The aqueous layer was acidified and the crude product was filtered, washed, and dried. It was then vacuum sublimed to give 0.5 g (40%) of **23**, mp 186–190°. *Anal.* ($C_{15}H_{18}O_2$) C, H.

Bioassays. Androgenic and myogenic activity was determined by the relative potency of the test compound compared to that of a standard androgen as measured by the change in weight of the ventral prostate, seminal vesicle, and levator ani of the immature castrate rat.

Uterotropic activity was determined by the relative potency of the test compound compared to that of a standard estrogen as measured by the change in weight of the uterus of the immature mouse.

Antiuterotropic activity was determined by the inhibitory effect of the test compound on the action of a standard estrogen as measured by the change in weight of the uterus of the immature mouse.

Antigonadotropic activity was determined by the inhibitory effect of the test compound compared with that of a standard androgen inhibitor on gonadotropic secretion of a castrate animal as measured by the change in weight of the ovary (and, secondarily, the uterus) of an immature intact rat parabiosed with an immature, castrate, male rat. (**Androgenic activity** was determined by the biological effect as measured by the change in weight of the ventral prostate, seminal vesicle, and levator ani as secondary information.)

Antiandrogenic and antimyogenic activity were determined by the inhibitory effect of the test compound on the action of a standard androgen as measured by the change in weight of the ventral prostate, seminal vesicle, and levator ani of the castrate rat. (**Androgenic and myogenic activity** were determined by the biological effect of the test compound alone on the secondary sex organs as secondary information.)

The Synthesis and Biological Evaluation of 16β-Amino-17α-hydroxy-20-ketopregnenes

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Primary and cyclic secondary amines were added to the ethylene ketals of 16,17α-epoxy-20-ketopregnenes giving the ethylene ketals of 16β-amino-17α-hydroxy-20-ketopregnenes. Acid hydrolysis gave the hydrochlorides of the 16β-amino-17α-hydroxy-20-ketopregnenes. The compounds were broadly screened and the results of the antiinflammatory, analgetic, and antibiotic tests are reported. Antiinflammatory activity was not favorably influenced by structural alterations which usually increase the activity of antiinflammatory steroids.

A previous publication[1] described the synthesis, structural confirmation, and biological evaluation of a series of 16β-amino-17α,20-dihydroxypregnanes. In this report the series is extended to include some of the corresponding 20-ethylene ketals and 20-ketones. The addition of primary and cyclic secondary amines to 16,17α-epoxypregnenolone 20-ethylene ketal 3-acetate gave the ethylene ketal of the 16β-amino-17α-hydroxypregnenolone. Hydrolysis with aqueous HCl in acetone gave the hydrochloride of the 16β-amino-17α-hydroxy 20-ketone. The structural assignment was confirmed by relating the 20-keto series to the 20-hydroxy series. 16β-Methylamino-3β,17α-dihydroxy-5-pregnen-20-one hydrochloride (**3b**) was reduced with $NaBH_4$ to 16β-methylamino-5-pregnene-3β,17α,20β-triol, the structure of which was established in the previous paper.[1]

The direct addition of amines to 16,17α-epoxy-20-keto steroids, as exemplified by the reaction of 16,17α-epoxypregnenolone with morpholine, gives rise not to 16-amino-17-hydroxy-20-keto steroids as claimed in a series of patents,[2] but rather to rearranged compounds which probably have a D-homo steroid structure. The morpholine adduct, **3f**, prepared by the indirect route through the 20-ketal has a methyl peak at 134 cps in the nmr spectrum while the morpholine adduct prepared by the direct route has a methyl peak at 84 cps and none further downfield. The structural requirement of a methyl adjacent to a carbonyl group is consistent with the 134-cps absorption but not with 84 cps, which is, however, consistent with a structure containing a methyl group attached to a carbon bearing a hydroxy and two alkyl residues. The well-known tendency of 17-hydroxy-20-keto steroids to undergo D-homoannulation under basic conditions would produce such a methyl group.[3]

An attempt to prepare 16β-dimethylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-ethylene ketal (**2d**) by the direct alkylation of the 16β-methylamine precursor **2b** with methyl iodide in methanol containing sodium bicarbonate gave only 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one 20-ethylene ketal (**1a**). This technique worked well in the 20β-hydroxy series[1] and the increased ease of displacement of the amine function can be ascribed to an increase of steric strain in the ketal series. The dimethyl derivative was successfully prepared by $LiAlH_4$ reduction of the N-carboethoxy derivative **6b**. Further indication of the severe crowding about the D ring was observed in the $LiAlH_4$ reduction of the N-methyl N-acetyl derivative **6a** which went mainly by cleavage of the N–CO bond to give the N-methyl derivative **2b**. Only a very small yield of the desired N-methylethyl derivative **2e** was obtained. Similar results have been previously noted in the $LiAlH_4$ reduction of hindered amides.[4]

Hydrolysis of the ketals to the ketones proceeded satisfactorily with aqueous HCl in acetone and the resulting hydrochlorides were easily purified by crystallization. However, the free amines, at least in the N-methyl series, appear to be unstable. Attempts to purify 16β-methylamino-3β,17α-dihydroxy-5-preg-

(1) C. G. Bergstrom, *J. Med. Chem.*, **10**, 440 (1967).

