Absorption Spectra of Ketones. Part I. α-Halogeno-ketones.

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The shift in position of $\lambda_{max.}$ of a ketone produced on substitution of halogen for an α-hydrogen atom is a function of the angle between the carbonyl group and the carbon–halogen bond. Thus the shift for an equatorial α-bromo*cyclo*hexanone is about −5 mμ, and for a polar one +28 mμ. The shift produced by bromination of camphor is intermediate.

The relation is used to assign configurations to some steroid and triterpenoid α-bromo-ketones.

In contrast to the well-known and invaluable relations established by Woodward (*J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; see also Evans and Gillam, *J.*, 1941, 815, and Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., 1949, p. 190) between the structure of an αβ-unsaturated ketone and the wave-length of the maximum of its intense absorption of ultra-violet light (230—260 mμ), very little is known about the factors that influence the position and intensity of the weak absorption band (*ca.* 280 mμ) shown by all unconjugated aldehydes and ketones (cf. Bowden, Braude, and E. R. H. Jones, *J.*, 1946, 948). The paucity of data is no doubt due partly to the practical difficulty in measuring accurately the position of the often rather flat, and always weak, maxima; and partly to the inability to interpret the data usefully. The present paper is concerned with the effect of halogen substitution at the α-position on the position and intensity of the maximum.

Table 1 lists the wave-length (in mμ) and the intensity of the carbonyl absorption bands of some steroid and triterpenoid α-halogeno-ketones. The change in intensity, with reference to the parent (non-halogenated) compound, is indicated by Δ log ε. By the use of the accepted conformations of steroid (Barton, *Experientia*, 1950, **6**, 316) and triterpenoid (Barton and Holness, *J.*, 1952, 78) compounds the carbon–halogen bonds can be classified as equatorial (e) or polar (p). The change in position of the absorption maximum produced by the substitution of an equatorial α-halogen atom is then indicated by $\Delta\lambda_e$ and the corresponding change for polar substitution by $\Delta\lambda_p$. In compiling Table 1 it has been assumed that substitution by bromine at $C_{(23)}$ in hecogenin has no effect on $\lambda_{max.}$

It will be seen from the Table that equatorial substitution by halogen has little effect on the absorption spectrum (Δλ *ca.* −5 mμ, Δ log ε *ca.* 0 to +0·3). Polar substitution on the other hand has a pronounced effect. For bromine Δλ is *ca.* +28 mμ and Δ log ε *ca.* +0·6. The measurements reported in the Table for the 6-bromo-7-oxocholestan-3β-yl acetates agree with those recorded earlier (Barr, Heilbron, E. R. H. Jones, and Spring, *J.*, 1938, 334), and support the configurations assigned to the epimers from their relative ease of dehydrobromination (Fieser and Fieser, *op. cit.*, p. 270).

R. N. Jones, Ramsay, Herling, and Dobriner (*J. Amer. Chem. Soc.*, 1952, **74**, 2828) have recently shown that the equatorial bromine atoms in 2α-bromo- (No. 17) and 2α : 4αdibromo-cholestan-3-one (No. 18) produce a marked shift in the infra-red carbonyl stretching frequency relative to that of the parent cholestan-3-one. Polar substitution on the other hand had little effect on the carbonyl frequency. Although the configurations of the bromine atoms in these compounds were not, at first, rigidly defined, adequate chemical evidence to support them has subsequently been presented (Fieser and Ettore, *J. Amer. Chem. Soc.*, 1953, **75**, 1700; Beereboom, Djerassi, Ginsburg, and Fieser, *ibid.*, p. 3500; Fieser and Huang, *ibid.*, p. 4837; Corey, *ibid.*, p. 4832). The ultra-violet measurements recorded in Table 1 may then be taken as confirmatory of the correctness of the configurations assigned. In general the effect of α-halogen substitution on the infra-red and the ultra-violet spectra of ketones are thus complimentary.

