

ATTEMPTS TO PREPARE 3-SUBSTITUTED PYRROLES

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ATTEMPTS TO PREPARE
3-SUBSTITUTED PYRROLES

A Thesis

by

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submitted in partial fulfillment of the
requirements for the degree of Master of Science

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ABSTRACT

1-Benzylpyrrole was prepared and subjected to bromination, nitration and formylation and the products isolated and identified. 1-Benzyl-3-bromopyrrole was converted to 1-benzyl-3-pyrrolicarboxylic acid and to methyl 1-benzyl-3-pyrrolicarboxylate; 1-benzyl-3-nitropyrrole was converted to 1-benzyl-3-acetamidopyrrole. 1-Benzyl-3-pyrrolicarboxaldehyde was oxidized to the 3-acid and 1-benzyl-2-pyrrolicarboxaldehyde was converted to the nitrile and thus to the 2-acid and the acid esterified to its methyl ester.

Identification of the compounds has been accomplished primarily by interpretation of nuclear magnetic resonance spectra in conjunction with infrared spectra and elemental analysis. Some interconversions of the derivatives were also successfully performed. Further evidence for the assigned structures of the 2- and 3-esters has been furnished by the synthesis of these compounds by unequivocal routes.

The catalytic reductive debenzylation of methyl 1-benzyl-3-pyrrolicarboxylate was attempted, but with no success.

Attempts were made to prepare 1-benzenesulfinylpyrrole and 1-(2,4-dinitrobenzenesulfinyl)-pyrrole but without success, the 2-substituted products being obtained in each case. The formylation of 1-(2,4-dinitrobenzenesulfinyl)-pyrrole gave only the 5-formyl derivative.

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DiscussionSection 1 Substitution reactions of Pyrrole and 1-Alkylpyrroles

A well known feature of the reactions of pyrrole is the susceptibility of the α -positions to electrophilic attack. Pyrrole can be represented as a number of resonance structures (Fig.I) but because of the smaller charge separation in structures (II) and (III) these assume a greater importance in the overall structure.

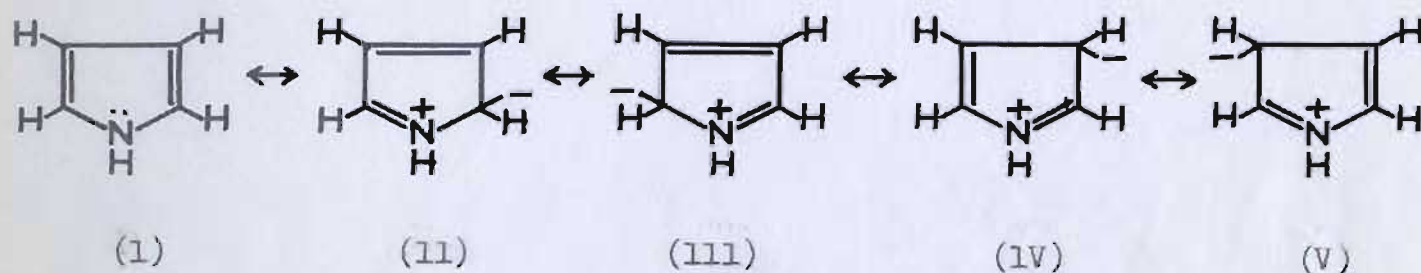


Fig. 1

The unshared pair of electrons on the nitrogen atom conjugates with the π electrons of the double bonds so that a situation analogous to that in benzene exists, in which the electrons form a "cloud" above and below the plane of the ring. Thus pyrrole reacts by substitution rather than by addition; it shows aromatic rather than diene-like behaviour.

Electrophilic substitution in pyrrole occurs almost exclusively in the α -position. Halogenation with sulfuryl chloride in ethereal solution (1) gave the 2,5-disubstituted pyrrole before any attack was apparent in the 3-position. Sulfonation, formylation, acylation and other substitution reactions also occur in the α -position. Nitration, however, gives a small amount of 3-substitution. Anderson (2) indicated a probable 7% of the 3-nitro isomer in the mononitration product when he nitrated pyrrole with a mixture of acetic anhydride and fuming nitric acid.

The presence of an alkyl group on the nitrogen atom has been shown to change the substitution pattern considerably. Nitration of 1-methylpyrrole with acetic anhydride and fuming nitric acid gives a mixture of isomers. Anderson (2), by column adsorption chromatography, isolated "roughly two parts of 2-nitro-1-methylpyrrole to one of the 3-isomer" while Fournari (3) applying the polarographic analysis technique, estimated 27% of the 3-isomer. Nitration of 1-phenylpyrrole (4) was shown to give a similar ratio of 2- and 3-nitro derivatives. On the other hand, metalation of 1-methylpyrrole with n-butyllithium (5), Friedel-Craft's acylation (6), formylation with phosphorus oxychloride and dimethylformamide (7) and other substitution reactions of 1-methylpyrrole all lead to the formation of 2-substituted product only.

1-Benzylpyrrole was chosen as the starting material for this study because first, it was expected that the substitution pattern in 1-benzylpyrrole would be similar to that of 1-methylpyrrole and 1-phenylpyrrole and would give a reasonable proportion of the 3-nitro isomer on nitration. Secondly, it was known that benzyl groups attached to tertiary nitrogen atoms readily undergo hydrogenolysis with the removal of the benzyl group (8). Furthermore Adkins and Coonradt (9) reported that hydrogenation of 1-benzylpyrrole was so slow over nickel that cleavage of the benzyl group occurred with the production of pyrrolidine (70% after 8 hours at 260°) and toluene. The present study has shown the β -directing effect of the benzyl group in 1-benzylpyrrole to be greater than that of the methyl and phenyl groups in 1-methyl and 1-phenyl pyrroles respectively. Nitration of 1-benzylpyrrole, using the same conditions as Anderson (2), gave a mixture of mononitro isomers which contained about 60% of the 3-isomer. Bromination too, under

conditions selected to minimize polybromination, gave the 3-bromo isomer as the major product - up to a maximum of about 66% of the crude product (Table IV, Reaction B3). Formylation of 1-benzylpyrrole with phosphorus oxychloride and dimethyl formamide also gave a mixture of isomers, but in this reaction the 2-isomer predominated; about 15% of the 3-aldehyde was obtained.

The ultraviolet spectra of pyrrole, 1-methylpyrrole and 1-benzylpyrrole (Table III) were very similar (λ_{max} 207-212.5 $m\mu$) but the intensity of the (K) band was greatest in 1-benzylpyrrole. The N-methyl group had a small bathochromic effect on the K band of pyrrole while the N-benzyl group had a small hypsochromic effect. However the differences were small and there appeared to be no significant electronic effect on the pyrrole ring by the N-benzyl group. Examination of a "space-filling" model of 1-benzylpyrrole showed there to be some interference between the α -hydrogen atoms of the benzene ring and the α -protons of the pyrrole ring. This steric interference is probably the reason for the unexpectedly large proportions of 3-substituted products obtained.

The 3-substituted products from the nitration, formylation and bromination reactions were studied and a variety of 1-benzyl-3-substituted pyrroles were prepared, including methyl 1-benzyl-3-pyrrolicarboxylate. This compound was treated with hydrogen in the presence of W-4 Raney-nickel under vigorous conditions in an attempt to remove the benzyl group, but no methyl 3-pyrrolicarboxylate was detected in the reaction mixture.

An attempt was then made to synthesize 1-benzenesulfonylpyrrole, in which the methylene bridge between the benzene and pyrrole rings is replaced by a sulfur atom. It was expected that this compound would have a substitution pattern similar to that of

1-benzylpyrrole and that the benzenesulfonyl group would be much more easily removed by catalytic reduction. However, this reaction was unsuccessful; the only product isolated appeared to be 2-benzenesulfonylpyrrole and this was obtained in poor yield. An attempt to prepare 1-(2,4-dinitrobenzenesulfonyl)-pyrrole which, because of the bulky nitro group in the α -position of the benzene ring, might be expected to give an even greater degree of β -substitution in the pyrrole ring, gave a good yield of the 2-substituted product. None of the hoped-for 1-substituted product was isolated. Formylation of 2-(2,4-dinitrobenzenesulfonyl)-pyrrole was attempted and this gave only the 5-formyl derivative.

Section 2 Preparation of 1-Benzylpyrrole

Alkylation of metal salts of pyrrole has been shown to produce a mixture of N- and C- substituted products. A study of the factors affecting the position of alkylation of alkali metal salts of pyrrole (10) has shown:

(i) for a given metal salt the most polar solvents gave the highest percentage of 1-alkylation.

(ii) for a given medium the relative percentage of 1-alkylation increases with decreasing coordinating ability of the cation in the order $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < (\text{CH}_3)_3\text{N}^+\text{C}_6\text{H}_5$.

Optimum conditions for the preparation of 1-benzylpyrrole would require the use of the trimethylphenylammonium salt of pyrrole with tetrahydrofuran as solvent. However the potassium salt, though not quite as efficient in its 1-directing effect, was much more convenient to prepare and use and was therefore chosen for the preparation. 1-Benzylpyrrole was prepared both in toluene and in tetrahydrofuran by reacting potassium pyrrole with benzyl bromide. The yield obtained in tetrahydrofuran was much better than that obtained in toluene and the product was cleaner. Thus the observations of Hobbs et al. (10) were confirmed.

Section 3Bromination of 1-Benzylpyrrole

Attempts were made to brominate 1-benzylpyrrole with a variety of brominating agents:

- (i) Bromine in carbon tetrachloride
- (ii) bromine in a mixture of glacial acetic acid and sodium acetate
- (iii) an aqueous solution of sodium hypobromite
- (iv) N-bromosuccinimide in carbon tetrachloride

Reagents (ii) and (iii) did not react since only 1-benzylpyrrole was identified by gas chromatography of the reaction mixture in each case. N-bromosuccinimide was unsuccessful when used with and without a catalyst (benzoyl peroxide). This reagent apparently polymerized the substrate with the production of a black powder but without the formation of any simple bromination products. Bromine in carbon tetrachloride proved to be successful but a sticky red byproduct, insoluble in carbon tetrachloride, was formed in addition to the simple pyrrole derivatives. The byproduct was presumably formed because the hydrogen bromide, produced during the reaction, catalyzed the polymerization of 1-benzylpyrrole. The amount of polymerization was reduced by removing most of the hydrogen bromide as it was formed by attaching the apparatus to a water pump and applying a slight suction.

