cooling, the benzene extracts deposited 1.2 g. of crystalline 2,5-dimethyl-D-mannitol (VI). This was recrystallized from benzene and from an acetone–benzene mixture. The material was hygroscopic, melted over a range 65–80° and had $[\alpha]^{21}D$ −18° (*c* 2, water).

*Anal.* Calcd. for $C_8H_{18}O_6$ (210): C, 45.7; H, 8.6; $OCH_3$, 29.5. Found: C, 45.8; H, 8.6; $OCH_3$, 29.1.

Periodate oxidation proceeded with an uptake of 1 g. mole per 200 g. of the dimethylmannitol; theory requires 1 g. mole per 210 g. for 2,5-dimethylmannitol.

Although both 2,5-dimethyl- and 2,4-dimethylmannitol could consume 1 mole of periodate per mole, the products would be different, *i.e.*, 2-methyl-D-glyceraldehyde in one case, and 2,4-dimethyl-D-arabinose in the latter. Therefore, 100 mg. of dimethylmannitol was treated with 1 mole equivalent, 0.22 g., of lead tetraacetate in dry benzene. After one hour, the precipitated lead acetate was removed by filtration and the benzene filtrate was concentrated to dryness. The resulting sirup, dissolved in 10 ml. of water, was treated with 8.5 ml. of perchloric acid–dinitrophenylhydrazine reagent[8] containing 0.24 g. of the precipitant.

After two hours, a light orange crystalline product (100 mg.) (VII) was collected and recrystallized from absolute ethanol. It melted at 145–147°, after slight softening at 141°.

*Anal.* Calcd. for $C_{10}H_{12}O_6N_4$ (286): N, 19.5; $OCH_3$, 10.8. Found: N, 19.8; $OCH_3$, 10.7.

**Acknowledgment.**—The authors wish to express their gratitude to the Nutrition Foundation, Inc., for the generous support of this work.

(8) C. Neuberg, A. Grauer and P. V. Pisha, *Anal. Chem. Acta*, **7**, 238 (1952).

BERKELEY, CALIFORNIA

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

# Terpenoids. I. Synthesis of the Gross Structure of Zingiberene[1]

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A synthesis of the gross structure proposed by Eschenmoser and Schinz for the monocyclic sesquiterpene hydrocarbon, zingiberene, has been achieved by the application of the Birch reduction. The synthetic product, which appears to be a mixture of bond isomers has been shown to be comparable with the natural zingiberene of Eschenmoser and Schinz, thus supporting their invalidation of the long-accepted structure suggested by Ruzicka and van Veen.

On the basis of degradative evidence Ruzicka and van Veen[3] suggested the structure I for zingiberene, a monocyclic sesquiterpene hydrocarbon, the main constituent of ginger oil from the rhizomes of *Zingiber officinale*, Roscoe. The assignment of the two double bonds in the side-chain was largely based on the assumption of 1,2-reduction of the conjugated system of double bonds in zingiberene by sodium and alcohol to give dihydrozingiberene which must have the structure II. The assumption of 1,2-reduction of the conjugated double bonds in I is not unwarranted in view of the observation by one of us[4] that 2-methyl-2,4-hexadiene on reduction with sodium and alcohol in liquid ammonia gave 2-methyl-2-hexene as the major product as shown by oxidation to acetone and *n*-butyraldehyde. However, the possibility of formation of dihydrozingiberene from such a structure as III was not considered by Ruzicka and van Veen.[3] Eschenmoser and Schinz[5] by a consideration of cationotropic cyclization experiments in the light of the structure of isozingiberene,[6] reinvestigated the structure of zingiberene and represented it by III. Their views were confirmed by ultraviolet and infrared absorption spectra and through condensation with dimethyl acetylenedicarboxylate.

Ruzicka's structure I was synthesized by one of us[7] and the similarity of its properties with those of natural zingiberene as exhibited in refractive indices and dehydrogenation experiments led to the conclusion of gross structural identity between synthetic I and the natural substance. The production of cadalene on sulfur dehydrogenation of I is not surprising in view of the fact that dihydrozingiberene (II) on similar treatment yielded some cadalene.[3] However, in view of Eschenmoser and Schinz's brilliant experiments we undertook the synthesis of the new structure III proposed by them.

