorptions at 1720 cm^{-1} and 1760 cm^{-1}, the peak at higher frequency corresponding to the N-ester carbonyl which appears at 1765 cm^{-1} in methyl 1-pyrrolecarboxylate.

2-Acetylpyrrole was prepared by the reaction of acetic anhydride with pyrrylmagnesium bromide as described by Oddo and Dainotti (11) and 2-pyrrolecarboxaldehyde by a Vilsmeier synthesis (59).

The action of isopropyl chloride on pyrrylmagnesium bromide produced the known mixture of 2- and 3-isopropylpyrrole (60). Repeated fractionation gave a sample of

2-isopropylpyrrole $>$ 95% pure as determined by gas-liquid partition chromatography. After conversion of this compound to the corresponding Grignard reagent, reaction with methyl chloroformate produced a moderate yield of the desired methyl 5-isopropyl-2-pyrrolecarboxylate. The n. m. r. spectrum was in agreement with the assigned structure.

The Friedel-Crafts alkylation reactions were carried out in carbon disulfide, ethylene chloride or nitromethane using anhydrous aluminum chloride, aluminum bromide, gallium chloride, ferric chloride, and titanium tetrachloride as catalysts. Analyses of all reaction mixtures were done by gas-liquid partition chromatography. Standardization against a series of mixtures of known proportions showed that this method gave results accurate to about 2% when peak areas were determined by triangulation. The instrument used was a Beckman GC-2A Gas Chromatograph equipped with a Beckman column of carbowax 4000 dioleate on firebrick, operating at 190°C, and using helium as the carrier gas".

Throughout the experiments no special purification of starting materials was undertaken except for the 2-substituted pyrrole substrates which were not used until the gas chromatographic patterns showed only a single peak. The solvents and isopropyl chloride were stored over molecular sieves; the catalysts were kept in a desiccator but no particular care was used in handling them beyond that which ordinary use demands. Some trial experiments with the ester and aldehyde showed that small quantities of water (0.1 - 0.2 ml) added to the reaction mixture had little effect on the product ratios. However, in a series of experiments with the ester where extra precautions were used to exclude all atmospheric moisture the extent of reaction was greatly decreased for the same time interval. In the main the alkylations were repeatable and gas chromatography gave consistent results except for some short time alkylations (particularly of the ester and the ketone). At least for the ester and the ketone, little destruction of the heterocyclic ring occurred during reaction as shown by the high percentage recovery of starting materials and products.

Column chromatography on alumina of reaction products from the isopropylation of methyl 2-pyrrolecarboxylate gave some unreacted starting material as well as three other compounds. One of the products was identified as the known 4-isopropyl-2-ester (61) by its melting point, by the n. m. r. spectrum, and by the melting point of the corresponding acid. Another product was shown by n. m. r. and elemental analysis to possess two isopropyl groups and to be the 4, 5-diisopropyl derivative. The third product was proven to be methyl 5-isopropyl-2-pyrrolecarboxylate by mixed melting point and comparison of its infrared spectrum with that of an authentic specimen prepared as described above.

When the 2-isopropylpyrrole used to prepare methyl-5-isopropyl-2-pyrrolecarboxylate contained more than a small amount of 3-isopropylpyrrole, then in the gas chromatographic pattern of the Grignard reaction product two additional peaks were observed. One of these corresponded to the

4-isopropyl-2-ester and the other had the same retention time as an unknown trace peak which appeared in the chromatogram of the reaction products from the isopropylation of the ester. The latter would thus appear to be methyl 3-isopropyl-2-pyrrolecarboxylate, the other possible monoisopropylation product. Miyazaki et al. (62) found that another Grignard synthesis from 3-isopropylpyrrole gave both 2- and 5-substitution. The amount of 3-substitution in the alkylation reactions was never greater and usually much less than 5%, and has been ignored in calculations of the product ratios. It has not been possible to isolate this substance in a pure state.

Further Friedel-Crafts isopropylation of the proven 4- and 5- isopropyl-2-esters produced the same diisopropyl-2-ester obtained in the original alkylation and the n.m.r. spectrum was in agreement with the assigned structure. Bromination of the 2-ester has been shown to produce the 4,5-dibromo-2-ester (63). Thus, there appears to be no reason to doubt the assignment of the two isopropyl-groups to the 4- and 5-positions.

Isopropylation of 2-pyrrolecarboxaldehyde gave only the 4-isopropyl derivative which was purified by steam distillation and crystallization from pentane. The n.m.r. spectrum and elemental analysis were in agreement with the assigned structure and oxidation with silver oxide produced the known 4-isopropyl-2-pyrrolecarboxylic acid (61).

Isopropylation of 2-acetylpyrrole gave three products, two of which were isolated by column chromatography on alumina and identified by their elemental analyses and n.m.r. spectra by analogy with previous results. These were the 4-isopropyl- and 4,5-diisopropyl-2-pyrryl methyl ketones. The third product, by analogy with the corresponding ester, was assumed to be the 5-isopropyl derivative. Reaction of acetic anhydride with the Grignard reagent of a mixture of isopropylpyrroles, of which more than 80% was the 2-isomer, gave as the major product a compound having the same retention time on the gas chromatograph as the supposed 5-isopropyl-2-pyrryl methyl ketone.

(ii) Results:

An investigation was undertaken of the effect of substituent, catalyst, solvent, and time on the rate of reaction and product distribution. The results of these experiments are detailed in Table II. We consider first the alkylations carried out in carbon disulfide with the normal 0.012 mole of catalyst per 0.01 mole of substrate.

In the aluminum chloride catalyzed isopropylation of methyl 2-pyrrolecarboxylate the observed behaviour was that roughly equal amounts of 4- and 5-isopropyl-2-ester were formed along with a small amount of diisopropyl-2-ester until about one hour had elapsed. The amount of both 4-isopropyl and of 4,5-diisopropyl-2-ester rose more rapidly during the second hour while the amount of 5-isopropyl-2-ester remained almost unchanged. The reaction was then nearly complete and not a great deal of change occurred during the next sixteen hours. The reaction mixture was largely heterogeneous at least in the initial stages. After about one hour the deposition of some yellow semisolid material on the bottom of the reaction vessel was observed. With larger amounts of catalyst a yellow oil separated. Aluminum bromide appeared to be a somewhat better catalyst while gallium chloride gave 94% conversion with, relatively speaking, very little of the 5-isopropyl and 4, 5-diisopropyl-2-esters. Aluminum bromide and gallium bromide are both soluble in carbon disulfide and oil formation occurred more quickly with these catalysts than with the aluminum chloride. Less than 2% reaction occurred with ferric chloride while with titanium tetrachloride no reaction occurred at all over a period of 18 hours at the boiling point of carbon disulfide.

Under similar conditions the 2-aldehyde proved to be very much more reactive, giving in less than an hour about 80% of the 4-isopropyl derivative (no other products) with the aluminum and gallium halides. Sixty percent conversion occurred with ferric chloride, and again none at all with titanium tetrachloride. The reagents, in these reactions, formed a red oil in the bottom of the flask immediately upon mixing and reaction appeared to occur mainly in this phase.*

Both aluminum chloride and aluminum bromide were quite effective in catalyzing the isopropylation of the 2-ketone, which while less reactive than the aldehyde was much more reactive than the ester. The main product was the 4-isopropyl-2-ketone but small amounts of the 5-isopropyl and 4,5-diisopropyl derivatives were observed in the product mixtures. As before, a red oil formed as the reaction progressed.

*Separate examination of the "red oil" and solvent phases revealed a higher proportion of product in the "red oil" than in the solvent. This was true for reactions of the ester and ketone as well as the aldehyde.

TABLE II

Isopropylation of 2-substituted pyrrole derivatives (at 50°)

2-Substituent	Catalyst (moles)	Solvent	Time (min.)	Conversion (mole %)	Product distribution (mole %)		
					4-isopropyl-	5-isopropyl-	4,5-diisopropyl-
$-COOCH_3$	$AlCl_3$(.012)	CS_2	15	5.7	4.3	trace	1.4
"	"	"	30	15.5	6.9	7.0	1.6
"	"	"	60	24.8	11.6	10.1	3.2
"	"	"	90	47.3	29.0	10.6	7.7
"	"	"	120	53.1	32.4	9.7	11.0
"	"	"	1080	61.8	34.6	11.6	15.6
"	$AlBr_3$(.012)	"	60	64.3	47.2	7.3	9.8
"	"	"	120	67.8	46.3	11.7	9.7
"	"	"	1080	77.1	51.9	17.3	7.8
"	$GaCl_3$(.012)	"	60	94.3	80.4	9.2	4.8
"	$FeCl_3$(.012)	"	1080	<2	trace	trace	-
"	$TiCl_4$(.012)	"	1080	0.0	-	-	-
"	$AlCl_3$(.020)	CH_3NO_2	1080	16.3	trace	12.2	4.1
"	" (.012)	$C_2H_4Cl_2$	60	86.8	62.4	8.8	15.7
"	" (.024)	CS_2	1080	78.0	8.0	70.0	trace

TABLE II (cont'd)

Isopropylation of 2-substituted pyrrole derivatives (at 50°)

2-Substituent	Catalyst (moles)	Solvent	Time (min.)	Conversion (mole %)	Product distribution (mole %)		
					4-isopropyl-	5-isopropyl-	4,5-diisopropyl-
-CHO	$AlCl_3$(.012)	CS_2	1	12.1	12.1	-	-
"	"	"	5	51.3	51.5	-	-
"	"	"	15	77.4	77.4	-	-
"	"	"	30	80.3	80.3	-	-
"	"	"	60	81.8	81.8	-	-
"	"	"	120	83.6	83.6	-	-
"	$AlBr_3$(.012)	"	1	22.7	22.7	-	-
"	"	"	5	50.7	50.7	-	-
"	"	"	15	74.1	74.1	-	-
"	"	"	30	77.2	77.2	-	-
"	"	"	60	83.2	83.2	-	-
"	"	"	120	83.8	83.8	-	-
"	$GaCl_3$(.012)	"	60	73.2	73.2	trace	trace
"	$FeCl_3$(.012)	"	60	46.9	46.9	-	-

TABLE II (cont'd)

Isopropylation of 2-substituted pyrrole derivatives (at 50°)

2-Substituent	Catalyst (moles)	Solvent	Time (min.)	Conversion (mole %)	product distribution (mole %)		
					4-isopropyl	5-isopropyl	4,5-diiso propyl
-CHO	$FeCl_3$(.012)	CS_2	120	52.2	52.2	-	-
"	$FeCl_3$(.012)	"	1080	59.2	59.2	-	-
"	$TiCl_4$(.012)	"	1080	0.0	-	-	-
"	$AlCl_3$(.020)	CH_3NO_2	1080	0	trace	-	-
"	$AlCl_3$(.012)	$C_2H_4Cl_2$	60	45.6	45.6	-	-
"	"	"	120	55.8	55.8	-	-
"	" (.024)	CS_2	120	89.1	89.1	trace	trace
$-COCH_3$	$AlCl_3$(.012)	CS_2	30	81.5	75.9	1.4	4.2
"	$AlBr_3$(.024)	"	60	75.5	71.1	2.7	1.6
"	$AlCl_3$(.024)	"	240	92.7	86.3	3.0	3.4
"	" (.020)	CH_3NO_2	1080	0.0	trace	-	-
"	$TiCl_4$).012)	CS_2	1080	0.0	-	-	-

In ethylene chloride (with aluminum chloride as catalyst) the ester reacted much more rapidly than the aldehyde, while in nitromethane (with the aluminum chloride-nitromethane complex as catalyst) only the ester reacted. Both solvents provided homogeneous reaction conditions (although in some cases in ethlene chloride small amounts of red oil were observed on the sides of the reaction vessel). In ethylene chloride the ester gave substantial amounts of the 5-isopropyl and 4,5-diisopropyl compounds in addition to the 4-isopropyl isomer which was the main reaction product; the aldehyde gave the 4-isomer only.

