58. *Constituents of* Zanthoxylum americanum (*Mill*). *Part III. The Constitution of Xanthoxyletin.*

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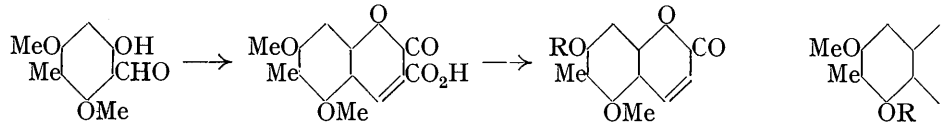
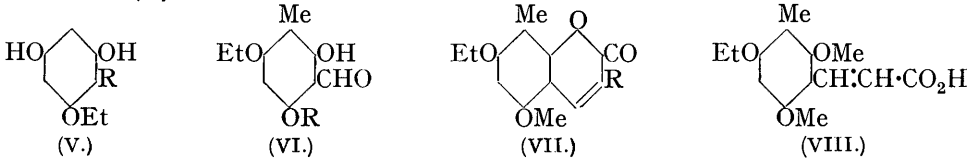
IN Part I (J., 1936, 627) it was clearly shown that *apo*xanthoxyletin was either 5-hydroxy-7-methoxy- or 7-hydroxy-5-methoxy-6-formylcoumarin and that the C_5 residue was present in a second heterocyclic system of the furan or (more probable) α-pyran type. The evidence described in the present memoir enables us to make a decision between each of these pairs of alternatives and consequently to develop complete structures for xanthoxyletin and its derivatives.

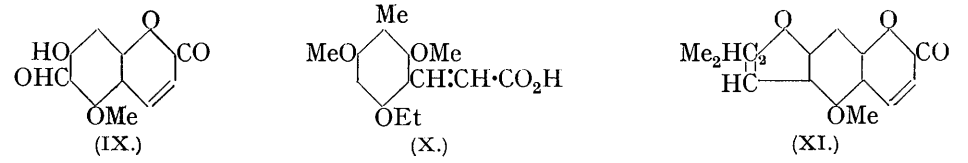
apo*Xanthoxyletin*.—Before proceeding to the orientation of this compound it was deemed advisable to confirm the structure of deoxy*apo*xanthoxyletin methyl ether (Part I, *loc. cit.*) by synthesis, a procedure now rendered possible by the recent preparation of *C*-methylphloroglucinol β-dimethyl ether (J., 1936, 1837). Accordingly, the *aldehyde* (I) was prepared from the latter ether in the usual manner and on condensation with cyanoacetic acid and subsequent hydrolysis of the product furnished the *coumarin-3-carboxylic acid* (II), which on decarboxylation gave rise to (III, R = Me), identical with the natural methyl ether of deoxy*apo*xanthoxyletin.



As it did not appear from the work of Curd and Robertson on derivatives of *C*-methylphloroglucinol (J., 1933, 437, 714) that a rational synthesis of the compounds having the structures possible for deoxy*apo*xanthoxyletin (type III, R = H, and IV, R = H) or for its *ethyl ether* was feasible, we decided to orient the latter ether by the following indirect method.

5-*Methoxy*-7-*ethoxy*-8-*methylcoumarin* (VII, R = H) was prepared from the *aldehyde* (VI, R = Me) by way of the *acid* (VII, R = CO_2H) and on hydrolysis and simultaneous methylation according to the general procedure (J., 1931, 1875) gave rise to 2 : 6-*dimethoxy*-4-*ethoxy*-3-*methylcinnamic acid* (VIII), identical with the cinnamic acid obtained from the isomeric deoxy*apo*xanthoxyletin ethyl ether by the same method. This result is possible only if the latter ether has the formula (III, R = Et), because a compound having the alternative structure (IV, R = Et) would give rise to 4 : 6-dimethoxy-2-ethoxy-3-methylcinnamic acid (X).





