were performed on fluorescent silica gel G plates, spots detected by uv or exposure to I_2 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 base[5] 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° (*c* 1, H_2O).‡ The nmr (D_2O) of this tartrate salt and tlc R_f (5% MeOH–$CHCl_3$) of the corresponding base were identical with those of the 6a*R* isomer.[6d] *Anal.* ($C_{19}H_{21}NO_2 \cdot C_4H_6O_6$) C, H, N.

(6aR)-10,11-Dimethoxyaporphine Hydrogen (2R,3R)-Tartrate (2). Mother liquors from isolation of the 6a*S* isomer were combined, concentrated, and converted to 3.7 g of base with 5% NaOH and Et_2O 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° (*c* 1, H_2O), was obtained and found to be identical by nmr (D_2O), tlc (5% MeOH–$CHCl_3$ on the base), and mixture melting point with an authentic sample prepared from apomorphine.[6d] *Anal.* ($C_{19}H_{21}NO_2 \cdot C_4H_6O_6$) C, H, N.

(6aS)-10,11-Dihydroxyaporphine Hydrochloride (1). The base obtained from 100 mg (0.224 mmol) of (6a*S*)-10,11-dimethoxyaporphine hydrogen (2*S*,3*S*)-tartrate by neutralization with saturated $NaHCO_3$ solution and EtOAc extraction was dissolved in 1.5 ml of Ac_2O and added to a mixture of 1.0 ml of 57% HI and 1.0 ml of Ac_2O. The HI–Ac_2O mixture was decolorized by warming on the steam bath with a few drops of H_3PO_2 and cooling to room temperature before addition of the aporphine. The mixture was stirred at reflux under CO_2 for 2 hr and cooled and 3 ml of H_2O was added. After concentrating under reduced pressure at 80–90°, 5 ml of H_2O was added and the solution was concentrated again. Excess saturated $NaHCO_3$ was added to the residue and the crude product extracted with EtOAc which was then washed (saturated NaCl–H_2O), dried (Na_2SO_4), 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 (6a*S*)-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; $[\alpha]^{25}$ 5780 Å +55.3°, 5460 Å +68.7°, 4360 Å +69.4° (*c* 0.15, O_2 free EtOH); λ max 2745 Å (ε 17,300), 3126 (3960), sh 2640–2700, 2810–2870.§ The nmr (DMSO-d_6) of this sample and tlc R_f (5% MeOH–$CHCl_3$) of the corresponding base were identical with those of an authentic sample of (6a*R*)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate. *Anal.* ($C_{17}H_{17}NO_2 \cdot HCl$) C, H, N.

Acknowledgment. The authors wish to thank Dr. B. H. Arison and W. R. McGaughran for the nmr spectra, E. L. Cresson for the uv spectra, and Dr. G. Smith and his staff for the optical rotations. We are also indebted to Dr. L. S. Watson for the cardiovascular data.

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‡ A sample of (6a*R*)-10,11-dimethoxyaporphine hydrogen (2*R*,3*R*)-tartrate, mp 177–182° dec, prepared from apomorphine and CH_2N_2,[6d] was found to have $[\alpha]^{25}D$ −65.9° (*c* 1, H_2O).

§ Found for an authentic sample of (6a*R*)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate: mp 220° darken, 258–268° dec; $[\alpha]^{25}$ 5780 Å 62.0°, 5460 Å 68.1°, 4360 Å 79.4° (*c* 0.15, O_2 free EtOH); λ max 2750 Å (ε 18,200), 3132 (3750), sh 2650–2680, 2810–2855.

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

John R. Carson* and Stewart Wong

McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034.
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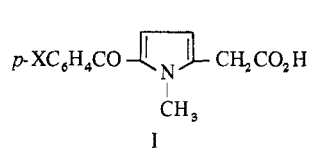
We recently disclosed some 5-benzoyl-1-methylpyrrole-2-acetic acids (I) which had antiinflammatory activity.[1] The potency of these compounds was intermediate between phenylbutazone and indomethacin (III).

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 aroyl group is flanked on both sides by a carbon substituent. The steric influence of the carbon substituents on the conformation of the aroyl group might account for the potency of these compounds.



