Steroids and Related Studies. Part 41.[1] Schmidt Reaction with 3β-Acetoxypregn-5-ene-7,20-dione

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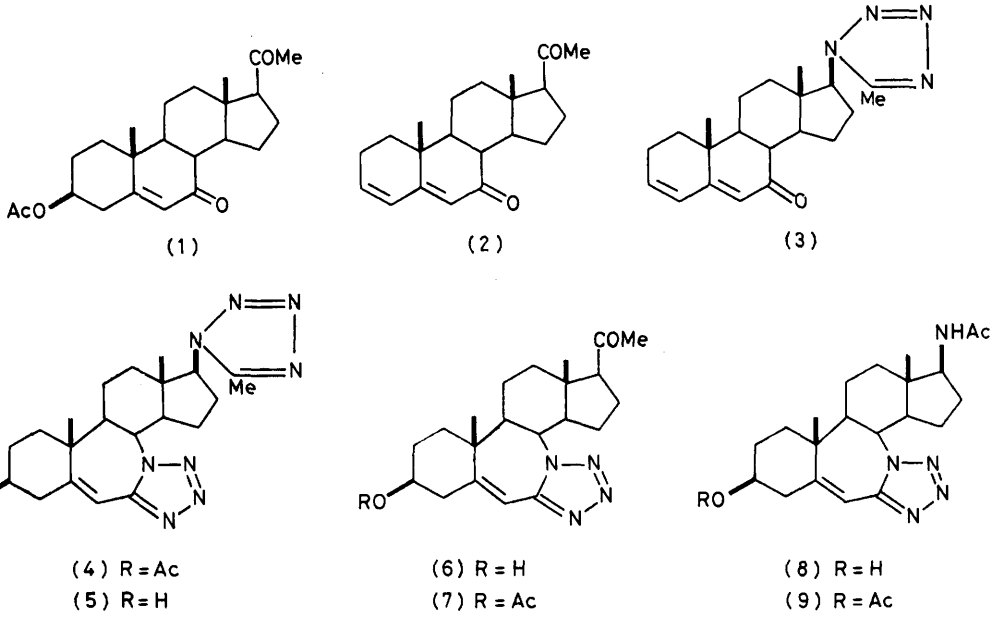
Treatment of 3β-acetoxypregn-5-ene-7,20-dione (1) with hydrazoic acid–boron trifluoride in chloroform gives a complex mixture. The major product is 17β-(5-methyltetrazol-1-yl)-7a-aza-B-homoandrost-5-eno[7a,7-*d*]-tetrazol-3β-ol (5), followed by 17β-acetamido-7a-aza-B-homoandrost-5-eno[7a,7-*d*]tetrazol-3β-ol (8). Other products are 3β-hydroxy-7a-aza-B-homopregn-5-eno-[7a,7-*d*]tetrazol-20-one (6), pregna-3,5-diene-7,20-dione (2), and 17β-(5-methyltetrazol-1-yl)androsta-3,5-dien-7-one (3).

It has been shown that under the conditions of the Schmidt reaction a 20-oxo-group is more reactive than a 4-en-3-one function; treatment of progesterone with an equimolar quantity of sodium azide in polyphosphoric acid gave 17β-acetamidoandrost-4-en-3-one, whereas use of an excess of sodium azide gave 17β-acetamido-3-aza-A-homoandrost-4a-en-4-one.[2] When the reaction was carried out with progesterone and an excess of hydrazoic acid in the presence of boron trifluoride, a mixture was obtained from which the products isolated were 17β-acetamido-3-aza-A-homoandrost-4a-eno[3,4-*d*]tetrazole and 17β-(5-methyltetrazol-1-yl)-3-aza-A-homoandrost-4a-eno[3,4-*d*]tetrazole.[3] It appeared of interest to examine the fate of 3β-acetoxypregn-5-ene-7,20-dione (1),[4] which contains an αβ-unsaturated ketone function in a sterically hindered environment; further complications might have been anticipated because of the 3β-acetoxy-function.

Treatment of compound (1) with an excess of hydrazoic acid in the presence of boron trifluoride in chloroform gave chloroform-soluble and chloroform-insoluble products. T.l.c. indicated both to be complex mixtures, the former showing nine spots and the latter only four of the same spots.

Chromatography of the chloroform-soluble product, a crystalline solid, on an alumina column yielded pure fractions (A), $C_{21}H_{28}O_2$, m.p. 146—148° (1.7%); (B), $C_{21}H_{28}N_4O$, m.p. 265—267° (0.76%); (C), $C_{23}H_{32}N_8O_2$, m.p. 298—299° (1.4%); (D), $C_{21}H_{30}N_4O_2$, m.p. 283—285° (2.4%); (E), $C_{21}H_{30}N_8O$, m.p. 328—330° (3.9%); and (F), $C_{21}H_{31}N_5O_2$, m.p. 298—300° (1.4%).



