

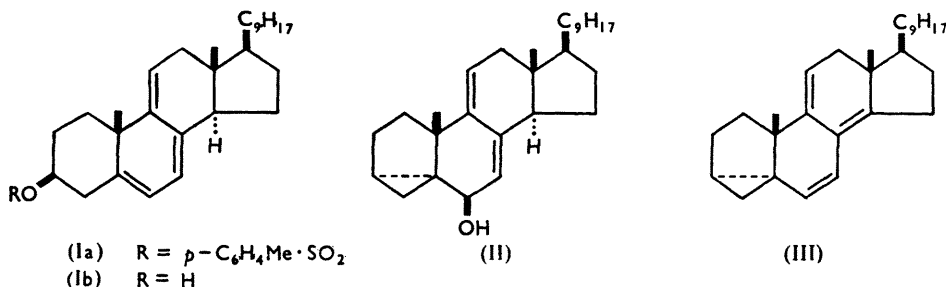
16. Steroids. Part XI.* The 3:5-cycloSteroid Rearrangement of Dehydroergosteryl Toluene-*p*-sulphonate.

By W. R. NES and C. W. SHOPPEE.

Buffered hydrolysis of dehydroergosteryl toluene-*p*-sulphonate in aqueous acetone proceeds rapidly at $\sim 63^\circ$ to give Nes's 3:5-cycloergostatrienol as the major product, with small amounts (2%) of hydrocarbon(s). A different 3:5-cycloergostatrienol obtained by Rees and Shoppee is probably a polymorph. Prolongation of the reaction time leads to the production of dehydroergosterol, with concomitant disappearance of the 3:5-cycloergostatrienol and formation of more hydrocarbon(s) (up to 20%); these observations appear to constitute the first example of the reversion of a 3:5-cyclosteroid to a Δ^5 -steroid in the presence of acetic acid.

HYDROLYSIS of dehydroergosteryl toluene-*p*-sulphonate (Ia) with aqueous acetone in the presence of potassium acetate has been reported by Rees and Shoppee¹ to yield dehydroergosterol (Ib), an isomeric alcohol, m. p. 47° , $[\alpha]_D +139^\circ$, λ_{\max} , 247 $m\mu$, and a hydrocarbon, m. p. 102° , $[\alpha]_D +81^\circ$, λ_{\max} , 252 $m\mu$. The last two compounds were tentatively formulated as 3:5-cycloergosta-7:9(11):22-trien-6 β -ol (II) and 3:5-cycloergosta-6:8(14):9(11):22-tetraene (III).

Subsequently, Nes² described the preparation of 3:5-cycloergosta-6:8(14):9(11):22-tetraene (III), m. p. 100° , $[\alpha]_D +65^\circ$, λ_{\max} , 244 and 295 $m\mu$, by another method. The ultraviolet spectrum thus differed from that of the earlier preparation, and was in much better agreement with that expected for structure (III); Rees and Shoppee's¹ hydrocarbon must



therefore have some other structure. Nes² also found that reduction of the time of reaction for the hydrolysis of dehydroergosteryl toluene-*p*-sulphonate furnished a 3:5-cycloergostatrienol, m. p. 125° , $[\alpha]_D +126^\circ$, λ_{\max} , 247 $m\mu$, ν_{\max} , 3600 cm^{-1} (in CS₂), in high yield, but was unable to obtain the 3:5-cycloergostatrienol, m. p. 47° , λ_{\max} , 247 $m\mu$, described as (II) by Rees and Shoppee.

Repetition of the buffered hydrolysis of dehydroergosteryl toluene-*p*-sulphonate under the conditions used by Rees and Shoppee¹ (reflux for 6 hours) yielded dehydroergosterol (Ib) as a minor product, Nes's 3:5-cycloergostatrienol, m. p. 125° , as the major product, and small amounts (8%) of hydrocarbon consisting mainly of 3:5-cycloergosta-6:8(14):9(11):22-tetraene, λ_{\max} , 244 and 295 $m\mu$, but containing also hydrocarbon(s) with λ_{\max} , 252 and 262 $m\mu$. The 3:5-cycloergostatrienol, m. p. 47° , could not be isolated; this material was either an impure preparation, or, more probably, a polymorph of the 3:5-cycloergostatrienol, m. p. 125° , a view supported by the similarity of the specific rotations and by the ultraviolet spectra which show similar slight inflections on both shoulders of the main absorption band.

Repetition of the buffered hydrolysis of dehydroergosteryl toluene-*p*-sulphonate under the conditions used by Nes² (reflux for 20 minutes) has confirmed that hydrolysis rapidly

* Part X, *J.*, 1955, 1370.

