

Hydroxy-steroids. Part 21.¹ The Preparation and Proton Nuclear Magnetic Resonance Spectra of 19-Norergosta-3,5,7,9,22-pentaene and -3,5,7,9-tetraene, 7-Methoxy-1,2-dihydronaphthalene, and Deuteriated Derivatives

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Efficient methods for the preparation of the compounds listed in the title have been developed. Examination of their ¹H n.m.r. spectra showed that in these substituted dihydronaphthalenes the ring containing the olefinic bond is conformationally mobile. Study of the deuteriated derivatives was useful in interpreting the gross spectrometric features of the parent compounds but did not simplify the detailed analysis.

THE conformational mobility of ring A in 19-norergosta-5,7,9-trien-3 β -ol (dihydroneo-ergosterol) (10a) and its 3 α -epimer¹ suggested that the derived Δ^3 -olefin (12b) should exist at normal temperature as a mixture of two rapidly interconverting forms each with ring A in the half-chair conformation. This situation had already been demonstrated in simple dihydronaphthalenes by computer analysis of the ¹H n.m.r. signals arising from the six-spin system of the alicyclic ring.^{2,3} A basic feature of the computer approach is that as many as possible of the observed lines are fitted to calculated transition at any early stage; the fitting of only a few signals can lead to a solution which, although having a low r.m.s. error, gives absurd values for some parameters. The ¹H n.m.r. spectrum of steroidal olefin (12b), although complex (see later), was analysed by the standard method † and led to the expected conclusion about the stereochemical details of ring A. However, since the analysis involved a number of assumptions it seemed prudent to strengthen confidence in the procedure by ancillary studies. The approach adopted here was to compare the spectra of parent 1,2-dihydronaphthalenes with those of specifically deuteriated analogues; it was thought that the simplified spectra of the latter would confirm the assignments made with the parent compounds and lead directly to approximate values for some of the coupling constants. In the present work this approach was developed with a simple system, 7-methoxy-1,2-dihydronaphthalene (3), and then applied to the steroidal olefin (12b).

The preparations of the 7-methoxy-1,2-dihydronaphthalenes are shown in the upper part of Scheme 1. For the purpose in hand it was essential to obtain products of high isotopic purity and to establish their deuterium content by a method other than ¹H n.m.r. spectrometry. The percentage of species containing increasing numbers of deuterium atoms in the inter-

mediate ketone (4) were found by making slow ion counts through the region of the parent ions in its mass spectrum and processing the results along standard lines;⁴ the normal mass spectra of the olefins (6), (8), and (9), while not establishing the percentages so precisely, showed that they satisfied the main feature of isotopic homogeneity. Pyrolysis of the 1-acetates, the method used for the parent compound (3),⁵ proceeded without loss or scrambling of deuterium. Preparation of the 4-deuterio-derivative (6) from the tosyl-hydrazone (5)⁶ by treatment with butyl-lithium followed by deuterium oxide was unsatisfactory, a variety of conditions giving material deuteriated to the extent of 86% at best. (It may be that tetrahydrofuran, the only common aprotic solvent in which the tosylhydrazone dissolved, protonates a certain amount of the intermediary alkenyl-lithium.) The method used previously for exchanging the C-2 hydrogens of the methoxy-tetralone (1) affords a mixture of the di-(83%) and mono-(17%) deuteriated derivatives.⁷ Reinvestigation of the exchange [Scheme 1; (1) \rightarrow (4)] established that the dideuterio-ketone (4) can be obtained almost exclusively (94%); under more forcing conditions the benzylic hydrogens at C-4 are also replaced to some extent. (Tables 2 and 3 in the Experimental section show the results of the m.s. analyses and the exchange reactions.) The work in Scheme 1 thus led to 7-methoxy-1,2-dihydronaphthalene (3), and the deuteriated analogues (6), (8), and (9) with isotopic purity exceeding 93%.

