# 242. *Infrared Spectra of Natural Products. Part XI.* Intramolecular Hydrogen-bonding and Stereochemistry of Triterpenoid Diols and Related Compounds.*

By A. R. H. Cole and (Miss) G. T. A. Müller.

The presence or absence of intramolecular hydrogen-bonds in compounds based on *cyclo*hexane rings can be readily determined from the hydroxyl stretching absorption. Neighbouring diaxial groups are too far apart to interact, while two equatorial groups or an equatorial and an axial will form an intramolecular bond of varying strength depending on the nature of the groups and their stereochemistry. Spectra are described for a series of 3 : 23-(or 24)-diols, 3-hydroxy-23(or 24)-carbonyl compounds and 23(or 24)-hydroxy-3-ketones of the triterpenoid series, and the application of the results to new compounds or degradative work is described.

Infrared absorption due to intramolecular hydrogen-bonding gives useful information about the stereochemistry of hydroxy-compounds [1-4] and few types of compound are as interesting for the investigation of this effect as those based on *cyclo*hexane rings with their axial and equatorial substituents. The present work is concerned with the stereochemistry of 3- and 4-substituents in triterpenoids. In a study of the infrared absorption of triterpenoid carboxylic acids [5] it was found that the spectrum of β-boswellic acid (I; R = $CO_2H$) in dilute solution in carbon tetrachloride showed no absorption due to intramolecular hydrogen-bonding, and that the high frequency of the 3-hydroxyl group (3638 cm.$^{-1}$) showed it to be axial.[6] This fixes the stereochemistry of ring A as (II; R = H), in agreement with the chemical evidence of Beton, Halsall, and Jones,[7] since only in the diaxial

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* Part X, preceding paper.

[1] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820, 6319.

[2] Kuhn, *ibid.*, p. 2492; 1954, **76**, 4323.

[3] Cole and Jefferies, *J.*, 1956, 4391.

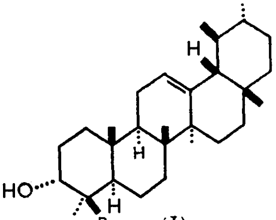
[4] Henbest and Lovell, *J.*, 1957, 1965.

[5] (*a*) Michell, Thesis, W. Australia 1956; (*b*) Cole and Michell, in the press.

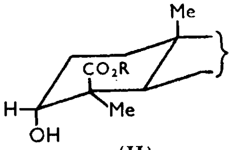
[6] Allsop, Cole, White, and Willix, *J.*, 1956, 4868.

[7] Beton, Halsall, and Jones, *J.*, 1956, 2904.

configuration are the hydroxyl and the carbonyl group sufficiently far apart to prevent hydrogen-bonding.



(I)



(II)

This work has now been extended to cover most of the known types of structure which might allow intramolecular hydrogen-bonding in this region.

*Experimental.*—The experimental conditions were as in Parts V and VIII.[8] All compounds were studied in dilute solution ($<0{\cdot}0035$M) in carbon tetrachloride in a cell 10·0 mm. in length. Preliminary measurements at different concentrations showed the hydrogen-bonding to be intramolecular since the relative intensities of the bands due to free and bonded hydroxyl groups were independent of concentration.

*Results and Discussion.*—The relevant absorption frequencies with peak apparent molar extinction coefficients [$\varepsilon = (1/cl) \log_{10} (T_0/T)$] [9] are given in the Table. Apart from determining whether hydrogen-bonding exists, it is possible to state which of the hydroxyl groups in the dihydroxy-compounds is the donor and which the acceptor in the bonded system by examining closely the stretching frequency of the free hydroxyl group. In this type of compound, primary hydroxyl groups absorb at 3640—3642, axial secondary at 3637—3639, and equatorial secondary at 3628—3631 cm.$^{-1}$.[6,10]

(a) 3 : 24- and 3 : 23-*Dihydroxy-triterpenoids.* Urs-12-ene-3α : 24-diol (III) has the diaxial structure with no hydrogen bonding, while the spectrum of its 3β-isomer (IV) indicates that the primary hydroxyl is bonded to the oxygen of the equatorial secondary group (free OH, 3629 cm.$^{-1}$). This direction of bonding is probably due to the preferred orientation of the axial primary group away from the axial 10-methyl group.

