330. *The Chemistry of Hop Constituents. Part XVI.*[1] *The Preparation of Hulupone and Cohulupone.*[2]

By D. WRIGHT.

The conversion of lupulone and colupulone into hulupone and cohulupone by direct oxidation is described. Hulupone has also been prepared by alkylation of 3-isovaleryl-5-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione, which is further evidence for the structure of the hulupones.

THE hulupones were earlier [1] formulated as 5-acyl-3,3-di-(3-methylbut-2-enyl)cyclopentane-1,2,4-triones and the present communication describes their synthesis. The oxidative method employed for the conversion of hexahydrocolupulone into tetrahydrocohulupone could not be applied to colupulone itself as autoxidation of the parent resin is apparently more complex than substitution of a hydroperoxy-group into the cyclohexane nucleus. Thus when a solution of colupulone (I; $R = H$, $R' = Pr^i$) in cyclohexane is shaken in oxygen, uptake is much faster than for the hexahydro-compound and 1·6 mol. are absorbed. The hydroperoxide produced has, however, similar light absorption properties to that of the hydroperoxide (II; $R = O{\cdot}OH$) formed from hexahydrocolupulone,[1] so it appears that the site of oxidation in the cyclohexane nucleus, at least in part, is the same in both compounds and that no breakdown of the colupulone skeleton occurs. It seems probable then that the extra oxygen taken up by colupulone is concerned in reactions with the unsaturated side-chains. In support of this, the iodine value on the resultant resin, showed only about 60% of the unsaturation present in colupulone. As the presence of hydroperoxy-groups might have vitiated the results the estimations were repeated after the product of the autoxidation had been treated with sodium sulphite in methanol: the outcome, however, was very similar to that given by the untreated autoxidation product.

If the double bonds of colupulone are attacked by oxygen or hydroperoxy-radicals, partial polymerisation may ensue with the formation of complex products, and many attempts to isolate distinct compounds after autoxidation of colupulone failed. A minute amount of crystalline material which had the light absorption of a hulupone salt was formed on one occasion when an oxygenated solution of colupulone was treated with sodium carbonate solution, but there was insufficient for complete characterization and the preparation could not be repeated. An attempt was also made to establish the presence of the simple hydroperoxide (I; $R = O{\cdot}OH$, $R' = Pr^i$) in the resin obtained by autoxidation of colupulone. If it were present it should be capable of being hydrogenated to give compound (II; $R = OH$) obtained from the hydroperoxide of hexahydrocolupulone (II; $R = O{\cdot}OH$). Completion of the remaining stages of the synthesis, however, gave only a low yield of a triketone which could not be identified with tetrahydrocohulupone. Possibly, therefore, only a small proportion of monomeric material is present in the autoxidation product of colupulone.

No reaction occurred when an attempt was made to introduce a hydroxyl group into colupulone directly with cumene hydroperoxide, as in the formation of humulinone from humulone.[3] However, during the estimation of iodine value that involved treatment with sodium sulphite in methanol (see above) the ultraviolet absorption of the peroxide-free resin ($\lambda_{max.}$ 255 mμ) differed from that of the starting material ($\lambda_{max.}$ 280 mμ). This led to a study of the effect of sodium sulphite in methanol upon colupulone itself; in the presence of oxygen a rapid uptake of gas occurred, giving resins consisting partly of cohulupone in the form of its sodium salt. Free cohulupone (IV; $R = Pr^i$) was isolated in about 30% yield with the infrared absorption of cohulupone [4] and ultraviolet absorption similar

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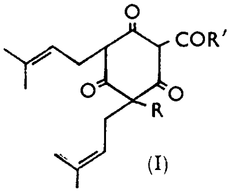
[1] Part XV, Stevens and Wright, preceding paper.

[2] Cf. Wright, *Proc. Chem. Soc.*, 1961, 315.

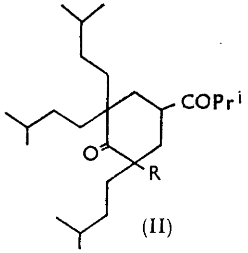
[3] Cook, Howard, and Slater, *J. Inst. Brewing*, 1955, **61**, 321.

[4] Spetsig and Steninger, *J. Inst. Brewing*, 1960, **65**, 413.

to that of tetrahydrocohulupone. With *o*-phenylenediamine and 2,3-naphthylenediamine cohulupone gave crystalline quinoxalines. Its relation to the established tetrahydrocohulupone[1] was confirmed by hydrogenation to a substance having the light absorption of oxyhumulinic acid;[3] reoxidation of the hydrogenation product gave tetrahydrocohulupone, identified by conversion into its sodium salt. Like the other hop resins, cohulupone is oxidised in air, changing gradually to a resin with a considerably lower carbon content than cohulupone and insoluble in light petroleum.



