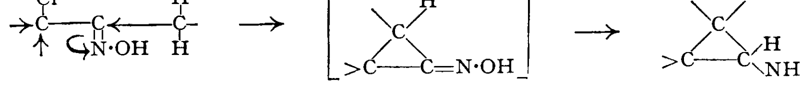
120. *The Chemistry of Humulene. Part II.**

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

The infra-red absorption spectra of some humulene derivatives have been determined. The vigorous oxidation of dihydrohumulene has yielded *as*-dimethylsuccinic acid and ββ-dimethyladipic acid. Ozonolysis of tetrahydrohumulene has given a C_{15} dicarboxylic acid, the thorium salt of which cannot be ketonized. Considerations of this physical and chemical information, together with the newer structures for β-caryophyllene advanced by Šorm *et al.* (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) and Dawson, Ramage, and Wilson (*Chem. and Ind.*, 1951, 464) suggest a provisional structure for humulene as 1 : 4 : 4 : 8-tetramethyl*cyclo*undeca-1 : 5 : 8-triene. The various transformations involved in these degradations are discussed.

THE investigation of the structure of the monocyclic triene sesquiterpene hydrocarbon humulene (α-caryophyllene) which we have shown to be identical with didymocarpene from *Didymocarpus pedicillata* (Clemo and Harris, *J.*, 1951, 22) has been continued. In that communication we described the preparation of α- and β-aminotetrahydrohumulene by hydrogenation of humulene nitrosochloride over Raney nickel at 100°/100 atm., and their further reduction with hydrogen over Adams's platinum oxide in acetic acid to aminohexahydrohumulenes. The decomposition of the corresponding α- and β-dimethylaminotetrahydrohumulene methiodides under Hofmann conditions yielded α- and β-dihydrohumulene, both of which would absorb two further molecules of hydrogen; the presence of two ethylenic linkages in the α-hydrocarbon has been confirmed by titration with perbenzoic acid. It was thought at first that in the tetrahydro-amine series both α- and β-compounds—these being most simply considered to be stereo-isomeric forms—contained a double bond which was difficult to hydrogenate, but after attempts to oxidize the highly crystalline α-acetamidotetrahydrohumulene with potassium permanganate in acetone, or with perbenzoic acid in chloroform, only unchanged material was identifiable. The α- and β-tetrahydro-amines therefore probably contain *cyclo*propane structures, which may arise by 1 : 3-dehydrohalogenation between a tertiary halide and a methylene group, activated by an α-nitroso- or hydroxyimino-structure, in the presence of the alkaline catalyst prior to reduction, thus :



Infra-red absorption spectra measurements on α-aminotetrahydrohumulene (Fig. 1) confirm this view, since this compound possesses an absorption band at 1020 cm.$^{-1}$, the fre-

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* Part I, Clemo and Harris, *J.*, 1951, 22.

quency associated with the *cyclo*propane structure (Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482). The presence in this spectrum of an absorption band at 970 cm.$^{-1}$ could be taken as indicative of the presence of the R·CH═CH·R group (see below), but it is difficult to reconcile a structure containing this group with the stability under the above conditions of oxidation and reduction. The 1020- and 970-cm.$^{-1}$ bands disappear on hydrogenation, as illustrated by the spectrum of aminohexahydrohumulene (Fig. 2).

The infra-red absorption spectra of α-dihydro-, tetrahydro-, and hexahydro-humulene,

