

The Caryophyllenes. Part XII. The Structure of Some
Derivatives of Humulene.*

By P. CLARKE and G. R. RAMAGE.

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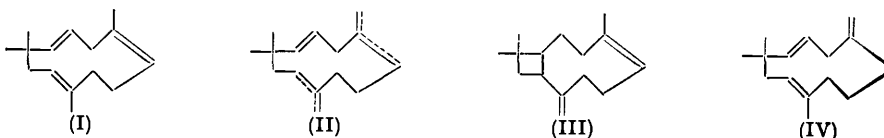
Degradation studies suggest that some humulene derivatives are based on the structure (I).

HUMULENE, a major constituent of hop oil present only in small amount in clove oil, was formulated as (II) by Clemo and Harris (*Chem. and Ind.*, 1951, 799) after evidence indicated that caryophyllene had the structure (III) (see Part X, p. 4336). Proof of the 1 : 1 : 4 : 8-tetramethylcycloundecane ring, with (IV) suggested as the formula for humulene, has been reported by Šorm, Streibl, Jarolím, Novotný, Dolejš, and Herout (*Chem. and Ind.*, 1954, 252) whereas Fawcett and Harris (*ibid.*, p. 405) explained their results on the basis of structure (V) and also suggested (VI). Šorm, Mleziva, Arnold, and Pliva (*Coll. Czech. Chem. Comm.*, 1949, **14**, 699) have given evidence for an exocyclic double bond in purified humulene.

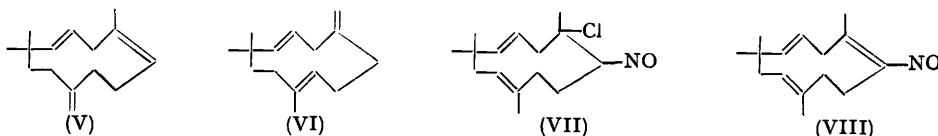
The highly insoluble humulene nitrosochloride was used in the present work in an

* Part XI, preceding paper.

attempt to exclude other unsaturated material. Ozonolysis of a suspension in 90% acetic acid yielded *as*-dimethylsuccinic, lævulic, nitric, and hydrochloric acids, whereas only *as*-dimethylsuccinic acid and more complex products were obtained in chloroform solution because of the stability of the nitrosyl chloride adduct.



Nitrosohumulene (Evans, Ramage, and Simonsen, *J.*, 1934, 1806) had no typical hydroxyimino-properties and on ozonolysis produced lævulic acid and *as*-dimethylsuccinic acid, and there was some evidence for the presence of acetaldehyde. Separation and estimation of lævulic and *as*-dimethylsuccinic acids were achieved by the formation of the 4-(*p*-nitrophenyl)phenacyl esters (Clarke, *Chem. and Ind.*, 1952, 450) which have very different solubilities. These derivatives were more readily separated than the corresponding *p*-phenylphenacyl esters. Alternatively the mixed acids were converted by diazomethane into their esters from which methyl lævulate was removed as its semicarbazone. The absorption spectrum of nitrosohumulene disclosed the absence of conjugated ethylenic linkages (the late Dr. A. E. Gillam, personal communication). These results suggest structure (VII) for the nitrosochloride and (VIII) for nitrosohumulene.



Hydrogenation of aminodihydrohumulene (Evans, Ramage, and Simonsen, *loc. cit.*) gave two aminotetrahydrohumulenes, one of which yielded an acetyl derivative which was probably identical with the α -acetamidotetrahydrohumulene (Clemo and Harris, *J.*, 1951, 22) obtained by a different route. Perbenzoic acid titrations of aminodihydrohumulene and the reduction products indicated di- and mono-unsaturation respectively.