(I)



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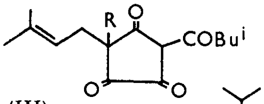

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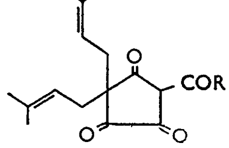

(IV)

Cohulupone appears to be more stable to alkali than humulone and about 50% was recovered unchanged as its sodium salt under conditions where humulone would be completely converted into humulinic acid.[5] The sodium salt (m. p. 255°) obtained in this fashion is distinct from that formed (m. p. 115—120°) when cohulupone is shaken with sodium hydrogen carbonate solution; both sodium salts, nevertheless, give cohulupone on treatment with mineral acid. These salts resemble the sodium salt of 3,3,5-tri-isopentylcyclopentane-1,2,4-trione[6] in being soluble in most organic solvents apart from light petroleum and only slightly soluble in water. Cohulupone was unstable to treatment with hydrochloric acid in aqueous methanol.

Hulupone (IV; R = Bu^{i}) itself has been prepared from synthetic lupulone[7] (I; R = H, R′ = Bu^{i}) in a similar manner to cohulupone, also by alkylation, with 3-methylbut-2-enyl bromide, of the sodium derivative of the triketone (III; R = H) obtained by oxidation of humulinic acid.[8] The two samples of hulupone were identical and yielded a quinoxaline with *o*-phenylenediamine. The general application of this method to the synthesis of the hulupones was indicated by the preparation of the analogue (III; R = Me) from the triketone (III; R = H) and methyl iodide.

The mechanism of the formation of the hulupones from the lupulones by oxygenation in the presence of sodium sulphite is obscure and no cohulupone was isolated when various other reagents were substituted for sodium sulphite. With sodium carbonate and sodium dihydrogen phosphite no reaction occurred; with sodium dithionite, or metabisulphite, or sulphur dioxide oxygen was absorbed but no cohulupone was isolated, perhaps because of the acidic conditions. The action of sulphite is not catalytic since the use of only 0·1 mol. caused oxygen uptake to cease prematurely. The usual yield of cohulupone was obtained when an extra 0·9 mol. of sodium sulphite was added to the reaction mixture, although usually a large excess of sulphite (6·35 mol.) was employed. Cohulupone, however, was obtained from colupulone by using ascorbic acid or glucose instead of sodium sulphite, in the first instance in about 30% yield, but the uptake of oxygen was much slower. Conversion of lupulones into the hulupones occurs during brewing and it has been shown[9] that 10% conversion into cohulupone occurs when colupulone is boiled with brewer's wort which is rich in reducing sugars.

The above oxidation procedure is applicable to certain other α-alkyl-β-diketones; thus,

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[5] Wöllmer, *Ber.*, 1916, **49**, 780.
[6] Howard, Pollock, and Tatchell, *J.*, 1955, 174.
[7] Riedl, *Chem. Ber.*, 1952, **85**, 692.
[8] Howard and Slater, *J.*, 1957, 1924.
[9] Stevens and Wright, *J. Inst. Brewing*, 1961, **67**, 496.

although dimedone (5,5-dimethylcyclohexane-1,3-dione) itself did not react, 2,5,5-trimethylcyclohexane-1,2-dione[10] gave rise to 4,4-dimethylcyclopentane-1,2-dione[11] and 3-methylpentane-2,4-dione yielded biacetyl although the isolated yield of the latter was very small. Surprisingly, however, hexahydrocolupulone was very slow to react and none of the expected tetrahydrocohulupone was isolated.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 40—60°.

Autoxidation of Colupulone in Cyclohexane.—(i) A freshly crystallized sample of colupulone (Found: I val., 179, 185. Calc. for $C_{25}H_{36}O_4$: I val. for 3 double bonds, 190) in cyclohexane (50 ml.) was shaken in oxygen until no more gas was absorbed (2—3 hr.; 1·6 mol.). Removal of the solvent left a pale yellow oil (Found: O·OH,[12] 4·0%; I val., 98, 100. $C_{25}H_{35}O_4{\cdot}O{\cdot}OH$ requires O·OH 7·6%; I val. for 3 double bonds, 176), $\lambda_{max.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 190). A portion (350 mg.) of the resin in methanol (5 ml.) was treated with sodium sulphite (1 g.) during 3 hr. After filtration and evaporation the residue was extracted with ether, to afford an oil (Found: O·OH, 0·0; I val., 92, 95), $\lambda_{max.}$ 255 mμ.

