320. *Constituents of the Bark of* Zanthoxylum americanum (*Mill*). *Part V. The Structure of* allo*Xanthoxyletin.*

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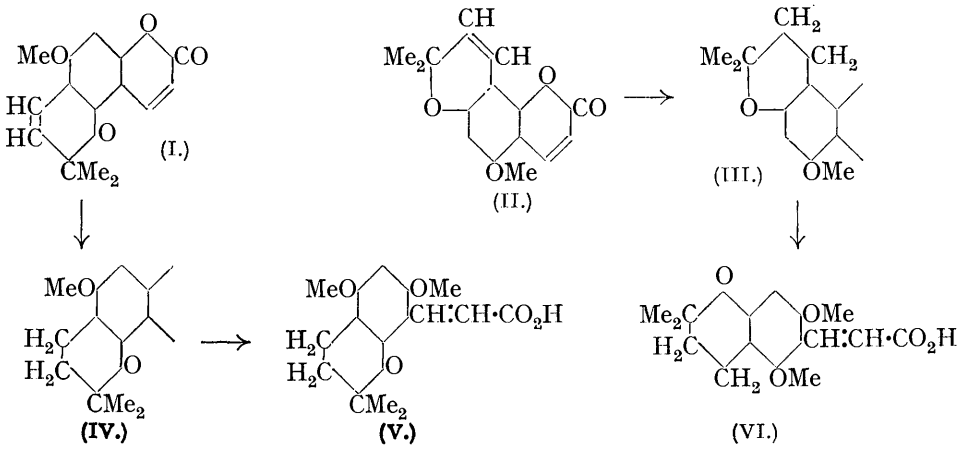
The structure of the new constituent *allo*xanthoxyletin, $C_{15}H_{14}O_4$, has been determined by application of the methods employed in the case of xanthoxyletin, with which it is isomeric. The behaviour of the compound on hydrolytic fission indicates that it is a 2 : 2-dimethyl-Δ^3-chromeno-α-pyrone derived from phloroglucinol monomethyl ether, and this view is supported by ozonolysis and hydrogenation experiments. In confirmation of the structures deduced for *allo*xanthoxyletin and its derivatives, a complete synthesis of dihydro*allo*xanthoxyletin from 7-hydroxy-5-methoxy-2 : 2-dimethylchroman is described.

Remarks on the absolute orientation of the monomethyl ethers of 5 : 7-dihydroxy-2 : 2-dimethylchroman and on the supposed occurrence of a furanocoumarin in the bark are included.

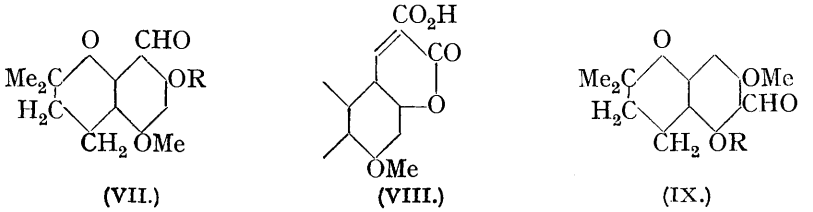
THE dark green oil, obtained in considerable quantities in the course of the isolation of xanthoxyletin (Part I, J., 1936, 627) by digesting the crude ethereal extract of the bark with light petroleum, did not yield solid material on being kept or on treatment with solvents, but on distillation in a high vacuum gave a fraction from which a small amount of a new compound, m. p. 115·5°, has been isolated. Occurring only in small quantities in the bark, this product, $C_{15}H_{14}O_4$, which is isomeric with xanthoxyletin and has been named allo*xanthoxyletin*, was separated in the first instance manually from mixtures of comparatively large crystals, and subsequently by a somewhat lengthy fractional crystallisation of the solid obtained on treating the distillate with a little light petroleum. It is a neutral substance devoid of hydroxyl or active carbonyl groups, contains one methoxyl group, and closely resembles xanthoxyletin in chemical properties. The behaviour of the compound with alcoholic sodium hydroxide is identical with that of the latter substance, indicating the presence of an α-pyrone system, and on hydrolytic fission with hot concentrated aqueous potassium hydroxide it gave rise to acetone and phloroglucinol monomethyl ether which, although obtained in insufficient quantity for purification by the usual methods, was recognised by the formation of the di-*p*-nitrobenzoate (compare Part I, *loc. cit.*). By analogy with xanthyletin (Part IV, preceding paper) and xanthoxyletin (Part III, this vol., p. 286), this result clearly indicates that *allo*xanthoxyletin is a 2 : 2-dimethyl-Δ^3-chromen derived from phloroglucinol monomethyl ether. With bromine water and dilute aqueous potassium permanganate *allo*xanthoxyletin behaves as a highly unsaturated

