chloride. The combined extracts were dried over magnesium sulfate. After filtration and removal of the solvent on the steam bath, there was obtained 1.26 g. (73%) of an orange liquid which crystallized upon standing in the refrigerator for 2 hr., m.p. 83–88°. Infrared and n.m.r. spectra showed the product to contain less than 5% of the sulfone. An analytical sample was prepared by chromatography on a short column of neutral alumina, eluting with methylene chloride. The clear liquid obtained crystallized upon standing in the refrigerator and the solid was recrystallized three times by dissolving in methylene chloride and adding low boiling petroleum ether (b.p. 30–60°) almost to the cloud point, m.p. 88.5–90°.

*Anal.* Calcd. for $C_5H_7NOS$: C, 46.47; H, 5.46; B, 10.84. Found: C, 46.78; H, 5.47; N, 10.67.

**Method B.**—Freshly distilled 2-methylthiopyrrole[4] (3.0 g., 26.6 mmoles) was dissolved in 3 ml. of acetic acid. Water was added until the solution became cloudy. The mixture was stirred magnetically and cooled in an ice bath, whereupon more solid formed. To this heterogeneous mixture was added 4 ml. of 30% hydrogen peroxide at such a rate as to maintain the temperature between 10–14°. The reaction mixture became homogeneous shortly after addition of the hydrogen peroxide; it was then allowed to warm to room temperature and was stirred for 13 hr. The reaction mixture was made slightly basic with 50% potassium hydroxide, extracted with four portions of methylene chloride, and the combined extracts were dried over magnesium sulfate. After removal of the drying agent and solvent, there was obtained 3.14 g. (81%) of tan colored crystals, m.p. 73–83°. Two recrystallizations as described in method A gave product melting at 87–89°.

**Reduction of 2-Methylsulfinylpyrrole (XVI) with Lithium Aluminum Hydride.**[11]—To a suspension of lithium aluminum hydride (0.19 g., 5 mmoles) in 12 ml. of dry ether was added in portions a solution of 2-methylsulfinylpyrrole (XVI) (0.488 g., 3.78 mmoles) in 20 ml. of ether. After the addition, the reaction mixture was refluxed for 6 hr. The excess lithium aluminum hydride was destroyed with water and the aluminum salts were dissolved by the addition of 10% hydrochloric acid. The two layers were separated and the aqueous phase was extracted with three more portions of ether. The combined ether extracts were dried over magnesium sulfate. Filtration and evaporation of the solvent yielded a yellow liquid. Distillation of the liquid through a 24-cm. heated column gave a 50% yield of 2-methylthiopyrrole (XV), identified by comparison of the infrared spectrum with that of an authentic sample.

**2-Methylsulfonylpyrrole (XVII).**—A solution of 2-methylsulfinylpyrrole (0.122 g., 0.94 mmoles) and 30% hydrogen peroxide (0.4 ml., 4.0 mmoles) in 2 ml. of glacial acetic acid was allowed to stand at room temperature for 43 hr. Ten milliliters of water was added and the reaction mixture was extracted with three portions of methylene chloride. The combined methylene chloride extracts were washed once with 10% sodium bicarbonate solution and once with water, followed by drying over magnesium sulfate. The drying agent was filtered off and the solvent removed on a steam bath to yield 71 mg. (52%) of a light yellow solid, m.p. 115–119°. The solid recrystallized from benzene–low boiling petroleum ether (b.p. 30–60°), m.p. 121.5–123°. This compound proved to be identical with 2-methylsulfonylpyrrole (XIV) as shown by melting point, mixture melting point, and comparison of the infrared and n.m.r. spectra.

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# The Methylpyrroles. Synthesis and Characterization

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Convenient syntheses have been devised for all the C-methylpyrroles with the exception of 3-methylpyrrole. Lithium aluminum hydride reduction of a C-acyl to a C-alkyl group was the key step in most of the syntheses. Attempts to use this method for the preparation of N-methylpyrroles were unsuccessful because reduction of C-acyl-N-methylpyrroles stopped at the hydroxymethyl stage, regardless of whether the acyl group was at the 2- or the 3-position. 1,2-Dimethylpyrrole and 1,2,3,5-tetramethylpyrrole were prepared, however, by methylation of the potassium salts of the required C-methyl derivatives. Infrared, ultraviolet, and proton magnetic resonance spectra are tabulated for pyrrole and fourteen N- and C-methylpyrroles.

In the course of a general study of the behavior of indoles and pyrroles in acidic media,[1] an extensive series of methylpyrroles was required. Although these compounds have been known for many years, most of the reported synthetic routes are tedious to carry out and the compounds themselves have not been well characterized.[2] Exceptions are 2,5-dimethylpyrrole and its N-substituted derivatives which can be prepared with ease from 1,4-diketones and the appropriate amines.[1b]

The pyrroles studied in the course of this work are listed in Table II. Pyrrole, 1-methylpyrrole, 2,4-dimethylpyrrole, and pentamethylpyrrole were purchased. Ring closure of the appropriate 1,4-diketone, the method used to prepare 2,5-dimethyl- and 1,2,5-trimethylpyrrole,[1b] was used for the synthesis of 2,3,4,5-tetramethylpyrrole. 1,2-Dimethyl- and 1,2,3,5-tetramethylpyrroles were prepared by N-methylation of the appropriate precursor. The other pyrroles were synthesized as described subsequently.

Profiting by the observations that carbonyl groups attached to positions 2 or 3 of the pyrrole ring can be reduced to hydrocarbon residues by lithium aluminum hydride,[3] we have devised relatively simple syntheses of only two or three steps for the remaining C-methylpyrroles, with the exception of 3-methylpyrrole. The methods are summarized in equations 1–6 and yields of products are given in Table I. Starting materials for the hydride reductions were prepared by methods in the literature as shown in the equations and cited in Table I. It should be noted that the conversion of a carbonyl group to an alkyl group is not new in the pyrrole series, Wolff–Kishner reductions having been used for many years for this purpose.[2,4] However, the present methods offer much greater freedom in the choice of starting materials.

(1) For leading references see: (a) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962); (b) E. B. Whipple, Y. Chiang, and R. L. Hinman, *ibid.*, **85**, 26 (1963); (c) Y. Chiang and E. B. Whipple, *ibid.*, **85**, 2763 (1963).

(2) For further discussion of this point and characterization of some of the higher alkylpyrroles, see P. S. Skell and G. P. Bean, *ibid.*, **84**, 4655 (1962).