Accordingly, it follows, therefore, that deoxy*apo*xanthoxyletin is 7-hydroxy-5-methoxy-6-methylcoumarin (III, R = H) and hence *apo*xanthoxyletin is 7-hydroxy-5-methoxy-6-formylcoumarin (IX). Further, since it has been clearly shown that the C_5 unit is

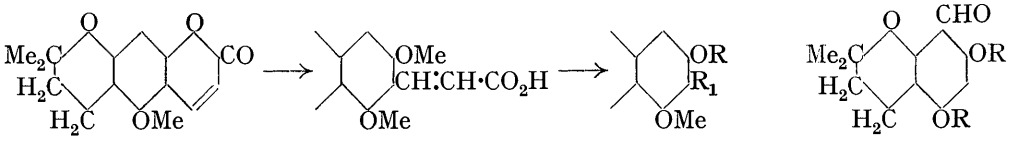
attached to the coumarin residue at the 6-position and to the oxygen atom appearing in the hydroxyl group in *apo*xanthoxyletin (Part I, *loc. cit.*), xanthoxyletin possesses the linear type of structure (XI).

The aldehyde (VI, R = Me) required for these experiments was conveniently prepared from phloroglucinol monoethyl ether by way of the stages (V, R = CHO), (V, R = Me), and (VI, R = H) and it may be noted that the successful production of (VI, R = Me) in this manner affords clear evidence that the orientations of the products formed by the application of the Gattermann reaction to phloroglucinol monoethyl ether and to (V, R = Me) and by the methylation of (VI, R = H) are identical with those of the analogous compounds obtained from the corresponding methyl ethers by the same methods respectively (Curd and Robertson, *loc. cit.*).

The 2 : 2-*Dimethyl*-Δ^3-*chromen Residue*.—The comparatively facile formation of acetone from xanthoxyletin by hydrolytic fission, in which respect there is a striking resemblance to toxicarol, led us to assume that xanthoxyletin contains a 2 : 2-dimethyl-Δ^3-chromen nucleus (compare Part I, *loc. cit.*), a view which is now completely vindicated.

Application of the Gattermann reaction to 5 : 7-dihydroxy-2 : 2-dimethylchroman gave rise to an *aldehyde* together with a compound which has not yet been fully investigated. Methylation of the former product yielded a dimethyl ether, which was characterised by the formation of a *semicarbazone* and a 2 : 4-*dinitrophenylhydrazone*. The same dimethyl ether of the formylchroman was obtained directly from specimens of 5 : 7-*dimethoxy*-2 : 2-*dimethylchroman* (XIV, R = Me; R_1 = H) prepared by the reduction of 5 : 7-dimethoxy-2 : 2-dimethylchroman-4-one and by the methylation of 5 : 7-dihydroxy-2 : 2-dimethylchroman.

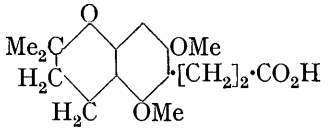
Ozonolysis of dihydroxanthoxyletin, which, as indicated in Part I (*loc. cit.*), we believed to contain a double bond in the α-pyrone ring, gave rise to a product (A) having the properties of an *o*-hydroxy-aldehyde and yielding a *monomethyl ether* which was characterised by the formation of a *semicarbazone* and a 2 : 4-*dinitrophenylhydrazone*. The same ether was also obtained by the oxidation of *O*-methyldihydroxanthoxyletinic acid with potassium permanganate or with ozone. Comparison of the semicarbazone and 2 : 4-dinitrophenylhydrazone of this ether with the respective derivatives of the dimethyl ether of the aldehyde obtained from 5 : 7-dihydroxy-2 : 2-dimethylchroman showed that the two compounds were isomeric and not identical, a result which we considered to be due to a difference in position of the formyl groups in the same chroman system rather than to the non-identity of the heterocyclic systems of the compounds.



(XII.) (XIII.) (XIV.) (XV.)

