the melting point was 170–173°, undepressed on admixture of XIV. The infrared spectra of the two materials were superimposable.

1-Benzamido-*trans*-2-(3,5-diiodo-4-hydroxyphenyl)cyclopropanecarboxylic Acid (XVIII).—To a solution of 2.97 g (0.01 mole) of XVI in 50 ml of 33% aqueous ethylamine was added slowly, with stirring, over 1 hr, 5.34 g (0.021 mole) of iodine in 125 ml of 10% aqueous KI. Stirring was continued for 1 hr at 25°. The solution was poured into ice–water, neutralized to pH 1, and cooled. The nearly colorless crystals were removed by filtration, air dried, and recrystallized from acetic acid; yield 3.0 g (55%), mp 210–214°. This material proved to be identical with XVIII prepared from XVII (see below) as shown by a comparison of their infrared spectra and mixture melting point which showed no depression.

1-(4-Acetoxy-3,5-diiodophenyl)-5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (XVII) was prepared from I by general procedure C; infrared, 1820 ($\nu_{C=O}$ oxazolone), 1765 ($\nu_{C=O}$ acetoxy), 1635 cm^{-1} ($\nu_{C=N}$ oxazolone); ultraviolet (CH_3CN), 263 mμ (ε 19,700).

A mixture of 17.8 g (0.031 mole) of XVII, 200 ml of 2% aqueous NaOH, and 200 ml of acetone was stirred under reflux for 4.5 hr and the acetone was removed under reduced pressure. The residue was poured into ice–water, acidified to pH 1, and cooled at 4° for 2 hr. The buff-colored crystals which separated were filtered, washed with H_2O, and dried over P_2O_5 to yield 14.0 g (82%) of XVIII, mp 214–215°. An analytical sample prepared by recrystallization from acetic acid had mp 215.5–216.5°; infrared, 3450 (ν_{OH} phenol), 3280 (ν_{NH} NHCO), 1700 ($\nu_{C=O}$ COOH), 1645 cm^{-1} ($\nu_{C=O}$ NHCO).

Anal. Calcd for $C_{17}H_{13}I_2NO_4$: C, 37.19; H, 2.39. Found: C, 37.09; H, 2.50.

This material was identical with that obtained by iodination of XVI (mixture melting point and infrared spectra).

Methyl 1-Benzamido-*trans*-2-(3,5-diiodo-4-hydroxyphenyl)-cyclopropanecarboxylate (XIX). A. From XVIII.—A mixture of XVIII (10 g, 0.018 mole), 50 ml of absolute methanol, 100 ml of 1,2-dichloroethane, and 0.5 g of *p*-toluenesulfonic acid was refluxed for 13 hr. The cooled reaction mixture was washed with H_2O, whereupon the product crystallized from the organic layer. The colorless crystals were filtered and recrystallized from methanol to yield 6.4 g (62%) of XIX, mp 195–197°. An analytical sample, recrystallized from methanol, had mp 199–200°; infrared, 3450 (ν_{OH} phenol), 3280 (ν_{NH} NHCO), 1725 ($\nu_{C=O}$ CO_2CH_3), 1645 cm^{-1} ($\nu_{C=O}$ NHCO).

Anal. Calcd for $C_{18}H_{15}I_2NO_4$: C, 38.39; H, 2.68. Found: C, 38.53; H, 2.84.

B. From XVII.—A mixture of XVII (16.4 g, 0.029 mole) and 3.24 g (0.06 mole) of sodium methoxide in 200 ml of absolute methanol was stirred under reflux for 3 hr. The solution was poured into ice–water and filtered, the filtrate was acidified to pH 3, and the mixture was cooled at 4° for 2 hr. The colorless crystals were filtered, washed with H_2O, and dried (vacuum, P_2O_5) to yield 15 g (93%) of XIX, mp 187–189°. The infrared spectrum of this material was identical with that of the product from method A above. Recrystallization from methanol gave colorless crystals, mp 197–199°.

Methyl 1-Benzamido-*trans*-2-[3,5-diiodo-4-(4-methoxyphenoxy)phenyl]cyclopropanecarboxylate (XX). A. From XIX.—A mixture of 15 g (0.026 mole) of XIX, 23.2 g (0.055 mole) of dianisyliodonium bromide,[10] 10 ml of triethylamine, 5 g of copper powder, and 200 ml of absolute methanol was stirred at 25° for 24 hr. It was filtered, the brownish crystals were dissolved in boiling methanol and filtered, and the filtrate was cooled to give 6.45 g (37%) of colorless XX, mp 185–187°. An analytical sample prepared by recrystallization from methanol had mp 186.5–187.5°; infrared, 3320 (ν_{NH} NHCO), 1735 ($\nu_{C=O}$ CO_2CH_3), 1645 ($\nu_{C=O}$ NHCO); nmr ($CDCl_3$), δ 7.78 (2 H, singlet, 2,6 protons of iodine-substituted ring), 7.48 (5 H, multiplet, phenyl protons of benzamido group), 6.72 (4 H, multiplet, protons of 1,4-disubstituted ring), 6.43 (1 H, broad singlet, $NHCOC_6H_5$), 3.75 (6 H, singlet, OCH_3, methyl ether and methyl ester), 3.08 (1 H, multiplet, cyclopropane CH), 2.03 (2 H, multiplet, cyclopropane CH_2); nmr (pyridine), δ 3.72 and 3.63 (3 H, singlet, OCH_3, methyl ether or methyl ester), 3.31 (1 H, multiplet, cyclopropane CH), 2.23 (2 H, multiplet, cyclopropane CH_2).