substance, and on hydrogenation with the aid of a palladium–charcoal catalyst gave rise to a *dihydro*-derivative. By the standard procedure this substance was converted into O-*methyldihydro*allo*xanthoxyletinic acid*, which was readily hydrogenated, yielding O-*methyltetrahydro*allo*xanthoxyletinic acid*.

On the basis of the foregoing analytical results, it appeared reasonably certain that *allo*xanthoxyletin is a 2 : 2-dimethyl-Δ^3-chromeno-α-pyrone which, in view of the established structure of xanthoxyletin (Part III, *loc. cit.*), must be represented by either of the angular formulæ, (I) or (II).



Further, since in xanthoxyletin the double bond in the chromen system is preferentially attacked by hydrogen in the presence of a catalyst, therefore by analogy dihydro*allo*-xanthoxyletin has either formula (III) or (IV), of which (III) is excluded because a compound having this structure would on simultaneous hydrolysis and methylation give rise to *O*-methyldihydroxanthoxyletinic acid (VI) (Part I, *loc. cit.*), whereas *O*-methyldihydro-*allo*xanthoxyletinic acid is isomeric with and not identical with (VI). Consequently, *O*-methyldihydro*allo*xanthoxyletinic acid must have formula (V), and hence *allo*xanthoxyletin and its dihydro-derivative are represented by the expressions (I) and (IV) respectively. In support of these conclusions it has been found that ozonolysis of dihydro*allo*xanthoxyletin gave rise to an *o*-hydroxyaldehyde which, since it was identical with a synthetical specimen obtained by the application of the Gattermann reaction to 7-hydroxy-5-methoxy-2 : 2-dimethylchroman, and since both natural and synthetical products gave rise to 5 : 7-dimethoxy-8-formyl-2 : 2-dimethylchroman (VII, R = Me), must be *7-hydroxy-5-methoxy-8-formyl-2 : 2-dimethylchroman* (VII, R = H).



The foregoing structures proposed for *allo*xanthoxyletin and its derivatives have been conclusively confirmed by the complete synthesis of dihydro*allo*xanthoxyletin. Interaction of the synthetical aldehyde (VII, R = H) with cyanoacetic acid in aqueous sodium hydroxide, and subsequent hydrolysis of the resulting salicylidenecyanoacetic acid, furnished the *coumarin-3-carboxylic acid* (VIII), which on decarboxylation gave rise to dihydro*allo*xanthoxyletin, identical in every way with the natural product.

It may be noted that the conversion of 7-hydroxy-5-methoxy-2 : 2-dimethylchroman into the 8-formyl derivative (VII, R = H) clearly serves to confirm the orientation of

the former compound and to distinguish it from the isomeric 5-hydroxy-7-methoxy-2 : 2-dimethylchroman (George and Robertson, this vol., p. 1539). The latter substance could give rise to two aldehydes by Gattermann's method, *viz.*, 5-hydroxy-7-methoxy-6-formyl- (IX, R = H) and -8-formyl-2 : 2-dimethylchroman, of which the former would yield (IX, R = Me) (Part III, this vol., p. 286) on methylation, whereas the latter, although it would furnish (VII, R = Me), could not be converted directly into a coumarin.

Experimental.

