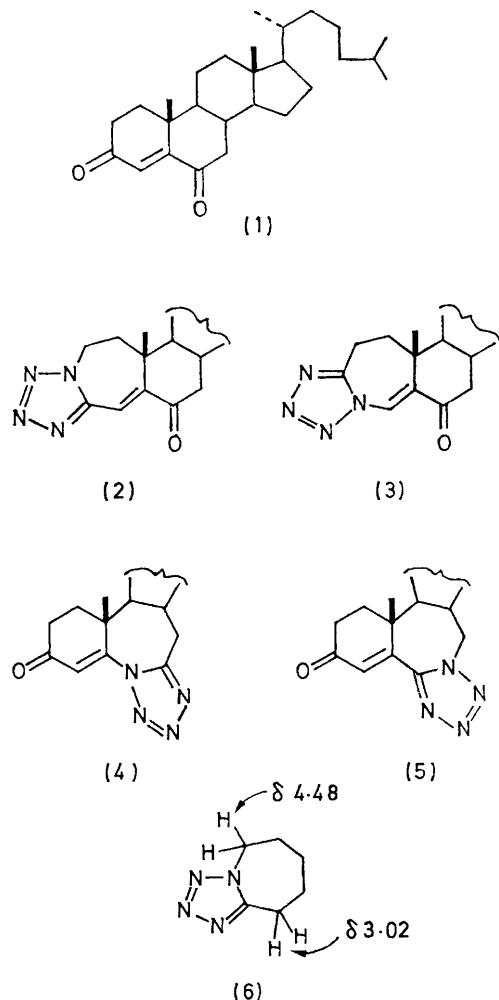


Steroids and Related Studies. Part XXXV.¹ Further Studies on the Schmidt Reaction with Cholest-4-ene-3,6-dione

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Treatment of cholest-4-ene-3,6-dione (1) with an excess of hydrazoic acid–boron trifluoride in chloroform yields 3-aza-A-homocholest-4a-eno[3,4-*d*]tetrazol-6-one (2), 3,6-diaza-AB-bishomocholest-4a-eno[3,4-*d*][6,7-*d*]bis-tetrazole (7), and 3-aza-A-homocholest-4a-ene-4,6-dione (11). The bistetrazole (7) was obtainable from the monotetrazole (2).

TREATMENT of cholest-4-ene-3,6-dione (1) with an equimolar quantity of sodium azide in polyphosphoric



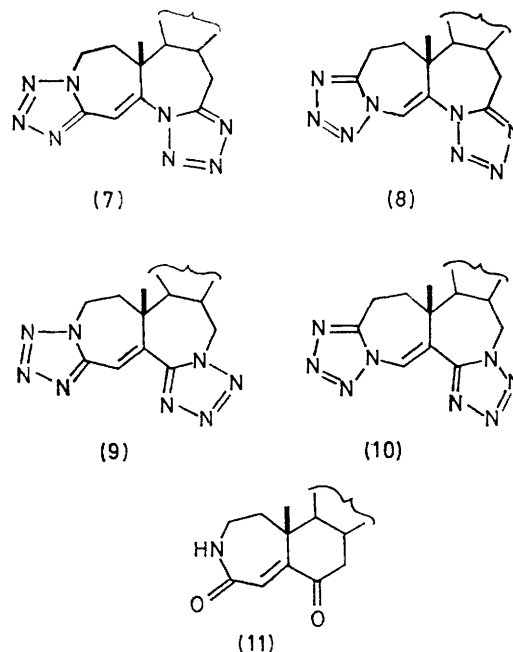
acid has been reported to yield the lactams 4-aza-A-homocholest-4a-ene-3,6-dione and 3-aza-A-homocholest-4a-ene-4,6-dione; 4,6-diaza-AB-bishomocholest-4a-ene-3,7-dione was obtained by use of 2 mol. equiv. of sodium azide.² This paper describes the products isolated when the Schmidt reaction of the enedione (1) was carried out with an excess of hydrazoic acid.

¹ Part XXXIV, H. Singh, R. K. Malhotra, A. S. Chawla, and N. K. Luhadiya, *Indian J. Chem.*, in the press.