In carbon disulfide and with a swamping amount of catalyst the ester gave almost exclusively methyl 5-isopropyl-2-pyrrolecarboxylate, the aldehyde gave only the 4-isomer, while in the reaction on the ketone only slightly more of the 5-isopropyl and 4,5-diisopropyl-2-ketones was formed than usually found with smaller amounts of catalyst.

Experiments were carried out to determine the extent of rearrangement and disproportionation accompanying these reactions. It was established that when pure methyl 5-isopropyl-2-pyrrolecarboxylate was refluxed for 1 to 2 hours in carbon disulfide in the presence of an excess of catalyst while a stream of anhydrous hydrogen chloride was admitted, no detectable change occurred. However, when methyl 4-isopropyl-2-pyrrolecarboxylate was subjected to the same conditions there was a rapid rearrangement in which roughly one-half of the 4-isomer was converted to the 5-isomer. At the same time there was a small amount of disproportionation in which nearly equal amounts of starting material and methyl 4,5-diisopropyl-2-pyrrolecarboxylate were formed. It was shown that the diisopropyl-2-ester was also unchanged by the reaction conditions over an 18 hour period, in the presence of starting material. Attempts to rearrange 4-isopropyl-2-pyrrolecarboxaldehyde were unsuccessful. The rearrangement experiments on 4-isopropylpyrryl methyl ketone were inconclusive although gas chromatography indicated that the extent of rearrangement must be very much less than for the corresponding ester. It was further shown that neither the 4,5-diisopropyl-2-ester nor the 4,5-diisopropyl-2-ketone disproportionated under reaction conditions in the presence of the appropriate starting material.

(iii) Discussion:

The results relating to the aluminum chloride catalyzed isopropylation of methyl 2-pyrrolecarboxylate in carbon disulfide have been discussed previously (1) and will be considered first. The pattern of the results is consistent with direct attack occurring primarily at the 4-position leading to the σ-complex, XV*, which may rearrange by an intramolecular 1, 2-shift mechanism (29, 43, 64) to give XVI. Loss of a proton from these carbonium ions would produce the two monoisopropyl-2-esters. The highly reactive 4-position of the 5-isopropyl-2-ester, could then acquire a second isopropyl group to form XVII and eventually the diisopropyl-2-ester. Although some direct

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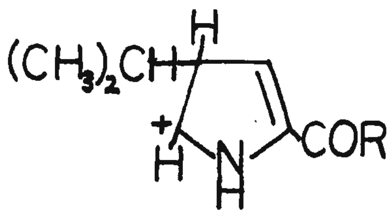
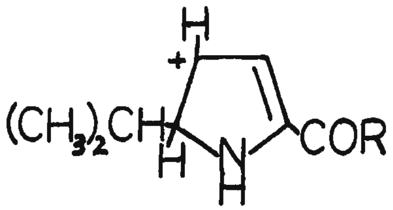
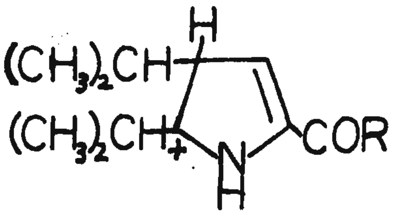
* The carbonyl groups of all such species undoubtedly remain complexed with the catalyst.



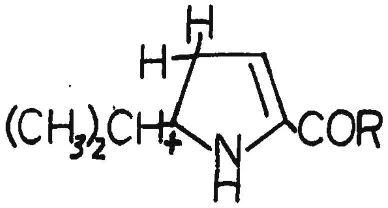
XV



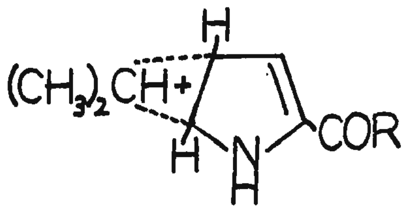
XVI



XVII



XVIII



XIX

$R = -H, -CH_3, -OCH_3$

alkylation at the 5-position probably occurs, on both theoretical and experimental ground it appears that the 4-position is greatly favoured as the initial site of attack.

In alkylation experiments where hydrogen chloride gas was admitted continuously throughout, yields were greatly decreased and the 5-isomer predominated. Here protonation of the 4-position exceeded alkylation and much of the XV that was formed rearranged to the 5-isomer. In rearrangement experiments on the latter and on the diisopropyl-2-ester, protonation of the 4-position gave XVIII and XVII respectively whose rearrangement or disproportionation would be expected to, and did, fail.

On the other hand methyl 4-isopropyl-2-pyrrolecarboxylate protonated to XV and did rearrange. Attempts to carry out this rearrangement in the absence of a stream of hydrogen chloride gas produced little of the 5-isomer. The small proton concentration which must have been present was probably supplied by the hydrogen chloride usually associated with commercial grade aluminum chloride. In addition to the monoisopropyl derivatives, this rearrangement gave small and approximately equal amounts of methyl 2-pyrrolecarboxylate and its 4,5-diisopropyl derivative. The fact that no overall loss of isopropyl groups was observed in the rearrangement reactions, indicates that the last two oompounds were probably formed from a direct intermolecular transalkylation (29) by XV on the 4-position of a molecule of methyl 5-isopropyl-2-pyrrolecarboxylate, rather than from the formation of a free isopropyl cation or its complex with the Lewis acid, followed by electrophilic attack on the 5-isopropyl-2-ester. In the latter case some loss of isopropyl groups might have been expected. The failure of the diisopropyl-2-ester to disproportionate under reaction conditions, provides additional evidence that the isomerization is intramolecular.

The reactivity of the 4-position is also supported by alkylation experiments using the monoisopropyl-2-ester. Here it was observed that 35% of the 5-isomer was converted to the diisopropyl-2-ester in fifteen minutes, while the 4-isopropyl-2-ester gave only 15% after one hour. In the latter experiment, rearrangement probably preceded alkylation to a large extent.

Alkylation experiments on methyl 2-pyrrolecarboxylate using swamping amounts of aluminum chloride or aluminum bromide as catalyst, gave high yields of product where the 5-isopropyl-2-ester predominated by far and where diisopropylation was negligible. This is analogous to Friedel-Crafts reactions on monoalkylbenzenes, where large amounts of catalyst lead to an increased proportion of <u>meta</u>-substitution (33). As discussed by Olah (30), several authors have studied complexes of the type $[ArH_2]^+[LAX]^-$, where LA refers to a Lewis acid.

McCauley and Lien (38, 65) have shown that for a mixture of xylenes in the presence of liquid HF-BF_3, the most basic isomer—<u>meta</u>-xylene—is preferentially extracted into the acid layer, leading to a shift of the equilibrium distribution in favour of this isomer. By analogy, an important factor contributing to the rearrangement of methyl 4-isopropyl-2-pyrrolecarboxylate to the 5-isomer, is the greater basicity of the latter, which makes it thermodynamically more stable under reaction conditions, owing to the formation of the σ-complex XVIII. It should be emphasized that protonation at the 4-position should be greatly favoured over 5-protonation, regardless of the number of alkyl substituents.

A small amount of the supposed 3-isopropyl-2-ester was detected among the rearrangement products of the 4-isopropyl isomer. While at least some direct attack may occur at the 3- and 5- positions during alkylation, it seems that most of the product with isopropyl groups at these positions arises through rearrangement from the kinetically favoured 4-position.

It was previously suggested (1) that the isopropyl group of methyl 4-isopropyl-2-pyrrolecarboxylate may rearrange intramolecularly to the 5-position by way of a Wagner-Meerwein intermediate, XIX. Loss of the isopropyl group group of this species to a molecule of methyl 5-isopropyl-2-pyrrolecarboxylate would produce equal amounts of methyl-2-pyrrolecarboxylate and its diisopropyl derivative, in agreement with experiment. However, location of such a species on a free energy profile could only be a matter of speculation. If the proposed 1, 2-shift mechanism is operative, XIX may more closely resemble a potential maximum (i.e. a transition state) than a minimum, since the redistribution of charge involved in the rearrangement probably requires considerable energy. Implicit in such a mechanism is the view that 5-isopropylation does not necessarily involve a common intermediate with 4-isopropylation, i.e. a π-complex. This is consistent with the suggestion that most of the 5-substituted product arises from rearrangement of the 4-isomer and not from direct attack.

That aluminum bromide and gallium bromide are more effective catalysts than aluminum chloride, is probably due in part to their much greater solubility in carbon disulfide. Of particular interest is the fact that gallium chloride gives 94% conversion with very much less of the 5-isopropyl and 4,5-diisopropyl-2-ester than observed with the aluminum halide catalysts. Thus in this case, consecutive isomerization appears to be greatly reduced. Under nearly homogeneous conditions in ethylene chloride with aluminum chloride as catalyst, 87% conversion of the unsubstituted ester was observed, with substantial amounts of the 5-isopropyl and 4,5-diisopropyl derivatives, being found in the product mixture. The greater solubility of aluminum chloride in ethylene chloride than in carbon disulfide would appear to account for the faster rate of reaction.

N.m.r. studies on complex formation between aluminum halide and the 2-substituted pyrrole substrates, indicate that the strength of carbonyl complex formation and hence the degree of deactivation of the ring to electrophilic substitution follows the order: aldehyde > ketone > ester (c.f. page55). It is therefore surprising to find that the rate of alkylation in carbon disulfide follows the same order, with the aldehyde reacting very much faster than the ester. This result may be attributed to differences in the physical states of the reaction mixtures.

The aluminum chloride catalyzed isopropylations of the ester (in carbon disulfide) gave heterogeneous reaction mixtures at least in the initial stages, with much of the catalyst remaining suspended in the solvent. On the other hand, the aldehyde and catalyst quickly formed a red oil on mixing in carbon disulfide , and reaction appeared to occur mainly in this phase. In this highly polar and acidic medium with a very high concentration of reactants, reaction would be expected to occur much faster than in the less polar and more dilute medium available to the ester, notwithstanding the greater degree of deactivation of the 2-formylpyrrole.

Molecular orbital calculations (c.f. page 28) have shown that electron withdrawal from the pyrrole ring leads to a greatly increased E_π value for the Wheland intermediate (and by the Hammond principle a greatly increased localization energy) for 5-substitution, relative to the very small increase in E_π (4-). Also the n.m.r. work on the Lewis acid-carbonyl complexes indicates that the decrease in π-electron density caused by complex formation is much greater at the 5-position than at the 4-position, and that this effect is much greater for the aldehyde than for the ester. That the ester but not the aldehyde rearranges under the reaction conditions, may be explained by assuming that the E_π(5-) value for the aldehyde is so large that it precludes 5-substitution either from direct attack or from rearrangement of the 4-alkyl group. On the other hand, the ester, not being as tightly complexed and therefore having lower energy Wheland intermediates for electrophilic substitution at the 4- and 5-positions, may undergo 5-isopropylation primarily by the 1,2-shift of a 4-isopropyl group. The behaviour of the 2-acetylpyrrole lies between that of the ester and the aldehyde; but in terms of 5- and di-alkylation the ketone more closely resembles 2-pyrrolecarboxaldehyde than the ester.

