624. *Steroids and Walden Inversion. Part LII.* The Bromination of 5α-Cholestan-2-one.*

By C. W. Shoppee and T. E. Bellas.

Acid-catalysed monobromination of 5α-cholestan-2-one at 20° gave 3α-bromo-5α-cholestan-2-one; dibromination at 85° gave 1α,3β-dibromo-5α-cholestan-2-one; and tribromination gave 1α,3,3-tribromo-5α-cholestan-2-one. 1α,3α-Dibromo-5α-cholestan-2-one has been prepared. Base-catalysed dibromination of 5α-cholestan-2-one at 90° gave 3,3-dibromo-5α-cholestan-2-one, which was dehydrobrominated to 3-bromo-5α-cholest-3-en-2-one and cholesta-3,5-dien-2-one.

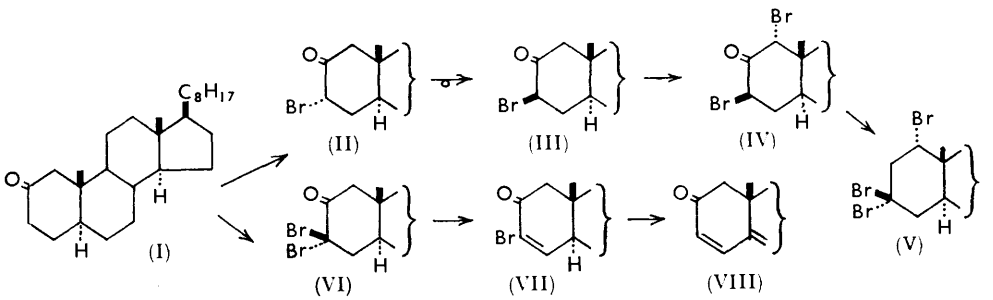
The molecular geometry, as disclosed by various optical properties, of a set of *gem*-dibromo-5α-cholestanones is considered.

Early in 1960 we commenced work on the bromination of 5α-cholestan-2-one. Through a letter from Professor C. Djerassi (Sept. 30th, 1960) we learnt of the work of Djerassi

* Part LI, *J.*, 1962, 2684.

and Nakano [1] on the monobromination of this ketone, and, by the courtesy of Professor Djerassi, received a copy of the paper before its publication. Accordingly, we confined our subsequent investigation to polybromination of the ketone.

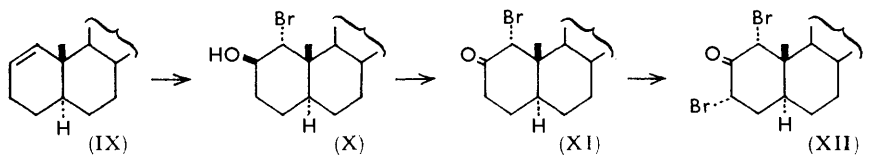
Monobromination of 5α-cholestan-2-one (I) in acetic acid in the presence of hydrogen bromide proceeded rapidly, to give 3α-bromo-5α-cholestan-2-one (II), previously described by Alt and Barton [2] and by Bird, Norymberski, and Woods,[3] and obtained by Djerassi and Nakano [1] from the enol acetate of the ketone (I) by kinetically controlled bromination; the 3α-bromo-compound is partly converted into 3β-bromo-5α-cholestan-2-one (III) by equilibration with hydrogen bromide in acetic acid at 20° (cf. ref. 1).



Further bromination of 3α-bromo-5α-cholestan-2-one (II) did not occur in acetic acid at 20°, but at 90° gave 1α,3β-dibromo-5α-cholestan-2-one (IV). It seems probable that the initial product is 3,3-dibromo-5α-cholestan-2-one (VI) which, in the presence of hydrogen bromide, rearranges to 1α,3β-dibromo-5α-cholestan-2-one (IV; 1α-Br, *ax*); this may be contrasted with the rearrangement of 2,2-dibromo-5α-cholestan-3-one [4,5] in the presence of hydrogen bromide to 2α,4α-dibromo-5α-cholestan-3-one (4α-Br, *eq*). Bromination of the ketone (I) or of 1α,3β-dibromo-5α-cholestan-2-one (IV) with an excess of bromine in acetic acid at 90° furnished 1α,3,3-tribromo-5α-cholestan-2-one (V).

