# A New and Convenient Synthesis of the 17α,21-Diacetoxy-20-oxopregnane Side-chain

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A convenient ' one-pot ' synthesis of the corticosteroid side chain has been developed. 20-Oxopregnane oximes have been converted into 20-acetylamino-17(20)-ene derivatives, which with lead tetra-acetate in dry benzene afford 17α-acetoxy-20-acetylimines. The latter are rearranged by acid to 20-enamides [as (IV)]. Further reaction with lead tetra-acetate then introduces an acetoxy-group at C-21. The 20-acetylimines are hydrolysed to the corresponding ketones by aqueous acid. Overall yields are high. Some preliminary experiments with 16α- and 16β-methylpregnanes are outlined.

THE dihydroxyacetone side chain is characteristic of many medicinally important analogues of the corticosteroids. Various syntheses of such compounds have been devised.[1] We have previously reported a new reaction whereby ketone oximes are reductively acylated to yield enimides and thence enamides.[2] We now describe the application of this reaction to a novel method for the conversion of 20-oxopregnanes into their 17α,21-diacetoxy-derivatives in a (potentially) 'one-pot' reaction in excellent overall yield.

The enimide (I; R = Ac) was isolated in 89% yield when 3β-acetoxypregn-5-en-20-one oxime[3] (II; R = OH) was heated in refluxing acetic anhydride and pyridine for 40 h. Chromatography of the product on alumina gave the enamide (I; R = H) (98%). N.m.r. spectroscopy clearly indicated that the new double bond was in the 17(20)-position, although we have no definite evidence concerning configuration about the double bond.[4] The enamide showed no tendency to rearrange to the 20(21)-ene isomer on treatment with acid. Ruschig and his co-workers have reported the preparation of the same enamide (I; R = H) and enimide (I; R = Ac), but in considerably lower yield, by acetylation of the imine (II; R = H).[5] The discrepancy between our constants and theirs may be due to isomerisation about the 17(20)-double bond.

We conceived that the enamide double bond of (I; R = H) would be smoothly acetoxylated by anhydrous lead tetra-acetate to give the 17α-acetoxy-20-acetylimine (III; X = NAc). We supposed that such an acetylimine, being considerably more hindered than a 3-acetylimino-steroid,[2] would not be hydrolysed unless water were deliberately added. Hence a compound like (III; X = NAc) should undergo with anhydrous acid the usual acetylimine ⟶ enamide rearrangement to give (IV), further acetoxylation of which to the acetylimine (V; X = NAc) followed by hydrolysis by addition of water would give the corticoid side-chain as in (V; X = O). In the event this conception could be reduced to practice without difficulty.

When the enamide (I; R = H) was treated with lead tetra-acetate in benzene both the 17α-acetoxy-20-acetylimine (III; X = NAc) and the 17α-acetoxy-20-ketone (III; X = O) were formed. However, if particular care was taken to ensure anhydrous conditions the acetylimine (III; X = NAc) was the only product (90% yield). In acetic acid, or preferably, acetic acid containing trichloroacetic acid, the acetylimine (III; X = NAc) rearranged to the enamide (IV) in essentially quantitative yield. Acetoxylation of the enamide (IV) with lead tetra-acetate in dry benzene proceeded best at 50 °C; the 17α,21-diacetoxy-20-acetylimine (V; X = NAc) was then isolated in 84% yield. The acetylimines (III or V; X = NAc) were hydrolysed quantitatively by aqueous acetic acid to the known α-acetoxy-ketones (III or V; X = O). An analogous series of reactions starting from 3β-acetoxy-5α-pregnan-20-one oxime[6] (II; R = OH, 5,6-dihydro) was performed with equal success. Details are given in the Experimental section.

