The Conversion of 17-Keto Steroids to 20-Oxygenated Steroids. A Facile Synthesis of 19-Norprogesterone

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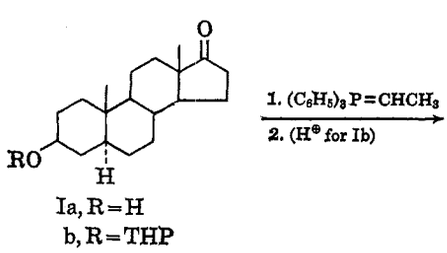
17-Keto steroids have been converted, in high yield and with high stereospecificity, into 20α-hydroxy steroids *via* an ethylidene Wittig reaction followed by hydroboration. A facile synthesis of 19-norprogesterone from estrone methyl ether utilizing this sequence is described.

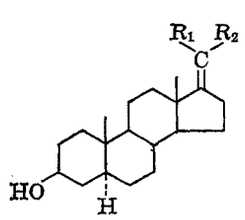
The addition of a two-carbon β-acetyl or β-(α-hydroxyethyl) side chain to a 17-keto steroid is an important part of the partial or total syntheses of pregnane derivatives. There have been two major procedures used in the past for effecting such a conversion, but neither is very attractive either because of length, overall yield, or impracticality on a large scale. The first method[1] involves cyanohydrin formation, dehydration, methyl Grignard addition, and hydrogenation. The second method[2] consists of ethynylation, acetylation, bromohydration, and zinc–acetic acid and metal–ammonia reduction. Both procedures afford 20-ketones.

We now describe a new high-yield sequence by which 20-hydroxy and 20-keto steroids are prepared in two and three steps, respectively, from 17-keto starting materials. This method involves introduction of the necessary two-carbon side chain by a Wittig reaction, functionalization of C-20 by hydroboration, and oxidation (if desired) to a 20-ketone.

Our initial experiments were carried out with isoandrosterone (Ia), and for the Wittig reaction we used the modification of Corey.[3] We found that isoandrosterone reacted rapidly with an excess of ethylidenetriphenylphosphorane in dimethyl sulfoxide (DMSO) at 50–60° to afford high yields of crude 17-ethylidene compound (II) which is a mixture of the two geometrical isomers. The major isomer was obtained pure by crystallization. Isoandrosterone tetrahydropyranyl (THP) ether (Ib) afforded 90–95% yields of crude Wittig product and, after hydrolysis and crystallization, afforded the identical material (II). This must be the *cis* isomer (IIb) since its physical properties differed from those reported by Reichstein[4] for the *trans* isomer (IIa), obtained by dehydration and saponification of 17α-ethylandrostane-3β,17β-diol 3-acetate.



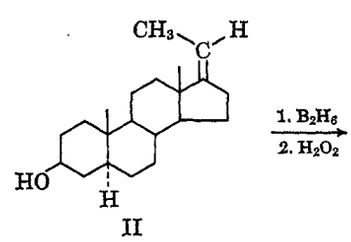
Ia, R=H
b, R=THP



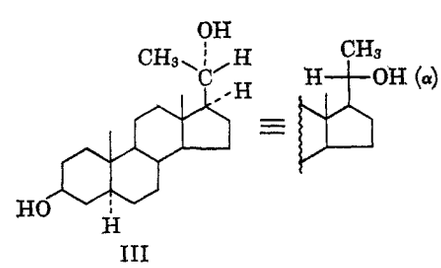
IIa, R_1=H; R_2=CH_3
b, R_1=CH_3; R_2=H

During the course of our work, Drefahl[5] reported the identical Wittig reaction with isoandrosterone acetate and also found the *cis* olefin to be the major product. We are in general agreement with their treatment of the stereochemistry of the Wittig reaction to account for the unusually high proportion of *cis* olefin, and this is further substantiated by the recent results of House.[6]

Additional evidence for the stereochemistry of II follows from our subsequent reactions. We found that II reacted with diborane in tetrahydrofuran (THF) solution (either generated *in situ* from $NaBH_4$ and BF_3[7] or, preferably, by employing a 1 *N* BH_3–THF complex[8]) to afford, after hydrogen peroxide treatment, 5α-pregnane-3β,20α-diol (III). This material and its diacetate were identical with authentic samples. Thus, the starting olefin must have been the *cis*-ethylidene compound IIb which was attacked from the rear by diborane.



