[Contribution from the Department of Chemistry, The Florida State University]

# Pyrroles XIV. Mannich Bases of 2,5-Substituted Pyrroles[1]

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Several pyrroles substituted in the 2- and 5-positions of the pyrrole nucleus were subjected to the Mannich reaction. The resulting bases were shown to be 3-dialkylaminomethyl- and 3,4-bisdialkylaminomethyl derivatives of pyrrole. Their utility as alkylating agents was investigated.

Previous work has shown that the *alpha* hydrogen atoms of pyrrole[3] and substituted pyrroles[4] are sufficiently reactive to participate in the Mannich reaction. The resulting Mannich bases resemble gramine in their ability to alkylate a variety of substances containing active hydrogen[5–8] and have become valuable intermediates in the synthesis of new pyrrole derivatives.

It therefore was of interest to study the susceptibility of the *beta* hydrogen atoms of the pyrrole nucleus to the Mannich reaction. When this investigation was begun, two such Mannich bases were recorded in the literature. Fischer and Nenitzescu[9] had obtained what was claimed to be 2,5-dimethyl-3-carbethoxy-4-diethylaminomethylpyrrole, and Bachman and Heisey[3a] had described a 3-piperidinomethyl-2,5-dimethylpyrrole which resulted from the reaction between 2,5-dimethylpyrrole, piperidine, and formaldehyde. No proof of structure was given in either instance, although it is conceivable that substitution might have taken place on the pyrrole nitrogen or on one of the methyl groups, nor was the utility of these substances as alkylating agents investigated. More recently, Treibs and Fritz[10] have reported the preparation of several 3-substituted Mannich bases and one, 2-methyl-5-carbethoxy-3-piperidinomethyl-4-$\beta$-carboxyethylpyrrole, has been used as an intermediate in the synthesis of uroporphyrin III.[11]

2,5-Dimethylpyrrole condensed readily with dimethylamine hydrochloride and formaldehyde to give a mono- and a disubstitution product, depending on the relative quantities of pyrrole derivative, base, and aldehyde. Properties of these and other Mannich bases are listed in Tables I and II. The structures of these substances were established unequivocally as 2,5-dimethyl-3-dimethylaminomethylpyrrole (I) and 2,5-dimethyl-3,4-bisdimethylaminomethylpyrrole (II) by means of the following: (a) presence of an —NH band in the infrared spectra of the Mannich bases which indicates that substitution had not taken place on the pyrrole nitrogen atom; (b) catalytic hydrogenolysis[4d] of I and II which led to 2,3,5-trimethylpyrrole and, respectively, 2,3,4,5-tetramethylpyrrole. The latter reaction, coupled with the excellent yields achieved in the Mannich reaction, constitutes a convenient preparative method for polyalkylpyrroles.

After the completion of this part of our work there appeared a paper[12] in which a product resulting from the reaction between 2,5-dimethylpyrrole, dimethylamine hydrochloride, and formaldehyde was assigned the structure 2,5-dimethyl-1-dimethylaminomethylpyrrole without experimental proof. The properties of this material roughly correspond to those of I and there can be little question that the Indian workers actually obtained 2,5-dimethyl-3-dimethylaminomethylpyrrole. In contrast to the indole series where the order of reactivity in the Mannich reaction is $\beta > N > \alpha$,[13] the order of substitution in the pyrrole series is therefore $\alpha > \beta$ the nitrogen apparently not being substituted at all.[14]

1,2,5-Trimethylpyrrole and 1-phenyl-2,5-dimethylpyrrole similarly formed mono- and di-Mannich bases although the yields were somewhat lower (see Table I). The facile formation of a disubstitution product from 1-phenyl-2,5-dimethylpyrrole

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[1] Paper XIII, W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958). This work was supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-436.

[2] Abstracted from the M.S. thesis of Robert L. Settine, August 1958.

[3] (a) G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, **68**, 2496 (1946); (b) W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **69**, 1698 (1947); (c) W. J. Burke and G. N. Hammer, *J. Am. Chem. Soc.*, **76**, 1294 (1954).

[4] (a) W. Herz and J. L. Rogers, *J. Am. Chem. Soc.*, **73**, 4291 (1951); (b) U. Eisner and R. R. Linstead, *J. Chem. Soc.*, 1655 (1956); (c) U. Eisner, A. Lichtarowicz, and R. R. Linstead, *J. Chem. Soc.*, 733 (1957); (d) A. Treibs and R. Zinsmeister, *Ber.*, **90**, 87 (1957).

