The Chemistry of Hop Constituents. Part VII. Colupulone.†*

By G. A. Howard, J. R. A. Pollock, and A. R. Tatchell.

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The major constituent of the β-soft resin of some varieties of English hops has been shown to be the hitherto unrecognised colupulone (I; R = Pr^i). The degradations of this compound by hydrogenolysis, alkaline hydrogen peroxide, acid, and alkali are described and the results are compared with those obtained with lupulone (I; R = Bu^i). New structures are proposed for lupuloxinic acid (Howard and Pollock, *J.*, 1952, 1902) and its degradation products. Degradations of synthetic lupulone and colupulone confirm the various structures put forward.

An important crystalline component, lupulone, of the " β-soft resin " of hops, isolated as long ago as 1863 by Lermer (*J. prakt. Chem.*, 1863, **90**, 254), was formulated by Bungener (*Bull. Soc. chim.*, 1886, **45**, 487) and Barth and Lintner (*Ber.*, 1898, **31**, 2022) as $C_{25}H_{36}O_4$. Wöllmer (*Ber.*, 1925, **58**, 672) favoured the formula $C_{26}H_{38}O_4$ although the analytical data support equally either formulation.

Catalytic hydrogenation of lupulone was shown by Wöllmer (*loc. cit.*) to yield 3-methylbutane and a compound, $C_{21}H_{34}O_4$ (II; R = Bu^i), characterised as its crystalline tribenzoate, $C_{42}H_{46}O_7$, m. p. 164—165°. The hydrogenolysis product was oxidised by air in the presence of lead acetate to tetrahydrohumulone, $C_{21}H_{34}O_5$, m. p. 82—84° (III; R = Bu^i), which on alkaline hydrolysis furnished 4-methylpentanoic acid and dihydrohumulinic acid (IV; R = Bu^i). In view of the sequel it is interesting that Carson (*J. Amer. Chem. Soc.*, 1951, **73**, 1850) was also able to prepare tetrahydrohumulone having m. p. 82—83° from lupulone derived from American hops.

By contrast with the foregoing results the crystalline " β-resin " isolated from three samples of English hops afforded a hydrogenolysis product (II) which was different from that described by earlier workers as it yielded a tribenzoate, $C_{41}H_{44}O_7$, m. p. 134°. Further, this product was oxidised in good yield to a " tetrahydrohumulone " which although it was not obtained crystalline afforded by alkaline hydrolysis a compound which proved to be identical with dihydrocohumulinic acid (IV; R = Pr^i) (Howard and Tatchell, *J.* 1954, 2400). It thus follows that the " β-soft resin " used for the degradation must accordingly possess the structure (I; R = Pr^i). This compound is conveniently termed colupulone as it bears the same relation to lupulone as cohumulone does to humulone. Colupulone appears to be the major constituent of the β-soft resin of all samples of English hops examined by us and, indeed, no evidence of the presence of any authentic lupulone (I; R = Bu^i) has been obtained.

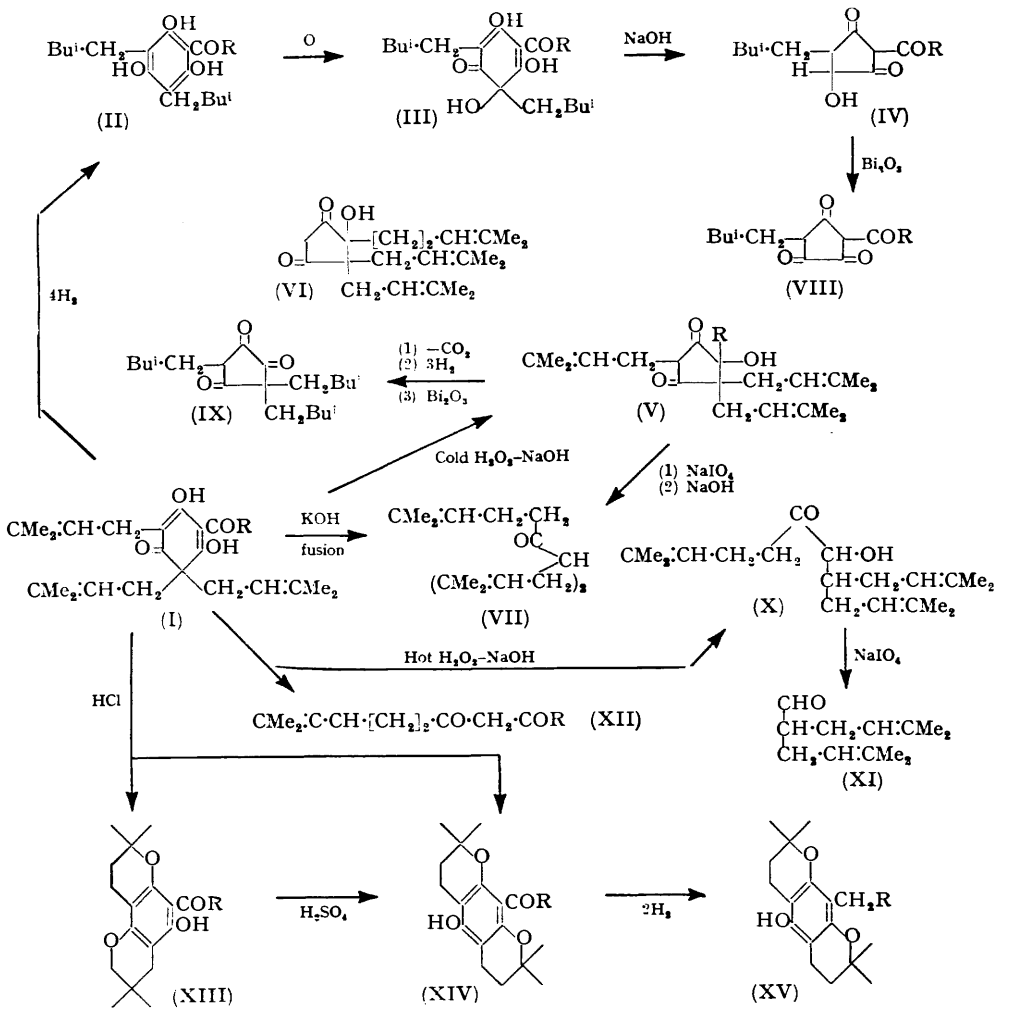
The material isolated from hops in the present work shows no depression of melting point when mixed with synthetic colupulone which had been incidentally prepared by Riedl (*Annalen*, 1954, **585**, 38) but exhibits a considerable depression with synthetic lupulone. By the methods already described, synthetic lupulone affords the tribenzoate of (II; R = Bu^i) having m. p. 164—165° as recorded by Wöllmer and by Carson (*locc. cit.*) whereas synthetic colupulone gives the tribenzoate of (II; R = Pr^i), having m. p. 134° identical with that from natural colupulone. Moerover, synthetic lupulone gives tetrahydrohumulone (III; R = Bu^i), m. p. 82—84°, whereas synthetic colupulone affords non-crystalline tetrahydrocohumulone (III; R = Pr^i).