Bromination of 5α-cholestan-2-one (I) in acetic acid in the presence of potassium acetate at 90° gave 3,3-dibromo-5α-cholestan-2-one (VI), which on dehydrobromination with lithium bromide and lithium carbonate in dimethylformamide [6] for 5 min. afforded 3-bromo-5α-cholest-3-en-2-one (VII) and after 3 hr. yielded cholesta-3,5-dien-2-one (VIII).

We have also prepared 1α,3α-dibromo-5α-cholestan-2-one (XII). Treatment of 5α-cholest-1-ene [7,8] (IX) with *N*-bromosuccinimide in t-butyl alcohol containing perchloric acid [9] gave 1α-bromo-5α-cholestan-2β-ol [1] (X), which is oxidised by chromic acid and



sulphuric acid in acetone [10] to 1α-bromo-5α-cholestan-2-one (XI); this, on monobromination in acetic acid in the presence of hydrobromic acid at 20°, gave 1α,3α-dibromo-5α-cholestan-2-one (XII).

[1] Djerassi and Nakano, *Chem. and Ind.*, 1960, 1385; Nakano, Hasegara, and Djerassi, *Chem. and Pharm. Bull.* (*Japan*), 1963, in the press.
[2] Alt and Barton, *J.*, 1954, 4284.
[3] Bird, Norymberski, and Woods, *J.*, 1957, 4149.
[4] Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 2125.
[5] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[6] Joly and Warnant, *Bull. Soc. chim. France*, 1958, 367.
[7] Henbest and Wilson, *J.*, 1956, 3289; Broome, Brown, Roberts, and White, *J.*, 1960, 1406.
[8] Shoppee, Roy, and Goodrich, *J.*, 1961, 1583.
[9] Henbest and Wilson, *J.*, 1959, 4136.
[10] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.

The ultraviolet, infrared, and optical rotatory dispersion characteristics of the various bromo-derivatives of 5α-cholestan-2-one are collected in Table 1; they are consistent with the formulæ assigned.

TABLE 1.

Absorption properties of bromocholestanones.

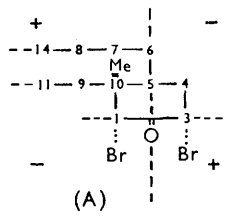
	Compound	$\lambda_{max.}$ (mμ) in cyclohexane	Δλ (mμ)	$\nu_{max.}$ (cm.$^{-1}$) in CCl_4	in $CHCl_3$	Δν (cm.$^{-1}$)	Hal. config.
(I)	5α-Cholestan-2-one	288 *	—	1711	1704	—	—
(XII)	1α-Bromo-2-one	309	+21	1715	1707	+4, +3	*ax*
(II)	3α-Bromo-2-one	312	+24	1715	1704	+4, 0	*ax*
(III)	3β-Bromo-2-one	282 †	−6	—	1718	+14	*eq*
(XIII)	1α,3α-Dibromo-2-one ...	339	+51	1714		+3	*ax, ax*
(IV)	1α,3β-Dibromo-2-one ...	304	+16	1736		+25	*ax, eq*
(VI)	3,3-Dibromo-2-one	305	+17	1731		+20	*eq, ax*
(V)	1α,3,3-Tribromo-2-one	329	+41	1731		+20	*ax, eq, ax*

* In EtOH, $\lambda_{max.}$ 280 mμ. † In dioxan.

	Cotton curve sign and molar amplitude, 10^{-2} *a*	Molar dispersion contribution of subst., Δ*a*	Posn. of 1st trough (or peak) λ* (mμ)	Δλ * (mμ)	Hal. config.
(I)	+102°	—	310	—	—
(XII)	−117	−219° (1α)	328	+18	*ax*
(II)	+260	+158 (3α)	335	+25	*ax*
(III)	+120	−18 (3β)	318	+8	*eq*
(XIII)	+20	−241 (1α), +137 (3α)	350	+40	*ax, ax*
(IV)	−128	−248 (1α), −11 (3β)	328	+18	*eq, ax*
(VI)	+252	+132 (3α), −8 (3β)	334	+24	*eq, ax*
(V)	+142	[−100 (1α), +250 (3α),] +122 (3β)	365	+55	*ax, eq, ax*

Δλ* represents the difference(mμ) between the first trough (peak) of the derivative and the parent ketone.

