trated to a sirup under reduced pressure and the residue of sirup was treated with 150 ml. of 1.0*M* methanolic potassium hydroxide. After standing for 2 hr. at room temperature, the mixture was diluted with 400 ml. of 10% aqueous saline solution and the Van Urk positive material was extracted with ethylene dichloride. The residue from the extract, after conversion to the acid maleate, yielded 0.30 g. of lysergic acid anilide acid maleate. A portion of the combined crops of product was recrystallized from methanol, yielding fine colorless needles; m.p. 200° (dec.); $[\alpha]_D^{25}$ +43.8° (*c*, 0.5 in ethanol).

Anal. Calcd. for $C_{22}H_{21}N_3O.C_4H_4O_4$: C, 67.96; H, 5.48; N, 9.15. Found: C, 68.34; H, 5.76; N, 9.11.

Ethyl +-lysergate. Potassium lysergate (3.0 g., 9.25 mmoles) was dissolved in 10 ml. of dry dimethylformamide. The solution was chilled and then 1.1 g. of ethyl chloroformate (10 mmol.) was added. The mixture was kept cold for 30 min. when 0.90 g. of morpholine (10.3 mmol.) was added. After 30 min. longer, the cold mixture was added to 50 ml. of ice water, causing a yellow, unstable solid to separate. The solid was collected in chloroform and dried with anhydrous magnesium sulfate. After evaporating the chloroform, the residue of brown sirup was dissolved in a few milliliters of methanol. The solution was then acidified with maleic acid, treated to turbidity with ether, and refrigerated for several days. The product, ethyl +-lysergate acid maleate, was obtained in the form of fine, yellow needles, which were collected, washed free of tarry material with methanol-ether solvent mixture (1:1), and dried. The needles weighed 0.78 g., m.p. 155–160° (dec.). Recrystallization from methanol and ether gave massive prisms, faintly yellow in color, m.p. 155–157° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_2O_2.C_4H_4O_4$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.19; H, 5.84; N, 6.92.

Ergonovine maleate preparation via the methanesulfonic acid anhydride. Lysergic acid monohydrate (1.43 g., 5.0 mmol.) was suspended in 25 ml. of dry dimethylformamide. The mixture was chilled to 0° and a cold solution of methanesulfonic acid anhydride in dry dimethylformamide (31.4 ml. of 0.35 molar solution) was added. The lysergic acid dissolved and after 30 min. in the cold, 2.2 g. of L-2-amino-1-propanol (20 mmol.) was added. The mixture was kept cold for 1 hr. and then worked up for ergonovine in the usual manner. The yield of ergonovine maleate was 0.55 g.

Acknowledgment. I wish to thank Dr. A. L. Kranzfelder and Dr. G. H. Svoboda for many helpful discussions during the course of this work. Also, appreciation is due Mr. H. L. Bird for paper chromatographic analyses, Mr. W. L. Brown for microanalyses, Dr. H. A. Rose for X-ray diffraction data, and Dr. H. E. Boaz for infrared spectra and microtitration data.

INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

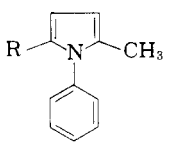
Aldehydes Derived from 1,2,5-Trisubstituted Pyrroles

RICHARD RIPS AND N. P. BUU-HOÏ

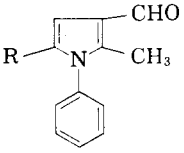
(*Received September 20, 1958*)

The formylation of 1-phenyl-2,5-dimethylpyrrole and 1,2-diphenyl-5-methylpyrrole was effected by means of dimethylformamide and phosphorus oxychloride, to give the corresponding monoaldehydes; 1-phenyl-2,3,5-trimethylpyrrole and 1,2-diphenyl-4,5-dimethylpyrrole were prepared by reduction of these aldehydes, and were also successfully formylated. A dialdehyde was also obtained from 1-phenyl-2,5-dimethylpyrrole.

