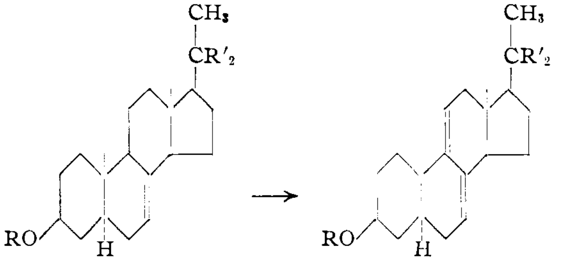
Steroids. XXIII.[1] $\Delta^{7,9(11)}$-Allopregnadiene-3β,20β-Diol and Related Compounds

BY J. ROMO, G. ROSENKRANZ AND CARL DJERASSI

In earlier papers from this Laboratory, there was described the preparation of $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol[2] and $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-acetate (IIa).[3] Such dienes have proved to be important intermediates for the oxidative introduction of an 11-keto group.[4,5] We have observed that $\Delta^{7,9(11)}$-allopregnadiene-3β,20β-diol (IIb) represents a particularly suitable substrate for similar oxidation experiment,[5a] since all intermediates are high melting solids and the absence of a keto group facilitates infrared interpretation of the various transformation products. The present note is concerned with the preparation of this diol IIb and certain related compounds.



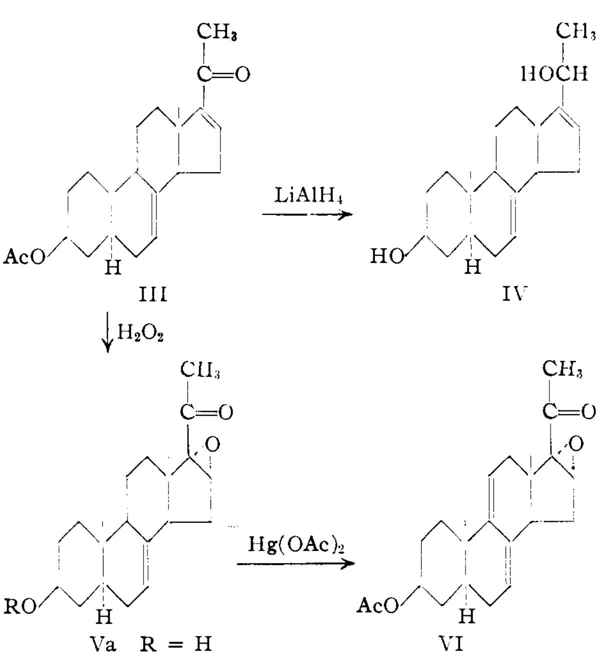
Ia, R = Ac; R'$_2$ = O IIa, R = Ac; R'$_2$ = O

b, R = H; R'$_2$ = $<^{H}_{OH}$ b, R = H; R'$_2$ = $<^{H}_{OH}$

c, R = Ac; R'$_2$ = $<^{H}_{OAc}$ c, R = Ac; R'$_2$ = $<^{H}_{OAc}$

Lithium aluminum hydride reduction of Δ^{7}-allopregnen-3β-ol-20-one 3-acetate (Ia)[3] afforded Δ^{7}-allopregnen-3β,20β-diol (Ib)[6] and upon acetylation the diacetate Ic. Dehydrogenation of the latter with mercuric acetate led to the corresponding diacetoxy diene IIc, which was also obtained upon lithium aluminum hydride reduction of $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-acetate (IIa).[3]

Concurrently with the above experiments, there was also prepared 16α,17α-oxido-$\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-acetate (VI) from $\Delta^{7,16}$-allopregnadien-3β-ol-20-one 3-acetate (III)[3] by alkaline hydrogen peroxide oxidation to the oxide V followed by mercuric acetate dehydrogenation. The oxido-diene VI represents an important starting material for the introduction of the 11-keto group and subsequent conversion[7] of the 16,17-oxido-20-keto function to the ketol side chain, characteristic of the cortical hormones.



III IV

Va R = H
b R = Ac

VI

Experimental[8]

Δ^{7}-Allopregnene-3β,20β-diol (Ib).[6]—A solution of 4.0 g. of Δ^{7}-allopregnen-3β-ol-20-one 3-acetate (Ia)[3] in 300 cc. of dry ether was added dropwise to a mixture of 2 g. of lithium aluminum hydride in 50 cc. of ether. After refluxing for ten minutes, the excess reagent was decomposed with dilute acid, the diol Ib was extracted with ether, the latter was washed with water, dried and evaporated. Recrystallization from ether–pentane yielded 2.5 g. (63%) of colorless crystals with m.p. 179–180°, $[\alpha]^{20}\text{D}$ −21.8°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.69; H, 10.44.

