amount was absorbed. The free base, bp 130–145° (1 mm), was isolated and converted into its hydrochloride which was recrystallized from ethanol; mp 163–165°; yield 17 g; ν^{CHCl_3} 3280, 1445, 1170, 1090, 1024, and 675 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO \cdot HCl$: C, 68.32; H, 8.54; N, 4.98. Found: C, 68.37; H, 8.36; N, 4.92.

(±)-*trans*-**N-Benzyl-N-methyl-2-(cyclohexyloxy)cyclopropylamine** (**22**).—A solution of 15 g of **21** and 6 g of formalin in 250 ml of methanol containing Raney nickel was reduced under 3.5 kg/cm^2 of hydrogen pressure. The theoretical amount of hydrogen was absorbed. After the catalyst was filtered and the filtrate was concentrated, the residual oil was distilled *in vacuo;* bp 115–124° (1 mm); yield 17 g; ν^{CHCl_3} 1445, 1165, 1096, 1026, and 698 cm^{-1}.

The base was converted into its hydrochloride and purified by recrystallization from 2-propanol; mp 158–159°.

Anal. Calcd for $C_{17}H_{24}NO \cdot HCl$: C, 69.15; H, 8.81; N, 4.74. Found: C, 68.93; H, 8.78; N, 4.77.

(±)-*trans*-**1-Methylamino-2-cyclohexyloxycyclopropane** (**23**).—A solution of 2.6 g of the tertiary amine **22** in 100 ml of absolute methanol containing 3 ml of 20% 2-propanolic HCl and 2 g of 10% Pd–C was shaken under 3 kg/cm^2 pressure of hydrogen until reduction was complete. The filtered solution was concentrated *in vacuo,* diluted with water, and made alkaline (NaOH), and the base was extracted with ether. The ethereal extracts were washed with water, dried, and evaporated, ν^{CHCl_3} was compatible: 3333, 1455, 1165, 1100, and 1023 cm^{-1}. The base was converted into its hydrochloride and recrystallized from ethyl acetate; mp 112–113°, yield 1.5 g.

Anal. Calcd for $C_{10}H_{19}NO \cdot HCl$: C, 58.53; H, 9.75; N, 6.82. Found: C, 58.20; H, 9.59; N, 6.82.

(±)-*trans*-**1-Dimethylamino-2-cyclohexyloxycyclopropane** (**24**).—A solution of 7.8 g of amine **9** and 9 g of formalin in 250 ml of methanol was reduced in the presence of Raney nickel and the hydrogen uptake ceased at theory. The solution was filtered, concentrated, and distilled, bp 48–53° (1 mm), yield 6.6 g. The base was converted into its hydrochloride and recrystallized from a mixture of ethanol–ethyl acetate; mp 187–189°; ν^{CHCl_3} 2500–2000 region, 1450, 1170, 1098, and 1024 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO \cdot HCl$: C, 60.27; H, 10.04; N, 6.39. Found: C, 60.47; H, 10.26; N, 6.25.

(±)-*trans*-(**2-Cyclohexyloxycyclopropyl**)**guanidine Nitrate** (**25**).—A mixture of 4 g of 1-guanyl-3,5-dimethylpyrazole nitrate[16] and 3.1 g of amine **9** in 40 ml of ethanol was refluxed for 6 hr under nitrogen. The solution was evaporated to dryness *in vacuo,* and the oily residue was triturated with eight 30-ml portions of anhydrous ether to remove 3,5-dimethylpyrazole. The residual oil crystallized on standing and was recrystallized from ethyl acetate; mp 110–111°; yield 3.1 g; ν^{CHCl_3} 3420–3140 region, 1667, 1610, 1390, 1340, 1023, and 823 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}N_3O \cdot HNO_3$: C, 46.15; H, 7.69; N, 21.53. Found: C, 46.10; H, 7.37; N, 21.47.

Acknowledgment.—The authors wish to express their gratitude to Dr. Al Steyermark and his staff for the microanalyses, to Mr. S. Traiman for the infrared spectra and interpretations, and to Messrs. H. J. Jenny and J. Manius for the gas–liquid partition chromatography.

(16) R. A. B. Bannard, A. A. Casselmen, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).

