

were performed on fluorescent silica gel G plates, spots detected by uv or exposure to I₂ vapor.

(6aS)-10,11-Dimethoxyaporphine Hydrogen (2S,3S)-Tartrate (2). A solution of 3.0 g (20 mmol) of (-)-tartaric acid in 20 ml of 50% EtOH-EtOAc was added to a solution of 5.0 g (17 mmol) of *rac*-10,11-dimethoxyaporphine base⁵ in 10 ml of EtOAc. After adding more EtOAc and cooling, the insoluble crude tartrate salt was recrystallized several times from EtOH-EtOAc-hexane to give 0.85 g of (+)-10,11-dimethoxyaporphine hydrogen (-)-tartrate with a constant melting point of 179–184° dec, $[\alpha]^{25}_D +64.0^\circ$ (*c* 1, H₂O).[‡] The nmr (D₂O) of this tartrate salt and tlc R_f (5% MeOH-CHCl₃) of the corresponding base were identical with those of the 6aR isomer.^{6d} *Anal.* (C₁₉H₂₁NO₂·C₄H₆O₆) C, H, N.

(6aR)-10,11-Dimethoxyaporphine Hydrogen (2R,3R)-Tartrate (2). Mother liquors from isolation of the 6aS isomer were combined, concentrated, and converted to 3.7 g of base with 5% NaOH and Et₂O extraction. After addition of 3 g of (+)-tartaric acid and several recrystallizations from EtOH-EtOAc-hexane, 500 mg of (-)-10,11-dimethoxyaporphine hydrogen (+)-tartrate, mp 177–183° dec, $[\alpha]^{25}_D -59.6^\circ$ (*c* 1, H₂O), was obtained and found to be identical by nmr (D₂O), tlc (5% MeOH-CHCl₃ on the base), and mixture melting point with an authentic sample prepared from apomorphine.^{6d} *Anal.* (C₁₉H₂₁NO₂·C₄H₆O₆) C, H, N.

(6aS)-10,11-Dihydroxyaporphine Hydrochloride (1). The base obtained from 100 mg (0.224 mmol) of (6aS)-10,11-dimethoxyaporphine hydrogen (2S,3S)-tartrate by neutralization with saturated NaHCO₃ solution and EtOAc extraction was dissolved in 1.5 ml of Ac₂O and added to a mixture of 1.0 ml of 57% HI and 1.0 ml of Ac₂O. The HI-Ac₂O mixture was decolorized by warming on the steam bath with a few drops of H₃PO₂ and cooling to room temperature before addition of the aporphine. The mixture was stirred at reflux under CO₂ for 2 hr and cooled and 3 ml of H₂O was added. After concentrating under reduced pressure at 80–90°, 5 ml of H₂O was added and the solution was concentrated again. Excess saturated NaHCO₃ was added to the residue and the crude product extracted with EtOAc which was then washed (saturated NaCl-H₂O), dried (Na₂SO₄), and filtered. Excess EtOH-anhydrous HCl solution (7 N) was added and after complete removal of solvent under reduced pressure at 40–50°, the residue was dissolved in 8 ml of 50% MeOH-EtOAc and filtered. The filtrate was concentrated at 15 mm of pressure and 40–50° until solid began to precipitate. After cooling, the product was filtered and dried immediately at 100° and 0.2 mm to give 35 mg (49%) of (6aS)-10,11-dihydroxyaporphine hydrochloride hydrate, mp 178–180° shrink, 220° darken, 258–268° dec. An analytical sample was obtained by drying at 138° (0.2 mm): mp 200° darken, 265.0–268.0° dec; $[\alpha]^{25}_D$ 5780 Å +55.3°, 5460 Å +68.7°, 4360 Å +69.4° (*c* 0.15, O₂ free EtOH); λ max 2745 Å (ϵ 17,300), 3126 (3960), sh 2640–2700, 2810–2870. \S The nmr (DMSO-*d*₆) of this sample and tlc R_f (5% MeOH-CHCl₃) of the corresponding base were identical with those of an authentic sample of (6aR)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate. *Anal.* (C₁₇H₁₇NO₂·HCl) C, H, N.

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[‡] A sample of (6aR)-10,11-dimethoxyaporphine hydrogen (2R,3R)-tartrate, mp 177–182° dec, prepared from apomorphine and CH₂N₂,^{6d} was found to have $[\alpha]^{25}_D -65.9^\circ$ (*c* 1, H₂O).

