

The ethanol and excess amine were removed *in vacuo* and the crystalline residue recrystallized from absolute ethanol three times. The salt forms white plates which melt at 226–228° (see Table II). This general procedure was used in the preparation of the other organic acid addition salts of 2-aminoheptane.

2-Aminoheptane Hydrochloride.—Dry hydrogen chloride gas was passed into a solution of pure 2-aminoheptane in anhydrous ether. Since no crystalline material formed the ether was evaporated off, leaving a residue which slowly crystallized. The salt was recrystallized from ether–ethanol. The 2-aminoheptane hydrochloride formed small, compact, white crystals which were somewhat hygroscopic. The product melted at 81–83°. The same product was obtained by mixing an excess of 2-aminoheptane with aqueous hydrochloric acid and evaporating the resulting solution. The crude crystalline residue melted at 78–81°; after recrystallizing from ether–ethanol the melting point was 81–83°.

These samples showed no change in melting point on repeated remelting or on standing for a period of over three years (see Table II).

2-Aminoheptane Hydrobromide.—An excess of 2-aminoheptane was added to a solution of 48% hydrobromic acid and ethanol. The solvents were evaporated *in vacuo* when the hydrobromide crystallized on cooling. The salt crystallized as small white plates from petroleum ether. The product melted at 65–67°.

The 2-aminoheptane hydrobromide showed no change in melting point on repeated remelting. A sample was heated at 100° in the molten state for two hours; on cool-

ing it remelted at 65–67°. A sample which has been kept for a period of more than three years has remained unchanged in melting point (see Table II).

2-Aminoheptane Chloroplatinate.—An aqueous solution of chloroplatinic acid was added to an aqueous solution of 2-aminoheptane hydrochloride. The chloroplatinate separated almost at once as yellow-orange plates. It was recrystallized three times from aqueous ethanol. The product began to darken at 215° and showed extensive decomposition at 225–235° (see Table II).

2-Aminoheptane Chloroaurate.—An aqueous solution of chloroauric acid was added to an aqueous solution of 2-aminoheptane hydrochloride. The mixture was cooled and the product recrystallized three times from water. After drying over phosphorus pentoxide it melted at 82–84°. It formed small yellow-orange plates. The melting point was unchanged on remelting (see Table II).

Summary

Some new aminoalkanes have been prepared for use as pressor substances.

Conditions for optimum pressor activity in aliphatic amines require that the amine group be in the C-2 position and that the compound have 7 or 8 carbon atoms.

The chemistry of 2-aminoheptane and its acid addition salts is discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF SMITH COLLEGE]

The Structure of Isozingiberene

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Direct evidence was obtained³ recently that the structure of the sesquiterpene cadinene is represented as I, in which the unsaturated linkages are in the 1,2 and the 6,7 positions. In the previous formula⁴ for cadinene, due to Ruzicka and Stoll,⁵ one double bond was fixed at 3,4 and the other was placed at either the 5,6 (α -cadinene) or the 6,7 (β -cadinene) position. The work which we wish to report indicates that the " β -cadinene" formula (II) of these investigators is actually that of another sesquiterpene, isozingiberene, and that their formula (IV) for cadinene dihydrochloride (III) represents the structure of isozingiberene dihydrochloride.

Isozingiberene (II) is the parent hydrocarbon of the dihydrobromide or dihydrochloride (IV)⁶ obtained from the sesquiterpene alcohol zingiberol,⁷ or, more commonly, from the monocyclic sesquiterpene zingiberene (V). The usual source for both of these natural products is ginger oil. The crystalline dihydrochloride yields only isozingiberene on treatment with alcoholic potas-

sium hydroxide. A dicyclic hydrocarbon with similar properties is obtained by direct cyclization of zingiberene with acidic reagents.⁸ Although this substance is readily converted to isozingiberene dihydrochloride, there is no proof that its double bonds are in exactly the same positions as those found in the hydrocarbon which is regenerated from the same derivative.