Ozonolysis of acetamidodihydrohumulene gave *as*-dimethylsuccinic and β -formyl-pivalic acids. The latter was characterised by the preparation of a *p*-nitro- and a 2:4-dinitro-phenylhydrazone. Perbenzoic acid titration of acetamidodihydrohumulene indicated two double bonds, and this was confirmed by hydrogenation which gave an acetamidohexahydrohumulene. These results showed that bicyclic products had not been formed. Ozonolysis of dimethylaminodihydrohumulene produced *as*-dimethylsuccinic acid. Emde reduction of its methiodide yielded a dihydrohumulene which furnished *iso*-butyraldehyde by ozonolysis.

The ready isolation of *as*-dimethylsuccinic acid from all simple derivatives fixes two of the double bond positions and the third double bond forms the nitrosochloride in an endocyclic position. In so far as ozonolysis of derivatives can be used as proof of structure the evidence requires (I) for humulene although the infra-red spectrum requires an exocyclic double bond. Bond mobility between adjacent endocyclic and exocyclic double bonds has been discussed in the preceding paper.

EXPERIMENTAL

Humulene Nitrosochloride.—Fractional distillation of caryophyllene (from Messrs. W. J. Bush and Co. Ltd.) gave a fraction of b. p. 118—120°/12 mm., which was treated in chloroform with ethyl nitrite and alcoholic hydrogen chloride. Nitrosochloride, representing a 1—2% yield on the original oil, was obtained, and then purified by standing with cold chloroform. The product was used without further purification since it and material crystallised from chloroform, in which it was only slightly soluble, each decomposed at 177°. By the kindness of Mr. M. Dewhurst, of Messrs. White, Tomkins and Courage Ltd., a portion of hop oil as used by Chapman (*J.*, 1928, 785) was available and a fraction of b. p. 132—136°/14 mm. gave a 55% yield of nitrosochloride.

Humulene Nitrosocyclohexylamide.—The above nitrosochloride (1 g.) was warmed gently with cyclohexylamine (3 c.c.) on the water-bath until a clear solution was obtained. Ethanol (3 c.c.) was added and the resulting *humulene nitrosocyclohexylamide* (0.9 g.) was filtered off and crystallised from ethanol as needles, m. p. 170° (Found: C, 76.1; H, 10.8. $C_{21}H_{36}ON_2$ requires C, 75.8; H, 10.9%).

p-Phenylphenacyl Lævulate.—This was prepared by Drake and Bronitsky's method (*J. Amer. Chem. Soc.*, 1930, 52, 3715) and the ester crystallised from light petroleum (b. p. 60–80°) as small plates, m. p. 93° (Found: C, 73.5; H, 6.2. $C_{19}H_{18}O_4$ requires C, 73.5; H, 5.8%). 4-(*p*-Nitrophenyl)phenacyl lævulate was prepared similarly and crystallised from ethanol as plates, m. p. 126° (Found: C, 63.8; H, 4.9. $C_{19}H_{17}O_6N$ requires C, 64.2; H, 4.8%).

Di-p-phenylphenacyl as-Dimethylsuccinate.—*as*-Dimethylsuccinic acid (0.15 g.) was heated under reflux with *p*-phenylphenacyl bromide (0.55 g.) and ethanol (10 c.c.). *N*-Sodium carbonate solution (2.0 c.c.) was added during 1 hr., and after 3 hr. the resulting product was filtered off after cooling. The ester (0.4 g.) crystallised from ethanol as needles, m. p. 145° (Found: C, 76.1; H, 6.0. $C_{34}H_{30}O_6$ requires C, 76.4; H, 5.7%). *Di*-4-(*p*-nitrophenyl)phenacyl *as*-dimethylsuccinate was prepared similarly and crystallised from butanol as short needles (0.45 g.), m. p. 185° (Found: C, 65.3; H, 4.3. $C_{34}H_{28}O_{10}N_2$ requires C, 65.4; H, 4.5%).