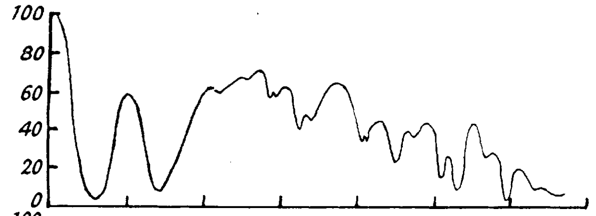


FIG. 1. *Aminotetrahydrohumulene.*

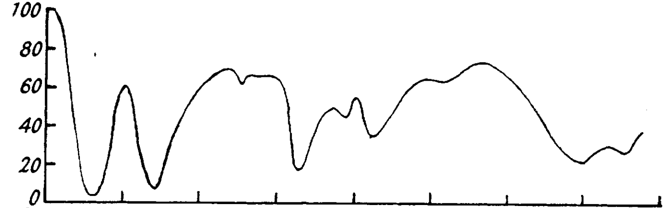


FIG. 2. *Aminohexahydrohumulene.*

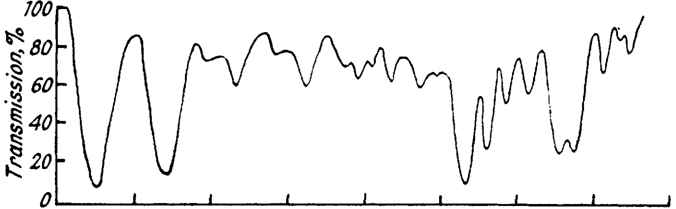


FIG. 3. *Dihydrohumulene.*

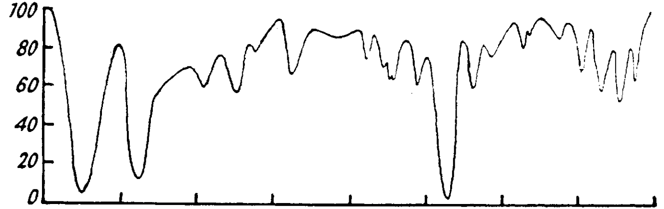


FIG. 4. *Tetrahydrohumulene.*

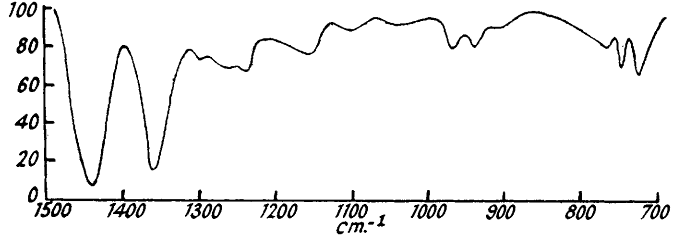
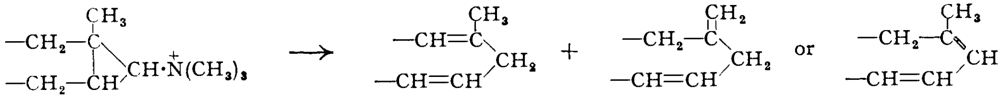


FIG. 5. *Hexahydrohumulene.*

all of which have been prepared from the highly purified crystalline parent α-aminotetrahydrohumulene hydrochloride, have also been measured (Figs. 3—5). The doubly unsaturated α-dihydrohumulene shows a marked absorption at 967 cm.$^{-1}$, which may be associated with the out-of-plane hydrogen deformation of the *trans*-arrangement of the group R·CH═CH·R (for references see Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915), while the band in the 12-μ region with peaks at 840 and 831 cm.$^{-1}$ suggests the presence of two arrangements of the group R·CH═CR′R″. The smaller absorption at 885 cm.$^{-1}$ in this substance could be associated with a third type of olefinic unsaturation, *viz.*, CH_2═CRR′, suggesting that this substance is, in fact, a mixture of hydrocarbons. Our inability to isolate a crystalline adduct with maleic anhydride suggests that there is no conjugation, but as we postulate a possible large-ring diene structure for these substances (see below) this may not be conclusive: evidence obtained on Stuart models indicates that such Diels–Alder adducts would be considerably strained. The recent observations that *cyclo*octa-1 : 3-diene does not form a simple adduct (Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128; Zeigler and Wilms, *Annalen*, 1950, **567**, 1) emphasise that conjugation in α-dihydrohumulene and presumably, therefore, in the parent humulene cannot be entirely excluded.

Ultra-violet absorption measurements show only end absorption below 2350 Å, but the observations by Pesch and Friess (*J. Amer. Chem. Soc.*, 1950, **72**, 5756) that absorption of cyclic conjugated dienes varies with ring size, and lack of information above *cyclo*octadiene make any decision on this evidence also difficult.

