SYNTHESES AND SUBSTITUTION REACTIONS OF SOME 3-SUBSTITUTED PYRROLES

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A THESIS

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Abstract

Product orientation and distribution in the Friedel-Crafts reaction and (or) Bromination of some 2- and 3-monosubstituted pyrrole derivatives have been studied.

It was found that the acetylation of methyl 2-pyrrolecarboxylate with acetic anhydride in the presence of excess aluminum chloride not only increased the yield, but also had the advantage of separating the reaction products.

Acetylations of 2-pyrrolecarbonitrile and 2-pyrrolecarboxaldehyde were found to give exclusively 4-substitution, while the 5-isomer was undoubtedly formed in minor amounts in the acetylation of methyl 2-pyrrolecarboxylate. The 4-acetylated acid obtained from the hydrolysis or oxidation of the corresponding acetylated products was converted to the known 3-acetylpyrrole.

5-Bromo and 5-isopropyl derivatives were the sole products isolated from the bromination and Friedel-Crafts isopropylation of methyl 3-pyrrolecarboxylate and 3-acetylpyrrole.

The structures of the products were confirmed primarily through nuclear magnetic resonance evidence. Further identification was accomplished by a study of some chemical interconversions.

The reaction of pyrrylmagnesium bromide with methyl chloroformate was carried out and several new products isolated and identified. The synthesis of 3-isopropylpyrrole *via* the ring closure of a glycidic ester was also attempted.

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DISCUSSION

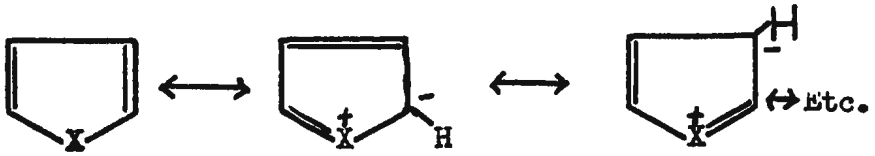
Section I

Friedel-Crafts Acetylation of 2-Substituted Pyrroles.

(1) General Considerations.

Many common reactions of aliphatic amines, ethers, and sulfides involve initial attack by an electrophilic reagent at a lone pair of electrons on the heteroatoms; salts, quarternary salts, coordination compounds, amine- and sulf-oxides, and sulfones are formed in this way. Corresponding reactions are very rare with the simple five-membered heteroaromatics with one heteroatom in the nucleus, e.g. pyrrole, thiophene, and furan. In these compounds, the lone pair of electrons of the heteroatoms participates in the aromatic resonance of the ring, so that they are not so readily available for proton capture. The resonance structures of these compounds (Ia - Ic) show that the heteroatoms possess partial positive charges which hinder reaction with electrophilic reagents, and the carbon atoms acquire partial negative charges which aid reaction with these reagents.

Fig. I.



(a) (b) (c)

X: NH, S, O.

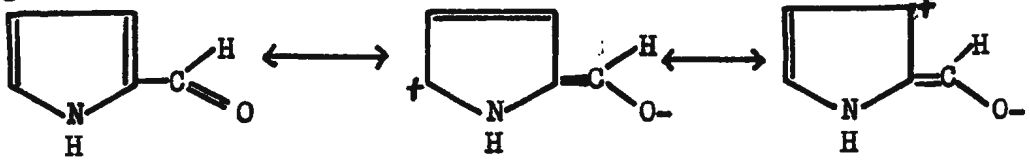
Since a smaller charge separation is involved in Ib and hence it has lower energy than Ic. This suggests that the α-positions are more susceptible to electrophilic attack than the β-positions. Experimental evidence fits very well to this prediction. As for example, the protonation (1), nitration (2), and acylation (3) of pyrrole; the

acylation of furan (4); and the sulfonation (5), nitration (6), and acylation (7) of thiophene, all occur predominantly or exclusively at the 2-position.

However, the situation may be altered substantially in the presence of an electron-withdrawing group (-R group) at the 2- or 3- position. In this case, the whole ring system is somewhat deactivated to electrophilic substitution by the effect of -R group, but is still fairly reactive to electrophilic attack.

The orientation of entering groups in the system with an -R group at the 2-position is expected to be influenced mainly by the α-directing influence of the heteroatom and, by the "meta" -directing influence of the -R group. As is illustrated by the resonance structures IIa, IIb, and IIc for 2-pyrrolecarboxaldehyde, it would be expected that, for electrophilic substitution, the product

Fig. II.



(a) (b) (c)

distribution should favor 4-substitution due to the further deactivation of 3- and 5-positions. A greater amount of 5-substituted product would be formed as weaker -R groups are used, since the effect of the heteroatom would be increased relative to the effect of -R group. The 3-position has the least capability of being attacked, as it is situated at the β-position to the heteroatom, and is further deactivated by the -R group.

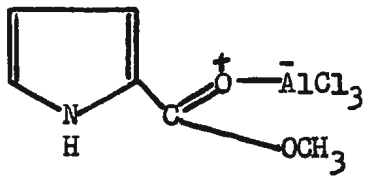
Nevertheless, the situation may entirely be changed, when the effect of a heteroatom overshadows that of the -R group. In that case the 5-position would be the easiest position to be attacked.

Experimental observations have shown that the 4-substituted products are the predominant ones in nearly all the cases as was found in the nitrations of several 2-substituted pyrroles (2, 8, 9), and thiophenes (2), as well as the brominations of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde (10). However, the brominations of furfural and methyl 2-furyl ketone (12, 13) were found to give predominantly the 5-bromo derivatives. This indicates that the oxygen in furan has a more profound effect than the sulfur or nitrogen in thiophene or pyrrole in the bromination reactions. Bromination of 2-thiophenecarboxaldehyde has also been reported by Gronowitz (11) 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.

The results of the brominations (10) of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde showed that the 4-substitution predominated. Similar results were obtained from the isopropylations of methyl 2-pyrrolecarboxylate (14), 2-pyrrolecarboxaldehyde (15), 2-acetylpyrrole (15), and 2-thienyl ketone (16). These suggest that in the pyrrole ring, the "meta" -directing group in the 2-position usually overcomes the α-directing heteroatom on the nucleus.

The Friedel-Crafts isopropylations of (15) methyl 2-pyrrolecarboxylate, 2-pyrrolecarboxaldehyde, and 2-acetylpyrrole under the same conditions showed that the order of reactivity of these carbonyl compounds was aldehyde >ketone>ester. It was also suggested by Anderson and Hopkins (14) that the effect of -R group is further enhanced by complexing with a Lewis acid as illustrated in III.

Fig. III.



The consequent further deactivation of position 3- and 5- should greatly enhance the amount of the 4-substituted products. The HMO calculations of Hopkins (17) supported the idea that Lewis acid complexing of the carbonyl greatly increased the required localization energy at all positions, but most markedly at the 3- and 5-positions. The same workers (15) indicated that this effect was felt most in the aldehyde and least in the ester. Thus the barrier to 5-substitution is lowest for the complexed ester.

On this basis, it would be expected that the Friedel-Crafts acylation of pyrrole, thiophene, and furan with an -R group at the 2-position would lead predominantly to the 4-substituted products, but the ratio of 5-substitution would be increased to some extent when a weaker -R group is used. However, the results of nearly all the acylation reactions that have been reported in the thiophene, furan and pyrrole series contradict to this prediction. The acetylation, benzoylation and butyrylation of methyl 2-furoate (18), and the acetylations of 2-acetylthiophene (19) and 2-benzoylpyrrole (20), were found to give exclusively the 5-substituted products. However, the acetylation of 1-methyl-2-nitropyrrole (8) was reported to give the 4-substituted product.