\S Found for an authentic sample of (6aR)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate: mp 220° darken, 258–268° dec; $[\alpha]^{25}_D$ 5780 Å 62.0°, 5460 Å 68.1°, 4360 Å 79.4° (*c* 0.15, O₂ free EtOH); λ max 2750 Å (ϵ 18,200), 3132 (3750), sh 2650–2680, 2810–2855.

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5-Benzoyl-1-methylpyrrole-2-acetic Acids as Antiinflammatory Agents. 2. The 4-Methyl Compounds

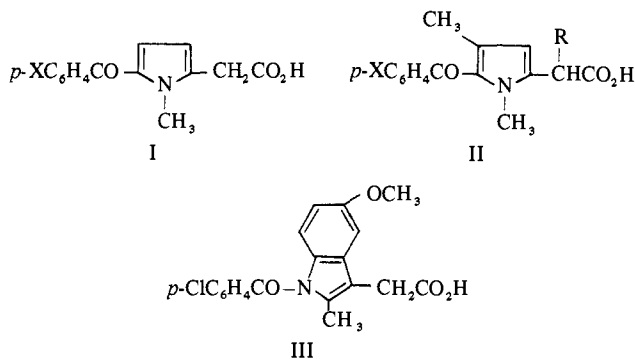
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We recently disclosed some 5-benzoyl-1-methylpyrrole-2-acetic acids (I) which had antiinflammatory activity.¹ The potency of these compounds was intermediate between phenylbutazone and indomethacin (III).

We would like to report on a structural modification that gives compounds with significantly greater potency. When a methyl group is introduced at the 4 position of the pyrrole ring, certain of the compounds (II) have a potency comparable to indomethacin.

Compounds of type I were designed as isosteres of the portion of the indomethacin molecule responsible for the activity. In both indomethacin and the compounds of type II, the aryl group is flanked on both sides by a carbon substituent. The steric influence of the carbon substituents on the conformation of the aryl group might account for the potency of these compounds.



Pharmacology. The relative potency of compounds of type II in the kaolin- and carrageenan-induced edema tests is shown in Table I. Further aspects of the pharmacology of these compounds will be published elsewhere.

Chemistry. The preparation of an appropriate pyrrole starting material VI was carried out by a modification of the Hantzsch pyrrole synthesis. Upon mixing diethyl acetone-dicarboxylate and aqueous methylamine, a transient precipitate of a white crystalline solid is formed. If chloroacetone is added rapidly with cooling before the disappearance of the precipitate, a good yield of ethyl 1,4-dimethyl-3-

Table I. Relative Potency (RP) of Type II Compounds in Edema Tests

Compound	RP kaolin edema (95% confidence limits)	RP carrageenan edema (95% confidence limits)
Indomethacin	1.00	1.00
I, X = CH ₃ ^a	0.28 (0.19-0.42)	0.38 (0.24-0.58)
II, X = Cl; R = CH ₃ ^b	4.25 (2.52-8.88)	1.30 (0.79-2.22)
II, X = F; R = H	1.06 (0.64-1.79)	1.62 (0.98-2.93)
II, X = CH ₃ ; R = H	0.48 (0.30-0.84)	0.19 (0.13-0.28)
II, X = Cl; R = H		1.88 (0.73-13.2)

^aDesignated as tolmetin. ^bDesignated as McN-2891.

ethoxycarbonylpyrrole-2-acetate (VI) is produced. In the conventional Hantzsch synthesis, ethyl 1,5-dimethylpyrrole-2-acetate would have been the expected product. A similar instance of anomalous substitution in a Hantzsch pyrrole synthesis was observed by Childs and Johnson.² They were able to obtain either methyl 1,2,5-trimethylpyrrole-2-carboxylate or methyl 1,2,4-trimethylpyrrole-2-carboxylate from methyl acetoacetate, chloroacetone, and methylamine by a "minor change in experimental conditions" but made no comment on the reason for this.

We feel that a plausible explanation for the anomalous reaction is that a methylamine salt IV of diethyl acetonedicarboxylate is the initially formed white precipitate. Upon isolation, it shows the ir characteristics and the solubility profile of an ammonium salt and is clearly spectrally different from the enamine which can be produced from it by dehydration. The diethyl acetonedicarboxylate anion then attacks the carbonyl group of chloroacetone to give adduct V. A similar adduct has been suggested in the Feist-Benary furan synthesis.³⁻⁵ Displacement of chloride by amine, condensation with the acetonedicarboxylate β-carbonyl, and dehydration complete the reaction. The structural assignment of VI was made by uv in analogy to that of Childs and Johnson. The remainder of the synthetic sequence leading to compounds of type II is illustrated in Scheme I.

