CHART I
TRIFLUOROMETHYL PYRAZOLE DERIVATIVES

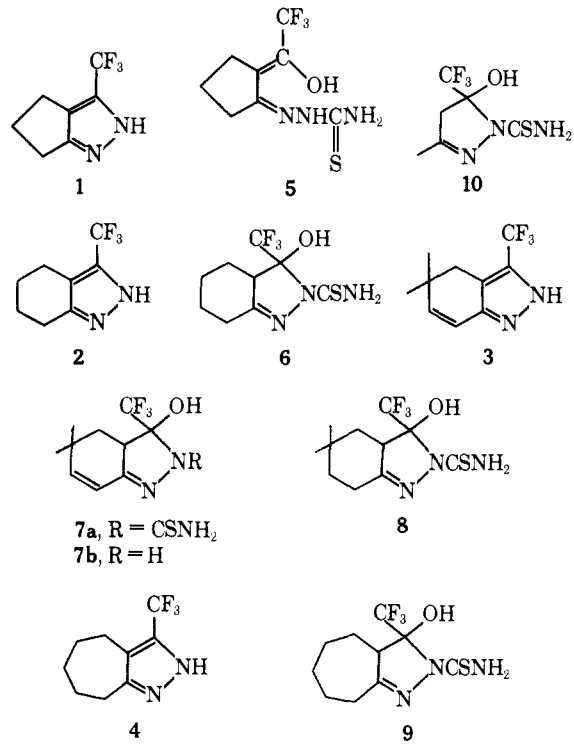

TABLE II
α-TRIFLUOROACETYL KETONES

Precursor of compd no.	% yield	Bp (mm), °C	Formula[a]
3, 7a, 7b	71	34–36 (0.1)	$C_{10}H_{11}F_3O_2$
8	24	31–33 (0.25)	$C_{10}H_{13}F_3O_2$

[a] *Anal.* C, H, F.

poured into H_2O, and the oily or solid material was collected, dried, and crystd to purity (see Table I).

3,4-Condensed-5-trifluoromethylpyrazoles. Method B.—The starting trifluoroacetyl ketone (0.025 mole) was dissolved in 50 ml of AcOH along with 5 ml (0.1 mole) of hydrazine hydrate and heated on the steam bath for 2 hr. Work-up was the same as described in method C.

5,5-Dimethyl-3-hydroxy-3-trifluoromethyl-3,3α,4,5-tetrahydroindazole (7b). Method C.—The starting trifluoroacetyl ketone (13.5 mmoles) was dissolved in 50 ml of 80% dioxane–H_2O and 2 ml (40 mmoles) of hydrazine hydrate was added. After standing 3 hr at room temp the sol was refrigerated overnight. The residual oil remaining after solvent removal at reduced pressure was extd into 5% NaOH, washed with Et_2O, acidified with 5% HCl, and extd back into Et_2O. Et_2O removal and recrystn from heptane gave **7b.**

2-(α,α,α-Trifluoro-β-hydroxyethylidene)cyclopentanone thiosemicarbazone was prepd and isolated as described in method B.

Antibacterial Screening.—The drug, in 1 ml of the appropriate dilu, was added to 9 ml of seed agar in sterile petri dishes. The hardened surface was inoculated with the test organism and incubated 18 hr at 35°. The end point, min inhibitory concn (MIC) in μg/ml was the least amt of drug that completely inhibited the test organism.

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Structure of the Diuretic Merbaphen

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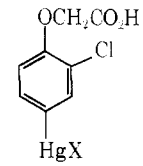
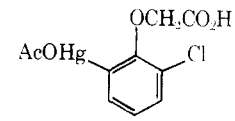
Although the clinical use of merbaphen has long since been abandoned, the compound is still of interest in structure–activity studies.[1] It was introduced as an antisyphilitic agent[2] but while being administered for that purpose it was found to have diuretic properties[3] greater than any drug then known. Thus it was demonstrated for the first time that profound diuresis could be induced by administration of a drug. This observation initiated a search for other potent, but less toxic, synthetic diuretics and so merbaphen became the predecessor of all the mercurial diuretics that followed and, in a sense, of the present-day potent nonmercurial diuretics. It is, therefore, surprising that the actual structure of merbaphen, apparently, never has been determined.

The chemical form of merbaphen used clinically is a combination formed with sodium diethylbarbiturate from the anhydro form[4] of the product that is obtained when 2-chlorophenoxyacetic acid is treated with $Hg(OAc)_2$.[5] It is obvious that the structure of the drug depends upon which of the 2 possible position isomers, Ia or II, is obtained in the mercuration reaction. In various papers and text books, structures of merbaphen are given which derive from Ia[6] or II.[7] No concrete evidence could be located to substantiate either structural assignment.