A series of reactions was performed (Table IV) in which the molecular proportions of the reactants and, in one example, the concentrations of the reactants were varied. The effect of concentration was not large but increased dilution did reduce somewhat the degree of polybromination. The composition of the mixture of products was shown to be influenced greatly by the molecular ratios of the starting materials, the degree of

polybromination increasing markedly as the proportion of bromine in the reaction mixture was increased. When reaction conditions were chosen to give maximum monobromination the reaction mixture was shown, by gas chromatography, to contain over 66% of one compound; its elemental analysis showed it to be a monobromo derivative. This compound was readily isolated by extracting the mixture with petroleum pentanes and recrystallizing the product. Other bromination products were then separated from the mother liquor by repeated chromatography on columns of alumina. It was found possible to isolate, in addition to the monobromo-derivative, one dibromo compound, one tribromo compound and the tetrabromo derivative. Another fraction was also isolated which appeared to consist of a mixture of dibromo isomers, but attempts to separate and identify these isomers failed because of the susceptibility of the mixture to oxidation. The products were initially identified on the basis of their nuclear magnetic resonance spectra (Table I) and elemental analysis and the structure of the major (monobrominated) product was confirmed by chemical means. The four compounds isolated were identified as 1-benzyl-3-bromopyrrole (major product), 1-benzyl-3,4-dibromopyrrole, 1-benzyl-2,3,4-tribromopyrrole and 1-benzyl-2,3,4,5-tetrabromopyrrole.

Discussion of the 3-substituted derivatives of 1-Benzylpyrrole and of the proof of their structures.

Attempts to react the monobromo derivative of 1-benzylpyrrole with magnesium in dry ether failed and the lack of reactivity of the bromine atom was also evident in the failure of the compound to react with n-butyllithium or with cuprous cyanide. It did, however, react with lithium metal when it was refluxed with

lithium wire in anhydrous ether. Carbonation of the reaction mixture gave the corresponding acid which reacted readily with diazomethane to give the methyl ester.

This ester was shown to be methyl 1-benzyl-3-pyrrole-carboxylate (Fig. 2, lll) by preparing another sample by an unequivocal route. The potassium salt of an authentic sample (ll) of methyl 3-pyrrolecarboxylate (Fig. 2, Vll) was reacted with benzyl bromide in tetrahydrofuran and the N-benzylated product isolated. A mixed melting point of the two samples of the ester showed no depression. It was therefore evident that they were the same compound, namely methyl 1-benzyl-3-pyrrolecarboxylate. Thus the acid was 1-benzyl-3-pyrrolecarboxylic acid (Fig. 2, ll) and the bromo compound was 1-benzyl-3-bromopyrrole (Fig. 2, lX).

The allocation of the 3-position to the substituents in the above compounds was supported by evidence from the nuclear magnetic resonance spectra of the compounds. The bromine atom had little effect upon the chemical shift of the remaining protons but with the electron withdrawing acid, ester, nitro, acetamido and oxime groups in the 3-position the 2-proton moved to lower field and was consistently the lowest field pyrrole proton, having values ranging from 7.20 to 7.46 p.p.m. In the bromo compound the 2 and 5 proton signals overlapped. The 4- and 5- proton signals moved closer together but their relative positions depended on the group in the 3-position. The values obtained for the coupling constants of the pyrrole protons were consistent with the assignment of the chemical shifts and were in reasonable agreement with similar values obtained by Gronowitz (12). J_{24} varied from 1.50 to 1.72 c.p.s., J_{25} varied from 2.30 to 2.60 c.p.s. and

J_{45} ranged from 2.50 to 3.10 c.p.s.

The reaction between lithium metal and 1-benzyl-3-bromopyrrole generated 1-benzyl-3-pyrrolyllithium. It has been established that an aryllithium compound can react with monohalogeno aromatic compounds to form benzyne-type intermediates (13). However, there was no evidence to suggest that such an intermediate was formed in this reaction and it appeared that the reaction proceeded by a simple metal-halogen exchange.

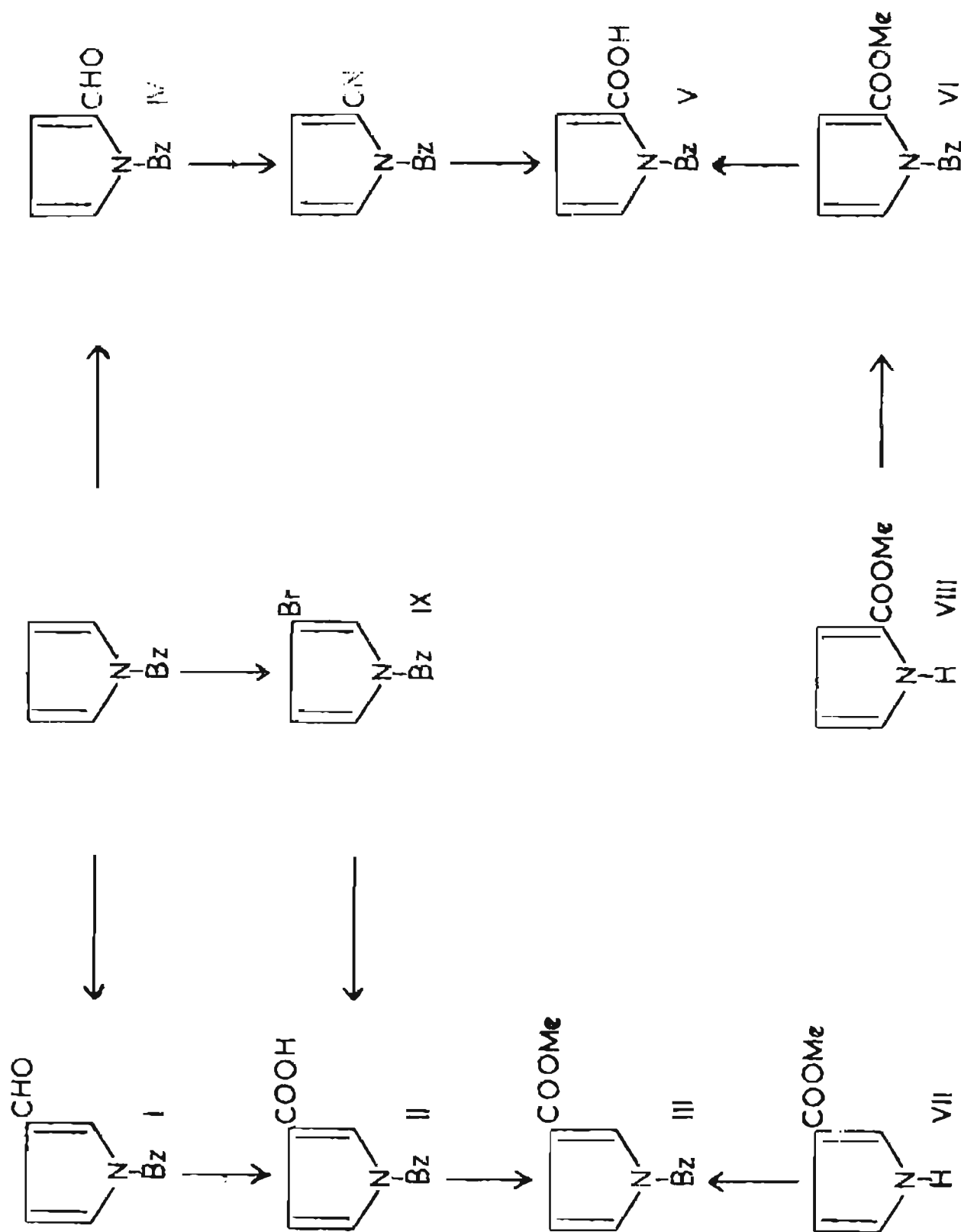


Fig. 2

Section 4 Nitration of 1-Benzylpyrrole

The method described by Anderson for the nitration of pyrrole and 1-methylpyrrole (2) was adopted. The nitrating mixture of fuming nitric acid and acetic anhydride, in its reaction with 1-benzylpyrrole, gave a mixture of the 2- and 3- mononitro derivatives. The higher melting 3-nitro isomer was pale yellow in colour; the 2-nitro isomer was white.

The position of the nitro group in each isomer was determined by a study of the n.m.r. spectra. (Table I). The presence of the nitro group moved the chemical shift of the adjacent protons to lower field, the greatest deshielding effect being due to the 3-nitro group on the 2-proton and the least being due to the 3-nitro group on the 4-proton. In the former case the δ -value of the 2-proton increased from 6.47 in 1-benzylpyrrole to 7.30 p.p.m. in 1-benzyl-3-nitropyrrole; in the latter instance the δ -value of the 4-proton increased from 6.06 in 1-benzylpyrrole to 6.58 p.p.m. in 1-benzyl-3-nitropyrrole. In the 2-nitro isomer there was some overlapping of the signals of the 3-proton with those of the benzene protons. In the 3-nitro isomer the chemical shift of the 2-proton moved below that of the benzene protons.

Reactions of 1-benzyl-3-nitropyrrole

The first attempts to reduce the 3-nitro compound to the amine were not successful because, as was shown in later reactions, the amine was unstable in the atmosphere. Catalytic reduction of an alcoholic solution of 1-benzyl-3-nitropyrrole in the presence of platinum oxide gave a product which began to go off colour as soon as it contacted the air. The amine was, however, readily acetylated with a mixture of acetic anhydride and sodium acetate,

but it was found more convenient to prepare 1-benzyl-3-acetamidopyrrole directly by catalytic reductive acetylation which gave an 85% yield. The amine hydrochloride was used in an attempt to replace the amino group by the nitrile group and by the bromine atom through diazotization, but without success. It was therefore not possible to confirm the position of the nitro group in the supposed 1-benzyl-3-nitropyrrole by direct comparison with the 3-substituted bromo and formyl derivatives. However, the nuclear magnetic resonance spectrum of 1-benzyl-3-acetamidopyrrole supports the allocation of the 3-position to the substituent group. As with the 3-nitro group the 3-acetamido group has a general deshielding effect and all the proton signals move to lower field.

Additional evidence of the correctness of the allocation of the 3-position to the higher melting nitro compound is obtained from a comparison of the ultraviolet spectra of the 2 and 3-nitro compounds with the spectra of the 2 and 3 substituted oximes and esters. (see p. 21)

Section 5Formylation of 1-Benzylpyrrole

1-Benzylpyrrole was formylated with dimethylformamide and phosphorous oxychloride (15) and the product was shown, by gas chromatographic analysis, to contain two products. A pure sample of the major product was obtained by fractional distillation of the reaction mixture under low pressure but the minor product could not be obtained by this method. The two products and the unreacted starting material were satisfactorily separated on a column of alumina but they remained coloured. However, each showed only one peak when analyzed by gas chromatography.

The major product (85%) was later shown to be 1-benzyl-2-pyrrolicarboxaldehyde and the minor product (15%) was shown to be 1-benzyl-3-pyrrolicarboxaldehyde. This is in contrast to the bromination and nitration reactions, in which the 3-bromo and 3-nitro isomers were the predominant mono-substitution products. However in the formylation of 1-methylpyrrole (7) no 3-formyl derivative was obtained, so that in spite of the small fraction of 3-formyl derivative in the product, 1-benzylpyrrole again demonstrated a greater tendency towards 3-substitution than did 1-methylpyrrole.

A mixture, later shown by gas chromatography to contain approximately 80% of 1-benzylpyrrole and 20% of 2-benzylpyrrole, was inadvertently formylated in one reaction. The crude product was shown to contain no unreacted 2-benzylpyrrole, but about 7% of 1-benzylpyrrole remained in the reaction mixture. It appeared therefore that 2-benzylpyrrole reacted with the formylating mixture faster than 1-benzylpyrrole. Apart from the two products described above (from 1-benzylpyrrole) two other compounds were separated, one pale yellow and the other orange in colour.

