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SOME REACTIONS OF 16-DIAZO-ANDROSTAN-3β-OL-17-ONE

SYNTHESIS OF D-NOR-STEROIDS

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Abstract—The preparation of 16-diazo-androstan-3β-ol-17-one (III) is described. Irradiation of III by U.V. light leads to contraction of the D-ring in the steroid molecule. The 16-diazo group has been replaced by 16β-acetate, 16α-halogen and 16ζ-alkoxy substituents.

DIAZOKETONES have been used as reactive intermediates in the preparation of a variety of compounds.[1] They have been employed in the steroid field by Reichstein[2] in the synthesis of 11-desoxycorticosterone, and more recently by Jeger[3] in a photolysis study of 21-diazo-pregnanes in order to construct an extra five-membered ring by the reaction of the intermediate ketocarbene with the C-18 methyl group.

In 1961, in a preliminary communication, the irradiation of 16-diazo-androstan-3β-ol-17-one leading to a novel D-ring contraction was described.[4] Subsequently, four separate preliminary reports of similar work, also leading in each case to D-nor steroids was published.[5–7] A detailed description of the work[4] plus further experiments is now given.

Androstan-3β-ol-17-one on treatment with isoamyl nitrite in basic medium yields 16-oximino-17-ketone (I); A modification of Huffman's technique[8]). The product, m.p. 245–247°, is in disagreement with the reported value, m.p. 218–219°.[8] The I.R. spectrum exhibits bands at 1740 and 1630 cm^{-1} for the C-17 keto group and the carbon–nitrogen double bond respectively. The elemental analysis of this compound is in agreement with the expected molecular formula $C_{19}H_{29}O_3N$. The structural assignment (I) is further supported by the U.V. spectra of the mono-oxime (I) and of the dioxime (II) in neutral and alkaline media. The keto-oxime (I) shows λ_{max}^{EtOH} 240 mμ (ε 7975) in neutral medium and λ_{max}^{EtOH} 290 mμ (ε 14100) in alkaline medium. The dioxime (II), prepared by the usual method, shows λ_{max}^{EtOH} 237 mμ (ε 6500) and λ_{max}^{EtOH} 275 mμ (ε 8620) in neutral and alkaline media respectively. Comparing these data with that recently published by Barton[9] for the 4-oximo-3-ketone and 3,4-dioxime systems (structures a, b, c and d) we may conclude that both our oxime and dioxime have the *anti* configuration. This configuration is the more stable for these systems,

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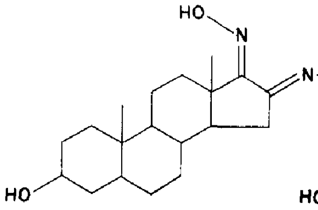
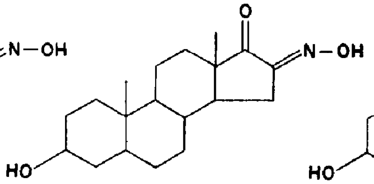
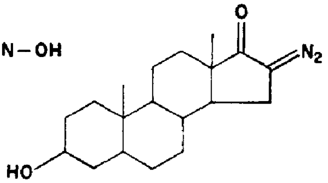


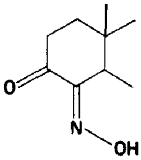
II



I



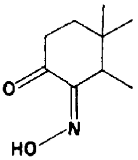
III



(a)

$\lambda_{\text{max.}}^{\text{EtOH}}$ 245 mμ (ϵ 7400)

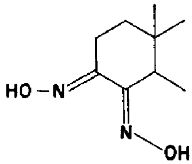
$\lambda_{\text{max.}}^{\text{EtOH}}$ (alkaline) 297 mμ (ϵ 11700)



(b)

$\lambda_{\text{max.}}^{\text{EtOH}}$ 276 mμ (ϵ 2500)