(3) (a) A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952); (b) A. Treibs and H. Derra-Scherer, *ibid.*, **589**, 188 (1954); (c) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); (d) acyl groups at the 3-position of the indole nucleus also are reduced to the hydrocarbon residue [E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953)], but acyl groups at the 2-position are reduced only to the carbinol [E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959)].

(4) (a) H. Fischer and B. Walach, *Ann.*, **450**, 109 (1926); (b) J. W. Cornforth and M. E. Firth, *J. Chem. Soc.*, 1091 (1958); (c) F. P. Doyle, M. D. Mahta, G. S. Sach, and J. L. Pearson, *ibid.*, 4458 (1958).

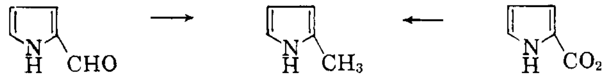
TABLE I

SUMMARY OF $LiAlH_4$ REDUCTIONS

| Pyrrole derivative reduced | Ref. to preparation of starting material | Yield of starting material | Moles of pyrrole deriv. reduced | Moles of $LiAlH_4$ | Vol. of[a] solvent, ml. | Product (as derivative of pyrrole) | Yield, % | Over-all yield, % |
|---|---|---|---|---|---|---|---|---|
| 2-Formyl | *b* | 80 | 0.2 | 0.4 | 700[c] | 2-Methyl | 63 | 48 |
| 2-Carboxylic acid | | 20 | 0.1 | 0.2 | 300 | 2-Methyl | 54 | 10 |
| 2-Methyl-3-carbethoxy[d] | *e* | 53 | 0.045 | 0.09 | 100 | 2,3-Dimethyl[a] | 61[a] | 30 |
| 1,3,4-Triscarbomethoxy | *f* | 40 | 0.02 | 0.08 | 150 | 3,4-Dimethyl | 50 | 20 |
| 3-Carbethoxy-4-methyl-2-carboxylic acid | *g* | 50 | 0.025 | 0.17 | 150 | 2,3,4-Trimethyl | 47 | 25 |
| 2,5-Dimethyl-3-formyl | | 62 | 0.04 | 0.08 | 100 | 2,3,5-Trimethyl[h] | 81 | 50 |
| 3-Carbethoxy-2,5-dimethyl | *i* | 60 | 0.15 | 0.30 | 200 | 2,3,5-Trimethyl[h] | 80 | 48 |
| 1-Methyl-2-formyl[j] | *k* | 62 | 0.05 | 0.10 | 250[l] | 2-Hydroxymethyl-1-methyl[f] | 76[j] | |
| 1,2,5-Trimethyl-3-formyl | | 99 | 0.05 | 0.10 | 125[m] | 3-Hydroxymethyl-1,2,5-trimethyl[n] | 44 | |

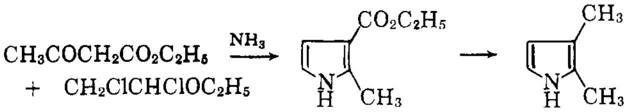
[a] Tetrahydrofuran except where noted otherwise. Reaction mixture refluxed overnight except where noted otherwise. [b] See ref. 6. [c] Ether, reflux time 4 hr. [d] Reduction of 2-methylpyrrole-3-carboxylic acid was effected in 40% yield. [e] E. Benary, *Ber.*, **44,** 493 (1911). [f] See ref. 11. [g] See ref. 10. [h] Picrate (from methanol), m.p. 83°. *Anal.* Calcd. for $C_7H_{11}N \cdot C_6H_3N_3O_7$: C, 46.15; H, 4.14; N, 16.75. Found: C, 46.15; H, 4.17; N, 16.56. [i] H. Fischer and B. Heyse, *Ann.*, **439,** 254 (1924), and G. Korschun, *Ber.*, **37,** 2196 (1904). [j] Reduction of 1-methylpyrrole-2-carboxylic acid was effected in tetrahydrofuran in 82% yield. [k] See ref. 8. [l] Ether. [m] Reflux time, 4 hr. [n] *Anal.* Calcd. for $C_8H_{13}NO$: C, 69.02; H, 9.41; N, 10.06. Found: C, 69.10; H, 9.32; N, 9.84.

**2-Methylpyrrole**



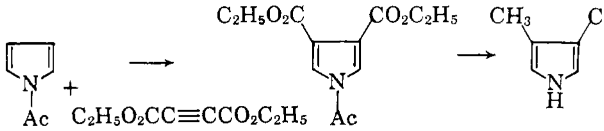
(1)

**2, 3-Dimethylpyrrole**



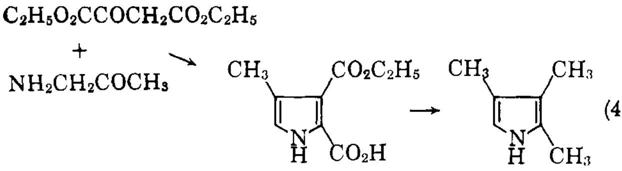
(2)

**3, 4-Dimethylpyrrole**



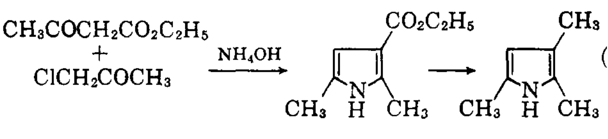
(3)

**2, 3, 4-Trimethylpyrrole**

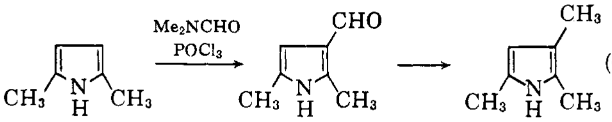


(4)

2,3,5-Trimethylpyrrole



(5)



(6)

A few points about the syntheses deserve special comment. Although in our hands the reduction of 3-carbethoxy-2-methylpyrrole gave 2,3-dimethylpyrrole in 61% yield, essentially the same procedure was reported by Treibs to give only tar.[3a] We have no simple explanation for this difference. However, Treibs proposed that the carbinols, which are presumed to be intermediate in the formation of the alkylpyrroles, would readily undergo polymerization, and polymerization of 1-methylpyrrole-2-carbinol has been reported to occur with explosive violence.[4c] In most of our experiments lithium aluminum hydride was present in 300% excess of that required to reduce the carbonyl group to the alkyl group. Since the previous workers[3a] appear to have used in general only small excesses of hydride, substantial quantities of carbinol may have been present at the time of work-up during which polymerization was observed. The success of our technique would then be due simply to the use of more drastic conditions for reduction. Treibs also reported[3b] that carboxyl groups are reduced more readily than are carbethoxy groups. Although our conditions were too severe to permit this distinction to be observed, in all cases studied higher yields of methylpyrroles were obtained from reduction of the esters than from the corresponding acids (Table I).

