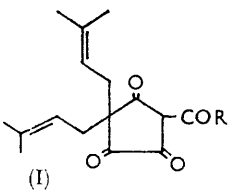
920. *Chemistry of Hop Constituents. Part XXI.*[1] *Adhulupone and Analogues of Hulupone.*

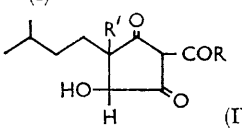
By P. Margaret Brown, J. S. Burton, and R. Stevens.

Analogues of hulupone (I; R = Bu^i) in which the acyl side chain is varied and in which one of the isopent-2-enyl side chains is replaced by allyl, prop-2-ynyl, or benzyl groups have been prepared. Some of these have been oxidized to the related hulupinic acids.

Hulupones (I), minor constituents of hops and bitter principles of beer, are derived by autoxidation of the β-acids or lupulones (II).[2] Since these occur naturally as a mixture of analogues with different acyl side chains [3] a similar mixture of hulupones is to be expected. The two predominant analogues, hulupone (I; R = Bu^i) and cohulupone (I; R = Pr^i) have been prepared by oxygenation of the corresponding lupulones in the presence of sodium sulphite, and hulupone itself has also been prepared by alkylation of dehydrohumulinic acid (III; R = Bu^i, R′ = H).[4]



(I)



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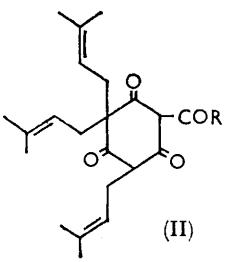

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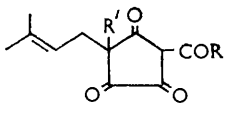

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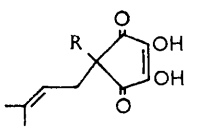

(V)

The yield of cohulupone by the former method was only 30% and alternative methods of oxidation were sought. The most satisfactory results were obtained with sodium persulphate at 20°. After 12 days the yield of cohulupone was 30%: in boiling ethanol the maximum yield (28%) was obtained after 15 minutes and after 2 hours only a trace of cohulupone remained, the major product being an uncharacterized high-boiling syrup.

Of the β-acids present in hop resins, only lupulone (II; R = Bu^i) and colupulone (II;

[1] Part XX, Burton, Elvidge, and Stevens, *J.*, 1964, 3816.

[2] (*a*) Spetsig and Steninger, *J. Inst. Brewing*, 1960, **65**, 413; (*b*) Stevens and Wright, *ibid.*, 1961, **66**, 496; (*c*) Lloyd, *Proc. Eur. Brewing Conv., Vienna*, Elsevier, 1961, p. 112.

[3] (*a*) Howard and Pollock, *Chem. and Ind.*, 1954, 991; (*b*) Howard, Pollock, and Tatchell, *J.*, 1955, 174; (*c*) Howard and Tatchell, *Proc. Eur. Brewing Conv., Baden-Baden*, Elsevier, 1955, p. 119; (*d*) Rigby, Shito, and Bars, *J. Inst. Brewing*, 1962, **68**, 60.

[4] Wright, *J.*, 1963, 1769.

R = Pr^i) have been isolated but considerable indirect evidence indicates that other analogues occur of which adlupulone (II; R = Bu^s) is the most important.[3] Accordingly adlupulone was synthesized by a modification of Riedl's method [5a,c] and was readily converted into adhulupone (I; R = Bu^s) by oxygenation in the presence of sodium sulphite or by use of sodium persulphate. In contrast, the ketone (II; R = Me) [5b] was oxidized to the hulupone (I; R = Me) only by the persulphate method.

The alkylation of dehydrohumulinic acid (III; R = Bu^i, R′ = H) has been studied further. Dehydrocohumulinic acid (III; R = Pr^i, R′ = H) was prepared and alkylated with 1-bromo-3-methylbut-2-ene to provide an alternative synthesis of cohulupone (I; R = Pr^i). In contrast, alkylation of dehydrohumulinic acid with 1-bromo-3-methylbutane was unsuccessful [6] although dihydrohulupone (III; R = Bu^i, R′ = CH_2·CH_2·$CHMe_2$) was prepared by alkylation of isohumulinic acid [3b] with the unsaturated halide. Dehydrohumulinic acid was also smoothly alkylated with allyl, prop-2-ynyl, and benzyl bromides to give the corresponding analogues of hulupone (Table 1). Hydrogenation [7] of the synthetic hulupones gave the corresponding saturated hydroxy-compounds (IV); the propyl analogue (IV; R = Bu^i, R′ = Pr) was oxidized back to the cyclopentane-1,2,4-trione.

