112. *Chemistry of Hop Constituents. Part XIII.* The Hydrogenation of* iso*Humulone.*

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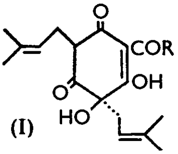
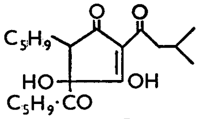
*iso*Humulone A and *iso*cohumulone A are hydrogenated in acetic acid over Adams catalyst to the corresponding tetrahydro-derivatives. Similar compounds are obtained by alkaline isomerisation of tetrahydrohumulone and tetrahydrocohumulone. Hydrogenation over the same catalyst in alkaline solution affords dihydro-derivatives, whereas in methanol solution other hydro-compounds are formed.

The conversion of humulone (I; R = CH_2Pr^i) into bittering substances such as occur in beer is a complex change, for several " *iso*humulones " are known while their characterisation is as yet incomplete and their inter-relations obscure.[1] Windisch *et al.*[2] suggested that humulone was converted in aqueous solution at differing pH levels into an inseparable mixture of " *iso*humulone " (now termed " *iso*humulone A " [1]), $C_{21}H_{30}O_5$, and " resin B ", $C_{17}H_{20}O_5$, which were formulated on the basis of earlier work by Wieland[3] as (II) and (III), respectively. This hypothesis appeared to be confirmed by the finding by Govaert and Verzele[4] that catalytic reduction of the supposed mixture under unspecified conditions afforded the corresponding tetrahydro*iso*humulone, m. p. 43° (equivalent weight 366), and the dihydro-derivative, m. p. 65° (equivalent weight 310), of "resin B", which were separated by chromatography. The latter compound was said to give dihydrohumulinic acid (IV) on oxidation with hypoiodite and both gave this acid on alkaline hydrolysis. Carson[5] subsequently isolated from the products resulting from treating humulone in alcoholic alkali a series of " *iso*humulones," some of which were crystalline (as distinct from earlier oily products). The existence of these products was subsequently confirmed and a system of nomenclature suggested to distinguish between them.[1] Hydrogenation of the crystalline *iso*humulones now designated B and C in methanol over palladised charcoal gave two different dihydro-derivatives, of high melting point, which were both hydrolysed by alkali to dihydrohumulinic acid, acetone, and *iso*butyraldehyde.[5] Since the hydrogenation of *iso*humulone thus appeared to offer a means both of detecting heterogeneity and of characterisation its effects have been investigated.



(I)



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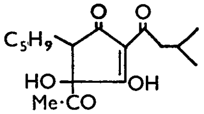

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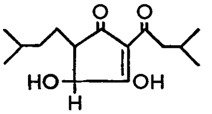

(IV)

Conditions closely parallel to those used by Windisch *et al.*[2] have been used regularly in the present studies to prepare *iso*humulone A without any evidence for the presence of resin B emerging. It was accordingly interesting to find that the hydrogenation of the product in methanol over palladised charcoal appeared at first, on the basis of solubility in benzene, to give two amorphous products identical in light absorption but softening at about 40° and 60° respectively and thus apparently comparable with the materials reported by Govaert and Verzele. Counter-current distribution, however, indicated that both had the same compound as the major constituent, and alkaline hydrolysis of each gave the same products in good yield: the reality of " resin B" as a separate entity is accordingly open

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* Part XII, *J.*, 1958, 1460.

[1] Howard, Slater, and Tatchell, *J. Inst. Brewing*, 1957, 237.

[2] Windisch, Kohlbach, and Schleicher, *Woch. Brau.*, 1927, **44**, 453 *et seq.*

[3] Wieland, *Ber.*, 1925, **58**, 2012.

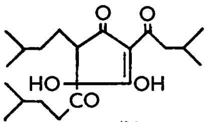
[4] Govaert and Verzele, *Congr. int. Industr. Ferm.*, 1947, 297.

[5] Carson, *J. Amer. Chem. Soc.*, 1952, **74**, 4615.

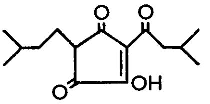
to doubt. In agreement with these results, chromatography of the material on silica gel, followed by distillation in a vacuum, gave a tetrahydro*iso*humulone, $C_{21}H_{34}O_5$, m. p. 32—34°, which counter-current distribution showed to be homogeneous. Catalytic hydrogenation of *iso*humulone A in acetic acid over Adams catalyst afforded a compound with identical physical properties and at present this provides the most convenient method of preparation. The compound was optically active, the magnitude of the rotation depending upon the pH, as in the case of humulone. The infrared and the ultraviolet light absorption, the hydrolysis to dihydrohumulinic and γ-methylvaleric acid, and the inability to take up iodine were consistent with its formulation as (V).

