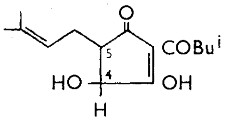
223. *Chemistry of Hop Constituents. Part XXIII.*[1,2] *The Structure of Humulinic Acid C and Other Acid-transformation Products of Humulinic Acids.*

By J. S. Burton, J. A. Elvidge, and R. Stevens.

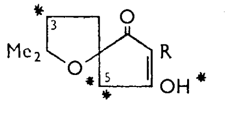
It is shown by oxidation, reduction, and proton magnetic resonance (p.m.r.) spectroscopy that humulinic acid C, an acid-isomerisation product of humulinic acid A (I), has the tetrahydrofuranspirocyclopentenone (IV); cohumulinic acid C is the analogue (V). Acid-isomerisation of dehydrohumulinic acid (VII) yields the dihydropyranocyclopentenedione (XI). Similar treatment of the dihydrohumulinic acids effects dehydration to the alkylidenecyclopentenolone (XIII), which was hydrogenated first to the acylcyclopentanedione (XIV) and then to the known deoxydihydrohumulinic acid (XVI). Deacylation of (XIV) gives the isopentylcyclopentanedione (XV). The isomeric isopentylcyclopentanedione (XIX) was prepared from the isopentylcyclopentanetrione (XVII).

We report an investigation of the products derived by acid treatment of humulinic acid A (I), dihydrohumulinic acid A, and dehydrohumulinic acid (VII). The isomerisations (I) ⟶ (IV) and (VII) ⟶ (XI) are established. Dihydrohumulinic acid is dehydrated to (XIII).

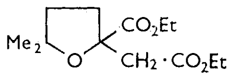
Humulinic Acid C (*Isomerisation of Humulinic Acid*).—We showed[3] by proton magnetic resonance (p.m.r.) that the humulinic acids A and B are the 4,5-*trans*- and 4,5-*cis*-stereoisomers (I) and (II),* and this was later confirmed.[4] A humulinic acid C, presumed from the molecular weight to be another isomer, was obtained by treatment of humulinic acid A with hydrochloric acid.[5] We also encountered this compound during a systematic study of the effect of perchloric acid upon hop constituents. Its identification, from the ultraviolet and infrared spectra published by Verzele,[5] was confirmed by comparison with a sample made by Verzele's method. We find that it is indeed a third humulinic acid isomer, $C_{15}H_{22}O_4$.



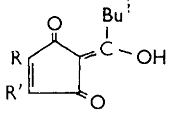
(I) 4,5-*trans*
(II) 4,5-*cis*



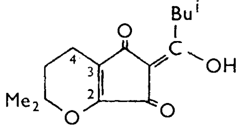
(III) R = $[CH_2]_2\cdot CHMe_2$
(IV) R = $CO\cdot\overset{**}{C}H_2\cdot CHMe_2$
(V) R = $COPr^i$



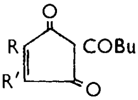
(VI)



(VII) R = $Me_2C{:}CH\cdot CH_2$, R' = OH
(VIII) R = $Me_2CH\cdot[CH_2]_2$, R' = OH
(IXb) R = $Me_2CH\cdot[CH_2]_2$, R' = H
(Xb) R = R' = Me



(XI)
(XII) 2,3-bond saturated



(IXa) R = $Me_2CH\cdot[CH_2]_2$, R' = H
(Xa) R = R' = Me

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* Only single tautomers are shown in this Paper for brevity.

[1] Part XXII, Burton, Stevens, and Elvidge, *J. Inst. Brewing*, 1964, **70**, 345.

[2] Preliminary communication, Burton, Elvidge, and Stevens, *Proc. Chem. Soc.*, **1964**, **220**.

[3] Burton, Elvidge, and Stevens, *J.*, 1964, 3816.

[4] (*a*) Lepoivre, Alderweireldt, Anteunis, and Verzele, *Bull. Soc. chim. belges*, 1964, **73**, **275**; (*b*) Alderweireldt and Anteunis, *ibid.*, p. 285.

[5] Anteunis, Brake, Verzele, and Alderweireldt, *Bull. Soc. chim. belges*, 1962, **71**, **623**.

