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THE CONVERSION OF ERGOSTEROL TO A RING C–BENZENOID STEROID BY A SELECTIVE AROMATIZATION REACTION[1,2]

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Abstract—Filtration of a benzene solution of 7,11,22,23-tetrabromoergost-8-en-3β-yl acetate (XIX) through alumina causes partial dehydrobromination to yield a benzenoid product in yields surpassing 90%. Evidence is presented that this product is a 12-methyl-18-norsteroid and can be assigned the structure, 22,23-dibromo-12-methyl-18-norergosta-8,11,13-trien-3β-yl acetate (XX).

THE selective aromatization of steroids possessing the customary angular methyl groups, either by methyl group migration or elimination, has been extensively studied and a useful review has recently appeared.[3] Three characteristic types of aromatic steroids occur naturally, as exemplified by estrone (I), the estrone isomer[4] (II) and the alkaloid, veratramine (III) representing respectively a ring A-, ring B- and modified (C-nor-D-homo) ring D-aromatic system.

From the viewpoint of partial syntheses from abundant naturally-occurring steroids, most attention has been paid to aromatization of ring A, utilizing dienones of type IV. For example, expulsion of the C-19 methyl group of such dienones can be accomplished by pyrolytic procedures, and gives the corresponding phenol (V), although usually in poor yield.[5] Acid catalyzed isomerization of the ring A dienones, customarily referred to as the "dienone-phenol rearrangement", yields predominantly the corresponding *p*-cresols (VI) and *m*-cresols (VII), the distribution being affected by solvent and other functional groups present;[6] derivatives of VII are isolated in particularly good yield in those cases in which a carbonyl group is located at C-6 or C-11 or an ethylenic function at C-6.[7] The action of zinc on dienones (IV) under mild conditions (refluxing pyridine, ethylene glycol), leading to the phenol (V) or

[1] The award of a research grant (O-3439) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service (to Robert Stevenson) is gratefully acknowledged.

[2] [a] C. F. Hammer, D. S. Savage, J. B. Thomson and R. Stevenson, *Tetrahedron Letters* 1261 (1963), described part of this work in preliminary communication.

[b] Presented in part at the XIX*th International Congress of Pure and Applied Chemistry* (London, 1963): R. Stevenson and C. F. Hammer, *Abstract*, p. 329.

[3] R. H. Shapiro, *Steroid Reactions* (Edited by C. Djerassi) pp. 371–402. Holden-Day, San Francisco (1963).

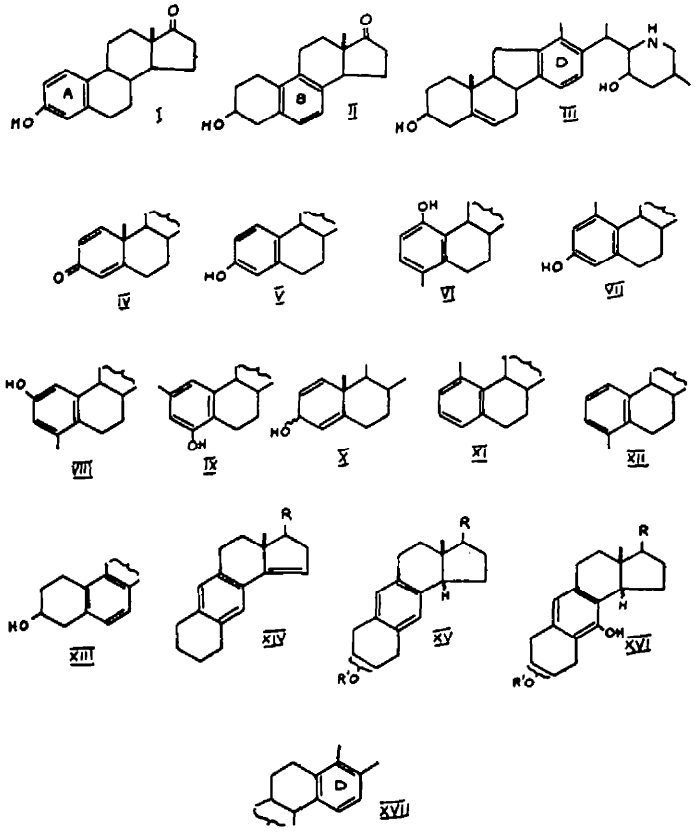
[4] R. D. H. Heard and M. M. Hoffman, *J. Biol. Chem.* **135**, 801 (1960); **138**, 651 (1961).

[5] Ref. 3, p. 382 gives pertinent references.

[6] [a] R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.* **72**, 494 (1950); [b] R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Heinz-Menzel, *Chem. Ber.* **86**, 594 (1953); [c] A. S. Dreiding and A. Voltman, *J. Amer. Chem. Soc.* **76**, 537 (1954); [d] S. M. Bloom, *Ibid.*, **80**, 6280 (1958); [e] Ref. 3, pp. 373–376 reviews reaction conditions and provides appropriate references; [f] L. F. Fieser and M. Fieser, *Steroids* pp. 327–329. Reinhold, New York (1959).

[7] Ref. 3: pp. 377–379 provides leading references.