In the framework of a general study on the chemical and pharmacological properties of substituted *N*-arylpyrroles,[1] we have investigated the behavior of 1-phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II) toward dimethylformamide in the presence of phosphorus oxychloride. The formylation of a large number of derivatives of pyrrole had already been performed and the nucleus found to be highly reactive in that respect,[2] but *N*-arylpyrroles had not yet been investigated.

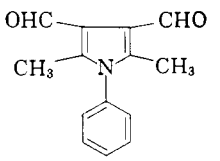


I, R = CH_3
II, R = C_6H_5

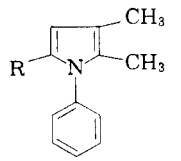


III, R = CH_3
IV, R = C_6H_5

Both pyrroles I and II readily underwent formylation to give 1-phenyl-2,5-dimethylpyrrole-3-aldehyde (III) and 1,2-diphenyl-5-methylpyrrole-4-aldehyde (IV) respectively, the best results being obtained when a diluent such as toluene was used for the reaction. In the case of 1-phenyl-2,5-dimethylpyrrole, small amounts of the corresponding *dialdehyde* (V) could also be isolated. The fact that 1,2-diphenyl-5-methylpyrrole, unlike I, gave no dialdehyde, points to a deactivating influence on the 3-position exerted by the 2-phenyl radical, and this effect justifies the assignment of structure IV to the formylation product of II. Wolff-Kishner reduction of aldehydes III and IV using Huang-



V

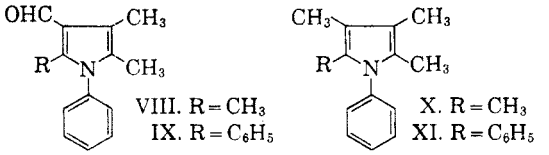


VI, R = CH_3
VII, R = C_6H_5

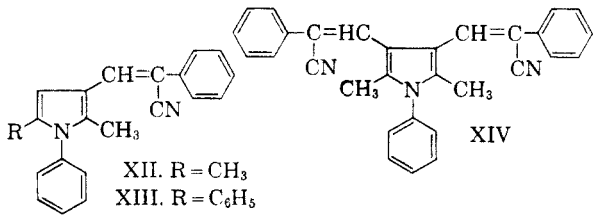
(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press.

(2) *Cf.* H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 145.

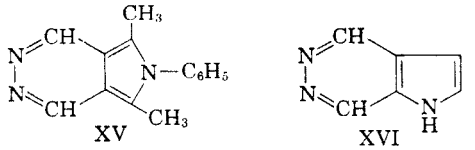
Minlon's technique,[3] furnished 1-phenyl-2,3,5-trimethylpyrrole (VI) and 1,2-diphenyl-4,5-dimethylpyrrole (VII) in excellent yields, and this reaction sequence constitutes a convenient method for the preparation of such substituted 3-methylpyrroles. Formylation of these two reduction products showed a remarkable difference in their respective reactivity, 1-phenyl-2,3,5-trimethylpyrrole giving aldehyde VIII in the usual way, whilst 1,2-diphenyl-4,5-dimethylpyrrole gave aldehyde IX only when drastic experimental conditions were adopted. The relative inertia of the 3-position in the molecule of VII is further proof of the deactivating influence of the 2-phenyl substituent. Wolff-Kishner reduction was successful in both cases, and furnished the completely substituted 1-phenyl-2,3,4,5-tetramethylpyrrole (X) (this same compound was obtained by similar reduction of dialdehyde V) and 1,2-diphenyl-3,4,5-trimethylpyrrole (XI) respectively.



