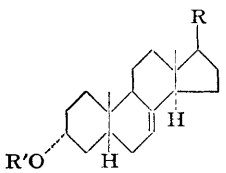
78. *The Application of the Method of Molecular Rotation Differences to Steroids. Part IX. Concerning* u-*Ergostadienol.*

By D. H. R. Barton and E. Miller.

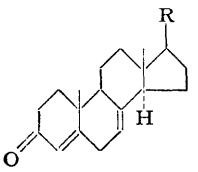
Partial catalytic hydrogenation of ergosterone in neutral solution affords a complex mixture of products from which *coproergosta*-7(8) : 22(23)-*diene*, ergosta-7(8) : 22(23)-dien-3-one, ergosta-7(8) : 22(23)-dien-3(β)-ol, and coproergosta-7(8) : 22(23)-dien-3(α)-ol have been isolated. The properties of coproergosta-7(8) : 22(23)-dien-3(α)-ol and its derivatives are identical with those recorded for *u*-ergostadienol, thus confirming the structure previously suggested for the latter.

Complete catalytic hydrogenation of *iso*ergosterone in neutral solution gives, after removal of unsaturated material, a mixture of ergostan-3(β)-ol and coproergostan-3(α)-ol.

In Part III of this series (*J.*, **1946**, **1116**) the formula (I; R = C_9H_{17}, R′ = H) was suggested for *u*-ergostadienol, principally from considerations of the optical rotatory powers of this substance and its derivatives (see Windaus and Auhagen, *Annalen*, 1929, **472**, 185). If this



(I.)



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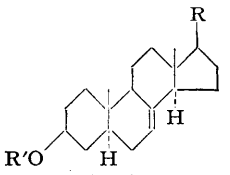
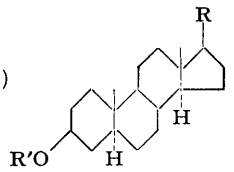
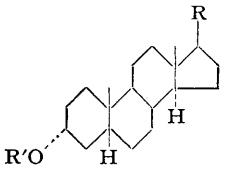


(III.)

(IV.)

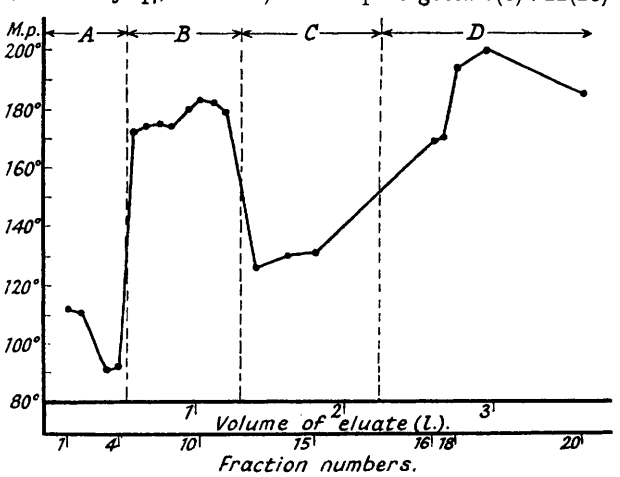




(V.)

view were correct it would be expected that partial catalytic hydrogenation of ergosterone (II; R = C_9H_{17}) in neutral solution would afford, amongst other products, ergosta-7(8) : 22(23)-dien-3(β)-ol (α-dihydroergosterol) (III; R = C_9H_{17}, R′ = H) and coproergosta-7(8) : 22(23)-

Fraction No.	*Elutriant.*
1—4	50 *Petrol* : 50 *benzene* (*A*)
5—12	50 *Petrol* : 50 *benzene* (*B*)
13—15	50 *Petrol* : 50 *benzene* (*C*)
16	66 *Benzene* : 34 *ether* (*D*)
17—19	*Ether* (*D*)
20	66 *Ether* : 34 *chloroform* (*D*)



dien-3(α)-ol (*u*-ergostadienol) by analogy with the behaviour of cholest-4(5)-en-3-one, which gives cholestan-3(β)-ol (IV; R = C_8H_{17}, R′ = H) and coprostan-3(α)-ol (V; R = C_8H_{17}, R′ = H) under similar conditions. In agreement with expectation we have found that catalytic hydrogenation of ergosterone in chloroform solution until 1·1 molar proportions of hydrogen have been absorbed gives a complex mixture of products which can be resolved by chromatography as illustrated in the diagram. The more easily eluted fractions (A) furnished on rechromatography a homogeneous hydrocarbon, $C_{28}H_{46}$, the constitution of which is discussed later. Fractions (B) on repeated recrystallisation, afforded ergosta-7(8) : 22(23)-dien-3-one (α-ergostadienone) (VI; R = C_9H_{17}), whilst fractions (C) gave unchanged ergosterone. Fractions (D) were combined and separated by digitonin treatment. By

TABLE I.