Hypocholesterolemic Agents. VI.[1] A- and B-Ring-Modified Azacholesterols

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

Divisions of Chemical and Biological Research, G. D. Searle & Company, Chicago, Illinois 60680

The potent hypocholesterolemic activity of certain diazacholesterol analogs prompted the synthesis of a series of diaza derivatives having the A and B rings modified from that of cholesterol. The comparative hypocholesterolemic activity of these compounds was examined and certain tentative suggestions regarding their structure–activity relationship were presented.

One successful approach to the development of hypocholesterolemic agents has been the preparation of compounds which will in some manner interfere with the synthesis of endogenous cholesterol. Several groups[2,3] have reported finding a significant suppression of hepatic cholesterol when cholesterol was fed to certain laboratory animals. This inhibitory effect has become known as a negative feedback control[4] mechanism involving the first irreversible step in the biosynthesis of cholesterol, that is, the conversion of hydroxymethylglutaryl-CoA to mevalonic acid.[5]

Previous publications[6,7] from these laboratories described a variety of synthetic diazacholesterol analogs which were prepared in an effort to simulate cholesterol in this feedback mechanism. Biological studies[8] demonstrated that a number of compounds were extremely potent inhibitors of cholesterol biosynthesis in animals. Subsequent clinical studies demonstrated that 22,25-diazacholestanol[9] and 20,25-diazacholesterol[10] (IIIa) caused a significant reduction in serum cholesterol levels in subjects with hypercholesterolemia and coronary atherosclerosis.

Structure–activity relationship studies with the azacholesterols suggested that a receptor site with dimensions specific for cholesterol was involved[6,7] and that adsorption of the inhibitor at the receptor site occurred *via* the less hindered α face of the steroid molecule.[1] Moreover, variation of the position of the nitrogen atom in the monoaza side-chain analogs resulted in dramatic changes in the hypocholesterolemic activity.[1] This paper represents a continuation in part of our structure–activity relationship studies and describes the synthesis and hypocholesterolemic activ-

(1) Paper V: R. E. Counsell, P. D. Klimstra, L. N. Nysted, and R. E. Ranney, *J. Med. Chem.*, **8**, 45 (1965).

(2) R. G. Gould and C. B. Taylor, *Federation Proc.*, **9**, 179 (1950).

(3) G. M. Tomkins, H. Sheppard, and I. L. Chaikoff, *J. Biol. Chem.*, **201**, 137 (1953); I. D. Frantz, Jr., H. S. Schneider, and B. T. Hinkelman, *ibid.*, **206**, 465 (1954).

(4) M. D. Siperstein, *Am. J. Clin. Nutr.*, **8**, 645 (1960); E. P. Madhava Bhattathiry and M. D. Siperstein, *J. Clin. Invest.*, **42**, 1613 (1963).

(5) M. D. Siperstein and M. J. Guest, *Am. J. Med.*, **27**, 325 (1959); *J. Clin. Invest.*, **38**, 1043 (1959); *ibid.*, **39**, 642 (1960).

(6) R. E. Counsell, P. D. Klimstra, R. E. Ranney, and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720 (1962).

(7) R. E. Counsell, P. D. Klimstra, and R. E. Ranney, *ibid.*, **5**, 1224 (1962).

(8) (a) R. E. Ranney, and R. E. Counsell, *Federation Proc.*, **21**, 96 (1962); *Proc. Soc. Exptl. Biol. Med.*, **109**, 820 (1962); (b) R. E. Ranney, D. L. Cook, W. E. Hambourger, and R. E. Counsell, *J. Pharmacol. Exptl. Therap.*, **142**, 132 (1963); (c) R. E. Ranney and D. L. Cook, *Arch. Intern. Pharmacodyn.*, **154**, 51 (1965).

(9) B. A. Sachs and L. Wolfman, *Circulation*, **26**, 669 (1962).

(10) J. M. Martt and C. R. Talbert, *ibid.*, **28**, 763 (1963); J. M. Martt, C. R. Talbert, and G. E. Lee, *Ann. Internal Med.*, **61**, 810 (1964); B. A. Sachs and L. Wolfman, *Arch. Internal Med.*, **116**, 336 (1965).

