

Studies in the Synthesis of Cortisone. Part X. Infra-red Absorption of 23a- and 23b-Bromo-isosapogenins.*

By D. H. W. DICKSON and J. E. PAGE.

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A series of infra-red absorption bands can be used to identify 23a- and 23b-bromo-isosapogenins (see Mueller and Norton, *J. Amer. Chem. Soc.*, 1954, **76**, 749) and to distinguish them from the corresponding unbrominated sapogenins.

THE preparation of 23-bromo-isosapogenins has been described by Djerassi, Martinez, and Rosenkranz (*J. Org. Chem.*, 1951, **16**, 303), Mueller, Stobaugh, and Winniford (*J. Amer. Chem. Soc.*, 1951, **73**, 2400), Hirschmann, Snoddy, and Wendler (*ibid.*, 1953, **75**, 3252), Mueller, Norton, Stobaugh, Tsai, and Winniford (*ibid.*, p. 4892), Schmidlin and Wettstein (*Helv. Chim. Acta*, 1953, **36**, 1241), Mueller and Norton (*J. Amer. Chem. Soc.*, 1954, **76**, 749), and Cornforth, Osbond, and Phillipps, (*J.*, 1954, 907), but only the last-named authors mentioned the infra-red absorption peaks characteristic of a 23a-bromo-22a-spirostan. Cornforth *et al.* quote these peaks as evidence that their compounds contain a 23a-bromo-22a-spirostan group, but do not comment on the origin of the assignment.

Mueller and Norton (*loc. cit.*) described a new series of isomeric bromo-isosapogenins, in which they believe that the bromine atom is located at C₍₂₃₎, but in which the carbon-bromine linkage has a different configuration from that in the original 23-bromo-isosapogenins; the latter were provisionally designated 23a-bromo-22a-spirostan in order to distinguish them from the new compounds, which were termed 23b-bromo-22a-spirostan. Mueller and Norton distinguished chemically between the two groups of isomers, but did not offer any infra-red evidence. We have found that the infra-red spectra of the two groups differ considerably in the 1050—850-cm.⁻¹ region, and we have identified absorption bands characteristic of the 23a- and 23b-bromo-isomers and available for distinguishing them from the corresponding unbrominated isosapogenins.

EXPERIMENTAL

The spectroscopic measurements were conducted as described by Dickson, Page, and Rogers.*

Compounds sufficiently soluble in carbon disulphide and carbon tetrachloride were examined as 1.0% (w/v) solutions in 1.0-mm. thick sodium chloride cells. Compounds that were insoluble in carbon disulphide were examined, if soluble, as 1.0% (w/v) solutions in solvents such as bromoform, chloroform, methylene chloride, and pyridine, or as Nujol mulls. Absorption intensities were measured as apparent molecular extinction coefficients calculated from the relationship: $\epsilon = 1/cl \log_{10} (T_0/T)$, where T_0 and T are respectively the % radiation transmitted by the solvent and by the solution at the frequency of the absorption peak, c is the solute concentration in moles per l. and l is the cell thickness in cm.

* Part IX, preceding paper.

The results are tabulated.

The 23a- and 23b-bromo-isosapogenins, which had been prepared in these laboratories (see previous and subsequent papers in the present series), had the properties given below, references being: (a) Cornforth *et al.*, (b) Schmidlin and Wettstein, (c) Mueller and Norton, (d) Mueller, Norton, Stobaugh, Tsai, and Winniford, *loc. cit.* :