[5] W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

[6] N. F. Albertson, *J. Am. Chem. Soc.*, **70**, 669 (1948).

[7] N. J. Leonard and E. H. Burk, *J. Am. Chem. Soc.*, **72**, 2543 (1950).

[8] W. Kutscher and O. Klamerth, *Ber.*, **86**, 352 (1953).

[9] H. Fischer and C. Nenitzescu, *Ann.*, **443**, 113 (1925).

[10] A. Treibs and G. Fritz, *Ann.*, **611**, 163 (1958).

[11] A. Treibs and W. Ott, *Naturwissenschaften*, **40**, 476 (1953); *Ann.*, **615**, 137 (1958).

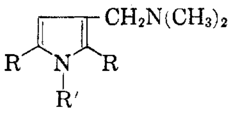
[12] S. Swaminathan, S. Ranginathan, and S. Sulochana, *J. Org. Chem.*, **23**, 707 (1958).

[13] S. Swaminathan and S. Ranginathan, *J. Org. Chem.*, **22**, 70 (1957).

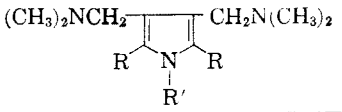
[14] This was established by using a large excess of dimethylamine hydrochloride and formaldehyde which did not result in further substitution on the pyrrole nitrogen atom.

TABLE I

COMPOUNDS OF TYPE (I)



AND (II)



| R | R′ | Yield, % | M.P. or B.P., °C. | Mm. | Type | Method | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | 92 | 99–100 | | I | A | $C_9H_{16}N_2$ | 71.00 | 10.59 | 18.4 | 71.25 | 10.31 | 18.1[a] |
| $CH_3$ | Phenyl | 49.5 | 130–131 | 1 | I | B | $C_{15}H_{20}N_2$[b] | 78.90 | 8.83 | 12.3 | 78.40 | 8.72 | 11.7[c] |
| $CH_3$ | $CH_3$ | 69 | 73–74 | 1 | I | B | $C_{10}H_{18}N_2$[d] | 72.24 | 10.91 | 16.9 | 72.05 | 10.89 | 17.3[e] |
| Phenyl | H | 73[f] | 124–125 | | I | B | $C_{19}H_{20}N_2$ | 82.57 | 7.29 | 10.14 | 81.97 | 7.29 | 10.18 |
| $CH_3$ | H | 90 | 144–145 | | II | A | $C_{12}H_{23}N_3$ | 68.99 | 11.01 | 20.1 | 68.93 | 10.89 | 19.9[g] |
| $CH_3$ | Phenyl | 61 | 150 | 1 | II | B | $C_{18}H_{27}N_3$ | 75.74 | 9.54 | 14.7 | 76.33 | 9.57 | 13.9[h] |
| $CH_3$ | $CH_3$ | 72.5 | 96–97 | 0.3 | II | B | $C_{13}H_{25}N_3$ | 69.90 | 11.28 | 18.8 | 70.00 | 11.23 | 18.2 |

[a] *Methiodide*, m.p. 130° (dec.). Calcd. for $C_{10}H_{19}IN_2$: C, 40.82; H, 6.51; N, 9.52. Found: C, 40.55; H, 6.69; N, 9.47. [b] $n_D^{25}$ 1.5500. [c] *Methiodide*, m.p. 211–212° (dec.). Calcd. for $C_{16}H_{23}IN_2$: C, 51.90; H, 6.26. Found: C, 52.39; H, 6.45. [d] $n_D^{25}$ 1.4951. [e] *Methiodide*, m.p. 140° (dec.). Calcd. for $C_{11}H_{21}IN_2$: C, 42.86; H, 6.87; N, 9.09. Found: C, 42.46; H, 6.74; N, 9.17. [f] Yield raised to 97.5% with two equivalents of dimethylamine hydrochloride and formaldehyde. [g] *Methiodide*, m.p. 139–140°. Calcd. for $C_{14}H_{29}I_2N_3$: C, 34.19; H, 5.89; N, 8.59. Found: C, 34.53; H, 5.90; N, 8.61. [h] *Methiodide*, m.p. 100° (dec.). Calcd. for $C_{20}H_{33}I_2N_3$: C, 42.19; H, 5.84; N, 7.28. Found: C, 41.73. H, 6.58; N, 7.04.