Analysis of the infrared and nuclear magnetic resonance spectra of the pale yellow formyl derivative indicated that it was 2-benzyl 5-pyrrolicarboxaldehyde. The infrared spectrum showed absorptions in the -N-H region at 3205 cm^{-1} and in the carbonyl region at 1630 cm^{-1} . The nuclear magnetic resonance spectrum showed two pyrrole signals, both quartets in carbon tetrachloride which became doublets when the solution was shaken with D_2O . The coupling constant of the two protons, 3.62 c.p.s., was consistent with other J_{34} values while the J_{13} and J_{14} values (2.20 c.p.s.) were also consistent with known values. (12)

The orange compound, which appeared to contain more than one benzylpyrrole nucleus, has not yet been identified and is still under investigation.

Discussion of the derivatives of 1-Benzyl-2- and 3-pyrrole-carboxaldehydes and the proof of their assigned structures.

Both 1-benzyl aldehydes reacted readily with hydroxylamine to give crystalline oximes, the 3-aldehyde giving a pale yellow oxime and the 2-aldehyde a white oxime. The nuclear magnetic resonance spectrum of 1-benzyl-2-pyrrolicarbaldoxime showed two peaks in the $-\text{CH}_2-$ region at δ 5.40 and δ 5.50 respectively which, when integrated, together corresponded to two protons. There were also two peaks in the $-\text{N}-\text{OH}$ region at δ 10.80 and δ 11.28 respectively which, when integrated together corresponded to one proton. This suggested the presence of two isomeric forms in the sample, the *syn*- and *anti*-configurations of the oxime respectively (Fig. 3) in which different environments exist for the $-\text{OH}$ and $-\text{CH}_2$ protons.



Fig. 3

The suspected 3-aldehyde was readily oxidized with alkaline silver oxide to the corresponding acid and a mixed melting point of this acid with the proven 3-acid (Fig.2,11) obtained from 1-benzyl-3-bromopyrrole, showed no depression. The minor formylation product was thus shown to be 1-benzyl-3-pyrrolecarboxaldehyde. (Fig.2,1).

The attempted oxidation of the suspected 1-benzyl-2-pyrrolecarboxaldehyde with Tollen's reagent was unsuccessful, so the required 2-acid was prepared by converting the aldehyde directly to the nitrile (16) and hydrolyzing the latter with concentrated sodium hydroxide solution. The nitrile was not isolated and purified but its presence was shown in the reaction mixture (before hydrolysis was attempted) by the presence of the characteristic -C-N stretching peak at 2210 cm^{-1} in its infrared spectrum. Hydrolysis of the nitrile was incomplete and both the corresponding amide and acid were isolated and identified. The position of the acid group was confirmed by preparing methyl 1-benzyl-2-pyrrolecarboxylate (Fig.2,V1) from an authentic sample of methyl 2-pyrrolecarboxylate (Fig.2,V11) by N-benzylating the latter in tetrahydrofuran.

The sample of methyl 1-benzyl-2-pyrrolecaboxylate was then hydrolyzed to the corresponding acid, (Fig.2,V) and a mixed melting point of this acid and the acid obtained from the nitrile showed no depression. Thus the assignment of the 2-position to the major substituent in the formylation reaction was confirmed.

Further evidence of the correctness of the assigned structure of the 2-substituted products comes from a study of their nuclear magnetic resonance spectra. (Table I). The chemical shift of the pyrrole -4 proton in each 2-substituted compound is the pyrrole proton to highest field, with the δ value ranging from 5.96 to 6.28 ppm. The relative chemical shifts of the 3 and 5 pyrrole protons are not consistent. The 5-proton of the amide and oxime is the one to lower field in each case; in the aldehyde the 3- and 5- protons overlap and for the nitro-compound, acid and ester, the 5-protons are to higher field. However the values obtained for the coupling constants are consistent with the assignments of the various protons. In these compounds the values of J_{34} vary from 3.60 to 4.10 c.p.s., the J_{35} values from 1.70 to 2.30 c.p.s. and the J_{45} values vary from 2.40 to 2.76 c.p.s.

Section 6 Attempted substitution of the Benzenesulfonyl and 2,4-Dinitrobenzenesulfonyl groups onto the Pyrrole Nitrogen

Attempts to prepare arylsulfonyl derivatives of pyrrole with the substituent on the nitrogen atom were unsuccessful. The reaction between potassium pyrrole and benzenesulfonyl chloride in toluene was unsatisfactory because of the poor yield of product obtained. The nuclear magnetic resonance spectrum of the crude product suggested that in fact, substitution had occurred in the 2-position. However, 2,4-dinitrobenzenesulfonyl chloride reacted with potassium pyrrole in toluene to give a good yield of product. Some uncertainty was experienced with this reaction because, as was later shown, the sample of pyrrole used contained an appreciable amount of impurity. The pyrrole (obtained from Aldrich Chemical Company) was first fractionated on a spinning band column and the constant boiling fraction collected but the nuclear magnetic resonance spectrum of the distillate showed some foreign peaks in the high field region. The product from the reaction of the potassium salt of this sample of pyrrole with 2,4-dinitrobenzenesulfonyl chloride was passed through a column of alumina and two products were isolated, the first collected being a bright red crystalline compound and the second an orange crystalline compound.

The nuclear magnetic resonance spectrum of the red compound contained two methyl groups at δ 2.10 and δ 3.55 and two pyrrole proton signals, which were doublets, with a J value of 2.65 c.p.s. There was no -N-H signal. The compound therefore appeared to be 1,3-dimethyl-2-(2,4-dinitrobenzenesulfonyl)-pyrrole and elemental analysis fitted the proposed formula. The reaction was then repeated in benzene so as to eliminate the only obvious source of

methyl groups (in toluene), but the red compound was again obtained. It was evident therefore that the pyrrole used contained a quantity of impurity, namely 1,3-dimethyl-pyrrole, which also reacted with the reagent. This was finally confirmed by obtaining pyrrole from another source (Ansul Chemical Company) and the reaction with potassium pyrrole repeated in toluene. No red compound was isolated.

The orange product was shown to be 2-(2,4-dinitrobenzenesulfonyl)-pyrrole. Its nuclear magnetic resonance spectrum in D_6 -DMSO showed the typical ABX pattern of the 2,4-dinitrophenyl protons together with three pyrrole proton signals, all quartets. The coupling constants indicated that these protons were in positions 3, 4 and 5. No N-H coupling was visible because of the solvent used but the presence of the N-H group was shown by the N-H stretching frequency at 3380 cm^{-1} in the infrared spectrum. The elemental analysis agreed with the proposed formula.

It was also observed that pyrrole reacted exothermically with 2,4-dinitrobenzenesulfonyl chloride in the presence of the weak base triethylamine, with a 76% conversion of the sulfonyl compound to the same orange product. Further the reaction of 2,4-dinitrobenzenesulfonyl chloride with a large excess of pyrrole in the absence of added base also gave 2-(2,4-dinitrobenzenesulfonyl)-pyrrole in 81% yield, based on the conversion of sulfonyl compound to product. In this latter reaction a quantity of black polymeric material was produced which suggested that the pyrrole acted as its own base, being itself polymerized in the process.

Two reaction mechanisms appear to be possible for this reaction:

(i) Addition-elimination;

2,4-Dinitrobenzenesulfonyl chloride is known to add readily across double bonds and has been used for the characterization of olefines (17). Pyrroles are known, in some cases, to behave as 1,3-dienes towards some reactive agents, though Diels-Alder type adducts have not been detected in the case of pyrrole itself (18). It is conceivable that, in the presence of the reactive 2,4-dinitrobenzenesulfonyl chloride, 2,5-addition, followed by elimination might have occurred. (Fig. 4). This mechanism would explain the absence of 1-(2,4-dinitrobenzenesulfonyl)-pyrrole in the product.

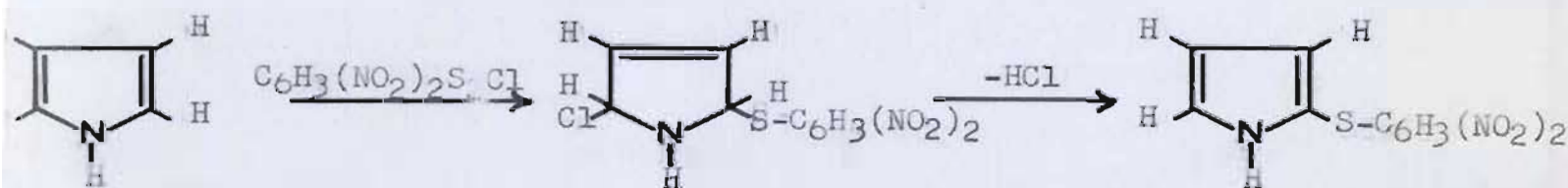


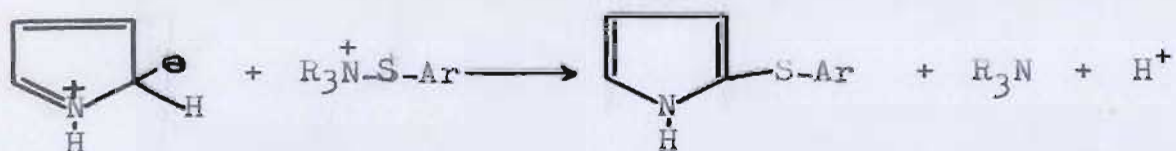
Fig. 4

(ii) Electrophilic substitution;

Benylation of potassium pyrrole in toluene gave a mixture of 1- and 2- benzylopyrroles but in the reaction of potassium pyrrole with 2,4-dinitrobenzenesulfonyl chloride in toluene no 1-substitution was apparent. The rate of the reaction appeared to be dependent upon the base present; its vigor appeared to decrease in the order potassium salt > triethylamine > pyrrole; this suggested that the reaction might be base catalyzed. The base might first react with the sulfonyl chloride to form a reactive intermediate;



and this might attack the pyrrole:



On the other hand the arylsulfenyl chloride might directly attack the electron rich α -carbon atom of pyrrole with the base acting as a proton acceptor in the final stage of the reaction.

It is evident that a further study of this reaction would be of interest:

(i) The reaction of potassium pyrrole with 2,4-dinitrobenzenesulfenyl chloride might be repeated in tetrahydrofuran so as to increase the tendency towards 1-substitution (10).

(ii) A study of the kinetics of the reaction might give some indications of the mechanism by which the substitution proceeds.

Section 7Ultraviolet Spectra

A comparison of the ultraviolet spectra of the 2- and 3-substituted 1-benzylpyrrole esters, oximes and nitro compounds (Table III) showed that the differences in band wavelengths and intensities between the 2- and 3-substituted compounds were consistent.

The K band of the 3-substituted benzylpyrroles was to longer wavelength than in the corresponding 2-isomer but the bathochromic shift was small. The intensity of the K band of the 3-isomer was greater than that of the 2-isomer in each case but again the (hyperchromic) effect is small. However although the effects observed were small they were consistent.