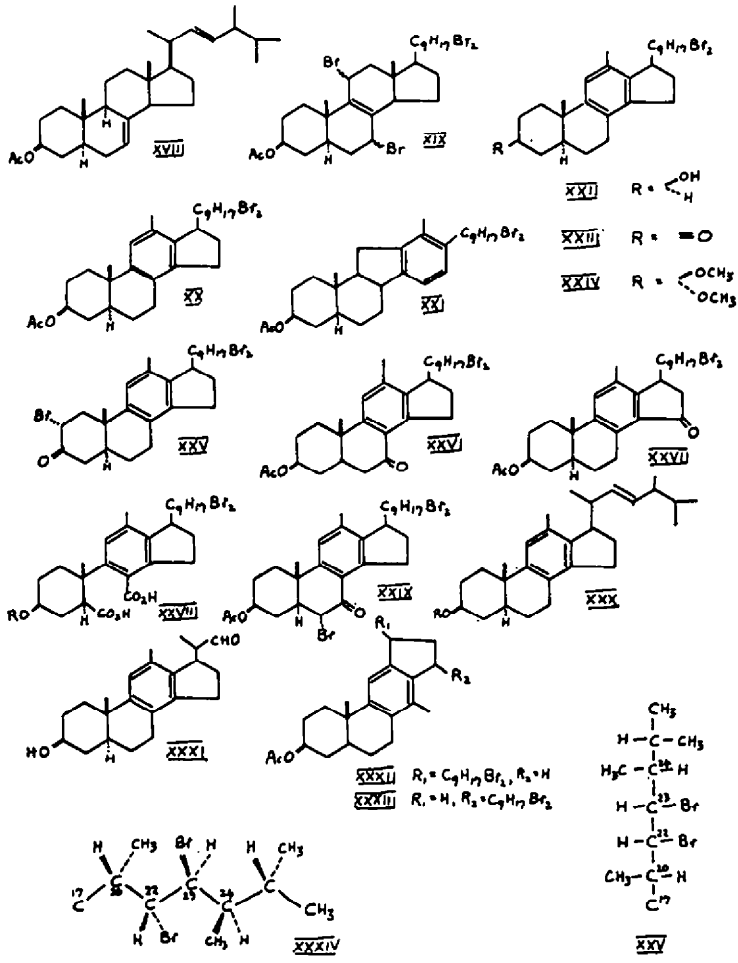
p-cresol (VI) in excellent yields, has recently been described.[8] By contrast, the products of photo-irradiation of ring A dienones (IV) have proved both complex and numerous; in addition to phenols of types (VI and VII, two others VIII and IX) have been isolated.[9–11] The dehydration of the corresponding ring A dienols (X) is known as the "dienol-benzene rearrangement" and produces the corresponding 1-methyl (XI) and 4-methyl (XII) benzenoid steroids.[12]



The conversion of ergosterol to neoergosterol (a benzenoid sterol of a type XIII now referred to as a neosterol) by photo-irradiation in absence of oxygen followed by pyrolysis of the 7,7′-bisergostatrienol product, provides the earliest example of a selective ring B aromatization.[13] The "anthrasteroid rearrangement" originally involved the acid treatment of Δ5,7,9,(11)-sterols to yield a modified steroid hydrocarbon

[8] K. Tsuda, S. Nozoe and coworkers, *J. Org. Chem.* **26**, 2614 (1961); **28**, 783, 786, 789, 795 (1963).
[9] H. Dutler, C. Ganter, M. Ryf, E. C. Rutzinger, K. Weinberg, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2346 (1962).
[10] C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2403 (1962).
[11] K. Weinberg, E. C. Utzinger, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **43**, 236 (1960).
[12] Ref. 3 pp. 379–381 gives leading references.
[13] For discussion, see ref. 6f, pp. 104–108.

with benzenoid ring B (XIV).[14,15] A modification of this interesting transformation involves the photochemical conversion of Δ5,7,9(11)-sterol derivatives, in the presence of *p*-toluenesulphonic acid catalyst, to isomeric C-14 epimers retaining the ring



A-hydroxylated function (XV).[16] Application of the dienone-phenol rearrangement to $\Delta^{5,8}$-unsaturated 7-ketones leads to anthrasteroid phenols (XVI).[17,18]

Ring D benzenoid D-homosteroids (XVII) have been obtained[19] from 17-ethynyl-carbinols by dehydration, ring enlargement and aromatization under the influence of acid. A selective aromatization of ring C, necessitating either elimination or migration

[14] W. R. Nes and E. Mosettig, *J. Amer. Chem. Soc.* **76**, 3182 (1954) and subsequent papers to Part X, J. A. Steele, L. A. Cohen and E. Mosettig, *Ibid.*, **85**, 1134 (1963).

[15] A. W. Burgstahler, *J. Amer. Chem. Soc.* **79**, 6047 (1957).

[16] K. Tsuda, R. Hayatsu, J. A. Steele, O. Tanaka and E. Mosettig, *J. Amer. Chem. Soc.* **85**, 1126 (1963).

[17] K. Tsuda, K. Arima and R. Hayatsu, *J. Amer. Chem. Soc.* **76**, 2933 (1954).

[18] P. Bladon, *J. Chem. Soc.* 2176 (1955).

[19] M. Dvolaitsky, A. M. Giroud and J. Jacques. *Bull. Soc. Chim. Fr.* 62 (1963).

of the C-18 methyl group does not appear to have been observed hitherto. Such a transformation is now described.

The action of bromine on 5-dihydroergosteryl acetate (XVIII) was reported[20] to yield a tetrabromoergostenyl acetate whose structure has recently been established[21] as 7,11,22,23-tetrabromoergost-8-en-3β-yl acetate (XIX). This tetrabromide is relatively stable in the solid state, particularly under vacuum, but undergoes rapid decomposition in polar solvents; it dissolves readily in benzene, however, to give a stable colorless solution. Filtration of a benzene solution through chromatographic alumina results in immediate reaction with formation of a greenish black band at the top of the column.[22] The nature of the eluted products varies with different commercial brands of alumina. With Spence Type H alumina (pH 9·10) or Woelm acid alumina (pH 3·75),[23] the tetrabromide, $C_{30}H_{46}O_2Br_4$ yields a dehydrobrominated product, $C_{30}H_{44}O_2Br_2$, in yields surpassing 90%.

The UV absorption spectrum of the dehydrobrominated product did not show high intensity absorption in the region associated with conjugated dienes or trienes, but exhibited low intensity maxima at 261, 268 and 277 mμ, i.e., typical benzenoid absorption. In support of this assignment, the product was recovered unchanged on attempted catalytic hydrogenation at atmospheric pressure and temperature. The mild conditions under which the dehydrobromination had occurred and the accumulated analytical data precluded the elimination of an angular methyl group and necessitated the conclusion that the benzenoid product had arisen as a consequence of molecular rearrangement associated with the dehydrobromination.

Acid or base hydrolysis of the dibromo benzenoid acetate gave the corresponding alcohol, attempted dehydration of which, using phosphorus oxychloride in pyridine, resulted in displacement of the hydroxyl group by a chlorine atom. Dehydration with phosphorus pentoxide in benzene, however, was successful and there were isolated two isomeric dibromo benzenoid ethylenes, in neither of which was the ethylenic bond conjugated with the benzenoid ring, as indicated by their UV spectra. From this, it was concluded that the ring adjacent to the original terminal ring A could not be the site of the benzenoid ring. With this restriction on the number of possible structures, we considered XX and XXI as the two most likely formulations. Both of these could have arisen by Wagner–Meerwein rearrangement of a carbonium ion or species electron deficient at C-12, XX by a 1,2-migration of the C-18 methyl group and XXI by similar shift of the C-13,14 bond. For the latter, a precedent exists in the solvolysis of a 12β-(equatorial) mesylate to give the C-nor-D-homo system.[25]

A distinction between XX and XXI was sought in examination of the IR spectrum.[26]

[20] R. C. Anderson, R. Stevenson and F. S. Spring, *J. Chem. Soc.* 2901 (1952).