¹ Rees and Shoppee, *J.*, 1954, 3422.

² Nes, *J. Amer. Chem. Soc.*, 1956, 78, 193.

gives the 3:5-cyclotrienol, m. p. 125°, accompanied by little if any dehydroergosterol. Dehydroergosterol is, however, formed slowly from the 3:5-cyclotrienol, m. p. 125°; for when the reaction is allowed to proceed for 20 hours, dehydroergosterol is essentially the only steroid alcohol present, and is readily separated chromatographically from the hydrocarbon fraction. The 5:7:9(11)-triene system with λ_{\max} 324 m μ characteristic of dehydroergosterol (Ib) was shown spectroscopically to be present before as well as after chromatography, so that rearrangement does not take place on the alkaline aluminium oxide employed. Although there is evidence² that active acidic aluminium oxide can convert the 3:5-cyclotrienol into dehydroergosterol, the 3:5-cyclotrienol was unchanged by the alkaline aluminium oxide used here.

To prove that the reaction sequence (Ia) \rightarrow 3:5-cyclotrienol \rightarrow (Ib) does in fact take place, we have followed the change in the intensity of the absorption maxima at 247 m μ

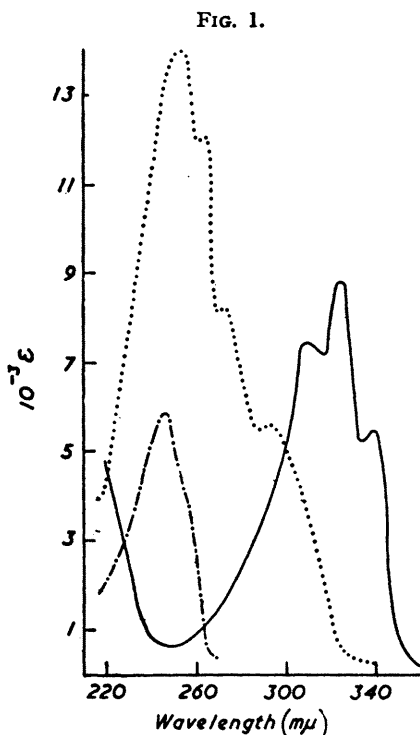


FIG. 1.

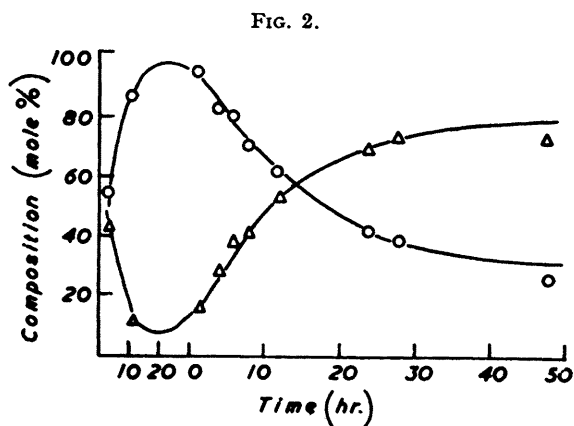


FIG. 2.

FIG. 2. Composition-time curves for buffered hydrolysis of dehydroergosteryl toluene-p-sulphonate (Ia).

○ 3:5-cycloTrienol.
 △ 5:7:9(11):22-Tetraen-3 β -ol (Ia or b).

FIG. 1. Absorption of (— · —) 3:5-cycloergosta-7:9(11):22-trien-6 β -ol, (—) ergosta-5:7:9(11):22-tetraen-3 β -ol (Ia or b), and (· · · ·) Rees and Shoppee's hydrocarbon,¹ m. p. 102°, $[\alpha]_D +81^\circ$ (all in isooctane).

associated with the 3:5-cyclotrienol and the appearance of the maximum at 324 m μ associated with the 5:7:9(11)-triene system (I) (Fig. 1). The results (Fig. 2) confirm the occurrence of this reaction sequence, in agreement with the suggestion by Shoppee and Summers³ and the supporting evidence adduced by Shoppee and Williams⁴ that formation of 3:5-cyclosteroids is kinetically controlled but that at equilibrium thermodynamic control leads to formation of Δ^5 -steroids. The present observations appear to constitute the first example of equilibrium attained under buffer conditions.³

The most probable structure for the 3:5-cyclotrienol appears on grounds of analogy to be 3:5-cycloergosta-7:9(11):22-trien-6 β -ol (II), but three facts cast doubt on this conclusion: (a) the ultraviolet absorption spectrum fails to show the three resolved maxima characteristic⁵ of the 7:9(11)-diene system (235, 243, 251 m μ); (b) the absorption maximum is displaced ~ 4 m μ toward longer wavelength; and (c) the cation (IV) appears to be either