Various reagents, *e.g.* potassium hydrogen sulphate at 150 °C,^{8,9} thionyl chloride and dimethylaniline at 60 °C,⁸ phosphoric oxide in boiling benzene,⁹ sodium ethoxide at 200 °C,¹⁰ have been used for the dehydration of 19-norergosta-5,7,9-trien-3 β -ol (dihydro-neoergosterol) (10b) or the Δ^{22} -alcohol (neoergosterol) (10a). Repetition of some of these reactions using the dihydro-alcohol (10b)

† We are grateful to Professor A. R. Katritzky for supplying full details (from Ph.D. Theses) of the work in ref. 2.

¹ Part 20, G. Felsky, P. M. Fredericks, and G. D. Meakins, preceding paper.

² M. J. Cook, A. R. Katritzky, F. C. Pennington, and B. M. Semple, *J. Chem. Soc. (B)*, 1969, 523.

³ M. A. Cooper, D. D. Elleman, C. D. Pearce, and S. L. Manatt, *J. Chem. Phys.*, 1970, **53**, 2343.

⁴ K. Biemann, 'Mass Spectrometry,' McGraw-Hill, New York, 1962.

⁵ W. S. Johnson, J. M. Anderson, and W. E. Shelberg, *J. Amer. Chem. Soc.*, 1944, **66**, 218.

⁶ R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, 1967, **89**, 5734.

⁷ N. S. Wulfson, V. I. Zaretskii, V. L. Sadovskaya, A. V. Zakharychev, S. N. Ananchenko, and I. V. Torgov, *Tetrahedron*, 1967, **23**, 3667.

⁸ J. W. Cook and G. A. D. Haslewood, *Chem. and Ind.*, 1934, 507.

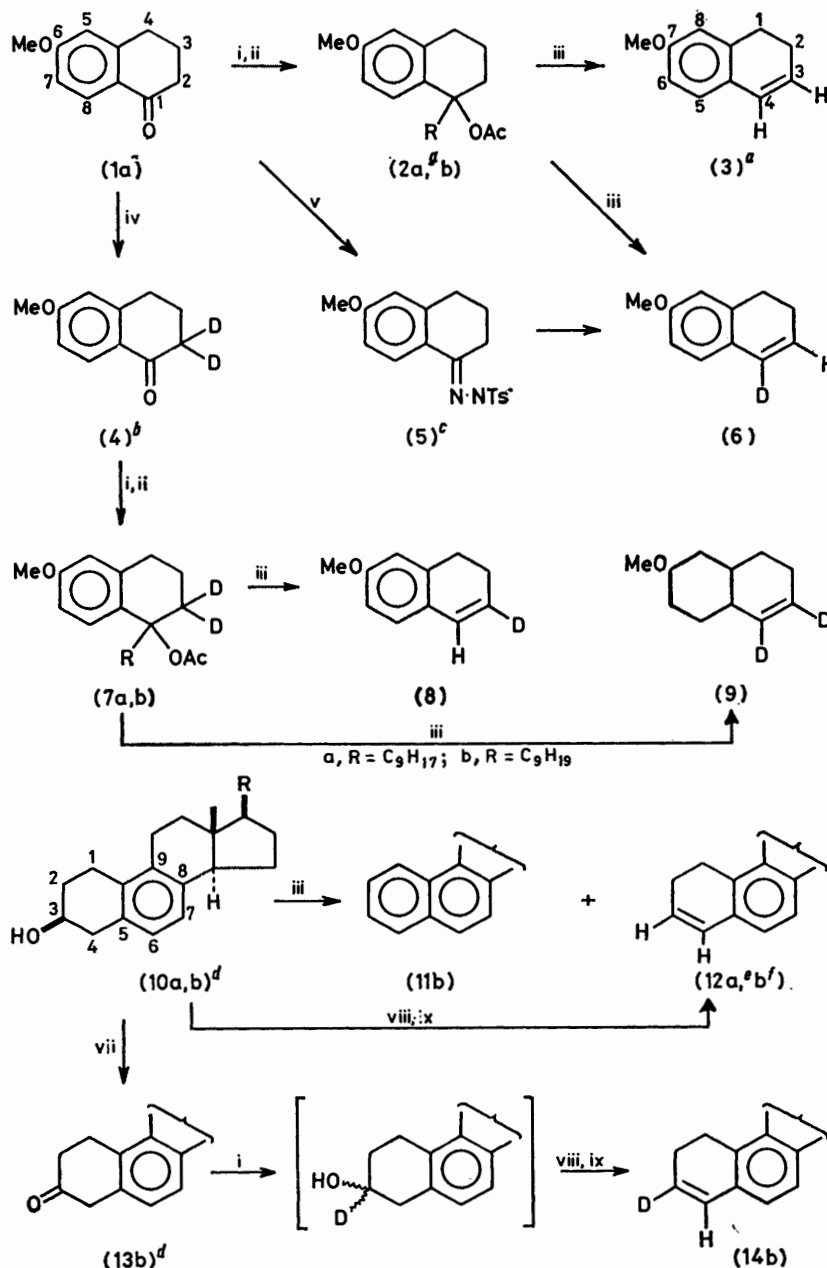
⁹ G. A. D. Haslewood and E. Roe, *J. Chem. Soc.* 1935, 465.