The starting material, 6-(4′-keto-1′-cyclohexenyl)-2-methyl-2-heptene (VI) was prepared according to Birch and Mukherji[8,9] with the modification that two-stage reduction of 6-(*p*-methoxyphenyl)-2-methyl-2,5-heptadiene (IV) was employed. The ketone VI was isomerized to the corresponding $\alpha,\beta$-unsaturated ketone VII by means of sodium ethoxide in ethanol under nitrogen. No solid derivative of VII could be prepared in spite of several attempts. However, the ultraviolet absorption spectrogram (Fig. 1) compares very well with that of cryptone[10] which is unequivocally an $\alpha,\beta$-unsaturated ketone of analogous structure. Moreover, the data conform to Woodward's rule for mono-alkyl substituted $\alpha,\beta$-unsaturated ketones.[11]

Reaction of methylmagnesium iodide on VII proceeded smoothly to give the corresponding carbinol VIII which was dehydrated with oxalic acid solution[12] to give 6-(4′-methyl-2′,4′-cyclohexadienyl)-2-methyl-2-heptene (III). The hydrocarbon thus obtained proved to be comparable with natural zingiberene[5] in its ultraviolet absorption spectra (Fig. 2).

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(1) A preliminary report of this work appeared in *Science and Culture*, **16**, 269 (1950).

(2) Punjab University, Hoshiarpur, East Panjab, India.

(3) L. Ruzicka and van Veen, *Ann.*, **468**, 143 (1929).

(4) S. M. Mukherji, unpublished work.

(5) A. Eschenmoser and H. Schinz, *Helv. Chim. Acta*, **33**, 171 (1950).

(6) M. D. Soffer, C. Steinhardt, G. Turner and M. E. Stebbins, THIS JOURNAL, **66**, 1520 (1944).

(7) S. M. Mukherji, *J. Indian Chem. Soc.*, **25**, 155 (1948).

(8) A. J. Birch, *J. Chem. Soc.*, 430 (1944); 809 (1945); 593 (1946); 102, 1642 (1947).

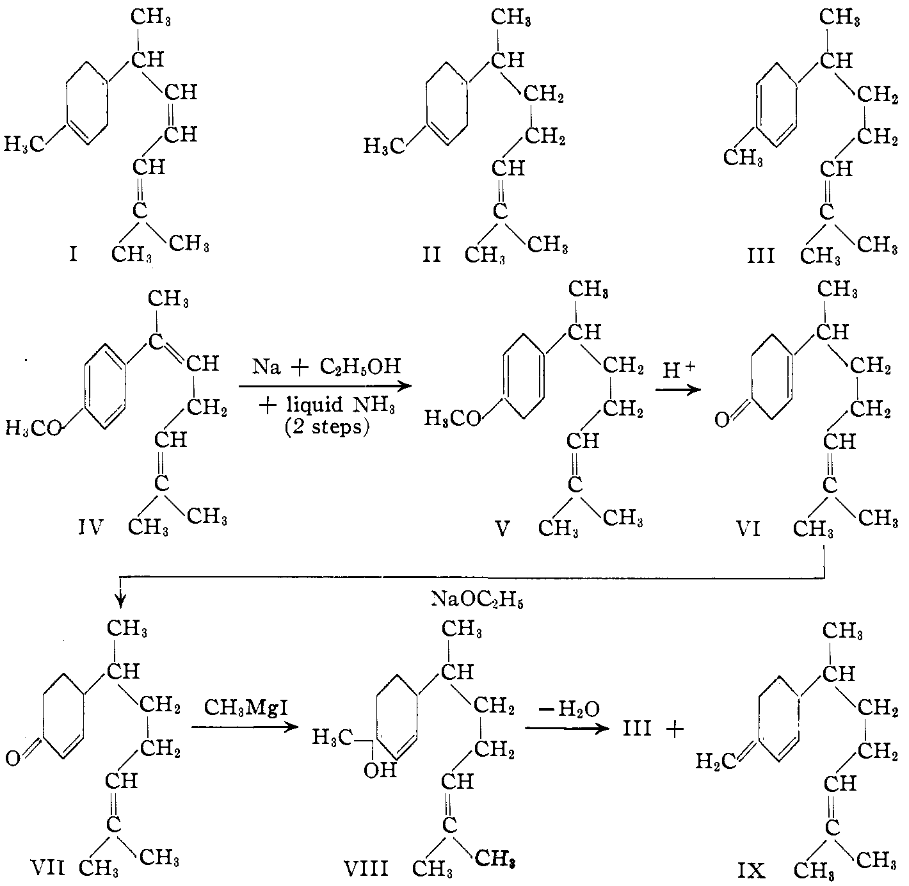
(9) A. J. Birch and S. M. Mukherji, *Nature*, **163**, 766 (1949); *J. Chem. Soc.*, 2531 (1949).