TABLE I

N-(DIMETHYLAMINO)PROPYL-17β-FORMAMIDOANDROSTANE DERIVATIVES

II[a]	Ref to ketone I	Recrystn media	Mp, °C	$[\alpha]^{25}D$, deg	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
b	b	Me_2CO	168–169.5	−75	62.6	$C_{25}H_{44}N_2O_2$	75.58	10.52		75.63	10.42	
c	c	Me_2CO–H_2O	50–54	+52.5	70.5	$C_{25}H_{44}N_2O$	77.66	10.95	7.25	77.66	10.82	6.87
d	d											
f		Me_2CO	138–139.5	−1.5	74.1	$C_{25}H_{46}N_2O_2$	74.21	10.96	6.48	74.29	10.84	6.66
g	e											
h	f	Me_2CO	118–119	+24.5	43.6	$C_{25}H_{42}N_2O$	77.66	10.95	7.25	77.93	11.03	7.39
i		Hexane	99–100	+17.5	74	$C_{25}H_{38}N_2O_2$	75.33	9.61	7.03	75.78	9.70	7.10

[a] Compounds IId [λ_{max} 234 mμ (log ε 4.27)] and IIg were oils which resisted crystallization from a variety of solvents. They were purified by forming their hydrochloride salts and liberating the free bases with Na_2CO_3. $LiAlH_4$ reduction was carried out directly without elemental analysis. [b] K. I. H. Williams, R. S. Rosenfeld, M. Smulowitz, and D. K. Fukushima, *Steroids*, **1**, 377 (1963). [c] S. Huwada and M. Miyasaki, *J. Pharm. Soc. Japan*, **57**, 874 (1937). [d] W. R. Nes and U. H. Kim, *Steroids*, **1**, 594 (1963); B. Camerino, R. DeCastiglione, and G. Bosisio, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 312 (1964). [e] H. Hirschmann, *J. Biol. Chem.*, **136**, 483 (1940). [f] J. Iriarte, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955).

TABLE II

N-METHYL-N-(DIMETHYLAMINO)PROPYL-17β-AMINOANDROSTANE DERIVATIVES

Compd[a]	$[\alpha]^{25}D$, deg	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Hydrochloride salts: Calcd, % Cl	Hydrochloride salts: Calcd, % N	Hydrochloride salts: Found, % Cl	Hydrochloride salts: Found, % N
IIIb	−62.5	$C_{25}H_{46}N_2O$	77.26	11.41	7.21	77.19	11.36	7.35	15.36	6.07	14.96	5.95
c	−43.5	$C_{25}H_{46}N_2$	80.58	11.90		80.81	11.50		15.92	6.29	15.32	6.24
d[b]	−77	$C_{25}H_{44}N_2$	81.02	11.42	7.56	80.99	11.11	7.75	15.98	6.32	15.39	5.91
f[c]	+12.5	$C_{25}H_{48}N_2O$	76.86	11.87	7.17	76.73	11.64	6.91	15.30	6.04	15.07	5.99
g[c]	+11.5	$C_{25}H_{48}N_2$	80.15	12.38		80.53	12.35		15.86	6.29	15.25	6.45
h	+46.5	$C_{25}H_{44}N_2$	80.58	11.90	7.52	80.27	11.95	7.52	15.92	6.29	15.50	6.05
i	+52.5	$C_{25}H_{40}N_2O$	78.07	10.48	7.29	78.10	10.42	7.58	15.50	6.13	15.09	6.02
IV	+70.5	$C_{25}N_{42}N_2$	77.66	10.95	7.25	77.65	10.95	6.83		6.10		6.00
Vc	+46	$C_{25}H_{44}N_2O$	77.26	11.41	7.21	76.91	11.44	7.05		6.07		6.16

[a] Most of the free bases were oils at room temperature and were purified for analysis through their dihydrochloride salts and with regeneration of the free bases by Na_2CO_3. The yield of product purified by this method ranged from 70 to 90%. [b] λ_{max} 234 mμ (log ε 4.26). [c] Recrystallized from acetone: IIIf, mp 119–121°; IIIg, mp 37–40°; Vc, mp 110–113°.

ity of a number of A- and B-ring-modified 20,25-diazacholesterol analogs.