The B band, which did not appear in 1-benzylpyrrole, occurs consistently to shorter wavelength in the 3-substituted compound than in the 2-substituted isomer. The hypsochromic shift of the 3-substituted pyrroles varied from 9.5 $m\mu$ in the 3-oxime to 48 $m\mu$ in the 3-nitro compound. There was also a hypochromic effect in the 3-nitro compound and 3-ester when compared with the 2-substituted compounds but the difference in intensity was negligible in the oximes.

It appeared therefore that there was a more efficient conjugation between the pyrrole ring and the substituent groups in the 2-position than in the 3-position.

The observations are in agreement with similar observations made in the thiophene series. Gronowitz (20) noted that larger bathochromic shifts were obtained for 2-substituted thiophenes having -I-M substituents than for the corresponding 3-substituted thiophenes.

Because the 2- and 3-nitro compounds fall into the pattern observed for other similar 2- and 3-substituted pyrroles and thiophenes it provides further evidence of the correctness of the assigned structures of the nitro compounds.

Table 1

Nuclear Magnetic Resonance Spectra

(A) Chemical Shifts (p.p.m.)

| | Solvent | $C_6H_5^\dagger$ | $-CH_2-$ | Pyrrole protons | | | | Other information |
|--------------------------------------|-------------|------------------|----------|-----------------|------|------|------|--|
| | | | | 2 | 3 | 4 | 5 | |
| 1-Benzylpyrrole | CCl_4 | 7.1 | 4.80 | 6.47 | 6.06 | 6.06 | 6.47 | |
| 1-Benzyl-3,4-dibromopyrrole | CCl_4 | 7.2 | 5.24 | - | 6.25 | 6.25 | - | |
| 1-Benzyl-2,3,4-tribromopyrrole | CCl_4 | 7.25 | 5.27 | 6.39 | - | - | - | |
| 1-Benzyl-2,3,4,5-tetrabromopyrrole | CCl_4 | 7.2 | 5.24 | - | - | - | - | |
| 1-Benzyl-3-bromopyrrole | CCl_4 | 7.23 | 4.96 | 6.53 | - | 6.09 | 6.53 | |
| 1-Benzyl-3-pyrrolecarboxylic acid | $CDCl_3$ | 7.33 | 5.08 | * | - | 6.67 | 6.67 | |
| Methyl 1-benzyl-3-pyrrolecarboxylate | CCl_4 | 7.2 | 4.96 | * | - | 6.49 | 6.49 | $-COOCH_3$ 3.68 |
| 1-Benzyl-3-nitropyrrole | CCl_4 | 7.25 | 5.07 | 7.44 | - | 6.60 | 6.53 | |
| 1-Benzyl-3-acetamidepyrrole | $CDCl_3$ | 7.27 | 4.97 | 7.40 | - | 6.03 | 6.51 | $-NHCOOCH_3$ 7.78 ; $-NHCOOCH_3$ 2.05 |
| 1-Benzyl-3-pyrrolecarbaldoxime | D_6 -DMSO | 7.24 | 5.10 | 7.46 | - | 6.37 | 6.79 | $-CH=N-$ 7.24; $=N-OH$ 10.92 |

† Centre of multiplet

* Chemical shifts not recorded because they are not distinguishable from the aromatic protons

Table 1 Continued

Nuclear Magnetic Resonance Spectra

(A) Chemical Shifts (p.p.m.)

| | Solvent | $C_6H_5^\dagger$ | $-CH_2-$ | Pyrrole protons | | | | Other information |
|---|------------|------------------|--------------|-----------------|------|------|------|--------------------------------------|
| | | | | 2 | 3 | 4 | 5 | |
| 1-Benzyl-2-pyrrolicarboxylic acid | $CDCl_3$ | 7.34 | 5.63 | - | * | 6.28 | 7.0 | $-COOH$ 11.70 |
| Methyl 1-benzyl-2-pyrrolicarboxylate | CCl_4 | 7.06 | 5.42 | - | 6.79 | 5.96 | 6.65 | $-COOCH_3$ 3.62 |
| 1-Benzyl-2-nitropyrrole | CCl_4 | 7.30 | 5.59 | - | * | 6.19 | 6.80 | |
| 1-Benzyl-2-pyrrolicarboxaldehyde | CCl_4 | 7.07 | 5.38 | - | 6.73 | 6.07 | 6.73 | $-CHO$ 9.38 |
| 1-Benzyl-2-pyrrolicarbaldoxime | D_6DMSO | 7.37 | 5.43 5.53 | - | 6.53 | 6.26 | 7.10 | $-CH=N$ 8.16; $=N-OH$ 10.83 11.31 |
| 1-Benzyl-2-pyrrolicarboxamide | $CDCl_3$ | 7.18 | 5.56 | - | 6.59 | 6.0 | 6.77 | |
| 2-Benzyl-5-pyrrolicarboxaldehyde | CCl_4 | 7.15 | 4.07 | - | 5.91 | 6.78 | - | $-CHO$ 9.25 |
| 2-(2,4-dinitrobenzenesulfonyl)-1,3-dimethylpyrrole ** | $CDCl_3$ | - | - | - | - | 6.15 | 6.90 | $C-CH_3$ 2.10; $N-CH_3$ 3.55 |
| 2-(2,4-dinitrobenzenesulfonyl)-pyrrole ** | D_6-DMSO | - | - | - | 6.64 | 6.36 | 7.22 | $N-H$ 11.25 |
| 2-(2,4-dinitrobenzenesulfonyl)-5-pyrrolicarboxaldehyde ** | Dioxane | - | - | - | 6.64 | 7.02 | - | CHO 9.45 |

† Centre of multiplet

* Chemical shifts not recorded because they are not distinguishable from the aromatic protons

** The aromatic protons are not recorded

Table I

Nuclear Magnetic Resonance Spectra(B) Coupling Constants (c.p.s.) for the pyrrole protons.

| | J_{13} | J_{14} | J_{15} | J_{24} | J_{25} | J_{34} | J_{35} | J_{45} |
|--------------------------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| 1-Benzylpyrrole | | | | | | | | |
| 1-Benzyl-3,4-dibromopyrrole | | | | | | | | |
| 1-Benzyl-2,3,4-tribromopyrrole | | | | | | | | |
| 1-Benzyl-2,3,4,5-tetrabromopyrrole | | | | | | | | |
| 1-Benzyl-3-bromopyrrole | | | | 1.72 | 2.42 | | | 2.62 |
| 1-Benzyl-3-pyrrolicarboxylic acid | | | | | | | | |
| Methyl 1-benzyl-3-pyrrolicarboxylate | | | | | | | | |
| 1-Benzyl-3-nitropyrrole | | | | 1.70 | 2.30 | | | 3.10 |
| 1-Benzyl-3-acetamidopyrrole | | | | 1.50 | 2.60 | | | 2.50 |
| 1-Benzyl-3-pyrrolicarbaldoxime | | | | 1.56 | 2.60 | | | 2.50 |

Table I Continued

Nuclear Magnetic Resonance Spectra

(B) Coupling Constants (c.p.s.) for the pyrrole protons

| | J_{13} | J_{14} | J_{15} | J_{24} | J_{25} | J_{34} | J_{35} | J_{45} |
|--|----------|----------|----------|----------|----------|----------|----------|----------|
| 1-Benzyl-2-pyrrolicarboxylic acid | | | | | | 3.60 | 1.80 | 2.60 |
| Methyl 1-benzyl-2-pyrrolicarboxylate | | | | | | 3.76 | 1.72 | 2.50 |
| 1-Benzyl-2-nitropyrrole | | | | | | 4.10 | 2.30 | 2.76 |
| 1-Benzyl-2-pyrrolicarboxaldehyde | | | | | | 3.96 | 2.00 | 2.50 |
| 1-Benzyl-2-pyrrolicarbaldoxime | | | | | | 3.60 | 1.80 | 2.60 |
| 1-Benzyl-2-amidopyrrole | | | | | | 3.74 | 1.70 | 2.40 |
| 2-Benzyl-5-pyrrolicarboxaldehyde | 2.20 | 2.20 | | | | 3.62 | | |
| 2-(2,4-dinitrobenzenesulfonyl)-1,3-dimethylpyrrole | | | | | | | | 2.65 |
| 2-(2,4-dinitrobenzenesulfonyl)-pyrrole | 2.20 | 2.80 | 2.70 | | | 3.50 | 1.56 | 2.80 |
| 2-(2,4-dinitrobenzenesulfonyl)-5-pyrrolicarboxaldehyde | | | | | | 3.60 | | |

Table 11

Major Infrared Absorption Bands

| | C=O stretching frequency | C=N stretching frequency | NO ₂ stretching Asym. | Sym. | N-H stretching frequency |
|--|-----------------------------|-----------------------------|-------------------------------------|------|-----------------------------|
| 1-Benzyl-3-pyrrolicarboxylic acid | 1655 | | | | |
| Methyl 1-benzyl-3-pyrrolicarboxylate | 1695 | | | | |
| 1-Benzyl-3-nitropyrrole | | | 1535 | 1360 | |
| 1-Benzyl-3-acetamidopyrrole | 1640 | | | | |
| 1-Benzyl-3-pyrrolicarbaldoxime | | 1645 | | | |
| 1-Benzyl-2-nitropyrrole | | | 1520 | 1355 | |
| 1-Benzyl-2-pyrrolicarboxaldehyde | 1660 | | | | |
| 1-Benzyl-2-pyrrolicarboxylic acid | 1670 | | | | |
| Methyl 1-benzyl-2-pyrrolicarboxylate | 1720 | | | | |
| 1-Benzyl-2-amidopyrrole | (i) 1610 (ii) 1637 | | | | 3160, 3360 |
| 1-Benzyl-2-pyrrolicarbaldoxime | | 1625 | | | |
| 2-Benzyl-5-pyrrolicarboxaldehyde | 1630 | | | | 3205 |
| 2-(2,4-dinitrobenzenesulfonyl)-pyrrole | | | 1505 | 1345 | 3380 |
| 2-(2,4-dinitrobenzenesulfonyl)-1,5-dimethylpyrrole | | | 1520 | 1340 | |
| 2-(2,4-dinitrobenzenesulfonyl)-5-pyrrolealdehyde | 1665 | | 1535 | 1350 | 3250 |

Table IIIUltraviolet Spectra

| | <u>K-Band</u> | | <u>B-Band</u> | |
|--------------------------------------|------------------------|------------------------------|------------------------|------------------------------|
| | λ_{max} | $\log \epsilon_{\text{max}}$ | λ_{max} | $\log \epsilon_{\text{max}}$ |
| Pyrrole ¹ | 209 | 3.8420 | | |
| 1-Methylpyrrole | 212.6 | 3.8363 | | |
| 1-Benzylpyrrole ² | 207 | 4.1310 | | |
| 1-Benzyl-2-nitropyrrole | 209 | 4.0629 | 333 | 4.0396 |
| 1-Benzyl-3-nitropyrrole | 210.5 | 4.1371 | 265 | 3.8433 |
| Methyl 1-benzyl-2-pyrrolicarboxylate | 207.5 | 3.9962 | 264 | 4.1336 |
| Methyl 1-benzyl-3-pyrrolicarboxylate | 211 | 4.1915 | 232 | 4.0632 |
| 1-Benzyl-2-pyrrolicarbaldoxime | 206 | 4.0266 | 260.5 | 4.1630 |
| 1-Benzyl-3-pyrrolicarbaldoxime | 208 | 4.3198 | 251 | 4.1693 |

Solvent: Absolute ethanol

1. Literature value λ_{max} 211 ; $\log \epsilon_{\text{max}}$ 3.8420. (27)2. Literature value λ_{max} 208 ; $\log \epsilon_{\text{max}}$ 4.14. (28)

EXPERIMENTAL

General:

Melting points were determined on a Fisher-John's apparatus and are uncorrected. Gas-liquid partition chromatography was carried out on a Beckman GC-2A gas chromatograph equipped with a $13\frac{1}{2}$ -inch column (number 70008) packed with Apiezon L on Firebrick and operated at 220° , with helium (at 30 p.s.i.g. inlet pressure) as the carrier gas. Retention times established for the pure compounds are recorded in Table V (p.55).

