Some Stereoselective and Regioselective Olefin Additions: Iodoacetoxylation and Related Electrophilic Additions across the 22(23)-Bond of 3α,5α-Cycloergosta-7,22-dien-6-one

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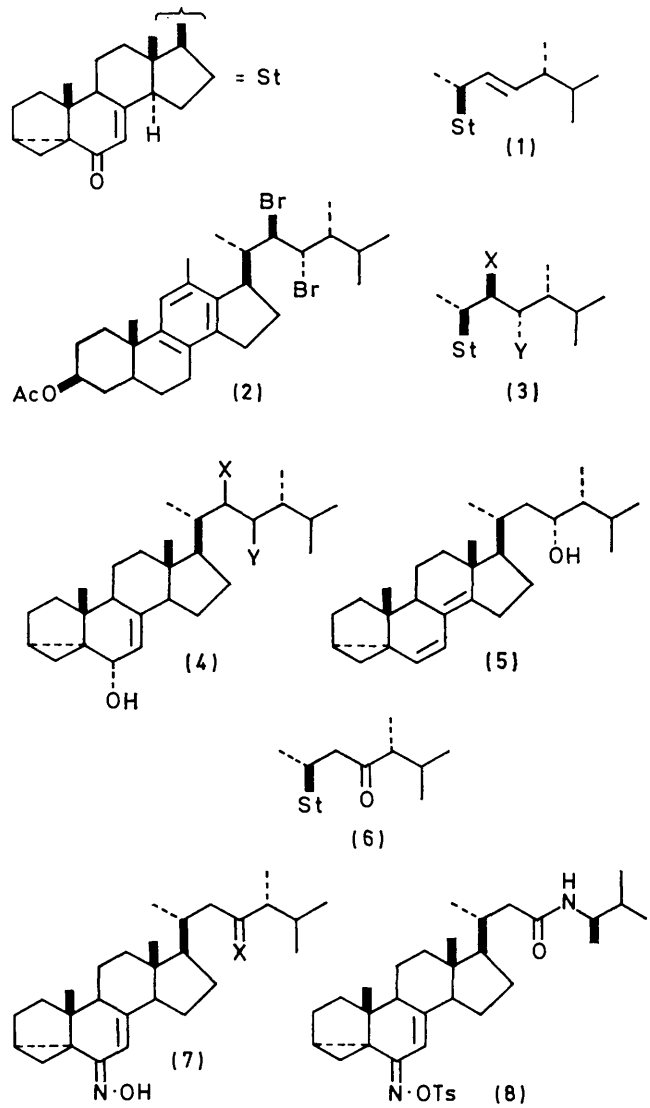
Iodoacetoxylation of the 22(23)-olefinic bond of 3α.5α-cycloergosta-7,22-dien-6-one proceeds in a stereoselective and regioselective manner: reactions with other electrophilic reagents proceed similarly. The structures of the adducts have been correlated chemically, by measurements of molecular rotation differences for the derived 22- and 23-alcohols, and by an *X*-ray crystallographic analysis of (23*R*)-23-hydroxy-3α.5α-cycloergost-7-en-6-one. Whereas lithium aluminium hydride reduction of the 23-ketone obtained from the latter alcohol proceeded according to the Cram rule, reduction of the corresponding 22-ketone did not. These results allow the stereoselective preparation of 22- and 23-hydroxy-steroids.

In a recent synthesis [1] of the insect moulting hormone ecdysone, from ergosterol, it was noticed that 3α,5α-cycloergosta-7,22-dien-6-one (1) yielded only one iodoacetate on treatment with iodine and silver acetate in glacial acetic acid. T.l.c. and ^{1}H n.m.r. analysis of the crude product revealed no significant amounts of any isomers. Such selective addition to the 22(23)-double bond had precedent in that the addition of bromine (or chlorine) in this position has been shown to give one major dihalide product in a variety of ergosterol derivatives.[2] The structure of one dibromide (2) has been determined by *X*-ray crystallography, and, as a consequence, on the assumption that no rearrangement occurs during experimental manipulation, this assignment can be extended to many of the dibromides reported.[3] It was of interest to determine what factors were responsible for this stereoselectivity. Furthermore, in the case of the production of the iodo-acetate, where there are four possible *trans*-addition products, a regioselective effect must also be operating.

Reduction of the iodo-acetate derivatives with freshly distilled tributyltin hydride [4] afforded an acetate (3; X = H, Y = OAc). In order to determine the position of the acetate group in the side chain it was necessary to convert it into the corresponding ketone system. Mild hydrolysis under a variety of conditions afforded mixtures; however, the following route proved satisfactory. Reduction with lithium aluminium hydride gave the diol (4; X = H, Y = OH), the 6α-orientation of which was established by its n.m.r. spectral properties. In the corresponding 6β-alcohols, obtained, for example, by solvolysis of ergosteryl toluene-*p*-sulphonate, the proton next to the hydroxy-group always gives rise to a broad signal with a half-band width of *ca.* 20 Hz. In the case of the 6α-alcohols this band width is much smaller (*ca.* 10 Hz). The orientation of reduction also corresponds to that preferred in the reduction of 3α,5α-cyclocholestan-6-ones.[5] The diol was sensitive to acid, and on treatment with dilute hydrochloric acid in acetic acid was dehydrated to the 6,8(14)-diene (5). Similarly, treatment with Jones reagent [6] afforded only a little of



[1] D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 1584.

[2] *E.g.*, R. Budziarek, F. Johnson, F. S. Spring, *J. Chem. Soc.*, 1952, 3410; R. C. Anderson, R. Stevenson, and F. S. Spring, *ibid.*, 1952, 2901; J. Elks, R. M. Evans, J. F. Oughton, and G. H. Thomas, *ibid.*, 1954, 463.

[3] T. N. Margulis, C. F. Hammer, and R. Stevenson, *J. Chem. Soc.*, 1964, 4396.

[4] H. G. Kuivila, L. W. Menapace, and C. R. Warne, *J. Amer. Chem. Soc.*, 1962, **84**, 3584; H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, 1963, **28**, 2165.

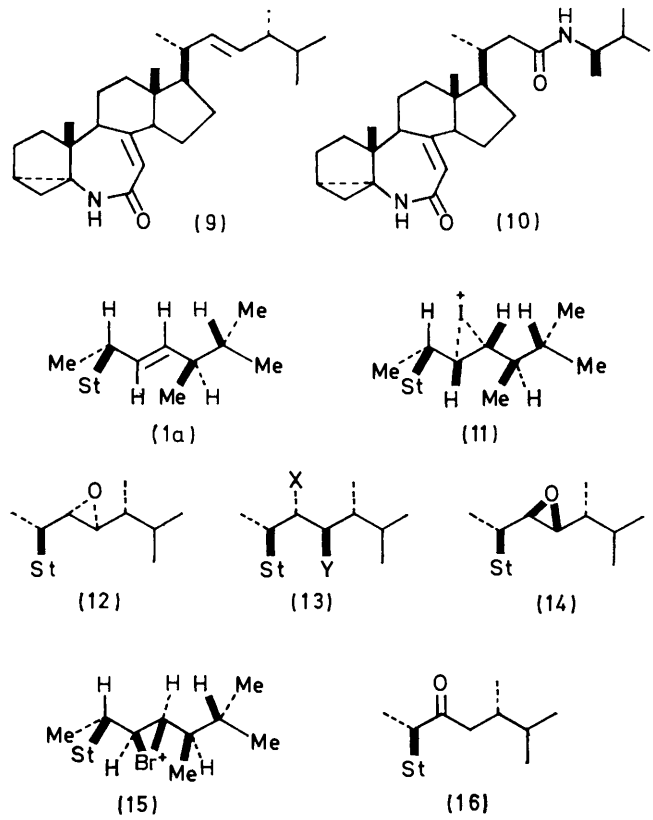
[5] J. Tadanier and W. Cole, *J. Org. Chem.*, 1962, **27**, 4610.

