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Spectroscopic Studies on Enols

Part 6. Enolisation and Hydrogen Bonding in 3-Acylcyclopentane-1,2,4-triones

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The nuclear magnetic resonance and infrared spectra of several 3-acylcyclopentane-1,2,4-triones, derived from hop resins, have been studied. Thus isohumulinic acid (5-isopentyl-3-isovalerylcyclopentane-1,2,4-trione), isocohumulinic acid (5-isopentyl-3-isobutyrylcyclopentane-1,2,4-trione) and dehydrohumulinic acid [3-isovaleryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione] are all di-enolic showing comparably weak hydrogen bonding as judged by signals due to the enolic protons at τ -2 to -3 and 2.3 to 2.5. Cohulupone [2-isobutyryl-5,5-di-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione] is mono-enolic with the signal from the enolic proton at τ -2 to -3. Occasionally two enolic forms were observed.

Various 3-acylcyclopentane-1,2,4-triones are known as degradation products of the hop resins. Thus from the degradation of humulone Wieland[1] isolated isohumulinic acid and assigned it the structure (1; R = Bu^i) which was supported by further degradation[2] and by its formation from dihydrohumulinic acid.[3] Similarly[4] cohumulone gave isocohumulinic acid (1; R = Pr^i). Subsequently Howard and Slater[5] oxidized humulinic acid with bismuth oxide and obtained the corresponding triketone with the unsaturated side chain, 3-isovaleryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione (2), for which we propose the trivial name dehydrohumulinic acid. Another group of hop resins, the hulupones, were recently isolated and assigned[6,7] the 3-acyl-5,5-di-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione structure (3) which was confirmed by the stepwise preparation of tetrahydrocohulupone from colupulone.[8] Cohulupone (3; R = $\mathrm{Pr^i}$) could also be prepared directly from colupulone while hulupone itself (3; R = $\mathrm{Bu^i}$) has been prepared by alkylation of dehydrohumulinic acid.[9]

Although these compounds have been called triketones, and are written here in this form, numerous possibilities for enolisation and hydrogen bonding occur, which provide for an extension of earlier studies of the β-tricarbonylmethane system (*cf.* Refs. [10–14]). The behaviour of 3-acylcyclopentane-1,2,4-triones is of special interest in relation to the properties of 2-acetylcyclopentane-1,3-diones and 2-acetylcyclopent-4-ene-1,3-diones[15] and of related studies on the tautomerism of the humulinic acids.[16] We have therefore examined nuclear magnetic resonance (NMR) and infrared spectra of representative compounds of this series.

It will be convenient to consider first the NMR spectra given by isohumulinic, isocohumulinic and dehydrohumulinic acids. That of the last compound is given in Fig. 1 and the data for the three compounds are collected in Table 1.

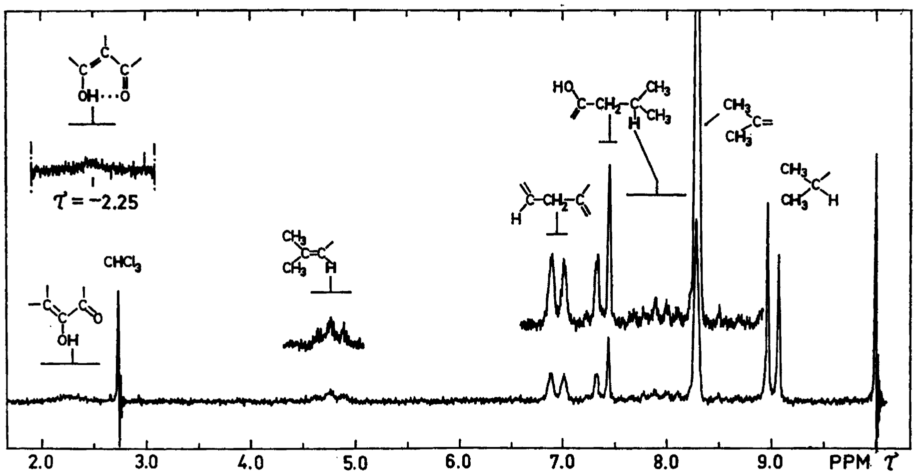
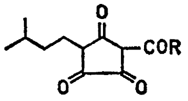


Fig. 1. NMR spectrum of dehydrohumulinic acid (2) in deuteriochloroform (60 Mc/s).

