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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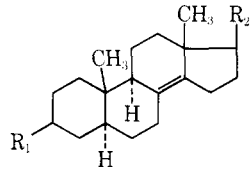
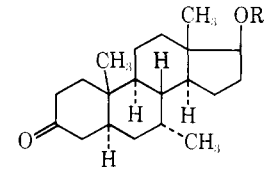
Received May 21, 1970

In a previous study,[2] we described results which led us to suggest that the enhancement of myotrophic–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).

TABLE I
ANDROGENIC–MYOTROPHIC ASSAY

Compound (total dose, mg)	Wt, mg[a] — Ventral prostate	Seminal vesicle	Levator ani	Body wt, g — Initial	Final
Castrate control	16.9 ± 1.07	12.0 ± 0.49	23.8 ± 2.05	54	92
Testosterone(0.3)	25.6 ± 2.47	15.1 ± 0.76	31.4 ± 2.50	55	96
p	<0.05	<0.05	<0.10-0.05		
Testosterone(0.6)	30.7 ± 3.50	17.2 ± 1.32	35.4 ± 1.71	55	94
p	<0.02	<0.05	<0.01		
Testosterone propionate(0.3)	55.5 ± 6.66	21.2 ± 1.25	34.8 ± 1.44	55	99
p	<0.01	<0.01	<0.02		
5 (3.0)	38.0 ± 8.62	12.5 ± 0.94	29.2 ± 2.65	54	91
p	ca 0.05	NS[b]	NS		
6 (3.0)	39.5 ± 6.38	13.1 ± 0.56	29.8 ± 3.31	54	92
p	<0.05	NS	NS		
7 (3.0)	39.0 ± 3.88	14.4 ± 0.59	27.6 ± 2.05	54	93
p	<0.01	<0.05	NS		
8 (0.3)	73.3 ± 4.64	26.5 ± 0.84	33.7 ± 1.93	54	98
p	<0.001	<0.001	<0.05		
9 (0.3)	111.8 ± 9.37	35.4 ± 2.84	41.4 ± 2.08	54	95
p	<0.001	<0.01	<0.01		

[a] Mean ± standard error. [b] Not significant

than testosterone (Table I). On the other hand, the $\Delta^{8(14)}$ compounds were only weakly active; in no case was potency higher than 0.2 of the corresponding testosterone activity observed. This could mean that the hypothesis of enhancement due to flattening toward the β face is incorrect. Alternatively, the presence of the double bond, or the absence of the 8β- or 14α-H may be responsible for the low order of activity.

Experimental Section[6]

5α-Androsta-8(14)-3,17-dione (2).—A solution of 2 g of 1[4] in 200 ml of Me_2CO was oxidized with Jones reagent at room temp. *i*-PrOH was added to destroy the excess Jones reagent, ice water was added, and the Me_2CO was removed under reduced pressure. The pptd powder was filtered to afford 1.8 g of product, mp 144–148°, which was recrystd from MeOH–H_2O to give a sample: mp 145–149°; nmr 0.93 (19 H_3), 1.10 (18 H_3), $[\alpha]^{20}D$ +347° (*c*, 1, $CHCl_3$). *Anal.* ($C_{19}H_{26}O_2$) C, H.

3,3-Dimethoxy-5α-androst-8(14)-en-17-one (3).—A solution of 1.5 g of **2** and 1.5 g of SeO_2 in 60 ml of MeOH was heated at 50° for 15 min. It was cooled to room temp and a solution of 2.5 g of KOH in 20 ml of MeOH was added to make the solution alkaline. It was poured into ice water, and the pptd powder was filtered to afford 1.5 g of crude product, mp 103–104°. It was recrystd from MeOH containing 1 drop of methanolic KOH to give **3**: mp 106–108°; nmr 0.70 (19 H_3), 1.07 (18 H_3), $[\alpha]^{20}D$ +222° (*c*, 1% $CHCl_3$). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.10; H, 9.28.

17β-Hydroxy-5α-androst-8(14)-en-3-one (5).—To a solution of 1.2 g of **3** in 40 ml of MeOH was added slowly a solution of 1.2 g of $NaBH_4$ in 20 ml of MeOH. Ice water was added and the pptd powder was filtered to afford 1.0 g of crude **4**, mp 184–187°. A solution of 1.0 g of this **4** in 5 ml of HOAc was warmed on a steam bath for 10 min and H_2O was added dropwise. The solution was cooled and the pptd powder was filtered to afford 0.7 g of **5**, mp 180–183°. It was recrystd from MeOH–H_2O to give material, mp 182–183°, $[\alpha]^{20}D$ +65° (*c*, 1% $CHCl_3$). *Anal.* ($C_{19}H_{28}O_2$) C, H.

17β-Hydroxy-5α-androst-8(14)-en-3-one Acetate (6).—A solution of 0.1 g of **5** in 1 ml of C_5H_5N was added to 0.1 ml of Ac_2O and the mixture was kept at room temp for 24 hr. Ice water was added and the pptd powder was filtered to afford 0.95 g of product, mp 145–147°, raised to mp 148–149° after recrystallization from MeOH, $[\alpha]^{20}D$ +41° (*c*, 1% $CHCl_3$). *Anal.* ($C_{21}H_{30}O_3$) C, H.

17β-Hydroxy-5α-androst-8(14)-en-3-one Propionate (7).—To a solution of 0.1 g of **5** in 1 ml of C_5H_5N was added 0.1 ml of $(C_2H_5CO)_2O$ and the mixture was kept at room temp for 24 hr. Ice water was added and the pptd powder was filtered to afford 0.105 g of product, mp 158–163°. It was recrystd from MeOH–H_2O to give material: mp 160–162°; nmr 0.90 (19 H_3), 0.98 (18 H_3), $[\alpha]^{20}D$ +38° (*c*, 1% $CHCl_3$). *Anal.* ($C_{22}H_{32}O_3$) C, H.

(6) Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Nmr spectra were obtained at a field strength of 60 MHz on samples in $CDCl_3$ solution on a Varian A 60A instrument using TMS as internal standard. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. 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.

Imidazole Derivatives. Histidine Decarboxylase Inhibitors

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Received March 13, 1970

Histamine has been implicated in a number of physiological processes,[2,3] among them, the regulation of the microcirculation,[4] gastric secretion,[5] growth and repair processes,[6] and certain hormone actions.[7] Some clinical conditions in which histamine plays a role are anaphylaxis and allergy, wound healing, inflamation, and mastocytosis. The discovery of an inducible, specific histidine decarboxylase (HD) in mammalian tissues and the development of sensitive assays[8] has opened up new approaches to the understanding of the physiological and pathological role of histamine. In recent years, interest in histidine decarboxylase inhibitors as tools in such studies and as agents for the treatment of disorders

(1) To whom inquiries should be directed.

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