[6] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

the required diketone (6). A better method for obtaining this diketone involved initial oxidation of the diol (4; X = H, Y = OH) with manganese dioxide,[7] which gave the alcohol (3; X = H, Y = OH) corresponding to the starting acetate (3; X = H, Y = OAc), followed by oxidation with Jones reagent. That the carbonyl group in the side chain was situated at position 23 was indicated by the mass spectral fragmentation pattern, which showed a parent ion at *m/e* 410 (85%) and ions at 395 (50%, *M* − 15) and 339 (40%, cleavage of 23,24-bond). This assignment was further supported by the results of investigating the products of the Beckmann rearrangement of the dioxime (7; X = NOH). This dioxime was prepared, with difficulty, from the diketone by use of a large excess of hydroxylamine hydrochloride in dry pyridine for 5 days. A small quantity of the 6-mono-oxime (7; X = O) was also isolated from the reaction mixture. The reluctance towards reaction of the 23-keto-group, adjacent to a secondary carbon atom at position 24, is reminiscent of the findings of Tsuda and Hayatsu that 22-oxocholesterol was sterically hindered and did not react with normal ketone reagents.[8]

Treatment of the dioxime (7; X = NOH) with toluene-*p*-sulphonyl chloride in dry pyridine at room temperature overnight did not give the expected ditoluene-*p*-sulphonate, but a mono-oxime toluene-*p*-sulphonate (8) in which the side-chain oxime system had already undergone Beckmann rearrangement. That the side-chain function had reacted was corroborated by a control experiment on the mono-oxime of the starting olefin (1), which afforded a toluene-*p*-sulphonate stable to the conditions of preparation. Rearrangement of the 6-hydroxyimino-ester fraction could be induced with alumina.[9] The model compound (1; as oxime *O*-toluene-*p*-sulphonate) thus produced the amide (9). That the 5,6-bond had migrated, with retention of configuration about C-5, was inferred on the basis both of precedent [10] and of the spectral properties of the product, which possessed the αβ-unsaturated amide group. Under similar conditions the amide ester (8) afforded the lactam (10), which exhibited the expected mass spectral fragmentation pattern. Thus, the molecular ion (*m/e* 440; base peak *m/e* >100) yields fragments at *m/e* 425 (22%, $M^+ - 15$), 397 (20%, $M^+ - C_3H_7$), 354 (20%, $M^+ - C_5H_{12}N$), and 312 (54%, cleavage across 20,22-bond), as required for an amide produced by the Beckmann rearrangement of a 23-oxime ester.[11]

As a consequence the original iodo-acetate (3; X = I, Y = OAc) must have the structure indicated. The configuration of the acetoxy-group was determined from molecular rotation differences of the alcohols (see later) and by a subsequent *X*-ray crystallographic study of the alcohol (3; X = H, Y = OH).[12]



Since the favoured conformation of the ergosterol-like side chain of the starting material (1) is probably similar to that in calciferol, which, for the solid state, has been defined by *X*-ray crystallography,[13] it can be represented as in (1a). In this staggered conformation allylic interactions between the vinylic hydrogen atoms and adjacent groups are minimised.[14] Approach of an encroaching electrophile (*e.g.* I^+) would be expected to occur from the less hindered side of the double bond to form the iodonium ion (11). Attack of the conjugate acetate ion in the anti-sense, preferably at position 23, *i.e.* remote from the bulky steroid substituent leads to the formulation of the adduct as the (22*R*,23*S*)-22-iodo-23-acetoxy-isomer. Such a rationale appears to be general and explains, for example, the observed stereochemistry of the major dibromide adducts.[3]

In order to define the limits of these preferred addition modes, the stereo- and regio-selectivity of bromohydrin formation and the stereoselectivity of the epoxidation of the 22(23)-olefinic bond in the title compound were also investigated. The bromohydrins were unstable and the initial products were therefore acetylated with acetic anhydride in pyridine. Careful preparative layer

[7] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. A. Walker, *J. Chem. Soc.*, 1952, 1094.

[8] K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, 1959, **81**, 5987.

[9] J. Cymerman-Craig and A. R. Naik, *J. Amer. Chem. Soc.*, 1962, **84**, 3410.

[10] M. S. Ahmad, Shafiullah, and M. Mushfiq, *Tetrahedron Letters*, 1970, 2739; for other examples see C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, *J. Chem. Soc.*, 1965, 5868.

[11] *Cf.* J. A. Gilpin, *Analyt. Chem.*, 1959, **31**, 935.

[12] D. H. R. Barton, J. P. Poyser, P. G. Sammes, M. B. Hursthouse, and S. Neidle, *Chem. Comm.*, 1971, 715.

[13] D. Crowfoot-Hodgkin, M. S. Webster, and J. D. Dunitz, *Chem. and Ind.*, 1957, 1148.

[14] *Cf.* F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, 1965, **87**, 5492.

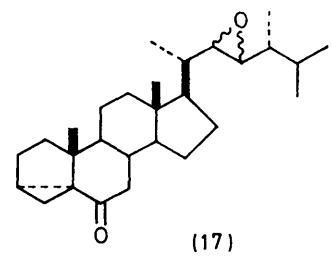
chromatography of the reaction mixture afforded three out of the four possible bromo-acetates (ratio *ca.* 9 : 4 : 1). Since the major isomer was reduced with tributyltin hydride to give the same acetate (**3**; X = H, Y = OAc) as was obtained from the iodo-acetate (**3**; X = I, Y = OAc), it must have structure (**3**; X = Br, Y = OAc). Furthermore, both the iodo-acetate and the major bromo-acetate afforded the same epoxide (**12**) on treatment with methanolic potassium carbonate. The same epoxide was also obtained from the second most abundant bromo-acetate (**13**; X = OAc, Y = Br), which must therefore arise from the same bromium ion as the major bromo-acetate (**3**; X = Br, Y = OAc), but by attack of water at the more hindered position (position 22). Direct bromoacetoxylation, for example with *N*-bromoacetamide and lithium acetate in a polar solvent,[15] would be expected to give less of this isomer. Of interest was the structure of the minor bromo-acetate (**3**; X = OAc, Y = Br), which was proven as follows. With methanolic potassium carbonate it gave the isomeric epoxide (**14**), indicating its formation from the isomeric bromonium ion (**15**), produced on the more hindered side of the starting olefin (**1**). Reduction with tribulyltin hydride gave the corresponding acetate (**3**; X = OAc, Y = H), which on reduction with lithium aluminium hydride followed by oxidation with manganese dioxide produced the alcohol (**3**; X = OH, Y = H). This alcohol was also prepared by reduction followed by allylic reoxidation, of the 22-ketone (**16**), the preparation of which is described later. The latter reduction also gave the isomeric alcohol (**13**; X = OH, Y = H), itself produced by appropriate reduction of the bromo-acetate (**13**; X = OAc, Y = Br).

Thus, in the case of the bromohydrins, initial bromonium ion formation occurs with high stereoselectivity, as was also observed for iodonium ion formation. However, subsequent opening of the bromonium ion by water (a relatively small nucleophile) is less regioselective than the opening of the iodonium ion by acetate ions. The isolation of small amounts of the third bromo-acetate (**3**; X = OAc, Y = Br) probably reflects the smaller size of the bromonium ion compared to the iodonium ion and, consequently, less stereoselective attack on the 22(23)-olefinic bond of the starting material (**1**). From models, quenching of this minor bromonium ion (**15**) by water does not appear to be preferred at either position 22 or 23, and our inability to isolate the fourth expected bromo-acetate [*viz*, (**13**; X = Br, Y = OAc)] derived from this bromonium ion possibly reflects isolation difficulties rather than lack of formation.

The structures of the three bromo-acetates were also correlated as follows. Heating either of the predominant bromo-acetates (**3**; X = Br, Y = OAc) and (**13**; X = OAc, Y = Br) at 140—150° for several minutes established a 1 : 1 equilibrium between the two compounds.[16] Similar thermal isomerisation of the minor bromo-acetate (**3**; X = OAc, Y = Br) also caused equilibration, with formation of small quantities of a new compound, presumed to be the fourth bromo-acetate; this, however, was not isolated.

Thermal isomerisation of the iodo-acetate (**3**; X = I, Y = OAc) also produced equilibration with a more polar isomer (**13**; X = OAc, Y = I).

Some selectivity in epoxide formation from the starting olefin (**1**) was also observed. The major product, obtained after oxidation with perphthalic acid, was the epoxide (**14**), obtained along with epoxide (**12**), in a **3** : **2** ratio. As anticipated from the foregoing arguments the more polar, minor epoxide (**12**) was identical with that produced by treatment with methanolic potassium carbonate from either of the two major bromo-acetates (**3**; X = Br, Y = OAc) and (**13**; X = OAc, Y = Br), or the iodo-acetate (**3**; X = I, Y = OAc). The less polar, major epoxide (**14**) was identical with that derived from the minor bromo-acetate (**3**; X = OAc, Y = Br). The epoxidation of 3α,5α-cycloergost-22-en-6-one gave a similar result to that of the related olefin (**1**). Thus treatment with monoperphthalic acid afforded two epoxides (**17**) in the ratio 6 : 5. The major isomer was again the less polar product and the minor isomer the more polar epoxide.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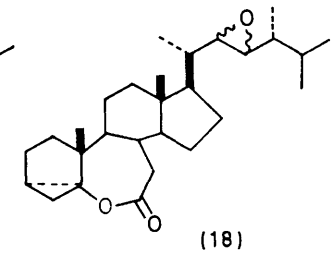
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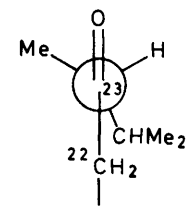
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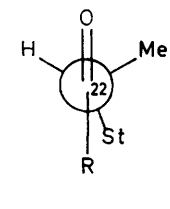
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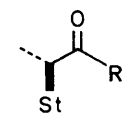
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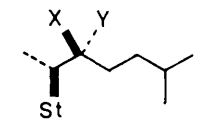

(21)

However, in contrast to the enone (**1**), the dihydro-compound was also attacked at the 6-keto-group to produce, as significant by products, the two lactones (**18**).[17]

[15] C. H. Robinson, L. Finckenor, M. Kirtley, D. Gould, and E. P. Oliveto, *J. Amer. Chem. Soc.*, 1959, **81**, 2195.

