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

HYDROXY AND THIOL DERIVATIVES OF 2,5-DIALKYLPYRROLES

NG. PH. BUU-HOÏ, NG. D. XUONG, AND J. M. GAZAVE

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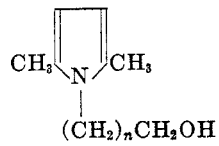
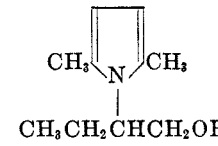
In a quest for substances of potential pharmacological interest for the local treatment of rhinitis and related nasal conditions, we focussed our attention on non-irritant sulfur-containing compounds which would have mild anesthetic, antiseptic, and cicatrisive properties. From this angle, we investigated esters of 2-thenoic acid with alcohols and phenols of the pyrrole group; previously, the benzoates of β-(1-pyrryl)ethanol and γ-(1-pyrryl)propanol had been investigated as possible local anesthetics (1), and thiophene derivatives are known to promote cicatrization.

In this series, β-(1-pyrryl)ethanol and γ-(1-pyrryl)propanol were prepared by Blicke and Blake (1) by hydrolysis of the corresponding acetates, obtained in the reaction of the potassium derivative of pyrrole with β-chloroethyl and γ-chloropropyl acetates; β-(2,5-dimethyl-1-pyrryl)ethanol (I) was prepared by Knorr and Rabe (2) by condensing acetonylacetone with β-aminoethanol. Although the alcohol (I), obtained by employment of the latter reaction, had some local anesthetic activity, its ester from 2-thenoic acid did not appear to be of pharmacological interest. The condensation of 3-aminopropanol with acetonylacetone readily gave γ-(2,5-dimethyl-1-pyrryl)propanol (II), whose 2-thenoate was not toxic, had a mild local anesthetic effect, and showed satisfactory bacteriostatic activity



I $n = 1$
II $n = 2$



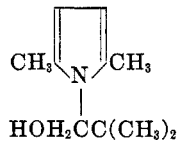
III

at a concentration of 1/400 against the following organisms: *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Escherichia coli*, *Klebsiella aerobacter*, and *Proteus vulgaris*.

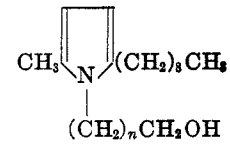
Some homologs of the alcohol (II) were also prepared, and an interesting case of steric hindrance was encountered in the Knorr-Paal reaction. Whilst 2-amino-*n*-butanol rapidly condensed with acetonylacetone to give β-(2,5-dimethyl-1-pyrryl)-*n*-butanol (III) in excellent yield, the sterically hindered 2-amino-2-

[1] The authors thank the Lederle Laboratories of the American Cyanamid Company, Pearl River, New York, for the supply of 3-aminopropanol.

methyl-*n*-propanol gave, under similar conditions, a very low yield of β-(2,5-dimethyl-1-pyrryl)-β,β-dimethylethanol (IV):



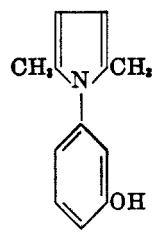
IV



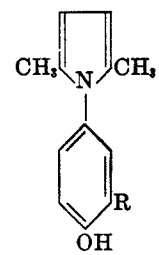
V $n = 1$
VI $n = 2$

Homologs of acetonylacetone were readily condensed with amino alcohols; thus, with β-aminoethanol, *n*-tetradecane-2,5-dione gave β-(2-methyl-5-*n*-nonyl-1-pyrryl)ethanol (V), and, with 3-aminopropanol, γ-(2-methyl-5-*n*-nonyl-1-pyrryl)propanol (VI).

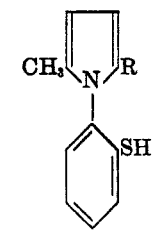
The Knorr-Paal condensation of acetonylacetone with *o*-amino-β-phenylethanol gave 2,5-dimethyl-1-(2-β-hydroxyethylphenyl)pyrrole; with *m*- and *p*-aminophenol, 2,5-dimethyl-1-*m*-hydroxyphenylpyrrole (VII) and the *para* isomer (VIII) were obtained in the form of readily autooxidizable solids; 2,5-dimethyl-1-(3-*n*-pentadecyl-4-hydroxyphenyl)pyrrole (IX), prepared from 2-*n*-pentadecyl-4-aminophenol, was even more unstable. On the other hand, 2,5-dimethyl-*o*-mercaptophenylpyrrole (X) and 2-methyl-5-pentyl-*o*-mercaptophenylpyrrole (XI),



VII



VIII R = H
IX R = n-$C_{15}H_{31}$



X R = CH_3
IX R = n-C_5H_{11}

prepared by interaction of 2-aminothiophenol with acetonylacetone or *n*-decane-2,5-dione respectively, were relatively stable oils.

