

*Absorption Spectra of Ketones. Part II.\* The Configuration of Some Bromo-derivatives of 6-Oxocholestan-6-one. Absorption Spectra of  $\alpha$ -Ketols.*

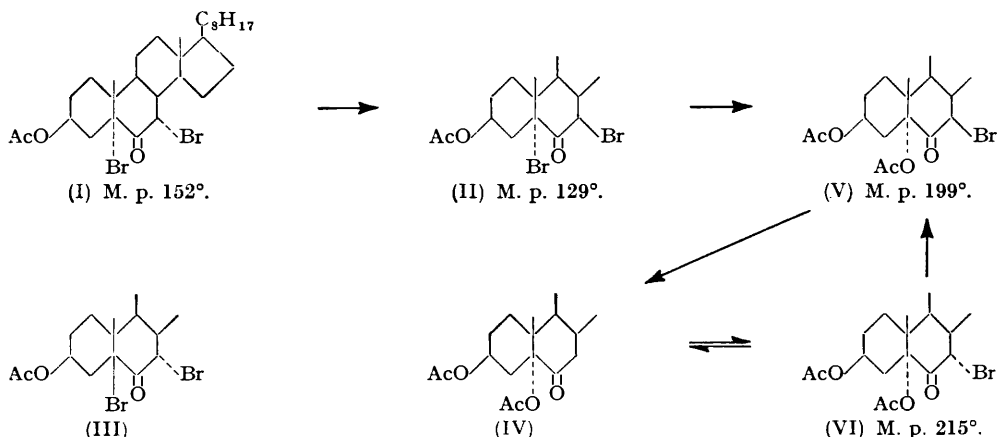
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$3\beta$  :  $5\alpha$ -Diacetoxy-7 $\beta$ -bromocholestan-6-one results from acetolysis of  $3\beta$ -acetoxy- $5\alpha$  :  $7\beta$ -dibromocholestan-6-one, and the  $7\alpha$ -epimer from bromination of  $3\beta$  :  $5\alpha$ -diacetoxycholestan-6-one.

The shift of the absorption band of a *cyclohexanone* caused by substitution of an  $\alpha$ -hydroxy- or  $\alpha$ -acetoxy-group in an equatorial or an axial configuration parallels the shift produced by an  $\alpha$ -bromine atom. Hydroxyl has a greater effect than acetoxy.

In a thorough investigation of the bromination of  $3\beta$ -acetoxycholestan-6-one Heilbron, Jackson, Jones, and Spring (*J.*, 1938, 102) found that the first product of bromination in acetic acid containing hydrogen bromide was a dibromide, m. p.  $152^\circ$ , which has since been shown by ultra-violet (Part I \*) and infra-red (Corey, *J. Amer. Chem. Soc.*, 1954, 76, 175) spectroscopy to be the  $5\alpha$  :  $7\alpha$ -dibromo-derivative (I). Longer reaction produces an isomeric dibromide, m. p.  $129^\circ$ , which has been shown by the same means to be either the  $5\alpha$  :  $7\beta$ - (II) or  $5\beta$  :  $7\alpha$ -dibromide (III). Although the yield of each dibromide is only



about 40% it seems reasonable to assume with Corey (*loc. cit.*) that the *trans*-dibromide of m. p.  $129^\circ$  is formed by isomerisation of that of m. p.  $152^\circ$ . In his analysis of the stereochemistry of steroid  $\alpha$ -bromo-ketones Corey (*loc. cit.*) assigned the configuration  $5\alpha$  :  $7\beta$  to the stable dibromide, m. p.  $129^\circ$ , on the assumption that the isomerisation of the  $5\alpha$  :  $7\alpha$ -dibromide in the presence of hydrogen bromide must take place through acid-catalysed enolisation and cannot therefore involve the tertiary  $5\alpha$ -bromine atom. An equally likely mechanism for the isomerisation would be by reduction of the bromo-ketone by hydrogen bromide, followed by re-bromination, and indeed Heilbron *et al.* (*loc. cit.*) showed that this very  $5\alpha$  :  $7\alpha$ -dibromo-ketone was reduced by hydrogen bromide in cold acetic acid to the  $7\alpha$ -monobromo-ketone. The isomerisation is in fact specifically catalysed by hydrogen bromide: the unstable dibromide is unchanged by even 7.5% perchloric acid in acetic acid after three days. This is consistent with the suggestion that the isomerisation takes place by the second mechanism, which also explains why the  $5\alpha$  :  $7\alpha$ -dibromide is stable to hydrogen bromide provided a large excess of bromine is present (Heilbron *et al.*, *loc. cit.*). Corey's reasoning is therefore fallacious.