The acetylation of some pyrroles with an -R group at the 2-position was thus carried out in order to investigate the product orientation and distribution.

(2) Results and Discussion.

The preparative acetylations of methyl 2-pyrrolecarboxylate, 2-pyrrolecarboxaldehyde, and 2-pyrrolecarbonitrile were all in conformity with the predictions discussed above. 4-Substituted products formed predominantly or exclusively, and thus did not agree with the other reports on the acylation reaction in this series of compounds.

Several workers (21, 22, 23) have found that yields of product generally improved with the amount of catalyst employed up to, or just above, the amount calculated for the stoichiometric equation. But some other workers (24, 25, 26) have observed that, in some cases, the yield fell off rapidly when more than the calculated amount of catalyst was used.

Table I. Acetylation of Methyl 2-Pyrrolecarboxylate

Ratio (catalyst/acylating agent)	Yield (mole%) 4-isomer	5-isomer	overall
1.1	51.7	4.8	56.5
2.6	62.0	4.1	66.1
3.0	62.0	5.6	67.6
3.2	73.4	7.6	81.0
4.0	48.0	5.4	53.4

Two mechanisms have been suggested when anhydrides are used as the acylating agents. In the formation of the reactive complex with $AlCl_3$, the stoichiometric equation for the utilization of both acyl residues of a carboxylic anhydride was proposed by Groggins et. al. (27) as: $(RCO)_2O + 3\ AlCl_3 \longrightarrow 2\ RCOCl \cdot AlCl_3 + AlOCl$; and hence, in this case, the optimum ratio Q (number of moles of catalyst to number of moles

of acyl component) is at least 3 (28). A corresponding equation for the utilization of only one acyl residue was given by Saboor (29) as:

$$(RCO)_2O + 2\ AlCl_3 \longrightarrow RCOCl.AlCl_3 + RCOOAlCl_2,$$

and the optimum ratio Q is in this case at least 2.

Experimental evidence (22, 27, 30, 31, 32) showed that two factors determined which mechanism would operate, viz. the amount of catalyst used, and the reactivity of the acyl group.

In the preparative acetylation of methyl 2-pyrrolecarboxylate, our value of the optimum ratio Q was found to be approximately 3.2. According to Anderson and Hopkins (14), a complex is formed between methyl 2-pyrrolecarboxylate and $AlCl_3$, consequently one unit is subtracted from the above value as a correction for the complex formation. Hence, the resulting value of the latter ratio is 2.2, which is in close agreement with Saboor's mechanism.

In addition to the higher yield obtained, it was easier to separate the products, when larger ratio Q was used, since most of the 4-isomer precipitated when the reaction complex was decomposed. On the other hand, when smaller ratio Q was used, the product was an oily liquid, therefore separation of the product was less easy.

As was discussed above, any electrophilic substitution reaction will favor 4-substitution for a strong -R group but give greater amounts of the 5-substituted product as weaker -R groups are used. This general trend has been observed by Tirouflet and Fournari (2) in the nitration of several 2-substituted pyrroles and thiophenes. They found that the percentage of 4-isomer decreased in the series: $NO_2 > CHO \sim COCH_3 \sim CN \sim COOH > CH(OCOCH_3)_2 > H$. The preparative

acetylation reactions of methyl 2-pyrrolecarboxylate, 2-pyrrolecarbonitrile, and 2-pyrrolecarboxaldehyde were found in agreement with their observations. The ester gave the mixture of 4- and 5-substituted products with 4-isomer predominating, while the nitrile and aldehyde gave exclusively the 4-substituted products. Thus the ester has a weaker "meta" -directing effect, while the others have a stronger effect. The nitrile and ester gave a fairly good yield, but the aldehyde suffered the disadvantage of low yield due presumably to its instability in the acidic media.

Under normal reaction conditions (at 50° with CS_2 as solvent), 2-pyrrolecarboxaldehyde was found to be destroyed very easily. Reacting at room temperature lead to the same result. Instead of aluminum chloride several catalysts were tried, such as polyphosphoric acid, 85% phosphoric acid, zinc chloride, stannous chloride dihydrate, aqueous perchloric acid, as well as zinc chloride with trace of cupric bromide, with the ratio Q ranging from 1.1 to 3,3 and temperature varied from room temperature to 50°. However, none of these reactions was successful. Replacing carbon disulfide by nitromethane gave a similar result. When acetyl chloride was used as the acylating agent, it caused the destruction of 2-pyrrolecarboxaldehyde even at the temperature of about -10° (bath temperature). Conducting the reaction at the temperature below -20° caused the recovery of the starting material.

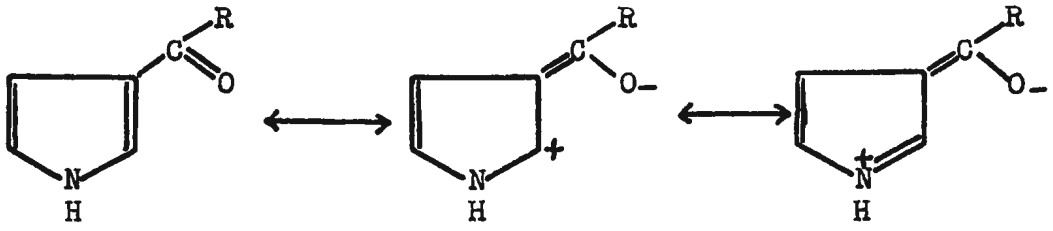
Finally it was found that under a stream of nitrogen, reacting at 0-4°, using nitromethane as solvent, and longer reaction time yielded 22% of the expected product, i.e., 4-acetyl-2-pyrrolecarboxaldehyde. The yield decreased to about 5.7% when carbon disulfide was used as solvent.

Section II

Bromination and Friedel-Crafts Isopropylation of 3-Substituted Pyrroles.

Prediction of the product orientation in the electrophilic substitution reactions of pyrrole compounds with an -R group at the 3-position is much simpler than for its 2-isomer.

Fig. IV.



(a) (b) (c)

From resonance structures (IVa-IVc) it is obvious that both inductive and resonance effects of the -R group strongly deactivate the 2-position toward electrophilic substitution, and one would thus expect monosubstitution to occur predominantly in the 5-position. The preferential substitution at the 5-position was further supported by considering the n.m.r. chemical shift positions of the ring protons of the complex between 3-carbonyl and $AlCl_3$. The fact of the greater shifts from the 2- and 4-positions toward lower field (see Table III) reveals a larger decrease in electron density at these positions and thereby leaves the 5-position the most susceptible to electrophilic attack. However, in agreement with the electrophilic substitution reactions of pyrrole with a weak -R group at the 2-position discussed previously, we would also expect that, in the present case, the 2-substituted product may be formed to a certain extent, when a weaker -R group is used. However, all the earlier experimental observations showed that the 5-substituted product formed exclusively. As for

example, brominations of 3-furoic acid (33) and 3-thiophenecarboxylic acid (34), acetylation of methyl 3-thiophenecarboxylate (35), and nitrations of ethyl 3-furoate (33), methyl 3-thiophenecarboxylate (36), 3-thiophenecarboxylic acid (34), 3-nitrothiophene (37), 3-thiophenecarboxaldehyde(38), methyl 3-pyrrolecarboxylate (39),and 1-methyl-3-nitropyrrole (40), all occurred exclusively at the 5-position.