[21] C. F. Hammer and R. Stevenson (to be published), cf., ref. 2.

[22] R. Stevenson, Ph.D. Thesis (Glasgow University) pp. 84, 120 (1952).

[23] The pH value refers to the pH of the decanted solution obtained by suspending the alumina (1·0 g) in distilled water (10 ml) for 45 min.

[24] The same product can be isolated, in much lower yields, with Merck acid, May and Baker, and Fisher alumina. The structures of other products obtained under these conditions will be the subject of a separate paper.

[25] R. Hirschmann, C. S. Snoddy, C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 4814 (1956).

[26] L. J. Bellamy, *Infra-red Spectra of Complex Molecules* (2nd Edition) pp. 64–65, 75–81. Methuen, London (1958).

Whereas XX is a pentasubstituted benzene and should exhibit an out-of-plane bending frequency in the region 900–860 cm^{-1}, XXI has two adjacent aromatic hydrogen atoms and should absorb at 860–800 cm^{-1}. The observed band at 869 (CS_2), 867 (KBr) and 862 cm^{-1} (nujol) supports XX. Although these values are sufficiently close to the borderline to be regarded as equivocal, comparison with closely-related models with narrower absorption ranges strengthens the conclusion.[27] Thus, tetra-substituted benzenes (e.g., *neo*steroids (XIII) and *sym*-octahydrophenanthrene) exhibit a sharp band at 812–795 cm^{-1} whereas the pentasubstituted ring in the anthrasteroids (XIV) show a moderate intensity band at 869–859 cm^{-1}. The nuclear magnetic resonance spectrum (Fig. 1) of the dibromo benzenoid acetate shows a signal at

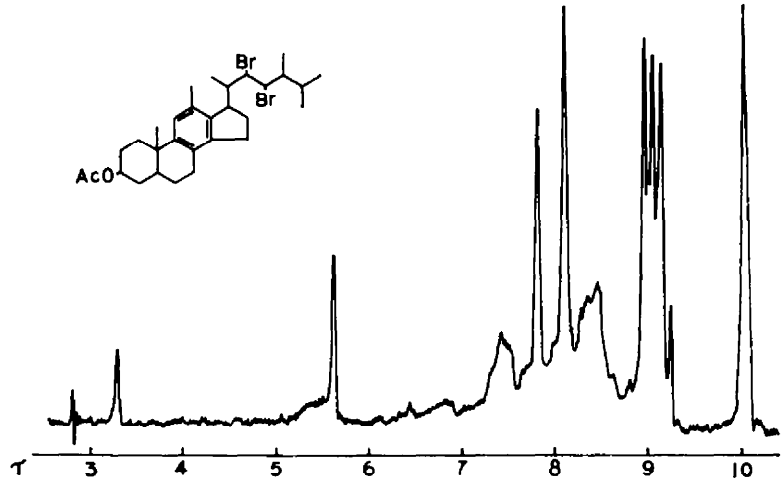


Fig 1. Nuclear magnetic resonance spectrum of XX.

τ7·78 with integrated intensity of three protons, characteristic of a methyl group attached to a benzene ring, and at τ3·22 with intensity of *one* proton, typical of an aromatic proton. This evidence rigorously excludes XXI and supports the structure 22,23-dibromo-12-methyl-18-norergosta-8,11,13-trien-3β-yl acetate (XX). This formulation is used in depicting the additional chemical evidence gained in support.

The alcohol (XXII), obtained from XX by either acid or base hydrolysis, was readily oxidized by chromium trioxide in pyridine to yield the corresponding ketone (XXIII), which could be crystallized from petroleum ether or isopropyl ether. In each case, solvent of crystallization was retained tenaciously after vigorous drying and was readily detected by the NMR spectrum. The NMR spectrum of the solvent-free ketone was measured on the pure specimen, readily obtained as a glass by chromatography. Simple crystallization of the ketone from methanol, by contrast, yielded a product which lacked carbonyl absorption in the IR spectrum, but had two methoxyl groups (τ6·87, 6·95) and is accordingly considered to be the dimethyl ketal (XXIV). It regenerates the ketone (XXIII) on chromatography on acid alumina. The ketone also yields the 2,4-dinitrophenylhydrazone derivative, whose UV spectrum is as expected for a non-conjugated ketone.[28]

[27] I. Scheer, W. R. Nes and P. B. Smeltzer, *J. Amer. Chem. Soc.* 77, 3300 (1955).
[28] C. Djerassi and F. Ryan, *J. Amer. Chem. Soc.* 71, 1000 (1949).

From the action of bromine on the ketone (XXIII) in acetic acid solution, there was isolated a monobromoketone whose IR absorption carbonyl frequency shows an increase of 15 cm^{-1} as compared to the unsubstituted parent ketone, indicative of an equatorial α-bromo atom.[29] The observed NMR multiplet splitting at τ5·42, attributable to the —CHBrCO— proton, is consistent with it being adjacent to a methylene rather than methine group. The bromoketone is accordingly formulated as the 2α-bromoketone (XXV). On treatment with 2,4-dinitrophenylhydrazine, it underwent elimination of hydrogen bromide to form the dinitrophenylhydrazone of a conjugated ketone. The UV (λ382 mμ) and NMR spectra (τ3·79 doublet (J = 11 cps) and 2·99 doublet (J = 11 cps)), are fully characteristic of the dinitrophenylhydrazone derivative of a Δ^1-unsaturated-3-ketone. This confirms the earlier conclusion that ring A is not adjacent to the benzene ring, that ring B (intact or modified) must be excluded as the site of the benzene ring, and establishes that at least three carbon atoms must separate the benzene ring from the ring-A oxygen function. The pattern of the bromination-dehydrobromination behaviour is, moreover, fully consistent with the behaviour of A/B-trans steroids with an axial C-19 methyl group.

