Pyrrole chemistry. VII. Syntheses and reactions of some *N*-substituted pyrroles

HUGH J. ANDERSON AND S. JOHN GRIFFITHS
Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland
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In nitration, bromination, and formylation reactions 1-benzylpyrrole showed a greatly increased proportion of 3-substitution over both pyrrole and 1-methylpyrrole. The products of these reactions have been identified and interrelated. A number of attempts at hydrogenolysis under increasingly vigorous conditions failed to remove the benzyl group from methyl 1-benzyl-3-pyrrolecarboxylate. An attempt to use the 2,4-dinitrobenzenesulfenyl group to block the pyrrole nitrogen failed when the group entered the 2-position instead.

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INTRODUCTION

The presence of a methyl group on the pyrrole nitrogen atom changes the normal nitration patterns of *N*-unsubstituted pyrroles substantially (1, 2). A large increase in the proportion of β-nitration was observed for both 1-methylpyrrole and those of its derivatives with electron-withdrawing groups in the 2-position. The 1-phenyl group was reported to have an effect on the nitration pattern similar to that of the 1-methyl group (3). No differences were observed, however, between the substitution patterns of pyrrole and 1-methylpyrrole in metalation with butyllithium (4), Friedel–Crafts acylation (5), or Vilsmeier formylation (6). In each case α-substitution occurred exclusively.

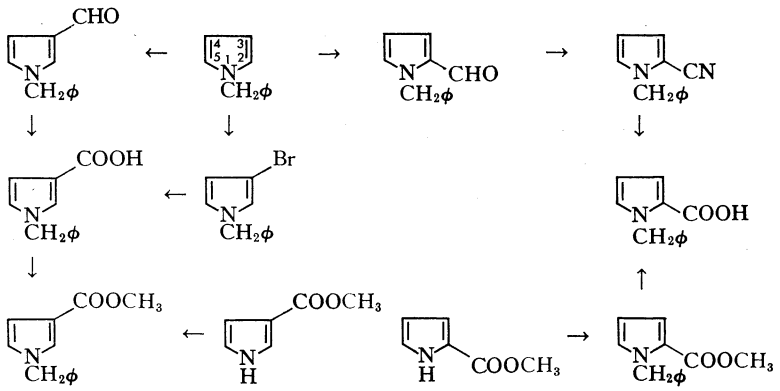
The possibility of finding a 1-substituent group which would survive electrophilic substitution and have a similar or stronger β-directing effect, but which could later be removed, appeared to provide a promising route to 3-substituted pyrroles. 1-Benzylpyrrole was chosen for this study because it was expected that it would give a reasonable proportion of 3-nitration, and because it was known that benzyl groups attached to a tertiary nitrogen atom are readily cleaved by hydrogenolysis (7). Furthermore, Adkins and Coonradt (8) reported that hydrogenation of 1-benzylpyrrole over nickel was so slow that cleavage of the benzyl group occurred, with the production of pyrrolidine and toluene. The benzyl group would not be expected to undergo electrophilic substitution or to interfere with any subsequent reactions carried out with the products.

Identification and Reactions of Products

Nitration of 1-benzylpyrrole with acetic anhydride – nitric acid gave a mixture of mononitro products containing about 60% of the 3-isomer. Bromination with bromine in carbon tetrachloride, under conditions selected to minimize polybromination and to remove hydrogen bromide as it was formed, gave 1-benzyl-3-bromopyrrole as the major product (up to 66% of the crude mixture in some experiments). The proportions of the bromination products were quite sensitive to conditions since polybromination took place very easily. The 2-bromo isomer was not isolated, but several other bromination products in addition to the 3-bromo compound were separated, purified, and identified. The Vilsmeier formylation of 1-benzylpyrrole also gave both monosubstitution products. Although the percentage of 3-attack was only about 15 in this reaction, it represented an increase in 3-substitution over that in the formylation of 1-methylpyrrole, where none of this isomer was found (6).

