Steroidal Analogues of Unnatural Configuration. Part 12.[1] Ring A Reactions of 9-Methyl-5β,9β,10α- and 9-Methyl-5α,9β,10α-estran-3-ones: Conformational Analysis and X-Ray Crystallography of Products

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Bromination of 17β-acetoxy-9-methyl-5β- and 17β-acetoxy-9-methyl-5α,9β,10α-estran-3-one, obtained through stereoselective reductions of the olefinic bond of the corresponding testosterone analogue, leads to complex mixtures of α-bromo-ketones. In both cases, bromination at C(2) is favoured, and the distributions of positional isomers are rationalised in terms of conformational transmission effects. It is shown that the respective epimeric pairs are readily interconverted. The crystal structures of 17β-acetoxy-9-methyl-5α,9β,10α-estran-3-one (3b) and its 2α- and 2β-bromo-derivatives (11) and (12) have been determined by X-ray analysis. Ring A of (3b) and (11) suffers slight deformation from a chair conformation, whereas that of (12) adopts a twist-boat conformation in response to the severe steric interaction between the 2β-bromo- and 9β-methyl groups. The solid-state conformations of the three compounds clarify anomalies in their spectroscopic properties.

THE physiological activity of certain 9β,10α-steroids has stimulated interest in their conformational properties,[2,3] and it has been recognised that non-bonded interactions upon the congested α-face of such molecules may give rise to skeletal deformations and sometimes, modified reactivity of functional groups. During our studies on related steroidal analogues derived from the cucurbitacins,[4] we encountered conformational aberrations which may be ascribed to similar causes.

Since very little is known about the behaviour of 9β,10α-steroids having the 19-nor-9-methyl system,[5-7] we undertook a study of some properties and reactions of the 9-methyl-9β,10α-estran-3-ones (2) and (3), derived from the testosterone analogue (1).[5] It was of particular interest to examine ring A brominations and related reactions of these compounds in order to assess the influence of long-range conformational transmission upon enolisation of the 3-oxo-group. The desired 5-isomers (2) and (3) were obtained through stereoselective reductions of the olefinic bond of (1).

Treatment of the 17-hydroxy-compound (1a) with lithium in liquid ammonia gave the expected 3-oxo-5β-compound (2a), whereas catalytic hydrogenation of (1a) over palladised charcoal in propan-2-ol gave mainly the 3-oxo-5α-compound (3a) (53%) accompanied by substantial amounts of hydrogenolysis products (4a) (13%) and the 5β-isomer (2a) (25%). Although hydrogenolysis was not suppressed when the 17-acetate (1b) was hydrogenated over palladised charcoal in the presence of acid, the stereoselectivity of reduction was improved and the 5α-isomer (3b) was obtained in 68% yield.

The configurational assignments made to the 4,5-dihydro-3-ketones are mechanistically reasonable, and also parallel those made to the products of similar

reactions in the related 9β-H,10α-Me (retro) series.[8,9] A comparison of the c.d. spectra of the 4,5-dihydro-compounds (Table 1) with those reported[9,10] for stereo-

a; R = H   b; R = Ac

chemically analogous compounds lacking a 9β-methyl group revealed that, whereas the 5β-isomers agree very well, the Cotton effect of the 5α-isomer (3b) is more strongly positive than that reported ($\Delta\varepsilon$ 0.55) for a 19-nor-5α,9β,10α-3-ketone. Since the 9β-methyl group in (3b) is close to a nodal plane and cannot be expected to contribute significantly to the Cotton effect, this difference suggests that the environment of the 3-oxo-group may be affected by interactions between the 9β-methyl group and elements of ring A (vide infra).

Reactions of the 3-Oxo-5β-compound (2b).—Bromination of the ketone (2b) was carried out by use of pyridinium hydrobromide perbromide (1.05 mol) in acetic acid at 15 °C, and the complex mixture of products and unreacted (2b) was separated by careful chromatography on

[1] Part XI, P. R. Enslin, J. Coetzer, and G. J. Kruger, J.C.S. Perkin II, 1977, 402.

[2] C. Romers, C. Altona, H. J. C. Jacobs, and R. A. G. de Graaff in 'Terpenoids and Steroids,' vol. 4, Chem. Soc. Specialist Periodical Report, 1975, pp. 531—583, and references therein.

[3] W. L. Duax, C. M. Weeks, and D. C. Rohrer, Topics in Stereochem., 1976, 9, 271, and references therein.

[4] J. R. Bull, A. J. Hodgkinson, and A. Tuinman, Tetrahedron, 1973, 29, 2415.

[5] J. R. Bull and A. Tuinman, Tetrahedron, 1973, 29, 1101.

[6] R. V. Coombs, J. Koletar, R. Danna, H. Mah, and E. Galantay, J.C.S. Perkin I, 1973, 2096.

[7] J. R. Bull, J. Floor, and A. Tuinman, Tetrahedron, 1975, 31, 2157.

[8] S. J. Halkes and E. Havinga, Rec. Trav. chim., 1965, 84, 889.

[9] W. Gibb, J. Jeffery, D. N. Kirk, and H. Mahdi, Biochem. J., 1975, 145, 483.

[10] H. J. C. Jacobs and E. Havinga, Tetrahedron, 1972, 28, 135.

silica gel. Although satisfactory separations were achieved, it was evident from t.l.c. of column fractions and of material recovered from m.p. determinations, that
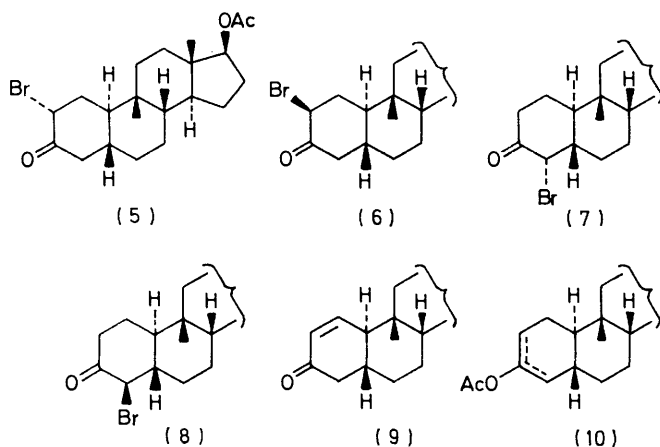
TABLE 1

Yields and spectroscopic properties of bromo-ketones

Compound	Yield (%)	C.d.[a]	N.m.r.[b]
5β-3-one (2b)		−1.3 (288)	
2α-Br-5β-3-one (5)	17	−5.0 (309)	4.33 (m, $W_{\frac{1}{2}}$ 8 Hz, 2β-H)
2β-Br-5β-3-one (6)	13	−1.3 (289)	4.65 (dd, J 12.5 and 6 Hz, 2α-H)
4α-Br-5β-3-one (7)	10	3.8 (309)	4.13 (t, J 2.5 Hz, 4β-H)
4β-Br-5β-3-one (8)	7	−0.8 (282)	4.41 (d, J 11 Hz, 4α-H)
5α-3-one (3b)		1.5 (287)	
2α-Br-5α-3-one (11)	48	1.0 (288)	4.51 (dd, J 12 and 6 Hz, 2β-H)
2β-Br-5α-3-one (12)	11	1.9 (284)	4.41 (dd, J 13 and 7 Hz, 2α-H)
4α-Br-5α-3-one (13)	5	1.3 (310)	4.36 (d, J 12 Hz, 4β-H)

[a] Data for methanol solutions given as $\Delta\varepsilon/nm$. [b] Data given as δ (width or multiplicity, splitting, assignment); compounds (5)—(8) in deuteriochloroform, and compounds (11)—(13) in deuteriobenzene.

the bromo-ketones isomerise readily. Accordingly, precautions were taken to obtain spectral and analytical data on freshly recrystallised samples.

In addition to unstable dibrominated material (13%), which was not further investigated, and starting material (2a) (25%), all four monobromo-ketones (5)—(8) were

(5)   (6)   (7)

(8)   (9)   (10)

isolated. Their positions of substitution were shown by dehydrobromination; thus (5) and (6) gave the 1-en-3-one (9), whereas (7) and (8) gave the 4-en-3-one (1b). The isomers were differentiated with the aid of spectroscopic data (Table 1). The axial bromo-ketones (5) and (7) displayed the expected Cotton effect increments in their c.d. spectra, and n.m.r. spectroscopy showed that the protons attached to the bromine-bearing carbon atoms were weakly coupled with adjacent protons; in the case of (7) the triplet seen for the 4β-proton in (7) may be ascribed to further coupling with the 2β-proton.

N.m.r. signals of the methine protons in the equatorial bromo-ketones (6) and (8) enabled unambiguous assignments to be made.

The formation of all four isomers during bromination suggested that equilibration may have occurred under the reaction conditions.[11] This was supported by experiments in which each of the pure isomers was treated with hydrogen bromide in acetic acid at 25 °C for 30 min to give a two-component mixture comprising the starting isomer and its epimer. No products of positional isomerisation were detected. The product distribution was similar to that of the respective epimeric pairs in the original bromination product, i.e slightly more of the axial epimer was present in each case.

The rates of bromination of the 2- and 3-enols of the ketone (2b) would not differ significantly since the steric surroundings of C(2) and C(4) are similar. Consequently, the retention of positional integrity during the equilibration experiments leads to the conclusion that the relative proportions of bromination at C(2) and C(4) provide a measure of the extent of enolisation toward those positions during the reaction. Despite some quantitative uncertainty owing to the formation of dibrominated material, it is evident that enolisation toward C(2) is favoured. In another experiment, the 3-ketone (2b) was treated with isopropenyl acetate–sulphuric acid to give a mixture of enol acetates (10); although the components could not be separated on a preparative scale, g.l.c. and n.m.r. showed that the product distribution is ca. 57 : 43 and that the 2-en-3-yl acetate is the major product.