From experiments on the oxidation of XX with chromium trioxide, the most readily isolated product was a phenyl ketone, whose IR carbonyl absorption (λ5·98 ($CHCl_3$), 5·94μ (Nujol)) indicated the presence of a tetralone, rather than indanone system, and is consequently considered to be the 7-ketone (XXVI). As isolated from the neutral fraction of the oxidation mixture, XXVI is obtained as a co-crystal with the precursor (XX) from which it is readily separated in a pure, but non-crystalline form by chromatography. A minor by-product of the reaction in another non-crystalline phenyl ketone whose IR absorption maximum at 5·84 μ indicates that it is an indanone and consequently the 15-ketone (XXVII). The isolation of XXVI and XXVII establishes that the benzenoid ring is flanked by a 6-membered and 5-membered ring. With a large excess of oxidizing agent, both XX and XXVI yielded an amorphous dicarboxylic acid, $C_{30}H_{42}O_6Br_2$ whose UV absorption spectrum closely resembled that of 5,6,7,8-tetrahydro-2-naphthoic acid[31] and is accordingly formulated as XXVIII.

Bromination of the phenyl 7-ketone (XXVI) in acetic acid solution gave a crystalline monobromoketone (XXIX) whose NMR spectrum included a doublet signal at τ5·63 (J = 14 cps) indicating that the proton at C-6 has an axial conformation and is adjacent to an axial methine proton. The bromine substituent consequently has the 6α-(equatorial) configuration as expected from its 1,3-relationship to the C-19 methyl group.

Within our experience, the dibromo benzenoid steroids encountered in this work proved generally more difficult to obtain crystalline than unrearranged 22,23- dibromoergostane derivatives.[20,32] In this respect, the Δ^{22}-derivatives of the benzenoid 18-norergostanes, readily obtained in excellent yield by debromination with zinc dust or Raney nickel in ethanol solution, proved still more recalcitrant. The dibromo benzenoid acetate (XX) yielded the non-crystalline acetate (XXX, R = Ac), which on alkaline hydrolysis gave the non-crystalline alcohol (XXX, R = H). A crystalline

[29] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).
[30] W. M. Schubert and W. A. Sweeney, *J. Amer. Chem. Soc.* **77**, 4172 (1955) and other references therein cited.
[31] W. G. Dauben, C. F. Hiskey and A. H. Markhart, *J. Amer. Chem. Soc.* **73**, 1393 (1951).
[32] R. Budziarek *et al.*, *J. Chem. Soc.* 3410, 4874 (1952); 534, 778, 956 (1953).

3,5-dinitrobenzoate derivative of the latter was, however, obtained. Sidechain degradation of XXX (R = Ac) established that no unexpected structural change had occurred with regard to the bromination-debromination sequence of the Δ^{22}-ethylenic bond. Addition of osmium tetroxide to XXX (R = Ac) and cleavage of the osmate ester with lithium aluminium hydride gave a 3,22,23-triol which after treatment with periodic acid yielded two carbonyl fragments, separated by steam distillation, and purified by chromatography of their 2,4-dinitrophenylhydrazone derivatives on alumina. The volatile fragment was identified as (—)-methylisovaleraldehyde by direct comparison of derivatives, and empirical analysis of the derivative of the non-volatile fragment was in agreement with its formulation as the bisnorallocholatrien-aldehyde (XXXI).

The NMR spectrum of the dibromo benzenoid acetate (XX) is reproduced in Fig. 1 and the principal assignments to this and a further ten dibromo benzenoid compounds, bearing substituents in rings A and B are summarized in Chart 1. In the high field region, four peaks, attributable to the methyl groups (C-19, C-21, C-28, C-26 and C-27) appear in the regions τ9·23–9·17, 9·10–9·07, 9·02–8·98 and 8·83–8·65. The signal in the last region, in which the greatest fluctuation with substitution occurs, can be assigned to C-19. In moving downfield, a broad unresolved band (τ8·38–8·18) due to methylene and methine protons is found, and the derivatives possessing the 3β-acetoxy group give a sharp 3-proton signal at τ8·05. The aromatic methyl group at C-12 gives a signal at τ7·77–7·75 in the first four derivatives listed, but is deshielded by a 7-keto or 3β-fluoroacetate group or a Δ^1-ethylenic bond to τ7·70–7·63. The protons adjacent to the aromatic ring ($H_{(7)}$,$H_{(15)}$ and $H_{(20)}$) give broad 5-proton signals at τ7·43–7·37; in the presence of the 7-keto group, the three remaining benzylic protons are deshielded (τ6·85–6·73). In every example, the $H_{(22)}$ and $H_{(23)}$ protons give a singlet peak at τ5·58–5·53. The aromatic proton at C-11, with integrated intensity of one proton in general gives a signal at τ3·23–3·22, which is deshielded by the 3-keto group and its 2,4-dinitrophenylhydrazone derivative (τ3·18–3·17) and more extensively by the phenyl conjugated 7-ketone (τ3·08–3·06).

The prediction of variation in chemical shift of angular methyl protons in steroids with the introduction of substituents into the parent molecule has been the subject of considerable work, and additivity relationships have been established.[33] Recently, attention has been drawn to the significance of structural symmetry on these relationships, with particular reference to C-19 methyl proton shifts and the rule formulated[34]—the same change in substituents at analogous positions (*vis-a-vis* the methyl group under study) will produce the same replacement constant. The data listed in Chart 1 permit an interesting test of this rule. In comparison with cholestane derivatives, it is to be expected, and found to be the case, that the C-19 methyl group signal of the ring C benzenoid norergostatriene compound is paramagnetically shifted. Although the conformation of ring B in the two systems must differ markedly, it was anticipated that ring A conformation should bear a close correspondence and that the "replacement constants" derived in the cholestane system[34] should be applicable in ring A, but inapplicable in ring B of the norergostatriene system. The τ values of the C-19 methyl protons for the two series are compared in Chart 2. In the four examples bearing

[33] [a] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80,** 5121 (1958); [b] R. F. Zurcher, *Helv. Chim. Acta* **44,** 1380 (1961); [c] J. Jacquesy, J. Lehn and J. Levisalles, *Bull. Soc. Chim. Fr.* 2444 (1961).

[34] E. R. Malinowsky, M. S. Manhas, G. H. Muller and A. K. Bose, *Tetrahedron Letters* 1161 (1963).