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

Infrared spectra ($625\text{--}4000\text{cm}^{-1}$ region) were recorded on a Perkin-Elmer 237B spectrophotometer using the potassium chloride disc technique (2 mg sample in 148 mg KCl). Ultraviolet spectra were determined in absolute ethanol on a Perkin-Elmer 202 recording spectrophotometer. The nuclear magnetic resonance spectra were determined at 60 Mc/second in the solvents stated in Table I using a Varian A-60 instrument. The chemical shifts are recorded in p.p.m. from tetramethylsilane as internal reference and are recorded on the δ scale.

Section 1 A. Preparation of 1-Benzylpyrrole in Toluene

Pyrrole (1.1 mole) and toluene (200 ml.) were placed in a one litre flask fitted with a stirrer, dropping funnel and condenser. Potassium (0.9 mole) was cut into small pieces, about 4g. added to the solution in the reaction vessel and the reaction mixture stirred and heated gradually until the reaction commenced. The heating mantle was removed and the remainder of the potassium added at such a rate that the reaction continued briskly without becoming too vigorous. After adding the potassium the heating mantle was replaced and the reaction mixture gently refluxed with stirring until potassium was no longer visible in the reaction mixture. Toluene was added as required to keep the mixture reasonably fluid.

Benzyl bromide (0.87 mole) was slowly added directly to the refluxing reaction mixture from the above reaction and after completing the addition the reaction mixture further refluxed for 2 hours when a coffee-coloured solution was obtained. The solution was filtered through a sintered glass crucible and the filtrate washed with water then dried over anhydrous sodium sulfate. The toluene was evaporated under reduced pressure on a rotary evaporator, the product transferred to a suitable flask and finally distilled under low pressure (5mm). The distillate was collected over the range 109-116°. Analysis of the product showed the presence of 2 impurities in small quantities. Yields for this reaction, based on the conversion of benzyl bromide averaged about 60%.

B. Preparation of 1-benzylpyrrole in tetrahydrofuran (10)

The above preparation of potassium pyrrole and its reaction with benzyl bromide were repeated in tetrahydrofuran. Pyrrole (.36 mole) was reacted with potassium (.256 mole) and the resulting

potassium salt reacted with benzyl bromide (.203 mole) as described above. The solvent was removed under reduced pressure and the resulting product was distilled at 5 mm pressure, the fraction boiling at 110-115⁰ being collected. The yield of distilled product was 31.4 g representing a 78.7% conversion of benzyl bromide.

Section 2 A. Bromination of 1-Benzylpyrrole (19)

The reaction vessel was a three necked round bottomed flask fitted with a stirrer, dropping funnel and condenser. Analysis of the reaction mixtures was accomplished by gas-liquid partition chromatography.

(i) With Sodium Hypobromite

1-Benzylpyrrole (.006 mole) and carbon tetrachloride (10 ml.) were placed in the reaction vessel and the solution cooled to 0°C. A solution of bromine (.003 mole) in 3M sodium hydroxide (10 ml.) was added dropwise to the cooled solution and the reaction mixture was stirred for 30 minutes at room temperature. The product was washed with 5% sodium bisulfite solution then with water, the aqueous layers extracted with ether and the combined organic extract dried over molecular sieves. The solvent was removed by distillation under reduced pressure and the residue analyzed. No bromination products were detected.

(ii) With Bromine in Acetic Acid

1-Benzylpyrrole (.006 mole) and a solution of glacial acetic acid (80 ml.) containing sodium acetate (0.1 mole) were placed in the reaction vessel and cooled in an ice bath. Bromine (.006 mole) in acetic acid (10 ml.) was added dropwise to the cold solution and the mixture was refluxed for 1 hour. The solvent was evaporated under reduced pressure on a rotary evaporator and the product taken up in ether. The solution of the product in ether was washed successively with 5% sodium bisulfite solution, 5% sodium bicarbonate solution then water, the aqueous layers combined and extracted with ether and the combined organic extracts dried over molecular sieves. Analysis of the product showed starting material but no bromination products present.

(iii) With N-Bromosuccinimide and Benzoyl Peroxide

1-Benzylpyrrole (.006 mole) in carbon tetrachloride (20 ml.) was treated with N-bromosuccinimide (.007 mole) at 0° . A little benzoyl peroxide (.001 mole) was added and the mixture stirred for 45 minutes at 0° . The product in carbon tetrachloride solution was filtered from the black residue, the residue extracted with ether and the extract combined with the carbon tetrachloride solution. The combined organic extracts were dried over molecular sieves and after evaporation of the solvents, the product was analyzed. There was no evidence of bromination products.

(iv) With N-Bromosuccinimide

Reaction (iii) was repeated except that no benzoyl peroxide catalyst was added to the reaction mixture. Analysis of the product showed no bromination products present.

(v) With Bromine in Carbon Tetrachloride

A series of reactions was performed in which the ratio of bromine to 1-benzylpyrrole was varied. Details of the quantities of reagents used in each reaction are recorded in Table IV.

The 1-benzylpyrrole (.006 mole) was placed in the reaction vessel together with the volume of carbon tetrachloride indicated in the table and the solution cooled to 0°C . The top of the condenser was then attached to a water pump and slight suction was applied to remove the hydrogen bromide produced by the reaction. The bromine (in carbon tetrachloride) was cooled to 0° then added dropwise to the cold reaction mixture, while the latter was being thoroughly stirred. After addition of the bromine the reaction mixture was stirred at 0° for a further 30 minutes.

TABLE IV

Bromination of 1-Benzylpyrrole with Bromine in Carbon TetrachlorideReactant: 1-benzylpyrrole (lg; .006 mole) Solvent: Carbon TetrachlorideTemperature: 0°C (except for reaction B-11 at room temperature)

Analysis of product was achieved by gas-liquid partition chromatography

| Reaction | Solvent in reaction vessel | Bromine added: mole Br ₂ /ml solvent | Total solvent used | Mole ratio 1-benzylpyrrole:Bromine | Analysis (%) of product | | | | |
|----------|----------------------------|--|--------------------|---------------------------------------|------------------------------------|------|------|--------|------|
| | | | | | A | B | C | D | E |
| B-1 | 22.5 ml. | .0015 mole/2.5 ml. | 25 ml. | 1: .25 | 90 | 1 | 9 | | |
| B-2 | 20.0 ml. | .003 mole/5.0 ml. | 25 ml. | 1: .5 | 60 | 6 | 33 | | |
| B-3 | 17.5 ml. | .0045 mole/7.5 ml. | 25 ml. | 1: .75 | 16.6 | 9.7 | 66.3 | 7.5 | |
| B-4 | 15.0 ml. | .006 mole/10 ml. | 25 ml. | 1: 1 | 3.0 | 7.5 | 57 | 33 | litt |
| B-5 | 37.5 ml. | .0075 mole/12.5 ml. | 50 ml. | 1: 1.25 | 1.5 | 4.1 | 20.2 | 33.7 | 40. |
| B-6 | 10.0 ml. | .009 mole/15 ml. | 25 ml. | 1: 1.5 | Further bromination appreciable | | | | |
| B-7 | 10.0 ml. | .012 mole/20 ml. | 30 ml. | 1: 2 | | | | | |
| B-8 | 42.5 ml. | .0045 mole/7.5 ml. | 50 ml. | 1: .75 | 35 | 10.6 | 55 | little | |
| B-9 | 40 ml. | .006 mole/10 ml. | 50 ml. | 1: 1 | 4.2 | 10.4 | 53 | 32 | litt |
| B-10 | 90 ml. | .006 mole/10 ml. | 100 ml. | 1: 1 | 4.5 | 9.0 | 59 | 27 | litt |
| B-11 | 40 ml. | .006 mole/10 ml. | 50 ml. | 1: 1 | 2.6 | 7.6 | 31.2 | 32.2 | 26. |

A: 1-benzylpyrrole

B: 2,3,4,5-tetrabromopyrrole

C: Mixture of 3-bromo-1-benzylpyrrole and 3,4-dibromo-1-benzylpyrrole

D: Unidentified mixture

E: 2,3,4-tribromopyrrole

The carbon tetrachloride solution was separated from an insoluble sticky red product, which resembled pyrrole red, and was washed successively with 5% sodium bicarbonate solution, 5% sodium bisulfite solution and water. The aqueous layers were combined and extracted with ether and the combined organic extract dried over molecular sieves. The solvent was evaporated and the product analyzed. The results of the analyses are recorded in Table IV. They show that the starting material was successfully brominated.

Separation of the Bromination products

A large scale bromination of 1-benzylpyrrole (0.18 mole) with bromine (0.18 mole) was carried out in two halves under conditions B9 (see Table IV). The product (45.9g) was worked up in the manner described below.

After evaporation of the solvent the product was extracted with boiling petroleum pentanes (b.p. 37-50°). The solution was filtered and the filtrate chilled in ice. 1-Benzyl-3-bromopyrrole crystallized from the solution and was purified by recrystallization from petroleum pentanes. The mother liquor was evaporated and the oil obtained fractionated by column adsorption chromatography on alumina (Fisher, neutral grade), eluting successively with petroleum pentanes, 20% benzene in petroleum pentanes then 40% benzene in petroleum pentanes. A partial separation was effected and a pure sample 1-benzyl-2,3,4-tribromopyrrole was obtained. The fractions collected were grouped together and each group rechromatographed on neutral alumina, eluting with a benzene-petroleum pentanes mixture, gradually increasing the percentage of benzene in the mixture. Finally the products described below were isolated and identified.

This separation was conveniently followed by gas-liquid

partition chromatography.