Although the 5β,10α-stereochemistry of (2b) does indeed suggest that enolisation of the 3-oxo-group toward C(2) should be favoured,[12] the absence of a more pronounced preference indicates that more remote conformational transmission effects may also be operative. A comparison of the effect of 2- and 3-olefinic bonds upon the ring-junction torsion angles (ϕ) in this skeleton reveals that $\phi_{7.8.9.10}$ would tend to be increased by the former function (Figure 1b) and decreased by the latter [12] (Figure 1c). Since the tendency of ring D to diminish $\phi_{11.9.8.14}$ [12] is transmitted as a like effect to $\phi_{7.8.9.10}$, owing to the B,C-cis-ring-junction (Figure 1a), it is clear that this will stabilise a 3- at the expense of a 2-ene. Consequently, the otherwise overwhelming stabilisation of a 2-ene occasioned by the A,B-trans-ring-junction, in addition to the steric interaction between 5β-H and 9β-CH₃ (which will tend to diminish $\phi_{6.5.10.9}$), is opposed but not overcome by the longer-range effect.

Reactions of the 3-Oxo-5α-compound (3b).—The compound (3b) was brominated under the same conditions as (2b), and the mixture of three products (11)—(13) separated by rapid chromatography under pressure, in order to minimise decomposition on the adsorbent. The bromo-ketones in this series were also susceptible to isomerisation. Although their positions of substitution were readily ascertained from the multiplicity of n.m.r.

[11] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 163—168, 385—386.
[12] R. Bucourt, Topics in Stereochem., 1974, 8, 159.

signals (Table 1), and by dehydrobromination to the appropriate α,β-unsaturated ketones (1b) and (14), only the minor product (13) could be structurally assigned with
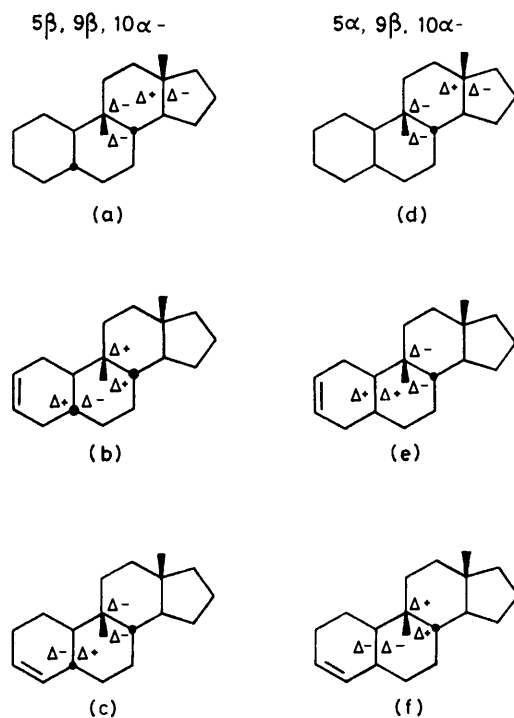

5β, 9β, 10α -   5α, 9β, 10α-

(a)   (d)

(b)   (e)

(c)   (f)

FIGURE 1 Effect of conformational transmission on ring-junction torsion angles. Δ+ represents an increase and Δ— a decrease in the magnitude of the torsion angle

confidence. Thus, the magnitude of n.m.r. coupling between 4- and 5α-H is compatible with a 4α-bromo-3-ketone having an undeformed ring A. However, the marked bathochromic shift of the c.d. maximum in (13) is not readily explained.

(11)   (12)

(13)   (14)   (15)
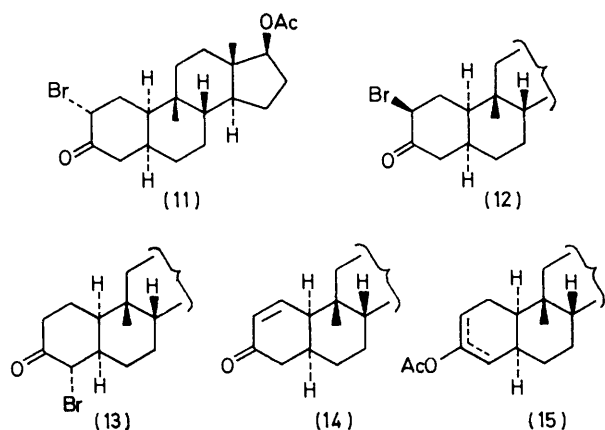
Although the 2-substituted isomers (11) and (12) could not be differentiated by n.m.r. and c.d. spectroscopy (Table 1), the data are consistent with products in which the bromo-group is equatorial or pseudo-equatorial. Models showed that the equatorial 2α-

isomer should be relatively strain-free, but that the severe non-bonded interactions in the axial 2β-isomer could force the substituent into a pseudo-equatorial orientation through deformation of ring A. In view of c.d. evidence that the parent ketone (3b) may itself be slightly deformed in response to smaller interactions (q.v.) a more drastic change in the 2β-bromo-3-ketone would be expected. The uncertainties in this series were resolved through X-ray crystallography of the parent ketone (3b) and the 2-bromo-compounds (11) and (12); it was thus established that the major product of bromination is the equatorial 2α-isomer (11) (vide infra).

Treatment of the pure 2-bromo-3-ketones (11) and (12) with hydrogen bromide in acetic acid at 25 °C for 30 min gave in each case, a ca. 4 : 1 mixture of isomers favouring the 2α-compound (11). This ratio of products is similar to that found in the original bromination mixture. After 24 h, traces of the 4α-isomer (13) were also detected (t.l.c.). Although positional isomerisation under these conditions is not unusual,[11] the small amount of the 4α-isomer (13) isolated after bromination of (3b) is more likely to have arisen through primary attack upon the derived 3-enol. Consequently the product distribution shows that attack at C(2) is highly favoured. Furthermore, it is probable that the otherwise favoured antiparallel[13] approach of the electrophile would be strongly inhibited by steric hindrance on the β-face, and that the major isomer (11) is also a primary reaction product.

Enol acetylation of (3b) using isopropenyl acetate–sulphuric acid gave a product (15) which appeared to be homogeneous (g.l.c.). Although the n.m.r. evidence is not conclusive, the width ($W_{\frac{1}{2}}$ 8 Hz) of the signal for the olefinic proton shows that it is coupled to two adjacent protons rather than one. Therefore the product (15) is taken to consist largely of the 2-en-3-yl acetate.

The strong preference for enolisation of (3b) toward C(2) is readily explained through conformational transmission;[12] a 2-ene will cause an increase in $\phi_{4.5,10.1}$ and, through the A,B-cis-ring-junction, a concomitant increase in $\phi_{6.5.10.9}$ (Figure 1e). These changes are reinforced by the tendency toward closure of $\phi_{7.8.9.10}$, occasioned by the ring D effect[12] (Figure 1d). By contrast, a 3-ene (Figure 1f) gives rise to opposing torsion angle effects from the two extremes of the skeleton. Furthermore, the 2-ene enjoys a greater degree of conformational mobility than the 3-ene, which may facilitate the relief of interactions between C(19) and elements of ring A.

Structure and Conformation of the 5α-Compounds (3b), (11), and (12).—The gross structures and configurations of the 3-oxo-5α-compound (3b) and its 2α- (11) and 2β-bromo-derivatives (12) were established by X-ray crystallography; that of the parent ketone (3b) is illustrated (Figure 2), showing the atom numbering system employed for all three compounds.

The conformation of the various rings can be con-

13 J. Valls and E. Toromanoff, Bull. Soc. chim. France, 1961, 758.

veniently compared by the method of Cremer and Pople.[14] For this purpose the atoms in each ring were considered in clockwise order starting from the lowest number in the
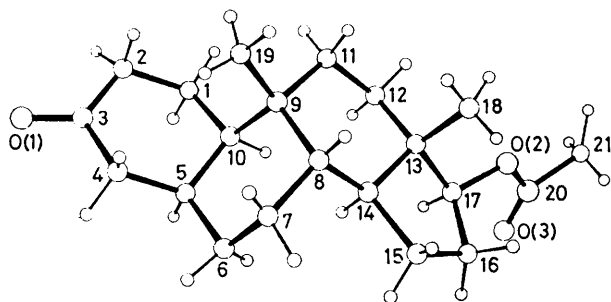

Figure 2   Structure and configuration of the 3-oxo-5α-compound (3b)

ring (as in Figure 3) to calculate the puckering parameters given in Table 2. For six-membered rings the

TABLE 2

Puckering parameters of 3-ketone (3b), 2α-bromo-3-ketone (11), and 2β-bromo-3-ketone (12)

Ring	Parameter	(3b)	(11)	(12)
A	$\phi/°$	257	336	325
	$\theta/°$	164	175	88
	$Q/Å$	0.44	0.52	0.76
B	$\phi/°$	204	239	186
	$\theta/°$	9	10	18
	$Q/Å$	0.53	0.55	0.50
C	$\phi/°$	252	273	256
	$\theta/°$	7	8	6
	$Q/Å$	0.56	0.56	0.58
D	$\phi/°$	350	346	353
	$q/Å$	0.47	0.43	0.49

puckering analysis yields a set of three 'polar' co-ordinates. The total degree of pucker is described by the radial co-ordinate Q, and the two angular co-ordinates θ and ϕ define the shape of the ring. The polar positions, θ 0 and 180°, correspond to the normal chair ($^1C_4$) and inverted chair ($^4C_1$) conformations. At the equator, θ 90°, a set of 12 boat (B) and twist-boat (T) conformations corresponding to different values of ϕ is found. This pseudo-rotational cycle is illustrated in Figure 3 which also shows the signs of the endocyclic torsion angles for the various conformations. For five-membered rings the zero position (ϕ 0) on the pseudo-rotational cycle is at the envelope conformation defined as ^0E for furanose rings by Altona and Sundaralingam [15] and as ^1E in the present notation.