Analytical results scarcely distinguish between lupulone and colupulone and their melting points are very similar, being 93° and 91—93° respectively (Riedl, *loc. cit.*). It is clear from degradative evidence that Wöllmer's material contained a high proportion of lupulone despite its low melting point (90·5—92°).

It will be recalled that Howard and Pollock (*loc. cit.*) showed that the oxidation of the crystalline " β-soft resin " of English hops by alkaline hydrogen peroxide affords crystalline

* Part VI, *J.*, 1954, 2400. † A preliminary account of part of this work has been reported (Howard and Pollock, *Chem. and Ind.*, 1954, 991).

lupuloxinic acid together with *iso*butyric acid. Whereas it was difficult to reconcile the production of the latter with the structure of lupulone its formation from colupulone clearly presents no problem. The initial oxidation of (I; R = Pr^i) is reminiscent of that of leptospermone (Briggs, Hassall, and Short, *J.*, 1945, 706) and directly affords *iso*butyric acid together with a product which is considered to undergo the type of ring-contraction encountered in the humulone series. Lupuloxinic acid is therefore formulated as (V;



R = CO_2H) while the product of its decarboxylation, lupulenol, becomes (V; R = H). Lupulenol was ascribed structure (VI) by Howard and Pollock (*loc. cit.*) on the grounds that it fails to reduce Fehling's solution, reacts as a monobasic acid, and reduces one equivalent of periodate to give a product which affords by alkaline hydrolysis a C_{18} ketone (VII). The failure to reduce Fehling's solution was regarded as precluding the presence of an acyloin group such as that in (V; R = H) and similar reasoning was applied to dihydrohumulinic acid (IV; R = Bu^i) in view of its failure to reduce the same reagent (Harris, Howard, and Pollock, *J.*, 1952, 1906). That the latter does in fact contain an acyloin group has, however, now been shown by oxidation with bismuth trioxide (cf. Rigby, *J.*, 1951, 793) to the corresponding α-diketone, *iso*humulinic acid (VIII; R = Bu^i) (cf. Harris, Howard, and Pollock, *loc. cit.*). The above conception of the formation and

structure of lupulenol is supported by the finding that hexahydrolupulenol is also smoothly oxidised by bismuth trioxide to a product having properties and light absorption consistent with its being 3 : 3 : 5-tri-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione (IX). It is of interest that the sodium salt of this compound is insoluble in water and light petroleum though freely soluble in ethanol and quite soluble in ether. These unusual properties together with the analytical data suggest that this salt is a chelate compound, $C_{40}H_{67}O_6Na$, similar in character to those formed by compounds such as salicylaldehyde (cf. Ephraim, " Inorganic Chemistry," Gurney and Jackson, London, 1948, p. 351).