The alkylations in nitromethane solution are noteworthy on two aounts. First only the ester reacted. No alkylation of the ketone or aldehyde was observed under the homogeneous conditions of the reaction. The n.m.r. results again provide an explanation, namely that the aldehyde and ketone are sufficiently deactivated by complexing, to rule out isopropylation catalyzed by the weak Friedel-Crafts catalyst-the nitromethane-aluminum chloride complex. In this case the medium of reaction was basic and reactant concentrations were low, in contrast to the conditions of alkylation in carbon disulfide. Although deactivated by complexing, the ester was still much more reactive than the aldehyde, and underwent 16% reaction over an 18 hour period. It is interesting to note that with ethylene chloride as solvent, where aluminum chloride is fairly soluble (although not deactivated by complexing with the solvent), and where the reaction mixture is nearly homogeneous (in contrast to reactions in carbon disulfide), the reaction proceeds more rapidly for the ester than for the aldehyde - the "expected" order.

The second interesting point concerning isopropylations in nitromethane is that virtually all the product from the alkylation consists of the 5- and 4,5-diisopropyl derivatives. Olah (23) has found that isopropylations carried out in nitromethane are highly selective and that the basic conditions of reaction largely eliminate consecutive rearrangement. One would expect that a highly selective electrophilic species would attack almost exclusively the 4-position of methyl 2-pyrrolecarboxylate. The observed results indicate that the first formed methyl 4-isopropyl-2-pyrrolecarboxylate rapidly rearranged to the 5-isomer before deprotonation of XV occurred. The 4% of the diisopropyl-2-ester found in the product mixture represents further alkylation of the 5-isopropyl derivatives. Olah (23) showed that no consecutive isomerization was possible in the "anhydrous" system, although he later carried out isomerizations of diisopropylbenzenes in nitromethane using water promoted aluminum chloride (29). How much water is necessary to initiate such rearrangements on an aromatic ring has not been investigated. It would appear, however, that rearrangement prior to deprotonation may be quite important and may account for much of the <u>meta</u>-isomer found in Olah's product mixtures from the isopropylations.

The results of Gilman <u>et al.</u> on the alkylation of various furan derivatives (48,52,53), are similar to results presented in the present work and may be explained in the same way. Thus, isopropylation of methyl 2-furoate gave only the 5-isomer, largely because of rapid rearrangement of the first formed 4-isomer, while the isopropylation of furfural gave only the 4-isopropyl derivative, because of the enhanced deactivation of the 3- and 5- positions caused by Lewis acid-carbonyl complexing. Spaeth and Germain (51) found that more than 90% of the product of isopropylation of methyl 2-thienyl ketone was the 4-isomer. Their low yield of the 5-isomer may have been due to further alkylations. However, they did not examine the diisopropylated product and did not use an external source of hydrogen chloride in rearrangement studies. Nonetheless, it would appear that the similarity to the behaviour of 2-acetylpyrrole in Friedel-Crafts isopropylation, is due to strong complexing of the ketone carbonyl with the catalyst.

6. SPECTRAL DATA:

(i) Nuclear magnetic resonance spectra:

The n. m. r. chemical shifts for several compounds reported in the present work are given in Table III. The deactivation of the pyrrole ring to electrophilic substitution by an electron-withdrawing 2-substituent is reflected in diminished π-electron density in the ring, and consequent lower field absorption bands (relative to pyrrole) for the aromatic protons". This deactivation follows the expected order: $CHO > COCH_3 > COOCH_3$. The absorption band of the 4-proton of the simple 2-substituted pyrroles occurs to high field of the absorption band of the 3- and 5- protons, indicating that the 4-position is the site of highest electron density and therefore should be the preferred site of electrophilic attack. Thus, the n. m. r. results corroborate the theoretical and experimental data discussed previously.

The small solvent effect on chemical shifts of the aromatic protons, observed in solvents more basic than carbon tetrachloride, would appear to result from specific interactions with the solvent.

Average coupling constants observed for the 2-substituted pyrroles and the isopropylated substrates are as follows:

J_{13} = 2.8 c.p.s. J_{34} = 3.8 c.p.s.
J_{14} = 2.5 c.p.s. J_{45} = 2.5 c.p.s.
J_{15} = 3.0 c.p.s. J_{35} = 1.5 c.p.s.

The values are in agreement with those reported by Gronowitz <u>et al.</u> (66).

TABLE III

N.M.R. Chemical Shifts (τ)

Compound	Solvent	Aliphatic		ester	Aromatic		
		C-CH_3*	C-H*	OCH_3	3-	4-	5-
Pyrrole					6.18	6.18	6.56
Methyl 1-pyrrolecarboxylate	CCl_4			6.15	-	3.84	2.80
Methyl 1,2-pyrroledicarboxylate	$CDCl_3$			6.00(N) 6.14(C)	3.05	3.76	2.61
Methyl 1,3-pyrroledicarboxylate	$CDCl_3$			5.96(N) 6.14(C)	2.07(2-)	3.32	2.96
Methyl 2-pyrrolecarboxylate	CCl			6.17	3.27	3.83	3.09
	$CDCl_3$			6.13	3.02	3.70	3.02
Methyl 4-isopropyl-2-pyrrolecarboxylate	CCl_4	8.81	7.12	6.19	3.32	-	3.32
Methyl 4-isopropyl-2-pyrrolecarboxylate	CCl_4	8.70	7.09	6.17	3.28	4.11	-
	$CDCl_3$	8.72	7.00	6.17	3.13	4.00	-
Methyl 4,5-diisopropyl 2-pyrrolecarboxylate	CCl_4	8.83(4-) 8.68(5-)	7.01 (2 overlap)	6.17 6.17	3.37 3.37	- -	- -
				aldehyde CHO			
2-Pyrrolecarboxaldehyde	CCl_4			0.52	3.06	3.73	2.81
	$CDCl_3$			0.47	2.96	3.64	2.79
	CH_2Cl_2			0.48	2.97	3.65	2.78
	CH_3NO_2			0.48	2.94	3.62	2.73

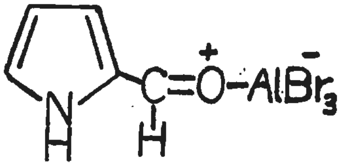
TABLE III (cont'd)

N.M.R. Chemical shifts (τ)

Compound	Solvent	Aliphatic C-CH_3*	 C-H*	ester OCH_3	Aromatic 3-	 4-	 5-
4-Isopropyl-2-pyrrole-carboxaldehyde	CCl_4	8.77	7.14	0.62	3.20	-	2.98
	$CDCl_3$	8.78	7.12	0.53	3.11	-	2.98
				ketone $COCH_3$			
2-Acetylpyrrole	CCl_4	-	-	7.58	3.17	3.85	2.94
4-Isopropyl-2-acetyl-pyrrole	CCl_4	8.81	7.18	7.63	3.28	-	3.11
4,5-Diisopropyl-2-acetylpyrrole	CCl_4	8.79(4-) 8.66(5-)	6.99 (2 overlap)	7.66	3.34	-	-

*All absorption bands assigned to isopropyl groups displayed the expected splitting. Thus the methyl group absorptions appeared as doublets and the methine proton resonances as discernible septets.

A study was made of the effect of complex formation with aluminum halide on the chemical shifts of the protons of the substrate molecules. Complexes between Lewis acids and carbonyl compounds are well known, the nature of these complexes having been shown by infrared spectroscopy to involve a dative bond between the oxygen and the Lewis acid (67). Thus the 2-pyrrolecarboxyaldehyde-aluminum bromide complex, for example, may be represented by XX, implying enhanced electron withdrawal from the ring and in particular from the 3- and 5- positions. This decrease in electron density should be reflected by changes in the resonance of the ring protons to lower field (negative $\Delta\tau$).



XX

This was found to be the case as shown by Table IV (wherein $\Delta\tau$ values are taken relative to chemical shifts for the uncomplexed pyrrole derivatives in the same solvent). It is immediately seen that, while all ring positions are deactivated, in each case electron withdrawal is much greater from the 3- and 5- positions than from the 4- positions. This parallels the general result from the m.o. calculations discussed previously; complex formation should lead to a great increase in the localization energies for electrophilic attack at the 3- and 5- positions thereby leaving the 4- position the most susceptible to electrophilic substitution. Complex formation by the ester leads to substantially less deactivation (by 0.3 to 0.5 p.p.m.)

TABLE IV

Effect of Complex Formation on Chemical Shifts

		$\Delta\tau$					
Complex	Solvent	3-	4-	5-	$COCH_3$	OCH_3	CHO
2-Acetyl-pyrrole. $AlBr_3$	CH_3NO_2	-0.92	-0.51	-0.89	-0.58		
Methyl-2-pyrrolecarboxylate. $AlBr_3$	CH_3NO_2	-0.52	-0.23	-0.42		-0.25	
2-Pyrrolecarboxaldehyde. $AlBr_3$	CH_3NO_2	-0.93	-0.54	-0.92			+0.67
2-Pyrrolecarboxaldehyde. $AlCl_3$	CH_3NO_2	-0.93	-0.54	-0.92			+0.67
2-Pyrrolecarboxaldehyde. $AlBr_3$	ethylene chloride	-0.89	-0.52	-0.86			+0.52

than was observed for the ketone and aldehyde. This suggests that the reason the 4-isopropyl-2-aldehyde and the 4-isopropyl-2-ketone do not rearrange lies in the great increase in activation energy (relative to the ester) for the formation of the 5- σ-complex brought about by complexing of the carbonyl. With the ester the deactivation is apparently not sufficient to preclude rearrangement. These results may also explain why the ester, but not the aldehyde on ketone, undergoes the Friedel-Crafts reaction in nitromethane solution.

The absorption bands of the ketone $-CH_3$ and ester $-OCH_3$ are moved to lower field by complex formation, while that of the aldehyde -CHO is changed to higher field. It is supposed that the low field position of the aldehydic proton resonance is due to the diamagnetic anisotropy of the carbonyl bond, which causes the proton to be in a deshielding portion of the induced magnetic field. Presumably the withdrawal of π-electrons from the bond through complex formation decreases the strength of the effective induced field and leads to a shift in the position of the absorption to higher field.

(ii) Ultraviolet spectra:

Ultraviolet spectra of some substituted pyrroles are recorded in Table V.

In general, substitution of alkyl groups shifts the absorption maxima to longer wavelengths. This is particularly true for the K-band. Changes in the extinction coefficient do not appear to follow any simple pattern.

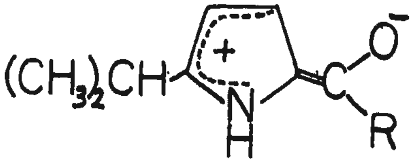
TABLE V

Ultraviolet spectra of substituted pyrroles

Substituent at position			Band E		Band K	
2-	4-	5-	λmax (mμ)	log ε	λmax (mμ)	log ε
$COOCH_3$	-	-	233.5	3.72	265.5	4.21
$COOCH_3$	i-Pr	-	232.5	3.95	273.5	4.20
$COOCH_3$	-	i-Pr	233	3.46	277.5	4.31
COOH	-	-	222[a]	3.65	258.	4.10
COOH	i-Pr	-	237	3.77	272.5	4.15
COOH	-	i-Pr	231	3.52	277	4.02
COOH	i-Pr	i-Pr	235	3.60	283.5	4.23
CHO	-	-	253[b]	3.70	289.5[b]	4.45
CHO	i-Pr	-	257.5	3.84	302.	4.20
Dimethyl 1,3-pyrroledicarboxylate			208	4.37	233	4.08

(a) Ref. (68). (b) Ref.(69) gives λmax = 252, 289.5 mμ (log ε 3.70, 4.22).

