The Total Synthesis of Retroprogesterones

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The first total syntheses (by three different routes) of 9β,10α-progesterones are described: (1) previously prepared tricyclic keto alcohol I was converted into retroprogesterone VI by a sequence involving the Wittig reaction, hydroboration, and A-ring annelation; (2) the $\Delta^{17(20)}$-olefin intermediate (IV) was converted into 16-dehydroretroprogesterone (IX) by another sequence consisting of A-ring annelation and photosensitized oxygenation as the key steps; (3) compound I was converted into 16-dehydroretroprogesterone by A-ring annelation, the Wittig reaction, and photosensitized oxygenation.

The successful conversion of 11α-hydroxyprogesterone into retroprogesterone by degradation to a BCD-tricyclic intermediate and stereospecific reconstruction of the tetracyclic skeleton has recently been reported.[1] Complementing this work, the total syntheses of both racemic[2] and optically active[3] 17β-hydroxy-$\Delta^{9(10)}$-des-A-androsten-5-ones and their efficient hydrogenation[4] to 17β-hydroxy-9β,10β-des-A-androstan-5-one (I) were achieved. In order to complete a total synthesis of retroprogesterones (related to the commercially available progestational agent dydrogesterone), all that remained was the introduction of the proper side chain at C-17 and the addition of the A ring to a tricyclic intermediate such as I. We would now like to report three different syntheses of retroprogesterones from totally synthetic optically active I.

Preparation of Retroprogesterone from I by the Wittig–Hydroboration–Annelation Reaction Sequence. —We have previously[5] described the conversion of representative 17-keto steroids into the corresponding pregnanes (20 ketones) by a three-step sequence involving the Wittig reaction, hydroboration, and oxidation. A similar scheme was used in the present work with the added feature of protecting the 5-ketone function. The tricyclic B/C *cis* intermediate I was ketalized in the normal manner[6] to II which was oxidized without additional purification with chromic oxide–N,N-dimethylformamide reagent[7] (containing concentrated sulfuric acid as catalyst) to give, after recrystallization, a high yield of the highly crystalline keto ketal III (see Scheme I). No hydrolysis of the ketal function occurred, agreeing with the results of Snatzke.[7]

Reaction of III with ethylidenetriphenylphosphorane according to our previously reported conditions[5] afforded high yields of product (90–95% after filtration through an alumina column) which consisted of 85% *cis* olefin (IVa), 7% *trans* olefin (IVb), and 8% impurity by vapor phase chromatographic (vpc) analysis. The total amount of useful (olefinic) material was 92% of the crude product, and our over-all yield from I was in the order of 80%.

The assignment of the *cis* stereochemistry to the major olefinic product was made on the basis of (a) analogy with our previously published work[5] and that of others,[8] where it was proven that the identical Wittig reaction with 17-keto steroids afforded mostly *cis* olefin, (b) conversion of the olefin into a 20α alcohol by hydroboration (*vide infra*), and (c) nmr spectral evidence.

Concerning this last point, the nmr spectrum of the crude Wittig product exhibited two C-18 methyl resonances, the major one at δ 0.90 and the minor one at 0.85. This is consistent with the deshielding effect of the 21-methyl group upon C-18 in the *cis* olefin.

The *cis* olefin IVa can be obtained pure by recrystallization but there is some disadvantage to purification at this stage, and it is best to hydroborate the crude Wittig product (using 1 *M* BH_3–THF complex in tetrahydrofuran[9]) and then oxidize *via* the standard alkaline hydrogen peroxide procedure. The crude alcohol mixture was then deketalized by warming in aqueous acetic acid. Vpc analysis of this material showed the presence of 84% 20α-ol (Va), 6% 20β-ol (Vb), and 10% assorted impurities. The total of 90% C-20 alcohols, compared with the 92% $\Delta^{17(20)}$ olefins originally present, indicates the high yield in this three-step sequence. Direct crystallization afforded 55–60% pure Va, leaving substantial quantities of this isomer as well as the potentially useful 20β isomer in the mother liquors.[10]