The structures of the nitration products were assigned principally on the basis of their ultraviolet (Table I) and nuclear magnetic resonance (n.m.r.) spectra (Table II). The spectra were consistent with those of correspondingly nitrated pyrroles and 1-methylpyrroles, whose structures have been proved (1, 9), as well as with the 2- and 3-substituted oximes and esters described below (see the spectral properties).

Reduction of 1-benzyl-3-nitropyrrole to the corresponding amine was most conveniently achieved by catalytic hydrogena-



REACTION SCHEME 1.

tion; however, since the amine decomposed rapidly in the air, it was acetylated to obtain a stable product. Direct reductive acetylation gave a very good yield of the same 1-benzyl-3-acetamidopyrrole. Attempts to diazotize the amine hydrochloride for conversion into the corresponding bromo or cyano compound by the Sandmeyer reaction were unsuccessful. The n.m.r. spectrum of 1-benzyl-3-acetamidopyrrole was consistent with the assigned structure.

The products isolated from the bromination reaction were identified by their elemental analyses and n.m.r. spectra as 1-benzyl-3-bromo-, 1-benzyl-2,5-dibromo-, 1-benzyl-2,3,5-tribromo-, and 1-benzyl-2,3,4,5-tetrabromo-pyrroles. The major product, 1-benzyl-3-bromopyrrole, was then proved and related to one of the formylation products by the reactions outlined in Reaction Scheme 1. The 3-bromo compound failed to form a Grignard reagent and to undergo metal–halogen interchange with butyllithium, but it reacted with lithium metal. Carbonation of this organolithium product gave an acid, which was converted into the corresponding methyl ester with diazomethane. This ester was shown to be methyl 1-benzyl-3-pyrrolecarboxylate by preparing another sample by the following route. The potassium salt of authentic methyl 3-pyrrolecarboxylate (10) was treated with benzyl bromide in tetrahydrofuran, and the 1-benzyl derivative was isolated. The melting point of a mixture of the two samples was not depressed and their infrared spectra were identical.

The two oily formylation products from 1-benzylpyrrole were separated and each was converted into its oxime for analysis. The aldehyde present as the minor component was oxidized to the corresponding acid and shown by mixture melting point and infrared spectrum to be identical with the 3-substituted compound obtained above. Oxidation of the major isomer failed, but a one-step conversion of this aldehyde into the nitrile (11) was successful and subsequent hydrolysis gave the expected 1-benzyl-2-pyrrolecarboxylic acid as shown in Reaction Scheme 1, together with some 1-benzyl-2-pyrrolecarboxamide. The identity of the acid was confirmed by comparison of its melting point and spectra with those of an authentic sample made by the 1-benzylation of methyl 2-pyrrolecarboxylate, followed by hydrolysis.

A series of unsuccessful attempts were made to debenzylate methyl 1-benzyl-3-pyrrolecarboxylate by catalytic hydrogenation over Raney nickel at temperatures up to 110 °C and pressures up to 1 900 p.s.i.g. The starting material was recovered unchanged, and without loss, even under the most strenuous conditions. Consequently, although the 1-benzyl group was successful in its directive purpose, it could not be used as a temporary blocking group.

The Benzenesulfenyl Group

The benzenesulfenyl group seemed likely

TABLE I
Ultraviolet spectra

Compound	Solvent	λ_{max} (mμ) (log ϵ)				Reference
Methyl 1-benzyl-2-pyrrolecarboxylate	EtOH	239*	(3.81)	264	(4.13)	
Methyl 1-methyl-2-pyrrolecarboxylate	EtOH	240	(3.78)	266	(4.16)	20
Methyl 2-pyrrolecarboxylate	EtOH	238*	(3.62)	263	(4.14)	18
Methyl 1-benzyl-3-pyrrolecarboxylate	EtOH	232	(4.06)	249*	(3.89)	
Methyl 3-pyrrolecarboxylate	EtOH	224	(3.90)	247	(3.73)	21
1-Benzyl-2-nitropyrrole	EtOH	240	(3.41)	333	(4.04)	
1-Methyl-2-nitropyrrole	EtOH	229	(3.37)	335	(3.95)	22
2-Nitropyrrole	MeOH	231	(3.61)	335	(4.23)	9
1-Benzyl-3-nitropyrrole	EtOH	285	(3.84)	311*	(3.81)	
1-Methyl-3-nitropyrrole	EtOH	282	(3.80)	315*	(3.82)	22
3-Nitropyrrole	MeOH	268	(3.86)	315	(3.73)	9
1-Benzyl-2-pyrrolecarbaldoxime	EtOH	280.5	(4.16)			
1-Methyl-2-pyrrolecarbaldoxime	EtOH	282	(4.28)			22
2-Pyrrolecarbaldoxime	EtOH	272	(4.25)			23
1-Benzyl-3-pyrrolecarbaldoxime	EtOH	256	(4.20)			