Such a mixture of dienes could be envisaged to arise contemporaneously with the opening of a *cyclo*propane ring in the following manner:

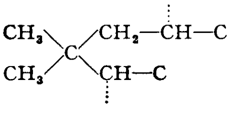


The infra-red absorption spectrum of the more highly reduced tetrahydrohumulene does not possess the marked unsaturation bands at 12 or 11·3 μ present in α-dihydrohumulene, but still retains the absorption associated with *trans*-R·CH=CH·R at 967 cm.$^{-1}$. All the spectra show the characteristic frequency due to the methyl (1360 cm.$^{-1}$) and saturated methylene group (1450 cm.$^{-1}$). The three bands determined in the spectra of tetrahydro- and hexahydro-humulenes between 770 and 720 cm.$^{-1}$ can be associated with rocking vibrations of different CH_2 groups (Shephard and Sutherland, *Nature*, 1947, **159**, 739; Szasz, Shephard, and Rank, *J. Chem. Phys.*, 1948, **16**, 704; Rasmussen, *ibid.*, p. 712; Barrow, *ibid.*, 1951, **19**, 345).

Further evidence of the structure has been obtained by chemical investigation. Vigorous oxidation of β-dihydrohumulene with potassium permanganate in acetone at 30°, followed by 50% nitric acid on the water-bath, in sufficient quantity to permit close fractionation of the methyl esters of the acid fraction, followed by chromatographic purification of the free acids, has yielded so far two solid acids, namely, *as*-dimethylsuccinic acid (thus confirming the presence of a *gem*-dimethyl group in the molecule) and ββ-dimethyladipic acid.

Tetrahydrohumulene has been obtained from α-dimethylaminohexahydrohumulene by quaternization and subsequent Hofmann decomposition (Clemo and Harris, *loc. cit.*); this tertiary base may be prepared either by direct reduction over platinum in acetic acid of α-dimethylaminohumulene or of α-aminotetrahydrohumulene with subsequent methylation of the resulting primary base. The products are identical as shown by the identity of the methiodides, but the reduction of the primary base proceeds much more rapidly. The presence of the R·CH=CH·R group in tetrahydrohumulene is confirmed as an endocyclic double bond since ozonolysis yields a C_{15} dicarboxylic acid. This acid is contaminated with a small amount of material which yields iodoform with sodium hypoiodite, but the absence of ketonic derivatives, an equivalent weight determination, and analysis of derivatives together with the above infra-red data suggest strongly that this material is adventitious. The acid on distillation with acetic anhydride gives an anhydride, and dry distillation of the thorium salt has not yielded any identifiable ketonic material.

This last observation was considered at first to be indicative of the presence of a four- or a five-membered ring system in tetrahydrohumulene (*cf.* Clemo and Harris, *Chem. and Ind.*, 1951, 50). However, the ββ-dimethyladipic acid can only arise from the system:

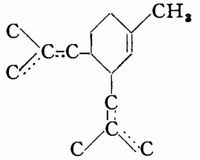


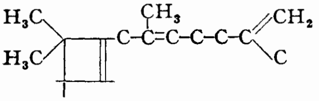
If it is assumed that the *gem*-dimethyl group is in a ring it is not feasible to accommodate this structure in less than a six-membered ring if it is to yield the above acid on oxidation.

The presence of a six-membered ring is difficult to reconcile with our inability to ketonize the thorium salt of the C_{15} acid. Also the infra-red spectrum of hexahydrohumulene would not appear to support a *cyclo*hexane system as the absorption at 967 cm.$^{-1}$ does not have a corresponding band between 1000 and 1055 cm.$^{-1}$ usually associated with this structure (cf. Marrison, *J.*, 1951, 1614); nevertheless, at present we would not preclude absolutely the possibility on this evidence.