The various monoaldehydes described gave condensation products with the usual reagents for the aldehyde group (semicarbazide, hydroxylamine, phenylhydrazine). A difference was observed, however, between the aldehydes having a free *ortho* position and the others, in their behavior toward benzyl cyanide in the presence of sodium hydroxide,[4] the former (III and IV) giving the corresponding acrylonitriles XII and XIII, whereas the latter (VIII and IX) failed to react. On the other hand, the dialdehyde V reacted with 2 moles of



benzyl cyanide under similar conditions, to give the *bis*-acrylonitrile (XIV). With hydrazine hydrate, it gave the cyclic azine (XV), which is derived from 5,6-diazaisoindole, a heterocyclic nucleus unknown hitherto although several derivatives of the isomeric 5,6-diazaindole (XVI) have already been reported in the literature.[5] This azine belongs to a group of compounds of biological interest as potential antagonists of purine bases.



(3) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(4) For similar condensations with other nitrogen heterocyclic aldehydes, see N. P. Buu-Hoï, R. Huls, and N. D. Xuong, *J. Org. Chem.*, **20**, 1407 (1955); R. Castle and W. Seese, *J. Org. Chem.*, **20**, 987 (1955).

EXPERIMENTAL

Preparation of intermediates. 1-Phenyl-2,5-dimethylpyrrole and 1,2-diphenyl-5-methylpyrrole were prepared by Knorr-Paal condensation of aniline with hexane-2,5-dione and phenacylacetone respectively[6]; the condensation products were purified by vacuum-distillation, followed by recrystallization from cyclohexane.

1-Phenyl-2,5-dimethylpyrrole-3-aldehyde (III). To a well stirred solution of 25 g. (0.146 mole) of 1-phenyl-2,5-dimethylpyrrole and 16 g. (1.5 mole) of dimethylformamide in 100 ml. of dry toluene, 27 g. (1.2 moles) of phosphorus oxychloride was added in small portions. The mixture was heated on a boiling water bath for 6 hr., and then shaken for 20 min. with 300 ml. of saturated aqueous sodium acetate. The reaction product was taken up in toluene, the toluene solution washed with 10% aqueous sodium carbonate, then with water, dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. Yield: 21 g. (73%) of an aldehyde, b.p. 190°/12 mm., crystallizing in colorless plates, m.p. 92°, from aqueous methanol. Brooker and Sprague[7] obtained this compound in 25% yield by using formamide and phosphorus oxychloride in ether medium, and gave m.p. 89–90°.

The corresponding *semicarbazone* crystallized from ethanol in colorless needles, m.p. 294°.

Anal. Calcd. for $C_{14}H_{16}N_4O$: N, 21.9. Found: N, 22.0. The *oxime* crystallized from ethanol in shiny colorless prisms, m.p. 210°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: N, 13.1. Found: N, 13.3.

1-Phenyl-2,5-dimethylpyrrole-3,4-dialdehyde (V). This dialdehyde was obtained by recrystallization from ethanol of the residue from the distillation of the foregoing monoaldehyde, the best yield (13%) being recorded when dimethylformamide was used in large excess (3 moles); it formed fine colorless needles, m.p. 203°, giving a yellow halochromy with sulfuric acid.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8. Found: C, 74.0; H, 6.0.

1,3-Dimethyl-2-phenyl-5,6-diazaisoindole (XV). A solution of 1 g. of the foregoing dialdehyde and 1 ml. of hydrazine hydrate in ethanol was refluxed for 2 hr., and the precipitate formed on cooling was recrystallized from aqueous methanol; yield: 0.9 g. of shiny colorless prisms, m.p. 288°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.3; H, 5.9; N, 18.8. Found: C, 75.2; H, 5.9; N, 19.0.