(2) (a) C. L. Hewett and D. S. Savage, British Patent 980,265 (1965); (b) L. Vargha, M. Rados, E. Kasztreiner, and L. Szporny, U. S. Patent 3,125,570 (1964); (c) L. Vargha, M. Rados, and L. Szporny, U. S. Patent 3,164,583 (1965).

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 578.

(4) D. F. Morrow, T. P. Culbertson, and R. M. Hofer, *J. Org. Chem.*, **32** 361 (1967).

CHART I

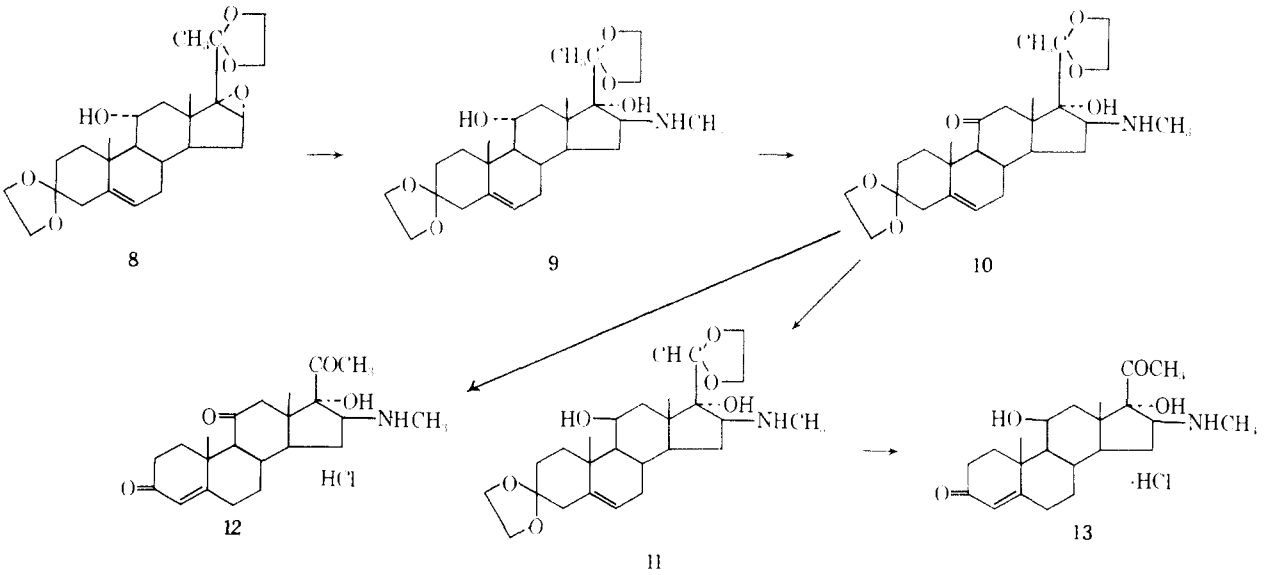
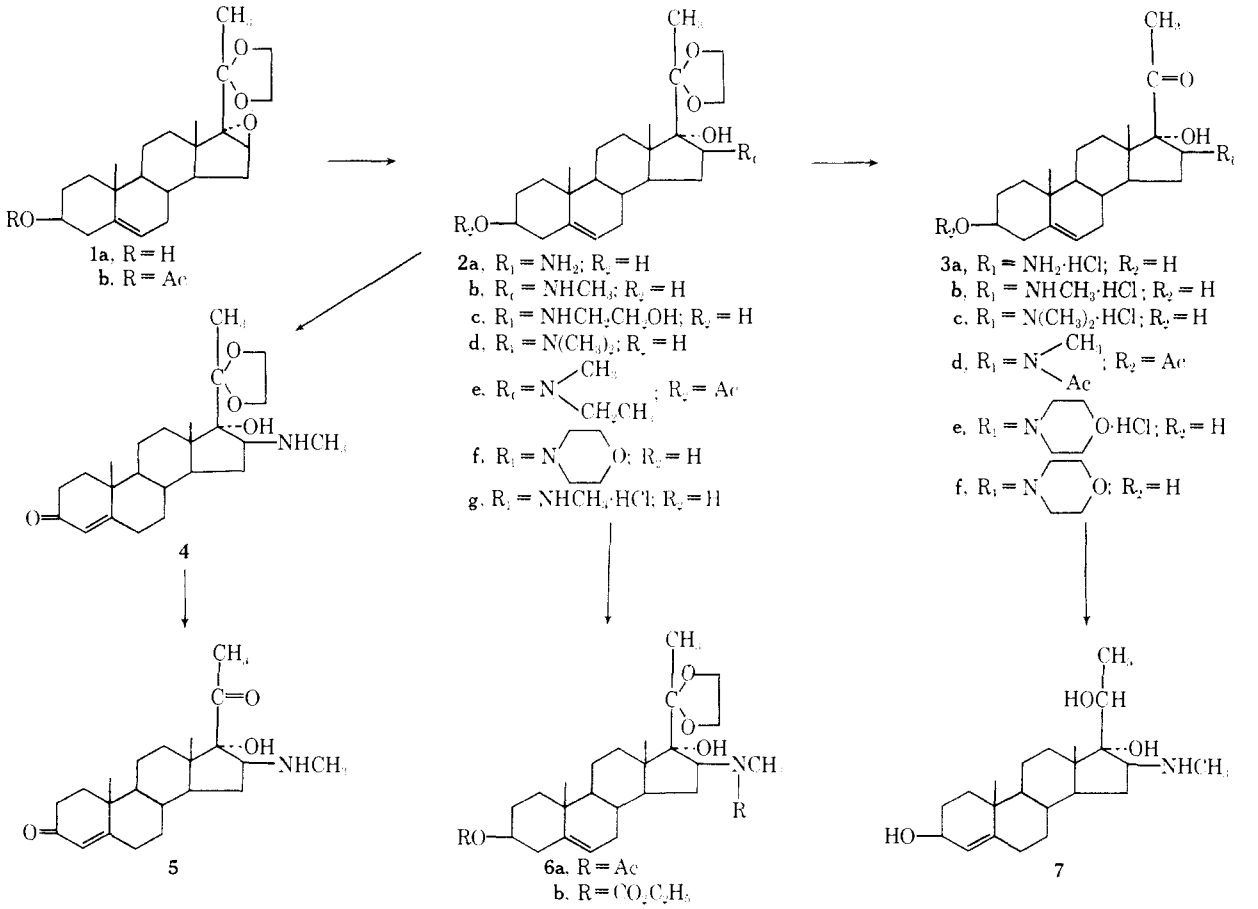


