$$\text{Ar-COCH}_2\text{COOEt} \longrightarrow \text{ArCOCCOOEt} \longrightarrow \underset{\underset{\text{NOH}}{\|}}{\text{ArCOCCOOEt}} \longrightarrow \text{Ar-CHOH—CH(NH}_2\text{)—ECOOt}$$

The products, capable of existing in two racemic forms, are obtained in the (±)-*erythro*-configuration.[4]

Experimental

Ethyl benzoyloximinoacetate, prepared by treating an ethereal solution of ethyl benzoylacetate with isopropyl nitrite according to the general procedure of Hartung and Munch[5] was obtained in 85–88.5% yields, formed white crystals m.p. 123–124° (uncor.) after two crystallizations from toluene.[6]

Anal. Calcd. for $C_{11}H_{11}O_4$: N, 6.33. Found: N, 6.35, 6.29.

Ethyl ester of *dl-erythro*-β-phenylserine, as obtained by catalytic hydrogenation is described by Chang and Hartung.[7]

Ethyl *p*-chlorobenzoyloximinoacetate was obtained from ethyl *p*-chlorobenzoylacetate and isopropyl nitrite[5] in yields 57–62.5%. Crystallized from toluene, the product melted 135–136° (uncor.).

Anal. Calcd. for $C_{11}H_{10}O_4NCl$: N, 5.49. Found: N, 5.45.

Ethyl ester of *dl-erythro*-β-*p*-chlorophenylserine was obtained by hydrogenating with Pd-on-C catalyst 7.0 g. of the oximino intermediate in 175 ml. ethanol in which was dissolved 20 g. of HCl. The H_2 uptake was 12% more than calculated, and it is possible that some of the chlorine was removed from the phenyl nucleus. Obtained 6.3 g. of the hydrochloride, 82.5%, m.p. 168–170°.

Anal. Calcd. for $C_{11}H_{14}O_3NCl{\cdot}HCl$: N, 5.22. Found: N, 5.19, 5.30.

(4) The configuration is assigned on the basis of correlation studies by (a) K. N. F. Shaw and S. W. Fox, abstracts, p. 28N, Chicago Meeting, American Chemical Society, 1950; (b) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **79**, 856 (1949); (c) D. Billet, *Compt. rend.*, **230**, 1074 (1950); (d) K. Vogler, *Helv. Chim. Acta*, **33**, 2111 (1950).

(5) W. H. Hartung and J. C. Munch, THIS JOURNAL, **51**, 2262 (1929).

(6) A. Bernton, *Arkiv. Kemi Mineral, Geol.*, **7**, No. 13, 1 (1919); *C. A.*, **14**, 2168 (1920), gives m.p. 121°.

(7) Y. T. Chang and W. H. Hartung, THIS JOURNAL, **75**, 89 (1953).

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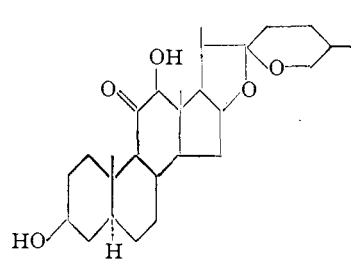
Steroidal Sapogenins. XXV.[1] Experiments in the Hecogenin Series (Part 4).[2] Degradation of 22a-5α-Spirostane-3β,12β-diol-11-one[3]

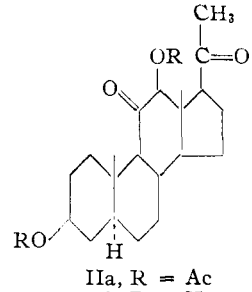
BY H. MARTINEZ, HOWARD J. RINGOLD, G. ROSENKRANZ AND CARL DJERASSI[4]

RECEIVED SEPTEMBER 17, 1952

It has been reported previously[2] that Gallagher's[5] procedure for the shift of the C-12 carbonyl function to position 11 developed in the bile acid series is inapplicable to the sapogenins, since the penultimate step—displacement of the C-12 hydroxyl group of 22a-5α-spirostane-3β,12β-diol-11-one (I)[6] by phosphorus tribromide—fails due to side reactions with the spiroketal system. It was necessary, therefore, to develop an alternate path through bismuth oxide oxidation[2] to an 11,12-dione and subsequent removal of the C-12 carbonyl group. Simultaneously with this work,[2] we have also investigated the feasibility of Gallagher's method[5] in the pregnane series and the present note deals briefly with such attempts.



