(regenerated from its semicarbazone) gave a 60% yield of retene, m.p. 99.5–100.5° (picrate m.p. 125.5–126.5°), undepressed with an authentic sample prepared from dehydroabietic acid.[5]

The structural identity of the synthetic *dl*-1-keto-7-isopropyl-12-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (Ic) with the C_{18} *d*-ketone recently obtained from dehydroabietic acid[6] is confirmed by comparison of their infrared spectra (Fig. 1).

The extension of this work to the stereospecific synthesis of the resin acids is being actively pursued.

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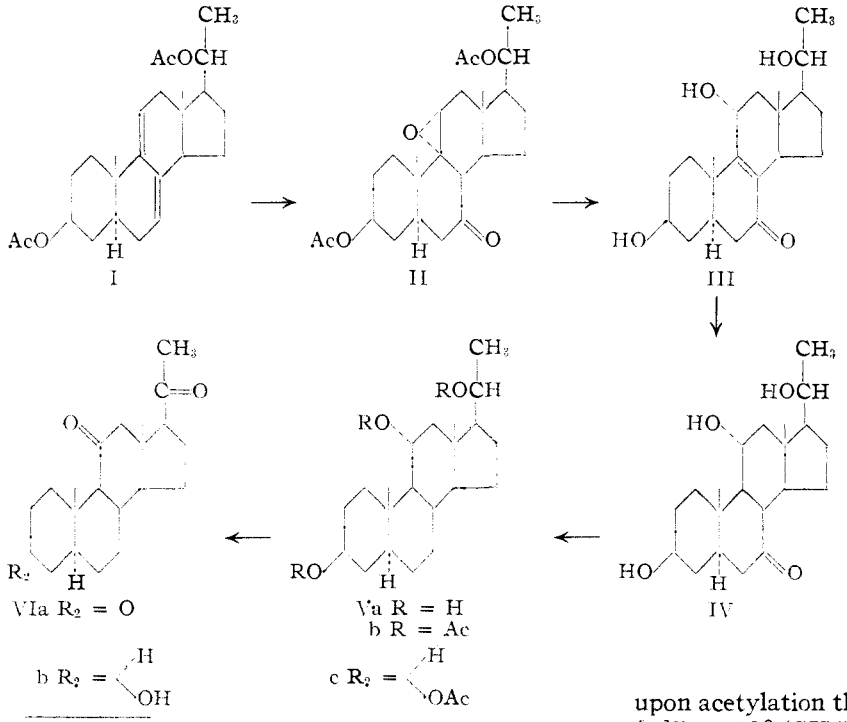
RECEIVED JUNE 15, 1951

(5) L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, **16**, 842 (1933).
(6) A. Brossi, H. Gutmann and O. Jeger, *ibid.*, **33**, 1730 (1950).
(7) National Institutes of Health Predoctoral Fellow, Harvard University, 1950–1951.

STEROIDS. XXIV.[1] INTRODUCTION OF THE 11-KETO AND 11α-HYDROXY GROUPS INTO RING C UNSUBSTITUTED STEROIDS

Sir:

The conversion of Δ^5-3β-hydroxy steroids to a number of $\Delta^{7,9(11)}$-dienes of the pregnane and sapogenin series with both the *allo* and *normal* configuration at C-5 has recently been reported from this Laboratory.[1–4] In two Communications[5,6] to the Editor, there is described the transformation of such $\Delta^{7,9(11)}$-dienes to 11-ketosteroids by way of Δ^8-unsaturated and thence saturated 7,11-diones. We should like to record herewith an alternate procedure for the synthesis of 11-oxygenated steroids from ring C unsubstituted steroids via $\Delta^{7,9(11)}$-dienes, which does not involve the above mentioned[5,6] intermediates. In addition to its versatility, the presently described method exhibits the attractive feature of representing a novel and convenient synthesis for the hitherto unknown 11α-hydroxyallopregnanes and sapogenins.[6a]