Anal. Calcd for $C_{25}H_{21}I_2NO_5$: C, 44.87; H, 3.16. Found: C, 44.69; H, 3.16.

B. From VI.—Treatment of VI with excess diazomethane in ether containing 16% methanol for 20 hr at 25° followed by evaporation of the solvent under reduced pressure furnished a residue which was crystallized from methanol–water. The resulting colorless crystals had mp 175–183°, undepressed (181–186°) by admixture of a sample obtained by method A from XIX. The infrared spectra of the two materials, and their respective nmr spectra in $CDCl_3$ and in pyridine, were identical.

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The Synthesis and Biological Evaluation of 16β-Amino-17α,20-dihydroxypregnanes

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The addition of primary and cyclic secondary amines to 16,17α-epoxy-20-hydroxypregnenes gave a series of 16β-amino-17α,20-dihydroxypregnenes. The amines were broadly screened and showed some activity as antihypertensive, antibacterial, antiprotozoal, and analgesic agents. The method of molecular rotation differences was shown to be applicable to the determination of configuration at C-20 in the 16,17α-epoxy-20-hydroxypregnane series.

The search for steroids with increased biological utility has led to the synthesis of such a profusion of compounds that hardly a position on the nucleus has resisted the introduction of a variety of new substituents. Molecular manipulation at the 16-carbon atom[1] has shown this to be one of the more profitable sites on which to operate. The introduction of a 16α-hydroxyl or a 16α-methyl group has been the most successful alteration to date. In the evolution of altered steroids the addition of nitrogen substituents has been a relatively recent development spurred by the success of the ring A pyrazoles.[2] Of the naturally occurring steroids the solanum alkaloids[3] and the apocynaceae[4] possess a C-16 nitrogen function and have been ex-

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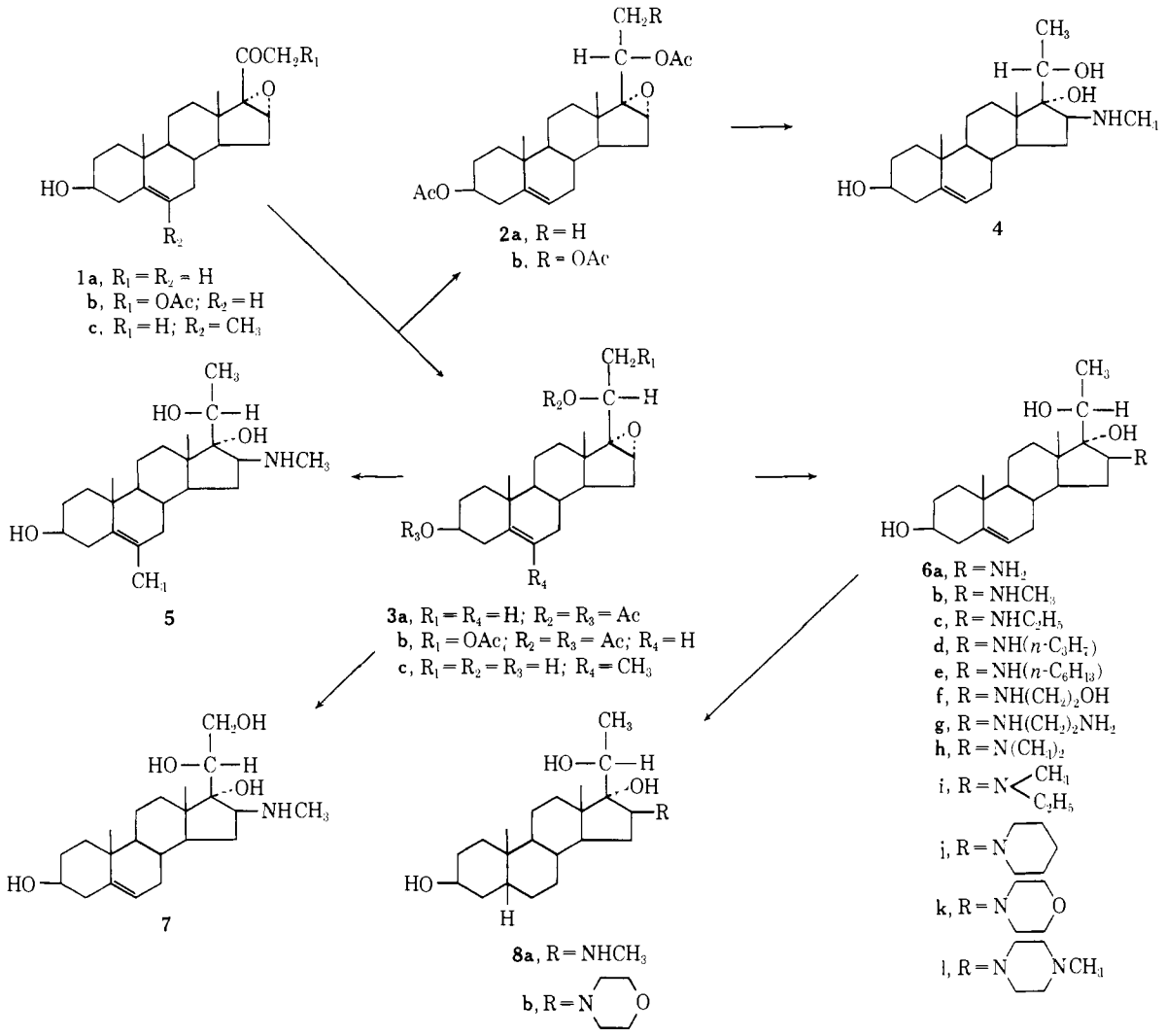
Chart I