Oxidation of the monomethyl ether of (A) with aqueous potassium permanganate gave rise to an *acid* (B), which on decarboxylation yielded an oily product (C). That the latter product is identical with 5 : 7-dimethoxy-2 : 2-dimethylchroman (XIV, R = Me; R_1 = H) is clearly proved by the fact that by means of the Gattermann reaction it was converted into a compound shown to be identical with the aldehyde obtained from the authentic chroman dimethyl ether by comparison of their respective semicarbazones and 2 : 4-dinitrophenylhydrazones. Further, since it has already been shown that xanthoxyletin possesses a linear type of structure, the acid (B) has the structure (XIV, R = Me; R_1 = CO_2H) and therefore the aldehyde (A) and its methyl ether must be 7-*hydroxy*-5-*methoxy*- (XIV, R = H; R_1 = CHO) and 5 : 7-*dimethoxy*-6-*formyl*-2 : 2-*dimethylchroman* (XIV, R = Me; R_1 = CHO) respectively. Consequently the isomeride of the latter compound obtained from 5 : 7-dimethoxy-2 : 2-dimethylchroman is the 8-*formyl* derivative (XV, R = Me). In this connexion it is of interest to note that the orientation of the aldehyde (XV, R = H) prepared from the dihydroxychroman, which follows from the structure of its dimethyl ether (XV, R = Me), differs from that expected by analogy with the behaviour of *C*-

methylphloroglucinol β-monomethyl ether when submitted to the Gattermann reaction (Curd and Robertson, *loc. cit.*).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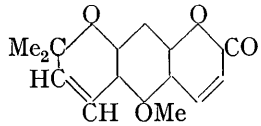
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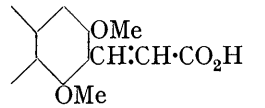
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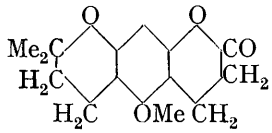
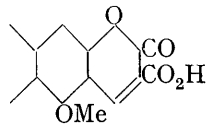
(XIX.) 


(XX.)

From the foregoing results it follows that dihydroxanthoxyletin contains the 2 : 2-dimethylchroman residue and is represented by formula (XII) and consequently that *O*-methyldihydro- and *O*-methyltetrahydro-xanthoxyletinic acid have formulæ (XIII) and (XVI) respectively. Further, since it contains two double bonds, one of which 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, in the α-pyrone ring, xanthoxyletin must be represented by the expression (XVII) and *O*-methylxanthoxyletinic acid by (XVIII). Finally, *tetrahydroxanthoxyletin*, which has now been obtained by catalytic reduction of dihydroxanthoxyletin in the presence of sodium hydroxide, followed by lactonisation of the resulting tetrahydro-acid, has the formula (XIX).

A partial synthesis of dihydroxanthoxyletin has been effected from the aldehyde (XIV, R = H; R_1 = CHO). Condensation of the latter compound with cyanoacetic acid and subsequent hydrolysis of the resulting salicylidenecyanoacetic acid gave rise to the *coumarin-3-carboxylic acid* (XX), which on decarboxylation yielded dihydroxanthoxyletin. Attempts to obtain xanthoxyletin by dehydrogenation of the latter compound have failed so far and the remaining step required to complete this synthesis, *viz.*, the conversion of the 5 : 7-dihydroxy-2 : 2-dimethylchroman into the aldehyde (XIV, R = H; R_1 = CHO), has not yet been effected.

In conclusion it may be noted that xanthyletin (J., 1936, 1828) and xanthoxyletin constitute a new type of natural chromeno-α-pyrone analogous to the chromenodihydro-γ-pyrones, deguelin, tephrosin, and toxicarol (J., 1932, 1380; 1935, 681).

Experimental.

2-Hydroxy-4 : 6-dimethoxy-5-methylbenzaldehyde (I).—In the course of the synthesis of *C*-methylphloroglucinol β-dimethyl ether (J., 1936, 1837) required for this experiment the following modification of Pratt and Robinson's procedure (J., 1924, **125**, 193) for the preparation of phloroglucinol dimethyl ether gave a satisfactory yield of phloroglucinol monomethyl ether; this method is superior to that starting from 3 : 5-dinitroanisole.

A solution of anhydrous phloroglucinol (50 g.) in methyl alcohol (200 c.c.) was saturated with dry hydrogen chloride in the course of 45 minutes; the rate of saturation was such that the alcohol did not boil. The mixture was then refluxed for 30 minutes, saturated again with hydrogen chloride at room temperature in the course of 45 minutes, kept for 12 hours, and evaporated in a vacuum. On isolation in the usual manner, followed by distillation in a vacuum, the product gave the monomethyl ether (25 g.) and the dimethyl ether (15 g.).

