Nitro-steroids. Part VI.[1] The Structure of 5α-Cholestano[2,3-*c*]furazan 2′-Oxide, and the Preparation of 6-Nitro-5α-cholestan-7-ones

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The structure of 5α-cholestano[2,3-*c*]furazan 2′-oxide, obtained from 2,3-bishydroxyimino-5α-cholestane, is established by its preparation from 2-nitro-5α-cholest-2-en-3-ol. Base-catalysed nitration of 5α-cholestan-7-one gives 6α- and 6β-nitro-derivatives, which adopt keto- rather than enol forms.

THE present work on steroidal α-nitro-ketones (see Scheme) had two objects, *viz.* to use such compounds in establishing the structure of a [2,3-*c*]furoxan (IX), and to prepare nitro-ketones (XII) and (XIII) having the functional groups in a non-terminal ring. In the Scheme, references are given to known compounds: the rest are new.

Conversion of 5α-cholestan-3-one (I) into the hydroxyimino-ketone (IV) with pentyl nitrite under acidic conditions was found to be more effective than the base-catalysed method.[2] The 2,3-dioxime (VIII), obtained in high yield *via* the diketone (VII) and formulated as the *anti*-form by comparison with related *anti*-[3] and *amphi*-compounds,[4] gave the furazan (X) and a furoxan (IX) by standard methods.[3] A minor product (III) of the reaction between 5α-cholestan-3-one and ethyl nitrate probably arises from ring-opening of a 2,4-dinitro-3-ketone followed by decarboxylation. The major product (II) formed an oxime (VI) (not fully characterised); conversion of this into the furoxan (IX) shows the latter to be the furazan 2′-oxide (IX). The yield of the furoxan (IX) from the dioxime is not sufficiently high to exclude the possibility that the isomeric 5′-oxide is a significant or even the major product.

The relative stabilities of steroids formally represented as α-nitro-ketones vary considerably with the positions of the substituents. In the 5α-series 2-nitro-3-ketones exist mainly as enols whereas the corresponding Δ^4-compounds and 16-nitro-17-ketones prefer the ketonic

[1] Part V, A. J. Baylis, J. R. Bull, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.* (*C*), 1968, 231.

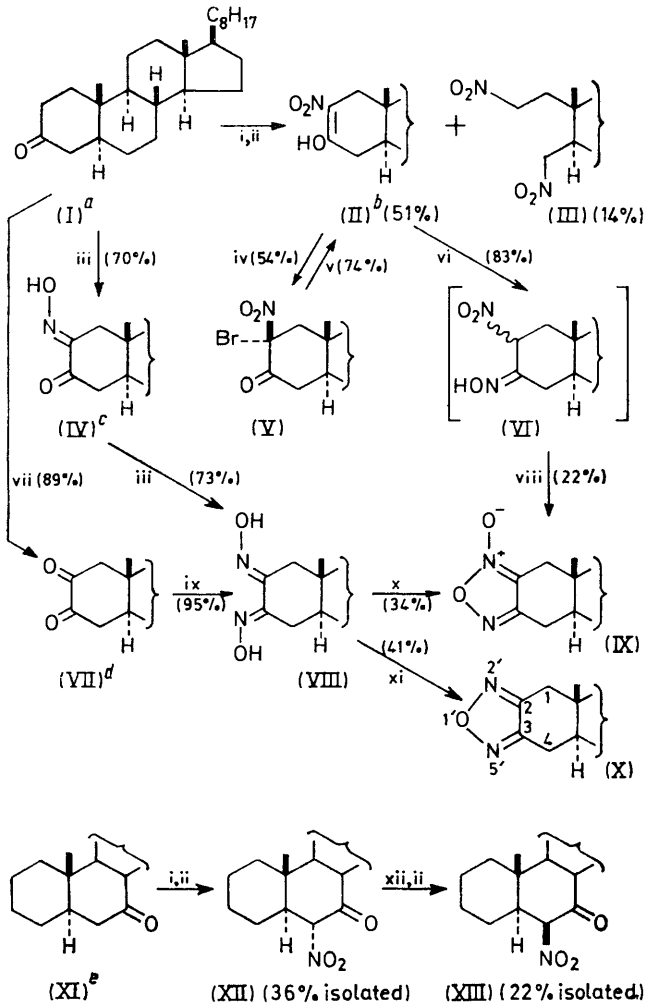
[2] (*a*) M. P. Cava, P. M. Weintraub, and E. J. Glamkowski, *J. Org. Chem.*, 1966, **31**, 2015; (*b*) J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.*, 1957, **79**, 6050.