In order to obtain a better understanding of the chemical properties of this series of compound, methyl 3-pyrrolecarboxylate and 3-acetylpyrrole were chosen in the preparative work to subject to the electrophilic substitution reactions, and the product distribution was analysed.

Both the preparative isopropylation and bromination of 3-acetylpyrrole and methyl 3-pyrrolecarboxylate showed that the 5-substituted products still formed exclusively (in the isopropylations, a trace amount of another isomer has also been found by analyzing through gas chromatography; however, due to the insufficient amount of the starting material used, attempted isolation of it was unsuccessful). Thus it is evident that the 5-substituted products are always the predominant ones in the electrophilic substitution reactions of pyrrole compounds with an -R group at the 3-position.

An interesting thing in the bromination of 3-acetylpyrrole and methyl 3-pyrrolecarboxylate is that these compounds seemed to be very reactive toward the brominating agents. Although bromine in carbon tetrachloride was found to be the better reagent for the 2-substituted pyrrole (10), it was found to be unsuitable for the bromination of 3-substituted pyrroles. It was thought this might be due to solubility restrictions. In carbon tetrachloride, tribromo derivatives formed

predominantly, with a small amount of two other isomers (one mono- and the other possibly a dibromo). However, by using bromine in dimethylformamide, under which condition the solubility restriction did not exist, still gave the same result as that found in bromine in carbon tetrachloride. Hence the solubility factor seems not to seriously influence the product orientation. This was further supported when dioxane-dibromide was used as the brominating agent, in which case, solubility restrictions still did not exist, but the products found were exclusively the 5-bromo derivatives. Obviously, dioxane-dibromide is a milder brominating agent than either bromine in carbon tetrachloride or bromine in dimethylformamide.

Section III Reaction of Pyrrylmagnesium Bromide with Methyl Chloroformate.

As was discussed previously (see section I), the hetero nitrogen in pyrrole is much less basic than that in secondary amines; for the same reasons, it should be more acidic. Pyrrole does behave as a weak acid of about the same strength as acetylene.

Pyrroles, as active hydrogen compounds, react with the Grignard reagent to give hydrocarbons and new pyrrole Grignard reagents, which react exceedingly readily with weak electrophilic reagents at either carbon or nitrogen or both (41).

The alkylation and acylation of the pyrrole Grignard reagent have long been investigated, and various results reported. In 1909, Oddo (42) claimed that with carbon dioxide or ethyl chloroformate, the 2-carboxylate derivatives of pyrrole were produced; but with methyl iodide (43), pyrrylmagnesium iodide gave 2- and 3- methyl pyrroles, dimethylpyrrole, and polyalkylpyrrolenines. However, these same workers claimed that alkylation with ethyl and n-propyliodide gave only the 3-alkylpyrroles and polyalkylpyrroles. Oddo and Moschini (44) also described the preparation of methyl 2-pyrrolecarboxylate in 90% yield by reaction of pyrrylmagnesium bromide with methyl chloroformate. However, these claims were refuted by several other workers who stated that ethylation and alkylation produced only the 2-alkyl and 2,5-dialkylpyrroles (45, 46) and reaction with methyl chloroformate (47, 48, 49) failed to duplicate the earlier results.

Recently, Skell and Bean (50) alkylated pyrrylmagnesium bromide with a series of alkyl halides and found that in every case pyrrole, the isomeric 2- and 3-alkylpyrroles and polyalkylpyrroles were produced. They also reported that the acylation (50) of pyrrylmagnesium bromide with either acyl halides or esters gave only the 2-acylpyrroles. Castro

et. al. (51) later found that 3-acylpyrrole was also formed in company with the isomeric 2-acylpyrroles. This fact was confirmed by the reinvestigation of Bean (52), except that when ethyl acetate was used as the acylating agent, the 3-acyl derivatives were not detected.

There has also been considerable controversy on the nature of the pyrrole Grignard reagent itself. On the basis of chemical evidence (50, 53, 54, 55), the pyrrole Grignard reagent might be represented by any of the structures Va-Vf or a mixture thereof (56).

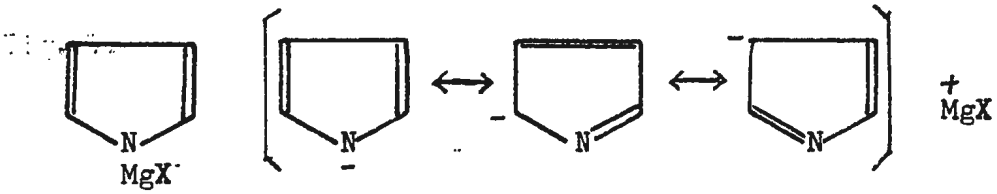
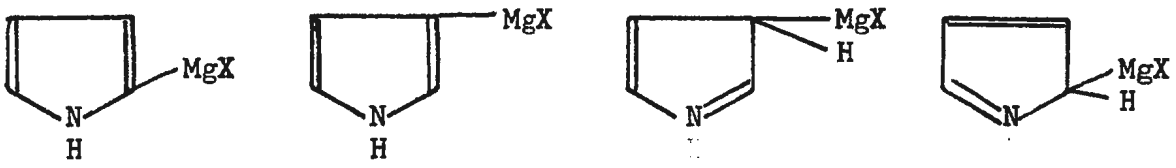


Fig. V.(a) (b)



(c) (d) (e) (f)

From the magnitude of the difference in electronegativity of the two elements, an ionic N-Mg bond is favored with the pyrrylmagnesium halide, consequently an associated ion pair Vb (57).

The n.m.r. and i.r. evidence have shown that pyrrole Grignard reagent existed as either Va structure or a resonance stabilized anion with the negative charge distributed between carbon and nitrogen Vb (56, 57). From this prediction, the formation of 1-substituted product would be expected, and indeed some was found on the alkylation of pyrrylmagnesium bromide (57, 58) and pyrrylmagnesium chloride (57), as well as on the ester formation from pyrrylmagnesium bromide (14, 49).

Mixtures are often formed in the normal pyrrole Grignard reactions, and the 2-substituted pyrroles often predominate. However, the proportions may be altered remarkably by changing the solvent, temperature or reagent. Thus, on the reaction with a chloroformate, pyrrole Grignard reagent formed 2-substituted product predominantly when equal or nearly equal amounts of pyrrole and the acylating agent were used (14, 59). On the other hand, 1,2-disubstituted product predominated when excess of the acylating agent was used, and the 2-substituted product became unimportant (49, 60).

In the preparative work, an attempt was made to decrease the yield of 1,2-disubstituted product, and to increase the amount of 1,3-disubstituted product, which can easily be converted into 3-monosubstituted derivatives (see section IV). The reaction was carried out using excess of pyrrole and the result showed that 2-substituted product still predominated; in addition, a small amount of some dipyrryl ketones also formed, possibly due to the further reaction of the excess pyrrole Grignard reagent with the initially formed products.

Section IV. Product Identification

(1) Hydrolysis and Oxidation:

Although 2-pyrrolecarbonitrile was hydrolyzed easily by potassium hydroxide in ethylene glycol (9), this reagent was not suitable for the hydrolysis of 4-acetyl-2-pyrrolecarbonitrile, which was decomposed under such condition. Attempted hydrolysis by acids (conc. H_2SO_4 : glacial AcOH : H_2O = 1 : 1 : 1 by volume) at 60-70° caused the recovery of starting material, while on refluxing it lead to the decomposition of the pyrrole ring. However, milder reaction, i.e., by refluxing with 40% aq. potassium hydroxide solution over a longer time (about 6 hours) gave a 37.5% yield of the desired acid.

