Studies in the Synthesis of Cortisone. Part V. Acid Rearrangement of 9α : 11α-Epoxy-Δ⁷-steroids having Hydroxy- or Acetoxy-groups at $C_{(5)}$.*

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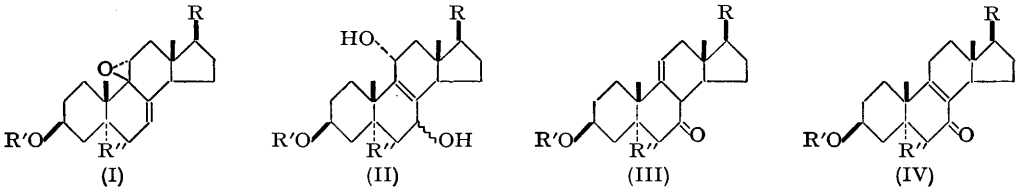
[Reprint Order No. 4645.]

Treatment of 3β : 5α-diacetoxy-9α : 11α-epoxyergosta-7 : 22-diene (I*a*) with aqueous sulphuric acid gives the 7-oxo-Δ⁹⁽¹¹⁾-compound (III*a*). On adsorption of this βγ-unsaturated ketone on alumina, the acetoxy-group at $C_{(5)}$ is eliminated, giving either the 7-oxo-Δ⁵:⁹⁽¹¹⁾-compound (V) or the 7-oxo-Δ⁵:⁸⁽⁹⁾-compound (VI), according to the kind of alumina used. The 9α : 11α-epoxy-Δ⁷-compounds (I*b* and *c*) also yield the corresponding 7-oxo-Δ⁹⁽¹¹⁾-compounds on acid treatment.

One of the more practicable methods of synthesising 11-keto-5α-steroids from 9α : 11α-epoxy-Δ⁷-compounds involves, as the first stage, acid rearrangement of the epoxide to the 7 : 11-dihydroxy-Δ⁸⁽⁹⁾-compound (Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; cf. also, Heusser, Heusler, Eichenberger, Honegger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 295; Budziarek, Hamlet, and Spring, *J.*, 1953, 778). The present work was undertaken to assess the usefulness of this approach when applied to compounds having hydroxy- or acetoxy-substituents at $C_{(5)}$, since these groups should be of value in the eventual formation of the 3-keto-Δ⁴⁽⁵⁾-system of cortisone.



(I) (II) (III) (IV)

Series (*a*) : R = C_9H_{17}, R′ = Ac, R″ = OAc.
Series (*b*) : R = C_9H_{17}, R′ = H, R″ = OH.
Series (*c*) : R = CHMe·CO_2Me, R′ = Ac, R″ = OH.

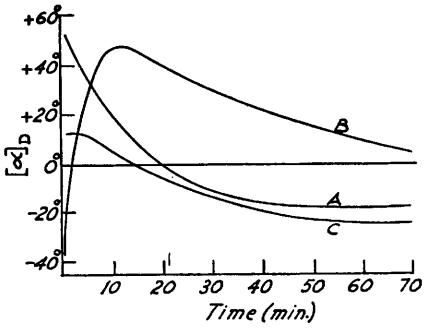
The epoxide (I*a*) was unaffected by aqueous sulphuric acid under the conditions that were found by Heusser *et al.* (*loc. cit.*, p. 2106) to convert 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (I; R = C_9H_{17}, R′ = Ac, R″ = H) rapidly into 3β-acetoxy-7ξ : 11α-dihydroxyergosta-8(9) : 22-diene (II; R = C_9H_{17}, R′ = Ac, R″ = H). A similar slowness in reaction of (I*a*), compared with the corresponding epoxide in the 5-hydrogen series, has been observed in connection with the boron trifluoride rearrangement of these compounds and may be attributed to steric interference of the 5-acetoxy-group (Part I, *J.*, 1953, 2921). When the acid rearrangement was followed polarimetrically, it was observed that stronger acid (0·67N-sulphuric acid as against a 0·3N-solution used by Heusser *et al.*) caused the rotation of the solution to drop steadily from that of the epoxide ($[\alpha]_D$ +50°) to about $[\alpha]_D$ −15° and to remain at this value for at least 16 hours (Fig., *A*). This behaviour may be contrasted with that of 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene, the rotation of whose solution increased in a few minutes from $[\alpha]_D$ −39° to a maximum (about $[\alpha]_D$ +50°), corresponding to complete formation of the 7ξ : 11α-di-hydroxy-Δ⁸⁽⁹⁾-compound, and then slowly dropped in value (eventually becoming negative) as the diol itself underwent rearrangement (Fig., *B*).