1-Phenyl-2,3,5-trimethylpyrrole (VI). A solution of 8 g. of aldehyde III and 3 g. of 95% hydrazine hydrate in 200 ml. of diethylene glycol was heated at 100° for 10 min.; 3.9 g. of potassium hydroxide was then added, and the mixture refluxed for 90 min., with removal of water. After cooling and acidification with dilute hydrochloric acid, the reaction product was taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent was removed, and the residue vacuum-distilled. Yield: 6.4 g. (86.6%) of a compound, b.p. 140°/18 mm., crys-

(5) *Cf.* for instance, H. Fischer and O. Wiedemann, *Hoppe-Seyler's Z. physiol. Chem.*, **155**, 52 (1926); H. Fischer, E. Sturm, and H. Friedrich, *Ann.*, **461**, 251 (1928); H. Fischer, H. Beyer, and E. Zaucker, *Ann.*, **486**, 61 (1931).

(6) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(7) L. G. Brooker and R. H. Sprague, *J. Am. Chem. Soc.*, **67**, 1869 (1945).

tallizing in colorless leaflets, m.p. 39°, from aqueous methanol.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.3; H, 8.2. Found: C, 84.2; H, 8.1.

1-Phenyl-2,3,5-trimethylpyrrole-4-aldehyde (VIII) was prepared in a manner analogous to the lower homolog of the foregoing pyrrole (VI) from 11.5 g. of the foregoing pyrrole, 6.8 g. of dimethylformamide, and 14.5 g. of phosphorus oxychloride in 100 ml. of dry toluene; yield: 11 g. (83.3%) of an aldehyde, crystallizing from methanol in long colorless needles, m.p. 134°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.8; H, 7.1; N, 6.6. Found: C, 78.8; H, 7.1; N, 6.6.

The *semicarbazone* crystallized from ethanol in shiny colorless prisms, m.p. 273°.

Anal. Calcd. for $C_{15}H_{18}N_4O$: N, 20.7. Found: N, 20.7.

1-Phenyl-2,3,4,5-tetramethylpyrrole (X) was prepared in the usual way from 5 g. of the foregoing aldehyde (VIII), 1.7 g. of hydrazine hydrate, and 2 g. of potassium hydroxide. This compound (3.5 g., 70%) was a colorless oil, b.p. 142°/12 mm., which darkened rapidly on exposure to air and light. The same compound was obtained by reduction of dialdehyde V.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.4; H, 8.6. Found: C, 84.1; H, 8.6.

1,2-Diphenyl-5-methylpyrrole-4-aldehyde (IV) was prepared from 15 g. of 1,2-diphenyl-5-methylpyrrole, 7 g. of dimethylformamide, and 15 g. of phosphorus oxychloride in 150 ml. of dry toluene. Yield: 16.5 g. (98%) of an aldehyde, b.p. 241–242°/13 mm., crystallizing in colorless prisms, m.p. 115–116°, from ethanol. No dialdehyde could be isolated in this reaction.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.7; H, 5.8. Found: C, 82.8; H, 5.8.

The *oxime* crystallized from ethanol in fine colorless prisms, m.p. 198°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: N, 10.1. Found: N, 10.1.

The *phenylhydrazone* crystallized from ethanol in silky colorless needles, m.p. 180°.

Anal. Calcd. for $C_{24}H_{21}N_3$: C, 81.8; H, 6.0; N, 12.0. Found: C, 81.7; H, 6.1; N, 12.2.

1,2-Diphenyl-4,5-dimethylpyrrole (VII) was prepared from 10 g. of the foregoing aldehyde (IV), 2.8 g. of hydrazine hydrate, and 3 g. of potassium hydroxide in 100 ml. of diethylene glycol. Yield: 8.2 g. (87%) of a product, b.p. 195°/12 mm., crystallizing from ethanol in colorless prisms, m.p. 79°, giving no coloration with sulfuric acid.

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.4; H, 6.9. Found: C, 87.3; H, 6.9.