- (1) 23a-Bromo-3 β -hydroxy-5 α : 22a-spirostan-12-one (I), m. p. 205° (decomp.) (a).
- (2) 3-Acetate of (1), m. p. 225—227° (a) [cf. m. p. 227—228° (decomp.) (b)].
- (3) 23a-Bromo-11 β : 12 β -epoxy-5 α : 22a-spirostan-3 β -ol, m. p. 207—209° (a).
- (4) 3-Acetate of (3), m. p. 233—235° (a) [cf. m. p. 232—234° (decomp.) (b)].
- (5) 23a-Bromo-12-oxo-5 α : 22a-spirost-9(11)-en-3 β -yl acetate, m. p. 228° (decomp.) [cf. m. p. 220—220.5° (decomp.) (c)].
- (6) 11 α : 23a-Dibromo-3 β -hydroxy-5 α : 22a-spirostan-12-one, m. p. 180° (decomp.).
- (7) 3-Acetate of (6), m. p. 189—191° (decomp.) (a) [cf. m. p. 198—199° (decomp.) (d), 180—183° (decomp.) (c)].
- (8) 11 α : 23a-Dibromo-12 β -hydroxy-5 α : 22a-spirostan-3 β -yl acetate, m. p. 197—202° (decomp.) (a) [cf. m. p. 205—206.5° (decomp.) (b)].
- (9) 11 α : 23a-Dibromo-12 α -hydroxy-5 α : 22a-spirostan-3 β -yl acetate, m. p. 198° (decomp.) (a).
- (10) 23a-Bromo-3 β : 12 β -dihydroxy-5 α : 22a-spirostan-11-one, m. p. 208° (decomp.) [cf. m. p. 233—234° (decomp.) (d)].
- (11) 3 : 12-Diacetate of (10), m. p. 195—196°.
- (12) 3 β : 12 α -Diacetoxy-23a-bromo-5 α : 22a-spirostan-11-one, m. p. 168—171°.
- (13) 12 α : 23a-Dibromo-11-oxo-5 α : 22a-spirostan-3 β -yl acetate, m. p. 229—232° (decomp.) (a).
- (14) 12 α : 23a-Dibromo-11 β -hydroxy-5 α : 22a-spirostan-3 β -yl acetate, m. p. 233—236° (decomp.) (a) [cf. m. p. 237—239° (decomp.) (b)].
- (15) 23a-Bromo-12 α -chloro-11 β -hydroxy-5 α : 22a-spirostan-3 β -yl acetate, m. p. 233—235° (decomp.) [cf. m. p. 236.5—242° (decomp.) (b)].
- (16) 23a-Bromo-12 α -chloro-11-oxo-5 α : 22a-spirostan-3 β -yl acetate, m. p. 230° (decomp.) [cf. m. p. 233—236° (decomp.) (b)].
- (17) 23b-Bromo-12-oxo-5 α : 22a-spirost-9(11)-en-3 β -yl acetate, m. p. 220° (decomp.) [cf. m. p. 220—221° (c)].
- (18) 11 α : 23b-Dibromo-12-oxo-5 α : 22a-spirostan-3 β -yl acetate, m. p. 168—169° (decomp.).

DISCUSSION

The strong peaks in the 1000—720-cm.⁻¹ region (see Tables) may be used to identify the two groups of bromo-compounds and to distinguish them from unbrominated 22a-

TABLE I. Frequency assignments (cm.⁻¹) for 23a-bromo-22a-spirostan in carbon disulphide solution.*

Compound	Hydroxy	Acetate	Ketone	Chlorine	23a-Bromo-22a-spirostan
1	3620, 1042	—	1710	—	1010, 947 > 919, 862, 725
2	—	1736, 1240	1712	—	1010, 946 > 920, 860, 724
3	3620, 1035	—	—	—	1010, 945 > 918, 866, 732
4	—	1732, 1240	—	—	1012, 944 > 916, 860, 732
5	—	1736, 1240	1675	—	1010, 945 > 918, 862, 728
6	3620, 1036	—	1730	—	1010, 946 > 918, 862, 726
7	—	1730, 1240	1730	—	1008, 944 > 917, 864, 726
8	3620	1731, 1238	—	—	1010, 944 > 916, 860, 724
9	3620	1736, 1242	—	—	1016, 948 > 917, 860, 724
10 †	3620, 3480	—	1705	—	1014, 944 > 918, 862, 724
11	—	{ 1752, 1220 1730, 1240	1730	—	1010, 946 > 918, 864, 728
12	—	{ 1758, 1218 1735, 1242	1735	—	1010, 945 > 918, 862, 724
13	—	1735, 1242	1710	—	1012, 946 > 916, 865, 728
14	3620	1735, 1238	—	—	1010, 944 > 915, 865, 726
15 †	3560	1717, 1266	—	776	1016, 948 > 918, 864, 728
16	—	1734, 1242	1718	762	1012, 946 > 918, 862, 726

* A dash indicates that an absorption band is absent from the spectrum and, e.g., "947 > 919" that the intensity of the absorption band at 947 cm.⁻¹ is greater than that of the band at 919 cm.⁻¹.