Humulinic acid C had the same enolised-tricarbonyl chromophore as the A isomer but lacked *s*-hydroxyl absorption in the infrared region. It did not react with iodine, or absorb hydrogen over palladium–barium sulphate catalyst, so there was no side-chain double bond. These findings pointed to a tetrahydropyranocyclopentanedione structure (XII) but this was precluded by the p.m.r. spectrum (Table), there being no resonance

TABLE.

Proton magnetic resonance results for 5—10% solutions in deuterochloroform containing 0·2% tetramethylsilane.

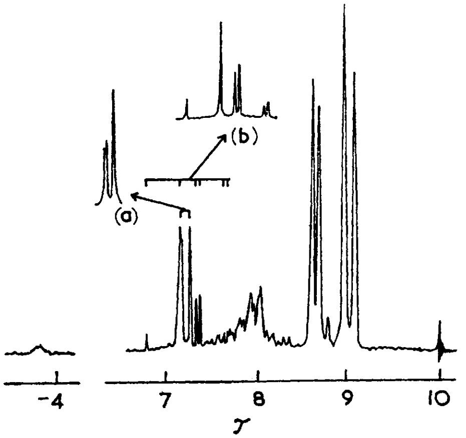
τ-values				Intensity; splitting * J (c./sec.)	Assignment
(III)	(VI)	(IV)	(V)		
9·11				6d (6)	Me_2 of alkyl chain
		9·02	8·84	6d (6; 7) †	Me_2 of acyl chain
	8·75			3t (7)	Me of $CH_2{\cdot}CO_2Et$
	8·70			3t (7)	Me of $\rightarrow C{\cdot}CO_2Et$
8·68	8·73	8·67	8·67	6s	$Me_2C<$
8·65	8·67	8·61	8·61	s	
~8·67				3	$CH_2{\cdot}CH$ of alkyl chain
	~7·95		~7·97	4	$CH_2{\cdot}CH_2$ of tetrahydrofuran ring
~7·98		~7·97		5	$CH_2{\cdot}CH_2$ of tetrahydrofuran ring CH of acyl chain
7·60				2t (7·5)	α-CH_2 of alkyl chain
7·33				2sb	$CH_2{\cdot}CO{\cdot}$ of ring
		7·46	7·37	1dd (20, 2; 19, 1·8) †	
		7·03	7·09	1d (20; 19) †	
	7·17			2s	$CH_2{\cdot}CO_2{\cdot}$
		7·19		2 ~d, A_2 part of A_2B	$CH_2{\cdot}CO{\cdot}$ of acyl chain
			6·39	1sep (7)	CH of acyl chain
	5·8			2q (7)	ester-CH_2 of $CH_2{\cdot}CO_2Et$
	5·85			2q (7)	CH_2 of $C{\cdot}CO_2Et$
0·63		−4·20	−3·17	1 (breadth, 0·4; 0·4; 0·7 p.p.m.) †	enolic OH
(XI)	(XIII)	(XIV)	(XVI)		
9·00		9·08		6d (6·5; 6) †	Me_2 of alkyl chain
	9·03		9·09	12d (6·5; 5·5) †	2 × Me_2
		9·00		6d (6·5)	Me_2 of acyl chain
8·56				6s	Me_2C
			8·92 to 8·03	8	2 × CH and 3 × CH_2 of side-chains
	~8·37			1	CH of $Me_2CH{\cdot}CH_2$
		8·85 to 8·2		5	$CH{\cdot}[CH_2]_2$ of alkyl chain
8·22				2t (6·5)	$\rightarrow C{\cdot}CH_2$ of dihydropyran ring
7·56				2t (6·5)	$CH_2{\cdot}C{=}$ of dihydropyran ring
7·89	7·92			1	CH of acyl chain
		8·2 to 7·1		4	$CH_2{\cdot}CH<$ of ring
	7·82			2t	CH_2 of alkenyl chain
			7·78	2t (7·5)	α-CH_2 of 2-isopentyl chain
7·38	7·17	7·19		2d, A_2 part or A_2B	$CH_2{\cdot}CO$ of acyl chain
	6·98		~7·38	2s; s b †	CH_2 of ring
			~7·12	1	CH of ring
	3·28			1tt (7·5, 2)	olefinic H
−1·92	−4·00	−3·40	−1·00	1 (breadth, 1·7; 0·3; 0·7; 0·4 p.p.m.) †	enolic OH
(XV)	(XVII)	(XIX)			
9·10	9·05	9·09		6d (6·0; 5·5; 5·5) †	Me_2 of alkyl chain
~8·72				4	$[CH_2]_2$ of alkyl chain
	8·59	8·72		2 A_2 part of A_2B	CH_2 of $Me_2CH{\cdot}CH_2$
8·55	8·41	8·53		1 B	CH of $Me_2CH{\cdot}CH_2$
	7·53	7·76		2t (7·5; 7·5) †	α-CH_2 of alkyl chain
		7·42		4s	$[CH_2]_2$ of ring
~7·36				3	$CH_2{\cdot}CH<$ of ring
	7·01			2s	CH_2 of ring
4·68				1s, b	=CH– of ring
−0·05	1·67	−1·33		1 (breadth, 0·3; 0·4 p.p.m.; s) †	enolic OH