A solution of *C*-methylphloroglucinol β-dimethyl ether (1 g.) and hydrogen cyanide (1·5 c.c.) was saturated at room temperature with dry hydrogen chloride and next day the aldimine was collected, well washed with ether, and hydrolysed with water (30 c.c.) on the steam-bath for 15 minutes. The resulting *aldehyde* (0·65 g.) formed slender colourless needles, m. p. 85°, from dilute alcohol, giving a dark red coloration with alcoholic ferric chloride [Found : C, 61·2; H, 6·2; OMe, 31·4. $C_8H_6O_2(OMe)_2$ requires C, 61·2; H, 6·1; OMe, 31·6%].

5 : 7-Dimethoxy-6-methylcoumarin (III, R = Me).—A mixture of the foregoing aldehyde (0·6 g.), cyanoacetic acid (5 c.c. of a solution prepared according to directions of Phelps and Tillotson, *Amer. J. Sci.*, 1908, **26**, 267), and 20% aqueous sodium hydroxide (4 c.c.) was agitated

for 2 hours and 1 hour later the resulting solution was acidified (Congo-red) with dilute hydrochloric acid. The yellow micro-crystalline precipitate of 4 : 6-dimethoxy-5-methylsalicylidenecyanoacetic acid (0·7 g.), m. p. 240—243° (decomp.), was collected, washed, and hydrolysed by being boiled with 4% hydrochloric acid for 40 minutes, yielding 5 : 7-*dimethoxy*-6-*methylcoumarin*-3-*carboxylic acid* (II), which separated from the hot reaction mixture in pale yellow needles (0·6 g.), m. p. 233—234° after recrystallisation from dilute alcohol (Found : C, 59·1; H, 4·7. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

This acid (0·4 g.) was decarboxylated by being boiled with quinoline (40 c.c.) containing copper-bronze (3 g.) for 20 minutes and after addition of excess of dilute hydrochloric acid to the filtered reaction mixture the *coumarin* was isolated with ether and purified by sublimation in a high vacuum (colourless needles) and then by recrystallisation from benzene–light petroleum (b. p. 60—80°), forming slender colourless needles (0·2 g.), m. p. 135—136°, undepressed by admixture with a natural specimen [Found : C, 65·4; H, 5·5; OMe, 27·8. Calc. for $C_{10}H_6O_2(OMe)_2$: C, 65·5; H, 5·5; OMe, 28·2%].

Vigorous acetylation of the aldehyde (I) (1·25 g.) with sodium acetate (3 g.) and acetic anhydride (3 c.c.) at 155—160° for 7 hours gave rise to an inferior yield of the same coumarin (0·1 g.), m. p. 134—135° after sublimation and recrystallisation.

2 : 4-*Dihydroxy*-6-*ethoxybenzaldehyde* (V, R = CHO).—Of a number of trial experiments the following gave the best yield of phloroglucinol monoethyl ether (compare Weidel and Pollak, *Monatsh.*, 1897, **18**, 355). Dry hydrogen chloride was led into a solution of phloroglucinol (60·0 g.) in alcohol (100 c.c.) for 45 minutes, at such a rate as to keep the temperature of the mixture at 60°. After being kept at room temperature for 18 hours, the reaction mixture was treated with water (20 c.c.) and then 8% aqueous sodium hydroxide (100 c.c.), and the product isolated with ether. By repeated distillation in a high vacuum this material was resolved into phloroglucinol monoethyl ether (20 g.), b. p. 157—160°/0·5 mm., and diethyl ether (20 g.), b. p. 143—145°/0·5 mm.