(ii) Colupulone (1·0 g.) in cyclohexane (50 ml.) was allowed to absorb only 1 mol. of oxygen and the solution was shaken with 2N-sodium carbonate (25 ml.). A small amount of solid which separated at the interface was removed, washed with sodium carbonate solution, and dissolved in ether. The dried ether solution was diluted with light petroleum and allowed to evaporate slowly. A small amount of crystalline material separated (7 mg.), having m. p. 120°, $\lambda_{max.}$ 255, 325 mμ; it gave an orange colour with ferric chloride solution.

(iii) Colupulone (0·5 g.) was oxygenated in cyclohexane until absorption was complete. After removal of the solvent the residue was taken up in methanol (30 ml.) and hydrogenated with platinum oxide (75 mg.). The catalyst and solvent were removed and the residue was boiled for 5 hr. with N-sodium hydroxide (14 ml.) and ethanol (3 ml.). The ethanol was evaporated and the residue extracted with ether. The material (250 mg.) obtained by evaporation of the ether was heated under reflux for 5 hr. with bismuth oxide (500 mg.) in acetic acid (4 ml.). Working up as in the preparation of tetrahydrocohulupone, and distillation at 100°/10^{-4} mm., gave a yellow oil (50 mg.) whose sodium salt appeared to differ from that of tetrahydrocohulupone. It had $\lambda_{max.}$ 255 and 325 mμ but gave crystals, m. p. 210°, from ethanol–hexane (Found: C, 64·05; H, 8·3%).

Oxygenation of Colupulone in Presence of Sodium Sulphite.—Colupulone (1·0 g.) was dissolved in methanol (10 ml.), and anhydrous sodium sulphite (2·0 g., 6·35 mol.) added. The mixture was shaken under oxygen until absorption of gas appeared complete (60 ml.; 2—3 hr.), then filtered and evaporated. The residue (1·34 g.) was extracted twice with warm light petroleum, leaving mixed salts (1·05 g.) which were dissolved in methanol and acidified by the gradual addition of dilute hydrochloric acid. After dilution with water the liquid was extracted with light petroleum, and the residue after removal of the solvent was distilled at 100° (bath)/ 10^{-4} mm. This gave a yellow oil (0·23 g., 29%) whose infrared absorption spectrum was identical with that of cohulupone[4] (Found: C, 71·95; H, 8·65%; I val., 156. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·15%; I val., 160). The *compound* gave a *sodium salt*, m. p. 115—120°, when its solution in light petroleum was shaken with sodium hydrogen carbonate solution. This salt was soluble in ethanol, ether, and chloroform but insoluble in light petroleum and carbon tetrachloride and could not be satisfactorily crystallized (Found: C, 64·45; H, 7·45. $C_{19}H_{25}NaO_4,0{\cdot}5H_2O$ requires C, 65·3; H, 7·4%). Pure cohulupone, obtained by regeneration from the sodium salt and distillation, had $\lambda_{max.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 276), $\lambda_{min.}$ 240 mμ ($E^{1\%}_{1\,cm.}$ 118) in acidified ethanol and $\lambda_{max.}$ 255 and 325 mμ ($E^{1\%}_{1\,cm.}$ 401, 274), $\lambda_{min.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 103) in alkaline ethanol. The compound gave a deep orange colour with ethanolic ferric chloride but no precipitate with methanolic lead acetate.

Cohulupone with *o*-phenylenediamine in ethanol–acetic acid gave a *quinoxaline* which after purification by chromatography and recrystallization from light petroleum had m. p. 107° Even after drying over phosphorus pentoxide it retained 0·5 mol. of water (Found: C, 75·4, 75·2; H, 7·8, 7·7; N, 6·9. $C_{25}H_{30}N_2O_2,0{\cdot}5H_2O$ requires C, 75·2; H, 7·8; N, 7·0%). In a

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[10] Desai, *J.*, 1932, 1079.
[11] Kon, *J.*, 1922, **121**, 513.
[12] Stuffins and Weatherall, *Analyst*, 1945, **70**, 403.

similar manner, cohulupone with 2,3-diaminonaphthalene gave a *quinoxaline* as orange prisms (from ethanol or hexane), m. p. 135° (Found: C, 78·9, 79·6; H, 7·8, 7·6. $C_{29}H_{32}N_2O_2$ requires C, 79·1; H, 7·3%).

