

## 5. A Contribution to the Chemistry of the Sesquiterpene Humulene.

By G. R. CLEMO and J. O. HARRIS.

The sesquiterpene didymocarpene has been identified as humulene. Preliminary degradative experiments on this substance are described which indicate that the compound is monocyclic.

DIDYMOCARPENE, the sesquiterpene isolated from the leaves of *Didymocarpus pedicellata* by Warsi and Siddiqui (*J. Indian Chem. Soc.*, 1939, **16**, 423), was described by these authors as yielding a blue nitrosite, m. p. 132—134°. Reinvestigation of this preparation has revealed that two products are formed: a blue mononitrosite, m. p. 115—116°, and a colourless, presumably bisnitrosite, m. p. 165—166°. This is reminiscent of the behaviour of humulene (cf. Chapman, *J.*, 1895, **67**, 780), and identity of these two sesquiterpenes has been established by the preparation of the same nitrosochloride, nitrolpiperidide, and nitroso-derivative from didymocarpene and humulene.

Humulene (C<sub>15</sub>H<sub>24</sub>), the chief sesquiterpene constituent of hop oil and a minor constituent of the high-boiling terpene fraction of clove oil, has been shown to be present in the essential oil of Egyptian hashish (Simonsen and Todd, *J.*, 1942, **188**), and in a variety of Japanese plants (Kohasa, *J. Chem. Soc. Japan*, 1942, **63**, 1483; Fujita, *ibid.*, 1941, **62**, 1014; 1944, **65**, 598; Huzita, *ibid.*, 1939, **60**, 1081; 1940, **61**, 137; 1941, **62**, 134; 424). Hitherto, little degradative work has been performed on it, presumably because of the difficulty of the separation of humulene from the other terpene constituents of these oils. The oil obtained from *Didymocarpus pedicellata* shows good constancy of chemical and physical properties, and we believe that material from this source consists essentially of one substance, and may safely be used for the degradation of this sesquiterpene.

Catalytic hydrogenation over Adams's platinum oxide in acetic acid revealed the presence of three double bonds, which was confirmed by titration with perbenzoic acid. Humulene therefore appears to be monocyclic. Catalytic reduction in alcohol over Adams's platinum oxide at atmospheric pressure reduced only one ethylenic linkage. Attempts to form a maleic anhydride adduct were abortive, and the absence of any conjugated system was confirmed by our inability to reduce the compound with sodium and alcohol. Dehydrogenation gave mainly unchanged material, together with a little azulene coloration. No picrate-yielding product was detected (cf. Simonsen and Todd, *loc. cit.*).

The liquid ozonide obtained in hexane yielded, on decomposition by steam, formaldehyde and l  vulaldehyde. More vigorous decomposition of the ozonide with potassium permanganate gave *as*-dimethylsuccinic acid.

Owing to the limited quantities of didymocarpene available, further degradations were performed on the highly crystalline nitrosochloride, easily obtainable from either hop oil or the high-boiling fractions of clove oil. Evans, Ramage, and Simonsen (*J.*, 1934, 1806) described the preparation of nitrosohumulene from this substance, and its subsequent reduction to aminodihydrohumulene. We have catalytically hydrogenated nitrosohumulene to the fully reduced aminohexahydrohumulene, in the hope that subsequent methylation and Hofmann decomposition would yield useful information, but the low yields and scarcity of starting material did not make this an attractive degradative route. We have found, however, that the nitrosochloride can be directly reduced over Raney nickel at 100 atmospheres and 100° to a mixture of isomeric aminotetrahydrohumulene hydrochlorides. This mixture can be separated by trituration with ether into a highly crystalline insoluble  $\alpha$ -isomer and an oily uncrystallizable  $\beta$ -isomer. Decomposition of these hydrochlorides yielded the free bases as colourless optically inactive oils. These substances were still unsaturated and both could be reduced further to the fully saturated aminohexahydrohumulenes by prolonged hydrogenation over Adams's platinum oxide in glacial acetic acid. The fully reduced material so obtained from the  $\alpha$ -isomer was the same as that obtained by direct reduction of nitrosohumulene in glacial acetic in the presence of Adams's platinum oxide, as shown by the identity of the acetyl derivatives.

