Hypocholesterolemic Agents. I. 20α-(2-Dialkylaminoethyl)aminopregn-5-en-3β-ol Derivatives

R. E. COUNSELL, P. D. KLIMSTRA, R. E. RANNEY, AND D. L. COOK

Divisions of Chemical and Biological Research of G. D. Searle & Co., Chicago 80, Illinois

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A series of 22,25-diaza analogs of cholesterol and cholestanol have been prepared as part of a program directed toward the development of potential *in vivo* inhibitors of cholesterol biosynthesis. Preliminary biological studies have shown that many of these compounds possess pronounced hypocholesterolemic activity.

Most of the clinical and experimental evidence to date suggests that atherosclerosis represents a metabolic disorder involving lipids and lipoproteins, especially cholesterol. These observations, together with consistent reports that human atherosclerosis is prominent in clinical states associated with abnormally high serum cholesterol levels, has stimulated an increasing interest in cholesterol-lowering procedures for the treatment of atherosclerosis. As yet, however, there is still no proof that depressing the cholesterol concentration in serum has a beneficial therapeutic effect in human atherosclerosis.

One approach to the development of hypocholesterolemic agents has involved the preparation and biological evaluation of compounds that inhibit the endogenous synthesis of cholesterol.[1] Theoretically, the biosynthesis of cholesterol can be stopped by interfering with any reaction in its metabolic pathway depicted in Fig. 1. As is indicated, the reactions beyond 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) are irreversible. In other words, mevalonic acid (MVA), except for being involved in the synthesis of coenzyme Q,[2] appears to be involved solely with the biosynthesis of sterols. Thus, compounds that exert their blocking action prior to HMG-CoA would also interfere with metabolic reactions other than the synthesis of cholesterol. Moreover, interruption of the sequence after squalene has undergone cyclization to form the steroid nucleus may result in the abnormal accumulation of steroid precursors of cholesterol, which may in themselves contribute to the development of atherosclerotic lesions.

(1) L. D. Wright, *Ann. Rev. Biochem.*, **30**, 525 (1961).
(2) U. Glorr and O. Wiss, *Arch. Biochem. Biophys.*, **83**, 216 (1959).

Acetyl-coenzyme A ⇄ Acetoacetyl-coenzyme A ⇄ 3-Hydroxy-3-methylglutaryl-coenzyme A → Mevalonic Acid → Squalene → Desmosterol → Cholesterol

Fig. 1.—Abbreviated outline of cholesterol biosynthesis.

In 1950, Gould and Taylor[3] noted that feeding cholesterol to animals resulted in a marked decrease in the rate at which the steroid was synthesized by the liver. This observation, which subsequently was confirmed by others,[4,5] indicated that the liver must normally possess a sensitive feedback mechanism whereby exogenous cholesterol served to block one or more of the reactions involved in the conversion of acetate to cholesterol. Further studies by Siperstein and Guest[6-8] suggested that the major biochemical site of this physiological regulation of cholesterol synthesis was the reductive transformation of HMG-CoA to MVA.

On the basis of this information, it was rationalized that one approach to hypocholesterolemic agents would be the synthesis of compounds which would simulate cholesterol in the feedback mechanism. If cholesterol is pictured as being bound to the surface of the feedback-inhibited enzyme through van der Waals forces and hydrogen-bonding, it seemed plausible that this adsorption could be enhanced by incorporating into the substrate molecule certain functional groups which would allow for the involvement of much stronger ionic forces. To test this hypothesis, a series of nitrogen isosteres of cholesterol was prepared and biologically evaluated. The present work is concerned with the synthesis of 22,25-diaza-substituted cholesterol analogs.