* s = singlet, d = doublet, t = triplet, q = quadruplet, dd = double doublet, tt = triple triplet, sep = septuplet, b = broadened, unspecified = complex band. † Respectively.

lines in the τ 6 region from a proton adjacent to ethereal oxygen, or any ring-methylene absorption near τ 8·5.

With Adams catalyst and hydrogen, humulinic acid C gave (as did the A isomer) [3] a reduction product in which the acyl side-chain was reduced to alkyl. The p.m.r. spectrum of this product, $C_{15}H_{24}O_3$, suggested the spiro-structure (III). Salient features of the spectrum (Table) were the doublet ($J = 6$ c./sec.) at τ 9·11 from the isopentyl methyl groups, the two lines at τ 8·68 and 8·65 from the almost equivalent geminal methyl groups adjacent to ethereal oxygen, the pattern approximating to symmetrical A_2B_2, centred at τ 7·98, from the 3- and 4-methylene protons of the tetrahydrofuran ring, and the broadened singlet at τ 7·33 from the isolated methylene in the mono-enolised cyclopentanedione ring.

The deduction of structure (III) for the reduction product implied that humulinic acid C had the spiro-structure (IV). Support for this was sought from oxidation. No characteristic degradation product of humulinic acid C was obtained with alkaline hydrogen peroxide or potassium permanganate. Periodate, however, gave a carboxylic product isolated as the di-(*p*-bromophenacyl) ester and as the liquid diethyl ester. The last gave a p.m.r. spectrum in accord with the expected tetrahydrofuran constitution (VI), showing lines at τ 8·73 and 8·67 from the non-equivalent geminal methyl groups adjacent to oxygen, and a near-symmetrical pattern centred at τ 7·97 from the 3- and 4-methylenes of the ring. The comparable *gem*-methyl group of eucalyptol appears at τ 8·75 [6a] and the β-methylene groups of tetrahydrofuran at τ 8·15.[6b] Both of these are at slightly higher field than in (VI), the latter because of the absence of ester groups, and the former for this reason and because of an enlarged ring. Further features in the p.m.r. spectrum of compound (VI) comprised two sets of A_2X_3 lines from the ethyl ester groups, and a two-proton singlet at τ 7·17. The last showed that the side-chain methylene protons were equivalent; in general this is not so when there are three different groups attached to the next carbon atom. However, a precedent was provided by the analogous methylene protons (τ 7·18) of diethyl malate (see Experimental section).



Proton magnetic resonance spectrum of humulinic acid C in deuterochloroform at 60 Mc./sec.

It thus became certain that humulinic acid C had the spiro-constitution (IV). The signals in the p.m.r. spectrum, except for those near τ 7, from four protons, could then be assigned by analogy with the spectrum of the reduction product (III) (Table). Assignments of the remaining lines were made, as indicated in the Figure, to the protons of the two methylene groups adjacent to carbonyl in structure (IV). The methylene group of the isovaleryl side-chain was expected to give rise to the distorted approximation to a doublet (the A_2 part of an A_2B system) which was a characteristic feature of the spectra of previously

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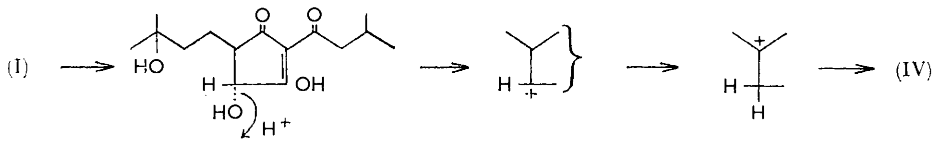
[6] Bhacca, Johnson, and Shoolery, " NMR Spectra Catalog," Varian Associates, Palo Alto, 1962, (*a*) No. 280, (*b*) No. 77.