TABLE II

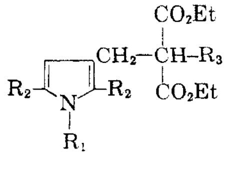
PICRATES OF MANNICH BASES

| R | R′ | Type | M.P., °C. | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | I | 117–118 | $C_{15}H_{19}N_5O_7$ | 47.24 | 5.02 | 18.4 | 46.94 | 5.38 | 18.7 |
| $CH_3$ | Phenyl | I | 137–138 | $C_{21}H_{23}N_5O_7$ | 55.14 | 5.07 | 14.7 | 54.64 | 4.79 | 14.7 |
| $CH_3$ | $CH_3$ | I | 137–138 (dec.) | $C_{16}H_{21}N_5O_7$ | 48.60 | 5.35 | 17.7 | 48.65 | 5.32 | 17.9 |
| Phenyl | H | I | 179–180 | $C_{25}H_{23}N_5O_7$ | 59.64 | 4.20 | 13.9 | 59.77 | 4.75 | 13.5 |
| $CH_3$ | H | II | 139–140 | $C_{24}H_{29}N_9O_{14}$ | 43.18 | 4.38 | 18.9 | 42.70 | 4.21 | 18.8 |
| $CH_3$ | Phenyl | II | 200–201 (dec.) | $C_{30}H_{33}N_9O_{14}$ | 48.95 | 4.85 | 16.9 | 49.12 | 4.40 | 16.5 |
| $CH_3$ | $CH_3$ | II | 181–182 (dec.) | $C_{25}H_{31}N_9O_{14}$ | 44.05 | 4.58 | 18.5 | 43.91 | 4.55 | 18.6 |

is in contrast to earlier observations with 1-phenylpyrrole[4a] where even under forcing conditions only one dialkylaminomethyl group could be introduced and the yield of monosubstituted product was considerably lower. One of two factors may account for this observation: (1) the two methyl groups may offset the deactivating effect of the phenyl group; (2) the phenyl group is forced out of the plane of the pyrrole nucleus by the two neighboring methyl groups and thus cannot affect the transition state. On the other hand, 2,5-diphenylpyrrole only formed a mono-Mannich base although the yield was improved considerably by the use of excess reagent.

The suitability of the 3-substituted pyrrole Mannich bases for alkylation reactions remained to be explored. It was also of interest to contrast the nitrogen-substituted bases which would be able to react only by the substitution mechanism with the nitrogen-unsubstituted compounds which might react by either the elimination-addition or substitution[15] mechanism.

In accordance with expectations, 3-dimethylaminomethyl-1-methyl- and 1-phenyl-2,5-dimethylpyrroles could not be brought into reaction with diethyl acetamidomalonate and diethyl malonate by refluxing with toluene in the presence of catalytic amounts of sodium hydroxide (elimination-addition conditions) while alkylations using I proceeded relatively smoothly. However, as has been observed previously in the pyrrole series[4a,5a,16] with compounds such as I which are capable of reacting by the elimination-addition mechanism, yields were much improved when I was quaternized before being used as an alkylating agent (substitution conditions), III and IV being formed in 95%, resp. 85% yield. Similarly, when the *N*-



III. $R_1 = H, R_2 = CH_3, R_3 = NH—\overset{\overset{O}{\|}}{C}—CH_3$
IV. $R_1 = H, R_2 = CH_3, R_3 = NHCHO$
V. $R_1 = H, R_2 = \text{phenyl}, R_3 = NHCHO$

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(15) For a discussion of these terms, as well as of the general problem of alkylation by means of indole and pyrrole Mannich bases, see the following reviews: (a) J. H. Brewster and E. L. Eliel, *Organic Reactions*, VII, 99 (1953); (b) H. Hellmann, *Angew. Chem.*, **65**, 473 (1953).

(16) W. Kutscher and O. Klamerth, *Ber.*, **86**, 352 (1953)

substituted Mannich bases were quaternized, the alkylation of malonic ester could be accomplished satisfactorily. These results furnish further evidence for the correctness of current views concerning alkylation by means of indole and pyrrole Mannich bases.