[16] D. H. R. Barton and J. F. King, *J. Chem. Soc.*, 1958, 4398; G. Alt and D. H. R. Barton, *ibid.*, 1954, 4284; D. H. R. Barton, *Bull. Soc. chim. France*, 1956, 973.

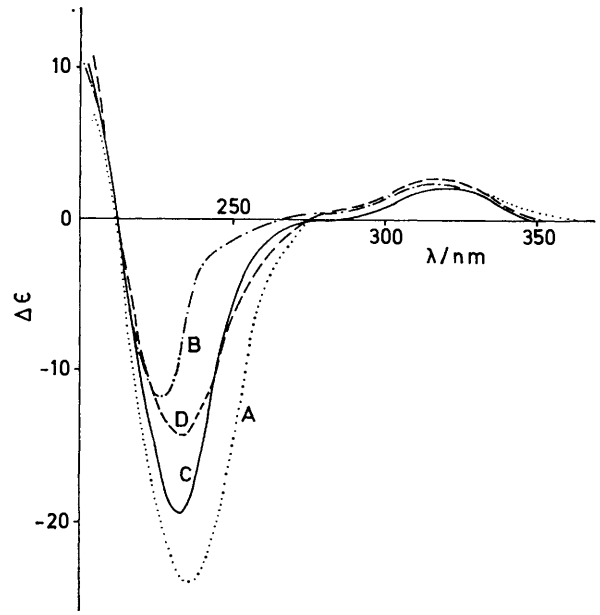
[17] *Cf.* C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, 1964, **29**, 2813.

Both the 22-ketone (16) and the 23-ketone (6) could be obtained from the bromo-acetates (13; X = OAc, Y = Br) and (3; X = Br, Y = OAc), respectively, *via* Jones oxidation of the corresponding alcohols (13; X = OH, Y = H) and (3; X = H, Y = OH). The reduction of these ketones was of interest. Treatment of either ketone with lithium aluminium hydride at −20°, in order to enhance stereoselectivity, followed by reoxidation of the 6α-alcohol function concurrently produced with manganese dioxide, gave a mixture of two epimeric alcohols. For the 23-ketone the ratio of the alcohols formed was 7 : 3. That alcohol (13; X = H, Y = OH) was the major component was consistent with the predictions of the Cram rule,[18] *viz.* non-catalytic reduction proceeding under kinetic control *via* conformation (19). The minor alcohol (3; X = H, Y = OH) from this reduction was identical with that derived from the iodo-acetate (3; X = I, Y = OAc) and which was used in the *X*-ray crystallographic analysis. A similar direction of reduction was also observed for 23-oxolanosterol.[19] The derived alcohols were correlated on the basis of molecular rotation differences, as compared with those of the related simple 4-methylpent-3-en-2-ols.[20]

In contrast, reduction of the 22-ketone (16) with lithium aluminium hydride, followed by oxidation with manganese dioxide, gave two alcohols in the ratio 7 : 1. The major, more polar isomer was the alcohol (3; X = OH, Y = H), *contrary* to that predicted on the basis of the Cram rule [see (20a)]. The minor, less polar alcohol had structure (13; X = OH, Y = H). In a parallel experiment, reduction of *i*-cholest-7-ene-6,22-dione (21; XY = O) was examined. Treatment with lithium aluminium hydride followed by oxidation with manganese dioxide to restore the ring B enone function again afforded two alcohols, in a ratio of 3 : 1. The major epimer was again the more polar component and was therefore identified as the (22*S*)-alcohol (21; X = OH, Y = H).

The direction of reduction of 22-oxo-steroids [21] has been the subject of much discussion, especially since earlier assignments [22] were based on the Cram rule. The situation has recently been clarified, both on the basis of a correlation with the *X*-ray analysis of ecdysone [23] and by applying Horeau's method involving partial resolution of esters of the 22-alcohols.[24] The results reported here are consistent with the latter work and confirm that 22-ketones of steroids prefer to be reduced in an 'anti-Cram rule' manner. For these 22-ketones the eclipsed conformation required for application of the Cram rule [*viz.* (20a)] must be too highly disfavoured to be formed, possibly owing to the severity of steric interactions between the pendant steroid nucleus and the side chain (20; R = isopentyl, *etc.*). When this interaction is relieved, as in the 22-aldehyde (20; R = H), the anticipated conformation (20a) can exist and addition occurs in the expected, kinetically controlled manner. Thus, selective addition of isopentylmagnesium bromide to the aldehyde (20; R = H) forms an epimeric mixture of two alcohols in which the major isomer is the predicted Cram-rule product (21; X = OH, Y = H).

Since the chemical and steric relationships between the foregoing 22- and 23-hydroxy-steroids had been determined, a comparison of their molecular rotation



C.d. curves for 22- and 23-benzoates: A, 22*R* (13; X = OBz, Y = H); B, 22*S* (3; X = OBz, Y = H); C, 23*R* (13; Y = OBz, X = H), D, 23*S* (3; Y = OBz, X = H)

properties was also made. Various checks were applied. Application of the Klyne and Stokes rule for cyclic alcohols [22] failed for these acyclic examples (Table 1). Furthermore, no general trend of behaviour could be discerned from the molecular rotations of either the derived acetates or the benzoates. Confirmation of the configurational assignments was also sought from the c.d. and o.r.d. curves of the four derived benzoates.* Whereas the o.r.d. curves were similar, the c.d. curves (Figure), although of the same shape, showed a greater magnitude for the negative Cotton effect at 230—235 nm in both the 22*R*- and 23*R*-epimers, as compared to the corresponding *S*-isomers. In these compounds the dispositions of the benzoate substituents are similar, always being adjacent to a primary and a secondary carbon

* We thank Dr. P. M. Scopes and her assistants (Westfield College, London) for these measurements.

[18] D. J. Cram and F. A. Abd-Elhafez, *J. Amer. Chem. Soc.*, 1959, **81**, 2748; J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, 1960, **82**, 3913.

[19] N. Entwistle and A. D. Pratt, *Tetrahedron*, 1969, **25**, 1449; *cf.* W. M. Stokes and W. Bergman, *J. Org. Chem.*, 1951, **16**, 1817.

[20] D. I. Dureen and J. Kenyon, *J. Chem. Soc.*, 1936, 1451.

[21] L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 5356; R. Hayatsu, *Chem. and Pharm. Bull. Japan*, 1957, **5**, 452.

[22] W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1954, 1979; A. Stabursvik, *Acta Chem. Scand.*, 1953, **7**, 1220; ref. 8.

[23] H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Chem. and Pharm. Bull. Japan*, 1968, **16**, 2416.

[24] E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, 1969, **17**, 1970; *cf.* A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.

centre. A comparison of the four curves (Figure) also shows that the difference between the two 23-isomers (adjacent to position 24*R*) is less than the observed differences between the two 22-benzoates (adjacent to position 20*S*). However, in these compounds the benzoate group is too far from the nuclear chromophore for application of the benzoate sector and related appear to always have a lower molecular rotation than the corresponding 23*S*-isomers (Table 2).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were taken for Nujol mulls and u.v. spectra and optical rotations for solutions in ethanol, unless otherwise