The spectrum of each compound shows two broad one-proton signals centred near τ 2.4 and -2.4. The low-field signal is attributed to a chelated enolic hydroxyl, *i.e.* to the acidic function of the compounds. This signal occurs at higher field than for many other chelated enols[16] of β-tricarbonyl compounds (τ generally between -7 and -9)[10–14] and even at higher field than in the enol of acetylacetone ($\tau = -5$). This seems to imply comparatively weak hydrogen bonding. Similar signals are found, however, in the spectra of cohulupone

Table 1. Proton magnetic resonance results for 10 % solutions in $CDCl_3$ containing 0.2 % $SiMe_4$

τ values (*J* c/sec)			Intensity (Splitting)	Assignment
Isohumulinic Acid	Isocohumulinic Acid	Dehydrohumulinic Acid		
9.06 (5.5)	9.07 (5.5)	—	6 (Doublet)	Me_2 of alkyl side chain
9.01 (6.5)	8.80 (7.0)	9.01(6.5)	6 (Doublet)	Me_2 of acyl side chain
8.53	8.53	—	2 (*ca.* Triplet)	β-CH_2 of isopentyl chain
—	—	8.27	6	$Me_2C=C$
8.28	8.28	—	1 (Broad multiplet)	Me_2CH of isopentyl chain
7.88	—	7.88	1 (Multiplet)	Me_2CH of isovaleryl chain
7.63 (7.0)	7.63 (7.0)	—	2 (Triplet)	α-CH_2 of isopentyl group
7.38	—	7.38	2 (*ca.* Doublet)	CH_2 of acyl side chain
—	—	6.95	2 (Doublet)	CH_2 of Me_2C:CH-CH_2
—	6.46	—	1 (Septuplet)	CH of isobutyryl side chain
—	—	4.75	1 (Triplet)	CH of Me_2C:CH-CH_2-
2.40 (broad, 1.2 p.p.m.)	2.50 (broad, 1.2 p.p.m.)	2.33	1	Enolic OH
−2.45 (broad, 0.7 p.p.m.)	−2.40 (broad, 0.7 p.p.m.)	−2.25	1	Enolic bonded OH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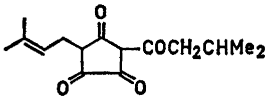
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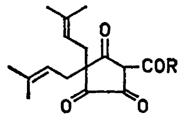
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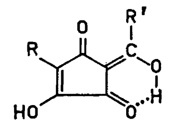
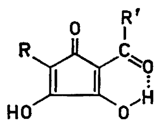

4a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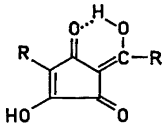
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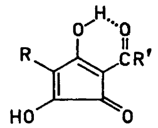
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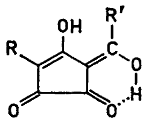
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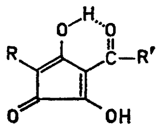

4f

R = $(CH_3)_2C=CHCH_2$– *or* $(CH_3)_2CHCH_2CH_2$–
R′ = $(CH_3)_2CH$– *or* $(CH_3)_2CHCH_2$–

(see below), 2-acetylcyclopentane-1,3-diones (τ *ca.* −4) and 2-acetylcyclopent-4-ene-1,3-diones (τ *ca.* −2).[15] The other low-field signal is due to a less acidic enolic hydroxyl which is only weakly hydrogen bonded, if at all, and can be compared with that in the mono-enolic 3-methylcyclopentane-1,2-dione ($\tau = 3.28$).[17] The compounds are therefore di-enolic. Signals corresponding to the triketone structures (1) and (2) or derived monoenols were not observed.