Dehydrohumulinic acid with methyl iodide and anhydrous potassium carbonate in acetone gave a mixture of the methyl analogue (III; R = Bu^i, R′ = Me) of hulupone and an *O*-methylated derivative. The latter product may be a complex mixture as treatment of dehydrohumulinic acid with diazomethane gave a mixture shown by proton magnetic resonance spectroscopy to consist of eleven *O*-methyl derivatives.[8] The allyl analogue (III; R = Bu^i, R′ = CH_2·CH:CH_2) was similarly prepared.

Autoxidation of hulupone and cohulupone in ethanolic solution gave the same hulupinic acid [9] (V; R = CH_2·CH:CMe_2) and this transformation product was obtained from adhulupone by similar treatment. Similarly, dihydrohulupinic acid (V; R = CH_2·CH_2·$CHMe_2$) and the benzyl analogue (V; R = CH_2Ph) were obtained. The former compound upon hydrogenation gave the tetrahydro-derivative identical with material obtained earlier. Although dehydrohumulinic acid (III; R = Bu^i, R′ = H) and the hulupones (I) are written here in their ketonic forms, proton magnetic resonance spectroscopy shows they exist, respectively, as a mixture of di- and mono-enolic forms.[10]

Experimental

Light petroleum refers to the fraction b. p. 40—60° unless otherwise stated. B. p.s refer to air-bath temperatures. The ultraviolet light absorption characteristics of the analogues of (I; R = Bu^i) were similar to previously reported data.[2,4,6,7,9]

Oxidation of Colupulone by Sodium Persulphate.—(*a*) Colupulone (1·0 g.) and sodium persulphate (2·5 g.) in methanol (10 ml.) were set aside for 12 days. After filtration and evaporation, the residue was taken up in light petroleum and separated from a small amount of inorganic matter. The petroleum extract was evaporated to leave a viscous syrup (0·62 g.) which was distilled, to give cohulupone, b. p. 115—120°/7 × 10^{-3} mm. (0·285 g.), characterized as the quinoxaline, m. p. and mixed m. p. 106—107°.

(*b*) Colupulone (1·0 g.) and sodium persulphate (2·0 g.) in ethanol (30 ml.) were heated under reflux for 15 min. and the mixture was cooled and filtered. The filtrate was evaporated *in vacuo* and the residue was extracted with light petroleum (3 × 30 ml.). After removal of the solvent the residue (0·68 g.) was distilled giving cohulupone, b. p. 115—120°/7 × 10^{-3} mm. (0·22 g.).

(*c*) Colupulone (5 g.) and sodium persulphate (12·5 g.) in ethanol (100 ml.) were heated under reflux for 2 hr. and worked up as above to give an orange syrup (3·82 g.). Examination

[5] (*a*) Riedl and Nickl, *Chem. Ber.*, 1956, **89**, 1863; (*b*) Riedl, *Chem. Ber.*, 1952, **85**, 692; (*c*) Tatchell, personal communication.
[6] Cf. Stevens and Wright, *J.*, 1963, 1763.
[7] Cf. Burton and Stevens, *J.*, 1963, 4382.
[8] Elvidge, personal communication.
[9] Burton, Stevens, and Elvidge, *J.*, 1964, 952.
[10] Forsén, Nilsson, Elvidge, Burton, and Stevens, *Acta Chem. Scand.*, 1964, **18**, 513.

of this product by reversed-phase paper chromatography [11] indicated that it contained no cohulupone. A portion (0·71 g.) of the residue was distilled giving a pale yellow syrup, b. p. 150°/9 × 10^{-3} mm. (0·40 g.) (Found: C, 73·0; H, 8·5. Calc. for $C_{15}H_{20}O_3$: C, 72·6; H, 8·1%).