*Hydroxyl and carbonyl absorption frequencies (cm.$^{-1}$, $CCl_4$ solutions), with peak apparent molar extinction coefficients in parentheses.*

| Compound | Free OH | Bonded OH | Free C–O | Bonded C–O |
|---|---|---|---|---|
| Urs-12-ene-3α : 24-diol (III) | 3641 (125) | — | | |
| Urs-12-ene-3β : 24-diol (IV) | 3629 (55) | 3550 $^{a}$ (45) | | |
| Me hederagenin (V) | 3643 (100)<br>3628 (sh) | 3532 $^{a}$ (70) | 1729 $^{b}$ (450) | |
| Me 3α-hydroxyurs-12-en-24-oate (II; R = Me) | 3638 (70) | — | 1723 (580) | |
| Me 3β-hydroxyurs-12-en-24-oate (VIIA–B) | 3627 $^{c}$ | 3548 $^{a}$ (75) | 1736 (70) | 1709 (530) |
| Me gypsogenin (VIIIA–B) | 3623 (50) | 3549 $^{a}$ (40) | 1729 $^{d}$ (575) | 1710 (200) |
| β-Boswellic acid (II; R = H) | 3638 (70)<br>3524 $^{e}$ | — | 1737 (165) | 1694 $^{f}$ (455) |
| Me hederagonate | 3630 $^{c}$<br>3602 (40) | 3540 $^{a}$ (20) | 1728 $^{b}$ (460) | 1697 (340) |
| Me icterogenin | 3635 (25) | 3518 (35) | 1746 $^{g}$ (450)<br>1718 $^{a, h}$ (435) | 1694 (310) |
| Cerin | 3615 | 3491<br>3436 $^{c}$ | 1715 | 1709 |

$^{a}$ Very broad. $^{b}$ Methoxycarbonyl. $^{c}$ Very weak. $^{d}$ Methoxycarbonyl plus non-bonded aldehyde. $^{e}$ Carboxyl-hydroxyl. $^{f}$ Dimeric acid (see ref. 5*b*). $^{g}$ Angelate carbonyl (see ref. 11). $^{h}$ Methoxycarbonyl plus non-bonded 3-ketone.

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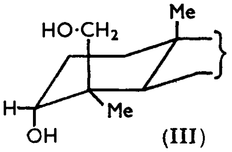
[8] (*a*) Cole and Thornton, *J.*, 1956, 1007; (*b*) Cole and Willix, *J.*, 1959, 1212.

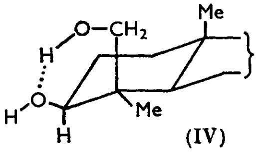
[9] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.

[10] Cole, Müller, Thornton, and Willix, *J.*, 1959, 1218.

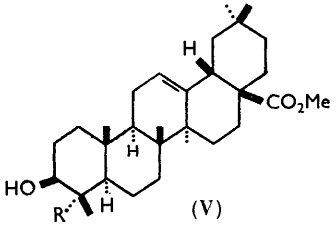
Methyl hederagenin (V; R = $CH_2$·OH), a 3β : 23-diol, exists mostly as (VA) (free primary OH 3643 cm.$^{-1}$) with a small proportion of (VB) [free secondary OH, 3628 cm.$^{-1}$ (shoulder)]. The methoxycarbonyl group absorbs at its normal position [8a] (1729 cm.$^{-1}$, see below).