We also carried out some preliminary experiments with 16α- and 16β-methylpregnanes. From a medicinal standpoint the presence of a 16-substituent is often highly desirable.[1] Thus, the oximes (VIa and b) afforded the enamides (VIIa and b; R = H) in yields of 55 and 73%, respectively. In the 16α-methyl series the intermediate enimide (VIIa; R = Ac) could not be induced to crystallise and was not fully characterised. Subsequent experiments in the 16β-methyl series established the feasibility of introducing a 17α-acetoxy-group using lead tetra-acetate in dry benzene, although the yield of actylimine (VIII) (61%) was lower than in the case of the unsubstituted series. Attempts at *in situ* rearrangement of the acetylimine (VIII) by addition of a solution of hydrogen chloride gas in chloroform gave the known[7] αβ-unsaturated ketone (IX) as the major product.

## EXPERIMENTAL

General directions are as previously.[2]

*3β-Acetoxy-20-diacetylaminopregna-5,17(20)-diene* (I; R = Ac).—3β-Acetoxypregn-5-en-20-one oxime[3] (400 mg) in dry

[1] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959; E. P. Oliveto in ' Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972, vol. II, pp. 127—236.

[2] R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell, and R. V. Stick, preceding paper.

[3] M. E. Wolff and R. C. Boguslaski, *J. Medicin. Chem.*, 1968, **11**, 285.

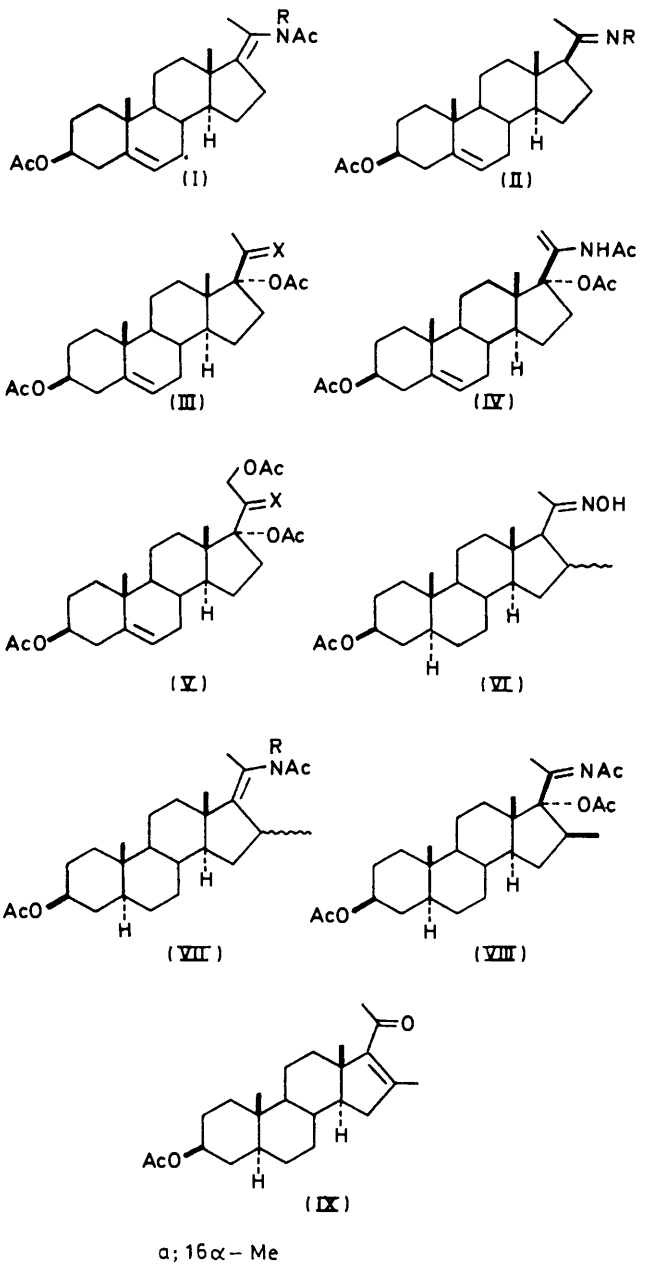
[4] For references to the corresponding enol acetates see D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968.

[5] H. Ruschig, W. Fritsch, J. Schmidt-Thomé, and W. Haede, *Chem. Ber.*, 1955, **88**, 883; 1963, **96**, 68.