Adlupulone.[5a,c]—A solution of 2-(2-methylbutyryl)-1,3,5-trihydroxybenzene (10·88 g.) in ether (50 ml.) was added to a stirred solution of sodium (3·6 g.) in methanol (40 ml.) at 0°. After 45 min., 1-bromo-3-methylbut-2-ene (23 g.) in ether (15 ml.) was slowly added and the mixture stirred for a further 1 hr. After dilution with ether, the sodium bromide was removed and the filtrate was washed successively with 2N-hydrochloric acid, water, saturated sodium hydrogen carbonate, and water and evaporated. The residue was dissolved in light petroleum and shaken with 2N-sodium hydroxide. After being washed with chloroform the alkaline extract was acidified (cooling) and extracted with light petroleum. Concentration of the solvent afforded adlupulone which, after recrystallization from light petroleum, had m. p. 79—79·5° (2·07 g.). The mother-liquors afforded a further crop (0·45 g.).

Adhulupone (I; R = Bu^s).—(*a*) Adlupulone (5·3 g.) in methanol (300 ml.) and sodium persulphate (10·6 g.) were heated under reflux for 1 hr. Working up gave *adhulupone*, b. p. 130°/7 × 10^{-3} mm. (1·51 g.) (Found: C, 72·5; H, 8·8. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·4%). The *quinoxaline*, prepared in the presence of boric acid, had m. p. 95° (Found: C, 75·8; H, 8·2; N, 6·9. $C_{26}H_{32}N_2O_2,0{\cdot}5H_2O$ requires C, 75·6; H, 8·0; N, 6·8%).

(*b*) Adlupulone (0·5 g.) in methanol (50 ml.) containing sodium sulphite (1·0 g.) was shaken in an atmosphere of oxygen, the calculated quantity being rapidly absorbed. After filtration, the filtrate was evaporated to small bulk, acidified, and extracted with light petroleum. The petroleum solution was treated with saturated sodium hydrogen carbonate and the insoluble salt and aqueous layer were separated and acidified. The oil which separated was extracted with light petroleum and the extract was dried, evaporated, and distilled to give adhulupone (0·16 g.), identical with that obtained above.

(*c*) Adlupulone rapidly autoxidized to give a gum, the light petroleum soluble portion of which, upon distillation, afforded adhulupone identified by the infrared spectrum.

3-Acetyl-5,5-di-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione (I; R = Me).—The ketone (II; R = Me) [5b] (0·34 g.) and sodium persulphate (0·68 g.) in ethanol (20 ml.) were heated under reflux for 30 min.; working up as before afforded the *trione*, b. p. 125—130°/3 × 10^{-4} mm. (0·08 g.) (Found: C, 70·6; H, 7·2. $C_{17}H_{22}O_4$ requires C, 70·4; H, 7·6%).

Cohumulinic Acid.—Cohumulone was separated from the mixed α-acids of Bullion hops by counter-current distribution.[12] The *α-naphthylurethane*, recrystallized from light petroleum (b. p. 80—100°), had m. p. 156—157° (Found: C, 72·1; H, 7·1. $C_{31}H_{35}NO_6$ requires C, 72·0; H, 6·8%). With 2,6-diaminopyridine it gave an *adduct*, m. p. 112—113° (from benzene–methanol) (Found: C, 65·6; H, 7·8. $C_{25}H_{35}N_3O_5$ requires C, 65·6; H, 7·7%). Cohumulinic acid was prepared by hydrolysis of cohumulone.[12] The most convenient way to isolate this compound is to separate, after acidification, the organic phase of the tubes containing cohumulone, from the counter-current distribution, and to extract this with 2N-sodium hydroxide (4 × 50 ml.). The alkaline extract is then heated under reflux for 30 min., whereafter acidification affords cohumulinic acid, m. p. 76—78° (after recrystallization). Alternatively, hydrolysis of the mixed α-acids gives mixed analogues of humulinic acid which can be separated by 100 transfers in the system 2,2,4-trimethylpentane–0·5M-sodium dihydrogen phosphate (adjusted to pH 3·2 by the addition of orthophosphoric acid).

3-Isobutyryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione (III; R = Pr^i, R′ = H).—Cohumulinic acid (1·62 g.) and bismuth oxide (3·3 g.) were heated under reflux in acetic acid (75 ml.) for 5 hr. The reaction mixture was poured into ice-cold dilute hydrochloric acid (100 ml.), and the precipitated oil was extracted with ether (3 × 50 ml.). The combined ethereal extracts were washed with water (50 ml.), dried, and evaporated to leave a solid residue. Pale yellow crystals of the *ketone* (0·58 g.), m. p. 127—128°, were obtained on recrystallization from light petroleum (Found: C, 67·0; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·25; H, 7·2%).