The 20α alcohol that we obtained was different from the oily 20β alcohol previously prepared by Uskokovic,[1] our alcohol being a crystalline solid, mp 110–111°. The nmr spectrum of the 20α-ol showed a C-18 methyl resonance at δ 0.77 compared with 0.83 for the 20β-ol. This is consistent with the C-18 methyl shifts for 20α- and 20β-hydroxy steroids.[11]

The 20α alcohol (Va) was annelated (*cf.* Uskokovic[1] for annelation of 20β alcohol) with methyl vinyl ketone in *t*-butyl alcohol at 50° using a catalytic amount of sodium hydroxide to afford 20α-hydroxyretropregn-4-en-3-one. This was oxidized to retroprogesterone (VI), identical in all respects with an authentic sample.[12] These transformations formally completed the total synthesis of retroprogesterone. Since retroprogester-

(1) (a) M. Uskokovic, J. Iacobelli, R. Philion, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966). (b) M. Uskokovic, J. Iacobelli, R. Philion, and T. Williams, *J. Org. Chem.*, **33**, 509 (1968).

(2) (a) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron Lett.*, 6495 (1966). (b) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967).

(3) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, 2039 (1968).

(4) (a) R. A. Micheli, Hoffmann-La Roche Inc., private communication, 1965. (b) F. Hoffmann-La Roche & Co. Ltd., South African Patent No. 67/1920.

(5) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

(6) Experiment first performed by Dr. W. Meier, F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland.

(7) G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).

(8) (a) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **98**, 604 (1965). (b) R. Rees, D. P. Strike, and H. Smith, *J. Med. Chem.*, **10**, 783 (1967).

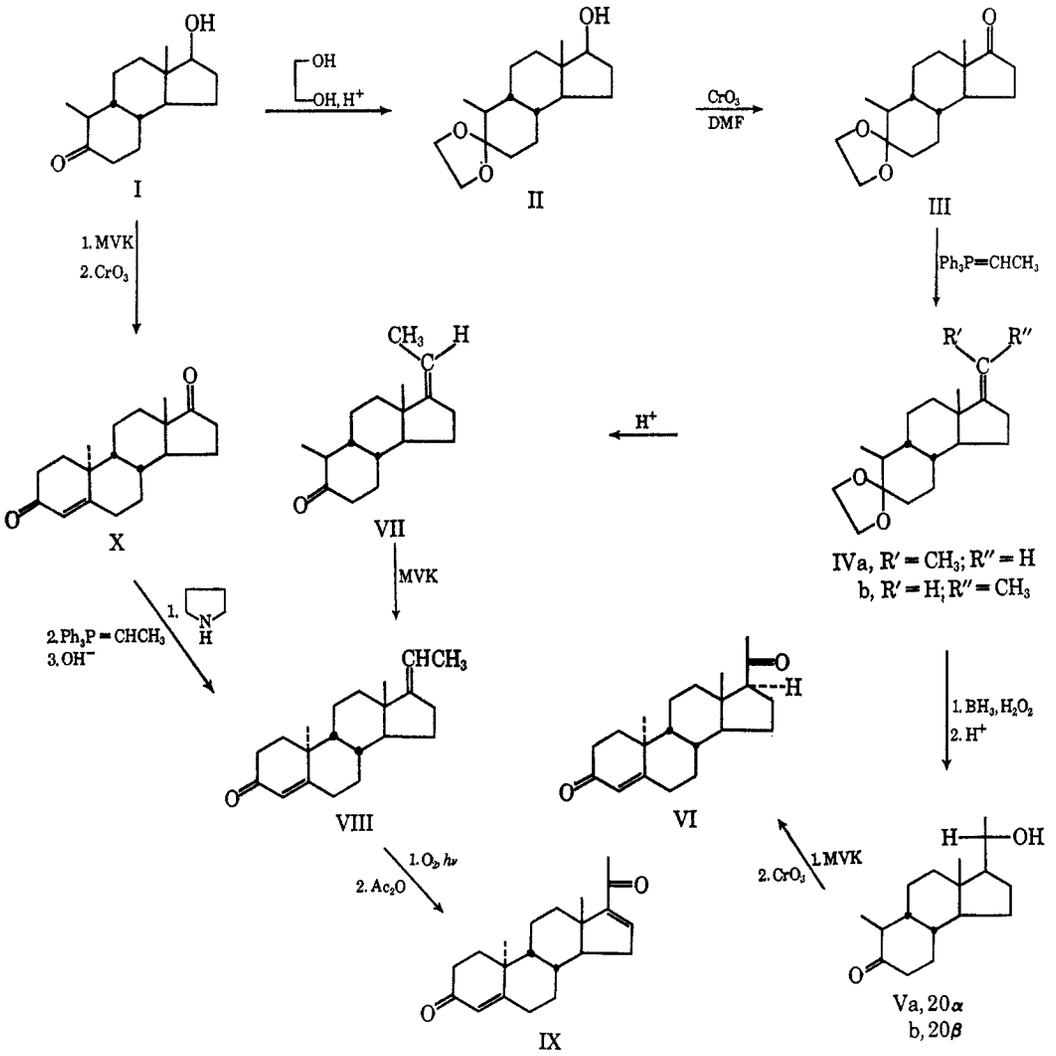
(9) *In situ* generation of diborane from sodium borohydride and boron trifluoride etherate was also used, but the above method was preferred for convenience.