*Shoulder.

to be a useful blocking group for the nitrogen. Desulfurization with Raney nickel might be used to remove this group after pyrrole ring substitution. However, it was found that the reaction of potassium pyrrole with benzenesulfenyl chloride, and a variety of similar preparative methods, gave only a small amount of a product which was apparently not the desired one. The reaction was repeated with 2,4-dinitrobenzenesulfenyl chloride, a more readily obtainable reagent. The principal product was then found to be 2-(2,4-dinitrobenzenesulfenyl)pyrrole, even under conditions which produced the best yields of 1-benzylpyrrole from benzyl halides and pyrrole salts (12). The Vilsmeier formylation of 2-(2,4-dinitrobenzenesulfenyl)pyrrole was found to occur at the 5-position. Consequently, the benzenesulfenyl blocking group was not investigated further.

Spectral Properties

As shown in Table I, the ultraviolet spectra of the 2- and 3-substituted-1-benzylpyrroles that were examined are closely similar to those of the corresponding 1-methyl and *N*-unsubstituted compounds (where these are known). The position and intensity of the longer wavelength band in similarly substituted compounds seems to be least affected by the presence or absence of a group on the nitrogen. The shorter wavelength band seems generally to undergo a hypsochromic shift with *N*-substitution. However, the number of examples is too few to draw many conclusions. The longer wavelength band of 2-substituted compounds is always at a longer wavelength than the corresponding band of 3-substituted ones, indicating that greater conjugation takes place at the 2-position. This is in agreement with the observations made with 2- and 3-substituted furans and thiophenes (13).

The n.m.r. spectra of the monosubstituted 1-benzylpyrrole derivatives were all consistent with the structures assigned, as shown in Table II. Where comparisons could be made, the spectra were in agreement with those of similarly substituted 1-methylpyrroles. The pyrrole ring coupling constants were within the usual limits (14) for $J_{4,5}$, but the $J_{2,4}$ and $J_{2,5}$ values in the 3-substituted compounds were generally at the upper limit of, or higher than, the ranges suggested by Gronowitz. However, the coupling constants were generally determined in dimethyl sulfoxide-d_6. As might be expected, electron withdrawal in the pyrrole ring was transmitted to the benzyl —CH_2— more strongly from the 2- than from the 3-position.

Two of the by-products obtained from the bromination reactions have not been proved completely. On the basis of their elemental analyses and n.m.r. spectra they have been identified tentatively as 1-benzyl-2,5-dibromopyrrole and 1-benzyl-2,3,5-tribromopyrrole. The low-field position of the