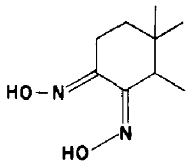
$\lambda_{\text{max.}}^{\text{EtOH}}$ (alkaline) 276 mμ (ϵ 2500)



(c)

$\lambda_{\text{max.}}^{\text{EtOH}}$ 234 mμ (ϵ 7700)

$\lambda_{\text{max.}}^{\text{EtOH}}$ (alkaline) 266 mμ (ϵ 7400)



(d)

$\lambda_{\text{max.}}^{\text{EtOH}}$ 225 mμ (ϵ 9000)

$\lambda_{\text{max.}}^{\text{EtOH}}$ (alkaline) 265 mμ (ϵ 10000)

and it is probable that the more acidic conditions used for the isolation of the keto-oxime, as compared with Huffman's conditions, leads to the formation of the *anti* compound. The small differences in the positions of the U.V. maxima of our mono-oxime and dioxime from those recorded by Barton[9] may arise from the fact that Barton's study was made on a six-membered ring and ours on a five-membered ring keto-oxime.

Treatment of the sodium salt of the keto-oxime with ammonia and sodium hypochlorite[10] yields the 16-diazo compound (III). The conditions for this preparation are critical and a slight variation of the reagent concentrations or of the temperature prevents precipitation, and lowers the yield. The structure of the diazo-ketone (III) is supported by analysis, and I.R. spectrum which shows characteristic bands[11] at 2075, 1650 and 1324 cm^{-1}.

The diazo-ketone (III) in solution in tetrahydrofuran–water (4 : 1) was irradiated with a Hanau S-700 mercury lamp, the temperature being maintained at 10°. The course of the reaction was followed by I.R. spectroscopy, the gradual disappearance of

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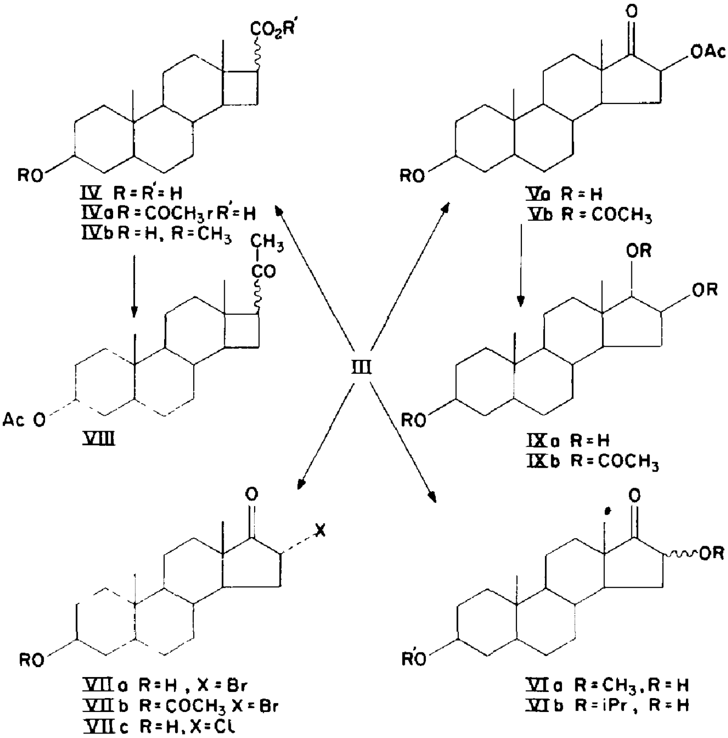
[10] M. O. Forster, *J. Chem. Soc.* **107**, 260 (1915).

