[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXI. Degradation of Hecololactone Acetate to Derivatives of 12,13-*seco*-16-Allopregnene-3β,13α-diol-12-carboxy-20-one 12,13-Lactone[2]

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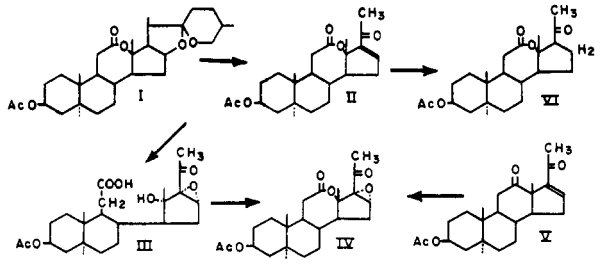
The degradation of hecololactone acetate to the 12,13-*seco*-16-allopregnene-20-ketone is described. The critical step in the procedure is the cleavage of the 16-acyloxy-20-ketone intermediate by means of a two-phase *t*-butyl alcohol–water–sodium bicarbonate mixture.

In paper XI[3] of this series, the peracid oxidation of steroidal C-12 ketosapogenins was shown to lead to the formation of seven-membered ring lactones. The present paper describes the degradation of hecololactone to 12,13-*seco*-16-allopregnene derivatives. The three-step Marker[4] procedure of sapogenin degradation involving the isomerization of the sapogenin acetate with acetic anhydride at 200° to a pseudosapogenin diacetate, subsequent oxidation to a 16-acyloxypregnane-20-one, and hydrolysis to a Δ^{16}-20-ketone is applicable to hecololactone acetate; however, modification of the hydrolytic conditions in the third step is necessary if the desired product is to be obtained.

Treatment of the 16-acyloxy oxidation product of the pseudosapogenin with strong alkali,[5] even when *t*-butyl alcohol was the medium, produced dark colored, non-crystalline material. Attempted cleavage by adsorption on alumina columns[6] also failed. However, *t*-butyl alcohol–water–sodium bicarbonate mixtures gave workable systems. While dark sirupy by-products also are formed in this system, the ether-insolubility of the 12,13-*seco*-16-allopregnene 12,13-lactone derivative (II), allowed its isolation in a highly pure form.



The ultraviolet absorption maximum at 227 mμ is lower than that usually observed but is the same as the value reported[6] for the Δ^{16}-12,20-diketones obtained by degradation of hecogenin and manogenin. The optical levorotation of the 12,13-*seco*-16-allopregnene-20-one 12,13-lactone derivative(II) is also unusual. In general, with the exception of the Δ^{16}-20-ketones and its oxide derivative, the molecular rotation value of compounds of the hecolactone series is of the same sign and is close in absolute value to that of the corresponding unaltered C-ring analog. Examples are seen in Table I.

TABLE I

M_D COMPARISONS IN THE HECOLOLACTONE AND TIGOGENIN SERIES

	M_D ($CHCl_3$)
Tigogenin acetate	−334
Hecololactone acetate	−318
Tigogenin	−270
Hecololactone	−232
Tigogenone	−219
3-Dehydrohecololactone	−230
3β-Acetoxy-16-allopregnene-3β-ol-20-one (II)	+108 −103
3β-Acetoxy-16α,17α-epoxy-allopregnane-20-one (IV)	+178 + 73
3β-Acetoxyallopregnane-20-one (VI)	+277 +236

We were also surprised to find that the 16,17-olefinic bond of the Δ^{16}-20-ketone II was inert to attack by perbenzoic acid. This double bond could, however, be attacked by alkaline hydrogen peroxide[6,7] to form the lactone epoxide IV. The alkaline medium caused some saponification of the lactone ring to form the epoxide of the hydroxy acid III, which could be relactonized by acetic anhydride leading to the same product IV bringing the over-all yield to 38%. This epoxide IV, m.p. 269–270°, $[\alpha]^{25}D$ +17.8°, we believe to be identical with the unknown compound, m.p. 271–272°, $[\alpha]^{25}D$ +19.4°, described by Mueller, Stobaugh and Winniford,[6] which they obtained by treating 3β-acetoxy-16-allopregnene-2,20-dione (V) with perbenzoic acid. We also have obtained this epoxide from the action of perbenzoic acid on 3β-acetoxy-16-allopregnene-12,20-dione using sulfuric acid catalysis.