The difference in the course of the two reactions became further apparent when the product of acid rearrangement of (I*a*) was worked up after the rotation of the solution had reached its minimum value. Since chromatography on alumina caused further changes (see below), the crude product was separated into its components on a charcoal

* Part IV, preceding paper.

column. Two pure compounds were isolated by this means, both of them isomeric with the original epoxide; there was no evidence of the presence of the required diol (II*a*). The minor, more strongly adsorbed component showed a maximum in the ultra-violet at 255 mμ and readily formed a 2 : 4-dinitrophenylhydrazone, consistently with its formulation as 3β : 5α-diacetoxyergosta-8(9) : 22-dien-7-one (IV*a*).

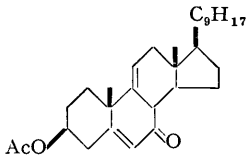
The major product of the acid rearrangement is formulated as 3β : 5α-diacetoxyergosta-9 : 22-dien-7-one (III*a*). This is supported by its ultra-violet spectrum, which showed no strong absorption above 220 mμ, by a ketone band at 1724 cm.$^{-1}$ in the infra-red spectrum, and by formation of a 2 : 4-dinitrophenylhydrazone. The displacement of the ketone band from its usual position at 1710 cm.$^{-1}$ is perhaps due to the 5-acetoxy-group.



Rotation changes during rearrangement of 9α : 11α-*epoxy*-Δ^7-*compounds.*

A, 3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene* (I*a*) *with* 0·67N-*sulphuric acid in aqueous dioxan.*
B, 3β-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene with* 0·3N-*sulphuric acid in aqueous dioxan.*
C, *Methyl* 3β-*acetoxy*-9α : 11α-*epoxy*-5α-*hydroxybisnor*-allo*chol*-7-*enoate* (Ic) *with* 0·3N-*sulphuric acid in aqueous dioxan.*

Further evidence that the compound has formula (III*a*) is provided by its conversion under very mild conditions into the ketones (V) and (VI), whose structures have been established (see the preceding paper). Thus, chromatography of (III*a*) on acetic acid-washed alumina gave 3β-acetoxyergosta-5 : 9(11) : 22-trien-7-one (V), a compound obtained



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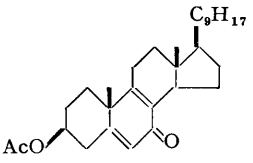

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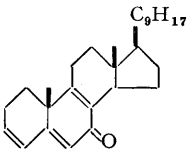
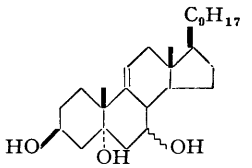


(VII)

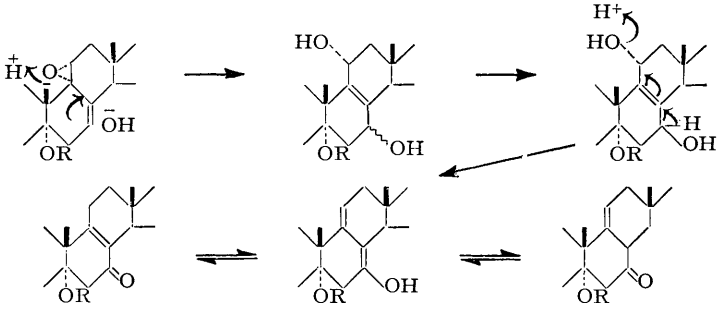


(VIII)