¹⁰ A. Windaus and M. Deppe, *Chem. Ber.*, 1937, **70**, 76.

showed that the materials described as the Δ^3 -olefin (12b) are formed in low yield and contain varying amounts of the naphthalene derivative (11b). (The components can be separated by preparative layer chromatography on

especially their rapid decomposition under basic conditions, prevented the introduction of deuterium at position 4 by exchange reactions. Nevertheless, the 3-deuterio-compound (14b) was obtained by reducing the

SCHEME 1 Preparation of 7-methoxy-1,2-dihydronaphthalenes and 19-norergosta-3,5,7,9-tetraenes. References are given to known compounds; the rest are new. a, R = H; b, R = D



Reagents: i, LiAlH₄ or LiAlD₄; ii, Ac₂O-C₅H₅N; iii, KHSO₄, heat; iv, NaOD-D₂O-THF(tetrahydrofuran), 65 °C; v, TsNH·NH₂; vi, BuⁿLi-THF, then D₂O; vii, H₂CrO₄-Me₂CO; viii, MeSO₂Cl-C₆H₅N; ix, NaOEt-EtOH. ^a Ref. 5. ^b Ref. 7. ^c Ref. 6. ^d Ref. 11. ^e Ref. 8. ^f Ref. 9.

silica impregnated with silver nitrate.) Both the Δ^3 -olefins (12a, b) were prepared in high yield and free from contamination *via* the β 3-methanesulphonyl esters as shown in the lower part of Scheme 1. The instability of 3-ketones derived from the neorgosterol system,¹¹

3-ketone (13b) with lithium aluminium deuteride and dehydrating the mixture of epimeric alcohols by the methanesulphonate sequence.

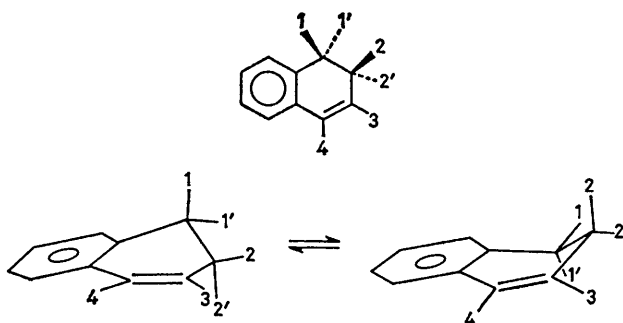
Since the method used in analysing the spectra of the substituted dihydronaphthalenes closely resembles that

developed in work on similar compounds^{2,3} only a brief outline of the present application is given. The following initial values (Hz) of the coupling constants (J) were taken as a basis for the calculations: (i) (averages from the observed spectra) $J_{2,3} = J_{2',3} = 4.3$, $J_{2,4} = J_{2',4} = -1.6$, $J_{3,4} = 10.4$, (ii) (assumed) $J_{1,3} = J_{1',3} = J_{1,4} = J_{1',4} = 0$, (iii) (from similar systems^{2,3}) $J_{1,1'} = -15$, $J_{1,2'} = 9$, $J_{1,2} = 7$, $J_{2,2'} = -17$, and (iv) $J_{H,D} = 0.14$ of the corresponding $J_{H,H}$. To facilitate fitting of the observed lines to the calculated transitions, the Lorentzian curves of the calculated spectra were compared with the experimental traces. The standard iterative processes were then carried out until solutions