† As Nujol mull.

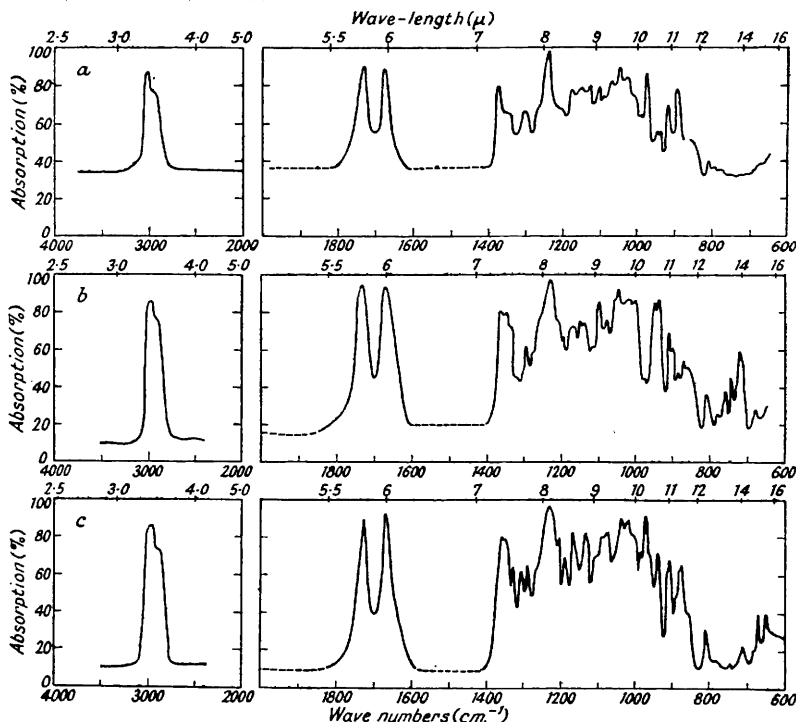
spirostans. 23a-Bromo-22a-spirostans absorb at about 1012, 946, 918, 862, and 726 cm^{-1} and 23b-bromo-22a-spirostans at about 1015, 972, 943, 905, and 880 cm^{-1} ; in the former compounds the absorption peak at 946 cm^{-1} (ϵ 320—250) is considerably stronger

TABLE 2. Frequency assignments (cm^{-1}) for 23b-bromo-22a-spirostans in carbon disulphide solution.

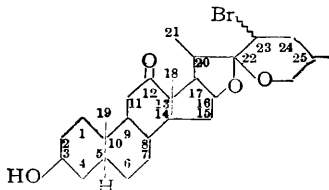
Compound	Acetate	Ketone	23b-Bromo-22a-spirostan
17	1736, 1240	1676	1013, 972, 944, 910, 878
18	1732, 1240	1732	1015, 972, 943, 904, 882

than that at 918 cm^{-1} (ϵ 140—100) and in the 23b-isomers the peak at 972 cm^{-1} (ϵ about 450) is considerably stronger than that at 943 cm^{-1} (ϵ about 150). These absorption peaks have the same relative intensities in Nujol mull and carbon disulphide, carbon tetra-

Infra-red spectra of (a) 12-oxo-5 α :22a-9(11)-en-3 β -yl acetate (C.S. no. 164), and (b) its 23a-bromo- (C.S. no. 165) and (c) 23b-bromo-derivative (C.S. no. 166).



chloride, and bromoform solution. The spectra of both bromo-isomers are free from strong peaks at about 980 and 898 cm^{-1} and are thus readily distinguished from those of unbrominated 22a-spirostans, which have peaks at about 980 (ϵ 440—304), 918 (ϵ 170—100),



and 898 cm^{-1} (ϵ 280—150); (cf. Wall, Eddy, McClennan, and Klumpp, *Analyt. Chem.*, 1952, 24, 1337; Jones, Katzenellenbogen, and Dobriner, *J. Amer. Chem. Soc.*, 1953, 75, 158).