The starting material for synthesis in this series was 20α-aminopregn-5-en-3β-ol 3-acetate (I) readily obtained by the Curtius degradation of 3β-acetoxy-5-bisnorcholenic acid according to the method of Julian, *et al.*[9] Acylation of I with chloroacetyl chloride gave 20α-chloroacetamidopregn-5-en-3β-ol 3-acetate (II) in excellent yield. Treatment of II with various secondary amines gave the corresponding 20α-dialkylaminoacetamido-derivatives (III) (Table I). When lithium aluminum hydride reduction of IIIa was performed in tetrahydrofuran at the reflux temperature, the product isolated in good yield was the corresponding 3β-ol (IV) resulting from cleavage of the ester function. The amide group was essentially unaffected

(3) R. G. Gould and C. B. Taylor, *Federation Proc.*, **9**, 179 (1950).
(4) G. M. Tomkins, H. Sheppard, and I. L. Chaikoff, *J. Biol. Chem.*, **201**, 137 (1953).
(5) I. D. Frantz, Jr., H. S. Schneider, and B. T. Hinkelman, *ibid.*, **206**, 465 (1954).
(6) M. D. Siperstein and M. J. Guest, *J. Clin. Invest.*, **38**, 1043 (1959).
(7) M. D. Siperstein and M. J. Guest, *Am. J. Med.*, **27**, 325 (1959).
(8) M. D. Siperstein and M. J. Guest, *J. Clin. Invest.*, **39**, 642 (1960).
(9) P. L. Julian, E. W. Meyer, and H. C. Printy, *J. Am. Chem. Soc.*, **70**, 887 (1948).

TABLE I

20α-(2-DIALKYLAMINO)ACETAMIDOPREGN-5-EN-3β-OL ACETATES (III)

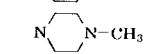
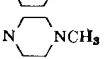
						Analyses, %					
						Calcd.			Found		
III	NR_2	M.p., °C.	$[\alpha]^{25}D$	Yield, %	Formula	C	H	N	C	H	N
a	$N(CH_3)_2$	159.5–161.5	−52.5°	90	$C_{27}H_{44}N_2O_3$	72.93	9.97	6.30	72.84	10.01	6.29
b	$N(C_2H_5)_2$	152–153	−44.5°	85	$C_{29}H_{48}N_2O_3$	73.68	10.24	5.93	73.50	10.04	5.80
c		157–160	−46.5°	89.5	$C_{29}H_{46}N_2O_3$	74.00	9.85	5.95	73.66	9.54	5.99
d		171–172.5	−46°	90	$C_{30}H_{48}N_2O_3$	74.33	9.98	5.78	74.07	9.84	5.64
e		173–176	−40°	91	$C_{29}H_{46}N_2O_4$	71.57	9.53	5.76	71.62	9.21	5.40
f		145–147	−41°	76	$C_{30}H_{49}N_3O_3$	72.10	9.88	8.41	72.08	9.97	8.26