The loss of the *N*-acetyl group from 1-acetyl-3,4-dicarbethoxypyrrole has a number of precedents of which the closest is found in the hydride reduction of 1-acylindoles.[5]

An attempt was made to prepare 2,3-dimethylpyrrole by formylation of 3-methylpyrrole with dimethylformamide,[6] followed by hydride reduction. The products of formylation consisted of a mixture of 2-formyl-3-methyl- and 2-formyl-4-methylpyrrole in a 4:1 ratio, as measured by n.m.r. Reduction of this mixture produced a mixture of 2,3- and 2,4-dimethylpyrroles, also in a 4:1 ratio. The ratio of products from the formylation reaction was foreshadowed by the 15:1 ratio[7] of conjugate acids of 3-methylpyrrole observed by n.m.r. in 12–18 *M* sulfuric acid,[1c] and foretells in turn the general pattern to be expected of electrophilic substitution of 3-methylpyrrole.

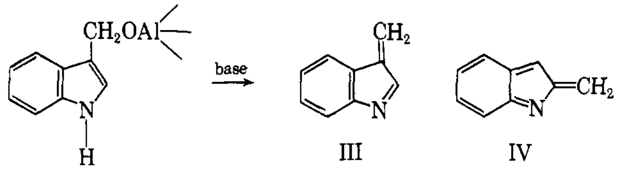
[5] (a) V. M. Mićović and M. Lj. Mihailović, *J. Org. Chem.*, **18,** 1190 (1953); (b) see also N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 575–590.

[6] R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36,** 74 (1956).

[7] Steric hindrance by the 3-methyl group to substitution at the 2-position by the bulky complex of dimethylformamide and phosphorus oxychloride [see, for example, G. F. Smith, *J. Chem. Soc.*, 3842 (1954)] would account for the decreased ratio of 2- to 5-substitution in formylation as compared to that for protonation.

An attempt to extend the general method to the reduction of acylpyrroles bearing an N-methyl group was not successful. It has been observed that N-methylpyrrole-2-carboxaldehyde (I) is similar to pyrrole-2-carboxaldehyde (II) in its failure to undergo many typical reactions of aldehydes,[8a] and earlier work[8b] had shown that inverse addition in the hydride reduction of 2-acylpyrroles leads to carbinols. However, even massive excesses of hydride (6 moles of hydride/mole of aldehyde) in the normal mode of addition did not carry the reduction of I beyond the carbinol stage. The reduction of N-methylpyrrole-2-carboxylic acid also stopped at the carbinol stage, as expected. This effect of an N-methyl group is, interestingly, conveyed also to the 3-position, as shown by the formation of 1,2,5-trimethylpyrrole-3-carbinol from the corresponding formyl compound in contrast to the clean reduction of the formyl to the C-methyl group in the des-N-methyl case (Table I).

These results bear on the mechanism proposed by Leete to explain a similar effect of an N-methyl group in the indole series.[3d] It was assumed in the earlier work[3d] that abstraction of hydrogen from the N–H of an indole-3-carbinol would be accompanied by loss of hydroxyl (in reality —O—Al—) from the carbinol to form a 3-methyleneindolenine III, which would in turn be reduced to the 3-alkylindole. An N-methyl group would prevent this 1,4-elimination. Significantly, 2-hydroxymethylindole did not undergo hydrogenolysis by lithium aluminum hydride, and the lack of reactivity was attributed to the difficulty of forming structure IV, which would be of higher energy than structure III. The clear preference for structures of type III as compared to type IV can be deduced from protonation studies.[1a] In the pyrrole series, structures of type IV are preferred in protonation, but the preference for IV over III is not as marked as is the inverse relationship in the indole series.[1b,c] With the protonation work as background the hydrogenolysis of carbinol groups at the 2- or 3-positions of pyrrole and the inhibition by N-methyl in both cases appears to be entirely consistent with the Leete mechanism.

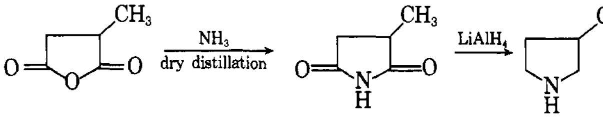


III IV

The preceding methods provide routes to all the C-methylpyrroles except 3-methyl, for which a simple synthesis has yet to be found. Of the more recent methods[4b,9,10] devised for the preparation of 3-methylpyrrole that of Lancaster and VanderWerf[10] is the most straightforward, leading to the desired product in 35% overall yield for the four steps. If 2,3,4-trimethyl- and 3,4-dimethylpyrrole are desired in addition to 3-methylpyrrole, this method becomes very attractive because the two additional pyrroles can be obtained by reduction of intermediates prepared *en route* to 3-methylpyrrole. The economy of effort more than makes up for the number of steps.

In attempting to devise a simpler route to 3-methylpyrrole, the reaction of 1-carbomethoxypyrrole with ethyl propiolate was carried out in a manner similar to that used for the reaction with dimethyl acetylenedicarboxylate. However, instead of the desired 1-carbomethoxy-3-carbethoxypyrrole, a product was obtained which contained ester and vinyl groups, and appeared to be a $\beta$-pyrrylacrylic acid ester, formed by conjugate addition of the pyrrole ring to the acetylenic ester. The preference of pyrroles to add to dienophiles in the conjugate manner rather than in Diels–Alder fashion is well known.[11]

A fairly extensive study of the dehydrogenation of 3-methylpyrrolidine also was made. The pyrrolidine is readily obtained by the sequence shown in equation 7.



(7)

The rhodium–alumina catalyst which has been used for the conversion of pyrrolidine to pyrrole[12] was effective, but at 600° where no pyrrolidine was recovered the product was a mixture of about 20% 3-methylpyrrole and 75% of what appeared from n.m.r. and v.p.c. data to be 2-methylpyrrole.[13] At 400° no 2-methylpyrrole was isolated, but 30–40% of the product mixture was unchanged 3-methylpyrrolidine. Despite the quite different boiling points of the two materials, separation by fractional distillation was difficult, probably because of association. Some higher boiling material, probably of the pyrrolidylpyrrole type found in the dehydrogenation of pyrrolidine,[12] and in the hydrogenation of pyrrole,[14] was obtained in each case, and an attempt to effect complete conversion by continuous recyclization of the product mixture at the lower temperatures led to increased quantities of the higher boiling materials. Attempts to carry out the reaction in a static system[15] under pressure at lower temperatures (<300°) were also unsuccessful.