The bathochromic shifts in the K-band appear to be greater per isopropyl group, than those observed by Eisner and Gore (70) for methyl substitution. In contrast to the results of these authors, who found the bathochromic shift to be independent of position of substitution, we find the shift for 5-substitution to be substantially greater than for substitution at the 4-position. This may be attributed to a more facile electron donation from the 5-isopropyl group (the 5-position being conjugated with the 2-substituent) and therefore a greater stabilization of the dipolar contribution, XXI, to the excited state.



$R = -OCH_3, -OH, -H$

XXI

This would result in a lower energy transition and a greater bathochromic shift for the 5-alkyl than for the 4-alkyl derivative.

(ii) **Infrared spectra:**

The carbonyl and N-H absorption frequencies for several substituted pyrrole derivatives are given in Table VI.

TABLE VI

I. R. Absorption of pyrroles

Compound	C=O(cm)	NH(cm^{-1})
Methyl 2-pyrrolecarboxylate	1681	3290
Methyl 4-isopropyl-2-pyrrolecarboxylate	1698	3297
Methyl 5-isopropyl-2-pyrrolecarboxylate	1690	3300
Methyl 4,5-diisopropyl-2-pyrrolecarboxylate	1680	3320
2-Pyrrolecarboxylic acid	1700	3355
4-Isopropyl-2-pyrrolecarboxylic acid	1695	3368
5-Isopropyl-2-pyrrolecarboxylic acid	1660	3404
4,5-Diisopropyl-2-pyrrolecarboxylic acid	1680	3297
2-Pyrrolecarboxyaldehyde	1660	3260
4-Isopropyl-2-pyrrolecarboxaldehyde	1655	-
2-Acetylpyrrole	1635	3280
4-Isopropyl-2-acetylpyrrole	1635	-
4,5-Diisopropyl-2-acetylpyrrole	1640	3290
Dimethyl 1,3-pyrroledicarboxylate	1720[a] 1760[b]	-
Dimethyl 1,2-pyrroledicarboxylate	1730[a] 1760[b]	-

(a) C-COOCH$_3$ (b) N-COOCH$_3$

7. EXPERIMENTAL

General:

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded by a Unicam SP100 Spectrophotometer using the potassium chloride disc technique (2 mg. of sample in 200 mg. KCl).

Ultraviolet spectra were determined with a Beckman DK-2A Recording Spectrophotometer; samples were dissolved in ethanol (95%) at a concentration of 10 mg. per litre. pKa's were determined spectrophotometrically as described by Jaffé and Orchin (71).

The nuclear magnetic resonance spectra were determined at 60 Mc/s in carbon tetrachloride, unless otherwise noted, 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.

Analyses of reaction mixtures were carried out by means of gas-liquid partition chromatography using a Beckman GC-2A Gas Chromatograph, equipped with a 30 inch column (Beckman number 70007) packed with Carbowax 4000 dioleate on firebrick and operated at 190°C with helium as the carrier gas (inlet pressure: 30 p.s.i.g.). Analyses were accurate to ± 2% as shown by gas chromatographic examination of a series of known mixtures.

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

Methyl 2-Pyrrolecarboxylate:

This compound was prepared by an adaptation of the Grignard method of Maxim et al. (55) for the ethyl ester. The reaction vessel was a 2 liter 3-neck round bottom flask equipped with a stirrer, dropping funnel and condenser. To a cold solution of ethylmagnesium bromide (1.40 moles) in 400 ml of ethyl ether was added pyrrole (96 g, 1.44 mole) in 100 ml of ether. The reaction mixture was stirred for 1 hour at room temperature and then cooled as methyl chloroformate (0.95 mole) in 100 ml of ether was added dropwise. The reaction mixture was stirred for one hour and then carefully hydrolysed with 250 ml of 10% ammonium chloride solution. The aqueous layer was separated and extracted with ether. After the combined ether extracts were dried over anhydrous sodium sulphate, the ether was removed by distillation and the product was vacuum distilled: b.p. 115-120° at 12 mm, yield 25%. The methyl 2-pyrrolecarboxylate was crystallized from methanol, m.p. 73° (57).

From the forerun was obtained a very small amount of methyl 1-pyrrolecarboxylate b.p. 57-59° at 14 mm (N_D^{22} 1.483). Gabel (72) reports b.p. 71-73° at 21 mm (N_D^{22} 1.487).

A higher boiling compound was separated from 2-ester residue by fractional crystallization from hexane to give a white solid, m.p. 142-143.5°. Infrared and n.m.r. spectra showed this compound to be methyl 1,3-pyrroledicarboxylate. Analysis, calculated: C, 52.46; H, 4.95; N, 7.65; found: C, 52.53; H, 5.06; N, 7.82.

Dimethyl 1,3-pyrroledicarboxylate was refluxed two hours in aqueous methanolic potassium hydroxide. The methanol was distilled and the aqueous solution was washed with ether to remove unreacted ester. Acidification with dilute hydrochloric acid resulted in copious evolution of carbon dioxide. The 3-pyrrolecarboxylic acid was extracted in ether and crystallized from methanol, m.p. 144.5 - 145.5°. Its infrared spectrum was identical to that of an authentic specimen of 3-pyrrolecarboxylic acid and the mixed melting point was not depressed.

Also isolated was the dimethyl 1,2-pyrroledicarboxylate reported by Hodge and Rickards (57), m. p. 44-45°. Its infrared spectrum was identical to that of an authentic specimen and the mixed melting point was undepressed.

2-Pyrrolecarboxaldehyde:

This was prepared by the method of Silverstein *et al.* (59). The reaction vessel was a 3 litre three-necked round bottomed flask, equipped with stirrer, dropping funnel, and condenser (with drying tube). To dimethylformamide (80 g, 1.1 moles) was added slowly phosphorus oxychloride (169 g, 1.1 moles), the internal temperature being maintained at 10 - 20°. The mixture was stirred at room temperature for fifteen minutes and then ethylene chloride (250 ml) was added and the solution cooled to 5° by application of an ice bath. A solution of pyrrole (67 g, 1.0 mole) in ethylene chloride (250 ml) was added over a period of one hour whereupon the ice bath was replaced by a heating mantle and the mixture stirred at the reflux temperature for 15 minutes during which time there was copious evolution of hydrogen chloride. The mixture was cooled to 25° and to it was added a solution of 750 g (5.5 moles) of sodium acetate trihydrate in 1 litre of water, very slowly at first, then as rapidly as possible. The reaction mixture was then refluxed for 30 minutes to complete the hydrolysis. The ethylene chloride layer was separated and the aqueous solution extracted with ether. The combined organic extracts were washed three times with 100 ml portions of saturated aqueous sodium carbonate solution, then dried over anhydrous sodium carbonate. The solvents were removed by distillation and the product vacuum distilled: b.p. 69-71° at 1 mm; yield: 70%. The 2-pyrrolecarboxaldehyde was crystallized from petroleum ether, m.p. 44-45°, literature m.p. 44-45°(59).

<u>2-Acetylpyrrole:</u>

2-Acetylpyrrole was prepared by the method of Oddo and Dainotti (11). To pyrrolemagnesium bromide (1.0 mole) in anhydrous ether (500 ml) was added acetic anhydride (108 g. 1.0 mole) in ether (100 ml) slowly with cooling. The reaction mixture was refluxed 30 minutes, then cooled and hydrolyzed with 800 ml of a 10% ammonium chloride solution. The aqueous layer was separated and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate, the solvent removed by distillation and the product vacuum distilled: b.p. 90-110° at 7 mm. yield 45%. The ketone was crystallized from methanol, m.p. 88-89°, literature m.p. 90° (11).

General Procedure for Alkylations:

The reaction vessel was a 100 ml three-neck round bottom flask, equipped with stirrer, dropping funnel, and condenser with drying tube, immersed in an oil bath maintained at 50°. 0.01 moles of the starting material (pyrrole-2-methyl ester, 2-aldehyde, 2-methylketone) and 0.012 moles of the anhydrous catalyst (aluminum chloride, aluminum bromide, gallium chloride, titanium tetrachloride, ferric chloride) were placed in the reaction vessel with 40 ml of carbon disulfide. Isopropyl chloride (0.01 mole) in 10 ml of carbon disulfide was added after fifteen minutes and the reaction mixture refluxed for the required period. The reaction was quenched by pouring on ice. The aqueous layer was separated, saturated with sodium chloride and extracted with ether. The combined organic extract was washed with sodium acetate (saturated aqueous solution) and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analysed by gas chromatography.

Isolation of Alkylation Products:

The various unreacted starting materials and most of the various isopropylated reaction products were separated by adsorption chromatography on alumina (Fisher Reagent Grade) and fractional crystallization from methanol. The melting points of the pure materials and the results from elemental analysis are given in Table VII, and their retention times on the gas chromatograph are presented in Table VIII. Spectral data are recorded elsewhere.

TABLE VII

Elemental Analysis

Compound	calculated C	calculated H	calculated N	found C	found H	found N
Methyl 4,5-diisopropyl-2-pyrrolecarboxylate, m.p. 120.5-121.0° $C_{12}H_{19}NO_2$.	68.87	9.15	6.69	68.77	9.43	6.92
Methyl 4-isopropyl-2-pyrrolecarboxylate, m.p. 89-90° (lit.90°(61)). $C_9H_{13}NO_2$.	64.65	7.84	8.29	65.05	7.74	8.50
Methyl 5-isopropyl-2-pyrrolecarboxylate, m.p.59.5-61° $C_9H_{13}NO_2$.	64.65	7.84	8.38	64.67	7.61	8.29
4-Isopropyl-2-pyrrolecarboxaldehyde m.p.31° $C_8H_{11}NO$.	70.04	8.09	10.20	70.42	8.06	10.16
4-Isopropyl-2-pyrrole carboxaldoxime, m.p.124° $C_8H_{12}N_2O$.	63.14	7.95	18.40	63.20	7.76	18.39
Semicarbazone of 4-isopropyl-2-pyrrolecarboxaldehyde m.p. 173-175°. $C_9H_{14}N_4O$	55.66	7.26	28.84	55.85	7.82	28.24
4-Isopropyl-2-acetylpyrrole, m.p. 46.5-47.5°. $C_9H_{13}NO$.	71.52	8.61	9.27	71.51	8.85	9.40
4,5-Diisopropyl-2-acetylpyrrole m.p. 103-4°. $C_{12}H_{19}NO$	74.57	9.91	7.25	74.58	9.85	7.41

TABLE VIII

Gas chromatograph retention times for 2-substituted pyrroles and their alkylation products

		Time(min.)	
Substituents	2-COOCH$_3$	2-CHO	2-COCH$_3$
Starting material	4.00	3.90	3.40
5-Isopropyl-	4.85	4.90	4.20
4,5-Diisopropyl-	6.55	6.85	5.70
4-Isopropyl-	7.40	8.40	7.00

Methyl 5-Isopropyl-2-pyrrolecarboxylate:

To a cold solution of 0.171 moles of ethylmagnesium bromide in 300 ml of ether was added a solution of 0.717 moles of isopropylpyrrole (> 95% purity) in 25 ml of ether. The reaction mixture was refluxed for one hour and then cooled while methyl chloroformate (0.171 mole) in 25 ml of ether was added dropwise. The reaction mixture was again refluxed one hour, then carefully hydrolyzed with 100 ml of 10% ammonium chloride solution. The aqueous layer was separated and extracted with ether. After the combined ether extracts were dried over anhydrous sodium sulfate, the ether was removed by distillation and the product, methyl 5-isopropyl-2-pyrrolecarboxylate, vacuum distilled. Gas chromatographic analysis showed that this material was homogeneous, the retention time (4.55 min.) corresponding to that of the alkylation product to which this structure had been tentatively assigned. The 5-isopropyl-2-ester was crystallized from methanol, m.p. 59.5-61°, and was shown to be identical to the alkylation product by mixed melting point and comparison of infrared spectra.