The solubility of cohulupone in water is 1·35 g./l. at 20°. Of a sample of cohulupone which had been stored in a desiccator for 3 weeks 40% was found to be insoluble in light petroleum. This amorphous material had $\lambda_{\text{max.}}$ 270 mμ ($E^{1\%}_{1\,\text{cm.}}$ 158), $\lambda_{\text{min.}}$ 240 mμ in ethanol, and $\lambda_{\text{max.}}$ 255 mμ ($E^{1\%}_{1\,\text{cm.}}$ 219) in alkaline ethanol (Found: C, 64·15; H, 7·8%; I val., 72).

Hydrogenation of Cohulupone.—A solution of cohulupone sodium salt (100 mg.) in methanol (10 ml.) was hydrogenated in the presence of platinum oxide (32 mg.). Absorption was complete after 2 hr. and the yellow solution had become colourless, its ultraviolet light absorption being very similar to that of oxyhumulinic acid.[3] After filtration and evaporation the white solid obtained was oxidised with bismuth oxide [13] and acetic acid. On distillation of the product at 100°/10^{-4} mm. a yellow oil (18 mg.) was obtained which gave a sodium salt, m. p. 225° (from ethanol–hexane) alone or mixed with the sodium salt of tetrahydrocohulupone.

Reaction of Cohulupone with Sodium Hydroxide Solution.—Cohulupone (98 mg.) was heated under reflux with N-sodium hydroxide (3 ml.) and ethanol (1 ml.) for 90 min. The ethanol was evaporated and the remaining mixture extracted with ether. Concentration of the dried ethereal solution deposited a *sodium salt* (42 mg.), m. p. 246° raised to m. p. 255° on recrystallisation from ethanol. The ultraviolet absorption spectrum of the salt was similar to that of cohulupone, $\lambda_{\text{max.}}$ 255 and 320 mμ ($E^{1\%}_{1\,\text{cm.}}$ 337, 240), $\lambda_{\text{min.}}$ 285 mμ ($E^{1\%}_{1\,\text{cm.}}$ 125); in acidified ethanol, $\lambda_{\text{max.}}$ was 280 mμ ($E^{1\%}_{1\,\text{cm.}}$ 125) (Found: C, 67·35, H, 7·5. $C_{19}H_{25}NaO_4$ requires C, 67·1; H, 7·35%). Acidification of a methanolic solution of this salt followed by extraction with light petroleum gave a yellow oil having the infrared absorption spectrum of cohulupone. Treatment of this sodium salt, m. p. 255°, with 2,3-naphthylenediamine in ethanol–acetic acid gave a quinoxaline, m. p. 136°, undepressed on admixture with that derived from cohulupone.

Oxygenation of Colupulone with Ascorbic Acid.—Colupulone (0·50 g.) and ascorbic acid (0·75 g.) in methanol (5 ml.) were shaken in oxygen for 60 hr. during which ~50 ml. were absorbed. The mixture was diluted with water and extracted with light petroleum. This extract was re-extracted with saturated sodium hydrogen carbonate solution (3 × 2 ml.); some sodium salt was precipitated. The sodium salt was dissolved in methanol and combined with the sodium hydrogen carbonate solution, and the combined extracts were acidified and extracted with light petroleum. The yellow oil from this solution was distilled (120 mg., 30%); it had $\lambda_{\text{max.}}$ 255, 325 mμ in alkaline ethanol.

Preparation of Hulupone from Synthetic Lupulone.—Synthetic lupulone [7] (833 mg.), sodium sulphite (1·66 g.), and methanol (8 ml.) were shaken together in oxygen for 40 min. after which uptake (65 ml.) had ceased. The mixture was filtered and the methanol evaporated, leaving a residue (1·17 g.) which was extracted with warm light petroleum which left a residue of salts (0·90 g.). This residue was dissolved in methanol and acidified and the liquid was extracted with light petroleum. The extract was shaken with saturated sodium hydrogen carbonate solution (3 × 2 ml.), and the insoluble sodium salt removed. This was acidified to give hulupone (199 mg.), b. p. 110° (bath)/10^{-4} mm. (144 mg., 22%), $\lambda_{\text{max.}}$ 255 and 325 ($E^{1\%}_{1\,\text{cm.}}$ 445, 308) in alkaline ethanol. With *o*-phenylenediamine it gave a *quinoxaline* that, after chromatography on silica gel,[7] separated from methanol as yellow prisms, m. p. 108—110° (Found: C, 76·9; H, 7·9. $C_{26}H_{32}N_2O_2$ requires C, 77·25; H, 7·9%). A mixed m. p. with the similar quinoxaline derived from cohulupone showed a depression to 88—94°.