earlier by chromatography of the product of chromic acid oxidation of 3β : 5α-diacetoxyergosta-7 : 9(11) : 22-triene (preceding paper). Consistently with the ease with which (V) is known to isomerise to 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one (VI) on mild treatment with alkali, the cross-conjugated ketone was the main product obtained by adsorption of (III*a*) on untreated grade 0 alumina. A minor product eluted from this column was a strongly lævorotatory compound: its analysis indicated that both acetoxy-groups had been eliminated and we have provisionally formulated it as ergosta-3 : 5 : 8(9) : 22-tetraen-7-one (VII); the maximum at 272 mμ in its ultra-violet spectrum lies between those of the individual chromophores of the cross-conjugated system (280 mμ for the 7-oxo-Δ$^{3:5}$- and 253 mμ for the 7-oxo-Δ$^{8(9)}$-system) (cf. preceding paper). The 7-oxo-5 : 8(9) : 22-triene (VI) was more conveniently obtained by treatment of (III*a*) with ethanolic potassium hydroxide and subsequent reacetylation.

The formation of (III*a*) and (IV*a*) has its parallel in the 5α-hydrogen series. Thus, Heusser *et al.* (*loc. cit.*, p. 2106) showed that, whereas treatment of 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (I; R = C_9H_{17}, R′ = Ac, R″ = H) with 0·3N-sulphuric acid for a few minutes gave the 7 : 11-dihydroxy-Δ$^{8(9)}$-compound (II; R = C_9H_{17}, R′ = Ac, R″ = H), prolonged treatment with very dilute sulphuric acid yielded the αβ-unsaturated ketone (IV; R = C_9H_{17}, R′ = Ac, R″ = H). Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler (*J. Amer. Chem. Soc.*, 1952, **74**, 2696)

moreover were able to obtain either the βγ-unsaturated ketone (III) or the αβ-unsaturated ketone (IV) from the epoxide (I; R = C_9H_{17}, R′ = R″ = H) by using sulphuric acid under appropriate conditions (cf. also Budziarek, Johnson, and Spring, *J.*, 1952, 3410). It is, then, apparent that the acid-catalysed rearrangement of epoxides of type (I) is complex and that the outcome is dependent upon the precise reaction conditions and upon the structure of the starting material. It is believed that the isomerisation proceeds as shown below. Some evidence that the 7 : 11-dihydroxy-$\Delta^{8(9)}$-compound is an intermediate in the formation of the 7-keto-steroids is provided by the observation of Heusser, Anliker, Eichenberger, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 936) that (II; R = C_9H_{17}, R′ = Ac, R″ = H) can be converted into the βγ-unsaturated ketone (III; R = C_9H_{17}, R′ = Ac, R″ = H) by means of peracetic acid (cf. Schoenewaldt *et al.*, *loc. cit.*).



If the rearrangement of (I*a*) was stopped after various shorter reaction times, with the intention of isolating the desired intermediate diol, unchanged epoxide or (III*a*) was the main product. It must be concluded, therefore, that in this particular instance the formation of the diol is the rate-determining stage in the sequence of changes postulated above and that this compound has only a transient existence in the reaction mixture. Similarly, acid treatment of 9α : 11α-epoxyergosta-7 : 22-diene-3β : 5α-diol (I*b*) [prepared by deacetylation of (I*a*) with lithium aluminium hydride] yielded 3β : 5α-dihydroxyergosta-9(11) : 22-dien-7-one (III*b*) instead of the diol (II*b*), and the relation between this βγ-unsaturated ketone and (III*a*) was demonstrated by reduction of both these compounds with lithium aluminium hydride to the same triol (VIII). The ready formation of these $\Delta^{9(11)}$-7-keto-steroids in the 5α-hydroxy- and acetoxy-series gives substance to the suggestion by Bladon, Henbest, Jones, Wood, Eaton, and Wagland (*J.*, 1953, 2916) that 3β-acetoxy-5α-hydroxyergost-9(11)-en-7-one is an intermediate in the performic acid oxidation of 3β-acetoxyergosta-7 : 9(11)-dien-5α-ol to 3β-acetoxy-9α : 11α-epoxy-5α-hydroxyergostan-7-one, the βγ-unsaturated ketone being formed by acid-catalysed isomerisation of the first-formed 9α : 11α-epoxy-Δ^7-compound (for an analogous reaction in the 5-hydrogen series see Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892).