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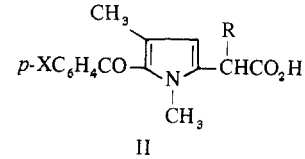

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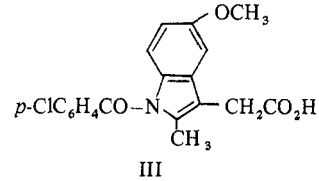


III

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 Hantzch pyrrole synthesis. Upon mixing diethyl acetonedicarboxylate 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)

[a]Designated as tolmetin. [b]Designated as McN-2891.

ethoxycarbonylpyrrole-2-acetate (VI) is produced. In the conventional Hantzch synthesis, ethyl 1,5-dimethylpyrrole-2-acetate would have been the expected product. A similar instance of anomolous substitution in a Hantzch 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 anomolous 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 (Me_4Si). 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]

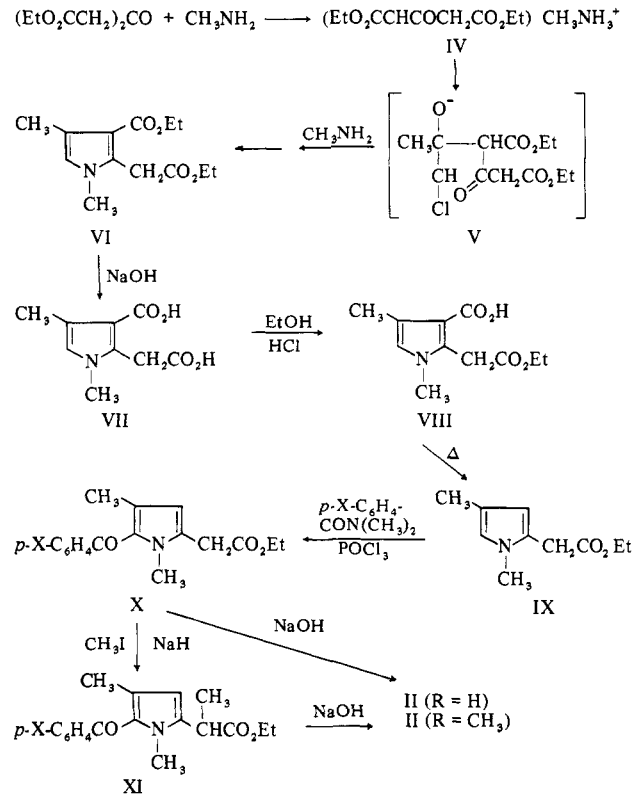
Chemistry. Ethyl 1,4-Dimethyl-3-ethoxycarbonylpyrrole-2-acetate (VI). A 20.2-g sample of diethyl acetonedicarboxylate (0.10 mol) was added rapidly to 75 ml of 40% aqueous CH_3NH_2 at 15°. A white precipitate formed. Addition of 18.5 g (0.20 mol) of chloroacetone was started immediately with cooling. 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 H_2O, and recrystallized from *i*-PrOH to give 17.5 g (70% yield), mp 71–73°. *Anal.* ($C_{13}H_{19}NO_4$) 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 Me_2CO–H_2O to give crystals, mp 220–222° dec. *Anal.* ($C_9H_{11}NO_4$) 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.* ($C_{11}H_{15}NO_4$) C, H.

Ethyl 1,4-Dimethylpyrrole-2-acetate (IX). A 70-g sample of VIII was heated under N_2 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.* ($C_{10}H_{15}NO_2$) 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 $POCl_3$ in 50 ml of $ClCH_2CH_2Cl$ was heated under reflux for 30 min. A solution of 18.1 g (0.1 mol) of IX in 30 ml of $ClCH_2CH_2Cl$ 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·$3H_2O$ in 120 ml of H_2O was added and the mixture was heated under reflux for 15 min. It was partitioned between H_2O and $CHCl_3$. The organic solution was dried ($MgSO_4$) 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 $PhCH_3$, 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 CH_3I was added dropwise. The mixture was stirred for 1 hr. It was poured into H_2O and extracted into Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was recrystallized from *i*-PrOH to give 128 g (70% yield) of tan crystals, mp 98–99°. *Anal.* ($C_{18}H_{20}ClNO_3$) 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, %	*Anal.*
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	*Anal.*
H	Cl	178–179 dec	83	*i*-PrOH	C, H, N
CH_3	Cl	153–155 dec	79	Benzene	C, H, N
H	F	176–178 dec	91	*i*-PrOH	C, H, N
H	CH_3	160–161 dec	82	*i*-PrOH	C, H, N