TABLE II

Nuclear magnetic resonance spectra*

Compound	Benzyl —CH_2—	Aromatic				Coupling constants			
		2-Proton	3-Proton	4-Proton	5-Proton	$J_{2,4}$ and $J_{3,5}$	$J_{4,5}$	$J_{2,5}$	$J_{3,4}$
1-Benzylpyrrole	4.80	6.49	6.08	6.08	6.49				
1-Benzyl-3-bromopyrrole	4.95	6.53	—	6.09	6.53	1.77	2.78	2.39	—
2-5-Dibromo	5.24	—	6.25	6.25	—				
2,3,5-Tribromo	5.28	—	—	6.39	—				
Tetrabromo	5.25	—	—	—	—				
2-Nitro	5.52	—	7.04	6.13	6.82	2.20	2.80	—	4.14
3-Nitro	5.08	7.48	—	6.53	6.63	1.86	3.19	2.48	—
3-Acetamido†	4.97	7.38	—	6.03	6.52	1.70	2.75	?	—
2-Ester	5.36	—	6.73	5.92	6.58	1.75	2.56	—	3.85
3-Ester	4.99	≃7.2	—	6.48	6.48	1.75	2.86	2.25	—
2-Aldehyde	5.50	—	6.87	6.18	6.87	1.8	2.55	—	3.86
2-Aldoxime‡§	5.53 (*syn*) 5.43 (*anti*)	—	6.50	6.23	7.10	1.80	2.65	—	3.70
3-Aldoxime‡‖	5.19	6.91	—	6.48	6.48	≃1.6	≃2.8	?	—

*Unless otherwise specified, the chemical shifts were determined in CCl_4; the coupling constants were determined in dimethyl sulfoxide-d_6.
†In $CDCl_3$.
‡In dimethyl sulfoxide-d_6.
§*syn* —CH=, 8.13; =N—OH, 10.82. *anti* —CH=, 7.45; =N—OH, 11.28.
‖—CH=, 7.48; =N—OH, 10.81.

benzyl —CH_2— in these two compounds, and similarly in the tetrabromo derivative, suggests that bromines occupy both the 2- and 5-positions of each molecule.

The n.m.r. spectrum of one sample of the oxime of 1-benzyl-2-pyrrolecarboxaldehyde showed both *syn* and *anti* forms to be present. The chemical shifts obtained in dimethyl sulfoxide-d_6 for the —CH= and =N—OH protons, and their separations, were in complete agreement with the recent observations of Kleinspehn (15). By using the Kleinspehn assignments, the *syn* isomer was found to be predominant in this sample. One interesting feature was the fact that the benzyl —CH_2— signal had different chemical shifts for the *syn* and *anti* isomers of the 1-benzyl-2-oxime. The *anti* isomer had the most shielded benzyl methylene protons. This must be attributed to the anisotropy of the C=N— bond, which will be oriented quite differently in the two forms. On the other hand, the 1-benzyl-3-oxime was a single isomer, and chemical shifts, and differences, did not permit a decision between the *syn* and *anti* forms.

EXPERIMENTAL

General

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Gas–liquid partition chromatography was carried out with a Beckman GC-2A chromatograph equipped with a 13½ in. column (No. 70008) packed with Apiezon L on Firebrick and operated at 220°, with helium as the carrier gas.

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

Infrared spectra (625 – 4 000 cm^{-1} region) were recorded on a Perkin–Elmer 237B spectrophotometer by the potassium chloride disk technique (2 mg sample in 148 mg of KCl). Ultraviolet spectra were determined in ethanol on either a Perkin–Elmer 202 or a Unicam S.P. 800 recording spectrophotometer. Nuclear magnetic resonance spectra were determined at 60 Mc.p.s. on a Varian A-60 instrument in the solvents stated. The chemical shifts are recorded in parts per million from tetramethylsilane as internal reference and are on the δ scale.

1-Benzylpyrrole

This compound was prepared from potassium pyrrole and benzyl bromide in tetrahydrofuran by the method of Hobbs *et al.* (12) in a 78% yield. Samples prepared with toluene as solvent were contaminated with 2-benzylpyrrole and required more careful purification.

Nitration of 1-Benzylpyrrole

1-Benzylpyrrole (0.047 mole) in acetic anhydride (25 ml) was treated with a solution of fuming nitric acid (0.066 mole) in acetic anhydride (15 ml), keeping the temperature below −10°. After hydrolysis in cold water for 3 h, the solution was neutralized with sodium hydroxide and the oily product separated from the aqueous layer. The aqueous layer was twice extracted with ether, and the combined organic extracts were washed with saturated sodium car-

bonate solution and with water, and dried over molecular sieves. Gas–liquid partition chromatography of the crude material showed two products.