Condensation of the monoethyl ether (8 g.) and hydrogen cyanide (10 c.c.) in ether (80 c.c.) with excess of hydrogen chloride gave an aldimine which on hydrolysis with water (100 c.c.) on the steam-bath during ½ hour furnished the *aldehyde*, forming yellow needles (7 g.) from dilute alcohol (charcoal). After sublimation in a high vacuum, followed by recrystallisation from dilute alcohol, the crystals, m. p. 169·5°, retained a pale yellow colour [Found : C, 59·4; H, 5·5; OEt, 24·8. $C_7H_5O_3(OEt)$ requires C, 59·3; H, 5·5; OEt, 24·7%]. This compound is insoluble in cold water, benzene, or light petroleum and gives an intense red coloration with aqueous or alcoholic ferric chloride. The 2 : 4-*dinitrophenylhydrazone*, which is almost insoluble in hot alcohol, separated from warm ethyl acetate in small, dark red prisms, m. p. 263—264° (Found : N, 15·3. $C_{15}H_{14}O_7N_4$ requires N, 15·5%).

Reduction of this aldehyde (3 g.), dissolved in acetic acid (100 c.c.), was readily effected with hydrogen (approx. 2 mols. absorbed) and a palladium–charcoal catalyst (prepared from 1 g. of charcoal and 20 c.c. of 1% palladium chloride solution) in about ½ hour. After removal of the catalyst the acetic acid was neutralised with aqueous sodium bicarbonate, and C-*methylphloroglucinol* β-*monoethyl ether* (V, R = Me) isolated with ether and purified by sublimation in a vacuum (about 140°/0·05 mm.) and then by crystallisation from chloroform, forming colourless slender prisms (2 g.), m. p. 130° after sintering at 128°, sparingly soluble in warm light petroleum or cold water and moderately soluble in warm benzene [Found : C, 64·5; H, 7·1; OEt, 26·8. $C_7H_7O_2(OEt)$ requires C, 64·3; H, 7·1; OEt, 26·8%]. The ferric reaction is pale blue in water and pale brown in alcohol.

2 : 6-*Dihydroxy*-4-*ethoxy*-3-*methylbenzaldehyde* (VI, R = H).—Application of the Gattermann reaction to the aforementioned phenol (1·8 g.) in ether (50 c.c.) gave rise to the aldimine, which on hydrolysis with water (100 c.c.) on the steam-bath for ½ hour yielded the *aldehyde* in pale yellow needles (1·5 g.), m. p. 196—197° after purification from 75% alcohol (Found : C, 61·3; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). With alcoholic ferric chloride this compound gave a dark red coloration. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in deep orange, slender needles, m. p. 260—261° (Found : N, 14·7. $C_{16}H_{16}O_7N_4$ requires N, 14·9%).

Methylation of this aldehyde (1 g.) in boiling acetone (30 c.c.) with methyl iodide and potassium carbonate was complete in about ½ hour and gave rise to 2-hydroxy-6-methoxy-4-ethoxy 3-methylbenzaldehyde (VI, R = Me), which formed almost colourless needles, m. p. 130° after sintering at 128°, from alcohol [Found : C, 63·0; H, 6·7; AlkylO, 15·2. Calc. for $C_8H_6O_2(OMe)(OEt)$: C, 62·9; H, 6·7; AlkylO, 15·2%]. This material was identical with a specimen, m. p. 130° after sintering at 128°, prepared according to Curd and Robertson (J., 1933, 719), who give m. p. 126—127°. In this connexion it may be noted that 2 : 4-dihydroxy-6-methoxy-3-methyl-

benzaldehyde, which Curd and Robertson (*loc. cit.*) describe as forming golden-yellow needles from alcohol, has again been found to retain this colour when purified by crystallisation only, but on sublimation in a high vacuum, followed by recrystallisation, formed pale yellow, almost colourless needles, m. p. 239—240°.

Catalytic reduction (approx. 2 mols. of hydrogen absorbed) of 2 : 6-dihydroxy-4-ethoxy-3-methylbenzaldehyde (1 g.), dissolved in acetic acid (100 c.c.) containing charcoal and palladium chloride (20 c.c. of a 10% solution), gave rise to 2 : 4-dihydroxy-6-ethoxy-*m*-xylene, m. p. 130—131°, having a pale blue ferric reaction (Herzig and Hauser, *Monatsh.*, 1900, **21**, 869) [Found : C, 65·7; H, 7·6; OEt, 24·7. Calc. for $C_8H_9O_2(OEt)$: C, 65·9; H, 7·7; OEt, 24·7%].

