[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

FURTHER STUDIES ON THE KNORR-PAAL SYNTHESIS OF 2,5-DIALKYLPYRROLES

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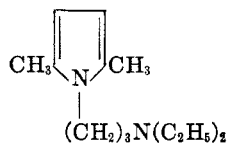
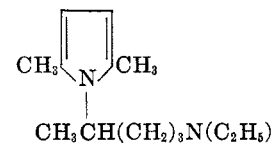
As part of a general investigation of the scope and limitations of the Knorr-Paal synthesis of 2,5-dialkylpyrroles by condensation of γ-diketones with primary amines (1), we have prepared a number of new amino derivatives of 2,5-dimethylpyrrole presenting potential pharmacological interest.

N,N-Diethyl-1,3-diaminopropane reacted vigorously with acetonylacetone to give 1-α-(γ-diethylaminopropyl)-2,5-dimethylpyrrole (I) in excellent yield. N,N-diethyl-1,4-diaminopentane reacted only sluggishly under the same conditions, and gave a poor yield of 1-β-(ω-diethylaminopentyl)-2,5-dimethyl-

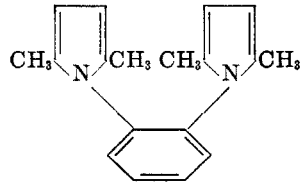


I

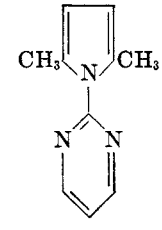


II

pyrrole (II). This marked difference in reactivity is probably due to steric hindrance, the amino group being located on a secondary carbon atom; cyclopentylamine, which has a similar structure, condensed with acetonylacetone to give 1-cyclopentyl-2,5-dimethylpyrrole, also in low yield, and amines with the functional group attached to a tertiary carbon atom (2) failed to react. It should be noted, however, that some anomalies in the reactivity of primary amines with acetonylacetone could not be accounted for merely on the grounds of steric hindrance. 2,5-Dichloroaniline, for instance, failed to give a pyrrole after several days' heating, whereas the probably more hindered 5-chloro-2-methoxyaniline readily gave 1-(5-chloro-2-methoxyphenyl)-2,5-dimethylpyrrole; similarly, *o*-phenylenediamine, condensed with two molecules of acetonylacetone, afforded 1-[2-(2,5-dimethyl-1-pyrryl)phenyl]-2,5-dimethylpyrrole (III) without difficulty. 2-Aminopyrimidine reacted with difficulty, to give 1-(2-pyrimidyl)-2,5-dimethylpyrrole (IV) in very poor yield, whereas 2-aminopyridines gave quantitative yields of the corresponding pyrroles (3), under the same conditions;



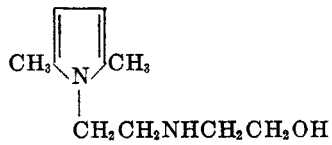
III



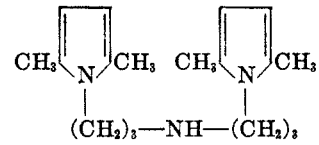
IV

this difference could perhaps be ascribed to the more pronounced tendency of 2-aminopyrimidine to react in the *imino* form.

More complex aliphatic amines were successfully condensed with acetonylacetone. Thus, N-(β-hydroxyethyl)-1,2-ethylenediamine gave 1-β-(β-hydroxyethylamino)ethyl-2,5-dimethylpyrrole (V), and di(γ-aminopropyl)amine gave di[γ-(2,5-dimethyl-1-pyrryl)-propyl]amine (VI). In the heterocyclic series,

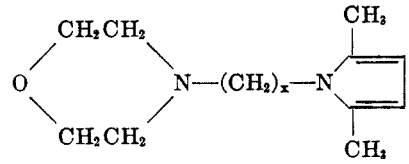


V



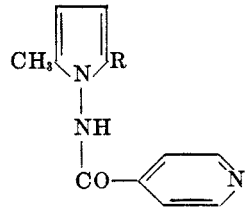
VI

N-(2-aminoethyl)morpholine and N-(3-aminopropyl)morpholine yielded on condensation 1-(β-N-morpholinylethyl)-2,5-dimethylpyrrole (VII) and 1-(γ-N-morpholinylpropyl)-2,5-dimethylpyrrole (VIII), respectively. All the pyrrole derivatives with amino functions thus prepared readily gave crystallized methiodides, and are undergoing biological tests for potential pressor activity or other effects on the blood vessels.

