

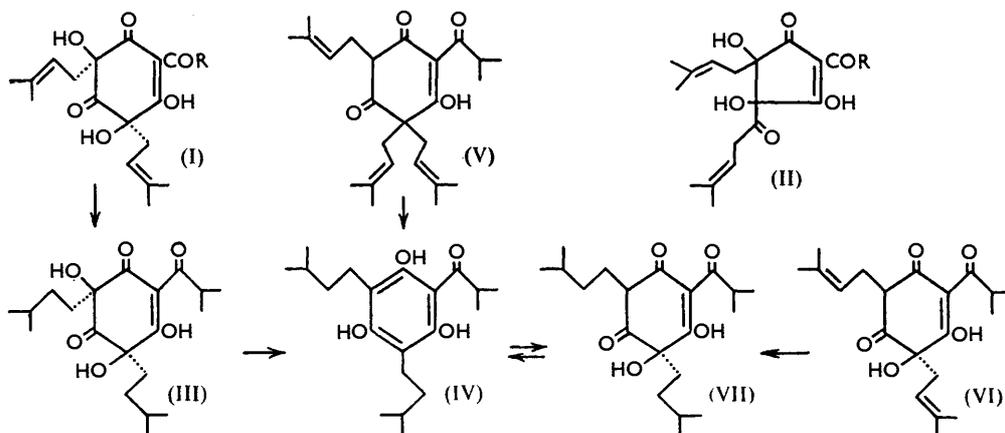
292. *The Chemistry of Hop Constituents. Part XII.\* The Structure of Humulinone.*

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Structures of type (I) are proved for humulinone and its analogues.

It was earlier suggested<sup>1</sup> that humulinone and its analogues had the general structure (I) rather than the alternative (II) involving a five-membered ring. More recently, on the other hand, the latter was preferred by Alderweireldt and Verzele,<sup>2</sup> primarily because of the low  $pK$  value and the infrared absorption of the compound. The present paper presents chemical evidence which proves the original structure (I).

Cohumulinone, which differs from humulinone only in the nature of its acyl side-chain,<sup>1</sup>



was hydrogenated to tetrahydrocohumulone (III), the only structural change being the saturation of the double bonds of the two alkyl side-chains. The same compound was also obtained by the oxidation, by cumenyl hydroperoxide, of tetrahydrocohumulone (VII)

\* Part XI, *J. Inst. Brewing*, 1957, 327.

<sup>1</sup> Cook, Howard, and Slater, *J. Inst. Brewing*, 1955, 321.

<sup>2</sup> Alderweireldt and Verzele, *Bull. Soc. Chim. belges*, 1957, **66**, 391.

itself derived from cohumulone (VI). Clemmensen reduction of the compound gave a phenol characterised as its tribenzoate, together with a hydrocarbon,  $C_{20}H_{40}$ . The phenolic product was also obtained by hydrogenolysis of colupulone<sup>3</sup> (V) and was oxidised to tetrahydrocohumulone (VII) by air in the presence of lead acetate.<sup>3</sup> No doubt is attached to the presence of six-membered rings<sup>3,4</sup> in compounds (V) and (VI), so that the new phenolic product must be 2 : 4 : 6-trihydroxy-3 : 5-diisopentylisobutyrophenone (IV). It follows that cohumulinone must likewise contain a six-membered ring and be regarded as (I; R = Pr<sup>i</sup>), the analogous compounds humulinone and adhumulinone<sup>5</sup> being as (I; R = Bu<sup>i</sup>) and (I; Bu<sup>s</sup>) respectively.

Neither humulinone nor cohumulinone is optically active when derived respectively, from the natural optically active humulone or cohumulone, presumably because the oxidation is so directed as to give internally compensated compounds.<sup>1</sup> Adhumulone differs from the analogues already mentioned in containing a further asymmetric carbon atom in the acyl side-chain. Adhumulinone derived from natural adhumulone might be expected therefore to differ from that obtained from synthetic (racemic) adhumulone. This has now been proved to be the case as "natural" adhumulinone prepared in these laboratories had m. p. 114—115° and  $[\alpha]_D +11^\circ$  "Synthetic" adhumulinone had m. p. 98°,  $\alpha$  0°.