The equatorial (2α) character of the bromine atom in 2-bromo-β-amyr-3-one (No. 23) is borne out by its infra-red spectrum: in carbon disulphide solution, β-amyr-3-one 1708 $cm.^{-1}$; 2-bromo-β-amyr-3-one 1726 $cm.^{-1}$ (*i.e.*, $\Delta\nu + 18$ $cm.^{-1}$). 7-Keto-steroids in carbon disulphide have the carbonyl band at *ca.* 1713 $cm.^{-1}$ (R. N. Jones, Humphries, and Dobriner, *ibid.*, 1950, **72**, 956). 6β-Bromo-7-oxocholestanyl acetate (No. 2) shows bands in this region at 1711 $cm.^{-1}$ due to the 7-carbonyl and at 1733 $cm.^{-1}$ due to the 3-acetoxyl (*i.e.*, $\Delta\nu - 2$ $cm.^{-1}$), whereas the epimer (No. 3) has a single band at 1734 $cm.^{-1}$ due to the carbonyl and ester groups superimposed (*i.e.*, $\Delta\nu + 21$ $cm.^{-1}$).

TABLE 1.

No.	Compound	$\lambda_{max.}$	log ε	Δ log ε	$\Delta\lambda_e$	$\Delta\lambda_p$	Solvent	Ref.
1	7-*Oxocholestanyl acetate*	283	1·75	—	—	—	Et–CH	1
		287	1·6	—	—	—	EtOH	2
2	6β-Bromo-	309	2·26	+0·51	—	+26	Et–Ch	1
		313	2·2	+0·6	—	+26	EtOH	2
3	6α-Bromo-	279	1·86	+0·11	−4	—	Et–Ch	1
		282	1·6	0	−5	—	EtOH	2
4	6α-8β-Dibromo-	304	2·2	+0·6	—	+22	EtOH	2
5	6-*Oxocholestanyl acetate*	280	1·6	—	—	—	EtOH	2
6	5α-Bromo-	308	2·1	+0·5	—	+28	EtOH	2
7	7α-Bromo-	310	2·2	+0·6	—	+30	EtOH	2
8	5α : 7α-Dibromo-	340	2·2	+0·6	—	+30	EtOH	2
9	5β : 7α-Dibromo-	305	2·1	+0·5	−5	—	EtOH	2
10	*Hecogenin acetate*	280	1·89	—	—	—	Et–Ch	1, 3
11	11α : 23-Dibromo-	274	2·20	+0·31	−6	—	Et–Ch	1, 3
12	5α : 22α-*Spirostan*-11-*on*-3β-*yl acetate*	294	1·74	—	—	—	Et–Ch	1, 3
13	12α : 23-Dibromo-	317	2·29	+0·55	—	+23	Et–Ch	1, 3
14	12-*Oxo-oleanolic lactone acetate*	297	1·80	—	—	—	Et–Ch	1, 4
15	11β-Bromo-	329	2·28	+0·48	—	+32	Et–Ch	1, 4
16	*Cholestan*-3-*one*	286	1·36	—	—	—	EtOH	1
17	2α-Bromo-	282	1·59	+0·23	−4	—	EtOH	1
18	2α : 4α-Dibromo-	[a]	—	—	—	—	EtOH	1
19	2 : 2-Dibromo-	294 [b]	2·13	+0·77	—	+12 [c]	EtOH	1
20	2α-Chloro-	279	1·60	+0·24	−7	—	EtOH	1
21	2 : 2-Dichloro-	294	1·63	+0·27	—	+15 [c]	EtOH	1
22	β-*Amyr*-3-*one*	291 [b]	1·50	—	—	—	EtOH	1
23	2α-Bromo-	286 [b]	1·81	+0·31	−5	—	EtOH	1

Et–Ch = 20% of chloroform in ethanol.

[a] Curve almost linear from 265 to 300 mμ; at 290 mμ, log ε = 1·76. [b] Point of inflexion. [c] In geminal position.

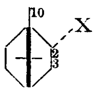
1, This paper. 2, Barr *et al.*, *loc. cit.* 3, Samples kindly provided by Dr. J. W. Cornforth (see Cornforth and Osbond, *Chem. and Ind.*, 1953, 919). 4, Samples kindly provided by Professor D. H. R. Barton and Mr. K. Overton.