γ-(2,5-Dimethyl-1-pyrryl)propyl 2-thenoate is undergoing clinical trials against rhinitis; detailed biological investigations, carried out with Dr. Pillot on the various compounds described here, will be reported elsewhere.

EXPERIMENTAL

β-(2,5-Dimethyl-1-pyrryl)ethanol and its derivatives. To 61 g. of redistilled β-aminoethanol (b.p. 171°), 114 g. of acetonylacetone was added in small portions; an exothermic reaction immediately took place, with formation of water. Distillation *in vacuo* of the reaction product yielded 120 g. of β-(2,5-dimethyl-1-pyrryl)ethanol, b.p. 156–157°/35 mm., as a glycerine-like oil which, on cooling, solidified to a crystalline mass, m.p. 50°; Knorr and Rabe (2) gave m.p. *circa* 46°.

β-(2,5-Dimethyl-1-pyrryl)ethyl 2-thenoate was prepared by adding, dropwise, 14 g. of 2-thenoyl chloride to a water-cooled, stirred benzene solution of 15 g. of the required al-

cohol and 10 ml. of anhydrous pyridine. The reaction mixture was kept for 15 minutes at room temperature, poured on ice, and the benzene layer was washed with aqueous sodium carbonate, then with water, and dried over sodium sulfate; yield 15 g.; b.p. 210–212°/15 mm.; shiny colorless leaflets, m.p. 87°, from ligroin.

Anal. Calc'd for $C_{13}H_{15}NO_2S$: C, 62.7; H, 6.0.
Found: C, 62.6; H, 6.3.

β-(2,5-Dimethyl-1-pyrryl)ethyl benzoate was prepared similarly from benzoyl chloride; b.p. 200–201°/13 mm.; it crystallized from ligroin in long silky needles, m.p. 84°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0.
Found: C, 74.0; H, 7.3.

γ-(2,5-Dimethyl-1-pyrryl)propanol (II). To 40 g. of redistilled 3-aminopropanol[1], 60 g. of acetonylacetone was added in small portions; when the exothermic reaction had subsided, the mixture was heated on the water-bath for five minutes, and fractionated *in vacuo*; yield, 81 g. of a glycerine-like oil, b.p. 149–150°/12 mm., n_D^{28} 1.5143, which darkened on exposure to the air and light.

Anal. Calc'd for $C_9H_{15}NO$: C, 70.7; H, 9.8.
Found: C, 70.7; H, 10.0.

γ-(2,5-Dimethyl-1-pyrryl)propyl 2-thenoate was prepared from 25 g. of the required alcohol and 25 g. of 2-thenoyl chloride; b.p. 228–230°/18 mm.; it crystallized from petroleum ether in colorless prisms, m.p. 75–76°; yield, 32 g.

Anal. Calc'd for $C_{14}H_{17}NO_2S$: C, 63.9; H, 6.4.
Found: C, 64.0; H, 6.4.

γ-(2,5-Dimethyl-1-pyrryl)propyl benzoate, b.p. 218–220°/13 mm., n_D^{23} 1.5528, crystallized from petroleum ether in shiny colorless leaflets, m.p. 39–40°.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.3.
Found: C, 74.4; H, 7.2.

β-(2,5-Dimethyl-1-pyrryl)-n-butanol (III) was prepared by refluxing for ten minutes a mixture of 50 g. of 2-amino-*n*-butanol and 65 g. of acetonylacetone; this *alcohol* was a colorless thick oil, b.p. 157–158°/23 mm., n_D^{21} 1.5122; yield: 86 g.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.9; H, 10.2.
Found: C, 71.8; H, 10.2.

β-(2,5-Dimethyl-1-pyrryl)-β,β-dimethylethanol (IV). A mixture of 89 g. of redistilled 2-amino-2-methyl-*n*-propanol (b.p. 160–162°) and 114 g. of acetonylacetone was refluxed for six hours. Yield, 16 g. of a colorless oil, b.p. 149–150°/16 mm., n_D^{26} 1.4941. No condensation product was obtained when the mixture was heated for only ten minutes.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.9; H, 10.2.
Found: C, 72.1; H, 10.3.

β-(2-Methyl-5-n-nonyl-1-pyrryl)ethanol (V). A mixture of 13 g. of *n*-tetradecane-2,5-dione and 8 g. of β-aminoethanol was refluxed for ten minutes. Yield: 15 g. of a pale yellow, viscous oil, b.p. 209–210°/14 mm., $n_D^{22.5}$ 1.4992.

Anal. Calc'd for $C_{16}H_{29}NO$: C, 76.4; H, 11.5.
Found: C, 76.5; H, 11.8.

The *benzoate* had b.p. 275–277°/18 mm., and crystallized from petroleum ether in shiny colorless leaflets, m.p. 38–39°.