In the alkylation of 1-methylgramine methiodide with hot aqueous sodium cyanide, two products were isolated.[17] The first was the expected product, 1-methyl-3-indoleacetonitrile, and the second, in much smaller yield, was 1,3-dimethyl-2-cyanoindole, presumably formed by an allylic rearrangement during the alkylation process. Under comparable conditions, the methiodides of 1,2,5-trimethyl- and 1-phenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole furnished volatile nitrile fractions in 26% and 45% yield, respectively. The presence of an unconjugated (2250 cm.$^{-1}$) nitrile band in the infrared spectra of these products suggested that no rearrangement had taken place. This was confirmed in the case of the 1,2,5-trimethyl derivative by hydrolysis to 1,2,5-trimethyl-3-pyrroleacetic acid which was synthesized independently from ethyl diazoacetate and 1,2,5-trimethylpyrrole.[18]

Hydrolysis of III was expected to furnish 2,5-dimethyl-3-pyrrolealanine which was of interest as a potential metabolite antagonist.[5a] The product which showed some activity against *E. coli* gave a positive ninhydrin test and appeared to be homogeneous on paper chromatography, but analysis indicated a considerable degree of contamination, as was observed previously in analogous cases.[1,4a,5a,19] Hydrolysis of IV yielded 2,5-diphenyl-3-pyrrolealanine which was inactive against *S. cervisiae*.

## EXPERIMENTAL[20]

*Mannich reactions of substituted pyrroles.* The following general procedures were used for the preparation of the Mannich bases listed in Table I.

*Method A:* A solution of 85 g. (1.05 mole) of dimethylamine hydrochloride in 79 g. (1.05 mole) of 40% formalin was added to 100 g. of 2,5-dimethylpyrrole in a three-necked flask fitted with stirrer, reflux condenser, nitrogen inlet tube, and dropping funnel at such a rate that the temperature did not exceed 60°. The mixture was diluted with water, extracted with ether, and the aqueous layer poured into 200 ml. of 25% sodium hydroxide solution. An oil separated which crystallized on standing and was recrystallized from ligroin (60–110°), yield 148 g. (92%), m.p. 99–100°.

For disubstitution, the quantities of dimethylamine hydrochloride and formalin were doubled.

*Method B:* A mixture of 20 ml. of a 33% aqueous solution of dimethylamine and 20 ml. of acetic acid was allowed to come to room temperature and mixed with 8.5 ml. of 40% formalin. The resulting solution was added dropwise to 17.1 g. (0.08 mole) of 1-phenyl-2,5-dimethylpyrrole in a nitrogen atmosphere, with stirring, and worked up as described previously. The oil which separated on pouring into alkali was extracted with ether, washed, and distilled *in vacuo*, b.p. 140–150° (3 mm.), yield 11.1 g. (49.5%).

For disubstitution, two moles of aqueous dimethylamine solution and two moles of formalin in sufficient acetic acid to ensure a homogeneous reaction mixture was added to 0.8 mole of pyrrole derivative.

*Picrates* (Table II) of the Mannich bases were precipitated by mixing alcoholic solutions of the base and picric acid and were recrystallized from ethanol.

*Methiodides* were prepared by adding the Mannich base, dissolved in a minimum of absolute ethanol, to 10% excess methyl iodide with vigorous stirring at ice bath temperature. The products were recrystallized from absolute ethanol.

*Hydrogenolysis of Mannich bases.* A small high-pressure bomb containing 20 g. of II in 100 ml. of ethanol and 4 g. of Raney nickel (W-2) was charged with hydrogen to a pressure of 80–100 atm. and heated at 100° for 48 hr. The solvent was removed *in vacuo* and the residue steam-distilled. The distillate contained 7.7 g. (72%) of 2,3,4,5-tetramethylpyrrole, m.p. 107–108°, lit.[4d] 107–108°.

In a similar manner, hydrogenolysis of 20 g. of I at 80–90° for 8 hr. furnished 1.5 g. of 2,3,5-trimethylpyrrole, b.p. 79–80° (15 mm.), lit.[21] 79–80° (15 mm.), and 7.5 g. of unreduced starting material. The yield of trimethylpyrrole could undoubtedly be improved by lengthening the reaction period.

*Diethyl 2,5-dimethyl-3-pyrrolemethyl-α-acetamidomalonate* (III). In a 300-ml. flask fitted with dropping funnel, condenser, and nitrogen inlet tube was placed 100 ml. of absolute ethanol and 1.72 g. of clean sodium. After the sodium had dissolved, 16.2 g. of diethyl acetamidomalonate and 11.5 g. of I were added. While cooling in an ice bath, 15.8 g. of dimethyl sulfate was added dropwise at such a rate that the temperature did not exceed 35°. Stirring was continued overnight, the solvent was removed at reduced pressure, the residue diluted with water, and chilled. The solid, wt. 18.4 g. (74%), m.p. 173–175°, was recrystallized from ethanol-water to a constant m.p. of 176–177°.