The presence of a dicyclic ring system and two unsaturated linkages was confirmed by Semmler and Becker,⁸ who obtained a tetrahydro derivative on catalytic hydrogenation. Zingiberene under the same conditions absorbed three molecules of hydrogen. The skeletal structure of the molecule has been established⁹ by dehydrogenation to 4-isopropyl-1,6-dimethylnaphthalene (cadalene) (VI), identified by synthesis.¹⁰

No experimental evidence has been reported for the location of the double bonds in isozingiberene. The formula proposed by Semmler and Becker,⁸ interpreted to fit the cadalene skeleton is shown as VII. More recently, Simonsen¹¹ has suggested

(8) Semmler and Becker, *Ber.*, **46**, 1814 (1913).

(9) Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, **5**, 345 (1922).

(10) Ruzicka and Seidel, *ibid.*, 369.

(11) "The Terpenes," Cambridge University Press, London, 1932, Vol. II, p. 498; Stewart and Graham, "Recent Advances in Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1936, Vol. II, pp. 113–115; Egloff, "Reactions of Pure Hydrocarbons," Reinhold Publishing Corporation, New York, N. Y., 1937, p. 825.

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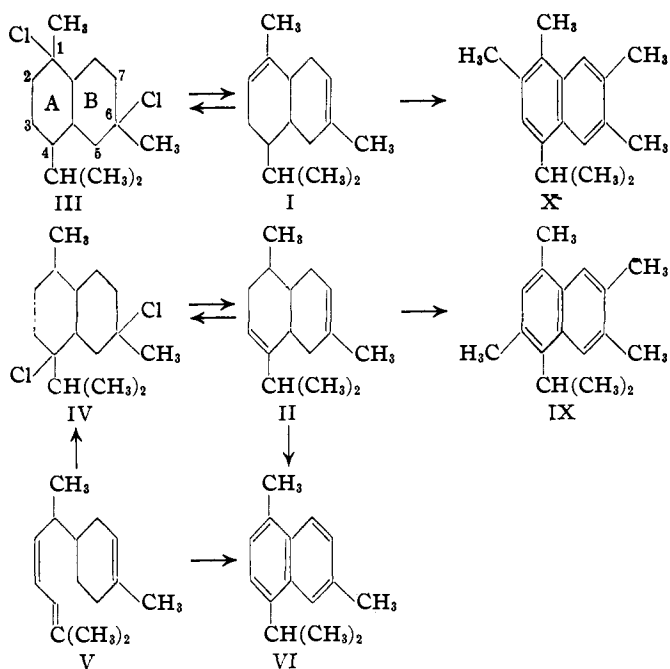
(3) Campbell and Soffer, *THIS JOURNAL*, **64**, 417 (1942).

(4) Due to a typographical error this formula appeared³ with the 6-methyl group in the 7 position.

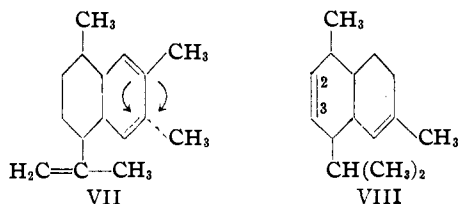
(5) Ruzicka and Stoll, *Helv. Chim. Acta*, **7**, 84 (1924).

(6) Formula IV is the Ruzicka and Stoll⁵ formula for cadinene dihydrochloride.

(7) Brooks, *THIS JOURNAL*, **38**, 431 (1916).



formula VIII. This conjecture, which places the double bond of ring A between two secondary carbon atoms is open to serious objection. The



known ease of double bond migration,⁵ under acidic conditions, to a position adjoining a tertiary carbon atom, and moreover, the regeneration of the hydrocarbon from the dihydrochloride, with the easy reconversion to the latter,⁸ would appear to preclude the 2,3 location and to require that the bond be situated in a tertiary position.

bisabolene, or even the dicyclic hexahydrocadalene, a closely related isomer of isozingiberene, which results¹³ from direct acid cyclization of bisabolene.