The oil obtained after evaporation of the ether was dissolved in benzene and chromatographed on alumina (Fisher, neutral grade). After separation of the starting material (2.0 g), the first product fraction (2.35 g) was collected and recrystallized from aqueous methanol. The crystals were needle-shaped and off-white in color. The ultraviolet and n.m.r. spectra (Tables I and II) showed them to be 1-benzyl-2-nitropyrrole, m.p. 36–36.5°.

Anal. Calcd. 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.

The second isomer collected was recrystallized from methanol (3.5 g) and then from a benzene – petroleum ether (b.p. 37–50°) mixture. The ultraviolet and n.m.r. spectra (Table I and II) of the pale-yellow crystals showed them to be 1-benzyl-3-nitropyrrole, m.p. 67.5–68°.

Anal. Calcd. 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.

Reductive Acetylation of 1-Benzyl-3-nitropyrrole

(*a*) Tin (1.7 g) was slowly added to a solution of 1-benzyl-3-nitropyrrole (0.0025 mole) in methanol saturated with hydrogen chloride, keeping the reaction mixture cool. The solution of the product was decanted from the unreacted tin, and the excess of methanol and hydrogen chloride was evaporated under reduced pressure. The oily residue was washed with water by decantation and treated with excess acetic anhydride (5 ml) in ether (25 ml); then the solution was made strongly alkaline with sodium hydroxide (6 *N*), keeping the mixture cold. After the mixture was thoroughly shaken, the ether layer was separated and dried over molecular sieves. The ether was evaporated and the resulting oil crystallized. Recrystallization from aqueous methanol and then from a benzene – petroleum ether mixture gave 1-benzyl-3-acetamidopyrrole (0.4 g, 80%), m.p. 130°. The n.m.r. spectrum is shown in Table II.

Anal. Calcd. 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.

(*b*) 1-Benzyl-3-nitropyrrole (0.002 mole) in methanol (15 ml) was shaken mechanically for 15 min with hydrogen at 35 p.s.i.g. in the presence of platinum oxide (0.05 g) on a Parr hydrogenator. The solution was filtered, but immediately began to go brown and thus 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 ether mixture. A mixture of the product and the 1-benzyl-3-acetamidopyrrole obtained by method *a* melted at 129–130°.

(*c*) 1-Benzyl-3-nitropyrrole (0.0022 mole) was dissolved in acetic anhydride (20 ml), and a saturated solution of sodium acetate (10 ml) was added. Platinum oxide (0.02 g) was added and the reaction mixture shaken mechanically for 15 min with hydrogen at 30 p.s.i.g. on a Parr hydrogenator. The solution was filtered and made alkaline with sodium hydroxide solution (6 *N*), and the crude product was removed by filtration (0.4 g, 85%). It was recrystallized from aqueous methanol and then from a benzene – petroleum ether mixture. A mixture of this product and the 1-benzyl-3-acetamidopyrrole obtained by method *a* melted at 130°.

Bromination of 1-Benzylpyrrole

1-Benzylpyrrole (0.18 mole) was placed in the reaction vessel with 100 ml of carbon tetrachloride and the solution was cooled to 0°. The top of the condenser was attached to a water pump, and slight suction was applied to help remove the hydrogen bromide produced by the reaction. Bromine (0.18 mole in carbon tetrachloride) was cooled to 0° and added dropwise to the cold reaction mixture, with vigorous stirring. The reaction mixture was then stirred at 0° for a further 30 min.

A small sample was analyzed by gas chromatography and showed the presence of 1-benzylpyrrole (4%), the tetrabromo compound (10%), the 3-bromo compound (55%), an unresolved mixture (30%), and the 2,3,5-tribromo compound (trace).

The carbon tetrachloride solution was separated from an insoluble sticky red product, 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 extracts were dried over molecular sieves.