(10) In theory, a mixture of 20α- and 20β-ols could be converted into retroprogesterone, although this was never attempted by us.

(11) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, p 23. (b) H. VanKamp, *Rec. Trav. Chim.*, **84**, 853 (1965).

(12) Kindly supplied by Dr. A. Fürst, F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland.

SCHEME I



one has previously been converted into 6-dehydroretroprogesterone (dydrogesterone),[13] this also constitutes the first total synthesis of this material. However, there were inherent disadvantages to this scheme, especially if a more versatile synthesis of complex retroprogesterones was desired, since hydroboration is precluded for those substrates which contain additional centers of unsaturation.

Preparation of 16-Dehydroretroprogesterone from I by the Wittig–Annelation–Photooxygenation Reaction Sequence.—An alternative method used by us with great success involves the photosensitized oxygenation of olefins studied in detail by Schenck[14a] and by Nickon[14b–d] and more recently applied to the side chain of steroids by Upjohn workers.[15] In this sequence (Scheme I), compound IVa was deketalized to VII which was annelated with methyl vinyl ketone to afford the retrosteroid VIII. This compound, in pyridine solution containing hematoporphyrine, was treated with a stream of oxygen while being illuminated with a fluorescent light source. The Δ^{16}-20-hydroperoxide was rapidly formed, as evidenced by tlc analysis. The hydroperoxide was directly dehydrated *in situ* with acetic anhydride to afford crude enone. Vpc analysis showed it to contain 88% IX,[16] and, after crystallization, 55% IX was obtained, identical with an authentic sample.[12]

It is noteworthy that the 3-keto-Δ^4 system of the steroid is completely inert to the reaction conditions. Other unrelated work which we have done with IVa, VII, and normal steroids has shown that, in agreement with the Upjohn[15] results, saturated ketones, dienones, and ethylene ketals are stable to the reaction conditions. In addition, we have found that steroidal aromatic A rings as well as certain hindered isolated double bonds (*e.g.*, $\Delta^{9(11)}$) are also unreactive. This method gives a greater flexibility to the total synthesis since the Δ^{16} double bond can be used as a handle for introduction of many groups at positions 16 and 17.

Preparation of 16-Dehydroretroprogesterone from I by the Annelation–Wittig–Photooxygenation Reaction Sequence.—One further transformation studied by us was conversion of I into VIII by the reverse process of annelation *followed* by side-chain introduction. First I was treated with methyl vinyl ketone, and the retrotestosterone obtained was oxidized with Jones reagent

(13) P. Westerhof and E. H. Reerink, *Rec. Trav. Chim.*, **79**, 771 (1960).

(14) (a) G. Schenck, O. Albrecht Neumüller, and W. Eisfeld, *Ann.*, **618**, 194, 202 (1958). (b) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1958). (c) A. Nickon, N. Schwartz, J. DiGiorgio, and D. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965). (d) A. Nickon and W. Mendelson, *ibid.*, **30**, 2087 (1965).

(15) (a) The Upjohn Co., U. S. Patent 3,281,415. (b) W. P. Schneider, D. E. Ayer, and J. E. Huber, Abstracts of Second International Congress of Hormonal Steroids, Milan, Italy, May 1966.

