**17β-Hydroxy-2α,6α,17α-trimethyl-5α-androstan-3-one (XIII).**—A solution of XII (1.5 g.) in ethanol (150 ml.) containing water (0.6 ml.) and concd. hydrochloric acid (0.08 ml.) was hydrogenated over 5% palladium on charcoal (0.5 g.) at room temperature and atmospheric pressure. Reduction was complete in 30 min. (negative ferric chloride test). The filtered solution was evaporated and the residue chromatographed on washed alumina (75 g.). Elution with benzene–hexane (70:30), and crystallization of the product from acetone–hexane gave 900 mg. (62.5%) of XIII, m.p. 138–140°, $[\alpha]_D$ + 7.2°. Further crystallization gave a product of m.p. 140–141°, $[\alpha]_D$ + 7.5°, $\nu_{max}$ 3690 (OH) and 1720 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91; O, 9.62. Found: C, 79.27; H, 10.76; O, 9.89.

## Spasmolytic 1,2,5-Trisubstituted Pyrroles

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In previous papers,[1] it has been shown that 1,2,5-trisubstituted pyrroles bearing a basic radical in position 1 are endowed with spasmolytic activity, especially of the musculotropic type, the most active substance of that series so far encountered being 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole (I); this compound[2] has since proven to be a useful antispasmodic, especially in dysmenorrhea and spasms of Oddi's sphincter.

It was of interest to introduce variations in the nature of the substituent both in position 1 and in position 5, to see whether the main pharmacologic features would be maintained. Six new compounds of this type are now reported, of which five bear a dialkylaminoalkyloxy chain in the *ortho* position on the 1-aryl substituent; earlier studies had shown this structure to be the most favorable one for pharmacologic activity.

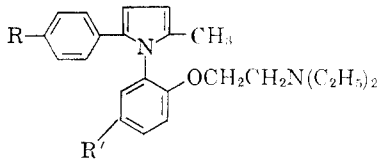
Knorr–Paal condensation[3] of 1-*p*-tolyl-1,4-pentanedione with *o*-aminophenol yielded 1-(*o*-hydroxyphenyl)-2-methyl-5-*p*-tolylpyrrole, whose β-diethylaminoethyl ether (II) is a methyl homolog of compound I. With 2-amino-4-chlorophenol, 1-phenyl-1,4-pentanedione

(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, **1**, 23, 319 (1959); **2**, 335 (1960).

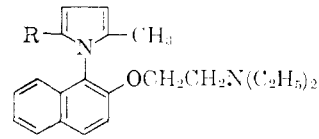
(2) Trademark Leioplegil®.

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

furnished 1-(5-chloro-2-hydroxyphenyl)-2-methyl-5-phenylpyrrole, whose β-diethylaminoethyl ether (III) is a chloro derivative of ompound I.

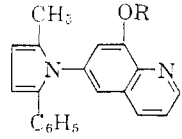


I, R = R′ = H
II, R = $CH_3$, R′ = H
III, R = H, R′ = Cl



IV, R = $C_6H_5$
V, R = p-$C_6H_4CH_3$
VI, R = $CH_3$

A more extensive modification of the 1-aryl group was achieved by condensing 1-phenyl- and 1-*p*-tolyl-1,4-pentanedione with 1-amino-2-methoxynaphthalene, then demethylating to 1-(2-hydroxy-1-naphthyl)-2-methyl-5-phenylpyrrole and 1-(2-hydroxy-1-naphthyl)-2-methyl-5-*p*-tolylpyrrole, whose ethers (IV) and (V) are benzo derivatives of compounds I and II, respectively. Hexane-2,5-dione and the same amine yielded 1-(2-methoxy-1-naphthyl)-2,5-dimethylpyrrole, which was demethylated and alkylated to 1-(2-β-diethylaminoethoxy-1-naphthyl)-2,5-dimethylpyrrole (VI). Demethylation of the methoxypyrroles by means of pyridine hydrochloride (a procedure which was found satisfactory in the phenyl series) produced very impure hydroxy compounds here; however, satisfactory de-