Ozonolysis of Nitrosohumulene.—Nitrosohumulene (6 g.) in methyl acetate (60 c.c.) was ozonised to completion in an ice-salt bath. Removal of solvent under a vacuum at room temperature left a brown ozonide which was decomposed by warm water (20 c.c.). The evolved gases were passed into an aqueous solution of Brady's reagent and gave a solid (0.2 g.) which after several crystallisations from ethanol had m. p. 147° alone or mixed with acetaldehyde 2 : 4-dinitrophenylhydrazone (Found: N, 25.4. Calc. for $C_8H_8O_4N_4$: N, 25.0%). The aqueous solution was treated overnight with hydrogen peroxide (100-vol.; 5 c.c.) and was separated into a neutral oil (trace) and an acid fraction (4.2 g.).

Examination of the Acid Fraction.—A sample (0.1 g.), 4-(*p*-nitrophenyl)phenacyl bromide (0.36 g.) (Clarke, *loc. cit.*), and ethanol (5 c.c.) were refluxed during the slow addition of *N*-sodium carbonate (1.15 c.c.) and for a further 2 hr. The solid (0.25 g.) was filtered off from the hot solution and crystallised from butanone as needles, m. p. 185° alone or mixed with *di*-4-(*p*-nitrophenyl)phenacyl *as*-dimethylsuccinate. The filtrate was diluted with water, and the resulting solid (0.13 g.) crystallised from light petroleum (b. p. 80–100°) as cream plates, m. p. 126° alone or mixed with 4-(*p*-nitrophenyl)phenacyl lævulate.

The remainder (4.1 g.) slowly deposited a solid (0.6 g.) which was filtered off and crystallised from water as prisms, m. p. 140° alone or mixed with *as*-dimethylsuccinic acid. The solid yielded a *p*-phenylphenacyl ester, m. p. 145°, and a 4-(*p*-nitrophenyl)phenacyl ester, m. p. 185°. The liquid acid was largely freed from *as*-dimethylsuccinic acid (1 g.; removed as the calcium salt), and the remainder was esterified by diazomethane. The freshly distilled ester fraction (2.2 g.), b. p. 85–90°/17 mm., yielded (*a*) a phenylsemicarbazone which crystallised from aqueous methanol as long colourless needles, m. p. 114° alone or mixed with methyl lævulate phenylsemicarbazone (Found: C, 59.4; H, 6.7. Calc. for $C_{13}H_{17}O_3N_3$: C, 59.3; H, 6.5%), and (*b*) a semicarbazone (1.1 g. from 2.0 g. of ester) which crystallised from methanol as needles, m. p. 150° alone or mixed with methyl lævulate semicarbazone (Found: C, 45.0; H, 7.0; N, 22.4. Calc. for $C_7H_{13}O_3N_3$: C, 44.9; H, 7.0; N, 22.5%). It was necessary to use redistilled ester, since contamination by lævulic acid caused the m. p. of the semicarbazone to be low, even after repeated crystallisation. The semicarbazone with Brady's reagent yielded yellow needles which after crystallisation from methanol had m. p. 141–142° alone or mixed with methyl lævulate 2 : 4-dinitrophenylhydrazone (Found: N, 18.1. Calc. for $C_{12}H_{14}O_6N_4$: N, 18.1%). The semicarbazone (0.5 g.) was heated under reflux (1 hr.) with 2*N*-sulphuric acid (5 c.c.); the material which was extracted by ether yielded a *p*-phenylphenacyl ester, m. p. 93° alone or mixed with *p*-phenylphenacyl lævulate.

as-Dimethylsuccinic acid (0.8 g.) was recovered from the mother-liquor obtained in the preparation of the semicarbazone.

Ozonolysis of Humulene Nitrosochloride.—Humulene nitrosochloride (3 g.), suspended in acetic acid (18 c.c.) and water (2 c.c.), was ozonised until all solid had disappeared. The issuing gas contained ozone from the outset and was passed through wash-water which gave a positive test for formaldehyde (note, however, Karrer and Kebrle, *Helv. Chim. Acta*, 1952, 35, 862), and for chloride and nitrate ions. Hydrogen peroxide (100-vol.; 2 c.c.) and water (20 c.c.) were added and after 24 hr. the solution was evaporated on the water-bath under reduced pressure. The residue (2.6 g.) was shown to contain lævulic and *as*-dimethylsuccinic acids, as in the preceding experiment.

