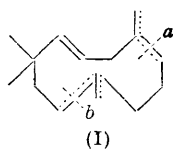


37. The Chemistry of Humulene. Part III.*

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Further investigation of the oxidation products of β -dihydrohumulene has led to the identification of succinic acid and $\beta\beta$ -dimethylpimelic acid. Formation of the latter is consistent with the formulation of humulene as a tetramethylcycloundecatriene. Less vigorous oxidation has resulted in the isolation also of a mono- or di-cyclic monoketo-carboxylic acid, $C_{15}H_{24}O_3$ (less probably $C_{15}H_{26}O_3$), and a dicyclic diketone, $C_{14}H_{22}O_2$. Attention is drawn to the resistance of α -tetrahydrohumulene to hydrogenolysis.

THAT the sesquiterpene humulene has a tetramethylcycloundecatriene structure (I) was suggested independently by Clemo and Harris (*Chem. and Ind.*, 1951, 799) and by Šorm, Streibl, Pliva, and Herout (*Chem. Listy*, 1951, 45, 308; 1952, 46, 30), the latter arguing from considerations of physical properties and the absence of large identifiable fragments on ozonolysis. In a further investigation of the products obtained from β -dihydrohumulene by potassium permanganate in acetone, followed by nitric acid (Clemo and Harris, Part II *), succinic and $\beta\beta$ -dimethylpimelic acid have been isolated. The former, because of its instability to potassium permanganate, presumably arises entirely from a secondary oxidation with nitric acid, and little structural significance can be attached to it. The formation of the latter acid, however, may be regarded as further substantive evidence for the proposed structure: it can arise by oxidation at points (a) and (b). Moreover the



sequence $C\cdot C\cdot CMe_2\cdot C\cdot C\cdot C\cdot C$ can arise only from a seven-membered or larger ring. The possibility of a pimelic acid arising from the fission of a suitably substituted β -carboxycyclohexanone system cannot be entirely excluded—cf. the chemistry of irone (Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, 1942, 25, 188; 1947, 30, 1807), although our experimental conditions, together with the inability to ketonize the C_{15} dicarboxylic acid obtained on the oxidation of tetrahydrohumulene (Clemo and Harris, *loc. cit.*), render this unlikely.

Oxidation of β -dihydrohumulene with potassium permanganate in acetone at 20–25° without subsequent treatment with nitric acid, gave *as*-dimethylsuccinic and $\beta\beta$ -dimethyladipic acid, together with a very small amount of a crystalline monoketo-carboxylic acid $C_{15}H_{24}O_3$ or $C_{15}H_{26}O_3$. Although the analytical data do not differentiate clearly between these two possibilities the former (presumably dicyclic) formula is preferred. It gives an ethyl ester 2 : 4-dinitrophenylhydrazone, and with alkaline hypiodite a positive test for the acetyl group. The neutral fraction from this oxidation yielded a very small amount of a dicyclic diketone, $C_{14}H_{22}O_2$, which readily forms a bis-2 : 4-dinitrophenylhydrazone.

* Part II, *J.*, 1952, 665.

This substance is highly reminiscent of the tricyclic diketone $C_{14}H_{20}O_2$ from β -caryophyllene, the genesis of which has been elucidated by Barton (*J.*, 1951, 2988; 1952, 2210), and it is attractive to assume a similar mechanism, under the alkaline conditions employed, for the formation of our C_{14} diketone. This is most easily envisaged as arising from a structure such as (II *a* or *b*).



Tetrahydrohumulene monoxide has been prepared from tetrahydrohumulene by treatment with perbenzoic acid. In preliminary investigations this appears to be unusually resistant to hydrogenolysis (see p. 186). The resistance to fission of dihydro- β -caryophyllene monoxide has already been noted by Šorm, Dolyš, and Pliva (*Coll. Czech. Chem. Comm.*, 1950, 15, 186), and this stability of oxides from large rings is of interest.

EXPERIMENTAL

Isolation of Succinic and $\beta\beta$ -Dimethylpimelic Acids.—Further investigation of fractions from the distillation of the methyl esters obtained by the oxidation of β -dihydrohumulene with potassium permanganate followed by nitric acid (Part II, *loc. cit.*) has given the following results. The fraction boiling at 100—110°/13 mm. (1.7 g.) was hydrolysed with methanolic potassium hydroxide. Chromatography of the crude free acidic material on silica gel, elution with ether, and purification by sublimation gave a colourless solid (30 mg.), m. p. 184° alone or mixed with authentic succinic acid (Found : C, 40.6; H, 5.2. Calc. for $C_4H_6O_4$: C, 40.7; H, 5.1%). The fraction boiling at 135—150°/13 mm. (4.0 g.) was similarly hydrolysed. The crude acid fraction distilled from a retort at 140—160° (bath-temp.)/0.01 mm. During 3—4 months at -5° the redistilled acids deposited a small amount of crystals, and decantation of the supernatant oil and repeated chromatography of a solution of the residual solid on silica gel, followed by elution with benzene-ether (3 : 2), gave a solid which recrystallized from concentrated hydrochloric acid in colourless prismatic needles (50 mg.), m. p. 100—101°, not depressed by authentic $\beta\beta$ -dimethylpimelic acid (Blanc, *Bull. Soc. chim.*, 1908, 4, 286) (Found : C, 57.5; H, 8.6. Calc. for $C_9H_{16}O_4$: C, 57.4; H, 8.5%).