Now, tetrahydrohumulone can be prepared by the hydrogenolysis of lupulone[6] and is hydrolysed by alkali to dihydrohumulinic and γ-methylvaleric acid. It was found that under controlled alkaline conditions tetrahydrohumulone is isomerised, though more slowly than humulone itself. The product was clearly a tetrahydro*iso*humulone and had the same light absorption and partition properties as that prepared from *iso*humulone A. It differed from that product, however, in having little or no optical activity, as would be expected from its origin, and also in having a higher melting point (49—53°, as compared with 32—34°). A similar situation arose with the case of the tetrahydro-derivatives of *iso*cohumulone. (—)-Cohumulone was converted by alkali into a dextrorotatory *iso*cohumulone A[1] which was smoothly reduced in acetic acid over Adams catalyst to a tetrahydro*iso*cohumulone, $C_{20}H_{32}O_5$, m. p. 40—46°, $K = 0{\cdot}47$ on counter-current distribution. Isomerisation in aqueous alkali of the (±)-tetrahydrocohumulone prepared from colupulone[7] afforded a tetrahydro*iso*cohumulone with the same partition coefficient but a melting point of 55—58°, whilst an analogous preparation in which alcoholic alkali was used gave a product with again the same partition coefficient and melting at 50—52°. The absorption spectra of the various tetrahydro*iso*-compounds were compared, with the object of ascertaining whether these differences in melting point were of stereochemical origin, for Carson[5] reported small but significant differences between the light absorption properties of the *iso*humulones B, C, and D. The samples of tetrahydro*iso*humulone prepared from (—)-humulone and synthetic lupulone had very similar absorption spectra, and this was true also of the corresponding *iso*cohumulone derivatives. The significance of the differences between the pairs of spectra is not easily assessed, but the close similarity both here and with the partition coefficients, suggests that the differences in melting points are due merely to the racemic or optically active nature of the compounds.

The tetrahydro*iso*-compounds, irrespective of their origin, were oxidised by bismuth oxide in acetic acid to the corresponding acyl*cyclo*pentanetriones: tetrahydro*iso*humulone, for example, afforded the *iso*humulinic acid (VI). Similar oxidation of *iso*humulone A afforded the corresponding compound (VII) which had previously been prepared by other routes.[8] The specificity of this oxidative reagent has not been closely investigated but, as it is said to affect the CO·CH·OH group,[9] it presumably also attacks the grouping CO·C(OH)·CO. On this assumption the isolation of the above oxidation products provides new evidence for the formulation of the *iso*-compounds and their reduction products as diacylhydroxy*cyclo*pentanediones.



(V)



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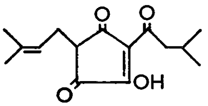

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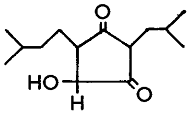

(VIII)

The hydrogenation of *iso*humulone A in methanol over Adams catalyst differed from

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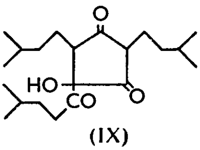
[6] Wöllmer, *Ber.*, 1925, **58**, 672.
[7] Howard, Pollock, and Tatchell, *J.*, 1955, 174.
[8] Howard and Slater, *J.*, 1957, 1924.
[9] Rigby, *J.*, 1951, 793.