CHART II



nen-20-one, prepared by the treatment of **3b** with NaOH, resulted in rapid rearrangement with loss of the CH_3CO peak in the nmr spectrum. The structure of the product was not determined but in view of the result obtained on reaction of 16,17-epoxypregnenolone with morpholine it is likely that the product is a D-homo steroid. The treatment of 16β-morpholino-3β,17α-dihydroxy-5-pregnen-20-one hydrochloride (**3e**) with NaOH gave the unrearranged compound **3f**. The much greater stability of the 16β-morpholino compound **3f** with respect to the 16β-methylamino compound is demonstrated by the observation that the morpholino compound survives unchanged after refluxing for 7 hr in acetone while the methylamino compound is largely rearranged in a few minutes.

Two representatives of the 3-keto-4-ene-11-deoxy series were prepared. The Oppenauer oxidation of 16β-methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-ethylene ketal (**2b**) gave the 3-keto-4-ene analog **4** and this was hydrolyzed to the free 20-keto compound **5**. The various transformations are summarized in Chart I.

Table I
Biological Data on Steroidal 16β-Amino-17α-hydroxy 20-Ketones and Ketals[a]

Compd	16 substituent	Other variant	Antiinflammatory: Cotton wad Ig	Antiinflammatory: Foot edema Sc	Antiinflammatory: Foot edema Ig	Analgetic	Antibacterial: *E. coli*	Antibacterial: *B. subtilis*	Antibacterial: *D. pneumoniae*	Antifungal: *T. mentagrophytes*	Antifungal: *C. albicans*	Antiprotozoal *T. gelleii*	Antialgal *C. vulgaris*	Clover seed germination
3β-Hydroxy-5-ene 20-Ethylene Ketals														
2a	$NH_2 \cdot HCl$			I25			I	I	I	I	I	A	I	I
2b	$NHCH_3$		L5, I2	A20	A5, I2[b]	A25[c]	I	A	I	I	I	A	A	A
4	$NHCH_3$	3-Keto-4-ene	A20, I10	A25	A5, I2	A50	A	A	I	A	A	A	A	A
2d	$N(CH_3)_2$		L20, A2, I1	A25	A5, I2		I	I	I	I	A	A	A	I
2f			A20, I5	A25	I5	I50	I	I	I	I	I	I	I	I
6a						A50			I	I	I	I	I	I
11-Oxygenated 3,20-Bisethylene Ketals														
9	$NHCH_3$	11α-OH	A20, I10	A25	I5	A25	A	A	I	I		A	I	I
11	$NHCH_3$	11β-OH		I25			A	A	I	I		A	A	A
10	$NHCH_3$	11-Keto	I20	A25	I5	A50	I	I	A	I	I	I	A	A
3-Hydroxy-5-ene 20-Ketones														
3b	$NHCH_3 \cdot HCl$		I20, A2, I1	A25	A5, I2	I50	I	I	A	I	A	A	A	I
3d		3-Ac		I25		I50			I	I	I	I	I	A
3c	$N(CH_3)_2 \cdot HCl$		L5	A25	A5, I2	A50	I	I	A	I	A	A	A	A
3e			I20	I25		I50	I	I	I	I	A	A	A	I
3,20-Diketo-4-enes														
5	$NHCH_3 \cdot HCl$		A5, I2	A25	I5	A25	I	A	I	A	A	A	A	A
13	$NHCH_3 \cdot HCl$	11β-OH	I20	I25		I50	I	I	I	I	I	I	I	I
12	$NHCH_3 \cdot HCl$	11-Keto	I20	A25	I5	A50	A	A	A	A	A	A	I	A