(16) Philips-Duphar, U. S. Patent 3,198,792.

to retroandrostenedione (X). This was converted into its pyrrolidine monoenamine[16] (at C-3), which was treated with ethylidenetriphenylphosphorane and then hydrolyzed with aqueous alkali. After purification, the expected retrosteroid VIII was obtained (38% from X) and proved to be identical with the earlier prepared sample.

Experimental Section[17]

5,5-Ethylenedioxy-9β,10β-des-A-androstan-17β-ol (II).—A mixture of 10.45 g of 5-keto-17β-hydroxy-9β,10β-des-A-androstane (I), 50 ml of ethylene glycol, 1.5 g of *p*-toluenesulfonic acid monohydrate, and 500 ml of benzene was refluxed overnight, using a Dean–Stark water trap. The cooled mixture was treated with solid sodium bicarbonate until CO_2 evolution ceased and was then washed with 5% sodium bicarbonate solution, water, and dried. The solvent was removed to afford 12.0 g of crude ketal, mp 110–112°. A sample recrystallized from *n*-hexane melted at 113.5–115.0°. The crude ketal showed no carbonyl absorption in the infrared spectrum and was used for the subsequent reaction: $[\alpha]^{25}D$ −9° (dioxane, 0.1%).

Anal. Calcd for $C_{17}H_{28}O_3$ (280.39): C, 78.82; H, 10.07. Found: C, 78.52; H, 10.07.

5,5-Ethylenedioxy-9β,10β-des-A-androstan-17-one (III).—Crude II as prepared above was dissolved in 500 ml of dry dimethylformamide (DMF). To this was added portionwise, with stirring, 12.0 g of chromic oxide, followed by a solution of 4.0 ml of concentrated sulfuric acid in 100 ml of dry DMF. After stirring overnight at room temperature, solid sodium bicarbonate was added, and the reaction was diluted with ether and washed with 5% sodium bicarbonate solution. The aqueous phase was extracted again with ether, and the organic extracts were washed three times with water. After drying and removal of the solvent, there was obtained 10.9 g of crude crystalline product. Recrystallization from *n*-hexane afforded 9.6 g of flat plates: mp 138–139°; $[\alpha]^{25}D$ +63.9°.

Anal. Calcd for $C_{17}H_{26}O_3$ (278.38): C, 73.34; H, 9.41. Found: C, 73.33; H, 9.38.

5,5-Ethylenedioxy-$\Delta^{17(20)}$-9β,10β-des-A-pregnene (IV).—Sodium hydride–mineral oil dispersion (23.8 g, 53.4% NaH) was washed three times with *n*-hexane and blown dry with nitrogen. Dry dimethyl sulfoxide (DMSO) (450 ml) was added, and the mixture was stirred vigorously under nitrogen at 70–75° until hydrogen evolution ceased (30–45 min). The light green solution was cooled to room temperature, and a solution of 224 g of ethyltriphenylphosphonium iodide in 900 ml of DMSO was rapidly added. To the deep red solution was added a solution of 40.0 g of III in 900 ml of DMSO. The reaction was heated at 60° overnight under nitrogen, cooled, and poured into ice water. After three extractions with petroleum ether, the combined organic extract was washed three times with water and dried. The solution was concentrated and filtered through a column of 130 g of alumina (grade I) with 2 l. of petroleum ether (bp 30–60°). Evaporation of the solvent afforded 38.4 g of semicrystalline product which analyzed by vpc for 85% *cis* olefin (IVa), 7% *trans* olefin (IVb), and 8% impurity. One recrystallization from ether–methanol afforded material (mp 71.5–73.5°) which was greater than 98% *cis* isomer. The nmr spectrum exhibited a C-18 methyl resonance at δ 0.90. The analytical sample had mp 73–75° and $[\alpha]^{25}D$ +7.5°.

Anal. Calcd for $C_{19}H_{30}O_2$ (290.43): C, 78.57; H, 10.40. Found: C, 78.43; H, 10.13.