The evidence for the structure of lupulenol as (V; R = H) is thus conclusive. Lupuloxinic acid must be (V; R = CO_2H) because it is smoothly decarboxylated to lupulenol and reacts as a dibasic acid, these considerations precluding attachment of the carboxyl group elsewhere in the molecule. The above implication requires that lupuloxinic acid acid (V; R = CO_2H) would be produced during the oxidation of lupulone as well as of colupulone. This has been confirmed by the oxidation of both synthetic colupulone and synthetic lupulone to lupuloxinic acid and its conversion into lupulenol and hexahydrolupulenol all of which, from both sources, were identical with the corresponding degradation products of natural colupulone. Incidentally *iso*valeric acid and *iso*butyric acid have been identified among the products of the oxidations of synthetic lupulone and synthetic colupulone respectively.

It has been observed that the degradation of colupulone with hydrogen peroxide in hot alkali can be made to follow alternative routes. Thus, if a solution of colupulone in warm alkaline hydrogen peroxide is allowed to cool overnight, subsequent heating at 100° affords a neutral oil, $C_{19}H_{32}O_2$, which is formulated as 7-hydroxy-2 : 11-dimethyl-8-(3-methylbut-2-enyl)dodeca-2 : 10-dien-6-one (X), since it reduces Fehling's solution and is oxidised by one equivalent of periodate to 5-methyl-2-(3-methylbut-2-enyl)hex-3-enal (XI) isolated as its 2 : 4-dinitrophenylhydrazone. On the other hand if the oxidation of colupulone is carried out wholly at 100°, hydrolytic fission occurs to give *iso*butyric acid together with the β-diketone 2 : 9-dimethyldec-8-ene-3 : 5-dione (XII; R = Pr^i), isolated as its crystalline copper salt.

The only work hitherto recorded on the crystalline " β-soft resin " of English hops is that by Walker (*J. Inst. Brewing*, 1924, 712; 1949, 266) who by acid degradation isolated two crystalline isomers, one a neutral substance, m. p. 91°, and the other a weak acid, m. p. 169·5°. These were given the molecular formula $C_{21}H_{30}O_4$ although analytical data are also consistent with $C_{20}H_{28}O_4$. The latter must in fact be correct as treatment of colupulone according to Walker's method affords the above two compounds, while similar treatment of synthetic lupulone yields two different substances. It is significant also that Walker must have been dealing with colupulone and not with lupulone.

The neutral compound, m. p. 91°, has now been synthesised by treating phloro*iso*butyrophenone with two equivalents of 1-bromo-3-methylbut-2-ene in dry chloroform. This suggests that it is a cyclisation product of 3 : 5-di-(3-methylbut-2-enyl)phloro*iso*butyrophenone and its infra-red absorption spectrum confirms the presence of a carbonyl group. A phenolic group is indicated by a strong colour with ferric chloride and formation of a methyl derivative. The substance is neutral and so must be an *o*-hydroxyaryl ketone (cf. Backhouse and Robertson, *J.*, 1939, 1257; Wolfrom *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 406); it is therefore 6-*iso*butyryl-3 : 4 : 9 : 10-tetrahydro-5-hydroxy-2 : 2 : 8 : 8-tetramethylbenzo[1,2-*b*, 3,4-*b*′]dipyran (XIII; R = Pr^i) (see Ring Index no. 1990). As the acidic isomer gives no colour with ferric chloride, contains one active hydrogen atom, and readily forms a monobenzoate and monomethyl ether, it is formulated as 10-*iso*butyryl-3 : 4 : 6 : 7-tetrahydro-5-hydroxy-2 : 2 : 8 : 8-tetramethylbenzo(1,2-*b*, 5,4-*b*′] dipyran (XIV; R = Pr^i) (Ring Index no. 1986). The ultra-violet absorption spectra of the two isomers in ethanol lend further support for those formulations (cf. Morton and Sawires, *J.*, 1940, 1052), and the close relation between the two compounds is borne out by the fact that the angular (XIII; R = Pr^i) is converted into the linear (XIV; R = Pr^i) by warm concentrated sulphuric acid. The acidic isomer undergoes reduction to a compound $C_{20}H_{30}O_3$, which is characterised as its monophenylurethane and mono-3 : 5-dinitrobenzoate and formulated as (XV; R = Pr^i). The chelate character of the hydroxy-ketone (XIII;

R = Pr^i) is further reflected by its failure to undergo similar reduction. The two compound obtained by acid degradation of synthetic lupulone are represented by the homologous formulations (XIII and XIV; R = Bu^i).

The presence of an *iso*valeryl side chain in lupulone was confirmed by Verzele and Govaert (*Bull. Soc. chim. Belg.*, 1949, **48**, 432; *J.*, 1952, 1954) who isolated *iso*valeric acid from the alkaline fusion of both lupulone (I; R = Bu^i) and its hydrogenolysis product (II; R = Bu^i). The crystalline " β-resin " from English hops gives, in similar circumstances, *iso*butyric acid. At the same time, 6-methylhept-5-en-2-one and the high-boiling ketone (VII) (cf. Verzele and Govaert, *loc. cit.*) are also formed.