The behaviour of methyl 3β-acetoxy-5α-hydroxy-9α : 11α-epoxybisnor*allo*chol-7-enoate (I*c*), on treatment with aqueous sulphuric acid under the conditions described by Heusser *et al.* (*Helv. Chim. Acta*, 1951, **34**, 2106), was seen to differ from that of (I*a*) and (I*b*) in that the rotation of the solution remained constant for some minutes before it underwent the usual steady fall (Fig., *C*). The structure of the methyl 3β-acetoxy-5α-hydroxy-7-oxobisnor*allo*chol-9(11)-enoate (III*c*) so formed was confirmed, as it was for (III*a*), by the absence of appreciable absorption in the ultra-violet above 220 mμ and the easy formation of a 2 : 4-dinitrophenylhydrazone.

Experimental

Optical measurements were determined on chloroform solutions (concentration limits 0·9—1·2) at room temperature, and, except where otherwise stated, ethanol was the solvent in light absorption measurements. A Perkin-Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra.

Acid Rearrangement of 3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene* (I*a*).—A solution

of the epoxide (Part I, *J.*, 1953, 2921) (4 g.) in dioxan (1 l.) and 2N-sulphuric acid (500 ml.) was kept at 20° for 3 hr. The product (3·8 g.; $[\alpha]_D$ −18°), obtained on isolation with ether, was dissolved in benzene and adsorbed on charcoal (100 g.; Sutcliffe and Speakman No. 5), the column then being eluted with benzene–ether (99 : 1; 7 × 100 ml.). The first fraction (185 mg.) had $[\alpha]_D$ −1° and was discarded. Rotations of the next six fractions varied between $[\alpha]_D$ −15° and $[\alpha]_D$ −18° and there was no significant absorption above 220 mμ; these fractions (2·3 g.) were combined and crystallised from methanol, giving 3β : 5α-*diacetoxyergosta*-9(11) : 22-*dien*-7-*one* (III*a*) as needles, m. p. 194—195°, $[\alpha]_D$ −21·5° (Found: C, 74·8; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Light absorption: Apparent max. 205 mμ (ε = 3300; *c*, 0·0099); $\nu_{max.}$ 1740 and 1240 (acetate), 1724 (ketone), 1670, 814, and 802 (trisubstituted ethylene), and 968 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in CS_2 (C.S. no. 64).* The ketone gave a yellow colour with tetranitromethane in chloroform.

Elution of the column with the same solvent mixture (3 × 100 ml.) and with benzene–ether (1 : 1; 200 ml.) yielded 3β : 5α-*diacetoxyergosta*-8(9) : 22-*dien*-7-*one* (IV*a*) (0·44 g.) which crystallised from methanol as plates, m. p. 188—190°, $[\alpha]_D$ −42° (Found: C, 74·75; H, 9·7. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%), $\lambda_{max.}$ 255 mμ (ε = 8700), $\nu_{max.}$ 1740 and 1240 (acetate), 1675 and 1593 (αβ-unsaturated ketone), and 969 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in CCl_4 (C.S. no. 65).

The 7-keto-$\Delta^{8(9):22}$-compound (IV*a*) readily formed a 2 : 4-dinitrophenylhydrazone derivative in Brady's reagent at 20°. The βγ-unsaturated ketone (III*a*) would only form a derivative in Brady's reagent at 40°.

Chromatography of 3β : 5α-*Diacetoxyergosta*-9(11) : 22-*dien*-7-*one on Alumina.*—(a) *Acid-washed alumina* (for preparation, see preceding paper). The ketone (0·5 g.) in light petroleum–benzene (1 : 1) was adsorbed on acetic acid-washed alumina (30 g.). Elution with the same solvent mixture and with benzene yielded 3β-acetoxyergosta-5 : 9(11) : 22-trien-7-one (V) (0·4 g.), which crystallised from methanol as plates, m. p. and mixed m. p. 168—172°, $[\alpha]_D$ −92°, $\lambda_{max.}$ 234 mμ (ε 12,750). Elks *et al.* (preceding paper) record for this compound, m. p. 169—172°, $[\alpha]_D$ −96°, $\lambda_{max.}$ 234·5 mμ (ε 12,800). The infra-red spectrum was identical with that of an authentic specimen.