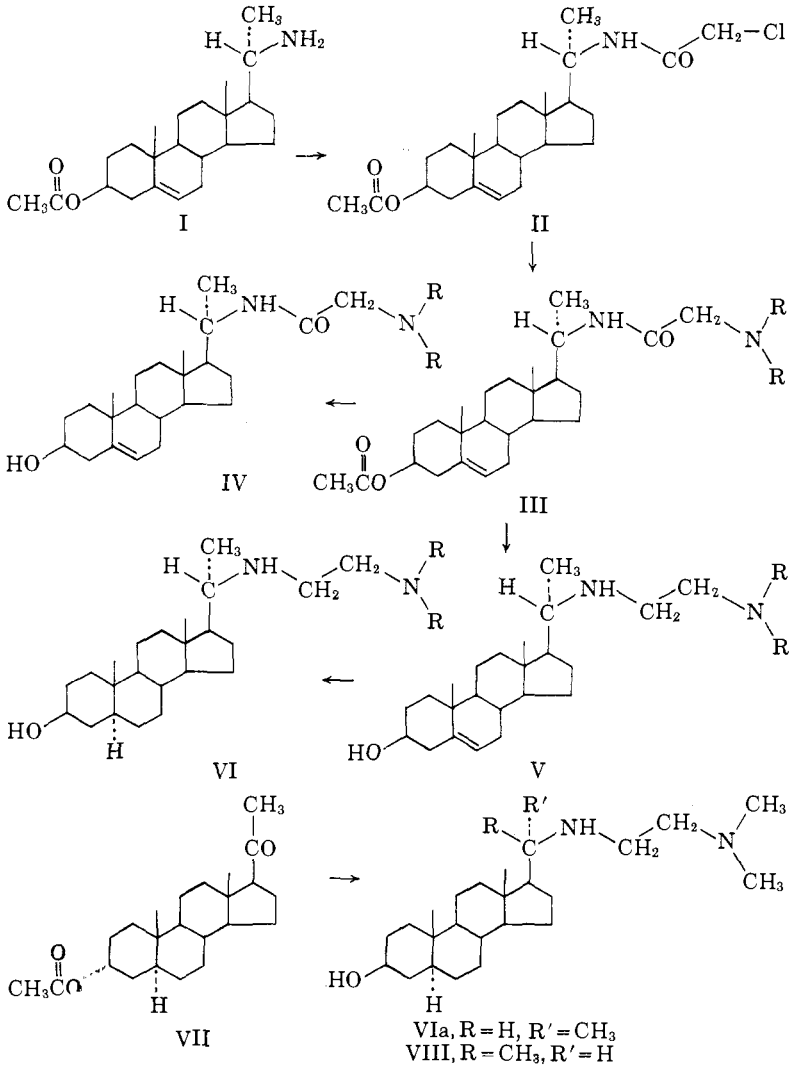
TABLE II

20α-(2-DIALKYLAMINOETHYL)AMINOPREGN-5-EN-3β-OLS (V)

						Analyses, %					
						Calcd.			Found		
V	NR_2	M.p., °C.	$[\alpha]^{25}D$	Yield, %	Formula	C	H	N	C	H	N
a	$N(CH_3)_2$	83–87/110–113	−41°	67	$C_{25}H_{44}N_2O$	77.26	11.41		77.66	11.45	
b	$N(C_2H_5)_2$	130–132	−43°	59.2	$C_{27}H_{48}N_2O$	77.82	11.61	6.72	78.08	11.09	6.85
c		111–113.5	−38°	83	$C_{27}H_{46}N_2O$	78.20	11.18	6.76	78.17	11.15	7.22
d		142–143.5	−41°	97.5	$C_{28}H_{48}N_2O$	78.45	11.29	6.54	78.42	11.11	6.59
e		145.5–147	−40°	91	$C_{27}H_{46}N_2O_2$	75.30	10.77		75.34	10.68	
f		147–148	−40.5°	88.7	$C_{28}H_{49}N_3O$	75.79	11.13	9.47	76.07	11.31	9.93

by these conditions. Substitution of dioxane for tetrahydrofuran, however, resulted in a smooth conversion of the 20α-dialkylamino-acetamido derivatives (III) to the desired 22,25-diaza analogs (V) of cholesterol (Table II).

The corresponding 5α-pregnane derivatives (VI) were obtained by catalytic hydrogenation of V over platinum oxide in acidic media (Table III). Although the initial assignment of the A/B *trans* configuration was based on the normal steric course of hydrogenation of



Δ^5-steroids,[10] this was later confirmed when reductive amination of *allo*-pregnanolone acetate (VII) with β-dimethylaminoethylamine afforded after saponification 20α-(2-dimethylaminoethyl)-amino-5α-pregnan-3β-ol (VIa) identical in all respects with that obtained by the catalytic hydrogenation of Va. The reductive amination experiment also gave another isomer (VIII) which has been tentatively assigned the 20β-configuration. This assignment is supported by the levorotatory shift in the optical rotation. A similar small negative shift in rotation has been observed previously in passing from cholesterol to 20-isocholesterol.[11] Additional chemical studies are now in progress to firmly establish the 20β-configuration of VIII.

Preliminary Biological Results.—The effectiveness of the compounds in reducing serum cholesterol levels was estimated with two *in vivo* bioassay procedures. The parenteral activity of the materials was measured in normal male rats (200–250 g.), 8 animals per group. Each compound was dissolved or suspended in corn oil and administered subcutaneously daily for a period of 9 days. Control groups received corn oil alone. Twenty-four hours after the last dose, blood samples were taken from the aorta and serum cholesterol concentrations were determined by the method of Zlatkis, *et al.*[12]

The oral potency of the compounds was estimated by a modification of the test described above. In this procedure moderate hypercholesterolemia was induced in young male rats (200–250 g.) by the inclusion of 0.01% of 6-propylthiouracil in the drinking water simultaneously with the initiation of steroid treatment. The compounds were dissolved or suspended in 20% propylene glycol in water and administered *per os* daily for a period of 10 days. Control animals received both the propylthiouracil and the propylene glycol vehicle. Treatment with propylthiouracil at the level used here does not effect a change in thyroid activity but does induce an increase of approximately 15% in the level of serum cholesterol values. Blood sampling and analysis were carried out as described above.