In this investigation, although at no time was *iso*valeric acid obtained, two other simple acids provisionally regarded as 2-methylbutanoic acid and 3-methylpentanoic acid were isolated from the alkaline fusion and characterised as their *p*-bromophenacyl esters. The occurrence of the former acid suggests the presence of a lupulone analogue of structure (I; R = CHMeEt). This accords with the recognition of adhumulone (Howard and Tatchell, *Chem. and Ind.*, 1954, 992). The isolation of the second acid suggests that still another analogue of lupulone is present in hops.

Experimental.

Isolation of Crystalline β-Soft Resin from Hops.—Freshly ground hops were extracted with cold methanol, the suspension was filtered, and the filtrate was treated with methanolic lead acetate (18% w/v) to remove α-soft resin. The filtrate from the lead salt was diluted with brine and extracted with light petroleum (b. p. 40—60°), and the extract was washed with water, dried, and concentrated to low bulk in a vacuum under nitrogen. The crystalline material which separated at 0° was filtered off, washed with light petroleum, and recrystallized three times from light petroleum and then once from methanol. The product had m. p. 92—93°, undepressed on admixture with synthetic colupulone but depressed to 76—84° on admixture with synthetic lupulone.

Hydrogenolysis of Colupulone.—Colupulone (5 g.; isolated from Fuggle hops of the 1950 crop) in methanol (100 ml.) was hydrogenated in the presence of aqueous palladous chloride (3 ml. of 5%), absorbing 1080 ml. of hydrogen in 1 hr. ($4H_2$, 1100 ml.). One-half of the solution was evaporated to dryness and the residue treated with benzoyl chloride (3 g.) in dry pyridine (30 ml.); this yielded a *tribenzoate*, m. p. 133°, prisms from aqueous methanol (Found: C, 75·5; H, 7·1. $C_{41}H_{44}O_7$ requires C, 75·9; H, 6·9%). The remainder of the solution from the hydrogenation was treated with lead acetate (2·5 g.) in water (5 ml.) and the solution was then shaken with oxygen (absorption 70 ml.; $\frac{1}{2}O_2$, 70 ml.). The lead salt of tetrahydrocohumulone was filtered off (2·0 g., 74%) and decomposed with hydrogen sulphide in methanol, giving a yellow resin; $\lambda_{max.}$ 240, 285, and 325 mμ ($E^{1\%}_{1\,cm.}$ 265, 178, and 191 in EtOH), 230 and 325 mμ ($E^{1\%}_{1\,cm.}$ 395 and 335 in alkaline ethanol). In similar experiments with colupulone isolated from Bullion hops and from Fuggles hops, both of the 1953 crop, the yields of tetrahydrocohumulone were 46% and 80% respectively.

Alkaline Hydrolysis of Tetrahydrocohumulone.—Tetrahydrocohumulone (1·5 g.) was heated under reflux with 2N-sodium hydroxide (50 ml.) for 3 hr. The solution was cooled, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was extracted with saturated aqueous sodium hydrogen carbonate; no material was removed by a further extraction with 2N-sodium hydroxide. The bicarbonate extracts yielded on acidification a mixture of acids which were isolated by means of ether. The resulting oil crystallized on treatment with aqueous methanol, affording dihydrocohumulinic acid, m. p. 89°, undepressed on admixture with material prepared by hydrogenating cohumulinic acid (Howard and Tatchell, *J.*, 1954, 2400) and depressed to 81° on admixture with dihydrohumulinic acid (Found: C, 66·3; H, 8·6; active H, 0·45. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7; 1H, 0·39%). On another occasion a portion of the hydrolysis product, insoluble in *cyclo*hexane, afforded, after crystallization from aqueous methanol, material of m. p. 152—153° which was not further examined.

Hexahydrolupulenol.—Colupulone (20 g.) was oxidised by alkaline hydrogen peroxide, and the product successively decarboxylated and hydrogenated (Howard and Pollock, *loc. cit.*), to give hexahydrolupulenol, m. p. 178° (9 g., 55% overall).

Oxidation of Hexahydrolupulenol with Bismuth Trioxide.—Hexahydrolupulenol (2 g.) and bismuth oxide (4 g.) were heated in refluxing acetic acid (25 ml.) for 24 hr., the suspension

was concentrated *in vacuo*, and the residue was diluted with ether and 2N-hydrochloric acid. The ethereal extract was washed with water, dried, and evaporated to leave an oil (2 g.). Distillation at 120° (bath-temp.)/10^{-4} mm. gave 3 : 3 : 5-3′-*methylbutyl*cyclo*pentane*-1 : 2 : 4-*trione* (1·8 g., 91%), m. p. 34° (Found: C, 74·5; H, 10·3. $C_{20}H_{34}O_3$ requires C, 74·6; H, 10·6%). Light absorption: In EtOH, $\lambda_{max.}$ 280 mμ (ε 9800); in alkaline ethanol, $\lambda_{max.}$ 230, 330 mμ (ε 12,500, 10,500); 3-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione has $\lambda_{max.}$ 276 mμ (ε 12,250 in EtOH) and 233 and 328 mμ (ε 10,500 and 10,800 in alkaline ethanol) (cf. Howard and Pollock *loc. cit.*). The substance afforded a green copper complex, m. p. 114—115°. Shaking a solution of the compound in light petroleum with aqueous sodium hydrogen carbonate caused precipitation of a *sodium salt* (Found: C, 71·4; H, 10·2. $C_{40}H_{67}O_6Na$ requires C, 72·0; H, 10·1%) which was insoluble in water and light petroleum but readily soluble in ethanol and acetone and somewhat soluble in ether.