9β,10β-Des-A-pregnan-20α-ol-5-one (Va) from Crude Wittig Product.—A sample (0.5 g) of the crude Wittig product (vpc analysis: 85% *cis* olefin, 7% *trans* olefin) dissolved in 30 ml of dry tetrahydrofuran (THF) was treated with 2.5 ml of 1.0 *M* borane–THF complex in THF. After standing at room temperature for 1.5 hr, 6.1 ml of 10% sodium hydroxide solution was cautiously added. The mixture was cooled to 0°, and 2.5 ml of 30% hydrogen peroxide was added. After stirring for 1.5 hr at 0°, the reaction mixture was diluted with water and extracted twice with ether. The organic layer was washed with 10% sodium bisulfite solution, water, and saturated brine, and dried. After removal of the solvent, the crude residue was heated at 55–60° with 15 ml of 70% aqueous acetic acid, cooled, and diluted with water. After two extractions with methylene chloride, the organic layer was washed with 5% sodium bicarbonate solution until neutral and dried, and the solvent was evaporated, to afford 429 mg of partially crystalline product. Vpc analysis showed the presence of 84% 20α-ol (Va) and 6% 20β-ol (Vb).

One recrystallization from ether–petroleum ether afforded 238 mg of product, mp 106–108.5°. The analytical sample had mp 110–110.5° and $[\alpha]^{25}D$ −8.1. The nmr spectrum exhibited a C-18 methyl resonance at δ 0.77.

Anal. Calcd for $C_{17}H_{28}O_2$ (264.39): C, 77.22; H, 10.67. Found: C, 77.49; H, 10.74.

9β,10α-Progesterone (VI) from Va.—The annelation of Va (2.64 g) with methyl vinyl ketone (0.53 g) was carried out in the identical manner with that described for the preparation of 9β,10α-testosterone from I (*vide infra*). After chromatography [1.16 g of starting material (Va) was recovered], the crude tetracyclic product was crystallized from isopropyl ether to afford 380 mg of material [mp 132–135°; λ_{max}^{EtOH} 241 mμ (ε 16,050)] which contained according to nmr and vpc analysis a small amount of a structural isomer. This material was dissolved in 19 ml of acetone and oxidized with a solution of 0.20 g of chromium trioxide in 2 ml of 6 *N* sulfuric acid. After standing overnight, the reaction was worked up with ether. The crude product (0.33 g) was crystallized from ether to give 0.244 g of VI, mp 140–153°. Pure VI was obtained by chromatography on 25 g of neutral alumina (grade III) and elution with benzene–ether (19:1) followed by crystallization from acetone–hexane. This material (124 mg) had mp 162–164° and was identical with an authentic sample of retroprogesterone.[12]

$\Delta^{17(20)}$-9β,10β-Des-A-pregnen-5-one (VII).—Once-recrystallized Wittig product (10.2 g) was dissolved in 225 ml of glacial acetic acid, and 60 ml of water was added. After stirring for 4 hr, at room temperature, the reaction was diluted with water, extracted twice with methylene chloride, washed to neutrality with 5% sodium bicarbonate solution, and dried. After removal of the solvent, there was obtained 8.48 g of product, mp 42–46°. The analytical sample was recrystallized from methanol–water: mp 45.5–48.0°; $[\alpha]^{25}D$ −0.95°.

Anal. Calcd for $C_{17}H_{26}O$ (246.38): C, 82.87; H, 10.64. Found: C, 82.85; H, 10.36.

9β,10α-Pregna-4,17(20)-dien-3-one (VIII) from VII.—A solution of 2.50 g of VII and 25 mg of sodium hydroxide in 75 ml of *t*-butyl alcohol was treated with a solution of 0.75 ml of methyl vinyl ketone in 12.5 ml of benzene as described for the synthesis of retrotestosterone (*vide infra*). The crude annelation product (3.54 g) was chromatographed on 250 g of neutral alumina (grade III). Elution with hexane–ether (19:1) afforded 1.237 g of starting material (VII). Hexane–ether (9:1) eluted 1.19 g of crude VIII which after crystallization from ether–hexane weighed 840 mg. The analytical sample was crystallized from ether–hexane: mp 119.0–119.5°; $[\alpha]^{25}D$ −130°; λ_{max}^{EtOH} 240.5 mμ (ε 16,050).

Anal. Calcd for $C_{21}H_{30}O$: (298.49): C, 84.55; H, 10.06. Found: C, 84.99; H, 10.36.