The method is substantially the same as that used to determine the nuclear double bond positions in cadinene,³ and in dextropimaric acid.¹⁴ Isozingiberene was converted to its dioxide by reaction with perbenzoic acid. The conditions necessary to accomplish this were previously determined by perbenzoic acid titrations in chloroform solution at approximately 7°. The results obtained, with a threefold excess of 0.461 *N* peracid in the first case, and a twofold excess of a 0.680 *N* solution in a larger run, are summarized in Table I. The course of the reaction is very similar to that observed in the case of cadinene under various conditions of temperature, solvent and concentration. In all cases there is a striking difference between the rates of absorption of the first and second atom of oxygen. The nature of the products obtained from cadinene monoxide suggest that, at least in this *cis*-hexahydronaphthalene¹⁵ series, the double bond which is one carbon atom removed from the ring junction is more reactive toward this reagent than the more distal unsaturated linkage.

Methyl groups, marking the positions of the double bonds in the original molecule, were introduced by treating the dioxide with excess methyl Grignard reagent. The product was dehydrated with anhydrous formic acid and dehydrogenated at low temperature with chloranil.¹⁶ Investigation of a low yield at this point showed that the reaction with chloranil did not serve to dehydrogenate all of the unsaturated hydrocarbon. An additional quantity of the desired naphthalenic product was obtained by the further action of selenium on the non-picrate forming material from the chloranil reaction. In the previous case,³ the

product obtained at this stage was a complex mixture of several closely related homologous hydrocarbons from which the desired substance could be directly obtained only by careful fractionation. In the present case the amount of crude aromatic hydrocarbon (1.9 g.) made this

TABLE I
ATOMS OF OXYGEN ABSORBED PER MOLE OF ISOZINGIBERENE

N	Excess	Time, minutes								
		1	5	15	80	90	180	360	950	1500
0.461	3×	..	1.63	..	1.94	1.98	2.02	..
.680	2×	1.42	..	1.66	1.72	1.78	1.84	1.90	1.96	1.96

The aim of the present work was to obtain direct evidence for the positions of the double bonds in the isozingiberene molecule. The isozingiberene used in this work was prepared exclusively from the pure crystalline dihydrochloride. Since it would be difficult, if not impossible, to separate the zingiberene from the bisabolene which accompanies¹² it in its natural source, it is not certain that the more readily available "isozingiberene" prepared directly^{8,12} by acid cyclization of zingiberene does not contain significant amounts of

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

(13) Ruzicka and Capato, *Helv. Chim. Acta*, **8**, 259 (1925).

(14) Ruzicka and Sternbach, *ibid.*, **22**, 124 (1940).

(15) According to the generalizations of Ruzicka, Koolhaus, and Wind, *ibid.*, **14**, 1171 (1931), the physical properties of isozingiberene and tetrahydroisozingiberene⁸ indicate a *cis* configuration between rings A and B.

(16) Arnold and Collins, *THIS JOURNAL*, **61**, 1407 (1939).

type of separation less feasible. Since the starting material is at the present time relatively inaccessible, the whole product was worked up through the picrate with no previous separation of the hydrocarbons. Although this procedure appreciably limited the yield of pure product, which in the other applications^{3,12} of the method has been quite low, we encountered no difficulty in isolating the desired dimethylcadalene in a high degree of purity.

The purified picrate crystallized from methanol in brilliant red needles melting at 156.0–156.5°. Mixed with an authentic sample of 4-isopropyl-1,3,6,7-tetramethylnaphthalene picrate (synthetic³; m. p. 156.5–157°) the melting point was 156.5–157°. A mixture with 4-isopropyl-1,2,6,7-tetramethylnaphthalene picrate (from cadinene³; m. p. 145°) melted at 131–137°. Similarly, the mixed melting point of the hydrocarbon (IX) (m. p. 96–97°), regenerated from the picrate, with a sample of 4-isopropyl-1,3,6,7-tetramethylnaphthalene (synthetic³; m. p. 96.5–97°) was 96–97°. The melting point was depressed to 71–74° by admixture with the corresponding hydrocarbon (4-isopropyl-1,2,6,7-tetramethylnaphthalene (X), m. p. 102–103°) obtained³ from cadinene.