5-Methoxy-7-ethoxy-8-methylcoumarin-3-carboxylic Acid (VII, R = CO_2H).—Acidification of the reaction mixture obtained by the interaction of 2-hydroxy-6-methoxy-4-ethoxy-3-methylbenzaldehyde and cyanoacetic acid (5 c.c. of Phelps and Tillotson's solution, *loc. cit.*) in 20% aqueous sodium hydroxide (6 c.c.) during 5 hours (agitate) gave rise to a salicylidenecyanoacetic acid, which on hydrolysis with boiling 4% hydrochloric acid for 1 hour yielded the *coumarin-3-carboxylic acid*. This compound, which was insoluble in benzene or alcohol, separated from acetone in slender needles, m. p. 238—239° after sintering at 230°, which decomposed at 250° (Found : C, 60·3; H, 5·0. $C_{14}H_{14}O_6$ requires C, 60·43; H, 5·1%).

5-Methoxy-7-ethoxy-8-methylcoumarin (VII, R = H).—The foregoing acid (0·5 g.) was boiled with quinoline (15 c.c.) containing copper-bronze (2 g.) for 5 minutes, and, after the addition of chloroform (500 c.c.), the filtered solution was washed with dilute hydrochloric acid to remove the quinoline, and then with aqueous sodium bicarbonate to remove traces of acid material. Evaporation of the solution left the *coumarin*, which formed slender colourless needles (0·3 g.), m. p. 167°, from alcohol, insoluble in hot benzene or light petroleum [Found : C, 66·7; H, 5·8; AlkylO, 14·3. $C_{10}H_6O_2(OMe)(OEt)$ requires C, 66·7; H, 6·0; AlkylO, 13·7%].

Fission of this coumarin (0·8 g.), followed by methylation of the resulting *o*-hydroxycinnamic acid with 20% aqueous sodium hydroxide and methyl sulphate according to Canter and Robertson's method (*loc. cit.*), gave the methyl ester of 2 : 6-*dimethoxy*-4-*ethoxy*-3-*methylcinnamic acid* (VIII), which formed colourless needles, m. p. 78°, from light petroleum (b. p. 40—60°). Hydrolysis of this ester with boiling 7% alcoholic potassium hydroxide for 15 minutes yielded the acid, which formed small colourless prisms (0·7 g.) from benzene, m. p. 164—165° [Found : C, 63·3; H, 6·8; AlkylO, 18·3. $C_{10}H_7O_2(OMe)_2(OEt)$ requires C, 63·2; H, 6·8; AlkylO, 18·0%].

*Deoxy*apo*xanthoxyletin Ethyl Ether* (III, R = Et).—Ethylation of deoxy*apo*xanthoxyletin (0·5 g.) in boiling acetone (30 c.c.) with ethyl iodide (two portions of 3 c.c.) and potassium carbonate (5 g.) during 1¾ hours gave rise to the *ethyl ether* as an oil, which solidified on trituration with water and then separated from alcohol in colourless needles (0·4 g.), m. p. 135°, insoluble in benzene or light petroleum [Found : C, 66·6; H, 6·1; AlkylO, 13·3. $C_{10}H_6O_2(OMe)(OEt)$ requires C, 66·7; H, 6·0; AlkylO, 13·7%]. Ethereal and alcoholic solutions of this coumarin exhibit a blue fluorescence.

By the usual procedure of hydrolysis and methylation this compound was converted almost quantitatively into *methyl* 2 : 6-*dimethoxy*-4-*ethoxy*-3-*methylcinnamate*, which formed clusters of needles, m. p. 78·5°, from light petroleum (b. p. 40—60°), identical with a synthetical specimen obtained from 5-methoxy-7-ethoxy-8-methylcoumarin (Found : C, 64·3; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1%).

Hydrolysis of the ester gave rise to the cinnamic acid (VIII), which was purified by means of aqueous sodium bicarbonate and then by crystallisation from benzene–light petroleum (b. p. 60—80°), forming small colourless prisms, m. p. 165°, undepressed by admixture with a synthetical specimen (Found : C, 63·2; H, 6·8; AlkylO, 17·7%).