Attempts to open the peroxide ring with hydrobromic acid and with lithium aluminum hydride did not lead to isolable, crystalline products.

Experimental

Degradation of Hecololactone Acetate (I) to 3β-Acetoxy-13α-hydroxy-12,13-*seco*-16-allopregnene-20-one-12-carboxylate 12,13-Lactone (II).—Hecololactone acetate, 24.4 g., in 75 ml. of acetic anhydride was heated 19 hours in a sealed tube at 185°. On cooling, 5 g. of crystalline starting material, m.p. 298°, precipitated and was removed. The sirupy filtrate after stirring with 13 ml. of H_2O to decompose the acetic anhydride, and diluting with 112 ml. of acetic acid was treated with 5 g. of sodium acetate trihydrate, and a solution of 8 g. of chromic anhydride in 30 ml. of 80%

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XX, M. E. Wall and S. Serota, THIS JOURNAL, **76**, 2850 (1954).

(3) E. S. Rothman, M. E. Wall and C. R. Eddy, *ibid.*, **76**, 527 (1954).

(4) See, for example, R. E. Marker, *et al.*, *ibid.*, **69**, 2167 (1947).

(5) M. E. Wall, H. E. Kenney, H. W. Jones and E. S. Rothman, Fifth Meeting in Miniature, Philadelphia Section A.C.S., Jan. 29, 1953, Abstracts of Papers, p. 10.

(6) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, THIS JOURNAL, **75**, 4888 (1953).

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

acetic acid added slowly during the course of 0.5 hour keeping the temperature below 15°. After stirring for 100 minutes at 20°, the mixture was poured into water and the steroid extracted with ether. The ether was washed well with water only and evaporated *in vacuo* with stirring to a heavy, gummy, yellowish residue. This was dissolved in 125 ml. of *t*-butyl alcohol, 125 ml. of 5% aqueous sodium bicarbonate was added and the mixture mechanically shaken overnight. On dilution with water and addition of ether 3.1 g. of crystalline material separated immediately. Evaporation of the ethereal layer and crystallization from ether gave 6.8 g. more of crystalline 3-acetoxy product. The over-all yield without regard to recovered starting material was 51%; the yield corrected for recovered starting material, 65%. The m.p. determined at a moderate heating rate was 185–191°; however, on slow heating a double melting was observed. The flattened needles melted at 173.5°, solidified to quadrilateral forms which reliquefied at 203–205° giving a doubly refracting melt when observed through polarizing filters, $[\alpha]^{25}D$ −26°; $\lambda^{227}_{max.}$ mμ 9880, log 4.0; $\lambda_{max.}$ 1677 cm.$^{-1}$ (CS_2).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.00, 70.91; H, 8.15, 7.83.

An aliquot containing 1 g. of the gummy yellowish residue described above was dissolved in 25 ml. of *t*-butyl alcohol, 1 g. of KOH in 1 cc. of H_2O was added and the mixture was stirred for 3 hours at 25°. The mixture of products was isolated with ether, washed with 5% hydrochloric acid, 5% sodium bicarbonate, dried and evaporated. The residue was a black tar yielding no crystallizable matter.

Another 1-g. aliquot in benzene solution was adsorbed on activated alumina overnight. Chloroform eluted 0.22 g. and methanol eluted 0.78 g. of glassy materials showing only moderate infrared absorption near 1677 cm.$^{-1}$ These materials could not be crystallized.