tensively studied. The study of unnatural steroids has led to the attachment of various heterocyclic systems, with nitrogen at C-16, to the D ring and among these are the 16-spiro-3′-[Δ¹-pyrazolines],[5] the [16,-17-*c*]isoxazolines,[6] the 16,17-aziridines,[7] the pyrazoles,[8] and the pyrroles and pyrrolidines.[9] The easy addition of nucleophiles to the conjugated system of the Δ¹⁶-20-keto steroids has led to the preparation of a variety of 16α-amino steroids.[1,10] Recently a series of 16β-amino steroids of the androstane[11] and pregnane[12] series have been reported, as have C-16 azides,[13] oximes,[14] alkoxyamines,[10b] and some miscellaneous amines.[15] This report will concern itself with the synthesis, structural confirmation, and biological evaluation of a series of 16β-amino-17α,20-dihydroxypregnanes.

16β-Amino-17α,20-dihydroxypregnenes were prepared by the reaction of a suitably substituted 16,17α-epoxy-20-hydroxypregnene with a primary or cyclic secondary amine at 130–200° for periods of time varying from several days to several weeks in the presence of a catalytic amount of *p*-toluenesulfonic acid.[16] Dimethylamine was not successfully added but acyclic tertiary amines were prepared by the direct alkylation of the secondary amine or by the reduction of an amide with lithium aluminum hydride. All of the amines are of the 3β-hydroxy-Δ⁵ series with the exception of two 5α-pregnanes, **8a** and **8b**. These two were prepared by the hydrogenation of the Δ⁵ compound. The configuration at C-5 was assigned by analogy to the known addition of hydrogen from the α side to other

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(16) T. Colclough, J. I. Cunneen, and C. G. Moore, *Tetrahedron*, **15**, 187 (1961).

Δ^5-steroids.[17] The various amines and the chemical transformations leading to them are summarized in Chart I.

The 16,17α-epoxy-20-hydroxy compounds from which the amines were synthesized were prepared by sodium borohydride reduction of the corresponding 20-keto steroid. The reduction of 16,17-epoxypregnenolone[18] gives a mixture of 20α and 20β epimers which, contrary to the usual case, can be cleanly and efficiently separated into the pure isomers because of the low solubility of the 20α-epimer. However, the broad melting points of the alcohols as well as the low solubility of the 20α-epimer made it convenient to effect the final purification of the isomers through their acetates. The assignment of configuration at C-20 can usually be made from the observation that the 20β-acetate has a greater positive rotation than the 20α-acetate.[19] However, in the case of certain 17,20-dihydroxy-21-carbethoxypregnanes it has been shown that rotational data can lead to a wrong conclusion.[20] In our case the diacetate of the major epimer **3a** has a rotation of 0.0° and the diacetate of the minor epimer **2a** has a rotation of −17.5°, which would place the major epimer in the 20β series. To settle this point a direct chemical comparison was made with a compound of known configuration at C-20.

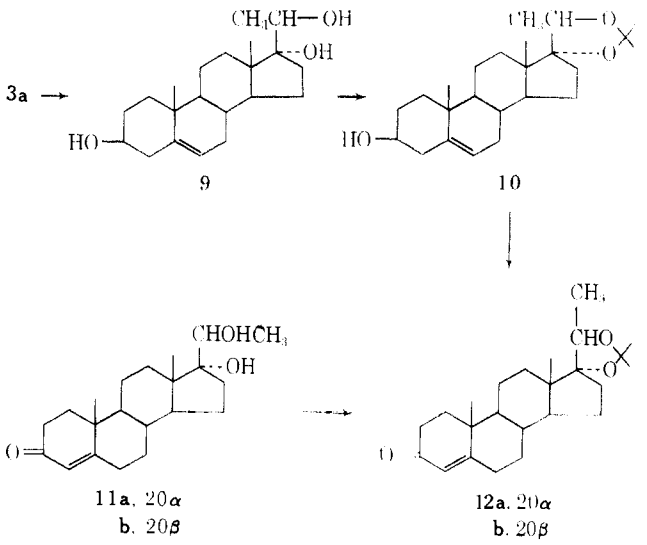
The availability in this laboratory of the acetonides[21] of the known C-20 epimers of 17α,20-dihydroxy-4-pregnen-3-one[22] made these compounds convenient reference samples with which to make the comparison. The diacetate of the major reduction product **3a** was reduced with $LiAlH_4$, the resulting triol, **9**, was converted into its acetonide **10** which was subjected to an Oppenauer oxidation. The product was identical (mixture melting point, infrared) with the acetonide of 17α,20β-dihydroxy-4-pregnen-3-one and not identical with the α-isomer, showing that the major isomer has the 20β configuration and the assumption of configuration based on the rotation of the acetates was correct. The reactions are summarized in Chart II.