5 : 7-Dihydroxy-8-formyl-2 : 2-dimethylchroman (XV, R = H).—The reaction mixture, obtained by saturating a solution of 5 : 7-dihydroxy-2 : 2-dimethylchroman (Robertson and co-workers, this vol., p. 285) (1 g.) in ether (50 c.c.) containing hydrogen cyanide (2 c.c.) with hydrogen chloride, was kept for one day and mixed with more ether (30 c.c.), and the ethereal solution decanted from the solid (wash with ether). A solution of the product in water (30 c.c.) was hydrolysed on the water-bath for 10 minutes; after cooling, the aqueous liquor was decanted from the oily material which had separated, and the residue triturated with water until it solidified. The dried solid was extracted several times with a boiling mixture of chloroform and light petroleum (b. p. 60—80°); on cooling, the extracts deposited a product in needles, which on recrystallisation from alcohol had m. p. 123—124° and gave a dark red ferric reaction in alcohol. The products obtained by treating this material with semicarbazide acetate and with 2 : 4-dinitrophenylhydrazine hydrochloride could not be purified.

After being heated on the steam-bath for 10 minutes, the combined aqueous liquor and

aqueous washings from the foregoing crude product slowly deposited the 8-*formylchroman*, which formed colourless needles (0·1 g.), m. p. 179—180°, from dilute alcohol (Found : C, 65·1; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). This compound gives with alcoholic ferric chloride a deep purple-red coloration which becomes bluish-red on the addition of much alcohol and wine-red on dilution with water.

The use of zinc chloride in the Gattermann reaction gave rise to a resinous product from which only the substance, m. p. 123—124°, could be isolated.

5 :7 -*Dimethoxy*-2 : 2-*dimethylchroman* (XIV, R = Me; R_1 = H).—A mixture of 5 : 7-dimethoxy-2 : 2-dimethylchromanone (Robertson and co-workers, *loc. cit.*) (1 g.), amalgamated zinc dust (20 g.), acetic acid (10 c.c.), and 12% hydrochloric acid (50 c.c.) was refluxed for 5 hours; after 3 hours more hydrochloric acid (50 c.c.) was added. The cooled acid liquors were extracted several times with ether, and the combined ethereal extracts washed with dilute aqueous sodium hydroxide and then with water, dried, and evaporated. Distillation of the residual oil in a high vacuum gave the *chroman* as an almost colourless oil (0·5 g.), b. p. 105°/0·05 mm. (Found : C, 70·4; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). The same compound, b. p. 105—106°/0·05 mm., was obtained by methylation of 5 : 7-dihydroxy-2 : 2-dimethylchroman (1 g.) in acetone (30 c.c.) with excess of methyl iodide and potassium carbonate during 3 hours (Found : C, 70·5; H, 8·3%).

5 : 7-*Dimethoxy*-8-*formyl*-2 : 2-*dimethylchroman* (XV, R = Me).—(A) Methylation of 5 : 7-dihydroxy-8-formyl-2 : 2-dimethylchroman, m. p. 179—180°, (0·4 g.) in acetone (30 c.c.) with methyl iodide and potassium carbonate during 3 hours gave the crude dimethyl ether, having a negative ferric reaction. An ethereal solution of this material was washed twice with aqueous sodium hydroxide, dried, and evaporated. Part of the resulting product was converted into the *semicarbazone*, which separated from hot alcohol in colourless needles, m. p. 217—218° (Found : C, 58·8; H, 6·7; N, 13·5. $C_{15}H_{21}O_4N_3$ requires C, 58·7; H, 6·8; N, 13·7%).

On addition of one drop of concentrated sulphuric acid to a solution of the remaining portion of the crude aldehyde and 2 : 4-dinitrophenylhydrazine (0·1 g.) in hot alcohol (5 c.c.) the 2 : 4-*dinitrophenylhydrazone* quickly separated in slender, dark red needles, m. p. 242—243° after recrystallisation from warm benzene (Found : C, 56·0; H, 5·2; N, 12·9. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1; N, 13·0%).

