Analogs of Steroid Hormones. II. 6-(Cyclopentyl) Derivatives of 2-Naphthalenone[1]

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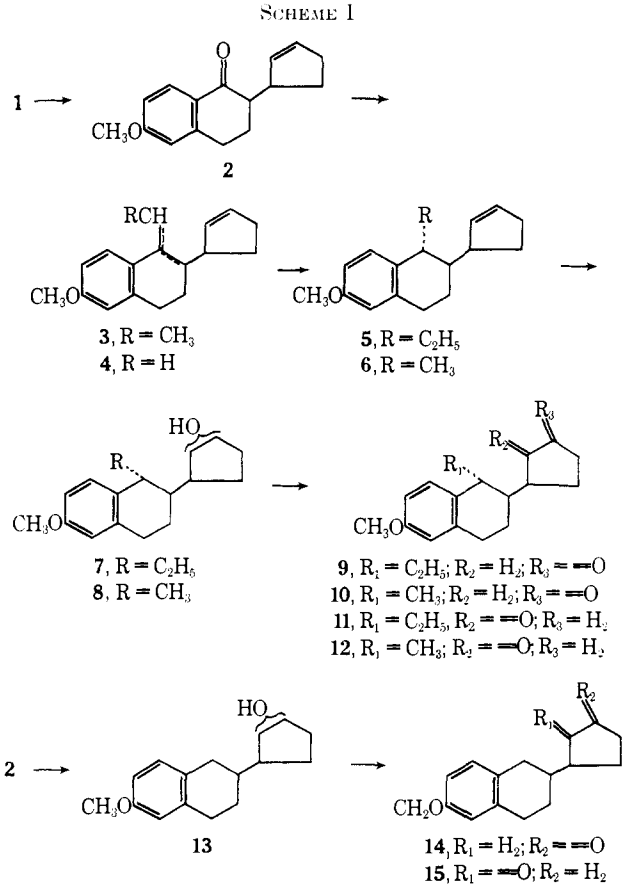
A number of 6-cyclopentyl derivatives of 2-naphthalenone have been prepared and tested for hormone and hormone antagonist activity. 3,4-Dihydro-2-(hydroxymethylene)-6-methoxy-1(2H)-naphthalenone was first alkylated with 3-bromocyclopentene. Further elaboration of the resulting cyclopentyl derivative was carried out by standard synthetic procedures to prepare the title compounds. None of the compounds showed significant activity when bioassayed for uterotropic, antiuterotropic, androgenic, antiandrogenic, and antigonadotropic activity.

In a previous paper,[2] the preparation and biological activities of some cyclohexyl and phenyl derivatives of 2-naphthalenone were reported. They had little biological activity so we decided to prepare some related compounds, having a five- rather than six-membered ring substituted at C-6, to study the effect of changing ring size on the biological properties of these compounds.

Starting with 3,4-dihydro-2-(hydroxymethylene)-6-methoxy-1(2H)-naphthalenone (**1**), suitably substituted methoxynaphthalenes were prepared using the sequence outlined in Scheme I. They were then converted to the test compounds by the Wilds[3,4] modification of the Birch reduction, followed by acid hydrolysis of the enol ethers.

SCHEME I



To prepare **3** and **4**, **1** was alkylated with 3-bromocyclopentene. The resulting ketone was allowed to react with methyl- or ethyllithium and the resulting carbinol was dehydrated to give a mixture of alkenes. With ethyllithium, enolization was an important side reaction so that it was necessary to repeat the reaction in order to get a satisfactory conversion. The nmr spectrum of the alkenes **3** and **4** showed 2.5 ethylenic protons present, indicating that the double bond was about equally distributed between the *endo* and *exo* positions. Reduction of the alkenes with lithium, ammonia, and proton source, as expected,[5,6] produced the *trans* isomers **5** and **6** exclusively. This was shown by reducing the two alkenes **5** and **6** catalytically and comparing the products with those obtained by hydrogenating the isomeric mixtures **3** and **4**. The latter products contained two isomers each while the former contained only one. The products obtained from the hydrogenation of **5** and **6** corresponded to the isomer migrating more slowly in the glpc and tlc chromatograms of the mixtures.

Hydroboration[7] of the cyclopentyl double bond gave rise to about equal amounts of the 2- and 3-substituted cyclopentanols. After oxidation of the mixed alcohols to ketones, the isomers were separated either by treatment with sodium bisulfite, the 2-substituted ketones failing to react (**15**), or by differences in their rates of reaction with semicarbazide (**11**).