It follows from Table 2 that the conformations of ring C ($^1C_4$) and ring D (^1E) are conserved fairly well in all three compounds, whereas those of ring B in the 3-ketone (3b) and the 2α-bromo-3-ketone (11) are slightly distorted in the direction of the $^2T_4$ and $^{2,5}B$ forms respectively. Ring B of the 2β-bromo-3-ketone (12) deviates more markedly from a chair conformation and is distorted

towards the $B_{4,1}$ form. This is a sympathetic response to severe deformation of ring A, the conformation of which lies on the equator of the ' sphere ' (Figure 3) and approximates very closely to a twist-boat ($^1T_3$). The higher degree of puckering measured for this ring than for those of the other compounds is an intrinsic property of such a conformation. Nevertheless, ring A of the 2α-bromo-compound (11) is itself more puckered than an ' ideal ' cyclohexanone [12] and is close to an inverted chair ($^4C_1$) conformation. By contrast, ring A of the parent ketone (3b) is less chair-like than that of (11) by ca. 11° and is abnormally flattened, even for a cyclohexanone ring.[12]

Crystallographic data for ring A of the three compounds were compared in order to rationalise steric interactions and relate them to spectroscopic properties.

Ring A of the 3-Ketone (3b).—The endocyclic torsion angles of (3b) demonstrate not only the overall flattening of ring A relative to cyclohexanone,[12] but dissymmetric deformation about the carbonyl group. The ring is more flattened at C(2) than at C(4) despite which the C(2) · · · C(19) separation (3.31 Å) is slightly less than that of C(4) · · · C(19) (3.39 Å). Although these two interactions, which are tantamount to 1,3-diaxial interactions between hydrogens and a t-butyl residue, are formally equivalent, the relative rigidity of the molecule about C(4) must be responsible for a skeletal adjustment to maximise the C(4) · · · C(19) separation and so tilt the
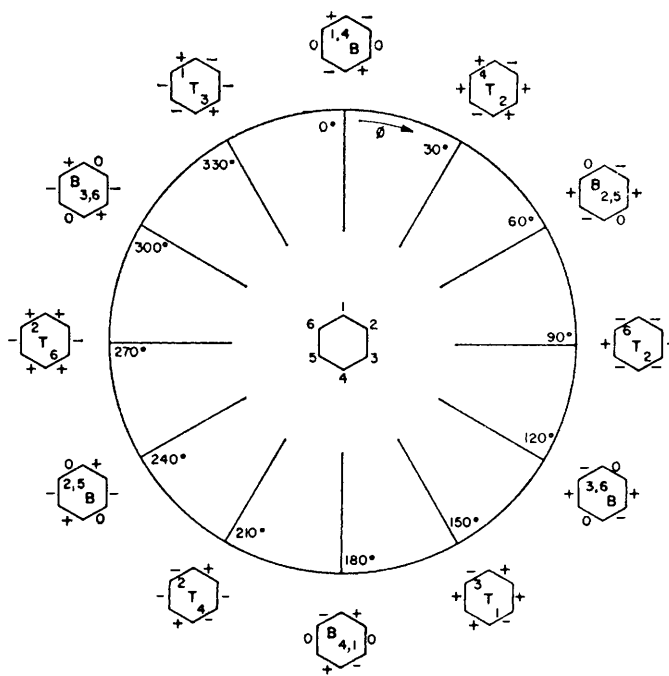

FIGURE 3   Pseudo-rotational cycle for cyclohexane showing the notations used for conformers on the equator (θ 90°)

9β-methyl group out of the ring A symmetry plane through C(3) · · · C(10). Dissymmetric flattening at the C(2) pivot, to alleviate the resultant close approach of the

[14] D. Cremer and J. A. Pople, *J. Amer. Chem. Soc.*, 1975, **97**, 1354.

[15] C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, 1972, **94**, 8205.

9β-methyl group, is facilitated by the greater conformational freedom of ring A at this position. These features are clearly seen in an octant projection (Figure 4) generated from the X-ray data, and provide a plausible explanation for the relatively strong, positive, Cotton effect of (3b). The octant contributions of the C(2)–C(1) and C(4)–C(5) bonds are no longer mutually cancelling, and the more skew disposition of the latter bond, in a positive octant, will outweigh the former; this additional contribution is superimposed onto the positive Cotton effect of the skeleton.[10] Furthermore the 9β-methyl group is perceptibly out of the nodal plane and in a positive octant; however, its contribution to perturbation of the chromphore is probably small.
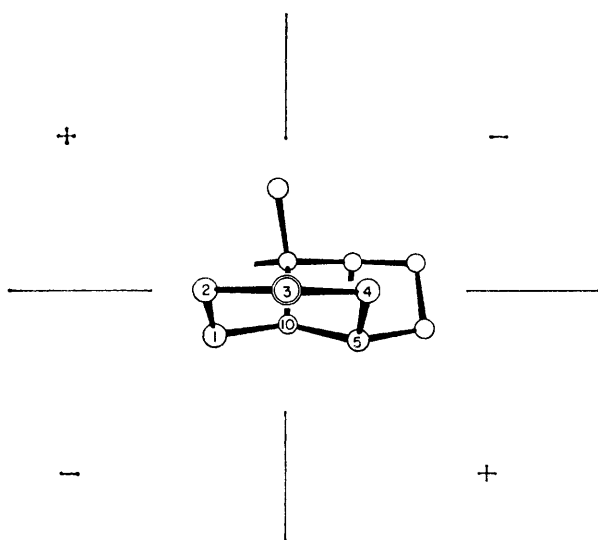
FIGURE 4 Octant projection of rings A and B of the 3-ketone (3b), generated from X-ray data

Ring A *of the* 2α-*Bromo-3-ketone* (11).—The more puckered state of ring A in (11) than in (3b), which is evident from a comparison of the endocyclic torsion angles (Table 3), should aggravate the C(2) · · · C(19) and C(4) · · · C(19) interactions. However, their respective separations of **3.24** and **3.43** Å show that ring A suffers a mode of dissymmetric deformation similar to that of (3b). The shorter C(2) · · · C(19) distance suggests that there is resistance to flattening at C(2), owing to the presence of the 2α-bromo-group. At least some of the potential steric compression between rings A and B in (11) is relieved through changes in valence bond angles (Table 4). The dissymmetric mode of ring A deformation in (11) may be discerned in the octant projection (Figure 5). That dissymmetry is less pronounced than in the parent ketone (3b) is also reflected in their respective Cotton effects (Table 1). N.m.r. data for (11) show that, despite some imprecision in determining the location of hydrogen atoms by X-ray crystallography, the measured torsion angles, $\phi_{2\beta,1\alpha}$ —176° and $\phi_{2\beta,1\beta}$ —51°, correlate quite well with J values of 12 and 6.5 Hz respectively.

A feature of the ring A conformation in (11) is the

near-coplanarity of the C(2)–Br and C(3)–O(1) bonds [$\phi_{Br,2,3,O(1)}$ —2.3°; *cf.* the related torsion angle,

TABLE 3

Torsion angles (°) involving non-hydrogen atoms only for 3-ketone (3b), 2α-bromo-3-ketone (11), and 2β-trans-3-ketone (12)