*Anal.* Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.24: H, 7.46; N, 8.64. Found: C, 59.69; H, 7.45; N, 8.38.

Reaction of 26 g. of I with 32.4 g. of diethyl acetamidomalonate in 300 ml. of toluene containing 1 g. of powdered sodium hydroxide, until the evolution of basic gases ceased, furnished 24 g. (45%) of the product, m.p. 175–177°.

*Diethyl 2,5-dimethyl-3-pyrrolemethyl-α-formamidomalonate.* Condensation of 20.3 g. of diethyl formamidomalonate and 11.5 g. of I in ethanol by quaternization *in situ* as described in the previous preparation yielded 19.2 g. (86%) of product, m.p. 137–138.5°.

*Anal.* Calcd. for $C_{12}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.24; H, 7.01; N, 9.20.

Hydrolysis of this material (6 g.) with 50 ml. of 25% sodium hydroxide solution for 2.5 hr., cooling, acidification to *p*H 6, filtering, acidification of the filtrate to *p*H 5, scratching to induce crystallization and chilling, yielded 3.3 g. of material, m.p. 280° (dec.), which gave a positive ninhydrin test. Several reprecipitations of this material and washing with ice water, ethanol, and ether gave a sample which gave only one spot on paper chromatography and inhibited *E. coli* at a level of 1 ml./ml. The analysis indicated the presence of inorganic contaminants which could not be removed by further crystallization or reprecipitation.

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[17] H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948).

[18] In view of the relatively low yields and the formation of undistillable noncrystallizable residues, presumably amides, which evolved ammonia on further treatment with base, the presence of a small amount of rearrangement product cannot be excluded with certainty, however.

[19] H. Behringer and H. Taul, *Ber.*, **90**, 1398 (1957).

[20] Melting points and boiling points are uncorrected. Analyses were carried out by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were run by Miss M. T. Esquivel on a Perkin-Elmer Model 21 double-beam recording spectrometer.

[21] C. D. Nenitzescu and E. Solomonica, *Ber.*, **64**, 1924 (1931).

*Diethyl 2,5-dimethyl-3-pyrrolemethyl malonate.* Alkylation of 50 g. of diethyl malonate with 31.5 g. of I by the quaternization procedure yielded 35.5 g. (78.5%) of product, b.p. 173–175° (2 mm.). The analytical sample boiled at 152° (0.3 mm.).

*Anal.* Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.25; H, 7.86; N, 5.21.

*Diethyl 2,5-diphenyl-3-pyrrolemethyl-α-formamidomalonate.* Reaction of 20.8 g. of 2,5-diphenyl-3-dimethylaminomethylpyrrole and 20.3 g. of diethyl formamidomalonate by the *in situ* quaternization method resulted in 31.05 g. (94.5%) of a colorless solid, m.p. 163–164°. The analytical sample, after recrystallization from ethanol-water, melted at 164–165°.

*Anal.* Calcd. for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.90; H, 6.12; N, 6.05.

*2,5-Diphenyl-3-pyrrolealanine.* A mixture of 5 g. of the preceding, 10 g. of potassium hydroxide, and 50 ml. of 80% ethanol was refluxed overnight in a stainless steel beaker fitted with cover and reflux condenser. The cooled solution was acidified to *p*H 5; the resulting solid, wt. 1.5 g. (42%), m.p. 217–218° (dec.), gave a positive ninhydrin test. It was purified repeatedly by dissolving in dilute base, reprecipitating with dilute acid, and washing with water, ether, and ethanol.

*Anal.* Calcd. for $C_{19}H_{17}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.31; N, 5.40; N, 8.71.

*Diethyl 1-phenyl-2,5-dimethyl-3-pyrrolemethyl malonate.* To 64 g. of diethyl malonate in which 1.84 g. of sodium had been dissolved was added 26 g. of the methiodide of 1-phenyl-2,5-dimethylaminomethylpyrrole. The solution was heated at 120°, with stirring, for 6 hr. in a nitrogen atmosphere until the evolution of basic gases had ceased. Water was added and the mixture was extracted with ether. Distillation gave 23.6 g. of malonic ester and 11.4 g. (48%) of product, b.p. 194–196° (0.6 mm.). The analytical sample boiled at 164–165° (0.1 mm.), $n_D^{25}$ 1.5230.