Hydrolysis of methyl 4-acetyl-2-pyrrolecarboxylate and methyl 2-isopropyl-4-pyrrolecarboxylate as well as the oxidation of 4-acetyl-2-pyrrolecarboxaldehyde gave the corresponding acids without difficulty.

Iodoform type oxidation of 2-isopropyl-4-acetylpyrrole was also attempted. However, n.m.r. evidence (see Table II) showed that the product was probably 2-isopropyl-3-iodo-4-acetylpyrrole, rather than the desired acid.

(2) Decarboxylation:

Various attempts were made to decarboxylate the 4-acetyl-2-pyrrolecarboxylic acid, however, none gave a satisfactory result. Heating the acid in an organic base such as quinoline in the presence of copper powder (61), copper bronze (62) or copper chromite catalyst (63) caused only decomposition. Similar result was obtained by heating the acid by itself or in ethylene glycol (64). Heating the mixture of the acid and sand (65) over a short time at the temperature just over its m.p. gave the decarboxylated product, i.e., 3-acetylpyrrole, with a yield of about 20%.

Attempted replacement of the carboxyl group by halogens was also carried out, but a substitution reaction proceeded instead of the desired replacement reaction. Thus, by reacting with iodine in ethanol (66), the 3,5-diiodo derivatives was obtained. Mixing with bromine in glacial acetic acid and exposing to UV lamp (67) gave a solid, which decomposed on recrystallization. Pyrolysis of the acid with soda-lime (67) was also tried, and trace of 3-acetylpyrrole (about 4%) was obtained.

(3) Replacement of bromine by deuterium:

It was reported that the bromine of the brominated pyrrole derivatives could easily be replaced by hydrogen or deuterium on catalytic hydrogenation or deuteration (62). In order to further prove the structure of bromopyrrole derivatives by n.m.r. spectra (see section IV-4), a modified catalytic deuteration (62) of the hydrogenation method of Linstead et. al. (68) was adopted except that Adams platinum oxide catalyst was used instead of palladium on charcoal. Gas-chromatography showed that the bromine of the bromopyrrole derivatives had completely been reduced and n.m.r. spectra confirmed that the 5-deuteriopyrrole derivatives had been obtained, since the signal of proton at 5-position had disappeared and that proton signals of pyrrole ring hydrogens (N-protons were uncoupled by D_2O exchange) had now become an AX system.

(4) Spectroscopic data:

The n.m.r., i.r. and u.v. spectra for several compounds reported in the present work are given in Table II -VI.

Average coupling constants (see Table IV) observed for the 2- and 3-substituted pyrroles and their derivatives are in agreement with the reported values (17, 62, 69).

In 3-acetyl-5-deuteriopyrrole and 2-isopropyl-3-iodo-4-acetylpyrrole, the n.m.r. signal of $COCH_3$ protons were split into a doublet when $CDCl_3$ was used as solvent. The same result was observed for 2-bromo-4-acetylpyrrole when CCl_4 was used as solvent, however, the latter compound gave the expected singlet signal when $CDCl_3$ or dioxane was used as solvent. Although this unusual splitting could not be observed in other 3-acetylpyrrole and methyl 3-pyrrolecarboxylate derivatives, the C=O stretching frequency in the infrared spectra of methyl 2-siopropyl -4-pyrrolecarboxylate was found to have two absorption bands in CCl_4, but only one band in $CHCl_3$. Presumably, the spatial arrangement of the carbonyl group as well as solvent effect may play a role in this phenomenon.

The effect of complex formation with $AlCl_3$ on the chemical shifts of the protons of the substrate molecules has also been studied. It was found by Anderson and Hopkins (15) that Lewis acid complexing of the 2-substituted pyrrole compounds had a marked effect on the n.m.r. chemical shift positions of the protons, and the signal positions of aromatic protons were all moved to lower field. Similar result was also obtained on the n.m.r. signals of 3-acetylpyrrole and methyl 3-pyrrolecarboxylate (see Table III).

Table II

Nuclear Magnetic Resonance Chemical Shifts†

	Aliphatic					Aromatic			
	CH_3CO-	CH_3O-	$(CH_3)C_2$-	-CH	CHO-	2	3	4	5
4-Acetyl-2-pyrrolecarboxaldehyde	2.49				9.59; 9.61;		7.39		7.73
4-Acetyl-2-pyrrolecarbonitrile	2.41						7.37		7.92
4-Acetyl-2-pyrrolecarboxylic acid (b)	2.35						7.33		7.52
" " (c)	2.37						7.10		7.62
Methyl 4-acetyl-2-pyrrolecarboxylate	2.47	3.93					7.38		7.67
Methyl 5-acetyl-2-pyrrolecarboxylate*	2.47	3.95					6.85	6.85	
4-Acetyl-3,5-diiodo-2-pyrrolecarboxylic acid	2.53								
3-Acetylpyrrole	2.43					7.41		6.63	6.75
" (b)	2.33					7.45		6.60	6.77
" (d)	2.40					7.43		6.63	6.80
" (f)	2.35					7.51		6.57	6.84
3-Acetyl-5-deuteriopyrrole	2.41					7.41		6.64	
3-Acetyl-5-bromopyrrole	2.41					7.37		6.63	
" (a)	2.39; 2.41;					7.05		6.07	
" (b)	2.31; 2.47;					7.34		6.59	
3-Acetyl-5-isopropylpyrrole	2.32		1.24	2.90		7.30		6.34	
" (a)	2.32		1.22	2.89		7.20		6.19	

Table II (cont'd)

	Aliphatic CH_3CO-	CH_3O-	$(CH_3)_2C$-	-CH	CHO-	Aromatic 2	3	4	5
3-Acetyl-4-iodo-5-isopropylpyrrole	2.43; 2.67;		1.25			7.52			
Methyl 3-pyrrolecarboxylate		3.80				7.40		6.63	6.75
" (b)		3.77				7.43		6.61	6.77
" (d)		3.79				7.42		6.62	6.76
" (f)		3.75				7.43		6.55	6.81
Methyl 5-deuterio-3-pyrrolecarboxylate		3.60				7.36		6.55	
Methyl 5-isopropyl-3-pyrrolecarboxylate		3.61	1.23	2.89		7.33		6.36	
" (a)		3.75	1.22	2.66		7.17		6.17	
5-Isopropyl-3-pyrrolecarboxylic acid (b)			1.19	2.60		7.19		6.17	
Methyl 5-bromo-3-pyrrolecarboxylate		3.79				7.33		6.55	
Methyl 2,4,5-tribromo-3-pyrrolecarboxylate (c)		3.76							
2,2'-Dipyrryl ketone							7.18	6.33	7.08
1,2'-Dipyrryl ketone						#	6.87	#	7.04

† $CDCl_3$ was used as solvent unless specifically indicated.

a: in CCl_4 ; b: in dioxane; c: in DMSO-d_6; d: in CH_2Cl_2 f: in CH_3NO_2

* Ref. 70 gives: CH_3CO-: 2.49; CH_3O-: 3.95; Aromatic protons; 6.95.

#. 2' : 7.41; 3' and 4' : 6.22; 5' : 7.41.

Table III

Complex Formation and Change in Chemical Shifts Position*†

Complex	2-	4-	5-	Side chain
3-Acetylpyrrole. $AlCl_3$	0.74	0.38	0.27	0.52 ($COCH_3$)
Methyl 3-pyrrolecarboxylate· $AlCl_3$	0.67	0.45	0.19	0.54 (OCH_3)

* Values are in p.p.m. and are all to lower field from the uncomplexed chemical shift positions given in Table II.