examined compounds of this series.[1,7] Graphical subtraction of this feature [(a) in the Figure] then left the lines from the 5′-methylene protons. These [shown at (b)] formed an AB quartet ($J = 20$ c./sec.) in which the higher-field pair of lines showed additional doublet splitting ($J = 2$ c./sec.). These deductions were supported by the spectrum of cohumulinic acid C (V) which showed, unobscured, an analogous pattern of lines in the τ 7 region (with $J = 19$, 1·8 c./sec.). In each case the small splitting is attributable to long-range coupling with a proton at C-3 of the tetrahydrofuran ring. This is reasonable because scale models show that there is a dihedral angle of about 180° between one proton at that position and a proton at C-5′, and the arrangement of the intervening σ-bonds is transoid. The p.m.r. spectrum of the reduction product (III) lacks corresponding fine structure, presumably because of flexing of the cyclopentenolone ring. The additional chelate ring in humulinic acid C (IV) evidently results in much greater rigidity, which is a requirement for the long-range coupling and for the marked non-equivalence of the 5′-methylene protons.

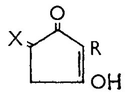
The formation of humulinic acid C (IV) from A (I) appears to involve hydration of the isopentenyl double bond, elimination of the *s*-hydroxyl group, isomerisation of the carbonium intermediate, and cyclisation:



When the isomerisation was performed with deuterium chloride in MeOD–D_2O, a humulinic acid C was isolated which had a simplified p.m.r. spectrum (Experimental section) in that the signals from six protons were missing. These appeared to be the protons marked * in (IV), consistent with the suggested mechanism and general expectations.

Isomerisation of Dehydrohumulinic Acid.—Treatment of dehydrohumulinic acid (VII) with perchloric acid gave an oily isomeric product, $C_{15}H_{20}O_4$, with a modified chromophore. The p.m.r. spectrum (Table) showed that this new compound was the fused-ring dihydropyranocyclopentenedione (XI). Immediately recognisable were the resonance signals from an exocyclically enolised isovaleryl group (with the $CH_2{\cdot}CO$ at τ 7·38) as previously found for isohumulinic acid (VIII) and for the starting material (VII), but there was no signal from an olefinic proton, as given by (VII). The rest of the spectrum comprised a six-proton singlet at τ 8·56, assignable to a geminal methyl grouping adjacent to oxygen, and two two-proton triplets ($J = 6{\cdot}5$ c./sec.) at τ 8·22 and 7·56. The two methylene groups responsible for the last signals are those which complete the dihydropyran ring in the structure (XI). A separate study of the reduction of the system (XI) is now in hand.

The cyclisation of dehydrohumulinic acid (VII) occurs straightforwardly to the dihydropyrano-compound (XI) presumably because dehydrohumulinic acid has a planar constitution.[7] In humulinic acid A (I) the hydroxyl group and olefinic bond are *trans*-disposed with respect to the plane of the cyclopentenolone ring. Simple acid-catalysed addition is therefore precluded.

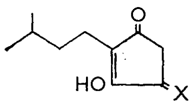


(XIII) $\mathrm{R = CO{\cdot}Bu^t,\ X = Me_2CH{\cdot}CH_2{\cdot}CH{=}}$

(XIV) $\mathrm{R = CO{\cdot}Bu^t,\ X = \begin{smallmatrix}Me_2CH{\cdot}[CH_2]_2\\ H\end{smallmatrix}\!>}$

(XV) $\mathrm{R = H,\ X = \begin{smallmatrix}Me_2CH{\cdot}[CH_2]_2\\ H\end{smallmatrix}\!>}$

(XVI) $\mathrm{R = [CH_2]_2{\cdot}CHMe_2,\ X = \begin{smallmatrix}R\\ H\end{smallmatrix}\!>}$



(XVII) $\mathrm{X = O}$

(XVIII) $\mathrm{X = <\!\begin{smallmatrix}OH\\ H\end{smallmatrix}}$

(XIX) $\mathrm{X = H_2}$

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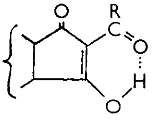
[7] Forsén, Nilsson, Elvidge, Burton, and Stevens, *Acta Chem. Scand.*, 1964, **18**, 513.