(10) R. G. Cooke and A. K. Macbeth, *ibid.*, 1408 (1938).

(11) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941).

(12) A. S. Galloway, J. Dewar and J. Read, *J. Chem. Soc.*, 1595 (1936).

FORMULAS



The absorption spectrum of the synthetic hydrocarbon indicates that the dehydration of VIII has proceeded at least partly in the alternative direction to give the conjugated structure with the exocyclic methylene group (IX). In fact the more prominent of the two maxima, that at 232 m$\mu$, corresponds to the calculated[13] value for the exocyclic structure (IX). The absorption spectrum of natural zingiberene was interpreted[5] as being due in part to the presence of such an isomer, and this was confirmed[5] by infrared data and ozonolysis. Indeed, Booker, Evans and Gillam[14] reported for zingiberene only a single maximum whose position, 235.5 m$\mu$, is not consistent with an homoannular diene.

However, the second maximum found, at 265 m$\mu$, is in the homoannular range and it is likely that the synthetic material is a mixture of several stereoisomers of the two gross structures III and IX assigned to natural zingiberene by Eschenmoser and Schinz.[5]

The comparability of the synthetic product with natural zingiberene[5] was further established by its condensation with diethyl acetylenedicarboxylate, which gave 4-methylphthalic acid following the procedure of Eschenmoser and Schinz.[5]

It may be pointed out that the formation of 4-methylphthalic acid does not exclude the presence of the exocyclic structure IX in the synthetic product because of the possibility of its rearrangement to the homoannular stage (III) followed by Diels–Alder addition as in the case of abietic acid.[15]

However, the above experiments strongly support Eschenmoser and Schinz's invalidation of Ruzicka's structure I for zingiberene which is established as III most probably accompanied by its bond isomer IX.

## Experimental

Melting points and boiling points are uncorrected.

**6-(4'-Keto-1-cyclohexenyl)-2-methyl-2-heptene (VI).** (a) **6-(*p*-Methoxyphenyl)-2-methyl-2-heptene.**—Dry liquid ammonia (1200 cc.) was taken in a 2-l. three-necked flask fitted with (i) a potassium hydroxide guard tube, (ii) glycerol-sealed mechanical stirrer and (iii) a dropping funnel (100 cc.) with a potassium hydroxide guard tube.

6-(*p*-Methoxyphenyl)-2-methyl-2,5-heptadiene (IV, 39 g.)[9] in 75 g. of absolute alcohol was added followed by 25 g. of clean dry sodium in small pieces during about 2.5 hours. Stirring was continued until the blue color was discharged completely. Water (500 cc.) was then added slowly with stirring and the outer side of the flask was continuously swept with a flow of tap water. This process helped to remove rapidly most of the ammonia during decomposition. The mixture was kept as such for another half an hour and then extracted thrice with ether. The clear colorless ethereal layer was washed twice with water and dried over anhydrous potassium carbonate. The residue, obtained after removing the ether, was fractionated *in vacuo* and the portion boiling at 135–138° (3 mm.) was collected; yield 31 g. (78%). This process was repeated to prepare larger amounts of this compound.

(b) **6-(4'-Methoxy-1',4'-cyclohexadienyl)-2-methyl-2-heptene (V).**—6-(*p*-Methoxyphenyl)-2-methyl-2-heptene (20 g.) was further subjected to metal–ammonia reduction with sodium (20 g.) and absolute alcohol (60 g.) in 1000 to 1100 cc. of liquid ammonia as described before. Fractionation afforded 17.8 g. (85%) of 6-(4'-methoxy-1',4'-cyclohexadienyl)-2-methyl-2-heptene (V) boiling at 135° (4 mm.).