9β,10α-Testosterone from I.—A solution of 4.73 g of I and 50 mg of sodium hydroxide in 100 ml of *t*-butyl alcohol was heated to 50° under nitrogen and treated dropwise with a solution of 1.05 g of methyl vinyl ketone (freshly distilled) in 10 ml of benzene. After the addition was complete (30 min), the reaction was kept at 50° for an additional 30 min, then cooled to 10°, and treated with 0.3 ml of glacial acetic acid. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on a column of 500 g of neutral alumina (grade III). Benzene–ether (19:1) eluted 2.76 g of starting material, mp 144–146°. A mixture of starting material and retrotestosterone (320 mg) was eluted with benzene–ether (9:1). Further elution with benzene–ether (9:1) afforded 1.69 g of impure retrotestosterone which after crystallization from ether weighed 1.08 g and had mp of 154–156°. Rechromatography of the mixed fractions described above afforded an additional 88 mg of I (mp 140–144°) and 180 mg of retrotesterone (mp 149–150°). The analytical sample [mp 154–156° $[\alpha]^{25}D$ −140.8° (dioxane, *c* 0.5%); λ_{max}^{EtOH} 240 mμ (ε 16,450)] was identical with an authentic sample.[12]

(17) All melting points are corrected. Nmr spectra were run in deuteriochloroform using tetramethylsilane as an internal standard. Optical rotations were run in chloroform (*c* 1%) unless otherwise specified. Solutions were dried over anhydrous sodium sulfate and solvents were evaporated at reduced pressure. Alumina for chromatography was Woelm neutral alumina, which was deactivated as required.

9β,10α-Androst-4-ene-3,17-dione (X).—9β,10α-Testosterone (30 g) in 600 ml of acetone was oxidized at 0° with 29.8 ml of 8 *N* chromic acid reagent. After the normal work-up with methylene chloride, the crude product was recrystallized from aqueous ethanol to afford 18.2 g of needles, mp 153.5–156.0°. A second crop, after further crystallization, afforded an additional 4.5 g of product, mp 151–153°.

***cis*-9β,10α-Pregna-4,17(20)-dien-3-one (VIII).**—A solution of 15.0 g of 9β,10α-androst-4-ene-3,17-dione in 150 ml of dry methanol was heated to reflux under nitrogen and treated with 8.0 ml of freshly distilled pyrrolidine. After 10 min at reflux, protecting from light, the orange solution was allowed to cool to room temperature, whereupon the enamine spontaneously crystallized. After cooling well in the freezer the crystals were filtered, washed well with dry methanol, and dried at 35°, affording 15.88 g of product. This material was dissolved in 300 ml of dry benzene containing a few drops of pyrrolidine and added to a solution of ethylidenetriphenylphosphorane in 600 ml of DMSO (prepared from 10.54 g of 54% sodium hydride dispersion and 99 g of ethyltriphenylphosphonium iodide). After heating at 50–55° overnight (protecting from light), 100 ml of 10% potassium hydroxide solution and 300 ml of methanol were added. Heating (50°) was continued for 1.5 hr. The reaction was then cooled, neutralized with acetic acid, and diluted with water. After extraction with three portions of ether, the combined extract was washed with water and 5% sodium bicarbonate solution, dried, and evaporated. The crude product was chromatographed on silica gel. Benzene and benzene–ethyl acetate (99:1) eluted 7.77 g of crystalline material which upon recrystallization from aqueous methanol weighed 5.62 g and had mp 111–114°. Further recrystallization from ether–hexane raised the melting point to 114.5–115.5°. This material was identical with the above-prepared sample by tlc and nmr analysis.

9β,10α-Pregna-4,16-diene-3,20-dione (IX).—A solution of VIII (1.0 g) and hematoporphyrine (20 mg) in 35 ml of pyridine was treated with a fine stream of oxygen while being illuminated with a series of two 15-W fluorescent lamps. After 4.5 hr, 5 ml of acetic anhydride was added, and the reaction mixture was allowed to stand at room temperature (somewhat exothermic) for 45 min and was then heated at 60° for an additional 30 min. After dilution with water, the product was extracted with methylene chloride and the organic phase washed thoroughly with 2 *N* HCl and then with 5% sodium bicarbonate solution. After drying, the methylene chloride solution was slurried with 15 g of neutral alumina (grade II) and filtered. The crystalline residue obtained after evaporation of the solvent was recrystallized twice from ether–petroleum ether to afford 562 mg of product, mp 151–153°. One further recrystallization raised the melting point to 165.5–167.0°, and this material was identical with an authentic sample[12] of this substance.