1-Benzyl-3-bromopyrrole, m.p. 73.5 - 74°

Calc'd for $C_{11}H_{10}NBr$: C, 55.95; H, 4.27; N, 5.93; Br, 33.85

Found : C, 55.84; H, 4.27; N, 5.96; Br, 33.86

1-Benzyl-3,4-dibromopyrrole, m.p. 78.0 - 78.5°

Calc'd for $C_{11}H_9NBr_2$: C, 41.94; H, 2.88; N, 4.44; Br, 50.74

Found : C, 42.05; H, 2.75; N, 4.53; Br, 50.82

1-Benzyl-2,3,4-tribromopyrrole m.p. 59.0 - 59.5°

Calc'd for $C_{11}H_8NBr_3$: C, 33.54; H, 2.04; N, 3.55; Br, 60.86

Found : C, 33.69; H, 2.02; N, 3.71; Br, 60.84

1-Benzyl-2,3,4,5-tetrabromopyrrole, m.p. 104.5 - 105°

Calc'd for $C_{11}H_7NBr_4$: C, 27.94; H, 1.49; N, 2.96; Br, 67.61

Found : C, 28.03; H, 1.43; N, 3.02; Br, 67.48

B. Preparation of 1-Benzyl-3-pyrrolicarboxylic Acid and its Methyl Ester

(i) Attempted Grignard reaction on 1-Benzyl-3-bromopyrrole

A 100 ml. three necked flask was equipped with a stirrer, dropping funnel and condenser. Drying tubes were attached to the funnel and condenser and the complete apparatus dried thoroughly in an oven. 1-Benzyl-3-bromopyrrole (.003 mole) and ethyl bromide (.003 mole) were dissolved in anhydrous ether (25 ml.) and the mixture added dropwise with stirring to magnesium (.02 mole) in anhydrous ether (25 ml.) contained in the flask. The reaction mixture was stirred for 1 hour at room temperature, then solid carbon dioxide was added down the condenser and the mixture stirred for a further 15 minutes. Ammonium chloride solution (15 ml. 10%) was added to hydrolyze the reaction mixture. The ether layer was separated, the aqueous layer extracted with ether and the combined organic extracts dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure but none of the expected acid was isolated.

(ii) The above reaction was repeated in tetrahydrofuran as solvent and the reaction mixture refluxed for 4 hours. This reaction was also unsuccessful.

(iii) A further modification of the Grignard reaction using a large excess of ethyl bromide was attempted. 1-Benzyl-3-bromopyrrole (.002 mole) and ethyl bromide (.02 mole) in dry tetrahydrofuran (25 ml.) was added dropwise with stirring to magnesium (.002 mole) in tetrahydrofuran (25 ml.) and the mixture refluxed until the magnesium had reacted completely. Then methyl chloroformate (.002 mole) in tetrahydrofuran (25 ml.) was added to the mixture and refluxing was continued for a further 2 hours. The tetrahydrofuran was washed with water, the water layer extracted with ether and the combined organic extract dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure on a rotary evaporator and an unidentified solid product (m.p. $49-50^{\circ}$) was isolated. It was apparently hydrocarbon. No ester was isolated.

(iv) Attempted Reaction of 1-Benzyl-3-bromopyrrole with n-Butyllithium

n-Butyllithium was prepared and standardised (20) with sulfuric acid (0.2 Normal). The product was shown to have a concentration of n-butyllithium of 1.1 moles/litre.

1-Benzyl-3-bromopyrrole (.0085 mole) in anhydrous ether (50 ml.) was placed in a 3 necked flask fitted with a stirrer, dropping funnel and a short condenser. The apparatus was thoroughly flushed with dry nitrogen then n-butyllithium solution (16 ml., .018 mole) added dropwise with stirring. After 15 minutes solid carbon dioxide was added to the reaction mixture and stirring was continued for a further 5 minutes. Water was added, then the mixture was acidified with hydrochloric acid. The aqueous layer was separated and extracted with ether, the organic extracts combined and the

combined extracts dried over molecular sieves. The solvent was removed by evaporation under reduced pressure and a brown, fruity-smelling liquid was obtained. The liquid decomposed on distillation under vacuum (5mm pressure). No acid was isolated.

(v) Reaction between 1-Benzyl-3-bromopyrrole and Lithium

The reaction vessel was a 100 ml. three necked flask fitted with a condenser, stirrer and dropping funnel. Freshly prepared lithium wire (.015 mole) was cut into small lengths and placed in anhydrous ether (25 ml.) in the previously dried flask, and 1-benzyl-3-bromopyrrole (.01 mole) in anhydrous ether (25 ml.) added with stirring. The reaction mixture was refluxed gently for $1\frac{1}{2}$ hours. After cooling, excess solid carbon dioxide was added down the condenser and stirring was continued for a further 10 minutes. The product was extracted with sodium hydroxide solution (10%) and the aqueous extract filtered. The filtrate was carefully acidified, keeping the temperature below 10° , and the product filtered. The yield of crude acid was 1.6g. (80%). The acid was purified by refluxing in methanol with activated charcoal (Norite) and recrystallizing from aqueous methanol. The acid was shown to be:

1-Benzyl-3-pyrrolicarboxylic acid m.p. $149.5-150^{\circ}$

Calc'd for $C_{12}H_{11}O_2N$: C, 71.63; H, 5.51; N, 6.96

Found : C, 71.61; H, 5.5 ; N, 7.10

(vi) Preparation of Methyl 1-Benzyl-3-pyrrolicarboxylate

An excess of a solution of diazomethane in ether was prepared (21) and added to 1-benzyl-3-pyrrolicarboxylate in ether (5 ml.) and left to stand overnight in a fume cupboard. The product in methanol was refluxed with decolourizing charcoal (Norite) and

recrystallized from aqueous methanol. It was shown to be:

Methyl 1-benzyl-3-pyrrolicarboxylate m.p. 52-52.5°.

Calc'd for $C_{13}H_{13}O_2N$: C, 72.5; H, 6.06; N, 6.50

Found : C, 72.1; H, 6.13; N, 6.62

C. Attempted Debenzylation of Methyl 1-Benzyl-3-pyrrolicarboxylate

W4 Raney nickel was prepared by the method of Pavlik and Adkins (22) using one-tenth the quantities described. The reactions were carried out in an autoclave hydrogenator and the products analyzed by gas-liquid partition chromatography.

(i) Methyl 1-benzyl-3-pyrrolicarboxylate (0.3g, .0014 mole) and W4 Raney nickel (0.3g) were placed in methanol (50 ml.) and the mixture transferred to the well of the bomb hydrogenator. Hydrogen was introduced at 1000 p.s.i.g. and the reaction allowed to proceed, while stirring the mixture slowly, for 8 hours. The Raney nickel was filtered and the methanol evaporated under reduced pressure. The product (0.3g) was taken up in ether and analyzed. No methyl -3-pyrrolicarboxylate was detected in the product.

(ii) The above reaction was repeated at 50°C and 1200 p.s.i.g. but there was no evidence that the required product was formed.

(iii) The reaction was repeated at 110°C and 1900 p.s.i.g. but these conditions again failed to bring about the required debenzylolation.

D. Preparation of Methyl 1-Benzyl-3-pyrrolicarboxylate from Methyl 3-Pyrrolicarboxylate

Methyl 3-pyrrolicarboxylate (.012 mole) in tetrahydrofuran was refluxed with potassium (.011 mole) and the product refluxed with benzyl bromide (.01 mole). Removal of the solvent gave a brown oil which was refluxed with activated charcoal in methanol. The ester was precipitated by adding water (m.p. 50.5-51.5°). A mixture of this product with the ester obtained from the 3-bromo compound melted at 51-52°.

Section 3 A. Nitration of 1-Benzylpyrrole (2)

1-Benzylpyrrole (0.047 mole) in acetic anhydride (25 ml.) was treated with a solution of fuming nitric acid (.006 mole) in acetic anhydride (15 ml.) keeping the temperature below -10° . After hydrolysis in cold water (3 hours) the solution was neutralized with sodium hydroxide and the oily product separated from the aqueous layer. The aqueous layer was twice extracted with ether, the ether layers combined with the oil and the combined organic extract washed with saturated sodium carbonate solution, then with water, and dried over molecular sieves. The crude product weighed 7.95g. It was analysed by gas-liquid partition chromatography and two products were shown to be present.

Separation of the Nitration Products

The oil obtained after evaporation of the ether was taken up in benzene and chromatographed on a column of alumina (Fisher, neutral grade), eluting with a benzene-petroleum pentanes mixture. The proportion of benzene in the mixture was gradually increased from 25% to 100%. A good separation of the two isomers was obtained. The separation was conveniently followed by gas chromatography. The retention times of the pure compounds are recorded in Table V. A very small peak (retention time, 5 minutes) was not identified. The first fraction (2.35 g) was collected and the solid obtained recrystallized from aqueous methanol, using very little water. The crystals were needle-shaped and off-white in colour. The nuclear magnetic resonance spectrum of this showed it to be the 2-nitro derivative. The second isomer collected was recrystallized from methanol then from a benzene-petroleum pentanes mixture. The nuclear magnetic resonance spectrum (Table I) of the pale yellow

crystals showed them to be the 3-nitro isomer.

1-Benzyl-2-nitropyrrole, m.p. 36-36.5°

Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.30; H, 4.98; N, 13.85

Found : C, 65.19; H, 5.32; N, 14.01

1-Benzyl-3-nitropyrrole m.p. 67.5-68°

Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.30; H, 4.98; N, 13.85

Found : C, 65.26; H, 5.01; N, 13.72

B. Reduction of 1-Benzyl-3-nitropyrrole

(i) Attempted Reduction with Alkaline Sodium Hypophosphite Solution

1-Benzyl-3-nitropyrrole (.0025 mole) was dissolved in methanol (5 ml.) and an excess of a solution of sodium hypophosphite in sodium hydroxide (6N) was added. The product was extracted with ether and the ether extract dried over molecular sieves. The solvent was then evaporated. The expected amine was not isolated.

(ii) Attempted Reduction with Zinc and Acetic Acid

1-Benzyl-3-nitropyrrole (.0025 mole) was suspended in water (5 ml.), some small pieces of granular zinc added and the solution acidified with acetic acid. The solution became hot as the zinc reacted. After 30 minutes the excess zinc was filtered and the solution made alkaline with sodium hydroxide. The alkaline solution was extracted with ether and the ether extract dried over molecular sieves. No residue was obtained on evaporation of the solvent.

(iii) Attempted Reduction with Zinc and Acetic Acid in the presence of Acetic Anhydride

1-Benzyl-3-nitropyrrole (.0025 mole) was dissolved in acetic anhydride (10 ml.) and the reduction carried out as in (ii). After filtering the excess zinc the solution was taken up in ether and the ether extract dried over molecular sieves. The volatile

components were evaporated under reduced pressure, and a small quantity of an oil was recovered. However this did not crystallize.

(iv) Attempted Reduction with Stannous Chloride Solution (23)

Tin was dissolved in concentrated hydrochloric acid and an excess of the solution added to 1-benzyl-3-nitropyrrole (.0025 mole) suspended in water (5 ml.). The product was made alkaline with sodium hydroxide and ether extracted, the ether layer being immediately added to an excess (10 ml.) of acetic anhydride. After evaporation of the ether and excess acetic anhydride a small quantity of oil remained which did not crystallize.