The reduced product (V, 17.8 g.) was heated with 60 cc. of 5% sulfuric acid solution on a steam-bath for 35–40 minutes. On cooling the oil was taken up in ether, the ether solution washed with water, sodium bicarbonate solution and then mechanically shaken with a saturated solution of sodium bisulfite for about 10 to 12 hours. The crystalline bisulfite addition compound was washed with ether and decomposed with 6–7% sodium hydroxide solution (150 cc.). The liberated oil was extracted with four 50-cc. portions of ether and the combined ether extracts washed with water and dried over potassium carbonate. The solvent being removed, the residue on vacuum distillation gave 12 g. (72%) of 6-(4'-keto-1'-cyclohexenyl)-2-methyl-2-heptene (VI), as a colorless liquid boiling at 138° (5 mm.). This compound showed no light absorption maximum in the region of 220–230 m$\mu$.

The semicarbazone prepared in the usual way and crystallized from ethanol melted at 111–112° (lit.[9] m.p. 114°).

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[13] R. B. Woodward, THIS JOURNAL, 64, 72 (1942).

[14] H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

[15] L. Ruzicka, Ankersmit and B. Frank, *Helv. Chim. Acta*, 15, 1289 (1932); Arbusov, *J. Gen. Chem.* (*U.S.S.R.*), 2, 806 (1932); R. G. R. Bacon and L. Ruzicka, *Chemistry and Industry*, 55, 546 (1936).

**6-(4'-Keto-2'-cyclohexenyl)-2-methyl-2-heptene (VII).**—To a solution of sodium ethoxide in alcohol (from 1.8 g. of sodium) was added dropwise a solution of 20.6 g. of VI in 50 cc. of absolute alcohol. The solution was heated on a water-bath at 60° for exactly 5 minutes and then poured into crushed ice and glacial acetic acid (12 cc.) when a thick oil separated. The mixture was saturated with salt and extracted thrice with ether. The ethereal layer was washed with sodium chloride solution, bicarbonate solution and dried over potassium carbonate. Ether being removed, the residue was fractionated when a colorless liquid came over at 148–152° (4 mm.); yield 16.1 g. (78%). This liquid developed a yellow color on standing; ultraviolet absorption spectra (ethanol), $\lambda_{\max}$ 225 mμ (log *E* 3.76) and 285 mμ, (log *E* 2.48); Fig. 1.

*Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.55; H, 10.68. Found: C, 81.03; H, 10.32.

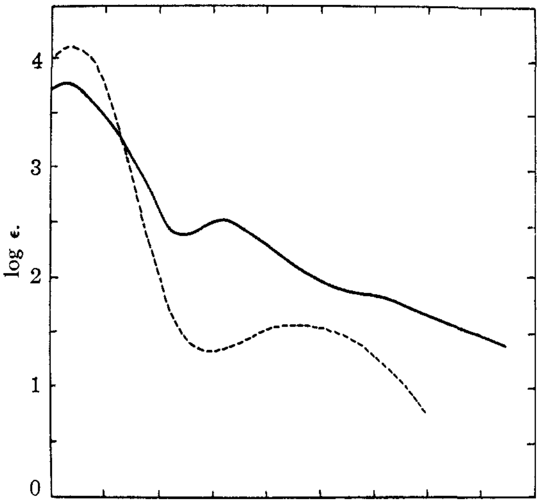

Fig. 1.—Ultraviolet absorption spectra of (VII) (—) and cryptone[10] (---) in ethanol.

**6-(4'-Methyl-4'-hydroxy-2'-cyclohexenyl)-2-methyl-2-heptene (VIII).**—The ketone (VII, 16 g.) in 50 cc. of dry ether was treated in the cold with methylmagnesium iodide (prepared from 2.3 g. of magnesium) in 160 cc. of dry ether. The reaction mixture after being kept overnight at room temperature was decomposed with ice and ammonium chloride and extracted with ether. The ethereal layer was washed with cold dilute sulfuric acid, sodium bicarbonate solution, and water and then dried over potassium carbonate. After removing the solvent the residue was distilled in vacuum, when 11.2 g. (65%) of the carbinol (VIII), a sweet smelling colorless liquid, came over at 133–135° (3 mm.); $n^{32}\mathrm{D}$ 1.4932.

*Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.08; H, 11.26. Found: C, 80.97; H, 11.09.