[6] P. Buchschacher, J. Kalvoda, D. Arigoni, and O. Jeger, *J. Amer. Chem. Soc.*, 1958, **80**, 2905.

[7] R. Mickova and K. Syhora, *Coll. Czech. Chem. Comm.*, 1965, **30**, 2771.

pyridine (30 ml) and acetic anhydride (20 ml) was refluxed under nitrogen for 40 h, after which no oxime or oxime acetate remained (t.l.c.). The solvent was evaporated off under reduced pressure, the residual black tar was taken up




a; 16α – Me
b; 16β – Me

in ether (200 ml), and N-sodium carbonate solution (100 ml) was added. The mixture was shaken and then filtered through a pad of Celite. The Celite was washed thoroughly with ether. The ether layer was separated, washed with water, dried, and evaporated. Chromatography of the residue on silica gel [benzene–ether (95 : 5 v/v)] afforded the enimide, which crystallised from methanol as plates (422 mg, 89%), m.p. 163—164°, (lit.,[5] 180—182°) $[\alpha]_D$ – 50°, $\nu_{max.}$ 1730, 1710, 1695, and 1240 cm$^{-1}$, $\tau$ 4.63 (1H, d, *J* 5 Hz, 6-H), 5.45 (1H, m, 3α-H), and 7.67, 7.70, 7.98, 8.07, 8.95, and 9.03 (each 3H, s), $M^+$ 441 (Found: C, 73.3; H, 8.9; N, 3.0. Calc. for $C_{27}H_{39}NO_4$: C, 73.4; H, 8.9; N, 3.2%).

3β-*Acetoxy*-20-*acetylaminopregna*-5,17(20)-*diene* (I; R = H).—The above enimide (200 mg) in benzene (5 ml) was adsorbed onto a column of alumina (Laporte type 0). Elution after 1 h with benzene–ether (1 : 1 v/v) gave the enamide (177 mg, 98%), m.p. (from methanol) 171—173° or 200—204° (lit.,[5] 152—153°), $[\alpha]_D$ –46°, $\nu_{max.}$ 3280, 1730, 1650, 1530, and 1245 cm$^{-1}$, $\tau$ 3.7br (1H, s, NH), 4.6 (1H, d, *J* 5 Hz, 6-H), 5.4 (1H, m, 3α-H), 7.98 (6H, s), and 8.02, 8.98, and 9.10 (each 3H, s), $M^+$ 399 (Found: C, 74.9; H, 9.4; N, 3.4. Calc. for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.3; N, 3.5%).

3β,17α-*Diacetoxy*-20-*acetyliminopregn*-5-*ene* (III; X = NAc).—The enamide (I; R = H) (150 mg) in dry benzene (40 ml) was further dried azeotropically by the distillation of benzene (10 ml). Dry lead tetra-acetate (250 mg) was added to the cooled solution, and the mixture stirred at room temperature for 45 min. Water (20 ml) was added and the mixture was shaken, and then filtered through Celite. The Celite was washed thoroughly with benzene. The benzene layer was separated, washed with N-sodium carbonate solution, then water, dried, and evaporated. Chromatography on silica gel [benzene–ether (95 : 5 v/v)] gave the *acetylimine* (155 mg, 90%), m.p. (from hexane) 155—157°, $[\alpha]_D$ –83°, $\nu_{max.}$ 1735, 1705, 1680, and 1240 cm$^{-1}$, $\tau$ 4.6 (1H, d, *J* 5 Hz, 6-H), (1H, m, 3α-H), and 7.85, 7.90, 7.97, 8.14, 8.96, and 9.23 (each 3H, s) (Found: C, 70.9; H, 8.85; N, 2.9. $C_{27}H_{39}NO_5$ requires C, 70.9; H, 8.6; N, 3.1%).

