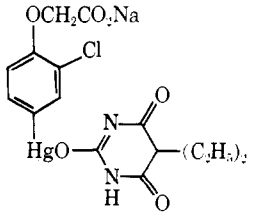
mercuri substitution product in 59% crude yield. Conversion to the chloromercuri compd was effected in 96% yield. This product, after recrystallization, was identical in mp and nmr spectrum with the 2-chloro-4-chloromercuri compd synthesized unequivocally.

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–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.

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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]

L. GUY DONARUMA* AND PATRICIA U. FLATH

Clarkson College of Technology, Potsdam, New York 13676

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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).

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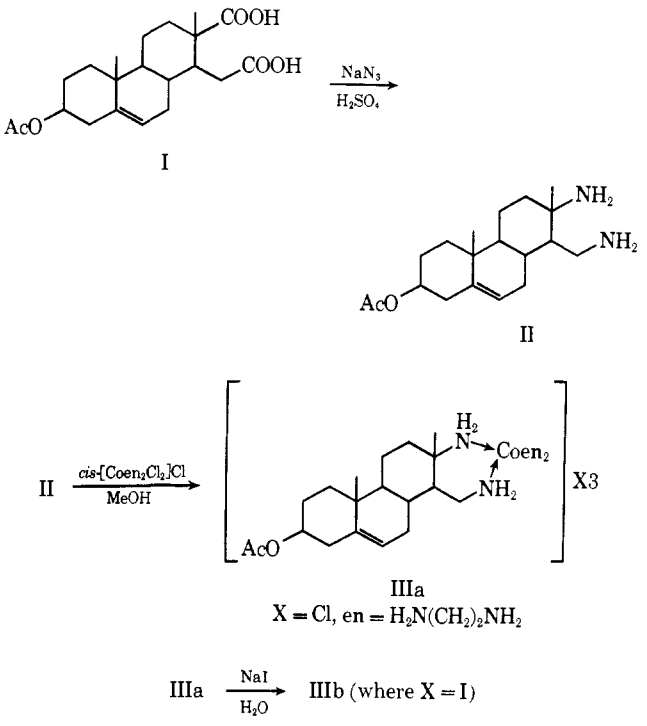
SCHEME I



When II was added to *cis*-dichlorobis(ethylenediamine)cobalt(3+) chloride in MeOH, [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), IIIa, was produced in 60% yield. The ir and nmr spectra of IIIa were consistent with the assigned structure. Ir maxima reported to be characteristic of Co–N bonds were present.[4] All elemental analyses for IIIa were within experimental error. Aq sols of IIIa gave 4 particle depressions of the freezing point of H_2O, and IIIa was diamagnetic. Reaction of IIIa with aq NaI yielded IIIb. The ir and nmr spectra of IIIb were consistent with the assigned structure, a 4 particle depression of the freezing point of aq sols was observed, the elemental analyses were within experimental error, and the compd was diamagnetic.

Biological Activity.—The capacity of the test compds to interfere with the incorporation of labeled acetate and/or mevalonate into cholesterol by rat liver homogenate was determined *in vitro* by the method of Dvornik, *et al.*[5] Any test compd producing 40% inhibition of cholesterol synthesis at 1×10^{-4} *M* is considered active and worth further work. IIIa was active as a hepatic cholesterogenesis inhibitor displaying 65% inhibition of cholesterol synthesis. II also was screened in identical fashion, but IIIa was more active than II. II showed only 26% inhibition of cholesterol synthesis. Activity testing continues.

Experimental Section[6]

7-Amino-8-(aminomethyl)-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydro-4a,7-dimethyl-2-phenanthrol β-Acetate (Ester) (II).—To a stirred soln of 0.50 g (1.8×10^{-3} mole) of I[3] in 10 ml of $CHCl_3$ was slowly added 3 ml of concd H_2SO_4; 0.5 g of NaN_3 was added very slowly to this mixture at a rate which kept the temp of the soln below 40°. After the addn was complete, the mixt was warmed to 40° for 2 hr, neutralized with concd NH_4OH at 0–5°, and filtered, and the filtrate was extd 4 times with $CHCl_3$. Removal of the solvent from the combined exts and recrystn from ligroin (bp 90–120°) yielded 0.20 g (54%) of product: mp 110–112°; $[\alpha]^{24}D$ −72°. *Anal.* ($C_{19}H_{32}N_2O_2$) C, H, N.