(III)

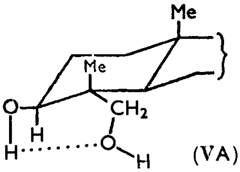


(IV)

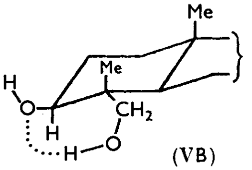


(V)

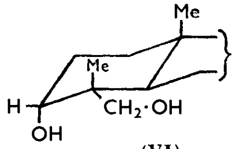
No sample of the second type of 3 : 23-diol (VI) was available. This structure would show hydrogen-bonding, probably as an equilibrium mixture as in (VA, VB), since the O–O distance in (VI) is the same as in (V) and the hydroxyl groups are not subject to steric repulsion by the 10-methyl group as in (IV).



(VA)

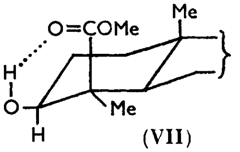


(VB)

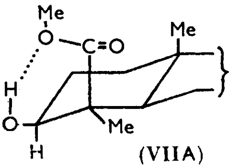


(VI)

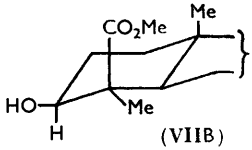
(b) *Carbonyl compounds.* This method of studying stereochemistry can be extended to cover 3-hydroxy-23 (or 24)-ketones and 23 (or 24)-hydroxy-3-ketones. Hydrogen-bonding lowers the frequency of both the hydroxyl and the carbonyl group. Thus, while methyl 3α-hydroxyurs-12-en-24-oate (β-boswellate) (I; R = $CO_2Me$) has no hydrogen-bonding (II; R = Me) and shows normal hydroxyl (axial, 3635 cm.$^{-1}$) and carbonyl absorption (1723 cm.$^{-1}$), its 3β-epimer exists almost completely in the hydrogen-bonded form (VII) (C = O 1709 cm.$^{-1}$). The frequency of the weak residual carbonyl band (1736 cm.$^{-1}$) is rather high compared with that of the 3α-compound and might indicate the presence of a small amount of material in which the hydrogen-bond is formed on to the other oxygen atom [4] (VIIA). The presence of a very small proportion of non-bonded material (VIIB) is shown by the weak shoulder at 3627 cm.$^{-1}$.



(VII)



(VIIA)



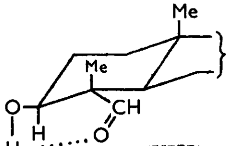
(VIIB)

The spectrum of methyl gypsogenin (V; R = CHO) indicates that the carbonyl group of an aldehyde is very much less effective as acceptor for a hydrogen-bond (VIII) than that of the methoxycarbonyl group, in agreement with the well-known electron-releasing properties of the methoxyl group. The high intensity of the free OH absorption band of this substance and the form of the carbonyl absorption show that in most of the molecules the hydroxyl group is free (VIIIA), although its frequency (3623 cm.$^{-1}$) is rather lower than usual for a secondary equatorial type. The carbonyl absorption consists of a major peak at 1729 cm.$^{-1}$ (methoxycarbonyl plus non-bonded aldehyde) with a shoulder at 1710 cm.$^{-1}$ due to the bonded carbonyl group.

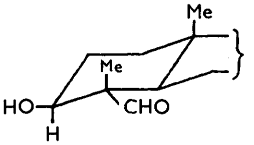
Methyl icterogenin [11] (IX) and methyl hederagonate (X) have respectively an axial and an equatorial primary 4-hydroxyl group which might be expected to form a hydrogen-bond

[11] Barton and de Mayo, *J.*, 1954, 887.

on to the 3-carbonyl group. The spectrum of the former is easily interpreted in terms of equilibrium between (IX) and (IXA) with the free hydroxyl of (IX) absorbing at 3635 cm.$^{-1}$ and its free carbonyl contributing to the peak at 1718 cm.$^{-1}$ which is rather broader than most carbonyl bands. Hydrogen-bonding causes the frequency of the greater part of the 3-carbonyl group to fall to 1694 cm.$^{-1}$.