I



IIa, R = Ac
b, R = H

It was planned to degrade the ketol I to the corresponding allopregnane derivative II where troublesome interference with phosphorus tribromide was not anticipated, and to effect the removal of the 12-hydroxyl function at this stage with the formation of allopregnan-3β-ol-11,20-dione, a substance which has already been converted to cortisone.[7,8] In contrast to the unsatisfactory side chain degradation of 22a-5α-spirostan-3β-ol-12-one (hecogenin),[9] the corresponding reaction with the 11-isomer[10] proceeded rather readily and it is interesting to observe that a similar degradation of the 3,12-diol-11-one (I) recorded in the present paper gave equally satisfactory results. The intermediate $\Delta^{20(22)}$-5α-furostene-3β,12β,26-triol-11-one has already been described earlier,[6] but for optimum yields of Δ^{16}-allopregnene-3β,12β-diol-11-one diacetate it was neither necessary nor desirable to isolate this intermediate furostene derivative. The Δ^{16}-20-ketone diacetate was hydrogenated readily to the corresponding saturated analog (IIa) but all attempts to saponify this diacetate completely to the diol IIb—a necessary operation before selective acylation at C-3 and subsequent displacement at C-12 with phosphorus tribromide can be carried out—resulted in very poor yields. This disappointing result may well be due to two factors, the ready isomerization of the ketol system under basic conditions to a mixture of isomeric ketols[5] and possibly also partial isomerization at C-17 to the α-epimer, which may be favored by the 12β-hydroxy substituent. At the present time, therefore, the only successful conversion of hecogenin to cortisone still remains the one through 22a-5α-spirostan-3β-ol-11,12-dione.[2]

(1) Paper XXIV, M. Velasco, J. Rivera, G. Rosenkranz, F. Sondheimer and C. Djerassi, *J. Org. Chem.*, **17**, December (1952).

(2) Part 3, C. Djerassi, H. J. Ringold and G. Rosenkranz, THIS JOURNAL, **73**, 5513 (1951).

(3) Our sapogenin nomenclature (G. Rosenkranz and C. Djerassi, *Nature*, **166**, 104 (1950)) has been changed slightly in accordance with the recommendations of the Ciba Conference on Steroid Nomenclature (*cf. Chemistry and Industry*, June 23, 1951, SN1).

(4) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(5) E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, **177**, 951 (1949).

(6) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

(7) J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, THIS JOURNAL, **73**, 4053 (1951).

(8) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951); **74**, 5615 (1952).

(9) R. B. Wagner, J. A. Moore and R. F. Forker, *ibid.*, **72**, 1856 (1950).

(10) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).

Incidental to the above experiments, there was also carried out the epoxidation of the initial degradation product Δ^{16}-allopregnene-3β,12β-diol-11-one diacetate with alkaline hydrogen peroxide. The resulting 16α,17α-oxide, isolated as the free diol, was transformed to the bromohydrin with hydrogen bromide in glacial acetic acid and immediately debrominated with palladized calcium carbonate catalyst[11] to yield allopregnane-3β,12β,17α-triol-11,20-dione.

Experimental[12]

Δ^{16}-Allopregnene-3β,12β-diol-11,20-dione Diacetate.—22a-5α-Spirostane-3β,12β-diol-11-one (I)[6] (4.9 g.) was converted into the furostene diacetate and directly oxidized with chromium trioxide and hydrolyzed with bicarbonate solution exactly as described for Δ^7-22a-5α-spirosten-3β-ol.[13] Chromatography through a short alumina column afforded 2.24 g. of colorless crystals with m.p. 213–215°, which upon further recrystallization from ether furnished the analytical sample with m.p. 214–216°, $[\alpha]^{20}D$ +22°, λ_{max}^{EtOH} 230 mμ (log ϵ 4.08),[14] $\lambda_{max}^{CS_2}$ 1736 (acetate) and 1680 cm.$^{-1}$ (Δ^{16}-20-ketone).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.39; H, 8.11.

Allopregnane-3β,12β-diol-11,20-dione Diacetate (IIa).—The catalytic hydrogenation of the above Δ^{16}-20-ketone (0.63 g.) was carried out in ethyl acetate solution (45 cc.) at room temperature and atmospheric pressure employing 0.11 g. of 10% palladized charcoal catalyst. The hydrogen uptake corresponding to one mole ceased within one hour, whereupon the catalyst was filtered, the filtrate evaporated to dryness and the residue was recrystallized from ether–pentane; yield 0.52 g., m.p. 155–157°, $[\alpha]^{20}D$ +29°, $\lambda_{max}^{CS_2}$ 1736 (acetate) and 1710 cm.$^{-1}$ (saturated 20-ketone).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.79; H, 8.03.

Attempts at partial saponification (limited amounts of bicarbonate at room temperature) furnished after chromatography some oily material and chiefly recovered diacetate. Potassium carbonate (room temperature or refluxing) afforded mixtures containing free diol, monoacetate and/or diacetate (free hydroxyl band as well as carbonyl bands at 1736 and 1706 cm.$^{-1}$). Saponification with boiling 5–10% methanolic potassium hydroxide yielded about 50% of solid with m.p. 147–155°, which after several recrystallizations from ether led to an analytical sample, m.p. 167–169°, $[\alpha]^{20}D$ +100°, which may be the desired diol IIb or an isomer (in ring C).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.47; H, 8.96.