The reduction of 16,17α-epoxy-3β,21-dihydroxy-5-pregnen-20-one 21-acetate gave a mixture of C-20 epimers which, after acetylation, were separated into the pure isomers by a combination of fractional crystallization and manual crystal picking. The major isomer **3b**, $[\alpha]_D$ +25.5°, was assigned the β configuration while the minor isomer **2b**, $[\alpha]_D$ −61°, was assigned the α configuration.

In the case of 6-methyl-16,17α-epoxy-3β-hydroxy-5-pregnen-20-one only one isomer of the reduction product was isolated and this was assigned to the 20β series because of the close correspondence of the nmr peaks for the C-18 and C-21 methyls and the C-16 and C-20 hydrogens with those of 16,17α-epoxy-5-pregnene-3β,-20β-diol.

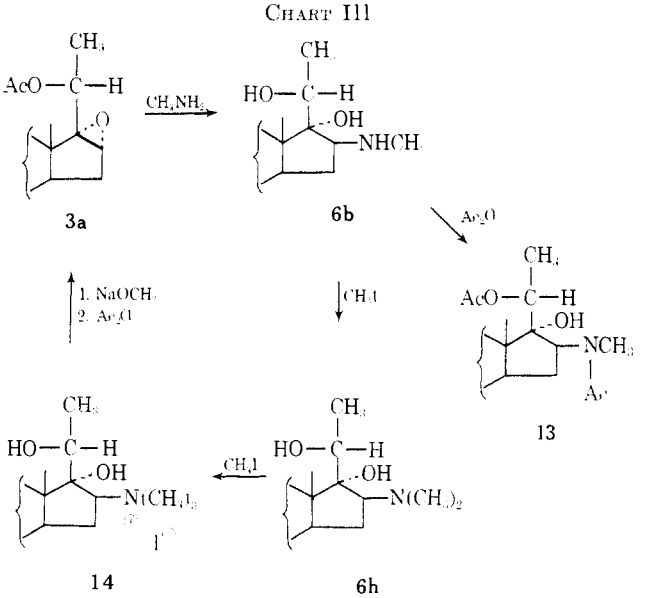
Having established the configuration at C-20 in the starting 16,17α-epoxides we turned to the question of the structure of the amine adducts. In spite of the subtleties involved in the conformations of ring D[23]

CHART II



the most rational assumption is that the amine addition proceeds to give the most nearly *trans* diaxial product,[24] *i.e.*, 16β-amino-17α-hydroxy. This view is supported by the work of Nagata[25] in which the elements of HCN are added as an organoaluminum cyanide to a 16,17α-epoxy-20-hydroxypregnane to give the 16β-cyano-17α-hydroxy product. Supporting chemical evidence was obtained from the transformations of the methylamine adduct of 16,17α-epoxy-5-pregnene-3β,20β-diol (**6b**), as illustrated in Chart III.

CHART III



Acetylation of **6b** gave a diacetate amide **13** in which one hydroxy group did not react, an observation consistent with the presence of the hindered, tertiary 17-hydroxy group. Stepwise methylation of **6b** with methyl iodide gave a dimethylamino compound **6h** and a quaternary ammonium iodide **14**. The quantitative conversion of **14** to the starting epoxide **3a** by sodium

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(23) (a) L. J. Chinn, *J. Org. Chem.*, **30**, 4165 (1965); (b) F. V. Brutcher, Jr., and E. J. Leopold, *J. Am. Chem. Soc.*, **88**, 3156 (1966).
(24) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(25) W. Nagata, M. Yoshioka, and T. Okumura, *Tetrahedron Letters*, 847 (1966).

methoxide in methanol followed by acetylation establishes the structural integrity of the pregnane system. It also eliminates the possibility of epoxide migration.[26] Such a migration would result in the conversion of the 16,17α-epoxy-20β-hydroxy system into a 16α-hydroxy-17β,20β-epoxy-17-isopregnane. Amine addition to the rearranged epoxide would be expected to give a 16α,20β-dihydroxy-17α-aminopregnane, which would not be converted to the 16,17α-epoxy-20β-hydroxy system on methylation and deamination as described above nor would it have a hindered hydroxy group.

Biological Evaluation.—The amines were broadly screened but only those categories showing the most interesting activities will be considered here. Antibacterial activity against *Diplococcus pneumoniae*[27] was observed with the ethylamino compound **6c**, the N-methylpiperazino compound **6l**, the 21-hydroxymethylamino compound **7**, and the 20α-hydroxymethylamino compound **4**. The ethylamino compound **6c** and the N-methylpiperazino compound **6l** also showed complete immobilization (death) of the protozoan *Tetrahymena geleii*,[28] while the dimethylamino compound **6h**, the 21-hydroxy-methylamino compound **7**, and the 20α-hydroxy-methylamino compound **4** killed about half of the organisms. Hypotensive activity, in pentobarbital-anesthetized dogs with cannulated femoral arteries,[29] was shown by the ethylamino compound **6c**, the *n*-propylamino compound **6d**, and the methylethylamino compound **6i**. Analgesic activity, as measured by the writhing mouse assay,[30] was noted with the following compounds: ethylamino **6c**, *n*-propylamino **6d**, ethanolamino **6f**, β-aminoethylamino **6g**, diethylamino **6h**, methylethylamino **6i**, piperidino **6j**, N-methylpiperazino **6l**, 21-hydroxymethylamino **7**, 4,5-dihydromorpholino **8b**.

