326. *Experiments on the Synthesis of Rotenone and its Derivatives. Part VII. Tetrahydrotubaic Acid.*

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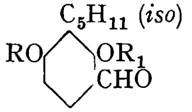
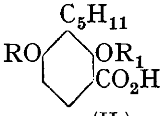
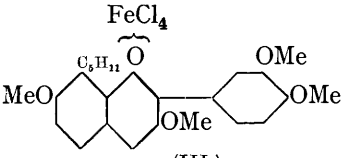
THE oxidation of O-*diacetyltetrahydrotubaic aldehyde* (I; R = Ac, R_1 = Ac) with potassium permanganate and subsequent deacetylation of the product (II; R = Ac, R_1 = Ac) gives rise to tetrahydrotubaic acid (II; R = H, R_1 = H) (compare Haller and La Forge, *J. Amer. Chem. Soc.*, 1932, **54**, 1988). In a similar manner the monomethyl ether of tetrahydrotubaic acid (II; R = Me, R_1 = H) is obtained from the acetate of (I; R = Me, R_1 = Ac). The formation of the *flavylium* salt (III) by the condensation of ω-methoxyacetoveratrone and the ether (I; R = Me, R_1 = H) serves to establish the orientation of the latter and hence that of the acid (II; R = Me, R_1 = H).



(I.)



(II.)



(III.)

The application of the Nencki reaction to homoasaronic acid and tetrahydrotubanol yields tetrahydroderritol methyl ether (Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, **1047**), but only traces of the latter are obtained by the application of the Hoesch condensation to this phenol and 2 : 4 : 5-*trimethoxyphenylacetonitrile.*

EXPERIMENTAL.

2 : 4-*Dihydroxy*-3-iso*amylbenzaldehyde* (*Tetrahydrotubaic Aldehyde*) (I; R = H, R_1 = H).—A solution of tetrahydrotubanol (J., 1933, 1163) (5 g.) in ether (80 c.c.) containing zinc cyanide (3 g.) and hydrogen cyanide (8 c.c.) was saturated with hydrogen chloride, and 24 hrs. later the product was washed with ether and hydrolysed by heating with water (200 c.c.) on the steam-bath for 20 mins. The resulting *aldehyde* separated from light petroleum (b. p. 60—80°) in tiny colourless plates (4 g.), m. p. 112·5°, readily soluble in alcohol, acetone, or benzene, and having a reddish-violet ferric chloride reaction (Found : C, 69·0; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). Crystallised from dilute alcohol, the *semicarbazone* formed irregular plates, m. p. 198° (Found : C, 58·8; H, 7·4. $C_{13}H_{19}O_3N_3$ requires C, 58·9; H, 7·2%). Acetylation of the aldehyde (2·5 g.) with acetic anhydride (8 c.c.) and pyridine (4 c.c.) for 24 hrs. at room temperature afforded the *diacetate* (3·3 g.), which separated from a small volume of light petroleum (b. p. 40—60°) in clusters of needles, m. p. 47·5°, readily soluble in alcohol or acetone (Found : C, 65·9; H, 7·1. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·8%).

2 : 4-*Dihydroxy*-3-iso*amylbenzoic Acid* (*Tetrahydrotubaic Acid*) (II; R = H, R_1 = H).—Oxidation of the aforementioned diacetate (1 g.) in acetone (75 c.c.) at 50—55° was effected by the gradual addition of potassium permanganate (1·2 g.) in water (60 c.c.), and after 15 mins. the solution was cleared with sulphur dioxide. Slow evaporation of the acetone gave the diacetate of the acid (0·9 g.), which separated from benzene–light petroleum (b. p. 60—80°) in tiny needles, m. p. 140—141°, unchanged on repeated crystallisation (Found : C, 62·4; H, 6·3. Calc. for $C_{16}H_{20}O_6$: C, 62·3; H, 6·5%) (Haller and La Forge, *loc. cit.*, give m. p. 143°). A solution of this compound (0·5 g.) in 2*N*-sodium hydroxide (30 c.c.) was kept for 2 hrs., and on acidification with dilute hydrochloric acid gave tetrahydrotubaic acid, which crystallised from benzene in irregular elongated plates, m. p. 203° (decomp.), having properties identical in every way with those of a specimen, m. p. 203°, prepared according to Haller (*J. Amer. Chem. Soc.*, 1933, **55**, 3032), who, however, gives m. p. 206° (Found : C, 64·4; H, 7·3. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