Rearrangement of Methyl 4-Isopropyl-2-pyrrolecarboxylate:

Methyl 4-isopropyl-2-pyrrolecarboxylate (0.001 mole) and aluminum chloride (0.0024 mole) in 10 ml of carbon disulfide were refluxed (50°) for two hours in the presence of a continuous stream of dry hydrogen chloride. The reaction mixture was worked up in the usual manner and the products analyzed by gas chromatography:

Product	Mole %
Methyl 4-isopropyl-2-pyrrolecarboxylate	35.2
Methyl 5-isopropyl-2-pyrrolecarboxylate	50.8
Methyl 2-pyrrolecarboxylate	6.9
Methyl 4,5-diisopropyl-2-pyrrolecarboxylate	7.0

Attempted Rearrangement of Methyl 5-Isopropyl-2-pyrrolecarboxylate:

The 5-isopropyl-2-ester and aluminum chloride in carbon disulfide were refluxed at 50° for two hours in the presence of dry hydrogen chloride. Gas chromatography revealed no rearrangement or disproportionation of isopropyl groups.

Isopropylation of Methyl 4-Isopropyl-2-pyrrolecarboxylate:

Methyl 4-isopropyl-2-pyrrolecarboxylate was reacted with isopropyl chloride and aluminum chloride using the general procedure. After a reaction time of one hour at 50° it was found that 15% dialkylation had occurred.

Isopropylation of Methyl 5-Isopropyl-2-pyrrolecarboxylate:

Methyl 5-isopropyl-2-pyrrolecarboxylate was reacted with isopropyl chloride and aluminum chloride using the general procedure. After a reaction time of fifteen minutes at 50° it was found that 35% of the starting material had been diisopropylated giving methyl 4,5-diisopropyl-2-pyrrolecarboxylate.

Attempted Disproportionation of Methyl 4,5-Diisopropyl-2-pyrrolecarboxylate:

Methyl 4,5-diisopropyl-2-pyrrolecarboxylate (0.001 mole) and methyl 2-pyrrolecarboxylate (0.001 mole) dissolved in 10 ml of carbon disulfide were refluxed for four hours in the presence of anhydrous aluminum chloride (0.0024 mole) while a continuous stream of dry hydrogen chloride was passed through the reaction mixture. The reaction mixture was worked up in the usual manner and the products analyzed by gas chromatography. No elimination or disproportionation of isopropyl groups was observed.

Preparation of Acids:

The corresponding acids of the alkylated esters were prepared by refluxing the esters in 20% aqueous potassium hydroxide solution for one to four hours. The unreacted ester was extracted in ether and the aqueous layer acidified with dilute hydrochloric acid. The acid derivative was extracted in ether, dried over sodium sulfate, and recrystallized from methanol or sublimed under vacuum. Spectral data are recorded elsewhere. Melting points and pKa's as determined spectrophotometrically are as follows:

Acid	M.P.	pKa
2-pyrrolecarboxylic acid	210 - 212° (d)[a]	4.55[b]
4-isopropyl-2-pyrrolecarboxylic acid	182 - 184° (d)[c]	4.77
5-isopropyl-2-pyrrolecarboxylic acid	133 - 134°	4.89
4,5-diisopropyl-2-pyrrolecarboxylic acid	93 - 94°	4.97

(a) Ref. (73) gives m. p. 204 - 205°

(b) Ref. (74) gives pKa 4.38.

(c) Ref. (61) gives m. p. 182 - 184°

4-Isopropyl-2-pyrrolecarbaldoxime:

4-Isopropyl-2-pyrrolecarboxaldehyde (1.8 g, 0.013 mole) in 5 ml of ethanol was added to a solution of hydroxylamine hydrochloride (0.90 g, 0.013 mole) and sodium acetate trihydrate (1.80 g. 0.013 mole) in 10 ml of water. The mixture was heated on a steam bath for five minutes, then refrigerated overnight. The oxime was filtered and recrystallized from ethanol, m. p. 124°; yield: 88 %.

4-Isopropyl-2-pyrrolecarboxaldehyde Semicarbazone:

The semicarbazone was prepared by the method of Vogel (75) m. p. 173-175° (ethanol/water).

Attempted Rearrangement, Disproportionation, and Alkylation of Isopropyl Derivatives of 2-Pyrrolecarboxaldehyde and 2-Acetylpyrrole:

Attempts to alkylate or rearrange 4-isopropyl-2-pyrrolecarboxaldehyde using the general procedure outlined for the ester and a reaction time of two hours led to only a trace ($< 1\%$) of the expected products as shown by gas chromatography.

Similar experiments on 4-isopropyl-2-acetylpyrrole while not conclusive, indicated that the extent of rearrangement is greatly reduced compared with the 4-isopropyl-2-ester; alkylation produced only a trace of the diisopropyl compound. An attempted disproportionation of 4,5-diisopropyl-2-acetylpyrrole was not successful.

Oxidation of 4-Isopropyl-2-pyrrolecarboxaldehyde:

4-Isopropyl-2-pyrrolecarboxaldehyde was oxidized to 4-isopropyl-2-pyrrolecarboxylic acid by the method of Hodge and Rickards (57). The mixed melting point with a specimen of the acid obtained from hydrolysis of the corresponding ester was not depressed.

APPENDIX 1. CALCULATION OF β .

A least squares plot of the logarithms of the partial rate factors (log f^{p}_{ArH}) for the nitration of several aromatic hydrocarbons against the corresponding localization energies gives a straight line of slope equal to β /2.303 RT (Figure 11).,

TABLE XIX

Partial rate factors[a] and localization energies for aromatic hydrocarbons

Hydrocarbon	position	log f^{p}_{ArH} [b]	E (p)[c]
Benzene	-	0.000	2.536
Diphenyl	2	1.477	2.400
Diphenyl	4	1.255	2.477
Naphthalene	1	1.672	2.299
Naphthalene	2	1.699	2.480
Phenanthrene	1	2.566	2.318
Phenanthrene	2	1.964	2.498
Phenanthrene	3	2.477	2.454
Phenanthrene	4	1.897	2.366
Phenanthrene	9	2.690	2.299
Pyrene	1	4.231	2.190
Triphenylene	1	2.778	2.378
Triphenylene	2	2.778	2.477
Chrysene	2	3.544	2.251
Perylene	3	4.887	2.140
Benzo(α)pyrene	6	5.035	1.961
Coronene	-	3.061	2.306
Anthracene	9	5.193	1.928

(a) Reactions carried out in acetic anhydride at 25°C.

(b) Ref. (76). (c) Ref. (6) page 336.

The equation of the line was found to be

$y = -7.172\ x + 19.42$

whence $\beta = -9.78$ k.cal.

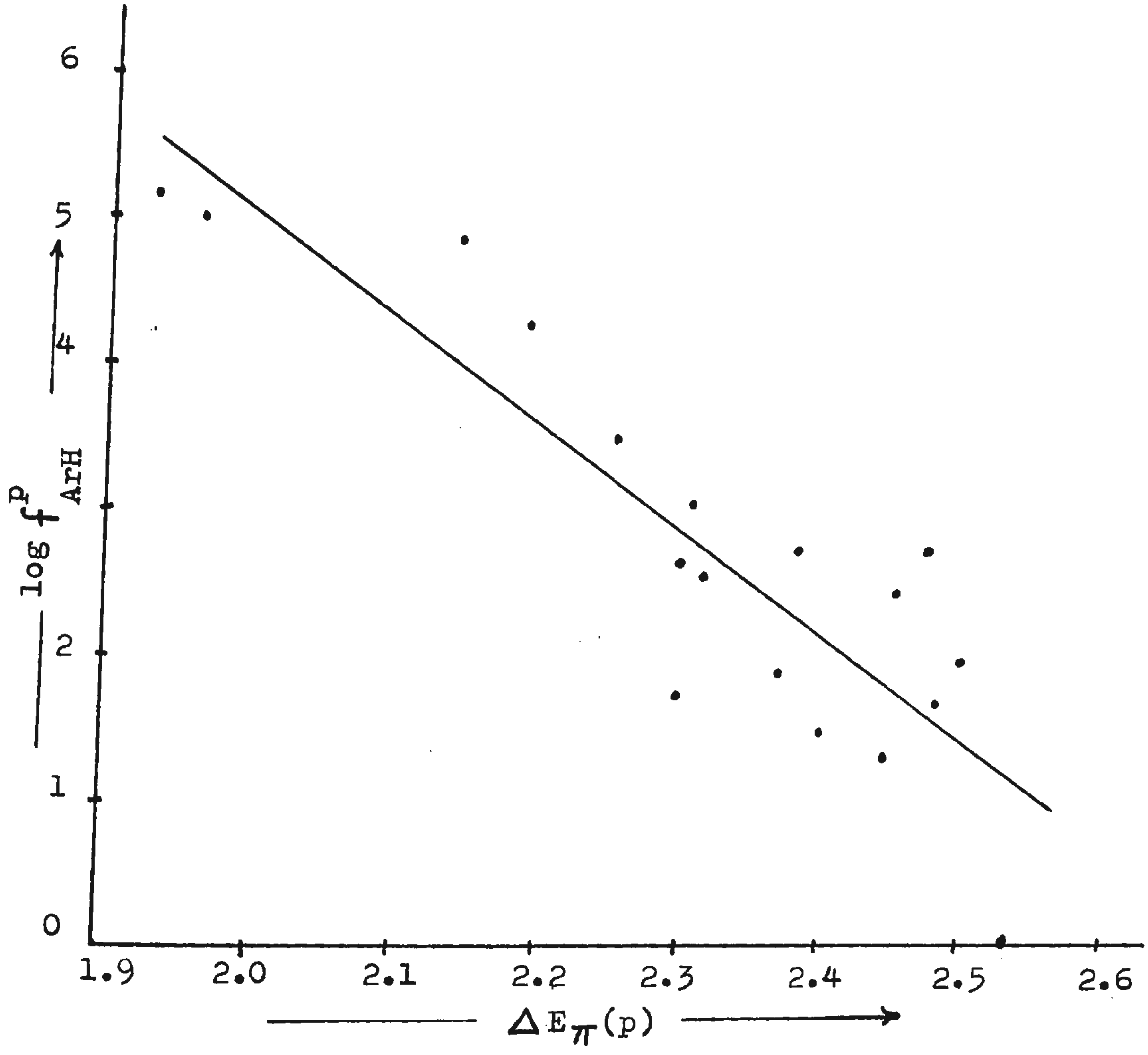
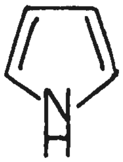


Figure 11. Plot of log f^{p}_{ArH} vs localization energies.