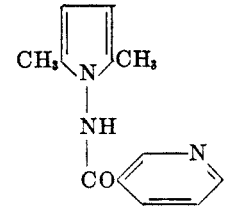


VII x = 2
VIII x = 3

It is known that substitution on the $—NH_2$ radical of isonicotinic hydrazide sometimes leads to useful tuberculostats (4). Condensation of this hydrazide with acetonylacetone, octane-2,5-dione, and tetradecane-2,5-dione afforded respectively 1-isonicotinylamino-2,5-dimethylpyrrole (IX), 1-isonicotinylamino-2-methyl-5-*n*-propylpyrrole (X), and 1-isonicotinylamino-2-methyl-5-*n*-nonylpyrrole (XI), compounds which, it is hoped, will show fewer side-effects on the nervous system than the parent hydrazide. 1-Nicotinylamino-2,5-dimethyl-



IX R = CH_3
X R = *n*-C_3H_7
XI R = *n*-C_9H_{19}



XII

pyrrole (XII), prepared from nicotinic hydrazide, is being tested for cardiotonic activity, in view of its resemblance to coramine (N,N-diethylnicotinamide).

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EXPERIMENTAL

1-α-(γ-Diethylaminopropyl)-2,5-dimethylpyrrole (I). N,N-Diethyl-1,3-diaminopropane (30 g.) was treated with 30 g. of acetonylacetone in small portions, and the mixture then was heated at 140–150° for one hour. Vacuum-fractionation yielded 42 g. of the compound (I), in the form of a colorless oil, b.p. 151–152°/18 mm., or 159–160°/23 mm., n_D^{23} 1.4945, with a faint amine odor.

Anal. Calc'd for $C_{13}H_{24}N_2$: C, 74.9; H, 11.4.
Found: C, 74.8; H, 11.8.

The corresponding *methiodide* crystallized from anhydrous ether in shiny, colorless prisms, m.p. 137–138°.

Anal. Calc'd for $C_{14}H_{27}N_2I$: N, 8.0. Found: N, 7.7.

1-β-(ω-Diethylaminopentyl)-2,5-dimethylpyrrole (II). A mixture of 10 g. of N,N-diethyl-1,4-diamino-*n*-pentane and 10 g. of acetonylacetone was gently refluxed for one hour, and the reaction product was vacuum-fractionated; yield: 10 g. of a colorless oil, b.p. 158°/13 mm., n_D^{22} 1.4919.

Anal. Calc'd for $C_{15}H_{28}N_2$: C, 76.2; H, 11.9.
Found: C, 76.3; H, 12.0.

The *methiodide* crystallized from ether in colorless leaflets, m.p. 86–87°.

Anal. Calc'd for $C_{16}H_{31}IN_2$: N, 7.4. Found: N, 7.1.

1-(5-Chloro-2-methoxyphenyl)-2,5-dimethylpyrrole. A mixture of 20 g. of 5-chloro-2-methoxyaniline and 20 g. of acetonylacetone was refluxed for 48 hours, to yield 29 g. of the *pyrrole*, b.p. 163–164°/13 mm., crystallizing from ligroin in shiny, colorless prisms, m.p. 89°.

Anal. Calc'd for $C_{13}H_{14}ClNO$: C, 66.2; H, 5.9.
Found: C, 66.0; H, 6.0.

Under the same conditions, no condensation product was obtained with 2,5-dichloroaniline.

1-[2-(2,5-Dimethyl-1-pyrryl)phenyl]-2,5-dimethylpyrrole (III). A mixture of *o*-phenylenediamine (1 mole) and acetonylacetone (2 moles) was refluxed for 24 hours, then vacuum-fractionated. The portion boiling at 190–195°/15 mm. crystallized from methanol in shiny, colorless leaflets, m.p. 161°.

Anal. Calc'd for $C_{18}H_{20}N_2$: N, 10.4. Found: N, 10.2.

1-(2-Pyrimidyl)-2,5-dimethylpyrrole (IV). A mixture of 7 g. of 2-aminopyrimidine and 7 g. of acetonylacetone was refluxed for 24 hours, to yield 2 g. of the compound (IV), b.p. 150–151°/12 mm., which crystallized from ligroin in shiny, colorless prisms, m.p. 112°. No condensation product was obtained when the heating was reduced to one hour.

Anal. Calc'd for $C_{10}H_{11}N_3$: N, 24.3. Found: N, 24.4.

1-Cyclopentyl-2,5-dimethylpyrrole. A mixture of 8 g. of cyclopentylamine and 12 g. of acetonylacetone was refluxed for one hour (unlike with the linear alkylamines, no reaction was observed at room temperature), to yield 6 g. of the *pyrrole*, b.p. 235–236°, n_D^{23} 1.5209.