In the 1α,3,3-tribromo-ketone (V) ring A is probably distorted; the calculated amplitude of the Cotton curve should be ~+40° [parent ketone (+102°) +Δ$a_{1α\text{-Br}}$ (−220°) +Δ$a_{3α\text{-Br}}$ (+158°) +Δ$a_{3β\text{-Br}}$ (0)], whereas the experimental figure is +140°, and this discrepancy is reflected in the molar dispersion contributions.



(A)

1α,3α-Dibromo-5α-cholestan-2-one (XII) is a further example of a rare type of compound exhibiting competing Cotton effects.[11] The secondary axial 1α-bromine atom controls the situation and superimposes its negative Cotton effect contribution, Δ*a* −219°, on the positive Cotton effect contribution, Δ*a* +158°, of the secondary axial 3α-bromine atom, reducing the molecular amplitude of the compound to $10^{-2}a$ −82° (calc., −60°). The negative influence of the 1α-bromine atom is dominant despite the fact that the angular 19-methyl group and the rest of the nuclear structure lie in the upper positive quadrant (cf. 5α-cholestan-2-one, $10^{-2}a$ +102°) defined by the octant rule [12] (see A).

Recently, we observed [11] that the spectroscopic properties of 7,7-dibromo-5α-cholestan-6-one indicate that the axial 7α-bromine atom simulates the usual behaviour of an equatorial bromine atom in an α-bromo-ketone, and we suggested that ring B in this dibromo-ketone is considerably distorted. The spectroscopic properties of 2,2-dibromo-5α-cholestan-1-one,[9,13,14] 3,3-dibromo-5α-cholestan-2-one, 2,2-dibromo-5α-cholestan-3-one,[5] and 3,3-dibromo-5α-cholestan-4-one [15] are set out in Table 2.

[11] Shoppee and Johnston, *J.*, 1962, 1246.
[12] Moffitt, Woodward, Klyne, and Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[13] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.
[14] Sigg and Tamm, *Helv. Chim. Acta*, 1960, **43**, 1402.
[15] Shoppee and Lack, *J.*, 1961, 3271.

TABLE 2.

Compound	Hal. confign.	$\Delta\lambda$ (mμ)	$\Delta\nu$ (cm.$^{-1}$)	Cotton effect sign and molar amplitude $10^{-2}a$	Molar dispersion contribn. of subst., Δa	Posn. of 1st trough (or peak) λ^* (mμ)	$\Delta\lambda$ * (mμ)	Ref.‡
5α-Cholestan-1-one								
2α-Bromo-	*eq*	−5,* −9	+15, +20	+5°, +10°	+4°, +9° (2α)	290, 295	−42, −43	8, 13, 14
2β-Bromo-	*ax*	+31	−3	−126	−127 (2β)	345	+14, +7	1, 14
2,2-Dibromo-	*eq, ax*	+23 *	+15	−151	−152 (2β)	345	+7, +13	8, 14
5α-Cholestan-2-one								
3β-Bromo-	*eq*	—	+14	+120	−18 (3β)	318	+8	1
3α-Bromo-	*ax*	+24	0, −5	+262, +260	+162, +158 (3α)	335	+25	1
3,3-Dibromo-	*eq, ax*	+17	+20	+252	+150 (3α)	334	+24	
5α-Cholestan-3-one								
2α-Bromo-	*eq*	−4	+15	+63	−2 (2α)	310	+3	16
2β-Bromo-	*ax*	+24	+2	+120 †	+55 † (2β)			3, *a*
2,2-Dibromo-	*eq, ax*	+8	+17	+186	+121 (2β)	330	+23	16
5α-Cholestan-4-one								
3β-Bromo	*eq*	−5	+20	−52	+42 (3β)	313	+6	
3α-Bromo-	*ax*	+24	0	−202	−108 (3α)	332	+24	15
3,3-Dibromo-	*eq, ax*	+20	+17	−194	−100 (3α)	325	+17	15

* The values given [8] for 5α-cholestan-1-one, its 2α-bromo-, and 2,2-dibromo-derivative for $\lambda_{max.}$ (in EtOH) require correction for a subsequently discovered scale displacement on the Uvispek instrument formerly used; the corrected values are 287, 282, and 310 mμ, which are consistent with values 297, 288, and 320 mμ found in hexane.[13, 14] † Provisional value. ‡ (*a*) Klyne, personal communication.