Experimental¹⁷

Isozingiberene Dihydrochloride (IV).—In a typical preparation, 1600 ml. of African ginger oil was stirred and heated for six hours at 60–65° with 2.5 times its volume of glacial acetic acid and 120 ml. of 50% sulfuric acid. The reaction mixture was poured into three times its volume of water and extracted with 35–60° petroleum ether. After washing with aqueous sodium carbonate, water, and a saturated solution of sodium chloride, and drying further over anhydrous magnesium sulfate, the solvent was removed and the residue distilled. The main fraction, b. p. 118–120° at 7 mm., was dissolved in an equal volume of glacial acetic acid and saturated at 0° with dry hydrogen chloride. The crystalline product, washed thoroughly with cold glacial acetic acid, separated from ethyl acetate as colorless glistening needles (42 g.) which melted sharply, with loss of hydrogen chloride, at 172°; $[\alpha]^{22}_D -17^\circ$. Further recrystallization did not change these physical properties.

Isozingiberene (II).—A solution of 26.0 g. of the dihydrochloride and 25 g. of 85% potassium hydroxide in 400 ml. of absolute ethanol was refluxed for four hours. After the addition of water to dissolve the precipitated potassium chloride, the hydrocarbon was extracted with hexane, and the extract washed thoroughly with water and dried over calcium oxide. The residue obtained on removal of solvent was distilled over calcium oxide in an atmosphere of nitrogen. After a small forerun, 15.7 g. (82%) of the product came over as a water-white oil with the following physical constants: b. p. 124–124.5° at 9 mm. (85–86° at 1.3 mm.), $d^{20}_4 0.9052$, $n^{20}_D 1.5021$, $[\alpha]^{22}_D -38^\circ$.

Perbenzoic Acid Titrations of Isozingiberene.—These were carried out essentially as described³ before. Control solutions in which the isozingiberene was omitted were prepared in each case. The values were determined by titrating 2-ml. aliquots at the intervals designated. The results are summarized in Table I.

4-Isopropyl-1,3,6,7-tetramethylnaphthalene (3,7-Dimethylcadalene) (IX) from Isozingiberene.—A 100-ml. solution of 11.89 g. of isozingiberene (0.0583 mole) in dry chloroform, was rinsed with 20 ml. of the same solvent into

1080 ml. of a 0.680 *N* solution of perbenzoic acid¹⁸ (0.367 mole) in chloroform. After fifteen hours, titration of an aliquot indicated a molar absorption of 2.0 gram-atoms of oxygen. No further absorption was indicated eleven hours later. The solution was shaken with 2 liters of water containing 42 g. of sodium carbonate and 150 g. of sodium thiosulfate, washed well with water, dried over anhydrous magnesium sulfate, and freed from solvent by distillation through a short column. Three consecutive distillations of the residual oil gave 6.0 g. of a colorless viscous product boiling at 109–133° at about 0.8 mm.

A solution of the foregoing crude dioxide in 50 ml. of anhydrous ether was added to the Grignard reagent, prepared from 45 g. of methyl iodide¹⁹ in 150 ml. of ether, at a rate sufficient to maintain gentle refluxing. After the addition, the refluxing was continued with external heating for twenty-four hours. The product was decomposed with ice water and ammonium chloride, and the ether layer was washed first with a small amount of a dilute solution of sodium thiosulfate, then with water, and with a saturated solution of sodium chloride, and finally dried with anhydrous sodium sulfate.