Registry No.—II, 10104-25-3; III, 17244-02-9; IVa, 17244-03-0; Va, 17244-04-1; VII, 17244-05-2; VIII, 17244-06-3; X, 571-45-9.

Acknowledgment.—We are indebted to Dr. V. Toome for the ultraviolet spectra, to Drs. F. Vane and T. Williams for the nmr spectra, and to Drs. A. Steyermark and F. Scheidl for the microanalyses. The valuable technical assistance of Mr. Harold Lucas and Mr. Fred DiMaria is greatly appreciated.

Transformations in the Morphine Series. III.[1a] Conversion of Thebaine into Methanobenzofuro[3,2-*d*]azocines

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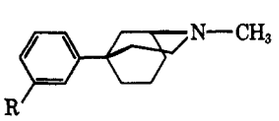
The synthesis of phenylmorphans containing an ether bridge comparable with that in morphine was undertaken. Thebaine was converted, by reported procedures, into 6-deoxy-14-hydroxydihydrocodeine (**4**), and the latter was converted into its methine base **5**, which was hydroxylated (OsO_4); periodate cleavage of triol **6** gave keto-aldehyde **7**. Selective reduction of ethylene dithioacetal **9b** with Raney nickel afforded **11b**. Bromination and cyclization gave **13**, which was hydrogenolyzed to **14**. Dry distillation eliminated CH_3Br, yielding **15a**. The carbonyl group in **15a** was reduced ($NaBH_4$) to the alcohol **16a**, which was mesylated to **16b**. The latter on treatment with $LiAlH_4$ unexpectedly gave the rearranged octahydroindole **17**. A modified Wolff–Kishner reduction of **15a**, by way of the intermediate hydrazone **15b**, afforded the desired methanobenzofuro[3,2-*d*]azocine **2**. Compound **15a** was inactive as an analgetic in mice while **2** had a potency about one-half that of codeine.

Earlier reports from this laboratory described the synthesis and biological activity of two compounds whose structures are related to morphine, namely 2-methyl-5-phenylmorphan[2,3] (**1a**) and 5-(*m*-hydroxyphenyl)-2-methylmorphan[2,3] (**1b**).

Compound **1b** had an analgesic potency equal to morphine, whereas **1a** was slightly less effective than meperidine; both were somewhat more toxic than morphine. It should be noted that both **1a** and **1b** are racemates, while morphine is levorotatory and meperidine is optically inactive.



1a, R = H
b, R = OH

It has been recognized for some time that certain structural features of morphine should be embodied in any modification of its structure in order to retain analgesic potency. They are (1) the phenyl nucleus, (2) the quaternary carbon attached to this nucleus, and (3) the tertiary nitrogen two carbon atoms (C-15 and C-16 in **3**) removed from the quaternary carbon. Further, it was the consensus that the tertiary nitrogen should be in a six-membered-ring formation.[4] Cleavage of the ether bridge and substitution in the aromatic nucleus of morphine appear to decrease activity,[5] while the pronounced analgesic properties of the

(1) (a) Part II: L. J. Sargent and B. C. Joshi, *J. Med. Chem.*, **11**, 336 (1968). (b) Author to whom correspondence should be addressed at the University of Pittsburgh, School of Pharmacy, Pittsburgh, Pa.

(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, **19**, 618 (1954); **20**, 1197 (1955).

(3) According to *Chemical Abstracts* nomenclature, these compounds are 2-methyl-5-phenyl-2-azabicyclo[3.3.1]nonane and 2-methyl-5-(*m*-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane, respectively.

(4) E. L. May and L. J. Sargent in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, 1965, p 123.

(5) E. L. May in "Medicinal Chemistry," 2nd ed, A. Burger, Ed., Interscience Publishers, Inc., New York, 1960, p 311.