Cohulupone (I; R = Pr^i).—To a solution of sodium (0·027 g.) in anhydrous methanol was added, at room temperature with stirring, 3-isobutyryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione (0·10 g.) in ether (2 ml.) and methanol (0·5 ml.). The resulting red solution was stirred at room temperature for 2 hr. *1-Bromo-3-methylbut-2-ene* (0·18 g.) in ether (3 ml.) was added and the mixture was stirred at room temperature for a further 20 hr. and then poured

[11] Whitear, *Chem. and Ind.*, 1962, 1464.
[12] Howard and Tatchell, *J.*, 1954, 2400.

into dilute hydrochloric acid (20 ml.). An oil was precipitated which was extracted with light petroleum (3 × 10 ml.). After being washed with water (10 ml.) and dried ($MgSO_4$), the extract was concentrated to 1 ml. Sodium hydrogen carbonate solution was added and the precipitated sodium salt was filtered off and dissolved in methanol (2 ml.). The solution was acidified with dilute hydrochloric acid and the precipitated oil was extracted with ether (3 × 10 ml.). The combined ethereal layers were washed, dried, and concentrated to an amber oil which was distilled to give cohulupone, b. p. 100—103°/10^{-4} mm. (0·04 g.). The material was identical with that obtained previously.[4] The quinoxaline was obtained in improved yield (60%) by allowing cohulupone (0·03 g.), *o*-phenylenediamine (0·011 g.), and boric acid (0·03 g.) to react at room temperature in acetic acid (4 ml.). The product had m. p. and mixed m. p. 107°.

Alkylation of Dehydrohumulinic Acid (III; R = Bu^i, R′ = H).—In a similar manner to the preparation of cohulupone, the triketone was alkylated to give the modified hulupones (III; R = Bu^i, R′ = CH_2·C:CH, CH_2·CH:CH_2, and CH_2Ph, respectively). The b. p.s, yields, and

TABLE 1.

Preparation of analogues of hulupone.

Compound (III; R = Bu^i) R′	B. p./mm.	Yield of distilled product (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
HC:C·CH_2	108°/4 × 10^{-4}	48	$C_{18}H_{22}O_4$	71·2	7·3	71·5	7·3
H_2C:CH·CH_2	128°/7 × 10^{-3}	73	$C_{18}H_{24}O_4$	71·2, 71·1	7·95, 7·9	71·0	7·9
Me_2CH·CH_2CH_2	123°/5 × 10^{-3}	69	$C_{20}H_{30}O_4$	72·0	9·2	71·8	9·0
Ph·CH_2	135°/5 × 10^{-4}	52	$C_{22}H_{26}O_4$	74·5, 74·1	7·7, 7·5	74·6	7·3
Pr (alkene side chain saturated)	128°/2 × 10^{-4}	85 *	$C_{18}H_{28}O_4$	70·3, 70·2	8·8, 8·7	70·1	9·0

* Obtained in the bismuth oxide oxidation.

analytical data are given in Table 1. Dihydrohulupone (III; R = Bu^i, R′ = CH_2·CH_2·$CHMe_2$) could not be obtained by this route but was prepared in the same way from isohumulinic acid [3b] and 1-bromo-3-methylbut-2-ene.

Hydrogenation of Hulupone Analogues.—The analogues of hulupone, listed in Table 2, were hydrogenated in methanolic solution. The mixtures were worked up as before [7] to give oils, the properties of which are given in Table 2.

5-Isopentyl-3-isovaleryl-5-propylcyclopentane-1,2,4-trione.—The hydrogenation product (IV; R = Bu^i, R′ = Pr) (1·1 g.) was oxidized by bismuth oxide to the *ketone* the properties of which are given in Table 1.

TABLE 2.

Hydrogenation of analogues of hulupone.

