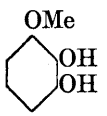
171. *Synthesis of Derivatives of Myristicin.*

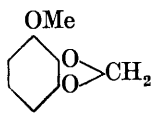
By WILSON BAKER, LOUIE VALERIE MONTGOMERY, and HILARY ANNOT SMITH.

THE naturally occurring substance myristicin (3-methoxy-4 : 5-methylenedioxy-1-allylbenzene) has been used as the starting material in the synthesis of the alkaloid narcotine and the anhalonium (cactus) alkaloid lophophorine. The syntheses have actually started from myristicinaldehyde (3-methoxy-4 : 5-methylenedioxybenzaldehyde) (IV) produced by isomerisation of myristicin to *iso*myristicin and subsequent oxidation; the preparation of the cotarnine fragment of narcotine was effected by Salway (J., 1910, **97**, 1208) and Decker and Becker (*Annalen*, 1913, **395**, 328) (the combination of cotarnine with meconine being first achieved by Perkin and Robinson, P., 1910, **26**, 46, 131), and that of lophophorine by Späth and Gangl (*Monatsh.*, 1923, **44**, 103). Both these syntheses are, however, incomplete, in that neither myristicin nor any of its derivatives has yet been synthesised. The present communication describes the synthesis of myristicinaldehyde and some related compounds.

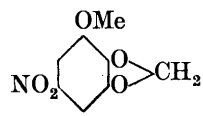
The completion of the synthesis of narcotine receives an added interest in the recent work of Rygh, Rygh, and Laland (*Z. physiol. Chem.*, 1932, **204**, 105; Laland, *ibid.*, p. 112; Rygh and Rygh, *ibid.*, p. 114), which indicates that *l*-narcotine may be the precursor of the antiscorbutic vitamin-C.*



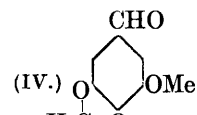
(I.)



(II.)



(III.)



* (Note added in proof.) Doubt has recently been expressed, however, by Smith and Zilva as to the correctness of this work. (See *J. Soc. Chem. Ind.*, 1932, **51**, 166.)

Pyrogallol 1-methyl ether (I) was readily prepared by oxidation of *o*-vanillin with hydrogen peroxide in *N*-alkali solution (Dakin, *Amer. Chem. J.*, 1909, **42**, 477), and methylenation of this compound with methylene sulphate (Baker, J., 1931, 2542) yielded 1-*methoxy*-2 : 3-*methylenedioxybenzene* (II) in excellent yield. Substance (II) was also prepared in small quantity by partial methylation of pyrogallol and subsequent methylenation without isolation of any intermediate product. Nitration of (II) readily yielded 5-nitro-1-methoxy-2 : 3-methylenedioxybenzene (III), but attempts to prepare myristicinic acid through the corresponding amino-compound by diazotisation were unsuccessful.

The synthesis of myristicinaldehyde (IV) was effected by the action of methylene sulphate and alkali on 4 : 5-dihydroxy-3-methoxybenzaldehyde (Bradley, Robinson, and Schwarzenbach, J., 1930, 811), and a direct comparison was made of the synthetic aldehyde with the aldehyde prepared from myristicin [Salway, J., 1909, **95**, 1208; the convenient method of oxidising *iso*apiole and asarone to the corresponding aldehydes by means of ethyl nitrite and hydrochloric acid devised by Fabinyi and Széki (*Ber.*, 1917, **50**, 1338) does not work satisfactorily with *iso*myristicin]. The synthetic aldehyde was also oxidised to myristicinic acid.

Experimental.