Oxidation of Dihydrohumulinic Acid with Bismuth Trioxide.—Dihydrohumulinic acid (122 mg.) and bismuth trioxide (140 mg.) were heated under reflux in acetic acid (10 ml.) for 24 hr. The cooled solution was diluted with 2N-hydrochloric acid (20 ml.) and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. The residue was crystallized from methanol, to give *iso*humulinic acid (50 mg.), m. p. and mixed m. p. 143—144°.

Oxidation of Colupulone with Hot Alkaline Hydrogen Peroxide.—(i) Colupulone (10 g.) was dissolved in warm 10% aqueous sodium hydroxide (500 ml.), aqueous hydrogen peroxide (30%; 100 ml.) was added, and the solution allowed to cool to room temperature overnight. Then it was heated for 3 hr. on the steam-bath and steam-distilled. The product, isolated from the distillate by extraction with ether, was a yellow oil (2·75 g.). Distillation afforded 7-*hydroxy*-2 : 11-*dimethyl*-8-(3-*methylbut*-2-*enyl*)*dodeca*-2 : 10-*dien*-6-*one*, b. p. 178—182°/35 mm., n_D^{20} 1·4872, d_{20}^{20} 0·8900 [Found: C, 77·6; H, 10·7; active H, 0·31%; *M* (Rast), 302. $C_{19}H_{32}O_2$ requires C, 78·1; H, 10·9; 1H, 0·34%; *M*, 292], which reduced Fehling's solution, absorbed 2·7 mols. of hydrogen on hydrogenation, and reduced 0·97 equiv. of periodate, but failed to form a 2 : 4-dinitrophenylhydrazone or a semicarbazone.

(ii) Colupulone (20 g.) in warm 10% aqueous sodium hydroxide (1 l.) was treated with aqueous hydrogen peroxide (30%; 150 ml.). The solution was heated at 100° for 3 hr., cooled, and extracted with ether. The ethereal extract afforded no α-ketol. The aqueous layer was acidified with sulphuric acid and extracted with ether. The ethereal extract was shaken with saturated aqueous sodium hydrogen carbonate, and acids were isolated from the aqueous phase in the usual way. The ethereal phase was extracted with 2N-sodium hydroxide to remove enols. The acidic fraction was distilled, affording *iso*butyric acid (0·87 g.), b. p. 146—148°, and another fraction (0·73 g.), b. p. 150—166°/25 mm. (Found: equiv., by titration, 257). The enolic fraction was obtained as an oil (2 g.) which afforded a green *copper complex*, m. p. 214° (from ethanol) (Found: C, 66·3; H, 8·4; Cu, 14·6. $C_{24}H_{38}O_4Cu$ requires C, 63·5; H, 8·4; Cu, 14·0%). A solution of this complex (0·72 g.) in ether was shaken with 2N-sulphuric acid, and the ethereal phase washed with water, dried, and evaporated to yield 2 : 9-*dimethyldec*-8-*ene*-3 : 5-*dione* (Found: C, 73·2; H, 10·5%; equiv., by titration 195; p*K* in aqueous ethanol, 6·7. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·3%; equiv., 196). The compound afforded bromoform when treated with sodium hypobromite.

Periodate Oxidation of 7-*Hydroxy*-2 : 11-*dimethyl*-8-(3-*methylbut*-2-*enyl*)*dodeca*-2 : 10-*dien*-6-*one*.—The compound (1·33 g.), dissolved in methanol (50 ml.), was treated with sodium metaperiodate (1 g.) in water (15 ml.), and the solution kept for 24 hr. Sodium iodate (0·68 g.) was filtered off, and the filtrate was diluted with water and extracted with ether. The extract was washed with water, with aqueous sodium hydrogen carbonate, and again with water, dried, and evaporated to dryness. The residual oily 5-methyl-2-(3-methylbut-2-enyl)hex-3-enal yielded a 2 : 4-*dinitrophenylhydrazone*, which, after chromatography on alumina in benzene, was isolated as orange needles, m. p. 89·5° (Found: C, 59·6; H, 6·6; N, 15·6. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·6%).