3β,17α-*Diacetoxypregn*-5-*en*-20-*one* (III; X = O).—The acetylimine (III; X = NAc) (100 mg) in acetic acid (30 ml) and water (1.6 ml) was heated on a steam-bath for 3 h. Work-up in the normal manner then afforded 3β,17α-diacetoxypregn-5-en-20-one (85 mg, 93%), m.p. (from methanol) 174—176°, mixed m.p. with an authentic sample 175—176°, $[\alpha]_D$ –66° (lit.,[8] m.p. 170—173°, $[\alpha]_D$ –63°), identical (i.r., n.m.r., and t.l.c.) with an authentic sample.

3β,17α-*Diacetoxy*-20-*acetylaminopregna*-5,20-*diene* (IV).—The acetylimine (III; X = NAc) (100 mg) in dry acetic acid (30 ml) containing trichloroacetic acid (100 mg) was left at room temperature overnight. Work-up in the normal manner then gave the *enamide* (94 mg, 94%), m.p. (from hexane) 154—156°, $[\alpha]_D$ –130°, $\nu_{max.}$ 3380, 1735, 1715, 1690, 1500, 1250, and 1235 cm$^{-1}$, $\tau$ 3.4br (1H, s, NH), 4.2br (1H, s, 21-H), 4.6 (1H, d, *J* 5 Hz, 6-H), 4.95 (1H, s, 21-H), 7.95 (6H, s), and 7.97, 8.95, and 9.28 (each 3H, s) (Found: C, 70.7; H, 8.6; N, 3.0. $C_{27}H_{39}NO_5$ requires C, 70.9; H, 8.6; N, 3.1%). When this rearrangement was repeated with the addition of 5% of acetic anhydride to the acetic acid, the above product was obtained together with 3β,17α-*diacetoxy*-20-*diacetylaminopregna*-5,20-diene (29%), m.p. (from hexane) 144—146°, $[\alpha]_D$ –39°, $\nu_{max.}$ 1730, 1700, 1675, and 1235 cm$^{-1}$ (Found: C, 69.8; H, 8.3; N, 2.9. $C_{29}H_{41}NO_6$ requires C, 69.7; H, 8.3; N, 2.8%), converted by chromatography into the enamide (IV).

3β,17α,21-*Triacetoxy*-20-*acetyliminopregn*-5-*ene* (V; X = NAc).—The enamide (IV) (200 mg) in dry benzene (60 ml) was dried by distillation of benzene (10 ml). Dry lead tetra-acetate (230 mg) was added and the mixture was heated at 50 °C for 40 h. Water (30 ml) was added and the mixture worked up as before. After preparative layer chromatography the *acetylimine* (190 mg, 84%) was obtained, m.p. (from benzene–hexane) 178—179°, $[\alpha]_D$ –50°,

[8] R. B. Moffett and H. V. Anderson, *J. Amer. Chem. Soc.*, 1954, **76**, 747.

$\nu_{max.}$ 1765, 1725, 1695, 1255, and 1225 $cm^{-1}$, $\tau$ 4.6 (1H, d, $J$ 5 Hz, 6-H), 5.2 (2H, ABq, 21-$H_2$), 5.4 (1H, m 3β-H), and 7.80, 7.90, 7.93, 7.95, 8.95, and 9.20 (each 3H, s) (Found: C, 67.45; H, 7.9; N, 2.7. $C_{29}H_{41}NO_7$ requires C, 67.55; H, 8.0; N, 2.7%).