Oxidation of β -Dihydrohumulene with Potassium Permanganate.—Finely divided potassium permanganate was added with continuous stirring to β -dihydrohumulene (33 g.) in acetone (30 c.c.) during 2 days at 20—25° until a permanent pink colour remained. The filtered sludge was extracted with hot water, and the extract combined with the residue from the distillation of the acetone filtrate and extracted with ether (to remove neutral products). The aqueous layer was acidified and re-extracted with ether, and the crude acids obtained were esterified with an excess of ethereal diazomethane. The crude esters (22.0 g.) were submitted to repeated fractional distillation. The fraction (1.0 g.) of b. p. <53°/0.1 mm. was hydrolysed with methanolic potassium hydroxide; the crude acid obtained crystallized from concentrated hydrochloric acid in colourless prisms, m. p. alone or mixed with *as*-dimethylsuccinic acid 140—141° (Found : C, 49.5; H, 7.2. Calc. for $C_6H_{10}O_4$: C, 49.3; H, 6.9%). The fraction (1.7 g.) of b. p. 55—65°/0.1 mm. was similarly hydrolysed and the acids, after distillation in a retort at 120° (bath-temp.)/0.01 mm., were chromatographed on silica gel; elution with benzene-ether (1 : 1), sublimation at 100°/0.1 mm., and crystallization from concentrated hydrochloric acid gave colourless prisms, m. p. alone or mixed with authentic $\beta\beta$ -dimethyladipic acid 82—83° (Found : C, 54.9; H, 6.9. Calc. for $C_8H_{14}O_4$: C, 55.2; H, 8.1%).

The fraction (0.7 g.) of b. p. 92—97°/0.1 mm. was similarly hydrolysed and the crude acid was distilled in a retort at 110° (bath-temp.)/0.01 mm. Chromatography on silica gel and elution with benzene gave a fraction which solidified on trituration with light petroleum (b. p. 60—80°). Sublimation at 100°/0.1 mm. then gave white prisms (15 mg.), m. p. 160—161° (Found : C, 71.3; H, 9.8. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.5. $C_{15}H_{26}O_3$ requires C, 70.9; H, 10.3%). This acid gave a strong iodoform reaction with alkaline hypoiodite, and no colour with alcoholic ferric chloride. It did not decolorize permanganate in acetone, but in alcohol gave the ethyl ester 2 : 4-dinitrophenylhydrazone as yellow needles, m. p. 204° (from alcohol) (Found : C, 59.8; H, 7.0. $C_{23}H_{32}O_6N_4$ requires C, 60.0; H, 6.9. $C_{23}H_{34}O_6N_4$ requires C, 59.8; H, 7.9%).

The neutral fraction from the oxidation was distilled, giving fractions: (1) b. p. 57—70°/0.1 mm. (0.4 g.), (2) b. p. 71—81°/0.1 mm. (0.2 g.), and (3) b. p. 84—100°/0.1 mm. (0.5 g.). Fraction (1) yielded no solid derivative with Brady's reagent but evidence for the presence of the same ketonic material in fractions (2) and (3) was obtained with this reagent. These last fractions with semicarbazide in the usual manner gave a *semicarbazone* (50 mg.), needles (from aqueous alcohol), m. p. 137° (Found: C, 57.4; H, 8.6. $C_{16}H_{28}O_2N_6$ requires C, 57.2; H, 8.4%). Decomposition of the crude semicarbazone with aqueous oxalic acid and distillation of the product at 120° (bath-temp.)/0.1 mm. gave a fraction which solidified. Trituration of this with light petroleum (b. p. 60—80°) and sublimation at 55° (bath-temp.)/0.1 mm. gave a colourless *diketone*, m. p. 111° (Found: C, 75.6; H, 10.1. $C_{14}H_{22}O_2$ requires C, 75.7; H, 9.9%), insoluble in aqueous sodium hydroxide and giving no colour with alcoholic ferric chloride. In alcohol it gave a *bis-2:4-dinitrophenylhydrazone*, orange needles (from pyridine), m. p. 282—283° (Found: C, 53.6; H, 5.3. $C_{24}H_{30}O_8N_8$ requires C, 53.5; H, 5.2%).

Tetrahydrohumulene Monoxide.—Tetrahydrohumulene (3.0 g.) in chloroform (50 c.c.) was treated with a slight excess of perbenzoic acid and the mixture left overnight, then washed with aqueous sodium hydrogen carbonate, and water, dried and distilled. The *monoxide* was obtained as a colourless liquid (2.4 g.), b. p. 88°/0.1 mm., n_D^{27} 1.4770 (Found: C, 80.3; H, 12.7. $C_{15}H_{28}O$ requires C, 80.4; H, 12.6%).

It was unaffected by hydrogen in the presence of Adams's platinum oxide at room temperature and pressure. It was also recovered unchanged, as shown by refractive index, analysis and inactivity towards sodium and phosphorus pentachloride, after treatment with lithium aluminium hydride in ether at room temperature and on the boiling-water bath.

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