

406. *Constituents of the Bark of Zanthoxylum americanum (Mill).*
Part II. Xanthyletin.

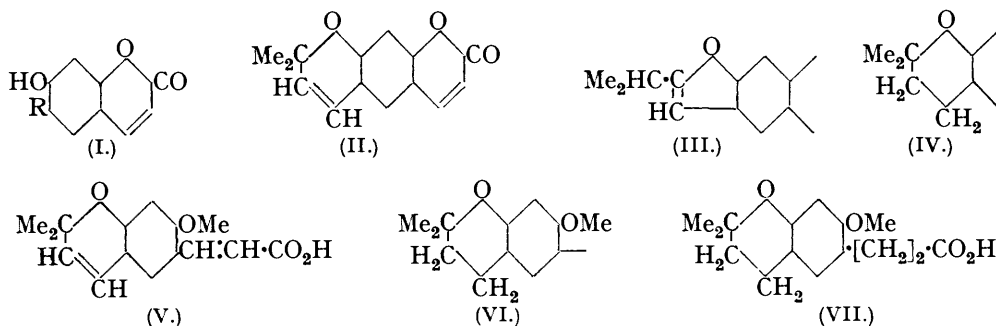
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IN Part I (this vol., p. 627) it was observed that the main difficulty encountered in the preparation of pure xanthoxyletin was due to the presence (in smaller amount) of another substance having approximately the same solubilities. This compound, which we have named *xanthyletin*, was first isolated by hand from mixtures of comparatively large crystals obtained on concentration of some alcoholic residues, but was subsequently observed to separate from several of the filtrates during the purification of xanthoxyletin. So far the isolation of the pure material has been to some extent fortuitous, because when, as often happens, the crude solid from the alcoholic filtrates contains a considerable proportion of xanthoxyletin, purification by fractional crystallisation is extremely tedious and uneconomical. This is due apparently to the tendency of the two compounds to form a mixed crystal melting at about 100—105°. Fortunately sufficient xanthyletin has been collected to enable us to investigate its composition.

Xanthyletin, which is devoid of hydroxyl, methoxyl, or reactive carbonyl groups and has the empirical formula $C_{14}H_{12}O_3$ corresponding to a demethoxyxanthoxyletin, closely resembles xanthoxyletin in chemical properties and consequently the investigation of its structure has followed the lines adopted for the latter compound. The behaviour of the substance with alcoholic sodium hydroxide is identical with that of xanthoxyletin, indicating the presence of an α -pyrone system, and on fission with boiling 25% aqueous sodium hydroxide it yields acetone and resorcinol. With bromine water and with aqueous potassium permanganate xanthyletin behaves as an unsaturated compound, and on catalytic hydrogenation it forms a *dihydro*-derivative. By means of methyl sulphate and aqueous sodium hydroxide according to Canter and Robertson's procedure (J., 1931, 1875) xanthyletin gave rise to *O-methylxanthyletinic acid*, and dihydroxanthyletin to *O-methyldihydroxanthyletinic acid*; on catalytic hydrogenation both acids yield the same *O-methyltetrahydroxanthyletinic acid*.

Ozonolysis of xanthyletin was accompanied by the loss of four atoms of carbon and furnished a product, $C_{10}H_6O_4$, which had the properties of an *o*-hydroxy-aldehyde, giving a ferric reaction and forming a *phenylhydrazone*, and on catalytic reduction gave rise to a phenolic deoxy-derivative, $C_{10}H_8O_3$, devoid of aldehydic properties. By analogy with *apoxanthoxyletin* (Part I, *loc. cit.*) it seemed likely that the compound $C_{10}H_6O_4$ was either 7-hydroxy-6-formyl- (I, R = CHO), 7-hydroxy-8 formyl-, or 5-hydroxy-6-formyl-coumarin and consequently that the reduction product was (I, R = Me), 7-hydroxy-8-methyl-, or 5-hydroxy-6-methyl-coumarin. Comparison of the properties of the substance $C_{10}H_6O_4$ with those of Späth and Pailer's 7-hydroxy-8-formylcoumarin (*Ber.*, 1935, 68, 940) showed that the two compounds were not identical, but it was found that the deoxy-compound $C_{10}H_8O_3$ was identical with *7-hydroxy-6-methylcoumarin* (I, R = Me) synthesised from 2:4-dihydroxy-5-methylbenzaldehyde. Therefore the compound $C_{10}H_6O_4$ is *7-hydroxy-6-formylcoumarin* (I, R = CHO).