[11] P. Yates. B. L. Shapiro, N. Yoda and J. Fugger, *J. Amer. Chem. Soc.* **79**, 5756 (1957).

the 2075 cm^{-1} band being observed at intervals using polyethylene cells.[12] After the reaction was complete, the product was partitioned into neutral and acidic fractions. A crystalline compound was obtained from the latter. Formulation of this product as the D-nor acid (IV) is strongly supported by the following evidence: (a) analysis and molecular weight determination; (b) the I.R. spectrum, which shows a very broad band between 3200 and 2700 cm^{-1} due to the associated carboxyl; (c) with diazomethane the acid gives the methyl ester (IVb), for which the compositional analysis and I.R. spectrum are in good agreement; (d) the irradiation product was recovered unchanged after attempted hydrogenation of ozonolysis, and bromine and permanganate tests were negative, thus excluding structures containing carbon–carbon double bonds; (e) the N.M.R. spectra of the methyl ester rules out possible cyclopropane carboxylic acids since the characteristic methylene absorption bands for this ring were absent[12a]. It was reported earlier that the irradiation of similar diazo-ketones such as diazocamphor[13] and diazohydrindanone[14] gives carboxylic acids with contraction of the ring. Acetylation of the acid (IV) gives the D-nor acid 3β-acetate (IVa). With thionyl chloride the acid (IVa) was converted into the corresponding acid chloride, not isolated in pure form, but treated directly with cadmium methyl to yield 3β-acetoxy-16 ξ-acetyl-D-norandrostane (VIII). These results did not permit allocation of the



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[13] L. Horner and E. Spietschka, *Chem. Ber.* **83**, 934 (1955).

[14] M. P. Cava, R. L. Litle and D. R. Napier, *J. Amer. Chem. Soc.* **80** 2257 (1958).

stereochemistry at C_{16} in any of the D-nor compounds. Other authors[5–7] have suggested that the side chain in these D-nor compounds is β-oriented, though no supporting evidence has been presented.

When the diazoketone (III) reacts with acetic acid in the presence of cuprous or cupric oxide, 16β-acetoxy-androstan-3β-ol-17-one (Va) is obtained. The configuration of the acetoxy group was shown to be *beta* by further acetylation at C-3 to the known 3β,16β-diacetoxy-androstan-17-one (Vb).[15] Lithium aluminium hydride reduction of the latter gives androstane-3β,16β,17β-triol (IXa), and from this 3β,16β,17β-triacetoxy-androstane (IXb) was prepared. Both derivatives have physical properties in agreement with the published values.[15,16]

The diazo-ketone (III) with methanol or isopropyl alcohol in the presence of boron trifluoride etherate affords the 16ξ-methoxy (VIa) and 16ξ-isopropoxy (VIb) derivatives, respectively. Treatment of (III) with hydrobromic acid gives the known 16α-bromo-androstan-3β-ol-17-one (VIIa).[17,18] Acetylation furnishes the 3β-acetate (VIIb), which also has physical constants similar to those published elsewhere.[17,18] Hydrochloric acid treatment of the diazo-ketone (III) yields the 16α-chloro analog (VIIc). The halogen atom is assigned the 16α-configuration since the optical rotatory dispersion curve of this derivative closely resembles the curve of the 16α-bromo compound (VIIa). With hydriodic acid the diazo-ketone is reduced to androstan-3β-ol-17-one.

EXPERIMENTAL[19]

Androstan-3β-ol-16-oximino-17-ketone (I). To 38 g potassium dissolved in 1500 ml anhydrous t-butyl alcohol 36 g androstan-3β-ol-17-one (m.p. 173–175°) were added with vigorous agitation. Isoamyl nitrite (63 ml) was added during 3 hr and the agitation continued a further 2 hr. The reaction mixture was poured into a flask containing 13 l. water and acidified with hydrochloric acid.

The keto-oxime separated immediately and after being kept for 24 hr at 5°, was filtered off, washed with water to neutrality and crystallized from methanol–water, m.p. 240–245°. Recrystallization from methanol raised the m.p. to 245–247° (23 g); λ_{max}^{EtOH} 240 mμ (ε 7975), $\lambda_{max}^{EtOH/KOH}$ 290 mμ (ε 14100): I.R. absorption bands at 1740 (C=O) and 1690 (C=N) cm^{-1}. (Found: C, 71·11; H, 9·21; O, 15·25; N, 4·42. $C_{19}H_{29}O_3N$ requires: C, 71·44; H, 9·15; O, 15·03; N, 4·39%).