In both of these tests a decrease in serum cholesterol concentration of more than 9–10% when compared to concurrent controls was routinely found to be statistically significant ($P < 0.05$). The initial dosages used were 10 mg./kg. orally or 8 mg./kg. parenterally. Deviations from this dose schedule are indicated in the tables. The free bases were more suitable for parenteral administration whereas the salts were preferred in the oral assay.

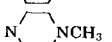
(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 272.

(11) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087 (1958).

(12) A. B. Zlatkis, B. Zak, and A. J. Boyle, *J. Lab. Clin. Med.*, **41**, 486 (1953).

TABLE III

20α-(2-DIALKYLAMINOETHYL)AMINOPREGNAN-3β-OLS (VI)

VI	NR_2	M.p., °C.	$[\alpha]^{25}D$	Yield,[a] %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	$N(CH_3)_2$	134–136	+22°	76	$C_{25}H_{46}N_2O$	76.86	11.87	7.17	77.23	12.25	7.27
b	$N(C_2H_5)_2$	140–142	+13°		$C_{27}H_{50}N_2O$	77.45	12.04	6.69	77.02	11.89	6.33
c		145–147	+18°		$C_{27}H_{48}N_2O$	77.82	11.61	6.72	77.49	11.28	6.93
d		133–135	+4°	83.4	$C_{28}H_{50}N_2O$	78.08	11.70	6.50	78.02	11.47	6.26
e		157–160	+11.5°	69	$C_{27}H_{48}N_2O_2$	74.95	11.18		75.30	10.87	
f		143–145	+10°	82.5	$C_{28}H_{51}N_3O$	75.45	11.53	9.43	75.52	11.39	9.16

[a] Calculated as the dihydrochloride salt.

TABLE IV

HYPOCHOLESTEROLEMIC ACTIVITY OF 20α-(2-DIALKYLAMINOETHYL)-AMINOPREGN-5-EN-3β-OL DERIVATIVES

Compound	Hypercholesterolemic rat (oral administration) dose: mg./kg.	% Reduction[a]	Normal rat (parenteral administration) dose: mg./kg.	% Reduction[a]	Compound	Hypercholesterolemic rat (oral administration) dose: mg./kg.	% Reduction[a]	Normal rat (parenteral administration) dose: mg./kg.	% Reduction[a]
Va	10	22	0.4	15	Vd	10	18	8.0	14[b]
Va.2HCl	1	35	1.0	19	Vd.2HCl	10	Inactive		
Vb	10	Inactive	8.0	29[b]	Ve			8.0	Inactive
Vb.2HCl	10	Inactive			Ve.2HCl	10	Inactive		
Vc	10	Inactive	2.0	26	Vf	10	Inactive		
Vc.2HCl	10	Inactive	2.0	Inactive	Vf.2HCl	10	Inactive		

[a] Values refer to the per cent. reduction of serum cholesterol. [b] Reduced body weight gain.