Application of the arguments employed in the deduction of two possible structures for xanthoxyletin (Part I, *loc. cit.*) to the foregoing experimental results * leads to the conclusion that xanthyletin is represented by either (II) or (III) and, since it has recently been shown



in these laboratories (private communication from Mr. T. S. Subramanian) that xanthoxyletin is a 2:2-dimethylchromeno- α -pyrone, therefore it is reasonably certain that xanthyletin is represented by the structure (II). Consequently dihydroxanthyletin, *O*-methylxanthyletinic acid, *O*-methyldihydroxanthyletinic acid, and *O*-methyltetrahydroxanthyletinic acid have formulæ (IV), (V), (VI), and (VII) respectively.

EXPERIMENTAL.

Xanthyletin.—On being kept, some of the alcoholic liquors left from the purification of xanthoxyletin deposited crystals of *xanthyletin* contaminated only by small amounts of xanthoxyletin. This material was extracted once with boiling light petroleum (b. p. 60–80°), the extract discarded, and the residue repeatedly crystallised from 95% alcohol, being finally obtained in colourless or almost colourless, comparatively large, flat prisms, m. p. 128–128.5°. For analysis the compound was recrystallised from light petroleum (b. p. 80–100°), in which it is sparingly soluble, forming colourless, elongated, flat prisms (Found: C, 73.6; H, 5.2; *M*, 219, 213. $C_{14}H_{12}O_3$ requires C, 73.7; H, 5.3%; *M*, 228). The solubilities of this substance in the usual organic solvents are almost identical with those of xanthoxyletin. A mixture of approximately equal parts of the two compounds melted at 100–105°.

In some cases where large crystals were deposited by the mother-liquors from xanthoxyletin it was possible to separate the two compounds manually, a procedure which was considerably assisted by the tendency of xanthyletin to separate from these concentrates in yellow or pale yellow crystals. Purification of the coloured material finally gave a colourless product.

So far it has not been possible to estimate accurately the total amounts of xanthyletin and xanthoxyletin present in the bark because a complete separation of all the residues from any particular batch of bark has not been effected.

Xanthyletin readily decolorises aqueous potassium permanganate and bromine water and forms an orange-red solution in concentrated sulphuric acid which becomes red and then dark brown on warming, identical with that obtained from xanthoxyletin. Dilution of this solution with water, however, gives a pale yellow liquid which exhibits a strong violet fluorescence in sunlight; a similar solution prepared from xanthoxyletin exhibits only a faint fluorescence under the same conditions. Xanthyletin does not form acyl derivatives and does not react with semicarbazide acetate or phenylhydrazine.

Dihydroxanthyletin.—Xanthyletin (1 g.), dissolved in alcohol (150 c.c.) containing palladium chloride (0.05 g.), rapidly absorbed hydrogen (approx. 1 mol.) at atmospheric pressure. On concentration and subsequent dilution with water the filtered alcoholic solution deposited the almost pure *dihydro*-derivative, which separated from light petroleum (b. p. 60–80°) in colourless needles (0.7 g.), m. p. 124–125° (Found: C, 73.1; H, 6.1; *M*, 225, 224. $C_{14}H_{14}O_3$ requires C, 73.1; H, 6.1%; *M*, 230). This substance is readily soluble in alcohol and sparingly soluble in hot water, from which it separates on cooling.

O-Methylxanthyletinic acid was prepared from xanthyletin (3 g.) by means of methyl sulphate

* The degradation of xanthyletin to α -hydroxyisobutyric acid has not been carried out, but the production of acetone by hydrolytic fission is considered sufficient to indicate that the C_5 residue has the isoprene skeleton.