[3] G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1445.

[4] L. H. Briggs, J. P. Bartley, and P. S. Rutledge, *J. Chem. Soc.* (*C*), 1971, 2115.

form:[5,6] 17β-hydroxy-4β-nitro-5β-androstan-3-one is entirely ketonic.[6]

We are not aware of a case in which both geometric isomers (*i.e.* the epimeric α- and β-nitro-derivatives) of a



SCHEME

Reagents: i, KOBu^t–EtONO$_2$–THF; ii, AcOH; iii, HCl–$C_5H_{11}ONO$; iv, Br_2–AcOH; v, Me_2CO–*hν*; vi, NH_2·OH,HCl–C_5H_5N; vii, KOBu^t–O_2; viii, H_3PO_4, 115 °C; ix, NH_2·OH; x, NaOH–Cl_2; xi, CH_2·CO·O·CO·CH_2, 180 °C; xii, $NaHCO_3$–EtOH, reflux.

[a] 'Encyclopædia of Organic Chemistry,' Elsevier, New York, 1940, vol. 14, p. 122. [b] Ref. 5b. [c] Ref. 2a. [d] Ref. 10. [e] G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whatelye, *J. Chem. Soc.* (*C*), 1966, 1266.

steroidal nitro-ketone have been isolated. The 6-nitro-7-oxo-system seemed suitable for this purpose since the enolic form is expected to be destabilised by a repulsive $NO_2 \cdots H_2C(4)$ interaction. Nitration of 5α-cholestan-7-one (XI) gave a mixture containing the more stable 6α-nitro-compound (XII) as the major component. Epimerisation of this under mild conditions led to an increased amount of the less stable 6β-epimer (XIII), which could then be isolated. Whereas the 2-nitro-compound (II) reacted easily with bromine in acetic acid, the 6α-nitro-7-ketone (XII) was unaffected, and no enolic form was detected by spectrometric study of the 6-nitro-7-ketones (XII) and (XIII) in neutral solutions.

The structures for the nitro-compounds (V), (XII), and (XIII) were originally proposed on general chemical grounds. The n.m.r. spectra establish the presence of 6- rather than 8-nitro-groups in compounds (XII) and (XIII); the configurations of these groups follow from the conformations indicated by i.r. and n.m.r. examination. With the bromonitro-compound (V) the structure is supported, but not rigorously established, by the position of its 19-H_3 signal (see Experimental section).

EXPERIMENTAL

General directions and the solvents normally used for recording spectra are as described previously.[7] Petrol refers to light petroleum, b.p. 60—80°, and THF to tetrahydrofuran.