The viscous, oily, crude di-tertiary glycol which remained after removal of the solvent was dehydrated by refluxing for fifteen minutes with 50 ml. of 98–100% formic acid. After the addition of 150 ml. of water the reaction mixture was extracted with low-boiling petroleum ether. The extract, washed with dilute alkali and with water, was allowed to stand over Norite and anhydrous magnesium sulfate before the solvent was removed. The residual oil, less viscous than the crude dioxide or glycol, was distilled over sodium. The water-white distillate (2.5 g.), b. p. 95–105° at 1.2 mm., gave a positive test for unsaturation with potassium permanganate and readily decolorized bromine.

The unsaturated hydrocarbon (2.0 g.) was refluxed with 6.7 g. of chloranil and 30 ml. of xylene for twenty-four hours. After cooling, the hydroquinone was more completely precipitated (5.9 g., 84%) by the addition of 30 ml. of 20–40° petroleum ether. The filtered solution was washed with aqueous sodium hyposulfite and excess alkali, washed again with water, and dried. After removal of solvent, 1.9 g. of colorless oil, b. p. 105–118° at 1.2 mm., was obtained by distillation over sodium.

Treatment with picric acid in ethanol in the usual way gave 0.56 g. of a red crystalline picrate, m. p. 115–135°. The melting point rose to 147.5–153° after one recrystallization from ethanol, and three more recrystallizations from methanol yielded 35 mg. of brilliant red needles, m. p. 156.0–156.5°, whose melting point was not changed by further recrystallization. The mixed melting point with an authentic sample³ of 4-isopropyl-1,3,6,7-tetramethylnaphthalene picrate (m. p. 156.5–157°), was 156.5–157°, and a mixture with 4-isopropyl-1,2,6,7-tetramethylnaphthalene picrate³ (m. p. 145°) melted at 131–137°.

The non-picrate forming material obtained from the mother liquors after removal of solvent was freed from picric acid by alkaline extraction of an ether solution. When the residue from the removal of ether was heated with 3 g. of selenium²⁰ and a small amount of sulfur, the evolution of gas ceased after one and one-half hours at 250–260°. No more gas was evolved when the temperature was raised, at this point, to 280°. A solution of the product in benzene was washed with alkali and water until the washings gave no test with lead acetate, and the extract, dried over anhydrous magnesium sulfate, was passed through a column of activated alumina. Removal of the solvent and distillation over sodium gave 0.52 g. of a colorless oil boiling at 125–148° at 2 mm. Treatment with picric acid and repeated recrystallization, as before, gave 10 mg. of

(18) Hibbert and Burt, *THIS JOURNAL*, **47**, 2240 (1925); Gilman and Blatt, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., second edition, 1941, p. 431.

(19) Methyl chloride, in a preliminary experiment, gave the same final product.

(20) Diels and Karstens, *Ber.*, **60**, 2323 (1927).

[17] All melting points are corrected.

red silky needles identical with the picrate isolated from the chloranil dehydrogenation.

The hydrocarbon regenerated from the pure picrate in ether-benzene-chloroform solution, by selective adsorption on activated alumina, crystallized from methanol in elongated colorless prisms, m. p. 96–97°. A mixture with 4-isopropyl-1,3,6,7-tetramethylnaphthalene (IX) (synthetic, m. p. 96.5–97°) melted at 96–97°. A mixture with 4-isopropyl-1,2,6,7-tetramethylnaphthalene (X) (from cadinine, m. p. 102–103°) melted at 71–74°.

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Summary

By the action of the methyl Grignard reagent on

isozingiberene dioxide, methyl groups were introduced marking the positions of the double bonds in isozingiberene. The dimethylcadalene obtained by subsequent dehydration and dehydrogenation was identical with synthetic 4-isopropyl-1,3,6,7-tetramethylnaphthalene, indicating that the double bonds are in the 3,4 and 6,7 positions in the isozingiberene molecule.