The systematic effect of equatorial and polar α-halogen substitution on ultra-violet absorption spectra is clearly of value in the assignment of configuration. Thus the 11-bromo-12-oxo-oleanolic lactone acetate (No. 15) of Barton, Holness, Overton, and Rosenfelder (*J.*, 1952, 3751) must be the 11β-compound. The 5- and the 7-bromo-6-oxocholestan-3β-yl acetates (Nos. 6 and 7) of Barr *et al.* (*loc cit.*) must both have the α-configuration.

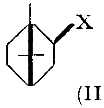
The *gem*-dihalides in Table 1 (Nos. 19 and 21) merit brief mention: The shift in λ_p is only about half of the normal. In contrast, the effects of two bromine atoms on either side of the carbonyl group appear to be additive. The dibromide (No. 4) formed by bromination of 7-oxocholestan-3β-yl acetate (Barr *et al.*, *loc. cit.*) cannot then be the

6 : 6-isomer. Since it is formed more rapidly, and in more than twice the yield, from 6α-bromo-7-oxocholestan-3β-yl acetate than from the 6β-isomer this dibromide must have the 6α : 8β-structure. The $\Delta\lambda$ value for 5 : 7-dibromo-6-oxocholestan-3β-yl acetate (No. 8) (Heilbron, Jackson, E. R. H. Jones, and Spring, *J.*, 1938, 102) points unmistakably to the 5α : 7α-configuration. From spectroscopic evidence the isomeric dibromide (No. 9) could be either the 5β : 7α- or the 5α : 7β-dibromide. The chemical evidence too (Heilbron *et al.*, *loc. cit.*) is consistent with either configuration, although the report that the 5-bromine atom is replaced by acetoxyl when the compound is treated with potassium acetate under conditions that do not alter the 5α-bromo-, the 7α-bromo-, or the 5α : 7α-dibromo-ketone rather favours the 5β : 7α-configuration.

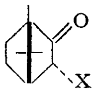
The $\alpha_e : \alpha'_e$ class of dibromide, represented by 2 : 4-dibromocholestan-3-one (No. 18), may prove less immediately recognisable since the expected $\Delta\lambda$ of −12 moves the carbonyl maximum back into the region of end-absorption from the bromine atoms, so that no maximum is observable. This type is easily differentiated, however, from the other three that contain polar bromine atoms by the low extinction at wave-lengths beyond the maximum of the parent ketone.



(I)



(II)



(III)

Before their spectra can be interpreted the configurations of the 3-halogeno-camphors must be determined. They are the more stable epimers. Thus, calculating from the optical rotations shows the equilibrium mixture of 3α-chloro- and 3β-chloro-camphor * to contain 91% of 3-α-chlorocamphor (Lowry and Steele, *J.*, 1915, **107**, 1382), and the equilibrium mixture of the two bromocamphors to contain 92% of 3-α-bromocamphor (Lowry, Steele, and Burgess, *J.*, 1922, **121**, 633). In camphane derivatives the usual order of stability of a substituent on a boat-form *cyclo*hexane is reversed (Shoppee, *Chem. and Ind.*, 1952, 86; Barton, *J.*, 1953, 1027) : the *endo* (p) configuration (I) is more stable than the *exo* (e) (II), because of compression of the *gem*-dimethyl group in the latter. To this steric effect, which raises the energy of the 3-*exo*-halogenocamphors relatively to their 3-*endo*-epimers (III), must be added the greater electrostatic repulsion between the $\mathrm{C}_3 \rightarrow \mathrm{Br}$ and

TABLE 2.