(100 c.c.) and 20% aqueous sodium hydroxide according to the method employed for the preparation of *O*-methylxanthoxyletinic acid (Part I, *loc. cit.*) and purified by crystallisation (3 times) from a small volume of methyl alcohol and then from 50% methyl alcohol, forming elongated, pale greenish-yellow prisms, m. p. 193—194° (decomp.) after sintering at 188°, readily soluble in alcohol or warm benzene [Found: C, 69.2; H, 6.3; OMe, 13.0. $C_{14}H_{13}O_3(OMe)$ requires C, 69.2; H, 6.2; OMe, 11.9%]. The preparation of this compound did not appear to proceed so smoothly as that of *O*-methylxanthoxyletinic acid and the crude product was accompanied by a considerable amount of resinous matter.

O-Methyldihydroxanthoxyletinic Acid.—Prepared from dihydroxanthyletin by the aforementioned procedure, this acid separated from benzene–light petroleum (b. p. 60—80°) and then from dilute methyl alcohol (charcoal) in colourless needles, m. p. 141—142° (Found: C, 68.6; H, 7.0. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%). It is readily soluble in alcohol, acetic acid, or benzene.

[With T. S. SUBRAMANIAM]. *O*-Methyltetrahydroxanthyletinic Acid.—Hydrogen (2 mols.) was rapidly absorbed (3 minutes) by *O*-methylxanthyletinic acid (0.2 g.) in acetic acid (15 c.c.) containing activated charcoal (0.5 g.) and aqueous palladium chloride (0.5 c.c. of a 10% solution). The reaction mixture was filtered, the charcoal washed with warm acetic acid, the combined filtrate and washings evaporated in a vacuum, and the residual oil triturated with water (10 c.c.). Crystallisation of the resulting solid from light petroleum (b. p. 60—80°) gave the acid in colourless flat prisms (0.13 g.), m. p. 99—100° (Found: C, 68.2; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%).

Hydrogenation of *O*-methyldihydroxanthyletinic acid (0.2 g.) under the same conditions gave rise to the same acid, m. p. and mixed m. p. 99—100° (Found: C, 68.5; H, 7.7%).

Hydrolytic Fission of Xanthyletin.—25% Aqueous sodium hydroxide (100 c.c.) containing well-powdered xanthyletin (3 g.) was refluxed for 1 hour; the solid dissolved in $\frac{1}{2}$ — $\frac{3}{4}$ hour, forming a dark brown solution, which was then distilled with the gradual addition of water to keep the volume of the reaction mixture constant. The distillate (200 c.c.) collected in the course of 2½ hours gave, on treatment with 2:4-dinitrophenylhydrazine hydrochloride in hydrochloric acid, an orange precipitate (0.8 g.), which crystallised from a little warm alcohol in orange-red needles, m. p. about 105°. Repeated crystallisation of this material from 50% acetic acid, alcohol, methyl alcohol, and finally alcohol gave acetone-2:4-dinitrophenylhydrazone, m. p. 126°, undepressed by admixture with an authentic specimen, m. p. 128° (Found: C, 45.5; H, 4.5. Calc. for $C_9H_{10}O_4N_4$: C, 45.4; H, 4.2%).

The cooled alkaline liquor remaining in the distilling flask was acidified with hydrochloric acid (Congo-red) and extracted several times with ether, the combined extracts were evaporated, the residue dissolved in a little warm water, and the solution filtered to remove a small amount of solid. Extraction of the acidified aqueous filtrate with ether gave resorcinol, which was purified by crystallisation from benzene, followed by sublimation in a vacuum, forming the characteristic sublimate, m. p. 108—109°. Mixed with an authentic specimen, m. p. 110°, it melted at 109—110°. A mixture of the product once recrystallised from benzene with an excess of *p*-nitrobenzoyl chloride in a little dry pyridine was kept at 60° for 15 minutes and then at room temperature for 2 days. The solid precipitated with excess of dilute hydrochloric acid was washed with water and extracted with aqueous sodium bicarbonate, leaving a residue of the *di-p*-nitrobenzoate of resorcinol, which separated from benzene–alcohol and then acetic acid–alcohol in colourless plates or needles, m. p. 184—185°, identical in every way with an authentic specimen (Found: C, 59.0; H, 2.9%). The authentic specimen was prepared from pure resorcinol in the same manner, m. p. 184—185° after purification (Found: C, 58.9; H, 3.0; N, 6.9. $C_{20}H_{12}O_8N_2$ requires C, 58.8; H, 2.9; N, 6.9%).