Table 1. This follows from the results that not only is $J_{1,2'} = J_{1',2}$ but, in addition, $J_{1,2} = J_{1',2'}$. Further the low field 3-H and 4-H signals are pairs of triplets arising from the equalities $J_{2,3} = J_{2',3}$ and $J_{2,4} = J_{2',4}$. Rapid interconversion between the forms shown in Table 1 is consistent with the ^1H n.m.r. parameters.

Although study of the deuteriated analogous was useful in clarifying some spectrometric features it was not so helpful as had been hoped at the outset. It transpired that H-D couplings could not be ignored since the shape of the signals is influenced appreciably by these interactions. Thus, for example, the spectrum of the dideuteriated compound (9) could not be satisfactorily

TABLE 1
Analysis of the ^1H n.m.r. spectra of the substituted 1,2-dihydronaphthalenes (Scheme 1)



The spectra of degassed solutions in CCl_4 were recorded at 90 MHz, each signal being examined at a sweep width of 100 Hz. Line positions were measured (in Hz, downfield from SiMe_4) using a frequency counter (accuracy ± 0.1 Hz). An LAOCN 3 programme^a was used for spectral analysis.

Compound	Lines observed	Transitions fitted	Chemical shifts (τ)				Coupling constants (Hz)						R.m.s. error	
			1,1'	2,2'	3	4	1,1'	2,2'*	1,2'; 1',2'	1,2; 1',2'	2,3; 2',3	2,4; 2',4		3,4
(3)	37	93	7.339	7.822	4.223	3.670	-14.8	-17.0	9.3	6.8	4.4	-1.7	9.6	0.109
(6)	25	82	7.341	7.821	4.239		-12.6	-17.0	9.9	6.4	4.3	0.0	0.0	0.098
(8)	15	48	7.337	7.819		3.689	-16.1	-17.0	9.2	7.2	0.5	-1.6	0.0	0.046
(9)	13	38	7.335	7.821			-15.5	-17.0	9.0	7.2	0.2	0.0	0.0	0.041
(12a)	26	84	7.380	7.813	4.813	3.698	-15.1	-17.0	8.7	7.5	4.3	-1.7	9.6	0.079
(12b)	24	88	7.384	7.860	4.186	3.700	-16.9	-17.0	9.3	7.3	4.3	-1.6	9.7	0.057
(14b)	13	41	7.383	7.858		3.709	-17.0	-17.0	9.3	7.5	0.4	-1.6	0.0	0.045

* Value assumed (see text)

^a D. F. Detar, 'Computer Programs for Chemistry', W. A. Benjamin, London, 1968, Vol. 1.

with acceptable r.m.s. errors emerged; the parameter values of these solutions are shown in Table 1. It may be noted that while the analysis does give a value for the difference between the geminal coupling constants ($J_{1,1'}$ and $J_{2,2'}$) it does not evaluate the sum of these constants.³ A value for one of the couplings must be assumed, and in the present work $J_{2,2'}$ was held constant at -17 Hz. (Fortunately, parameters other than $J_{1,1'}$ and $J_{2,2'}$ are not appreciably affected by the precise value of the sum of the geminal coupling constants.)