$10^{-2}a$ (standard values): 5α-cholestan-1-one, +1°, -2-one, +102°; -3-one, +65°; -4-one, −94°.

In the four *gem*-dibromo-ketones, the equatorial bromine atoms make the normal contribution $\Delta\nu = +15$—20 cm.$^{-1}$ to the infrared stretching frequency of the carbonyl group; except in the case of 2,2-dibromo-5α-cholestan-3-one,[16] the axial bromine atoms likewise make the normal contribution $\Delta\lambda = +17$—23 mμ to the wavelength of the ultraviolet absorption maximum of the carbonyl group. It thus appears that, unlike ring B in 7,7-dibromo-5α-cholestan-6-one, ring A in these *gem*-dibromo-ketones is not appreciably distorted.

It is of interest that 6,6-dibromo-7-oxo-5α-cholestan-3β-yl acetate ($\lambda_{max.}$ 304 mμ; log ε 2·1), originally prepared by Barr, Heilbron, Jones, and Spring [17] and regarded by Cookson [16] as the 6α,8β-dibromo-ketone because he observed the normal increment $\Delta\lambda = +17$ for an axial bromine atom ($\lambda_{max.}$ 304 mμ; log ε 2·2), has been shown by Takeda and Komeno [18] to be the 6,6-dibromo-ketone ($\lambda_{max.}$ 302 mμ; log ε 2·08; $\Delta\lambda + 15$. $\nu_{max.}$ 1724 cm.$^{-1}$; $\Delta\nu + 15$ cm.$^{-1}$). These values suggest that here ring B is not seriously distorted.

EXPERIMENTAL

For general experimental directions see *J.*, 1959, 345. M. p.s were determined on a Kofler block and are corrected. $[\alpha]_D$ refer to $CHCl_3$ solutions at room temperature. Ultraviolet absorption spectra were determined for cyclohexane solutions, unless otherwise stated, on a Perkin-Elmer 4000 A model spectrophotometer. Infrared absorption spectra were measured for CCl_4 solutions by use of a Perkin-Elmer model 221 spectrophotometer. Chromatography was on silica gel (Davison 40—200 mesh) or aluminium oxide (Spence's type H, activity II).

3α-Bromo-5α-cholestan-2-one (II).—(*a*) 5α-Cholestan-2-one [19] (192 mg.) in acetic acid (10 c.c.) was treated with bromine (1·1 mol) and a solution of hydrogen bromide in acetic acid (1 drop) at 20°. The colour was discharged after 20 min., and after 1 hr. the solution was poured into

[16] Cookson, *J.*, 1954, 282.
[17] Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334.
[18] Takeda and Komeno, *Chem. and Pharm. Bull.* (*Japan*), 1956, **4**, 432.
[19] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.

ether and worked up in the usual manner. Chromatography of the product on silica gel (25 g.) in hexane and elution with ether–hexane (1 : 99) gave 3α-bromo-5α-cholestan-2-one, m. p. 151—153° (from chloroform–methanol), $\lambda_{max.}$ 312 mμ (log ε 2·08), $\nu_{max.}$ 1715 cm.$^{-1}$.

(*b*) 2β,3β-Epoxy-5α-cholestane [2] (800 mg.) in chloroform (40 c.c.) was shaken with aqueous 45% hydrobromic acid (12 c.c.) at 20° for 7 min.; this gave 3α-bromo-5α-cholestan-2β-ol (700 mg.), m. p. 137° (from methanol) (lit.,[2] 133—135°). This bromohydrin (400 mg.) in acetone (100 c.c.) was oxidised with sodium dichromate–sulphuric acid by the method of Bowden *et al.*,[10] to give 3α-bromo-5α-cholestan-2-one, m. p. 154° (lit.,[1,2] 153°), whose infrared spectrum was identical with that of preparation (*a*).