16,17-*Dioximino-androstan-3β-ol* (II). The oximino-ketone (I) (1 g) was mixed with 0·5 g hydroxylamine hydrochloride and the mixture dissolved in pyridine–ethanol. After being kept 2 hr under reflux, the solution was poured into water and the product recrystallized from ethanol–water, m.p. 243–245° (mixed m.p. with the monoxime, 228–230°); λ_{max}^{EtOH} 237 mμ (ε 6500), $\lambda^{EtOH/KOH}$ 275 mμ (ε 8620). (Found: C, 68·45; H, 9·06; O, 14·43; N, 8·45. $C_{19}H_{30}O_3N_2$ requires: C, 68·23; H, 9·04; O, 14·35; N, 8·34%).

16-*Diazo-androstan-3β-ol-17-one* (III). Oximino-ketone (I; 23 g) dissolved in a 2% solution of sodium hydroxide was heated at 80°. At this temp. 92 ml 57% ammonium hydroxide and 114 ml sodium hypochlorite (8% active chlorine) were added simultaneously. Precipitation began immediately

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[19] U.V. spectra were determined with a Beckman DK-2 spectrophotometer using ethanol as solvent. I.R. spectra were determined with a Perkin Elmer model 21 recording spectrophotometer fitted with a sodium chloride prism. Except where stated I.R. spectra were measured in chloroform solutions. N.M.R. spectra were taken in chloroform using a Varian Associates Spectrometer Model A-60. The line positions are given in τ values.[20] The microanalyses were performed by Dr. Franz Pascher at Bonn, Germany, and optical rotatory dispersions were made at Syntex, S. A. laboratories, Mexcio City, Mexico. The m.p.s are not corrected.

[20] G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

and was complete in ca. 10 min. After attaining room temp, the yellow precipitate was collected, m.p. 165–168° (17 g, 75 % yield). Recrystallization from acetone–hexane raised the m.p. to 177–178°; I.R. (Nujol) characteristic bands for diazoketones[11] at 2075, 1650 and 1324 cm^{-1}; U.V. λ_{max}^{EtOH} 250 mμ (ε 4139) and 297 mμ (ε 3592). (Found: C, 72·04; H, 8·95; O, 10·28; N, 8·93. $C_{19}H_{28}O_2N_2$ requires: C, 72·11; H, 8·92; O, 10·11; N, 8·85 %).

D-*Norandrostan*-3β-*ol*-16ξ-*carboxylic acid* (IV). The diazoketone (III) (4 g) dissolved in 160 ml distilled tetrahydrofuran and 40 ml water was irradiated by immersing in the solution a Hanau S-700 mercury lamp in a jacketed flask and maintaining the temp of the solution at 10 ± 1°. After 1 hr a sample showed complete removal of the 2075 cm^{-1} band from the I.R. spectrum and that the reaction was complete. The mixture was poured into 600 ml water and extracted with ether; the organic layer was extracted with a saturated solution of sodium bicarbonate and on acidification with hydrochloric acid the D-nor acid (IV) precipitated as a foamy solid. After being kept for 6 hr at 5° the product was filtered off, washed with water, decolorized with Norit charcoal and crystallized from methanol, m.p. 200–205° (3 g, 75 % yield). By recrystallization from methanol the m.p. was raised to 205–206°. The I.R. spectrum exhibits very broad bands between 3200 and 2700 cm^{-1} overlapping with the C—H band, characteristic of the associated carboxyl group, and $\nu_{C=O}$ (acid) at 1690 cm^{-1} (Nujol) and 1710 cm^{-1} ($CHCl_3$). (Found: C, 74·21; H, 9·93; O, 15·83. $C_{19}H_{30}O_3$ requires: C, 74·27; H, 9·87; O, 15·66 %).

