

*The Chemistry of Humulene. Part IV.**

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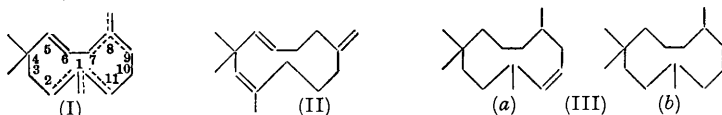
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3 : 7 : 7 : 10- or 2 : 6 : 6 : 9-Tetramethylundecane-1 : 11-dioic acid has been prepared and shown to be identical with the C₁₅ dicarboxylic acid obtained by degradation of tetrahydrohumulene (Clemo and Harris, *J.*, 1952, 665). The identity is confirmed by cyclisation to the acyloins and oxidation to the same 4 : 8 : 8 : 11- or 3 : 7 : 7 : 10-tetramethylcycloundecane-1 : 2-dione.

These experiments show the structure of humulene to be based on a 1 : 4 : 4 : 8-tetramethylcycloundecane skeleton.

The preparation of 2 : 6 : 6 : 9-tetramethyldecane-1 : 10-dioic, 2 : 5 : 5-trimethyloctane-1 : 8-dioic, and 4 : 4-dimethyloctane-1 : 8-dioic acids is also described.

HUMULENE (α -caryophyllene), on degradative evidence, has been provisionally formulated as a 1 : 4 : 4 : 8-tetramethylcycloundecatriene (I) (Clemo and Harris, *J.*, 1951, 22 ; 1952, 665 ; Harris, *J.*, 1953, 184) directly derivable from the established structure of β -caryophyllene. This structure and an alternative (II) based on 1 : 3 : 3 : 8-tetramethylcycloundecane, not so related to β -caryophyllene, have also been proposed by Šorm, Streibl, Pliva, and Herout (*Chem. Listy*, 1951, 45, 308 ; 1953, 46, 30).



The trimethylammonium iodide from hexahydrohumulene, prepared by the catalytic hydrogenation of humulene nitrosochloride with subsequent methylation and quaternization, gives on Hofman degradation a monounsaturated tetrahydrohumulene; this on ozonolysis yields a C₁₅ dibasic acid (Clemo and Harris, *loc. cit.*, 1952). Tetrahydrohumulene is most readily formulated as (IIIa or b) which would give 3 : 7 : 7 : 10- or 2 : 6 : 6 : 9-tetramethylundecane-1 : 11-dioic acid under these conditions. In order to confirm the presence of this unique ring system in the phytochemical pattern, and to reach a decision on the precise position of the alkyl group, the synthesis of a suitable tetramethylundecanedioic acid was undertaken by the annexed route.

The first steps are self-explanatory. When the dimethyl ester from the acid (VI) was fractionated, one main fraction was obtained; there being no evidence for the presence of a second isomer this fraction was hydrolysed. The acid, further purified by distillation, was obtained as a viscous oil, characterised as its bis-*p*-bromobenzylthiuronium salt, m. p. 140°, and was converted into the cyclic anhydride (VII), which with one equivalent of sodium methoxide gave the salt of an acid ester. The corresponding free acid ester was converted into the ester-chloride (VIII) and then homologized by the Arndt-Eistert procedure to the diester (IXa or b). Chromatography of the derived dicarboxylic acid gave a viscous oil which yielded a crystalline bis-*p*-bromobenzylthiuronium salt undepressed in m. p. by the compound obtained from the C₁₅ degradation acid from natural sources. The methyl esters of the natural and the synthetic acid showed identical infra-red spectra from 5 to 14 μ but there was little resolution in the main finger-print region (9—14 μ).

To confirm the identity of these acids, both the natural and the synthetic ester were cyclized to the acyloins. These unsolidifiable oils were oxidized directly to the corresponding α -diketones with chromic acid. The infra-red absorption spectra showed identity of positions of all the bands but differences of strength for some of them. It may be assumed that the diketones were mixtures of stereoisomers in different proportions which

* Part III, *J.*, 1953, 184.

crude product was slowly fractionated and *dimethyl 2 : 6 : 6 : 9-tetramethyldecane-1 : 10-dioate* distilled as a colourless liquid (16 g., 62% calc. from the tetracarboxylic ester), b. p. 113—6°/0.5 mm. (Found : C, 67.4; H, 10.6. $C_{16}H_{30}O_4$ requires C, 67.1; H, 10.5%).