	Coproergosta-7(8) : 22(23)-dien-3(α)-ol.		*u*-Ergostadienol.		
Derivative.	M. p.	$[\alpha]_D$ in $CHCl_3$.	M. p.	$[\alpha]_D$ in $CHCl_3$.	Refs.
Alcohol.....	170·5°	+43°	170°	+42°	1
Acetate	130	+59	128	+58	1
Benzoate	159	+51	159	—	2

1. Windaus and Auhagen, *Annalen*, 1929, **472**, 185.
2. Laucht, *Z. physiol. Chem.*, 1937, **246**, 171.

resolution of the insoluble digitonide, α-dihydroergosterol (III; R = C_9H_{17}, R′ = H) was obtained, whilst from the non-digitonide-forming fraction coproergosta-7(8) : 22(23)-dien-3(α)-ol was isolated. The properties of the latter and its derivatives are summarised in Table I and compared with those recorded in the literature for *u*-ergostadienol and its derivatives. The agreement between the sets of figures, combined with the evidence previously adduced, is sufficient to establish beyond doubt the correctness of the view we have advocated as to the identity of these substances.

The hydrocarbon, $C_{28}H_{46}$, obtained from the more easily eluted fractions of the chromatogram must contain two ethylenic linkages. The possible formulæ for this substance, which has m. p. 122·5°, $[\alpha]_D$ +34° (in chloroform), are (VII; R = C_9H_{17}), (VIII; R = C_9H_{17}),

TABLE II.

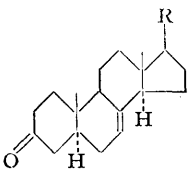
		$[M]_D$,			
Substance.	Solvent.	3(α)-ol.	3-H.	Δ.	Refs.
Coprostan-3(α)-ol	$CHCl_3$	+124°	+ 97°	−27°	1, 2, 3
Coproergostan-3(α)-ol	$CHCl_3$	+101	+ 77	−24	4, 5
3(α)-Hydroxycholanic acid methyl ester	Me_2CO	+129	+ 94	−35	6, 7
3(α)-Hydroxychol-11(12)-enic acid methyl ester	MeOH	+163	+127 *	−36	7, 8
3(α)-Hydroxy-11(α) : 12(α)-oxidocholanic acid methyl ester	Me_2CO	+145	+113	−32	7, 8
3(α)-Hydroxy-12-ketoætiocholanic acid methyl ester	$CHCl_3$	+501	+473	−28	9, 10
Average	—	—	—	−30	—
Coproergosta-7(8) : 22(23)-dien-3(α)-ol	$CHCl_3$	+171	+129	−42	11
Anomalous.					
3(α) : 7(α)-Dihydroxyætiocholanic acid methyl ester	$CHCl_3$	+ 7	+104	+97	9

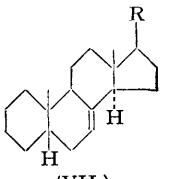
* In Me_2CO.

1. Isiguro and Watanabe, *J. Pharm. Soc. Japan*, 1938, **58**, 260.
2. Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 572.
3. *Idem, ibid.*, p. 575.
4. Wetter and Dimroth, *Ber.*, 1937, **70**, 1665.
5. Laucht, *Z. physiol. Chem.*, 1937, **246**, 171.
6. Seebeck and Reichstein, *Helv. Chim. Acta.*, 1943, **26**, 536.
7. Alther and Reichstein, *ibid.*, 1942, **25**, 805.
8. Press and Reichstein, *ibid.*, p. 878.
9. Lardon, *ibid.*, 1947, **30**, 597.
10. Wenner and Reichstein, *ibid.*, 1944, **27**, 965.
11. Exptl.

and (IX; R C_9H_{19}). Of these (VIII; R = C_9H_{17}) is that already allotted to α-ergostadiene, m. p. 124—125°, $[\alpha]_D$ −10° (in chloroform) (Heilbron *et al.*, *J.*, 1932, 1705), and although the rotation should probably be somewhat more negative there is no reason to doubt the essential homogeneity of this compound. Formula (IX; R = C_9H_{19}) is unlikely because

all the other substances isolated possessed an ethylenic linkage at the 22 : 23-position. Formula (VII; R = C_9H_{17}), on the other hand, would be related in molecular rotation to coproergosta-7(8) : 22(23)-dien-3(α)-ol in the manner indicated in Table II. The agreement between the Δ value calculated assuming this relationship and the Δ values found for comparable substances


(VI.)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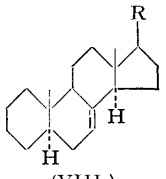
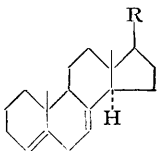
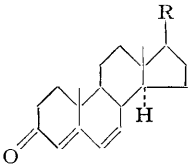

(VIII.)