2-*Hydroxy*-4-*methoxy*-3-iso*amylbenzaldehyde* (I; R = Me, R_1 = H).—2 : 4-Dihydroxy-3-*iso*amylbenzaldehyde (2·7 g.) was methylated in boiling acetone (40 c.c.) with methyl iodide (1·6 c.c.) and potassium carbonate (6 g.) during 2 hrs.; after 1 hr., more iodide (1·6 c.c.) was added. On isolation, the monomethyl ether was obtained as a colourless oil (2·6 g.), b. p. 180°/15 mm., which gave a reddish-violet ferric chloride reaction. The *semicarbazone* separated from benzene in slender needles, or from dilute alcohol in irregular plates, m. p. 193° (Found : C, 60·4; H, 7·5; N, 14·5. $C_{14}H_{21}O_3N_3$ requires C, 60·2; H, 7·5; N, 15·0%). Condensation of this ether (0·5 g.) and ω-methoxyacetoveratrone (1 g.) in ethyl acetate with hydrogen chloride gave 3 : 7 : 3′ : 4′-tetramethoxy-8-*iso*amylflavylium chloride, which crystallised from 8% hydrochloric acid in clusters of deep red rectangular prisms. The *ferrichloride* (III) separated from acetic acid in red plates with a green reflex, m. p. 131—132° (Found : C, 48·7; H, 5·0. $C_{24}H_{29}O_5Cl_4Fe$ requires C, 48·4; H, 4·9%).

2-*Hydroxy*-4-*methoxy*-3-iso*amylbenzoic Acid* (II; R = Me, R_1 = H).—Acetylation of the foregoing ether (1·9 g.) with acetic anhydride (8 c.c.) and pyridine (4 c.c.) at room temperature for 12 hrs. and then on the water-bath for 2 hrs. gave the acetate as a viscous oil (2·0 g.). Oxidation of this material (1 g.) in acetone (75 c.c.) at 50—55° with potassium permanganate (1·2 g.) in water (60 c.c.), and subsequent deacetylation of the product (0·9 g.) with 8% aqueous sodium hydroxide (50 c.c.) at room temperature for 3 hrs., gave rise to 2-hydroxy-4-methoxy-3-*iso*-

amylbenzoic acid, which, after the removal of a little unchanged 4-*O*-methyltetrahydrotubaic aldehyde by means of aqueous sodium bicarbonate, separated from light petroleum (b. p. 60—80°) in elongated leaflets (0·3 g.), m. p. 154·5°, identical in every way with the monomethyl ether of tetrahydrotubaic acid for which Haller and La Forge (*J. Amer. Chem. Soc.*, 1932, **54**, 1988) and Takei and co-workers (*Ber.*, 1932, **65**, 285) gave m. p. 156° (Found : C, 65·8; H, 7·5. Calc. for $C_{13}H_{18}O_4$: C, 65·5; H, 7·6%).

2 : 4 : 5-*Trimethoxyphenylpyruvic Acid.*—The azlactone of asarylaldehyde (Takei and co-workers, *ibid.*, p. 1047) (6·8 g.) was boiled with 12% aqueous sodium hydroxide (60 c.c.) for 6 hrs., cooled, and saturated with sulphur dioxide. After the separation of the precipitated benzoic acid, the liquid on being heated with concentrated hydrochloric acid (30 c.c.) on the water-bath gradually deposited the pyruvic *acid* (4·3 g.), which formed pale yellow prisms from acetic acid, m. p. 198° (decomp.) (Found : C, 56·8; H, 5·3. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%). The compound is sparingly soluble in water, alcohol, or benzene.

2 : 4 : 5-*Trimethoxyphenylacetonitrile.*—The foregoing keto-acid (3 g.) was oximated with hydroxylamine hydrochloride (3 g.) in warm 10% aqueous sodium hydroxide (40 c.c. at 50—55°), and 24 hrs. later the oxime (3·4 g.) was precipitated with concentrated hydrochloric acid. Prepared from the crude oxime (3 g.) by means of warm acetic anhydride (10 c.c.), the *nitrile* (1·9 g.) crystallised from dilute alcohol in colourless, elongated, rectangular prisms, m. p. 85°, readily soluble in alcohol, acetone, or benzene (Found : C, 64·0; H, 6·4; N, 6·9. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3; N, 6·8%). Hydrolysis of this compound (2 g.) with a boiling solution of potassium hydroxide (1 g.) in water (4 c.c.) for 3 hrs. gave rise to 2 : 4 : 5-trimethoxyphenylacetic acid, which separated from water as the hydrate in needles, m. p. 81°. Dried in a vacuum over phosphoric oxide, the anhydrous material had m. p. 106° (La Forge and co-workers, *J. Amer. Chem. Soc.*, 1931, **53**, 4402, and Takei and co-workers, *loc. cit.*, record m. p. 83° and 87° respectively).

Solution of the crude oxime in boiling water was accompanied by decomposition, and the product which separated on cooling consisted mainly of 2 : 4 : 5-trimethoxyphenylacetonitrile, m. p. and mixed m. p. 85° after five recrystallisations (Found : C, 63·8; H, 6·2; N, 6·7%).

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