To prepare **14** and **15**, **2** was hydroborated directly and the benzylic hydroxyl was removed by hydrogenolysis (Scheme II). The isomeric ketones were again separated by treatment with sodium bisulfite.

To prepare the test compounds **16–18** and **21**, ketal derivatives of **9**, **10**, **14**, and **15** were made and reduced by the Birch method. The enol ether and ketal groups were then hydrolyzed in cold formic acid solution. The resulting unsaturated ketone **16** was submitted for bioassay without further treatment. The others were refluxed in dioxane–aqueous HCl solution in order to rearrange the major proportion of the mixture into the conjugated isomer. The proportion varied from 70–90% in **17**, **19**, **21**, **22** but was only 24% in **18** and **20** which contained a C-5 ethyl group. An examination of the models of **18** and **20** suggests that there is increased crowding between the C-5 ethyl and C-6 cyclopentyl groups in the conjugated isomer, so that the stabilization conferred by the conjugation is offset by

(1) Supported by a research grant (CA-05077) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) R. E. Juday, D. P. Page, and G. A. DuVall, *J. Med. Chem.*, **7**, 549 (1964).

(3) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).

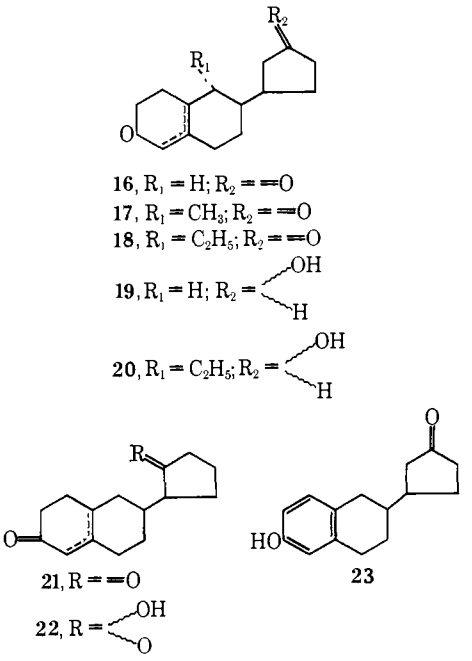
(4) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 1807 (1960).

(5) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 61 ff.

(6) D. Lednicer, D. E. Emmert, G. W. Duncan, and S. C. Lyster, *J. Med. Chem.*, **10**, 1051 (1967). An example of this reduction.

(7) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

SCHEME II



the crowding making the nonconjugated isomer the more stable one.

To prepare **19**–**20** and **22**, the ketone groups were reduced with $NaBH_4$ before reducing the ring. The ether group of **13** was cleaved by heating with pyridine hydrochloride to produce **23**.

Bioassay Results.[8]—Compound **23** was found to be inactive when tested for uterotropic and antiuterotropic activity. The other compounds, **16**–**22**, showed no significant activity when tested for androgenic, antigonadotropic, and antiuterotropic activity. Thus, one may conclude that neither the cyclopentyl nor cyclohexyl derivatives of 2-naphthalenone show promise as hormone antagonists.

Experimental Section[9-11]