Experimental Section

All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were obtained using a Varian A-60 instrument (Me₂Si). Elemental analyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark. Where analyses are indicated by the symbols of the elements, the analytical results obtained for these elements are within ±0.4% of the theoretical values. The details of the pharmacological methods have been previously reported.¹

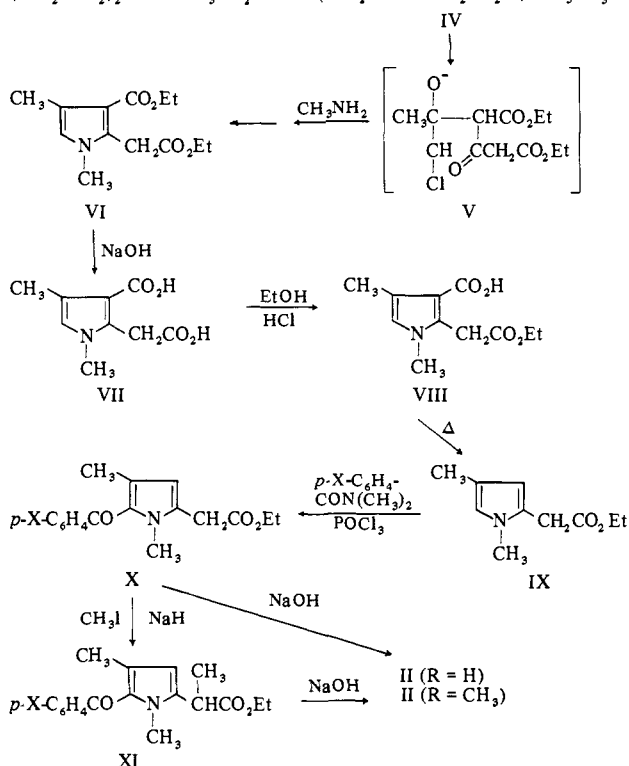
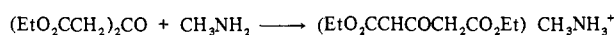
Chemistry. Ethyl 1,4-Dimethyl-3-ethoxycarbonylpyrrole-2-acetate (VI). A 20.2-g sample of diethyl acetonedicarboxylate (0.10 mol) was added rapidly to 75 ml of 40% aqueous CH₃NH₂ at 15°. A white precipitate formed. Addition of 18.5 g (0.20 mol) of chloroacetone was started immediately with cooling. The rate of addition was adjusted to keep the temperature below 40°. The mixture was allowed to come to room temperature. After completion of the addition (1 hr), the mixture was poured into ice-HCl. The precipitate was filtered, washed with H₂O, and recrystallized from *i*-PrOH to give 17.5 g (70% yield), mp 71-73°. *Anal.* (C₁₃H₁₉NO₄) C, H, N.

3-Carboxy-1,4-dimethylpyrrole-2-acetic Acid (VII). Heating 176 g (0.7 mol) of VI in 1760 ml of 25% NaOH under reflux for 3 hr gave, upon acidification, filtration, and air drying, 130 g (98% yield) of a gray solid. It was recrystallized from Me₂CO-H₂O to give crystals, mp 220-222° dec. *Anal.* (C₉H₁₁NO₄) C, H.

Ethyl 3-Carboxy-1,4-dimethylpyrrole-2-acetate (VIII). A solution of 60.4 g (0.31 mol) of VII in 1300 ml of 0.5% dry HCl in EtOH was heated under reflux for 20 min.⁶ Upon cooling, a precipitate separated which was collected and dried, 48 g (70% yield), mp 182-184°. *Anal.* (C₁₁H₁₅NO₄) C, H.

Ethyl 1,4-Dimethylpyrrole-2-acetate (IX). A 70-g sample of VIII was heated under N₂ at 190-210° until gas evolution ceased.

Scheme I



The residue was distilled to give 41 g (73% yield) of a colorless oil, bp 82-90° (0.025 mm). *Anal.* (C₁₀H₁₅NO₂) C, H.