The foregoing experimental data cannot be accommodated on either of the formulæ so far presented for humulene. Structure (I) (Wolfrom and Mishkin, *J. Amer. Chem. Soc.*, 1950, **72**, 5350) does not contain a *gem*-dimethyl group and is derived from an obsolete formula for β-caryophyllene, and structure (II) (Klein and Lahey, *Chem. and Ind.*, 1951, 761) whilst attractive on biogenetic grounds, being directly derivable from the structure (III) proposed by Šorm, Dolyš, and Plíva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) for β-caryophyllene, cannot arise from the more recent modifications (IV) proposed by Dawson, Ramage, and Wilson (*Chem. and Ind.*, 1951, 464). Also, formula (II) does not account for the formation of ββ-dimethyladipic acid, or permit 1 : 3-dehydrohalogenation during reduction of the nitrosochloride.

(I)





(II)

We are aware that several interpretations, which can be further complicated by potential intramolecular rearrangements, are feasible on the evidence under discussion. The possibility of such rearrangements, however, is limited since the infra-red spectrum of hexahydrohumulene prepared by the direct reduction of humulene (Šorm *et al.*, *Coll. Czech. Chem. Comm.*, 1949, **14**, 691) is very similar to that determined above. However, one novel structure (V) for humulene presents itself which may also be considered to have some support on biosynthetic grounds. This eleven-membered ring formula is directly derivable by fission of the four-membered ring, from either structure (III) or the modification (IV) of this *bicyclo*[7 : 2 : 0]undecane ring system. The major transformations encountered are envisaged to occur as shown in the scheme; the C_{15} dicarboxylic acid, now formulated as a tetramethylnonane-1 : 9-dicarboxylic acid, could be expected to undergo ketonization only with difficulty (cf. Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 670, 686; Prelog, *J.*, 1950, 420), although it should readily form an anhydride (cf. Adams and Anderson, *J. Amer. Chem. Soc.*, 1951, **73**, 136).

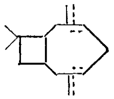
The large ring also accommodates the *trans*-arrangement of the R·CH═CH·R band indicated by the infra-red absorption spectra (see above) of both dihydro- and tetrahydrohumulene, although variations of this characteristic olefinic band have not yet been correlated with the R·CH═CH·R band deformation in ring structures. However, if all the above assumptions are correct the frequency at 840 cm.$^{-1}$ would be associated with an endocyclic R·CH═CR′R″ group, and Plíva and Herout (*Coll. Czech. Chem. Comm.*, 1950, **15**, 160) have pointed out that when such a structure is associated with a five- or a six-membered ring this value is shifted to higher frequencies, hence the smaller value encountered here might be considered to support the hypothesis of a larger ring.

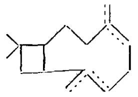
The 1 : 5 : 8-endocyclic arrangement of the double bonds would be unique in accounting for the formation of *as*-dimethylsuccinic acid and lævulaldehyde as primary oxidation products, and in this case conjugation in the parent hydrocarbon is excluded. However, it should be noted that Šorm *et al.* (*ibid.*, 1949, **14**, 699) did not identify lævulaldehyde as a product of ozonolysis of highly purified humulene and further investigation in this connection is desirable.* A proportion of an isomer with an exocyclic methylene group would account for the formation of formaldehyde on ozonolysis.

* See addendum.