3β-*Acetoxy-D-norandrostane*-16ξ-*carboxylic acid* (IVa). Treatment of the 3β-hydroxy-D-nor acid with acetic anhydride and pyridine and recrystallization of the product from methanol furnished the 3β-acetate m.p. 243–244°; I.R. absorption at 1690 (COOH) and 1730 cm^{-1} (acetate C=O). (Found: C, 72·65; H, 9·21; O, 18·21. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26; O, 18·37 %).

3β-*Hydroxy*-16ξ-*carbomethoxy-D-norandrostane* (IVb). A solution of 1 g D-nor acid (IV) in 2 ml methanol and 50 ml anhydrous ether was treated with excess diazomethane in ether at 10°. After 15 hr at 25°, the residual diazomethane was evaporated and the product crystallized from hexane, m.p. 130–132°. Two crystallizations from acetone–hexane raised the m.p. to 132–133°. (Found: C, 75·18; H, 9·71; O, 14·94. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06; O, 14·98 %).

3β-*Acetoxy*-16ξ-*acetyl-D-norandrostane*. To a solution of 1 g D-nor acid (IVa) in 25 ml benzene, 2 ml recently distilled thionyl chloride were added. After refluxing for 30 min the solution was evaporated to dryness *in vacuo*. Benzene (10 ml) was added and the mixture evaporated to dryness again. This operation was repeated 3 times to eliminate the thionyl chloride. The dry crude product exhibited I.R. absorption at 1780 (—COCl) and 1730 (acetate C=O) cm^{-1} and was used without further purification for the next step.

A mixture of 5 ml methyl magnesium bromide (3 M in ether) and 500 mg anhydrous cadmium chloride was refluxed for 30 min. The ether was distilled off and 30 ml anhydrous benzene added. The acid chloride previously obtained (ca. 1·1 g) was dissolved in chloroform–benzene and added dropwise during a 45 min. The solution was refluxed for 4 hr and the product then hydrolysed with 5 % sulfuric acid, the organic layer washed successively with water, dil bicarbonate solution and water, and the methyl ketone (VIII) isolated by evaporation, m.p. 158–161°. A pure sample, obtained by recrystallization from methanol, m.p. 163–164° exhibited I.R. absorption (CCl_4) at 1700 cm^{-1}. (Found: C, 76·08; H, 10·07; O, 13·85. $C_{22}H_{34}O_3$ requires: C, 76·26; H, 9·89; O, 13·85 %).

16β-*Acetoxy-androstan*-3β-*ol*-17-*one* (Va). To the diazoketone (III) (750 mg) dissolved in 35 ml acetic acid were added 75 mg cuprous oxide and the mixture kept at room temp (ca. 22°) for 24 hr, then poured in 200 ml water and extracted with ether. The ether layer was washed with a 5 % solution of sodium bicarbonate, with water and finally dried over sodium sulfate. Evaporation gave a solid (530 mg), m.p. 214–218°. Recrystallization from methanol and from acetone–hexane afforded the 16β-acetate (Va), m.p. 219–220°, with I.R. absorption at 3430 (OH) and 1730 (acetate C=O) cm^{-1}. N.M.R, 7·92τ (acetate CH_3). (Found: C, 72·06; H, 9·19; O, 18·70. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26; O, 18·37 %).

3β-16β-*Diacetoxy-androstan*-17-*one* (Vb). A solution of the acetate Va (500 mg) in 2 ml pyridine and 4 ml acetic anhydride was heated on a steam bath for 1 hr and the diacetate Vb isolated in the normal way, m.p. 156–157° from ethanol. (Lit.[15] m.p. 156–157°).