The ^1H n.m.r. work demonstrates that the 1,1',2,2' spin system is symmetrical, corresponding to the AA'BB' rather than the ABCD type. Thus, in each of the columns of Table 1 which shows two parameters, equality of the parameters is established by the spectral analysis. The most probable interpretation of the symmetry is that the ring containing the olefinic bond is conformationally mobile in all the compounds shown in

analysed as a four spin system. Broad band deuterium decoupling, a facility not available in the present work, would be required in order to take full advantage of the simplification of the ^1H n.m.r. spectrum associated with deuteration at specific positions.

EXPERIMENTAL

General directions were as described in the preceding paper except that routine i.r. spectra were recorded using solutions in CCl_4 unless otherwise stated, and petrol refers to light petroleum, b.p. 60–80 °C.

7-Methoxy-1,2-dihydronaphthalene (3).—A solution of 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (1) (commercially available material; 10 g) in Et_2O was boiled under reflux for 1 h with LiAlH_4 (2 g). Work-up gave material (9.3 g), ν_{max} 3 620 cm^{-1} , which was treated with Ac_2O (40 ml)– C_6H_6 (40 ml) at 90 °C during 1 h. Work-up and rapid distillation of the product gave 1-acetoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (2a) (8.8 g), b.p. 126–

133 °C/0.8 mmHg (lit.,⁵ 132—139 °C/1—2 mmHg) (Found: C, 70.5; H, 7.2. Calc. for C₁₃H₁₆O₃: C, 70.9; H, 7.3%), ν_{\max} (CCl₄) 1 735 cm⁻¹. Heating a mixture of this compound (3.3 g) and KHSO₄ (20 mg) in a distillation apparatus at 120 °C/20 mmHg gave fractions of AcOH and then 7-methoxy-1,2-dihydronaphthalene (3) (2.4 g), b.p. 84—86 °C/1 mmHg (lit.,⁵ 75—76 °C/0.3 mmHg), ν_{\max} 3 036 cm⁻¹, one spot on t.l.c.

7-Methoxy-1,2-dihydro[4-²H]naphthalene (6).—(a) Via the 1-acetate (2b). The procedures of the preceding experiment were used. Treatment of the ketone (1) (2.5 g) with LiAlD₄ (205 mg) gave material (2.3 g), ν_{\max} 3 620 cm⁻¹, which afforded the 1-acetate (2b) (2.2 g), ν_{\max} 1 735 cm⁻¹, and then *7-methoxy-1,2-dihydro[4-²H]naphthalene* (1.7 g) of isotopic composition shown in Table 2, b.p. 81—83 °C/0.8 mmHg (Found: C, 81.6. C₁₁²H₁₁O requires C, 81.9%), one spot on t.l.c.

(b) Via the hydrazone (5). A solution of the ketone (1) (10 g) and toluene-4-sulphonylhydrazine (12.5 g) in EtOH (70 ml) was boiled under reflux for 30 min and then cooled. Collection of the insoluble material gave 6-methoxy-1-(*p*-tolylsulphonylhydrazono)-1,2,3,4-tetrahydronaphthalene (5) (19.3 g), m.p. 208—210 °C (lit.,⁶ 207—210 °C). A solution of this compound (dried at 100 °C *in vacuo*; 1 g) in dry tetrahydrofuran (30 ml) was added during 30 min to 1.4M-BuⁿLi in hexane (10 ml) which was stirred under N₂ at 10—15 °C. After a further 20 min D₂O (10 ml) was added slowly, the temperature of the mixture being kept below 20 °C, and stirring was continued for 10 h. Work-up and distillation gave material (580 mg) shown by m.s. examination to contain the 4-²H olefin (6) (86%) and the non-substituted olefin (3) (14%).

The Deuteriated 1,2-Dihydronaphthalenes (8) and (9).—Na (30 mg) was added to D₂O (15 ml). A solution of the ketone (1) (5 g) in dry tetrahydrofuran (25 ml) was added, and the solution was boiled under reflux for 8 h with exclusion of atmospheric moisture, cooled, and shaken with dry Et₂O. The Et₂O layer was separated, dried (MgSO₄), and evaporated to give 6-methoxy-1-oxo-1,2,3,4-tetrahydro[2,2-²H₂]naphthalene (4) (4.6 g) of isotopic composition shown in Table 2, m.p. 78—79 °C (lit.,⁷ 76°), ν_{\max} (CHCl₃) 1 670 cm⁻¹; τ 7.13 (2 H, t with *J* 6 Hz, 4-H) and 7.97 (2 H, t with *J* 6 Hz, 3-H).