(b) *Untreated alumina.* The ketone (2 g.) in light petroleum–benzene (4 : 1) was adsorbed on alumina (Peter Spence, Grade 0; 60 g.). Elution with the same solvent mixture and light petroleum–benzene (1 : 1) yielded (?)*ergosta*-3 : 5 : 8(9) : 22-*tetraene*-7-*one* (VII) (402 mg.), needles (from methanol), m. p. 170—172°, $[\alpha]_D$ −172° (Found: C, 85·5; H, 10·45. $C_{28}H_{40}O$ requires C, 85·65; H, 10·25%), $\lambda_{max.}$ 215—217 (ε 19,000) and 272 mμ (ε 14,600), $\nu_{max.}$ 1642, 1610, and 1586 (carbonyl in conjugation with at least three double bonds), 1656 and 968 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in CCl_4 (C.S. no. 66); no bands associated with acetoxy- or hydroxy-groups). The compound readily formed a 2 : 4-dinitrophenylhydrazone in Brady's reagent. It gave a strong yellow colour with tetranitromethane in chloroform.

Elution of the column with benzene and ether yielded a solid (0·72 g.) which, on crystallisation from methanol, gave 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one (VI) as needles, m. p. 202—204°, $[\alpha]_D$ −30°, $\lambda_{max.}$ 246 mμ (ε 12,800). Elks *et al.* (preceding paper) record m. p. 199—204°, $[\alpha]_D$ −32°, $\lambda_{max.}$ 245 mμ (ε 11,800). The infra-red spectrum was identical with that of authentic material.

Treatment of 3β : 5α-*Diacetoxyergosta*-9(11) : 22-*dien*-7-*one with Alkali.*—Potassium hydroxide (1 g.) in water (3 ml.) was added to a solution of the ketone (1 g.) in ethanol (250 ml.), the solution then being kept at 20° for 1 hr. Isolation with ether yielded a solid which was re-acetylated in acetic anhydride–pyridine at 20° overnight. Crystallisation from methanol gave 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one (0·45 g.) as needles, m. p. 201—205°, $[\alpha]_D$ −30°, $\lambda_{max.}$ 246 mμ (ε 12,100). Evaporation of the mother-liquors yielded impure (VII) (0·09 g.), $[\alpha]_D$ −95°, $\lambda_{max.}$ 270 mμ (ε 8400), inflexion at 254—257 mμ (ε 7500).

9α : 11α-*Epoxyergosta*-7 : 22-*diene*-3β : 5α-*diol* (I*b*).—3β : 5α-Diacetoxy-9α : 11α-epoxyergosta-7 : 22-diene (2 g.) in ether (40 ml.) was treated with excess of lithium aluminium hydride in ether. The solution was kept at 20° for 1 hr., then refluxed for a further hour. After decomposition of the complex with ice, the solution was shaken with 2N-tartaric acid (50 ml.) to remove aluminium hydroxide. Isolation with chloroform followed by crystallisation from aqueous acetone gave the *diol epoxide* (1·3 g.) as needles, m. p. 209—213°, $[\alpha]_D$ −1° (Found:

* Infra-red spectra thus marked have been deposited with the Society. Photo-copies (price, 3*s.* 0*d.* each per copy) may be obtained on application, quoting the C.S. no., to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

C, 78·55; H, 10·2. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%), having no significant absorption above 220 mμ., $\nu_{max.}$ 3620 and 3520 (hydroxyl), 1660 and 970 (*trans*-1 : 2-disubstituted ethylene), and 1635, 848, and 816 cm.$^{-1}$ (trisubstituted ethylene) in Nujol (C.S. no. 67).