TABLE 1

Molecular rotation properties † of 22- and 23-alcohols

	M_D	Δ(OH) [a]	Δ(OAc)	Δ(OBz)	Δ_1	Δ_2	Δ_3 [b]
(22*R*)-22-Hydroxy-3α,5α,-cycloergost-7-en-6-one (13; X = OH, Y = H)	+346°	+49					+134
(22*R*)-22-Acetoxy-3α,5α-cycloergost-7-en-6-one (13; X = OAc, Y = H)	+282		−15		−64		
(22*R*)-22-Benzoyloxy-3α,5α-cycloergost-7-en-6-one (13; X = $PhCO_2$, Y = H)	+180			−177		−166	
(22*S*)-22-Hydroxy-3α,5α-cycloergost-7-en-6-one (3; X = OH, Y = H)	+198	−99					+14
(22*S*)-22-Acetoxy-3α,5α-cycloergost-7-en-6-one (3; X = OAc, Y = H)	+175		−122		−23		
(22*S*)-22-Benzoyloxy-3α,5α-cycloergost-7-en-6-one (3; X = $PhCO_2$, Y = H)	+357			+60		+159	
(23*R*)-23-Hydroxy-3α,5α-cycloergost-7-en-6-one (3; X = H, Y = OH)	+224	−73					+83
(23*R*)-23-Acetoxy-3α,5α-cycloergost-7-en-6-one (3; X = H, Y = OAc)	+298		+1		+74		
(23*R*)-23-Benzoyloxy-3α,5α-cycloergost-7-en-6-one (3; X = H, Y = $PhCO_2$)	+307			+10		+83	
(23*S*)-23-Hydroxy-3α,5α-cycloergost-7-en-6-one (13; X = H, Y = OH)	+237	−60					−23
(23*S*)-23-Acetoxy-3α,5α-cycloergost-7-en-6-one (13; X = H, Y = OAc)	+259		−38		+22		
(23*S*)-23-Benzoyloxy-3α,5α-cycloergost-7-en-6-one (13; X = H, Y = $PhCO_2$)	+192			−105		−45	

† Δ(OH) = M_D (C*—OH) − M_D(C*—H); Δ(OAc) = M_D(C*—OAc) − M_D(C*—H); Δ(OBz) = M_D(C*—OBz) − M_D(C*—H); Δ_1 = M_D(C*—OAc) − M_D(C*—OH); Δ_2 = M_D(C*—OBz) − M_D(C*—OH); Δ_3 = M_D(C*=O) − M_D(C*—OH).

[a] 3α,5α-Cycloergost-7-en-6-one, M_D +297°. [b] 3α,5α-Cycloergost-7-ene-6,22-dione, M_D +212°; 3α,5α-cycloergost-7-ene-6,23-dione, M_D +214°.

TABLE 2

Molecular rotation differences between *R*- and *S*-alcohols

	22*R* (23*R*)	22*S* (23*S*)	Δ(*R* − *S*)	Ref.
2β,3β,14α,22,25-Pentahydroxy-5β-cholest-7-en-6-one	+271°	−14°	+285°	*a*
22,25-Dihydroxy-3α,5α-cycloergost-7-en-6-one	+387	+352	+35	*b*
22,25-Dihydroxy-5α-cholestane-3,6-dione	+30	−39	+69	*c*
3β,22-Dihydroxy-5α-cholestane	+73	+12	+61	*c*
3β,22-Dihydroxycholest-5-ene	−153	−217	+64	*d*
3β-Benzoyloxy-22-hydroxycholest-5-ene	−91	−142	+51	*d*
22-Hydroxy-3α,5α-cyclocholest-7-en-6-one	+399	+325	+74	*e*
22-Hydroxy-3α,5α-cycloergost-7-en-6-one	+346	+198	+148	*e*
23-Hydroxy-3α,5α-cycloergost-7-en-6-one	−73	−60	−13	*e*
3β,23-Dihydroxylanosta-8(9),24-diene	+234	+322	−88	*f*
4-Methylpent-3-en-2-ol	−4·0	+4·0	−8·0	*g*

[a] A. Butenandt and P. Karlson, *Z. Naturforsch.*, 1954, **9***b*, 389; J. B. Siddall and J. H. Fried, *Tetrahedron Letters*, 1966, 3457. [b] J. P. Poyser, Ph.D. Thesis, London University, 1971. [c] H. Mori, K. Shibata, K. Tsuneda, M. Sawai, and K. Tsuda, *Chem. and Pharm. Bull. Japan*, 1968, **16**, 1407. [d] E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 103. [e] This paper. [f] N. Entwistle and A. D. Pratt, *Tetrahedron*, 1969, **25**, 1449. [g] D. I. Duneen and J. Kenyon, *J. Chem. Soc.*, 1936, 1451.

chirality rules.[25] It remained to compare directly the molecular rotation differences with those of related 22- and 23-hydroxy-steroids of known configuration (Table 2). For the 22-alcohols it was found that the 22*R*-epimers consistently possessed a more highly positive rotation than their 22*S*-counterparts. So far no simple 22-alcohols which violate this generalisation have been found. In contrast, for the 23-alcohols the 23*R*-epimers

[25] N. Harada, M. Ohashi, and K. Nakanishi, *J. Amer. Chem. Soc.*, 1968, **90**, 7349; N. Harada and K. Nakanishi, *ibid.*, p. 7351; M. Koreeda, N. Harada, and K. Nakanishi, *Chem. Comm.*, 1969, 548.

specified. ^{1}H N.m.r. spectra were recorded with a Varian A60 or HA100 spectrometer, with deuteriochloroform as solvent and tetramethylsilane as internal reference. Light petroleum refers to the fraction of boiling range 40—60°. Preparative layer chromatography (p.l.c.) was carried out on 20 × 60 cm plates, 0·5 mm thick, and t.l.c. on 20 × 20 cm plates, 0·1 mm thick, both with Merck silica gel GF_{254}. Solutions were dried over anhydrous sodium sulphate.

(22R,23S)-23-*Acetoxy*-22-*iodo*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = I, Y = OAc).[1]—The olefin (1) [26] (500 mg) in glacial acetic acid (12 ml) was stirred with silver acetate

[26] G. H. R. Summers, *J. Chem. Soc.*, 1958, 4489.

(0·5 g) at room temperature while powdered iodine (0·37 g) was added in portions during 15 min. After 3 h the mixture was diluted with chloroform (100 ml) and filtered. The filtrate was washed with water (2 × 50 ml), saturated sodium hydrogen carbonate solution (2 × 25 ml), and finally water (2 × 25 ml). The dried solution was evaporated to dryness before separation by p.l.c. (1 : 19 acetone–light petroleum). Besides some unchanged starting material the major component was the *iodo-acetate* (390 mg, 53%), m.p. (benzene–light petroleum) 157—159°, $[\alpha]_D^{28}$ +53° (*c* 0·52), $\nu_{max.}$ 1730, 1654, and 1230 cm^{-1}, $\lambda_{max.}$ 243·5 nm (ε 14,200), τ 4·2 (1H, dd, C-7 vinyl proton), 4·5 (1H, d, *J* 10 Hz, proton α to acetate), 5·75 (1H, d, *J* 10 Hz, proton α to iodide), 7·93 (3H, s, OAc), and 9·0, 9·05, and 9·25, *m/e* 580 (M^+), 453 (M^+ — I), 393 (M^+ — I — AcOH), and 267 (M^+ — side chain) (Found: C, 62·0; H, 7·8; I, 21·6. $C_{30}H_{45}IO_3$ requires C, 62·1; H, 7·8; I, 21·9%). No related isomers were eluted from the p.l.c. plate.

(23R)-23-*Acetoxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = H, Y = OAc).—The iodo-acetate (3; X = Z, Y = OAc) (350 mg) in dry, redistilled tetrahydrofuran (25 ml) was stirred under nitrogen at room temperature for 24 h with freshly distilled tri-n-butyltin hydride (1·0 g). More tri-n-butyltin hydride (1·0 g) was then added and stirring was continued for a further 16 h before addition of ether (100 ml) and extraction with water. The dried organic phase was evaporated to dryness and the residue was purified by p.l.c. (1 : 10 acetone–light petroleum). The product (230 mg, 84%) was recrystallised from methanol to give the *acetate*, m.p. 149—150°, $[\alpha]_D^{25}$ +66° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 1718, 1655, and 1256 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 14,100), τ 4·28 (1H, t), 4·98br (1H), 8·00 (3H, s), 8·72, 8·80, 9·04, 9·10, 9·16, and 9·36, *m/e* 454 (M^+), 394 (M^+ — AcOH), 341, 325, 311, 297, 296, 269, 267, 243, and 71 (Found: C, 79·0; H, 10·0. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%).

Reduction of the bromo-acetate (3; X = Br, Y = OAc) (1·54 g) under similar conditions afforded the same acetate (3; X = H, Y = OAc) (1·08 g, 82%), m.p. and mixed m.p. 147—150°.