Nitration of 5α-Cholestan-3-one (I).—A solution of the ketone (dried by azeotropic distillation with C_6H_6; 9·36 g) in dry THF (150 ml) was added slowly during 30 min to a stirred solution of KOBu^t (freshly sublimed; 4·14 g) in THF (140 ml) at −40 °C. EtO·NO_2 (freshly distilled; 3·3 ml) was added during 5 min, and the temperature of the stirred solution was allowed to rise to 0 °C during 45 min. Acidification with AcOH, dilution with H_2O, and isolation with Et_2O gave material (10·74 g), which was chromatographed on SiO_2 (400 g). Petrol–C_6H_6 (4 : 1) eluted 2-nitro-5α-cholest-2-en-3-ol (II) (5·35 g), m.p. 133—134° (from EtOAc), $[\alpha]_D$ +108° (*c* 0·6), $\lambda_{max.}$ (C_6H_{14}) 327 nm (ε 8400), $\lambda_{max.}$ (EtOH) 327 nm (ε 8800), $\lambda_{max.}$ (KOH–EtOH) 345 nm (ε 12,900), $\nu_{max.}$ (CCl_4) 1628 and 1515 cm^{-1}, τ 9·19 (19-H_3) and 9·33 (18-H_3) [lit.,[5b] m.p. 135—136·5°, $\nu_{max.}$ (KBr) 1610 and 1520 cm^{-1}]. Petrol–C_6H_6 (1 : 1) eluted 2,4-*dinitro*-2,3-*seco*-A-*nor*-5α-*cholestane* (III) (1·5 g), m.p. 169—172° (from EtOAc), $[\alpha]_D$ +31° (*c* 0·6) (Found: C, 69·2; H, 10·4; N, 6·4. $C_{26}H_{46}N_2O_4$ requires C, 69·3; H, 10·3: N, 6·2%), $\nu_{max.}$ 1560 cm^{-1}, τ 9·13 (19- and 18-H_3).

2α-Bromo-2β-nitro-5α-cholestan-3-one (V).—The 2-nitro-compound (II) (157 mg) was shaken with AcOH (100 ml) at 20 °C until a clear solution was obtained (*ca.* 4 d). Br_2 in AcOH [1·9 ml of a solution made by mixing Br_2 (1·545 g) and AcOH (50 ml)] was added, and the solution was kept in the dark at 20 °C for 2 h. Isolation with Et_2O, chromatography on SiO_2 (10 g), and elution with petrol–C_6H_6 (4 : 1) gave the *bromonitro-compound* [101 mg, m.p. 151—155° (from C_6H_{14})], $[\alpha]_D$ +57° (*c* 1·0) (Found: C, 63·5; H, 8·7; N, 2·45. $C_{27}H_{44}BrNO_3$ requires C, 63·5; H, 8·6; N, 2·75%), $\nu_{max.}$ 1745 and 1570 cm^{-1}, τ 9·18 (19-H_3) and 9·34 (18-H_3) [*cf.* the 19-H_3 signals of ketone (I), and its 2α- and 2β-bromo-derivatives[8] at τ 8·99, 8·92, and 8·77, respectively, and the expectation[1] that a 2α- and a 2β-NO_2 group would, respectively, deshield and shield the 19-protons].

A solution of the bromonitro-compound (V) (64 mg) in

[5] (*a*) A. Hassner and J. M. Larkin, *J. Amer. Chem. Soc.*, 1963, **85**, 2181; (*b*) A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, 1968, **30**, 1733.

[6] R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, 1964, **20**, 373.

[7] C. W. Davey, E. L. McGinnis, M. McKeown, G. D. Meakins, M. W. Pemberton, and R. N. Young, *J. Chem. Soc.* (*C*), 1968, 2674.

[8] C. W. Shoppee, T. E. Bellas, R. E. Lack, and S. Sternhell, *J. Chem. Soc.*, 1965, 2483.

Me_2CO (*ca.* 2 ml) was kept at 20 °C in sunlight. After 1 day the insoluble material was collected and recrystallised from EtOAc to give the nitro-compound (II) (40 mg), m.p. and mixed m.p. 132—133°.