The diacetate Ic was recrystallized from methanol, m.p. 104–106°, $[\alpha]\text{D}^{20}$ −3.2°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.57; H, 9.32.

$\Delta^{7,9(11)}$-Allopregnadiene-3β,20β-diol Diacetate (IIc) (A) By Mercuric Acetate Dehydrogenation of Δ^{7}-Allopregnene-3β,20β-diol Diacetate (Ic).—A mixture of 1.0 g. of diacetate Ic, 2.0 g. of C.P. mercuric acetate, 25 cc. of chloroform and 40 cc. of acetic acid was shaken at room temperature for 18 hours. After working up in the usual manner[2,3] and recrystallizing from methanol, there was obtained 0.41 g. of the **diacetate IIc** with m.p. 113–115°, $[\alpha]^{20}\text{D}$ +23.5°, ultraviolet absorption maxima at 236 mμ (log ϵ 4.11) and 242 mμ (log ϵ 4.14).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.28; H, 9.18.

(B) By Lithium Aluminum Hydride Reduction of $\Delta^{7,9(11)}$-Allopregnadien-3β-ol-20-one 3-Acetate (IIa).—The dienolone IIa (2.0 g.) was reduced with 1 g. of lithium aluminum hydride exactly as described above for Ia. Recrystallization from acetone afforded 1.41 g. (71%) of colorless prisms of the **diene diol IIb** with m.p. 183–185°, $[\alpha]^{20}\text{D}$ + 24°, ultraviolet absorption maxima at 235 mμ (log ϵ 4.09) and 242 mμ (log ϵ 4.13).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.86; H, 9.91.

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[1] Paper XXII, L. Miramontes, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3540 (1951).

[2] G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).

[3] C. Djerassi, J. Romo and G. Rosenkranz, *ibid.*, **16**, 754 (1951).

[4] E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951).

[5] L. F. Fieser, J. E. Herz and W. Huang, *ibid.*, **73**, 2397 (1951).

[5a] G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951).

[6] The 20β-configuration is assumed provisionally by analogy to the course of the lithium aluminum hydride reduction of Δ^{5}-pregnen-3β-ol-20-one (W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950)), and the dextrorotatory shift observed on acetylation (W. Klyne and D. H. R. Barton, THIS JOURNAL, **71**, 1500 (1949)). It should be noted, however, that this shift is much less pronounced in the dienes IIb and IIc, which might indicate a vicinal effect of the diene system.

[7] P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

[8] All melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba for the microanalyses.

Acetylation produced the **diacetate IIc** with m.p. 113–114°, undepressed upon admixture with a specimen produced according to procedure (a), $[\alpha]^{20}D$ +23.9°.

$\Delta^{7,16}$-Allopregnadiene-3β, 20β (?)-diol (IV).—Produced in 70% yield by lithium aluminum hydride reduction of III[3]; colorless crystals (from ether–hexane), m.p. 145–147°, $[\alpha]^{20}D$ +6.6°, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.36; H, 10.26.

16α,17α-Oxido-Δ^7-allopregnen-3β-ol-20-one (Va).—To a solution of 5.0 g. of $\Delta^{7,16}$-allopregnadien-3β-ol-20-one 3-acetate (III)[3] in 400 cc. of methanol, cooled to 18°, was added dropwise simultaneously from two separatory funnels 10 cc. of 30% hydrogen peroxide and a solution of 2.3 g. of sodium hydroxide in 10 cc. of water and 25 cc. of methanol. After stirring for one hour at room temperature, the mixture was left in the ice-box overnight and then diluted with water. Filtration yielded 4.6 g. of a mixture of free alcohol (Va) and acetate (Vb), which did not show any ultraviolet absorption maximum at 240 mμ. The crude material was saponified by boiling with methanolic potassium bicarbonate solution for one hour and the colorless crystals were recrystallized from acetone–water yielding 4.2 g. (90%) of the alcohol Va with m.p. 124–126°, $[\alpha]^{20}D$ +32.5°.

Anal. Calcd. for $C_{21}H_{50}O_3$: C, 76.32; H, 9.15. Found: C, 76.38; H, 9.41.

The acetate Vb exhibited m.p. 153–155°, $[\alpha]^{20}D$ +28°; yellow color with tetranitromethane.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.54.

16α,17α-Oxido-$\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-Acetate (VI).—The mercuric acetate dehydrogenation of the oxide Vb was carried out exactly as described above for Ic and after recrystallization from methanol afforded large prisms of the diene VI with m.p. 153–155°, $[\alpha]^{20}D$ +102°, ultraviolet absorption maxima at 234° mμ (log ϵ 4.13) and 242 mμ (log ϵ 4.17). The product gave an orange color with tetranitromethane.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.64; H, 8.48.