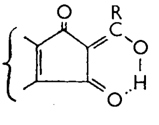
Dehydration of Dihydrohumulinic Acid.—In initial experiments concerning the relationship between the humulinic acids A and B, we examined the dehydration of the two forms of dihydrohumulinic acid. Birch and English [8] had dehydrated dihydrohumulinic acid A to a compound (IXa), m. p. 75—76°, with the chromophore of calythrone (Xa). Despite many attempts, we were unable to obtain this product. In our hands, the dehydration of both dihydrohumulinic acid A and B, using polyphosphoric acid or a mixture of hydrochloric and glacial acetic acids led to an oil isomeric with (IX). (No change was effected by perchloric acid in acetic acid.) The dehydration product failed to crystallise and the light-absorption differed from that of Birch's compound and calythrone. The p.m.r. spectrum (Table) showed it to have the structure (XIII) and this was supported by ozonolysis to give isovaleraldehyde.

There was an olefinic proton signal in the p.m.r. spectrum of the dehydration product (XIII) which was split as a triple triplet ($J = 7{\cdot}5$, 2 c./sec.). This indicated coupling to the protons of an adjacent methylene group (at τ 7·82) and also to another methylene at longer-range, in the "allylic" position. The latter methylene group gave a broadened signal at τ 6·98, indicative of its position in the cyclopentane ring adjacent to the tautomeric 1,3-dicarbonyl system. The higher-field methylene group of the alkenyl chain appeared as a triplet because of equal coupling to protons, one on each side. Also consistent with the structure (XIII) was the fact that the doublet signal from the terminal *gem*-methyl group of the alkenyl chain had moved downfield slightly from its position in the spectrum of the dihydrohumulinic acid [3] to coincide with the signal from the geminal methyl of the acyl side-chain.

The structure (XIII) is of interest in connection with the reluctance of the cyclopentanediones to assume a cyclopentadiene configuration.[7] Humulinic and dihydrohumulinic acids have the *endo*-enol structure (A),[3] but dehydrohumulinic acid [7] and 4-acetylcyclopentene-3,5-dione [9] have the *exo*-enol structure (B), evidently because the alternative direction of enolisation would lead to the unfavourable cyclopentadienone form. If the dehydration product of dihydrohumulinic acid is not to take up a cyclopentadienone configuration, one of the double bonds must migrate. Presumably the carbonium ion formed in the dehydration is more easily rearranged than the chelated enol system, so that the structure (XIII) results. An extension of this argument suggests that Birch's compound (IXa) and calythrone (Xa) will have the fine structures (IXb) and (Xb), respectively.



(A)



(B)

Mild hydrogenation of the dehydration product (XIII) saturated the *exo*-double bond at C-4, as confirmed by the p.m.r. spectrum (Table), to give 4-isopentyl-2-isovalerylcyclopentane-1,3-dione (XIV). This had the same chromophore as the recently synthesised 2-acetylcyclopentane-1,3-dione which was reported [10] to be readily deacylated. Our compound (XIV) was stable to both dilute acid and alkali, but was deacylated with 95% sulphuric acid to give the enolised 4-isopentylcyclopentane-1,3-dione (XV). The p.m.r. spectrum (Table) confirmed the structure. An important feature in the spectrum was the singlet at τ 4·68 from the olefinic proton of the ring, a part of the enolised 1,3-dicarbonyl system. The enol proton was at τ —0·05.

Hydrogenation of compound (XIII) over Adams catalyst gave a further reduction product, $C_{15}H_{26}O_2$, identical with the "deoxydihydrohumulinic acid" [11,12] originally

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[8] Birch and English, *J.*, 1957, 3805.

[9] Nilsson, personal communication.

[10] Merenyi and Nilsson, *Acta Chem. Scand.*, 1963, **17**, 1801.

[11] Wieland and Martz, *Ber.*, 1926, **59**, 2352.