Vilsmeier Aroylation of IX. A solution of 0.1 mol of the *p*-X-*N,N*-dimethylbenzamide and 15.4 g (0.1 mol) of POCl₃ in 50 ml of ClCH₂CH₂Cl was heated under reflux for 30 min. A solution of 18.1 g (0.1 mol) of IX in 30 ml of ClCH₂CH₂Cl was added. The mixture was heated under reflux for 1 hr and cooled to room temperature (where X = F, it was stirred overnight at room temperature). A solution of 68 g (0.5 mol) of NaOAc·3H₂O in 120 ml of H₂O was added and the mixture was heated under reflux for 15 min. It was partitioned between H₂O and CHCl₃. The organic solution was dried (MgSO₄) and evaporated *in vacuo*. The residue was recrystallized from *i*-PrOH. The products obtained are shown in Table II.

Ethyl 5-*p*-Chlorobenzoyl-1,4,α-trimethylpyrrole-2-acetate (XI, X = Cl). To a NaH suspension (28.8 g of 50% NaH in mineral oil, washed with PhCH₃, 0.6 mol) in 800 ml of dry dimethoxyethane was added 173 g (0.6 mol) of X (X = Cl) in portions. The solution was stirred at room temperature for 3 hr. A 94-g (0.66 mol) sample of CH₃I was added dropwise. The mixture was stirred for 1 hr. It was poured into H₂O and extracted into Et₂O. The Et₂O solution was washed with H₂O, dried (MgSO₄), and evaporated *in vacuo*. The residue was recrystallized from *i*-PrOH to give 128 g (70% yield) of tan crystals, mp 98-99°. *Anal.* (C₁₈H₂₀ClNO₂) C, H.

Saponification of Esters X and XI. A 0.1-mol sample of the ester was refluxed for 30 min with 110 ml of 1 N NaOH. The solu-

Table II. Ethyl 5-Aroyl-1,4-dimethylpyrrole-2-acetates

Product	Mp, °C	Yield, %	<i>Anal.</i>
X, X = Cl	108-110	52	C, H
X, X = F	86-87	36	C, H
X, X = CH ₃	90-91	40	C, H

Table III. 5-Aroyl-1,4-dimethyl- and 1,4,α-Trimethylpyrrole-2-acetic Acids

R	X	Mp, °C	Yield, %	Crystn solvent	<i>Anal.</i>
H	Cl	178-179 dec	83	<i>i</i> -PrOH	C, H, N
CH ₃	Cl	153-155 dec	79	Benzene	C, H, N
H	F	176-178 dec	91	<i>i</i> -PrOH	C, H, N
H	CH ₃	160-161 dec	82	<i>i</i> -PrOH	C, H, N

tion was poured into HCl. The precipitate was filtered and air-dried. The products II (R = CH₃) are described in Table III.

Acknowledgment. The authors thank Mrs. Susan Libsch for assistance in chemical synthesis and Dr. Harold R. Almond for analytical data.

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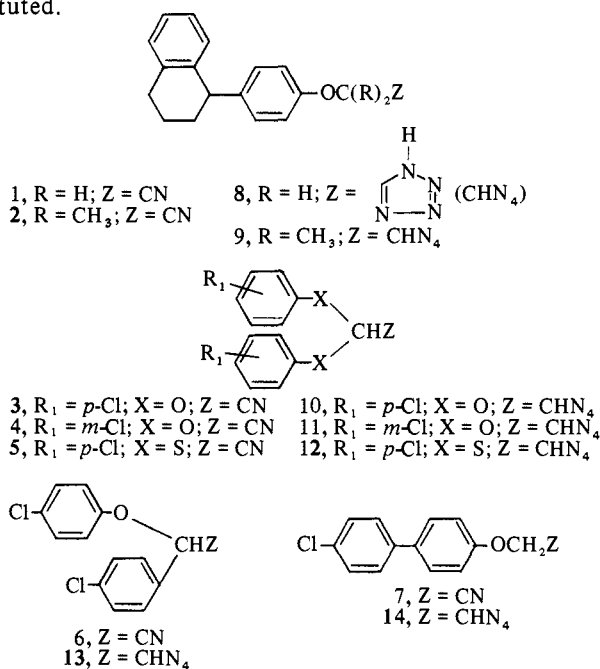
Hypocholesterolemic 5-Methyltetrazole Derivatives[†]

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There remains a great need for developing superior agents for the control of hyperlipoproteinemia and associated atherosclerotic disease. This note describes the synthesis and biological evaluation of a number of related compounds that have resulted from our continued interest in 5-substituted tetrazoles as potential hypolipidemic agents.²

Chemistry. In general, the tetrazoles 8–14 were prepared from the corresponding nitriles 1–7 by standard synthetic methods (see Tables I and II and Experimental Section). The yields varied, with generally poor conversions resulting when the α carbon of the nitrile precursor was highly substituted.