(23R)-23-*Hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = H, Y = OH).—The acetate (3; X = H, Y = OAc) (99 mg) was treated with lithium aluminium hydride (36 mg) in anhydrous ether (5 ml) at room temperature for 2 h. Wet ether was added (to destroy any excess of reducing agent), followed by an excess of water. The ether layer was decanted and the aqueous layer was re-extracted with ether. The dried ether extract was evaporated to afford (23*R*)-3α,5α-*cycloergost*-7-*ene*-6α,23-*diol* (4; X = H, Y = OH), m.p. (methanol) 165—169°, $[\alpha]_D^{20}$ +112° (*c* 0·1 in $CHCl_3$), $\nu_{max.}$ 3370 cm^{-1}, τ 4·83 (1H, m), 5·79 (1H, d, *J* 2 Hz), 6·35 (1H, m), 9·02, 9·05, 9·12, 9·21, and 9·40, *m/e* 414 (M^+), 396 (M^+ — H_2O), 271 (M^+ — side chain), and 253 (396 — side chain) (Found: C, 80·9; H, 11·3. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%). The yield was quantitative. Treatment of this diol (30 mg) in chloroform (10 ml) with manganese dioxide (250 mg) under nitrogen for 5 h afforded, after filtration and evaporation, (23R)-23-*hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = H; Y = OH) (25 mg, 84%), m.p. (methanol) 188—192°, $[\alpha]_D^{20}$ +54° (*c* 0·3 in $CHCl_3$), $\nu_{max.}$ 3420, 1640, and 1618 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 12,300), τ 4·26 (1H, t), 6·34br (1H), 8·93, 8·98, 9·04, 9·12, 9·20, and 9·30, *m/e* 412 (M^+), 397, 394, 341 (M^+ — side chain from C-23), 297 (M^+ — side chain from C-20), 269 (M^+ — side chain), and 149 (269 — ring A) (Found: C, 81·2; H, 10·7. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

The diol (4; X = H, Y = OH) was unstable to acid. Thus, treatment of this diol (40 mg) in ether (5 ml) containing glacial acetic acid (1 ml) and N-hydrochloric acid (0·6 ml) for 10 min, followed by washing with water until the solution was acid-free, gave, after drying and evaporation, the diene, (23R)-23-*hydroxy*-3α,5α-*cycloergosta*-6,8(14)-*diene* (5) (30 mg, 78%), m.p. (light petroleum) 95—98°, $[\alpha]_D^{23}$ +147° (*c* 0·4 in $CHCl_3$), $\nu_{max.}$ 3500 cm^{-1}, $\lambda_{max.}$ 255 and 261 nm (ε 19,700 and 20,300), τ 3·91 (1H, d, *J* 10 Hz, C-7 H), 4·87 (1H, d, *J* 10 Hz, C-6 H), 6·36br (1H), 9·00, 9·06, 9·09, 9·13, and 9·25, *m/e* 396 (M^+), 381, 363, 265, 253 (M^+ — side chain), and 199 (253 — C_4H_6) (Found: C, 84·7; H, 11·0. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

Benzoylation of the Alcohol (3; X = H, Y = OH).—The alcohol (22 mg) and freshly distilled benzoyl chloride (30 mg) in dry pyridine (3 ml) were left for 16 h. The mixture was then poured into water and extracted with ether (2 × 20 ml). The combined organic extracts were washed with N-hydrochloric acid (3 ml), saturated sodium hydrogen carbonate solution, and water. P.l.c. (6 : 94 acetone–light petroleum) gave (23R)-23-*benzoyloxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = H, Y = $PhCO_2$) (18 mg, 70%), m.p. (methanol) 186—188°, $[\alpha]_D^{20}$ +59° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 1710, 1650, 1610, 1280, and 720 cm^{-1}, $\lambda_{max.}$ 233 and 247 nm (ε 19,500 and 13,300), τ 2·04 (2H, m), 2·62 (3H, m), 4·32 (1H, t), 4·71br (1H), 8·98, 9·02, 9·06, 9·08, 9·13, 9·19, and 9·44, *m/e* 516 (M^+), 501, 394 (M^+ — $PhCO_2H$), 379, 296 (M^+ — side chain from C-20), 268 (M^+ — side chain), 243, 105, and 77 (Found: C, 81·3; H, 9·45. $C_{35}H_{48}O_3$ requires C, 81·35; H, 9·4%). Its c.d. curve showed Δε +9·37 (204 nm), −19·46 (233 nm), and +2·28 (319 nm), and its o.r.d. curve [φ] +91,500 (212 nm), −29,100 (252 nm), and −10,400 (298 nm).

3α,5α-*Cycloergost*-7-*ene*-6,23-*dione* (6).—The alcohol (3; X = H, Y = OH) (410 mg) in 1 : 19 chloroform–acetone (50 ml) was oxidised with a slight excess of Jones reagent [from chromium trioxide (2·67 g) and conc. sulphuric acid (2·3 ml) made up to 10 ml with water] for 30 min. After addition of a few drops of methanol, to consume the excess of oxidant, the mixture was poured into water and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness. The residue was crystallised from methanol to give the *diketone* (320 mg, 78%), m.p. 177—180°, $[\alpha]_D^{19}$ +52° (*c* 0·1 in $CHCl_3$), $\nu_{max.}$ 1705 and 1655 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 12,700), τ 4·28 (1H, t), 8·78, 8·94, 9·00, 9·08, 9·14, 9·20, and 9·30, *m/e* 410 (M^+), 395, 339 (M^+ — side chain from C-23), 311 (M^+ — side chain from C-22), 297, 296 (M^+ — side chain from C-20), 99, and 71 (Found: C, 81·8; H, 10·4. $C_{28}H_{42}O_4$ requires C, 81·9; H, 10·3%).

6,23-*Bis-hydroxyimino*-3α,5α-*cycloergost*-7-*ene* (7; X = N·OH).—The dione (6) (107 mg) was stirred with hydroxylamine hydrochloride (500 mg) in anhydrous pyridine (3 ml) for 5 days. The solvent was evaporated off under reduced pressure and the residue was extracted into benzene. The extract was washed with water, dried, and evaporated to afford, as a white solid, the *dioxime* (80 mg, 70%), m.p. (tetrahydrofuran–methanol) 234—236°, $[\alpha]_D^{29}$ −23° (*c* 0·35 in dioxan), $\nu_{max.}$ 3300, 1645, 1638, 975, 950, and 935 cm^{-1}, $\lambda_{max.}$ 239 and 266 nm (ε 12,500 and 8150), τ 3·59 (1H, t, C-7 vinylic H), 8·80, 9·07, 9·14, 9·21, and 9·37, *m/e* 440 (M^+), 423, 410, 397, 312, 296, 280, and 241 (Found: C, 76·2; H, 10·0; N, 6·3. $C_{28}H_{44}N_2O_2$ requires C, 76·3; H, 10·1; N, 6·4%). From a preliminary experiment p.l.c. also afforded the less polar 6-hydroxyimino-3α,5α-cyclo-

ergost-7-en-23-one (7; X = O), which was not completely characterised but which possessed $\nu_{max.}$ 3300, 3240, 1710, 1645, 1638, 975, 950, and 935 cm^{-1}, *m/e* 425 (M^+), 409, 394, and 241. The latter monoxime was also present in the preparative reaction mixture.

6-*Hydroxyimino*-3α,5α-*cycloergosta*-7-22-*diene* (1; *as Oxime*).—The ketone (1) (125 mg) in water (1·5 ml) and ethanol (4 ml) was treated with hydroxylamine hydrochloride (45 mg) and sodium acetate (45 mg). After filtration the solution was heated under reflux for 5 days. On cooling, crystals of the *oxime* formed (40 mg, 31%), m.p. (ethanol) 201—206°, $[\alpha]_D^{27}$ −16° (*c* 0·5 in dioxan), $\nu_{max.}$ 3280, 3210, 1635, and 1620 cm^{-1}, $\lambda_{max.}$ 239 and 266 nm (ε 10,000 and 7500), τ 2·3br (1H), 4·22 (1H, m), 4·83 (2H, m), 8·93, 9·06, 9·17, 9·24, 9·33, and 9·36 (Found: C, 81·9; H, 10·3; N, 3·3. $C_{28}H_{43}NO$ requires C, 82·1; H, 10·6; N, 3·4%).

6-*Hydroxyimino*-3α,5α-*cycloergosta*-7,22-*diene* O-*Toluene*-p-*sulphonate* (1; *as Oxime* O-*Toluene*-p-*sulphonate*).—Treatment of the oxime (1; as oxime) (350 mg) in dry pyridine (5 ml) with toluene-*p*-sulphonyl chloride (340 mg) at room temperature for 16 h afforded, after normal work-up, the oxime toluene-*p*-sulphonate (435 mg, 90%), m.p. (benzene–light petroleum) 151—154° (decomp.), $[\alpha]_D^{24}$ −20° (*c* 0·5 in benzene), $\nu_{max.}$ 1622, 1600, 1195, 1177, and 675 cm^{-1}, $\lambda_{max.}$ 230 and 251 nm (ε 21,600 and 22,200), τ 2·24 (2H, d, *J* 8 Hz), 2·80 (2H, m), 3·78 (1H, dd, C-7 vinylic H), 4·85 (2H, m, side-chain vinylic protons), 7·63 (3H, s, aromatic Me), 8·96, 9·03, 9·06, 9·12, 9·21, and 9·41, *m/e* (M^+ not observable) 547, 409 (elimination of toluene-*p*-sulphonic acid), 393, 378, 268, 253, 241, 172, and 91 (Found: C, 74·5; H, 8·6; N, 2·4; S, 5·8. $C_{35}H_{49}NO_3S$ requires C, 74·6; H, 8·8; N, 2·5; S, 5·7%).

