

STUDIES IN SESQUITERPENES—PART I

Synthesis of 5:8—Dimethyl Cadalene

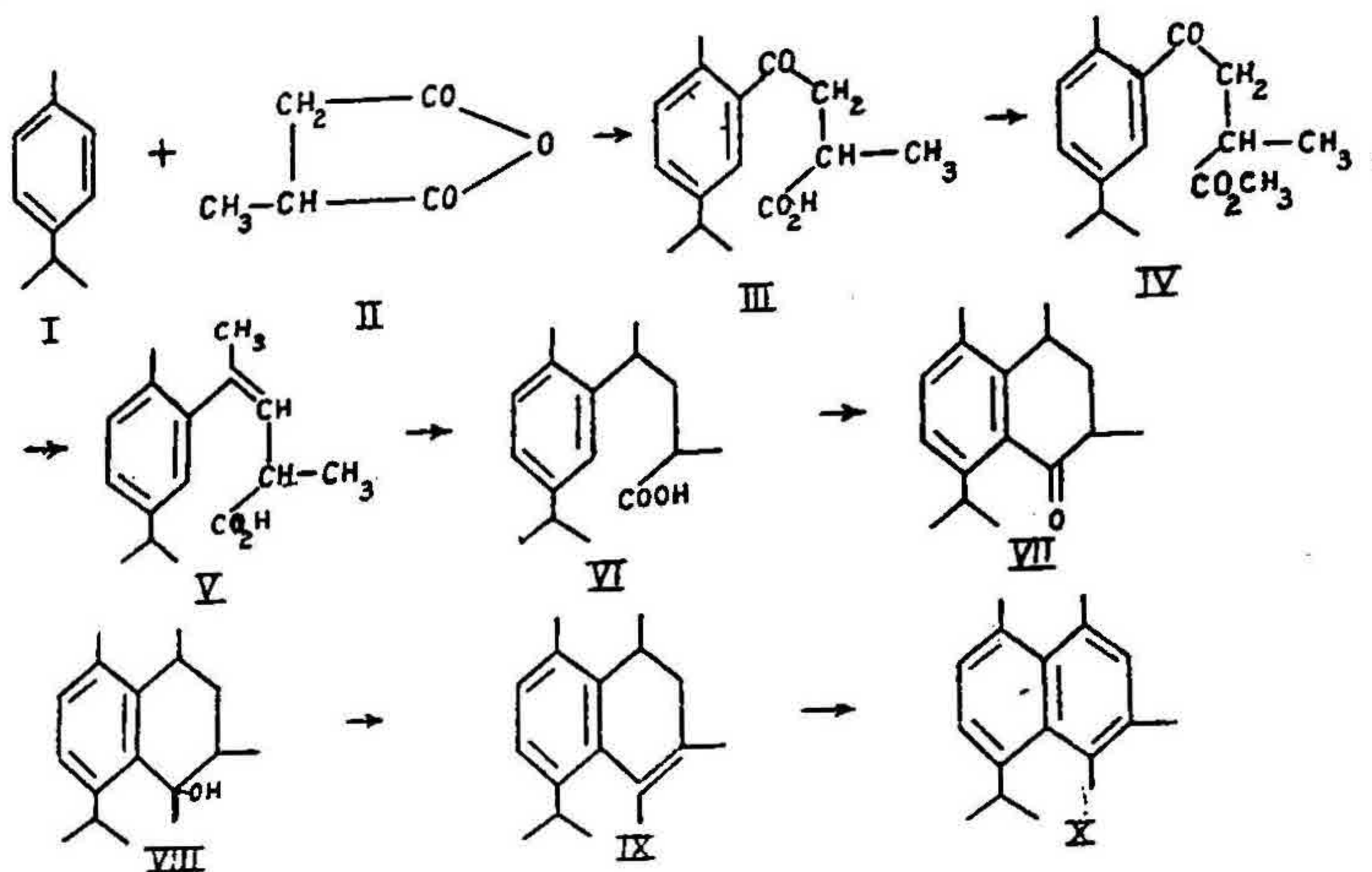
(1:5:6:8—Tetramethyl-4-Isopropyl Naphthalene)

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In connection with the investigations on the structure of sesquiterpenes of the cadinene group, dimethyl-cadalenes form valuable reference compounds, for locating double bonds in the sesquiterpene molecules. Dioxide prepared by the action of two molecules of perbenzoic acid on one mole of cadinenic sesquiterpene hydrocarbon would react with methyl magnesium iodide introducing two additional methyl groups into the sesquiterpene molecule. The position of the additional methyl groups in the cadalene molecule would reveal the position of the ethylenic linkages in the original sesquiterpene. This method was first used by Ruzicka and Sternbach (*Helv. Chim. Acta*, 1940, 23, 124) and also by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, 64, 417) for locating the position of double bonds in cadinene and isozingiberene. 2:7- and 3:7-dimethyl-cadalenes were synthesized by Campbell and Soffer (*loc. cit.*) in their investigations of the structures of cadinene and isozingiberene.