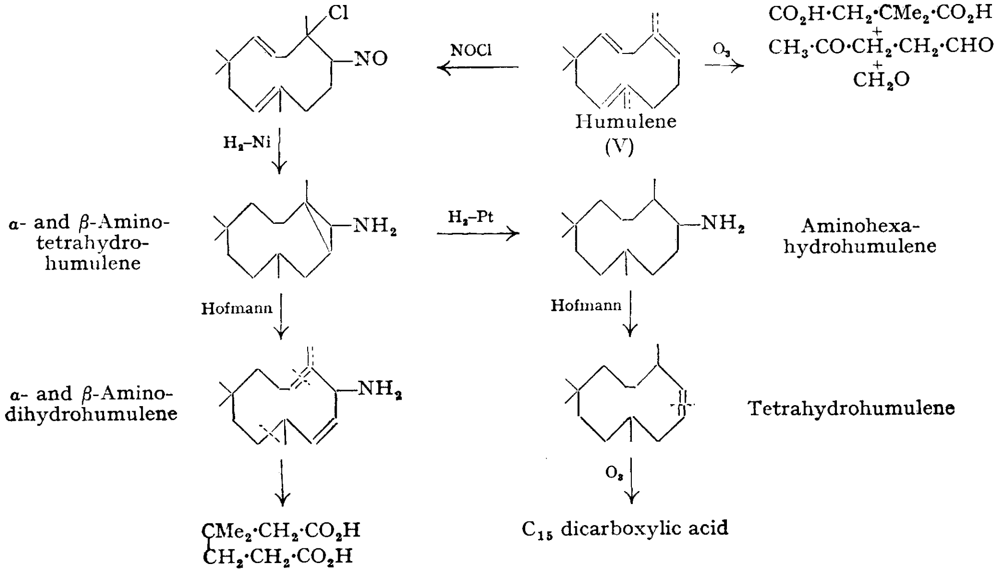
Support for the presence of the three different classes of double bonds, *viz.*, R·CH=CH·R′, (*trans*-)RR′C=CH·R″, and RR′C=CH_2, required on this formulation is given in the infra-red spectrum of pure humulene recorded by Plíva and Šorm (*ibid.*, p. 274) which has maxima at 970, 825—830, and 890 cm.$^{-1}$ associated respectively with these olefinic types.

(III)





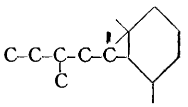
(IV)



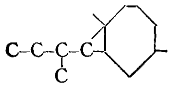
The Stuart model of this optically inactive " head-to-tail isoprenic " alkyl *cyclo*undecatriene has a compact strainless structure.

[*Addendum, October 30th,* 1951.] We have now identified lævulaldehyde as an ozonolysis product of humulene (n_D^{17} 1·5063, *d* 0·8920, $[\alpha]_D^{17}$ +0·39°) purified by chromatography.

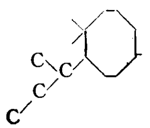
On the assumption that humulene arises by a simple coiling of the farnesene chain, contains a cyclic *gem*-dimethyl group, and is a single substance or mixture of closely related isomers differing only by an endo–exo-cyclic bond arrangement, examination of the possible monocyclic carbon skeletons (VI)—(XI) with ring size greater than six shows that only a



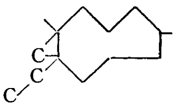
(VI)



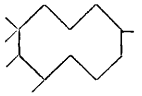
(VII)



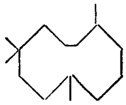
(VIII)



(IX)



(X)



(XI)

structure based on (XI) can accommodate the formation of *as*-dimethylsuccinic acid and lævulaldehyde as primary fission products. In this connection Šorm and Dolejš (*ibid.*, 1950, **15**, 96) have recently shown that a structure derived from (VI) is not possible for humulene.

EXPERIMENTAL

All the infra-red spectra were measured on a Grubb-Parsons single-beam spectrometer, with a variable slit opening (2—6 cm.$^{-1}$ at 6·5—14 μ). The liquid samples were studied as films of 0·05 mm. thickness between sodium chloride plates.

α-Dihydrohumulene (Clemo and Harris, *loc. cit.*) was titrated in chloroform with perbenzoic acid, duplicate determinations giving 2·05 and 2·2 double bonds per mole.

Attempted Oxidation of α-Acetamidotetrahydrohumulene.—α-Acetamidotetrahydrohumulene (0·1 g.) in acetone (15 c.c.) was left with excess of finely ground potassium permanganate for 24 hours. Filtration and removal of the solvent, after the passage of sulphur dioxide, gave a residue which, after chromatographic purification, was identical with the starting material. A similar attempt to oxidize this substance with perbenzoic acid in chloroform in the cold overnight again yielded as identifiable material only the original amide. This substance gives no colour with tetranitromethane.