II



III

The diol III was oxidized by standard procedures to 5α-pregnane-3,20-dione to complete formally the introduction of the 17-acetyl group.[9]

(1) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

(2) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958).

(3) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(4) H. Reich, M. Sutter, and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

(5) G. Drefahl, K. Ponsold, and H. Schick, *Ber.*, **98**, 604 (1965).

(6) H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, **29**, 3327 (1964).

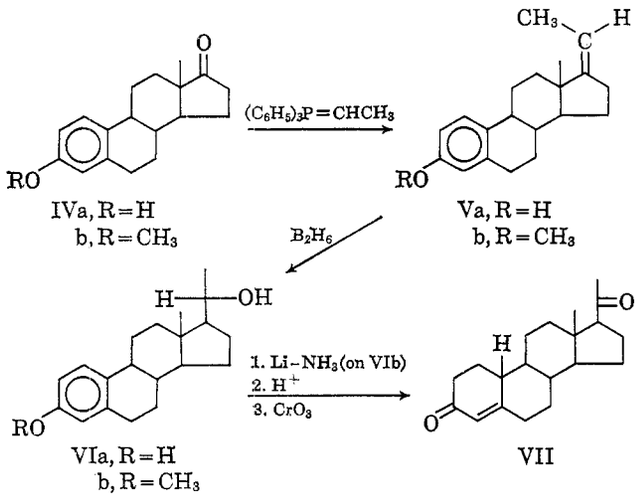
(7) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960).

(8) Available from Metal Hydrides, Inc., Beverly, Mass.

(9) Oxidation of crude diol affords crude dione which contains 5–7% of 17-iso material, by n.m.r. analysis. Presumably, this results from a small amount of topside attack by diborane.

The above reaction sequence has been applied to ring-A aromatic steroids and further extended to provide a facile new synthesis of 19-norprogesterone. Both estrone (IVa) and estrone methyl ether (IVb) were subjected to the above Wittig and hydroboration reactions to afford the 20-alcohols (VIa and b). The configuration at C-20 was assumed to be α, by analogy with the above results.

The 20-alcohol (VIb) was converted to 19-norprogesterone (VII) by the known sequence of Birch reduction, hydrolysis, and oxidation.



This sequence probably constitutes the most convenient method for the preparation of 19-norprogesterone from readily available starting materials, with high stereospecificity during each step. In addition, the sequence can be modified to produce other 19-norpregnanes with additional oxygen functions in the side chain.

Experimental Section[10]

Ethyltriphenylphosphonium Iodide.—A solution of 308 g. (1.17 moles) of triphenylphosphine and 210 ml. (420 g., 2.69 moles) of ethyl iodide in 1 l. of benzene was heated under reflux overnight. The voluminous precipitate was filtered, washed well with benzene, and dried under reduced pressure at 60°, yield 492 g. (100%), m.p. 163–164.5°.

Ethylidenetriphenylphosphorane.—Three grams of sodium hydride (53.4% dispersion in mineral oil; 67 mmoles) was washed three times with hexane and blown dry with nitrogen. To this was added 50 ml. of DMSO (Matheson Coleman and Bell, reagent grade) and the mixture was heated with stirring under nitrogen at 70–75°. After 30–45 min., a light green solution resulted, and no hydrogen evolution could be detected. This solution was cooled to room temperature and a solution of 27.9 g. (67 mmoles) of ethyltriphenylphosphonium iodide in 100 ml. of DMSO was added rapidly to produce a deep red solution (assumed to contain 67 mmoles of phosphorane) which was used for all Wittig reactions described below.

***cis*-$\Delta^{17(20)}$-5α-Pregnen-3β-ol (IIb). A.**—A solution of 3.88 g. (13.3 mmoles) of isoandrosterone (Ia) in 100 ml. of DMSO was added rapidly to a solution of 67 mmoles of ethylidenetriphenylphosphorane in DMSO. The mixture was heated at 55–60° under nitrogen for 5 hr., cooled, and poured into ice–water. After ether extraction (three times), back washing with water (three times), drying, and evaporation, the residue was dissolved in a minimal amount of hot hexane–benzene (3:1) and filtered through a column of 120 g. of alumina (grade III) with the above solvent. The total eluate was evaporated, and the residue was slurried with 200 ml. of ether and filtered. The filtrate was evaporated and this residue was crystallized from methanol to give 1.65 g., m.p. 153–154°, $[\alpha]^{25}D$ +19.9° (*c* 2.00%). A second crop of 900 mg. was obtained, m.p. 150–152° (total yield 63%).