† CH_3NO_2 was used as solvent.

Table IV

Nuclear Magnetic Resonance Spectra (Coupling Constants for the Pyrrole Protons c.p.s.)#

	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{1,5}$	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
Methyl 4-acetyl-2-pyrrolecarboxylate									1.6	
4-Acetyl-2-pyrrolecarbonitrile*		2.2		3.1					1.6	
4-Acetyl-2-pyrrolecarboxaldehyde									1.4	
4-Acetyl-2-pyrrolecarboxylic acid*									1.6	
3-Acetylpyrrole						1.6	1.9			2.98
3-Acetyl-5-deuteriopyrrole	2.81					1.60				
Methyl 5-isopropyl-3-pyrrolecarboxylate	3.1		2.6			1.64				
Methyl 5-bromo-3-pyrrolecarboxylate	2.90		2.58			1.75				
5-Isopropyl-3-pyrrolecarboxylic acid	3.0					1.6				
Methyl 3-pyrrolecarboxylate						1.6	2.1			2.89
Methyl 5-deuterio-3-pyrrolecarboxylate	3.0		2.4			1.6				
5-Isopropyl-3-acetylpyrrole	3.0		2.7			1.66				
5-Bromo-3-acetylpyrrole	3.12		2.54			1.60				
3-Acetyl-4-iodo-5-isopropylpyrrole	3.3									
1,2' -Dipyrryl ketone					2.27	2.27	2.27			
2,2' -Dipyrryl ketone		3.66	3.72	2.90				3.84	1.36	2.61

#The N-protons were uncoupled by D_2O exchange and $CDCl_3$ was used as solvent unless specifically indicated.

*in DMSO -d_6

Table V

I. R. Absorption of Pyrroles†

Compound	C=O stretching frequency		N-H stretching frequency
Methyl 4-acetyl-2-pyrrolecarboxylate	1700,	1635	3180
Methyl 5-acetyl-2-pyrrolecarboxylate	1715,	1660	3260
4-Acetyl-2-pyrrolecarbonitrile	1650		3070
4-Acetyl-2-pyrrolecarboxaldehyde	1670	1650	3200
3-Acetylpyrrole	1630		3180
Methyl 3-pyrrolecarboxylate	1730	1700[a.e.]	3300[a]
2-Isopropyl-4-acetylpyrrole	1630		3220
Methyl 2-isopropyl-4-pyrrolecarboxylate	1675 [b,c]		3265
2-Bromo-4-acetylpyrrole	1635		3130
Methyl 2-bromo-4-pyrrolecarboxylate	1685		3175
2-Isopropyl-4-pyrrolecarboxylic acid	1650		3350
4-Acetyl-3,5-diiodo-2-pyrrolecarboxylic acid	1640	1630	3130
Methyl 2,4,5-tribromo-4-pyrrolecarboxylate	1685		3140
1, 2' -Dipyrryl ketone	1650[d]		3285
2, 2' -Dipyrryl ketone	1605[d]		3260[a]

† KCl disc technique was used unless specifically indicated.

a: in $CHCl_3$, b: in CCl_4, 1715 and 1685 (C=O stretching).

c: in $CHCl_3$, 1705 (C=O stretching). d: in $CHCl_3$, 1660 (C=O stretching).

e: Ref. (71) gave 1712 and 1698 cm^{-1} .

Table VI

Ultraviolet spectra of substituted pyrroles†

	Band E		Band K	
	λ max (mμ)	log ε	λ max (mμ)	log ε
3-Acetylpyrrole	203	4.13	244	3.80
Methyl 3-pyrrolecarboxylate#	200	4.14	247	3.38
Methyl 4-acetyl-2-pyrrolecarboxylate	226	4.17	277	4.13
4-Acetyl-2-pyrrolecarbonitrile	217	4.17	265	3.56
4-Acetyl-2-pyrrolecarboxaldehyde	229	4.26	265	4.19
4-Acetyl-2-pyrrolecarboxylic acid	225,5	4.17	273.5	4.13
Methyl 5-acetyl-2-pyrrolecarboxylate	220	3.96	290	4.14
Methyl 2-isopropyl-4-pyrrolecarboxylate	201	4.16	260	3.28
2-Isopropyl-4-acetylpyrrole	205	4.14	244	3.99
2-Isopropyl-4-pyrrolecarboxylic acid	201	4.16	255	3.27
4-Acetyl-3,5-diiodo-2-pyrrolecarboxylic acid	223	4.14		
2-Bromo-4-acetylpyrrole	206	4.15	239	3.56
Methyl 2-bromo-4-pyrrolecarboxylate	204	4.18	256	3.80
2,4,5-Tribromo-3-pyrrolecarboxylic acid	208	4.16		
1, 2' -Dipyrryl ketone	238	3.66	295	4.15
2, 2' -Dipyrryl ketone*	255	3.36	337	4.17

† Ethanol (95%) was used as solvent.

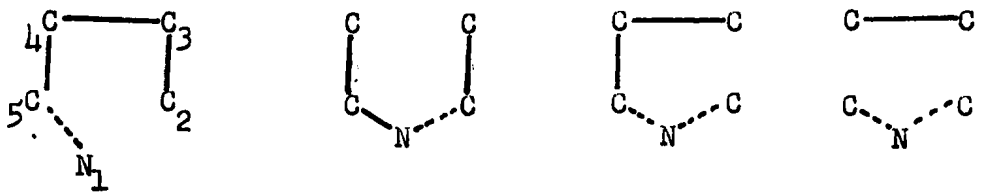
Ref. (72) gives λmax = 257, 334 mμ (ε max = 5,350, 25,000).

* Ref. (71) gives λmax = 240 mμ (log ε_{max} 3.82).

Section V. Attempted Synthesis of 3-Isopropylpyrrole via Ring Closure of a Glycidic Ester.

The methods of synthesizing the pyrrole rings may be divided into those which involve only the C-N bond (VIa) formation, and those which involve formation of the 3:4 bond (VIb), the 2:3 bond (VIc), and both the 2:3 bond and the 4:5 bonds (VId).

Fig. VI



(a) (b) (c) (d)

The most practically important methods are Baar-Knorr, Knorr and Hantzsch methods.

Despite the large variety of ways have been used to establish one or both C-N bonds, few examples were found which lead finally to the 3-monosubstituted pyrroles with a reasonable yield. Methyl- (39, 73, 74, 75, 76) and ethyl- (73) 3-pyrrolecarboxylates, 3-isopropyl- (65) and 3-acetyl- (39) pyrroles, as well as 2,3-pyrroledicarboxylates (77, 78) have been synthesized. The 2,3-pyrroledicarboxylates may be converted into the 3-pyrrolecarboxylates by the selective hydrolysis and decarboxylation. However, these methods suffered from the disadvantage of either (A) difficulty in obtaining the starting material, or (B) low yield, or both. Therefore an attempt was made to synthesize 3-isopropylpyrrole from a compound which is easily obtainable.