In the course of preparing 3-methylpyrrolidine it was found that the base forms a hydrate from which water cannot be removed by ordinary dessicants such as calcium sulfate. The water, which was identified by v.p.c. and n.m.r., could be removed by calcium hydride. In the v.p.c. the hydrate gives rise to two peaks, one for water and one for the pyrrolidine, from which the composition of the hydrate is estimated as 3-methylpyrrolidine $\cdot 2H_2O$. In the usual method of isolation of the pyrrolidine the hydrate distils first at 92–94°, and the free base comes over at 103–104° after all of the hydrate has been removed. When the crude mixture was treated with calcium hydride before distilla-

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(8) (a) W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958); (b) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *ibid.*, **76**, 4485 (1954).

(9) H. Plieninger and W. Bühler, *Angew. Chem.*, **71**, 163 (1959).

(10) R. E. Lancaster, Jr., and C. A. VanderWerf, *J. Org. Chem.*, **23**, 1208 (1958).

(11) N. W. Gabel, *ibid.*, **27**, 301 (1962); *cf.* R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 457 (1961).

(12) J. M. Patterson and P. Drenchko, *J. Org. Chem.*, **24**, 878 (1959).

(13) Isomerization of alkylpyrroles at high temperatures has been noted previously. For leading references see I. A. Jacobson, H. H. Heady, and G. V. Dineen, *J. Phys. Chem.*, **62**, 1563 (1958); I. A. Jacobson and H. B. Jensen, *ibid.*, **66**, 1245 (1962); also ref. 2.

(14) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).

(15) H. Adkins and L. G. Lundsted, *ibid.*, **71**, 2964 (1949).

TABLE II

SPECTRAL PROPERTIES OF PYRROLES

| | | | | | | Ultraviolet bands[v] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Free base (in $H_2O$) | | Conjugate acid[w] | | |
| Pyrrole | B.p. [m.p.] (mm.), °C. | Lit. B.p. [m.p.] (mm.), °C. | $n_D$ (°C.) | Infrared bands, μ[p] NH[q] | >C═C< (?)[t] | $\lambda_{max}$ mμ | $\epsilon_{max}$ | $\lambda_{max}$ mμ | $\epsilon_{max}$ | |
| Pyrrole[a] | 132 | 130–131 (761)[b] | | 2.96[r] | 6.38 (w),<br>6.46 (w),<br>6.53 (m)[u] | 205[x] | 6700[x] | 241 | 3900 | (7.6) |
| 1-Methyl[a] | 116 | 112–114[c] | | | 6.50 (sh),<br>6.56 (sh),<br>6.66 (s) | 210 | 5800 | 247 | 4100 | (7.2) |
| 2-Methyl | 146–149 | 148 (755)[d] | 1.5017 (23)[n] | 2.93 | 6.35 (m),<br>6.43 (w) | 208 | 7100 | 233 | 4500 | (4.3) |
| 3-Methyl | 143–143.5 | 80 (70)[e] | 1.4961 (25)[o] | 2.92 | 6.40 (m) | 208 | 5900 | 258 | 4800 | (4.8) |
| 1,2-Dimethyl | 139–141 (760) | 139–140[c] | 1.4910 (25)[f] | | 6.26 (w),<br>6.48 (m),<br>6.70 (s) | 210 | 7200 | 240 | 4500 | (5.1) |
| 2,3-Dimethyl | 97 (65) | 65 (14)[g] | 1.4978 (25) | 2.95 | 6.30 (m),<br>6.51 (w) | 208 | 5600 | 246 | 3800 | (5.7) |
| 2,4-Dimethyl[a] | 166 | 160–165 (760)[h] | | 2.96 | 6.30 (m),<br>6.64 (w) | 209 | 5800 | 249 | 5200 | (4.0) |
| 2,5-Dimethyl | [i] | | | 2.90 | 6.25 (w),<br>6.55 (w) | 209 | 7700 | 237,<br>275[y] | 2900,<br>740[y] | (2.5) |
| 3,4-Dimethyl | 66–67 (16) | 65–66 (14)[j] | | 2.92[s] | 6.36 (w),<br>6.70 (w)[t] | 205[z] | 4400 | 271 | 5800 | (4.0) |
| 1,2,5-Trimethyl | [i] | | | | 6.24 (w),<br>6.38 (m),<br>6.62 (s) | 211 | 8300 | 243[aa] | 3100[aa] | (3.0) |
| 2,3,4-Trimethyl | 79 (15)<br>[39.5–40] | [39][j] | | 2.90 | 6.25 (w) | 208 | 5100[bb] | 262 | 5000[bb] | (6.8) |
| 2,3,5-Trimethyl | 78–80 (15–16) | 75–76 (14–15)[k] | 1.5045 (24) | 2.99 | 6.22 (s),<br>6.46 (w),<br>6.60 (w) | 212 | 6600 | 252 | 5700 | (4.0) |
| 1,2,3,5-Tetramethyl | 80–81 (16) | 62–64 (5)[l] | 1.4950 (25) | | 6.30 (m),<br>6.60 (m) | 216 | 7500 | 259 | 5600 | (5.1) |
| 2,3,4,5-Tetramethyl | [110] | [112][j] | | 2.90 | 6.20 (m),<br>6.42 (w) | 216 | 5800[cc] | 265 | 5200[cc] | (2.0) |
| 1,2,3,4,5-Pentamethyl[a] | [70] | [69–70][m] | | | 6.28 (w),<br>6.54 (w) | 216 | 7000 | 269 | 5600 | (5.1) |