Anal. Calc'd for $C_{23}H_{33}NO_2$: C, 77.7; H, 9.2.
Found: C, 77.5; H, 9.5.

γ-(2-Methyl-5-n-nonyl-1-pyrryl)propanol (VI) was prepared as for V from 7 g. of *n*-tetradecane-2,5-dione and 3 g. of 3-aminopropanol; yield, 7.5 g. of a pale yellow, viscous oil, b.p. 220–222°/18 mm., n_D^{24} 1.4960.

Anal. Calc'd for $C_{17}H_{31}NO$: C, 76.9; H, 11.7.
Found: C, 76.7; H, 11.7.

The corresponding *2-thenoate* was a thick yellow oil, b.p. 280–282°/22 mm., n_D^{22} 1.5188.

Anal. Calc'd for $C_{22}H_{33}NO_2S$: C, 70.5; H, 8.8.
Found: C, 70.6; H, 9.0.

2,5-Dimethyl-1-m-hydroxyphenylpyrrole (VII) was prepared in quantitative yield by

refluxing (5 min.) 15 g. of *m*-aminophenol and 20 g. of acetonylacetone. This compound, b.p. 191–192°/18 mm., crystallized from petroleum ether in shiny colorless needles, m.p. 72°, which darkened rapidly on exposure to the air and light.

Anal. Calc'd for $C_{12}H_{13}NO$: C, 77.0; H, 6.9.
Found: C, 77.1; H, 6.7.

2,5-Dimethyl-1-p-hydroxyphenylpyrrole (VIII). This compound crystallized from methanol in colorless prisms, m.p. 107°, b.p. 201–202°/25 mm.

Anal. Calc'd for $C_{12}H_{13}NO$: C, 77.0; H, 6.9.
Found: C, 76.9; H, 7.0.

Its *allyl ether* was a colorless oil, b.p. 194–195°/15 mm., n_D^{22} 1.5698.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.3; H, 7.5.
Found: C, 79.5; H, 7.8.

2-Methyl-5-n-pentyl-1-p-hydroxyphenylpyrrole, prepared from 3.5 g. of *p*-aminophenol and 5 g. of *n*-decane-2,5-dione, was a viscous yellow oil, b.p. 221–222°/18 mm., which solidified to a crystalline mass melting at room temperature.

Anal. Calc'd for $C_{16}H_{21}NO$: C, 79.0; H, 8.6.
Found: C, 78.7; H, 8.5.

2,5-Dimethyl-1-(3-n-pentadecyl-4-hydroxyphenyl)pyrrole (IX) was prepared in quantitative yield by refluxing (15 min.) 30 g. of 2-*n*-pentadecyl-4-aminophenol and 20 g. of acetonylacetone. This compound, b.p. 293–295°/17 mm., n_D^{24} 1.5232, crystallized from petroleum ether in silky, highly oxidizable needles, m.p. 39–40°.

Anal. Calc'd for $C_{27}H_{43}NO$: C, 81.6; H, 10.8.
Found: C, 81.3; H, 11.0.

2,5-Dimethyl-1-o-mercaptophenylpyrrole (X). This substance was prepared by refluxing (15 min.) a mixture of 12.5 g. of *o*-aminothiophenol and 15 g. of acetonylacetone; yield, 23 g. of a viscous, colorless oil, b.p. 164–165°/18 mm., n_D^{25} 1.6009.

Anal. Calc'd for $C_{12}H_{13}NS$: C, 70.9; H, 6.4.
Found: C, 71.0; H, 6.7.

2-Methyl-5-n-pentyl-1-o-mercaptophenylpyrrole (XI) was similarly obtained from 4.5 g. of *o*-aminothiophenol and 5 g. of *n*-decane-2,5-dione; yield, 7 g. of a pale yellow oil, b.p. 197–198°/18 mm., n_D^{20} 1.5718.

Anal. Calc'd for $C_{16}H_{21}NS$: C, 74.1; H, 8.1.
Found: C, 74.2; H, 8.1.

2,5-Dimethyl-1-(2-β-hydroxethylphenyl)pyrrole. A mixture of 63 g. of acetonylacetone and 60 g. of *o*-amino-β-phenylethanol (3) (b.p. 210°/40 mm., n_D^{20} 1.5745) was refluxed for 3 hours; the reaction product was a thick colorless oil, b.p. 204°/30 mm., n_D^{23} 1.5745.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 7.9.
Found: C, 78.2; H, 8.2.

SUMMARY

1. The Knorr-Paal condensation of various amino alcohols, aminophenols, and 2-aminothiophenol with γ-diketones has been investigated.

2. A number of new pyrroles have been prepared for pharmacological evaluation.

PARIS Ve, FRANCE

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