Other experiments on the deuteration of the ketone (1) are summarised in Table 3.

In separate experiments the deuteriated ketone (4) (2.5 g) was reduced with LiAlH₄ and with LiAlD₄, and the products were dehydrated as described earlier for the ketone (1). The sequences gave, respectively, *7-methoxy-1,2-dihydro[3-²H]naphthalene* (8) (1.6 g), b.p. 86—87 °C/1 mmHg (Found: C, 81.7. C₁₁²H₁₁O requires C, 81.9%), and *7-methoxy-1,2-dihydro[3,4-²H₂]naphthalene* (9) (1.7 g), b.p. 81—83 °C/0.8 mmHg (Found: C, 81.2. C₁₁²H₂H₁₀O requires C, 81.5%); the isotopic compositions of these products, each of which gave one spot on t.l.c., are shown in Table 2.

*Dehydration of 19-Norergosta-5,7,9-trien-3 β -ol*¹¹ (10b).—The following results are broadly typical of those obtained by repetition of several procedures.⁸⁻¹⁰ An intimate mixture of 19-norergosta-5,7,9-trien-3 β -ol (2.8 g) and KHSO₄ (fused and powdered immediately before use; 5.6 g) was heated for 1 h at 160 °C in a stream of CO₂. The material (2.53 g) obtained by dilution with H₂O and extraction with Et₂O was adsorbed on neutral Al₂O₃ (200 g). Elution with CHCl₃ gave an oil (522 mg) which was separated by p.l.c. [repeated development with petroleum using layers

of SiO₂ impregnated with AgNO₃ (5%)] into, in order of descending *R_F*, fractions A (24 mg), B (48 mg), C (52 mg), and D (47 mg). Fraction B afforded 19-norergosta-1,3,5,7,9-pentaene (11b) (42 mg; m.p. 72—74 °C after crystallisation

TABLE 2

Abundancies (%) in the parent ion regions of mass spectra

<i>m/e</i>	180	179	178	177	176	175	174
Compound (1) *			1.3	14.3	100	8.9	0.4
Compound (4) *	1.7	14.8	100	13.5	1.4		

<i>m/e</i>	164	163	162	161	160	159	158	157
Compound (3)			1	14	100	41	5	1
Compound (6) †	1	14	100	42	8	1		
Compound (8)	2	15	100	47	13	1		
Compound (9)	1	14	100	45	16	2		

* Normalised results, the base-peak being at *m/e* 148 in both spectra; the percentages of the deuteriated species in compound (4) are 1.0 (²H₀), 4.6 (²H₁), 93.5 (²H₂), 0.5 (²H₃), and 0.4 (²H₄). † Base-peaks. ‡ Prepared *via* the acetate (2b).

from Me₂CO-hexane), [α]_D +21° (*c* 0.8) (Found: C, 89.1; H, 10.5. C₂₇H₃₈ requires C, 89.4; H, 10.6%), ν_{\max} (CHCl₃) 3 060 and 3 010 cm⁻¹; λ_{\max} 226 nm (ϵ 78 000);

TABLE 3

Deuteration of 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (1)

Ketone (g)	Na (mg)	D ₂ O (ml)	C ₅ H ₅ N (ml)	THF (ml)	MeOD (ml)	Time (h)	Temp (°C)	Dideuteration *
0.18	6	0.2	1.5			1	20	25
0.18	6	0.2	1.5			1	65	50
0.18	6	0.2	1.5			5	80	60
0.18	6	0.2	1.5			5	85	62
5	12	16		15		17	20	ca. 2
5	100	2		50		48	20	62
5	12	16		15		7	65	30
5	20	26		25		1	65	76
8	20	46		25		22	65	94
2	100	2			10	24	65	88 + 32 †

* At C-2 unless stated otherwise. † At C-4.