This method of labelling the double bonds has been extended to ketones, primary and secondary alcohols. Bradfield (*J. Chem. Soc.*, 1936, 667) fixed the position of carbonyl in tetrahydro-eremophilone according to this procedure. Secondary and primary alcoholic groups can be oxidized to ketones and aldehydes and the method of labelling the keto groups by additional methyl groups can be followed. The importance of the syntheses and study of the properties of all the possible and unknown dimethyl cadalenes is apparent. The synthesis of 5:8-dimethyl-cadalene was accomplished according to scheme outlined below.



p-Cymene (I) was condensed with methyl-succinic anhydride (II) in the presence of anhydrous aluminium chloride according to the method of Sukh Dev and Guha (J. Indian Chem. Soc., 1948, 25, 13). β-(*p*-cymoyl-2-)-α-methyl propionic acid (III), thus obtained, was esterified with methyl-alcohol and sulphuric acid. The methyl ester (IV), when treated with methyl magnesium iodide (inverse addition) yielded γ-(*p*-cymyl-2-)-α-γ-dimethyl-vinylacetic acid (V). The latter could not be purified by distillation under reduced pressure as it tended to lactonise. The crude acid itself was refluxed with a mixture of hydroiodic acid and red phosphorus for 12 hours at 130-160°C. γ-(*p*-cymyl-2-)-α-γ-dimethyl butyric acid (VI), thus obtained, was cyclised in presence of anhydrous aluminium chloride to yield 2:4:5-trimethyl-4-isopropyl-tetralone-1 (VII). The latter was treated with methyl magnesium iodide and the crude carbinol (VIII) isolated was dehydrated by 85% formic acid yielding 1:5:6:8-tetramethyl-4-isopropyl-dihydronaphthalene (IX) which on dehydrogenating with sulphur furnished 5:8-dimethyl-cadalene (X).

Experimental

(i) β-(*p*-cymoyl-2-)-α-methyl propionic acid (III) : Condensation of methyl-succinic anhydride (II) with *p*-cymene (I).—Methyl-succinic

anhydride (II, 28 g. 1 mol) was condensed with *p*-cymene (I, 35 g. 41 c.c., 1.1 mol) in nitrobenzene (150 c.c.) solution in presence of anhydrous aluminium chloride (74 g., 2.2 mols). (For details, see Sukh Dev and Guha, J. Indian Chem. Soc., 1948, 25, 13). The crude acid (III) was obtained in 62.3% yield (38 g.). It crystallised in colourless plates from a mixture of ether and petroleum ether; m.p. 118-9°C.

(ii) *Methyl-β (p-cymoyl-2-)-α-methyl-propionate (IV)*.—The acid (38 g.) methanol (75 c.c.) and concentrated sulphuric acid (6 c.c.) were refluxed for 10 hours and worked up in the usual manner. The ester was purified by distilling. b.p. 145°C/0.5 m.m. Yield 30.0 g. 75%.

(iii) *γ-(p-cymyl-2-)-α-γ-dimethyl-vinylacetic acid (V)*.—A Grignard solution of magnesium methyl iodide was prepared from magnesium (2 g., 1.6 mol), methyl iodide (11.4 g., 1.6 mol) and anhydrous ether (35 c.c.). The ester (13.1 g., 1 mol) was dissolved in dry ether (40 c.c.) and chilled in ice salt mixture and the Grignard solution was added in a very thin stream with continuous shaking. The reaction mixture was left as such over-night and thereafter refluxed for 2 hours. A viscous liquid separated. The flask was cooled in ice and the complex decomposed with dilute hydrochloric acid (50 c.c., 1:2). As soon as all the complex dissolved, the ether layer was separated and aqueous solution was extracted once with ether. The ether extract was washed once with water and extracted four times with sodium carbonate solution. The alkaline extract was treated with norite, chilled and acidified with dilute hydrochloric acid (congo red), and the liberated oil was extracted with ether (thrice). The ethereal solution was dried over anhydrous sodium sulphate and the solvent removed, when a viscous liquid was obtained. Yield 6 g.