(IX.)




(X.)

of known structure (see Table II) is support for our view that the unknown hydrocarbon is *coproergosta*-7(8) : 22(23)-*diene* (VII; R = C_9H_{17}). It should be pointed out that the comparison of molecular rotations made here is not invalidated by the possibility of " vicinal action " as will be seen from a consideration of our earlier study of this subject (*J.*, 1948, 783). Further proof for the correctness of the formula (VII; R = C_9H_{17}) was obtained by the catalytic hydrogenation of the diene in neutral solution. This gave a hydrocarbon, $C_{28}H_{48}$, m. p. 107°, $[\alpha]_D$ +48° (in chloroform), whose molecular rotation difference with respect to its progenitor was +55° and corresponded therefore to the average value of +61° (see Part II; *J.*, 1946, 512) required for the reduction of the 22(23)-ethylenic linkage in the sterol side chain. In consequence this reduction product is formulated as *coproergost*-7(8)-*ene* (VII; R = C_9H_{19}).

One of the former objections to the formulation of *u*-ergostadienol as coproergosta-7(8) : 22(23)-dien-3(α)-ol was the fact that *u*-ergostanol, the fully saturated derivative of *u*-ergostadienol, did not correspond to the fully saturated alcohol obtained by Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) by hydrogenation of ergosterone under drastic conditions, and which was tentatively formulated by them as coproergostan-3(α)-ol (V; R = C_9H_{19}, R′ = H) (compare Part III, *loc. cit.*). We have provided confirmation for this formula of Wetter and Dimroth by a study of the hydrogenation of *iso*ergosterone (X; R = C_9H_{17}) in neutral solution. After removal of unsaturated material from the reaction product and resolution with digitonin ergostan-3(β)-ol (IV; R = C_9H_{19}, R′ = H) and coproergostan-3(α)-ol (V; R = C_9H_{19}, R′ = H) were obtained, the latter agreeing in all respects with the alcohol of Wetter and Dimroth. Since we have fully established the identity of *u*-ergostadienol and coproergosta-7(8) : 22(23)-dien-3(α)-ol it follows that our views (Part III, *loc. cit.*) as to the inhomogeneity of *u*-ergostanol now receive confirmation.

Experimental.

(M. p.s are uncorrected.)

The substances whose rotations are listed below were dried in a vacuum at 20° below their m. p.s, or at 120°, whichever was the lower temperature. All rotations are for the Na_D line and in chloroform solution. They were taken in 1 dm. macro- or micro-tubes, the use of the latter being specifically indicated after each recorded measurement.

Standard chemical operations were carried out as in Part IV (*J.*, 1948, 783) unless specified to the contrary.

Partial Hydrogenation of Ergosterone in Neutral Solution.—10 G. of ergosterone (prepared by Oppenauer oxidation of ergosterol), dissolved in 150 ml. of chloroform, were shaken with 500 mg. of reduced platinum oxide catalyst in an atmosphere of hydrogen until the volume of gas absorbed corresponded to 1·1 molar proportions. The catalyst was removed by filtration and the solvent by evaporation under reduced pressure. The residue was dissolved in the minimum of light petroleum (b. p. 40—60°) and chromatographed over a column of Birlec alumina, 40 cm. long and 3 cm. in diameter. The resulting chromatogram, shown in the diagram, was treated as outlined below.

Fractions (A) were combined and rechromatographed over the same quantity of alumina. Elution with light petroleum furnished, after crystallisation from ethyl acetate, long needles of *coproergosta*-7(8) : 22(23)-*diene*, m. p. 122·5°, $[\alpha]_D$ +34° (*c*, 2·04; micro-tube), $[M]_D$ +129° (Found : C, 87·7; H, 12·0. $C_{28}H_{46}$ requires C, 88·0; H, 12·0%).

Catalytic hydrogenation of coproergosta-7(8) : 22(23)-diene in ethyl acetate solution using a platinum oxide catalyst until there was no further absorption of hydrogen gave, after recrystallisation from ethyl acetate–methanol, *coproergost*-7(8)-*ene*, m. p. 107°, $[\alpha]_D$ +48° (*c*, 1·84; micro-tube), $[M]_D$ +184° (Found : C, 87·5; H, 12·1. $C_{28}H_{48}$ requires C, 87·5; H, 12·5%). The hydrocarbon gave a strong colour when tested for unsaturation with tetranitromethane.