Experimental Section[31]

16,17α-Epoxy-5-pregnene-3β,20-diol 3,20-Diacetate (2a and 3a).—To a stirred suspension of 200 g of 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one (**1a**) in 2 l. of methanol containing 20 ml of 10% aqueous NaOH was carefully added 11 g of $NaBH_4$. After 1 hr the suspension was cooled and 20 ml of acetic acid was added. Precipitation with water gave 184 g of a mixture of 20α- and 20β-diols and this was stirred with 450 ml of cold pyridine. Filtration gave 45 g of crude 20α-diol which was acetylated with acetic anhydride and pyridine giving 54 g of diacetate. One crystallization from acetone gave 27 g (11%) of pure **2a**: mp 166–167.5° (lit.[18] mp 168°); $[\alpha]_D^{26}$ −17.5° (*c* 1, EtOH); principle nmr peaks at 58 (18-H), 63 (19-H), 76, 83 (21-H), 122 (acetate CH_3's), 200 (16-H), 260–290 (3-H), 318, 325, 329, 336 (20-H), 315–330 (6-H).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.08; H, 8.44.

The pyridine filtrate was treated with acetic anhydride and, after standing overnight at room temperature, was added to water, precipitating 165 g of crude 20β-acetate. Crystallization from ether gave 88 g (35%) of pure **3a**. The analyzed sample was crystallized from acetone–hexane and had the following properties: mp 136–137.5°, partial recrystallization and complete fusion 147–148° (lit.[18] mp 150°); $[\alpha]_D^{27}$ 0.00 (*c* 1, EtOH); nmr peaks at 53 (18-H), 62 (19-H), 62, 69 (21-H), 121 (3-acetate), 124 (20-acetate), 194 (16-H), 260–290 (3-H), 315–330 (6-H), 328, 335, 342, 348 (20-H).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.07; H, 8.82.

16,17α-Epoxy-5-pregnene-3β,20,21-triol 3,20,21-Triacetate (2b and 3b).—The reduction of 30 g of 16,17α-epoxy-3β,21-dihydroxy-5-pregnen-20-one 21-acetate (**1b**) with 6 g of $NaBH_4$ was carried out as described above. The product, being noncrystalline, was extracted into ethyl acetate, isolated, and acetylated with acetic anhydride in pyridine to give 36 g of crude triacetate. Four crystallizations from acetone–hexane gave 13 g (35%) of pure **3b**: mp 179–181.5°; $[\alpha]_D^{26}$ +25.5° (*c* 1, EtOH); nmr peaks at 54 (18-H), 62 (19-H), 122, 127 (acetate methyls), 202 (16-H), 225, 228, 237, 243, 245, 247, 253, 258 (21-H), 260–290 (3-H), 315–327 (6-H), 341, 346, 348, 353 (20-H).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.61; H, 8.14.

The mother liquor was allowed to slowly evaporate at room temperature and from the residual crystalline mass nodules of prisms were removed by hand. Four crystallizations from acetone–hexane gave 1.1 g (3%) of pure **2b**: mp 129.5–131°; $[\alpha]_D^{26}$ −61° (*c* 1, EtOH); nmr peaks at 58 (18-H), 62 (19-H), 121, 123, 124 (acetate methyls), 197 (16-H), 230, 243, 252, 263, 266, 276, 278 (21-H), 255–290 (3-H), 315–327 (6-H), 332, 335, 341, 343 (20-H).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.31; H, 7.84.

16,17α-Epoxy-6-methyl-5-pregnene-3β,20β-diol (3c).—The reduction of 20 g of 3β-hydroxy-16,17α-epoxy-6-methyl-5-pregnen-20-one with 1.1 g of $NaBH_4$ in 0.20 l. of methanol containing 2 ml of 10% aqueous NaOH was carried out as described above. The crude product was crystallized five times from acetone–hexane, giving 8.0 g (40%) of pure **3c**: mp 183.5–190.5°; $[\alpha]_D^{27}$ −52° (*c* 1, EtOH); nmr peaks at 50 (18-H), 57 (19-H), 60, 67 (21-H), 93 (6-CH_3), 197 (16-H), 190–220 (3-H), 258, 264 (20-H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.15; H, 9.70.

The Addition of Amines to 16,17-Epoxy-20-hydroxy-5-pregnenes.—A 10-g quantity of the appropriate epoxide and 100 ml of amine with 1 g of *p*-toluenesulfonic acid monohydrate were heated either at reflux or in a bomb. The excess solvent was largely removed by evaporation and the residue was washed with water. The crude amine was either crystallized directly (isolation D) or was converted to its hydrochloride (isolation H). The hydrochlorides were prepared by adding HCl in 2-propanol or in water to an ether solution of the amine. The amine hydrochlorides were separated as a solid or an aqueous solution or as both and the free amines were regenerated by adding NaOH to a solution in water or methanol. No attempt was made to find optimum conditions for the amine preparations. The yields are calculated from the weight of the analyzed sample. The pertinent data are summarized in Table I.