2-(2-Cyclopenten-1-yl)-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (**2**).—Freshly distilled 3-bromocyclopentene (16 g, 0.11 mole) was added all at once to a mixture of **1** (15 g, 0.064 mole), NaH (1.76 g, 0.084 mole), and 70 ml of anhydrous DMF at −10°. An immediate temperature rise of about 20° was noted. After the reaction subsided, the mixture was stirred at room temperature for a few minutes and then treated with H_2O and C_6H_6. The benzene layer was washed twice (H_2O) and concentrated *in vacuo*. The residue was refluxed 30 min with a mixture of 25 ml of 95% EtOH and 25 ml 25% aqueous KOH. H_2O and C_6H_6 were again added and the benzene layer was washed with H_2O and concentrated *in vacuo*. The residue was distilled to give 10.8 g (74%) of product distilling at 174–178° (1.3 mm), $n^{20}D$ 1.5885. *Anal.* ($C_{16}H_{18}O_2$) C, H.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentyl Acetate and 2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentyl Acetate (**24**).—A solution of **2** (20.6 g, 0.085 mole) was hydroborated using the method of Brown and Rao.[7] The mixture of carbinols was dissolved in 40 ml of AcOH and hydrogenated over 5% Pd–C in the presence of 0.2 g of methanesulfonic acid. The product was recovered by dilution, solvent extraction, and distillation to give 15.0 g (61%) of material distilling at 165° mm). *Anal.* ($C_{18}H_{24}O_3$) C, H.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanol and 2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (**13**).—A mixture of **23** (15.6 g, 0.54 mole), $NaBH_4$ (4.6 g, 0.12 mole), and 125 ml of 95% EtOH was refluxed 2 hr. (While $NaBH_4$ does not reduce esters, it catalyzes ester exchange.) The crude product was recovered by dilution with H_2O and solvent extraction and distilled *in vacuo* to give 13.0 g (98%) of **13**, bp 155° (0.01 mm). *Anal.* ($C_{11}H_{22}O_2$) C, H.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanone (**14**) **and 2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanone** (**15**).—A mixture of **13** (14.0 g, 0.57 mole) and CrO_3 (14.0 g, 0.14 mole) in pyridine (300 ml)[12] was stirred for 6 hr at 30°. H_2O and C_6H_6 were added and the mixture was filtered. The crude product was recovered from the benzene and distilled *in vacuo* to give 13.0 g (94%) of mixed isomers, bp 165° (0.01 mm). A solution of the isomers in 50 ml of ether was shaken for 24 hr with a solution of sodium metabisulfite (90 g, 0.48 mole) in 130 ml of H_2O and 20 ml of MeOH. The bisulfite addition compound of **14** was removed and decomposed with concentrated HCl. The ketone was recovered by extracting with C_6H_6, evaporating, and distilling *in vacuo* to give 6.5 g (35%) of **14**, bp 165° (0.01 mm). *Anal.* ($C_{16}H_{20}O_2$) C, H. Compound **15** was recovered from the filtrate of the bisulfite reaction mixture and purified by converting to the semicarbazone. Nonketonic material was washed away from the semicarbazone with ether. The semicarbazone was hydrolyzed by refluxing in an AcOH–H_2O solution of pyruvic acid.[13] The product was recovered by solvent extraction and distilled to give 7.0 g (37%) of **15**, bp 162° (0.01 mm). *Anal.* ($C_{16}H_{20}O_2$) C, H.

Mixture of 2-(2-Cyclopenten-1-yl)-1-ethyl-3,4-dihydro-6-methoxynaphthalene and 2-(2-Cyclopenten-1-yl)-1-ethylidene-1,2,3,4-tetrahydro-6-methoxynaphthalene (**3**).—A solution of **2** (17.6 g, 0.073 mole) in C_6H_6 was treated with excess EtLi at −10°. After hydrolyzing the mixture, the crude product was dehydrated by heating to 110°, *in vacuo*, with powdered $KHSO_4$ Since about one-third of the ketone failed to react, the above processes were repeated using reduced quantities of reagents. The final product was distilled to give 16.5 g (89%) of **3**, bp 150° (0.01 mm). *Anal.* ($C_{18}H_{22}O$) C, H.

Mixture of 2-(2-cyclopenten-1-yl)-3,4-dihydro-6-methoxy-1-methylnaphthalene and 2-(2-cyclopenten-2-yl)-6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (**4**) was prepared using the method outlined for **3**, using MeLi instead of EtLi. In this case it was not necessary to repeat the reaction with the MeLi as no enolate was formed. Starting with 9.5 g of **2** a yield of 8.6 g (92%) of **4**, bp 140° (0.01 mm), was obtained. *Anal.* ($C_{18}H_{22}O$) C, H.

trans-**2-(2-Cyclopenten-1-yl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene** (**5**).—A solution of **3** (17.8 g, 0.07 mole) in 150 ml of dry ether was added to a solution of Li (4.2 g, 0.6 g-atom) in 300 ml of liquid NH_3 at −40°. After 10 min a solution of H_2O (15 g, 0.83 mole) in 16 ml of dioxane was added slowly until the color of the Li was discharged. NH_4Cl (23 g, 0.43 mole) was next added and the NH_3 was allowed to evaporate. The product was isolated by solvent extraction followed by distillation to give 14.5 g (81%) of **5**, bp 130° (0.01 mm). Results from tlc (silica gel H_f developed by C_6H_6–MeOH) indicated that a single isomer was present. *Anal.* ($C_{18}H_{24}O$) C, H.