	(3b)	(11)	(12)
Br–C(2)–C(1)–C(10)		−172.0	−168.3
Br–C(2)–C(3)–O(1)		−2.3	15.2
Br–C(2)–C(3)–C(4)		173.6	−165.2
O(1)–C(3)–C(2)–C(1)	−145.0	−124.7	142.3
O(1)–C(3)–C(4)–C(5)	141.8	121.9	156.8
O(2)–C(17)–C(13)–C(12)	78.2	91.9	83.6
O(2)–C(17)–C(13)–C(14)	−166.8	−155.0	−162.1
O(2)–C(17)–C(13)–C(18)	−47.7	−35.3	−43.9
O(2)–C(17)–C(16)–C(15)	143.6	137.7	142.3
O(3)–C(20)–O(2)–C(17)	1.3	7.9	6.1
C(1)–C(2)–C(3)–C(4)	34.4	51.2	−38.1
C(1)–C(10)–C(5)–C(4)	−50.4	−50.9	−32.4
C(1)–C(10)–C(5)–C(6)	−178.8	−178.2	−164.6
C(1)–C(10)–C(9)–C(8)	177.5	173.8	172.0
C(1)–C(10)–C(9)–C(11)	−63.0	−67.2	−63.4
C(1)–C(10)–C(9)–C(19)	56.5	53.4	50.1
C(2)–C(1)–C(10)–C(5)	48.4	48.4	−26.9
C(2)–C(1)–C(10)–C(9)	−84.9	−84.6	−158.1
C(2)–C(3)–C(4)–C(5)	−37.6	−54.1	−22.7
C(3)–C(2)–C(1)–C(10)	−41.3	−49.6	65.0
C(3)–C(4)–C(5)–C(6)	176.1	−176.7	−166.3
C(3)–C(4)–C(5)–C(10)	47.0	56.2	60.2
C(4)–C(5)–C(6)–C(7)	−81.8	−77.3	−93.6
C(4)–C(5)–C(10)–C(9)	82.2	81.0	97.0
C(5)–C(6)–C(7)–C(8)	−56.2	−60.1	−49.8
C(5)–C(10)–C(9)–C(8)	48.0	45.3	42.7
C(5)–C(10)–C(9)–C(11)	167.5	164.3	167.3
C(5)–C(10)–C(9)–C(19)	−73.0	−75.1	−79.2
C(6)–C(5)–C(10)–C(9)	−46.3	−46.3	−35.2
C(6)–C(7)–C(8)–C(9)	60.0	59.5	59.9
C(6)–C(7)–C(8)–C(14)	−64.8	−63.8	−63.8
C(7)–C(6)–C(5)–C(10)	48.2	51.1	37.8
C(7)–C(8)–C(9)–C(10)	−52.9	−50.6	−55.3
C(7)–C(8)–C(9)–C(11)	−173.2	−170.6	−178.0
C(7)–C(8)–C(9)–C(19)	71.4	73.4	68.5
C(7)–C(8)–C(14)–C(13)	−178.4	−176.2	−176.1
C(7)–C(8)–C(14)–C(15)	−55.5	−51.4	−52.0
C(8)–C(9)–C(11)–C(12)	49.5	46.1	50.4
C(8)–C(14)–C(13)–C(12)	−59.9	−61.5	−62.5
C(8)–C(14)–C(13)–C(17)	178.4	175.1	178.9
C(8)–C(14)–C(13)–C(18)	62.6	59.1	64.1
C(8)–C(14)–C(15)–C(16)	−162.9	−164.6	−164.6
C(9)–C(8)–C(14)–C(13)	56.7	60.0	57.9
C(9)–C(8)–C(14)–C(15)	179.5	−175.2	−178.1
C(9)–C(11)–C(12)–C(13)	−55.0	−51.7	−53.3
C(10)–C(9)–C(8)–C(14)	72.2	73.3	71.1
C(10)–C(9)–C(11)–C(12)	−69.1	−74.0	−71.7
C(11)–C(9)–C(8)–C(14)	−48.1	−46.8	−51.6
C(11)–C(12)–C(13)–C(14)	55.6	54.1	57.0
C(11)–C(12)–C(13)–C(17)	165.8	164.3	164.5
C(11)–C(12)–C(13)–C(18)	−68.8	−69.5	−69.7
C(12)–C(11)–C(9)–C(19)	166.6	162.0	168.2
C(12)–C(13)–C(14)–C(15)	168.5	166.7	167.2
C(12)–C(13)–C(17)–C(16)	−156.8	−150.8	−158.0
C(13)–C(14)–C(15)–C(16)	−34.4	−34.6	−35.6
C(13)–C(17)–O(2)–C(20)	−159.7	−86.5	−160.0
C(13)–C(17)–C(16)–C(15)	21.4	16.7	23.0
C(14)–C(8)–C(9)–C(19)	−163.5	−162.8	−165.1
C(14)–C(13)–C(17)–C(16)	−41.8	−36.9	−43.3
C(14)–C(15)–C(16)–C(17)	8.3	10.5	6.8
C(15)–C(14)–C(13)–C(17)	46.8	43.4	48.7
C(15)–C(14)–C(13)–C(18)	−69.1	−72.6	−66.2
C(16)–C(17)–O(2)–C(20)	81.2	156.8	85.5
C(16)–C(17)–C(13)–C(18)	77.3	82.8	74.5
C(17)–O(2)–C(20)–C(21)	179.7	−173.0	−172.8

$\phi_{2\alpha-H,2,3,O(1)}$ —21.8°, in the parent ketone (3b)]. Furthermore, the O · · · Br separation (**3.01** Å) is smaller than the sum (**3.35** Å) of their respective van der Waals

radii.[16] Such an orientation appears to be favoured in equatorial α-halogenocyclohexanones,[17-19] and it has been suggested [17] that an attractive interaction between

TABLE 4

Bond angles (°) between non-hydrogen atoms for compounds (3b), (11), and (12)

Angle	(3b)	(11)	(12)	Mean
C(17)-O(2)-C(20)	117.9(4)	119.5(8)	116.1(14)	117.8(4)
C(2)-C(1)-C(10)	116.6(5) *	116.0(8)	109.3(14) *	114.0(4)
C(1)-C(2)-C(3)	115.7(5) *	113.3(12)	110.5(15)	113.2(4)
O(1)-C(3)-C(2)	120.5(5) *	124.7(11)	122.5(17)	122.6(4)
O(1)-C(3)-C(4)	122.5(5)	122.9(12)	122.8(18)	122.7(4)
C(2)-C(3)-C(4)	117.0(5) *	112.3(11)	114.6(17)	114.6(4)
C(3)-C(4)-C(5)	116.1(4) *	111.7(10)	112.0(18)	113.3(4)
C(4)-C(5)-C(6)	111.4(4)	111.7(10)	113.6(17)	112.2(4)
C(4)-C(5)-C(10)	114.3(4) *	113.9(10)	110.0(15)	112.7(4)
C(6)-C(5)-C(10)	112.7(4)	111.4(11)	115.9(15)	113.3(4)
C(5)-C(6)-C(7)	112.1(4)	111.3(12)	115.7(18)	113.0(4)
C(6)-C(7)-C(8)	113.0(4)	112.1(11)	112.4(17)	112.5(4)
C(7)-C(8)-C(9)	111.4(4)	111.1(8)	112.2(14)	111.6(4)
C(7)-C(8)-C(14)	111.6(4)	111.1(12)	113.8(17)	112.2(4)
C(9)-C(8)-C(14)	111.0(3) *	110.3(7)	108.2(13)	109.8(3)
C(8)-C(9)-C(10)	107.9(4) *	110.1(9)	109.7(14)	109.2(4)
C(8)-C(9)-C(11)	109.3(4)	108.2(8)	112.2(15)	109.9(4)
C(8)-C(9)-C(19)	108.7(4)	107.6(9)	109.4(16)	108.6(4)
C(10)-C(9)-C(11)	110.5(4)	109.8(8)	108.7(14)	109.7(4)
C(10)-C(9)-C(19)	114.2(4)	113.5(8)	111.4(15)	113.0(4)
C(11)-C(9)-C(19)	106.1(4)	107.4(9)	105.4(16)	106.3(4)
C(1)-C(10)-C(5)	108.7(4)	107.9(8)	112.2(13)	109.6(3)
C(1)-C(10)-C(9)	115.3(4)	115.1(9)	113.2(14)	114.5(4)
C(5)-C(10)-C(9)	116.8(4)	117.1(9)	117.1(14)	117.0(4)
C(9)-C(11)-C(12)	116.6(4)	118.5(10)	114.6(19)	116.6(4)
C(11)-C(12)-C(13)	110.5(4)	112.4(9)	111.0(16)	111.3(4)
C(12)-C(13)-C(14)	107.6(4)	106.1(8)	109.0(13)	107.6(3)
C(12)-C(13)-C(17)	116.5(4)	118.4(9)	114.1(15)	116.3(4)
C(12)-C(13)-C(18)	110.3(4)	109.7(11)	112.1(15)	110.7(4)
C(14)-C(13)-C(17)	99.2(3)	98.1(10)	98.0(13)	98.4(3)
C(14)-C(13)-C(18)	113.6(4)	114.2(9)	113.9(15)	113.9(4)
C(17)-C(13)-C(18)	109.3(4)	110.1(8)	109.0(14)	109.5(4)
C(8)-C(14)-C(13)	114.7(4)	115.3(10)	114.7(15)	114.9(4)
C(8)-C(14)-C(15)	119.8(4) *	118.5(9)	116.9(14)	118.4(4)
C(13)-C(14)-C(15)	102.7(4) *	104.4(8)	105.5(15)	104.2(4)
C(14)-C(15)-C(16)	103.9(4)	104.0(11)	104.2(17)	104.0(4)
C(15)-C(16)-C(17)	106.4(5)	107.7(14)	104.4(19)	106.2(5)
O(2)-C(17)-C(13)	110.8(4)	110.5(10)	111.2(14)	110.8(4)
O(2)-C(17)-C(16)	115.1(4) *	108.1(11)	110.6(16)	111.3(4)
C(13)-C(17)-C(16)	105.1(4)	105.8(10)	103.9(16)	104.9(4)
O(2)-C(20)-O(3)	123.7(5)	123.3(10)	122.8(18)	123.3(4)
O(2)-C(20)-C(21)	112.3(5)	111.6(10)	110.4(20)	111.4(4)
O(3)-C(20)-C(21)	124.0(6)	125.1(11)	126.8(21)	125.2(5)
Br-C(2)-C(1)		109.6(7)	111.9(12)	110.8(6)
Br-C(2)-C(3)		109.5(8)	112.4(12)	111.0(7)

* These bond parameters are significantly different from the mean.

oxygen and halogen may be responsible. Such an interaction would have to be more powerful than the repulsive dipole interaction,[20] and in the case of (11) would also have to overcome the β-face steric interactions which oppose the concomitant puckering of ring A.

Ring A of the 2β-Bromo-3-ketone (12).—The severe steric interaction between the 2β-bromo- and 9β-methyl groups in an all-chair conformation of (12) is clearly intolerable, and is overcome by the assumption of a puckered twist-boat conformation for ring A. This conformation clarifies the spectroscopic findings (Table 1).