Ia, X = AcO
b, X = Cl



II

Since we were unable to obtain a sample of commercial merbaphen, we decided to remove, by synthetic procedures, the ambiguity surrounding its structure. To this end, 2-chloro-4-chloromercuriphenoxyacetic acid (Ib) was prepared by an unequivocal synthesis from 4-amino-2-chlorophenoxyacetic acid by the method of Weiner, *et al.*,[1] and compared with the chloromercuri compound obtained *via* the original mercuration procedure.[5]

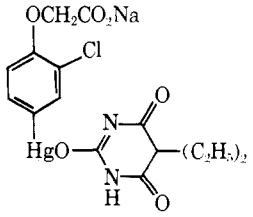
The original method[5] of heating 2-chlorophenoxyacetic acid with $Hg(OAc)_2$ in H_2O gave the acetoxy-

(1) I. M. Weiner, R. I. Levy, and G. H. Mudge, *J. Pharmacol. Exp. Ther.*, **138**, 96 (1962).
(2) K. Zeiler, *Muenchen Med. Wochenschr.*, **64**, 1257 (1917).
(3) (a) P. Saxyl and R. Heilig, *Wien. Klin. Wochenschr.*, **33**, 943 (1920); (b) A. Vogel, *Amer. Heart J.*, **39**, 881 (1950).
(4) Bayer and Co., German Patent 264,267 (1912).
(5) Bayer and Co., German Patent 261,229 (1912).
(6) (a) E. C. White, *Ind. Eng. Chem.*, **16**, 1034 (1924); (b) J. H. Crawford and J. F. McIntosh, *J. Clin. Invest.*, **1**, 333 (1925); (c) "May's Chemistry of Synthetic Drugs," Longmans Green and Co., London, 1959, p 320; (d) Jenkins and Hartung, "Chemistry of Organic Medical Products," Wiley, New York, N. Y., 1949, p 507.
(7) (a) H. T. A. Haas, *Pharmazie*, **2**, 1 (1947); (b) J. G. Topliss, *Med. Chem.*, 979 (1970).

mercuri substitution product in 59% crude yield. Conversion to the chloromercuri compd was effected in 96% yield. This product, after recrystallization, was identical in mp and nmr spectrum with the 2-chloro-4-chloromercuri compd synthesized unequivocally.

In order to determine the isomer distribution produced in the mercuration reaction, the crude chloromercuri derivative was treated with I_2. The total product of iodination was converted to Me ester and submitted to gas chromatography; it was found to contain 5% of 2-chlorophenoxyacetic acid and 94% of a fraction shown to be 2-chloro-4-iodophenoxyacetic acid. No 2-chloro-6-iodophenoxyacetic acid that would arise *via* ortho-mercuration could be detected in the chromatogram.

It has thus been demonstrated that the original mercuration procedure leads to para substitution and that merbaphen therefore has the structure that is derived from Ia. Hence, its structure, as depicted by conventional methods, is represented by III.



III

Experimental Section[8]

4-Amino-2-chlorophenoxyacetic Acid (IV).—2-Chloro-4-nitrophenoxyacetic acid[9] (77.0 g, 0.331 mole) was dissolved in satd Na_2CO_3 soln (700 ml) at 90°. To the hot soln $Na_2S_2O_4 \cdot 2H_2O$ (192 g) was added over 19 min with vigorous stirring. After cooling to 0°, the soln was acidified with 12 *N* HCl and evapd to dryness under reduced pressure. The residue was dissolved in hot H_2O (1.5 l.), and the soln was filtered and adjusted to pH 8 with 20% NaOH. After it was acidified to pH 5 with AcOH, the mixt was stored at 5° for 16 hr. The ppt was collected and air-dried. The product (32 g) is a tan powder, mp >350°. For analysis a sample was recrystd 3 times from $H_2O \cdot$AcOH (5:1). *Anal.* ($C_8H_8ClNO_2$) C, H, N.

2-Chloro-4-chloromercuriphenoxyacetic Acid (Ib). A. By Diazotization and Mercuration.—4-Amino-2-chlorophenoxyacetic acid (5 g) was dissolved in hot 12 *N* HCl (25 ml). The soln was cooled to 4° in an ice bath. A soln of $NaNO_2$ (2.5 g) in H_2O (5 ml) was added with stirring over a period of 2 min. The mixt was kept for an addnl 2 min and then filtered through sintered glass. The filtrate was cooled in an ice bath and to it was added a mixt of $HgCl_2$ (8 g), concd HCl (8 ml), and ice (8 g) followed by freshly prepd Cu powder (4 g). The mixt was kept at 0° for 4 hr and then made basic with 40% NaOH. The green to black ppt was removed by filtration. The filtrate was acidified with HCl. The tan ppt was purified by alternate repptn from NaOH soln with HCl and recrystn from 95% EtOH to obtain 0.7 g of product, mp 194–195°. *Anal.* ($C_8H_6Cl_2HgO_3$) C, H, Hg; nmr (C_2D_6SO) δ 4.84 (s, 2, CH_2), 7.12 (d, 1, J = 9 Hz, ArH^6), 7.51 (doublet of doublets, 1, J = 9, 1 Hz, ArH^5), 7.70 (d, 1, J = 1 Hz, ArH^3).