The above two primary amines were separately methylated with formaldehyde and formic acid to the corresponding  $\alpha$ - and  $\beta$ -dimethylaminotetrahydrohumulenes. These were converted into the crystalline  $\alpha$ - and  $\beta$ -tetrahydrohumulene-trimethylammonium iodides which

were decomposed under Hofmann conditions to yield two isomeric hydrocarbons,  $\alpha$ - and  $\beta$ -dihydrohumulene, respectively.

Attempts to isolate maleic anhydride adducts from either of those two hydrocarbons were unsuccessful.

$\alpha$ -Dimethylaminotetrahydrohumulene could be hydrogenated further in glacial acetic acid in the presence of Adams's platinum oxide to  $\alpha$ -dimethylaminohexahydrohumulene, the quaternary ammonium iodide from which gave on Hofmann degradation a tetrahydrohumulene.

The fact that complete reduction of some of the above substances could only be achieved by hydrogenation in the presence of Adams's platinum oxide, one double bond being resistant to hydrogen over Raney nickel at 100° and 100 atmospheres suggests the presence of an ethylenic linkage between highly alkylated carbon atoms.

Oxidative experiments on these hydrocarbons are in progress.\*

#### EXPERIMENTAL.

The oil obtained by steam-distillation and fractionation of the pedicellin-free filtrate from the ethereal extract of the leaves of *Didymocarpus pedicellata* was redistilled. Almost the whole of the very pale yellow liquid boiled at 74–76°/0.1 mm. and had  $n_D^{20}$  1.5003 (Found: C, 87.9; H, 11.6. Calc. for  $C_{15}H_{24}$ : C, 88.2; H, 11.8%).

*Nitrosomitrosite*.—Didymocarpene (2.5 g.) in light petroleum (b. p. 40–60°) (2.5 c.c.) was well shaken at 0–5° with saturated sodium nitrite solution (2.5 c.c.). Glacial acetic acid (8.5 c.c.) was slowly added, and shaking continued for 2 hours. A deep blue colour developed, and the blue crystals deposited (0.5 g.) were collected and recrystallized from methanol to yield sky-blue prismatic needles, m. p. 115–116° (decomp.), of a *nitrosomitrosite* (Found: N, 9.9.  $C_{15}H_{24}O_2N_2$  requires N, 10.0%). The filtrate, when kept overnight in the refrigerator, deposited very light-yellow needles (0.1 g.) which on recrystallization from light petroleum (b. p. 60–80°) formed colourless needles, m. p. 165–166° (decomp.) (Found: N, 9.8%) (cf. Chapman, *loc. cit.*).

*Nitrosochloride*.—Didymocarpene (7.0 g.) in a mixture of methylated spirit (15 c.c.), glacial acetic acid (15 c.c.), and ethyl nitrite (7.0 c.c.) was cooled in a freezing-mixture. A well-cooled mixture of glacial acetic acid (7 c.c.) and concentrated hydrochloric acid (7 c.c.) was added with constant stirring. The white precipitate (4.8 g.), after removal and washing with ether, melted at 173–174° (decomp.), not depressed on admixture with humulene nitrosochloride prepared in a similar manner from a sample of hop oil (Chapman, *J.*, 1895, **67**, 54).

*Nitroso-derivative*.—The above didymocarpene nitrosochloride (4.5 g.) was refluxed with pyridine (6 c.c.) for 5 minutes, and the mixture poured into water and extracted with ether. The ethereal extract was washed (dilute hydrochloric acid), dried ( $Na_2SO_4$ ), and evaporated, and the residue on distillation yielded a semi-solid mass (bath-temp. 145–155°/1  $\times 10^{-5}$  mm.). On recrystallization from aqueous ethanol (80%) it yielded colourless plates, m. p. 128–129°, not depressed on admixture with nitrosobumulene prepared similarly (Evans, Ramage, and Simonsen, *J.*, 1934, 1806).

*Nitropiperidide*.—Didymocarpene nitrosochloride (0.5 g.) and piperidine (3 c.c.) were heated to boiling, and after the rapid reaction had subsided the residue was triturated with a little cold alcohol, the mixture filtered, and the solid recrystallized twice from ethanol. The product (0.2 g.) separated as colourless prisms, m. p. 154–155°, not depressed on admixture with a similar sample prepared from humulene (Chapman, *J.*, 1895, **67**, 780).

