values for -OMe (see footnote e, Table I). Evidence for the validity of this assumption comes from a study of the steric effects in hapten–antibody interactions.[8] In this study, the value of E_s was found to be 0.40. This is close to that of the calculated value used in Table I. Use of 0.40 actually gives a slightly better fit with eq 5. It is of particular interest that E_s as estimated for -OMe and -NHAc gives quite satisfactory results in two very different biological systems.

The negative coefficient with the E_s terms means that the rate of reduction is increased by bulky groups in the 4 position. Mechanistically, this is probably best rationalized in terms of Koshland's induced-fit hypothesis.[9] The rigid positioning of the substituent in the 4 position appears to be quite important. A small effect is produced by groups such as -OMe and -NHAc which can adjust to positions of minimum repulsion while large effects are brought about by CF_3 and NO_2. The use of a polarizability term in eq 5 in place of $E_s - 4$ results in a much poorer correlation, indicating volume alone is not the determining factor.

(8) E. Kutter and C. Hansch, *Arch. Biochem. Biophys.*, **135**, 126 (1969).
(9) D. E. Koshland, Jr. and K. E. Neet, *Annu. Rev. Biochem.*, **37**, 359 (1968).

Metal Chelate Steroid Analog. [7-Amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine]bis(ethylenediamine)cobalt(3 +) Trichloride[1]

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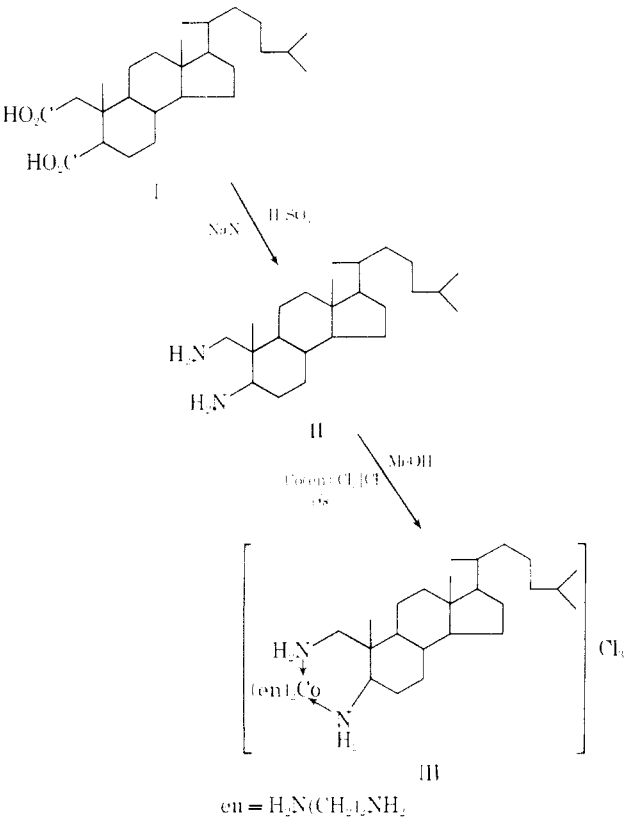
Over the last decade, much work has been done concerning the synthesis of steroid analog systems wherein various ring carbon atoms have been replaced with N, O, or S. Some of the aza, oxa, and thia steriods possess biological activity. We wondered if it might be possible to synthesize a molecule which contained a metal chelate ring within a reasonable facsimile of a steroid ring system. Scheme I shows the reaction employed to prepare the requisite ligand, 7-amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine (II).

Compound II was prepared in 86% yield by reaction of A-nor-2,3-secocholestan-2,3-dioic acid (I)[2] in $CHCl_3$ mixed with concentrated H_2SO_4 and NaN_3. The ir spectrum was in agreement with structure II in all respects. All elemental analyses of bis derivatives, α-naphthylurea, benzensulfonamide, *p*-chlorobenzamide, prepared from II by standard procedures[3] were within experimental error (±0.3%), and the ir spectra of the derivatives were consistent with the expected structures. The dihydrochloride of II(IIa) was prepared by precipitation from C_6H_6 with dry HCl. Compound II was added to *cis*-dichlorobisethylenediaminecobalt(3+) chloride in MeOH to yield 96% of golden crystalline [7-amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[e]indene-6-methylamine]bis(ethylenediamine)cobalt(3+) trichloride (III). The ir spectrum was consistent with the assigned structure. Ir maxima reported to be characteristic of Co–N bonds were present.[4] Finally, III, which is completely water soluble, gave a 4 particle depression of the freezing point in aqueous solutions and was diamagnetic. Thus, all the data confirm the structures assigned for II and III.