Heilbron *et al.* acetolysed the *trans*-dibromide with potassium acetate in acetic acid to

\* Part I, *J.*, 1954, 282.

a  $3\beta : 5\alpha$ -diacetoxy-7-bromocholestan-6-one which was reduced to  $3\beta : 5\alpha$ -diacetoxycholestan-6-one (IV). The ultra-violet absorption (see Table, No. 7) of this substance,  $\Delta\lambda -6 \text{ m}\mu$  ( $\Delta\lambda$  as defined in Part I), shows that it is  $3\beta : 5\alpha$ -diacetoxy-7 $\beta$ -bromocholestan-6-one (V) with an equatorial bromine atom. Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, 1949, **71**, 3938) have already assigned this constitution to a compound obtained by bromination of  $3\beta : 5\alpha$ -diacetoxycholestan-6-one in the presence of boron trifluoride in acetic acid. The two isomers both give  $3\beta : 5\alpha$ -diacetoxycholestan-6-one on reduction with zinc dust in cold acetic acid and therefore differ only in the configuration at  $C_{(7)}$ . As required by the revised structure (VI), Fieser and Rajagopalan's bromo-ketone (No. 9) has  $\Delta\lambda +27 \text{ m}\mu$  and the corresponding  $5\alpha$ -ol (No. 8)  $\Delta\lambda +34 \text{ m}\mu$ , characteristic of an axial bromine atom. The unusually low extinction (cf. Part I) of the 5-acetate was not changed by further recrystallisation of the sample.

Although the  $7\alpha$ -bromide (VI) is stable to perchloric acid in acetic acid, it is isomerised by hydrogen bromide in acetic acid to the  $7\beta$ -bromide (V). So, in this case at least, the isomerisation does involve reduction and rebromination, rather than simple acid-catalysed enolisation.

The fact that (VI), which would be an intermediate in the conversion of (III) into (V), is unchanged under the conditions of the acetolysis shows that the stable dibromide must have the alternative *trans*-configuration,  $3\beta$ -acetoxy- $5\alpha : 7\beta$ -dibromocholestan-6-one (II). The isomerisations of (I) to (II) and of (VI) to (V) then become analogous. Although Heilbron *et al.* (*loc. cit.*) considered that the dibromide (I) could not be an intermediate in the formation of its isomer (II) since they could isolate only  $3\beta$ -acetoxy- $7\alpha$ -bromocholestan-6-one after treatment of (I) with hydrogen bromide in acetic acid, there can now be little doubt that Corey (*loc. cit.*) is justified in regarding (I) as the kinetically controlled product of dibromination of  $3\beta$ -acetoxycholestan-6-one and (II) as the thermodynamically controlled product. Retention of configuration in the acetolysis of (II) can plausibly be attributed to the intermediate formation of  $3\beta : 6\alpha$ -diacetoxy- $7\beta$ -bromo- $5\beta : 6\beta$ -epoxycholestane.

We take the opportunity of reporting the absorption spectra of some halogeno-derivatives of cholestan-2- and -3-one of known configuration recently prepared by Alt and Barton (*J.*, 1954, 4284) who kindly gave us samples (Nos. 10—14). The spectrum of  $3\alpha$ -bromocholestan-2-one (No. 12) is normal for an axial bromo-ketone.  $3\alpha$ -Chlorocholestan-2-one (No. 11) and  $2\beta$ -chlorocholestan-3-one (No. 14) provided values of  $\Delta\lambda$  for axial chlorine, which were lacking previously: as expected, chlorine causes a smaller shift than bromine.