Fraction (A), $\lambda_{max.}$ 275 nm, δ 5.65 (1 H, s) and 6.17 (2 H, s) (vinylic), was identified as pregna-3,5-diene-7,20-dione (2).[4] Fraction (B) (3) also had the 3,5-dien-7-one function, but the 17-acetyl function had reacted to form 17β-(5-methyltetrazol-1-yl) system [δ 2.55 (Me)].[3] The elemental analytical data for this fraction, however, were not very satisfactory.

Fraction (C), a bistetrazole, $\lambda_{max.}$ 235 nm is assigned structure (4) on the basis of its n.m.r. signals, δ 2.60 (3 H, s), 4.2—4.9 (3 H, m), and 6.64 (1 H, s), assignable to the methyl group of a 17β-(5-methyltetrazol-1-yl) system, the 3α-, 8β-, and 17α-protons, and the vinylic 6-proton, respectively, in the light of our earlier discussions.[3] Fraction (E) was identified as the corresponding 3β-ol (5), which gave (4) on acetylation.

The i.r. spectrum of fraction (D) (6) showed bands due

[1] Part 40, H. Singh, D. Paul, T. R. Bhardwaj, K. K. Bhutani, and J. Ram, *J. Chromatog.*, 1977, **137**, 202.
[2] N. J. Doorenbos and H. Singh, *J. Pharm. Sci.*, 1962, **51**, 418.
[3] H. Singh, R. K. Malhotra, and N. K. Luhadiya, *J.C.S. Perkin I*, 1974, 1480.
[4] C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Amer. Chem. Soc.*, 1957, **79**, 6308.

to OH (3 275 cm^{-1}) and C(20)=O (1 709 cm^{-1}). It was too insoluble in chloroform for an n.m.r. study. The acetyl derivative (7) showed a singlet at δ 2.16 for the 21-methyl group. Thus the 20-oxo-function is intact and the 5-en-7-one group has reacted, contrary to expectation on the basis of the earlier studies.[3]

Fraction (F) was assigned structure (8); it showed carbonyl absorption at 1 669 cm^{-1} and the acetyl derivative (9) exhibited n.m.r. singlets at δ 2.01 and 2.04. Compound (8) was also synthesised from 17β-acetamido-3β-acetoxyandrost-5-en-7-one, prepared in turn by oxidation of 17β-acetamido-3β-acetoxyandrost-5-ene.[5]

The chloroform-insoluble product, a sticky mass, was crystallised from methanol to yield the bistetrazole (5) (19.5%). The residue from the supernatant liquid on preparative t.l.c. gave the amide (8) (3.3%).

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. U.v. and i.r. spectra were obtained for solutions in methanol and for potassium bromide discs, respectively. N.m.r. spectra (60 MHz) were recorded for solutions in deuteriochloroform containing tetramethylsilane as internal reference. T.l.c. was carried out on silica gel G (Merck) and plates were developed by exposure to iodine vapour and cerium(IV) sulphate solution (2 g in 100 ml of 10% v/v sulphuric acid), followed by heating at 150 °C. Anhydrous sodium sulphate was employed as drying agent.

Schmidt Reaction with 3β-*Acetoxypregn*-5-*ene*-7,20-*dione* (1).—Freshly distilled boron trifluoride–ether complex (1.75 ml) was added to a freshly prepared solution of hydrazoic acid (6—8%) in chloroform (105 ml) kept at 0 °C. A solution of the acetate (1) (3.5 g) in dry chloroform (60 ml) was added in small portions during 4 h to the above mixture maintained at 0 °C. The mixture was then left at room temperature (25—30 °C) for 20 h. A sticky mass separated. The supernatant chloroform layer was separated, washed repeatedly with water, dried, and evaporated to leave a residue (1.7 g).

T.l.c. of the chloroform-soluble portion revealed nine spots. The mixture was chromatographed on a column of alumina (100 g) in benzene. Elution with benzene yielded fraction (A). Crystallisation from acetone gave pregna-3,5-diene-7,20-dione (2) (0.05 g, 1.7%), m.p. 146—148°, $[\alpha]_D^{30}$ −219° (*c* 0.20), $\lambda_{max.}$ 275 nm (log ε 4.35), $\nu_{max.}$ 2 900, 1 710, 1 667, 1 630, and 1 598 cm^{-1}, δ 0.71 (3 H, s), 1.14 (3 H, s), 2.15 (3 H, s), 5.65 (1 H, s), and 6.17 (2 H, s) (Found: C, 80.9; H, 9.1. Calc. for $C_{21}H_{28}O_2$: C, 80.5; H, 9.05%).