After evaporation of the solvent, the product was extracted with boiling petroleum ether. 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 ether. The mother liquor was evaporated and the oil chromatographed on neutral alumina. A partial separation was effected and a pure sample of a 1-benzyltribromopyrrole was obtained. The fractions that were collected were grouped together and each group was rechromatographed on neutral alumina. Finally the products described below were isolated and identified. The n.m.r. spectra are shown in Table II.

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

Anal. Calcd. 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-2,5-dibromopyrrole, m.p. 78.0–78.5°.

Anal. Calcd. 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-2,3,5-tribromopyrrole, m.p. 59.0–59.5°.

Anal. Calcd. for $C_{11}H_8NBr_3$: C, 33.54; H, 2.04; N, 3.55; Br, 60.88. 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°.

Anal. Calcd. 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.

1-Benzyl-3-pyrrolecarboxylic Acid and Its Methyl Ester

Freshly prepared lithium wire (0.015 mole) was cut into small lengths and placed in anhydrous ether

(25 ml) in a previously dried, 100 ml, three-necked flask; then 1-benzyl-3-bromopyrrole (0.01 mole) in anhydrous ether (25 ml) was added, with stirring. The reaction mixture was refluxed gently for 1½ h and cooled. Excess solid carbon dioxide was added down the condenser and stirring was continued for a further 10 min. The product was extracted with 10% sodium hydroxide solution, and the aqueous extract was filtered and carefully acidified. The yield of crude acid was 1.6 g (80%). After crystallization from methanol, the 1-benzyl-3-pyrrolecarboxylic acid melted at 149.5–150°.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.61; H, 5.50; N, 7.10.

An excess of a solution of diazomethane in ether was added to 1-benzyl-3-pyrrolecarboxylic acid in ether (5 ml) and left overnight. The product, methyl 1-benzyl-3-pyrrolecarboxylate, was recrystallized from aqueous methanol, m.p. 52–52.5°. The ultraviolet and n.m.r. spectra are shown in Tables I and II.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.50; H, 6.06; N, 6.50. Found: C, 72.10; H, 6.13; N, 6.62.

Benzylation of Methyl 3-Pyrrolecarboxylate

Methyl 3-pyrrolecarboxylate (10) (0.012 mole) in tetrahydrofuran was refluxed with potassium (0.011 mole), and the product was refluxed with benzyl bromide (0.01 mole). Removal of the solvent gave a brown oil which was decolorized with activated charcoal in methanol; the ester was precipitated by adding water. A mixture of this product and the ester obtained above from the 3-bromo compound melted at 51–52°.

Attempted Debenzylation of Methyl 1-Benzyl-3-pyrrolecarboxylate

Raney nickel (W4) was prepared by the method of Pavlik and Adkins (16). The hydrogenolysis attempts were carried out in an Autoclave Engineers high-pressure reaction vessel and the products analyzed by gas–liquid partition chromatography.

(*i*) Methyl 1-benzyl-3-pyrrolecarboxylate (0.3 g, 0.0014 mole) and Raney nickel (W4, 0.3 g) were added to methanol (50 ml) in the well of the reaction vessel. After the vessel was sealed, hydrogen was introduced at 1 000 p.s.i.g. and the mixture was agitated slowly for 8 h. The Raney nickel was removed by filtration and the methanol evaporated under reduced pressure. The product (0.3 g) was dissolved in ether and analyzed. No methyl 3-pyrrolecarboxylate was detected in the product, which appeared to be entirely unchanged.

(*ii*) The above reaction was repeated at 50° and 1 200 p.s.i.g. of hydrogen, but there was no evidence that the required product was formed.

(*iii*) The reaction was repeated at 110° and 1 900 p.s.i.g. of hydrogen, but these conditions again failed to bring about the required debenzylation.

Formylation of 1-Benzylpyrrole

This reaction was carried out in the usual way (6), with 0.09 mole of 1-benzylpyrrole. The solvent was evaporated under reduced pressure and the residue analyzed by gas–liquid partition chromatography. Two products in the ratio of 14.7:1 were found, along with some unreacted starting material.