2 : 6 : 6 : 9-Tetramethyldecane-1 : 10-dioic Acid.—The above ester (16.0 g.) was refluxed overnight in methanolic potassium hydroxide (35%; 50 c.c.). The methanol was removed and after acidification the free acid was extracted with sodium carbonate solution. Distillation of the product gave *2 : 6 : 6 : 9-tetramethyldecane-1 : 10-dioic acid* as a colourless viscous gum (14.0 g., 95%), b. p. 95—105° (bath-temp.)/0.001 mm. (Found : C, 65.2; H, 10.4. $C_{15}H_{28}O_4$ requires C, 65.1; H, 10.1%). The *p-bromobenzylthiuronium* salt formed colourless needles (from acetone), m. p. 140° (Found : C, 48.4; H, 6.2. $C_{31}H_{46}O_4N_4Br_2S_2$ requires C, 48.1; H, 5.9%).

2 : 6 : 6 : 9-Tetramethyldecane-1 : 10-dioic Anhydride.—The dicarboxylic acid (14 g.) was heated (1 hr.) with acetic anhydride (14 g.) at 135°. The temperature was raised so that the acetic acid and excess of acetic anhydride slowly distilled off. The last traces of acetic anhydride were removed at the water-pump, and the residual *anhydride* distilled as a viscous oil which partially solidified (12.5 g., 96%), b. p. 100° (bath-temp.)/0.001 mm. (Found : C, 70.2; H, 10.2. $C_{14}H_{24}O_3$ requires C, 70.0; H, 10.0%).

9-Methoxycarbonyl-2 : 5 : 5 : 9- or -2 : 6 : 6 : 9-tetramethylnonan-1-oic Acid.—*2 : 6 : 6 : 9-Tetramethyldecane-1 : 10-dioic anhydride* (12.5 g.) in dry ether (20 c.c.) was refluxed with a solution from sodium (1.195 g.) in absolute methanol (40 c.c.) (1 hr.). The methanol was removed, the residue dissolved in dilute sodium carbonate solution, the neutral material extracted with ether, and the acid ester extracted (after acidification) with ether, dried (Na_2SO_4), and fractionated. Two fractions were obtained : (i) acid ester (6.9 g.), b. p. 147—50°/0.4 mm. (Found : equiv., 261) and (ii) dibasic acid (with some unchanged anhydride) (4.0 g.), b. p. 146—168°/0.2 mm. (Found : equiv., 180). From the sodium carbonate extract dimethyl ester was recovered (2.8 g.). This material was combined with fraction (ii), hydrolysed with alcoholic potassium hydroxide, converted into the anhydride, and reopened to the acid ester. Total yield of *acid ester* was 9.2 g. (65%) (Found : C, 66.3; H, 10.2. $C_{15}H_{28}O_4$ requires C, 66.2; H, 10.3%).

9-Methoxycarbonyl-2 : 6 : 6 : 9-tetramethylnonan-1-oyl Chloride (or its Isomer).—The above acid ester (9.2 g.) and thionyl chloride (4.5 g.) were warmed at 40° until the evolution of hydrogen chloride subsided. The temperature was gradually raised and the mixture refluxed (30 min.). Excess of thionyl chloride was removed at the water-pump, and the residue distilled. The *ester-chloride* was a colourless liquid which gradually darkened and had b. p. 102.5°/0.3 mm. (8.0 g., 81%) (Found : C, 62.3; H, 9.7. $C_{15}H_{27}O_3Cl$ requires C, 62.0; H, 9.3%).

2 : 6 : 6 : 9- or 3 : 7 : 7 : 10-Tetramethylundecane-1 : 11-dioic Acid.—The ester chloride (8.0 g.) was added with stirring to an ethereal diazomethane solution containing twice the theoretical amount of diazomethane and set aside for 1 hr. The ether and excess of diazomethane were removed below 25° and the diazo-ketone dissolved in methanol (20 c.c.) at 0°. This solution was heated at 60° and the diazoketone decomposed by the addition of small portions of silver oxide, added at intervals, until the evolution of nitrogen ceased. The solution was refluxed for 1 hr. further, then filtered, and the methanol was removed from the filtrate. The residue was fractionated and the fraction (3.8 g., 48%), b. p. 102.7°/0.1 mm., collected (Found : C, 68.0; H, 11.0. $C_{17}H_{32}O_4$ requires C, 68.0; H, 10.7%). A sample of the *dimethyl ester* (500 mg.) was hydrolysed in methanolic potassium hydroxide (35%; 15 c.c.), and the free acid purified by chromatography on a silica column with subsequent elution with benzene-light petroleum (b. p. 60—80°) (1 : 2). *2 : 6 : 6 : 9- or 3 : 7 : 7 : 10-Tetramethylundecane-1 : 11-dioic acid* (400 mg.), obtained by distillation after removal of the solvent, had b. p. 175° (bath-temp.)/0.001 mm. It remained a colourless gum (Found : C, 66.5; H, 10.5. $C_{15}H_{28}O_4$ requires C, 66.2; H, 10.3%). The *bis-p-bromobenzylthiuronium* salt recrystallised from acetone as colourless plates, m. p. 160.5° (Found : C, 49.1; H, 5.8. $C_3H_4O_4N_4$ requires C, 48.8; H, 6.0%). This was not depressed on admixture with the *bis-p-bromobenzylthiuronium* salt from the natural C_{15} acid (Clemo and Harris, *loc. cit.*). The acid recovered from this salt was converted into the dimethyl ester with diazomethane, and the infra-red absorption recorded; bands occur at 1739, 1587, 1429, 1341, 1250, 1183, 1149, 1075, and 1005 cm^{-1} .