2,3-*Bishydroxyimino-5α-cholestane* (VIII).—(a) *From the hydroxyimino-ketone* (IV). 5α-Cholestan-3-one (1 g) in Et_2O (30 ml) was mixed with 10N-HCl (7 ml)–MeOH (4 ml). The mixture was stirred vigorously at 20 °C, and pentyl nitrite (0·35 ml) in Et_2O (20 ml) was added during 20 min. After a further 15 min the insoluble material was collected, washed with H_2O, dried, and crystallised from EtOH to give 2-hydroxyimino-5α-cholestan-3-one (IV) (0·75 g), m.p. 240—242° (decomp.) (lit.,[2a] 268—270°; lit.,[2b] 205—207°), $[\alpha]_D$ (C_5H_5N) +42° (*c* 1·0), $\lambda_{max.}$ 242 nm (ε 7300) (lit.,[2a] 235 nm (ε 8200)], $\nu_{max.}$ 3300, 3150, and 1730 cm^{-1}. A solution of this material (200 mg) and NH_2OH,HCl (60 mg) in C_5H_5N (20 ml) was heated at 100 °C for 1 h, cooled, and poured into H_2O. The insoluble material was dried and crystallised from EtOH to give the *dioxime* (VIII) (152 mg), m.p. 218—220°, $[\alpha]_D$ (C_5H_5N) +71° (*c* 1·0) (Found: C, 74·5; H, 10·5; N, 6·9. $C_{27}H_{46}N_2O_2$ requires C, 75·2; H, 10·7; N, 6·5%), $\lambda_{max.}$ 238 nm (ε 6600), $\lambda_{max.}$ (KOH–EtOH) 279 nm (ε 6500), $\nu_{max.}$ 3390, 3160, and 1620 cm^{-1}. A solution in THF gave a red precipitate with aq $NiSO_4$.

(b) *From the diketone* (VII). Oxygenation of 5α-cholestan-3-one (5·25 g) by Barton's method [9] and crystallisation of the product from EtOH gave a mixture of the diketone and enol forms (4·82 g), m.p. 117—134°, $\lambda_{max.}$ 272 nm (ε 5350), $\nu_{max.}$ 3440, 1680, and 1665 cm^{-1} [lit.,[10b] m.p. 132—134°, $\lambda_{max.}$ 270 nm (ε 3700)]. A solution of this mixture (4·12 g), NH_2OH,HCl (2·6 g), and NaOAc (6 g) in EtOH (180 ml)–H_2O (20 ml) was heated under reflux for 1 h. The dioxime (VIII) (4·2 g; m.p. and mixed m.p. 216—218°) separated on cooling.

5α-*Cholestano*[2,3-c]*furazan 2′-Oxide* (IX).—(a) *From the dioxime* (VIII). A solution of NaOH (4 g) in H_2O (20 ml) was saturated with Cl_2 at 5 °C. This was added during 20 min to a stirred suspension of the dioxime (1 g) in NaOH (3 g) –MeOH (90 ml) –H_2O (30 ml) at 0 °C. The insoluble material was collected, washed with H_2O, dried, and crystallised twice from C_6H_6–MeOH to give the *furazan 2′-oxide* (342 mg), m.p. 202—203°, $[\alpha]_D$ +62° (*c* 1·0) (Found: C, 75·1; H, 10·4; N, 6·8. $C_{27}H_{44}N_2O_2$ requires C, 75·7; H, 10·3; N, 6·6%), $\lambda_{max.}$ (Et_2O) 267 nm (ε *ca.* 8000), $\nu_{max.}$ 1630 and 1475 cm^{-1}, τ 9·17 (19-H_3) and 9·31 (18-H_3).

(b) *From the 2-nitro-compound* (II). A solution of the 2-nitro-compound (500 mg) and NH_2OH,HCl (250 mg) in C_5H_5N (2·5 ml) –EtOH (50 ml) –H_2O (2·5 ml) was heated under reflux for 6 h, and poured into H_2O. The insoluble material was dried to give a product (430 mg), m.p. 70—75°, $\nu_{max.}$ 3580, 3240, 1620, and 1550 cm^{-1}, presumed to be the nitro-oxime (VI), which could not be crystallised. A portion (206 mg) was heated under N_2 with H_3PO_4 (2 ml) at 115 °C for 1 h. Isolation with Et_2O, chromatography on SiO_2 (20 g), and elution with C_6H_6 gave the furazan 2′-oxide (43 mg), m.p. 202—203°, identical (mixed m.p., i.r. spectrum) with the product of route (a).