The aliphatic α,β-epoxy carbonyl compounds may be used to synthesize different heterocyclic compounds. Since two of the three

active carbons are used in the formation of rings, it would be expected that three different kinds of rings may be formed. This was born out by experiments. In the ring formation, different reagents led to different rings by acting at various positions. Thus, 1-benzoyl-2-phenylethylene oxide, on reacting with thiourea, gave 2-amino-4α hydroxybenzyl-5-phenylthiazole (79); but on reacting with guanidine or its homologs, gave a series of compounds, the structures of which were assigned as 4-benzoyl-5-phenylimidazoline-2 with an amino or a substituted amino group at position 2 (80); on the other hand, 4-hydroxy-4,5-dihydropyrazole derivatives was obtained by reacting with phenylhydrazine (81). 2,3-Epoxybutanal, on reacting with benzthioamide, gave 4-hydroxy-5-(α-hydroxyethyl)-2-phenyl-2-thiazoline (82); but reacting with benzamidine to give 4(5)-(α-hydroxyalkyl)-imidazole derivative (82).

An elegant method of preparing methyl 3-methyl-2-furoate (83) was carried out by simply heating a specific α, β-epoxy ester, i.e., ethyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate. This method suffers none of the disadvantages mentioned above, and was therefore adopted for the attempted synthesis of 3-isopropylpyrrole.

In the preparative work, methyl 3-isopropyl-2,3-epoxy-5,5-dimethoxypentanoate was used as the starting material and was prepared by the method of Burness (83).

The ring closure reaction was undertaken at various conditions either by mixing with liquid ammonia or by refluxing with various ammonium salts (such as ammonium acetate, ammonium carbonate, or ammonium chloride) in different solvents (such as methanol, ethanol, water, dioxane or ethylene glycol) and either in the presence or absence

of acid (conc. HBr, conc. HCl or conc. H_2SO_4) and catalyst ($FeCl_3$ or Al_2O_3). All the attempts were unsuccessful. It was found that under milder conditions, the starting material usually recovered, while at vigorous conditions, especially when the temperature exceeded 150°, 3-propylfuran derivatives, e.g., acid, ester or amide, often formed. It appeared that much more drastic conditions would be necessary to make this reaction become successful.

EXPERIMENTAL

General:

Melting points were observed by using a Fisher-John's melting point block, and are uncorrected.

Infrared spectra were recorded by a Perkin-Elmer 237B spectrophotometer using the potassium chloride disc (2 mg sample in 200 mg KCl) and (or) solution (0.5 mm. NaCl cell) techniques.

Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer 202 recording spectrophotometer.

The nuclear magnetic resonance spectra were determined by a Varian A-60 spectrophotometer at 60 Mc/sec. The chemical shifts are in p. p. m. from tetramethylsilane as internal reference and are recorded on the δ scale.

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

Analysis of the reaction mixtures was carried out by means of gas-liquid partition chromatography using a Beckman GC-2A chromatograph, equipped with a 13½ -in. column (number 70006) packed with Apiezon L on firebrick and operated at 220° with helium as the carrier gas. Established for pyrrole compounds were:

Compound	operating pressure (psig.)	retention time (min.)
3-Acetylpyrrole	25	3.0
2-Isopropyl-4-acetylpyrrole	25	5.1
2-Bromo-4-acetylpyrrole	25	6.8
Methyl 3-pyrrolecarboxylate	25	2.2
Methyl 2-bromo-4-pyrrolecarboxylate	25	5.3
Methyl 2-isopropyl-4-pyrrolecarboxylate	25	4.2
Methyl 4-acetyl-2-pyrrolecarboxylate	30	5.8
Methyl 5-acetyl-2-pyrrolecarboxylate	30	3.0
4-Acetyl-2-pyrrolecarboxaldehyde	30	4.8
Methyl 1-pyrrolecarboxylate	30	0.4
Methyl 2-pyrrolecarboxylate	30	0.7
Methyl 3-pyrrolecarboxylate	30	1.5
Methyl 1,2-pyrroledicarboxylate	30	1.2
Methyl 1,3-pyrroledicarboxylate	30	1.9
1,2' -Dipyrryl ketone	30	4.5
2,2' -Dipyrryl ketone	30	10.9

Section I. Friedel-Crafts Acetylation of 2-Substituted Pyrroles

General:

Methyl 2-pyrrolecarboxylate was prepared by an adaption of the Grignard method of Maxim et al.(68) for ethyl ester as described in Ref. (17).

2-Pyrrolecarboxaldehyde was prepared by the method of Silverstein et al. (84).

2-Pyrrolecarbonitrile was prepared by the method of Anderson (9).

Methyl 2-pyrrolecarboxylate:

In a 1 litre three-neck round bottom flask equipped with a sealed stirrer, dropping funnel and double-surface condenser (with drying tube) was placed anhydrous aluminum chloride (120 g, 0.9 mole) and carbon disulfide (250 ml.). The mixture was cooled, and methyl 2-pyrrole-carboxylate (35.5 g, 0.284 mole) in carbon disulfide (150 ml.) was added with care while stirring. The flask was then immersed in an oil bath maintained at 50°. Acetic anhydride (30.6 g, 0.3 mole) in carbon disulfide (100 ml.) was added drop by drop, and stirring continued for a further 15 hours. The reaction was then quenched by pouring into a dilute hydrochloric acid and ice mixture. After the lumpy reaction complex was completely decomposed (about 1 day), the solid was filtered off, washed thoroughly with water and dried. It was then dissolved in chloroform, and passed through a neutral alumina column. Removing the solvent by flash evaporation gave crude methyl 4-acetyl-2-pyrrole-carboxylate with only a very small amount of methyl 5-acetyl-2-pyrrole-carboxylate. Recrystallization from benzene twice gave pure methyl 4-acetyl-2-pyrrolecarboxylate (33.2 g, 70%), m.p. 110-111°, needless, literature m.p. 109-110° (70). Calc'd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.43; Found: C, 57.29; H, 5.62; N, 8.31.

The corresponding acid, obtained by hydrolysis with 15% aq. potassium hydroxide solution, gave m.p. 221.5-223° (decompn.) Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15; Found: C, 55.22; H, 4.69; N, 9.15.

The aqueous layer from the acetylation reaction was separated, saturated with sodium chloride and extracted with ether. The mother liquor was then combined with organic layers, washed with sodium acetate (saturated aqueous solution) and dried over anhydrous magnesium sulfate. The solvent was removed and the products were separated by adsorption chromatography on neutral alumina. A further 1.6 g (3.4%) of methyl 4-acetyl-2-pyrrolecarboxylate was obtained, along with 5-acetyl-2-pyrrole-carboxylate, which on recrystallization from benzene-petroleum ether yielded 3.6 g (7.6%), m.p. 109-110°, prisms, literature m.p. 110-111.5° (65).

2-Pyrrolecarbonitrile:

This compound was acetylated by the same procedure described above. Thus, to a mixture of 2-pyrrolecarbonitrile (3.68 g, 0.04 mole) and anhydrous aluminum chloride (16.08 g, 0.12 mole) in carbon disulfide (80 ml.), was added dropwise of acetic anhydride (4.49 g, 0.044 mole) in carbon disulfide (20 ml). The temperature was maintained at 50° and stirring continued for 5 h. The mixture was then carefully hydrolyzed by dilute hydrochloric acid and ice mixture. The solid was filtered off, washed with water thoroughly and dried. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium acetate solution and dried. The solid obtained was dissolved in ethanol and combined with organic layers, passed through a neutral alumina column. Crude 4-acetyl-2-pyrrole-carbonitrile was isolated by evaporating the solvent. On recrystallization

from ethanol-water, a yield of 3.82 g (71.3%) was obtained, m.p. 216-217° (decompn.) prisms. Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.88; Found: C, 62.80; H, 4.68; N, 21.17.

4-Acetyl-2-pyrrolecarbonitrile, on refluxing with 40% aq. potassium hydroxide gave the corresponding 4-acetyl-2-pyrrolecarboxylic acid with a yield of 34.5%, m.p. 221-222° (decompn.).