[a] Indicates pyrroles which were purchased; all others were prepared in this laboratory. [b] G. L. Ciamician and M. Dennstedt, *Ber*, **16**, 1536 (1883). [c] H. Rapaport and E. Jorgensen, *J. Org. Chem.*, **14**, 664 (1949). [d] Ref. 4b. [e] Ref. 2. [f] Reported $n^{25}D$ 1.4913 (footnote *c*). [g] O. Piloty, *Ber.*, **45**, 2586 (1912). [h] Ref. 22. [i] Ref. 1b. [j] Ref. 4a. [k] G. Korschun, *Ber.*, **38**, 1125 (1905). [l] F. Ya Perveev and E. M. Kuznetsova, *Zh. Obshch. Khim.*, **28**, 2360 (1958). [m] Private communication from supplier, Aldrich Chemical Co. [n] Reported $n^{25}D$ 1.5002 (ref. 2). [o] Reported $n^{25}D$ 1.4955 (ref. 2). [p] Measurements made on pure liquid. [q] All bands very strong. [r] Reported for $CCl_4$ solution: 2.8 μ (ref. 21b). [s] Values reported for 3,4-diethylpyrrole (pure liquid): 2.97, 6.39, 6.60 μ (ref. 21b). [t] Assignment on basis of ref. 21a. [u] Reported: 6.34, 6.40, 6.53 μ (ref. 21a). [v] Measurements made on $10^{-4}$–$10^{-5}$ *M* solutions of pyrroles. [w] Figures in parentheses are molarities of sulfuric acid solutions on which measurements were made. [x] $\lambda_{max}$ (95% EtOH) 208 mμ ($\epsilon_{max}$ 7300) $\lambda_{max}$ (*n*-hexane) 217 mμ ($\epsilon_{max}$ 7900). Each value is the average of two determinations on freshly distilled material. [y] Values assigned to β-protonated isomer (ref. 1b). [z] Broad. [aa] Long tail absorption to 300 mμ due to β-protonated isomer (ref. 1c). [bb] Uncertain because of impurities observed in n.m.r. [cc] Uncertain because absorption intensity of free base decreases very rapidly with time. Spectrum of conjugate acid undergoes little change.

tion only material of b.p. 103–104° was obtained. Recognition of the existence of the hydrate explains a discrepancy in boiling points for 3-methylpyrrolidine reported some sixty years apart in the literature.[16]

For the syntheses of the N-methylpyrroles methylation of the potassium salt proved the best procedure for 1,2-dimethyl- and 1,2,3,5-tetramethylpyrrole. Synthesis of 1,2-dimethylpyrrole by way of the appropriate 2,5-dimethoxytetrahydrofuran[17] also was carried out, but the last step, conversion of the tetrahydrofuran to the pyrrole by the action of methylamine in acetic acid gave only low yields of product.

Finally it should be noted that the synthesis of 2,3,4,5-tetramethylpyrrole from commercially available 3,4-dimethylhexane-2,5-dione[18a] is much more convenient than that reported recently in *Organic Syntheses*,[18b] and has the added advantage of being simply extended to the synthesis of N-alkyl derivatives by the substitution of the appropriate amine for ammonia.

As mentioned at the beginning of this report, characterization of the methylpyrroles (and of the alkylpyrroles generally[2]) has in the past been minimal. We report here the infrared, ultraviolet, and proton magnetic resonance spectra at 60 Mc. of all the simple C-methylpyrroles that have been synthesized or purchased, as well as data for some of their N-methyl derivatives (Tables II and III).

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(16) F. F. Blicke and C. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952), reported 92–94°, whereas H. Oldach, *Ber.*, **20**, 1657 (1887), gave 103–105°.

(17) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952).

(18) (a) This reaction previously had been carried out with liquid ammonia under pressure; see L. A. Brooks and M. Markarian, U. S. Patent 2,417,046; *Chem. Abstr.*, **41**, 3821c (1947). (b) A. W. Johnson and R. Price, *Org. Syn.*, **42**, 92 (1962).

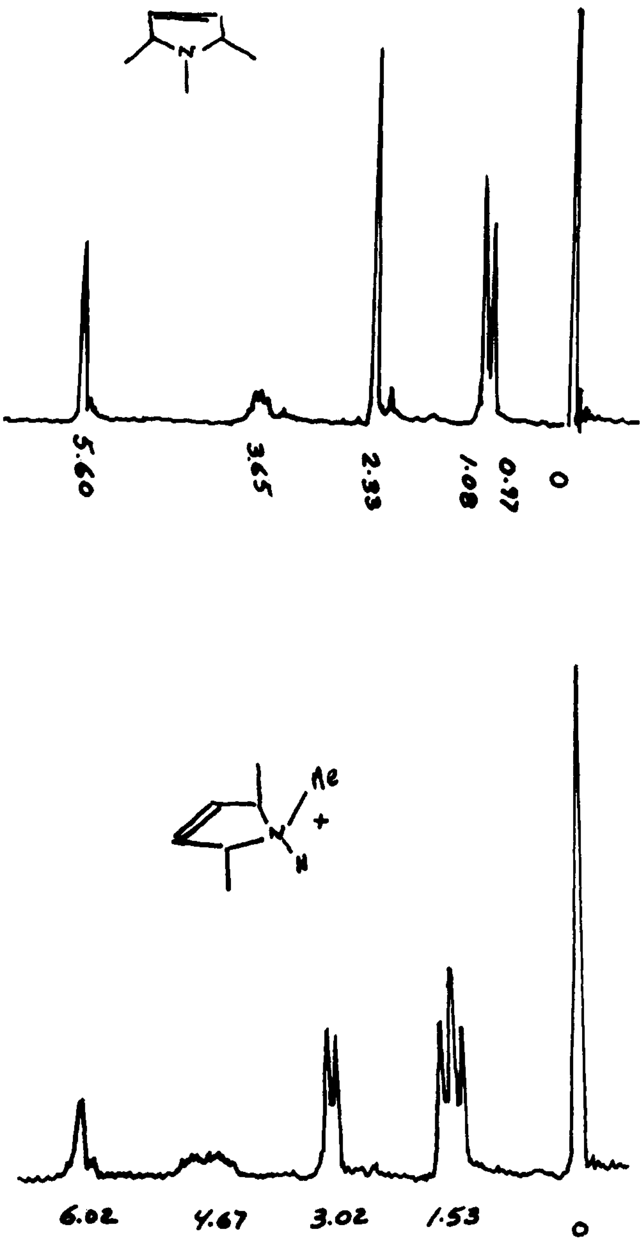

Fig. 1.—Proton magnetic resonance spectra of 1,2,5-trimethyl-$\Delta^3$-pyrroline; values in p.p.m. relative to internal tetramethylsilane; upper, in carbon tetrachloride, lower, in trifluoroacetic acid.