Androstane-3β,16β,17β-*triol* (IXa). The diacetate (Vb) (200 mg) in 25 ml anhydrous ether and 570 mg lithium aluminum hydride in ether were mixed and refluxed 1 hr. After working up in the normal manner (Na_2SO_4 technique), 150 mg of the triol (IXa), m.p. 252–254° was obtained from ethanol (Lit. m.p. 253–256°[15] and 251–253°[16]).

3β,16β,17β-Triacetoxy-androstane (IXb). Androstane-3β,16β,17β-triol (IXa, 50 mg) was acetylated to the triacetate (IXb) which crystallized from ethanol, m.p. 186–189°. (Lit.[15] m.p. 190–191°).

16ξ-Methoxy-androstan-3β-ol-17-one (VIa). To a solution of 500 mg diazoketone (III) in 50 ml methanol, 624 mg boron trifluoride etherate were added and the mixture refluxed for 4 hr. Water (100 ml) was added and after kept for 12 hr the methyl ether (VIa) (400 mg) was collected, m.p. 65–70°. Crystallization from acetone–water afforded a pure sample, m.p. 65–66°, with proton resonance at 6·6τ (methoxy CH_3). (Found: C, 74·57; H, 10·03; O, 15·38. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06; O, 14·98%).

16ξ-Isopropoxy-androstan-3β-ol-17-one (VIb). A solution of 1 g diazoketone (III) in 50 ml isopropanol and 1·25 g boron trifluoride etherate was refluxed 4 hr, diluted with 100 ml water and the product extracted with ether. The organic layer was washed with 5% bicarbonate solution, and with water, and dried over sodium sulfate. Evaporation gave an oily product which was chromatographed over 40 g washed neutral alumina. Elution with 9:1 and 4:1 benzene–ether yielded the isopropyl ether (VIb), m.p. 120–128°. Recrystallization from ethanol afforded the analytical sample, m.p. 140–141°. (Found: C, 75·35; H, 10·62; O, 14·01. $C_{22}H_{36}O_3$ requires: C, 75·81; H, 10·41; O, 13·77%).

16α-Chloro-androstan-3β-ol-17-one (VIIc). To 500 mg diazoketone (III) in 25 ml ethyl ether, cooled to 5°, was added 0·3 ml conc hydrochloric acid. After 10 min and occasional shaking, the mixture was diluted with 100 ml water and the ether layer washed with 5% bicarbonate solution and water to neutrality. On evaporation 450 mg of the α-chloro-ketone (VIIc) m.p. 140–145°, was obtained, which was recrystallized from methanol, m.p. 170–171°. (Found: C, 70·76; H, 8·92; O, 9·61 Cl, 10·84. $C_{19}H_{29}O_2Cl$ requires: C, 70·23; H, 8·99; O, 9·84; Cl, 10·90%).

16α-Bromo-androstan-3β-ol-17-one (VIIa). To a solution of 500 mg 16-diazo-ketone (III) in 25 ml ethyl ether at 5°, 0·4 ml of a saturated solution of hydrobromic acid in water was added. After 10 min no more nitrogen was evolved. The organic phase was separated, washed with 5% sodium bicarbonate solution, and with water, and dried (Na_2So_4), after evaporation 460 mg of the α-bromo-ketone (VIIa), m.p. 137–140°, was obtained. Recrystallization from methanol gave a sample, m.p. 160–161° (Lit.[17] 155–156°; Lit.[18] m.p. 164–165°). (Found: C, 61·97; H, 7·91; O, 8·67; Br, 21·30. Calc. for $C_{19}H_{29}O_2Br$: C, 61.75; H, 7·92; O, 8·66; Br, 21·63%).

3β-Acetoxy-16α-bromoandrostan-17-one (VIIb). The 3β-hydroxy-17-ketone (VIIa) (100 mg) was acetylated to the 3β-acetate (VIIb) which was crystallized from methanol–hexane, m.p. 172–174°. (Lit.[18] m.p. 171–172°).

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