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.59; H, 11.41.

B.—A solution of 5.0 g. (13.3 mmoles) of isoandrosterone THP ether (Ib) in 100 ml. of dry THF was added rapidly to a solution of 67 mmoles of ethylidene–triphenylphosphorane in DMSO. The reaction mixture was heated at 50–55° under nitrogen overnight, cooled, and poured into ice–water. After extraction with hexane (three times), back washing with water (three times), drying, and concentration, the hexane solution, including some precipitated triphenylphosphine oxide, was applied to a short column of alumina (grade I) and eluted with hexane to afford 4.7 g. (90%) of product, m.p. 67–73°, probably a mixture of diastereomers of the ether, as well as double-bond isomers. To avoid the problem of diastereoisomerism, this material was hydrolyzed to the free alcohol. Crude Wittig product (500 mg.) was dissolved in 15 ml. of 0.2 *N* ethanolic HCl, and allowed to stand at room temperature for 1.5 hr. After dilution with ether, washing with 5% $NaHCO_3$ solution (two times), drying, and evaporation, the residue was crystallized from methanol to afford 200 mg. of IIb, m.p. 153–154°.

5α-Pregnane-3β,20α-diol (III).—Three milliliters of 1 *M* BH_3–THF complex[8] in THF was added to a solution of 500 mg. (1.65 mmoles) of *cis*-$\Delta^{17(20)}$-5α-pregnen-3β-ol (IIb) in 20 ml. of dry THF with stirring under nitrogen. After 1 hr. at room temperature, 12 ml. of 10% NaOH solution was added dropwise cautiously. After cooling to 0°, 8 ml. of 30% H_2O_2 was added dropwise with stirring, over a 10-min. period, and stirred for 1 additional hr. at 0°. The reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with 10% $NaHSO_3$ and water, dried, and evaporated to afford 507 mg. (95%) of product, m.p. 212–217° (lit.[11] m.p. 218–219°). This material was acetylated in the usual fashion and the diacetate was recrystallized from methanol, m.p. 163–165°, $[\alpha]^{25}D$ −1.4° (*c* 2.01%) [lit.[11] m.p. 163–165°, $[\alpha]^{25}D$ −0.3° ($CHCl_3$)]. This material was identical with an authentic sample.[12]

5α-Pregnane-3,20-dione.—A solution of 150 mg. of CrO_3 in 20 ml. of 95% acetic acid was added to a solution of 202 mg. of crude diol (III) in 20 ml. of 95% acetic acid. After 1 hr. at 15°, a few drops of methanol was added and most of the acetic acid was removed under reduced pressure. After partitioning between ether and water, the organic layer was washed with 5% $NaHCO_3$ until neutral, dried, and evaporated. The crude product (200 mg.) was recrystallized from ethanol to afford material, m.p. 195–197°, $[\alpha]^{25}D$ +107° (*c* 2.00%), identical with an authentic sample[12] [lit.[13] m.p. 200–201°, $[\alpha]^{25}D$ +121° ($CHCl_3$)].

3-Methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (Vb).—A solution of 31.0 g. (109 mmoles) of estrone methyl ether (IVb) in 600 ml. of benzene was added rapidly to a solution of 467 mmoles of ethylidenetriphenylphosphorane in 1200 ml. of DMSO. After heating at 60° overnight, the reaction was processed as for the second preparation of IIb. The crude product, dissolved in petroleum ether (b.p. 30–60°), was filtered through 225 g. of alumina (grade I). The residue from the eluate consisted of 95% *cis* and 5% *trans* isomers, as determined by v.p.c. analysis. After recrystallization from ether–methanol, there was obtained 26.33 g. (82%) of *cis* isomer, m.p. 76.5–77.5°, $[\alpha]^{25}D$ +60.4° (*c* 1.00%).

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.96; H, 9.71.

***cis*-19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol (Va).**—A solution of 14.0 g. (50 mmoles) of estrone (IVa) in 400 ml. of DMSO was added rapidly to a solution of 234 mmoles of ethylidenetriphenylphosphorane in 600 ml. of DMSO. After heating at 60° under nitrogen overnight, the reaction was processed as for the first preparation of IIb. The crude product, dissolved in petroleum ether–ethyl acetate (1:1), was filtered through a column of 300 g. of silica gel and the product was crystallized from ethanol–water to afford 11.0 g. (80%) of material, m.p. 137–139°, $[\alpha]^{25}D$ +56.8° (*c* 1.02%).