3,3-*Dibromo-5α-cholestan-2-one* (VI).—3α-Bromo-5α-cholestan-2-one (340 mg.) in acetic acid (25 c.c.) containing anhydrous potassium acetate (1·5 g.) and bromine (163 mg., 1·4 mol.) were heated at 90° for 40 min. The yellow solution was cooled, then poured into water, and the product isolated with ether in the usual way. Chromatography on silica gel (30 g.) in pentane and elution with pentane (250 c.c.) afforded 3,3-*dibromo-5α-cholestan-2-one*, m. p. 181—184° (decomp.), $\lambda_{max.}$ 305 mμ (log ε 2·06), $\nu_{max.}$ 1731 cm.$^{-1}$, after recrystallisation from ether [Found (after drying at 20°/0·1 mm. for 12 hr.): C, 59·6, 59·8; H, 8·2, 8·1. $C_{27}H_{44}Br_2O$ requires C, 59·55; H, 8·15%], optical rotatory dispersion in MeOH [ϕ] +11,600° (332·5 mμ, peak), −12,950° (282·5 mμ, trough), $10^{-2}a$ + 245. Further elution with pentane and ether–pentane (1 : 9) gave fractions (114 mg.), which by crystallisation from chloroform–methanol furnished 3α-bromo-5α-cholestan-2-one, m. p. 152°.

1α,3β-*Dibromo-5α-cholestan-2-one* (IV).—3α-Bromo-5α-cholestan-2-one (140 mg.) in acetic acid–chloroform (3 : 1) was treated with one drop of a 45% solution of hydrogen bromide in acetic acid and then a solution of bromine (55 mg.) in acetic acid at 85—87° for 3 hr. (sealed tube). The product, obtained by dilution with water and ether-extraction, was chromatographed on silica gel (20 g.) in pentane. Elution with ether–pentane (1 : 500) yielded 1α,3β-*dibromo-5α-cholestan-2-one*, m. p. 135—138° (from ether–methanol), $[\alpha]_D$ −3° (*c* 0·9 in $CHCl_3$), $\lambda_{max.}$ 304 mμ (log ε 2·30), $\nu_{max.}$ 1736 cm.$^{-1}$ [Found (after drying at 20°/0·1 mm. for 12 hr.): C, 59·5; H, 8·2%], optical rotatory dispersion in $CHCl_3$ [ϕ] −5900° (327·5 mμ, trough), +6940° (282·5 mμ, peak), $10^{-2}a$ −128.

1α,3,3-*Tribromo-5α-cholestan-2-one* (V).—(*a*) 3α-Bromo-5α-cholestan-2-one (330 mg.) in acetic acid–chloroform (3 : 1) was treated with 3 drops of a 45% solution of hydrogen bromide in acetic acid and then a solution of bromine (520 mg.) in acetic acid at 93° for 4 hr. (sealed tube). The product was isolated in the usual way and chromatographed on silica gel (30 g.) in pentane. Elution with pentane (200 c.c.) gave 1α,3,3-*tribromo-5α-cholestan-2-one*, m. p. 158—162° (decomp.) (from ether–methanol), $[\alpha]_D$ +80° (*c* 0·65), $\lambda_{max.}$ 329 mμ (log ε 2·08), $\nu_{max.}$ 1735 cm.$^{-1}$ [Found (after drying at 20°/0·1 mm. for 12 hr.): C, 52·3; H, 6·9. $C_{27}H_{43}Br_3O$ requires C, 52·0; H, 6·95%], optical rotatory dispersion in $CHCl_3$ [ϕ] +6850° (365 mμ, peak), −7350° (307·5 mμ, trough), $10^{-2}a$ +142.

(*b*) 1α,3β-Dibromo-5α-cholestan-2-one (IV), on similar bromination with an excess of bromine and subsequent chromatography, gave 1α,3,3-tribromo-5α-cholestan-2-one, whose infrared spectrum was identical with that in preparation (*a*).