Further elution with chloroform afforded fraction (B) which crystallised from acetone to afford 17β-(5-methyltetrazol-1-yl)androsta-3,5-dien-7-one (3) (0.025 g, 0.76%), m.p. 265—267°, $\lambda_{max.}$ 275 nm (log ε 4.22), $\nu_{max.}$ 2 900, 1 667, 1 630, 1 600, 1 515, 1 449, 1 428, 1 395, and 1 380 cm^{-1}, δ 0.82 (3 H, s), 1.15 (3 H, s), 2.55 (3 H, s), 5.64 (1 H, s), and 6.15 (2 H, s) (Found: C, 70.85; H, 8.15; N, 13.9. Calc. for $C_{21}H_{28}N_4O$: C, 71.55; H, 8.0; N, 15.9%).

Elution was continued with solvents of increasing polarity. Fraction (C), obtained with chloroform–methanol (99 : 1), crystallised from methanol to give 17β-(5-*methyltetrazol*-1-*yl*)-7a-*aza*-B-*homoandrost*-5-*eno*[7a,7-d]*tetrazol*-3β-*yl acetate* (4) (0.06 g, 1.4%), m.p. 298—299°, $[\alpha]_D^{30}$ −167.9° (*c* 0.33), $\lambda_{max.}$ 235 nm (log ε 4.29), $\nu_{max.}$ 2 941, 1 740, 1 678, 1 524, 1 445, 1 386, 1 368, and 1 248 cm^{-1}, δ 0.93 (3 H, s), 1.35 (3 H, s), 2.06 (3 H, s), 2.60 (3 H, s), 4.2—4.9 (3 H, m), and 6.64 (1 H, s) (Found: C, 61.3; H, 7.15; N, 24.9. $C_{23}H_{32}N_8O_2$ requires C, 61.0; H, 7.15; N, 24.8%).

Further elution with the same solvent afforded fraction (D). Crystallisation from methanol gave 3β-*hydroxy*-7a-*aza*-B-*homopregn*-5-*eno*[7a,7-d]*tetrazol*-20-*one* (6) (0.085 g, 2.4%), m.p. 283—285°, $\nu_{max.}$ 3 275, 2 915, 1 709, 1 675, 1 515, 1 449, 1 361, and 1 085 cm^{-1} (Found: C, 68.05; H, 8.2; N, 14.95. $C_{21}H_{30}N_4O_2$ requires C, 68.1; H, 8.15; N, 15.1%).

A mixture of the tetrazole (6) (0.05 g), pyridine (0.2 ml), and acetic anhydride (0.1 ml) was heated on a steam-bath for 90 min. The mixture was cooled, poured into ice-cold water, and then processed in the usual way to obtain a residue which on crystallisation from methanol gave 3β-*acetoxy*-7a-*aza*-B-*homopregn*-5-*eno*[7a,7-d]*tetrazol*-20-*one* (7) (0.04 g, 71.9%), m.p. 185—187°, $[\alpha]_D^{30}$ −104° (*c* 0.25), $\lambda_{max.}$ 235 nm (log ε 4.49), $\nu_{max.}$ 2 941, 1 739, 1 710, 1 678, 1 510, 1 475, 1 445, 1 370, and 1 242 cm^{-1}, δ 0.82 (3 H, s), 1.30 (3 H, s), 2.05 (3 H, s), 2.16 (3 H, s), 4.27 (1 H, m), 4.76 (1 H, m), and 6.62 (1 H, s) (Found: C, 67.05; H, 7.85; N, 13.5. $C_{23}H_{32}N_4O_3$ requires C, 66.95; H, 7.8; N, 13.6%).

Elution with chloroform–methanol (98.5 : 1.5) gave fraction (E). Crystallisation from chloroform–methanol yielded 17β-(5-*methyltetrazol*-1-*yl*)-7a-*aza*-B-*homoandrost*-5-*eno*[7a,7-d]*tetrazol*-3β-*ol* (5) (0.15 g, 3.9%), m.p. 328—330°, $\nu_{max.}$ 3 300, 2 900, 1669, 1 524, 1 513, 1 447, 1 389, 1 351, and 1 075 cm^{-1} (Found: C, 61.9; H, 7.4; N, 27.05. $C_{21}H_{30}N_8O$ requires C, 61.45; H, 7.35; N, 27.3%).

A mixture of the bistetrazole (5) (0.15 g), pyridine (0.25 ml), and acetic anhydride (0.2 ml) was heated on a steam-bath for 90 min and then poured into ice-cold water. The residue obtained from the usual work-up was crystallised from methanol to yield the acetate (4) (0.125 g, 75.6%), m.p. 298—300°.