**6-(4'-Methyl-2',4'-cyclohexadienyl)-2-methyl-2-heptene (III) and 6-(4'-Methylene-2'-cyclohexenyl)-2-methyl-2-heptene (IX).**—To a warm solution of oxalic acid (32 g.) in water (64 cc.) was added the carbinol (VIII, 10.5 g.). The mixture was refluxed over a free flame for 2.5 hours, cooled and extracted thrice with ether. The organic layer was washed with water and sodium bicarbonate solution and dried over sodium sulfate. Ether was removed and the residue, on distillation under diminished pressure, afforded colorless, mobile liquid, b.p. 118° (4 mm.). The oil was then heated with phthalic anhydride on an oil-bath at 170–180° for 20–25 minutes in nitrogen atmosphere. It was dissolved in ether, washed with 5% sodium hydroxide solution and dried over anhydrous potassium carbonate. Ether was evaporated and the residue, on distillation *in vacuo*, gave an oil, b.p. 110° (2 mm.), $n^{32}\mathrm{D}$ 1.4948, yield 7.2 g. (75%), ultraviolet absorption spectra (ethanol), $\lambda_{\max}$ 232 mμ (log *E* 3.52); *265 mμ* (log *E 3.26*); *Fig. 2.*

*Anal.* Calcd. for $C_{15}H_{24}$: C, 88.23; H, 11.77. Found: C, 87.99; H, 11.32.

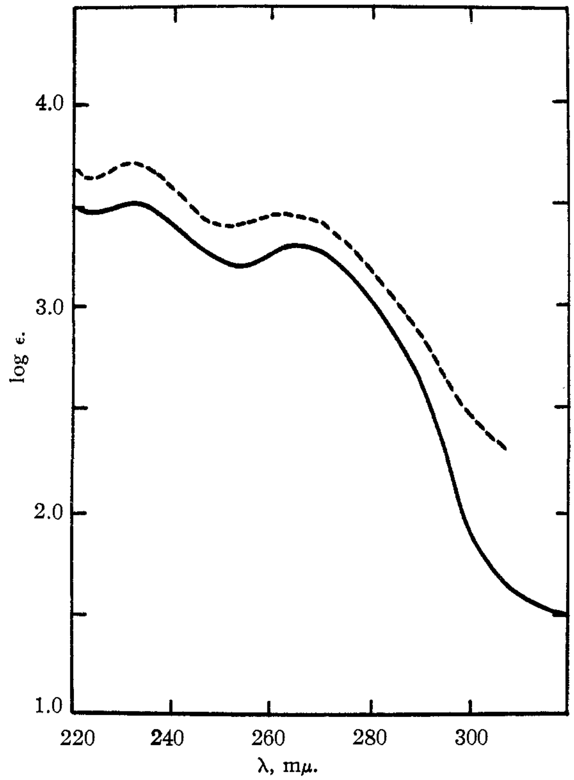

Fig. 2.—Ultraviolet absorption spectra of natural zingiberene[5] (---) and synthetic product (—) in ethanol.

**Condensation of the Synthetic Hydrocarbon with Diethyl Acetylenecarboxylate.**—The synthetic hydrocarbon (4.65 g.) was mixed with 5 g. of freshly distilled diethyl acetylenedicarboxylate and the mixture heated on an oil-bath for two hours at 200–210°. Fractionation of the reaction product gave 3.8 g. of the diethyl phthalate, boiling at 190–205° (7–8 mm.). It was refractionated to yield 3.1 g. of a clear pale yellow liquid, b.p. 188–193° (6–7 mm.). This diester was refluxed on the steam-bath with methanolic potash (5 g. of potassium hydroxide in 50 cc. of methyl alcohol) for 6 hours. Most of the methyl alcohol was removed and the cooled residue dissolved in the minimum amount of water and the solution washed with ether. The aqueous solution was acidified with concentrated hydrochloric acid when a red viscous oil separated on cooling. It was taken up in ether, washed with water and dried over anhydrous sodium sulfate. The ether being removed, the residue sublimed at 195–200° (5–6 mm.). Part of this sublimate was crystallized from benzene as fine colorless cubic crystals which sharply melted at 149–150°; mixed m.p. with an authentic sample of 4-methylphthalic acid, 149–150°. The acid was also crystallized from dilute methyl alcohol but benzene was found to be a better solvent.

The rest of the sublimate was heated at a temperature of 170° for 1.5 hours and distilled, the distillate dissolved in benzene and the benzene solution washed with 1% sodium bicarbonate solution until it was alkaline. Benzene was removed and the residue when distilled *in vacuo* came over at 150–160° (7–8 mm.) as a viscous oil. Fractional crystallization of this oil from dry benzene gave 4-methylphthalic anhydride, m.p. 90–91°, undepressed when mixed with an authentic sample of 4-methylphthalic anhydride.

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