Performic acid oxidation of $\Delta^{7,9(11)}$-allopregnadiene-3β,20β-diol diacetate (I)[1] readily led to 9α,11α-oxidoallopregnane-3β,20β-diol-7-one diacetate (II) (m.p. 260–262° (all m.p.s are uncorrected), $[\alpha]^{20}D$ −55° ($CHCl_3$), no ultraviolet maximum, $\lambda_{max.}^{nujol}$ 1736 cm.$^{-1}$ (acetate) and 1718 cm.$^{-1}$ (7-ketone), no free hydroxyl band; found: C, 68.95; H, 8.39). Alkaline hydrolysis was accompanied by isomerization and afforded in high yield Δ^8-allopregnene-3β,11α,20β-triol-7-one (III) (m.p. 250–252°, $[\alpha]^{20}D$ −25° (EtOH), $\lambda_{max.}^{EtOH}$ 254 mμ, log ε 4. 11, $\lambda_{max.}^{nujol}$ 1662 cm.$^{-1}$, found: C, 72.52; H, 8.97; triacetate, m.p. 203–205°; found: C, 68.21; H, 8.06). Catalytic hydrogenation (palladized charcoal in ethanol solution) of III produced 78% of allopregnane-3β,11α,20β-triol-7-one (IV) (m.p. 246–248°, $[\alpha]^{20}D$ −112° (EtOH), no ultraviolet maximum, $\lambda_{max.}^{nujol}$ 1718 cm.$^{-1}$; found: C, 71.58; H, 10.01). Wolff–Kishner reduction gave allopregnane-3β,11α,20β-triol(Va) (m.p. 253–255°, $[\alpha]^{20}D$ −28° (EtOH), no carbonyl band in infrared; found: C, 74.63; H, 10.83), which formed a triacetate (Vb) (m.p. 162–164°, $[\alpha]^{20}D$ −16° ($CHCl_3$), $\lambda_{max.}^{CS_2}$ 1736 cm.$^{-1}$ (acetate), no free hydroxyl band; found: C, 70.47; H, 9.26). Chromium trioxide oxidation of the triol Va led to the known[7] allopregnane-3,11,20-trione (VIa) (m.p. 211–213°, $[\alpha]^{20}D$ +129° (EtOH); found: C, 76.19; H, 9.39), which on Raney nickel reduction smoothly yielded allopregnane-11,20-dione-3β-ol (VIb) (m.p. 192–194°, $[\alpha]^{20}D$ +99° ($CHCl_3$); found: C, 75.44; H, 9.55) and upon acetylation the acetate (VIc)[8] (m.p. 143–144°, $[\alpha]^{20}D$ +89° ($CHCl_3$), $\lambda_{max.}^{CS_2}$ 1736 and 1710 cm.$^{-1}$, no

(1) Paper XXIII, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, in press.
(2) R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, (1951) in press.
(3) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).
(4) C. Djerassi, J. Romo and G. Rosenkranz, *ibid.*, **16**, 754 (1951).
(5) L. F. Fieser, J. E. Herz and W. Huang, THIS JOURNAL, **73**, 2397 (1951).
(6) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Alminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951).

(6a) W. T. Long, T. W. Marshall, and T. F. Gallagher, *J. Biol. Chem.*, **165**, 197 (1946), have prepared 11a-hydroxy compounds in the bile acid series.
(7) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938), prepared the trione VIa by degradation of corticosterone and reported m.p. 212–216°, $[\alpha]^{20}D$ +133° (EtOH). A mixed melting point determination, kindly performed by Prof. T. Reichstein, further confirmed the identity of the two specimens.
(8) Ref. 5 records m.p. 141–143°, $[\alpha]D$ +88°.

free hydroxyl band; found: C, 73.24; H, 8.88). The presently described procedure is equally applicable to the steroidal sapogenins as exemplified by the performic acid oxidation of $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol acetate[3] to 9α,11α-oxido-22-isoallospirostan-3β-ol-7-one acetate (m.p. 295–297°, $[\alpha]^{20}D$ −128° ($CHCl_3$), $\lambda_{max.}^{nujol}$ 1736 and 1718 cm.$^{-1}$; found: C, 71.74; H, 8.94). Analogous transformations of this oxidoketone to 11-oxygenated 22-isoallospirostan-3β-ols have already been completed and will be reported shortly in a detailed paper.

Since the starting diol (I)[5] has been prepared from both diosgenin[3,4] and Δ^5-pregnen-3β-ol-20-one[4] (which is also available from stigmasterol), the above described experiments constitute the conversion of the two most abundant plant steroids into 11-oxygenated pregnane derivatives.

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RECEIVED JUNE 11, 1951

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ACYLALKYLCARBONATES AS ACYLATING AGENTS FOR THE SYNTHESIS OF PEPTIDES

Sir:

Mixed anhydrides of carbonic with carboxylic acids have been found to be excellent acylating agents for the preparation of amides. In particular, anhydrides between branched chain alkyl carbonic acids and N-substituted amino acids or peptides react readily at low temperature with amino acid or peptide esters, or with a salt of an amino acid, to give the corresponding peptide or higher peptide in good yield. The by-products of the reaction, carbon dioxide and an alcohol, are readily removed and the peptide is obtained initially in a very high state of purity.