[16] L. Pauling, ' The Nature of the Chemical Bond,' 3rd edn., Cornell University Press, Ithaca. New York, 1960.
[17] J. A. Wunderlich and W. N. Lipscomb, *Tetrahedron*, 1960, **11**, 219.
[18] J. Lapasset and J. Falgueirettes, *Acta Cryst.*, 1971, **B27**, 624.

Thus, the Cotton effect of (12) is dominated by the positive contributions of the skew-bonds (Figure 6), and the pseudo-axial orientation of the 2α-proton gives rise to J values of 13 and 7 Hz, which are compatible with the measured torsion angles, $\phi_{2\alpha,1\beta}$ —169.3 and $\phi_{2\alpha,1\alpha}$ 71.4°. The ring A conformation is associated with substantial closure of $\phi_{1.10.5,4}$; the sympathetic closure of $\phi_{9.10,5.6}$ is responsible for moderate deformation of ring B, resulting
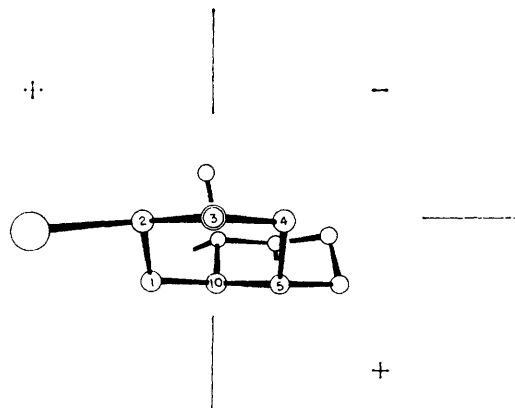

FIGURE 5 Octant projection of rings A and B of the 2α-bromo-3-ketone (11), generated from X-ray data

in a further measure of relief from the steric interactions between the 9β-methyl group and C(4). This factor may be responsible for the failure of ring A to adopt a $B_{3.6}$ conformation (Figure 3), in which the C(2)-Br and C(3)-O(1) bonds would approach coplanarity. The measured torsion angle ($\phi_{Br.2,3,O(1)}$ 15.2°) shows that other steric constraints can overcome the postulated [17] attractive

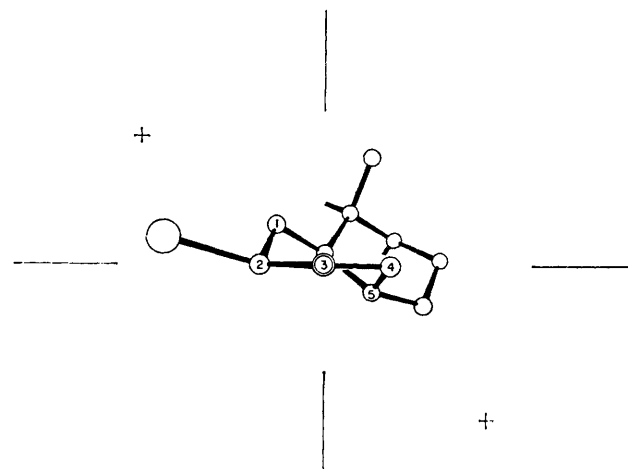FIGURE 6 Octant projection of rings A and B of the 2β-bromo-3-ketone (12), generated from X-ray data

interaction between oxygen and halogen, even in a case where there is sufficient conformational freedom to accommodate it.

[19] R. A. G. de Graaff, M. Th. Giesen, E. W. M. Rutten, and C. Romers, *Acta Cryst.*, 1972, **B28**, 1576.
[20] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ' Conformational Analysis,' Interscience, New York, 1965, pp. 460—469.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Unless otherwise specified, spectra were recorded as follows: i.r., Perkin-Elmer 237, chloroform solutions; u.v., Unicam SP 800, methanol solutions; n.m.r., Varian HA 100, deuteriochloroform solutions, with tetramethylsilane as internal standard; mass, A.E.I. MS 9; and c.d., JASCO J 20, methanol solutions. Optical rotations were determined for solutions in chloroform at 24 °C with a Perkin-Elmer 241 polarimeter. Silica gel refers to Kieselgel 60 (Merck).

Reduction of 17β-*Hydroxy*-9-*methyl*-9β,10α-*estr*-4-*en*-3-*one* (1a).—(a) The compound (1a) (0.576 g) in tetrahydrofuran (3 ml) was added to lithium (0.1 g) in stirred liquid ammonia (dried by prior distillation from sodium; ca. 40 ml), tetrahydrofuran (10 ml), and toluene (10 ml). After 5 min dibromoethane (0.4 ml) was added, followed by methanol–acetic acid (4 : 1; 5 ml). Water was added and the product was isolated by extraction with ethyl acetate and filtered through silica gel (30 g) with ethyl acetate to give 17β-*hydroxy*-9-*methyl*-5β,9β,10α-*estran*-3-*one* (2a) (0.503 g), m.p. 133—137 °C (from ether–hexane); $[\alpha]_D$ −17° (c 0.7), $v_{max.}$ 3 600 and 1 706 cm⁻¹; δ 0.8 (13β-Me), 0.93 (9β-Me), and 3.75 (1 H, t, J 8 Hz, 17α-H) (Found: C, 78.5; H, 10.6%; M^+, 290. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%; M, 290).

The derived 17-*acetate* (2b) had m.p. 159—161 °C (from ethanol); $[\alpha]_D$ −24° (c 1.1); $v_{max.}$ 1 723 and 1 711 cm⁻¹; δ 0.81 (13β-Me), 0.89 (9β-Me), 2.01 (OAc), and 4.73 (1 H, dd, J 8.5 and 7.5 Hz, 17α-H) (Found: C, 76.2; H, 10.0%; M^+, 332. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%; M, 332).

(b) The compound (1a) (0.2 g) in propan-2-ol (3 ml) was added to prereduced palladium–charcoal (5%; 0.02 g) in propan-2-ol (20 ml), and the mixture was shaken in hydrogen. Uptake ceased after 45 min (ca. 1.1 mol), and the filtered solution was evaporated. Chromatography of the residue on silica gel (20 g) with ethyl acetate–benzene (1 : 1) gave the impure 4-olefin (4a) as an oil (0.025 g); $v_{max.}$ 3 600 cm⁻¹; m/e 274 (M^+); δ 0.79 (13β-Me), 0.96 (9β-Me), 3.72 (1 H, dd, J 8.5 and 7.5 Hz, 17α-H), and 5.48br (ca. ' 0.8H,' $W_{\frac{1}{2}}$ 10 Hz, 4- and 6-H). G.l.c. of this material revealed the presence of minor impurities, probably the 5- and/or 5(10)-isomers. Further elution gave 17β-*hydroxy*-9-*methyl*-5α,9β,10α-*estran*-3-*one* (3a) (0.107 g), m.p. 122—124 °C (from ether–hexane); $[\alpha]_D$ +28° (c 0.6); $v_{max.}$ 3 600 and 1 702 cm⁻¹; δ 0.79 (13β-Me), 1.18 (9β-Me), and 3.69 (1 H, t, J 8 Hz, 17α-H) (Found: C, 78.3; H, 10.6%; M^+, 290), followed by the 5β-isomer (2a) (0.05 g), m.p. and mixed m.p. 133—137 °C.

Reduction of 17β-*Acetoxy*-9-*methyl*-9β,10α-*estr*-4-*en*-3-*one* (1b).[6]—The compound (1b) (0.46 g) was added to prereduced palladium–charcoal (5%; 0.1 g) in acetic acid (100 ml) containing 3N-hydrochloric acid (1 ml), and the mixture was shaken in hydrogen. After 2 h the uptake was ca. 1.05 mol. The mixture was filtered and the filtrate evaporated to give a residue which was adsorbed on silica gel (50 g). Elution with ethyl acetate–benzene (1 : 9) gave a mixture of olefins (4b) (0.11 g); $v_{max.}$ 1 725 cm⁻¹; m/e 316 (M^+); g.l.c. revealed the presence of three components in a ratio of 12 : 5 : 3. Further elution gave 17β-*acetoxy*-9-*methyl*-5α,9β,10α-*estran*-3-*one* (3b) (0.32 g), m.p. 110—112 °C (from pentane); $[\alpha]_D$ +14° (c 1.0); $v_{max.}$ 1 725 and 1 710 cm⁻¹; δ 0.79 (13β-Me), 1.33 (9β-Me), 1.99 (OAc), and 4.66 (1 H, t, J 8 Hz, 17α-H) (Found: C, 75.9; H, 9.75%; M^+, 332), followed by the 5β-isomer (2b) (0.024 g), m.p. and mixed m.p. 159—161 °C.