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.95; H, 9.05.

(10) All melting points are uncorrected. Infrared spectra and rotations were determined in chloroform. N.m.r. spectra were run in deuteriochloroform using tetramethylsilane as internal standard. All solutions were dried over sodium sulfate.

(11) W. Klyne and D. H. R. Barton, *J. Am. Chem. Soc.*, **71**, 1500 (1949).

(12) Purchased from Preparations Laboratories, Huntington, Long Island, N. Y.

(13) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

3-Methoxy-19-norpregna-1,3,5(10)-trien-20α-ol (VIb).—Forty milliliters of 1 *M* BH_3–THF complex in THF was added rapidly to a stirred solution of 4.5 g. of 3-methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (Vb) in 200 ml. of dry THF under nitrogen. After stirring at room temperature for 72 hr. (2 hr. is probably sufficient), 120 ml. of 10% NaOH solution was added cautiously, and, after cooling to 0°, 40 ml. of 30% H_2O_2 was added over 15 min. After an additional 1.5 hr. at 0°, the reaction mixture was partitioned between ethyl acetate and water and the original layer was washed with 10% $NaHSO_3$ and water, dried, and evaporated. The crude product was chromatographed on a column of 150 g. of alumina (grade I). The material, eluted with benzene–ether (7:3), was recrystallized from ether–petroleum ether to yield 1.78 g. of product, m.p. 104–105°, $[\alpha]^{25}D$ +76.4° (*c* 2.00%).

Anal. Calcd. for $C_{21}H_{30}O$: C, 80.21; H, 9.02. Found: C, 79.92; H, 9.75.

19-Norpregna-1,3,5(10)-triene-3,20α-diol (VIa).—A solution of 3.0 g. of *cis*-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (Va) in 90 ml. of dry THF was treated at room temperature with 22 ml. of BH_3–THF complex for 2 hr., and then processed as above (40 ml. of 10% NaOH, 15 ml. of 30% H_2O_2). After the reaction was complete, 2 *N* HCl was added until the mixture was slightly acidic and the mixture was partitioned between CH_2Cl_2 and water and processed as above. The crude product, 2.7 g., was recrystallized from CH_2Cl_2–ether to give 1.375 g., m.p. 178–179°, $[\alpha]^{25}D$ +77.2° (*c* 1.00%). A second crop of 238 mg., m.p. 173–175°, was obtained (total 1.61 g., 50%).

Anal. Calcd. for $C_{20}H_{28}O$: C, 79.95; H, 9.39. Found: C, 80.20; H, 9.25.

19-Nor-4-pregnen-3-on-20α-ol.—To a solution of 250 mg. of 3-methoxy-19-norpregna-1,3,5(10)-trien-20α-ol (VIb) in 25 ml. of dry THF was added, by distillation, about 25 ml. of ammonia. While stirring, 250 mg. of lithium wire was added rapidly as small pieces. After 15 min., 4 ml. of absolute ethanol was added rapidly. The blue color disappeared after 15 min. and the ammonia was evaporated, water and ether were added, and the organic extract was washed with water, dried, and evaporated. The crude product (240 mg.) was dissolved in 8 ml. of methanol, treated with 5 ml. of 4 *N* HCl, and heated at reflux for 1 hr. After pouring into saturated salt solution, extraction with ether, and washing the organic layer with 5% $NaHCO_3$ solution, it was dried and evaporated to afford 202 mg. of product. This material was chromatographed on a column of 6 g. of alumina (grade I). The benzene and benzene–ether (9:1) eluates (180 mg.) were combined and recrystallized from ether–petroleum ether, m.p. 124–127°. This material, without further characterization, was oxidized to 19-norprogesterone, as described below.

19-Norprogesterone (VII).—To a solution of 50 mg. of 19-nor-4-pregnen-3-on-20α-ol in 4 ml. of dry DMF was added 50 mg. of CrO_3 followed by 0.7 ml. of DMF containing 0.02 ml. of concentrated H_2SO_4. After 1 hr. at room temperature, the reaction mixture was partitioned between ether and water. The ether extracts were washed with water, dried, and evaporated to afford 46 mg. of crystalline product, m.p. 139–141°, which, after crystallization from ether, melted at 141.5–142.5° and was identical with an authentic sample[14] (lit.[2] m.p. 141–144°).