3β : 5α-*Dihydroxyergosta*-9(11) : 22-*dien*-7-*one* (III*b*).—The above diol epoxide (1 g.) in dioxan (400 ml.) was treated with 2N-sulphuric acid (150 ml.), the solution then being kept at 20° for 3 hr. Isolation with ether and crystallisation from ethyl acetate yielded the *ketone* (0·4 g.) as threads, m. p. 220—221°, $[\alpha]_D$ −67° (Found : C, 78·7; H, 10·65. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%), no significant absorption above 220 mμ, $\nu_{max.}$ 3530 and 3350 (hydroxyl), 1700 (ketone), 1650, 840, and 812 (trisubstituted ethylene) and 965 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene) in Nujol (C.S. no. 68).* The 2 : 4-dinitrophenylhydrazone was formed in Brady's reagent at 20° (2 hr.).

Ergosta-9(11) : 22-*diene*-3β : 5α : 7ξ-*triol* (VIII).—(*a*) Excess of ethereal lithium aluminium hydride was added to 3β : 5α-diacetoxyergosta-9(11) : 22-dien-7-one (1 g.) in ether (60 ml.), and the solution was refluxed for 1 hr. After decomposition of the complex with ice, the solution was shaken with 2N-tartaric acid (50 ml.). Isolation with chloroform and crystallisation from acetone yielded the *triol* as threads, m. p. 239—240°, $[\alpha]_D$ −12·5° (Found : C, 78·45; H, 11·0. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%), $\nu_{max.}$ 3450 (hydroxyl), 1660 and 964 (*trans*-1 : 2-disubstituted ethylene), 1645, 822, and 815 cm.$^{-1}$ (trisubstituted ethylene) in Nujol. Acetylation in acetic anhydride–pyridine at 20° overnight gave the 3-*monoacetate*, threads (from methanol), m. p. 188—191°, $[\alpha]_D$ −18·5° (Found : C, 76·55; H, 10·1. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%), $\nu_{max.}$ 3520 and 3350 (hydroxyl), 1738 and 1240 (acetate), 1658 and 970 (*trans*-1 : 2-disubstituted ethylene), 1645, 830, and 820 cm.$^{-1}$ (trisubstituted ethylene) in CS_2.

(*b*) On reduction of 3β : 5α-dihydroxyergosta-9(11) : 22-dien-7-one (150 mg.) with ethereal lithium aluminium hydride as described above, the triol was obtained as threads, m. p. and mixed m. p. 230—232°, $[\alpha]_D$ −17·5°. The infra-red spectrum was identical with that of the triol obtained by method (*a*).

Acid Rearrangement of Methyl 3β-*Acetoxy*-9α : 11α-*epoxy*-5α-*hydroxybisnor*allo*chol*-7-*enoate* (I*c*).—The epoxide (Part I, *loc. cit.*) (1 g.) in dioxan (140 ml.) was treated with 2N-sulphuric acid (22 ml.), the solution then being kept at 20° for 80 min. Isolation with ether and crystallisation from methanol gave *methyl* 3β-*acetoxy*-5α-*hydroxy*-7-*oxobisnor*allo*chol*-9(11)-*enoate* (III*c*) (0·41 g.), m. p. 227—230°, $[\alpha]_D$ −45·5° (*c*, 0·5) (Found : C, 69·4; H, 8·35. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%), $\nu_{max.}$ 3600 (hydroxyl), 1732 and 1240 (acetate), 1712 (carboxylic ester and ketone), and 1160 cm.$^{-1}$ (carboxylic ester) in Nujol (C.S. no. 69). The peak at 1712 cm.$^{-1}$ has twice the normal intensity, indicating two carbonyls; the peak at 1160 cm.$^{-1}$ suggests that one of the carbonyls occurs in an ester group, leaving the second as an unconjugated carbonyl.

The 2 : 4-*dinitrophenylhydrazone* separated from Brady's reagent as yellow-orange needles, m. p. 240° (decomp.) (Found : C, 60·6; H, 6·65. $C_{31}H_{40}O_9N_4$ requires C, 60·75; H, 6·6%), $\lambda_{max.}$ 368 mμ (ε 38,500) in $CHCl_3$. The derivative was identical with that obtained on treatment of the epoxide (I*c*) with Brady's reagent.

Thanks are due to Mr. W. F. Wall for assistance in the experimental work.

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* Burke, Turnbull, and Wilson (*J.*, 1953, 3237) give m. p. 212—214°, $[\alpha]_D$ −61° (in $CHCl_3$).