B. By Mercuration of 2-Chlorophenoxyacetic Acid.—2-Chlorophenoxyacetic acid (28 g, 0.15 mole) was added to a soln of $Hg(OAc)_2$ (57.2 g, 0.18 mole) in H_2O (1050 ml). The suspension was stirred and heated at 80–85° for 3.5 hr. The solid product was collected, washed with H_2O, and oven-dried at 65°. The wt of crude acetoxymercuri-2-chlorophenoxyacetic acid was 39.2 g (59%).

This material (20 g, 0.045 mole) was added to 200 ml of a 2% NaOH soln; insol material was removed by filtration. The filtrate was chilled and treated with 6 *N* HCl (35 ml). The crude chloromercuri-2-chlorophenoxyacetic acid that pptd weighed 18.2 g (96%), mp 169–170°. *Anal.* ($C_8H_6Cl_2HgO_3$) C, H, Hg; calcd: 47.59; found 46.97.

A sample, after recrystn from 95% EtOH (50% recovery), had mp 191–194°; mmp with 2-chloro-4-chloromercuriphenoxyacetic acid undepressed; nmr spectrum identical with that of the same compd.

Isomer Distribution by Iodination.—A mixt of crude chloromercuri-2-chlorophenoxyacetic acid (4.2 g, 0.01 mole), I_2 (2.5 g, 0.01 mole), and AcOH (30 ml) was stirred at 25° for 3 hr and then dild with H_2O (80 ml). The ppt was collected, dried, and extd with boiling C_6H_6 (60 ml). The ext was filtered and evapd to give 2.4 g (78%) of crude chloroiodophenoxyacetic acid, mp 127–140°, shown by glpc analysis to contain 2-chlorophenoxyacetic acid (5%, identified by admixt of authentic material) and one fraction of longer retention time (94%). The latter fraction was shown to be 2-chloro-4-iodophenoxyacetic acid by the nmr spectrum (C_2D_6SO): δ 4.90 (s, 2, CH_2), 7.01 (d, 1, J = 9 Hz, ArH^6), 7.77 (doublet of doublets, 1, J = 9, 2 Hz, ArH^5), 7.81 (d, 1, J = 2 Hz, ArH^3). A sample recrystd from C_6H_6 had mp 136–138.5° (lit. mp of 2-chloro-4-iodophenoxyacetic acid is 138–141°).[10]

2-Chlorophenoxyacetic acid does not react with I_2 under the conditions of this experiment.

Acknowledgment.—The authors thank K. B. Streeter and Y. C. Lee for microanalytical data, W. R. McGaughran for nmr spectra, and A. Augenblick for glpc analyses.

(8) Melting points were determined in capillary tubes and are uncorrected. Nmr spectra were taken on a Varian A-60 spectrometer and are reported in δ ppm *vs.* TMS standard. Glpc analysis was obtd on an F and M Model A-10 gas chromatography with 6 ft × 3 mm glass column packed with 5% QF-1 silicone on chromosorb G, at 200°. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical value.

(9) J. P. Brown and E. B. McCall, *J. Chem. Soc.*, 3687 (1955).

(10) M. S. Newman, W. Fones, and M. Renoll, *J. Amer. Chem. Soc.*, **69**, 719 (1947).

Metal Chelate Steroid Analogs. 2. [7-Amino-8-(aminomethyl)-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydro-4a,7-dimethyl-2-phenanthrol]-bis(ethylenediamine)cobalt(3+) Trichloride β-Acetate (Ester)[1]

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In a previous publication,[2] we reported the synthesis, characterization, and properties of the first metal chelate steroid analog. Since then, our studies in these areas have continued, and in this paper we would like to describe a homosteroidal metal chelate analog (III). Scheme I displays the reactions employed to prepare III and the requisite ligand (II).

II was prepared in 86% yield by reaction of I[3] with HN_3. The ir and nmr spectra of II were in agreement with structure II in all respects. Elemental analyses performed on II, its 2HCl salt, and selected bis derivatives (α-naphthylurea, benzenesulfonamide, *p*-chlorobenzamide), prepared in a fashion identical with analogous derivatives described previously,[2] were all within experimental error.

(1) Taken in part from the thesis submitted by Patricia U. Flath in partial fulfillment of the requirements for the M.S. degree and in part from the thesis to be submitted by Mrs. Flath in partial fulfillment of the requirements for the Ph.D. degree.

(2) L. G. Donaruma and P. U. Flath, *J. Med. Chem.*, **13**, 966 (1970).

(3) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956); A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1960).