16α,17α-Oxidoallopregnane-3β,12β-diol-11,20-dione.—An ice-cold solution of 0.5 g. of Δ^{16}-allopregnene-3β,12β-diol-11,20-dione diacetate in 40 cc. of methanol was treated with 1.25 cc. of 30% hydrogen peroxide followed by the addition of a solution of 0.5 g. of sodium hydroxide in 2 cc. of water. After 89 hours in the refrigerator, the solution was diluted with chloroform, washed with water until neutral, dried and evaporated. Recrystallization from acetone–hexane furnished 0.24 g. of colorless crystals with m.p. 183–185°, $[\alpha]^{20}D$ +105°, $\lambda_{max}^{CS_2}$ 1718 cm.$^{-1}$ and free hydroxyl band. The method of preparation and the physical constants do not preclude the possibility of epimerization of the ketol system in ring C.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.42; H, 8.44.

Allopregnane-3β,12β,17α-triol-11,20-dione.[15]—A solution of 2.49 g. of the above oxide in 25 cc. of glacial acetic acid was treated for 15 minutes at 18° with 5 cc. of a 32% solution of hydrogen bromide in glacial acetic acid and then diluted with much water. The bromohydrin was filtered, washed well with water, air-dried, and then hydrogenated directly with 9.0 g. of 2% palladized calcium carbonate in 75 cc. of 95% ethanol at room temperature and atmospheric pressure for 16 hours. After filtration of the catalyst and evaporation of the filtrate to dryness, the residue was allowed to stand at room temperature for two hours in 1% methanolic potassium hydroxide solution in order to saponify any 3-acetate formed during the oxide opening. Neutralization with acetic acid and concentration *in vacuo* followed by chilling afforded (two crops) 2.08 g. of crystals with m.p. 270–274°. The analytical sample was obtained from acetone and exhibited m.p. 278–282° (Fisher block), $[\alpha]^{20}D$ +52° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.29; H, 8.82.

(11) F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

(12) Melting points are uncorrected. Unless indicated otherwise, 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.

(13) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(14) It is interesting to note that the ultraviolet absorption maximum is at the rather low wave length of 230 mμ, also observed with a 12-keto (ref. 9) and 8(14)-unsaturated (O. Mancera, D. H. R. Barton, G. Rosenkranz and C. Djerassi, *J. Chem. Soc.*, 1026 (1952)) Δ^{14}-20-ketone, in contrast to the expected maximum (*ca.* 238 mμ) found with the corresponding 11-ketone (ref. 10) and 12α-acetoxy derivatives (C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 660 (1949)).

(15) As pointed out above, the preparation of the oxide with alkaline hydrogen peroxide, though carried out at low temperature, may nevertheless involve isomerization of the ketol system (*cf.* ref. 5). Since the triol was obtained from the oxide, this reservation concerning the stereochemistry of the ketol system (in ring C) applies to both substances.

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Condensation of Trisodium Tricarballylate with Propionic Anhydride

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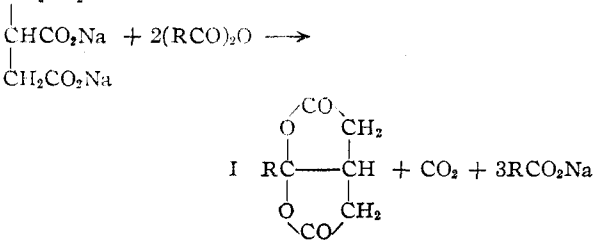
The condensation of trisodium tricarballylate with an acid anhydride to form a β-acylglutarobislactone (I) appears to be a fairly general reaction.[1,2] The method has been applied successfully to acetic anhydride,[3] *n*-butyric anhydride,[4] isobutyric anhydride,[4] benzoic anhydride[5] and phthalic anhydride.[6] The yields of I ranged from 5 to 43%. The position of condensation, at the site of the central carboxyl group of trisodium tricarballylate, was proved beyond question.



Trisodium camphoronate (II) has also been reported to form β-aceto-α,α,β-trimethylglutarobislactone (III) by reaction with acetic anhydride.[7]

The bislactones I were reported to undergo hydrolysis to β-acylglutaric acids IV on being boiled

(1) R. Fittig, *Ber.*, **30**, 2145 (1897).
(2) R. Fittig, *Ann.*, **314**, 1 (1901).
(3) R. Fittig and E. Roth, *ibid.*, **314**, 16 (1901).
(4) R. Fittig and T. Guthrie, *ibid.*, **314**, 40 (1901).
(5) R. Fittig and H. Salomon, *ibid.*, **314**, 58 (1901).
(6) R. Fittig and O. Gottsche, *ibid.*, **314**, 74 (1901).
(7) R. Fittig and H. Salomon, *ibid.*, **314**, 89 (1901).