Bromination of the 3-*Oxo*-5β-*compound* (2b).—Pyridinium hydrobromide perbromide (0.3 g) was added in small portions to the 3-ketone (2b) (0.3 g) in acetic acid (15 ml) at

10 °C under nitrogen. After 2 h at 15 °C the mixture was poured on ice and extracted with ethyl acetate. The combined extracts were washed (water, aqueous sodium hydrogen carbonate, and aqueous sodium chloride), evaporated *in vacuo*, and the residue adsorbed on silica gel (40 g). Elution with ethyl acetate–benzene (5 : 95) gave a mixture of dibromo-derivatives [0.057 g; m/e 488, 490, and 492 (1 : 2 : 1)], which was too unstable for further characterisation, followed by a mixture (0.1 g) of the 2α- (5) and the 4α-bromo-compound (7). Elution with ethyl acetate–benzene (1 : 9) gave 17β-*acetoxy*-2β-*bromo*-9-*methyl*-5β,9β,10α-*estran*-3-*one* (6) (0.047 g), m.p. 155—180 °C (from acetone–ethanol); $[\alpha]_D$ −80° (c 1.0); $v_{max.}$ 1 725br cm⁻¹; δ 0.85 (13β-Me), 0.94 (9β-Me), 2.05 (OAc), 4.65 (1 H, dd, J 12.5 and 6 Hz, 2α-H), and 4.74 (1 H, t, J 8 Hz, 17α-H) (Found: C, 61.6; H, 7.7%; M^+, 410, 412. $C_{21}H_{31}BrO_3$ requires C, 61.3; H, 7.6%; M, 410, 412), and the 4β-*bromo-compound* (8) (0.025 g), m.p. 142—150 °C (from acetone–ethanol); $[\alpha]_D$ +56° (c 0.6); $v_{max.}$ 1 725br cm⁻¹; δ 0.85 (13β-Me), 0.93 (9β-Me), 2.05 (OAc), 4.41 (1 H, d, J 11 Hz, 4α-H), and 4.76 (1 H, d d, J 8.5 and 7.5 Hz, 17α-H) (Found: C, 61.7; H, 7.7%; M^+, 410, 412). Further elution with ethyl acetate–benzene (1 : 9) afforded starting material (2b) (0.075 g).

TABLE 5

Crystal data and details of crystallographic analysis for 3-ketone (3b), 2α-bromo-3-ketone (11), and 2β-bromo-3-ketone (12)

Compound	(3b)	(11)	(12)
Formula	$C_{21}H_{32}O_3$	$C_{21}H_{31}BrO_3$	$C_{21}H_{31}BrO_3$
M	332.5	411.4	411.4
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a/Å	13.85(1)	13.00(1)	21.45(1)
b/Å	12.39(1)	7.38(1)	12.39(1)
c/Å	11.18(1)	11.55(1)	7.38(1)
β/°		115.9(1)	
U/Å³	1 918.4	996.3	1 961.3
D_c/g cm⁻³	1.151	1.371	1.393
F(000)	728	432	864
Z	4	2	4
μ(Mo-K_α)	0.42	20.11	20.43 cm⁻¹
Scan width/°	0.9	1.2	0.9
Scan time/s	30	30	30
Step size/s	0.03	0.04	0.03
$\theta_{max.}$/°	20	20	20
Observed intensities	1 733	1 014	1 026
F cut-off	3σ	1σ	2σ
Weighting	Counting statistics	Unit weights	Unit weights
R	0.064	0.046	0.061

The mixture (0.1 g) of bromo-compounds, (5) and (7), was rechromatographed under pressure on silica gel (Merck prepacked Kieselgel 60; size B) with ethyl acetate–hexane (1 : 9) to give the 2α-*bromo-compound* (5) (0.06 g), m.p. 48—55 °C (from methanol); $[\alpha]_D$ −185° (c 0.4); $v_{max.}$ 1 720 and 1 703 cm⁻¹; δ 0.84 (13β-Me), 0.9 (9β-Me), 2.02 (OAc), 2.88 (1 H, dd, J 14 and 12 Hz, 4α-H), 4.33br (1 H, $W_{\frac{1}{2}}$ 8 Hz, 2β-H), and 4.7 (1 H, dd, J 9 and 7 Hz, 17α-H) (Found: C, 61.35; H, 7.45%; M^+, 410, 412), followed by the 4α-*bromo-compound* (7) (0.035 g), m.p. 125—138 °C (from methanol); $[\alpha]_D$ +103° (c 0.4); $v_{max.}$ 1 720 and 1 703 cm⁻¹; δ 0.82 (13β-Me), 0.89 (9β-Me), 2.02 (OAc), 3.17 (1 H, dt, J 14, 14, and 6 Hz, 2α-H), 4.13 (1 H, t, J 2.5 Hz, 4β-H), and 4.74 (1 H, dd, J 8.5 and 7.5 Hz, 17α-H) (Found: C, 61.0; H, 7.4%; M^+, 410, 412).

T.l.c. examination revealed that the four bromo-ketones (5)—(8) underwent partial isomerisation during chromatography and upon heating to their m.p.s. Pure samples were obtained by careful crystallisation of column eluates.

TABLE 6

Fractional co-ordinates with e.s.d. in parentheses

(a) 3-Ketone (3b)

Atom	x/a	y/b	z/c
O(1)	−3 076(4)	1 278(5)	−1 656(4)
O(2)	815(3)	311(3)	5 990(4)
O(3)	−6(4)	−859(4)	7 096(4)
C(1)	−1 318(5)	192(5)	375(6)
C(2)	−1 626(5)	671(6)	−813(6)
C(3)	−2 531(4)	1 294(5)	−797(6)
C(4)	−2 744(5)	1 922(5)	303(6)
C(5)	−2 462(4)	1 393(5)	1 480(5)
C(6)	−2 653(4)	2 143(5)	2 540(5)
C(7)	−1 861(4)	2 943(5)	2 710(5)
C(8)	−872(4)	2 416(4)	2 863(4)
C(9)	−595(3)	1 723(4)	1 746(4)
C(10)	−1 445(3)	919(4)	1 494(5)
C(11)	343(4)	1 101(5)	2 006(5)
C(12)	383(4)	476(5)	3 179(5)
C(13)	165(3)	1 218(4)	4 231(4)
C(14)	−823(4)	1 752(4)	3 995(4)
C(15)	−1 059(5)	2 274(6)	5 200(6)
C(16)	−635(5)	1 493(5)	6 117(6)
C(17)	−59(4)	674(5)	5 418(5)
C(18)	1 005(5)	2 048(5)	4 411(6)
C(19)	−368(5)	2 482(5)	706(6)
C(20)	741(5)	−446(5)	6 814(6)
C(21)	1 704(7)	−752(8)	7 332(9)
H(1,1)	−682(39)	15(38)	279(43)
H(1,2)	−1 844(36)	−321(39)	499(44)
H(2,1)	−1 715(32)	−39(38)	−1 546(41)
H(2,2)	−1 152(36)	1 129(39)	−938(43)
H(4,1)	−2 499(35)	2 594(40)	203(42)
H(4,2)	−3 410(37)	2 299(37)	372(41)
H(5)	−2 882(35)	829(40)	1 558(42)
H(6,1)	−2 675(34)	1 557(41)	3 101(43)
H(6,2)	−3 261(35)	2 535(36)	2 330(42)
H(7,1)	−1 744(33)	3 447(39)	2 130(44)
H(7,2)	−2 014(34)	3 537(39)	3 373(43)
H(8)	−418(34)	3 020(41)	2 871(42)
H(10)	−1 347(35)	328(37)	2 195(44)
H(11,1)	796(38)	1 562(37)	1 956(41)
H(11,2)	522(33)	689(37)	1 302(48)
H(12,1)	−43(36)	−57(42)	3 238(44)
H(12,2)	1 087(36)	199(36)	3 244(42)
H(14)	−1 291(34)	1 153(40)	3 898(43)
H(15,1)	−831(37)	2 817(44)	5 126(43)
H(15,2)	−1 670(39)	2 365(37)	5 363(41)
H(16,1)	−1 147(33)	1 088(37)	6 682(43)
H(16,2)	−276(35)	1 975(38)	6 484(43)
H(17)	−441(35)	−18(40)	5 330(43)
H(18,1)	855(39)	2 531(45)	4 900(49)
H(18,2)	1 124(35)	2 637(41)	3 650(49)
H(18,3)	1 556(40)	1 618(40)	4 482(48)
H(19,1)	−48(39)	2 085(44)	185(52)
H(19,2)	−854(43)	2 943(46)	437(49)
H(19,3)	43(39)	2 972(45)	920(46)
H(21,1)	1 640(38)	−208(46)	7 797(51)
H(21,2)	1 830(40)	−1 325(56)	7 076(49)
H(21,3)	2 308(40)	−590(43)	6 850(50)

(b) 2α-Bromo-3-ketone (11) *

Atom	x/a	y/b	z/c
Br	9 693(1)	5 000	7 967(1)
O(1)	10 333(7)	7 111(16)	6 150(9)
O(2)	1 527(5)	5 820(11)	1 223(6)
O(3)	1 738(6)	5 784(13)	3 270(7)
C(1)	7 613(8)	5 713(14)	5 763(9)
C(2)	8 805(8)	5 121(25)	6 087(9)
C(3)	9 416(11)	6 365(19)	5 523(12)
C(4)	8 733(11)	6 679(20)	4 133(12)
C(5)	7 534(11)	7 386(19)	3 830(12)
C(6)	6 846(12)	7 819(22)	2 391(14)
C(7)	6 380(10)	6 065(19)	1 585(12)
C(8)	5 590(7)	5 012(24)	2 003(8)
C(9)	6 236(8)	4 436(13)	3 477(9)
C(10)	6 846(8)	6 128(15)	4 325(9)
C(11)	5 335(10)	3 664(18)	3 893(10)
C(12)	4 234(9)	4 691(17)	3 523(9)

(Table 6 Continued)