APPENDIX 2: MOLECULAR ORBITAL CALCULATIONS

(1) Pyrrole



The secular determinant for pyrrole is written as follows:

$$\begin{vmatrix} x + h & 1 & 0 & 0 & 1 \\ 1 & x + h' & 1 & 0 & 0 \\ 0 & 1 & x & 1 & 0 \\ 0 & 0 & 1 & x & 1 \\ 1 & 0 & 0 & 1 & x + h' \end{vmatrix} = 0$$

whence the polynomial equation becomes:

$$x^5 + (2h' + h)\, x^4 + (h'^2 + 2hh' - 5)\, x^3 + (hh'^2 - 6h' - 3h)\, x^2 - (h'^2 + 4hh' - 5)\, x - (hh'^2 - 2h' - h - 2) = 0.$$

The roots of this equation and the corresponding E_π values are tabulated on the following page.

h' = 0	ROOTS OF POLYNOMIAL					E π(pyrrole)
h = -1.0	-1.861	-0.618	-0.254	1.618	2.115	-5.466
-0.8	-1.881	-0.618	-0.319	1.618	2.000	-5.636
-0.6	-1.904	-0.618	-0.388	1.618	1.893	-5.820
-0.4	-1.931	-0.618	-0.462	1.618	1.793	-6.022
-0.2	-1.963	-0.618	-0.539	1.618	1.702	-6.240
0.0	-2.000	-0.618	-0.618	1.618	1.618	-6.472
0.2	-2.043	-0.618	-0.698	1.618	1.541	-6.718
0.4	-2.094	-0.618	-0.778	1.618	1.472	-6.980
0.6	-2.154	-0.618	-0.856	1.618	1.410	-7.256
0.8	-2.223	-0.618	-0.930	1.618	1.354	-7.542
1.0	-2.303	-0.618	-1.000	1.618	1.303	-7.842
1.2	-2.393	-0.618	-1.064	1.618	1.257	-8.150
1.4	-2.495	-0.618	-1.121	1.618	1.215	-8.468
1.6	-2.607	-0.618	-1.171	1.618	1.179	-8.792
1.8	-2.730	-0.618	-1.216	1.618	1.145	-9.128
2.0	-2.861	-0.618	-1.254	1.618	1.115	-9.466

h' = 0.20						
h = 0.0	-2.083	-0.766	-0.633	1.566	1.516	-6.964
0.2	-2.126	-0.766	-0.708	1.566	1.434	-7.200
0.4	-2.176	-0.766	-0.783	1.566	1.360	-7.450
0.6	-2.234	-0.766	-0.859	1.566	1.293	-7.718
0.8	-2.301	-0.766	-0.931	1.566	1.232	-7.996
1.0	-2.378	-0.766	-1.000	1.566	1.178	-8.288
1.2	-2.464	-0.766	-1.064	1.566	1.129	-8.588
1.4	-2.562	-0.766	-1.123	1.566	1.085	-8.902
1.6	-2.669	-0.766	-1.176	1.566	1.045	-9.222
1.8	-2.787	-0.766	-1.223	1.566	1.009	-9.552
2.0	-2.913	-0.766	-1.264	1.566	0.977	-9.886

h' = 0	ROOTS OF POLYNOMIAL				$E\ \pi$(pyrrole)
h = 0.0	-2.105	-0.804	-0.637	1.554	-7.096
0.2	-2.147	-0.804	-0.711	1.554	-7.324
0.4	-2.198	-0.804	-0.785	1.554	-7.572
0.6	-2.255	-0.804	-0.859	1.554	-7.836
0.8	-2.321	-0.804	-0.931	1.554	-8.112
1.0	-2.397	-0.804	-1.000	1.554	-8.402
1.2	-2.483	-0.804	-1.064	1.554	-8.702
1.4	-2.580	-0.804	-1.123	1.554	-9.014
1.6	-2.686	-0.804	-1.177	1.554	-9.334
1.8	-2.802	-0.804	-1.225	1.554	-9.662
2.0	-2.927	-0.804	-1.267	1.554	-9.996

(2) Wheland intermediate for α-substitution in pyrrole

The secular determinant for the Wheland intermediate for α-substitution in pyrrole is written as follows:

$$\begin{vmatrix} x+h & 0 & 0 & 1 \\ 0 & x & 1 & 0 \\ 0 & 1 & x & 1 \\ 1 & 0 & 1 & x+h' \end{vmatrix} = 0$$

whence the polynomial equation becomes:

$$x^4 + (h+h')x^3 + (hh' - 3)x^2 - (2h+h')x - (hh' - 1) = 0$$

The roots of this equation and the corresponding E_π values are tabulated below. Note that the corresponding models for radical (r) and nucleophilic (n) substitution differ from the one shown for electrophilic (e) substitution by the one and two extra π-electrons respectively that are placed in the lowest unoccupied molecular orbital, in this case an antibonding m. o.

h' = 0.0	ROOTS OF POLYNOMIAL				$E_{\pi}(\alpha e)$
h = -1.0	-1.532	-0.347	1.000	1.897	-3.758
-0.8	-1.543	-0.387	0.929	1.801	-3.860
-0.6	-1.557	-0.434	0.852	1.738	-3.982
-0.4	-1.573	-0.487	0.772	1.688	-4.120
-0.2	-1.593	-0.549	0.693	1.649	-4.284
0.0	-1.618	-0.618	0.618	1.618	-4.472
0.2	-1.649	-0.693	0.549	1.593	-4.684
0.4	-1.688	-0.772	0.487	1.573	-4.920
0.6	-1.738	-0.852	0.433	1.557	-5.180
0.8	-1.801	-0.929	0.387	1.543	-5.460
1.0	-1.879	-1.000	0.347	1.532	-5.758
1.2	-1.973	-1.062	0.313	1.522	-6.070
1.4	-2.084	-1.114	0.284	1.514	-6.396
1.6	-2.209	-1.157	0.260	1.507	-6.732
1.8	-2.347	-1.192	0.238	1.501	-7.078
2.0	-2.496	-1.220	0.220	1.496	-7.432
h' = 0.20					
h = 0.0	-1.695	-0.645	0.590	1.550	-4.680
0.2	-1.726	-0.712	0.517	1.526	-4.876
0.4	-1.766	-0.783	0.441	1.507	-5.098
0.6	-1.815	-0.857	0.379	1.493	-5.344
0.8	-1.875	-0.930	0.325	1.480	-5.610
1.0	-1.949	-1.000	0.279	1.470	-5.898
1.2	-2.038	-1.063	0.240	1.462	-6.202
1.4	-2.143	-1.118	0.207	1.454	-6.522
1.6	-2.261	-1.165	0.178	1.448	-6.852
1.8	-2.392	-1.204	0.154	1.443	-7.192
2.0	-2.535	-1.236	0.133	1.438	-7.542

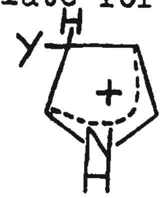
h' = 0.25	ROOTS OF POLYNOMIAL				$E_\pi(\alpha e)$
h' = 0.0	-1.716	-0.652	0.583	1.534	-4.736
0.2	-1.747	-0.716	0.502	1.511	-4.926
0.4	-1.786	-0.786	0.429	1.493	-5.144
0.6	-1.835	-0.858	0.365	1.478	-5.386
0.8	-1.895	-0.931	0.309	1.466	-5.652
1.0	-1.968	-1.000	0.262	1.456	-5.936
1.2	-2.056	-1.063	0.221	1.448	-6.238
1.4	-2.158	-1.119	0.187	1.441	-6.554
1.6	-2.275	-1.167	0.157	1.435	-6.884
1.8	-2.405	-1.207	0.132	1.430	-7.224
2.0	-2.546	-1.240	0.111	1.425	-7.572

The ΔE_π values for α-substitution in pyrrole are given in the following table:

	$\Delta E_\pi(\alpha e)^a$	$\Delta E_\pi(\alpha r)^a$	$\Delta E_\pi(\alpha n)^a$	$\Delta E_\pi(\alpha e)^b$	$\Delta E_\pi(\alpha e)^c$
h = -1.0	1.708	2.709	3.708	-	-
-0.8	1.776	2.705	3.634	-	-
-0.6	1.838	2.690	3.542	-	-
-0.4	1.902	2.674	3.446	-	-
-0.2	1.956	2.649	3.342	-	-
0.0	2.000	2.618	3.236	2.284	2.356
0.2	2.034	2.583	3.132	2.324	2.400
0.4	2.060	2.547	3.034	2.352	2.428
0.6	2.076	2.509	2.942	2.374	2.448
0.8	2.082	2.469	2.856	2.386	2.460
1.0	2.084	2.431	2.778	2.390	2.466
1.2	2.080	2.393	2.706	2.386	2.464
1.4	2.072	2.356	2.640	2.380	2.458
1.6	2.060	2.320	2.580	2.370	2.450
1.8	2.050	2.288	2.526	2.360	2.436
2.0	2.034	2.254	2.474	2.344	2.422

(a) h' = 0.0; (b) h' = 0.2; (c) h' = 0.25.

(3) Wheland Intermediate for β-substitution in pyrrole



The secular determinant for the Wheland intermediate for β-substitution in pyrrole is written as follows:

$$\begin{vmatrix} x + h & 1 & 0 & 1 \\ 1 & x + h' & 0 & 0 \\ 0 & 0 & x & 1 \\ 1 & 0 & 1 & x + h' \end{vmatrix} = 0$$

whence the polynomial equation becomes:

$$x^4 + (h + 2h')x^3 + (2hh' + h'^2 - 3)x^2 + (hh'^2 - 3h' - h)x - (hh' - 1) = 0$$

The roots of this equation and the corresponding E_π values are as follows:

h' = 0.0	ROOTS OF POLYNOMIAL				E_π (β e)
h = -1.0	-1.356	-0.477	0.738	2.095	-3.666
-0.8	-1.394	-0.505	0.717	1.982	-3.798
-0.6	-1.439	-0.533	0.695	1.877	-3.944
-0.4	-1.491	-0.561	0.671	1.781	-4.104
-0.2	-1.550	-0.590	0.645	1.695	-4.280
0.0	-1.618	-0.618	0.618	1.618	-4.472
0.2	-1.695	-0.645	0.590	1.550	-4.680
0.4	-1.781	-0.671	0.561	1.491	-4.904
0.6	-1.877	-0.695	0.533	1.439	-5.144
0.8	-1.982	-0.717	0.505	1.394	-5.398
1.0	-2.095	-0.738	0.477	1.356	-5.666
1.2	-2.217	-0.756	0.451	1.322	-5.946
1.4	-2.347	-0.773	0.426	1.293	-6.240
1.6	-2.483	-0.788	0.403	1.269	-6.542
1.8	-2.626	-0.802	0.381	1.247	-6.856
2.0	-2.775	-0.814	0.360	1.228	-7.178