3 : 6 : 6 : 10- or 3 : 7 : 7 : 10-Tetramethylcycloundecane-1 : 2-dione.—Sodium (1.2 g.) and purified xylene (150 c.c.) were heated in a current of pure dry nitrogen with high-speed stirring. After the sodium had been finely dispersed dimethyl *2 : 6 : 6 : 9- or 3 : 7 : 7 : 10-tetramethylundecane-1 : 11-dioate* was added during 15 min. Stirring and heating were continued for a further 15 min., the mixture was cooled to 0°, and the sodium salts were decomposed by the

slow addition (at $<30^\circ$) of methanol (50 c.c.). The xylene layer was washed with water until neutral, then dried (Na_2SO_4), the solvent removed at the water-pump, the residue fractionated, and a crude acyloin fraction (0.5 g., 24%), b. p. 125—140° (bath-temp.)/0.6 mm., collected.

The acyloin fraction, in acetic acid (2 c.c.), was added slowly with stirring to a solution of chromic anhydride (0.2 g.) in water (1 c.c.) and acetic acid (2 c.c.) cooled in ice-salt. The mixture was allowed to come to room temperature overnight. The diketone was extracted with ether, the extract was neutralised with dilute sodium carbonate solution, washed with water, and dried (Na_2SO_4), the solvent removed, and the residue distilled. The 3 : 6 : 6 : 10- or 3 : 7 : 7 : 10-tetramethylcycloundecane-1 : 2-dione (0.17 g., 35%), b. p. 90—110° (bath-temp.)/0.3 mm., distilled as a bright yellow liquid (Found : C, 76.0; H, 11.1. $\text{C}_{15}\text{H}_{26}\text{O}_2$ requires C, 75.7; H, 10.9%). Infra-red absorption bands were observed at 3500, 3008, 1720, 1470, 1302, 1254, 1170, 1087, 1044, 1007, 975, 947, 932, 919, 906, 863, 782, 756, and 740 cm^{-1} .

The diketone gave, with 2 : 4-dinitrophenylhydrazine in alcohol solution on the boiling-water bath, a red amorphous uncrystallizable precipitate. The decanted supernatant liquor on cooling gave a solid *bis*-2 : 4-dinitrophenylhydrazone which recrystallised from ethyl acetate as needles, m. p. 231° (Found : C, 54.5; H, 6.0. $\text{C}_{23}\text{H}_{26}\text{O}_8\text{N}_8$ requires C, 54.2; H, 5.7%).

The C_{15} dibasic acid (Clemo and Harris, *loc. cit.*) was esterified with diazomethane, to give a colourless ester, b. p. 106—10°/0.1 mm., the infra-red absorption spectrum of which was identical with that of the synthetic ester. This ester was cyclised as above. The crude acyloin fraction (0.4 g., 20%) distilled over the range 90—120°/0.3 mm. This was oxidized, as previously described, to the bright yellow 3 : 6 : 6 : 10- or 3 : 7 : 7 : 10-tetramethylcycloundecane-1 : 2-dione (0.21 g., 53%), b. p. 90—115° (bath-temp.)/0.3 mm. (Found : C, 75.9; H, 11.1%). The infra-red absorption bands were all at the positions recorded for the synthetic product. This material gave with 2 : 4-dinitrophenylhydrazine a *bis*-2 : 4-dinitrophenylhydrazone, which crystallised from ethyl acetate as needles, m. p. alone or mixed the similar compound above, 231° (Found : C, 54.5; H, 6.0%).