1α,3α-*Dibromo-5α-cholestan-2-one* (XIII).—1α-Bromo-5α-cholestan-2-one [1] (m. p. 94—96°; 107 mg.) in acetic acid (20 c.c.) was treated with 3 drops of a 45% solution of hydrogen bromide in acetic acid and with bromine (45 mg., 1·2 mol.) at 20°. The colour was discharged after 30 min., and the product, isolated in the usual way, was chromatographed on silica gel (10 g.) in pentane. Elution with ether–pentane (3 : 100) gave 1α,3α-*dibromo-5α-cholestan-2-one*, m. p. 165—168° (from acetone), $\lambda_{max.}$ 339 mμ (log ε 2·13), $\nu_{max.}$ 1718 cm.$^{-1}$ [Found (after drying at 20°/0·1 mm. for 12 hr.): C, 59·7; H, 8·6%], optical rotatory dispersion in MeOH [ϕ] +2340° (350 mμ, peak), +350° (325 mμ, trough), $10^{-2}a$, +20.

Dehydrobromination of 3,3-*Dibromo-5α-cholestan-2-one* (VI).—(*a*) A solution of the dibromo-ketone (125 mg.) in dimethylformamide (3 c.c.) containing lithium bromide (200 mg.) and lithium carbonate (270 mg.) was refluxed in nitrogen for 5 min. The product, isolated by dilution with water and extraction with ether, crystallised on evaporation of the ethereal solution. Recrystallisation from ether–methanol gave 3-*bromo-5α-cholest-3-en-2-one* (VII), m. p. 99—103° (decomp.), $\lambda_{max.}$ 257 mμ (log ε 3·80), $\nu_{max.}$ 1696 cm.$^{-1}$ [Found (after drying at 20°/0·1 mm. for 12 hr.): C, 69·8; H, 9·2. $C_{27}H_{43}BrO$ requires C, 70·0; H, 9·35%].

(*b*) The dibromo-ketone (90 mg.), after similar treatment for 3 hr. and repeated chromatography, gave *cholesta-3,5-dien-2-one* (VIII) (8 mg.), m. p. 119° (softening at 110°) (from

methanol), $\lambda_{max.}$ 290 mμ (log ε 3·99); the infrared spectrum in Nujol was identical with that of a genuine specimen prepared by the procedure of Ruzicka, Plattner, and Furrer.[20]

3α-*Bromo-* *and* 3β-*Bromo*-5α-*Cholestan*-4-*one*.—A reputed sample of 3β-bromo-5α-cholestan-4-one, m. p. 111—113°, supplied by Dr. A. Magnani, exhibited twin peaks of equal intensity, $\nu_{max.}$ 1732 and 1713 cm.$^{-1}$, and by chromatography on silica gel and elution with ether–benzene (1 : 99) yielded 3α-bromo-5α-cholestan-4-one,[15] m. p. 125°, $\nu_{max.}$ 1713 cm.$^{-1}$, optical rotatory dispersion in methanol: [ϕ] −7400° (335 mμ trough), +9700° (290 mμ, peak) [$10^{-2}a$ −171, cf. $10^{-2}a$ −194 [15]]. Further elution with ether–benzene (2 : 98) gave 3β-*bromo*-5α-*cholestan*-4-*one*, m. p. 139°, $\lambda_{max.}$ 280 mμ, $\nu_{max.}$ 1732 cm.$^{-1}$, optical rotatory dispersion in methanol: [ϕ] −1200° (313 mμ, trough) +4000° (280 mμ, peak) [Found: C, 69·6; H, 9·8. $C_{27}H_{45}BrO$ requires C, 69·6; H, 9·7%]. Equilibration of either bromo-ketone with hydrogen bromide in acetic acid at 25° for 48 hr. gave a 1 : 1-mixture, m. p. 111—113°, $\nu_{max.}$ 1732 and 1713 cm.$^{-1}$, identical with the original preparation provided by Dr. Magnani. These findings have subsequently been confirmed by Dr. Magnani and Mr. Cooper of Julian Laboratories, Inc., Franklin Park, Illinois.

We thank Professor W. Klyne, University of London, for measuring the optical rotatory dispersion curves, Professor C. Djerassi, Stanford University, for the optical rotatory dispersion data for 1α-bromo-5α-cholestan-2-one, and Dr. A. Magnani of Julian Laboratories Inc., Franklin Park, Ill., U.S.A., for a specimen of 3β-bromo-5α-cholestan-4-one. One of us (T. E. B.) acknowledges the award of a Research Scholarship by the Commonwealth Scientific and Industrial Research Organisation.

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[20] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 524.