

A NOVEL TYPE OF THE RING OPENING OF THE STEROIDAL

16 $\alpha$ ,17 $\alpha$ -EPOXIDES

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BY oxidation of 16-methylpregna-5,16-dien-3 $\beta$ -ol-20-one acetate<sup>1</sup> with hydrogen peroxide in alkaline methanolic solution we have prepared 16 $\beta$ -methyl-16,17-oxidopregn-5-en-3 $\beta$ -ol-20-one (Ia), m.p. 192-193 $^{\circ}$ ,  $[\alpha]_D$  -21 $^{\circ}$  (Found: C, 76.58; H, 9.55. C<sub>22</sub>H<sub>32</sub>O<sub>3</sub> requires: C, 76.70; H, 9.36); acetate (Ib) m.p. 177-178.5 $^{\circ}$ ;  $[\alpha]_D$  -20 $^{\circ}$  (Found: C, 74.85; H, 8.66. C<sub>24</sub>H<sub>34</sub>O<sub>4</sub> requires: C, 74.57; H, 8.87). Reaction of the above compound (Ia) with hydrogen bromide in acetic acid - dichloromethane, unexpectedly, yielded a bromine-free isomer of Ia, for which the structure of 16-methylenepregn-5-en-3 $\beta$ ,17 $\alpha$ -diol-20-one (IIa) has been established; m.p. 253-255 $^{\circ}$ . (Found: C, 76.40; H, 9.24. C<sub>22</sub>H<sub>32</sub>O<sub>3</sub> requires: C, 76.70; H, 9.36). The compound was further characterized as the 3-acetate (IIb); m.p. 204-206 $^{\circ}$ ;  $[\alpha]_D$  148 $^{\circ}$ ; I.R.-spectrum  $\lambda_{max}$  1652, 1692, 1725, 3080, 3480, 3605 cm<sup>-1</sup> (Found: C, 74.80; H, 8.88; H<sub>active</sub>, 0.30. C<sub>24</sub>H<sub>34</sub>O<sub>4</sub> (one -OH) requires: C, 74.57; H, 8.87; H<sub>active</sub>, 0.26); and the 3-formate (IIc); m.p. 220-222 $^{\circ}$ ;  $[\alpha]_D$  -158.5 $^{\circ}$  (Found: C, 74.28; H, 8.87. C<sub>23</sub>H<sub>32</sub>O<sub>4</sub> requires: C, 74.16; H, 8.66).

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<sup>1</sup> A. Wettstein, Helv. Chim. Acta 27, 1803 (1944).

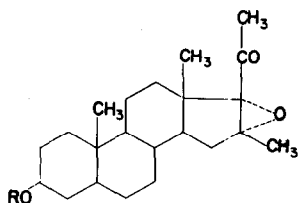
The same product (IIa) was obtained by reaction of the epoxide Ia with other acidic reagents, such as hydriodic acid in aqueous dioxane or perchloric acid in methanol. In both cases a second isomer of unidentified structure was also isolated, similar in physical properties to IIa; m.p. 275-278 $^{\circ}$  (Found: C, 76.80; H, 9.52.  $C_{22}H_{32}O_3$  requires: C, 76.70; H, 9.36); 3-acetate, m.p. 212-214 $^{\circ}$ ;  $[\alpha]_D -166^{\circ}$ ; I.R.-spectrum  $\lambda_{max}$  1695, 1725, 3490, 3605  $cm^{-1}$ . (Found: C, 74.50; H, 8.81;  $H_{active}$ , 0.32.  $C_{24}H_{34}O_4$  (one -OH) requires: C, 74.57; H, 8.87;  $H_{active}$ , 0.26). This compound contains no 16-methylene grouping. The isomerization also proceeds by the action of formic acid in Ia, the 3-formate (IIc) being obtained directly.

The structure II was proved by reduction of the 3-acetate (IIb) with sodium borohydride to the 17,20-diol, followed, without isolation, by oxidative cleavage with periodic acid to the known<sup>2</sup> 16-methylene-androst-5-en-3 $\beta$ -ol-17-one acetate (V) and acetaldehyde (identified as the dimedone derivative). The presence of the 16-methylene grouping in II was also verified by the ozonization of compounds IIb, IIc and V and identification of the formaldehyde formed by means of the modified Schiff reagent.

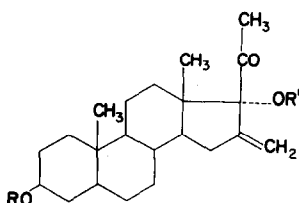
The generality of the above isomerization was demonstrated by a similar reaction sequence in the 5 $\alpha$ -pregnane series. Addition of diazomethane to 5 $\alpha$ -pregn-16-en-3 $\beta$ -ol-20-one acetate afforded the corresponding pyrazoline, m.p. 150-151 $^{\circ}$  (decomp.) (Found: C, 72.12; H, 9.20.  $C_{24}H_{36}N_2O_3$  requires: C, 71.96; H, 9.06), which on thermal decomposition at 150-170 $^{\circ}$  gave 16-methyl-5 $\alpha$ -pregn-16-en-3 $\beta$ -ol-20-one acetate; m.p. 169-170 $^{\circ}$  (Found: C, 77.08; H, 9.72.  $C_{24}H_{36}O_3$  requires: C, 77.37; H, 9.74). On oxidation with hydrogen in alkaline

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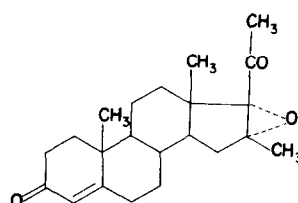
<sup>2</sup> P. L. Julian, E. W. Meyer and H. C. Printy, J. Amer. Chem. Soc. 70, 3872 (1948).