Anal. Calc'd for $C_{11}H_{17}N$: C, 80.9; H, 10.5.
Found: C, 81.2; H, 10.8.

Under the same conditions, amines of the general formula $R(CH_2)_n-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-NH_2$ gave no condensation products.

1-β-(β-Hydroxyethylamino)ethyl-2,5-dimethylpyrrole (V). To 15 g. of N-(β-hydroxyethyl)-1,2-ethylenediamine was added 13 g. of acetonylacetone (an exothermic reaction occurred at room temperature), and the mixture then was heated at 140–150° for one hour. Yield: 23 g. of a pale yellow viscous oil, b.p. 220–222°/20 mm., n_D^{19} 1.5280.

Anal. Calc'd for $C_{10}H_{18}N_2O$: C, 65.9; H, 10.0.

Found: C, 66.0; H, 10.0.

The *methiodide* crystallized from ether in colorless prisms, m.p. 180°.

Di[γ-(2,5-dimethyl-1-pyrryl)propyl]amine (VI). To 20 g. of di(γ-aminopropyl)amine was cautiously added 45 g. of acetonylacetone, thereby producing a vigorous exothermic reaction. The mixture then was heated for one hour, and fractionated *in vacuo*; yield: 40 g. of a pale yellow viscous oil, b.p. 221–222°/2 mm., n_D^{22} 1.5394.

Anal. Calc'd for $C_{18}H_{29}N_3$: C, 75.2; H, 10.2.

Found: C, 75.1; H, 10.1.

The *methiodide* crystallized from ether in yellowish prisms, m.p. 163–164°.

Anal. Calc'd for $C_{19}H_{32}N_3I$: N, 9.7. Found: N, 9.5.

1-(β-N-Morpholinylethyl)-2,5-dimethylpyrrole (VII). N-(2-Aminoethyl)morpholine (30 g.) began to react with acetonylacetone (23 g.) at room temperature, and the condensation was completed by a brief heating at 140–150°. Yield: 37 g. of a colorless oil with a faint amine odor, b.p. 172–173°/12 mm., n_D^{22} 1.5216.

Anal. Calc'd for $C_{12}H_{20}N_2O$: C, 69.2; H, 9.7.

Found: C, 69.2; H, 9.9.

The *methiodide* crystallized from ether in fine yellowish prisms, decomposing around 253°.

1-(γ-N-Morpholinylpropyl)-2,5-dimethylpyrrole (VIII). A mixture of 30 g. of N-(3-aminopropyl)morpholine and 25 g. of acetonylacetone, treated as for VII, yielded 37 g. of a colorless oil, b.p. 180–181°/12 mm., n_D^{23} 1.5189.

Anal. Calc'd for $C_{13}H_{22}N_2O$: C, 70.2; H, 10.0.

Found: C, 70.0; H, 10.0.

The *methiodide* crystallized from ether in yellowish prisms, m.p. 222–223°.

Anal. Calc'd for $C_{14}H_{25}IN_2O$: N, 7.7. Found: N, 7.9.

1-Isonicotinylamino-2,5-dimethylpyrrole (IX). A mixture of 15 g. of isonicotinic hydrazide and 15 g. of acetonylacetone was kept at 180° for one hour; the crystalline mass obtained on cooling was washed with water, and recrystallized from aqueous acetone; yield: 20 g. of silky, colorless needles, m.p. 145–146°, sparingly soluble in water.

Anal. Calc'd for $C_{12}H_{15}N_3O$: N, 19.5. Found: N, 19.2.

1-Isonicotinylamino-2-methyl-5-n-propylpyrrole (X). This substance, similarly prepared from isonicotinic hydrazide and octane-2,5-dione, crystallized from aqueous acetone as silky, colorless needles, m.p. 140°.

Anal. Calc'd for $C_{14}H_{17}N_3O$: N, 17.3. Found: N, 17.5.

1-Isonicotinylamino-2-methyl-5-n-nonylpyrrole (XI) crystallized from aqueous methanol in colorless leaflets, m.p. 77°.

Anal. Calc'd for $C_{20}H_{29}N_3O$: C, 73.4; H, 8.9.

Found: C, 73.5; H, 9.1.

1-Nicotinylamino-2,5-dimethylpyrrole (XII) crystallized from aqueous acetone in colorless needles, m.p. 80°.

Anal. Calc'd for $C_{12}H_{13}N_3O$: N, 19.5. Found: 19.4.

SUMMARY

1. The Knorr-Paal reaction of acetonylacetone with various polyamino compounds and hydrazides was used to prepare a series of new pyrroles of possible biological interest.

2. Certain abnormalities, observed in the course of this investigation, have been related to steric hindrance.

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