Two general conclusions may be reached from an examination of the biological activity of the compounds listed in Tables IV and V. It is evident that the compounds possessing the terminal group most similar to that of cholesterol, *i.e.*, the dimethylamino compounds Va and VIa, were the most effective hypocholesterolemic agents. Further, it appears that the pregn-5-ene derivatives have a greater potency in reducing serum cholesterol levels than the saturated analogs. It is evident, therefore, that simple substitution of nitrogen for carbon at the 22 and 25 position of the cholesterol molecule results in compounds possessing a profound hypocholesterolemic activity. The superficial structural similarities of these 22,25-diazacholesterols and 22,25-diazacholestanols to cholesterol carries over to biochemical studies. It has been reported[13] elsewhere that the dihydrochloride salt of VIa,[14] the most intensively studied of these compounds, does mimic the effect of cholesterol feeding in several enzymatic systems. In a rat liver homogenate it inhibited acetate-1-C^{14} incorporation into cholesterol by 64%, but when mevalonate-2-C^{14} was used as a labeled substrate 42% inhibition of incorporation resulted. Concomitant with the inhibition of cholesterol synthesis from labelled acetate there was an increased incorporation of C^{14} into fatty and keto acids. Finally, whereas acetate-1-C^{14} inclusion into 3-hydroxy-3-methylglutarate was essentially unimpaired, there was a significant reduction of radioisotope incorporation into mevalonate. Thus, the preliminary evaluation of the site of action of compound VIa dihydrochloride and presumably its analogs implies that its primary site of action may be the specific inhibition of HMG-CoA reductase, the suggested site of action of exogenous cholesterol in reducing cholesterol synthesis. For this reason, the term "cholesteromimetic" has been used to denote the type of biological action exhibited by these compounds.[13]

Experimental[15]

20α-Chloroactamidopregn-5-en-3β-ol Acetate (II).—To a solution of 3β-acetoxy-20α-aminopregn-5-ene[9] (18 g.) in benzene (300 ml.) and triethylamine (10 ml.) was added dropwise with stirring chloroacetyl chloride (7.5 g.) in benzene (25 ml.). The dropping funnel was rinsed with additional benzene (25 ml.) and the mixture refluxed with stirring for 1 hr. After allowing to cool to room temperature, the reaction mixture was washed with water (5 × 50 ml.). The benzene

(13) R. E. Ranney and R. E. Counsell, *Proc. Soc. Expil. Biol. Med.*, **109**, 820 (1962).

(14) This compound has been evaluated biologically and clinically under the number SC 11952.

(15) The analytical data and optical rotations were furnished by our Analytical Department under the supervision of Dr. R. T. Dillon. The optical rotations were obtained in chloroform unless otherwise specified.

TABLE V

HYPOCHOLESTEROLEMIC ACTIVITY OF 20α-(2-DIALKYLAMINOETHYL)-AMINO-5α-PREGNAN-3β-OL DERIVATIVES

Compound	Hypercholesterolemic rat (oral administration) dose: mg./kg.	% Reduction[a]	Normal rat (parenteral administration) dose: mg./kg.	% Reduction[a]
VIa	25	33[b]	2	36
VIa·2HCl	1	12	0.4	23
VIb·2HCl	10	18[b]	2	Inactive
VIc	25	23[b]	2	29
VId			4	21
VId·2HCl	10	Inactive		
VIe			2	Inactive
VIe·2HCl	10	Inactive	2	Inactive
VIf			8	30[b]
VIf·2HCl	10	Inactive		

[a] Values refer to per cent. reduction of serum cholesterol. [b] Reduced body weight gain.

phase was dried and partially decolorized over a mixture of anhydrous potassium carbonate and Darco and the solvent removed by distillation. Recrystallization of the residue from ethanol afforded 17.8 g. (82%) of II, m.p. 195–199°. One additional recrystallization from benzene gave an analytical sample, m.p. 196–199°, $[\alpha]^{26}D$ −44°.

Anal. Calcd. for $C_{25}H_{38}ClNO_3$: Cl, 8.13; N, 3.21. Found: Cl, 8.10; N, 3.23.

20α-(2-Dimethylamino)-acetamidopregn-5-en-3β-ol Acetate (IIIa).—To a solution of II (8.72 g.) in a mixture of toluene (100 ml.) and methyl ethyl ketone (25 ml.) contained in a pressure bottle was added a solution of dimethylamine (9 g.) in toluene (30 ml.). The bottle was sealed and kept at 50–55° for 40 hr. After refrigeration, the contents were transferred to a separatory funnel and washed with water. The organic phase was dried over a mixture of anhydrous potassium carbonate and Darco and the solvent removed by distillation. Crystallization of the resulting residue from ethanol–water afforded 8.0 g. (90%) of IIIa, m.p. 157–159°. One additional recrystallization from the same solvent mixture gave an analytical sample, m.p. 159.5–161.5°, $[\alpha]^{25}D$ −52.5°.