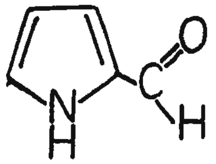
h' = 0.2	ROOTS OF POLYNOMIAL				E_{π} (β e)
h = 0.0	-1.721	-0.726	0.526	1.521	-4.894
0.2	-1.793	-0.749	0.493	1.449	-5.081
0.4	-1.874	-0.771	0.459	1.386	-5.290
0.6	-1.964	-0.793	0.424	1.332	-5.514
0.8	-2.063	-0.813	0.389	1.286	-5.752
1.0	-2.170	-0.832	0.356	1.246	-6.004
1.2	-2.286	-0.849	0.323	1.212	-6.270
1.4	-2.410	-0.865	0.291	1.183	-6.550
1.6	-2.541	-0.880	0.262	1.158	-6.842
1.8	-2.678	-0.894	0.235	1.137	-7.144
2.0	-2.822	-0.906	0.210	1.118	-7.456

h' = 0.25					
h = 0.0	-1.748	-0.756	0.506	1.498	-5.008
0.2	-1.819	-0.778	0.471	1.425	-5.194
0.4	-1.898	-0.799	0.436	1.361	-5.394
0.6	-1.987	-0.819	0.400	1.306	-5.612
0.8	-2.083	-0.839	0.363	1.260	-5.844
1.0	-2.190	-0.857	0.328	1.220	-6.094
1.2	-2.304	-0.874	0.293	1.186	-6.356
1.4	-2.426	-0.890	0.260	1.156	-6.632
1.6	-2.556	-0.905	0.229	1.132	-6.922
1.8	-2.692	-0.918	0.200	1.110	-7.220
2.0	-2.835	-0.931	0.174	1.092	-7.532

	$\Delta E_{\pi}(\beta e)^{a}$	$\Delta E_{\pi}(\beta r)^{a}$	$\Delta E_{\pi}(\beta n)^{a}$	$\Delta E_{\pi}(\beta e)^{b}$	$\Delta E_{\pi}(\beta e)^{c}$
h = 1.0	1.800	2.538	3.276	-	-
-0.8	1.838	2.555	3.272	-	-
-0.6	1.876	2.571	3.266	-	-
-0.4	1.918	2.589	3.260	-	-
-0.2	1.960	2.605	3.250	-	-
0.0	2.000	2.618	3.236	2.070	2.084
0.2	2.038	2.628	3.218	2.116	2.132
0.4	2.076	2.637	3.198	2.160	2.178
0.6	2.112	2.645	3.178	2.204	2.222
0.8	2.144	2.649	3.154	2.244	2.268
1.0	2.176	2.653	3.130	2.284	2.308
1.2	2.204	2.655	3.106	2.318	2.346
1.4	2.228	2.654	3.080	2.352	2.380
1.6	2.250	2.653	3.056	2.380	2.412
1.8	2.272	2.653	3.034	2.408	2.440
2.0	2.288	2.648	3.008	2.430	2.462

(a) h' = 0.00; (b) h' = 0.20; (c) h' = 0.25.

(4) 2-Pyrrolecarboxaldehyde



The secular determinant for 2-pyrrolecarboxaldehyde is written as follows:

$$\begin{vmatrix} x+h & 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & x+h' & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & x & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & x & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & x+h' & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & x+1' & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & x+1 \end{vmatrix} = 0$$

The coefficients of x^n for the resulting polynomial are tabulated below:

coefficient	x^n
1^*	x^7
$2h' + h + (l + l')$	x^6
$h'^2 + 2hh' + 2h'(l + l') + h(l + l') + ll' - 7$	x^5
$hh'^2 + h'^2(l + l') + 2hh'(l + l') + 2h'll' + hll' - 9h' - 5h - 5(l + l') - l$	x^4
$hh'^2(l + l') + h'^2 ll' + 2hh'll' - 6h'(l + l') - 3h(l + l') - 7hh' - 2h'^2 - lh - lh' - 5ll' + 13$	x^3
$hh'^2 ll' - 2hh'^2 - 6h'll' - 4hh'(l + l') - hh'l - 3hll' - h'^2(l + l') + 9h' + 6h + 3l + 5(l + l') + 2$	x^2
$-4hh'll' - hh'^2(l + l') - h'^2 ll' + 2h'(l + l') + h(l + l') + h'^2 + 5hh' + 2h'(l + l') + 2lh + lh' + 5ll' + 2(l + l') - 6$	x^1
$hh'^2 + hh'l - hh'^2 ll' + hll' + 2h'll' + 2h' + 2ll' - h - l - 2$	x^0

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* The number 1 is denoted by 1^* in this and subsequent equations where there is possibility of confusion between 1^* and the Coulomb inductive parameter, unstarred l.

The roots of the equation and the resulting E_π values are as follows:

ROOTS OF POLYNOMIAL

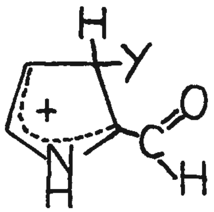
h = 1.28; h' = 0.00; l' = 0.00

								E_π (ald)
l = 0.00	-2.525	-1.316	-1.083	-0.439	0.765	1.465	1.853	-10.726
1.00	-2.539	-1.698	-1.087	-0.708	0.492	1.445	1.816	-12.064
2.00	-2.643	-2.306	-1.089	-0.843	0.365	1.436	1.800	-13.612
3.00	-3.342	-2.474	-1.091	-0.899	0.302	1.431	1.792	-15.612
4.00	-4.252	-2.492	-1.092	-0.926	0.266	1.428	1.787	-17.524

h = 1.28; h' = 0.00; l' = 0.20

l = 1.00	-2.552	-1.754	-1.087	-0.712	0.410	1.430	1.785	-12.210
2.00	-2.673	-2.314	-1.090	-0.867	0.269	1.422	1.772	-13.888
3.00	-3.363	-2.476	-1.092	-0.935	0.203	1.418	1.766	-15.732
4.00	-4.264	-2.496	-1.094	-0.969	0.166	1.415	1.762	-17.646

(5) Wheland intermediate for 3-substitution in 2-pyrrolecarboxaldehyde.



The secular determinant for the Wheland intermediate corresponding to 3-substitution in 2-pyrrolecarboxaldehyde is written as follows:

$$\begin{vmatrix} x + h & 1 & 0 & 0 & 1 & 0 \\ 1 & x + h' & 1 & 0 & 0 & 0 \\ 0 & 1 & x & 0 & 0 & 0 \\ 1 & 0 & 0 & x + h' & 1 & 0 \\ 0 & 0 & 0 & 1 & x + l' & 1 \\ 0 & 0 & 0 & 0 & 1 & x + l \end{vmatrix} = 0$$

The coefficients of x^n for the resulting polynomial are tabulated below:

coefficients	x^n
1^*	x^6
$2n' + h + (l + l')$	x^5
$h'^2 + 2hh' + 2h'(l + l') + h(l + l') + ll' - 5$	x^4
$hh'^2 + h'^2(l + l') + 2hh'(l+l') + 2h'll' + h ll' - 6h' - 3h - 3(l + l') - l$	x^3
$hh'^2(l + l') + h'^2 ll' + 2hh'll' - h'^2 - 4hh' - lh - lh' - h(l + l') - 3h'(l + l') - 3ll' + 6$	x^2
$hh'^2 ll' - hh'^2 - hh'l - hh'(l + l') - 3h'll' - hll' + 3h' + 2h + 2l + (l + l')$	x^1
$-hh'll' + hh' + hl + ll' - 1^*$	x^0

The roots of the equation and the corresponding E_π values are as follows:

ROOTS OF POLYNOMIAL

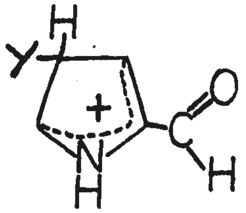
$h = 1.28;\ h' = 0.00;\ l' = 0.00$

							$E_\pi(3)$
l = 0.00	-2.348	-1.306	-0.660	-0.264	1.180	1.589	- 8.628
1.00	-2.365	-1.698	-0.792	-0.052	1.114	1.513	- 9.710
2.00	-2.555	-2.221	-0.873	-0.196	1.080	1.486	-11.298
3.00	-3.336	-2.305	-0.913	-0.259	1.061	1.472	-13.108
4.00	-4.250	-2.317	-0.935	-0.291	1.050	1.464	-15.004

$h = 1.28;\ h' = 0.00;\ l' = 0.20$

l = 1.00	-2.380	-1.753	-0.793	-0.092	1.070	1.468	- 9.852
2.00	-2.592	-2.224	-0.889	-0.256	1.032	1.448	-11.410
3.00	-3.357	-2.307	-0.941	-0.324	1.012	1.438	-13.210
4.00	-4.263	-2.321	-0.970	-0.358	1.000	1.432	-15.108

(6) Wheland intermediate for 4-substitution in 2-pyrrolecarboxaldehyde



The secular determinant for the Wheland intermediate corresponding to 4-substitution in 2-pyrrolecarboxaldehyde is written as follows:

$$\begin{vmatrix} x+h & 1 & 0 & 1 & 0 & 0 \\ 1 & x+h' & 0 & 0 & 0 & 0 \\ 0 & 0 & x & 1 & 0 & 0 \\ 1 & 0 & 1 & x+h' & 1 & 0 \\ 0 & 0 & 0 & 1 & x+l' & 1 \\ 0 & 0 & 0 & 0 & 1 & x+l \end{vmatrix} = 0$$

The coefficients of x^n for the resulting polynomial are tabulated below:

coefficients	x^n
1^*	x^6
$2h' + h + (l + l')$	x^5
$h'^2 + 2hh' + 2h'(l + l') + h(l + l') + ll' - 5$	x^4
$hh'^2 + h'^2(l + l') + 2hh'(l + l') + 2h'll' + hll' - 6h' - 3h - 3(l + l') - 1$	x^3
$hh'^2(l + l') + h'^2ll' + 2ll'hh' - h'^2 - 4hh' - lh' - lh - 3h'(l + l') - h(l + l') - 3ll' + 5$	x^2
$ll'hh' - hh'^2 + lhh' - hh'(l + l') - ll'h - 3ll'h' + 3h' + h + (l + l') + 1$	x^1
$-ll'hh' + hh' + ll' - 1^*$	x^0

The roots of the equation and the corresponding E_π values are as follows:

ROOTS OF POLYNOMIAL

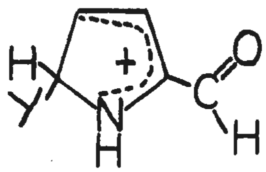
$h = 1.28; \quad h' = 0.00; \quad l' = 0.00$

							$E_\pi(4)$
l = 0.00	-2.385	-1.302	-0.561	+0.419	0.768	1.781	-8.496
1.00	-2.408	-1.668	-0.811	+0.314	0.566	1.726	-9.774
2.00	-2.589	-2.204	-0.925	+0.213	0.523	1.703	-11.436
3.00	-3.340	-2.324	-0.969	+0.154	0.510	1.690	-13.266
4.00	-4.251	-2.342	-0.992	+0.119	0.504	1.681	-15.170

$h = 1.28; \quad h' = 0.00; \quad l' = 0.20$

l = 1.00	-2.427	-1.718	-0.812	0.265	0.531	1.681	- 9.914
2.00	-2.626	-2.207	-0.941	0.132	0.502	1.660	-11.548
3.00	-3.362	-2.327	-0.997	0.063	0.494	1.649	-13.372
4.00	-4.264	-2.348	-1.025	0.024	0.490	1.642	-15.274

(7) Wheland intermediate for 5-substitution in 2-pyrrolecarboxaldehyde



The secular determinant for the Wheland intermediate corresponding to 5-substitution in 2-pyrrolecarboxaldehyde is written as follows:

$$\begin{vmatrix} x+h & 0 & 0 & 1 & 0 & 0 \\ 0 & x & 1 & 0 & 0 & 0 \\ 0 & 1 & x & 1 & 0 & 0 \\ 1 & 0 & 1 & x+h' & 1 & 0 \\ 0 & 0 & 0 & 1 & x+l' & 1 \\ 0 & 0 & 0 & 0 & 1 & x+l \end{vmatrix} = 0$$

