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HETEROCYCLIC STEROIDS—VII

TRANSFORMATIONS OF 17β-HYDROXY-1,3-SECO-2-NOR-5α-ESTRAN-4-ON-1-OIC ACID[1]

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Abstract—The acetylester (Ib) has been transformed into several derivatives. The direction of bromination of the 4-ketone under acid conditions has been shown as proceeding toward C-3 by the isolation of bromosteroids (Ic) and V. In addition, the 2-oxa lactone (III) has been prepared.

IN CONSIDERING approaches to the partial synthesis of heterocyclic steroids three steps must be envisaged: namely; cleavage of the ring and removal of one or more carbon atoms, introduction of the heteroatom, and closure of the ring. Occasionally, the last two steps of the sequence can be accomplished in a combined manner, e.g., *via* Beckmann rearrangement or Baeyer-Villiger oxidation. However, with these reactions a norsteroid should be employed in order to obtain a heterosteroid with a "normal" ring system. Hence, removal of a carbon atom is necessary prior to actual insertion of the heteroatom.

The formation of acetyl acids Ia and II by the hydrogen peroxide oxidation[3] of 1-hydroxy-4-methyl-1,3,5(10)-trienes provided us with potentially versatile intermediates for the synthesis of heterocyclic steroids. Indeed, we have already utilized the existing functional features of these products to construct 4-methyl-2,3-diazasteroids[1b,3a] (steroidal pyridazones and pyridazinones). In addition Ib was amenable to relatively facile removal of the acetyl moiety at C-5 to yield a β-ketoester, which we have employed for the synthesis of 2,4-diazasteroids[4] (steroidal pyrimidines).

In the preceding instances not all of the available carbons were incorporated into the reformed ring A, some being attached to the ring as a methyl group and others removed. The acid Ia has five carbon atoms available for construction of a modified ring A which, supplemented by a heteroatom, could form steroids with oxygen, nitrogen, etc. at position 2. For this a hydrogen of the methyl at C-3 must be suitably replaced.

In addition, we had hoped that certain transformations could furnish steroids with a ketol chain at C-5. This is of interest, since such moieties are the characteristic

[1] [a] This work was supported by Grants A5326, CA07137 and FR-05528 from the U.S. Public Health Service; [b] Part VI. D. M. Piatak, R. I. Dorfman, D. Tibbetts and E. Caspi, *J. Med. Chem.* 7, 590 (1964).

[2] Recipient of Public Health Service Research Career Program Award CA-K3-16614 from the National Cancer Institute.

[3] [a] E. Caspi, P. K. Grover and D. M. Piatak, *Chem. & Ind.* 1495 (1963); [b] E. Caspi, P. K. Grover, D. M. Piatak and Y. Shimizu. *J. Chem. Soc.* 3052 (1965).

[4] [a] E. Caspi and D. M. Piatak, *Experimentia* **19**, 465 (1963); [b] D. M. Piatak and E. Caspi, *Steroids* 3, 631 (1964).

feature of corticosteroids. Additional incentive was provided by the observations of Jacques *et al.*[5] on reverse steroids with a ketol group at C-3.

In approaching the problem of functionalization of the methyl the first task was to establish the direction of bromination of the C-4 ketone. Acid catalyzed bromination was therefore explored. Should enolization occur toward the methyl, a functional group could be introduced and eventually appropriately manipulated. When ester Ib was brominated a good yield of a monobrominated product was obtained. The structure was established by NMR as being Ic, since the signal for the acetyl methyl at 135·0 c/s originally present in ester Ib was no longer visible and a singlet at 242·5 c/s equivalent to two protons appeared. Thus, a route to an oxygenated moiety could be projected. In fact the α-acetoxyketone Id was formed *via* a potassium iodide–potassium acetate[6] displacement of the bromide. Characterization of Id was achieved by analysis, a positive blue tetrazolium test,[7] and the appearance of IR bands at 1750 and 1720 cm^{-1}. The shift of the C-4 ketone in Id to a higher wavenumber (1720 cm^{-1}) duplicates that observed for 21-acetoxylation of 20-ketopregnanes. The NMR spectrum showed, among others, two doublets at 274·5 and 289·0 c/s (J = 16·5 c/s) for the C-3 methylene and singlets at 129·5 c/s for C-3 acetate and at 122·5 c/s for the 17-acetate. Subsequently, Id was directly prepared from Ib by the boron trifluoride–lead tetraacetate method.[8] Thus, the bromination step could be circumvented, markedly increasing the yield.