Aminohexahydrohumulene.—α-Aminotetrahydrohumulene (10·3 g.) in glacial acetic acid (150 c.c.) was shaken with hydrogen at room temperature and pressure for 24 hours over platinum oxide (1·1 g.), after which reduction ceased and the theoretical amount of hydrogen had been absorbed. The solvent was removed, the residue basified, extracted with ether, and dried (Na_2SO_4), the solvent removed, and the residual *hexahydro-amine* distilled as a colourless oil (10·2 g.), b. p. 82°/2 mm., n_D^{22} 1·4813 (Found: C, 79·8; H, 13·7. $C_{15}H_{31}N$ requires C, 80·0; H, 13·8%). This was methylated with formaldehyde and formic acid, and the tertiary base converted into the methiodide, which, recrystallised from water, had m. p. 164° (decomp.) not depressed by admixture with the methiodide prepared from dimethylaminohexahydrohumulene (Clemo and Harris, *loc. cit.*).

Hexahydrohumulene.—Tetrahydrohumulene (0·6 g.) was hydrogenated in glacial acetic acid over platinum oxide. Hydrogen uptake ceased at 1 mole/mole. The solvent was removed, and the residue, in ethereal solution, washed with sodium carbonate, dilute acid, water, dried, and finally distilled from sodium as a colourless oil (0·5 g.), 70—75° (bath-temp.)/0·1 mm., n_D^{24} 1·4714 (Found: C, 85·9; H, 14·2. $C_{15}H_{30}$ requires C, 85·7; H, 14·3%).

Oxidation of Dihydrohumulene with Potassium Permanganate and Nitric Acid.—β-Dihydrohumulene (50 g.) in acetone (750 c.c.) was oxidised with finely divided potassium permanganate (200 g.) added during 2 days so that the temperature did not rise above 30°. The mixture was filtered, the manganese dioxide extracted five times with boiling water, and the aqueous extract combined with the residue obtained from the acetone filtrate by removal of solvent. The whole was made alkaline to phenolphthalein and extracted with ether. The aqueous layer was acidified and repeatedly extracted with ether, the ethereal solution was dried (Na_2SO_4), and the solvent removed. The acid residue was further oxidized by the cautious addition of nitric acid (200 c.c.; *d* 1·23), heating overnight on the water-bath, and concentration in an evaporating basin until no appreciable amount of mineral acid remained. The residue was dissolved in ether and treated with an excess of diazomethane, and the mixed esters were distilled into two main fractions, (A) (20 g.) b. p. 110°/0·1 mm., and (B) (8 g.) b. p. 110—140°/0·1—0·3 mm. Distillate (A) was refractionated in a 6″ I.C.I. (Dixon) precision column; it distilled continuously from 90° to 170° at 13 mm., the only approximate plateau being at *ca.* 126°/13 mm. A fraction boiling at 89—94°/13 mm. (0·65 g.) was hydrolysed with methanolic potassium hydroxide and the acid fraction was separated. This slowly solidified, and recrystallised from light petroleum (b. p. 60—80°) as colourless crystals, m. p. alone or mixed with *as*-dimethylsuccinic acid, 138—139°.

The above fraction of (A) boiling at 125·5—127°/13 mm. (2·0 g.) was refluxed with methanol (6 c.c.) and potassium hydroxide (2 g.) for 3 hours, and the free acid distilled at 75—95° (bath-temp.)/0·01 mm. This partly solidified during three weeks in a refrigerator. The solid (0·1 g.) was separated and purified by adsorption on silica gel (10 g.) and subsequent elution with benzene–ether (7 : 3). This chromatographic purification was repeated three times and was followed by repeated sublimation at 70°/0·1 mm. In this manner a colourless solid, m. p. 85—86°, was obtained (Found: C, 55·4; H, 8·0. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·05%).