Scheme I



The preparation of other metal chelate steroid analogs is underway, and the complete conformational characterization of II and III by X-ray diffraction methods will soon be initiated. It is interesting to note that models of III show that the normal shape of the "A" ring is not completely distorted, and the two external rings present due to the bidentate ethylenediamine ligands might be said to be structurally somewhat similar to compounds such as the ethylene ketal of cholestanone.

Biological Activity.—The capacity of the test compound 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 compound producing 40% inhibition of cholesterol synthesis at 1×10^{-4} *M* is considered active and a lead worth further work. III was biologically active as a hepatic cholesterogenesis inhibitor displaying 58% inhibition of cholesterol synthesis. II also was put through the same screens as III, but III was more active than II. II showed only

(1) Taken in part from the thesis submitted by Patricia U. Flath in partial fulfillment of the requirements for the M.S. degree.
(2) A. Windaus and C. Ubrig, *Ber.*, **47**, 2387 (1914).
(3) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th ed, Wiley, New York, N. Y., 1964.
(4) E. P. Bertin, I. Nakagawa, S. Misushima, T. J. Lane, and J. V. Quagliano, *J. Amer. Chem. Soc.*, **80**, 525 (1958).
(5) D. Dvornik, M. Kraml, and J. Dulaw, *Proc. Soc. Exp. Biol. Med.*, **116**, 537 (1964).

8% inhibition of cholesterol synthesis. Activity testing continues.

Experimental Section[6]

7-Amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine (II).—To a stirred solution of 4.00 g (9.52×10^{-3} mole) of I_2 in 35 ml of $CHCl_3$ was slowly added 12 ml of concd H_2SO_4. To this was added very slowly 1.855 g (2.86×10^{-2} mole) of NaN_3 so that the temp of the solution did not exceed 45°. After the addition was complete, the mixture was warmed at 40–45° for 15 min. The mixture was then cooled to 0–5° and concd NH_4OH was slowly added to neutralize the acid. The resulting mixture was extracted 4 times with $CHCl_3$. The extracts were evapd on a steam bath to give 3.00 g (86.5%) of the crude product. A sample of the highly hygroscopic product was recrystd using decolorizing charcoal in $CHCl_3$; mp 73–75°; $[\alpha]^{28}D + 10°$ ($CHCl_3$).

7-Amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine Dihydrochloride (IIa).—II (1 g, 2.77×10^{-3} mole) was dissolved in 15 ml of dry C_6H_6. HCl gas was bubbled through the soln for 5 min. The white gelatinous mass was filtered and washed with C_6H_6. The solvent was removed to give 1.05 g (87.6%) of the desired product. A sample was purified rigorously by dissolving some of the product in a minimum volume of hot H_2O, cooling the soln, and adding concd HCl. The resulting ppt was filtered, washed with dry C_6H_6, and dried; mp 230–232°. *Anal.* ($C_{24}H_{48}Cl_2N_2$) C, H, Cl, N, neut equiv.

A series of derivatives of 7-amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine (II) were prepared and characterized to confirm the functionality of the diamine. Among the derivatives prepared were the α-naphthylurea, the benzenesulfonamide, and the *p*-chlorobenzamide.

α-Naphthylurea.—II (0.2 g, 5.52×10^{-4} mole) was placed in a 25-ml flask and stoppered with a serum cap. α-Naphthylisocyanate (0.2 ml, 2.10×10^{-2} moles) was added to the diamine by injecting the sample through the serum cap with a syringe. The solution was heated at 40–50° in a H_2O bath for 30 min. Absolute EtOH was added and the ppt filtered to give 0.300 g (77.6%) of product. A sample was recrystd from abs EtOH; mp 234–235.5°. *Anal.* ($C_{46}H_{60}N_4O_2$) C, H, N.

Benzenesulfonamide.—II (0.3 g, 8.28×10^{-4} mole) 10 ml of 10% aq NaOH and 0.50 ml (3.92×10^{-3} mole) of $PhSO_2Cl$ were shaken vigorously, cooled, and aq HCl was added. The ppt was filtered, washed with ligroin, dried, and recrystd from EtOH to give 0.30 g (87%) of the product; mp 92–93.5°. *Anal.* ($C_{36}H_{54}N_2S_2O_4$) C, H, N, S.

***p*-Chlorobenzamide.**—To a soln of 0.50 g (1.38×10^{-3} mole) of II in 5 ml of dry C_5H_5N and 10 ml of dry C_6H_6 was added a slight excess (0.60 ml, 4.75×10^{-3} mole) of *p*-ClC_6H_4COCl. The resulting mixture was heated on a H_2O bath at 60–70° for 30 min, poured into 100 ml of H_2O, the C_6H_6 layer was separated and the aq layer washed with 10 ml of C_6H_6. The combined C_6H_6 extracts were washed with H_2O and 5% aq Na_2CO_3 soln and dried ($MgSO_4$). The C_6H_6 soln was evapd to a small volume (3–4 ml), and hexane (20 ml) was stirred into the soln. This mixture was cooled. The solid substituted benzamide was filtered and washed with hexane. Recrystallization was effected from cyclohexane–hexane. The yield was 0.30 g (34%) mp 88–89°. *Anal.* ($C_{38}H_{52}Cl_2N_2O_2$) C, H, Cl, N.