allo*Xanthoxyletin*.—(A) Evaporation of the solvent from the light petroleum liquors obtained in the course of the isolation of xanthoxyletin (Part I, *loc. cit.*) left a viscous dark green oil which on distillation in a high vacuum gave an almost colourless fraction, b. p. 180—210°/0·04 mm. This material (50 g., from 200 g. of crude oil), which solidified at approximately 0°, was mixed with light petroleum (b. p. 60—80°) and on slow evaporation of the solvent the solution gradually deposited a crystalline product (2 g.) during 7 days. On isolation, the solid was washed with light petroleum (b. p. 40—60°) (20 c.c.) and then dissolved in boiling light petroleum (b. p. 60—80°) (30 c.c.), the solution was cleared (charcoal), one hour later the liquor was decanted, and the residual crystals were washed with fresh solvent (3—4 c.c.). On being kept at room temperature, the combined light petroleum liquor and washings, which had been warmed and allowed to cool, gradually deposited allo*xanthoxyletin* in pale yellow, elongated, thick prisms (0·2 g.), which on repeated crystallisation from light petroleum (b. p. 60—80°) was obtained in colourless, elongated prisms, m. p. 115·5°, easily soluble in benzene or ether and sparingly soluble in cold alcohol [Found : C, 69·8; H, 5·4; OMe, 13·0; *M*, 270. $C_{14}H_{11}O_3$(OMe) requires C, 69·8; H, 5·4; OMe, 12·0%; *M*, 258]. This compound, which appears to be slightly more soluble in organic solvents than xanthoxyletin or xanthyletin, does not give a ferric reaction, and is insoluble in aqueous sodium hydroxide. The orange solution of the substance in concentrated sulphuric acid changes to orange-red in about a minute, and on being warmed on the water-bath becomes bright red and then colourless (compare xanthoxyletin; Part I, *loc. cit.*).

(B) *allo*Xanthoxyletin can be isolated from the distillate by the following alternative procedure. A solution of the oil (100 g.) in absolute alcohol (200 c.c.) was mixed with 60% aqueous potassium hydroxide solution, heated on the steam-bath for 10 minutes, diluted with water (600 c.c.), and extracted three times with ether. The alkaline aqueous liquors were then cleared with charcoal, filtered, and saturated with carbon dioxide, and the colourless crystalline precipitate which separated during 5 days was collected, washed, and dried. Fractional crystallisation of this material from warm light petroleum (b. p. 60—80°) finally gave *allo*-xanthoxyletin, m. p. 115·5°, identical with that obtained by method (A).

(C) Evaporation of the combined liquors obtained by repeated crystallisation of the crude mixture of chromenocoumarins (20 g.) (Part I, *loc. cit.*), consisting mainly of xanthoxyletin and xanthyletin, from much light petroleum, (b. p. 80—100°) gave a product from which *allo*-xanthoxyletin (0·1 g.) was obtained by fractional crystallisation from light petroleum (b. p. 60—80°).

Hydrolytic Fission of allo*Xanthoxyletin*.—Well-powdered *allo*xanthoxyletin (0·5 g.) was boiled with 25% aqueous sodium hydroxide (50 c.c.) for 30 minutes (the solid dissolved in the course of about 5 minutes), and the pale brown solution, which had gradually become deep reddish-brown, was then distilled with the frequent addition of water so as to keep the volume of the alkaline liquor constant. Treatment of the distillate (100 c.c.) with an excess of 2 : 4-dinitrophenylhydrazine hydrochloride in hydrochloric acid gave an orange-yellow precipitate of acetone-2 : 4-dinitrophenylhydrazone (0·2 g.), which was purified by repeated crystallisation from dilute alcohol; m. p. 125° undepressed by admixture with an authentic specimen, m. p. 127° (Found : N, 23·2. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%).

The cooled alkaline solution remaining in the distillation flask was acidified (Congo-red) with hydrochloric acid, saturated with ammonium sulphate, and repeatedly extracted with ether. Evaporation of the combined dried extracts left a dark brown viscous residue, from which by distillation in a high vacuum a small amount of a pale yellow distillate, m. p. about 65°, was obtained, giving a negative reaction with alcoholic ferric chloride and a pale blue coloration with the aqueous reagent, identical with the behaviour of phloroglucinol monomethyl ether. Interaction of this product with excess of *p*-nitrobenzoyl chloride in the presence of pyridine gave rise to the di-*p*-nitrobenzoate of phloroglucinol monomethyl ether, m. p. and mixed m. p. 199—200° (Found : C, 57·6; H, 3·3; N, 6·3. Calc. for $C_{21}H_{14}O_9N_2$: C, 57·5; H, 3·2; N, 6·4%).

*Dihydro*allo*xanthoxyletin* (IV).—Hydrogen (approx. 1 mol.) was rapidly absorbed at atmospheric pressure by *allo*xanthoxyletin (0·5 g.), dissolved in acetic acid (30 c.c.) containing a palladium–charcoal catalyst (from 0·5 g. of charcoal and 5 c.c. of 1% aqueous palladium chloride), and after the removal of the catalyst and the evaporation of the solvent in a vacuum, the *product* separated from light petroleum (b. p. 80—100°) in thick colourless prisms (0·4 g.), m. p. 155° after sintering at 153° (Found: C, 69·3; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). This substance is moderately soluble in alcohol or benzene and readily soluble in chloroform.