[a] I = inactive, A = active, L = lethal. Accompanying numbers represent dose in milligrams per rat. [b] Brewers yeast (0.1 ml, 10% solution) used as irritant. [c] Doses are in milligrams per kilogram.

The observation that several of the 11-deoxy-16β-amino-17α-hydroxy compounds showed antiinflammatory activity made it important to prepare some 11-oxygenated analogs and this was done as described in Chart II. The 3,20-bisethylene ketal of 11α-hydroxy-16,17α-epoxy-4-pregnene-3,20-dione (**8**) was converted to the 16β-methylamino-17α-hydroxy derivative **9**. Oxidation with CrO_3–H_2SO_4 in acetone gave the 11-ketone **10** which was reduced to the 11β-hydroxy compound **11**. Hydrolysis of the 20-ketals of the 11-keto and 11β-hydroxy compounds gave the 20-keto compounds **12** and **13**.

Biological Evaluation.—The compounds were screened broadly and the results of the antiinflammatory, analgetic, and antibiotic tests are summarized in Table I. Antiinflammatory activity was measured by the cotton wad granuloma[5] and foot edema[6] tests. It is important to note that the antiinflammatory activity is not increased by the addition of an 11-oxygen function, nor is it increased by oxidation of a 3β-hydroxy-5-ene to the 3-keto-4-ene, nor is it increased by removal of the ketal groups. Any of these changes would be expected to have a marked activity-enhancing effect in the antiinflammatory steroid group. Antiinflammatory activity appeared to be increased by adding methyl groups to the 16β-nitrogen as illustrated by the series NH_2 (**2a**), $NHCH_3$ (**2b**), and $N(CH_3)_2$ (**2d**). Changes about C-20 were also significant since the 20β-hydroxy series did not show antiinflammatory activity.

Analgetic activity as measured by the writhing mouse assay[7] was observed in this series of compounds as well as in the previously described 20-hydroxy series.[1] Antibiotic activity was also shown by this series as it had been with the 20-hydroxy compounds. Antibacterial activity was measured against *Escherichia coli*, *Bacillus subtilis*, and *Diplococcus pneumoniae*.[8] Antifungal activity was measured against *Trichophyton mentagrophytes* and *Candida albicans*[8] while antialgal activity was measured against *Chlorella vulgaris*.[8] *Tetrahymena gelleii* was used to measure antiprotozoal activity,[9] and the inhibition of clover seed germination[10] measured the inhibition of dicotyledenous seed germination.

(5) The cotton wad granuloma test was a modification of that described by W. E. Dulin, *Proc. Soc. Exptl. Biol. Med.*, **90**, 115 (1955). Male rats of the Sprague–Dawley strain weighing 180–200 g were implanted subcutaneously with 4–6-mg pellets of dental cotton 4 days after adrenalectomy. The test compound was administered in saline solution by stomach tube on the day of implantation and on the following day. The pellets and surrounding granuloma were removed, dried, and weighed 48 hr after implantation. The compound was rated active if it caused a significant decrease in the weight of granuloma tissue when compared to a group of concurrently treated control animals. Intragastric hydrocortisone is active at 1 mg.

(6) The foot edema test was a modification of the procedure of C. A. Winter, E. A. Risley, and G. W. Nuss, *ibid.*, **111**, 544 (1962). An inflammatory reaction was induced in intact male rats weighing about 120 g by injecting 0.1 ml of a 1% solution of carrageenin (Type 402, Marine Colloids) under the plantar surfaces of the hind feet. The test compound was administered subcutaneously in saline 1 hr before injection of the irritant and if active received additional testing intragastrically. The circumferences of the feet measured 5 hr after injection of the irritant served as a measure of the inflammatory response. Hydrocortisone was active at 0.4–0.8 mg intragastrically and at 0.5 mg subcutaneously.