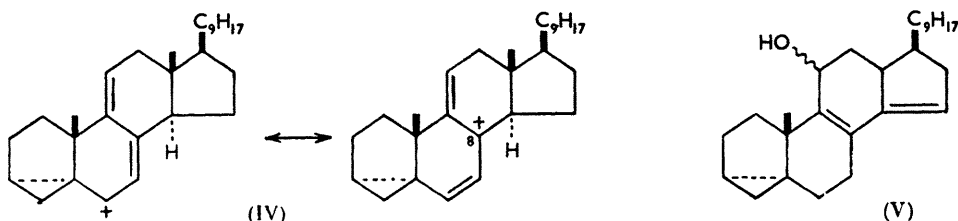
³ Shoppee and Summers, *J.*, 1952, 3361.

⁴ Shoppee and Williams, *J.*, 1956, 2488.

⁵ Doriman, *Chem. Rev.*, 1953, 53, 47.

not common to, or not the only cation involved in, the forward (Ia \rightarrow 3 : 5-cyclotrienol) and reverse (3 : 5-cyclotrienol \rightarrow Ib) reactions. If the 3 : 5-cyclotrienol has structure (II), the forward and the reverse reaction would be expected to proceed through the mesomeric cation (IV), and the compound (III), formed by loss of a proton at C₍₁₄₎, should constitute the hydrocarbon fraction of the reaction mixture. Removal of the elements of toluene-*p*-sulphonic acid from (Ia) has been shown² to give this tetraene (III) under other conditions. However, this is not the (only) hydrocarbon formed under the buffered hydrolytic conditions, and we have confirmed the original observations by Rees and Shoppee¹ that the material possesses a maximum at 252 m μ (Fig. 1) when isolated after 20 hours' refluxing. The yield of hydrocarbon rises sharply with the time of reaction (2% after 20 minutes, 8% after 6 hours, 20% after 48 hours), and this strongly suggests that the mechanism of formation of the hydrocarbon is related to the mechanism of the conversion of the 3 : 5-cyclotrienol into dehydroergosterol (Ib). This is difficult to understand if structure (II) is assigned to the 3 : 5-cyclotrienol.

There are three alternative heteroannular diene systems for the 3 : 5-cyclotrienol, *viz.*, $\Delta^6:8(14)$, $\Delta^7:14$, and $\Delta^8:14$; the first two can be excluded because the former would have λ_{\max} . 261 m μ since⁶ it contains a diene system "conjugated" with the 3 : 5-cyclostructure,



whilst the latter contains a cisoid diene system with an extinction coefficient lower than that actually observed. If the 3 : 5-cyclotrienol should prove to possess a $\Delta^8:14$ -diene system (with which the absorption spectrum is in agreement),⁶ the interesting possibility arises that the hydroxyl group may be situated at position 11 (cf. V).

The structure of the hydrocarbon(s) formed during the conversion of the 3 : 5-cyclotrienol into dehydroergosterol is uncertain. A completely heteroannular, cross-conjugated, 7 : 9(11) : 14-triene system is most unlikely because it should be associated with an absorption maximum below 243 m μ . It is, however, possible that contamination by 3 : 5-cycloergosta-6 : 8(14) : 9(11) : 22-tetraene (III) alters the true nature of the absorption spectrum.

EXPERIMENTAL

For general experimental directions, see *J.*, 1956, 2492. Ultraviolet absorption spectra were determined in *isooctane*, unless otherwise stated, on a Unicam SP 500 spectrometer with corrected scale. Aluminium oxide used for chromatography was Spence, type H, activity \sim II.

Dehydroergosteryl toluene-*p*-sulphonate was prepared according to the directions of Rees and Shoppee¹ and exhibited λ_{\max} . 222, 311, 325, and 341 m μ (ϵ 18,000, 10,300, 11,600, and 7300).

Buffered Hydrolysis of Dehydroergosteryl Toluene-p-sulphonate (Ia).—(a) *For 20 minutes.* Dehydroergosteryl toluene-*p*-sulphonate (1.3 g.) in water (30 c.c.) and acetone (90 c.c.) containing potassium acetate (2.6 g.) was refluxed for 20 min. Acetone (12 c.c.) was removed by distillation from the clear, colourless solution, which became turbid. After cooling of the mixture to 0°, the resulting crystalline precipitate was filtered off and recrystallised from aqueous acetone, to give colourless crystals (0.61 g., 68%), m. p. 123–125°, λ_{\max} . 247 m μ (ϵ 13,200). The compound was chromatographed on aluminium oxide; elution with ether yielded the 3 : 5-cyclotrienol, m. p. 122°, λ_{\max} . 247 m μ (ϵ 14,400). No dehydroergosterol could be detected.