Pyrogallol 1-Methyl Ether (I).—*o*-Vanillin (15 g.), dissolved in *N*-sodium hydroxide (97 c.c.), was treated with 3% aqueous hydrogen peroxide (46 c.c.; 1·25 equivs.); rise of temperature occurred and the solution darkened. After ¼ hour, a slight excess of dilute sulphuric acid was added, then sodium bicarbonate to produce alkalinity, and the solution was repeatedly extracted with ether. The extracts, dried by sodium sulphate and evaporated, yielded an oil, of which the fraction, b. p. 140—160°/25 mm., solidified, and separated from ligroin in colourless prisms, m. p. 39—41°. The diacetate, obtained by boiling with acetic anhydride and sodium acetate, separated from alcohol in colourless needles, m. p. 91—93°. Herzig and Pollak (*Monatsh.*, 1904, **25**, 99) give m. p. 38—41° and 91—93° respectively.

1-*Methoxy*-2 : 3-*methylenedioxybenzene* (II). — (A) Pyrogallol 1-methyl ether (13 g.) in 50% aqueous acetone (100 c.c.) containing sodium hydroxide (12 g.) was slowly treated with methylene sulphate (12 g.) in an atmosphere of coal gas. The mixture was kept at 45° for 1 hour, diluted, and extracted with ether. The extracts left a product which at once crystallised and was purified by distillation (b. p. 215—230°; yield, 10 g.). Crystallisation from ligroin gave colourless needles, m. p. 41° (Found : C, 63·3; H, 5·1. $C_8H_8O_3$ requires C, 63·2; H, 5·3%).

(B) To a stirred mixture of pyrogallol (126 g.), water (500 c.c.), and methyl sulphate (69 g.) was slowly added a solution of sodium hydroxide (44 g.) in water (200 c.c.), air being excluded by coal gas. After ½ hour's stirring, the liquid was heated on the water-bath for 2 hours and cooled. Acetone (250 c.c.) and methylene sulphate (121 g.) were now added and a solution of sodium hydroxide (90 g.) in water (200 c.c.) was slowly introduced into the mixture, which was stirred for several hours. After being made strongly alkaline, the liquid was submitted to steam distillation. The colourless solid (5·3 g.) in the distillate crystallised from ligroin in needles, m. p. 41°, which was not depressed on admixture with a specimen made by method (A).

5-*Nitro*-1-*methoxy*-2 : 3-*methylenedioxybenzene* (III).—The preceding compound (5 g.) in glacial acetic acid (25 c.c.) was treated with a solution of nitric acid (5 c.c.; *d* 1·5) in acetic acid (20 c.c.) at 0°. After 2 hours, the partly crystalline mixture was treated with water and the solid was collected and crystallised first from alcohol (yield, 4·1 g.) and then from ethyl acetate, being obtained in almost colourless prisms, m. p. 146—148° (Found : N, 7·3. Calc. for $C_8H_7O_5N$: N, 7·1%) (Salway, J., 1909, **95**, 1161, records m. p. 143—144°). Reduction with stannous chloride and hydrochloric acid gave a poor yield of the corresponding amino-compound, which separated from water in colourless leaflets, m. p. 82—86° (Salway records m. p. 85—86°).

Myristicinaldehyde (3-*Methoxy*-4 : 5-*methylenedioxybenzaldehyde*) (IV).—4 : 5-Dihydroxy-3-methoxybenzaldehyde (10 g.) in a solution of potassium hydroxide (22 g.) in water (50 c.c.) was treated with methylene sulphate (15 g.) in portions at about 50°. The mixture was diluted, warmed for ¼ hour, and the aldehyde isolated by steam distillation as a crystalline solid (0·5 g.). By crystallisation from hot water it was obtained in colourless needles, m. p. 131°, either alone or when mixed with a specimen of myristicinaldehyde prepared from natural myristicin (Found : C, 60·3; H, 4·5. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·4%).

The synthetic aldehyde was oxidised by a hot dilute alkaline solution of potassium permanganate, and yielded a carboxylic acid which separated from hot water in colourless needles, m. p. 209—210° (alone or mixed with myristicinic acid, m. p. 209—210°, prepared from natural myristicin).

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, February* 18*th*, 1932.