No.	Compound	$\lambda_{\text{max.}}$	log ε	Δ log ε	$\Delta\lambda_{\text{endo}}$	$\Delta\lambda_{\text{exo}}$	Solvent	Ref.
24	*Camphor*	288	1·45	—	—	—	CH	5
		292	1·36	—	—	—	CH	1
		289·5	1·51	—	—	—	EtOH	1
25	3α-Bromo-	310	1·95	+0·50	+22	—	CH	5
		307·5	1·98	+0·62	+15·5	—	CH	1, 6
		306	2·00	+0·49	+16·5	—	EtOH	1, 6
26	3β-Bromo-	312	1·95	+0·50	—	+24	CH	5
27	3α-Chloro-	305	1·72	+0·27	+17	—	CH	5
28	3β-Chloro-	306	1·75	+0·30	—	+18	CH	5
29	3 : 3-Dibromo-	323	1·88	+0·45	+11 [c]	+13 [c]	CH	5
30	3-Bromo-3-chloro-	315	1·84	—	—	—	CH	5
31	3 : 3-Dichloro-	310	1·82	+0·37	+ 4 [c]	+ 5 [c]	CH	5
32	10-*Bromocamphor*	293	1·39	—	—	—	CH	5
33	3α-Bromo-	308	2·03	+0·64	+15	—	CH	5
34	3α-Chloro-	306	1·67	+0·28	+13	—	CH	5
35	*Camphor*-10-*sulphonic acid*...	285	1·54	—	—	—	W	5
36	3α-Bromo-	303	1·93	+0·39	+18	—	WK	5
37	3α-Chloro-	300	1·59	+0·05	+15	—	WK	5
38	3α : 8-Dibromocamphor	312	2·05	—	—	—	CH	5
39	3β : 8-Dibromocamphor	309	2·02	—	—	—	CH	5

CH = *cyclo*Hexane. W = water. WK = Potassium salt in water.
[a]—[c] and 1—4, See Table 1. 5, Lowry and Owen, *J.*, 1926, 606. 6, Sample kindly provided by Dr. A. Nickon.

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* α and β are used in the customary steroid sense for formulæ set up as (I)—(III). These configurations have hitherto been termed, *e.g.*, 3 and 3′.

$C_2 \rightarrow O$ dipoles in the former ("equatorial" bromine) than in the latter (" polar " bromine) (cf. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301). The electrostatic effect will be much less important in the camphor than in the *cyclo*hexanone series (see below). The stable 3-halogenocamphors have then the *endo*-configuration (III). This has been confirmed by *X*-ray crystallography (Bijvoet and Wiebenga, *Naturwiss.*, 1944, **32**, 45; Wiebenga and Krom, *Rec. Trav. chim.*, 1946, **65**, 663).

Although the *cyclo*hexane ring in camphane has been referred to as a boat and the two $C_{(2)}$–H bonds as polar and equatorial, the anchoring of the bow and the stern to the same carbon atom imposes considerable distortion on the boat form and weakens the distinction between the two types of bond.

In considering 2-halogeno-ketones it will be convenient to define θ as the angle between the projections of the $C_{(1)}{=}O$ bond and the $C_{(2)}$–Halogen bond on the plane at right angles to the $C_{(1)}$–$C_{(2)}$ bond (that is, the apparent angle between the $C_{(1)}{=}O$ and $C_{(2)}$–Halogen bonds, when viewed down the axis of the $C_{(1)}$–$C_{(2)}$ bond). Then in a 2-halogeno*cyclo*hexanone (chair), $\theta_e =$ *ca.* $-15°$ and $\theta_p =$ *ca.* $+105°$. But in a 3-halogenocamphor $\theta_e =$ *ca.* $-55°$ and $\theta_p =$ *ca.* $+65°$, values closer to a normal *cyclo*pentanone than to a *cyclo*hexanone. So, if $\Delta\lambda$ is a function of θ, one would expect the $\Delta\lambda$ values for the camphor series to be different from those in the *cyclo*hexanone series, and perhaps intermediate between $\Delta\lambda_e$ and $\Delta\lambda_p$. The light absorption of the camphor derivatives given in Table 2 bears out this expectation.

The average values for a 3-bromine atom (*endo* and *exo* series combined) are $\Delta\lambda$ +20 mμ and $\Delta \log \varepsilon$ +0·50, and for a 3-chlorine atom $\Delta\lambda$ +16 mμ, $\Delta \log \varepsilon$ +0·23. $\Delta\lambda$ for bromine in a geminal grouping (No. 29) is again approximately half of the normal. A remeasurement of the light absorption of camphor and of 3α-bromocamphor on a modern instrument gave a rather lower value for $\Delta\lambda$, which was scarcely changed by substitution of ethanol for *cyclo*hexane as solvent.