Degradation of Colupulone under Acidic Conditions.—A solution of colupulone (10 g.) in methanol (500 ml.) and 12N-hydrochloric acid (150 ml.) was refluxed for 3·5 hr. (odour of isoprene) and then concentrated to 300 ml. The concentrate was extracted with ether (1 × 200; 2 × 100 ml.); the combined extracts were washed with water, dried, and evaporated. The residue was dissolved in light petroleum (b. p. 40—60°; 20 ml.) and the solution seeded and stored at 0° for 18 hr. The light petroleum solution was decanted and the crystals were washed with light petroleum and recrystallized from aqueous methanol, affording 10-iso*butyryl*-3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 5,4-b′)*dipyran* (XIV; R = Pr^i)

(1·6 g.), m. p. 169·5° (Found: C, 72·0; H, 8·3; active H, 0·43. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·4; 1H, 0·3%). Light absorption: in concentrated H_2SO_4, $\lambda_{max.}$ 325 mμ (ε 24,500); in EtOH, 282 (ε 4000); in alkaline ethanol, 282 mμ (ε 4280); 5-hydroxy-7-methoxy-2 : 2-dimethyl-8-β-phenylpropionylchroman has $\lambda_{max.}$ 284 mμ (ε 5570; cf. Morton and Sawires, *loc. cit.*). The above light petroleum solution was chromatographed on alumina (Merck; washed with acetic acid and methanol), light petroleum (b. p. 40—60°) being the developing solvent. The rapidly moving yellow band was eluted and gave material which, recrystallized from aqueous methanol, afforded yellow plates of 6-iso*butyryl*-3 : 4 : 8 : 9-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 3,4-b′)*dipyran* (XIII; R = Pr^i) (1·3 g.), m. p. 83° (Found: C, 71·9; H, 8·4; active H, 0·32. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·4; 1H, 0·3%). Light absorption in concentrated H_2SO_4, $\lambda_{max.}$ 325 mμ (ε 24,000); in EtOH, 298 mμ (ε 16,500); in alkaline ethanol, 300 mμ (ε 19,900); 7-hydroxy-5-methoxy-2 : 2-dimethyl-8-β-phenylpropionylchroman has $\lambda_{max.}$ 291 mμ (ε 18,700; cf. Morton and Sawires, *loc. cit.*). Methylation (cf. methylation of dihydro*iso*pomiferitin dimethyl ether, etc.; Wolfrom *et al.*, *loc. cit.*) afforded a resinous *methyl ether* (Found: C, 72·9; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

The compound (XIV; R = Pr^i) is soluble in 12N-hydrochloric acid to give a deep yellow solution and in aqueous sodium hydroxide, but insoluble in aqueous sodium hydrogen carbonate; it forms a *monobenzoate*, m. p. 159° (Found: C, 74·4; H, 7·5. $C_{27}H_{32}O_5$ requires C, 74·3; H, 7·4%), and a crystalline sodium salt but failed to react with phenyl *iso*cyanate. Methylation as for (XIII; R = Pr^i) afforded a *methyl ether*, m. p. 134° (Found: C, 73·0; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%). The isomer (XIII; R = Pr^i) was insoluble in alkali; it failed to react with benzoyl chloride in pyridine and absorbed no hydrogen on attempted hydrogen in the presence of palladous chlorde. Compound (XIII; R = Pr^i) exhibited maximal absorption at the following wave-lengths in the infra-red: 3·7 (w), 6·24 (s), 7·07 (m), 7·33 (m), 7·43 (m), 7·56 (m), 7·80 (m), 7·94 (m), 8·0 (s), 8·15 (m), 8·50 (m), 8·65 (s), 8·74 (s), 8·84 (s), 8·96 (s), 9·53 (w), 9·61 (w), 9·89 (w), 10·1 (w), 10·46 (m), 10·75 (w), 10·9 (w), 11·14 (w), 11·26 (w), 11·42 (w), 11·8 (w), 12·1 (w), 12·49 (w), 13·45 (w), 13·9 (w) and 14·6 (w) μ where (s) = strong, (m) = medium, (w) = weak. We are indebted to Professor Sir Alexander Todd, F.R.S., for this spectrum.

Hydrogenation of the Dipyran (XIV; R = Pr^i).—The compound (2 g.) was hydrogenated in methanol in the presence of palladous chloride, 274 ml. of hydrogen being absorbed ($2H_2$ and $C_{20}H_{28}O_4$ require 270 ml.). The solution was filtered and diluted with water, and 10-iso*butyl*-3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 5,4-b′)*dipyran* (XV; R = Pr^i) (1·7 g.) was filtered off. The compound recrystallized as colourless needles, m. p. 88°, from aqueous methanol (Found: C, 75·0; H, 9·7; active H, 0·28. $C_{20}H_{30}O_3$ requires C, 75·2; H, 9·5; 1H, 0·32%). The compound showed only end-absorption in the ultra-violet and formed a *phenylurethane*, colourless prisms, m. p. 181—182°, from aqueous methanol (Found: C, 73·9; H, 8·2. $C_{27}H_{35}O_4N$ requires C, 74·1; H, 8·1%) and a 3 : 5-*dinitrobenzoate*, yellow plates, m. p. 221°, from aqueous methanol (Found: C, 62·8; H, 6·4; N, 5·6. $C_{27}H_{32}O_8N_2$ requires C, 63·1; H, 6·3; N, 5·5%).