[12] Harris, Howard, and Pollock, *J.*, 1952, 1906.

obtained by Clemmensen reduction of dihydrohumulinic acid. Confirmation of Wieland and Martz's [11] structure (XVI) came from the p.m.r. spectrum (Table). The same compound was also obtained by hydrogenation of isohumulinic acid (VIII) in glacial acetic acid containing perchloric acid.[13]

Hydrolysis of isohumulinic acid (VIII) removed the acyl side-chain to afford the cyclopentanetrione (XVII) which has been synthesised.[12] The p.m.r. spectrum showed that this compound was mono-enolic and that the enolisation was confined to that 1,3-dicarbonyl system which embraced the side-chain. There was a two-proton singlet at τ 7·01 from the ring methylene group, a somewhat broadened singlet at τ 1·67 from the one enol proton, and the rest of the resonance signals obviously came from the isopentyl side-chain which was attached to a carbon atom not bearing hydrogen (Table). It is of interest that there was no enolisation in the sense alternative to that already indicated, or to a dienolic cyclopentadienone, at least in deuterochloroform at 38°.

Hydrogenation of the enolised cyclopentanetrione (XVII) using Adams catalyst gave the hydroxy-dione (XVIII), not examined in detail, whilst, in the additional presence of perchloric acid, there was formed the dione (XIX), isomeric with (XV). Salient features in the p.m.r spectrum of the dione (XIX) were a four-proton singlet at τ 7·42, from the equivalent protons of the two methylene groups of the ring, and a triplet at τ 7·76 from the terminal methylene of the isopentyl chain. These signals, and that at low field from one enolic proton, proved that the 1,3-dicarbonyl system was mono-enolised, as indeed was now expected. The two enol tautomers of (XIX) are equivalent, and probably for this reason the enol signal is sharp.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 40—60°. Unless otherwise stated, reaction mixtures were extracted three times with the solvent, and the combined extracts washed with water, dried over anhydrous magnesium sulphate, and evaporated. Absorption spectra were measured (A) in acidified ethanol (B) in alkaline ethanol. B. p.s refer to bath temperatures.

Humulinic Acid C (IV).—(*a*) Humulinic acid A (1·0 g.) in glacial acetic acid (50 ml.) and perchloric acid (1 ml.) was set aside at 20° for 5 days. Dilution with water (20 ml.) and extraction with ether afforded *humulinic acid* C as an orange syrup, b. p. 125—130°/4 × 10^{-4} mm. (0·54 g.) (Found: C, 67·7; H, 8·4. $C_{15}H_{22}O_4$ requires C, 67·6; H, 8·3%), $\lambda_{max.}$ (A) 225 (ε 14,200) and 265 (10,050), (B) 250 (18,100) and 269 mμ (15,300).

(*b*) Humulinic acid A (4·7 g.) in methanol (320 ml.) and concentrated hydrochloric acid (80 ml.) was heated under reflux for 4 hr. The solution was concentrated under reduced pressure to 150 ml. and extracted with ether, to give humulinic acid C, b. p. 120—125°/10^{-4} mm., having the same infrared absorption as the sample above.

(*c*) In a similar manner, humulinic acid A (0·56 g.) in methanol (40 ml.) and 47% hydrobromic acid (20 ml.) gave humulinic acid C (0·41 g.).

Cohumulinic Acid C (V).—By method (*b*) cohumulinic acid A[2] (0·13 g.) gave *cohumulinic acid C*, b. p. 105—110°/10^{-3} mm. (0·09 g.) (Found: C, 66·95; H, 8·05. $C_{14}H_{20}O_4$ requires C, 66·6; H, 7·9%).

Deuterated Humulinic Acid C.—Deuterium oxide (25 ml.) was added to cooled dry sodium methoxide (from 30 g. of sodium), and the deuterated methanol (30 ml.), b. p. 68—71°, collected under anhydrous conditions. Deuterium oxide (5 ml.) was added dropwise to acetyl chloride (20 ml.), and the gas [14] collected in deuterium oxide (20 ml.), to give a DCl solution (9·88N). To a mixture of this solution (3 ml.) and the deuterated methanol (12 ml.) was added humulinic acid A (0·23 g.), and the mixture heated under reflux for 4 hr. After dilution with deuterium oxide, the product was extracted with ether and distilled, b. p. 95—100°/10^{-3} mm. (0·19 g.). It had τ (in $CDCl_3$) 9·02 (Me_2 of acyl chain; doublet, $J = 6$ c./sec.), 8·67 and 8·61 ($Me_2C<$), $\sim$7·92 (CH_2-CH of tetrahydrofuran ring + CH of acyl chain; complex).