In another experiment under the same conditions, the total hydrocarbon content of the

⁶ Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397.

reaction mixture was evaluated chromatographically by elution with pentane. From 2.0 g. of (Ia) 27 mg. of hydrocarbon were obtained.

(b) *For 6 hours.* Dehydroergosteryl toluene-*p*-sulphonate (2.0 g.) was refluxed for 6 hr. in a solution of water (100 c.c.) and acetone (250 c.c.) containing potassium acetate (4.2 g.). The acetone was removed under reduced pressure and the semicrystalline material was extracted with ether. The residue from the washed and dried ethereal solution was dissolved in pentane (20 c.c.), and the solution, which showed λ_{\max} . 247, 311, 324, and 341 ($D_{247}/D_{324} = 3.1$), poured on a column of aluminium oxide (45 g.). Elution with pentane (150 c.c.) yielded 96 mg. of hydrocarbon (λ_{\max} . 244 and 295 $m\mu$, shoulder at 252 $m\mu$). Further elution with pentane (4×150 c.c.) gave a total of 14 mg. of hydrocarbon (λ_{\max} . 244, 262, 275, and 295 $m\mu$). Elution with ether (300 c.c.) gave a mixture showing λ_{\max} . 247, 310, 324, and 340 $m\mu$ ($D_{247}/D_{324} = 4$). Further elution with ether (300 c.c.) eluted material showing only the maximum at 247 $m\mu$. The material from the first ether fraction was rechromatographed (alumina, 60 g.). Elution with ether (90 c.c.) and crystallisation from ethanol yielded slightly impure dehydroergosterol (0.12 g.), m. p. 135° (unsharp), λ_{\max} . 310, 324, and 340 $m\mu$ (ϵ 9000, 10,000, and 6600 in EtOH); recrystallisation from ethanol raised the m. p. to 141–143°. Further elution with ether (60 c.c.) gave 11 mg. of a mixture (λ_{\max} . 247, 310, 324, and 340 $m\mu$), but continued use of ether (500 c.c.) eluted the 3 : 5-cycloergostatrienol, which was combined with that from the last ether fraction of the original chromatogram. These combined fractions by crystallisation from aqueous acetone yielded 0.6 g. of colourless crystals, m. p. 123–125°, λ_{\max} . 247 $m\mu$ (ϵ 14,200 in EtOH).

(c) *For 20 hours.* Dehydroergosteryl toluene-*p*-sulphonate (0.52 g.) was refluxed for 20 hr. in water (12 c.c.) and acetone (35 c.c.) containing potassium acetate (1.0 g.). The clear, colourless solution was cooled to 15° and yielded 0.3 g. of crystalline material, melting poorly at 80–100°, λ_{\max} . 250–255, 310, 324, and 341 $m\mu$ ($D_{324}/D_{350} = 2.4$). Chromatography of 0.2 g. of this material on aluminium oxide (9 g.) by elution with pentane (60 c.c.) gave long colourless prisms (17 mg.) (from acetone), m. p. 96–98°, λ_{\max} . 252, 262, and 295 $m\mu$ (ϵ 14,000, 12,000, 5600). Further elution with pentane failed to yield material, but use of ether–pentane (1 : 1; 30 c.c.) eluted dehydroergosterol (70 mg.), colourless flakes (from ethanol), m. p. 147–149°, λ_{\max} . 311, 324, and 340 $m\mu$ (ϵ 9800, 11,200, and 7000), λ_{\min} . 245–250 (ϵ 780). Further elution with ether furnished an additional quantity of dehydroergosterol.

In another experiment, under similar conditions for 48 hr., the total weight of hydrocarbon was evaluated by chromatography. From 1.0 g. of dehydroergosteryl toluene-*p*-sulphonate elution with pentane gave 134 mg. of hydrocarbon.

(d) *With spectroscopic control.* A solution of dehydroergosteryl toluene-*p*-sulphonate (0.98 g.) in acetone (125 c.c.) and water (50 c.c.) containing potassium acetate (2.1 g.) was refluxed for 48 hr. At specific intervals aliquot parts (1.0 c.c.) were evaporated rapidly to dryness under reduced pressure, and the residues dissolved in ether. The ultraviolet spectrum was then determined and the concentrations of (Ia) and (Ib), and of the 3 : 5-cyclotriolenol were calculated from the intensities of absorption at 324 and 247 $m\mu$, to afford the curves reproduced in Fig. 2.

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