16β-Dimethylamino-5-pregnene-3β,17α,20β-triol (6h).—A solution of 5.00 g of 16β-methylamino-5-pregnene-3β,17α,20β-triol (**6b**) in 0.50 l. of methanol containing 0.10 l. of CH_3I and 10 g of $NaHCO_3$ was refluxed for 6 hr. The solvents were largely distilled under vacuum and the product was precipitated with water. Four crystallizations from aqueous methanol gave 2.85 g (55%) of **6h**, mp 161.5–176.5°.

Anal. Calcd for $C_{23}H_{39}NO_3$: C, 73.16; H, 10.41; N, 3.71. Found: C, 72.88; H, 10.35; N, 3.64.

16β-Methylethylamino-5-pregnene-3β,17α,20β-triol (6i).—To a stirred suspension of 1.50 g of $LiAlH_4$ in 0.20 l. of THF was added 5.00 g of N-acetyl-16β-methylamino-5-pregnene-3β,17α,20β-triol 3,20-diacetate (**13**) and the mixture was refluxed for 72 hr. The cooled reaction mixture was treated with 0.30 l. of ethyl acetate and 0.10 l. of saturated aqueous Rochelle salt solution. The layers were separated and the aqueous phase was washed with

(26) G. B. Payne, *J. Org. Chem.*, **27**, 3819 (1962).

(27) The compounds were placed directly on the surface of blood agar plates which had been inoculated with the test organism. After an incubation period of 24 hr at 36° active compounds showed a clear zone, free of bacterial growth, around the compound.

(28) Approximately 5 mg of compound was added to 1.0 ml of a 24-hr culture and the effect was measured after 24 hr at room temperature.

(29) The amines were administered intravenously at 5 mg/kg. Active compounds showed at least a 20% decrease in blood pressure lasting 5 min or longer in 50% or more of the dogs. The method is described by A. L. A. Boura and A. F. Green in "Evaluation of Drug Activities: Pharmacometrics," D. R. Laurence and A. L. Bacharach, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 19.

(30) This test is a modification of the procedure of E. T. Eckhardt, F. Cheplovitz, M. Lipo, and W. M. Govier, *Proc. Soc. Exptl. Biol. Med.*, **98**, 186 (1958). One hour following the oral administration of 60 mg or less of compound each mouse was challenged with the intraperitoneal administration of 0.2 ml of 0.5% aqueous HCl. The compound is rated active if at least 20% of the animals do not show the writhing response.

(31) Melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Nmr spectra were taken with a Varian A-60 instrument using $CDCl_3$ as solvent unless otherwise indicated. The data are given in cycles per second downfield from internal Me_4Si.

TABLE I

THE PREPARATION OF 16β-AMINO-17α,20-DIHYDROXY-5-PREGNENES

Compd	16-Substit	Other variant	Time, days	Temp, °C	Press., psi	Isolation[a]	Recryst solvent[b]	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
4	$NHCH_3$	20α-OH	6	150	700	D	M–W	218–225	75	$C_{22}H_{35}NO_3$	72.68	72.88	10.26	10.49	3.85	4.02
5	$NHCH_3$	6-CH_3[c]	5	132	700	D	M	234–252	46	$C_{23}H_{39}NO_3$	73.16	73.36	10.41	10.40	3.71	4.00
6a	NH_2	d	3.5	147	1200	M	M	243–265	9	$C_{21}H_{35}NO_3$	72.16	72.08	10.09	10.00	4.01	4.04
6b	$NHCH_3$		4	130	700	D	M	229–242	58	$C_{22}H_{37}NO_3$	72.68	72.58	10.26	10.27	3.85	3.87
6c	NHC_2H_5		4	189	750	M	A–H	177.5–184.5	25	$C_{23}H_{39}NO_3$	73.16	73.44	10.41	10.35	3.71	3.69
6d	$NH(n\text{-}C_4H_7)$		3	150	200	M	M–W	169.5–173.5	76	$C_{25}H_{43}NO_3$	73.61	73.73	10.55	10.41	3.38	3.48
6e	$NH(n\text{-}C_6H_{13})$		8	Reflux		M	A–W	101.5–102.5	76	$C_{27}H_{47}NO_3$	74.78	74.89	10.92	11.26	3.25	3.30
6f	$NH(CH_2)_2OH$		0.5	Reflux		M	M–A	212–216	65	$C_{23}H_{39}NO_4 \cdot 0.5M^f$	68.92	69.12	10.09	9.95	3.42	3.49
6g	$NH(CH_2)_2NH_2$		104	Reflux		M	M	183.5–195.5	22	$C_{23}H_{40}N_2O_3$	70.36	70.15	10.27	10.13	7.14	7.06
6j			7	150	90	M	A	212–221	31	$C_{26}H_{43}NO_3$	74.77	74.92	10.38	10.45	3.35	3.22
6k			66	Reflux		M	M–W	140–147	47	$C_{25}H_{41}NO_4$	71.56	71.71	9.85	9.89	3.34	3.31
6l			18	Reflux		D	A	233–256	47	$C_{26}H_{44}N_2O_3$	72.18	72.44	10.25	10.31	6.48	6.75
7	$NHCH_3$	21-OH	4	133	575	D	M–A	228–240 dec	25	$C_{22}H_{37}NO_4$	69.62	69.87	9.85	9.82	3.69	3.92

[a] D = direct isolation, H = *via* hydrochloride. [b] A = acetone, M = methanol, H = hexane, W = water. [c] 2 g of *p*-toluenesulfonic acid monohydrate used as catalyst. [d] 1:1 Et_3N–NH_3 used as solvent.

ethyl acetate. The combined organic layers were concentrated to dryness under vacuum and the residue was crystallized twice from ether giving 1.45 g (36%) of **6i**, mp 192–205°.

