319. *Constituents of the Bark of* Zanthoxylum americanum (*Mill*). *Part IV. The Constitution of Xanthyletin.*

By (Miss) Janet C. Bell, Walter Bridge, and Alexander Robertson.

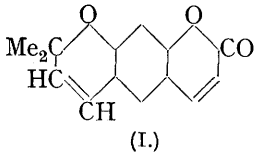
The present investigation, which is a continuation of that described in Part II (J., 1936, 1828), was undertaken to obtain confirmatory evidence for the structures suggested for xanthoxyletin and its derivatives.

The orientation of cresorcylaldehyde and the ozonolysis and synthesis of dihydroxanthyletin are described. The results obtained, in conjunction with the analytical evidence described in Part II, serve to place the constitution of xanthyletin and its derivatives beyond doubt.

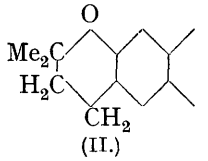
From the analytical evidence and the close similarity of the properties of xanthyletin and xanthoxyletin it was suggested in Part II (J., 1936, 1828) that the former compound is a chromeno-α-pyrone having the linear type of structure (I), and in the present memoir

conclusive analytical and synthetical evidence is described substantiating this expression in every detail. The evidence for this linear type of formula relies on the orientation of 7-hydroxy-6-methylcoumarin (Part II, *loc. cit.*) derived from the structure which Gattermann (*Annalen*, 1907, **357**, 340) proposed for cresorcylaldehyde but which had not been confirmed experimentally. The almost quantitative conversion of cresorcylaldehyde into *m*-xylorcin by Clemmensen's method of reduction, however, now serves to verify the orientation of this aldehyde and hence that of 7-hydroxy-6-methylcoumarin. On catalytic reduction, cresorcylaldehyde, unlike phloroglucinolaldehyde and its derivatives (J., 1936, 1837; this vol., p. 286), did not give satisfactory results and only small yields of *m*-xylorcin were obtained.

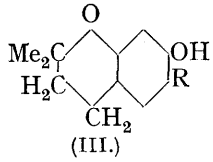
On ozonolysis, dihydroxanthyletin, which as indicated in Part II (*loc. cit.*) we believed to contain a double bond in the α-pyrone ring, gave rise to a product having the properties of an *o*-hydroxy-aldehyde, which, by analogy with the product obtained in a similar manner from dihydroxanthoxyletin (Part III, this vol., p. 286), was considered to be *7-hydroxy-6-formyl-2 : 2-dimethylchroman* (III, R = CHO). The nature of this compound, in which the position of the formyl group clearly follows from the linear structure established for xanthyletin, was confirmed by its synthesis from 7-hydroxy-2 : 2-dimethylchroman (III, R = H), and consequently dihydroxanthyletin is represented by the expression (II). In this connexion it may be noted that, when submitted to the Gattermann reaction, the chroman (III, R = H) behaves in a manner strictly analogous to cresorcin (cf. remarks on 5 : 7-dihydroxy-2 : 2-dimethylchroman; Part III, *loc. cit.*).



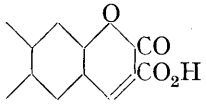
(I.)



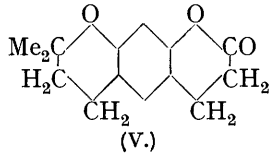
(II.)



(III.)



(IV.)



(V.)