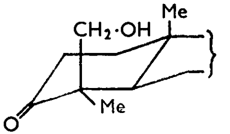


(VIII)

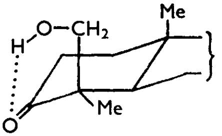


(VIIIA)

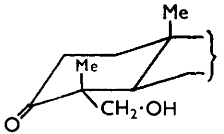
On the other hand, the spectrum of methyl hederagonate is more difficult to interpret. The high-frequency part the hydroxyl absorption is broad with a weak shoulder at about 3630 and its centre at 3602 cm.$^{-1}$, while there is a normal, fairly weak hydrogen-bond band centred at 3540 cm.$^{-1}$. That there is considerable hydrogen-bonding is illustrated by the



(IX)



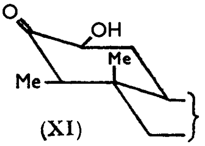
(IXA)



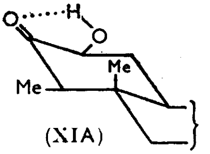
(X)

low 3-carbonyl frequency (1697 cm.$^{-1}$) and absence of free carbonyl near 1710—1715 cm.$^{-1}$ The weak absorption near 3630 cm.$^{-1}$ undoubtedly represents a small amount of free hydroxyl group, and the intramolecular hydrogen-bond might be influenced by the proximity of the $\pi$-electron system of the carbonyl group which is in approximately the same plane as the primary hydroxyl system.

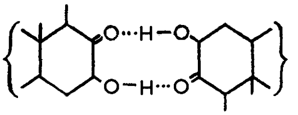
Cerin [12] (XI) belongs to a different class of compound and is included here because it forms an intramolecular hydrogen bond. It is sparingly soluble in carbon tetrachloride, indicating the formation of strong intermolecular hydrogen-bonds in the crystal, and it probably forms dimers similar to those of carboxylic acids (XII). Its hydroxyl spectrum has a " free " band at 3615 cm.$^{-1}$ (a low frequency for a secondary group, due to the presence of the carbonyl group), and two broad hydrogen-bond bands [3491, 3436 cm.$^{-1}$ (weak)]. The first of these is probably due to (XIA) and the second to a small amount of (XII) in solution. In the carbonyl absorption two bands of approximately equal intensity [1715 (free), 1709 cm.$^{-1}$ (bonded)] are just resolved from one another. More examples of compounds with neighbouring ketone and hydroxyl groups must be studied before more conclusions can be drawn about the nature of the interaction.



(XI)



(XIA)



(XII)

*Applications*.—The identification of systems involving intramolecular hydrogen-bonds by their infrared absorption has proved useful in the investigation of new compounds in this laboratory. A degradation product (XIII) of A$_1$-barrigenol [13] has a band at 3629 cm.$^{-1}$ ($\varepsilon$ 53) due to the equatorial 3-hydroxyl group, while the bonded enol absorbs at 3415

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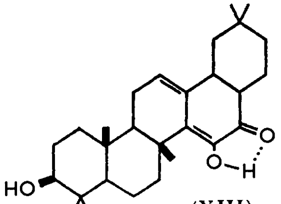
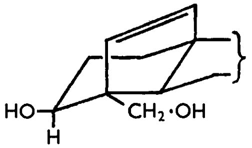
[12] Corey and Ursprung, *J. Amer. Chem. Soc.*, 1955, **77**, 3668; Brownlie, Spring, Stevenson, and Strachan, *J.*, 1956, 2419.

[13] Cole, Downing, Watkins, and White, *Chem. and Ind.*, 1955, 254.

cm.$^{-1}$ and the conjugated and bonded carbonyl group at 1625 cm.$^{-1}$. A diterpenoid triol[14] isolated from *Beyeria leschenaultii* var. drummondii which has the probable A/B ring system (XIV) and a number of its degradation products show hydroxyl absorption similar to that of (V), indicating the steric relation of two of the hydroxyl groups. Measurements in this region of the spectrum would assist in the location of hydroxyl groups on ring E of triterpenoids such as treleasegenic acid.[15]



(XIII)



(XIV)

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Nedlands, Western Australia.

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[14] Cole, White, and Woods, unpublished results.

[15] Djerassi and Mills, *J. Amer. Chem. Soc.*, 1958, **80**, 1236.