(iv) *γ-(p-cymyl-2-)-α-γ-dimethyl butyric acid (VI)*.—The above acid (V, 19.1 g.) hydriodic acid (100 g.) and red phosphorus (12 g.) were refluxed for 12 hours at 130°-140°C. The reaction mixture was cooled, diluted with water and extracted with ether

several times. The ethereal extract was washed twice with water and extracted with dilute sodium carbonate solution (4 times). The ethereal solution containing neutral products was kept apart to be treated later. The alkaline extract was treated with norite and acidified with dilute hydrochloric acid (congo red). The liberated acid was extracted with ether (thrice) and the ethereal extract was washed with sodium thiosulphate solution to remove any iodine and then it was washed with water and dried over anhydrous sodium sulphate. The ether was removed and the crude acid purified by distilling under reduced pressure. A colourless viscous liquid was obtained; b.p. 145-155°C/0.5 m.m. Yield 10 g. (Found: C, 77.12; H 9.32. $C_{16}H_{24}O_2$ requires C, 77.41; H, 9.67 per cent).

The ethereal solution containing the neutral products was washed with dilute sodium thiosulphate solution and then with water. After drying, the ether was removed and the residue fractionated; b.p. 115-117°C/1 m.m. It was identified to be 2:4:5-trimethyl-8-isopropyl-tetralone-1 (VII) by preparing 2:4-dinitrophenyl-hydrazone as bright red needles. m.p. 206.5°C. Mixed m.p. with authentic sample remained undepressed. (Found: N, 13.69. $C_{23}H_{36}N_2O_4$ requires N, 13.658 per cent).

(v) 2:4:5-Trimethyl-8-isopropyl-tetralone-I (VII). — The acid chloride was prepared from the above acid (VI, 3.4 g., 1 mol) and phosphorus pentachloride (3.33 g., 1.1 mol.) in the usual manner and without being isolated was cyclised in the presence of anhydrous aluminium chloride (2.1 g., 1.1 mol). For details see the preparation of 2:5-dimethyl-8-isopropyl-tetralone-1 (Sukh Dev and Guha, *ibid.* 1948, 25, 18). The tetralone (VII) was obtained as colourless mobile liquid. b.p. 115-117°/1 m.m.: yield 2½ g. 2:4-Dinitrophenyl-hydrazone was prepared (sulphuric acid method) and crystallised from alcohol in bright red needles. m.p. 206.5°C. (Found: N, 13.69. $C_{23}H_{36}N_2O_4$ requires N, 13.658 per cent).

(vi) 1:5:6:8-Tetramethyl-4-isopropyl-dihydronaphthalene (IX). — Grignard solution was prepared from magnesium (0.84 g., 1.6 mol),

methyl iodide (5 g.) and dry ether (50 c.c.) and chilled in ice. A solution of the ketone (VII, 5 g., 1 mol) in dry ether (15 c.c.) was added in a thin stream with continuous shaking. The reaction mixture was left at room temperature for 2 hours and then refluxed for four hours. A white complex separated which was decomposed by pouring out the mixture into ammonium chloride solution (ammonium chloride 30 g., water 20 c.c., ice 100 g.). After stirring for 30 minutes, the ethereal layer was separated and washed once with saturated ammonium chloride solution and dried over anhydrous sodium sulphate. Ether was removed and the crude carbinol (VIII) thus obtained was dehydrated by refluxing with formic acid (20 c.c.) for 3 hours. The mixture was cooled, diluted with water and extracted (thrice) with ether. The ethereal extract was washed with water (twice) and dried over anhydrous sodium sulphate. Ether was removed and the hydrocarbon purified by distillation. b.p. 120-123°C/1 m.m. Yield 3.48 g. (Found: C, 89.46; H, 10.60. $C_{17}H_{24}$ requires C, 89.48; H, 10.52 per cent).

(vii) 1:5:6:8-Tetramethyl-4-isopropyl naphthalene:5:8-dimethyl-cadalene (X).—The above hydrocarbon (IX, 2 g.) was dehydrogenated with sulphur (0.3 g.) by heating together at 230° for 30 minutes and at 260° for further half an hour. The dimethyl-cadalene was purified by distilling over sodium (twice). b.p. 130-5°C/1 m.m. Yield 1 g. (Found: C, 90.27; H, 9.74, $C_{17}H_{22}$ requires C, 90.265 H, 9.735 per cent).

The trinitrobenzene derivative of 5:8-dimethyl-cadalene was prepared by mixing hot alcoholic solutions of trinitrobenzene and the hydro-carbon and allowing to crystallise slowly. Golden yellow needles separated; m.p. 144-5°C. Further crystallisations did not raise the melting point.

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