Several interconvertible di-enolic forms are possible (4 *a-f*). Of these *a* and *b* as well as *c* and *d* should be rapidly interconvertible since the hydrogen bonds need not be broken in the transformations. Generally it is not possible to distinguish such tautomers by NMR spectroscopy. On the other hand if the pairs *a-b* and *c-d* coexist in solution they will be slowly interconverted and it would be possible to observe these forms by NMR spectroscopy. No splitting which could be attributed to the occurrence of more than one form was observed.

Of the possible di-enolic structures those containing a cyclopentadienone structure (4*b* 4*d* and 4*f*) are considered unlikely on theoretical grounds. As was predicted by calculation[18] cyclopentadienone readily dimerizes,[19] a tendency not observed in the present series. Further the related compound cyclopentene-3,5-dione is not enolic and shows no tendency to enolise into a hydroxycyclopentadienone.[20,21] The structures remaining for consideration (4*a*, 4*c*, and 4*e*) all contain an exo-cyclic enolic double-bond. Preliminary quantum-mechanical calculations[22] also indicate these enols to be favoured. Mention should also be made of the generalization of Brown, Brewster and Shechter[23] that in simple compounds with five membered rings, in contrast to the cyclohexane series, exo-cyclic double bonds are favoured over those within the ring.

Although reactivity data do not permit any safe conclusions regarding the enol equilibria[24] it should be mentioned that alkylation and hydrogenation first affect positions 5 and 1, respectively, in compounds 1 and 2. Thus alkylation with methyl iodide or 3-methylbut-2-enyl bromide (sodium methoxide in methanol-ether) gives the 5-alkyl derivatives, or hulupone.[9] On catalytic hydrogenation the carbonyl group at C—1 is reduced first. On further hydrogenation the acyl side chain is reduced to an alkyl group, the reduction thus leading eventually to cyclopentane-1,3-dione derivatives.[16,25]

Further evidence for the di-enolic structures in the case of isohumulinic and isocohumulinic acids ($R=Bu^i$, Pr^i, respectively) comes from the chemical shift (τ 7.63) of the lower field of the two methylene groups in the 5-isopentyl side chain which indicates proximity to a double bond. The signal is split as a triplet ($J=7$ c/sec.) by the adjacent methylene (at τ 8.53) and the absence of further splitting confirms that there is no proton at the 5-position of the ring. Indeed there is no triplet signal in the spectra which could be reasonably attributed to a proton at C—5.

There is no ambiguity in the assignment of the methylene signals from isocohumulinic acid (Table 1), and it is also clear that of the two six-proton doublets, at τ 9.07 and 8.80, that at higher field arises from the gem-dimethyl group at the end of the isopentyl chain. The other signal comes from the methyl groups attached β to the double bond in the enolised isobutyryl chain. Each signal is split as a doublet because of coupling to an adjacent proton. These CH group protons give broad multiplet signals as expected, at τ 8.28 and 6.46. The latter position is at lower field than for the CH signal of isopropyl methyl ketone (τ 7.58). Incidentally, the gem-dimethyl group of this ketone gives a doublet signal at τ 8.93. The additional deshielding of the side-chain protons in isocohumulinic acid must arise from the nearby enolic 1,3-dicarbonyl system and the chelate ring.

In the spectrum of isohumulinic acid the two signals from the pair of gem-dimethyl groups have almost the same chemical shift, but it is appropriate to assign that at highest field to the methyls of the saturated isopentyl chain. There is an additional methylene-group signal at τ 7.38 which appears as a characteristically distorted approximation to a doublet, recognizable as the A_2 part of an A_2B spin multiplet system, and so this signal must be assigned to the methylene group of the isovaleryl chain. The CH group in the latter gives a broad multiplet signal at τ 7.88, at higher-field than the corresponding CH group in isocohumulinic acid, as expected from its more remote position from the enol double bond and the cyclopentene ring. The remaining signals in the spectrum of isohumulinic acid (Table 1) parallel those from isocohumulinic acid.