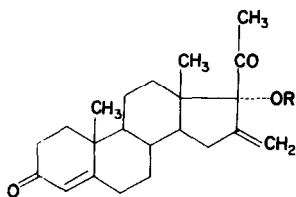
I a  $\Delta^5$ ; R=H—  
 b  $\Delta^5$ ; R=Ac—  
 c  $5\alpha$ ; R=H—



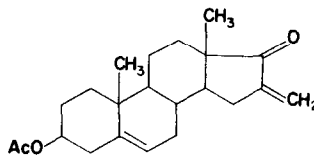
II a  $\Delta^5$ ; R=R'=H  
 b  $\Delta^5$ ; R=Ac—; R'=H—  
 c  $\Delta^5$ ; R=HCO—; R'=H—  
 d  $5\alpha$ ; R=R'=H—  
 e  $5\alpha$ ; R=Ac—; R'=H—  
 f  $\Delta^5$ ; R=HCO—; R'=Ac—



III



IV a R=H—  
 b R=Ac—



V

methanolic solution, the latter compound gave 16 $\beta$ -methyl-16,17-oxido-5 $\alpha$ -pregnan-3 $\beta$ -ol-20-one (Ic); m.p. 186-188 $^{\circ}$ ;  $[\alpha]_D +54.5^{\circ}$ . (Found: C, 76.01; H, 9.62.  $C_{22}H_{34}O_3$  requires: C, 76.26; H, 9.89). The same product was obtained by hydrogenation of Ia on Pd/CaCO $_3$  in methanol. The isomerization of Ic with hydrogen bromide in acetic acid - dichlormethane afforded 16-methylene-5 $\alpha$ -pregnan-3 $\beta$ ,17 $\alpha$ -diol-20-one (IIId), m.p. 236-239 $^{\circ}$ ; (Found: C, 76.31; H, 9.83.  $C_{22}H_{34}O_3$  requires: C, 76.26; H, 9.89); 3-acetate (IIe);

m.p. 180-182°;  $[\alpha]_D -88^\circ$ . (Found: C, 73.97; H, 9.08. C<sub>24</sub>H<sub>36</sub>O<sub>4</sub> requires: C, 74.19; H, 9.34).

A similar isomerization was brought about by the action of hydriodic acid on a dioxan solution of 16 $\beta$ -methyl-16,17-oxidopregn-4-en-3,20-dione (III); m.p. 165° (Found: C, 77.01; H, 9.02. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub> requires: C, 77.15; H, 8.83), obtained by Oppenauer oxidation of Ia. The product of the isomerization reaction - 16-methylenepregn-4-en-17 $\alpha$ -ol-3,20-dione (IVa); m.p. 218-221°;  $[\alpha]_D -3.8^\circ$ ;  $E_{\max}^{\text{EtOH}}$  240 m $\mu$  (log  $\epsilon$  4.24) (Found: C, 77.12; H, 8.91. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub> requires: C, 77.15; H, 8.83) was identical with the product of a mild hydrolysis (potassium hydrogen carbonate) of 17 $\alpha$ -acetoxy-16-methylenepregn-4-en-3,20-dione (IVb)\*; m.p. 231-233°;  $[\alpha]_D -56^\circ$ ;  $E_{\max}^{\text{EtOH}}$  240 m $\mu$  (log  $\epsilon$  4.41) (Found: C, 74.75; H, 8.22. C<sub>24</sub>H<sub>32</sub>O<sub>4</sub> requires: C, 74.97; H, 8.39). This in turn was obtained from IIc by acetylation of the 17 $\alpha$ -hydroxyl group with acetic anhydride and toluene-p-sulphonic acid to the corresponding 3-formate 17-acetate (IIIf); m.p. 178-180°;  $[\alpha]_D -169.5^\circ$  (Found: C, 74.25; H, 8.12. C<sub>25</sub>H<sub>34</sub>O<sub>5</sub> requires: C, 72.43; H, 8.27), followed by Oppenauer oxidation of the latter compound.

The unusual course of the epoxide ring cleavage may be ascribed mainly to the ditertiary character of the epoxide ring in conjunction with the steric conditions on the highly substituted and relatively rigid cyclopentanone system. The usual attack of the halogen anion from the "front" side is in this case hindered by the 16 $\beta$ -methyl group and thus the structure formed by

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\* A paper which, judging by the title, also deals with the preparation of IVb, has recently been submitted for publication<sup>3</sup>, though no details are yet known.

<sup>3</sup> D. N. Kirk, V. Petrow, M. Stansfield and D. M. Williamson, J. Chem. Soc. No. 4, xi (1960).

fission of the C<sub>(16)</sub>-O linkage in the protonated epoxide is stabilized by elimination of the hydrogen from the neighbouring carbon atom. This reaction course formally recalls formation of the  $\Delta^{8(14)}$ -11 $\beta$ -ol-system by the action of strong acids on the 9 $\beta$ ,11 $\beta$ -epoxide ring, stabilization in this case, however, proceeding through transannular hydrogen transfer.<sup>4</sup>

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<sup>4</sup> N. L. Wendler, R. P. Graber, C. S. Snoddy, Jr. and F. W. Bollinger, J. Amer. Chem. Soc. 79, 4476 (1957); J. Fried and E. F. Sabo, Ibid. 79, 1130 (1957).  
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