7-Hydroxy-6-formylcoumarin (I, R = CHO).—A slow stream of ozone and oxygen was passed into a solution of xanthyletin (1 g.) in dry chloroform (125 c.c.) for 1½ hours and after evaporation of the solvent the product was left in contact with water (50 c.c.) at room temperature for 24 hours. The mixture was then warmed on the water-bath for $\frac{1}{4}$ hour and, after cooling, the solid was collected and well ground with 1% aqueous sodium hydroxide (20 c.c.). Acidification of the filtered alkaline extract with hydrochloric acid gave the *hydroxyformylcoumarin*, which formed tiny prisms (0.2—0.3 g.), m. p. 253° (decomp.), from acetic acid (charcoal) (Found: C, 63.0; H, 3.4. $C_{10}H_8O_4$ requires C, 63.2; H, 3.2%). This compound is soluble in alcohol or ethyl acetate and insoluble in carbon tetrachloride, forms a yellow solution in aqueous sodium hydroxide, and gives a deep port-wine coloration with alcoholic ferric chloride. It gave a faint coloration with Schiff's reagent, a silver mirror with ammoniacal silver nitrate at 60°, and a 2:4-dinitrophenylhydrazone.

On being warmed with excess of phenylhydrazine in acetic acid, the hydroxyformylcoumarin yielded a *phenylhydrazone*, which formed yellow prisms, m. p. 255—257° (decomp.), from alcohol (Found : N, 10.0. $C_{18}H_{12}O_3N_2$ requires N, 10.0%).

7-Hydroxy-6-methylcoumarin (I, R = Me).—(A) A mixture of 2 : 4-dihydroxy-5-methylbenzaldehyde (Gattermann, *Annalen*, 1907, **357**, 340) (2 g.), sodium acetate (2 g.), and acetic anhydride (20 c.c.) was kept at 180—185° for 18 hours. On isolation in the usual manner the *acetate* of the coumarin separated from a small volume of alcohol in long colourless needles, m. p. 145—146° (Found : C, 65.8; H, 4.8. $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.6%). This material, dissolved in the minimum amount of alcohol, was deacetylated by warm 8% aqueous sodium hydroxide in 5 minutes. Acidification of the dark solution gave the *coumarin*, which, after having been crystallised from dilute alcohol (charcoal) and sublimed in a high vacuum, separated from dilute alcohol in masses of long needles, m. p. 248° (Found : C, 68.3; H, 4.7. $C_{10}H_8O_3$ requires C, 68.2; H, 4.6%). This compound, which has a negative ferric reaction and is readily soluble in methyl alcohol and sparingly soluble in water, exhibits an intense blue fluorescence in aqueous alcohol. A cleaner product was subsequently obtained by deacetylation with a boiling mixture of alcohol and concentrated hydrochloric acid.

(B) 7-Hydroxy-6-formylcoumarin (0.3 g.), dissolved in acetic acid (150 c.c.), was reduced with hydrogen (approx. 2 mols. absorbed) and a palladium-charcoal catalyst (from 0.1 g. of palladium and 1.2 g. of activated charcoal). Evaporation of the filtered solution in a vacuum left 7-hydroxy-6-methylcoumarin, which was purified by sublimation in a high vacuum and crystallisation from dilute alcohol, forming characteristic needles, m. p. 248°, undepressed by admixture with the synthetical compound (Found : C, 68.5; H, 4.7%). The solubilities and fluorescence of this material were identical with those of the authentic specimen.

In another experiment the coumarin was isolated with ether from the filtered reaction mixture which had been almost neutralised with aqueous sodium bicarbonate.

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