The structure of dihydroxanthyletin (II) is confirmed by a complete synthesis of the compound from the synthetical aldehydo-chroman (III, R = CHO): Interaction of the latter compound with cyanoacetic acid in aqueous sodium hydroxide and subsequent hydrolysis of the resulting salicylidenecyanoacetic acid gave rise to the *coumarin-3-carboxylic acid* (IV), which on decarboxylation furnished dihydroxanthyletin, identical in every way with a natural specimen. This result also serves to substantiate the formulæ proposed in Part II (*loc. cit.*) for *O*-methyldihydro- and for *O*-methyltetrahydro-xanthyletinic acid, and clearly shows that in xanthyletin the C_5 unit is present in a 6-atom-ring system. Catalytic hydrogenation of the disodium derivative of xanthyletinic acid, and subsequent lactonisation of the resulting tetrahydroxanthyletinic acid, gave rise to an almost quantitative yield of *tetrahydroxanthyletin*, thus confirming the presence of two double bonds in xanthyletin indicated by the formation of *O*-methyltetrahydroxanthyletinic acid. Of the ethylenic linkages, one is embodied in the C_5 residue and is preferentially attacked by hydrogen in the presence of a catalyst and by ozone, and the other, less reactive, is present in the α-pyrone ring, and consequently xanthyletin must be a chromeno-α-pyrone represented by the structure (I). Hence the tetrahydro-derivative has formula (V), and the structure suggested for *O*-methylxanthyletinic acid in Part II (*loc. cit.*) is substantiated.

Experimental.

Orientation of 2 : 4-*Dihydroxy-5-methylbenzaldehyde.*—The cresorcin, m. p. 104—105°, employed for the preparation of this aldehyde, which was used in the synthetical experiments described in Part II (*loc. cit.*), was prepared by the reduction of resorcylaldehyde according to

the method of Clemmensen (*Ber.*, 1914, **47**, 62), who, however, gives m. p. 83—84° for the phenol. The m. p. of the cresorcin obtained by us was identical with that given by Wallach (*Ber.*, 1882, **15**, 2835) for material prepared by an independent method, and in view of this discrepancy the following experiments are described :—Pure resorcylaldehyde (10 g.), suspended in a little dilute hydrochloric acid, was added to a boiling mixture of 15% hydrochloric acid (120 c.c.) and alcohol (200 c.c.), containing amalgamated zinc dust (60 g.), during 1 hour, and after the addition of concentrated hydrochloric acid (15 c.c.) the mixture was refluxed for 2 hours. On isolation, the product had m. p. 88—89° after being once recrystallised from benzene, but on being purified by distillation in a vacuum, followed by repeated recrystallisation from benzene with or without sublimation in a vacuum, cresorcin, m. p. 104—105°, was finally obtained. This phenol having the same m. p. was also obtained when the reduction was effected with amalgamated zinc and 15% hydrochloric acid (8 hours), and it seems likely that the material described by Clemmensen as cresorcin was contaminated with small amounts of impurities encountered in these experiments and which are best removed by crystallisation from benzene.

Reduction of pure resorcylaldehyde (2 g.), dissolved in acetic acid (50 c.c.), with hydrogen (approx. 2 mols. absorbed) and a palladium–charcoal catalyst (from 5 g. of charcoal and 0·5 g. of palladium chloride) for 40 minutes gave an oily product from which a small amount of cresorcin, m. p. 106—107°, was obtained by crystallisation from benzene, followed by sublimation in a high vacuum. Mixed with material prepared by Clemmensen's procedure, it melted at 105—106°.

2 : 4-Dihydroxy-5-methylbenzaldehyde (5 g.), prepared from cresorcin, m. p. 104—105° (Gattermann, *Annalen*, 1907, **357**, 340), was reduced with boiling 15% hydrochloric acid and amalgamated zinc dust (30 g.) in the course of 3 hours, giving rise to *m*-xylorcin, m. p. 116—118°, after distillation in a vacuum. On being twice recrystallised from benzene, this compound had m. p. 124° and was identical in every way with an authentic specimen (Robertson and Robinson, J., 1927, 2196). *m*-Xylorcin was also obtained in small yield by the reduction of 2 : 4-dihydroxy-5-methylbenzaldehyde, dissolved in acetic acid, with hydrogen and a palladium–charcoal catalyst, and had m. p. and mixed m. p. 123° after being purified by sublimation in a vacuum, followed by recrystallisation from benzene.