Hydrogenation of Humulinic Acid C.—The acid (0·41 g.) in methanol (20 ml.) was hydrogenated in the presence of Adams catalyst. After removal of catalyst and solvent, the residue was crystallised from methanol–water, to afford the *alkylcyclopentanedione* (III), m. p. 133—

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[13] Cf. Boyce and Whitehouse, *J.*, 1959, 2022.

[14] Dewar and Fahey, *J. Amer. Chem. Soc.*, 1963, **85**, 2247.

134° (Found: C, 71·9; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%), $\lambda_{max.}$ (A) 252 (ε 18,700), (B) 274 mμ (26,300).

Periodate Oxidation of Humulinic Acid C.—Sodium metaperiodate (11·2 g.) in water (100 ml.) was set aside with humulinic acid C (2·8 g.) in ethanol (100 ml.) for 3 days. After filtration the residual sodium iodate was washed with ethanol and the combined filtrate and washings, after dilution with water, were extracted with ether. The crude product was esterified by heating under reflux with 5% ethanolic sulphuric acid for 4 hr. The mixture was diluted with water and extracted three times with ether. The combined extracts were washed twice with 2N-sodium hydroxide and twice with water, to give *ethyl* 2-*ethoxycarbonyl*-5,5-*dimethyl*-2-*tetrahydrofurylacetate* (VI) as an oil, b. p. 70—75°/1·23 × 10^{-4} mm., n_D^{21} 1·4450 (0·30 g.) (Found: C, 60·9, 60·7; H, 8·6, 8·4. $C_{13}H_{22}O_5$ requires C, 60·4; H, 8·6%). Acidification of the sodium hydroxide washings afforded unreacted humulinic acid C, identified by the p.m.r. spectrum.

The ester (VI) (0·39 g.) in ethanol (2 ml.) was hydrolysed with 2N-sodium hydroxide (2 ml.) to the corresponding *acid* [Found: Equiv., 101. $C_7H_{12}O(CO_2H)_2$ requires Equiv., 101], which was converted into the *di*-p-*bromophenacyl ester*, m. p. 145° (from ethanol) (Found: C, 50·3; H, 4·1. $C_{25}H_{24}Br_2O_7$ requires C, 50·4; H, 4·1%).

Isomerisation of Dehydrohumulinic Acid (VII).—Dehydrohumulinic acid (1·34 g.) in glacial acetic acid (75 ml.) was set aside with perchloric acid (1·5 ml.) for 48 hr. After dilution with water and extraction into light petroleum, the *pyran* (XI) was obtained, b. p. 120—130°/3 × 10^{-4} mm. (0·74 g.) (Found: C, 67·8; H, 7·75. $C_{15}H_{20}O_4$ requires C, 68·1; H, 7·6%), $\lambda_{max.}$ (A) 260 (ε 25,700) and 280sh (21,500), (B) 265 (31,700) and 280 mμ (33,900).

Dehydration of Dihydrohumulinic Acid.—(*a*) Dihydrohumulinic acid A (0·2 g.) was added to phosphoric oxide (4 g.) in phosphoric acid (6 ml.) and the mixture heated to 130° for 10 min. After cooling and dilution with water the mixture was extracted with ether, to afford 2-*isovaleryl*-4-(3-*methylbutylidene*)*cyclopentane*-1,3-*dione* (XIII), b. p. 90—100°/3 × 10^{-4} mm. (0·08 g.) (Found: C, 71·7; H, 9·1. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%), $\lambda_{max.}$ (A) 238 (ε 13,620) and 305 (10,280), (B) 240 (13,020) and 270 mμ (16,880).

(*b*) Dihydrohumulinic acid A (0·48 g.) in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (9 ml.) was heated under reflux for 1 hr. The solution was poured into water (100 ml.) and extracted with light petroleum to give a product (0·34 g.) identical with that obtained above.

(*c*) Dihydrohumulinic acid B[2] (0·53 g.) was heated as in (*b*), to give the same product and a trace (10 mg.) of starting material.

Ozonolysis of Dehydration Product (XIII).—Ozone was passed through a solution of the dehydration product (0·74 g.) in acetic acid (26 ml.) for about 1 hr. Zinc dust (10 g.) was added to the solution, and the mixture was heated under reflux in a current of nitrogen which was then passed through a 0·1% solution of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid, to give isovaleraldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 122—123° (from ethanol) (Found: C, 49·6; H, 5·6; N, 21·8. Calc. for $C_{11}H_{14}N_4O_4$: C, 49·6; H, 5·3; N, 21·1%). It had the same R_F as an authentic sample on thin-film chromatography.