CHART 1. CHEMICAL SHIFTS (τ-VALUES) OF 22,23-DIBROMO-12-METHYL-18-NORERGOSTA-8,11,13-TRIENE DERIVATIVES

	CH_3 (Sidechain)			C-19	$>CH_2$[a] and $>CH$	CH_3CO_2-3β	12-CH_3	$PhCH_2$[a] and PhCH<	$H_{(22)(23)}$	$H_{(11)}$	Other
3β-Acetate (XX)	9·20	9·10	9·00	8·90	8·34	8·05	7·77	7·39	5·55	3·22	5·37 $H_{(3)}$
3β-Alcohol (XXII)	9·22	9·10	9·00	8·92	8·38	—	7·75	7·42	5·58	3·22	—
3-Ketone (XXIII)	9·20	9·08	8·98	8·73	8·23	—	7·77	7·43	5·55	3·17	—
3,3-Dimethylketal (XXIV)	9·18	9·07	8·98	8·93	8·38	—	7·75	7·38	5·53	3·23	6·95 Methoxyl 6·85 Methoxyl
3-Ketone 2′,4′-dinitrophenylhydrazone	9·17	9·07	8·98	8·73	8·18	—	7·72	7·38	5·57	3·17	2·20 H(6′) 1·83 H(5′) 1·05 H(3′) −1·08 NH
2α-Bromoketone XXV	9·20	9·08	9·00	8·65	8·22	—	7·75	7·43	5·55	3·18	5·20 (quadruplet) $H_{(2)}$
Δ^1-3-Ketone 2′,4′-dinitrophenylhydrazone	9·18	9·07	8·98	8·77	8·20	—	7·70	7·37	5·55	3·06	3·79 doublet (J11) $H_{(1)(2)}$ 2·99 doublet (J11) 2·13 H(6′) 1·78 H(5′) 1·08 H(3′) −1·08 NH
7-Keto-3β-alcohol	9·23	9·10	9·00	8·33	8·22	-	7·63	6·73	5·53	3·07	—
7-Keto-3β-acetate (XXVI)	9·23	9·08	9·00	8·82	8·27	8·05	7·67	6·85	5·57	3·07	—
6α-Bromo-7-keto-3β-acetate (XXIX)	9·20	9·08	9·02	8·82	8·23	8·03	7·65	6·77	5·55	3·08	5·35 H(3) 5·63 doublet (J14)H(6)
3β-Trifluoracetate	9·20	9·08	8·98	8·85	8·30	—	7·67	7·38	5·55	3·23	—

[a] Centre of broad unresolved band.

CHART 2. CHEMICAL SHIFTS OF C-19 METHYL PROTONS (τ VALUES)

	Cholestane	Norergostatriene	Difference
3β-Acetate	9·17	8·90	0·27
3β-Alcohol	9·19	8·92	0·27
3-Ketone	9·01	8·73	0·28
2α-Bromo-3-ketone	8·91	8·65	0·26
7-Keto-3β-alcohol	8·94	8·83	0·11
7-Keto-3β-acetate	8·93	8·82	0·11
6α-Bromo-7-keto-3β-acetate	8·85	8·82	0·03

ring A substituents, the additivity of the replacement constant holds within the error of $\pm$0·01 ppm, but is inapplicable to the three examples with ring B substituents.

The evidence presented is consistent with the formulation of the aromatic steroid as XX, but does not exclude alternative structures e.g. XXXII and XXXIII, for which mechanisms of formation can be readily derived, but which may be considered unlikely due to the involvement of 4-membered spiran intermediates. Consideration of the UV fine structure of the B-band permitted a distinction between benzenoid compounds with angular annulation (e.g. neosteroids (XIII)) and those with linear annulation (e.g. dihydroanthrasteroids (XV)).[27] Comparison of the general shapes and molecular extinction coefficients of the maxima of the dibromo benzenoid acetate supports its angular annulated formulation (XX), rather than the linear structures (XXXII and XXXIII).

An X-ray crystallographic structure study of the dibromo benzenoid acetate, undertaken with Dr. T. N. Margulis of this department and to be reported separately, has confirmed structure XX. It establishes that the β-configuration of the sidechain had been retained during the aromatization reaction and permits assignment of configuration to the sidechain bromine atoms. The perspective drawing (XXXIV) of the sidechain shows the complete staggering of the bromine and methyl substituents along the chain. As arranged in Fischer projection (XXXV), according to the Plattner–Fieser nomenclature convention,[35] the halogen atoms in XX and hence all derivatives have 22α,23α-orientations.

EXPERIMENTAL

Specific rotations were determined in chloroform solution and UV absorption spectra were measured in ethanol solution (unless otherwise stated). All m.ps. were determined using a Gallenkamp m.p. apparatus. NMR spectra were determined in CCl_4 solution with tetramethylsilane as an internal standard, using a Varian 4300B spectrometer at 60 mc.

22,23-Dibromo-12-methyl-18-norergosta-8,11,13-trien-3β-yl acetate (XX)

A solution of 7,11,22,23-tetrabromoergost-8-en-3β-yl acetate (4·29 g) in benzene (150 ml) was added to a column (1 in. diameter) of Spence Type H alumina (45 g) causing formation of a dark green violet coloured band at the top. The product was immediately eluted with additional benzene (140 ml), solvent removal yielding a residual glass (3·19 g, 96% yield). Crystallization from acetone–methanol gave 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*yl acetate* as needles (2·75 g, m.p. 135–136°). An analytical sample had m.p. 136–137·5°, $[\alpha]_D$ −4° (*c*, 1·6); λ220 inf. (13500), 261(247), 268(279), 277 sh. (216) mμ in iso-octane, λKBr 3·41, 3·50, 5·78, 6·21 w., 6·84, 6·89, 11·50 (pentasubstituted aromatic) μ, λCS_2 869 cm^{-1}. It gives a deep yellow colour with tetranitromethane

[35] For a discussion of nomenclature of sidechain stereochemistry, see ref. 5(f), pp. 337–340.

in chloroform solution. (Found: C, 60·4; H, 7·5. Calc. for $C_{30}H_{44}O_2Br_2$: C, 60·40; H, 7·43%). The dibromo acetate was quantitatively recovered after attempted catalytic hydrogenation at atmospheric pressure using platinum catalyst.