6-*Aza*-3α,5α-*cyclo*-B-*homoergosta*-8,23-*dien*-7-*one* (9).—The oxime tosylate (1; as oxime tosylate) (120 mg) in dry benzene (1 ml) was added to a column of alumina (grade 1; 10 g; acid-washed) and the column was left for 15 min before elution. Elution with light petroleum, followed, in order, by benzene, 1 : 2 chloroform–benzene, and chloroform gave, from the latter fractions the *lactam* (60 mg, 60%), m.p. (methanol) 192—195°, $[\alpha]_D^{23}$ +160° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 3300—3200, 1675, and 1632 cm^{-1}, $\lambda_{max.}$ 224 nm (ε 15,100), τ 4·10 (1H, dd, C-8 vinylic H), 4·47 (1H, s, lactam NH), 4·86 (2H, m), 8·92, 8·98, 9·04, 9·06, 9·44, 9·21, and 9·39, *m/e* 409 (M^+), 394, 366, 214, and 149 (none of these fragmentation ions were abundant) (Found: C, 81·9; H, 10·5; N, 3·3. $C_{28}H_{43}NO$ requires C, 82·1; H, 10·6; N, 3·4%).

Beckmann Rearrangement of the Dioxime (7; X = N·OH).—The dioxime (7; X = N·OH) (60 mg) in pyridine (1 ml) was treated with toluene-*p*-sulphonyl chloride (60 mg) at room temperature for 16 h. The mixture was then poured into water and extracted with ether. Evaporation of the dried extract afforded the amide oxime toluene-*p*-sulphonate (8) (72 mg, 90%), m.p. 98—102°, $[\alpha]_D^{29}$ +4° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 3430, 3340, 1647, 1605m, 1550, 1119, 1182, and 675 cm^{-1}, $\lambda_{max.}$ 230·5 and 250·5 nm (ε 18,800 and 18,600), τ 2·24 and 2·77 (AA'BB' system), 3·78 (1H, dd), 4·66br (1H), 6·16br (1H), 6·9br (1H), 7·62 (3H, s), 8·76, 8·92, 8·98, 9·09, 9·12, and 9·38 (3H, s), *m/e* (no M^+ observable) 440 (M^+ — toluene-*p*-sulphonic acid), 425, 352 (amide fragmentation), 312 (440 — side-chain cleavage at C-20), 172, 155, 149, and 91.

The oxime ester (8) (50 mg) was rearranged on alumina as already described. The column was eluted with benzene, chloroform–benzene, and finally chloroform. Some starting material (30 mg) was recovered from the first fractions; later fractions gave the *amide lactam* (10) (10 mg), m.p. (chloroform) 123—127°, $[\alpha]_D^{31}$ +140° (*c* 0·3 in $CHCl_3$), $\nu_{max.}$ 3330, 1670, 1650, 1625, and 1555 cm^{-1}, $\lambda_{max.}$ 223 nm (ε 13,500), 4·15 (1H, dd), 4·48 (1H, s) 4·75br (1H), 6·2br (1H), 6·9br (1H), 8·93, 9·00, 9·09, and 9·39, *m/e* 440 (M^+) ($C_{28}H_{44}N_2O_2$ requires *M*, 440), 425, 397, 354 (amide cleavage in side chain), 325, 312, 284, 258, and 244.

Bromo-acetoxylation of 3α,5α-*Cycloergosta*-7-22-*dien*-6-*one* (1).—*N*-Bromosuccimimide (500 mg) was added in portions during 10 min to a stirred solution of the olefin (1) in aqueous tetrahydrofuran (1 : 4; 100 ml) at 0° under nitrogen. After 2 h the excess of solvent was removed under reduced pressure, below 40°, and the resulting mixture was poured into ice–water (150 ml) and extracted with benzene (3 × 50 ml). The combined extracts were dried and evaporated to small bulk under reduced pressure below 40°. The crude product was dissolved in 2 : 1 pyridine–acetic anhydride (15 ml) and left at room temperature overnight. Work-up in the normal way afforded an oily residue which was purified by p.l.c. [1 : 19 acetone–light petroleum (five elutions)]. The major, least polar bromo-acetate (500 mg, 37%) crystallised from methanol as needles of (22R,23S)-23-*acetoxy*-22-*bromo*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = Br, Y = OAc), m.p. 166—169°, $[\alpha]_D^{24}$ +42° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 1735, 1650, and 1230 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 12,000), τ 4·25 (1H, t, C-7 vinylic H), 4·63 (1H, dd, *J* 11 and 3 Hz, proton α to acetate), 5·88 (1H, dd, *J* 11 Hz, proton α to bromide), 7·98 (3H, s, acetate), 8·76, 8·93, 9·01, 9·08, 9·15, and 9·32, *m/e* 534, 532 (M^+), 519, 517 (M^+ — Me), 394 (M^+ — Br — OAc), 393 (M^+ — HBr — OAc), 392 (M^+ — HBr — HOAc), 269 (M^+ — side chain), and 267 (Found: C, 67·7; H, 8·2. $C_{30}H_{45}BrO_3$ requires C, 67·5; H, 8·4%).

Elution of the second most polar product from the p.l.c. plate afforded a second bromo-acetate (280 mg, 21%). Crystallisation from methanol afforded (22S,23R)-22-*acetoxy*-23-*bromo*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = OAc, Y = Br), m.p. 146—148°, $[\alpha]_D$ +43° (*c* 0·4 in $CHCl_3$), $\nu_{max.}$ 1725, 1650, 1620, and 1240 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 11,700), τ 4·28 (1H, t), 4·80 (1H, dd, *J* 10 Hz), 5·77 (1H, dd, *J* 10 Hz), 7·96 (3H, s), 8·78, 8·94, 9·06, 9·11, and 9·31, *m/e* 534, 532 (M^+), 519, 517, 394, 393, 392, 269, and 267 (Found: C, 67·6; H, 8·6. $C_{30}H_{45}BrO_3$ requires C, 67·5; H, 8·4%).

Elution of the most polar product from the p.l.c. plate afforded (22R,23S)-22-*acetoxy*-23-*bromo*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = OAc, Y = Br) (60 mg, 9%), m.p. (methanol) 152—153°, $[\alpha]_D^{25}$ +36° (*c* 0·1 in $CHCl_3$), $\nu_{max.}$ 1725, 1650, 1620, and 1240 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 11,700), τ 4·3 (1H, t), 4·8br (1H, d, *J* 10 Hz), 5·77br (1H, d, *J* 10 Hz), 7·96 (3H, s), 8·78, 8·94, 9·06, 9·11, and 9·31, *m/e* 534, 532 (M^+), 529, 517, 394, 393, 392, 269, and 267 (Found: C, 67·6; H, 8·6. $C_{30}H_{45}BrO_3$ requires C, 67·5; H, 8·4%).

Epoxidation of 3α,5α-*Cycloergosta*-7,22-*dien*-6-*one* (1).—The olefin (400 mg) in ether (20 ml) was oxidised with monoperphthalic acid [300 mg; solution in ether (6 ml)] at room temperature for 16 h. The solution was then washed with saturated sodium hydrogen carbonate solution, dried, and evaporated to dryness. Separation by p.l.c. (1 : 19 acetone–light petroleum; four elutions) gave, as the major product, the less polar epoxide, (22R,23R)-22,23-*epoxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (14) (153 mg, 41%), m.p. (methanol) 158—160°, $[\alpha]_D^{27}$ +74° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 1650, 1625, 970, and 925—900 cm^{-1}, $\lambda_{max.}$ 244 nm (ε 13,100),

τ 4·22 (1H, t), 7·25 (2H, m), 8·92, 9·03, 9·15, 9·25, and 9·35 (Found: C, 82·0; H, 10·4. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%).

The more polar, minor epoxide isolated was (22S,23S)-22,23-*epoxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (12) (95 mg, 25%), m.p. (methanol) 179—182°, $[\alpha]_D^{24}$ +40° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ 1655, 1625, 970, and 920—900 cm^{-1}, $\lambda_{max.}$ 244 nm (ε 13,000), τ 4·2 (1H, t), 7·45 (2H, m), 8·92, 9·01, 9·13, 9·24, and 9·35 (Found: C, 81·7; H, 10·3. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%).