Anal. Calcd. for $C_{27}H_{44}N_2O_3$: C, 72.93; H, 9.97; N, 6.30. Found: C, 72.84; H, 10.01; N, 6.29.

20α-(2-Pyrrolidino)-acetamidopregn-5-en-3β-ol Acetate (IIIc). General Method.—A solution of II (4.4 g.) and pyrrolidine (1.7 g.) in benzene (50 ml.) was refluxed on the steam bath for 15 hr. Ether (100 ml.) was added to the cooled reaction mixture and the solution washed with water (3 × 50 ml.). After drying the organic phase over a mixture of anhydrous potassium carbonate and Darco, the solvent was removed by distillation. Crystallization of the residue from ethanol-water afforded 4.2 g. (89.5%) of IIIc as platelets, m.p. 157–160°, $[\alpha]^{25}D$ −46.5°.

Anal. Calcd. for $C_{29}H_{46}N_2O_3$: C, 74.00; H, 9.85; N, 5.95. Found: C, 73.66; H, 9.54; N, 5.99.

Lithium Aluminum Hydride Reduction of Amides. 1. In Tetrahydrofuran.—A solution of IIIa (7.5 g.) in tetrahydrofuran (75 ml.) was added dropwise with

stirring to a suspension of lithium aluminum hydride (5.0 g.) in tetrahydrofuran (75 ml.) at such a rate as to maintain gentle reflux. After refluxing the reaction mixture for an additional 4 hr., ethyl acetate (20 ml.) was added dropwise with stirring to the externally cooled mixture. The mixture was then treated with saturated sodium sulfate solution until the precipitate began to adhere to the sides of the flask. Anhydrous sodium sulfate was added and the salts were removed by filtration. They were washed with ethyl acetate and the filtrate was evaporated to dryness. Recrystallization of the resulting solid from acetone–Skellysolve C afforded 3.75 g. (56%) of 20α-(2-dimethylamino)-acetamidopregn-5-en-3β-ol (IV), m.p. 187.5–189.5°, $[\alpha]^{26}D$ −47°.

Anal. Calcd. for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.52; N, 6.96. Found: C, 74.63; H, 10.38; N, 7.09.

2. **In Dioxane. General Method.**—A solution of IIIc (3.0 g.) in purified dioxane (25 ml.) was added dropwise with stirring to a refluxing slurry of lithium aluminum hydride (1.5 g.) in purified dioxane[16] (40 ml.). The dropping funnel was rinsed with purified dioxane (10 ml.) and the mixture was refluxed and stirred for 16 hr. Excess hydride was decomposed by successive dropwise addition of water (1.5 ml.) in dioxane (25 ml.), 20% sodium hydroxide solution (1.2 ml.), and water (5.3 ml.) to the refluxing mixture. The reaction mixture was cooled and the insoluble salts were removed by filtration and washed with dioxane. The solvent was removed from the filtrate under reduced pressure. This afforded 2.6 g. of a yellow oil which upon crystallization from acetone gave 2.2 g. (83%) of 20α-(2-pyrrolidinoethyl)-aminopregn-5-en-3β-ol (Vc) as needles, m.p. 111–113.5°, $[\alpha]^{25}D$ − 38°.

Anal. Calcd. for $C_{27}H_{46}N_2O$: C, 78.20; H, 11.18; N, 6.76. Found: C, 78.17; H, 11.15; N, 7.22.

Dihydrochloride Salts.—The crystalline free base was dissolved in anhydrous ether containing sufficient isopropyl alcohol for solubilization. Addition of a solution of hydrogen chloride in isopropyl alcohol precipitated the dihydrochloride salt which was recrystallized from aqueous ethanol or aqueous isopropyl alcohol. All the salts gave satisfactory elemental analyses.