2-Pyrrolecarboxaldehyde:

A slow stream of nitrogen was conducted into a flask containing anhydrous aluminum chloride (6.04 g, 0.06 mole) and nitromethane (20 ml). The flask was cooled in a ice-salt mixture and 2-pyrrolecarboxaldehyde (1.9 g, 0.02 mole) in nitromethane (15 ml) was added with stirring. Acetic anhydride (2.56 g, 0.025 mole) in nitromethane (15 ml) was then added gradually at a rate such that the temperature could be maintained below 0°. The mixture was stirred for an additional 3 h. The stream of nitrogen was then discontinued and the temperature allowed to come to 3-4° for 60 h. The reaction was then quenched by pouring into a dilute hydrochloric acid and ice mixture. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium acetate solution and dried. Removing the solvent gave 4-acetyl-2-pyrrolecarboxaldehyde, which on recrystallization from benzene-cyclohexane yielded 0.6 g (22%), m.p. 136-137°, prisms. Calcd. for $C_7H_7N_2O$: C, 61.30; H, 5.14; N, 10.21; Found C, 61.98; H, 5.21; N, 10.40.

Oxidation of 4-acetyl-2-pyrrolecarboxaldehyde by silver oxide (86) gave the corresponding acid with a yield of 37.5%, m.p. 220-222° (decompn.).

Section II Attempted Decarboxylation of 4-Acetyl-2-pyrrolecarboxylic Acid, Heating with sand:

4-Acetyl-2-pyrrolecarboxylic acid (10 g, 0.065 mole) and 50 g of sand were mixed thoroughly and heated at 220-230° for 30 minutes. The mixture was cooled and extracted with ether. The extract was dried and the product was isolated by evaporation of the solvent. Recrystallization from benzene-petroleum ether gave 1.47 g (20.6%) of 3-acetylpyrrole, m.p. 114-115°, prisms, literature m.p. 115-116°. (39).

Attempted replacement of carboxyl-group by iodine:

The mixture of 4-acetyl-2-pyrrolecarboxylic acid (1 g) in ethanol (20 ml.) and anhydrous sodium acetate (0.56 g) in water (3 ml.) was boiled on steam bath, and treated with iodine (1.68 g) in ethanol (15 ml.) over 1 hour (66). It was heated for further 1½ hours, then hot water (75 ml.) was added with stirring. After cooling, the crystals were filtered off, and on recrystallization from ethanol-water gave 4-acetyl-3,5-diiodo-2-pyrrolecarboxylic acid (0.4 g), m.p. 173-175°, prisms.

Attempted displacement of carboxyl-group with bromine:

The mixture of 4-acetyl-2-pyrrolecarboxylic acid (1.43 g, 0.01 mole) in glacial acetic acid (50 ml.) and bromine (4.8 g, 0.03 mole) in glacial acetic acid (25 ml.) was exposed to UV lamp over 20 minutes (67). The glacial acetic acid was then removed by flash evaporator under room temperature. The residue was poured into ice-water mixture containing sodium carbonate (3.2 g), and extracted with ether. The solvent was then dried. Removing the solvent gave a solid, which decomposed on recrystallization.

Section III. The Brominations and Friedel-Crafts Isopropylations of Methyl 3-Pyrrolecarboxylate and 3-Acetylpyrrole

General:

Methyl 3-pyrrolecarboxylate:

Methyl 1,3-pyrroledicarboxylate (4 g, 0.0216 mole) was dissolved in a minimum amount of methanol, and 12 ml. of cold aqueous potassium hydroxide solution was added. The mixture was mechanically shaken for 6 h and cooled. The solid was filtered off, washed with water and dried. The aqueous layer was extracted with ether. The residue obtained by evaporation of the solvent was combined with the solid. After recrystallization from methanol-water, 2.29 g (64%) of methyl 3-pyrrolecarboxylate was obtained, m.p. 86-87°, prisms, literature m.p. 88° (39).

3-Acetylpyrrole:

This compound was prepared by decarboxylation of 4-acetyl-2-pyrrolecarboxylic acid (see section II) or by the method of Castro et al. (51).

General procedure for brominations:

The mixture of methyl 3-pyrrolecarboxylate or 3-acetylpyrrole (0.016 mole) and anhydrous sodium acetate (2.46 g) in dioxane (150 ml) was stirred at room temperature and the dioxane-dibromide solution (from 0.015 mole of bromine with 100 ml. of dioxane) was added at a rate such that bromine color did not persist. It was stirred for a further 4 hours, and the dioxane was then removed by flash evaporator under room temperature. The residue was poured into an ice-water mixture containing 5% sodium carbonate (40 ml.). It was then extracted with ether, and the ether layer was washed with saturated sodium chloride solution, dried, and the solvent was removed by evaporation. The

residue was then analyzed by gas chromatography and separated by adsorption chromatography on neutral alumina.

Products obtained were:

Methyl 2-bromo-4-pyrrolecarboxlate, 1.56 g (51.7%), m.p. 106-108° (decompn.), prisms (from cyclohexane-chloroform). Calcd. for $C_6H_6BrNO_2$: C, 35.32; H, 2.96; N, 6.87; Br, 39.17; Found: C, 35.51; H, 3.08; N, 6.67; Br, 39.16.

2-Bromo-4-acetylpyrrole, 1.77 g (62.8%), m.p. 151-152.5°, prisms (chloroform-cyclohexane). Calcd. for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45; Br, 42.50; Found: C, 38.25; H, 3.33; N, 7.32; Br, 42.61.

General Procedure for isopropylations:

To the cold mixture of 0.04 mole of methyl 3-pyrrolecarboxylate (or 3-acetylpyrrole) in 50 ml. carbon disulfide and anhydrous aluminum chloride (0.08 mole in 50 ml. carbon disulfide), was added 0.037 mole of isopropyl chloride (or isopropyl bromide) in 50 ml. carbon disulfide with stirring. Stirring continued for a further 30 minutes. The reaction mixture was then immersed in an oil bath maintained at 50° and stirred for 20 hours. The reaction was quenched by pouring into an ice-water mixture. The aqueous layer was separated, saturated with sodium chloride, and extracted with ether. The combined organic layers were washed with saturated sodium chloride solution, and dried. Evaporation of the solvent gave the crude product, which was then dissolved in benzene, and passed through a neutral alumina column. The solvent was removed and the solid recrystallized from cyclohexane twice. Products obtained were:

Methyl 2-isopropyl-4-pyrrolecarboxylate, 3.64 g (59%), m.p. 74-75.5° (prisms). Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38; Found: C, 64.60; H, 7.73; N, 8.28.

2-Isopropyl-4-acetylpyrrole; 3.48 g (62.2%), m.p. 66.5-69.5° (prisms). Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; Found C, 71.41; H, 8.49; N, 9.23.

Bromination of methyl 3-pyrrolecarboxylate with bromine in carbon tetrachloride:

A mixture of methyl 3-pyrrolecarboxylate (0.048 mole) and anhydrous sodium acetate (4.1 g) in 100 ml. carbon tetrachloride was cooled in an ice-salt bath. Bromine (0.04 mole) in 50 ml. carbon tetrachloride was then added drop by drop with stirring. Stirring continued for a further 3 hours. The reaction mixture was then poured into an ice-water mixture containing 10 ml. of 10% sodium hydroxide solution. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and dried. The residue obtained by evaporation of the solvent was separated by adsorption chromatography on neutral alumina. The product isolated was methyl 2,4,5-tribromo-3-pyrrolecarboxylate, which on recrystallization from benzene-cyclohexane gave a yield of 1.9 g (41%), m.p. 207-208.5° (decompn.), prisms. Calcd. for $C_6H_4Br_3NO_2$: C, 19.92; H, 1.11; N, 3.87; Br, 66.26; Found: C, 20.14; H, 1.11; N, 3.70; Br, 66.21.