The recent revision of the formula for cadinene is supported by the evidence that one of the previous formulas for cadinene, and the formula previously assigned to cadinene dihydrochloride, represent the structures of isozingiberene and isozingiberene dihydrochloride.

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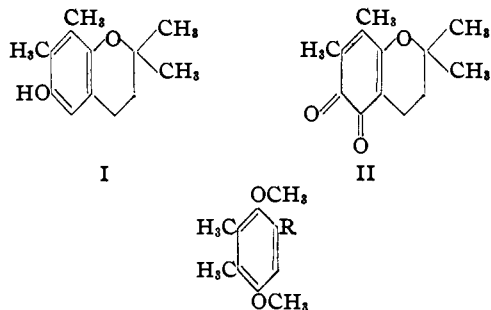
RECEIVED JULY 6, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Vitamin E. XLIII.¹ Synthesis of 2,2,7,8-Tetramethyl-6-hydroxychroman and its Behavior upon Oxidation

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In a previous paper,³ it was reported that 2,2,7,8-tetramethyl-6-hydroxychroman (I), when oxidized by action of silver nitrate in ethanol, gave the red ortho-quinone II, m. p. 109.5–110.5°. However, the substance actually oxidized was an oil obtained by extracting, with Claisen alkali,



III, R = H VI, R = CH₂CH₂COCH₃
 IV, R = CH₂Cl VII, R = CH₂CH₂C(OH)(CH₃)₂
 V, R = CH₂CH(COCH₃)COOC₂H₅

the product of a condensation between *o*-xylohydroquinone and isoprene. The condensation product was itself an oil, and although from the method of preparation it was reasonable to assume that the alkali-soluble fraction of this oil would consist largely of I, the material was not analyzed, and it was characterized only by its conversion into II upon oxidation. Recently, some question arose concerning the generality of the statement previously made³ with reference to the behavior upon oxidation of *p*-hydroxychromans, such as I, and in order to acquire more definite information,

the chroman I has now been prepared in a pure state, and the behavior upon oxidation has been studied. The results confirm the previous work—oxidation of the pure chroman, m. p. 84.5–85.5°, by action of silver nitrate in ethanol, gave the red *o*-quinone II, m. p. 109.5–110.5°, in a yield of 26%.

The chroman I cannot be prepared in a pure form by condensation of *o*-xylohydroquinone with isoprene, for the product of this reaction is an inseparable mixture of I, the double chroman, the hydroquinone and polymers of isoprene. Although this mixture can be separated into two fractions by extraction with Claisen alkali, these fractions are both oils and no pure I can be obtained from the alkali-soluble fraction. It was necessary, therefore, to synthesize I by a method which would lead only to the desired compounds and in which the intermediates could be readily purified. The synthetic route involved the sequence of compounds III, IV, V, VI, VII and I.

Experimental Part⁴

2,3-Dimethylphenol⁵ was coupled with diazotized sulfanilic acid according to the procedure previously developed,⁶ and the azo compound was reduced to 2,3-dimethyl-4-aminophenol by action of aqueous sodium hydrosulfite.⁷ A small sample of the aminophenol, recrystallized several times from benzene, formed white needles which melted at 172–173°.⁸

Anal. Calcd. for C₉H₁₁ON: C, 70.04; H, 8.08. Found: C, 69.99; H, 8.33.

(4) Microanalyses by Stanley T. Rolfsen.

(5) Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941).

(6) Smith, Opie, Wawzonek and Prichard, *ibid.*, **4**, 318 (1939).

(7) For an example of the procedure, see Smith, Hoehn and Whitney, *THIS JOURNAL*, **62**, 1863 (1940).

(8) Hinkel, Collins and Ayling, *J. Chem. Soc.*, 2968 (1923), give the m. p. as 175°.

(1) XLII, *THIS JOURNAL*, **65**, 745 (1943).

(2) Abstracted from a thesis by R. W. H. Tess, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, March, 1944.

(3) Smith, Irwin and Ungnade, *THIS JOURNAL*, **61**, 2424 (1939).