For peptide synthesis, the over-all reaction is given by

$$X\text{-}NHCH(R)COOCOOR''' + H_2NCH(R')COOR'' \longrightarrow X\text{-}NHCH(R)CONHCH(R')COOR'' + R'''OH + CO_2\uparrow$$

where X is a blocking group, R and R′ are amino-acid residues and R″ is an esterifying or salt forming group. Best results have been obtained when R‴ is a *s*- or isobutyl radical.

The mixed anhydrides are formed by treating *s*- or isobutylchlorocarbonate with a solution of the triethylamine salt of an N-substituted aminoacid or peptide in an inert solvent as toluene or chloroform at 0 to −10°. The reaction is complete in 25–30 minutes. A solution of the amino acid or peptide ester to be acylated, also in an inert solvent, is then added and the reaction mixture is allowed to warm to room temperature and stand overnight. Carbon dioxide evolution begins immediately upon addition of the base and is substantially complete after several hours. In some cases, the formed N-substituted peptide ester crystallizes directly from the reaction mixture and is essentially pure after washing with water to remove triethylamine hydrochloride. More generally, the reaction mixture is washed with water and with dilute sodium bicarbonate solution, dried and diluted with petroleum ether to crystallize the product.

Amino acids may be used in this procedure by preparing a solution in one equivalent of 2 *N* alkali and adding this to the preformed mixed anhydride. The heterogeneous mixture is then stirred rapidly for 1–2 hours and the aqueous phase is separated, extracted with ether and acidified to precipitate the formed peptide acid.

In general, *s*-butylchlorocarbonate gave slightly higher yields than the isobutyl isomer. Peptide ethyl esters prepared using these reagents to form the reactive mixed anhydrides include those of carbobenzoxyglycyl-L-tyrosine[1] (68%); m.p. 129–130°, $[\alpha]^{24}D$ +19.3° (*c* = 10, ethanol); dicarbobenzoxy-L-lysylglycine[2] (64%), m.p. 89–90°, $[\alpha]^{24}D$ −12.0° (*c* = 4, ethanol); carbobenzoxy-L-leucyl-L-tyrosine[3] (63%), m.p. 116–118°, $[\alpha]^{24}D$ −14.9° (*c* = 10, ethanol); phthalylglycyl-L-leucine[3] (61%), m.p. 142–143°, $[\alpha]^{24}D$ −23.2° (*c* = 5, ethanol); carbobenzoxyglycyl-DL-phenylalanylglycine[3] (83%), m.p. 134–135° (from carbobenzoxyglycyl-DL-phenylalanine and ethyl glycinate); phthalyl - DL - phenylalanylglycylglycine[3] (67%), m.p. 164–165° (from phthalyl-DL-phenylalanine and ethyl glycylglycinate) and carbobenzoxyglycyl-DL-phenylalanyl-DL-phenylalanylglycylglycine[3] (59%), m.p. 188–193° (from carbobenzoxyglycyl-DL-phenylalanine and ethyl DL-phenylalanylglycylglycinate).

Peptide acids prepared by the free aminoacid procedure include carbobenzoxyglycyl-DL-phenylalanine[4] (63%), m.p. 160–162°; carbobenzoxyglycyl-DL-valine[5] (49%), m.p. 127–128° and 146–147° and carbobenzoxy-DL-alanyl-DL-phenylalanine[5] (50%), m.p. 145–146°.

ADDED IN PROOF. We have just received a publication by R. A. Boissonnas (*Helv. Chim. Acta*, **34**, 874 (1951)) on this same general subject matter.

(1) M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **118**, 405 (1937).
(2) M. Bergmann, *et al.*, *Z. physiol. Chem.*, **224**, 26 (1934).
(3) Carbon, hydrogen and nitrogen analysis was satisfactory.
(4) H. Neurath, *et al.*, *J. Biol. Chem.*, **170**, 221 (1947).
(5) T. Wieland and R. Sehring, *Ann.*, **519**, 122 (1950).

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RECEIVED MAY 31, 1951

THE TOTAL SYNTHESIS OF SOME NATURALLY OCCURRING STEROIDS

Sir:

We have resolved methyl *dl*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate[1] by the following method. Reduction of the keto-ester with sodium borohydride in ethanol gave a mixture of the corresponding 3-α and 3-β-hydroxy-esters. Treatment with excess digitonin,[2] followed by decomposition of the precipitated complex, gave material enriched in the desired *d*-3-β-hydroxy-ester. Further resolution was achieved by two repetitions of this procedure, and

(1) Woodward, Sondheimer, Taub, Heusler and McLamore, THIS JOURNAL, **73**, 2403 (1951).
(2) *Cf.* Windaus, Klänhardt and Weinhold, *Z. physiol. Chem.*, **126**, 308 (1923).