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Mercurial Diuretics. V. Stability of Mercury–Olefin Addition Compounds to Hydrochloric Acid

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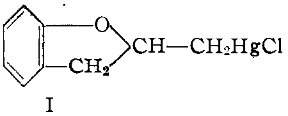
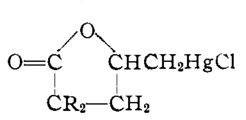
The products obtained by the addition of mercuric salts to olefins in water or alcohol are as a general rule decomposed by mineral acids. Certain exceptions to this rule have been noted: for example, 2-chloromercurimethyl-2,3-dihydrobenzofuran (I) obtained by the mercuration of *o*-allylphenol, exhibits stability to acids which is remarkable when compared with other olefin–mercuric salt addition compounds.[1] Recently the formation of δ-chloromercuri-γ-valerolactones, II, III, by the reaction of allyl acetic acids with mercuric salts, has been reported.[2] The similarity of the structures of I, II and III suggested the study of the stability of II and III toward mineral acid.



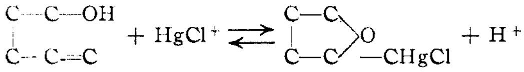
I



II, R = H
III, R = C_6H_5

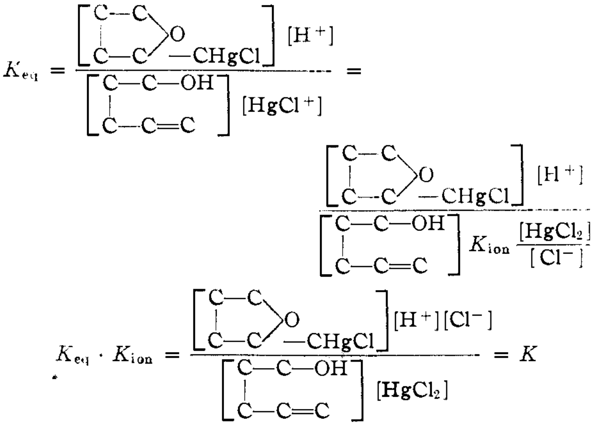
Formation of mercuric chloride from the δ-chloromercuri-γ-valerolactones was studied polarographically. With 0.07 *N* aqueous hydrochloric acid, II was decomposed rapidly while III did not react; III was decomposed, however, by 1 and 6 *N* hydrochloric acid. The pronounced difference in the ease of formation of mercuric chloride from II and from III may be related to stabilization of III by alpha substitution, but it would appear probable that this difference is largely a result of difference in solubility, II being quite soluble in water while III is very insoluble.

Since our study of the rate of decomposition of III in 1 *N* acid apparently measured the rate of solution of III, attention was directed to the equilibria involved in the acid decomposition of II and III. On the basis of the mechanism resulting from the study of Lucas, Hepner and Winstein,[3] the reaction under consideration would be



Since

$$K_{\text{ion}} = \frac{[\text{HgCl}^+]\,[\text{Cl}^-]}{[\text{HgCl}_2]}$$



The value of *K* has been determined previously for the reaction of ethylene with mercuric chloride in water.[4]

Although decomposition of 0.0001 mole of II by 100 ml. of 0.07 *N* hydrochloric acid was essentially complete, only 50% decomposition occurred with 0.01 *N* acid (note Table I). Accordingly, the value of *K* for the reaction of allylacetic acid with mercuric chloride in water was calculated to be 0.19.[5] When the equilibrium was approached by reaction of allylacetic acid with mercuric chloride in an aqueous solution which was originally 0.01 *M* in both reactants, the equilibrium concentration of mercuric chloride was determined polarographically to be 0.0019 *M;* on the basis of this observation, the value of *K* was 0.15.

No mercuric chloride was detected after agitation of III and 0.07 *N* hydrochloric acid for 312 hours.

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[1] R. Adams, F. L. Roman and W. N. Sperry, THIS JOURNAL, **44**, 1781 (1922).

[2] R. L. Rowland, W. L. Perry and H. L. Friedman, *ibid.*, **73**, 1040 (1951).

[3] H. J. Lucas, F. R. Hepner and S. J. Winstein, *ibid.*, **61**, 3102 (1939); J. Chatt, *Chem. Revs.*, **48**, 37 (1951).

[4] J. Sand and F. Breest, *Z. physik. Chem.*, **59**, 424 (1907).

[5] In this and subsequent calculations, the value of $HgCl_2$ was corrected for the formation of $HgCl_3^-$ and $HgCl_4^=$ utilizing the constants $[HgCl_3^-]/[HgCl_2][Cl^-]$ = 7 and $[HgCl_4^=]/[HgCl_2][Cl^-]^2$ = 70, determined by B. Lindgren, A. Jonsson and L. G. Sillen, *Acta Chem. Scand.*, **1**, 479 (1947).