VII, R = H
VIII, R = $CH_2CH_2N(C_2H_5)_2$

methylation was achieved by means of potassium hydroxide in diethylene glycol. This same method was used for preparing 1-(8-hydroxy-6-quinolyl)-2-methyl-5-phenylpyrrole (VII) (obtained from 1-phenyl-1,4-pentanedione and 6-amino-8-methoxyquinoline), which was converted into the β-diethylaminoethyl ether (VIII).

All the basic ethers described here yielded well-crystallized, water-soluble hydrochlorides. Their *in vitro* biological evaluation was performed on rat duodenum fragments, in a regularly oxygenated Tyrode medium at 38°, according to a technique previously described in detail[1]; the compounds were tested in concentrations of 0.5 to 5 mcg. per 10 ml. of medium, and the comparison was made with the effect produced by papaverine hydrochloride in a concentration of 12.5 mcg.

per 10 ml. of medium. In these conditions, the substances tested showed a high degree of spasmolytic activity of the musculotropic type; however, the introduction of a chlorine atom (*viz.*, compound III) in the molecule of compound I considerably reduced this activity (to less than one-tenth). A detailed report of the properties of each substance will be published later.

## Experimental

**Preparation of Intermediates.**—Hexane-2,5-dione and the various amines used were obtained commercially; 1-phenyl-1,4-pentanedione and 1-*p*-tolyl-1,4-pentanedione were synthesized by Friedel and Crafts reactions of levulinyl chloride with benzene and toluene in the presence of aluminum chloride.[4]

**Knorr-Paal Condensations.**—A mixture of the appropriate arylamine and γ-diketone (the latter in 10% excess) was gently refluxed until steam had ceased to evolve, and the product was then vacuum-fractionated. Purification was effected by crystallization from heptane or cyclohexane for the hydroxy compounds, and from methanol for the methoxy compounds. The 2-methylpyrroles thus prepared are listed in Table I.

**Demethylation of Methoxypyrroles.**—To a solution of 18 g. of 1-(2-methoxy-1-naphthyl)-2-methyl-5-phenylpyrrole in 100 ml. of diethylene glycol, 56 g. of potassium hydroxide was added, the mixture warmed with stirring until complete dissolution and heated for 8 hr. at 230°. After cooling and dilution with water, the precipitate of 1-(2-hydroxy-1-naphthyl)-2-methyl-5-phenylpyrrole was filtered, and purified by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid. Crystallization from cyclohexane gave a 70% yield of colorless prisms, m.p. 118°.

*Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.3; H, 5.7; O, 5.3. Found: C, 84.0; H, 5.6; O, 5.4.

The following compounds were thus prepared:

**1-(2-Hydroxy-1-naphthyl)-5-*p*-tolylpyrrole**, m.p. 100–101° (yields: 17% after 8 hr. heating at 235°, 72% after 35 hr. at 235°, almost quantitative after 5 min. at 255°).

*Anal.* Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.5. Found: C, 84.2; H, 6.2; N, 4.3.

**1-(2-Hydroxy-1-naphthyl)-2,5-dimethylpyrrole**, m.p. 135–136° (yield: 80% after 14 hr. at 235°).

*Anal.* Calcd. for $C_{16}H_{15}NO$: C, 81.0; H, 6.4; N, 5.9; O, 6.7. Found: C, 80.7; H, 6.4; N, 6.0; O, 6.8.

**1-(8-Hydroxy-6-quinolyl)-2-methyl-5-phenylpyrrole**, shiny yellow leaflets (from methanol), m.p. 216–217° (yield 58% after 7 hr. at 235°).

*Anal.* Calcd. for $C_{20}H_{16}N_2O$: C, 80.0; H, 5.4; N, 9.4; O, 5.3. Found: C, 79.8; H, 5.4; N, 9.4; O, 5.5.