Atom	x/a	y/b	z/c
C(13)	3 631(7)	5 134(21)	2 068(8)
C(14)	4 514(8)	6 111(16)	1 765(9)
C(15)	3 813(11)	6 934(21)	410(12)
C(16)	2 692(15)	7 429(25)	406(18)
C(17)	2 672(11)	6 595(19)	1 591(12)
C(18)	3 163(12)	3 353(20)	1 288(14)
C(19)	7 064(11)	2 885(18)	3 573(12)
C(20)	1 144(9)	5 574(17)	2 135(12)
C(21)	−85(10)	4 992(30)	1 553(13)
H(1,1)	7 243(75)	4 522(140)	6 181(84)
H(1,2)	7 702(76)	7 195(143)	6 210(89)
H(2,1)	8 943(80)	3 639(149)	5 797(89)
H(4,1)	8 774(82)	5 835(139)	3 750(95)
H(4,2)	8 937(89)	7 816(173)	3 855(98)
H(5)	7 639(81)	8 387(158)	4 484(94)
H(6,1)	6 285(84)	8 869(151)	2 171(90)
H(6,2)	7 324(89)	7 984(160)	2 257(98)
H(7,1)	7 016(74)	5 345(170)	1 684(76)
H(7,2)	5 996(76)	6 628(145)	650(98)
H(8)	5 219(81)	3 773(147)	1 515(88)
H(10)	6 107(84)	7 061(146)	4 327(91)
H(11,1)	5 802(78)	3 344(146)	4 947(94)
H(11,2)	5 134(79)	2 318(152)	3 431(94)
H(12,1)	3 740(82)	4 212(143)	3 769(92)
H(12,2)	4 473(83)	5 904(157)	3 927(88)
H(14)	4 825(80)	7 320(150)	2 349(95)
H(15,1)	3 859(81)	6 152(152)	−47(93)
H(15,2)	4 379(81)	8 043(156)	445(95)
H(16,1)	2 145(82)	6 966(157)	−326(94)
H(16,2)	2 463(85)	5 895(162)	551(95)
H(17)	2 507(92)	5 981(151)	1 971(104)
H(18,1)	3 727(85)	2 426(154)	1 434(91)
H(18,2)	2 815(79)	2 493(152)	2 026(92)
H(18,3)	2 637(108)	3 349(161)	338(123)
H(19,1)	7 122(80)	2 102(155)	4 195(103)
H(19,2)	7 722(90)	3 140(152)	3 326(98)
H(19,3)	6 311(83)	1 958(148)	2 840(92)
H(21,1)	−571(81)	6 045(164)	1 202(97)
H(21,2)	−402(81)	4 562(145)	728(93)
H(21,3)	−596(75)	4 431(132)	2 057(86)

(c) 2β-Bromo-3-ketone (12) *

Atom	x/a	y/b	z/c
Br	2 670(1)	−1 696(2)	5 879(3)
O(1)	2 031(6)	463(12)	5 767(21)
O(2)	6 634(5)	1 124(11)	2 987(16)
O(3)	6 580(7)	600(12)	77(18)
C(1)	3 657(8)	−119(15)	6 284(26)
C(2)	3 031(9)	−317(16)	5 267(27)
C(3)	2 592(10)	596(14)	5 582(28)
C(4)	2 886(9)	1 677(19)	5 582(30)
C(5)	3 512(8)	1 682(16)	4 543(26)
C(6)	3 753(9)	2 799(16)	4 133(34)
C(7)	4 199(9)	3 263(19)	5 498(29)
C(8)	4 723(8)	2 490(14)	5 961(31)
C(9)	4 477(8)	1 411(15)	6 782(25)
C(10)	3 985(8)	897(14)	5 472(24)
C(11)	5 010(11)	579(19)	7 107(35)
C(12)	5 458(9)	433(16)	5 493(28)
C(13)	5 693(8)	1 515(15)	4 815(22)
C(14)	5 145(9)	2 218(14)	4 359(28)
C(15)	5 416(10)	3 180(19)	3 278(29)
C(16)	5 950(13)	2 688(19)	2 192(36)
C(17)	5 993(9)	1 472(17)	2 896(26)
C(18)	6 159(9)	2 038(16)	6 145(30)
C(19)	4 191(11)	1 635(21)	8 697(29)
C(20)	6 883(10)	734(18)	1 421(35)
C(21)	7 568(9)	528(17)	1 648(29)
H(1,1)	3 979(64)	−921(112)	6 453(196)
H(1,2)	3 503(64)	231(112)	7 586(214)
H(2,1)	3 150(64)	−534(110)	3 855(222)
H(4,1)	2 637(67)	2 536(116)	5 208(183)
H(4,2)	2 987(65)	1 971(128)	6 519(209)
H(5)	3 363(70)	1 303(112)	3 412(211)
H(6,1)	3 373(61)	3 423(111)	4 361(195)
H(6,2)	3 953(71)	2 862(119)	3 029(228)

* The configuration defined by these co-ordinates is different from the known absolute configuration.

TABLE 6 (Continued)
(c) 2β-Bromo-3-ketone (12)   (Continued)

Atom	x/a	y/b	z/c
H(7,1)	4 353(65)	3 946(126)	4 883(198)
H(7,2)	3 925(69)	3 596(119)	6 234(216)
H(8)	4 994(69)	2 883(113)	6 958(215)
H(10)	4 121(63)	633(108)	4 427(235)
H(11,1)	5 177(67)	897(112)	8 066(202)
H(11,2)	4 805(65)	−274(117)	7 537(210)
H(12,1)	5 179(64)	−139(111)	4 534(205)
H(12,2)	5 817(67)	−33(113)	6 275(217)
H(14)	4 827(63)	1 808(120)	3 460(189)
H(15,1)	5 541(70)	3 755(126)	3 788(215)
H(15,2)	5 058(69)	3 744(116)	2 972(203)
H(16,1)	6 420(68)	3 055(116)	2 151(200)
H(16,2)	5 904(84)	2 369(143)	1 990(230)
H(17)	5 789(70)	813(120)	2 120(217)
H(18,1)	6 360(65)	2 778(114)	5 590(214)
H(18,2)	6 562(65)	1 768(124)	6 565(179)
H(18,3)	5 907(68)	2 454(115)	7 389(212)
H(19,1)	4 176(63)	885(126)	9 346(222)
H(19,2)	3 789(69)	2 113(115)	8 732(20)
H(19,3)	4 410(65)	2 277(117)	9 408(232)
H(21,1)	7 799(65)	221(120)	454(213)
H(21,2)	7 650(66)	−14(118)	2 770(229)
H(21,3)	7 749(80)	1 318(125)	1 972(218)

Dehydrobromination of the 2-Bromo-3-ketones, (5) and (6).—
(a) A mixture of the 2α-bromo-3-ketone (5) (0.07 g), lithium carbonate (0.1 g), and lithium bromide (0.1 g) in dimethyl-formamide (2.5 ml) under nitrogen was kept at 110 °C for 3 h. The product was isolated by extraction with ethyl acetate, and chromatographed on silica gel (7 g) with ethyl acetate–hexane (1 : 3) to give 17β-acetoxy-9-methyl-5β,9β,10α-estr-1-en-3-one (9) (0.034 g), m.p. 127—129 °C (from acetone–hexane); $[\alpha]_D$ +11° (c 0.6); $\nu_{max.}$ 1 727, 1 675, and 1 609 cm^{-1}; $\lambda_{max.}$ 232 nm (ε 9 519); δ 0.83 (13β-Me), 0.92 (9β-Me), 2.01 (OAc), 4.68 (1 H, dd, J 8.5 and 7.5 Hz, 17α-H), 5.98 (1 H, dd, J 10 and 3 Hz, 2-H), and 6.95 (1 H, dd, J 10 and 1.5 Hz, 1-H) (Found: C, 76.3; H, 9.2%; M^+, 330. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%; M, 330). Further elution gave the 4-en-3-one (1b) (0.002 g), m.p. and mixed m.p. 176—179 °C (from ethanol).

(b) Similar treatment of the 2β-bromo-3-ketone (6) gave the same result.

Dehydrobromination of the 4-Bromo-3-ketones, (7) and (8).—
(a) Treatment of the 4α-bromo-3-ketone (7) (2 mg) with lithium carbonate (3 mg) and lithium bromide (3 mg) in dimethylformamide (0.2 ml), as described in the preceding experiments, gave the 4-en-3-one (1b), contaminated with traces of the 1-en-3-one (9) (t.l.c.).

(b) Similar treatment of the 4β-bromo-3-ketone (8) gave the same result.

Treatment of Bromo-ketones with Hydrogen Bromide.—
Each of the pure bromo-ketones (5)—(8), (1 mg) was dissolved in acetic acid (0.1 ml) and treated with hydrogen bromide in acetic acid (40%; 20 μl). T.l.c. monitoring revealed that (5) and (6) afforded similar mixtures of (5) + (6), whereas (7) and (8) afforded similar mixtures of (7) + (8), after 30 min at 25 °C. The distribution of each pair of epimers in the reaction mixtures was similar to that found in the crude bromination product of (2b); no further changes were detected after 24 h.

Enol Acetylation of the 3-Oxo-5β-compound (2b).—A solution of the ketone (2b) (0.06 g) in isopropenyl acetate (5 ml) containing sulphuric acid (5 μl) was refluxed under nitrogen for 1 h. Water was added and the product was extracted into ether. The extract was washed with aqueous sodium hydrogen carbonate and aqueous sodium chloride

and evaporated *in vacuo*. Chromatography of the product on silica gel (6 g) with ethyl acetate–hexane (1 : 4) gave an oil (0.035 g), shown by g.l.c. to be a *ca.* 57 : 43 mixture of the 2- and 3-en-3-yl acetates (10), $\nu_{max.}$ 1 737br cm^{-1}; m/e 374 (M^+); δ 0.79 (13β-Me), 0.89 (' 1.3H,' s, 9β-Me of 3-ene), 0.91 (' 1.7H,' s, 9β-Me of 2-ene), 1.99 (OAc), 2.06 (OAc), 4.67 (1 H, t, J 8.5 Hz, 17α-H), 5.11 (' 0.43H,' t, J 1.5 Hz, 4-H of 3-ene), and 5.29br (' 0.57H,' $W_{\frac{1}{2}}$ 8 Hz, 2-H of 2-ene). Further elution afforded starting material (2b) (0.019 g).