The most convenient route to the A- and B-ring-modified diazacholesterol derivatives (III) was that of Leuckart reductive amination of the readily available 17-keto steroids (I) to form the intermediate N-(dimethylamino)propyl-17β-formamidoandrostane derivatives (II, see Table I and Scheme I) in good yields. Subsequent reduction of these compounds with lithium aluminum hydride in dioxane gave the desired N-methyl-N-(dimethylamino)propyl-17β-aminoandrostanes (III, see Table II). The stereochemistry of the products and nature of these reactions was reported on previously.[6] Alternatively, the saturated compounds IIIe[7] and IIIg were prepared by catalytic hydrogenation of the corresponding dehydro analogs IIIa and IIIh. Compound IIIg was identical with that obtained by the Leuckart reductive amination approach starting with Ig.

Several groups[11,12] have shown that cholestenone (cholest-4-en-3-one) will inhibit cholesterogenesis and depress serum cholesterol levels in experimental animals. On the basis of this information, it was contemplated that conversion of 20,25-diazacholesterol to the cholestenone analog would lead to an enhancement of hypocholesterolemic activity. Oppenauer oxidation of IIIa afforded 20,25-diazacholestenone (IV) in good yield. Furthermore, reduction of this product with lithium tri-*t*-butoxyaluminum hydride provided V, the double-bond isomer of 20,25-diazacholesterol.

In an effort to ascertain the necessity of the steroid nucleus for hypocholesterolemic activity, a compound containing the diazacholesterol side chain but lacking the A, B, and C rings of the steroid nucleus was prepared. Lithium aluminum hydride reduction of the Leuckart reductive amination product of 2-methylcyclopentanone with dimethylaminopropylamine gave the desired N-(2-methyl)cyclopentyl derivative (VIII).

The steric configuration of VIII was shown by nmr[13] to be a mixture of *cis* and *trans* isomers probably resulting because of the lack of the fused steroidal ring system on the cyclopentane, which apparently controls the stereoselectivity of the Leuckart reaction in the case of the diazacholesterol derivatives. Moreover, the nmr spectrum as obtained in various solvent systems (*i.e.*, deuteriochloroform, deuterioacetic acid, and pyridine) was complex but indicated an isomer ratio of about 2:1. Preliminary vapor phase chromatography studies, however, have revealed only one component. From the stereochemical considerations of the Leuckart reaction one would expect the *trans* isomer to predominate.

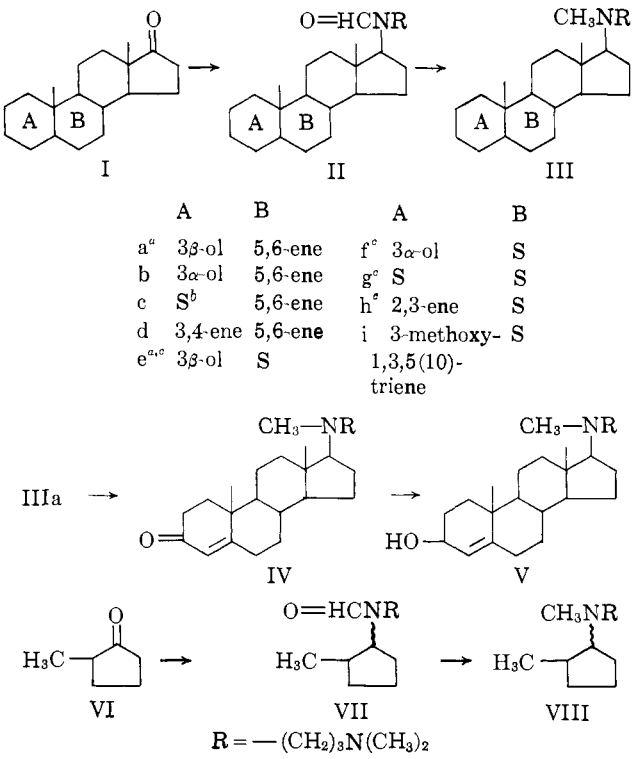
Preliminary Biological Results.—The oral hypocholesterolemic activities of A- and B-ring-modified

(11) G. M. Tomkins, C. W. Nichols, Jr., D. D. Chapman, S. Hotta, and I. L. Chaikoff, *Science*, **125**, 936 (1957).

(12) D. Steinberg, D. S. Fredrickson, and J. Avigan, *Proc. Soc. Exptl. Biol. Med.*, **97**, 784 (1958).

(13) We wish to thank Dr. R. H. Bible of our laboratories for interpretation of the nmr spectrum.