5α-*Cholestano*[2,3-c]*furazan* (X).—A mixture of the dioxime (VIII) (500 mg) and succinic anhydride (500 mg) was heated at 180 °C for 8 min. The material obtained by work-up with H_2O and $CHCl_3$ was chromatographed on SiO_2 (15 g). C_6H_6 eluted the *furazan* (198 mg), m.p. 103—105° (from EtOH), $[\alpha]_D$ +50° (*c* 0·9) (Found: C, 78·4; H, 10·6; N, 6·6. $C_{27}H_{44}N_2O$ requires C, 78·9; H, 10·7; N, 6·8%), $\lambda_{max.}$ 215 nm (ε 4150), $\nu_{max.}$ 1405, 1226, and 1010 cm^{-1}.

6α- *and* 6β-*Nitro*-5α-*cholestan*-7-*one* (XII) and (XIII).—The procedure described above for nitrating 5α-cholestan-3-one (I) was used with 5α-cholestan-7-one (XI) (2·09 g) in THF (30 ml), $KOBu^t$ (1 g) in THF (30 ml), and $EtO{\cdot}NO_2$ (1·2 ml), and the product was chromatographed on SiO_2 (200 g). Petrol–C_6H_6 (3 : 2; 1·8 l) eluted a mixture (1·22 g) [C=O bands at 1735 and 1697 cm^{-1}, relative intensities 2 : 1, attributed (see below) to the 6α- (XII) and 6β- (XIII) isomers, respectively]. Two crystallisations from petrol gave 6α-*nitro*-5α-*cholestan*-7-*one* (XII) (830 mg), m.p. 137—139°, $[\alpha]_D$ +3° (*c* 1·0) (Found: C, 75·0; H, 10·3; N, 2·9. $C_{27}H_{45}NO_3$ requires C, 75·1; H, 10·5; N, 3·25%), $\lambda_{max.}$ (EtOH) 240 nm (ε 1600) but no selective absorption in the range 250—350 nm, $\nu_{max.}$ (CCl_4) 1735 and 1565 cm^{-1}, τ (CCl_4) 5·00 (d, *J* 12·6 Hz, 6-H), 8·87 (19-H_3), and 9·33 (18-H_3).

A solution of the 6α-nitro-compound (452 mg) in EtOH 180 ml) –H_2O (20 ml) saturated with $NaHCO_3$ was heated under reflux for 2 h, concentrated under reduced pressure to a volume of *ca.* 50 ml, and diluted with H_2O. Acidification with AcOH at 20 °C and extraction with Et_2O afforded a mixture ($\nu_{max.}$ 1735 and 1697 cm^{-1}, approx. equally intensity). Two crystallisations from EtOAc gave 6β-*nitro*-5α-*cholestan*-7-*one* (XIII) (96 mg), $[\alpha]_D$ +2° (*c* 1·0) (Found: C, 75·2; H, 10·6; N, 3·0%), $\nu_{max.}$ 1696 and 1550 cm^{-1}, τ (CCl_4) 5·55 (m, 6-H), 9·13 (19-H_3), and 9·31 (18-H_3). This compound melts in the range 155—170°, the temperature depending on the rate of heating, to give material in which the relative intensities of the C=O bands (1735 and 1696 cm^{-1}) vary with the duration of the heating.

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[9] E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1965, 1578.

[10] (*a*) L. Ruzicka, Pl. A. Plattner, and M. Furer, *Helv. Chim. Acta*, 1944, **27**, 524; (*b*) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 1938, 353.