O-*Methyldihydro*allo*xanthoxyletinic Acid.*—The foregoing compound (1 g.) was hydrolysed, and the resulting cinnamic acid methylated with excess of methyl sulphate and 20% aqueous sodium hydroxide by the standard procedure used for the preparation of xanthoxyletinic acid (Part I, *loc. cit.*). A solution of the product in a mixture of alcohol (70 c.c.) and water (30 c.c.), containing sodium hydroxide (6 g.), was kept at 80° for 10 minutes, diluted with water (400 c.c.), and acidified with hydrochloric acid. The *acid*, which had separated in colourless needles, was purified by means of aqueous sodium bicarbonate and then by recrystallisation from benzene–light petroleum (b. p. 60—80°), forming slender needles (0·7 g.), m. p. 178° (decomp.), having a negative ferric reaction [Found: C, 65·9; H, 6·8; OMe, 22·0. $C_{14}H_{14}O_3(OMe)_2$ requires C, 65·8; H, 6·9; OMe, 21·2%].

In the course of the purification of this acid a trace of an acidic compound, m. p. 205°, was isolated which gave a red ferric reaction.

Hydrogenation of *O*-methyldihydro*iso*xanthoxyletinic acid (0·15 g.) in acetic acid (20 c.c.) with a palladium–charcoal catalyst afforded O-*methyltetrahydro*allo*xanthoxyletinic acid*, which separated from light petroleum (b. p. 60—80°) in short colourless prisms (0·1 g.), m. p. 108·5°, readily soluble in aqueous sodium bicarbonate, benzene or alcohol [Found: C, 65·2; H, 7·4; OMe, 20·7. $C_{14}H_{16}O_3(OMe)_2$ requires C, 65·3; H, 7·5; OMe, 21·1%].

7-*Hydroxy*-5-*methoxy*-8-*formyl*-2 : 2-*dimethylchroman* (VII, R = H).—(A) A stream of ozone and oxygen (rate, approx. 100 c.c./min.) was led into a solution of dihydro*allo*xanthoxyletin (1 g.) in dry chloroform (50 c.c.) maintained at 0° for 2 hours; the colourless solution gradually became pale yellow. After the removal of the solvent in a vacuum the residue was digested with water (20 c.c.) at room temperature for 12 hours and then on the water-bath for 10 minutes, and the oily product isolated with ether. A solution of this material in ether (30 c.c.) was extracted with 2% aqueous sodium hydroxide (6 × 5 c.c.) and, on being saturated with carbon dioxide, the combined alkaline extracts gradually deposited the *aldehydo-chroman* as a pale yellow precipitate, which was collected, washed, and recrystallised from 50% alcohol, forming colourless slender needles (0·25 g.), m. p. 90° [Found: C, 66·1; H, 6·9; OMe, 13·3. $C_{12}H_{13}O_3(OMe)$ requires C, 66·1; H, 6·8; OMe, 13·1%]. The pure material, which is sparingly soluble in dilute aqueous sodium hydroxide, gives a wine-red coloration with alcoholic ferric chloride, and reduces warm Fehling's solution and ammoniacal silver nitrate. It separates from hot light petroleum (b. p. 60—80°) in clusters of colourless prisms.

(B) A slow stream of hydrogen chloride was led into a solution of 7-hydroxy-5-methoxy-2 : 2-dimethylchroman (George and Robertson, *loc. cit.*) (0·8 g.) in absolute ether (20 c.c.), containing hydrogen cyanide (1·2 c.c.), for 3 hours and the mixture kept for 12 hours. After the addition of more ether (200 c.c.) the reaction mixture was kept for 2 hours to allow the fine precipitate to coagulate, the solvent decanted, and the aldimine hydrochloride collected, washed with ether, and hydrolysed with water (30 c.c.) on the steam-bath for 30 minutes. The pale yellow aldehydo-chroman was collected, washed, dried, and crystallised from light petroleum (b. p. 60—80°), forming thick colourless prisms (0·6 g.), m. p. 90°, identical in every way with the compound obtained from dihydro*allo*xanthoxyletin (Found: C, 66·2; H, 6·8; OMe, 12·8%). Attempts to prove the presence of an expected isomeric product, 7-hydroxy-5-methoxy-6-formyl-2 : 2-dimethylchroman, in the residues left on purification of this compound were unsuccessful, but it must be noted that the amounts of material available were too small to enable us to certify the complete absence of the isomeride.