Epoxidation of 3α,5α-*Cycloergost*-22-*en*-6-*one*.[27]—The olefin (500 mg) in ether (17 ml) was treated with monoperphthalic acid (700 mg) at room temperature for 24 h. The mixture was then processed in the usual manner. P.l.c. (3 : 97 acetone–light petroleum; three elutions) enabled the mixture to be separated into five components, the least polar fraction being recovered starting material (50 mg). The major product was the less polar epoxide, (22R,23R)-22,23-*epoxy*-3α,5α-*cycloergostan*-6-*one* (17) (138 mg, 30%), m.p. (methanol) 128—130°, $[\alpha]_D^{29}$ +27° (*c* 0·66 in $CHCl_3$), $\nu_{max.}$ 1690 and 915 cm^{-1}, τ 7·35 (2H, m), 8·87, 9·00, 9·07, 9·10, and 9·30 (Found: C, 81·6; H, 10·6. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

The second major product was the more polar epoxide, (22S,23S)-22,23-*epoxy*-3α,5α-*cycloergostan*-6-*one* (17) (120 mg, 25%), m.p. (methanol) 151—153°, $[\alpha]_D^{26}$ −18° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 1685 and 920 cm^{-1}, τ 7·38 (2H, m), 9·00, 9·10, and 9·29 (Found: C, 81·5; H, 10·6. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

Two by-products were also obtained. The less polar of these was identified as (22R,23R)-22,23-*epoxy*-6-*oxa*-B-*homo*-3α,5α-*cycloergostan*-7-*one* (18) (70 mg, 14%), m.p. (methanol) 145—147°, $[\alpha]_D^{25}$ +20° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 1740, 1260, and 922 cm^{-1}, τ 7·4 (2H, m), 8·54, 8·76, 8·93, 8·98, 9·03, 9·07, 9·10, 9·14, and 9·25 (Found: C, 78·3; H, 10·3. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). The final, more polar lactone epoxide was identified as (22S,23S)-22,23-*epoxy*-6-*oxa*-B-*homo*-3α,5α-*cycloergostan*-7-*one* (18) (70 mg, 14%), m.p. (methanol) 195—197°, $[\alpha]_D^{26}$ −44° (*c* 0·6 in $CHCl_3$), τ 7·45 (2H, m), 8·54, 8·73, 8·92, 9·00, 9·10, and 9·26 (Found: 78·2; H, 10·2. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Correlation of the Iodo-acetate (3; X = I, Y = OAc) *and the Corresponding Bromo-acetates* via *their Epoxides*.—The general procedure involved heating the halogeno-acetate (2—5 mg) in aqueous methanol (1 : 9; 2—5 ml) containing potassium carbonate (20—50 mg) under nitrogen at reflux for 1 h. The reactions were followed by t.l.c. By this method the iodo-acetate (3; X = I, Y = OAc) and the bromo-acetates (3; X = Br, Y = OAc) and (13; X = OAc, Y = Br) afforded the most polar epoxide (12). The minor bromo-acetate (3; X = OAc, Y = Br) afforded only the least polar epoxide (14).

Thermal Isomerisation of the Halogeno-acetates.—The general procedure involved isomerisation of the halogeno-acetate (*ca.* 1 mg), sealed in a capillary tube, in a bath pre-heated to 140—150°, for 10 min. The products of the thermal equilibration were compared (t.l.c.) with authentic samples. The bromo-acetates (3; X = Br, Y = OAc) and (13; X = OAc, Y = Br) gave mixtures containing similar quantities of each other. Some decomposition products were also observed. The minor bromo-acetate (3; X = OAc, Y = Br) gave rise to an 'equilibrium' mixture, containing, besides general decomposition products, a predominant new isomer, less polar than any of the three known isomers, and identified as the fourth bromo-acetate (13; X = Br, Y = OAc).

Equilibration of the iodo-acetate (3; X = I, Y = OAc) also gave a new product. A repeat experiment with a larger quantity of the iodo-acetate (40 mg), followed by t.l.c. separation of the more polar new isomer, afforded (22R,23S)-23-*acetoxy*-22-*iodo*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = OAc, Y = Br) (5 mg), m.p.(ether–light petroleum), 138—141°, $[\alpha]_D^{25}$ +42° (*c* 0·1 in $CHCl_3$), $\nu_{max.}$ 247 nm (ε 11,000), *m/e* 580 (M^+), 520, 453, 394, 393, 392, 341, 297, 269, and 267 (Found: M^+ 580·2391. $C_{30}H_{45}IO_3$ requires *M*, 580·2415).

(22R)-22-*Acetoxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = OAc, Y = H).—The bromo-acetate (13; X = OAc, Y = Br) (511 mg) was debrominated with tributyltin hydride, as already described. The crude product was purified by p.l.c. Recrystallisation from light petroleum afforded the *acetate* (363 mg, 83%), m.p. 100—110°, $[\alpha]_D^{22}$ + 62° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 1730, 1650, and 1250 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 13,300), τ 4·16 (1H, t), 4·91br (1H), 7·93 (3H, s), 8·90, 8·98, 9·06, 9·16, and 9·31, *m/e* 454 (M^+), 439, 394, 315, 313, and 311 (Found: C, 79·0; H, 10·0. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%).

(22R)-22-*Hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = OH, Y = H).—The acetate (13; X = OAc, Y = H) (360 mg) was reduced with lithium aluminium hydride (0·5 g) in dry ether as described previously. The reaction afforded, by direct crystallisation from methanol, (22R)-3α,5α-*cycloergost*-7-*ene*-6α,22-*diol* [as (4; X = OH, Y = H)] (300 mg, 94%), m.p. 93—96°, $[\alpha]_D^{25}$ +117° (*c* 0·25 in $CHCl_3$), $\nu_{max.}$ 3380 cm^{-1}, τ 4·85 (1H, dd, *J* 2 and 3 Hz), 5·70br (1H), 6·32br (1H), 9·07, 9·15, 9·21, 9·25, and 9·42, *m/e* 414 (M^+), 399, 396, 381, 353, 253, and 161 (Found: C, 80·9; H, 11·0. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

Oxidation of the diol (4; X = OH, Y = H) (250 mg) with manganese dioxide as already described gave, by direct crystallisation from methanol, the alcohol (13; X = OH, Y = H) (220 mg, 89%), m.p. 219—222°, $[\alpha]_D^{24}$ +86° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 3390, 1635, and 1618 cm^{-1}, $\lambda_{max.}$ 245 nm (ε 13,000), τ 4·30 (1H, t), 6·31br (1H), 8·79, 8·96, 9·10, 9·16, 9·22, and 9·34, *m/e* 412 (M^+), 397, 394, 379, 298, 283, and 243 (Found: C, 81·3; H, 10·8. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

3α-5α-*Cycloergost*-7-*en*-6,22-*dione* (16).—Jones oxidation of the alcohol (13; X = OH, Y = H) (80 mg) in acetone (35 ml) gave, by direct crystallisation, the *dione* (70 mg, 88%), m.p. (methanol) 182—184°, $[\alpha]_D^{20}$ +52°, (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 1715 and 1650 cm^{-1}, $\lambda_{max.}$ 246 nm (ε 12,800), τ 4·28 (1H, t), 8·87, 8·93, 9·11, 9·15, 9·22, and 9·32, *m/e* 410 (M^+), 395 (M^+ − Me), 341 (M^+ − side chain from C-23), 325 (M^+ − side chain from C-22), 297 (M^+ − side chain from C-20), 269, 243, 113, and 89 (Found: C, 81·75; H, 10·4. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%).

(22R)-22-*Benzoyloxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = $PhCO_2$, Y = H).—The alcohol (13; X = OH, Y = H) (50 mg) was benzoylated with benzoyl chloride in pyridine to give, after p.l.c. (1 : 11 acetone–light petroleum), the *benzoate* (39 mg, 63%), m.p. (methanol) 206—208°, $[\alpha]_D^{20}$ +35° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 1710, 1652, 1285, and 720 cm^{-1} $\lambda_{max.}$ 233 and 247 nm (ε 23,500 and 15,400), τ 2·00 (2H, m) 2·67 (3H, m), 4·24 (1H, t), 4·83br (1H), 8·93, 9·02, 9·11, 9·19, 9·23, and 9·32, *m/e* 516 (M^+), 501, 394, 347, 268, 243, 105, and 77 (Found: C, 81·3; H, 9·5. $C_{35}H_{48}O_3$ requires C,

[27] M. J. Thompson, C. F. Cohen, and S. M. Lancaster, *Steroids*, 1965, **5**, 745.

81·4; H, 9·4%). Its c.d. curve showed Δε +6·54 (205 nm), −24·13 (236 nm), and +2·86 (315 nm), and its o.r.d. curve [φ] +65,100 (201 nm), +54,760 (215 nm), −20,720 (253 nm), and +2960 (352 nm).