(7) This test was a modification of the procedure of E. T. Eckhardt, F. Cheplovitz, M. Lipo, and W. M. Govier, *ibid.*, **98**, 186 (1958). One hour following the oral administration of the indicated dose 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.

(8) The compounds were placed directly on the surfaces of appropriate agar plates which had been inoculated with the test organism. After an incubation period active compounds showed a clear zone, free of growth, around the compound.

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

(10) Ten seeds of white clover were placed near the edge of a moist 4.25-cm filter paper in a 6.0-cm Petri dish. Approximately 5 mg of compound was placed at the center. The effect of the compound was observed after 5 days.

Experimental Section[11]

16β-Amino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2a).—A mixture of 20 g of 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one 3-acetate 20-ethylene ketal (**1b**),[12] 200 ml of liquid NH_3, and 200 ml of DMSO was heated at 150° and 84.5 kg/cm² for 5 days. The NH_3 was evaporated and a product was precipitated with H_2O and was crystallized from MeOH–H_2O; yield 15.67 g, mp 158.5–191.5°. This partially purified product was added to a cold, stirred mixture of 3 l. of 0.1 *N* aqueous HCl and 1.5 l. of EtOAc. The mixture was filtered, the filtrate was separated, and the aqueous phase was neutralized with 0.12 l. of aqueous NaOH. While washing the neutralized aqueous phase with 0.5 l. of EtOAc and two 0.1-l. portions of CH_2Cl_2, there separated 3.26 g (15%), mp 249–251° dec, of **2a**·HCl·0.5H_2O. Recrystallization from MeOH–Et_2O gave 1.21 g, mp 240–250° dec. The ir spectrum was as expected and the nmr spectrum was not determined due to insolubility. *Anal.* ($C_{23}H_{37}NO_4$·HCl·0.5H_2O) C, H, Cl, N.

After removal of the hydrochloride the aqueous phase was made strongly basic with NaOH and 2.88 g of **2a**, mp 202.5–215°, was precipitated. Four crystallizations from MeOH–H_2O gave the analyzed sample, 1.35 g (7%), mp 210.5–219.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{23}H_{37}NO_4$) C, H, N.

16β-Amino-3β,17α-dihydroxy-5-pregnen-20-one (3a).—A solution of 525 mg of ketal **2a** in a mixture of 26 ml of acetone and 16 ml of 1 *N* aqueous HCl was refluxed for 2 hr. The reaction mixture was evaporated at room temperature and the residue was crystallized twice from MeOH–Me_2CO giving 173 mg (34%) of **3a**, mp 258–259.5° dec. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{21}H_{33}NO_3$·HCl) C, H, Cl, N.

16β-Methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2b).—A solution of 50 g of 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one 3-acetate 20-ethylene ketal (**1b**) in 0.50 l. of $MeNH_2$ was heated at 140° and 58 kg/cm² for 10 days. The excess $MeNH_2$ was evaporated and the residue was crystallized from acetone–hexane. The yield of **2b** was 24.95 g (51%), mp 181.5–191°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{24}H_{39}NO_4$) C, H, N.

16β-Methylamino-3β,17α-dihydroxy-5-pregnen-20-one Hydrochloride (3b).—A mixture of 23.57 g of **2b**, 1.18 l. of acetone, and 0.24 l. of 1 *N* aqueous HCl was refluxed for 5 hr. The solvent was evaporated with N_2 at room temperature and the residue was crystallized twice from MeOH–anhydrous Et_2O. The yield of **3b** was 17.62 g (74%), mp 240.5–245.5° dec. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{22}H_{35}NO_3$·HCl) C, H, Cl, N.

16β-Methylamino-17α-hydroxy-4-pregnene-3,20-dione 20-Ethylene Ketal (4).—A mixture of 10.00 g of **2b**, 0.50 l. of PhMe, and 80 ml of cyclohexanone was refluxed for 30 min. After washing with saturated aqueous potassium sodium tartrate solution and with H_2O the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The residual syrup was rinsed with pentane and was crystallized twice from acetone–hexane. The yield of **4** was 3.68 g (37%), mp 140.5–146.5°. Absorption bands of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{24}H_{37}NO_4$) C, H, N.

16β-Methylamino-17α-hydroxy-4-pregnene-3,20-dione Hydrochloride (5).—The mother liquors left after the purification of **4** were concentrated and the residue was refluxed for 4 hr with 0.25 l. of acetone and 50 ml of 1 *N* aqueous HCl. The mixture was concentrated at room temperature and the residue was crystallized twice from MeOH–anhydrous Et_2O. The yield of **5** was 3.01 g (31% from **2b**), mp 222–227° dec. Absorption bands of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{22}H_{33}NO_3$·HCl) C, H, Cl, N.