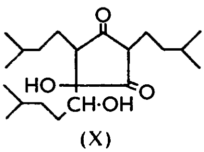
that in acetic acid, the product being an oil, $C_{21}H_{38}O_4$ or $C_{21}H_{36}O_4$, containing one oxygen atom less than the starting material. No crystalline derivatives could be obtained and the compound, designated here *neo*hydro*iso*humulone, was stable to alkali and gave no volatile products on ozonolysis. A compound with the same properties was formed similarly from tetrahydro*iso*humulone. In acidic methanol it had $\lambda_{max.}$ 253 mμ (ε 11,800) and in alkaline methanol $\lambda_{max.}$ 274 mμ (ε 17,200). This light absorption is virtually identical with that of a compound, $C_{14}H_{24}O_3$, obtained by the hydrogenation of cohumulinic acid, $C_{14}H_{20}O_4$. The latter reduction product failed to give *iso*butyric acid on oxidation [10] and its infrared absorption was consistent with the presence of free hydroxyl, enolic hydroxyl, and conjugated carbonyl groups, but there was no absorption due to a free carbonyl group. It is accordingly formulated as (VIII). The light absorption of *neo*hydro*iso*humulone suggests that it also is a substituted *cyclo*pentane-1 : 3-dione, since compounds of this type have maximal light absorption at 240—250 mμ in acidic media and at about 270 mμ in the enol form,[11,12] whereas 2-acyl*cyclo*alkanones absorb at longer wavelengths,[12] *e.g.*, 2-acetyl*cyclo*pentanone has $\lambda_{max.}$ 285 mμ (ε 7500) in acidic and $\lambda_{max.}$ 305 mμ (ε 19,800) in alkaline ethanol.

Oxidation of *neo*hydro*iso*humulone by hot alkaline hydrogen peroxide gave *ca.* two equivalents of γ-methylvaleric acid and no *iso*valeric acid. Further, the corresponding *neo*hydro*iso*cohumulone reduced two mols. of periodate to give material which gave γ-methylvaleric acid but neither *iso*butyl nor *iso*hexyl methyl ketone on hydrolysis. These results, together with the light absorption properties, suggest that the *neo*hydro*iso*-compounds are to be formulated as (IX) or (X). The infrared absorption was similar to that of compound (VIII), except for the indicated presence of a free carbonyl group, the absorption due to free hydroxyl being relatively weaker than was the case with (VIII). Structure (IX) is therefore proposed for *neo*hydro*iso*humulone. It is to be noted, however, that although *neo*hydro*iso*humulone, like (VIII), failed to form a copper complex it had three active hydrogen atoms. It is, on the other hand, not uncommon in this field for active hydrogen analyses to give unexpected results. The hydrogenation of *iso*cohumulone A or its tetrahydro-derivative in methanol likewise affords a corresponding *neo*hydro*iso*cohumulone, and the ultraviolet light absorption of its reduction product suggests that *iso*humulone C behaves likewise.

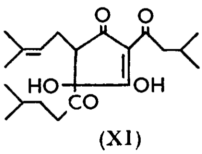
It is noteworthy that, whereas *iso*humulone A afforded a tetrahydro-derivative, the isomers B and C gave only dihydro-compounds under apparently similar conditions of hydrogenation.[5] Since the latter substances had high melting points, further attempts to prepare a dihydro*iso*humulone A were made. The difference between the course of hydrogenation of *iso*humulone A in neutral and acidic solvents prompted an investigation into its behaviour in alkaline solution. Over Adams catalyst in aqueous sodium carbonate it afforded a resinous product different from both tetrahydro- and *neo*hydro-*iso*humulone. Its empirical formula, $C_{21}H_{32}O_5$, iodine value, and light absorption in both the ultraviolet and the infrared region all suggest that it was a dihydro-derivative, (XI) or (XII), of *iso*humulone. The isolation of humulinic acid after alkaline hydrolysis provides some support for the former structure, but little reliance can be placed on this because of the low yield. No additional reliable confirmatory evidence could be obtained and, in view of the non-crystalline nature of the material, it was not investigated further.



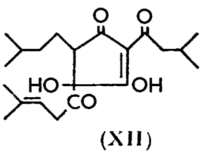
(IX)



(X)



(XI)



(XII)

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[10] Howard and Tatchell, *J.*, 1954, 2400.
[11] Howard and Pollock, *J.*, 1952, 1902.
[12] Eistert and Weiss, *Chem. Ber.*, 1954, **87**, 108.

EXPERIMENTAL

Hydrogenation of iso*Humulone A*.—(*a*) *iso*Humulone A (853 mg.) was hydrogenated in methanol (70 ml.) over Adams catalyst (100 mg.). That part of the crude product which was extractable from ether by aqueous sodium carbonate was isolated in the usual way and distilled at 130° (bath)/2 × 10^{-3} mm., to give neo*hydro*iso*humulone* (Found: C, 71·2; H, 10·5; active H, 0·83. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·2; 3 active H, 0·85%), $\lambda_{\text{max.}}$ 253 mμ (ε 11,800) in acidic ethanol and 274 mμ (ε 17,200) in alkaline ethanol. The reduction product tasted bitter, gave no copper complex soluble in chloroform, failed to reduce Fehling's solution, gave a positive iodoform reaction, and was unaffected by boiling N-ethanolic alkali or by potassium hydrogen sulphate in boiling toluene. A trace (0·06 mol.) of acetone was produced by ozonolysis. Attempts to prepare an oxime, semicarbazone, 2 : 4-dinitrophenylhydrazone, or benzoate failed to give crystalline products.