*Degradation Experiments*.—The degradations described for the original sesquiterpene were all performed on the constant-boiling material obtained from the leaves of *Didymocarpus pedicellata* as described above. The starting material for all other experiments was the highly crystalline humulene nitrosochloride, obtained from the high-boiling terpene fraction of clove oil in a manner identical with that described by Evans, Ramage, and Simonsen (*loc. cit.*) or from the high-boiling residues of hop oil; these residues (130 c.c.) yielded humulene nitrosochloride (60 g.) (cf. Chapman, *ibid.*, p. 54).

*Hydrogenation Experiments*.—Humulene (28.9 mg.) in glacial acetic acid (5 c.c.) was hydrogenated in the presence of Adams's platinum oxide (0.1 g.) at atmospheric pressure. Hydrogen uptake was continuous, and practically ceased after 2.8 mols. of hydrogen per mol. of humulene had been absorbed.

*Titration of Humulene with Perbenzoic Acid*.—Humulene was treated with excess of perbenzoic acid in chloroform, and the solution left in a refrigerator for 6 days. Duplicate determinations of unchanged perbenzoic acid with iodine and thiosulphate indicated the presence of 2.9 double bonds per mol. of humulene.

*Attempted Addition of Maleic Anhydride to Humulene*.—Humulene (0.5 g.) in benzene (5 c.c.) containing maleic anhydride (0.3 g.) was refluxed overnight. Removal of the solvent and recrystallization of the residue yielded only unchanged maleic anhydride.

*Ozonolysis Experiments*.—Humulene (1.0 g.), dissolved in pure hexane (25 c.c.) and cooled in "Cardice," was ozonized to completion, whereupon a crystalline ozonide separated. The reaction mixture was allowed to warm to room temperature, and the solvent decanted from the tacky ozonide.

\* Since submission of this paper, our attention has been drawn to a communication by Šorm (*Czech. Chem. Comm.*, 1949, **14**, 274) in which we understand the infra-red data on tetrahydrohumulene are discussed. We have examined humulene derivatives twice by the same method during the past three years, but in neither case would our experts commit themselves to any conclusions as to structure.

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The latter was distilled in a current of steam, the first 5 c.c. distilling being treated with dimedone solution. The white precipitate produced was crystallized from a small volume of methylated spirit (m. p. alone or mixed with formaldehyde dimedone compound, 189°). The bulk of the steam-distillate was treated with an excess of 2:4-dinitrophenylhydrazine hydrochloride solution; a tacky solid separated, which, after trituration with ether and methanol followed by crystallization from dioxan and recrystallization from nitrobenzene, yielded a red micro-crystalline powder, m. p. alone or mixed with lævulaldehyde bis-2:4-dinitrophenylhydrazone, 235.5° (Found: C, 44.4; H, 3.5. Calc. for C<sub>17</sub>H<sub>16</sub>O<sub>8</sub>N<sub>8</sub>: C, 44.4; H, 3.5%).

A further sample of ozonide (1.0 g.) was refluxed with saturated aqueous potassium permanganate solution (30 c.c.) for 5 hours. The reaction mixture was saturated with sulphur dioxide, acidified (concentrated hydrochloric acid), refluxed for 1 hour, cooled, and extracted with ether in a continuous extractor. The solvent was removed, and the residue extracted with 2N-sodium carbonate. The alkaline solution was removed, acidified, and again extracted with ether. Removal of the solvent yielded a small amount of solid material (ca. 10 mg.), m. p. alone, or mixed with an authentic sample of *as*-dimethylsuccinic acid, 137–138° (Found: C, 48.8; H, 6.85. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>4</sub>: C, 49.3; H, 6.85%).

*Attempted Dehydrogenation of Humulene.*—(i) Humulene (1.6 g.) was heated with selenium (2.0 g.) at 280–300° for 40 hours. Some hydrogen selenide was evolved, but unchanged selenium (1.8 g.) was recovered. Distillation of the oil yielded only material which gave no precipitate with picric acid, and after prolonged oxidation with chromic acid on the water-bath, followed by ether extraction, no solid acid material could be isolated. A sample of the recovered oil behaved under catalytic hydrogenation in a manner identical with the starting material. (ii) Attempted dehydrogenation with sulphur at 230–258° for 15 hours, and over palladized charcoal in a furnace at 345–360° at 10 mm., gave similar results.