1 : 5-Dibromo-3 : 3-dimethylpentane.—3 : 3-Dimethylpentane-1 : 5-diol (6.0 g.), from the lithium aluminium hydride reduction of diethyl $\beta\beta$ -dimethylglutarate, was brominated as described above for the dibromohexane. 1 : 5-Dibromo-3 : 3-dimethylpentane distilled as a colourless liquid which gradually darkened (3.9 g., 33%), b. p. 82.4°/3 mm., n_D^{25} 1.5059 (Found : C, 32.9; H, 5.7. $\text{C}_7\text{H}_{14}\text{Br}_2$ requires C, 32.0; H, 5.5%). Similar yields were obtained on bromination with phosphorus tri- and penta-bromide.

Diethyl 7-Bromo-5 : 5-dimethylheptane-2 : 2-dicarboxylate.—A solution from sodium (0.32 g.) in absolute alcohol (10.6 c.c.) was added with stirring during 1 hr. to a mixture of 1 : 5-dibromo-3 : 3-dimethylpentane (6.9 g.) and diethyl methylmalonate (2.35 g., 1 equiv.) at 100° and the temperature maintained for a further 2 hr. The mixture was cooled, water added, and the bromo-ester separated with ether and dried (Na_2SO_4). The solvent was removed and the residue fractionated to give (i) recovered diethyl methylmalonate (2 g.), (ii) recovered dibromide (3 g.), and (iii) the required bromo-ester (1.1 g.), b. p. 99—101°/0.1 mm. (Found : C, 51.7; H, 7.3. $\text{C}_{15}\text{H}_{27}\text{O}_4\text{Br}$ requires C, 51.3; H, 7.7%).

2 : 5 : 5-Trimethyloctane-1 : 8-dioic Acid.—The above bromo-ester (7.0 g.) was refluxed (24 hr.) with potassium cyanide (3.8 g.) in absolute alcohol (100 c.c.). The alcohol was removed and the nitrile extracted with ether.

The residue after evaporation of the ether was hydrolysed by refluxing alcoholic potassium hydroxide (20%, 50 c.c.) for 48 hr. The alcohol was removed, the residue acidified, and the acid isolated through sodium carbonate solution and dried (Na_2SO_4). The solvent was removed and the product distilled at 140—160°/0.001 mm. 2 : 5 : 5-Trimethyloctane-1 : 8-dioic acid was obtained as a colourless gum, which solidified in the refrigerator (m. p. 41°; 1.8 g., 38%), b. p. 130—140° (bath-temp.)/0.001 mm. (Found : C, 61.2; H, 9.3. $\text{C}_{11}\text{H}_{20}\text{O}_4$ requires C, 61.2; H, 9.3%). The *di*-*p*-phenylphenacyl ester crystallised as needles (from ethanol), m. p. 110° (Found : C, 77.3; H, 6.9. $\text{C}_{39}\text{H}_{40}\text{O}_6$ requires C, 77.5; H, 6.6%).

1 : 6-Dicyano-3 : 3-dimethylhexane.—1 : 6-Dibromo-3 : 3-dimethylhexane (4.0 g.) was refluxed (60 hr.) with potassium cyanide (2.3 g.) in alcohol (15 c.c.) and water (2 c.c.). The alcohol was removed, the residue extracted with ether and dried (Na_2SO_4), and the solvent removed. The dinitrile distilled as a colourless liquid (1.6 g., 66%), b. p. 148—151°/3 mm. (Found : C, 73.0; H, 10.0. $\text{C}_{10}\text{H}_{16}\text{N}_2$ requires C, 73.2; H, 9.8%).

4 : 4-Dimethyloctane-1 : 8-dioic Acid.—The dinitrile was heated at 150° with potassium hydroxide (0.5 g.) in alcohol (2 c.c.). Water was added, the mixture acidified, the acid extracted through sodium carbonate solution, and the solvent removed. The residue was distilled in a high vacuum and the gum obtained purified on a silica column with elution with benzene—

chloroform (1 : 1). 4 : 4-Dimethyloctane-1 : 8-dioic acid redistilled as a colourless gum which solidified in the refrigerator (0.4 g., 54%), b. p. 140—160° (bath-temp.)/0.001 mm. (Found : C, 59.3; H, 8.7. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.9%). The acid was characterised as its *bis-p-bromobenzylthiuronium* salt, m. p. 155° (Found : C, 44.8; H, 5.29. $C_{26}H_{26}O_4N_4S_2Br_2$ requires C, 45.0; H, 5.2%), and as its *di-p-phenylphenacyl* ester, m. p. 36° (Found : C, 77.6; H, 6.7. $C_{38}H_{38}O_6$ requires C, 77.3; H, 6.45%).

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