**Preparation of β-Diethylaminoethyl Ethers.**—A solution of the hydroxy compound (0.2 mole) in 300 ml. of absolute ethanol was treated with sodium hydroxide (0.2 mole) dissolved in 20 ml. of water; the solution was warmed for 5 min.,

(4) J. H. Helberger, *Ann.*, **522**, 269 (1936); R. Rips, Ch. Derappe, and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 390 (1960).

TABLE I

| 2-Methylpyrrole | M.p., °C. | Yield, % | Formula | Carbon % Calcd. | Carbon % Found | Hydrogen % Calcd. | Hydrogen % Found | Nitrogen % Calcd. | Nitrogen % Found |
|---|---|---|---|---|---|---|---|---|---|
| 1-(*o*-Hydroxyphenyl)-5-*p*-tolyl[a] | 93 | 80 | $C_{18}H_{17}NO$ | 82.1 | 82.3 | 6.5 | 6.6 | 5.3 | 5.4 |
| 1-(*o*-Methoxyphenyl)-5-*p*-tolyl-[b] | 76–77 | 85 | $C_{19}H_{19}NO$ | 82.3 | 82.1 | 6.9 | 6.8 | 5.1 | 5.2 |
| 1-(5-Chloro-2-hydroxyphenyl)-5-phenyl-[c] | 111 | 73 | $C_{17}H_{14}ClNO$ | 71.9 | 71.8 | 5.0 | 5.0 | 4.9 | 4.8 |
| 1-(5-Chloro-2-methoxyphenyl)-5-phenyl-[d] | 80 | 73 | $C_{18}H_{16}ClNO$ | — | — | — | — | 4.6 | 4.9 |
| 1-(2-Methoxy-1-naphthyl)-5-phenyl-[e] | 67–68 | 52 | $C_{22}H_{19}NO$ | 84.3 | 84.0 | 6.1 | 6.1 | 4.5 | 4.5 |
| 1-(2-Methoxy-1-naphthyl)-5-*p*-tolyl-[f] | 123 | 62 | $C_{23}H_{21}NO$ | 84.4 | 84.2 | 6.5 | 6.2 | 4.3 | 4.4 |
| 1-(2-Methoxy-1-naphthyl)-5-methyl-[g] | 92–93 | 71 | $C_{17}H_{17}NO$ | 81.3 | 81.0 | 6.8 | 6.7 | 5.6 | 5.8 |
| 1-(8-Methoxy-6-quinolyl)-5-phenyl-[h] | 139 | 53 | $C_{21}H_{18}N_2O$ | — | — | — | — | 8.9 | 9.1 |

[a] Calcd.: O, 6.1. Found: O, 6.1. [b] B.p. 219° (18 mm.); calcd.: O, 5.8. Found: O, 5.9. [c] Calcd.: Cl, 12.5. Found: Cl, 12.7. [d] B.p. 223–224° (18 mm.); calcd.: Cl, 11.9. Found: Cl, 12.1. [e] B.p. 250–252° (17 mm.). [f] B.p. 255–259° (17 mm.); calcd.: O, 4.9. Found: O, 4.9. [g] B.p. 191–192° (19 mm.); calcd.: O, 6.4. Found: O, 6.5. [h] B.p. 279–280° (15 mm.); calcd.: O, 5.1. Found: O, 5.2.