1,2-Diphenyl-4,5-dimethylpyrrole-3-aldehyde (IX). When the usual formylation technique was applied to the foregoing pyrrole (VII), no aldehyde was obtained, even after 30 hours' heating. The following procedure, however, furnished the expected aldehyde, in good yield. To a mixture of 5.5 g. of pyrrole VII and 2.4 g. of dimethylformamide, 4 g. of phosphorus oxychloride was added in small portions, and the sticky dark violet mass obtained was heated for 10 hr. on a water bath. After cooling, a 15% aqueous solution of sodium hydroxide was added, and the reaction product worked up in the usual way. Yield: 4.7 g. (77%) of an aldehyde, b.p. 254°/17 mm., crystallizing from cyclohexane in colorless, rhombohedric prisms, m.p. 200°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.9; H, 6.2; O, 5.8. Found: C, 82.9; H, 6.2; O, 5.8.

The *oxime* crystallized from ethanol in shiny colorless prisms, m.p. 238–239°.

Anal. Calcd. for $C_{19}H_{18}N_2O$: N, 9.7. Found: N, 9.7.

1,2-Diphenyl-3,4,5-trimethylpyrrole (XI) was prepared from 6 g. of the foregoing aldehyde (IX), 1.4 g. of hydrazine hydrate, and 1.4 g. of potassium hydroxide in 50 ml. of diethylene glycol. Yield: 4 g. (70%) of a compound crystallizing in shiny colorless needles, m.p. 121°, from cyclohexane or acetic acid.

Anal. Calcd. for $C_{19}H_{19}N$: C, 87.3; H, 7.3. Found: C, 87.3; H, 7.2.

α-Phenyl-β-(1-phenyl-2,5-dimethyl-3-pyrryl)acrylonitrile (XII). A solution of aldehyde III (1 mole) and benzyl cyanide (1 mole) in ethanol was refluxed for 5 min. with a few drops of aqueous sodium hydroxide (5*N*). The precipitate formed on cooling and diluting with water, was washed with water and recrystallized from ethanol, giving silky yellowish needles, m.p. 139°. Yield: 70%. Under the same experimental conditions, no condensation products were obtained with aldehydes VIII and IX.

Anal. Calcd. for $C_{21}H_{17}N_2$: N, 9.4. Found: N, 9.5.

α-Phenyl-β-(1,2-diphenyl-5-methyl-4-pyrryl)acrylonitrile (XIII). Similarly prepared from aldehyde IV and benzyl cyanide, this nitrile crystallized from ethanol in silky yellowish needles, m.p. 145°.

Anal. Calcd. for $C_{26}H_{20}N_2$: N, 7.8. Found: N, 8.1.

bis-*Acrylonitrile* (XIV). This compound, prepared from 1 mole of dialdehyde V with 2 moles of benzyl cyanide, crystallized from ethanol in pale yellow needles, m.p. 171°.

Anal. Calcd. for $C_{30}H_{23}N_3$: N, 9.9. Found: N, 9.9.

PARIS VE, FRANCE

[CONTRIBUTION FROM THE RESEARCH DIVISION, AMERICAN CYANAMID CO., BOUND BROOK LABORATORIES]

Reactions of 2,3-Dichloro-1,4-naphthoquinone with 2-Aminopyridine and Related Amines[1]

WILLIAM L. MOSBY AND RICHARD J. BOYLE

Received September 22, 1958

2,3-Dichloro-1,4-naphthoquinone reacts with 2-aminopyridine to yield a 1:1 and a 1:2 condensation product. The former is shown to have structure I, and the latter is believed to have structure X. Various substitution products of I are described, as are several analogous quinones derived from other heterocyclic amines.

During the preparation of a number of naphtho-[2,3-*b*]pyrrocolinediones *via* the convenient synthesis elaborated by Pratt *et al.*,[2,3] we became interested in the nature of the products which might

(1) Paper presented at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958; *Abstracts*, p. 66N.

(2) E. F. Pratt, R. W. Luckenbaugh, and R. L. Erickson, *J. Org. Chem.*, **19**, 176 (1954).

(3) E. F. Pratt, R. G. Rice, and R. W. Luckenbaugh, *J. Am. Chem. Soc.*, **79**, 1212 (1957).