trans-**2-(2-Cyclopenten-1-yl)-1,2,3,4-tetrahydro-6-methoxy-1-methylnaphthalene** (**6**).—The procedure used to prepare **5** was followed. Starting with **4** (8.6 g, 0.036 mole) a yield of 8.1 g (93%) of **6**, bp 130° (0.01 mm), was obtained. Results from glpc (3% SE-30 on Aeropak, 230°) indicated that only one isomer was present. *Anal.* ($C_{17}H_{22}O$) C, H.

cis- **and** *trans*-**2-(Cyclopentyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalenes.**—Two samples were prepared, the first by hydrogenating 2.0 g of **3** and the second by hydrogenating 2.0 g of **5**, both in EtOH solution using 5% Pd–C. Both samples distilled at 130° (0.01 mm) and were obtained in almost quantitative yields. Both samples were subjected to tlc. The sample from **3** contained equal amounts of the *cis* and *trans* isomers, while the sample from **5** contained only one isomer identical with the isomer from **3** having the lower R_f value. *Anal.* ($C_{18}H_{26}O$) C, H.

cis- **and** *trans*-**2-(Cyclopentyl)-1,2,3,4-tetrahydro-6-methoxy-1-methylnaphthalenes.**—The two samples were prepared from **4**

(8) See Experimental Section for a description of bioassays.

(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical.

(10) Combustion analyses were run by Galbraith Laboratories, Knoxville, Tenn.

(11) The uv spectra were run on a Coleman-Hitachi spectrophotometer purchased by Grant GP-6988, National Science Foundation.

(12) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1690 (1948).

(13) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

and **6** as outlined for the 1-ethyl analog. The isomers failed to separate on tlc, so they were subjected to glpc. Again, the product from **4** contained equal amounts of the *cis* and *trans* isomers, while the sample prepared from **6** contained only one, identical with the slower moving isomer in the first sample. The products were obtained in almost quantitative yields, bp 128° (0.01 mm). *Anal.* ($C_{17}H_{24}O$) C, H.

***trans*-2- and *trans*-3-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanols (7).**—Compound **5** (10.7 g, 0.042 mole) was hydroborated using the method of Brown and Rao.[3] A yield of 10.1 g (88%) of **7** was obtained, bp 163° (0.01 mm). *Anal.* ($C_{18}H_{26}O_2$) C, H.

***trans*-2- and *trans*-3-(1,2,3,4-Tetrahydro-6-methoxy-1-methyl-2-naphthyl)cyclopentanols (8).**—Compound **6** (16.0 g, 0.006 mole) was hydroborated using the method of Brown and Rao.[3] A yield of 12.9 g (74%) of **8** was obtained, bp 158°. *Anal.* ($C_{17}H_{24}O_2$) C, H.

***trans*-3-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanone (9).**—The same procedure used to oxidize **13** was followed. Starting with **7** (11.2 g, 0.041 mole) a yield of 10.1 g (90%) of the isomeric ketones **9** and **11**, bp 152° (0.01 mm), was obtained. The crude product was stirred in a solution of semicarbazide hydrochloride (12.0 g, 0.11 mole) in 45 ml of MeOH, 40 ml of H_2O, and 18 ml of pyridine for 24 hr at room temperature. The precipitate was washed (Et_2O) and dried. It was hydrolyzed by refluxing 30 min in an AcOH–H_2O solution of pyruvic acid.[6] Addition of H_2O, solvent extraction, and distillation of the crude product gave 6.0 g (59%) of **9**, bp 152° (0.01 mm). The tlc chromatogram indicated only one ketone isomer was present in the final product. The semicarbazone of **11** did not hydrolyze and **11** was not recovered. *Anal.* ($C_{18}H_{24}O_2$) C, H.

***trans*-3-(1,2,3,4-Tetrahydro-6-methoxy-1-methyl-2-naphthyl)cyclopentanone (10).**—The same procedure used to oxidize **13** was followed. Starting with **8** (6.3 g, 0.024 mole of mixed carbinols), a yield of 1.9 g (38%) of **10**, bp 150° (0.01 mm), was obtained. *Anal.* ($C_{17}H_{22}O_2$) C, H.

7-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-1,4-dioxaspiro[4.4]nonane (25).—A mixture of ethylene glycol (5.9 g, 0.11 mole), **14** (7.0 g, 0.029 mole), and methanesulfonic acid (0.3 g) was refluxed 4 hr in dry benzene (175 ml) using a Dean–Stark trap to remove H_2O. The product was recovered by adding $NaHCO_3$ bicarbonate solution and extracting (C_6H_6). The solvent was evaporated and the residue distilled *in vacuo* to give 7.5 g (90%) of **25**, bp 130° (0.01 mm). *Anal.* ($C_{18}H_{24}O_3$) C, H.