The crude formylation product was chromatographed on a column of alumina. A separation was effected, but the oily fractions that were collected were colored. However, each gave only one peak on the gas chromatograph. The minor compound was identified as 1-benzyl-3-pyrrolecarboxaldehyde, and the major as the 2-aldehyde (see also Table II), by means of the physical properties of their oximes and by conversion into the corresponding acids and esters as described below.

Preparation of Oximes

Oximes were prepared from the two aldehydes in the usual way (17). 1-Benzyl-2-pyrrolecarbaldoxime was obtained in an 87% yield as white crystals, m.p. 111–112°, after crystallization from aqueous methanol. The n.m.r. and ultraviolet spectra are shown in Tables I and II.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.13; H, 6.15; N, 13.84.

1-Benzyl-3-pyrrolecarbaldoxime was obtained in a 65% yield as pale-yellow crystals after crystallization from benzene – petroleum ether, m.p. 146–147°. The ultraviolet and n.m.r. spectra are shown in Tables I and II.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.23; H, 5.84; N, 13.92.

Conversion of Aldehydes into the Corresponding Acids

(*a*) 1-Benzyl-3-pyrrolecarboxaldehyde (0.5 g, 0.003 mole) was oxidized with Tollen's reagent as described by Hodge and Rickards (18). The product (0.12 g, 22%) was recrystallized from aqueous methanol. It melted at 148–149°, and the mixture melting point of this product and the acid obtained above from the metalation and carbonation of 1-benzyl-3-bromopyrrole was 150°. The infrared spectra were identical.

(*b*) According to the method of Van Es (11), 1-benzyl-2-pyrrolecarboxaldehyde (0.01 mole), hydroxylamine hydrochloride (0.80 g, 0.01 mole), sodium formate (1.25 g), and formic acid (15 ml, 98–100%) were refluxed for 1 h. The product was diluted with water, extracted with ether, dried over anhydrous sodium sulfate, and evaporated to give a brown oil. The oil was washed through a short column of alumina, giving a colorless oil with a nitrile band at 2 210 cm^{-1}. The yield of crude nitrile was 0.8 g (45%).

The nitrile was then refluxed for 6 h with sodium hydroxide (5 ml, 40% solution). After dilution with water, an insoluble white solid (A) was collected. The alkaline solution was extracted with ether, and the aqueous layer was cooled and carefully acidified with concentrated sulfuric acid. The white crystalline precipitate (B) was removed by filtration.

Solid A was recrystallized from a benzene – petroleum ether mixture and was shown by its infrared and n.m.r. spectra to be 1-benzyl-2-pyrrolecarboxamide, m.p. 112–113°.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 6.06; N, 13.78.

Solid B was recrystallized from aqueous methanol, giving 1-benzyl-2-pyrrolecarboxylic acid (0.5 g, 55%), m.p. 130–131°.

Anal. Calcd. 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.

Benzylation of Methyl 2-Pyrrolecarboxylate

Methyl 2-pyrrolecarboxylate (0.055 mole) in toluene was reacted with potassium (0.05 mole) followed by benzyl bromide (0.047 mole). The solvent was removed on a flash evaporator and the resulting product chromatographed twice on alumina. The product (2.55 g, 25%), a yellow oil, crystallized when left overnight in a freezer. Distillation under vacuum yielded a colorless liquid which crystallized readily to give methyl 1-benzyl-2-pyrrolecarboxylate, m.p. 31–31.5°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.50; H, 6.06; N, 6.50. Found: C, 72.70; H, 6.07; N, 6.75.

The product was shown to have the same retention time on gas–liquid chromatography as the ester obtained by oxidation and methylation of the major formylation product from above. Their infrared and n.m.r. spectra were identical.

Methyl 1-benzyl-2-pyrrolecarboxylate (0.2 g) was then hydrolyzed in 20% aqueous potassium hydroxide for 4 h. After acidification, the product was extracted with ether, dried, and evaporated, and the crude product was recrystallized from aqueous methanol. The yield of recrystallized product was 0.068 g (46%); its melting point was 131–131.5°.