Preparation of 20α-(2-Dialkylaminoethyl)amino-5α-pregnan-3β-ol Derivatives (VI). 1. By Catalytic Hydrogenation[17] of the Appropriate Pregn-5-ene Derivative (V). General Method.—A solution of 20α-(2-dimethylaminoethyl)-aminopregn-5-en-3β-ol (Va, 0.5 g.) in 95% ethanol (12 ml.) containing concd. hydrochloric acid (0.3 ml.) was hydrogenated over platinum oxide (0.1 g.) at atmospheric pressure and 25°. After hydrogen uptake ceased (5 hr.), the catalyst was removed by filtration and washed with 95% ethanol. The solvent was removed from the filtrate by distillation and the solid residue recrystallized from ethanol–water. This gave 0.45 g. (76%) of 20α-(2-dimethylaminoethyl)-amino-5α-pregnan-3β-ol dihydrochloride, $[\alpha]^{25}D$ +11.5° (CH_3OH).

Anal. Calcd. for $C_{25}H_{46}N_2O \cdot 2HCl$: Cl, 15.30; N, 6.04. Found: Cl, 15.13; N, 6.21.

The free base was prepared by treating a methanol–water (1:4) solution of the dihydrochloride with aqueous sodium hydroxide solution. Collection of the precipitate and recrystallization from ethyl acetate gave 20α-(2-dimethylaminoethyl)-amino-5α-pregnan-3β-ol (VIa), m.p. 134–136°, $[\alpha]^{25}D$ +22°.

(16) Obtained from Pierce Chemical Company.

(17) We are indebted to Messrs. W. M. Selby and M. G. Scaros for performing the catalytic hydrogenations.

Anal. Calcd. for $C_{25}H_{46}N_2O$: C, 76.86; H, 11.87; N, 7.17. Found: C, 77.23; H, 12.25; N, 7.27.

2. By Reductive Amination.—A solution of *allo*-pregnanolone acetate (VII, 28.8 g.), β-dimethylaminoethylamine (14.1 g.), and acetic acid (19.2 g.) in absolute ethanol (500 ml.) was hydrogenated over platinum oxide (3.0 g.) at 70.3 kg./cm.^{2} and 46°. After hydrogen uptake ceased (11 hr.), the catalyst was removed by filtration and washed with ethanol. Sodium hydroxide (25 g.) and water (100 ml.) were added to the filtrate and the solution refluxed on the steam bath for 1.5 hr. The solution was then concentrated to one half the original volume and slowly poured into ice water. The resulting gum was extracted with methylene chloride. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the oily residue dissolved in isopropyl alcohol–ether (1:4, 500 ml.). A solution of hydrogen chloride in isopropyl alcohol was added dropwise with stirring until precipitation was complete. The precipitate was collected by filtration and washed with acetone and ether. The crude dihydrochloride (39 g.) was dissolved in ethanol–water (1:4) and the solution made basic with 20% sodium hydroxide solution. The resulting precipitate was washed with water and slowly recrystallized from acetone to afford 7.5 g. of material, m.p. 110–120°. Several recrystallizations from ethyl acetate gave pure VIa (3.1 g., 10%) identical in all respects with that obtained above. A second crop of material (12.3 g.) obtained from the initial recrystallization was recrystallized several times from ethyl acetate to give a lower melting isomer (VIII), m.p. 72–74°, $[\alpha]^{25}D$ +9.

Anal. Calcd. for $C_{25}H_{46}N_2O$: C, 76.86; H, 11.87. Found: C, 76.53; H, 11.74.

Thyroxine Analogs. VI.[1] Synthesis and Antigoitrogenic Activity of 3,5-Diiodo-4-(4′-Aminophenoxy)-L-Phenylalanines, Including the 4′-Amino Analog of 3,5,3′-Triiodo-L-Thyronine

EUGENE C. JORGENSEN AND PETER SLADE

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California

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The synthesis of several analogs of thyroxine, in which the 4′-hydroxyl group has been replaced by an amino group, is described. The 4′-amino analogs of 3,5,3′-triiodo-L-thyronine and 3,5-diiodo-3′,5′-dimethyl-L-thyronine show thyroxine-like activity in the rat antigoiter assay.

One of the ways in which thyroxine might exert its biological effects is by interaction with oxidation-reduction systems. Niemann[2] has

(1) Paper V, E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.*, **26**, 897 (1961).

(2) C. Niemann, *Fortschr. Chem. org. Naturstoffe*, **7**, 167 (1950).