Conversion of 16β-Methylamino-3β,17α-dihydroxy-5-pregnen-20-one Hydrochloride (3b) to 16β-Methylamino-5-pregnene-3β,17α,20β-triol (7).—An ice-cooled suspension of 0.50 g of $NaBH_4$ in 25 ml of MeOH was treated dropwise with a cold solution of 0.50 g of **3b** in 25 ml of MeOH. After 2.75 hr the mixture was diluted (H_2O) and the product was filtered off, yield 0.45 g, mp 229–237.5°. Crystallization from MeOH gave 0.32 g, mp 234.5–243°. Mixture melting point with **7** showed no depression and the ir spectra were equivalent.

N-Acetyl-16β-methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal 3-Acetate (6a).—A solution of 4.00 g of **2b** in a mixture of 10 ml of pyridine and 5 ml of Ac_2O was kept at room temperature for 20 hr. Precipitation with H_2O gave 5.38 g of product, mp 197.5–207°. Crystallization from acetone–hexane gave 3.42 g (71%) of **6a**, mp 198.5–205.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{26}H_{39}NO_5$) C, H, N.

16β-Methylethylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal 3-Acetate (2e).—A mixture of 3.30 g of **6a** and 1.00 g of $LiAlH_4$ in 0.10 l. of THF (decanted from Drierite[13]) was refluxed for 3 days. Excess hydride was destroyed with EtOAc and the mixture was washed with saturated aqueous potassium sodium tartrate solution. The THF solution was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure. The residue was partitioned between ether and aqueous 1 *N* HCl. The aqueous phase which contained a white solid was made strongly basic with aqueous NaOH and then filtered. Two crystallizations from MeOH–Me_2CO gave 0.28 g (9.5%) of 16β-methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-ethylene ketal hydrochloride (**2g**), mp 229–231.5°. The absorption bands of the spectra (ir, nmr) were as expected and the sample was identical (ir, mixture melting point) with a sample of **2g** prepared from **2b**. *Anal.* ($C_{24}H_{39}NO_4$·HCl) C, H, N; Cl: calcd, 8.02; found, 7.54.

The mother liquor remaining after removal of **2g** was made basic with aqueous NaOH and dilution with water precipitated 680 mg of material which was acetylated with Ac_2O (0.7 ml) and pyridine (1.4 ml). The acetylated mixture was partitioned between ether and aqueous 1 *N* HCl. The aqueous phase contained a white solid which was filtered off and dissolved in MeOH. The MeOH solution was made basic with aqueous NaOH and dilution with H_2O gave crude **2e**, 118 mg, mp 138–146°. Four crystallizations from MeOH–H_2O gave the analyzed sample, 64 mg (2%), mp 144.5–148.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{26}H_{43}NO_4$) C, H, N.

N-Acetyl-16β-methylamino-3β,17α-dihydroxy-5-pregnen-20-one 3-Acetate (3d).—A solution of 1.00 g of **3b** in a mixture of 10 ml of pyridine and 5 ml of Ac_2O was kept at room temperature for 18 hr. Precipitation with H_2O gave 1.09 g of crude **3d**, mp 163.5–189.5°. Two crystallizations from acetone–hexane gave 0.64 g (58%) of **3d**, mp 181–190°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{26}H_{39}NO_5$) C, H, N.

16β-(β-Hydroxyethylamino)-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2c).—A solution of 1.00 g of 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one 20-ethylene ketal 3-acetate (**1b**) in 25 ml of ethanolamine was refluxed for 19 hr. Most of the ethanolamine was removed by distillation at reduced pressure and the residue was washed (H_2O) giving 1.02 g of crude **2c**, mp 153–177°. Three crystallizations from acetone–hexane gave 0.44 g (42%) of **2c**, mp 178–188°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{25}H_{41}NO_5$) C, H, N.

The Conversion of 16β-Methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2b) to 16,17α-Epoxy-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (1a).—A mixture of 0.50 g of **2b**, 50 ml of MeOH, 5.0 ml of MeI, and 2.0 g of $NaHCO_3$ was stirred at reflux for 24 hr. The solvents were mostly evaporated and the product was precipitated with H_2O. The yield of **1a** was 0.43 g (92%), mp 184.5–188° (**1a**, mp 184.5–188.5°). Identity was established by ir and mmp.

N-Carboethoxy-16β-methylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal 3-Ethylcarbonate (6b).—A solution of 3.83 g of **2b** in 38 ml of pyridine was treated cautiously with 3.8 ml of ethyl chloroformate. After 18 hr the product was precipitated with H_2O, yield 2.38 g, mp 162–167°. Three crystallizations from Me_2CO–H_2O gave 1.40 g (27%) of **6b**, mp 170–174.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{30}H_{47}NO_8$) C, H, N.