Fractions B were combined and repeatedly recrystallised from ethyl acetate–methanol to give ergosta-7(8) : 22(23)-dien-3-one (α-ergostadienone), m. p. 184—185°, undepressed by admixture with an authentic specimen (Part V, *J.*, 1948, 1354).

Fractions C were combined and recrystallised from ethyl acetate–methanol to furnish unchanged ergosterone, m. p. 131°, undepressed on admixture with the starting material.

Fractions D were combined, dissolved in 95% ethyl alcohol and treated with excess of digitonin dissolved in the same solvent (Schönheimer, *Z. physiol. Chem.*, 1933, **215**, 59). The digitonide that separated was decomposed by pyridine and the digitonin precipitated with excess of dry ether. After removing the digitonin by filtration the solution was evaporated under reduced pressure and the residue recrystallised from ethyl acetate–methanol to give ergosta-7(8) : 22(23)-dien-3(β)-ol (α-dihydroergosterol), m. p. 175°, undepressed on admixture with an authentic specimen (Part V, *loc. cit.*).

The alcoholic mother liquors remaining from the separation of the above mentioned digitonide were evaporated under reduced pressure and the residue extracted with dry ether. Evaporation of the filtered ethereal solution afforded, after crystallisation from ethyl acetate–methanol, coproergosta-7(8) : 22(23)-dien-3(α)-ol, m. p. 170·5°, $[\alpha]_D$ +43° (*c*, 2·32), +44° (*c*, 0·80), $[M]_D$ +171°. Acetylation of this alcohol gave the acetate, recrystallised from ethyl acetate–methanol, m. p. 130°, $[\alpha]_D$ +59° (*c*, 4·77; micro-tube), $[M]_D$ +260°, whilst benzoylation furnished the corresponding benzoate, recrystallised from ethyl acetate, m. p. 159°, $[\alpha]_D$ +50° (*c*, 4·65; micro-tube), +51° (*c*, 2·70; micro-tube), $[M]_D$ +256°. Coproergosta-7(8) : 22(23)-dien-3(α)-ol and its derivatives gave negative Tortelli–Jaffé tests, thus confirming the absence of contaminants having a 7(8)-ethylenic linkage and the ergostane configuration at C_5.

Hydrogenation of iso*Ergosterone in Neutral Solution.*—2·8 G. of *iso*ergosterone, prepared by isomerisation of ergosterone in chloroform solution with dry hydrogen chloride, were dissolved in 75 ml. of ethyl acetate, 100 mg. of platinum catalyst were added, and the resulting solution shaken in an atmosphere of hydrogen for 36 hours until there was no further absorption. The catalyst was removed by filtration and the solvent by evaporation under reduced pressure. The residue was taken up in carbon tetrachloride and subjected to the Anderson–Nabenhauer procedure (*J. Amer. Chem. Soc.*, 1924, **46**, 1957) for the removal of unsaturated material. The crystalline product from this treatment was dissolved in 95% ethyl alcohol and excess of digitonin in the same solvent was added (Schönheimer, *loc. cit.*). The precipitated digitonide was resolved in the same way as is detailed above and furnished ergostan-3(β)-ol, m. p. 143—144°, undepressed on admixture with an authentic specimen (Part V, *loc. cit.*). The mother liquors from filtration of the insoluble digitonide were worked up in a similar manner to that detailed above to give coproergostan-3(α)-ol, m. p. 139°. By acetylation coproergostan-3(α)-yl acetate, recrystallised from methanol, m. p. 99°, $[\alpha]_D$ +39° (*c*, 3·07; micro-tube), +38° (*c*, 2·57; micro-tube), $[M]_D$ +173°, was obtained. Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) give m. p. 139—140°, $[\alpha]_D$ +25° (in chloroform), $[M]_D$ +101°, for their coproergostan-3(α)-ol and m. p. 99° for the corresponding acetate. The difference in molecular rotation (Δ_1 value) for Wetter and Dimroth's alcohol compared with the acetate obtained here is +72° which is in satisfactory agreement with the average value for this constant given in Part III (*J.*, 1946, 1116). For *u*-ergostanyl acetate which, as we have argued, should be identical with coproergostan-3(α)-yl acetate, Windaus and Auhagen (*Annalen*, 1929, **472**, 185) give m. p. 96°, $[\alpha]_D$ +39° (in chloroform), whilst Dithmar and Achtermann (*Z. physiol. Chem.*, 1932, **205**, 55) record m. p. 97°, $[\alpha]_D$ +41° (in chloroform).

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