TABLE III

PROTON MAGNETIC RESONANCE SPECTRA OF PYRROLES IN CARBON TETRACHLORIDE

| | Chemical shifts at ring positions indicated[a] | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Pyrrole[d,e] | 7.7 | 6.62 | 6.05 | 6.05 | 6.62 |
| 1-Methyl | (3.60) | 6.37 | 5.92 | 5.92 | 6.37 |
| 2-Methyl[d,e] | 7.2 | (2.16) | 5.72 | 5.89 | 6.36 |
| 3-Methyl | [b] | 6.28 | (2.05) | 5.85 | 6.42 |
| 1,2-Dimethyl | (3.48) | (2.16) | 5.67 | 5.77 | 6.30 |
| 2,3-Dimethyl[e] | 7.1 | (2.02) | (1.96) | 5.82 | 6.28 |
| 2,4-Dimethyl[c,e] | 7.0 | (2.07) | 5.57 | (2.00) | 6.08 |
| 3,4-Dimethyl[c] | [b] | 6.27 | (1.95) | (1.95) | 6.27 |
| 2,5-Dimethyl[e] | 7.1 | (2.13) | 5.57 | 5.57 | (2.13) |
| 1,2,5-Trimethyl | (3.27) | (2.10) | 5.52 | 5.52 | (2.10) |
| 2,3,5-Trimethyl[c] | [b] | (2.02) | (1.87) | 5.42 | (2.08) |
| 2,3,4-Trimethyl[c] | [b] | (2.08) | (1.84) | (1.92) | 6.15 |
| 1,2,3,5-Tetramethyl | (3.28) | (2.05) | (1.89) | 5.41 | (2.10) |
| 2,3,4,5-Tetramethyl[c] | 6.8 | (1.98) | (1.80) | (1.80) | (1.98) |
| Pentamethyl | (3.27) | (2.02) | (1.82) | (1.82) | (2.02) |

[a] Referred in p.p.m. to internal tetramethylsilane with positive sense in direction of decreasing magnetic field. Figures in parentheses denote shifts of methyl group protons. [b] Not measured (all NH peaks are very broad). [c] For reported values at 60 Mc. relative to an internal dioxane reference, see R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959). [d] For values at 40 Mc., see G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, **83**, 5020 (1961); R. Abraham and H. Bernstein, *Can. J. Chem.*, **39**, 905 (1961); also ref. 2. [e] For measurements on pure liquids, see *ibid.*, **37**, 1057 (1959).

From the ultraviolet data it is apparent that the introduction of methyl groups generally causes small bathochromic shifts in the 205-mμ band of pyrrole. Increases in intensity accompany 2-substitution, whereas introduction of a 3-methyl group has the reverse effect. In this connection it should be noted that an erroneous early report of the ultraviolet spectrum of pyrrole in hexane ($\lambda_{max}$ 210, 240 mμ; $\epsilon_{max}$ 15000, 300)[19a] has been quoted by a number of authors without verification[19b,20] and has led to incorrect conclusions about the perturbing effect of methyl substituents,[20] in particular that alkyl substitution generally causes a decrease in intensity of absorption.[20a] Redetermination of the spectrum of purified pyrrole revealed successive bathochromic shifts and increases in $\epsilon_{max}$ in changing from solutions in water to 95% ethanol to *n*-hexane, but even in the last case $\epsilon_{max}$ was only about half the value reported earlier and in the concentration range of our experiments there was no evidence of a a peak at 240 mμ (Table II). Bathochromic shifts accompanying methyl substitution in the pyrrole conjugate acids are much larger than those observed for the free bases. The additivity of substituent effects on the 241 mμ band of pyrrole conjugate acid[1c] and the fact that the absorption maximum of a 3-protonated conjugated acid appears at longer wave lengths than its 2-protonated isomer[1b] have been pointed out in other work from this laboratory.

In the infrared spectra, weak bands assigned to the vinyl C–H appear in the customary place from 3.18 to 3.26 μ and methyl CH appears as a strong band in the region from 3.37–3.46 μ. Neither band is shifted much by ring substitution. In the region of 6.25–6.70 μ appear bands that have been previously assigned to carbon–carbon double bonds of pyrrole.[21] This assignment should be accepted with caution, however, since pyrrolidine and 3-methylpyrrolidine both have bands of medium intensity at 6.38 and 6.44 μ. Almost all the pyrroles studied had bands of weak intensity between 5.9 and 6.0 μ. On the assumption that these were due to carbonyl groups formed by autoxidation, a sample of 2,4-dimethylpyrrole, in which this absorption was particularly strong, was distilled from sodium under a nitrogen atmosphere. The intensity of this band in the distillate was greatly reduced, although it was still visible. As the distillate stood open to the atmosphere during fifteen minutes, the intensity of the band increased greatly. By the next day crystals

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(19) (a) C. Menczel, *Z. Physik. Chem.* (Leipzig), **125**, 161 (1927); (b) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(20) (a) G. H. Cookson, *ibid.*, 2789 (1953); (b) V. Eisner and P. H. Gore, *ibid.*, 922 (1958).

(21) (a) P. Mirone, *Gazz. chim. ital.*, **86**, 165 (1956); (b) V. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

had formed in the red oil.[22] To minimize autoxidation all distillations were carried out under nitrogen and spectral measurements were made as soon as possible on freshly distilled material.

For characterization of pyrroles picrates would be useful solid derivatives, were it not for the tendency of pyrroles to dimerize under acidic conditions.[1] The more highly substituted pyrroles such as the 2,3,4-[4a] and 2,3,5-trimethyl- (this work, Table I) and 2,3,4,5-tetramethyl-[4a] pyrroles form picrates of the parent monomers. 2,3-Dimethylpyrrole[23] yields a picrate of its dimer, which is nevertheless useful as a derivative. 3-Methylpyrrole also formed a product melting sharply at 103–103.5°, but a satisfactory analysis for the picrate of either the monomer or the dimer could not be obtained. No products were obtained from attempts to prepare trinitrobenzene derivatives of the pyrroles in methanol.