[7-Amino-3-(1,5-dimethylhexyl)dodecahydro-3a,6-dimethyl-1*H*-benz[*e*]indene-6-methylamine]bis(ethylenediamine)cobalt(3+) Trichloride (III).—To a mixture of 1.00 g (3.51×10^{-3} mole) of *cis*-dichlorobisethylenediamine Co^{3+} chloride in 6 ml of MeOH was added a soln of 1.27 g (3.51×10^{-3} mole) of II in 10 ml of dry C_6H_6. The mixture was stirred for 48 hr, filtered, and recrystd from H_2O–EtOH to yield 2.18 g (96%) of III: mp 240–242° dec; λ_{max} 468 mμ; $[\alpha]^{28}D + 2°$ (H_2O). Cryoscopic particle number: Calcd, 4.00. Found, 4.06, 3.97. *Anal.* ($C_{28}H_{62}Cl_3CoN_6$) C, H, Cl, Co, N.

(6) Melting points were taken on a hot stage and are corrected. Infrared spectra were taken in KBr wafers on a Beckmann IR-12 spectrophotometer. Optical rotations were determined using a Rudolph polarimeter. Where analyses are indicated only by the symbols of the elements or functions, analytical data were within ±0.3% of the calculated values for those elements or functions.

Acknowledgments.—We are indebted to the National Science Foundation for 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 III for us. Activity testing was done by Ayerst Laboratories.

Synthesis and Myotrophic–Androgenic Activity of 17β-Hydroxy-5α-androst-8(14)-en-3-one Derivatives[1]

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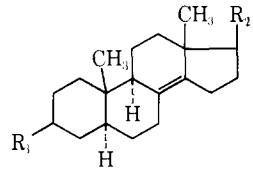
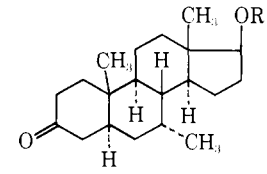
In a previous study,[2] we described results which led us to suggest that the enhancement of mytropohic-androgenic activity by the 7α-methyl group[3] in steroids is due to flattening of the molecule towards the β face. An examination of molecular models revealed that a $\Delta^{8(14)}$ double bond would cause a similar effect, and the preparation of a number of 5α-androst-8-(14)-ene derivatives (**5–7**) was undertaken on this basis. The compounds were prepared from 3β,17β-dihydroxyandrost-8(14)-ene[4] (**1**) by the methods described in the Experimental Section.



1, R_1 = OH; R_2 = OH
2, R_1 = O; R_2 = O
3, R_1 = $(MeO)_2$; R_2 = O
4, R_1 = $(MeO)_2$; R_2 = OH
5, R_1 = O; R_2 = OH
6, R_1 = O; R_2 = OAc
7, R_1 = O; R_2 = $OCOC_2H_5$



8, R = H
9, R = Ac

The data from the pharmacological testing[5] are displayed in Table I. Since it appears likely that the active androgen is actually 5α-dihydrotestosterone, 5α-*H*-$\Delta^{8(14)}$ steroids were used in the present work. The enhancing effect of the 7α-methyl substituent in the 5α-H system was established by testing **8** and **9** which had been obtained in our previous study.[2] Both of these compounds were found to be far more active

(1) This investigation was supported in part by a Public Health Service Research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) M. E. Wolff, G. Zanati, G. Shanmugasundaram, S. Gupte, and G. Aadahl, *J. Med. Chem.*, **13**, 53 (1970).

(3) This enhancement has been reported, *inter alia* by (a) A. Segaloff, *Steroids*, **1**, 299 (1963), and J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *ibid.*, **1**, 317 (1963), for testosterone derivatives; (b) G. Anner, J. Kalvoda, and P. Wieland, *Chimia*, **20**, 434 (1966), for 19-nortestosterone derivatives; and by (c) H. Kaneko, K. Nakamura, Y. Yamato, and M. Kurokawa, *Chem. Pharm. Bull. (Tokyo)*, **17**, 11 (1969), for 7α-akylthio and 7α-arylthio derivatives.

(4) R. Antonucci, S. Bernstein, D. Giancola, and K. Sax, *J. Org. Chem.*, **16**, 1891 (1951).

(5) Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis., using essentially the method of L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175 (1953).