(22S)-22-*Acetoxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = OAc, Y = H).—The bromo-acetate (3; X = OAc, Y = Br) (50 mg) was debrominated with tributyltin hydride, in the usual manner, to give by p.l.c. (1 : 19 acetone–light petroleum) the *acetate* (10 mg), m.p. (methanol) 150—155°, $[\alpha]_D^{27}$ +38° (*c* 0·3 in $CHCl_3$), $\nu_{max.}$ 1723, 1650, 1625, and 1243 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 11,000), τ 4·27 (1H, t), 4·94br (1H), 8·00 (3H, s), 8·93, 8·98, 9·04, 9·16, 9·20, 9·34, 9·42, and 9·52, *m/e* 454 (M^+), 439, 394, 379, 269, 268, and 267 (Found: C, 77·7; H, 9·9. $C_{30}H_{46}O_{30}$,0·5H_2O requires C, 77·7; H, 10·2%).

(22S)-22-*Hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = OH, Y = H).—Reduction of the acetate (3; X = OAc, Y = H) with lithium aluminium hydride as previously described, followed immediately by oxidation with manganese dioxide, afforded the *alcohol* (12 mg, 67%), m.p. (methanol) 204—208°, $[\alpha]_D^{28}$ +31° (*c* 0·26 in $CHCl_3$), $\nu_{max.}$ 3420 and 1640 cm^{-1}, $\lambda_{max.}$ 248 nm (ε 12,800), τ 4·26 (1H, t), 6·29br (1H), 8·93, 9·03, 9·10, 9·16, 9·22, and 9·33, *m/e* 412 (M^+), 397, 394, 327 (M^+ − side chain from C-22), 298 (M^+ − side chain from C-20), 269, and 243 (Found: C, 81·3; H, 10·8. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

(22S)-22-*Benzoyloxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (3; X = $PhCO_2$, Y = H).—Benzoylation of the alcohol (3; X = OH, Y = H) (25 mg) in the normal manner but during several days gave the *benzoate* (6 mg, 19%), isolated by p.l.c. (1 : 19 acetone–light petroleum) as a non-crystalline solid, $[\alpha]_D^{29}$ +69° (*c* 0·14 in $CHCl_3$), $\nu_{max.}$ 1715, 1658, 1275, and 718 cm^{-1}, $\lambda_{max.}$ 231 and 247 nm (ε 21,900 and 13,600), τ 2·00 (2H, m), 2·58 (3H, m), 4·28 (1H, t), 4·68br (1H), 8·76, 8·85, 8·94, 9·16, 9·32, and 9·42, *m/e* 516 (M^+), 501, 394, 379, 347, 284, 268, 256, and 243 (Found: M^+, 516·3578. $C_{35}H_{48}O_3$ requires *M*, 516·3602). Its c.d. curve showed Δε +9·9 (202 nm), −11·95 (227 nm), and +2·12 (316 nm), and its o.r.d. curve [φ] +44,000 (215 nm), 37,600 (240 nm), −27,000 (250 nm), and −44,000 (254 nm).

Reduction of the 23- *and* 22-*Ketones* (6) *and* (16).—By the usual procedure (lithium aluminium hydride reduction, followed by manganese dioxide oxidation) the title ketones were separately converted into their epimeric alcohol mixtures. In order to arrive at an estimate of the epimer ratio the reductions were repeated at −20°. The 22-ketone afforded the alcohols (3; X = OH, Y = H) and (13; X = OH, Y = H) in the ratio 7 : 1, identical (t.l.c., m.p., mixed m.p., and spectral comparisons) with the alcohols produced from the respective bromo-acetates.

The 23-ketone (6) afforded the epimeric 23-alcohols. P.l.c. gave, as the major product (ratio 7 : 3) the less polar (23S)-23-*hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = H, Y = OH), m.p. (methanol) 178—179°, $[\alpha]_D^{25}$ +57° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 3395 and 1635 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 13,400), τ 4·27 (1H, t), 6·44br (1H), 8·76, 8·93, 9·07, 9·13, 9·18, 9·26, and 9·32, *m/e* 412 (M^+), 397, 394, 379, 384, 341 (M^+ − side chain from C-23), 311, 297 (M^+ − side chain from C-20), and 269 (Found: C, 81·3; H, 10·5. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%). The minor, most polar alcohol from the reduction was the 23*R*-alcohol (3; X = H, Y = OH), identical with the corresponding alcohol produced by reduction of the bromo-acetate (3; X = Br, Y = OAc) (t.l.c., m.p., mixed m.p., and spectral comparison).

Acylation of (23S)-23-*Hydroxy*-3α,5α-*cycloergost*-7-*en*-6-*one* (13; X = H, Y = OH).—Acetylation of the title alcohol, under the usual conditions, afforded the 23S-*acetate* (13; X = H, Y = OAc), m.p. (methanol) 86—89°, $[\alpha]_D^{23}$ +57° (*c* 0·3 in $CHCl_3$), $\nu_{max.}$ 1730, 1650, 1625, and 1248 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 12,400), τ 4·27 (1H, t), 5·03br (1H), 8·03 (3H, s), 8·77, 8·94, 9·04, 9·11, 9·16, 9·23, and 9·35, *m/e* 454 (M^+), 439, 394, 379, 341, 311, 297, 296, 269, and 267 (Found: C, 79·1; H, 10·1. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%).

The title alcohol was also benzoylated, to give the *benzoate* (13; X = H, Y = $PhCO_2$), m.p. (methanol) 168—170°, $[\alpha]_D^{32}$ +37° (*c* 0·25 in $CHCl_3$), $\nu_{max.}$ 1710, 1650, 1620, 1290, and 730 cm^{-1}, $\lambda_{max.}$ 234 and 249 nm (ε 20,500 and 13,800), τ 1·98 (2H, m), 2·57 (3H, m), 4·26 (1H, m), 4·71br (1H), 8·76, 8·95, 9·08, 9·13, 9·36, and 9·42, *m/e* 516 (M^+), 394, 379, 296, 277, 267, 243, 149, and 105 (Found: C, 81·5; H, 9·15. $C_{35}H_{48}O_3$ requires C, 81·35; H, 9·4%). Its c.d. curve showed Δε +11·20 (204 nm), −14·30 (234 nm), and +2·52 (316 nm) and its o.r.d. curve [φ] +34,800 (204 nm), −26,400 (256 nm), and −9900 (295 nm).

Reduction of 3α,5α-*Cyclocholest*-7-*ene*-6,22-*dione* (21; XY = O).—The ketone (33 mg) was reduced with lithium aluminium hydride in the normal manner, then oxidised with manganese dioxide. The epimer mixture (ratio 3 : 1; u.v. estimation) was separated by p.l.c. (1 : 9 acetone–light petroleum). The major, more polar alcohol was identified as (22S)-22-*hydroxy*-3α,5α-*cyclocholest*-7-*en*-6-*one* (21; X = OH, Y = H), m.p. (ethyl acetate–light petroleum) 186—189°, $[\alpha]_D^{28}$ +82° (*c* 0·7 in $CHCl_3$), $\nu_{max.}$ 3600, 1650, and 1620 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 11,300), τ 4·23 (1H, t), 6·35br (1H), 887 (3H, s), 9·05 (3H, d), 9·15 (3H, d), and 9·30 (3H, s) (Found: C, 81·2; H, 10·6. $C_{27}H_{42}O_2$ requires C, 81·4; H, 10·6%).

The minor alcohol was (22R)-22-*hydroxy*-3α,5α-*cyclocholest*-7-*en*-6-*one* (21; X = H, Y = OH), m.p. (ethyl acetate–light petroleum) 170—173°, $[\alpha]_D^{26}$ +100° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ 3400, 1635, and 1618 cm^{-1}, $\lambda_{max.}$ 247 nm (ε 11,700), τ 4·28 (1H, dd), 6·45br (1H), 8·94 (3H, s), 9·05 (3H, d), 9·11 (3H, d), 9·15 (3H, d), and 9·34 (3H, s) (Found: C, 81·5; H, 10·4%. $C_{27}H_{42}O_2$ requires C, 81·4; H, 10·6%).

Grignard Reaction on (20S)-3α,5α-*Cyclo*-20-*formylpregn*-7-*en*-6-*one* (20; R = H).[1]—The aldehyde (300 mg) in ether (20 ml) was treated with a solution of isopentylmagnesium bromide [from pentyl bromide (1·05 g) and magnesium turnings (0·125 g) in ether (5 ml)] at room temperature under nitrogen. After 5 min the mixture was heated to reflux for a further 5 min, then cooled, and ice-cold, saturated aqueous ammonium chloride solution was added to decompose the complex. The ethereal solution was washed with water, dried, and evaporated to afford an oil. The products were separated by p.l.c. (1 : 9 acetone–light petroleum) to afford the two epimeric 22-alcohols (ratio 6 : 1). The major, more polar isomer was the 22*S*-alcohol (21; X = OH, Y = H), identical with the alcohol produced by lithium aluminium hydride reduction of the 22-ketone (t.l.c., m.p., and mixed m.p.). The less polar, minor product, was the 22*R*-alcohol (21; X = H, Y = OH), identical with the product obtained by reduction of the 22-ketone (t.l.c., m.p., and mixed m.p.).

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