22,23-*Dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*ol* (XXII)

(a) The dibromo acetate (250 mg) was dissolved in methanolic NaOH solution (2%, 25 ml), the mixture heated under reflux for 1 hr, worked up in the usual way through ether and the product crystallized from pet. ether to give 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*ol* as felted needles (90 mg), m.p. 111–113°, $[\alpha]_D$ +5° (*c*, 1·1), λ268(400) and 276 mμ (260), ν_{nujol} 3390 (hydroxyl), 1598 and 865 (aromatic) cm^{-1}. (Found: C, 60·2; H, 7·6. Calc. for $C_{28}H_{42}OBr_2$: C, 60·66; H, 7·64%). The alcohol crystallized from ethanol as needles, m.p. 100–102°, $[\alpha]_D$ +3° (*c*, 1·9) with ethanol of crystallization. (Found: C, 59·92; H, 7·85. Calc. for $C_{28}H_{42}OBr_2 \cdot C_2H_5OH$: C, 60·00; H, 8·06%).

(b) The dibromo acetate (497 mg) was heated under reflux for 1 hr with methanolic H_2SO_4 aq. (18%, 100 ml) and allowed to stand overnight at room temp. Colourless needles (450 mg, m.p. 90–98°) separated and on recrystallization from aqueous methanol gave the dibromo alcohol, m.p. 108–110°, $[\alpha]_D$ +5°, with IR spectrum identical to that of specimen obtained as in (a). Acetylation regenerated the acetate, m.p. 136–137°, $[\alpha]_D$ −2° (*c*, 1·2). The trifluoroacetate was isolated as a colorless glass which resisted crystallization.

22,23-*Dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3-*one* (XXIII)

To a solution of the dibromo alcohol (2·61 g) in pyridine (20 ml) was added a suspension of bis(pyridine)chromium oxide (4·0 g, Eastman Organic Chemical) in pyridine (25 ml) and the mixture allowed to stand at room temp. for 18 hr. The product was worked up through ether in the usual way to yield a light brown gum (2·2 g, λ$CHCl_3$ 2·78 (weak) and 5·83 μ (strong)) which was purified by chromatography on Spence Type H alumina (80 g). Elution with benzene (250 ml) yielded 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3-*one* as a colourless glass (1·62 g), which crystallized from pet. ether (b.p. 64–69°) or isopropyl ether as small needles, m.p. 101–102° (in each case containing solvent of crystallization not removed by heating at 78°/10^{-3} mm Hg for 8 hr). A sample (150 mg) was rechromatographed by the preparative thin layer technique on silica gel (1 mm). Development with benzene–chloroform (3:7) gave a band (R_f 0·35) which on elution with methylene chloride gave the ketone as a colourless glass (120 mg), yielding (from pet. ether) needles (103 mg) m.p. 103·5–105°, $[\alpha]_D$ +23° (*c*, 1·05), λKBr 3·42, 5·83 μ, λ222 inf. (11,200), 261(270), 268(350) and 275 inf. mμ (250). (Found (from pet. ether): C, 64·21; H, 7·97; (from isopropyl ether): C, 61·78; H, 7·24; Br, 28·13. Calc. for $C_{28}H_{40}OBr_2$: C, 60·87; H, 7·30; Br, 28·93%). The NMR spectrum determined on the pure sample (glass state) gave a total integrated intensity of 40 protons.

22,23-*Dibromo*-3,3-*dimethoxy*-12-*methyl*-18-*norergosta*-8,11,13-*triene* (XXIV)

Crystallization of the glassy pure dibromoketone from methanol yielded the *dimethylketal* as small needles, m.p. 138·5–140°, $[\alpha]_D$ +14° (*c*, 1·5), λ220 inf. (13000), 266 mμ (386), λ$CHCl_3$ 3·42, 5·83 (weak, indicating ca. 5% ketone), 8·73, 9·03, 9·14, 9·67 μ (methoxyl). Two recrystallizations from aqueous dimethylformamide reduced ketone content to ca. 2%. (Found: C, 60·31; H, 7·73. Calc. for $C_{30}H_{50}O_2Br_2$: C, 60·20; H, 7·75%). Crystallization of the glass ketal from 1% HCl in methanol gives a ketone (16):ketal (84) mixture. The ketone is readily regenerated from the ketal by filtration of a solution through a column of Woelm acid alumina.

22,23-*Dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3-*one* 2′,4′-*dinitrophenylhydrazone*

Boiling the ketone with a solution of 2,4-dinitrophenylhydrazine in acetic acid yielded the 2,4-dinitrophenylhydrazone as orange plates from chloroform-acetic acid, m.p. 227–228°, λ$CHCl_3$ 367(20800) and 260 sh. (9900) mμ. (Found: C, 55·20; H, 5·91; N, 7·54. Calc. for $C_{34}H_{44}N_4O_4Br_2$: C, 55·74; H, 6·05; N, 7·65%).

2α,22,23-*Tribromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3-*one* (XXV)

A solution of bromine (58 mg) in acetic acid (1·0 ml was added dropwise to a solution of the dibromoketone (200 mg, crystallized from pet. ether) in acetic acid (3 ml) with swirling and slight warming. White needles, which began to separate before addition was complete, were collected

(160 mg, m.p. 172·5–173·5°) after the mixture had been allowed to stand at room temp. for 2 hr. This product was purified by thin layer chromatography on silica gel (1 × 20 × 20 mm plate) with elution with benzene–chloroform (1:3). A band (R_f 0·5) yielded, after extraction with methylene chloride, a white solid (82 mg) which was crystallized twice from methylene chloride–methanol to give 2α,22,23-*tribromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3-*one* as needles m.p. 184–184·5° dec., $[\alpha_D]$ +40° (*c*, 1·7), λ222 inf. (14700), 262 sh. (327), 267(338), 275 sh. (282) mμ., λKBr 3·42, 5·78 μ. (Found: C, 53·19; H, 6·38; Br, 37·51. Calc. for $C_{28}H_{39}OBr_3$: C. 53·26; H, 6·23; Br, 37·97%).

22,23-*Dibromo*-12-*methyl*-18-*norergosta*-1,8,11,13-*tetraen*-3-*one* 2′4′-*dinitrophenylhydrazone*

Boiling the 2α-bromoketone with a solution of 2,4-dinitrophenylhydrazine in acetic acid resulted in dehydrobromination and give the conjugated ketone 2,4-dinitrophenylhydrazone. It crystallized from chloroform–acetic acid as red-orange needles, m.p. 223·5–224·5°, λCHCl$_3$ 382(35600), 286 inf. (12,700) and 256 mμ (21400). (Found: C, 55·60; H, 5·51; N, 7·75. Calc. for $C_{34}H_{42}N_4O_4Br_2$: C, 55·90; H, 5·80; N, 7·67%).