With the introduction of oxygen α to the ketone the necessary sixth atom was now available. Closure of the ring by linking C-1 to the heteroatom would then provide a 2-oxasteroid[9] III. Obviously, the simplest approach to ring formation is saponification of the ester moieties and subsequent dehydration. We first attempted the saponification of the 3-acetate and C-1 ester with potassium bicarbonate. However, a selective attack on the ketol moiety occurred, giving largely a neutral product Ie and a minor amount of an acid. The structure of Ie follows from the disappearance of the 1750 cm^{-1} band in the IR and the appearance of a hydroxy band at 3460 cm^{-1}. In addition, the characteristic IR shift observed upon conversion of 21-acetoxy-20-ketopregnanes to 21-hydroxy-20-ketopregnanes occurred and the 4-ketone appeared at 1705 cm^{-1}. Further verification was obtained by an NMR spectrum which showed a signal at 122·0 c/s only for the 17-acetate, confirmed by the unchanged chemical shift of the 18-methyl at 48·5 c/s. The acid was characterized as being the half acid ester IVa and was converted to the diester IVb. Hypobromite oxidation of Ia followed by diazomethane esterification and acetylation, also gave IVb.

Interestingly, the oxidation of α-hydroxyketone Ie with periodic acid in aqueous methanol gave acidic and neutral fractions. The acid was found to be the half acid ester IVa, as expected. The neutral product was diester IVb. Evidently, the periodic

[5] M. Dvolaitzky, H. B. Kagan and J. Jacques, *Bull. Soc. Chim. Fr.* 598 (1961) and preceding papers of the series.

[6] For examples see *Steroid Reactions* (Edited by C. Djerassi) p. 598. Holden-Day, San Francisco (1963).

[7] C. Chen, J. Wheeler and H. E. Tewell, Jr., *J. Lab. and Clin. Med.* **42**, 749 (1953).

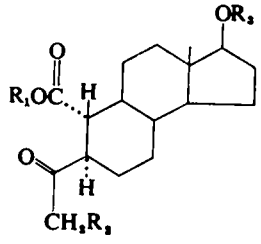
[8] [a] J. D. Cocker, H. B. Henbest, G. H. Phillips, G. P. Slater and D. A. Thomas, *J. Chem. Soc.* 6 (1965); [b] Application of this reagent to Ia gives totally different results, which will be reported in a later communication.

[9] R. Pappo and C. J. Jung, *Tetrahedron Letters* 365 (1962), have reported that 2-oxasteroids possess significant biological activity.

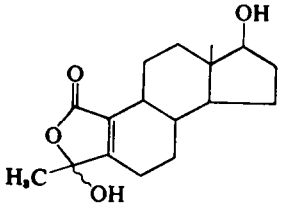
acid was strong enough to cause an acid catalyzed esterification even in the presence of water.

Since the potassium bicarbonate did not hydrolyze the ester at C-1, the reaction of Id with sodium hydroxide was examined. The resulting acid If was characterized as its diacetate Ig, which could be methylated to starting material Id. The acid If was then suspended in chloroform and dehydrated to lactone III with phosphorus pentoxide. The structure of III follows from its elemental analysis and IR spectrum having a 1740 cm^{-1} peak which we assigned to the C-1 carbonyl and a 1720 cm^{-1} peak for the C-4 carbonyl. The IR spectrum of III did not show enolization of the C-4 carbonyl similar to compounds where this ring system is attached to an aromatic moiety.[10]

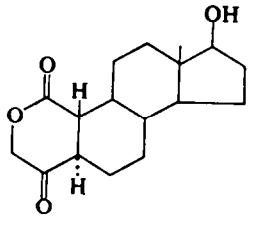
After completion of this part of the work, additional aspects of bromination under acid conditions were explored. We began with the α-acetoxyketone Id and used conditions similar to those employed for 17α-bromination of 21-acetoxy-20-ketopregnanes.[11] The reaction product analyzed as a monobromo compound and its IR spectrum exhibited sharp peaks at 1780, 1730 and 1720 cm^{-1}. The appearance of the 1780 cm^{-1} band, concomitant with the disappearance of the 1750 cm^{-1} band