In the course of this work we had occasion to carry out reductions of 1,2,5-trimethyl- and 2,3,4,5-tetramethylpyrrole with zinc and hydrochloric acid by the procedure reported for the former.[24] The $\Delta^3$-pyrrolines were the principal products in both cases. The *trans* configuration was assigned to the methyls of 1,2,5-trimethyl-$\Delta^3$-pyrroline on the basis of the n.m.r. spectrum taken in trifluoroacetic acid (Fig. 1). In carbon tetrachloride the C-methyls appear as a doublet centered at 1.03 p.p.m. (tetramethylsilane reference), with a coupling constant of 7 c.p.s., but in the conjugate acid the methyl resonance is a triplet centered at 1.53 p.p.m., indicating that the two methyls are in different environments. The remainder of the spectrum is assigned as follows: doublet at 3.02 p.p.m. ($N-CH_3$); broad multiplet at 4.67 p.p.m. (ring protons at 2- and 5-position); singlet at 6.01 p.p.m. (vinyl protons). The technique of assigning stereochemistry by the use of the n.m.r. spectrum of the conjugate acid of an N-alkylamine may be useful in other cases.[25]

## Experimental[26]

**2,5-Dimethyl-3-formylpyrrole.**—The procedure was similar to that used for the synthesis of pyrrole-2-carboxaldehyde.[6] While holding the temperature at 20–25°, 16.9 g. (0.11 mole) of phosphorus oxychloride was added dropwise with stirring to 10 g. of dimethylformamide in a flask protected from atmospheric moisture. A solution of 2,5-dimethylpyrrole (9.5 g., 0.1 mole) in 2 g. of dimethylformamide was added slowly to the stirred mixture while the temperature was maintained at 20–25°. The mixture was stirred at 50° for 30 min., then poured onto 100 g. of ice. The mixture was made alkaline with 125 ml. of 20% sodium hydroxide and heated to boiling for 1 min. After cooling a brown solid separated and was removed by filtration. The filtrate was extracted with ether, the ether was evaporated, and the residual solid was combined with the brown solid isolated by filtration. Crystallization of the combined solids from acetone yielded 7.6 g. (62%) of pale yellow solid, m.p. 144–144.5° (lit.[27] m.p. 144°).

**3-Formyl-1,2,5-trimethylpyrrole.**—The procedure was similar to and on the same scale as that described previously, but 20 ml. of ethylene dichloride was added to the phosphorus oxychloride–dimethylformamide mixture, followed by 1,2,5-trimethylpyrrole in 5 ml. of ethylene dichloride. The reaction mixture was then heated to 50–60° for 15 min. and finally for 2–3 min. at 85°. After the reaction mixture had cooled to room temperature, 200 ml. of water was added and the mixture was then made alkaline with a solution of 25 g. of sodium hydroxide in 100 ml. of water. The mixture was heated at 85° for 10 min., cooled, and the dichloroethylene layer was separated. The aqueous phase was extracted with two 25-ml. portions of chloroform. The combined chloroform and dichloroethylene solutions were dried over sodium sulfate and the solvents were removed *in vacuo*. The solid residue was crystallized from an acetone–ether mixture, yielding 13 g. (99%) of 3-formyl-1,2,5-trimethylpyrrole, m.p. 96.5–97° (lit.[27] m.p. 96°).

**2,3,4,5-Tetramethylpyrrole.**—This compound was prepared in 74% yield from 3,4-dimethylhexane-2,5-dione[28] and ammonia by the method reported previously for 2,5-dimethylpyrrole.[1b] The product was a white solid, m.p. 110° (lit.[4a] m.p. 112°).

**Reductions with Lithium Aluminum Hydride.**—These reactions were all carried out by essentially the same procedure, the compound to be reduced being added to the stirred slurry of the hydride. The conditions are summarized in Table I. Decomposition of excess hydride was effected by the addition in succession of *n* ml. of water, *n* ml. of 15% sodium hydroxide solution, and 3 *n* ml. of water,[5a] where *n* is the number of grams of hydride originally used. The inorganic solids were removed by filtration, the organic layer was dried over magnesium or sodium sulfate, and the solvents were then removed *in vacuo* and the residue was distilled through a 12-in. spinning-band column.

**V.p.c. Analysis of Methylpyrroles.**—The purity of all methylpyrroles was established by n.m.r. and v.p.c. analysis. With a Perkin-Elmer Model 154-B chromatograph, equipped with an O column, and using helium as the carrier gas at a flow rate of about 80 ml./min., all purified pyrroles showed a single peak of retention time greater than 6 min. at a temperature 15–20° below their boiling points. Under these conditions 2-methyl- and 3-methylpyrrole were easily separated (see section on dehydrogenation of 3-methylpyrrolidine). These isomers could also be identified in their mixtures by infrared spectra,[2] but we found the v.p.c. method more sensitive.

**Dehydrogenation of 3-methylpyrrolidine.**—The procedure was adapted from that used for the dehydrogenation of pyrrolidine.[12] The reaction chamber was a Pyrex tube 34 × 1.3 cm., preceded by a preheater 22 × 1.3 cm. The preheater contained 15 ml. of Berl saddles, while the reaction tube contained 25 ml. of rhodium-alumina catalyst[12] with a 3-ml. layer of Berl saddles above it and a 7-ml. layer beneath it. Charges of 5–10 g. of 3-methylpyrrolidine were dropped slowly into the reaction tube under dry nitrogen at a flow rate of 150 ml./min. Under these conditions the product mixture obtained as analyzed by v.p.c. is given in Table IV.

TABLE IV

PRODUCT MIXTURE OBTAINED AS ANALYZED BY V.P.C.

| | Yields of products[a] | | |
|---|---|---|---|
| Compound | 600° | 500° | 400° |
| 3-Methylpyrrolidine | none | 10% | 30–40% |
| 3-Methylpyrrole | 20% | 40% | 60–70% |
| 2-Methylpyrrole | 75% | 40% | None |
| Higher boiling materials | 5% | Some | Some |

[a] Temperatures are of catalyst bed.

On a Perkin-Elmer O column, column temperature 70°, and flow rate of helium about 80 ml./min., 2-methyl and 3-methylpyrrole had retention times of 12 and 13 min., respectively.

**2,3,4,5-Tetramethyl-$\Delta^3$-pyrroline.**—The procedure was a modification of that described for the reduction of 1,2,5-trimethylpyrrole.[24] Ten grams of tetramethylpyrrole was dissolved in 50 ml. of methanol and 50 g. of zinc powder was added. Then 300 ml. of 10% hydrochloric acid in methanol was added dropwise to the stirred mixture while the temperature was held at 15–20°. Finally, 50 ml. of concentrated hydrochloric acid was added and

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[22] H. Fischer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 217.

[23] O. Piloty and S. J. Thannhauser, *Ann.*, **390**, 201 (1912).

[24] G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

[25] The authors are indebted to Dr. E. B. Whipple for suggesting and carrying out this experiment.

[26] Boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model-21 recording spectrophotometer, equipped with sodium chloride optics. Ultraviolet spectra were determined with a Beckman DK-2 recording spectrophotometer using quartz cuvettes of 1-cm. light path.

[27] E. Ghizi and A. Drusiani, *Atti. accad. sci. ist. Bologna, Classe sci. fis.*, **11**, 14 (1957); *Chem. Abstr.*, **52**, 11818a (1958).