The spectrum of dehydrohumulinic acid (2) shows the same signals as isohumulinic acid attributable to the isovaleryl side chain. The 3-methylbut-2-enyl side chain gives signals from the methyl groups (τ 8.3) and the methylene group (τ 6.95) which are, as expected, at lower fields than from these groups in the saturated compounds (1). The methylene signal at τ 6.95 from dehydrohumulinic acid is split as a doublet by the adjacent olefinic proton, and as there is no sign of further multiplicity, there cannot be a proton at C—5 in the ring. The olefinic proton, at τ 4.77 is split into a triplet which shows signs of further splitting (by the gem-methyl protons), as expected.

The infrared spectra of dehydro-, iso-, and isoco-humulinic acids are all very similar whether measured in chloroform solution or in potassium bromide discs. All show a strong broad band in the region 1618—1645 cm^{-1}, which may be two overlapping bands, as a shoulder is sometimes observed at *ca.*

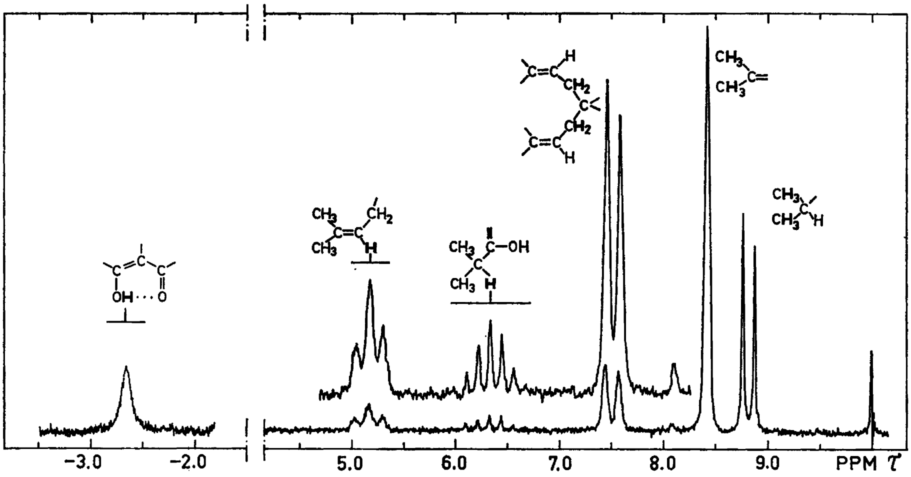


Fig. 2. NMR spectrum of cohulupone [3, R= -CH $(CH_3)_2$] in deuteriochloroform (60 Mc/s).

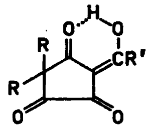
1667 cm^{-1}, and in other cases a much weaker band in the region 1710—1724 cm^{-1}. The spectra differ from that of cohulupone (see below), which shows two bands below 1700 cm^{-1}, and 2-acetyl-4-methylcyclopent-4-ene-1,3-dione,[15] in which the low frequency band is resolved into two bands at 1660 and 1615 cm^{-1}. The band at 1710 cm^{-1}, however, has a counterpart in other spectra and indicates that in at least dehydrohumulinic acid there is one conjugated ring carbonyl group which is not involved in strong hydrogen bonding.