I

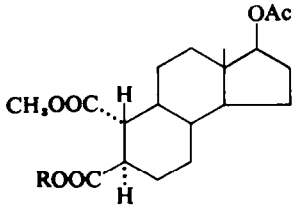


II

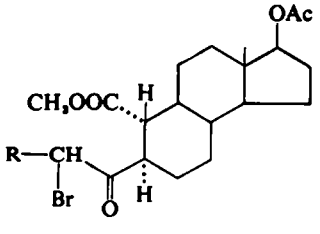


III

a. $R_1 = R_2 = R_3 = H$
b. $R_1 = CH_3$; $R_2 = H$; $R_3 = Ac$
c. $R_1 = CH_3$; $R_2 = Br$; $R_3 = Ac$
d. $R_1 = CH_3$; $R_2 = OAc$; $R_3 = Ac$
e. $R_1 = CH_3$; $R_2 = OH$; $R_3 = Ac$
f. $R_1 = H$; $R_2 = OH$; $R_3 = H$
g. $R_1 = H$; $R_2 = OAc$; $R_3 = Ac$
h. $R_1 = CH_3$; $R_2 = R_3 = H$



a. R = H
b. $R = CH_3$ IV



a. R = AcO
b. R = Br V

[10] E. B. Knott, *J. Chem. Soc.* 402 (1963).
[11] C. R. Engel, *U.S. Patent* 2,985,672 (May 23, 1961).

of the C-3 acetate, suggested that bromination occurred within the immediate vicinity of the acetate as in Va and not at C-5. That indeed it was the case was obvious from an NMR in which the doublets at 274·5 and 289·0 c/s (J = 16·5 c/s) for the acetoxymethyl were absent and a new resonance equivalent to one proton appeared at 412·0 c/s. This evidence established the product as having structure Va. It is apparent that bromination under acid conditions occurs predominantly, if not exclusively, at C-3, whether or not C-3 is functionalized. The formation of a 21-acetoxy-21-bromo-17α-hydroxy-20-ketopregnane as a minor product of N-bromosuccinimide reaction with 3α,17α-dihydroxy-21-acetoxy-5β-pregna-11,20-dione has been reported.[12] However, enolization in the latter instance can only proceed toward C-21.

Further documentation of the strong enolization of the C-4 ketone towards the C-3 methyl was evidenced by the bromination of Ib with 2 moles of bromine. The product VI analyzed correctly for a dibromide. The single proton signal at 358·5 c/s definitely confirmed the *gem*-dibromide structure Vb.

Formation of the *gem*-dibromide is not totally unexpected in the light of the bromination results with the acetoxy ketone Id. The results do indicate a dissimilarity of behaviour of this methyl ketone with 20-ketopregnanes.[13]

At present further studies are in progress to exploit the acetyl acids Ia and II for other heterocyclic steroid synthesis.

EXPERIMENTAL[14]

Methyl 17β-*acetoxy*-3-*bromo*-1,3-*seco*-2-*nor*-5α-*estran*-4-*on*-1-*oate* (Ic)

To a solution of Ib (360 mg) in glacial AcOH (16 ml) was added a 1M solution of Br_2 in AcOH (1·02 ml). The reaction was stored in the dark for 6 hr, whereupon the original red color faded to yellow with the concomitant formation of HBr. The mixture was diluted with ether and washed with a sat $NaHCO_3$aq then water. Evaporation of the solvent *in vacuo* gave 444 mg of crude product. Recrystallization from CH_2Cl_2–MeOH gave colorless crystals; m.p. 179–181°, ν_{max} 1730, 1720 cm^{-1}; NMR 242·5, 223·5, 125·5, 50·0 c/s. (Found: C, 55·52; H, 6·46. $C_{30}H_{39}BrO_5$ requires: C, 55·94; H, 6·81%.)

Methyl 3,17β-*diacetoxy*-1,3-*seco*-2-*nor*-5α-*estran*-4-*on*-1-*oate* (Id)

(a) A mixture of Ic (100 mg) NaI (38 mg), freshly fused AcOK (110 mg), glacial AcOH (0·03 ml) and acetone (2·0 ml) was heated at reflux for 22 hr. The mixture was diluted with water and the steroids were taken up in ether. After washing with $NaHCO_3$aq the ether was evaporated and the solid was recrystallized from MeOH to give colorless crystals; m.p. 142–146°; ν_{max} 1750, 1725, 1245, 1230 cm^{-1}; NMR 274·5, 289·0 (doublets) (J = 16·5 c/s) 221·0, 129·5, 122·5, 49·0 c/s. (Found: C, 64·54; H, 7·73. $C_{32}H_{38}O_7$ requires: C, 64·68; H, 7·90%.)