*Anal.* Calcd. for $C_{20}H_{25}NO_4$: C, 69.90; H, 11.28; N, 18.82. Found: C, 70.00; H, 11.23; N, 18.20.

*Diethyl 1,2,5-trimethyl-3-pyrrolemethylmalonate.* By the above procedure there was obtained, after 24 hr., 6.8 g. (36%) of a clear liquid, b.p. 145–146° (0.9 mm.), $n_D^{25}$ 1.4670.

*Anal.* Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.80; H, 7.95; N, 4.87.

*1,2,5-Trimethyl-3-pyrroleacetonitrile.* In a 500-ml. three-necked flask fitted with nitrogen inlet and condenser was heated, with stirring, 55 g. of the methiodide of 1,2,5-trimethyl-3-dimethylaminomethylpyrrole, 30 g. of sodium cyanide, and 200 ml. of water until the evolution of basic gas (identified as trimethylamine) had ceased. The solution was extracted with ether and the dried extract distilled *in vacuo*, yield 5.5 g. (26%), b.p. 135–137° (1.5 mm.). The analytical sample boiled at 90° (0.2 mm.), $n_D^{25}$ 1.1527, nitrile band at 2250 cm.$^{-1}$ The pot residue consisted of a tarry solid which liberated ammonia on treatment with base and probably contained some amide, due to partial hydrolysis of the nitrile.

*Anal.* Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.9. Found: C, 72.78; H, 8.32; N, 18.7.

*1,2,5-Trimethyl-3-pyrroleacetic acid.* (*A.*) A mixture of 5 g. of the preceding nitrile, 5 g. of potassium hydroxide, and 50 ml. of 80% ethanol was refluxed for 8 hr., diluted with water, and poured over crushed ice containing 10 ml. of concentrated hydrochloric acid. The oil which separated was taken up in ether. Removal of ether furnished 3.2 g. (82%) of a solid, m.p. 117–118°. The analytical sample, recrystallized from petroleum ether (b.p. 60–110°) melted at 120–121°.

*Anal.* Calcd. for $C_9H_{13}NO_2$: C, 64.65; N, 7.84; N, 8.38. Found: C, 64.72; H, 8.09; N, 8.16.

(*B.*) To a 300-ml. flask fitted with nitrogen inlet tube, condenser, stirrer, and dropping funnel and containing 90 g. of 1,2,5-trimethylpyrrole and 4 g. of powdered copper was added dropwise, with stirring and slight warming 48 g. of ethyl diazoacetate. After completion of the exothermic reaction, stirring was continued for 3 hr., the copper was removed, and the filtrate distilled at reduced pressure. This resulted in recovery of 72.5 g. of 1,2,5-trimethylpyrrole, b.p. 70–72° (22 mm.), and isolation of 18.8 g. (59%) of the desired ethyl 1,2,5-trimethyl-3-pyrroleacetate, b.p. 124–125° (5 mm.). The analytical sample boiled at 90–91° (0.1 mm.), $n_D^{27}$ 1.4919.

*Anal.* Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.57; H, 8.70; N, 7.27.

Hydrolysis of the ester with 80% aqueous alcoholic alkali furnished 2.76 g. (63%) of a solid m.p. 117–120° which on recrystallization melted at 120–121° and did not depress the m.p. of the substance obtained by hydrolysis of the nitrile.

*1-Phenyl-2,5-dimethyl-3-pyrroleacetonitrile.* Alkylation of 30 g. of sodium cyanide with 40 g. of the methiodide of 1-phenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole in the manner described for the 1-methyl analog yielded 9 g. (45%) of a fraction, b.p. 144–145° (0.6 mm.), $n_D^{25}$ 1.5246, nitrile band at 2250 cm.$^{-1}$

*Anal.* Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.41; H, 7.07; N, 13.2.

*1-Phenyl-2,5-dimethyl-3-pyrroleacetic acid.* On saponification of 3 g. of the preceding nitrile there was obtained 2.5 g. (48%) of an acid, m.p. 151–152° after recrystallization from petroleum ether (b.p. 60–110°).

*Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.53; H, 6.50; N, 6.46.

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TALLAHASSEE, FLA.