Preparation of Hulupone from 3-*Isovaleryl*-5-(3-*methylbut*-2-*enyl*)*cyclopentane*-1,2,4-*trione* [8] (III; R = H).—Into a stirred solution of sodium (2·7 mol., 118 mg.) in dry methanol (1 ml.) at 0° the triketone (III) (500 mg., 1 mol.) in dry ether (2 ml.) and methanol (0·5 ml.) was introduced with extra methanol (0·5 ml.) and ether (1 ml.). After 2 hours' stirring at 0° 3-methylbut-2-enyl bromide (764 mg., 2·7 mol.) in ether (1 ml.) was added in 2 portions at an interval of 15 min. and the remaining bromide washed in with ether (0·5 ml.). After 1 hour's stirring at 0° the mixture was stirred overnight at room temperature and then diluted with ether. The ethereal extract was washed with water and dilute hydrochloric acid and dried ($MgSO_4$). After removal of solvent the residue was dissolved in light petroleum and the solution shaken with a saturated solution of sodium hydrogen carbonate (2 × 5 ml.). The solid so obtained was washed with light petroleum and sodium hydrogen carbonate solution and was dissolved

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[13] Rigby, *J.*, 1951, 793.

in methanol. The solution was acidified with dilute hydrochloric acid and then extracted with light petroleum which removed hulupone (470 mg.), b. p. 110° (bath)/10^{-4} mm. (340 mg., 54%), with the infrared absorption of material obtained by oxygenation of lupulone and $\lambda_{max.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 268), $\lambda_{min.}$ 245 mμ ($E^{1\%}_{1\,cm.}$ 125) in acidified ethanol, and $\lambda_{max.}$ 255 and 325 ($E^{1\%}_{1\,cm.}$ 446, 299), $\lambda_{min.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 110) in ethanol. With *o*-phenylenediamine it gave a quinoxaline, m. p. and mixed m. p. 108—110°.

3-*Isovaleryl*-5-*methyl*-5-(3-*methylbut*-2-*enyl*)*cyclopentane*-1,2,4-*trione* (III; R = Me).—In a manner similar to the above, treatment of the sodium salt of the triketone (III; R = H) with methyl iodide gave a yellow *ketone*, b. p. 100—110° (bath)/10^{-4} mm. (35%) (Found: C, 68·8; H, 8·15. $C_{16}H_{22}O_4$ requires C, 69·1; 7·9%), $\lambda_{max.}$ (in acidified ethanol) 280 mμ ($E^{1\%}_{1\,cm.}$ 339), $\lambda_{min.}$ 240 mμ ($E^{1\%}_{1\,cm.}$ 133), $\lambda_{max.}$ (in alkaline ethanol) 250 and 325 mμ ($E^{1\%}_{1\,cm.}$ 499 and 360), $\lambda_{min.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 106).

Oxygenation of Dihydro-1,1,4-*trimethylresorcinol*.—2,5,5-Trimethylcyclohexane-1,2-dione [10] (0·50 g.) and sodium sulphite (1·0 g.) in methanol (5 ml.) were shaken in oxygen; about 70 ml. (1 mol.) were absorbed in 3 hr. The mixture was filtered and the methanol evaporated. The residue was extracted with light petroleum and the insoluble residue was shaken with a mixture of dilute hydrochloric acid and ether. The residue from the dried ether (310 mg.) gave, as a pale yellow oil, 4,4-dimethylcyclopentane-1,2-dione,[11] b. p. 100—120°/0·3 mm. (150 mg.), which crystallized. The compound gave a disemicarbazone, m. p. 248° (lit., 251°) (Found: C, 45·0; H, 6·75. Calc. for $C_9H_{16}N_6O_2$: C, 45·0; H, 6·65%), and a 2,4-dinitrophenylosazone, m. p. 207° (from dimethylformamide–ethanol).

Oxygenation of 3-*Methylpentane*-2,4-*dione*.[14]—The dione (1 g.) was dissolved in methanol (35 ml.), sodium sulphite (7·0 g.) was added and the whole shaken in oxygen. Uptake of gas was very slow but after 18 hr. the odour of biacetyl was noticed and a drop of the solution after being warmed with hydroxylamine gave a bright red colour with nickel acetate solution. The sodium sulphite was filtered off and the mixture distilled. Addition of methanolic 2,4-dinitrophenylhydrazine to the distillate gave biacetyl 2,4-dinitrophenylosazone (110 mg.), m. p. and mixed m. p. 321—323° (from dimethylformamide).

The interest of Dr. A. H. Cook, F.R.S., is gratefully acknowledged.

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[*Received, September 14th,* 1962.]

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[14] Sprague, Beckham, and Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 2665.