Other products were decomposed before separation. No further attempt was made to isolate these products.

Section IV. Some Reactions of Brominated and Isopropylated Methyl 3-pyrrolecarboxylate and 3-Acetylpyrrole.

Catalytic deuteration of brominated pyrrole derivatives:

The modified method (62) for the hydrogenation described by Linstead et al.(68) was adopted, but using cyclohexane for the reservoir instead of using petroleum ligroine, and using Adams platinum oxide catalyst (washed with CH_3COOD beforehand) to replace palladium on charcoal. Nuclear magnetic resonance spectrum showed that brominated pyrrole derivatives were completely deuterated in the desired position.

Hydrolysis of methyl 2-isopropyl-4-pyrrolecarboxylate:

Methyl 2-isopropyl-4-pyrrolecarboxylate gave, after refluxing with 15% aqueous potassium hydroxide solution, the corresponding acid with a yield of 81.7%, m.p. 126-127° (decompn.), prisms (from methanol-water). Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.20; Found: C, 62.77; H, 7.54; N, 9.14.

Attempted Oxidation of 2-isopropyl-4-acetylpyrrole:

2-Isopropyl-4-acetylpyrrole (0.046 g) was dissolved in a minimum amount of warm dioxane, then sodium hypoiodite (prepared by mixing 1.52 g iodine and 2.7 g potassium iodide in 13.5 ml. water with 0.32 g sodium hydroxide in 3 ml. water) was added, and the mixture was warmed at 60° for 1 hour. Cold water (10 ml.) was then added, and the precipitate removed. After recrystallization from ethanol-water, 2-isopropyl-3-iodo-4-acetylpyrrole (0.31 g) was obtained, m.p. 177-179°. Which, on exposing to air, gradually decomposed.

Section V. Reaction of Pyrrylmagnesium Bromide with Methyl Chloroformate

This reaction was carried out by a modification of the method of Maxim et al.(59) for ethyl ester. To a stirred, cold solution of ethylmagnesium bromide (1.9 mole) in 600 ml. ether was added dropwise pyrrole (2 mole) in 200 ml. of ether. The reaction mixture was then refluxed for 20 minutes. After cooling, ether (100 ml.) was added, and methyl chloroformate (1 mole) in 150 ml. ether was added dropwise. The reaction mixture was again refluxed for 30 minutes, then cooled and carefully hydrolyzed with 10% ammonium chloride solution. The aqueous layer was separated and extracted with ether. The combined ether layers were dried, the ether removed by flash evaporation and the product was vacuum distilled. Fractions collected were: 80-120°/13-20 mm; 120-127°/13 mm; 127-135°/13 mm; 133-142°/12 mm; 144-154°/12 mm; 137-145°/ 3 mm; 159-172°/ 3 mm; 147-150° /0.4-0.5 mm; 150-180° /0.4-0.5 mm. The residue was then extracted fractionally with benzene, ethanol, and dioxane. Products in each fraction were separated repeatedly by adsorption chromatography on neutral alumina using appropriate solvents as eluents, until a $>95\%$ pure sample was obtained using gas chromatography for analysis. Each sample was then recrystallized from a suitable solvent so that a melting point within a 2 degree range could be obtained .

Products obtained were:

Compound	Average yield
Pyrrole	12.89 g
Methyl 1-pyrrolecarboxylate	0.3 g (0.24%)
Methyl 2-pyrrolecarboxylate	28 g (22.4%)
Methyl 3-pyrrolecarboxylate	trace (unisolated)
Methyl 1,2-pyrroledicarboxylate	10.1 g (5.5%)
Methyl 1,3-pyrrolecarboxylate	8.53 g (4.7%)
1, 2'-Dipyrryl ketone*	0.53 g (0.4%)
2,2' -Dipyrryl ketone‡	1.7 g (1.1 %)

* m.p. 58.5-60°, prisms (from petroleum ether).

Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.34; N, 17.49;

Found: C, 67.24; H, 5.26; N, 17.40.

‡ m.p. 160-161°, prisms (from ethanol-benzene), literature m.p. 160-161° (87). Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.34; N, 17.49;

Found: C, 67.52; H, 5.26; N, 17.43

Section VI. Attempted Synthesis of 3-Isopropylpyrrole via the ring closure of a Glycidic Ester.

Methyl 5,5-dimethoxy-3-isopropyl-2,3-epoxypentanoate:

This compound was prepared by the method of Burness (83), but using 1,1-dimethoxy-4-methyl-3-pentanone (88) instead of 1,1-dimethoxy-3-butanone. Product was obtained by vacuum distillation: b.p. 96-97°/1 mm (57%).

Methyl 3-isopropyl-2-furoate:

This compound was prepared by the method of Burness (83), but using methyl 5,5-dimethoxy-3-isopropyl-2,3-expoxypentanoate instead of using methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate. Product was obtained by vacuum distillation: b.p. 68-71°/2 mm (61%). On refluxing with 30% aqueous potassium hydroxide solution this gave the corresponding acid with a yield of 87%, m.p. 93-94°, (decompn), needles (from chloroform-cyclohexane). Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54; Found: C, 62.51; H, 6.46.

Attempted synthesis of 3-isopropylpyrrole via the ring closure of methyl 5,5-dimethoxy-3-isopropyl 2,3-epoxypentanoate:

The ring closure reaction was carried out under various conditions:

(1) By shaking mechanically with 10% aqueous ammonium carbonate solution (dioxane was added to increase the solubility) for 1 day or by refluxing for 2 hours.

(2) By mixing with ammonium chloride and excess liquid ammonia, and allowed to evaporate to dryness.

(3) Refluxing with ammonium acetate in methanol for 8 hours.

(4) Refluxing with ammonium chloride and ammonia-saturated methanol solution for 8 hours.

(5) Refluxing with ammonium chloride in 95% ethanol over 4 hours.

(6) Refluxing with ammonium chloride in benzene over 6 hours.

(7) Hydrobromic acid 48% was added with stirring while cooling, large excess of concentrated ammonium hydroxide was then added and warmed at 40-50° for 3 hours.

(8) Concentrated ammonium hydroxide was added and stirred at 40-50° for 3 hours, then cooled and concentrated sulfuric acid was added. The mixture was stirred for a further 3 hours.

(9) Refluxing with 48% hydrobromic acid for 1 hour, then cooled and added concentrated ammonium hydroxide. The mixture then stood overnight.

(10) Refluxing with ammonium carbonate in dioxane for 6 hours.

(11) Refluxing with aluminum oxide in ethylene glycol, and concentrated ammonium hydroxide was added at intervals.

(12) Refluxing with ferric chloride in ethylene glycol, while concentrated ammonium hydroxide was added at intervals.

At the end of each of the above operations the reaction mixture was then neutralized and extracted with ether. The residue after evaporating the solvent was vacuum distilled or crystallized from appropriate solvent. All the attemps were unsuccessful. It was found that under milder conditions (in methods 1-6), the starting material was recovered. While with vigorous conditions, 3-isopropylfuran derivatives, e.g. acid (method 7), ester (methods 11 and 12) or amide (method 9) were formed.

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