16β-Dimethylamino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2d).—A mixture of 7.14 g of **6b** and 7.14 g of $LiAlH_4$ in 0.72 l. of THF was refluxed for 3 days. Excess reducing agent was destroyed with 50 ml of EtOAc and then 0.10 l. of saturated aqueous potassium sodium tartrate was added. The organic layer was decanted and dried (Na_2SO_4). The solvent was evaporated at reduced pressure and the residue was par-

(11) Melting points were taken in a Thomas–Hoover melting point apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(12) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **71**, 766 (1949).

(13) W. S. Hammond, Drierite Co., Xenia, Ohio.

titioned between 155 ml of ether and 70 ml of aqueous 1 *N* HCl. The aqueous layer contained a white solid. The ether was decanted and the aqueous layer was further washed (Et_2O). The suspension of amine hydrochloride was diluted with 155 ml of H_2O and 31 ml of aqueous 10% NaOH. The yield of crude **2d** was 5.30 g, mp 150.5–158°. Crystallization from MeOH–H_2O gave 4.29 g (62%) of **2d**, mp 149.5–163°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{25}H_{41}NO_4$) C, H, N.

16β-Dimethylamino-3β,17α-dihydroxy-5-pregnen-20-one Hydrochloride (3c).—A solution of 2.55 g of **2d** in a mixture of 128 ml of acetone and 25.5 ml of aqueous 1 *N* HCl was refluxed for 6.5 hr. The solvent was evaporated at <35° and the residue was crystallized from MeOH–Et_2O and twice from MeOH–H_2O. The yield of **3c** was 1.21 g (48%), mp 273–274.5° dec. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{23}H_{37}NO_3 \cdot HCl$) C, H, Cl, N.

Reaction of 16,17α-Epoxypregnenolone with Morpholine.—A solution of 10.0 g of 16,17α-epoxypregnenolone and 2.7 g of phenol in 30 ml of morpholine was refluxed for 23 hr. Precipitation with water gave 11.93 g of crude adduct, mp 173–221°. Crystallization from Me_2CO gave 7.27 g (57%), mp 219–226°. Successive crystallizations from Me_2CO gave crystals with mp ~219–226°, then mp 223–229°, also mp 187–190°, and finally, after six crystallizations, the analyzed sample: 2.31 g; mp 185.5–189° (lit.[2a] 182–186°); $[\alpha]D$ −65° (*c* 1.01, EtOH) (lit.[2a] −66.6°); nmr peaks ($CDCl_3$), 61 (19-H), 67 (18-H), 84 (CH_3-CR_2OH), 159, 164, 168, 172 (NCH_2), 219, 223, 228 (OCH_2), 190–240 (3-H), 315–330 cps (6-H). *Anal.* ($C_{25}H_{39}NO_4$) C, H, N.

16β-Morpholino-3β,17α-dihydroxy-5-pregnen-20-one 20-Ethylene Ketal (2f).—A mixture of 20 g of 3β-hydroxy-16,17α-epoxy-5-pregnen-20-one 20-ethylene ketal 3-acetate (**1b**) and 200 ml of morpholine was heated in a bomb at 180° for 5 days. The mixture was concentrated at reduced pressure and the product was precipitated with H_2O, yield 15.07 g, mp 112–115°. Two crystallizations from MeOH–H_2O gave 12.48 g (56%) of **2f**: mp 114–117.5°; nmr ($CDCl_3$), 53 (19-H), 61 (18-H), 97 (21-H), 150, 155, 160, 165, 170, 175 (NCH_2), 214, 219, 223 (OCH_2), 236 (ketal), 315–330 (6-H). *Anal.* ($C_{27}H_{43}NO_5$) C, H, N.

16β-Morpholino-3β,17α-dihydroxy-5-pregnen-20-one Hydrochloride (3e).—A mixture of 6.10 g of **2f**, 305 ml of acetone, and 61 ml of aqueous 1 *N* HCl was refluxed for 18.5 hr. The reaction mixture was concentrated at reduced pressure and <25°. The yield of solid product was 3.87 g, mp 221–230° dec. Two crystallizations from MeOH–anhydrous Et_2O gave 2.29 g (38%) of **3e**, mp 242.5–245° dec. Low solubility prevented determination of the nmr spectrum. *Anal.* ($C_{25}H_{39}NO_4 \cdot HCl$) C, H, Cl, N.