The new measurements recorded in the Table combined with the absorption spectra of some 11 : 12-ketols recently published by Schindler and Reichstein (*Helv. Chim. Acta*, 1954, **37**, 667) show that the absorption of light by  $\alpha$ -hydroxy- and  $\alpha$ -acetoxy-ketones depends on the geometry of the systems, the effects being generally similar to those shown by  $\alpha$ -bromo-ketones (Part I). Substitution of a hydroxyl group for an equatorial hydrogen atom shifts the maximum  $12 \text{ m}\mu$  to shorter wave-length; an axial hydroxyl group causes a shift of  $15\text{--}23 \text{ m}\mu$  to longer wave-length. An acetoxy-group shows  $\Delta\lambda_e -5 \text{ m}\mu$  and  $\Delta\lambda_a +7$  to  $+11 \text{ m}\mu$  (subscripts refer to conformation). Since the parent, unoxxygenated, ketone may not always be available for comparison perhaps a more useful generalisation is that acetylation of an equatorial 1-hydroxycyclohexanone moves the absorption maximum to a longer wave-length, while acetylation of an axial one moves the maximum to a shorter wave-length. By this criterion cevagenin (Nos. 28 and 29) is an equatorial  $\alpha$ -ketol as proposed by Barton, Jeger, Prelog, and Woodward (*Experientia*, 1954, **10**, 81). Caudoside (No. 32), although undoubtedly an 11 : 12-ketol (Schindler and Reichstein, *loc. cit.*), appears to be an exception to the rule.

The reported maximum of methyl  $3\alpha$ -acetoxy-11-oxocholanoate (No. 16) seemed to be at an improbably long wave-length: a remeasurement of the light absorption of this substance showed that its maximum was in fact at the same position as that of the corresponding  $\alpha$ -titanate (No. 15). This revised value has been used in calculating the values of  $\Delta\lambda$  for derivatives of 11-oxocholanic acid, which now fall into line with the other ketols in the Table. In a few examples calculation of  $\Delta\lambda$  involves the assumption that

esterification of a carboxyl or hydroxyl in a remote part of the molecule does not change  $\lambda_{\max}$ . The axial 13-lactone group in the oleanolic acid series (Nos. 34 and 35) has an effect similar to that of an axial acetoxy-group.

$\Delta\lambda$  produced by introduction of hydroxyl, like that of chlorine and bromine (Part I),