SCHEME I



	A	B		A	B
a[a]	3β-ol	5,6-ene	f[c]	3α-ol	S
b	3α-ol	5,6-ene	g[c]	S	S
c	S[b]	5,6-ene	h[c]	2,3-ene	S
d	3,4-ene	5,6-ene	i	3-methoxy-1,3,5(10)-triene	S
e[a,c]	3β-ol	S			

[a] The preparation and properties of these compounds are reported in *J. Med. Chem.*, **5**, 1224 (1962). [b] S = saturated ring. [c] In these examples, a 5α hydrogen is present.

diaza cholesterol analogs are shown in Table III and were determined in male rats made hypercholesterolemic with 6-propylthiouracil.[8b] The minimal effective dose (MED) necessary to lower serum cholesterol 10% below that of concurrently tested control animals after a 10-day treatment period was taken as the criterion of biological activity.

TABLE III

ORAL HYPOCHOLESTEROLEMIC ACTIVITY OF A- AND B-RING-MODIFIED AZACHOLESTEROLS

Compd[a]	MED[b] (rats), mg/kg
IIIa	0.3
b	2.0
c	8.0
d	2.0
e	2.0
f	0.5
g	2.6
h	0.6
i	3.0
IV	0.5
V	0.3
VIII	Inactive

[a] All compounds were evaluated as their hydrochloride salts. [b] Minimal effective dose.

It is apparent from Table III that none of the A- and B-ring modifications of the cholesterol analog IIIa produced enhancement in hypocholesterolemic activity. High activity, however, appears to be associated with the localization of electrons in the vicinity of the C-3 atom. For example, compound IIIc without a functional group in the A ring showed a much lower order of activity than IIIa.

The completely saturated moiety, IIIg,[14] demonstrated a reduction in activity while the additional unsaturation involving the A and B rings (IIId) did not enhance the hypocholesterolemic effect of IIIa. The configuration of the 3-hydroxyl group in the 5-cholesterol series seems important for optimal activity, since IIIb (3-axial OH) had less than one-sixth the activity of IIIa. On the other hand, the reverse was true in the cholestanol series since compound IIIf (3-axial OH) was several times more potent than IIIe (3-equatorial OH). Therefore, no real conclusion can be drawn with regard to the steric effect of the 3-hydroxyl group in this series of compounds.

The inclusion of a diazacholesterol analog possessing an aromatic A ring (IIIi) was of interest not only because of the conformational and electronic changes introduced by such a system, but also because of the similarity of this substance to known estrogenic compounds which themselves are known to have a profound effect on serum lipid levels in man.[15,16] Although IIIi showed significant hypocholesterolemic activity, it still was only one-tenth that of IIIa. The estrogenic activity of IIIi as measured by the increase in weight of the immature mouse uterus was only 0.12% when compared to estrone. While compounds possessing estrogenic activity normally produce hypocholesterolemic response, it is unlikely that this minimal estrogenic response was entirely responsible for the hypocholesterolemic activity of IIIi. Similar results were recently reported for 22,25-diaza-19-norcholesta-1,3,5(10)-trien-3-ol by Plotka and co-workers.[17,18]

In contrast with our expectations, conversion of IIIa to the cholestenone analog IV caused a slight lowering of hypocholesterolemic activity. Reduction of IV to V, however, restored the original activity.

The nonsteroidal analog VIII was completely devoid of hypocholesterolemic activity at a dose of 10 mg/kg. This result along with those reported[19] for other aliphatic diamines indicates that the steroid nucleus is essential for optimal hypocholesterolemic activity in this series.

Experimental Section[20]

N-(3-Dimethylamino)propyl-17β-formamidoandrost-5-en-3α-ol (IIb). General Method.—Formic acid (40 ml, 98-100%) was added cautiously with stirring and external cooling to a mixture of Ib (10 g) in 3-dimethylaminopropylamine (20 g). The reaction mixture was heated in an oil bath maintained between 170–180° for 20 hr. After allowing to cool, the solution was poured into ice and water (750 ml) containing NaOH (40 g). The gelatinous precipitate was extracted with chloroform. The combined extracts were washed several times with water and dried (Na_2SO_4). Solvent removal with heating *in vacuo* gave

(14) It is of interest to point out the unexplained toxicity of this substance at a dose of 10 mg/kg. Five out of eight animals did not survive the 10-day test period.