Oxidation of 22,23-*Dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*yl acetate with chromium trioxide*

(a) *Using* 2·2 *mole* O. A solution of chromium trioxide (131 mg) in water (0·5 ml) and acetic acid (2 ml) was added to a solution of dibromo acetate (535 mg) in acetic acid (25 ml). The mixture was allowed to stand at room temp. for 20 hr, diluted with water and the resultant flocculent precipitate (474 mg, m.p. 88–100°) collected, washed with water and dried. Two recrystallizations from methanol gave a mixed crystal of starting dibromo acetate and derived 7-ketodibromo acetate as needles, m.p. 126·5–128·5°, $[\alpha]_D$ −5° (*c*, 2·04), λCHCl$_3$ 3·41, 3·50, 5·78, 5·98, 6·26 μ. (Found: C, 60·02; H, 7·40. Calc. for $C_{30}H_{44}O_2Br_2$ (dibromo acetate): C, 60·40; H, 7·43. Calc. for $C_{30}H_{42}O_3Br_2$ (keto dibromo acetate): C, 59·02; H, 6·94%). The NMR and IR spectra indicated that the mixed crystal contained ca. 60% ketone.

Concentration of the crystallization mother liquors yielded rosettes (80 mg, m.p. 191–193·5° dec, IR spectrum showed hydroxyl present and acetoxyl absent) which on recrystallization from methylene chloride–methanol gave 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*ol*-7-*one* as rosettes, m.p. 195–196·5° (dec), $[\alpha]_D$ −7° (*c*, 2·1), λ219(26600), 264(12500), 309 mμ (2800), λCHCl$_3$ 2·78, 2·90, 3·42, 3·50, 5·99, 6·28 μ. (Found: C, 59·36; H, 7·09. Calc. for $C_{28}H_{40}O_2Br_2$: C, 59·16; H, 7·09%).

Acetylation, using pyridine and acetyl chloride, gave the corresponding acetate as a colourless glass whose IR spectrum was identical with specimen isolated in (b) below.

(b) *Using* 3·3 *mole* O. A solution of chromium trioxide (254 mg) in water (few drops) and acetic acid (5 ml) was added to a solution of the dibromo acetate (690 mg) in acetic acid (30 ml), the mixture allowed to stand at room temp. for 20 hr and worked up as in (a). The resulting product (689 mg, m.p. 102–106°) was dissolved in benzene and chromatographed on Merck acid alumina (40 g). Elution with benzene yielded unchanged dibromo acetate (53 mg, identical NMR spectrum). Elution with chloroform–benzene (1:1, 170 ml) gave 3β-*acetoxy*-22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-7-*one* (XXVI) as a colourless glass which could not be crystallized, $[\alpha]_D$ −4·5° (*c*, 2·3), λ219(23800), 266(12100) and 311 mμ (2600), λKBr 3·42, 3·50, 5·78, 5·99, 6·29, 6·90, 11·48 μ. It was recovered unchanged from attempted semicarbazone and 2,4-dinitrophenylhydrazone formation. Alkaline hydrolysis yielded the corresponding alcohol.

Further elution with chloroform–benzene (1:1, 20 ml) gave a colourless glass (53 mg, λCHCl$_3$ 5·78(-OAc), 5·84(indanone carbonyl) and 5·99 μ (tetralone carbonyl) and with chloroform (70 ml) gave a light yellow glass (81 mg, IR spectrum showed hydroxyl, indanone and tetralone absorption). These fractions were combined with corresponding fractions from repeat experiments (total = 613 mg) and rechromatographed on Merck acid alumina (20 g) with collection of 10 ml volumes of chloroform–benzene (1:1) eluates. The fourth fraction yielded a colourless glass (46 mg, λCHCl$_3$ 5·78, 5·84 μ) which could not be crystallized and which is regarded as 3β-*acetoxy*-22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-15-*one* (XXVII) on consideration of the IR and NMR spectrum. It was recovered unchanged from attempted 2,4-dinitrophenylhydrazone formation.

(c) *Using* 12 *atoms* O. A solution of chromium trioxide (1·05 g) in acetic acid (15 ml) was added to a solution of the dibromo acetate (900 mg) in acetic acid (50 ml) and the mixture allowed to stand at room temp. for 2 days, then worked up through ether to give neutral and acid fractions. The acid

fraction (500 mg) was an amorphous white solid which did not crystallize from the usual solvents and was purified by repeated precipitation from an acetic acid solution by addition of water to give 6,7-*seco*-3β-*acetoxy*-22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*triene*-6,7-*dioic acid* (XXVIII), m.p. 150–170° dec, λ257 (11000) and 300 mμ (3000), ν_{nujol} 3300–2850 and 1720–1710 cm^{-1}. (Found: C, 54·6; H, 6·7. Calc. for $C_{30}H_{42}O_6Br_2$: C, 54·73; H, 6·43%). Treatment of 3β-acetoxy-22,23-dibromo-12-methyl-18-norergosta-8,11,13-trien-7-one under the same oxidation conditions gave the amorphous dicarboxylic acid in 50% yield.

3β-*Acetoxy*-6α,22,23-*tribromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-7-*one* (XXIX)

A solution of bromine (147 mg) in acetic acid (5 ml) was added dropwise to a solution of the 7-ketodibromo acetate (563 mg) in acetic acid (10 ml). A drop of HBr (48%) was added, the mixture allowed to stand at room temp. for 1 hr, then poured into water (300 ml). The resultant precipitate was collected and crystallized from aqueous acetic acid to give needles (449 mg, m.p. 191–194° dec). Recrystallization of an analytical sample from the same solvent gave 3β-*acetoxy*-6α, 22,23-*tribromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-7-*one* as fine needles, m.p. 201–202° dec, $[\alpha]_D$ −23° (*c*, 2·7), λ220(20,100), 274(11,960) and 306 sh. mμ. (3100), λ$CHCl_3$ 3·41, 5·78, 5·94, 6·27 μ. (Found: C, 52·27; H, 6·13; Br, 35·05. Calc. for $C_{30}H_{41}O_3Br_3$: C, 52·26; H, 6·00; Br, 34·78%). The bromoketone was recovered in good yield on attempted semicarbazone and 2,4-dinitrophenylhydrazone formation.