² H. Singh, S. Padmanabhan, A. K. Bose, and I. Kugajevsky, *J.C.S. Perkin I*, 1972, 993.

Reaction with an excess of hydrazoic acid in the presence of boron trifluoride in chloroform gave a complex mixture, separated by column chromatography on alumina into products (A), C₂₇H₄₂N₄O (33.4%), (B), C₂₇H₄₂N₈ (5%), and (C), C₂₇H₄₃NO₂ (5.6%).

For the product (A), evidently a monotetrazole, λ_{\max} 260 nm, ν_{\max} 1 695 (C=O) and 1 626 cm⁻¹ (C=C), structures (2)–(5) were considered. The methylene functions in the tetrazole (6)³ are reported to exhibit the n.m.r. multiplets as indicated. The spectrum of product (A) exhibited a broad two-proton multiplet at δ 4.65, which in the light of our previous studies^{4,5} favours structures (2) and (5). During our earlier work,⁵ it was noted that in steroidal 3-aza-A-homo-4a-eno[3,4-*d*]tetrazoles the vinylic 4a-proton signal at δ 6.50 was characteristically *ca.* 0.75 p.p.m. downfield of the signal of a vinylic 4-proton (δ 5.75) in 4-en-3-ones. The product (A) showed a vinylic proton signal at δ 7.20,



downfield by 1.03 p.p.m. from the signal at δ 6.17 in the spectrum of compound (1). This supports the

³ G. DiMaio and V. Permutti, *Tetrahedron*, 1966, **22**, 2059.

⁴ H. Singh, R. B. Mathur, and P. P. Sharma, *J.C.S. Perkin I*, 1972, 990.

⁵ H. Singh, R. K. Malhotra, and N. K. Luhadiya, *J.C.S. Perkin I*, 1974, 1480.

assignment of structure (2). Structure (5) may also be excluded in view of the greater reactivity of the 3-carbonyl group.^{6,7}

For the product (B), apparently a bistetrazole, λ_{\max} 246 nm, ν_{\max} 1 681 cm^{-1} (C=C), structures (7)–(10) were considered. Two-proton n.m.r. multiplets at δ 4.85 and 3.43 could be assigned to the methylene groups in (7) or (10), excluding structures (8) and (9). Treatment of the monotetrazole (2) with hydrazoic acid–boron trifluoride in chloroform gave a mixture from which the bistetrazole (7) was obtained in 10% yield. However, when this reaction was carried out in benzene solution,⁸ the bistetrazole (7) was isolated in 73% yield. The product (B) therefore has structure (7).

The monolactam (C) was assigned structure (11)² on the basis of spectral comparison. However, the m.p. was higher than that reported.²

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. I.r. spectra were obtained for potassium bromide discs. 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); plates were developed by exposure to iodine vapour. Anhydrous sodium sulphate was employed as drying agent.

Schmidt Reaction with Cholest-4-ene-3,6-dione (1).—A solution of compound (1) (5.0 g) in dry chloroform (200 ml) was added to a mixture of boron trifluoride–ether complex (5 ml) and hydrazoic acid solution in chloroform (300 ml)⁴ during 4 h at 0 °C. The mixture was kept at 23–25 °C for 20 h, then washed successively with aqueous sodium hydrogen carbonate (10%) and water. The chloroform layer was dried and evaporated, and the brown residue (4.32 g), which gave five spots on t.l.c. (chloroform–methanol, 32:1) was chromatographed on a column of alumina (250 g) in dry benzene. Elution with benzene–chloroform (9:1; 23 × 100 ml) yielded a solid residue (2.04 g), which afforded 3-aza-A-homocholest-4a-eno[3,4-d]tetrazol-6-one (2) (1.5 g, 33.4%), m.p. 220–222° (from methanol), $[\alpha]_{\text{D}}^{25}$ –42.5° (*c* 0.30), λ_{\max} (MeOH) 260 nm (log ϵ 4.16), ν_{\max} 2 941, 1 695, 1 626, 1 527, 1 460, 1 418, and 1 389 cm^{-1} , δ 0.75 (3 H, s), 1.15 (3 H, s), 4.65 (2 H, m), and 7.20 (1 H, s) (Found: C, 73.85; H, 9.55; N, 12.4. $\text{C}_{27}\text{H}_{42}\text{N}_4\text{O}$ requires C, 73.9; H, 9.65; N, 12.75%).