Clemmensen Reduction of the Dipyran (XIV; R = Pr^i).—A solution of the compound (180 mg.) in 12N-hydrochloric acid (10 ml.) and ethanol (10 ml.) containing zinc amalgam (2 g.) was boiled under reflux for 2 hr. The colourless supernatant solution was diluted with water, and the product recrystallized from aqueous methanol to give the phenol (XV; R = Pr^i) (50 mg.), identical with the material prepared by catalytic hydrogenation of (XIV; R = Pr^i).

Isomerisation of the Angular Dipyran (XIII; R = Pr^i).—The yellow solution of the compound (0·5 g.) in concentrated sulphuric acid was warmed for 5 min. at 60° and poured on ice. The mixture was extracted with ether, and the ethereal extract shaken with saturated aqueous sodium hydrogen carbonate and with 2N-sodium hydroxide. The latter extract on acidification gave the isomer (XIV; R = Pr^i), m. p. 168° undepressed by material prepared directly from colupulone.

Alkaline Fusion of Crystalline β-Soft Resin.—(i) The material (10 g.) was dissolved in air-free 2N-potassium hydroxide (50 ml.), and solid potassium hydroxide (20 g.) was added. The mixture was distilled under nitrogen almost to dryness, water (40 ml.) added, and the mixture again distilled, the process being repeated five times. The residue was adjusted almost to neutrality with 12N-hydrochloric acid, silica filtered off, and the filtrate acidified with 2N-hydrochloric acid and saturated with sodium chloride. The solution was extracted with ether (3 × 100 ml.), and the extract was washed with saturated brine, dried (Na_2SO_4), and evaporated. The residue (4 g.) was distilled, the fraction of b. p. 146—178° (2·1 g.) being collected. Redistillation afforded (*a*) material, b. p. 152—156° (417 mg.), giving *p*-bromophenacyl *iso*butyrate, m. p.

and mixed m. p. 71°, and (*b*) material, b. p. 156—160°, n_D^{20} 1·4038 (389 mg.), giving a *p*-bromophenacyl ester, m. p. 54—55° (Found: C, 51·9; H, 4·7; Br, 27·2. Calc. for $C_{13}H_{15}O_3Br$: C, 52·1; H, 5·0; Br, 26·8%); *p*-bromophenacyl α-methylbutyrate has m. p. 55° (Murahashi, *Sci. Papers Inst. Phys. Chem. Research, Tokyo*, 1938, **34**, 155).

(ii) Crystalline β-resin (20 g.) was added to 2N-potassium hydroxide (100 ml.), and solid potassium hydroxide (40 g.) was added. The solution was evaporated nearly to dryness, water (100 ml.) added, and the process repeated four times. The distillate was extracted with light petroleum (b. p. 60—80°), and the extract dried and evaporated to dryness. Fractional distillation gave (*a*) a product (0·606 g.), b. p. 135—142°/28 mm., which gave a 2 : 4-dinitrophenylhydrazone which could not be crystallized, (*b*) 6-methylhept-5-en-2-one (0·4 g.), b. p. 170—172°/28 mm. (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 78°), and (*c*) the ketone (VII) (1·148 g.), b. p. 160—185°/15 mm., n_D^{20} 1·4819, d_4^{20} 0·861. Howard and Pollock (*loc. cit.*) give b. p. 196°/40 mm., n_D^{12} 1·4832.

The residue from the fusion experiment was freed from silica as before and acidified. The acids, isolated as under (i) above, were distilled, affording (*a*) *iso*butyric acid, b. p. 150—158° (identified as the *p*-bromophenacyl ester), (*b*) an acid, b. p. 160—164°, and (*c*) an acid, b. p. 124—132°/45 mm. [*p*-bromophenacyl ester, m. p. 40° (Found: C, 53·3; H, 5·3; Br, 25·6. Calc. for $C_{14}H_{17}O_3Br$: C, 53·6; H, 5·4; Br, 25·6%)]. *p*-Bromophenacyl (±)-3-methylpentanoate has m. p. 36° (Sabetay and Panousse, *Compt. rend.*, 1945, **225**, 887).

*Phloro*iso*butyrophenone*.—A mixture of anhydrous phloroglucinol (19 g.), aluminium chloride (61 g.), and carbon disulphide (70 ml.) was stirred for 30 min., nitrobenzene (45 ml.) was then added, and the solution stirred and refluxed for a further 30 min. *iso*Butyryl chloride (16·4 g.) in nitrobenzene (5 ml.) was added to the boiling solution during 30 min. and the whole then stirred and heated for 1 hr. The thick syrup was poured into water (500 ml.), sodium potassium tartrate (500 g.) added, and the solution adjusted to neutrality. Volatile material was removed by steam-distillation (25 min.), the residue cooled until crystallization was complete, and the product filtered off. Recrystallization from water gave phloro*iso*butyrophenone (13 g., 44%), m. p. 78—82° (hydrate) or 138—140° (anhydrous).

*Phloro*iso*valerophenone*.—The compound, prepared from phloroglucinol and *iso*valeryl chloride in an analogous manner, had m. p. 145° (anhydrous).

Synthesis of Colupulone.—Phloro*iso*butyrophenone (6·67 g.) was converted into colupulone by Riedl's method (*loc. cit.*), giving 1·87 g. (14%) of pure product, m. p. 90—92°.