7-Amino-8-(aminomethyl)-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydro-4a,7-dimethyl-2-phenanthrol β-Acetate (Ester)·2HCl.—II (1 g, 3.13×10^{-3} mole) was dissolved in 15 ml of dry C_6H_6. HCl gas was bubbled through the soln for 5 min. After filtration and recrystn (H_2O-concd HCl), 1.18 g (96%) of product was obtained: mp 225–227°; neut equiv, calcd, 197; found 195, 198. *Anal.* ($C_{19}H_{34}Cl_2N_2O_2$) C, H, Cl, N.

Bis derivatives of II (α-naphthylurea, benzenesulfonamide, *p*-chlorobenzamide) were prepd in the same manner as previously reported analogs:[2] α-naphthylurea, 85% yield (recryst EtOH), mp 230–231° [*Anal.* ($C_{41}H_{46}N_4O_4$) C, H, N]; benzenesulfonamide, 70% yield (recryst EtOH), mp 147–148° [*Anal.* ($C_{31}H_{40}NO_{26}S_2$) C, H, N, S]; *p*-chlorobenzamide, 86% yield (recryst EtOH), mp 111–112° [*Anal.* $C_{33}H_{38}Cl_2N_2O_4$) C, H, Cl, N].

[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) (IIIa).—To 0.625 g (2.19×10^{-3} mole) of *cis*-dichlorobis(ethylenediamine)cobalt(3+) chloride in 30 ml of MeOH was added a soln of 0.70 g (2.19×10^{-3} mole) of II in 10 ml of dry C_6H_6. After stirring for 48 hr, the product was filtered and recrystd from H_2O–EtOH. The yield of gold-colored crystals was 0.80 g (60%): mp 215–217°; λ_{max} 472 mμ; $[\alpha]^{28}D$ −7°; cryoscopic particle no., calcd, 4.00; found, 4.14, 4.11. *Anal.* ($CoC_{23}H_{48}Cl_3N_6O_2$) Co, C, H, Cl, N.

[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+) Triiodide β-Acetate (Ester) (IIIb).—IIIa (0.1 g) was dissolved in a min vol of H_2O. A 10-fold excess of NaI was added to the soln. The orange ppt was filtered and recrystd from hot H_2O. The yield of product, mp 256–257°, λ_{max} 475 mμ, was quantitative; cryoscopic particle no., calcd, 4.00; found, 4.02, 4.06. *Anal.* ($CoC_{23}H_{48}I_3N_6O_2$) Co, C, H, I, N.

Acknowledgments.—We are indebted to the National Science Foundation for partial support of this work under Traineeship Grant GE-7878, and we are indebted to Dr. K. L. Loening of the Chemical Abstracts Service for naming compounds II and IIIa for us. Activity testing was done by Ayerst Laboratories.

Where anal. are indicated only by the symbols of the elements or functions, analytical data were within experimental error relative to the calcd values for those elements or functions. Nmr spectra were taken on a Varian A60A spectrometer in $CDCl_3$ or D_2O. Visible spectra were taken on a Perkin-Elmer 202 spectrophotometer. Optical rotations were measured in a Rudolph Model 62 polarimeter in $CHCl_3$.

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(6) Melting points were taken on a hot stage and are corrected. Ir spectra were taken in KBr wafers on a Beckmann IR-12 spectrophotometer.

Synthesis and Hypoglycemic Activity of 3-Aryl(or Pyridyl)-5-alkyl(or aryl)amino-1,3,4-thiadiazoles and Some Sulfonylurea Derivatives of 4*H*-1,2,4-Triazoles

M. Y. MHASALKAR, M. H. SHAH, P. D. PILANKAR, S. T. NIKAM, K. G. ANANTANARAYANAN, AND C. V. DELIWALA*

Haffkine Institute, Bombay 12, India

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We have described[1,2] the synthesis and study of 1,2,4-triazole derivatives and have shown that many

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