When warmed with resorcinol and concentrated sulphuric acid, this acid gave a reddish-brown solution, which on dilution and treatment with alkali became deep crimson with a violet fluorescence. The colour was discharged by acid, but returned on basification (cf. Crossley and Renouf, *J.*, 1906, 1552). The m. p. of this acid was depressed on admixture with α-*iso*propylglutaric, αα′-trimethylglutaric, αββ-trimethylglutaric, β-methyl-β-ethylglutaric, αα-dimethyladipic, or *cis*- or *trans*-caryophyllenic acid, but not with ββ-dimethyladipic acid.

The acids other than *cis*- and *trans*-caryophyllenic acids (for these we are gratefully indebted to Dr. G. R. Ramage) were prepared by the recorded methods, except ββ-dimethyladipic acid, which was obtained from ββ-dimethylglutaric acid anhydride as follows: The anhydride (10 g.) was refluxed with methanol (5·5 c.c.) for 2 hours, and the acid-soluble portion separated and distilled, giving methyl hydrogen ββ-dimethylglutarate as a colourless oil (8·5 g.; b. p. 85°/0·3 mm.), which with thionyl chloride at 60° (1 hour) gave monomethyl ester chloride (7·5 g.; b. p. 45°/0·2 mm.). This ester acid chloride (7·5 g.) was added to an excess of diazomethane in ether, and the diazo-ketone which remained after removal of the solvent was treated in methyl-alcoholic solution at 60° with silver oxide (0·2 g.), added during 1 hour in small portions. The reaction was completed on the water-bath. The crude methyl ester was isolated, distilled (5·0 g.; b. p. 58°), and hydrolysed with alcoholic potassium hydroxide, and the crude acid recrystallised from concentrated hydrochloric acid, forming colourless needles (4·2 g.; m. p. 86°) (Found: C, 54·9; H, 7·9%).

Ozonolysis of Tetrahydrohumulene.—Tetrahydrohumulene (2·3 g.) was dissolved in hexane, and ozone was passed in at −80° until the solution became blue. The solution was allowed to come to room temperature, the hexane decanted, the remaining solvent allowed to evaporate, and the residual oily ozonide heated in acetic acid (25 c.c.) on the water-bath overnight. The solvent was removed in a vacuum, the distillate on dilution giving no precipitate with Brady's reagent. The residue was extracted with sodium hydroxide solution and ether. The aqueous fraction was acidified and extracted with ether, and the dried ethereal solution treated with excess of diazomethane. The ester was distilled and the bulk collected at 120°/0·3 mm. (Found: C, 68·2; H, 10·5; ester OMe, 21·0. Calc. for $C_{17}H_{32}O_4$: C, 68·0; H, 10·7%; ester OMe, 21·0%). It was hydrolysed with methanolic potassium hydroxide, and the crude acid (1·3 g.) (Found: equiv., 143) isolated. This was dissolved in cold alkali, treated with excess of iodine, and left overnight, and a small amount of iodoform (0·1 g.; m. p. 119°) was removed. The filtrate was saturated with sulphur dioxide and extracted with ether, and the crude acid slowly heated in a retort with acetic anhydride to 150°. The residue was distilled in a high vacuum (bath-temp., 180°/0·1 mm.). The non-solidifying oily distillate gave no ketonic reactions and was insoluble in sodium carbonate, but dissolved in warm aqueous sodium hydroxide. The acid recovered from this solution was redistilled in a high vacuum (bath-temp., 80—90°/0·1 mm.) and obtained as an oil (Found: C, 66·4; H, 10·0%; equiv., 140. Calc. for $C_{15}H_{28}O_4$: C, 66·2; H, 10·3%; equiv., 136).

The *di*-p-*bromophenylthiuronium* salt was prepared by treating the neutral solution with two equivalents of *p*-bromophenylthiuronium bromide in alcohol and crystallized from acetone as clusters of feathery needles, m. p. 160·5° (Found: C, 49·1; H, 6·0. $C_{31}H_{46}O_4N_4Br_2S_2$ requires C, 48·8; H, 6·0%).

The thorium salt (0·75 g.), prepared by addition of thorium nitrate to a neutral solution of the acid in aqueous ammonia, yielded on dry distillation up to 320° under reduced pressure (water-pump) a trace of distillate which gave no ketonic reactions.

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