*Catalytic Reduction of Nitrosohumulene.*—Nitrosohumulene (1.0 g.), prepared as described by Evans, Ramage, and Simonsen (*loc cit.*), was shaken in glacial acetic acid (30 c.c.) with Adams's platinum oxide (0.1 g.) and hydrogen at 100 lbs./sq. in. for 3 hours. Filtration and removal of solvent yielded a basic liquid, which was converted into its *acetyl* derivative with acetic anhydride. This crystallized from light petroleum (b. p. 40–60°) in colourless needles, m. p. 125–126° (Found: C, 76.8; H, 12.5. C<sub>17</sub>H<sub>33</sub>ON requires C, 76.4; H, 12.4%).

*Catalytic Reduction of Humulene Nitrosochloride.*—Humulene nitrosochloride (44 g.) in methyl alcohol (200 c.c.) was shaken with Raney Nickel (4.0 g.) and hydrogen at 100 atm. and 90–100° for 4 hours. Filtration and removal of solvent yielded a tacky solid; on trituration with ether this gave a highly crystalline *hydrochloride* (16.5 g.) which crystallized from aqueous alcohol in colourless, prismatic needles, m. p. 290–291° (Found: C, 69.7; H, 11.75. C<sub>15</sub>H<sub>23</sub>N.HCl requires C, 69.4; H, 11.6%).

The bulk of the above hydrochloride was dissolved in hot water and basified, the oily layer extracted with ether and dried, and the resulting *α*-aminotetrahydrohumulene distilled as an optically inactive, colourless liquid (10 g.), b. p. 76–77°/0.01 mm., *n*<sub>D</sub><sup>20</sup> 1.4994 (Found: C, 80.7; H, 12.8. C<sub>15</sub>H<sub>23</sub>N requires C, 80.7; H, 13.0%). Quantitative hydrogenation over Adams's platinum oxide in acetic acid revealed the presence of one double bond, and acetylation of the fully reduced base gave an *acetyl* derivative, m. p. 125°, identical with that obtained by direct hydrogenation of nitrosohumulene.

*α*-Aminotetrahydrohumulene with acetic anhydride immediately deposited *α*-acetamidotetrahydrohumulene as a white solid which crystallized from light petroleum (b. p. 60–80°) as colourless needles, m. p. 182° (Found: C, 76.7; H, 11.9. C<sub>17</sub>H<sub>31</sub>ON requires C, 77.0; H, 11.7%); it decolorized an acetone solution of potassium permanganate only very slowly.

The ethereal solution from the trituration of the above hydrochloride on evaporation yielded an uncrystallizable glass which was easily soluble in water. The aqueous solution on basification yielded an oil which, on extraction, drying, and subsequent distillation, gave *β*-aminotetrahydrohumulene (17.5 g.), optically inactive, b. p. 79°/0.3 mm., *n*<sub>D</sub><sup>20</sup> 1.5000 (Found: C, 80.7; H, 12.8%). Attempts to prepare a crystalline hydrochloride, picrate, or *acetyl* derivative were unsuccessful. Quantitative hydrogenation over Adams's platinum oxide in glacial acetic acid revealed the presence of one double bond.

*α*-Dimethylaminotetrahydrohumulene.—*α*-Aminotetrahydrohumulene (18 g.), 40% aqueous formaldehyde (12 c.c.), and formic acid (95%; 12 c.c.) were heated on the steam-bath overnight. The mixture was basified and extracted with ether, and after drying and removal of the solvent, *α*-dimethylaminotetrahydrohumulene was obtained as a colourless oil (18 g.), b. p. 82°/0.3 mm., *n*<sub>D</sub><sup>20</sup> 1.4948 (Found: C, 81.0; H, 13.1. C<sub>17</sub>H<sub>33</sub>N requires C, 81.2; H, 13.15%).

*β*-Dimethylaminotetrahydrohumulene.—*β*-Aminotetrahydrohumulene (48 g.) was treated as above, giving *β*-dimethylaminotetrahydrohumulene (18 g.) as a colourless oil, b. p. 84°/0.3 mm., *n*<sub>D</sub><sup>20</sup> 1.4990 (Found: C, 81.2; H, 13.0%).