TABLE II

| Compound | M.p., °C. | B.p.°(mm.) | Formula | Carbon | | Hydrogen | | Chlorine | | Nitrogen | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| II | — | 234–235 (15) | $C_{24}H_{30}N_2O$ | 79.5 | 79.4 | 8.3 | 8.1 | — | | 7.7 | 7.7 |
| Hydrochloride of II-HCl | 141–142 | — | $C_{24}H_{31}ClN_2O$ | — | | — | | 8.9 | 8.8 | 7.0 | 6.9 |
| III | 62–63 | 254–255 (18) | $C_{23}H_{27}ClN_2O$ | 72.1 | 72.1 | 7.1 | 7.1 | 9.3 | 9.2 | 7.3 | 7.5 |
| Hydrochloride of III-HCl | 182–183 | — | $C_{23}H_{28}Cl_2N_2O$ | 65.9 | 65.8 | 6.7 | 6.7 | 16.9 | 17.1 | 6.7 | 6.7 |
| IV | — | 271–272 (17) | $C_{27}H_{30}N_2O$ | 81.4 | 81.1 | 7.6 | 7.5 | — | | 7.0 | 6.8 |
| Hydrochloride of IV-HCl | 117–118 | — | $C_{27}H_{31}ClN_2O$ | — | | — | | 8.2 | 8.4 | 6.4 | 6.3 |
| V | — | 212–213 (0.5) | $C_{28}H_{32}N_2O$ | — | | — | | — | | 6.8 | 6.5 |
| Hydrochloride of V-HCl | *ca.* 100–101 | — | $C_{28}H_{33}ClN_2O$ | not analyzed | | | | | | | |
| VI | — | 240–242 (22) | $C_{22}H_{28}N_2O$ | 78.5 | 78.2 | 8.4 | 8.2 | — | | 8.3 | 8.5 |
| Hydrochloride of VI-HCl | 186–187 | — | $C_{22}H_{29}ClN_2O$ | — | | — | | — | | 7.5 | 7.4 |
| VIII[a] | 125–126 | 305–310 (20) | $C_{26}H_{29}N_3O$ | 78.2 | 78.4 | 7.3 | 7.2 | — | | 10.5 | 10.7 |

[a] With hydrogen chloride in ether, this compound gave an unstable salt, m.p. 122–123°, which analyzed as a monohydrochloride. *Anal.* Calcd. for $C_{26}H_{30}ClN_3O$: Cl, 8.1; N, 9.6. Found: Cl, 8.1; N, 9.3.

β-diethylaminoethyl chloride (0.22 mole) (prepared from the hydrochloride by basification with aqueous sodium hydroxide) was added with stirring, the mixture was refluxed for 5 min. and, after cooling, basified with aqueous sodium hydroxide. The reaction product was extracted in methylene chloride, the solution dried over sodium sulfate, the solvent distilled and the residue vacuum-fractionated. The hydrochlorides were prepared with hydrogen chloride in ether solution, and recrystallized from benzene or cyclohexane. The ethers and their hydrochlorides are listed in Table II. Most of the ethers were non-crystalline viscous oils; those which were solid were recrystallized from heptane.

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## Phenyl-bridged Analogs of Phenylbutazone

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The side-reactions of phenylbutazone[1] which limit its useful anti-inflammatory activity spurred a search for less toxic analogs. The suggestion by Bavin and co-workers[2] that the toxicity is associated with the hydrazobenzene portion of the molecule seemed logical. Since the character of hydrazobenzene might be sharply affected by bridging the *ortho* positions of the phenyl rings, we prepared a few such analogs as shown in Table I.

At the start of this work the closest analogs to this series were two benzo[c]cinnoline derivatives (I, X = —, R = H, Bu) reported by Kühn and Erlenmeyer.[3] Quite recently several sulfone-bridged analogs (I, X = $SO_2$) have been reported by Michel and Matter[4] at Haco, A. G., and two Belgian patents[5] indicate that workers at Geigy have also explored the series reported here.

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 322.
(2) E. M. Bavin, D. J. Drain, D. E. Seymour, and P. D. Waterhouse, *J. Pharm. Pharmacol.*, **7**, 1022 (1955).
(3) H. Kühn and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 531 (1955).
(4) K. Michel and M. Matter, *ibid.*, **44**, 2204 (1961).
(5) J. R. Geigy, S. A., Belgian Patents 605,985, and 607,062.