As a rough guide, the following relations between θ and $\Delta\lambda$, based on average values for monobromo-compounds in Tables 1 and 2 (revised value), can now be proposed:

θ	15°	65°	105°
$\Delta\lambda$ (mμ)	−5	+16	+28

This relation may be contrasted with the results of Leonard and Mader's investigation of the absorption spectra of α-diketones (*J. Amer. Chem. Soc.*, 1950, **72**, 5388).

EXPERIMENTAL

Measurements were made with a Unicam SP500 spectrophotometer, the wave-length scale of which was set on the hydrogen line at 486·1 mμ. The setting was checked periodically against the absorption maxima of an ethanolic solution of ergosteryl acetate (271·4 and 281·8 ± 0·2 mμ). Measurements of optical density of ketone solutions, in a 1-cm. cell, were made at intervals of 0·5 mμ in the region of the maximum. The wave-lengths of points of inflection were determined graphically.

Absolute ethanol and chloroform were spectroscopically pure commercial samples. *cyclo*Hexane was shaken with sulphuric acid, boiled over sodium, and distilled. Camphor was sublimed after recrystallisation from aqueous ethanol. The other ketones were recrystallised until their physical constants (m. p. and/or rotation) reached those recorded. Dr. J. W. Cornforth kindly warned us that the sample of hecogenin acetate might contain a trace of the 9(11)-dehydro-derivative, that cannot conveniently be removed by physical methods. Since for a recrystallised sample ε at 243 mμ was only 370, with no change in gradient of the end-absorption in that region, the proportion of unsaturated ketone cannot have exceeded *ca.* 2%.

Epimeric 6-*Bromo*-7-*oxocholestan*-3β-*yl Acetates* [with Mr. C. H. ROBINSON].—Bromination of 7-oxocholestan-3β-yl acetate according to Barr *et al.* (*J.*, 1938, 334) gave the 6β-bromide as blades, m. p. 178—180°, $[\alpha]_D$ +33·5° (*c*, 1·85 in $CHCl_3$), after crystallisation from acetone.

The 6α-isomer, isolated from the mother-liquors, tended to separate as a gel. It crystallised readily from methanol, however, after chromatography on neutralised alumina, and then had m. p. 138—141°, $[\alpha]_D$ −6° (*c*, 1·57 in $CHCl_3$).

2α-*Bromo*-β-*amyr*-12-*en*-3-*one* [with Mr. O. P. ARYA].—A 3% solution of bromine in acetic acid (18·5 ml.) was added dropwise to one of β-amyr-12-en-3-one (1·5 g.) in acetic acid (30 ml.)

at room temperature during 20 min. The mixture was diluted with water and extracted with ether, which was washed with sodium hydrogen carbonate solution and water. Crystallisation of the involatile portion of the extract from acetone yielded long needles of the bromo-ketone, m. p. 197—198° (decomp.), $[\alpha]_D$ +22° (*c*, 1·8 in $CHCl_3$) (Found: Br, 15·5. Calc. for $C_{30}H_{47}OBr$: Br, 15·9%).

This bromide (1·24 g.) was dehydrobrominated by being boiled for 3 hr. in freshly distilled collidine (6 ml.). The cooled solution was diluted with chloroform, which was washed with dilute sulphuric acid and then water. The residue left on evaporation of the chloroform crystallised from acetone. β-*Amyra*-2 : 12-*dien*-3-*one* has m. p. 174—175°, $[\alpha]_D$ +141° (*c*, 1·5 in $CHCl_3$), $\lambda_{max.}$ 230 mμ (ε 9700) (Found: C, 85·1; H, 10·8. $C_{30}H_{46}O$ requires C, 85·3; H, 10·9%).

The infra-red spectra were kindly measured by Dr. J. E. Page of Glaxo Laboratories Ltd. I am also indebted to the colleagues who generously gave compounds for measurement, and especially to Professor D. H. R. Barton for valuable advice and encouragement.

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