A typical NMR spectrum of cohulupone is given in Fig. 2 together with the assignments. Only one enolic proton is found at around τ -3 to -2 (somewhat dependent on concentration), a similar field to that in the other acyltriketones examined. The signals attributable to the isobutyryl side chain are at similar field strengths to those in isocohumulinic acid. Those signals attributable to the 3-methylbut-2-enyl side chains are at the same fields as from these chains in hulupinic acid,[26] but at higher fields than from the chain in dehydrohumulinic acid in which there is a double bond at the point of attachment. A sample of cohulupone kept under nitrogen for several months showed the signal for the enolic proton at a lower field and split into two signals (τ -3.08 and -2.90). Each of the signals from the isobutyryl grouping also showed doublet splitting. This splitting disappeared on addition of a small amount of triethylamine and could be due to the presence of two enolic forms (*cf.* Refs.[10,11,14,15]). Possibly the other samples contained minor amounts of acidic autoxidation products which catalysed the interconversion of the enolic forms. Further indications that cohulupone can exist in more than one enolic form came from its infrared absorption. The infrared spectrum of hulupone was reported by Spetsig and Steninger[7] to show four bands between 1580 and 1780 cm^{-1}. There are, however, differences between the spectra in carbon tetrachloride and chloroform solutions (Table 2). The main bands in the carbonyl region are similar but all the bands show shoulders which are more marked for the chloroform than for the carbon tetrachloride solution. In the spectrum of the chloroform solution the shoulders account for approximately 30 % of the peak area. while in the carbon tetrachloride spectrum the value is only *ca.* 10 %. This subsidiary absorption may well arise from a second enolic form. It is perhaps noteworthy that, in the splitting of the enol signal in the NMR spectrum observed on the one occasion, the ratio of the intensity of the signals was approximately 30:70 again suggesting that the chloroform solution contained 30 % of a second enolic form.

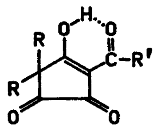
Table 2. Infrared absorptions for cohulupone in the carbonyl region given in cm^{-1}. Figures in brackets refer to the shoulders.

Chloroform	1750(1760)	1706(1690)	1650(1640)	1577(1564)
Carbon tetrachloride	1755(1765)	1710(1690)	1652(1640)	1580(1565?)

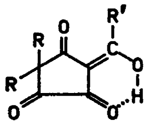
The possible enolic forms which may be considered for cohulupone are 5 *a*-*e*. Of these, 5*e* can be excluded because the enolic signal in the NMR spectrum is at much lower field than would be expected for such a weakly



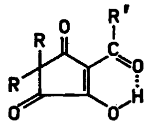
5a



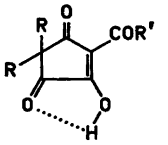
5b



5c



5d



5e

R = $(CH_3)_2C=CHCH_2$-
R' = $(CH_3)_2CH$-

bonded structure, and because of the infrared absorption. For the remaining structures similar arguments to those advanced above apply favouring the exo-cyclic enols 5*a* and 5*c*. As with isohumulinic acid hydrogenation occurs first at C—1 followed by reduction of the acyl side chain.[25]

EXPERIMENTAL

Methods. The NMR spectra were recorded on Varian A60 spectrometers for 10—20 % solutions in carbon tetrachloride or deuteriochloroform. The probe temperature was 40 ± 1° in Stockholm and 38 ± 1° in London. The calibration of the spectrometers were frequently checked and are accurate to within ± 1 c/s. The values for the enolic protons are dependent upon concentration.

The infrared spectra were recorded on Perkin Elmer spectrometers with sodium chloride optics, Model No. 21 in Stockholm and No. 137 at Nutfield.

Solution spectra were measured for *ca.* 0.1 M solutions in 0.1 mm cells.

Materials. Isohumulinic, isocohumulinic and dehydrohumulinic acids were prepared as described in the literature [3,4,16,5] and had the recorded m.p.'s. Cohulupone was prepared from colupulone using the method of Wright[9] and stored in sealed ampoules under nitrogen. Spectra were also taken for samples which had been occasionally exposed to the air and for a sample which was freshly purified *via* the sodium salt and redistilled (b.p. 100—102°/10^{-3} mm).

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