Similar hydrogenations of two crystalline *iso*humulones (m. p. 123—124°, $[\alpha]_D$ −15·7° in methanol; m. p. 129—130°, $[\alpha]_D$ −40·6° in methanol) gave products which failed to distil at 135°/10^{-4} mm., but had ultraviolet light absorption identical with that of *neo*hydro*iso*humulone.

(*b*) A solution of the compound (617 mg.) in acetic acid (20 ml.) was hydrogenated over Adams catalyst. A portion of the product (580 mg.) was analysed by counter-current distribution which showed it to be mainly (70%) tetrahydro*iso*humulone, and the remainder afforded this compound (m. p. 31—33°) on distillation *in vacuo*.

(*c*) A solution of the compound (616 mg.) in methanol (5 ml.) and aqueous 2N-sodium carbonate (50 ml.) was hydrogenated over Adams catalyst, the product chromatographed on silica gel, and the portion eluted by benzene (375 mg.) distilled, to give *dihydro*iso*humulone A* as an oil (Found: C, 69·1; H, 9·1. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·8%), $\lambda_{\text{max.}}$ 225 and 274 mμ ($E^{1\%}_{1\,\text{cm.}}$ 310 and 256) in acidic ethanol and 252 and 272 (inflexion) mμ ($E^{1\%}_{1\,\text{cm.}}$ 405 and 350) in alkaline ethanol, and iodine value 72. This gave a brown colour with ferric chloride in methanol; attempts to hydrolyse it with aqueous-ethanolic alkali failed to give recognisable products, except a volatile acid isolated in low yield and considered to be γ-methylvaleric acid (gas chromatography).

(*d*) Hydrogenation in methanol over palladium–charcoal gave a product with ultraviolet light absorption like that of *iso*humulone or its di- or tetra-hydro-derivative. Trituration with benzene gave a soluble and an insoluble fraction in the proportions 2 : 1. Alkaline hydrolysis of either fraction afforded dihydrohumulinic and γ-methylvaleric acid (70—80% yield in each case), the former identified by m. p. and mixed m. p., and the latter as the *p*-bromophenacyl ester and by gas chromatography. The fraction soluble in benzene had 71% of material having a partition coefficient identical with that of tetrahydro*iso*humulone when examined by counter-current distribution. A similar analysis of the fraction insoluble in benzene indicated the presence of 50% of tetrahydro*iso*humulone. Chromatography on silica gel of the portion soluble in benzene afforded material eluted by benzene, which distilled at 125° (bath)/10^{-5} mm. to give *tetrahydro*iso*humulone*, m. p. 32—34° (Found: C, 69·1; H, 9·1. $C_{21}H_{34}O_5$ requires C, 68·8; H, 9·3%), $[\alpha]_D$ +24·5° in neutral methanol, $[\alpha]_D$ +98° in alkaline methanol, $\lambda_{\text{max.}}$ 230 and 275 mμ ($E^{1\%}_{1\,\text{cm.}}$ 250 and 250) in acidic ethanol and 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 456) in alkaline ethanol. Hydrogenation in methanol over Adams catalyst afforded a product identical in ultraviolet absorption with *neo*hydro*iso*humulone.

Tetrahydro*iso*humulone had a partition coefficient 1·04 in the system 2-methylheptane–phosphate buffer (0·5M; pH 6·5).

*Hydrogenation of Dihydro*iso*humulone* —In methanol over Adams catalyst this afforded a product with the ultraviolet light absorption of *neo*hydro*iso*humulone. Reduction over Adams catalyst in acetic acid afforded an oil which distilled at 120°/5 × 10^{-4} mm., to give a *product* whose infrared absorption and counter-current distribution were unlike those of tetrahydro*iso*humulone although the two compounds had similar ultraviolet absorption (Found: C, 71·4; H, 10·5. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·2%).