3β-Acetoxy-13α-hydroxy-16α,17α-epoxy-12-carboxy-12,13-*seco*-allopregnane-20-one 12,13-Lactone (IV). (a) From II.—From Δ 16-20-ketone II, 9.8 g., in 660 ml. of methanol was treated with 37 ml. of 30% hydrogen peroxide at 10° and 4.1 g. of sodium hydroxide in 21 ml. of water added. The mixture was let stand overnight at 10°, diluted with 500 ml. of water containing 3.74 g. of hydrochloric acid, and the solution repeatedly extracted with chloroform until test evaporations of the chloroform showed no residue. A sample of the white crystalline residues in the last extracts was identified as the oxide of the 3β-acetoxy derivative of the 13α-hydroxy-12-carboxylic acid produced by the partial saponification of the lactone, *viz.*, 3β-acetoxy-16α,17α-epoxy-13α-hydroxy-12-carboxy-12,13-*seco*-allopregnane-20-one (III), m.p. 210–213.5°, $[\alpha]^{25}D$ +38.4° (MeOH).

Anal. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.26; H, 8.12.

Treatment of the combined extracts with pyridine–acetic anhydride overnight at room temperature gave ring closure to the lactone IV in 38% yield. The product m.p. 265–267° gave hexagonal scales from ether, m.p. 269–270°, after transition to octagonal forms, $[\alpha]^{25}D$ +17.8°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.07; H, 8.03.

(b) From 3β-Acetoxy-16-allopregnene-12,20-dione (V).—Two grams of V, m.p. 179–180, *i.e.*, 5.37 millimoles, was mixed at 5° with 44.32 ml. of chloroform containing 21.48 millimoles of perbenzoic acid. One milliter of 10% sulfuric acid in acetic acid was added and the mixture let stand for two weeks. The chloroform was washed with dilute sodium hydroxide and with water and evaporated. The residue was triturated with ether whereupon 190 mg. of a crystalline precipitate formed melting over 300° which was filtered off. The mother liquors deposited 350 mg. of a white crystalline product m.p. 231–241°, which on recrystallization once from acetone melted at 266–270° and had an infrared spectrum essentially identical with that of the preparation described above.

3β-Acetoxy-13α-hydroxy-12,13-*seco*-allopregnane-20-one-12-carboxylate 12,13-Lactone (VI).—Two grams of II in 75 cc. of tetrahydrofuran were shaken with 1 g. of 5% palladium-on-carbon catalyst at three atmospheres for six hours. The catalyst was filtered and washed with acetone. The solvents were evaporated and the resulting glassy residue was crystallized from ether to give 0.4 g. of crystalline material, m.p. 178–183°. This product on slow crystallization from acetone gave large hexagonal tablets having a double melting point 172.5°, 184–189°, $[\alpha]^{25}D$ +60.4°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.54; H, 8.65.

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Steroidal Sapogenins. XXII.[2] Conversion of Hecogenin Acetate to a Hecololactone Derivative with the Adrenal Cortical Hormone Side Chain *via* Allopregnane-3β,17α,21-triol-12,20-dione Diacetate

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Allopregnane-3β,17α-diol-12,20-dione 3-acetate is described as having physical properties different from those previously reported. This material was in turn converted to allopregnane-3β,17α,21-triol-12,20-dione 3,21-diacetate, a diketone, which suffers oxidative attack by perbenzoic acid only at the C-12 carbonyl group to form 12-carboxy-12,13-seco-allopregnane-3β,13α,17α,21-tetrol-20-one 12,13-lactone 3,21-diacetate.

In the preceding article of this series[2] the direct degradation of hecololactone acetate to the *seco*-allopregnene derivative 12-carboxy-12,13-*seco*-16-allopregnene-3β,13α-diol-20-one 12,13-lactone 3-acetate was described. The *seco*-allopregnene product presented difficulties in subsequent transformations. In particular the attempted opening of the epoxide ring of its 16α,17α-epoxy derivative did not lead to isolation of crystalline products. For this reason, an alternative approach to our problem of synthesis of hecololactone types having the dihydroxyacetone side chain was considered. The results of this approach involving the lactonization of the C-ring as the *final* reaction step are presented here.

Starting with 16-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate (I), a compound first synthesized by Mueller, Stobaugh and Winniford,[3] we

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(2) Paper XXI, E. S. Rothman and M. E. Wall, THIS JOURNAL, **77**, 2228 (1955).

(3) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.* **75**, 4888 (1953).