5 : 7-*Dimethoxy*-8-*formyl*-2 : 2-*dimethylchroman* (VII, R = Me).—On being distilled in a high vacuum, the product formed by the application of the Gattermann reaction to 5 : 7-dimethoxy-2 : 2-dimethylchroman (1·0 g.) (Part III, *loc. cit.*) was obtained as a thick oil which gradually solidified and then separated from light petroleum (b. p. 60—80°) in clusters of colourless thick prisms (0·4 g.), m. p. 107° [Found: C, 67·3; H, 7·2; OMe, 25·0. $C_{12}H_{12}O_2(OMe)_2$ requires C, 67·2; H, 7·2; OMe, 24·8%].

Methylation of 7-hydroxy-5-methoxy-8-formyl-2 : 2-dimethylchroman (0·2 g.), obtained from dihydro*allo*xanthoxyletin, with methyl iodide (2 c.c.) and potassium carbonate (2 g.)

for 3 hours gave rise to 5 : 7-dimethoxy-8-formyl-2 : 2-dimethylchroman (0·15 g.), m. p. 107°, after purification, identical in every way with a synthetical specimen (Found: C, 67·2; H, 7·3; OMe, 24·7%). The semicarbazone separated from hot alcohol in slender needles, m. p. 217—218°, undepressed by admixture with an authentic specimen (Part III, *loc. cit.*).

*Dihydro*allo*xanthoxyletin-3-carboxylic Acid* (VIII).—A mixture of synthetical 7-hydroxy-5-methoxy-8-formyl-2 : 2-dimethylchroman (0·3 g., well powdered), 20% aqueous sodium hydroxide (7 c.c.), and cyanoacetic acid (6 c.c. of a solution prepared according to Phelps and Tillotson, *Amer. J. Sci.*, 1908, **26**, 267) was agitated for 24 hours. The filtered bright yellow solution was acidified (Congo-red) with hydrochloric acid, and the canary-yellow precipitate collected, washed with water, and boiled with 4% hydrochloric acid (50 c.c.) for ½ hour. The solid dissolved in 5 minutes and was gradually replaced by a pale yellow crystalline precipitate of the *acid* (VIII) (0·35 g.), which formed slender yellow needles (0·3 g.), m. p. 240° (decomp.), from warm 50% alcohol, sparingly soluble in benzene or light petroleum, and readily soluble in aqueous sodium bicarbonate (Found: C, 63·1; H, 5·4. $C_{16}H_{16}O_6$ requires C, 63·1; H, 5·3%).

This acid (0·2 g.) was boiled with quinoline (4 c.c.), containing Kahlbaum's "Naturkupfer" (0·5 g.), for 10 minutes, the reaction mixture treated with chloroform (200 c.c.), and the filtered solution repeatedly extracted with 8% hydrochloric acid to remove the quinoline, washed with water, dried, and evaporated. The residue was triturated with aqueous sodium bicarbonate to remove traces of acidic material, and on being sublimed in a high vacuum (110°/0·03 mm.) the resulting dihydro*allo*xanthoxyletin formed small thick prisms (0·1 g.). Purified from light petroleum, it had m. p. and mixed m. p. 155° after sintering at 152°, and was identical in every way with a natural specimen (Found: C, 69·3; H, 6·3%).

Appendix.

In their memoir on the constituents of *Zanthoxylum fraxineum* (Wild) [*Zanthoxylum americanum* (Mill)], Dieterle and Kruta (*Arch. Pharm.*, 1937, **275**, 475) mention the presence of a furanocoumarin, m. p. 99—100°, but, although our investigation of the constituents of this bark is not yet completed, we have been unable to detect the presence of a pure compound answering to this description. In view of the isolation of *allo*xanthoxyletin, it is conceivable that small amounts of the chromeno-α-pyrone (II), as well as of the analogous isomeride of xanthyletin, may be present, and in our search for compounds of this type we have examined in some detail the mixture, m. p. about 100—105°, which tends to separate in the course of the isolation of xanthoxyletin and xanthyletin (Part II, J., 1936, 1828). By a series of somewhat lengthy fractional crystallisations from alcohol and inoculating the liquors alternately with crystals of xanthoxyletin and of xanthyletin, we have been able to resolve this product into xanthyletin and xanthoxyletin in addition to traces of *allo*-xanthoxyletin (see present paper).

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