Hydrogenation of iso*Cohumulone A*.—Hydrogenation of *iso*cohumulone A (892 mg.) in acetic acid (30 ml.) over Adams catalyst afforded a low-melting solid, which was purified by elution from silica gel with benzene (85% recovery) and finally by distillation at 145° (bath)/10^{-3} mm., to give *tetrahydro*iso*cohumulone*, m. p. 40—46° (Found: C, 67·8; H, 9·4. $C_{20}H_{32}O_5$ requires C, 68·2; H, 9·1%). It had $[\alpha]_D$ +28° in methanol, and +89° in alkaline methanol, a partition coefficient of 0·47 between 2-methylheptane and phosphate buffer (pH 6·5), and $\lambda_{\text{max.}}$ 230 and 273 mμ ($E^{1\%}_{1\,\text{cm.}}$ 294 and 274) in acidic ethanol and 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 515) in alkaline ethanol.

(±)-*Tetrahydro*iso*cohumulone*.—(*a*) A solution of (±)-tetrahydrocohumulone [10] (480 mg.) in aqueous N/15-sodium hydroxide (74 ml.) was heated under reflux under nitrogen for 9 min. The product was isolated in the usual way and purified by chromatography on silica gel. The material eluted by benzene had m. p. 53—54° and afforded tetrahydro*iso*cohumulone, m. p. 55—58°, on distillation at 105° (bath)/10^{-5} mm. (Found: C, 68·4; H, 8·9%). It had a partition coefficient (cf. above) of 0·46, $[\alpha]_D$ +6° in both neutral and alkaline ethanol, and $\lambda_{\text{max.}}$ 230 and 273 mμ ($E^{1\%}_{1\,\text{cm.}}$ 264 and 284) in acidic ethanol and $\lambda_{\text{max.}}$ 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 494) in alkaline ethanol.

(*b*) (±)-Tetrahydrocohumulone (2·86 g.) was isomerised in ethanolic alkali as described for humulone by Carson; [5] the product (2·53 g.) crystallised and 70% of it had the same partition coefficient as tetrahydro*iso*cohumulone in the usual system. Chromatography on silica gel followed by distillation at 128° (bath)/10^{-3} mm. afforded tetrahydro*iso*cohumulone, m. p. and mixed m. p. 50—52°, $\lambda_{\text{max.}}$ 230 and 273 mμ ($E^{1\%}_{1\,\text{cm.}}$ 260 and 250) in acidic and 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 574) in alkaline ethanol (Found: C, 68·4; H, 9·4%).

(±)-*Tetrahydro*iso*humulone*.—A solution of tetrahydrohumulone (668 mg.) in aqueous N/15-sodium hydroxide (100 ml.) was boiled under reflux under nitrogen for 9 min. The product was isolated and purified by chromatography on silica gel as was tetrahydro*iso*cohumulone, and then distilled at 110° (bath)/10^{-5} mm., to give *tetrahydro*iso*humulone*, m. p. 49—53°, $[\alpha]_D$ −2° in neutral and +13° in alkaline methanol, $K = 1·04$ between 2-methylheptane and phosphate buffer (pH 6·5), $\lambda_{\text{max.}}$ 230 and 275 mμ ($E^{1\%}_{1\,\text{cm.}}$ 250 and 265) in acidic and 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 480) in alkaline ethanol (Found: C, 68·5; H, 9·4. $C_{21}H_{34}O_5$ requires C, 68·8; H, 9·3%).

*Alkaline Hydrolysis of Tetrahydro*iso*humulone*.—A solution of tetrahydro*iso*humulone (478 mg.) in ethanol (3 ml.) and aqueous N-sodium hydroxide (7 ml.) was boiled under reflux under nitrogen for 3 hr. The hydrolysate was acidified and concentrated by distillation, the distillate being collected. The crystalline material (260 mg., 74%) present in the distillation residue had m. p. 122—124°, and afforded dihydrohumulinic acid, m. p. and mixed m. p. 126°, on recrystallisation from methanol. From the distillate obtained above, the acids were isolated in the usual way. Analysis by gas chromatography indicated the presence of γ-methylvaleric acid (80%), and the *p*-bromophenacyl ester, m. p. and mixed m. p. 77—78°, was obtained in 20% yield in the usual way.