[28] Aldrich Chemical Co., Milwaukee, Wis.

the mixture was stirred for four more hours. Residual zinc was removed by filtration, and the methanol was removed under reduced pressure. The residue was diluted with water, brought to pH 10 with 10% sodium hydroxide solution, and extracted with ether. The combined extracts were dried over potassium carbonate and distilled. The first fraction, b.p. 140–144°, weighed 2 g. and appeared to be the pyrrolidine. A second fraction of 4.5 g. (45%), distilling at 149°, was the $\Delta^3$-pyrroline. The infrared spectrum (pure liquid) had a band at 6.10 $\mu$. The 60-Mc. n.m.r. spectrum in carbon tetrachloride (tetramethylsilane reference) showed a doublet centered at 8.92 p.p.m. with coupling constant of 7 c.p.s., assigned to the 2- and 5-methyls (*cf.* 1,2,5-trimethylpyrrole). A singlet at 8.48 p.p.m. is assigned to the 3- and 4-methyls, and a broad peak at 6.40 p.p.m. is due to the ring protons at the 2- and 5-positions.

The **perchlorate**, recrystallized from methanol and ether, melted at 172°.

*Anal.* Calcd. for $C_8H_{10}ClNO_4$: C, 42.58; H, 7.14; N, 6.20. Found: C, 42.60; H, 7.13; N, 6.46.

**1-Methylpyrrole-2-carboxylic Acid.**—Fifteen grams of 1-methylpyrrole-2-carboxaldehyde was dissolved in a solution of 10 g. of sodium hydroxide in 300 ml. of water, and 20 g. of potassium permanganate was added in three portions to the stirred mixture. The temperature rose to 60–70° and was maintained there for 3–4 hr. The filtrate obtained by removal of the manganese dioxide was cooled to 5° and acidified to pH 2 with 5% hydrochloric acid. The product separated in white needles which were recrystallized from water, yielding 3.4 g. (20%) of pure material, m.p. 134–135° (lit.[29] m.p. 135°).

**1,2-Dimethylpyrrole.**—2-Methylpyrrole (8.19, 0.1 mole) was added dropwise to a stirred mixture of 4.7 g. (0.12 g.-atom) of potassium metal in 200 ml. of anhydrous ether, contained in a flask which was under a positive pressure of nitrogen and which had been previously dried over an open flame while purging with nitrogen. The mixture was refluxed overnight, cooled, and then 30 g. of methyl iodide was added. The resulting solution was refluxed for 4 hr., cooled, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in ether, about 1 g. of potassium metal was added, and the mixture was refluxed for 4 hr. A chaser of 5 ml. of phenyl ether was added and the pyrrole was distilled. The colorless liquid, weighing 6.2 g. (65%), distilled at 74° (65 mm.), and its vapor chromatogram showed a single peak.

**1,2,3,5-Tetramethylpyrrole.**—The procedure was similar to that presented previously for the preparation of 1,2-dimethylpyrrole, but 1,2-dimethoxyethane was used as the solvent, and the second treatment with potassium was not needed. The product, which weighed 17 g. (67% based on 22 g. of 2,3,5-trimethylpyrrole), was a colorless liquid that distilled at 80–81° (16 mm.).

*Anal.* Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 78.11; H, 10.75; N, 11.57.

When more than a 20% excess of potassium was used, the product was contaminated by what appeared from n.m.r. data to be pentamethylpyrrole.

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[29] E. Fischer, *Ber.*, **46**, 2510 (1913).

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# Arrested Deamination in the Fischer Indole Synthesis. The Synthesis of 1,2,3,3a,4,8b-Hexahydropyrrolo[3,4-*b*]indoles with Angular Substitution[1]

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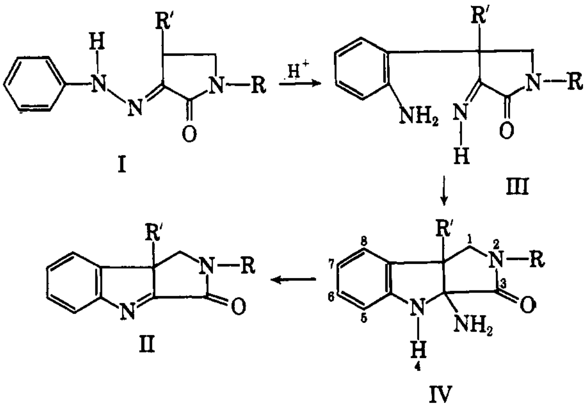
Phenylhydrazones of 1-substituted 4-benzyl-2,3-dioxopyrrolidines (I) rearrange in methanol–hydrochloric acid mixtures to yield 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV). This type of transformation represents a normal Fischer indole synthesis arrested at the point at which ammonia is usually eliminated. The compounds IV were converted into a variety of other products containing the hexahydropyrrolo[3,4-*b*]indole ring system. Thus, it was possible to reduce the lactam carbonyl to a methylene group, to replace the angular 3a-amino function by hydrogen or hydroxyl, to acylate the 4-nitrogen, and to obtain products embodying two or more of such changes. It was shown that compounds of this series resemble alkaloids of the indoline type with respect to ultraviolet spectra and certain color tests.

Compounds in the pyrrolo[3,4-*b*]indole series have recently been made available by application of the Fischer indole synthesis to phenylhydrazones of 2,3-dioxopyrrolidines.[4] In order to make possible a more complete assessment of the potential biological activity of compounds containing this new heterocyclic ring system it was considered of interest to prepare members of the series of the type II, in which an angular substituent and an indolenine rather than an indole nucleus is present. Reduction of such compounds was expected to lead to structures of the type IX, related to the heterocyclic ring system of eserine, but with the position of the nitrogen changed in the outer pyrrolidine ring.

It was anticipated that the compounds II would result from the Fischer indole reaction of phenylhydrazones of 4-substituted 2,3-dioxopyrrolidines (I). When four phenylhydrazones of a series of recently obtained 1-substituted 4-benzyl-2,3-dioxopyrrolidines[5] (I, R′ = benzyl; R = methyl, isopropyl, cyclohexyl, or benzyl) were heated for a short time with methanolic hydrochloric acid, however, rearrangement products which



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[2] National Science Foundation Undergraduate Research Participant, 1961–1962.

[3] National Science Foundation Cooperative Predoctoral Fellow, 1959–1960. This paper is based principally on a thesis submitted by Richard J. Owellen in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, September, 1960.

[4] P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, **25**, 1133 (1960).

[5] P. L. Southwick and E. F. Barnas, *ibid.*, **27**, 98 (1962).