The spectra of 12-oxo-5 α : 22a-spirost-9(11)-en-3 β -yl acetate and its 23a- and 23b-bromo-derivatives may be compared in the Figure. Similar relations are shown by hecogenin acetate (C.S. no. 162) and its 23a-bromo-derivative (C.S. no. 163).*

The 1350—1500-cm.⁻¹ region of the spectrum of a steroid in carbon tetrachloride solution provides information on the individual methyl and methylene groups (Jones and Cole, *ibid.*, 1952, 74 5648; Jones, Cole, and Nolin, *ibid.*, p. 5662) and it was thought that the spectra now available might indicate the location and conformation of the bromine atom. This, however, is not possible.

The spectra summarised in the Tables show that substituents in rings A, B, and C of a 23-bromo-22a-spirostan absorb at their normal frequencies. The displaced acetoxy C=O (from 1732 to 1717 cm.⁻¹) and C—O stretching frequencies (from 1240 to 1266 cm.⁻¹) in the Nujol mull spectrum of 23a-bromo-12 α -chloro-11 β -hydroxy-5 α : 22a-spirostan-3 β -yl acetate are attributed to intermolecular hydrogen bonding.

A 12-ketone (*e.g.*, no. 2), that normally absorbs at about 1712 cm.⁻¹, absorbs at about 1675 cm.⁻¹ when a 9(11)-double bond is introduced (no. 5) and at about 1730 cm.⁻¹ when an 11 α -bromine atom (equatorial) is introduced (no. 7). The latter displacement is in harmony with Jones, Ramsay, Herling, and Dobriner's hypothesis (*ibid.*, p. 2828) that an equatorial bromine atom on the α -carbon atom to a ketone group in a cyclohexanone ring in the chair configuration displaces the C=O stretching frequency and that an axial bromine atom causes little or no displacement. The hypothesis is further supported by the behaviour of the 12 α -bromine atom (axial) in 12 α : 23a-dibromo-11-oxo-5 α : 22a-spirostan-3 β -yl acetate (no. 13) and of the 12 α -chlorine (axial) in 23a-bromo-12 α -chloro-11-oxo-5 α : 22a-spirostan-3 β -yl acetate, which have little effect on the absorption frequency of the 11-ketone.

It is noteworthy that both a 12 α -acetoxy (axial), and a 12 β -acetoxy-group (equatorial) displace the C=O stretching frequency of an 11-ketone (nos. 11 and 12) by about 25 cm.⁻¹ to higher values; a 12 α - has a slightly greater effect than a 12 β -acetoxy group. The C=O and C—O stretching frequencies for the 12-acetoxy-group are displaced by about 20 cm.⁻¹ in a positive and in a negative direction, respectively. Thus in the spectrum of 3 β : 12 β -diacetoxy-23a-bromo-5 α : 22a-spirostan-11-one (no. 11) the 3-acetoxy-group shows normal absorption at about 1730 and 1240 cm.⁻¹, but the 12 β -acetoxy-group absorbs at about 1752 and 1220 cm.⁻¹ and the 11-ketone group at about 1730 cm.⁻¹; the absorption band at 1730 cm.⁻¹ accommodates the C=O stretching vibrations of both the 11-ketone and the 3-acetoxy-group and has twice the normal intensity. These frequency displacements, which we have also observed in the spectra of the corresponding unbrominated *isosapogenins*, are attributed to dicarbonyl interaction and are probably similar to the 21-acetate-20-ketone interaction reported by Jones, Humphries, Herling, and Dobriner (*ibid.*, p. 2820).

The two 12 α -chloro-compounds listed exhibit a C—Cl stretching band at about 760—775 cm.⁻¹; the corresponding C—Br bands for the four 11 α - and two 12 α -bromo-compounds probably appear between 600 and 500 cm.⁻¹ and cannot be detected by a spectrometer equipped with sodium chloride optics (see Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 269). We originally believed that the absorption band at about 726 cm.⁻¹ in the spectrum of a 23a-bromo-22a-spirostan was associated with a C—Br stretching vibration, but it was later found that the band does not appear in the spectrum of a 23b-bromo-22a-spirostan; the absence of the band in the latter compounds may, however, be due to the different configuration of the C—Br linkage.

GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX.

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* Spectra thus designated have been deposited with the Chemical Society. Photocopies, price 3s. 0d. per copy per spectrum, may be obtained on application, citing the C.S. no., to the General Secretary, the Chemical Society, Burlington House, Piccadilly, London, W.1.