7-Hydroxy-6-formyl-2 : 2-dimethylchroman (III, R = CHO).—(A) Interaction of 7-hydroxy-2 : 2-dimethylchroman (Robertson and co-workers, this vol., p. 1532) (3 g.), dissolved in ether (110 c.c.), with hydrogen cyanide (7 c.c.) in the presence of excess of hydrogen chloride for 48 hours afforded a crystalline aldimine which, after the addition of more ether (80 c.c.), was collected, washed several times with ether, and hydrolysed with water (100 c.c.) on the steam-bath for 20 minutes. From the resulting product, which was isolated with ether, the *aldehyde* was extracted by means of excess of warm light petroleum (b. p. 40—60°) and purified by recrystallisation from the same solvent, followed by sublimation (twice) in a high vacuum, being finally obtained in colourless prisms, m. p. 104° (Found : C, 69·9; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). With alcoholic ferric chloride the substance gave a brown-red coloration. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange-red, elongated, rectangular prisms, m. p. 302° (decomp.) (Found : N, 14·7. $C_{18}H_{18}O_6N_4$ requires N, 14·5%).

(B) A slow stream of ozone and oxygen was led into a solution of dihydroxanthyletin (*loc. cit.*) (1 g.) in dry chloroform (75 c.c.) for 1¾ hours, the solvent removed in a vacuum, and the residue hydrolysed with water (30 c.c.) at room temperature for 16 hours and then on the water-bath for 10—15 minutes. The resulting aldehyde was separated from a little unchanged dihydroxanthyletin with the aid of 1% aqueous sodium hydroxide, and crystallised from dilute alcohol or dilute acetic acid and then from light petroleum, forming colourless prisms, m. p. 103°, identical in every way with a synthetical specimen (Found : C, 69·8; H, 6·8%). The dinitrophenylhydrazone had m. p. 301—302° (decomp.) (Found : N, 14·3%).

Dihydroxanthyletin-3-carboxylic Acid (IV).—A solution of 7-hydroxy-6-formyl-2 : 2-dimethylchroman (1 g.) and cyanoacetic acid (4 c.c., of a solution prepared according to Phelps and Tillotson, *Amer. J. Sci.*, 1908, **26**, 267) in 20% aqueous sodium hydroxide (10 c.c.) was kept at room temperature for 24 hours and acidified (Congo-red) with dilute hydrochloric acid. On being boiled with 4% hydrochloric acid (60 c.c.) for ½ hour, the yellow precipitate of the salicylidenecyanoacetic acid gave rise to the insoluble *coumarin-3-carboxylic acid*, which formed slender straw-coloured prisms, m. p. 158—159°, from 50% alcohol (Found : C, 65·7; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%). An alcoholic solution of this compound exhibits a blue fluorescence.

Dihydroxanthyletin (II).—Decarboxylation of the foregoing acid (0·4 g.) was effected at 220° with the aid of copper-bronze in the course of 15 minutes, and the resulting dihydroxanthyletin

(0·25 g.) isolated from the reaction mixture by sublimation in a high vacuum at about 130°. Recrystallised from light petroleum (b. p. 60—80°), it formed colourless prisms, m. p. 125°, undepressed by admixture with a natural specimen (Found: C, 73·1; H, 6·2. Calc. for $C_{14}H_{14}O_3$: C, 73·0; H, 6·1%).

[With T. S. SUBRAMANIAM.] *Tetrahydroxanthyletin* (V).—20% Aqueous sodium hydroxide (2 c.c.) was added dropwise to xanthyletin (1 g.), dissolved in alcohol kept at 50°, the almost colourless solution was diluted with water (50 c.c.), and the disodium derivative of xanthyletinic acid was hydrogenated with an active palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 1 g. of charcoal) and hydrogen at atmospheric pressure (approx. 200 c.c. absorbed; theoretical for $\frac{=}{2}$, 205 c.c.) in the course of 1 hour. After the removal of the catalyst by filtration (wash with 20 c.c. of water), the solution was acidified (Congo-red) with 8% hydrochloric acid, and the colourless precipitate of tetrahydroxanthyletinic acid, m. p. 160° (efferv.), was collected, washed, and dried. On being kept at 180° for ½ hour, this compound was converted by loss of water into *tetrahydroxanthyletin*, which on being sublimed in a high vacuum was obtained in colourless rhombic prisms. Recrystallised from alcohol, it formed clusters of prisms, m. p. 156°, mixed m. p. with dihydroxanthyletin 115—117° (Found: C, 72·4; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

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