*Oxidation of Tetrahydro*iso*humulone with Bismuth Oxide*.—A solution of tetrahydro*iso*humulone (200 mg.) prepared from either humulone or synthetic lupulone, in acetic acid (10 ml.), was boiled under reflux with bismuth trioxide (450 mg.) for 5 hr. A yellow solid (181 mg.) was extracted from the acidified solution by ether after dilution with water. Recrystallisation from light petroleum (b. p. 40—60°) afforded *iso*humulinic acid, m. p. and mixed m. p. 142—143° (oxime, m. p. and mixed m. p. 208°). The product gave the same colour (blue-purple) with methanolic ferric chloride and had the same ultraviolet light absorption as *iso*humulinic acid. Tetrahydro*iso*humulone was recovered unchanged when boiled with acetic acid alone.

*Oxidation of Tetrahydro*iso*cohumulone with Bismuth Oxide*.—A solution of tetrahydro*iso*cohumulone (286 mg.), prepared from either cohumulone or colupulone, in acetic acid (6 ml.) was boiled with bismuth oxide (450 mg.) for 4 hr. The product isolated in the usual way was *iso*cohumulinic acid (52 mg.), m. p. and mixed m. p. 121—123°.

Oxidation of iso*Humulone A by Bismuth Oxide*.—A solution of *iso*humulone A (298 mg.) in acetic acid (6 ml.) was boiled under reflux with bismuth oxide (450 mg.) for 1 hr., longer boiling causing extensive decomposition. The solution was acidified with hydrochloric acid, diluted with water, and extracted with ether. The extract was washed with water, dried, and evaporated and the residue recrystallised from light petroleum, thus giving a product (2·5 mg.), m. p. 131—133° unchanged when mixed with 5-(3-methylbut-2-enyl)-3-*iso*valeryl*cyclo*pentane-1 : 2 : 4-trione.

Oxidation of neo*Hydro*iso*humulone by Alkaline Hydrogen Peroxide*.—A solution of *neo*hydro-*iso*humulone (500 mg.) in aqueous 2N-sodium hydroxide (14 ml.) was boiled under reflux and 30% hydrogen peroxide (5 ml.) was added; similar additions were made at hourly intervals for 3 hr. After 4 hr. the solution was acidified at 0° and extracted with ether, and the acids were extracted with aqueous sodium hydrogen carbonate, then recovered as an oil (370 mg.) which afforded *p*-bromophenacyl γ-methylvalerate, m. p. and mixed m. p. 75—77°.

In a similar experiment, 98% of the oxidation product was soluble in aqueous sodium hydrogen carbonate, and examination of it by gas chromatography using an internal standard showed that 73% of it was a mixture of *iso*valeric, γ-methylvaleric, and a C_7 acid in the ratios 6 : 78 : 17. A portion of the material soluble in aqueous sodium hydrogen carbonate was distilled with steam, the non-volatile acids were again oxidised by hydrogen peroxide in boiling alkali, and the material soluble in aqueous sodium hydrogen carbonate was isolated. This then contained 22% of γ-methylvaleric acid Thus the oxidation of *neo*hydro*iso*humulone finally afforded *ca.* 1·9 mol. of γ-methylvaleric acid. The acidic product which was not volatile with steam had $\lambda_{\text{max.}}$ 230 mμ in acidic, and 263 mμ in alkaline, ethanol but did not crystallise.

Hydrogenation of iso*Humulone*.—Humulone (6·37 g.) was isomerised by Carson's method, and the product diluted with light petroleum, thus affording crystalline material (729 mg., 15%) which was recrystallised successively from light petroleum, methanol, and light petroleum to give " *iso*humulone," m. p. 124—125°, $[\alpha]_D$ +10·4° and +56° in neutral and alkaline methanol respectively (Found: C, 69·7; H, 8·45. Calc. for $C_{21}H_{30}O_5$: C, 69·6; H, 8·2%). Counter-current distribution with 2-methylheptane and phosphate–citrate buffer (pH 5·0) indicated the presence of one major component with *K* 1·42, together with minor components. The residue remaining after the original removal of crystalline " *iso*humulone " was dissolved in ether and shaken with aqueous 2N-sodium hydroxide, and the insoluble sodium salt was removed. The oily *iso*humulone then obtained (3·8 g.) consisted primarily (75%) of *iso*humulone A as judged by counter-current distribution. A portion (978 mg., $[\alpha]_D$ +27·5° in methanol) was hydrogenated over Adams catalyst in acetic acid, 2 mols. of hydrogen being absorbed, to give a product (915 mg., $[\alpha]_D$ +7° in methanol) of which 60% was tetrahydro*iso*humulone as judged by its behaviour on counter-current distribution. Chromatography on silica gel gave material eluted by benzene (87% of original sample) which partially crystallised. The crystalline material was recrystallised from light petroleum to give a product, m. p. 152—154°. The non-crystalline product distilled at 128° (bath)/10^{-3} mm., had $[\alpha]_D$ +20° in neutral and +90° in alkaline methanol, $\lambda_{\text{max.}}$ 230 and 275 mμ ($E^{1\%}_{1\,\text{cm.}}$ 240 and 255) in acidic and 253 mμ ($E^{1\%}_{1\,\text{cm.}}$ 466) in alkaline ethanol and also, although not crystalline, gave analyses correct for tetrahydro*iso*humulone (Found: C, 68·8; H, 9·5. Calc. for $C_{21}H_{34}O_5$: C, 68·8; H, 9·3%).