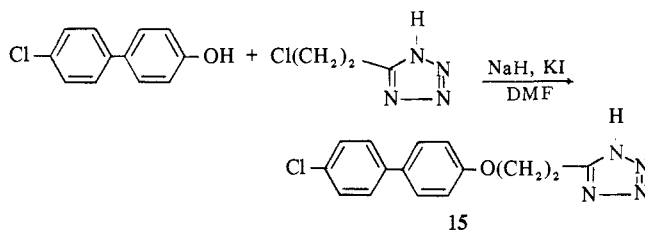
Compound 15 was prepared by tetrazolylation of *p*-(4-chlorophenyl)phenol.²

Biological Evaluation. In the hypocholesterolemic screen the tetrazoles were administered orally to rats once daily for 4 days (0.5% suspension in carboxymethylcellulose). Serum

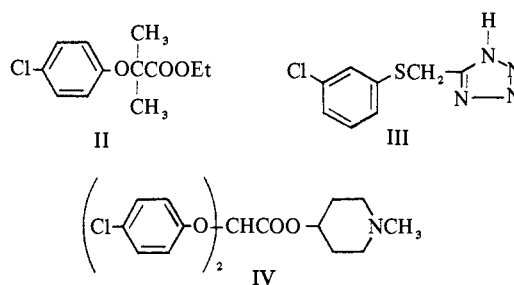
Table I. Nitriles

No.	Yield, ^a %	Recrystn solvent	Mp or bp, °C (mm)	Formula	Analyses
1	91		164–169 (0.05)	C ₁₈ H ₁₇ NO	
2	26		<i>b</i>	C ₂₀ H ₂₁ NO	
3	68.2		<i>b</i>	C ₁₄ H ₉ Cl ₂ NO ₂	
4	96.6		151–152 (0.1)	C ₁₄ H ₉ Cl ₂ NO ₂	
5	37.9	2-PrOH	109.5–110.5	C ₁₄ H ₉ Cl ₂ NS ₂	C, H, N, S
6	72.7		139–145 (0.025)	C ₁₄ H ₉ Cl ₂ NO	C, H, N
7	95	CCl ₄	78–80	C ₁₄ H ₁₀ ClNO	C, H, N

^aYield from penultimate intermediate. ^bUsed in the crude state.



cholesterol values were determined by the method of Zlatkis, *et al.*,³ as modified for the autoanalyzer (method Np-24) and are recorded in Table III. In general, compounds that lowered serum cholesterol by at least 20% proved to be significantly active. The most active compound at 100 mg/kg is the bis(*p*-chlorophenoxy)methyl derivative 10. Significant activity is lost if: (a) oxygen is replaced by sulfur (12); (b) chlorine is in the meta position relative to the ether linkages (11); (c) one *p*-chlorophenoxy group is replaced by a *p*-chlorophenyl group (13). The remaining compounds listed have generally poor hypocholesterolemic activity. In this assay compound 10 has greater activity than the reference agent ethyl 2-methyl-2-(*p*-chlorophenoxy)propionate (clofibrate, II) (MED \approx 400 mg/kg)⁴ and 5-(3-chlorophenylthiomethyl)tetrazole (III) (MED \approx 200 mg/kg)² but less activity than 1-methyl-4-piperidyl bis(*p*-chlorophenoxy)acetate⁵ (IV)



(MED \approx 25 mg/kg in our assay). Using Lofland's semi-automated procedure for the determination of triglycerides,⁶ compound 10 was found to significantly lower serum triglyceride levels (–44%) when administered orally to male Sprague-Dawley rats at 50 mg/kg per day for 2 weeks.

Experimental Section[‡]

Nitriles (Table I). *p*-(1,2,3,4-Tetrahydro-1-naphthyl)phenoxyacetonitrile (1) and 4-(*p*-Chlorophenyl)phenoxyacetonitrile (7).

[‡]The melting points were obtained in capillary tubes with a Thomas-Hoover Unimelt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within $\pm 0.4\%$ of the theoretical values (see also Tables I and II). Spectral data (ir and nmr) for all compounds were consistent for the reported structures and were recorded on Beckmann Model IR9 and Varian Model A-60 recording spectrometers, respectively.

[†]Some of these compounds have been described in ref 1.