Bromination of the 3-Oxo-5α-compound (3b).—The ketone (3b) (0.115 g) was brominated with pyridinium hydrobromide perbromide (0.12 g), as described for (2b). Chromatography of the product under pressure on silica gel (Merck prepacked Kieselgel 60, size B) with ethyl acetate–hexane (1 : 9) gave the following fractions: 17β-acetoxy-2α-bromo-9-methyl-5α,9β,10α-estran-3-one (11) (0.069 g), m.p. 135—150 °C (from acetone–methanol); $[\alpha]_D$ −26° (c 0.8); $\nu_{max.}$ 1 728br cm^{-1}; δ (C_6D_6) 0.67 and 0.68 (13β- and 9β-Me), 1.71 (OAc), 4.51 (1 H, dd, J 12 and 6.5 Hz, 2β-H), and 4.67 (1 H, dd, J 9 and 8 Hz, 17α-H) (Found: C, 61.5; H, 7.5%; M^+, 410, 412); the 4α-bromo-compound (13) (0.007 g), m.p. 157—166 °C (from acetone–hexane); $[\alpha]_D$ +60° (c 0.3); $\nu_{max.}$ 1 727br cm^{-1}; δ (C_6D_6) 0.54 (9β-Me), 0.64 (13β-Me), 1.71 (OAc), 4.36 (1 H, d, J 12 Hz, 4β-H), and 4.71 (1 H, dd, J 9 and 8 Hz, 17α-H) (Found: C, 61.45; H, 7.7%; M^+, 410, 412); and the 2β-bromo-compound (12) (0.015 g), m.p. 95—100 °C (from hexane); $[\alpha]_D$ + 54° (c 0.6); $\nu_{max.}$ 1 728br cm^{-1}; δ (C_6D_6) 0.56 (9β-Me), 0.64 (13β-Me), 1.71 (OAc), 4.41 (1 H, dd, J 13 and 7 Hz, 2α-H), and 4.75 (1 H, dd, J 9 and 8 Hz, 17α-H) (Found: C, 61.6; H, 7.7%; M^+, 410, 412).

The facility with which the compounds underwent isomerisation during chromatography or upon heating necessitated careful handling of column fractions, and recrystallisation of samples below 40 °C.

TABLE 7

Bond lengths (Å) between non-hydrogen atoms, with estimated standard deviations in parentheses, for compounds (3b), (11), and (12)

Bond	(3b)	(11)	(12)	Mean
Br–C(2)		1.965(9)	1.93(2)	1.948(8)
O(1)–C(3)	1.222(6)	1.22(1)	1.22(2)	1.221(5)
O(2)–C(17)	1.440(6) *	1.50(2)	1.44(2)	1.460(6)
O(2)–C(20)	1.318(7) *	1.36(1)	1.36(3)	1.346(6)
O(3)–C(20)	1.197(7)	1.21(1)	1.20(2)	1.202(6)
C(1)–C(2)	1.516(9)	1.49(1) *	1.56(2)	1.522(6)
C(1)–C(10)	1.551(7)	1.55(1)	1.56(2)	1.554(6)
C(2)–C(3)	1.473(8) *	1.53(2)	1.49(2)	1.498(7)
C(3)–C(4)	1.484(8)	1.47(2)	1.48(3)	1.478(8)
C(4)–C(5)	1.521(8)	1.53(2)	1.55(3)	1.534(8)
C(5)–C(6)	1.528(7)	1.54(2)	1.51(2)	1.526(6)
C(5)–C(10)	1.527(7) *	1.56(2)	1.56(2)	1.549(6)
C(6)–C(7)	1.490(7) *	1.55(2)	1.50(3)	1.513(6)
C(7)–C(8)	1.527(7)	1.52(2)	1.52(3)	1.522(6)
C(8)–C(9)	1.564(6)	1.59(1)	1.56(2)	1.571(5)
C(8)–C(14)	1.510(7)	1.54(2)	1.53(3)	1.527(6)
C(9)–C(10)	1.567(6)	1.57(1)	1.57(2)	1.569(5)
C(9)–C(11)	1.539(7)	1.56(2)	1.56(3)	1.553(6)
C(9)–C(19)	1.528(7)	1.54(2)	1.57(3)	1.546(6)
C(11)–C(12)	1.525(7)	1.51(2)	1.54(3)	1.525(6)
C(12)–C(13)	1.523(7)	1.55(1)	1.52(3)	1.531(6)
C(13)–C(14)	1.542(6) *	1.52(2)	1.50(2)	1.521(6)
C(13)–C(17)	1.520(7) *	1.58(2)	1.56(2)	1.553(6)
C(13)–C(18)	1.566(8)	1.56(2)	1.54(2)	1.555(7)
C(14)–C(15)	1.531(8)	1.55(2)	1.55(3)	1.544(8)
C(15)–C(16)	1.527(8)	1.50(2)	1.53(3)	1.519(8)
C(16)–C(17)	1.509(7) *	1.50(2)	1.60(3)	1.536(6)
C(20)–C(21)	1.503(10)	1.50(2)	1.50(3)	1.501(9)

* These bond parameters are significantly different from the mean.

Dehydrobromination of the 2-Bromo-3-ketones, (11) *and* (12).—(*a*) Treatment of the 2α-bromo-3-ketone (11) (0.045 g) with lithium carbonate and lithium bromide in dimethylformamide as described in previous experiments, and chromatography of the product on silica gel (5 g) with ethyl acetate–hexane (3 : 7) gave 17β-*acetoxy*-9-*methyl*-5α,9β,10α-*estr*-1-*en*-3-*one* (14) (0.035 g), m.p. 158—160 °C (from acetone–hexane); $[\alpha]_D$ —124° (*c* 0.6); $\nu_{max.}$ 1 727, 1 671, and 1 615 cm^{-1}; $\lambda_{max.}$ 235 nm (ε 9 208); δ 0.83 (13β-Me), 1.0 (9β-Me), 2.02 (OAc), 4.71 (1 H, dd, *J* 9 and 7.5 Hz, 17α-H), 6.11 (1 H, dd, *J* 10 and 1.5 Hz, 2-H), and 6.99 (1 H, dd, *J* 10 and 6 Hz, 1-H) (Found: C, 76.1; H, 9.0%; M^+, 330).

(*b*) Similar treatment of the 2β-bromo-3-ketone (12) gave the same result.

Dehydrobromination of the 4α-*Bromo*-3-*ketone* (13).— Dehydrobromination of the bromo-ketone (13) (0.008 g) under the conditions already described, and chromatography of the product on silica gel (1 g) with ethyl acetate–hexane (1 : 1) gave the 4-en-3-one (1b) (0.005 g), m.p. and mixed m.p. 176—179 °C.

Treatment of Bromo-ketones with Hydrogen Bromide.— Each of the pure bromo-ketones (11)—(13) (1 mg) was treated with hydrogen bromide in acetic acid as already described. In the case of (11) and (12), a *ca.* 4 : 1 ratio of (11) + (12) was present after 30 min (t.l.c.); after 24 h the additional presence of (13) was detected in small amount. The 4α-bromo-compound (13) failed to undergo significant isomerisation during 24 h.

Enol Acetylation of the 3-*Oxo*-5α-*compound* (3b).—The ketone (3b) (0.05 g) was treated with isopropenyl acetate as described previously, and the product was chromatographed on silica gel (5 g) with ethyl acetate–hexane (1 : 4) to give (15) (0.03 g) as an oil, $\nu_{max.}$ 1 730br cm^{-1}; *m/e* 374 (M^+); δ

* Final observed and calculated structure factors and atom thermal parameters are listed in Supplementary Publication No. SUP 22233 (26 pp., 1 microfiche). For details, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

0.78 (13β-Me), 0.97 (9β-Me), 1.99 (OAc), 2.05 (OAc), 4.67 (1 H, t, *J* 8 Hz, 17α-H), and 5.29br (*ca.* 0.8H, $W_{\frac{1}{2}}$ 8 Hz, 2-H). G.l.c. showed a single peak.

Crystallography.—After preliminary photographic examination accurate cell constants were determined and data collected on a Philips PW 1100 automatic diffractometer at the National Physical Research Laboratory by use of graphite–crystal monochromated Mo-K_α radiation. Data reduction consisted of compensation for background, merging of equivalent reflections, and Lorentz polarisation corrections. The structure of the parent compound (3b) was solved by direct methods and those of the bromoketones (11) and (12) by standard heavy-atom techniques. After partial anisotropic refinement by full-matrix least squares all hydrogen atoms were located on difference maps. Convergence was considered complete when all parameter shifts were <0.01σ, at which stage difference-Fourier excursions from zero nowhere exceeded 0.4 eÅ^{-3}. No attempt was made to redetermine absolute configuration and where necessary parameter signs were simply changed to conform to the known configuration. The program SHELX 76 [21] was used for structure analyses, and scattering factors were taken from ref. 22. Details of the structure determinations and refinements are summarised in Table 5.*

Refined atom parameters are listed in Table 6 according to the atomic numbering scheme illustrated in Figure 2. Hydrogen atoms are numbered according to the numbers of the carbon skeleton to which they are attached. Calculated bond lengths are listed in Table 7, valence angles in Table 4, and torsion angles in Table 3.

[21] G. M. Sheldrick, personal communication, 1976.
[22] 'International Tables for *X*-Ray Crystallography,' vol. 4, Kynoch Press, Birmingham, 1974.