The coefficients of x^n for the resulting polynomial are tabulated below:

coefficients	x^n
1^*	x^6
$(l + l') + h + h'$	x^5
$hh' + h'(l + l') + h(l + l') + ll' - 5$	x^4
$hh'(l + l') + ll'h' + ll'h - 3(l + l') - 2h' - 4h - l$	x^3
$hh'll' - h'(l + l') - 2h(l + l') - 2hh' - 3ll' - hl + 5$	x^2
$-hh'(l + l') - 2ll'h - ll'h' + 3h + h' + l + (l + l')$	x^1
$-hh'll' + hh' + hl + ll' - 1^*$	x^0

The roots of the equation and the corresponding E_π values are as follows:

ROOTS OF POLYNOMIAL

h = 1.28; h' = 0.00; l' = 0.00

							$E_\pi(5)$
l = 0.00	-2.211	-1.133	-1.000	0.216	1.000	1.849	-8.688
1.00	-2.258	-1.543	-1.083	-0.048	0.844	1.808	-9.768
2.00	-2.557	-2.012	-1.089	-0.198	0.785	1.791	-11.316
3.00	-3.340	-2.115	-1.090	-0.273	0.757	1.782	-13.090
4.00	-4.251	-2.138	-1.092	-0.316	0.741	1.776	-14.962

h = 1.28; h' = 0.00; l' = 0.20

l = 1.00	-2.290	-1.578	-1.083	-0.088	0.785	1.774	-9.902
2.00	-2.590	-2.012	-1.089	-0.269	0.728	1.759	-11.382
3.00	-3.361	-2.121	-1.092	-0.359	0.702	1.751	-13.148
4.00	-4.264	-2.148	-1.093	-0.409	0.688	1.746	-15.010

(8) Localization energies for electrophilic substitution of 2-pyrrolecarboxaldehyde.

	$\Delta E_\pi(3)$	$\Delta E_\pi(4)$	$\Delta E_\pi(5)$
h = 1.28;	h' = 0.00;	l' = 0.00	
l = 0.00	-2.098	-2.230	-2.038
1.00	-2.354	-2.290	-2.296
2.00	-2.464	-2.326	-2.446
3.00	-2.504	-2.346	-2.522
4.00	-2.520	-2.354	-2.562

h = 1.28; h' = 0.00; l' = 0.00

l = 1.00	-2.358	-2.296	-2.308
2.00	-2.478	-2.340	-2.506
3.00	-2.522	-2.360	-2.584
4.00	-2.538	-2.372	-2.636

REFERENCES

(1) H. J. Anderson and L. C. Hopkins. Can J. Chem. 42, 1279 (1964).

(2) C. Friedel and J. M. Crafts. Compt. rend. 84, 1392, 1450 (1877).

(3) G. A. Olah and R. E. A. Dear. In Friedel-Crafts and Related Reactions. Vol. I. Edited by G. A. Olah. Interscience Publishers, Inc., London. 1963. Page 13.

(4) L. M. Jackman. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press Ltd., London. 1959. Page 18.

(5) F. A. Kekulé. Ann. 162, 77 (1872).

(6) E. Hückel. Z. Physik. 70, 204 (1931); 72, 310 (1931); 76, 626 (1932).

(7) A. Streitwieser, Jr. Molecular Orbital Theory for Organic Chemists. John Wiley and Sons, Inc., New York. 1961. Page 256.

(8) Y. Chiang and E. B. Whipple. J. Am. Chem. Soc. 85, 2763 (1963).

(9) H. J. Anderson. Can. J. Chem. 35, 21 (1957).

(10) J. Tirouflet and P. Fournari. Bull Soc. Chim. France. 1651 (1963).

(11) B. Oddo and C. Dainotti. Gazz. chim. ital. 42, 727 (1912).

(12) R. M. Acheson. An Introduction to the Chemistry of Heterocyclic Compounds. Interscience Publishers, Inc., New York. 1960. Page 84.

(13) (Miss) S.-F. Lee. M. Sc. Thesis, Memorial University of Newfoundland, 1965.

(14) P. Hodge and R. W. Rickards. Personal communication.

(15) S. Gronowitz. Arkiv Kemi, 12, 295 (1958).

(16) H. C. Longuet-Higgins and C. A. Coulson. Trans. Faraday Soc. 43, 87 (1947); but see (17, 18).

(17) R. D. Brown. Austral. J. Chem. 8, 100 (1955).

(18) R. D. Brown and B. A. W. Coller. Austral. J. Chem. 12, 1953 (1959).

(19) J. Hine. Physical Organic Chemistry. McGraw-Hill Book Co., Inc., New York. 1956. Page 327.

(20) G. S. Hammond. J. Am. Chem. Soc. 77, 334 (1955).

(21) S. Glasstone, K. J. Laidler and H. Eyring. The Theory of Rate Processes. McGraw-Hill Book Co., Inc., New York. 1941.

(22) H. C. Brown and J. Jungk. J. Am. Chem. Soc. 77, 5584 (1955); 78, 2182 (1956). H. C. Brown and M. Grayson. J. Am. Chem. Soc. 75, 6285 (1953).

(23) G. H. Olah, S. F. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuk. J. Am. Chem. Soc. 86, 1046 (1964).

(24) H. Ulich and G. Heyne. Z. Electrochem. 41, 509 (1935).

(25) C. D. Nenitzescu and E. I. P. Cantuniari. Ber. 66, 1097 (1933).

(26) A. S. Evans and M. Polanyi. J. Chem. Soc. 252 (1947), et seq.

(27) G. A. Olah, M. W. Meyer, and N. A. Overchuk. J. Am. Chem. Soc. 86, 2310 (1964).

(28) G. A. Olah, M. W. Meyer, and N. A. Overchuk. J. Am. Chem. Soc. 86, 2313 (1964).

(29) G. A. Olah, M. W. Meyer, and N. A. Overchuk. J. Am. Chem. Soc. 86, 2315 (1964).

(30) G. A. Olah. In Friedel-Crafts and related reactions. Edited by G. A. Olah. Interscience Publishers, Inc., London. 1963. Page 855.

(31) L. Ruzicka, P. Pieth, T. Reichstein, and L. Ehman. Helv. Chim. Acta, 16, 275 (1933).

(32) G. A. Olah and M. W. Meyer. In Friedel-Crafts and related reactions. Edited by G. A. Olah. Interscience Publishers, Inc., London. 1963, Page 710.

(33) C. C. Price. In Organic reactions, Vol. 3. Edited by R. Adams. John Wiley and Sons, Inc., New York. 1946. Page 1.

(34) H. C. Brown and K. L. Nelson. J. Am. Chem. Soc. 75, 6292 (1953).

(35) H. C. Brown and C. R. Smoot. J. Am. Chem. Soc. 78, 6255 (1956).

(36) G. A. Olah, S. J. Kuhn, and S. H, Flood. J. Am. Chem. Soc. 78, 6255 (1956).

(37) R. H. Allen and L. D. Yats. J. Am. Chem. Soc. 83, 2799 (1961).

(38) D. A. McCaulay and A. P. Lien. J. Am. Chem. Soc. 73, 2013 (1951).

(39) H. C. Brown and J. D. Brady, J. Am. Chem. Soc. 74, 3570 (1952).

(40) D. A. McCaulay and A. P. Lien. J. Am. Chem. Soc. 74, 6246 (1952).

(41) R. H. Allen, T. Alfrey, Jr., and L. D. Yats. J. Am. Chem. Soc. 81, 42 (1959).

(42) R. H. Allen, L. D. Yats, and D. S. Erley. J. Am. Chem. Soc. 82, 4853 (1960).

(43) R. H. Allen. J. Am. Chem. Soc. 82, 4856 (1960).

(44) B. N. Campbell and E. C. Spaeth. J. Am. Chem. Soc. 81, 5933 (1959).

(45) P. B. D. de la Mare and J. H. Ridd. Aromatic Substitution. Butterworths, London. 1959, Page 83.

(46) M. F. Lappert. J. Chem. Soc. 817 (1961); 522 (1962).

(47) B. Mori, J. Gohring, D. Cassimatis, and B. P. Susz. Helv. Chim. Acta, 45, 77 (1962).

(48) H. Gilman and N. O. Calloway. J. Am. Chem. Soc. 55, 4197 (1933).

(49) T. Reichstein, H. R. Rosenberg, and R. Eberhardt. Helv. Chim. Acta, 18, 721 (1935).

(50) C. D. Hurd and G. L. Oliver. J. Am. Chem. 76, 50 (1954).

(51) E. C. Spaeth and C. B. Germain. J. Am. Chem. Soc. 77, 4066 (1955).

(52) H. Gilman, N. O. Calloway, and R. R. Burtner. J. Am. Chem. Soc. 57, 906 (1935).

(53) N. Elming. Acta Chem. Scand. 6, 605 (1952).

(54) C. A. Coulson. Valence. Oxford University Press, London, 1961.

(55) N. Maxim, I. Zugranescu, and I. Fulga. Chem. Abstr. 32, 2938 (1938).

(56) R. M. Acheson and J. M. Vernon. J. Chem. Soc., 457 (1961).

(57) P. Hodge and R. W. Rickards. J. Chem. Soc. 2543 (1963).

(58) H. Rapoport and D. Wilson. J. Org. Chem. 26, 1102 (1961).

(59) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard. In Organic Syntheses, Vol. 36. Edited by N. J. Leonard, page 74.

(60) P. S. Skell and G. P. Bean. J. Am. Chem. Soc. 84, 4655 (1962).

(61) T. Sugawa, Y. Sanno, and A. Kurita. Chem. Abstr. 50, 4119 (1956).

(62) M. Miyazaki, H. Watanabe, C. Mizumo, T. Takano, and A. Morimoto. Chem. Abstr. 50, 10078 (1956).

(63) I. J. Rinkes. Rec. trav. chim. 60, 303 (1941).

(64) G. Baddeley, G. Holt, and D. Voss. J. Chem. Soc. 100 (1952).

(65) D. A. McCaulay, B. H. Shoemaker, and A. P. Lien. Ind. Eng. Chem. 42, 2103 (1950).

(66) S. Gronowitz, A. -B. Hörnfeldt, B. Gestblom, and R. A. Hoffman. Arkiv. Kemi, 15, 133 (1961).

(67) N. N. Greenwood and K. Wade. In Friedel-Crafts and related reactions, Vol. I. Edited by G. A. Olah Interscience Publishers, London, 1963. Pages 583,584.

(68) R. Andrisano, G. Papalardo, and L. Bolognari. Gazz, Chim. Ital. 85, 1430 (1955).

(69) R. Andrisano and G. Papalardo. Gazz. Chim. Ital. 95, 1430 (1955).

(70) U. Eisner and P. H. Gore. J. Chem. Soc. 922 (1957).

(71) H. H. Jaffé and M. Orchin. Theory and applications of ultraviolet spectroscopy. John Wiley and Sons, Inc. New York. 1962.

(72) N. W. Gabel. J. Org. Chem. 27, 301 (1962).

(73) O. Süs, K. Möller, R. Dietrich, H. Eberhardt, M. Glos, M. Grundkötter, and H. Hoffman. Chem. Abstr. 50, 7828 (1956).

(74) C. M. McCay and C. L. A. Schmidt. J. Gen. Physiol. 9, 333 (1926).

(75) A. I. Vogel. A Textbook of Practical Organic Chemistry. Longmans, Green and Co. London 1957, page 344.

(76) M. J. S. Dewar, T. Mole, and E. W. T. Warford. J. Chem. Soc. 3581 (1956).