(v) Reduction with Tin and a Saturated Solution of Hydrogen Chloride in Methanol

Tin (1.7g) was reacted with a solution of 1-benzyl-3-nitropyrrole (.0025 mole) in methanol saturated with hydrogen chloride, keeping the reaction mixture cool by immersing the flask in cold water. When the tin had nearly all dissolved the solution of the product was decanted from the unreacted tin and the excess of methanol and hydrogen chloride evaporated under reduced pressure. The oily residue was shaken up with water and the aqueous solution decanted. This solution was treated with excess acetic anhydride (5 ml.) in ether (25 ml.) and the solution made strongly alkaline with sodium hydroxide (6N), keeping the mixture cold by immersing the flask in an ice bath. After thoroughly shaking the mixture the ether layer was separated and dried over molecular sieves. The ether was evaporated and an oil obtained, which crystallized. The crystals were recrystallized from aqueous methanol then from a benzene-petroleum pentanes mixture. 1-Benzyl-acetamidopyrrole (.4g; 80% yield) was obtained.

1-Benzyl-3-acetamidopyrrole m.p. 130°

Calc'd for $C_{13}H_{14}N_2O$: C, 72.85; H, 6.58; N, 13.07

Found : C, 72.87; H, 6.72; N, 13.18

(vi) Catalytic reduction of 1-Benzyl-3-nitropyrrole (14)

1-Benzyl-3-nitropyrrole (.002 mole) in methanol (15 ml.) was shaken mechanically for 15 minutes with hydrogen at 35 p.s.i.g. in the presence of platinum oxide (.05g) on a Parr hydrogenator. The solution was filtered and it immediately began to go brown, so the solution was treated with a mixture of acetic anhydride and sodium acetate. The solvent was evaporated under reduced pressure and the product recrystallized from a benzene-petroleum pentanes mixture. It was shown to be the same compound as that obtained in the above experiment. A mixture of the product with the 1-benzyl-3-acetamidopyrrole obtained in (v) melted at 129°.

(vii) Catalytic Reductive Acetylation of 1-Benzyl-3-nitropyrrole

1-Benzyl-3-nitropyrrole (.0022 mole) was dissolved in acetic anhydride (20 ml.) and a saturated solution of sodium acetate (10 ml.) was added. Platinum oxide (.02g) was added and the reaction mixture shaken mechanically for 15 minutes with hydrogen at 30 p.s.i.g. on a Parr hydrogenator. The solution was filtered,, made alkaline with sodium hydroxide solution (6N) and the crude product filtered (yield .4g; 85%). It was recrystallized from aqueous methanol, then sublimed and then recrystallized from a benzene-petroleum pentanes mixture. A mixed m.p. with the 1-benzyl-3-acetamidopyrrole obtained in (v) showed no depression. (130°).

Section 4 A. Formylation of 1-Benzylpyrrole (15)

The reaction vessel was a three-necked flask (500 ml.) fitted with a stirrer, dropping funnel and condenser. Dimethyl formamide (0.103 mole) was placed in the reaction vessel and cooled to 0°. Phosphorus oxychloride (0.102 mole) was then added, with stirring over a 15-minute period, keeping the temperature between 10° and 20°. The mixture was further stirred for 15 minutes at room temperature, then the ice bath was replaced, ethylene dichloride (25 ml.) added and the mixture cooled to 5°. A solution of 1-benzylpyrrole (.09 mole) in ethylene dichloride (25 ml) was added from a dropping funnel over a period of 10 minutes and the mixture refluxed for a further 30 minutes. It was then cooled to 25-30°; a solution of sodium acetate (0.8 mole) in water (250 ml.) was added rapidly to the reaction mixture and the mixture again refluxed for 15 minutes. After cooling the ethylene dichloride layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed with saturated sodium carbonate solution then with water and finally dried over molecular sieves. The solvent was evaporated under reduced pressure and the product (in ether) analyzed by gas-liquid partition chromatography. Two products in the ratio 14.7:1 were indicated on the analytical chromatogram along with some unreacted starting material. The retention times are recorded in Table V.

Separation of the Products(i) By Distillation under Vacuum

The brown formylation product was distilled at 0.3mm and the fraction boiling at 128-131° collected. This was a colourless liquid and was the major product of the reaction. Only a small portion of the product was recovered because of decomposition at

this high temperature. Only the one product was recovered. Its nuclear magnetic resonance spectrum corresponded to :

1-Benzyl-2-pyrrolicarboxaldehyde b.p. 128-131° at 0.3mm

Calc'd for $C_{12}H_{11}NO$: C, 77.8; H, 5.98; N, 7.56

Found : C, 77.63; H, 6.08; N, 7.69

(ii) By Column Chromatography

The formylation product was placed on a column of alumina (Fisher, Adsorption Grade) and eluted with petroleum pentanes until the unreacted 1-benzylpyrrole was recovered, then with a benzene-petroleum pentanes mixture, gradually increasing the ratio of benzene in the mixture. A separation of the products was effected but the oily fractions collected were coloured. However, each gave only one peak on the gas chromatograph. 1-Benzyl-3-pyrrolicarboxaldehyde was indentified by its nuclear magnetic resonance and infrared spectra but it was not analyzed for C, H, and N.

Formylation of a Mixture of 1- and 2- Benzylpyrroles

A mixture containing about 20% 2-benzylpyrrole and 80% 1-benzylpyrrole was formylated as described in A above. Analysis of the reaction mixture by gas chromatography showed (a) that all the 2-benzylpyrrole had reacted but some 1-benzylpyrrole remained in the reaction mixture, (b) that three products were to be expected, two of which were those obtained in the formylation of pure 1-benzylpyrrole. The 1-benzyl-2 and 3-carboxaldehydes were separated by column chromatography as previously described then the column stripped with methanol, the dark brown methanol solution being collected and set on one side to evaporate slowly. A dark oil separated which after two or three days deposited pale yellow crystals. These were separated and recrystallized from

aqueous methanol. This compound was identified from its nuclear magnetic resonance and infrared spectra to be :

2-benzyl-5-pyrrolicarboxaldehyde m.p. 93.5-94.5°

Calc'd for $C_{12}H_{11}NO$: C, 77.8; H, 5.98; N, 7.56

Found : C, 77.6; H, 6.18; N, 7.74

The black oil remaining was dissolved in methanol and refluxed with decolourizing charcoal (Norite). The solution obtained was orange and orange crystals were obtained on evaporating. The crystals were recrystallized from benzene-petroleum pentanes and melted at 121-122°. This compound has not been identified.

B. Preparation of Derivatives of 1-Benzyl-2-pyrrolicarboxaldehyde and 1-Benzyl-3-pyrrolicarboxaldehyde

(i) Preparation of Oximes (24)

Hydroxylamine hydrochloride (0.5g) was dissolved in water (2 ml.) and a solution of sodium hydroxide (2 ml. 10%) added. The aldehyde was then added together with enough ethanol to give a clear solution. The mixture was then refluxed for 30 minutes and the product poured into twice its own volume of water and cooled in an ice bath.

(a) 1-Benzyl-2-pyrrolicarboxaldehyde (0.2g) yielded 0.19g, (87%) of oxime. It gave white crystals, m.p. 111-112°, from aqueous methanol.

Calc'd for $C_{12}H_{12}ON_2$: C, 71.96; H, 6.05; N, 13.99

Found : C, 72.13; H, 6.15; N, 13.84

(b) 1-Benzyl-3-pyrrolicarboxaldehyde (0.3g) yielded 0.2g (65%) of oxime. The bright yellow product, recrystallized from a benzene-petroleum pentanes mixture, gave pale yellow crystals, m.p. 146-147°

Calc'd for $C_{12}H_{12}ON_2$: C, 71.96; H, 6.05; N, 13.99

Found : C, 72.23; H, 5.84; N, 13.92

(iii) Conversion to the Corresponding Acids(a) Oxidation of 1-Benzyl-3-pyrrolicarboxaldehyde

This was oxidized with Tollen's reagent as described by Hodge and Rickards (25). Silver nitrate (.007 mole) was dissolved in water (125 ml.) and a solution of sodium hydroxide (0.25 mole) in water (250 ml.) added with stirring. The aldehyde (0.5g; 0.003 mole) was dissolved in methanol (25 ml.) then added to the reaction mixture and the latter stirred at room temperature for 2 hours. The residue was filtered and the filtrate ether extracted. The aqueous solution was carefully acidified while cooling in ice and the product salted out with sodium chloride. The filtered product (0.12g; 22%) was recrystallized from aqueous methanol. It melted at 148-149° and a mixed melting point of this acid with the acid obtained (p. 38) from 1-benzyl-3-bromopyrrole (m.p. 150°) showed no depression (mixed m.p. 148-151°).

(b) Oxidation of 1-Benzyl-2-pyrrolicarboxaldehyde

(i) The method described in (a) was attempted but only a very small amount of product (0.04g) was obtained from 1 gm. of the aldehyde.

(ii) Preparation of 1-Benzyl-2-pyrrolenitrile (16)

1-Benzyl-2-pyrrolicarboxaldehyde (.01 mole), hydroxylamine hydrochloride (0.80g; 0.01 mole), sodium formate (1.25g; excess) and formic acid (15 ml.; 98-100%) were refluxed for 1 hour. The product was diluted with water and the solution ether extracted; the solution was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a brown oil. This was placed on a short column of alumina (Adsorption grade) and eluted with a petroleum pentanes-benzene mixture. Evaporation of the solvents under reduced

pressure gave a colourless oil. The infrared spectrum of this oil (Table 11) indicated the presence of the nitrile group. The yield of crude nitrile was .8g (45%).

(iii) Hydrolysis of the Nitrile

The nitrile obtained above was refluxed for 6 hours with sodium hydroxide (5 ml. 40% solution). The product was added to water and the insoluble white solid (A) filtered. The alkaline solution was ether extracted, then the aqueous layer was cooled in an ice-salt bath and carefully acidified with concentrated sulfuric acid, keeping the solution cold. The white crystalline precipitate (B) was filtered.

The white solid, (A) was recrystallized from a benzene-petroleum pentanes mixture. It was shown, by its nuclear magnetic resonance spectrum to be :

1-Benzyl-2-pyrrolicarboxamide, m.p. 112-113°

| | |
|-------------------------------|-------------------------------|
| Calc'd for $C_{12}H_{12}ON_2$ | : C, 72.00; H, 6.03; N, 14.00 |
| Found | : C, 71.85; H, 6.06; N, 13.78 |

The white acid B, was recrystallized from aqueous methanol.