22,23-*Dibromo*-3ξ-*chloro*-12-*methyl*-18-*norergosta*-8,11,13-*triene*

A solution of the dibromo alcohol (85 mg) in pyridine (10 ml) was warmed on the steam bath with phosphorus oxychloride (1 ml) for 1 hr, allowed to stand overnight at room temp., then worked up in the usual manner. Crystallization of the product (60 mg, m.p. 190–193°) from chloroform–methanol gave 22,23-*dibromo*-3ξ-*chloro*-12-*methyl*-18-*norergosta*-8,11,13-*triene* as needles, m.p. 195–197°, $[\alpha]_D$ +13° (*c*, 1·7), λ215(25000), 258(467), 267(476) and 276 mμ (400). It gives a deep yellow colour with tetranitromethane in chloroform. (Found: C, 58·65; H, 7·30; Br, 27·2; Cl, 6·05. Calc. for $C_{28}H_{41}BrCl$: C, 58·69; H, 7·21; Br, 27·90; Cl, 6·19%).

Action of phosphorus pentoxide on 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*ol*

A solution of the dibromo alcohol (160 mg) in dry benzene (5 ml) was shaken at room temp. for 22 hr with P_2O_5 (160 mg). After addition of water, the reaction mixture was worked up in the usual manner to give a pale yellow gum (140 mg) which slowly crystallized from acetone to give a *compound* (regarded as the Δ^2 (or Δ^3)-ethylene) as blades (70 mg), m.p. 124–125°, $[\alpha]_D$ +53° (*c*, 0·7), λ208(30,000) and 269 mμ (370). (Found: C, 62·65; H, 7·7. Calc. for $C_{28}H_{40}Br_2$: C, 62·69; H, 7·52%). From the mother liquors there separated needles (30 mg, m.p. 123–128°). Recrystallization from chloroform–methanol gave an *isomer* (regarded as the Δ^3 (or Δ^4)-ethylene) as needles, m.p. 128–131°, $[\alpha]_D$ +41° (*c*, 0·6), λ208(30,000) and 269 mμ (370). (Found: C, 62·5; H, 7·5. Calc. for $C_{28}H_{40}Br_2$: C, 62·69; H, 7·52%). A mixture of the two products showed m.p. 124–125°.

Debromination of 22,23-*dibromo*-12-*methyl*-18-*norergosta*-8,11,13-*trien*-3β-*yl acetate*

(a) Zinc dust (4 g, activated by washing with 10% NH_4Cl aq. was added to a solution of the dibromo acetate (400 mg) in ether–ethanol (100 ml) and the mixture heated under reflux for 4 hr. Working up in the usual way through ether gave 12-*methyl*-18-*norergosta*-8,11,13,22-*tetraen*-3β-*yl acetate* (XXX, R = Ac), as a colourless gum (290 mg), $[\alpha]_D$ +60° (*c*, 1·6) which could not be crystallized.

(b) The same product (205 mg, $[\alpha]_D$ +60°) was obtained by heating under reflux the dibromo acetate (300 mg) in benzene–ethanol (100 ml) for 3 hr with Raney nickel sludge (ca. 6 ml; 3·6 g).

12-*Methyl*-18-*norergosta*-8,11,13,22-*tetraen*-3β-*yl*-3′,5′-*dinitrobenzoate*

Alkaline hydrolysis of the above debrominated acetate yielded the corresponding 12-*methyl*-18-*norergosta*-8,11,13,22-*tetraen*-3β-*ol* (XXX, R = H) as a colourless gum, $[\alpha]_D$ +77° (*c*, 1·1). Treatment of the alcohol in pyridine solution at room temp. overnight with 3,5-dinitrobenzoyl chloride gave the 3,5-*dinitrobenzoate* as yellow blades, m.p. 156–157°, $[\alpha]_D$ −52° (*c*, 2·5) from chloroform–methanol. (Found: C, 71·4; H, 7·2; N, 4·6. Calc. for $C_{35}H_{44}N_2O_6$: C, 71·41; H, 7·53; N, 4·76%).

Sidechain degradation of 12-*methyl*-18-*norergosta*-8,11,13,22-*tetraen*-3*β*-*yl acetate*

Osium tetroxide (1·0 g) was added to a solution of the acetate (940 mg) in dry ether (75 ml) and the mixture left for 6 days at room temp. Lithium aluminum hydride (3 g) was then added, the mixture refluxed for 3 hr, cooled and water and dil. H_2SO_4 aq. added. The dried ether layer on evaporation yielded the 3,22,23-*triol* as a solid froth (990 mg, $[\alpha]_D$ −60° (*c*, 1·0)). The triol (912 mg) was dissolved in ethanol (100 ml) and treated with a solution of periodic acid (950 mg) in water (3 ml) for 30 hr at room temp. The reaction mixture was neutralized (to litmus) with $NaHCO_3$, $Na_2S_2O_3$ aq. (10%, 100 ml) added, and steam distilled.

Addition of an aqueous ethanolic solution of 2,4-dinitrophenylhydrazine sulphate to the distillate produced an orange precipitate (180 mg, m.p. 95–110°) which was dissolved in pet. ether–benzene (2:1, 15 ml) and chromatographed on alumina (6 g). Elution with the same solvent (75 ml) gave a residue (97 mg) which crystallized from *n*-hexane as orange plates, m.p. 100–104°. Further recrystallization from ethanol yielded (−)-methylisovaleraldehyde 2,4-dinitrophenylhydrazone, m.p. 110–114°, $[\alpha]_D$ −20° (*c*, 0·8) whose identity was established (mixed m.p., IR spectrum) by comparison with an authentic specimen. Further elution with the same solvent (100 ml) yielded a second fraction (43 mg) which crystallized from ethanol as orange needles, m.p. 164–166° and was identified as acetaldehyde 2,4-dinitrophenylhydrazone (presumably formed by solvent oxidation).

The non-volatile residue was obtained by ether extraction and yielded 3*β*-*hydroxy*-12-*methyl*-18-*nor*-*bisnorallochola*-8,11,13-*trienaldehyde* (XXXI) as a solid froth (630 mg), $[\alpha]_D$ −18° (*c*, 1·0), λ208(30000), 268(530), ν_{nujol} 3378 cm^{-1} (OH) and 1724 cm^{-1} (aldehyde). On treatment with Brady's reagent it gave the 2,4-*dinitrophenylhydrazone* on crystallization from ethanol, as lemon yellow blades, m.p. 194–197°. (Found: C, 66·3; H, 6·6; N, 11·1. Calc. for $C_{28}H_{34}O_5N_4$: C, 66·37; H, 6·76; N, 11·06%).

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