*α*-Tetrahydrohumulene trimethylammonium Iodide.—*α*-Dimethylaminotetrahydrohumulene (15 g.), in acetone (200 c.c.), was treated with freshly distilled methyl iodide (10 c.c.) and a precipitate was immediately deposited. The reaction mixture was left overnight, and the *α*-tetrahydrohumulene trimethylammonium iodide (19.5 g.) was filtered off and crystallized from acetone as prismatic needles, m. p. 264° (decomp.) (Found: C, 54.95; H, 9.35. C<sub>18</sub>H<sub>36</sub>NI requires C, 55.0; H, 9.2%).

*β*-Tetrahydrohumulene trimethylammonium Iodide.—*β*-Dimethylaminotetrahydrohumulene (28 g.) in acetone (200 c.c.) was treated with methyl iodide (15 c.c.), and the whole left overnight. The solution was concentrated to ca. 30 c.c. and allowed to crystallize; *β*-tetrahydrohumulene trimethylammonium iodide was obtained as needles (26.5 g.) of indistinct m. p. beginning to decompose at 188° (Found: C, 54.8; H, 9.1%).

*α-Dihydrohumulene.*—*α*-Tetrahydrohumulenetrिमethylammonium iodide (18 g.) was decomposed by being shaken overnight with an excess of freshly precipitated silver oxide (18 g.) suspended in water (200 c.c.). The combined washings and filtrate (250 c.c.) were treated with sodium hydroxide (250 g.); trimethylamine was evolved and an oil separated. The whole was refluxed for 1.5 hours, and the mixture diluted, and extracted with ether. The ethereal solution was washed with dilute acid and water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated, and the residue distilled from sodium, *α-dihydrohumulene* being obtained as a colourless liquid, b. p.  $50^\circ/0.1$  mm.,  $n_D^{21}$  1.4908 (Found: C, 87.3; H, 12.3.  $\text{C}_{15}\text{H}_{26}$  requires C, 87.4; H, 12.6%). Quantitative hydrogenation over Adams's platinum oxide in acetic acid at room temperature and pressure revealed the presence of two double bonds.

*β-Dihydrohumulene.*—When *β*-tetrahydrohumulenetrिमethylammonium iodide (25 g.) was decomposed and the product worked up as above, *β-dihydrohumulene* (6.6 g.) distilled as a colourless oil, b. p.  $53^\circ/0.2$  mm.,  $n_D^{21}$  1.4960 (Found: C, 87.7; H, 12.3%). Quantitative hydrogenation under the conditions used for the *α*-isomer again indicated the presence of two double bonds.

*Dimethylaminohexahydrohumulene.*—*α*-Dimethylaminotetrahydrohumulene (10 g.) in glacial acetic acid (95 c.c.) was shaken with Adams's platinum oxide (250 mg.) and hydrogenated for 20 hours at atmospheric pressure and room temperature, more catalyst (200 mg.) was added, and the hydrogenation continued for another 30 hours. A third addition of catalyst (150 mg.) was made, and the hydrogenation continued for another 24 hours, reduction then appearing to be complete. The liquid was concentrated and basified and, after extraction of the oil and subsequent distillation, dimethylaminohexahydrohumulene was obtained as a colourless oil (9.1 g.; b. p.  $133^\circ/2$  mm.).

The above tertiary amine (9.0 g.), acetone (50 c.c.), and methyl iodide (10 c.c.) were mixed and kept for 3 days, and the solvent was then removed; the quaternary salt obtained (14.5 g.) recrystallized from a small volume of acetic acid as prisms, m. p.  $135$ – $145^\circ$  (decomp.) (Found: C, 54.7; H, 9.4.  $\text{C}_{18}\text{H}_{38}\text{NI}$  requires C, 54.7; H, 9.6%).

This quaternary ammonium iodide (14.0 g.) was decomposed as above, and the hydrocarbon fraction separated and distilled; *tetrahydrohumulene* was obtained as a colourless oil (4.0 g.), b. p.  $86^\circ/1$  mm. (Found: C, 86.5; H, 13.35.  $\text{C}_{15}\text{H}_{28}$  requires C, 86.5; H, 13.5%). Quantitative catalytic hydrogenation showed the presence of one double bond.

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UNIVERSITY OF DURHAM, KING'S COLLEGE,  
NEWCASTLE-ON-TYNE, 1.

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