Catalytic Reduction of Aminodihydrohumulene.—Redistilled base (3 g.) was shaken under hydrogen with 10% palladium-charcoal (1 g.) in ethanol. After filtration and addition of an excess of alcoholic hydrogen chloride, most of the solvent was distilled off before addition of water (10 c.c.). The solid hydrochloride (1.4 g.) was filtered off from the ice-cold mother-liquor and had m. p. 282°. An aminotetrahydrohumulene (1 g.) was recovered from the hydrochloride and characterised as its acetyl derivative which crystallised from light petroleum (b. p. 100—120°) as long needles, m. p. 180° (Found C, 76.9; H, 11.7. Calc. for $C_{17}H_{31}ON$: C, 76.9; H, 11.8%). The mother-liquor yielded a colourless basic oil (1.6 g.), b. p. 147—150°/13 mm., which gave an *acetamidotetrahydrohumulene*. It crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 151° (Found: C, 76.6; H, 11.9. $C_{17}H_{31}ON$ requires C, 76.9; H, 11.8%).

Methyl β -Formylpivalate 2:4-Dinitrophenylhydrazone.—Methyl β -carboxypivalate (1.0 g.) (Bone, Sudborough, and Sprankling, *J.*, 1904, 85, 534) was treated with thionyl chloride (3 c.c.) at room temperature for 4 days. The excess of thionyl chloride was evaporated under a vacuum and the product was shaken in dry xylene at 100° with 1% palladium-calcium carbonate (2 g.) under hydrogen. The filtrate was shaken with an aqueous solution of Brady's reagent and the xylene was removed under a vacuum. The product was chromatographed in light petroleum (b. p. 60—80°) on alumina. The 2:4-dinitrophenylhydrazone crystallised from the same solvent as fine needles (0.2 g.), m. p. 106° (Found: C, 48.4; H, 4.8. $C_{13}H_{16}O_6N_4$ requires C, 48.1; H, 5.0%).

β -Formylisovaleric Acid 2:4-Dinitrophenylhydrazone.—Methyl β -carboxyisovalerate (*idem*, *loc. cit.*) was treated as in the preceding experiment. The resulting ester was hydrolysed by cold dilute sulphuric acid, and yielded an alkali-soluble 2:4-dinitrophenylhydrazone (0.2 g.) which crystallised from ethanol and had m. p. 260° (Found: C, 46.3; H, 4.1. $C_{12}H_{14}O_6N_4$ requires C, 46.4; H, 4.5%).

Ozonolysis of Acetamidodihydrohumulene.—Acetamidodihydrohumulene (3 g.) was ozonised, as for nitrosohumulene. No volatile carbonyl compounds were detected on decomposition of the ozonide with water. Hydrogen peroxide (100-vol.; 5 c.c.) was added to the resulting solution, and the whole was left for 24 hr. The resulting acid fraction (1.8 g.) deposited a solid (0.7 g.) which crystallised from water and had m. p. 140° alone or mixed with *as*-dimethylsuccinic acid (Found: C, 49.1; H, 6.9. Calc. for $C_6H_{10}O_4$: C, 49.3; H, 6.9%). The liquid acid gave *β -formylpivalic acid p-nitrophenylhydrazone* which crystallised from chloroform as fine yellow needles, m. p. 150° (Found: C, 53.8; H, 5.8. $C_{12}H_{15}O_4N_3$ requires C, 54.3; H, 5.7%), and the corresponding 2:4-dinitrophenylhydrazone which crystallised from chloroform as fine orange needles, m. p. 173° (Found: C, 46.5; H, 4.4. $C_{12}H_{14}O_6N_4$ requires C, 46.4; H, 4.5%). The 2:4-dinitrophenylhydrazone was treated with diazomethane, and the resulting ester crystallised from light petroleum (b. p. 60—80°) as fine yellow needles, m. p. 106° alone or mixed with the above methyl β -formylpivalate 2:4-dinitrophenylhydrazone (Found: C, 48.2; H, 5.0; N, 17.6. Calc. for $C_{13}H_{16}O_6N_4$: C, 48.1; H, 5.0; N, 17.3%).