Synthesis of Lupulone.—Phloro*iso*valerophenone (15 g.) was similarly converted into lupulone (8·3 g., 29%), m. p. 89—90°, depressed to 76—82° on admixture with synthetic colupulone.

Hydrogenolysis of Synthetic Colupulone.—Synthetic colupulone (232 mg.) was hydrogenated in methanol in the presence of palladous chloride, the mixture filtered, and the filtrate evaporated to dryness *in vacuo*. The residue in pyridine (0·8 ml.) was treated with benzoyl chloride (0·4 g.), kept under nitrogen for 3 days, diluted with water, and extracted with ether, and the extract washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and with water, dried, and evaporated. The product was crystallized from methanol and had m. p. 135—137°, undepressed on admixture with material similarly obtained from natural colupulone.

Hydrogenolysis of Synthetic Lupulone.—Synthetic lupulone (2·6 g.) was hydrogenated in methanol (70 ml.) containing palladous chloride, 592 ml. of hydrogen being absorbed ($4H_2$, 563 ml.). The mixture was filtered and a portion of the filtrate (20 ml.) benzoylated as above, giving material, m. p. 164—166° (Wöllmer, *loc. cit.*, gives m. p. 164—165°). Lead acetate (1·6 g.) was added to the remainder of the filtrate and the whole shaken with oxygen. The lead salt (1·542 g., 59%) was filtered off and decomposed with methanolic hydrogen sulphide, and the product isolated in the usual way. Recrystallized from aqueous acetic acid it had m. p. 82—84° (Wöllmer, *loc. cit.*, gives m. p. 82—84°).

Oxidation of Synthetic Colupulone with Alkaline Hydrogen Peroxide.—Synthetic colupulone (1·5 g.) was oxidised with hydrogen peroxide (30% w/v; 6 ml.) in 10% aqueous sodium hydroxide (75 ml.) as described previously (Howard and Pollock, *loc. cit.*). The non-volatile acidic product was decarboxylated by 5 minutes' boiling in toluene to material (420 mg., 33%), m. p. 117—119° undepressed on admixture with lupulenol obtained from natural colupulone. Hydrogenation of a portion (310 mg.) of the material in methanol over Adams's catalyst (uptake 74 ml. Calc. for $3H_2$ for $C_{20}H_{30}O_3$, 67 ml.) gave hexahydrolupulenol (226 mg.), m. p. 178—180° undepressed on admixture with material similarly prepared from natural colupulone. The volatile acid fraction of the oxidation was isolated in the usual manner and distilled. The distillate (114 mg.) gave *p*-bromophenacyl *iso*butyrate, m. p. and mixed m. p. 75—77°.

Oxidation of Synthetic Lupulone with Alkaline Hydrogen Peroxide.—Synthetic lupulone (5 g.) was oxidised in the usual manner. The volatile acidic material (730 mg.) had b. p. 172° and gave an anilide, m. p. 113—114°, and a *p*-bromophenacyl ester, m. p. 66—67°, both undepressed on admixture with the corresponding derivatives of *iso*valeric acid. The non-volatile acidic material (2·75 g.) was heated in boiling toluene (20 ml.) for 5 min., to give lupulenol (1·61 g.), m. p. 118—119° undepressed on admixture with material prepared from natural or synthetic colupulone. Hydrogenation of the material (1 g.) gave hexahydrolupulenol (1 g.), m. p. 176—178° undepressed on admixture with material prepared from natural or synthetic colupulone.

Synthesis of Compound (XIII; R = Pr^i).—To a suspension of phloro*iso*butyrophenone (3·25 g.) in chloroform (30 ml.), previously dried over phosphoric oxide, 1-bromo-3-methylbut-2-ene (4·93 g.) was added. Heat was evolved and hydrogen bromide was liberated while the phloro*iso*butyrophenone slowly dissolved. The clear solution was diluted with chloroform (40 ml.) and successively shaken with saturated aqueous sodium hydrogen carbonate, 2N-sodium carbonate, and N-sodium hydroxide. The extracted chloroform layer was evaporated to dryness, affording the dipyran (XIII; R = Pr^i) (0·349 g., 6·4%), m. p. 86—88°, undepressed by material prepared directly from colupulone.

Acid Degradation of Lupulone.—A degradation of synthetic lupulone (1·9 g.) carried out as for colupulone above afforded 3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethyl*-10-β-*methylbutyrylbenzo*(1,2-b, 5,4-b′)*dipyran* (XIV; R = Bu^i), as colourless plates, m. p. 102—104° (0·67 g.), from aqueous methanol (Found: C, 72·7; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), and 3 : 4 : 8 : 9-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethyl*-6-β-*methylbutyryl*-*benzo*(1,2-b, 3,4-b′)*dipyran* (XIII; R = Bu^i), b. p. 155—160° (bath-temp.)/10^{-3} mm. (Found: C, 73·0; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

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BREWING INDUSTRY RESEARCH FOUNDATION,
NUTFIELD, SURREY.

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