2-*Isovaleryl*-4-(3-*methylbutyl*)*cyclopentane*-1,3-*dione* (XIV).—The dehydration product (V) (0·81 g.) in methanol (25 ml.) was shaken with 5% Pd–$BaSO_4$ catalyst in hydrogen until 1 mol. of the gas had been absorbed. After removal of catalyst and solvent the residue was distilled, to give a colourless oil, b. p. 100—105°/2 × 10^{-3} mm., which slowly crystallised. The *product* had m. p. 25—27° (Found: C, 71·1; H, 9·55. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%), $\lambda_{max.}$ (A) 225 (ε 11,100) and 265 (8500), (B) 245 (23,900) and 265 mμ (17,100).

4-(3-*Methylbutyl*)*cyclopentane*-1,3-*dione* (XV).—2-Isovaleryl-4-(3-methylbutyl)cyclopentane-1,3-dione (200 mg.) was heated in 95% sulphuric acid (2 ml.) at 160—185° (5 min.). The mixture was poured on to ice, diluted with water, and extracted into ether. Distillation afforded the *dione* (XV) as a viscous syrup, b. p. 150—155°/2 × 10^{-4} mm. (Found: C, 71·85; H, 9·7. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), $\lambda_{max.}$ (A) 241·5 (ε 18,900), (B) 260 mμ (31,000).

2,4-*Di-isopentylcyclopentane*-1,3-*dione* (XVI).—(*a*) The dehydration product (V) (0·17 g.) was hydrogenated in methanol (20 ml.) using Adams catalyst. Removal of catalyst and solvent gave a solid residue which was recrystallised from methanol–water, to give the *product* (0·04 g.), m. p. 142—144° undepressed by " deoxydihydrohumulinic acid " [11, 12] (Found: C, 75·5; H, 10·8. $C_{15}H_{26}O_2$ requires C, 75·5; H, 11·0%), $\lambda_{max.}$ (A) 252 (ε 16,700), (B) 273 mμ (27,400).

(*b*) Similar hydrogenation of the saturated dione (XIV) (0·25 g.) gave the same product (0·06 g.), m. p. and mixed m. p. 141—142°.

(*c*) Isohumulinic acid (VIII) (0·5 g.) in glacial acetic acid (30 ml.) containing perchloric acid (0·6 ml.) was hydrogenated using Adams catalyst. After filtration, the filtrate was diluted with water and the precipitated material collected and recrystallised from methanol–water, to give the same dione (XIV) (0·22 g.), m. p. and mixed m. p. 142—143°.

4-*Hydroxy*-2-(3-*methylbutyl*)*cyclopentane*-1,3-*dione* (XVIII).—3-(3-Methylbutyl)cyclopentane-1,2,4-trione [12] (XVII) (0·71 g.) in methanol was hydrogenated in the presence of Adams catalyst. After filtration and evaporation, crystallisation of the residue from benzene–light petroleum afforded the *hydroxy-dione*, m. p. 135—137° (Found: C, 65·4; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·1; H, 8·7%), $\lambda_{max.}$ (A) 250 mμ (ε 12,600), (B) 275 mμ (20,700).

2-(3-*Methylbutyl*)*cyclopentane*-1,3-*dione* (XIX).—3-(3-Methylbutyl)cyclopentane-1,2,4-trione (XVII) (0·63 g.) in acetic acid (45 ml.) containing perchloric acid (0·9 ml., 70%) was hydrogenated using Adams catalyst. The filtrate was diluted with water and the precipitated oil extracted into ether. After evaporation, the residue was crystallised from methanol, to give the *dione* (0·35 g.), m. p. 148—149° (Found: C, 71·1; H, 9·75. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), $\lambda_{max.}$ (A) 250 (ε 19,100), (B) 270 mμ (33,400).

Diethyl DL-*Malate*.—This had b. p. 95—96°/2 mm., n_D^{20} 1·4350, τ (in $CDCl_3$) 8·73 and 8·70 (ester Me's; triplets), 5·80 and 5·73 (ester CH_2's; quadruplets, J = 7 c./sec.), 7·18 ($CO{\cdot}CH_2$; doublet, J = 5·5 c./sec.), 6·44 (OH), 5·48 (>CH·O triplet, J = 5·5 c./sec.).

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