Acknowledgment.—We are indebted to Dr. A. Steyermark for the microanalyses, Dr. F. Vane for the n.m.r. spectra, and Mr. H. Lucas for technical assistance.

(14) Kindly supplied by Dr. A. Bowers, Syntex Corp.

16-Alkylated Corticoids. IV.[1] Synthesis of 16β-Methyl Analogs of Cortisone, Prednisone, and 9α-Fluoroprednisolone[2]

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The synthesis of 16β-methyl analogs of cortisone, prednisone, 9α-fluoroprednisolone, and related compounds is described, starting with intermediates readily prepared from bile acids.

It is well known that the introduction of a chlorine or fluorine atom at the C-9 position of the natural adrenal substances cortisone and hydrocortisone (and their 1-dehydro analogs) markedly enhances the anti-inflammatory activity of these agents and is accompanied by a striking increase in both salt and water retention.[4] These undesirable side effects, manifested generally by 9-halo steroids, preclude their use systemically in the management of disorders normally responsive to adrenocortical steroid therapy.

Introduction of a 16α-hydroxyl or 16α-methyl group into the 9α-fluorocorticoid molecule has suppressed these severe electrolyte disturbances,[4a,c] but other side effects have been reported.[4a,5]

The first reports of the synthesis of 16β-methyl cortical steroids and their efficacy as antiinflammatory agents came from these laboratories in 1958.[2a,b]

We now wish to report the detailed synthesis of several 16β-methyl steroids, one of which (9α-fluoro-16β-methylprednisolone[6]) is the most potent anti-inflammatory steroid marketed and is also devoid of electrolyte imbalance and water retention at clinically effective dose levels.[7]

The readily available 3α-acetoxy-16-methyl-16-pregnene-11,20-dione[8] (I) was catalytically reduced using palladium on charcoal in acetic acid to give 3α-acetoxy-16β-methylpregnane-11,20-dione (II) (Scheme I). Reaction of II with *p*-toluenesulfonic acid in hot acetic anhydride produced the 17(20)-enol acetate III. Epoxidation with peracetic acid in benzene[9] gave the

(1) Paper III: E. P. Oliveto, *et al.*, *J. Am. Chem. Soc.*, **80**, 6687 (1958).

(2) A portion of this work was communicated earlier: (a) E. P. Oliveto, *et al.*, *ibid.*, **80**, 4428 (1958); (b) paper III, ref. 1. See also (c) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *ibid.*, **80**, 4435 (1958); (d) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, **82**, 4012 (1960); (e) T. R. Carrington, *et al.*, *J. Chem. Soc.*, 4560 (1961); (f) G. G. Nathansohn, G. Winters, and E. Testa, *Experientia*, **17**, 448 (1961); D. Kluepfel and C. Coronelli, *ibid.*, **18**, 441 (1962).

(3) Hoffman-LaRoche, Inc., Nutley, N. J.

(4) (a) For a discussion of the effects of antiinflammatory steroids on electrolyte metabolism, see G. W. Liddle, *Ann. N. Y. Acad. Sci.*, **82**, 854 (1959); (b) L. H. Sarett, *ibid.*, **82**, 802 (1959); (c) J. Fried, *Vitamin Hormones*, **16**, 304 (1958); (d) L. H. Sarett, A. A. Patchett, and S. A. Steelman, *Progr. Drug Res.*, **5**, 11 (1963).

(5) (a) R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis Rheumat.*, **1**, 215 (1958); (b) J. J. Bunim, R. L. Black, L. Lutwak, R. E. Peterson, and G. D. Whedon, *ibid.*, **1**, 313 (1958); (c) M. Pechet, E. L. Carroll, M. Mitchell, and M. J. Wegner, *J. Clin. Invest.*, **37**, 921 (1958).

(6) Celestone is the registered trademark for the Schering Corp. brand of 9α-fluoro-16β-methylprednisolone (Betamethasone).

(7) (a) M. M. Pechet, personal communications; (b) reports to the Clinical Division, Schering Corp.; (c) Swiss Conference on Celestone, Zurich, 1961; (d) *Praxis* (Bern), **51**, 238 (1962).

(8) *Cf.* (a) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); (b) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(9) E. P. Oliveto and E. B. Hershberg, *ibid.*, **76**, 5167 (1954).