Anal. Calcd for $C_{24}H_{41}NO_3$: C, 73.61; H, 10.55; N, 3.58. Found: C, 73.62; H, 10.46; N, 3.54.

16β-Methylamino-5α-pregnane-3β,17α,20β-triol (8a).—The hydrogenation of 5.0 g of 16β-methylamino-5-pregnene-3β,17α,-20β-triol (**6b**) was carried out at 4.2–3.15 kg/cm² in a Parr bomb using 0.25 l. of ethanol containing 1.1 equiv of HCl as solvent and 0.5 g of PtO_2 catalyst. Filtration, concentration of the filtrate, neutralization with $NaHCO_3$, and watering out gave 5.56 g of product, mp 230–244°. Two crystallizations from methanol gave 2.83 g (56%) of pure **8a**, mp 236–252°.

Anal. Calcd for $C_{22}H_{39}NO_3$: C, 72.28; H, 10.75; N, 3.83. Found: C, 72.55; H, 10.61; N, 3.53.

16β-Morpholino-5α-pregnane-3β,17α,20β-triol (8b).—A solution of 10.0 g of 16β-morpholino-5-pregnene-3β,17α,20β-triol (**6k**) in 0.25 l. of ethanol containing 1.0 g of 10% Pd–C was hydrogenated in a Parr bomb at 4.2–2.8 kg/cm.[2] Filtration and evaporation of the filtrate gave a crude product which was crystallized twice from ethyl acetate giving 8.00 g (80%) of **8b**, mp 135.5–139°.

Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.22; H, 10.28; N, 3.32. Found: C, 71.16; H, 10.20; N, 3.25.

Nmr Data.—No nmr data on 16β-aminopregnanes have appeared in the literature and so the principle nmr peaks of the 16β-amino-17α,20-dihydroxypregnanes are listed in Table II. Because of the low solubility of these compounds in $CDCl_3$ the spectra were run in Cl_3CO_2D and consequently the recorded peaks are actually those of the amine salt. For convenience the additive constants[32] for the various amines have been calculated for the C-18 and C-19 methyl groups. The effect of the amino group on the C-19 methyl group is negligible (0–1 cps) while a significant downfield shift is observed for the C-18 methyl, being 11–12 cps for the secondary amines having only carbon substituents and 15–16 cps for the tertiary amines. The C-21 methyl and the 20-hydrogen comprise an A_3X system, the methyl group appearing as a doublet (J = 6–8 cps) and the single hydrogen as a quartet, although the outer peaks were not always visible. The deshielding effect of the nitrogen is also observable on these protons, being about 10–17 and 15–27 cps, respectively.

Synthesis of 17α,20β-Dihydroxy-4-pregnen-3-one Acetonide (12b) from the Major $NaBH_4$ Reduction Product of 16,17α-Epoxy-3β-hydroxy-5-pregnen-20-one (1a).—A suspension of 2.00 g of $LiAlH_4$ in a solution of 10.0 g of 16,17α-epoxy-5-pregnene-3β,20β-diol 3,20-diacetate (**3a**) in 0.50 l. of THF was stirred at room temperature for 69 hr. The suspension was treated cautiously with 75 ml of saturated aqueous Rochelle salt solution and the THF solution was decanted. The solvent was removed under vacuum and the residue was crystallized from acetone giving 6.52 g (79%) of 5-pregnene-3β,17α,20β-triol (**9**), mp 233–235°.[33] A 5.00-g sample of the triol **9** in 100 ml of acetone containing 0.1 ml of 70% $HClO_4$ was kept at room temperature for 15 min. Saturated aqueous $NaHCO_3$ solution and then water were added. The resulting precipitate was crystallized from acetone containing a trace of pyridine giving 4.82 g (86%) of acetonide **10**, mp 168.5–169.5°.[33] A 1.00-g sample of acetonide **10** in 25 ml of toluene was oxidized to the conjugated ketone with 8 ml of cyclohexanone and 4 ml of 25% w/v aluminum isopropoxide in toluene by refluxing for 30 min. The reaction mixture was worked up with saturated aqueous Rochelle salt and with water. Distillation of the toluene at reduced pressure left a syrupy residue which was crystallized from acetone containing a trace of pyridine. The yield of **12b** was 236 mg (24%), mp 193–194.5°.[33] Identity with authentic **12b** was established by mixture melting point and the equivalence of the infrared spectra. Mixture melting point with the 20α-acetonide **12a** showed a 10° depression and the infrared curves were not equivalent.

17α,20α-Dihydroxy-4-pregnen-3-one Acetonide (12a).—A solution of 500 mg of 17α,20α-dihydroxy-4-pregnen-3-one[22] in 25 ml of acetone containing 0.15 ml of 70% $HClO_4$ was kept at room temperature for 70 min. The acid was neutralized with $NaHCO_3$ and the product was precipitated with water. The yield was 469 mg, mp 164–183°.[33] Four crystallizations from aqueous acetone containing a trace of pyridine gave 280 mg (50%) of *pure* **12a**, mp 191–192°,[33] λ_{max}^{MeOH} 241 mμ (ε 16,300), $[\alpha]^{24}D$ +32° (*c* 1, $CHCl_3$).