Further elution with the same solvent (13 × 100 ml) yielded a solid residue (0.3 g), which afforded 3,6-diaza-AB-

bishomocholest-4a-eno[3,4-d][6,7-d]bistetrazole (6) (0.25 g, 5%), m.p. 206–210° (from ethanol), $[\alpha]_{\text{D}}^{25}$ –11.9° (*c* 0.37), λ_{\max} (EtOH) 246 nm (log ϵ 4.29), ν_{\max} 2 933, 1 681, 1 538, 1 471, 1 435, and 1 377 cm^{-1} , δ 0.74 (3 H, s), 0.92 (3 H, s), 3.43 (2 H, m), 4.85 (2 H, m), and 7.10 (1 H, s) (Found: C, 68.05; H, 8.95; N, 23.2. $\text{C}_{27}\text{H}_{42}\text{N}_8$ requires C, 67.75; H, 8.85; N, 23.4%).

Elution with solvents of increasing polarity was carried out; fractions (8 × 100 ml) obtained with benzene–chloroform (1:1) yielded a solid (0.31 g), which afforded 3-aza-A-homocholest-4a-ene-4,6-dione (11) (0.27 g, 5.6%), m.p. 213–215° (from methanol) (lit.,² 200–204°), $[\alpha]_{\text{D}}^{25}$ –124° (*c* 0.15), λ_{\max} (MeOH) 234 nm (log ϵ 4.20), ν_{\max} 3 125, 2 933, 1 695, 1 667, 1 639, and 1 608 cm^{-1} , δ 0.71 (3 H, s), 1.04 (3 H, s), 3.25 (2 H, m), 5.98 (1 H, d, *J* 1.5 Hz, collapsing to s on deuterium exchange), and 7.34 (1 H, m, disappearing on deuterium exchange) (Found: C, 77.9; H, 10.7; N, 3.45. Calc. for $\text{C}_{27}\text{H}_{43}\text{NO}_2$: C, 78.4; H, 10.5; N, 3.4%).

3,6-Diaza-AB-bishomocholest-4a-eno[3,4-d][6,7-d]bistetrazole (6) from the Monotetrazole (2).—(a) A solution of compound (2) (1.0 g) in dry chloroform (20 ml) was added to a mixture of boron trifluoride–ether complex (1 ml) and hydrazoic acid solution in chloroform (30 ml)⁴ during 4 h at 0 °C. The mixture was kept at 25–28 °C for 24 h, then washed successively with aqueous sodium hydrogen carbonate (10%) and water. The chloroform layer was dried and evaporated; the residue (0.65 g), which showed six spots on t.l.c. (chloroform–methanol, 3:1), was partially separated on a column of alumina (22 g) in benzene to give a two-component mixture (0.3 g). Further chromatography of this on an alumina column (25 g) in benzene [elution with benzene (8 × 100 ml)] gave a solid which on crystallisation from methanol afforded the product (6) (0.1 g, 10%), m.p. 209–210°.

(b) Compound (2) (0.1 g) in benzene (5 ml) was added to a mixture of boron trifluoride–ether complex (1 ml) and hydrazoic acid solution in benzene (15 ml).⁸ The mixture was heated at 40 ± 5 °C for 15 h. Crushed ice was added and the mixture was washed successively with aqueous sodium hydroxide (5%) and water. The benzene layer was dried and evaporated; the residue (0.1 g) was crystallised from methanol to afford the product (6) (0.08 g, 73%), m.p. 206–208°.

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⁶ J. Décombe, R. Jacquemain, and J. Rabinovitch, *Bull. Soc. chim. France*, 1948, 447.

⁷ L. F. Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.

⁸ R. Mechoulam, *Israel J. Chem.*, 1968, **6**, 909.