#### EXPERIMENTAL

*Tetrahydrocohumulinone* (III).—(a) A solution of tetrahydrocohumulone<sup>3</sup> (3.1 g.) in ether (10 ml.) containing cumenyl hydroperoxide (3.1 ml.) was kept over saturated aqueous sodium hydrogen carbonate (50 ml.) for 3 days. The colourless sodium salt (2.75 g., 81%) was filtered off and afforded in the usual manner *tetrahydrocohumulinone*, m. p. 64—65°, which could not be recrystallised (Found: C, 65.1; H, 8.8.  $C_{20}H_{32}O_6$  requires C, 65.2; H, 8.7%). It had  $\lambda_{max}$ . 230 and 270 m $\mu$  ( $\epsilon$  9160 and 10,200 respectively) in acidic ethanol and  $\lambda_{max}$ . 255 and 270 (infl.) m $\mu$  ( $\epsilon$  22,500 and 20,400 respectively) in alkaline ethanol. The compound was bitter, gave an orange-red colour with methanolic ferric chloride and a yellow colour with concentrated sulphuric acid and, like tetrahydrocohumulone, failed to reduce Fehling's solution.

(b) Cohumulinone (344 mg.) was hydrogenated overnight in acetic acid over Adams platinum oxide. The solution was filtered, the filtrate evaporated *in vacuo*, and the residue shaken with ether and saturated aqueous sodium hydrogen carbonate. The sodium salt thus formed afforded tetrahydrocohumulinone as colourless needles, m. p. 62—64° undepressed on admixture with the compound prepared from tetrahydrocohumulone.

*Clemmensen Reduction of Tetrahydrocohumulone*.—A solution of tetrahydrocohumulone (0.68 g.) in ethanol (5 ml.) was boiled with amalgamated zinc (20 g.) in concentrated hydrochloric acid (12 ml.) for 1.75 hr. The product was extracted by light petroleum and the extract kept overnight in pyridine (5 ml.) containing benzoyl chloride (0.78 g.). The product isolated in the usual way crystallised from methanol as colourless prisms (0.14 g.), m. p. 137—138°, undepressed on admixture with 2 : 4 : 6-tribenzoyloxy-3 : 5-diisopentylisobutyrophenone prepared from colupulone.<sup>3</sup>

*Clemmensen Reduction of Tetrahydrocohumulinone*.—A solution of tetrahydrocohumulinone (0.38 g.) in ethanol (5 ml.) was heated with amalgamated zinc (20 g.) and concentrated hydrochloric acid (12 ml.) for 4.75 hr. The product was isolated and the crude benzoylation product chromatographed on alumina. The fraction eluted by 4 : 1 light petroleum-ether recrystallised from methanol, giving prisms (20 mg.), m. p. 136—137° undepressed on admixture with the preceding tribenzoate. The fraction eluted from the chromatogram by light petroleum was rechromatographed on silica gel (from Messrs. Hopkin and Williams). The substance (75 mg.) eluted by light petroleum had b. p. 110—115° (bath)/6  $\times 10^{-4}$  mm.,  $n_D^{25}$  1.4600 (Found: C, 86.1; H, 13.9.  $C_{20}H_{40}$  requires C, 85.7; H, 14.3%).

*Adhumulinone from Natural Adhumulone*.—A solution of the (–)-adhumulone (0.75 g.), isolated from hops,<sup>6</sup> in ether (3 ml.) containing cumenyl hydroperoxide (0.7 ml.) was kept over

<sup>3</sup> Howard, Pollock, and Tatchell, *J.*, 1955, 174.

<sup>4</sup> Howard, *Chem. and Ind.*, 1956, 1504.

<sup>5</sup> Cook, Howard, and Slater, *J. Inst. Brewing*, 1956, 220.

<sup>6</sup> Rigby and Bethune, *J. Amer. Chem. Soc.*, 1955, 77, 2828.

saturated aqueous sodium hydrogen carbonate (10 ml.) for 7 days. The sodium salt (0.52 g., 63%) was filtered off and the free acid recrystallised from light petroleum (b. p. 60—80°), as needles, m. p. 114—115° (Found: C, 66.7; H, 8.1. Calc. for  $C_{21}H_{30}O_6$ : C, 66.6; H, 7.9%). On admixture with adhumulinone from synthetic adhumulone it had m. p. 102—109°. It had  $[\alpha]_D + 11^\circ$  (*c* 5.36 in MeOH), tasted bitter, gave an orange colour with methanolic ferric chloride and a cherry-red colour with concentrated sulphuric acid and rapidly reduced Fehling's solution.

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