(32) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(33) The melting point was determined on a Fisher-Johns block and is uncorrected.

Table II

Nmr Peaks[b] of 16β-Amino-17α,20-dihydroxy-5-pregnenes in Perdeuterioacetic Acid

Compd	16β-Substit	C-18	Shift[a]	C-19	Shift	C-21		C-20				NCH_3
9	H	52		63		68	74	236	242	248	255	
6a	NH_2	63	11	63	0	79	86		260	267		
6b	$NHCH_3$	64	12	64	1	80	87	256	261	267	273	166
6c	NHC_2H_5	64	12	64	1	78	87	257	263	268	278	
6d	$NH(n\text{-}C_3H_7)$	64	12	64	1	81	87		263	270		
6e	$NH(n\text{-}C_6H_{13})$	64	12	64	1	80	87		262	269		
6f	$NH(CH_2)_2OH$	65	13	64	1	82	88		263	269		
6g	$NH(CH_2)_2NH_2$	67	15	64	1	83	88		261	267		
6h	$N(CH_3)_2$	67	15	63	0	84	92		263	271		184
6i	$N(CH_3)C_2H_5$	68	16	64	1	86	92	259	265	272	278	179
6j		67	15	64	1	85	92		268	275		
6k		67	15	63	0	85	92	261	269	276	282	
6l		63	11	63	0	83	89		257	264		174
					Miscellaneous Compounds							
5	$NHCH_3$[c]	64		64		80	86		258	264		166
8a	$NHCH_3$[d]	63		52		79	86		259	266		166
8b	 [d]	64		51		84	91		265	272		
7	$NHCH_3$[e]	63		63								164
4	$NHCH_3$[f]	53		63		75	81					168

[a] A positive value denotes a downfield shift from the corresponding 16-H compound **9**. [b] Cps at 60 Mc using Me_4Si as internal standard. [c] 6-CH_3. [d] 5,6-Dihydro. [e] 21-Hydroxy. [f] 20α-Hydroxy.

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.43; H, 9.85.

17α,20β-Dihydroxy-4-pregnen-3-one Acetonide (12b).—A 500-mg sample of 17α,20β-dihydroxy-4-pregnen-3-one[22] was converted to its acetonide as described for the preparation of the 20α-acetonide **12a**. The yield of pure acetonide **12b** was 343 mg (61%), mp 193–194°,[33] $[\alpha]^{26}D$ +54° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.32; H, 9.70.

N-Acetyl-16β-methylamino-5-pregnene-3β,17α,20β-triol 3,20-Diacetate (13).—Treatment of 1.00 g of 16β-methylamino-5-pregnene-3β,17α,20β-triol (**6b**) with a mixture of 10 ml of pyridine and 5 ml of acetic anhydride for 18 hr at room temperature gave, after precipitation with water, 1.32 g, mp 205–213°, of crude product. Two crystallizations from acetone–hexane gave 1.01 g (75%) of pure **13**: mp 214–217°; $\lambda_{max}^{CHCl_3}$ 2.76 μ (17-OH); $[\alpha]D$ −55° (*c* 1, $CHCl_3$); nmr peaks at 52, 54 (18-H), 63 (19-H), 69, 75 (21-H), 123 (acetate methyls), 127, 134 (N-acetyl), 174, 180 (NCH_3).

Anal. Calcd for $C_{28}H_{43}NO_6$: C, 68.68; H, 8.85; N, 2.86. Found: C, 68.84; H, 9.07; N, 3.05.

16β-Dimethylamino-5-pregnene-3β,17α,20β-triol Methiodide (14).—A solution of 1.04 g of 16β-dimethylamino-5-pregnene-3β,17α,20β-triol (**6h**) in 20 ml of nitrobenzene and 5 ml of CH_3I was refluxed for 3 hr. The product precipitated and was collected on a filter after cooling in ice and was recrystallized from methanol–ethyl acetate giving 0.54 g (38%) of **14**: mp 229–234° dec; nmr peaks (in pyridine) at 64 (19-H), 74 (18-H), 103, 109 (21-H), 215 (16-H), 225 (NCH_3).

Anal. Calcd for $C_{24}H_{42}INO_3$: C, 55.48; H, 8.15; I, 24.43; N, 2.70. Found: C, 55.34; H, 8.00; I, 24.62; N, 2.62.

The Conversion of 16β-Dimethylamino-5-pregnene-3β,17α,-20β-triol Methiodide (14) to 16,17α-Epoxy-5-pregnene-3β,20β-diol 3,20-Diacetate (3a).—A solution of 100 mg of methiodide **14** and 100 mg of sodium methoxide in 10 ml of methanol was kept at room temperature under N_2 for 4 hr. The reaction mixture was partitioned between ethyl acetate and water, the ethyl acetate layer was washed with water and after drying (Na_2SO_4) was concentrated under vacuum. The crystalline residue (62 mg) was acetylated with acetic anhydride in pyridine. The yield of acetate was 68 mg, mp 132–134°, and thin layer chromatography showed a single spot migrating at the same rate as **3a**. Recrystallization from acetone–hexane gave 52 mg (65% from **14**) of epoxide **3a**, mp 135–136°, identical with authentic **3a** by mixture melting point and a comparison of infrared spectra.

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