6-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-1,4-dioxaspiro[4.4]nonane (26).—The procedure used to prepare **25** was followed. Starting with **14** (5.9 g, 0.024 mole), a yield of 6.5 g (94%) of **26**, bp 140° (0.01 mm), was obtained. *Anal.* ($C_{18}H_{24}O_3$) C, H.

***trans*-7-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-1,4-dioxaspiro[4.4]nonane (27).**—The procedure used to prepare **25** was followed. Starting with **9** (5.3 g, 0.019 mole), a yield of 6.0 g (98%) of **27**, bp 145° (0.01 mm), was obtained. *Anal.* ($C_{20}H_{28}O_3$) C, H.

***trans*-7-(1,2,3,4-Tetrahydro-6-methoxy-1-methyl-2-naphthyl)-1,4-dioxaspiro[4.4]nonane (28).**—The procedure used to prepare **25** was followed. Starting with **10** (7.1 g, 0.0275 mole) a yield of 7.6 g (92%) of **28** was obtained, bp 140° (0.01 mm). *Anal.* ($C_{19}H_{26}O_3$) C, H.

***trans*-3-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (29).**—A solution of **9** (4.0 g, 0.015 mole) and $NaBH_4$ (1.4 g, 0.037 mole) in 100 ml of 95% EtOH was stirred for 1 hr at room temperature. The solution was diluted with 3 *N* HCl and the product was recovered by solvent extraction and distillation to give 3.9 g (98%) of product, bp 155° (0.01 mm). The glpc chromatogram showed the product to be an isomeric mixture containing 71% of one epimer and 29% of the other, which were not otherwise identified. *Anal.* ($C_{18}H_{26}O_3$) C, H.

Mixture of 4,4a,5,6,7,8-Hexahydro-6-(3-oxocyclopentyl)-2(3H)-naphthalenone and 3,4,5,6,7,8-Hexahydro-6-(3-oxocyclopentyl)-2(1H)-naphthalenone (16).—In this and the following reductions, the procedure of Wilds and Nelson[3] were generally followed. A 5–10 molar excess of Li was used with 50–60 ml of liquid NH_3/g of metal. THF was used as an auxiliary solvent. The reduction was completed by adding an excess of anhydrous EtOH. The enol ether (and the ketal group when present) was hydrolyzed at room temperature in a 90% AcOH–90% HCO_2H mixture and the product was recovered by dilution with H_2O, solvent extraction, and distillation. Starting with **25** (7.5 g, 0.026 mole), a yield of 3.8 g (63%) of **16**, bp 140° (0.01 mm), λ_{max}^{95} 238 mμ (ε 9100), was obtained. The product was found to contain 57% of the conjugated isomer by glpc, and 55% of the conjugated isomer by nmr spectroscopy.[14,15] Based on these data, the extinction coefficient of the conjugated ketone was estimated to be 16,000. This value was used to determine the amount of conjugated isomer in samples of the other compounds (**17**–**22**) submitted for bioassay. *Anal.* ($C_{16}H_{22}O_2$) C, H.

3-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (30). The procedure used to prepare **28** was followed. Starting with **14** (4.9 g, 0.02 mole) a yield of 4.7 g (96%) of **30**, bp 157° (0.01 mm), was obtained. *Anal.* ($C_{16}H_{22}O_2$) C, H.

2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (31).—The procedure used to prepare **28** was followed. Starting with **15** (7.7 g, 0.032 mole) a yield of 7.4 g (95%) of **31**, bp 156° (0.01 mm), was obtained. *Anal.* ($C_{18}H_{22}O_2$) C, H.

Mixture of 4,4a,5,6,7,8-Hexahydro-6-(2-oxocyclopentyl)-2(3H)-naphthalenone and 3,4,5,6,7,8-Hexahydro-6-(2-oxocyclopentyl)-2(1H)-naphthalenone (21).—The procedure used to prepare **16** was followed. Starting with **26** (6.5 g, 0.023 mole), a yield of 4.0 g (77%) of **21**, bp 153° (0.01 mm), was obtained, which was estimated to contain 26% of the conjugated isomer.[16] After refluxing the initial product in a solution of 5 ml of 20% HCl in 30 ml of dioxane for 10 min, the composition of the recovered product was changed to 82% of the conjugated isomer. *Anal.* ($C_{15}H_{20}O_2$) C, H.