tion was poured into HCl. The precipitate was filtered and air-dried. The products II (R = CH_3) 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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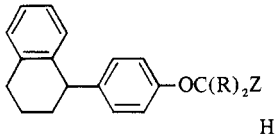
Hypocholesterolemic 5-Methyltetrazole Derivatives†,[1]

Ronald L. Buchanan* and Vilmars Sprancmanis

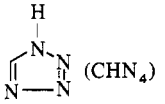
Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201. *Received July 14, 1972*

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]

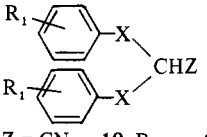
Chemistry. In general, the tetrazoles **8–14** were prepared from the corresponding nitriles **1–7** by standard synthetic methods (see Tables I and II and Experimental Section). The yields varied, with generally poor conversions resulting when the α carbon of the nitrile precursor was highly substituted.



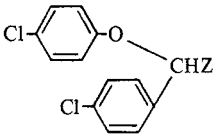
1, R = H; Z = CN
2, R = CH_3; Z = CN



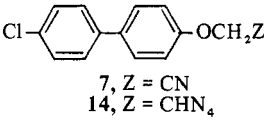
8, R = H; Z = CHN_4
9, R = CH_3; Z = CHN_4



3, R_1 = *p*-Cl; X = O; Z = CN
4, R_1 = *m*-Cl; X = O; Z = CN
5, R_1 = *p*-Cl; X = S; Z = CN
10, R_1 = *p*-Cl; X = O; Z = CHN_4
11, R_1 = *m*-Cl; X = O; Z = CHN_4
12, R_1 = *p*-Cl; X = S; Z = CHN_4



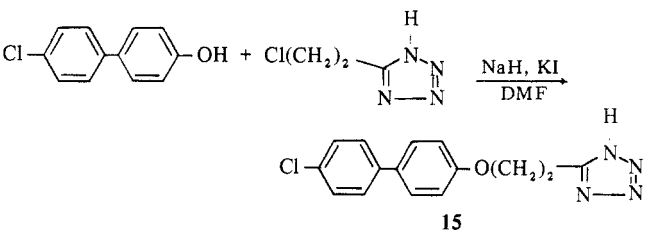
6, Z = CN
13, Z = CHN_4



7, Z = CN
14, Z = CHN_4

Compound **15** was prepared by tetrazolylethylation 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 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 ≃ 400 mg/kg)[4] and 5-(3-chlorophenylthiomethyl)tetrazole (III) (MED ≃ 200 mg/kg)[2] but less activity than 1-methyl-4-piperidyl bis(*p*-chlorophenoxy)acetate[5] (IV)



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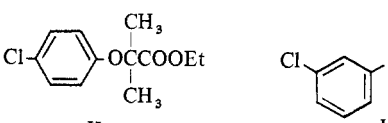

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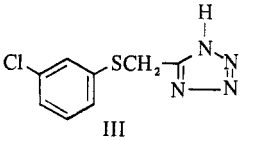
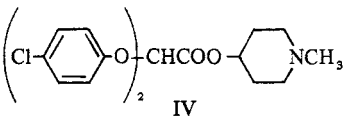


III



IV

(MED ≃ 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).

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		*b*	$C_{20}H_{21}NO$	
3	68.2		*b*	$C_{14}H_9Cl_2NO_2$	
4	96.6		151–152 (0.1)	$C_{14}H_9Cl_2NO_2$	
5	37.9	2-PrOH	109.5–110.5	$C_{14}H_9Cl_2NS_2$	C, H, N, S
6	72.7		139–145 (0.025)	$C_{14}H_9Cl_2NO$	C, H, N
7	95	CCl_4	78–80	$C_{14}H_{10}ClNO$	C, H, N

[a] Yield from penultimate intermediate. [b] Used in the crude state.

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

‡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 ±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.