16β-Morpholino-3β,17α-dihydroxy-5-pregnen-20-one (3f).—A solution of 0.44 g of hydrochloride **3e** in 0.07 l. of H_2O was made strongly alkaline with aqueous 10% NaOH. The resulting precipitate weighed 0.31 g, mp 147.5–167.5°. Three crystallizations from acetone–hexane gave 0.18 g (44%) of **3f**, mp 166.5–173°. The ir spectrum was not identical with that of the product of the reaction of 16,17α-epoxypregnenolone and morpholine and the mmp was 154.5–184.5°; nmr ($CDCl_3$), 51 (18-H), 60 (19-H), 134 (21-H), 130–160 (NCH_2), 217, 223, 227 (OCH_2), 315–328 (6-H). *Anal.* ($C_{25}H_{39}NO_4$) C, H, N.

11α-Hydroxy-16,17α-epoxy-5-pregnene-3,20-dione 3,20-Bisethylene Ketal (8).—A mixture of 25 g of 11α-hydroxy-16,17α-epoxy-5-pregnene-3,20-dione, 1.00 l. of C_6H_6, 25 ml of ethylene glycol, and 0.15 g of *p*-toluenesulfonic acid was refluxed while vigorously stirring with water removal for 8 hr. The reaction mixture was neutralized with aqueous $NaHCO_3$ and washed with H_2O, and 1 ml of pyridine was added. After drying (Na_2SO_4), the mixture was concentrated at reduced pressure and the residue was crystallized twice from acetone–hexane containing a few drops of pyridine, yield 9.92 g (32%), mp 185–187.5°. The analyzed sample had mp 189.5–192°. Absorption bands of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{25}H_{36}O_6$) C, H.

16β-Methylamino-11α,17α-dihydroxy-5-pregnene-3,20-dione 3,20-Bisethylene Ketal (9).—A mixture of 39.95 g of **8** and 400 ml of $MeNH_2$ was heated in a bomb at 130° and 43 kg/cm² for 8 days. The excess $MeNH_2$ was evaporated and the residue was crystallized twice from Me_2CO, yield 13.76 g (32%), mp 228–235°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{26}H_{41}NO_6$) C, H, N.

16β-Methylamino-17α-hydroxy-5-pregnene-3,11,20-trione 3,-20-Bisethylene Ketal (10).—A solution of 3.87 g of **9** in 507 ml of Me_2CO at 5° was treated with 3.87 ml of CrO_3 reagent (26.72 g of CrO_3, 23 ml of H_2SO_4, and water to 100 ml). After 2 min the reaction mixture was added to a mixture of 190 ml of saturated aqueous $NaHCO_3$ solution and 1.5 l. of H_2O. The product was extracted into EtOAc. After drying (Na_2SO_4) the solvent was evaporated at reduced pressure and the residue was twice crystallized from acetone–hexane and twice from Me_2CO–H_2O. The yield of **10** was 0.65 g (17%), mp 176.5–179.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{26}H_{39}NO_6$) C, H, N.

16β-Methylamino-17α-hydroxy-4-pregnene-3,11,20-trione Hydrochloride (12).—A mixture of 387 mg of **10**, 30 ml of acetone, and 4 ml of aqueous 1 *N* HCl was refluxed for 3.3 hr. The solvent was evaporated at room temperature and the residue was crystallized twice from MeOH–anhydrous Et_2O. The yield of **12** was 183 mg (53%), mp 231–242° dec. Absorption bands of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{22}H_{31}NO_4 \cdot HCl \cdot 0.5H_2O$) C, H, Cl, N.

16β-Methylamino-3β,11β-dihydroxy-5-pregnene-3,20-dione 3,20-Bisethylene Ketal (11).—A solution of 9.04 g of **10** in 362 ml of MeOH containing 3.6 ml of aqueous 10% NaOH was treated with 9.04 g of $NaBH_4$. After 6 hr an additional 9.04 g of $NaBH_4$ was added and the mixture was kept overnight at room temperature. Water was added and the product was extracted into EtOAc. After drying (Na_2SO_4) the solvent was evaporated at reduced pressure. The residual syrup was crystallized twice from acetone–hexane. The yield of 11, which crystallized as a hemiacetone solvate, was 4.23 g (43%), mp 107.5–118° with gas evolution. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* [$C_{26}H_{41}NO_6 \cdot 0.5(CH_3)_2CO$] C, H, N.

16β-Methylamino-11β,17α-dihydroxy-4-pregnene-3,20-dione Hydrochloride (13).—A solution of 3.84 g of 11 in 192 ml of acetone containing 38 ml of aqueous 1 *N* HCl was refluxed for 1 hr. The mixture was concentrated at reduced pressure and <30° and after cooling the product was collected on a filter, yield 2.52 g (80%). The sample had no definite melting point: when inserted into the bath at 250° it darkened above 265°, sintered a little at 278°, and gradually changed to a dark brown cinder which was unchanged up to 360°. Absorption bands of spectra (uv, ir) were as expected. No suitable solvent was found for the determination of the nmr spectrum. *Anal.* ($C_{22}H_{33}NO_4 \cdot HCl$) C, H, Cl, N.

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