Hydrogenation of Acetamidodihydrohumulene.—Acetamidodihydrohumulene (1 g.) was shaken with 10% palladium-charcoal (2 g.) in ethanol and absorbed 166 c.c. of hydrogen (theor. 85 c.c. per double bond). Acetamidohexahydrohumulene (0.8 g.) crystallised from aqueous methanol as needles, m. p. 119° (Found: C, 76.7; H, 12.4. Calc. for $C_{17}H_{33}ON$: C, 76.3; H, 12.4%). The product is considered to be identical with that described by Clemo and Harris (*J.*, 1951, 22).

Dimethylaminodihydrohumulene.—Dimethylaminodihydrohumulene methiodide (10 g.) (prepared from aminodihydrohumulene, methyl iodide, and methanolic potassium hydroxide) was heated from 180° to 230° at 12 mm. The yellow viscous distillate (4.3 g.) was separated into (i) a hydrocarbon (1.4 g.), b. p. 126—128°/12 mm., n_D^{20} 1.5051, which yielded a nitrosochloride, m. p. 177° (decomp.) alone or mixed with humulene nitrosochloride, and (ii) *dimethylaminodihydrohumulene* (2.8 g.), b. p. 146—148°/12 mm., n_D^{20} 1.4979, d_4^{25} 0.8912 (Found: C, 82.2; H, 12.7; N, 5.4. $C_{17}H_{31}N$ requires C, 81.9; H, 12.5; N, 5.6%). The *methiodide*, crystallised from acetone-ether, had m. p. 212° (decomp.) (Found: C, 55.1; H, 8.6. $C_{13}H_{34}NI$ requires C, 55.2; H, 8.8%). The *picrolonate* crystallised from 2-ethoxyethanol as plates, m. p. 240° (decomp.) (Found: C, 63.7; H, 7.7. $C_{27}H_{39}O_6N_5$ requires C, 63.1; H, 7.7%).

Emde Reduction of Dimethylaminodihydrohumulene Methiodide.—The methiodide (8 g.) in water (400 c.c.) was added to sodium amalgam (30 g. of sodium, 600 g. of mercury) and heated on the water-bath for 48 hr. while a slow stream of carbon dioxide was passed into the solution. The dihydrohumulene, freed from bases, distilled as a colourless liquid (3.8 g.), b. p. 124—126°/11 mm., n_D^{20} 1.4910.

Ozonolysis of the hydrocarbon (1 g.), as for nitrosohumulene, yielded an ozonide which was warmed with water. The evolved gases were passed into an aqueous solution of Brady's reagent and gave a solid (0.2 g.) which crystallised from ethanol as yellow needles, m. p. 182° alone or mixed with *isobutyraldehyde* 2 : 4-dinitrophenylhydrazone. The aqueous solution contained *isobutyric acid* but only traces of *as*-dimethylsuccinic and β -formylpivalic acids.

Dimethylaminohexahydrohumulene.—Dimethylaminodihydrohumulene (1 g.) in methanol (150 c.c.) with 10% palladium-charcoal (0.5 g.) absorbed hydrogen equivalent to two double bonds. The product was a colourless oil (0.95 g.), b. p. 142—145°/12 mm., n_D^{20} 1.4889, and gave a *methiodide*, m. p. 268° (decomp.) (Found : C, 55.2; H, 9.7. $C_{18}H_{38}NI$ requires C, 54.7; H, 9.7%).

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THE TECHNICAL COLLEGE, HUDDERSFIELD.

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