| No. | Compound   | $\lambda_{\max}$<br>(in EtOH) | log $\epsilon$ | $\Delta\lambda_c$  | $\Delta\lambda_a$    | Ref.      |
|-----|--|-------------------------------|----------------|--------------------|----------------------|-----------|
| 1   | 3 $\beta$ -Acetoxycholestan-6-one  | 280<br>279                    | 1.6<br>1.65    | —<br>—             | —<br>—               | 1, 2<br>3 |
| 2   | 3 $\beta$ -Acetoxy-7 $\alpha$ -bromocholestan-6-one                          | 310                           | 2.2            | —                  | +30(Br)              | 1, 2      |
| 3   | 3 $\beta$ -Acetoxy-5 $\alpha$ :7 $\alpha$ -dibromocholestan-6-one            | 340<br>339                    | 2.2<br>2.12    | —<br>—             | +30(Br)<br>+30(Br)   | 1, 2<br>3 |
| 4   | 3 $\beta$ -Acetoxy-5 $\alpha$ :7 $\beta$ -dibromocholestan-6-one, m. p. 129° | 305<br>304                    | 2.1<br>2.03    | —<br>—             | —<br>—               | 1, 2<br>3 |
| 5   | 3 $\beta$ -Acetoxy-5 $\alpha$ -hydroxycholestan-6-one                        | 299.5                         | 1.77           | —                  | +20.5(OH)            | 3         |
| 6   | 3 $\beta$ :5 $\alpha$ -Diacetoxycholestan-6-one                              | 290                           | 1.93           | —                  | +11(OAc)             | 3         |
| 7   | 3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\beta$ -bromocholestan-6-one             | 284                           | 1.96           | -6(Br)             | —                    | 3         |
| 8   | 3 $\beta$ -Acetoxy-7 $\alpha$ -bromo-5 $\alpha$ -hydroxycholestan-6-one      | 333.5                         | 2.04           | —                  | +34(Br)<br>+23.5(OH) | 3         |
| 9   | 3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\alpha$ -bromocholestan-6-one            | 317                           | 1.69           | —                  | +27(Br)<br>+7(OAc)   | 3         |
| 10  | Cholestan-2-one  | 279.5                         | 1.39           | —                  | —                    | 3         |
| 11  | 3 $\alpha$ -Chlorocholestan-2-one  | 305                           | 1.79           | —                  | +25.5(Cl)            | 3         |
| 12  | 3 $\alpha$ -Bromocholestan-2-one   | 312                           | 2.04           | —                  | +32.5(Br)            | 3         |
| 13  | Cholestan-3-one  | 285                           | 1.40           | —                  | —                    | 3         |
| 14  | 2 $\beta$ -Chlorocholestan-3-one   | 299.5                         | 1.53           | —                  | +14.5(Cl)            | 3         |
| 15  | Methyl 3 $\alpha$ -acetoxy-11-oxo $\alpha$ -tanoate                          | 297.5                         | 1.44           | —                  | —                    | 4         |
| 16  | Methyl 3 $\alpha$ -acetoxy-11-oxocholanoate                                  | 305<br>298                    | 1.50<br>1.47   | —<br>—             | —<br>—               | 5<br>3    |
| 17  | 3 $\alpha$ :12 $\alpha$ -Dihydroxy-11-oxocholanoic acid                      | 313                           | 1.69           | —                  | +15(OH)              | 6         |
| 18  | Methyl 3 $\alpha$ :12 $\alpha$ -diacetoxy-11-oxocholanoate                   | 308                           | 1.84           | —                  | +10(OAc)             | 6         |
| 19  | Methyl 3 $\alpha$ :12 $\beta$ -dihydroxy-11-oxocholanoate                    | 285.5                         | 1.67           | -12.5(OH)          | —                    | 4         |
| 20  | Methyl 3 $\alpha$ :12 $\beta$ -diacetoxy-11-oxocholanoate                    | 294<br>292                    | 1.47<br>1.50   | -4(OAc)<br>-6(OAc) | —<br>—               | 4<br>5    |
| 21  | 12-Oxocholanoic acid   | 290                           | 1.76           | —                  | —                    | 4         |
| 22  | Methyl 3 $\alpha$ -hydroxy-12-oxocholanoate                                  | 290                           | 1.69           | —                  | —                    | 5         |
| 23  | 3 $\alpha$ :11 $\alpha$ -Dihydroxy-12-oxocholanoic acid                      | 278                           | 1.90           | -12(OH)            | —                    | 4         |
| 24  | Methyl 3 $\alpha$ -acetoxy-11 $\alpha$ -hydroxy-12-oxocholanoate             | 279                           | 1.89           | -11(OH)            | —                    | 4         |
| 25  | Methyl 3 $\alpha$ :11 $\alpha$ -diacetoxy-12-oxocholanoate                   | 285<br>285                    | 1.85<br>1.87   | -5(OAc)<br>-5(OAc) | —<br>—               | 4<br>5    |
| 26  | Methyl 3 $\alpha$ -acetoxy-11 $\beta$ -hydroxy-12-oxocholanoate              | 307<br>307                    | 1.85<br>1.82   | —<br>—             | +17(OH)<br>+17(OH)   | 4<br>5    |
| 27  | Methyl 3 $\alpha$ :11 $\beta$ -diacetoxy-12-oxocholanoate                    | 298.5                         | 2.06           | —                  | +8.5(OAc)            | 4         |
| 28  | Cevagenin  | 279                           | 1.71           | —                  | —                    | 3         |
| 29  | Cevagenin <i>ortho</i> acetate diacetate                                     | 283                           | 1.49           | —                  | —                    | 3         |
| 30  | Sarmutoside  | 287                           | 1.89           | —                  | —                    | 4         |
| 31  | Sarmutogenin diacetate   | 293.5                         | 1.94           | —                  | —                    | 4         |
| 32  | Caudoside  | 295                           | 1.76           | —                  | —                    | 4         |
| 33  | Caudogenin diacetate   | 295                           | 1.94           | —                  | —                    | 4         |
| 34  | Methyl 3 $\beta$ -acetoxyolean-28-oate                                       | 287                           | 1.47           | —                  | —                    | 3         |
| 35  | 12-Oxo-oleanolic lactone acetate   | 297                           | 1.80           | —                  | +10(lactone)         | 2         |
| 36  | Camphor  | 289                           | 1.51           | —                  | —                    | 3         |
| 37  | 3 $\alpha$ -Hydroxycamphor   | 297.5                         | 1.47           | +8.5(OH)           | —                    | 3         |

1, Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334. 2, Cookson, *J.*, 1954, 282. 3, This paper. 4, Schindler and Reichstein, *Helv. Chim. Acta*, 1954, 37, 667. 5, Wintersteiner, quoted in ref. 4. 6, Baumgartner and Tammi, quoted in ref. 4.

into a cyclopentanone (Nos. 36—37) is intermediate between  $\Delta\lambda_c$  and  $\Delta\lambda_a$ . The substance known as " $\alpha$ "-hydroxycamphor is assigned the *endo*-configuration, 3 $\alpha$ -hydroxycamphor, since it is evidently the more stable epimer (Bredt and Fischer, *J. pr. Chem.*, 1931, 131, 56; Lapworth and Chapman, *J.*, 1901, 79, 384; cf. Part I).

#### EXPERIMENTAL

Ultra-violet absorption measurements were made in EtOH as described previously (Part I). Optical rotations were measured in CHCl<sub>3</sub> in a 1-dm. tube.

3 $\beta$ -Acetoxy-5 $\alpha$ :7 $\alpha$ -dibromocholestan-6-one, made according to Heilbron, Jackson, Jones, and Spring (*J.*, 1938, 102), had m. p. 152—153°, [ $\alpha$ ]<sub>D</sub> -140°. The isomeric dibromide, made by Woodward and Clifford's method (*J. Amer. Chem. Soc.*, 1941, 63, 2727), had m. p. 129°, [ $\alpha$ ]<sub>D</sub> -57°.

3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\beta$ -bromocholestan-6-one.—3 $\beta$ -Acetoxy-5 $\alpha$ :7 $\beta$ -dibromocholestan-6-one (m. p. 129°) (1.11 g.) was heated on the steam-bath for 7 hr. with freshly fused potassium acetate (2.2 g.) in acetic acid (100 ml.). The mixture was then diluted with water, and the precipitate recrystallised thrice from acetic acid, to give the diacetate, m. p. 198—199° (248 mg.). When reaction was for only 1.5 hr., as described by Heilbron *et al.* (*loc. cit.*), only unchanged dibromide could be isolated by crystallisation.

3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\alpha$ -bromocholestan-6-one.—Prepared according to Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, 1949, 71, 3938), 3 $\beta$ -acetoxy-5 $\alpha$ -hydroxy-7 $\alpha$ -bromocholestan-6-one had m. p. 170—171°, [ $\alpha$ ]<sub>D</sub> +7°, and its 5-acetate, m. p. 215—216°, [ $\alpha$ ]<sub>D</sub> +39°.

*Reduction with Zinc and Acetic Acid.*—3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\beta$ -bromocholestan-6-one (42 mg.) was dissolved in warm acetic acid (5 ml.). When the solution had cooled to room temperature zinc dust was added in portions to the stirred mixture during 3 hr. Next day the filtered solution was diluted with water, and the precipitate crystallised twice from methanol. The m. p. of the resulting needles, 170—171°, was unchanged when they were mixed with an authentic sample of 3 $\beta$ :5 $\alpha$ -diacetoxycholestan-6-one of the same m. p.

The 7 $\alpha$ -epimer gave the same product on reduction.

*Epimerisation of 3 $\beta$ :5 $\alpha$ -Diacetoxy-7 $\alpha$ -bromocholestan-6-one.*—A solution of 3 $\beta$ :5 $\alpha$ -diacetoxy-7 $\alpha$ -bromocholestan-6-one (55 mg.) in acetic acid (15 ml.) containing hydrogen bromide (5%) was left at room temperature for 40 hr. The mixture was then poured into water, and the precipitate collected, washed with water, and recrystallised twice from acetic acid. The resulting crystals (25 mg.) melted at 201—202°, alone or mixed with 3 $\beta$ :5 $\alpha$ -diacetoxy-7 $\beta$ -bromocholestan-6-one made by acetolysis of the 5 $\alpha$ :7 $\beta$ -dibromide.

When perchloric acid was substituted for hydrogen bromide the 7 $\alpha$ -isomer was recovered under the above conditions. It was also unchanged by 9 hours' heating on the steam-bath with potassium acetate in acetic acid.

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