τ 2—3 (6 H, m with most intense signals at 2.63 and 2.79, ArH), and 9.39 (18-H). Fraction C was identified as 19-norergosta-3,5,7,9-tetraene (12b) by comparison with the product of the following experiment.

19-Norergosta-3,5,7,9-tetraene (12b). A solution of 19-norergosta-5,7,9-trien-3 β -ol (5.75 g) and MeSO₂Cl (2.6 ml) in C₆H₅N (20 ml) was kept at 20 °C for 3 d. Work-up, which included washing the solution in Et₂O with aq. CuSO₄, afforded the 3 β -methanesulphonate (6.15 g), m.p. 121—123 °C (from Et₂O), τ 4.89 (m, 3 α -H) and 6.99 (s, MeSO₂). Na (45 mg) was dissolved in EtOH (9 ml), the sulphonate (700 mg) was added, and the solution was boiled under reflux for 1 h. Work-up, filtration of a solution of the product in petrol through Al₂O₃, evaporation, and sublimation at 150 °C (bath temp.)/0.1 mmHg gave 19-norergosta-3,5,7,9-tetraene (459 mg), m.p. 69—70 °C (lit.,⁹ 63—64 °C), [α]_D +53° (*c* 0.8) (Found: C, 88.6; H, 11.2. Calc. for C₂₇H₄₀: C, 88.9; H, 11.1%), ν_{\max} (CHCl₃) 3 070, 3 040, and 3 010 cm⁻¹; λ_{\max} 267 nm (ϵ 11 200); τ 3.20 (2 H, s, 6-H and 7-H), 3.68 (1 H, m, 4-H), 4.17 (1 H, m, 3-H), and 9.41 (18-H).

19-Norergosta-3,5,7,9,22-pentaene (12a).—The procedures of the preceding experiment were used to convert 19-norergosta-5,7,9,22-tetraen-3 β -ol¹¹ (10a) (2.4 g) into its

¹¹ E. L. McGinnis, G. D. Meakins, and D. J. Morris, *J. Chem. Soc., (C)*, 1967 1238.

3 β -methanesulphonate (3.1 g), m.p. 135—138 °C (from Et₂O) (lit.,¹² 110—111 °C), and thence into 19-norergosta-3,5,7,9,22-pentaene (1.75 g), m.p. 87—88 °C (from petrol), [α]_D +46° (*c* 0.8) (lit.,⁹ m.p. 93—94 °C, [α]_D +51°) (Found: C, 89.3; H, 10.4. Calc. for C₂₇H₃₈: C, 89.4; H, 10.6%), λ_{max} 267 nm (ϵ 11 800); τ 3.20 (2 H, s, 6-H and 7-H), 3.70 (1 H, m, 4-H), 4.18 (1 H, m, 3-H), 4.75 (2 H, m, 22-H and 23-H), and 9.41 (18-H).

[3-²H]-19-Norergosta-3,5,7,9-tetraene (14b).—A solution of LiAlD₄ (105 mg) in Et₂O (20 ml) was added to a stirred solution of 19-norergosta-5,7,9-trien-3-one (2.1 g) in Et₂O (35 ml) at 0 °C, and stirring was continued for 3 h. Work-up gave material (1.92 g), lacking the signal at τ 5.9 observed

with 3 α - and 3 β -hydroxy-19-norergosta-5,7,9-triene.¹ This material, treated as in the preparation of the tetraene (12b), afforded [3-²H]-19-norergosta-3,5,7,9-tetraene (85 mg), m.p. 68—69 °C, [α]_D +54° (*c* 0.3) (Found: C, 88.5. C₂₇²HH₃₉ requires C, 88.7%), τ 3.20 (2 H, s, 6-H and 7-H), 3.69 (1 H, broad s, 4-H), and 9.41 (18-H).

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¹² S. G. Levine and A. C. Ghosh, *Tetrahedron Letters*, 1969, 39.