3β,17α,21-*Triacetoxypregn-5-en-20-one* (V; X = O).—The acetylimine (V; X = NAc) (90 mg) in acetic acid (30 ml) and water (1.6 ml) was heated on a steam-bath for 3 h. Work-up in the normal manner then gave the triacetate (80 mg, 97%), m.p. (from hexane) 204—206°, mixed m.p. with an authentic sample 205—207°, $[\alpha]_D$ −57° (lit.,[9] m.p. 209—211°, $[\alpha]_D$ −51°), identical (i.r., n.m.r., and t.l.c.) with an authentic sample. An analogous series of experiments starting from 3β-acetoxy-5α-pregnan-20-one oxime[6] afforded the following new compounds: 3β-*acetoxy*-20-*diacetylamino*-5α-*pregn*-17(20)-*ene*, m.p. (from hexane) 191—192.5°, $[\alpha]_D$ −6° (Found: C, 72.9; H, 9.2; N, 3.2. $C_{27}H_{41}NO_4$ requires C, 73.1; H, 9.3; N, 3.2%); 3β-*acetoxy*-20-*acetylamino*-5α-*pregn*-17(20)-*ene*, m.p. (from methanol) 188—189°, $[\alpha]_D$ +31° (Found: C, 74.7; H, 9.7; N, 3.7. $C_{25}H_{39}NO_3$ requires C, 74.8; H, 9.8; N, 3.5%); 3β,17α-*Diacetoxy*-20-*acetylimino*-5α-*pregnane*, m.p. (from hexane) 162—163°, $[\alpha]_D$ −33° (Found: C, 70.6; H, 8.8; N, 3.0. $C_{27}H_{41}NO_5$ requires C, 70.55; H, 9.0; N, 3.05%); 3β,17α-*diacetoxy*-20-*acetylamino*-5α-*pregn*-20-*ene*, m.p. (from hexane) 175—177°, $[\alpha]_D$ −54° (Found: C, 70.4; H, 9.0; N, 2.9. $C_{27}H_{41}NO_5$ requires C, 70.55; H, 9.0; N, 3.05%).

3β-*Acetoxy*-16α-*methyl*-5α-*pregnan*-20-*one Oxime* (VIa).—3β-Acetoxy-16α-methyl-5α-pregnan-20-one (1 g) and hydroxylamine hydrochloride (500 mg) in pyridine (30 ml) were heated on a steam-bath for 5 h. The solution was poured into ice–water, then filtered, to yield the *oxime* (990 mg), needles (from methanol), m.p. 153—155°, $[\alpha]_D$ −17° (Found: C, 73.9; H, 9.9; N, 3.4. $C_{24}H_{39}NO_3$ requires C, 74.0; H, 10.1; N, 3.5%). Treatment with acetic anhydride and pyridine at room temperature overnight afforded the *oxime acetate*, m.p. (from hexane) 132—124°, $[\alpha]_D$ −3°, $\nu_{max.}$ 1770, 1725, 1240, and 1200 $cm^{-1}$, $\tau$ 5.3 (1H, m, 3α-H), 7.82, 7.99, 8.06, 9.17, and 9.30 (each 3H, s), and 8.99 (3H, d, $J$ 7 Hz, 16α-$CH_3$) (Found: C, 72.2; H, 9.6; N, 3.15. $C_{26}H_{41}NO_4$ requires C, 72.35; H, 9.6; N, 3.25%).

3β-*Acetoxy*-20-*acetylamino*-16α-*methyl*-5α-*pregn*-17(20)-*ene* (VIIa; R = H).—3β-Acetoxy-16α-methyl-5α-pregnan-20-one oxime (500 mg) in dry pyridine (25 ml) and acetic anhydride (20 ml) was refluxed for 52 h. Work-up as for similar experiments above, including chromatography on alumina, then afforded the *enamide* (295 mg, 55%), m.p. (from methanol) 197—199°, $[\alpha]_D$ +78°, $\nu_{max.}$ 3220, 1730, 1640, and 1240 $cm^{-1}$ (Found: C, 74.9; H, 9.8; N, 3.05. $C_{26}H_{41}NO_3$ requires C, 75.1; H, 9.9; N, 3.4%).