Elution from the column was continued; fraction (F), obtained with chloroform–methanol (49 : 1) was crystallised from methanol to give 17β-*acetamido*-7a-*aza*-B-*homoandrost*-5-*eno*[7a,7-d]*tetrazol*-3β-*ol* (8) (0.05 g, 1.4%), m.p. 298—300°, $\nu_{max.}$ 3 247, 2 915, 1 669, 1 645, 1 553, 1 513, 1 449, 1 385, 1 351, and 1 056 cm^{-1} (Found: C, 65.0; H, 7.95; N, 18.55. $C_{21}H_{31}N_5O_2$ requires C, 65.4; H, 8.1; N, 18.15%).

A mixture of compound (8) (0.1 g), pyridine (0.2 ml), and acetic anhydride (0.1 ml) was heated on a steam-bath for 90 min. The mixture was cooled and poured into ice-cold water, and then processed in the usual way. The residue crystallised from methanol to give 17β-*acetamido*-7a-*aza*-B-*homoandrost*-5-*eno*[7a,7-d]*tetrazol*-3β-*yl acetate* (9) (0.085 g, 76.7%), m.p. 270—271°, $[\alpha]_D^{30}$ −200° (*c* 0.42), $\lambda_{max.}$ 235 nm (log ε 4.11), $\nu_{max.}$ 3 280, 2 915, 1 735, 1 667, 1 550, 1 445, 1 370, and 1 250 cm^{-1}, δ 0.87 (3 H, s), 1.25 (3 H, s), 2.01 (3 H, s), 2.04 (3 H, s), 4.24—4.82 (3 H, m), 5.61 (1 H, m), and 6.62br (1 H, s) (Found: C, 64.75; H, 7.8; N, 16.35. $C_{23}H_{33}N_5O_3$ requires C, 64.6; H, 7.8; N, 16.4%).

The chloroform-insoluble sticky material obtained after the separation of chloroform layer was crystallised from methanol to yield the bistetrazole (5) (0.75 g, 19.5%), m.p. 328—330°.

T.l.c. of the mother liquor indicated three spots. Preparative t.l.c. on silica gel G (Merck) in chloroform–methanol (8 : 2) afforded compound (8) (0.12 g, 3.3%), m.p. 298—300°.

[5] P. de Ruggieri, C. Ferrai, and C. Gandolfi, *Gazzetta*, 1961, **91**, 655.

No other product was obtained from the mother liquor by crystallisation or by preparative t.l.c.

17β-*Acetamido*-3β-*acetoxyandrost*-5-*en*-7-*one*.— 17β-Acetamido-3β-acetoxyandrost-5-ene (2 g) was dissolved in dry carbon tetrachloride (13 ml), acetic anhydride (2.5 ml), and glacial acetic acid (6 ml). To this was added t-butyl chromate reagent (16 ml) dropwise with stirring. The mixture was refluxed for 12 h, cooled in an ice-bath, and treated carefully with oxalic acid (10%; 40 ml). After 15 min solid oxalic acid (2.5 g) was added; the mixture was stirred vigorously for 2 h, then extracted with carbon tetrachloride (4 × 25 ml), and the extract was worked up as usual. The residue was crystallised from methanol to give 17β-*acetamido*-3β-*acetoxyandrost*-5-*en*-7-*one* (0.45 g, 21.7%), m.p. 231—233°, $[\alpha]_D^{30}$ −217.8° (*c* 1.01), $\lambda_{max.}$ 235 nm (log ε 4.08), $\nu_{max.}$ 3 356, 3 279, 2 941, 1 745, 1 724, 1 675, 1 520, 1 465, 1 380, and 1 250 cm^{-1}, δ 0.71 (3 H, s), 1.22 (3 H, s), 1.98 (3 H, s), 2.04 (3 H, s), 3.92 (1 H, m), 4.73 (1 H, m), 5.72 (1 H, s), and 5.80 (1 H, m) (Found: C, 70.5; H, 8.7; N, 3.55. $C_{23}H_{33}NO_4$ requires C, 71.3; H, 8.6; N, 3.6%).

Schmidt Reaction with 17β-*Acetamido*-3β-*acetoxyandrost*-5-*en*-7-*one*.—A solution of the androstenone (1 g) in dry chloroform (15 ml) was added during 4 h to a mixture of boron trifluoride–ether complex (0.25 ml) and freshly prepared hydrazoic acid in chloroform (15 ml) at 0 °C. The mixture was kept at room temperature (25—30 °C) for 20 h. The chloroform layer was washed repeatedly with water and worked up as usual to leave a residue (0.1 g). No product was obtained from this portion.

The remaining chloroform-insoluble sticky material (1.4 g) was chromatographed on a column of alumina in chloroform–methanol (4 : 1). Elution with the same solvent afforded a residue, which was crystallised from methanol to give compound (8) (0.5 g, 50.25%), m.p. 298—300°.

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