Compound (III; R = Bu^i) R′	Catalyst	Product (IV; R = Bu^i) R	B. p./mm.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
CH_3	PtO_2	CH_3	125°/7 × 10^{-3}	$C_{16}H_{26}O_4$	68·2	9·65	68·1	9·2
HC:C·CH_2	Pd–$BaSO_4$	Pr	136°/2 × 10^{-4}	$C_{18}H_{30}O_4$	70·4	9·2	69·7	9·7
H_2C:CH·CH_2	Pd–$BaSO_4$	Pr	138°/5 × 10^{-4}	$C_{18}H_{30}O_4$	70·1	9·3	69·7	9·7
Ph·CH_2	Pd–C	Ph·CH_2	135°/5 × 10^{-3}	$C_{22}H_{30}O_4$	74·2	8·4	73·7	8·4

Alkylation of Dehydrohumulinic Acid.—(*a*) Dehydrohumulinic acid (0·53 g.) and methyl iodide (0·56 g.) in anhydrous acetone (20 ml.) were heated under reflux for 20 hr. with anhydrous potassium carbonate (0·56 g.). The reaction mixture was diluted with water, acidified with 2N-hydrochloric acid, and extracted with ether (3 × 20 ml.). The combined ethereal extracts were dried and evaporated and the residue was distilled (b. p. 130—135°/7 × 10^{-3} mm.; 0·39 g.). This material was not homogeneous and was fractionated by dissolution in light petroleum (3 ml.) and treatment with a saturated solution of sodium hydrogen carbonate, an insoluble salt being formed at the interface. The organic phase was separated and the precipitate and aqueous layer were washed with light petroleum (20 ml.). The combined petroleum extracts were washed with water, dried, and evaporated and the residue was distilled to give a methyl ether (mixture of isomers), b. p. 105—110°/8 × 10^{-3} mm. (0·12 g.) (Found: C, 69·8; H, 8·3; OMe,

11·5. Calc. for $C_{15}H_{19}O_3$·OMe: C, 69·1; H, 7·9; OMe, 11·2%), $\lambda_{max.}$ 280 mμ (ε 8420) in acidified ethanol.

The sodium hydrogen carbonate solution together with the insoluble material was acidified and extracted with ether (2 × 15 ml.). The ethereal extracts were dried, evaporated, and distilled (b. p. 100—105°/3 × 10^{-3} mm.), to give the ketone (III; R = Bu^i, R′ = Me) identical with a specimen obtained by Wright.[4]

(*b*) By using allyl bromide, the ketone (III; R = Bu^i, R′ = CH_2·CH:CH_2), b. p. 115—120°/2 × 10^{-3} mm., was prepared in a similar manner, but the fraction containing the allyl ether was discarded.

(*c*) Dehydrohumulinic acid was recovered unchanged from a similar preparation involving isopentyl bromide.

Hulupinic Acid from Adhulupone.—Adhulupone (0·37 g.) in ethanol (500 ml.) was heated under reflux for 3 days during which a continuous stream of oxygen was passed through the solution. Evaporation gave a residue from which hulupinic acid (V; R = CH_2·CH:CMe_2), m. p. and mixed m. p. 166°, separated. The compound formed a yellow lead salt insoluble in methanol which softened at 193° and decomposed at 225° (Found: C, 38·1, 38·0; H, 4·2, 4·1; Pb, 42·75, 42·4. $C_{15}H_{18}O_4Pb$ requires C, 38·4; H, 3·8; Pb, 44·0%).

Dihydrohulupinic Acid.—Dihydrohulupone (III; R = Bu^i, R′ = CH_2·CH_2·$CHMe_2$) (0·74 g.) was similarly oxidized in ethanol (500 ml.) for 4 days. The solvent was removed *in vacuo* and the residue was washed three times with light petroleum and crystallized from methanol–water. A further recrystallization from methanol–water gave *dihydrohulupinic acid* (0·02 g.), m. p. 123—124° (Found: C, 67·6; H, 8·3. $C_{15}H_{22}O_4$ requires C, 67·3; H, 8·4%).

The Acid (V; R = CH_2Ph).—The ketone (III; R = Bu^i, R′ = CH_2Ph) (2·1 g.) in ethanol (400 ml.) was oxidized in a similar manner and the solvent was evaporated. The residue was extracted with light petroleum and the extract discarded when the remainder partially solidified. After storage on porous tiles the solid material was twice recrystallized from methanol–water, to give the *acid*, m. p. 184—185° (18 mg.) (Found: C, 71·3, 71·1; H, 6·5, 6·7. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

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