3β-*Acetoxy*-16β-*methyl*-5α-*pregnan*-20-*one Oxime* (VIb).—3β-Acetoxy-16β-methyl-5α-pregnan-20-one (5.5 g) in the minimum amount of boiling methanol necessary for dissolution was treated with a hot filtered solution prepared from hydroxylamine hydrochloride (2.5 g) and anhydrous sodium acetate (3 g) in methanol. The solution was refluxed for 4 h, then worked up to afford the *oxime* (5.7 g), m.p. 162—164°, $[\alpha]_D$ +40°, $\tau$ 5.3 (1H, m, 3α-H), 7.98, 8.11, 9.03, and 9.16 (each 3H, s), and 8.97 (3H, d, $J$ 7 Hz, 16β-$CH_3$) (Found: C, 73.8; H, 9.9; N, 3.6. $C_{24}H_{39}NO_3$ requires C, 74.0; H, 10.1; N, 3.6%). Treatment with pyridine and acetic anhydride at room temperature gave the *oxime acetate*, m.p. (from methanol) 153—154°, $[\alpha]_D$ +56°, $\nu_{max.}$ 1750, 1730, 1260, 1250, and 1230 $cm^{-1}$, $\tau$ 5.3 (1H, m, 3α-H), 7.80, 7.98, 8.05, 8.96, and 9.15 (each 3H, s) and 8.96 (3H, d, $J$ 7 Hz, 16β-$CH_3$) (Found C, 73.0; H, 9.3; N, 3.1. $C_{26}H_{41}NO_4$ requires C, 73.35; H, 9.6; N, 3.25%).

3β-*Acetoxy*-20-*diacetylamino*-16β-*methyl*-5α-*pregn*-17(20)-*ene* (VIIb; R = Ac).—3β-Acetoxy-16β-methyl-5α-pregnan-20-one oxime (500 mg) in dry pyridine (25 ml) and acetic anhydride (20 ml) was refluxed under nitrogen for 50 h. Work-up as above with chromatography on silica then gave the *enimide* (459 mg, 78%), m.p. (from hexane) 165—167°, $[\alpha]_D$ −78°, $\nu_{max.}$ 1735, 1705, 1260, and 1240 $cm^{-1}$, $\tau$ 5.3 (1H, m, 3α-H), 7.68, 7.74, 7.98, 8.08br, 9.02, and 9.16 (each 3H, s), and 9.03 (3H, d, $J$ 7 Hz, 16β-$CH_3$) (Found: C, 73.3; H, 9.4; N, 2.6. $C_{28}H_{43}NO_4$ requires C, 73.5; H, 9.5; N, 3.1%). Chromatography of the enimide on alumina [benzene–ether (60 : 40 v/v)] gave 3β-*acetoxy*-20-*acetylamino*-16β-*methyl*-5α-*pregn*-17(20)-*ene* (VIIb; R = H) (94%), m.p. 206—208°, $[\alpha]_D$ −49°, $\nu_{max.}$ 3280, 1730, 1650, and 1240 $cm^{-1}$ (Found: C, 75.0; H, 9.8; N, 3.2. $C_{26}H_{41}NO_3$ requires C, 75.1; H, 9.9; N, 3.4%).

3β,17α-*Diacetoxy*-20-*acetylimino*-16β-*methyl*-5α-*pregnane* (VIII).— 3β-Acetoxy-20-acetylamino-16β-methyl-5α-pregn-17(20)-ene (200 mg) in dry benzene (50 ml) was treated with lead tetra-acetate (225 mg) as described above to yield the *acetylimine* (138 mg, 61%), m.p. (from hexane) 156—157°, $[\alpha]_D$ −19°, $\nu_{max.}$ 1730, 1680, 1255, 1240, and 1220 $cm^{-1}$, $\tau$ 5.3 (1H, m, 3α-H), and 7.87, 7.89, 7.98, and 8.20 (each 3H, s) (Found: C, 70.8; H, 9.1; N, 2.8. $C_{28}H_{43}NO_5$ requires C, 71.0; H, 9.15; N, 3.0%). The acetylimine in dry benzene was treated with a saturated solution of hydrogen chloride gas in chloroform. After 3 days at room temperature the solvent was evaporated off, and the residue chromatographed on silica gel. Elution with benzene afforded 3β-acetoxy-16-methyl-5α-pregn-16-en-20-one (IX) (201 mg, 56%), m.p. (from hexane) 168—170°, $[\alpha]_D$ −21° (lit.,[7] m.p. 167—169°, $[\alpha]_D$ −23°), $\nu_{max.}$ 1730, 1650, 1245, and 1235 $cm^{-1}$, $\tau$ 5.3 (1H, m, 3α-H), 7.73 (3H, s), 7.98 (6H, s), and 9.04 and 9.13 (each 3H, s).

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