The mixture melting point of this product and the acid obtained above from the major formylation product, 1-benzyl-2-pyrrolecarboxaldehyde, via the nitrile was 130–132°.

Attempted Preparation of 1-Benzenesulfenylpyrrole

A solution of pyrrole (0.029 mole) in toluene (10 ml) was placed in a three-necked flask, and potassium (0.022 mole) was added, with gentle heating and stirring. The mixture was then refluxed until all of the potassium had reacted. Benzenesulfenyl chloride (0.019 mole), prepared in a 64% yield from thiophenol (19), in toluene (10 ml) was added at −70° under an atmosphere of nitrogen. The mixture was stirred at −70° for a further 30 min; then the temperature was gradually raised to room temperature. The solvent was evaporated and an attempt was made to purify the product by distillation under reduced pressure (8 mm). Most of the product decomposed, but a few drops of clear distillate were obtained. It appeared, from its n.m.r. spectrum, to be 2-benzenesulfenylpyrrole.

Attempted Preparation of 1-(2,4-Dinitrobenzenesulfenyl)pyrrole

(*a*) Potassium pyrrole (0.046 mole) was prepared as described above and the slurry cooled to −10° by means of an ice–salt bath. 2,4-Dinitrobenzenesulfenyl chloride (9.8 g, 0.041 mole), partly dissolved and partly suspended in toluene, was slowly added. The first few milliliters of reagent produced a deep-blue coloration which darkened rapidly. The mixture was stirred at −10° for 30 min. The solvent was flash evaporated, and the product was dissolved in a minimum of methanol, refluxed with activated charcoal (Norit), and then crystallized from aqueous methanol. The n.m.r. spectrum of the yellow product (5.8 g) showed it to be 2-(2,4-dinitrobenzenesulfenyl)pyrrole, m.p. 149.5–150°.

Anal. Calcd. for $C_{10}H_9N_3O_4S$: C, 45.29; H, 2.66; N, 15.80; S, 12.09. Found: C, 45.55; H, 2.80; N, 15.60; S, 12.16.

(*b*) Pyrrole (0.057 mole) and triethylamine (0.075 mole) were mixed together in an Erlenmeyer flask. 2,4-Dinitrobenzenesulfenyl chloride (0.05 mole) in dioxane (50 ml) was added, with stirring. The mixture became hot and was allowed to stand for 1 h. The same yellow compound, 2-(2,4-dinitrobenzenesulfenyl)pyrrole, was obtained after chromatography on alumina, yield 8.85 g (68.6%).

(*c*) Pyrrole (0.057 mole) and 2,4-dinitrobenzenesulfenyl chloride (0.025 mole) were mixed at room temperature in sufficient dioxane to make a homogeneous solution. The reaction mixture was stirred for 4 h. A yellow solution was left after the black solid was removed by filtration. The solution was flash evaporated and then passed down a column of neutral alumina. The orange solution was collected and evaporated to give yellow 2-(2,4-dinitrobenzenesulfenyl)pyrrole (4.8 g, 70%).

Formylation of 2-(2,4-Dinitrobenzenesulfenyl)pyrrole

The reaction was carried out as described for the formylation of 1-benzylpyrrole, except that double the volume of ethylene chloride was used. However, the 2-(2,4-dinitrobenzenesulfenyl)pyrrole (0.02 mole) failed to dissolve completely and was added as a paste. During the reaction it dissolved completely; after the product was hydrolyzed with sodium acetate solution and cooled, yellow crystals (2.45 g, 42%) appeared. The n.m.r. spectrum of the product showed it to be 2-(2,4-dinitrobenzenesulfenyl)-5-pyrrolecarboxaldehyde, m.p. 212–214° after crystallization from benzene – petroleum ether.

Anal. Calcd. for $C_{11}H_7N_3O_5S$: C, 45.05; H, 2.41; N, 14.33; S, 10.93. Found: C, 45.23; H, 2.38; N, 14.14; S, 10.67.

From the ethylene chloride layer, 3.1 g of unreacted 2-(2,4-dinitrobenzenesulfenyl)pyrrole was recovered.

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