(15) E. M. Russ, H. A. Eder, and D. P. Barr, *Am. J. Med.*, **19**, 4 (1955).

(16) M. E. Davis, R. J. Jones, and C. Jarolim, *Am. J. Obstet. Gynecol.*, **82**, 1003 (1961).

(17) L. Velluz, D. Bertin, L. Nedelec, and C. Plotka, *Compt. Rend.*, **255**, 6 (1962).

(18) C. Plotka, R. Dergedt, J. Pottier, P. Zirinis, and R. Jequier, *Arch. Intern. Pharmacodyn.*, **152**, 319 (1964).

(19) M. Kraml, L. G. Humber, J. Dubuc, and R. Gandry, *J. Med. Chem.*, **7**, 500 (1964).

(20) The elemental analyses, optical rotations, and infrared spectra were furnished by Mr. E. Zielinski and Mr. J. Damascus of our analytical department under the supervision of Dr. R. T. Dillon. The optical rotations and infrared spectra were obtained in chloroform. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

nearly a quantitative yield of which was suitable for subsequent reduction. Recrystallization from acetone, however, gave IIb (8.9 g), mp 168–169.5°, $[\alpha]^{25}D$ −75°.

Anal. Calcd for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.52. Found: C, 74.63; H, 10.42.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-5-en-3α-ol (IIIb). General Method.—A solution of IIb (6.0 g) in purified dioxane (60 ml) was added with stirring to a refluxing slurry of $LiAlH_4$ (3.0 g) in purified dioxane (140 ml) over 0.5 hr. The reaction was refluxed for 18 hr, and the excess hydride was decomposed by the successive dropwise addition of aqueous dioxane (1:6, 20 ml), 20% NaOH solution (2.5 ml), and water (11 ml). The inorganic salts were removed by filtration and washed with additional dioxane (50 ml). Solvent removal *in vacuo* with heating gave an oily residue which solidified. Recrystallization from acetone gave IIIb (5.2 g), mp 119–121°, $[\alpha]^{25}D$ −62.5°.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrostane (IIIg).—A solution of the dihydrochloride in IIIh (1.25 g) in 95% ethyl alcohol (100 ml) was hydrogenated at atmospheric pressure (Parr shaker) and 25° using PtO_2 (100 mg) as catalyst. The catalyst was removed by filtration and washed with additional 95% ethyl alcohol. The solvent was removed *in vacuo* to leave a solid residue which was recrystallized from ethyl alcohol to give pure IIIg dihydrochloride (1.2 g), $[\alpha]^{25}D$ +11° (MeOH).

Anal. Calcd for $C_{25}H_{46}N_2 \cdot 2HCl$: N, 6.28. Found: N, 6.23.

A 10% aqueous solution of Na_2CO_3 (2.5 ml) was added with stirring to the dihydrochloride (0.5 g) in methanol (0.8 ml) and water (5 ml). The mixture was diluted with water (20 ml) and filtered to yield the free base IIIg (0.4 g), identical with that prepared by the Leuckart procedure described above.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-4-en-3-one (IV).—A solution of IIIa (4.0 g) and cyclohexanone (20 ml) in toluene (100 ml) was distilled until 20 ml had been collected. Aluminum isopropoxide (8.0 g) in toluene (75 ml) was added dropwise with stirring to the hot solution. Slow distillation of the reaction mixture was continued for 2 hr. After cooling to room temperature, a concentrated solution of Rochelle salts (120 ml) was added slowly with rapid stirring. The mixture was steam distilled for 1 hr. After cooling, the residual mixture was extracted with ether; the extract was treated with three 150-ml portions of 5% HCl. The aqueous acid fraction was washed with ether and made basic with 20% NaOH solution. The oily precipitate was extracted with ether, washed with water, and dried (Na_2SO_4 containing Darco); solvent removal *in vacuo* gave IV (3.5 g) as an oil ($[\alpha]^{20}D$ +70.5°), which solidified upon standing but resisted recrystallization from a variety of solvents. The ultraviolet spectrum displayed the characteristic absorption maximum for a 4-dehydro-3-keto system, at 240 mμ (log ε 4.19).