Mixture of 4,4a,5,6,7,8-Hexahydro-6-(3-hydroxycyclopentyl)-2(3H)-naphthalenone and 3,4,5,6,7,8-Hexahydro-6-(3-hydroxycyclopentyl)-2(1H)-naphthalenone (19).—The procedure used to prepare **16** was followed except that Na was used instead of Li; *i*-PrOH was added before the Na and the NH_3 was redistilled. Refluxing for 90 min in an acidic medium[6] changed the amount of conjugated isomer from 37 to 90%. Starting with **30** (5.4 g, 0.022 mole) a yield of 2.7 g (52%) of **19**, bp 160° (0.01 mm), was obtained. *Anal.* ($C_{15}H_{22}O_2$) C, H.

Mixture of 4,4a,5,6,7,8-Hexahydro-6-(2-hydroxycyclopentyl)-2(3H)-naphthalenone and 3,4,5,6,7,8-Hexahydro-6-(2-hydroxycyclopentyl)-2(1H)-naphthalenone (22).—The method used to prepare **16** was followed. Starting with **31** (6.8 g, 0.028 mole) a yield of 1.9 g (30%) of **22**, bp 150° (0.01 mm), was obtained, estimated to contain 26% of the conjugated isomer. Refluxing for 90 min in an acidic medium[6] changed the composition to 90% of the conjugated isomer. *Anal.* ($C_{15}H_{22}O_2$) C, H.

Mixture of *trans*-5-Ethyl-3,4,5,6,7,8-hexahydro-6-(3-oxocyclopentyl)-2(1H)-naphthalenone and *trans*-5-Ethyl-4,4a,5,6,7,8-hexahydro-6-(3-oxocyclopentyl)-2(3H)-naphthalenone (18).—The procedure used to prepare **16** was followed. Starting with **27** (6.0 g, 0.019 mole) a yield of 3.5 g (71%) of **18**, bp 155° (0.01 mm), was obtained. Refluxing in an acidic medium[15] changed the amount of conjugated isomer from 22 to 24%. *Anal.* ($C_{17}H_{24}O_2$) C, H.

Mixture of *trans*-5-Ethyl-3,4,5,6,7,8-Hexahydro-6-(3-hydroxycyclopentyl)-2(1H)-naphthalenone and *trans*-5-Ethyl-4,4a,5,6,7,8-hexahydro-6-(3-hydroxycyclopentyl)-2(3H)-naphthalenone (20).—The procedure used to prepare **16** was followed. Starting with **29** (8.8 g, 0.033 mole) a yield of 1.9 g (26%) of **20**, bp 160° (0.01 mm), was obtained. Refluxing in an acidic medium[15] changed the amount of conjugated isomer from 22 to 24%. *Anal.* ($C_{16}H_{26}O_2$) C, H.

Mixture of *trans*-4,4a,5,6,7,8-Hexahydro-5-methyl-6-(3-oxocyclopentyl)-2(3H)-naphthalenone and *trans*-3,4,5,6,7,8-Hexahydro-5-methyl-6-(3-oxocyclopentyl)-2(1H)-naphthalenone (17).—The procedure used to prepare **16** was followed. Starting with **28** (8.5 g, 0.028 mole), a yield of 4.5 g (65%) of **17**, bp 149° (0.01 mm), was obtained. Refluxing in an acidic medium[6] changed the amount of conjugated isomer from 9 to 72%. *Anal.* ($C_{16}H_{22}O_2$) C, H.

3-(1,2,3,4-Tetrahydro-6-hydroxy-2-naphthyl)cyclopentanone (23).—A mixture of **14** (1.3 g, 0.0053 mole) and 29 g of pyridine hydrochloride was heated for 60 min at 195–200°. The melt was cooled, diluted with water, and extracted twice with C_6H_6. The benzene solution was washed twice with 10% KOH solution,

(14) We are indebted to Drs. Graeme Baker and Richard Geer, Montana State University, Bozeman, Mont., for the glpc chromatograms and nmr spectrum.

(15) This slight discrepancy may be explained on the basis of less than 1% impurity that was detected in the gas chromatogram but was not separately evaluated in the nmr spectrum.

(16) See procedure for preparing **16**.

(17) See procedure for preparing **21**.

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).