Analysis of its nuclear magnetic resonance spectrum showed it to be:

1-Benzyl-2-pyrrolicarboxylic acid, m.p. 130-131°. Yield .5gm (55%)

| | |
|-------------------------------|------------------------------|
| Calc'd for $C_{12}H_{11}O_2N$ | : C, 71.63; H, 5.51; N, 6.96 |
| Found | : C, 71.41; H, 5.31; N, 7.02 |

C. Preparation of 1-Benzyl-2-pyrrolicarboxylic Acid from Methyl 2-Pyrrolicarboxylate

(i) Methyl 2-pyrrolicarboxylate (0.055 mole) in toluene was reacted with potassium (0.05 mole) and the mixture refluxed to complete the reaction. Benzyl bromide (0.047 mole) was then added and the mixture refluxed for a further 1 hour. The solvent was removed by evaporation under reduced pressure on a flash evaporator

and the product obtained chromatographed on a column of alumina (Fisher, Adsorption grade) and eluted with petroleum pentanes. The yellow liquid obtained was analyzed by gas-liquid partition chromatography and was shown to contain benzyl bromide and product. The yield of crude material was 4.4g (44%); The product was rechromatographed on a column of alumina (Fisher, Neutral grade) and 2.55g of product (25%) free of benzyl bromide was obtained. The yellow oil crystallized on standing overnight in a freezer. The coloured crystals were distilled under vacuum and a colourless liquid, which crystallized readily, was obtained.

Methyl 1-Benzyl-2-pyrrolicarboxylate m.p. 31-31.5°

Calc'd for $C_{13}H_{13}O_2N$: C, 72.5; H, 6.06; N, 6.50

Found : C, 72.70; H, 6.07; N, 6.75

The product was compared with the sample of methyl 1-benzyl-2-pyrrolicarboxylate prepared in B (iv) above. Both were shown to have the same retention time on gas-liquid chromatography and to have identical nuclear magnetic resonance spectra.

(ii) Methyl 1-benzyl-2-pyrrolicarboxylate (0.2g) prepared in (i) was refluxed with excess potassium hydroxide (20%) until the oily ester was no longer visible (4 hours). The solution was filtered, diluted with an equal volume of water then cooled in ice.

Concentrated sulfuric acid was added drop by drop to the cold solution until the solution was acidic and the product was ether extracted. The ether was evaporated and the crude product recrystallized from aqueous methanol. The yield of recrystallized product was .068g (46%); its melting point 131-131.5°.

The mixed m.p. of the product with the acid obtained from 1-benzyl-2-pyrrolicarboxaldehyde via the nitrile (p.48) was 130-132°.

Section 5 Attempted Substitution of the Benzenesulfonyl and 2,4-Dinitrobenzenesulfonyl groups onto the Pyrrole Nitrogen

A. (i) Preparation of Benzenesulfonyl Chloride (26)

A brisk stream of dry chlorine was bubbled through carbon tetrachloride (150 ml.) which was cooled in an ice-salt bath. The mixture was stirred and a solution of thiophenol (.057 mole) in carbon tetrachloride (50 ml.) was added slowly under anhydrous conditions. The excess chlorine and carbon tetrachloride were evaporated under reduced pressure from the reddish solution and a red liquid remained. Further distillation at 9mm pressure produced an oily red distillate at 73-77°. The yield of redistilled product was 5.46g; (64%).

(ii) Attempted Preparation of 1-Benzenesulfonylpyrrole

(a) A solution of pyrrole (.029 mole) in toluene (10 ml.) was placed in a three-necked flask and potassium (.022 mole) was added with gentle heating and stirring. The mixture was then refluxed until all the potassium had reacted. Benzenesulfonyl chloride (.019 mole) in toluene (10 ml.) was slowly added with stirring to the hot solution and the mixture refluxed for one hour. Much charring occurred. The reaction mixture was filtered and the toluene solution washed with water then dried over molecular sieves. The solvent and excess pyrrole were evaporated under reduced pressure. The reaction was unsuccessful.

(b) The above reaction was repeated but the benzenesulfonyl chloride was added to the potassium pyrrole at 0°. The mixture was then gradually brought up to reflux temperature but the product was still very dark and oxidized on attempted distillation.

(c) The reaction was again repeated at -70° under an atmosphere of nitrogen, the reaction flask being cooled in a "Dry-Ice"-acetone

bath. The benzenesulfonyl chloride was added over a period of 20 minutes and the mixture stirred at -70° for a further 30 minutes, then the temperature gradually raised to room temperature. The solution obtained was much cleaner. The solvent was evaporated and an attempt was made to purify the product by distillation under low pressure (8 mm). Most of the product again decomposed but a few drops of clear distillate was obtained. It appeared, from its nuclear magnetic resonance spectrum, to be 2-benzenesulfonyl-pyrrole.

B. (i) Attempted Preparation of 1-(2,4-Dinitrobenzenesulfonyl)-Pyrrole

Pyrrole (obtained from Aldrich Chemical Company) was purified and distilled by fractionating on a spinning band column. The constant boiling fraction was collected. Potassium pyrrole (.046 mole) was prepared as described above in (Section 5A(ii)) and the slurry cooled to -10° by means of an ice-salt bath. 2,4-Dinitrobenzenesulfonyl chloride (9.8g; .041 mole), partly dissolved, partly suspended in toluene was slowly added. The first few ml. of reagent added produced a deep blue colouration on coming into contact with the potassium pyrrole but it darkened rapidly. The mixture was stirred at -10° for 30 minutes, then the temperature raised to room temperature. The solvent was evaporated on a flash evaporator and the product dissolved in a minimum of methanol. It was refluxed with activated charcoal (Norite) and then recrystallized from aqueous methanol. The nuclear magnetic resonance spectrum of the yellow product (Table I) showed it to be the 2-substituted pyrrole derivative:

2-(2,4-dinitrobenzenesulfonyl)-pyrrole, m.p. $149.5-150^{\circ}$

Calc'd for $C_{10}H_9N_3O_4S$: C, 45.29; H, 2.66; N, 15.8; S, 12.09

Found : C, 45.55; H, 2.80; N, 15.6; S, 12.16

(ii) Reaction B (i) was repeated under the same conditions but the crude product was run (in two batches) down a 12-inch column of alumina (Adsorption grade). Two fractions were collected. The first gave a ruby red oil (4.7g) which crystallized on standing to give bright red crystals, which were recrystallized from a benzene-petroleum pentanes mixture. The second fraction (5.8g) contained the compound isolated in B (i). The nuclear magnetic resonance spectrum of the red product showed it to be:

1,3-dimethyl-2-(2,4-dinitrobenzenesulphenyl)-pyrrole m.p. 107-112°

Calc'd for $C_{12}H_{11}N_3O_4S$; C, 49.14; H, 3.78; N, 14.32; S, 10.92

Found ; C, 49.33; H, 3.90; N, 14.16; S, 11.00

(iii) The above reaction, B (ii) was carried out in benzene as solvent instead of toluene thus eliminating the only apparent source of methyl groups. However the same two products were obtained.

(iv) Reaction between Pyrrole and 2,4-Dinitrobenzenesulphenyl Chloride in the presence of Triethylamine

Pyrrole (.057 mole) and triethylamine (0.075 mole) were mixed together in an Erlenmeyer Flask. 2,4-Dinitrobenzenesulphenyl chloride (.05 mole) in dioxane (50 ml.) was added with stirring. The mixture became hot and was allowed to stand for one hour. The solvent was evaporated on a rotary evaporator and the dark oil chromatographed (in two batches) on a 12-inch column of alumina (Adsorption grade). Only the yellow compound, 2-(2,4-dinitrobenzenesulphenyl)-pyrrole, was obtained. (Yield 8.85g; 68.6%). No red product was isolated.

(v) Reaction between Pyrrole and 2,4-Dinitrobenzenesulfonyl Chloride
with no added base

Pyrrole (.057 mole) and 2,4-dinitrobenzenesulfonyl chloride (.025 mole) were mixed at room temperature in sufficient dioxane to make a homogeneous solution. The reaction mixture was stirred for 4 hours. Much blackening occurred but a yellow solution was left after filtering the black solid. The solution was evaporated on a flash evaporator then passed down a 12-inch column of neutral grade alumina. The orange solution was collected and evaporation of this gave 2-(2,4-dinitrobenzenesulfonyl)-pyrrole, the yellow product obtained in B (i). (Yield 4.8g; 70%).

The black material was insoluble in the common solvents but burned leaving a residue of carbon. It was probably a polymeric material.

(vi) Reaction B (ii) was repeated with pyrrole obtained from an entirely different source (Ansul Chemical Company). The product was passed through a column of neutral alumina. No red product, 1,3-dimethyl-2-(2,4-dinitrobenzenesulfonyl)-pyrrole, was isolated.

C. Formylation of 2-(2,4-Dinitrobenzenesulfonyl)-pyrrole

The method used employed dimethylformamide (.002 mole) and phosphorus oxychloride (.002 mole) as the formylating mixture. The reaction was carried out, as described on page 44, for the formylation of 1-benzylpyrrole, except that double the volume of ethylene dichloride was used in an attempt to dissolve all the 2-(2,4-dinitrobenzenesulfonyl)-pyrrole (.02 mole). However the 2-(2,4-dinitrobenzenesulfonyl)-pyrrole failed to dissolve completely and was added as a paste. During the reaction however it went completely into solution and, on cooling, after hydrolyzing the product with sodium acetate solution, yellow crystals appeared

which were filtered off. (Yield 2.45g; 42%). These crystals were recrystallized from aqueous ethanol then from a benzene-petroleum pentanes mixture. The nuclear magnetic resonance spectrum of the product showed it to be 2-(2,4-dinitrobenzenesulfonyl)-5-pyrrolealdehyde m.p. 212-214°

Calc'd for $C_{11}H_7N_3O_5S$: C, 45.05; H, 2.406; N, 14.33; S, 10.93

Found : C, 45.23; H, 2.38 ; N, 14.14; S, 10.67

The ethylene dichloride layer was separated and the aqueous phase extracted with ether and the combined organic extracts dried over molecular sieves. Evaporation of the solvents gave a red oil which was taken up in methanol. Water was added to the solution and an oil, which crystallized on standing, was obtained (yield 3.1g). The crystals were recrystallized from a benzene-petroleum pentanes mixture and melted at 134-135°. This compound was shown to be recovered starting material; a mixed melting point of the crystals with starting material showed no depression.

Column No. 70006 (Apiezon on Firebrick).

Temperature: 220°C

Pressure : 30 p.s.i.g.

| <u>Compound</u> | <u>Retention time(minutes)</u> |
|--------------------------------------|--------------------------------|
| 1-Benzylpyrrole | 1.6 |
| 1-Benzyl-3-bromopyrrole | 6.0 |
| 1-Benzyl-3,4-dibromopyrrole | 8.2 |
| 1-Benzyl-2,3,4-tribromopyrrole | 26.3 |
| 1-Benzyl-2,3,4,5-tetrabromopyrrole | 3.7 |
| 1-Benzyl-2-nitropyrrole | 7.8 |
| 1-Benzyl-3-nitropyrrole | 18.0 |
| 1-Benzyl-2-pyrrolicarboxaldehyde | 4.8 |
| 1-Benzyl-3-pyrrolicarboxaldehyde | 11.6 |
| Methyl 3-pyrrolicarboxylate | 1.5 |
| Methyl 2-pyrrolicarboxylate | .7 |
| Methyl 1-benzyl-2-pyrrolicarboxylate | 5.4 |
| Methyl 1-benzyl-3-pyrrolicarboxylate | 14.1 |
| 2-Benzylpyrrole | 2.5 |
| 2-Benzyl-5-pyrrolicarboxaldehyde | 10.8 |

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