Periodate Oxidation of neo*Hydro*iso*cohumulone*.—To a solution of *neo*hydro*iso*cohumulone (867 mg.) in ethanol (20 ml.) was added one of sodium metaperiodate (1·2 g.) in water (20 ml.), and the mixture set aside overnight. Sodium iodate was filtered off and washed with ethanol, and the combined filtrates and washings were acidified, saturated with sodium chloride, and extracted with ether. The extract was washed with brine, evaporated to low bulk, and then boiled under reflux for 2 hr. with aqueous 2N-sodium hydroxide (20 ml.). The cooled hydrolysate was extracted with ether, and the extract washed with brine, dried, and evaporated cautiously. The residue was treated with alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride, and the resulting hydrazones examined chromatographically in alumina. No evidence could be obtained of the presence of ketones of low molecular weight. The alkaline solution remaining after the hydrolysis was acidified and distilled with steam. Extraction of the distillate with ether in the usual way afforded γ-methylvaleric acid (260 mg. of impure material), characterised by gas chromatography and as the *p*-bromophenacyl ester, m. p. and mixed m. p. 78°.

Infrared Spectra.—*neo*Hydro*iso*cohumulone, as a film, had absorption peaks at 2·90 (m), 3·1 to 3·4 (m), 3·4 (s), 3·8 (m), 5·85 (s), 6·1 to 6·5 (s), 6·85 (s), 7·25 and 7·35 (s), 8·0 (s), 8·57 (m), 8·85 (m), 9·22 (m), 9·4 (m), 10·3 (w), 10·85 (w), 11·8 to 12·3 (w), and 12·9 (w) μ.

Dihydro*iso*humulone, as a film, had absorption peaks at 2·85 (m), 3·35 (s), 3·7 (w), 5·85 (s), 6·1 to 6·4 (s), 6·8 and 6·9 (s), 7·2 and 7·3 (s), 7·8 (m), 8·15 (m), 8·55 (m), 9·1 to 9·3 (m), 10·15 (w) 10·40 (w), 10·8 (w), and 11·9 (w) μ.

Tetrahydro*iso*humulone, as a film, had absorption peaks at 2·85 (m), 3·35 (s), 3·7 (w), 5·85 (s), 6·1 to 6·35 (s), 6·8 (s), 7·3 (s), 7·55 (m), 7·85 (m), 8·2 (m), 8·55 (s), 8·8 (s), 10·85 (m), and 12·0 (w) μ. Tetrahydro*iso*humulone in carbon disulphide gave a similar spectrum, but with additional shoulders at 3·41, 5·75, and 7·15 μ. In carbon tetrachloride solution, distinct peaks were observable at 6·15 and 6·32 μ with shoulders at 6·60 and 6·95 μ. The spectra of samples derived from (—)-humulone and synthetic lupulone were very similar. Samples of tetrahydro*iso*cohumulone derived from (—)-cohumulone or colupulone had very similar absorption spectra when examined as films or dissolved in carbon disulphide or carbon tetrachloride and differed from the tetrahydro*iso*humulone samples chiefly in that the bands at 7·85 and 8·2 μ were absent and there was a strong band at 9·15 μ.

2-*iso*Butyl-4-hydroxy-5-*iso*pentyl*cyclo*pentane-1 : 3-dione (VIII) in Nujol had significant absorption peaks at 2·92 (m), 3·8 (s), 6·45 (s), 7·2 (s), 7·45 (s), 7·6 (s), 7·85 (m), 8·07 (m), 8·85 (m), 9·44 (m), 10·1 (m), 11·8 (m), and 12·95 (m) μ.

The spectra were determined with a Perkin-Elmer spectrophotometer Model 137.

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