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-4-en-3β-ol (V).—A solution of IV (1.7 g) in dry tetrahydrofuran (THF) (40 ml) was added with stirring dropwise to a suspension of $LiAlH_4$ (1.0 g) in THF (60 ml). The reaction mixture was refluxed for 3.5 hr. After cooling to room temperature, the excess hydride was decomposed by the successive dropwise addition of water (1 ml) in THF (20 ml), 20% NaOH (0.75 ml), and water (3.5 ml). The inorganic salts were removed by filtration and washed with additional THF (20 ml). The filtrate was concentrated to dryness *in vacuo* to give an oil which solidified upon standing. Recrystallization from acetone afforded V (1.3 g), mp 110–113°, $[\alpha]^{25}D$ +46°.

N-(Dimethylamino)propyl-1ξ-formamido-2ξ-methylcyclopentane (VII).—To a stirred solution of 2-methylcyclopentanone (50.0 g) in formic acid (330 ml, 98–100%) was added 3-dimethylaminopropylamine (250 g) dropwise over 20 min. The reaction was heated in a sealed container at 172–175° for 24 hr. The mixture was cooled and poured into a solution of NaOH (480 g) in water (2 l.). The resulting oily material was extracted with ether. The extract was washed repeatedly with water, until the aqueous portions were nearly neutral, and dried (Na_2SO_4). Solvent removal *in vacuo* gave VII as an oil which was distilled with the fraction boiling at 138–140° (9–10 mm) and collected (20.5 g), $n^{25}D$ 1.4688.

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39. Found: C, 68.07; H, 11.39.

N-Methyl-N-(dimethylamino)propyl-1ξ-amino-2ξ-methylcyclopentane (VIII).—A solution of VII (14.0 g) in dioxane (100 ml) was added dropwise with stirring and heating to a slurry of $LiAlH_4$ (12.0 g) in dioxane (100 ml) over 0.5 hr. The mixture was refluxed for 16 hr and the excess hydride was decomposed by the successive dropwise addition of aqueous dioxane (1:3, 36 ml), 20% aqueous NaOH solution (9 ml), and water (41 ml). The salts were removed by filtration and washed with additional dioxane. The filtrate was concentrated *in vacuo* leaving a viscous oil. Distillation gave the product VIII (10.4 g), bp 84–85° (9–10 mm), $n^{25}D$ 1.4523, $[\alpha]^{25}D$ +0.5°.

Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21. Found: C, 72.25; H, 12.83.

The **hydrochloride** salt of VIII gave the following analysis.

Anal. Calcd for $C_{12}H_{26}N_2 \cdot 2HCl$: N, 10.33. Found: N, 10.41.

Hydrochloride Salts.—The free base diamines were dissolved in a mixture of ether and acetone (1:1) and sufficient 7 *N* HCl in isopropyl alcohol was added dropwise with agitation. After stirring a few minutes, the dihydrochloride salts were collected by filtration and washed with acetone and ether. Recrystallization from ethanol or isopropyl alcohol gave the pure salts.

The Synthesis of Potential Anabolic Agents. Steroidal Oxadiazoles[1]

ROBERT E. HAVRANEK, G. BROOKE HOEY, AND DAVID H. BAEDER

Research Laboratories, Medicinal Division, Mallinckrodt Chemical Works, St. Louis, Missouri

Received October 13, 1965

The synthesis of several steroidal oxadiazoles and their N-oxide analogs, derived from cholesterol and 17α-methyltestosterone, is described and the results of their preliminary screening as anabolic agents are discussed. All the compounds tested showed some anabolic–androgenic activity. 17α-Methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol (**4**) is the most potent of those prepared, showing enhanced anabolic–myotropic activity and diminished androgenic response.

The incorporation of a heterocyclic ring fused onto ring A of selected steroids has been shown to lead to compounds therapeutically useful as anabolic agents.[2a] Clinton and co-workers,[2b] found that certain steroidal pyrazoles such as 17α-methyl-5α-androstano[3,2-*c*]-[1′,2′,5′]pyrazol-17β-ol (**1a**) represented a novel class of compounds with a high degree of separation of anabolic from androgenic activity. More recently, Manson

(1) Presented to the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) (a) P. de Ruggieri, G. Gandolfi, U. Guzzi, D. Chiaramonti, and C. Ferrari, *Farmaco* (Pavia), *Ed. Sci.*, **20**, 280 (1965); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961); (c) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Philips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).