(b) To a solution of Ib (500 mg) in benzene (19 ml) was added BF_3-etherate (2·5 ml) MeOH (1·0 ml) and lead tetraacetate (650 mg). After stirring for 4 hr the reaction was diluted with water and ether, and the steroids were recovered by extraction. Crystallization of the residue from MeOH gave 420 mg, identical to the above sample.

[12] [a] E. B. Hershberg, C. Gerold and E. P. Oliveto, *J. Amer. Chem. Soc.* **74**, 3849 (1952); [b] E. P. Oliveto and C. E. Gerold, *U.S. Patent* 2,684,376 (July 20, 1954).

[13] Ref. 6 pp. 201–202. Under acid conditions dibromination of 3-ketones gives 2,4-dibromo-3-ketones, due to the facile rearrangement of the 2,2-dibromoketone formed initially. The 2,2-dibromo-3-ketone can only be isolated under buffered bromination conditions. *Ibid.* p. 183.

[14] M.p. were taken on a micro hot stage and are corrected. Unless otherwise stated IR spectra were recorded on KBr wafers. NMR spectra were performed on $CDCl_3$ sols. Preparative TLC was accomplished on 20 cm by 20 cm plates coated with silica gel HF_{254} supplied by Brinkmann, Inc. The solvents indicated in each case were used for development.

Methyl 17β-*acetoxy*-3-*hydroxy*-1,3-*seco*-2-*nor*-5α-*estran*-4-*on*-1-*oate* (Ie)

A solution of $KHCO_3$ (600 mg) in water (10 ml) was mixed with a solution of Id (200 mg) in MeOH (24 ml), then the mixture was set aside for 20 hr at room temp. The reaction was diluted with water and the neutral product isolated by extraction with Et_2O–$CHCl_3$ (3–1). Removal of the dried (Na_2SO_4) solvents *in vacuo* gave 130 mg of crystalline Ie. Repeated recrystallizations from AcOEt–pentane gave an analytical sample; m.p. 115–117°; ν_{max} 3460, 1725, 1705, 1245 cm^{-1}; NMR 256·0, 219·0, 122·0, 48·5 c/s. (Found: C, 65·93; H, 8·17. $C_{30}H_{50}O_6$ requires: C, 65·55; H, 8·25%.)

The potassium bicarbonate soluble fraction was processed as described below.

Methyl 17β-*acetoxy*-1,4-*seco*-2,3-*bisnor*-2α-*estran*-1-*oate*-4-*carboxylic acid* (IVa)

(a) The potassium bicarbonate solution from the hydrolysis of Id was acidified with dil HCl and the acidic material recovered by extraction with AcOEt. Evaporation of the AcOEt gave 30 mg of IVa which crystallized from AcOEt–pentane as colorless crystals; m.p. 172–182°; ν_{max} 3140, 1730, 1720, 1687 cm^{-1}. (Found: C, 65·00; H, 8·07. $C_{19}H_{28}O_6$ requires: C, 64·75; H, 8·01%.)

(b) To Ie (100 mg) in MeOH (10 ml) was added periodic acid (140 mg) in water (2·0 ml). The reaction was stored for 3·5 hr, then diluted with water. The steroids were extracted into ether and separated into neutral and acidic materials with $NaHCO_3$. Recovery of the acid portion gave 40 mg IVa which was identical to the above sample.

The neutral material is described below in part (c).

Dimethyl 17β-*acetoxy*-1,4-*seco*-2,3-*bisnor*-5α-*estrane*-1,4-*dioate* IVb

(a) The Ia (750 mg) was dissolved in 4% NaOHaq (15 ml) and cooled to 10°. Br_2 (0·42 ml) was added to a cooled solution of 8% NaOH (15 ml). The two solutions were then admixed and stored at room temp for 16 hr. The mixture was extracted with ether to remove the bromoform. Extraction of the acidified aqueous layer yields 720 mg of hydroxy diacid IV.

A portion of the diacid was methylated with diazomethane to the diester, then acetylated as usual (Ac_2O–pyridine). The IVb obtained was recrystallized from MeOH to yield colorless crystals; m.p. 125–127°; ν_{max} 1730 cm^{-1}; NMR 224·0, 221·5, 124·5, 50·0 c/s. (Found: C, 65·52; H, 8·37. $C_{30}H_{50}O_6$ requires: C, 65·55; H, 8·25%.)

(b) Methylation of IVa in ether with ethereal diazomethane gave IVb which was identical to the sample prepared in part a.

(c) The neutral fraction from the above periodic acid oxidation had the solvent removed to yield 65 mg of crystalline IVb, identical to the above samples.

3,17β-*Diacetoxy*-1,3-*seco*-2-*nor*-5α-*estran*-4-*on*-1-*oic- acid* (Ig)

The Id (100 mg) was saponified in MeOH (5 ml) with 2N NaOH (0·5 ml) by refluxing for 1·5 hr. The MeOH was removed under a stream of N_2 and the solution was acidified with 2N HCl. The acid was then isolated by extraction with ether. The material was acetylated as usual (Ac_2O–pyridine). Crystallization of the diacetate from MeOH–CH_2Cl_2 gave colorless crystals; m.p. 232–234°; ν_{max} 3240, 1760, 1725, 1680 cm^{-1}, NMR 128·5, 123·0, 49·0 c/s. (Found: C, 63·51; H, 7·18. $C_{31}H_{50}O_7$ requires: C, 63·94; H, 7·66%.)

Methylation of a small portion with ethereal diazomethane gave starting material Id.

17β-*Hydroxy*-2-*oxa*-5α-*estra*-1,4-*dione* (III)

A sample of Id (200 mg) was saponified in 10 ml MeOH with 2N NaOH (1·0 ml) as above. The If was recovered as above and the syrup was shaken for 3·5 hr with 100 ml $CHCl_3$ containing P_2O_5. The mixture was then poured on ice and $NaHCO_3$. Extraction with ether gave 54 mg of neutral material, which was recrystallized from AcOEt–pentane to m.p. 174–176°; ν_{max} 3520, 1740, 1720 cm^{-1}; NMR 279·0, 47·5 c/s. (Found: C, 69·42; H, 8·31. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%.)

Methyl 3-*bromo*-3,17-*diacetoxy*-1,3-*seco*-2-*nor*-5α-*estran*-4-*on*-1-*oate* (Va)

To Id (100 mg) in glacial AcOH (1·0 ml) containing a trace of anhydrous HBr was added 1 M Br_2 in AcOH (0·25 ml). The mixture was heated at 45–50° for 1–2 hr, then stored at room temp

[16] We wish to thank Dr. H. B. Bhat for this experiment.

overnight. After dilution of the mixture with water, the steroids were extracted into ether and washed with sat. $NaHCO_3$aq, then water. Removal of the solvents *in vacuo* gave a syrup which was chromatographed on a thin layer plate ($CHCl_3$–AcOEt, 3:2). The less mobile zone corresponded to starting material as evidenced by its R_f value. The more mobile zone was eluted to yield 45 mg of Va; m.p. 142–154° (from MeOH); ν_{max} 1780, 1730, 1720 cm^{-1}; NMR 412·0. 217·0, 134·0, 123·0, 50·0 c/s. (Found: C, 54·12; H, 6·37; $C_{23}H_{31}BrO_7$ requires: C, 54·21; H, 6·41%.)

To a solution of Ib (200 mg) in glacial AcOH (8·5 ml) was added a Br_2–AcOH (1·10 ml; 1·83 g Br_2/10 ml). The mixture was stored at ambient temp for 3·5 hr then heated to 40° for 1·5 hr after the addition of a few drops of AcOH saturated with HBr. The light yellow reaction was diluted with water and the steroids were taken up into ether, then washed with $NaHCO_3$aq and water. Evaporation of the ether gave solid material which gave 190 mg of crystals from MeOH. The analytical sample, m.p. 189–192° had ν_{max} 1725 cm^{-1}; NMR 358·5; 217·0, 120·5, 48·5 c/s. (Found: C 47·46; H, 5·56. $C_{20}H_{28}Br_2O_5$ requires: C, 47·26; H, 5·55%.)