(B) The crystalline aldimine, obtained by saturating a solution of 5 : 7-dimethoxy-2 : 2-dimethylchroman (0·5 g.) in dry ether (30 c.c.), containing hydrogen cyanide (1 c.c.), with hydrogen chloride, was washed with ether and hydrolysed with water (30 c.c.) on the steam-bath for 20 minutes. The resulting aldehyde gave an almost quantitative yield of the semicarbazone, which separated from alcohol in needles, m. p. and mixed m. p. 217—218°.

Ozonolysis of Dihydroxanthoxyletin.—A stream of ozone and oxygen (rate of 40 c.c. per minute) was led into a solution of the dihydro-compound (1 g.) in chloroform (100 c.c.) for 2 hours, the solvent was evaporated in a vacuum, and the residue hydrolysed with water (50 c.c.) at room temperature for 16 hours and then on the steam-bath for 10 minutes. An ethereal solution of the product was extracted eight times with 8% aqueous sodium hydroxide (4 c.c.) and the combined extracts were diluted with twice their volume of water, treated with a little charcoal, filtered, and saturated with carbon dioxide. The precipitated 7-*hydroxy*-5-*methoxy*-6-*formyl*-2 : 2-*dimethylchroman* (XIV, R = H; R_1 = CHO) was collected and purified by distillation in a high vacuum and then by crystallisation from dilute alcohol, forming colourless flat prisms, m. p. 85—86°, which were readily soluble in alcohol, light petroleum, or benzene, gave a dark claret coloration with alcoholic ferric chloride, reduced ammoniacal silver nitrate, and formed a red 2 : 4-dinitrophenylhydrazone [Found : C, 65·9; H, 6·8; OMe, 13·0. $C_{12}H_{13}O_3$(OMe) requires C, 66·1; H, 6·8; OMe, 13·1%].

5 : 7-*Dimethoxy*-6-*formyl*-2 : 2-*dimethylchroman* (XIV, R = Me; R_1 = CHO).—(A) Methylation of the foregoing aldehyde (0·6 g.) in boiling acetone (25 c.c.) with methyl iodide and potassium carbonate was complete after 2 hours (indicated by the disappearance of the yellow colour of the reaction mixture) and yielded 5 : 7-*dimethoxy*-6-*formyl*-2 : 2-*dimethylchroman*, which, after having been distilled in a high vacuum, separated from light petroleum in colourless prisms, m. p. 81—82° [Found : C, 67·0; H, 7·2; OMe, 25·2. $C_{12}H_{12}O_2(OMe)_2$ requires C, 67·2; H, 7·2; OMe, 24·8%]. The semicarbazone formed slender needles, m. p. 215—216°, from alcohol.

(B) A solution of *O*-methyldihydroxanthoxyletinic acid (Part I, *loc. cit.*) (2 g.) in acetone (80 c.c.), maintained at 50°, was treated with 1·4% aqueous potassium permanganate (200 c.c.) in the course of 2 hours. After having been cleared with sulphur dioxide, the reaction mixture was heated on the steam-bath with 8% sulphuric acid (10 c.c.) for 10 minutes and then extracted eight times with ether and the combined extracts were washed with aqueous sodium bicarbonate to remove acidic material, dried, and evaporated, leaving a residue which had the properties of

the aldehyde prepared by method (A) and was converted into the *semicarbazone*. This derivative separated from alcohol in slender needles (0·4 g.), m. p. 215·5—216·5°, identical with a specimen prepared by method (A) (Found : C, 58·4; H, 7·1; N, 12·8. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8; N, 13·7%).

A hot solution of 2 : 4-dinitrophenylhydrazine hydrochloride (0·13 g.) in alcohol (5 c.c.) containing 2 drops of concentrated sulphuric acid was added to a solution of the semicarbazone (0·2 g.) in the same solvent (10 c.c.), and the mixture boiled for 1 minute. The reaction mixture quickly became dark red and the 2 : 4-*dinitrophenylhydrazone* separated in dark red needles. Recrystallised from ethyl acetate–alcohol, it formed rectangular prisms, m. p. 215—216° (Found : C, 56·0; H, 5·2; N, 12·7. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1; N, 13·0%).

(C) A stream of ozone and oxygen (rate of approx. 50 c.c. per minute) was led into a solution of *O*-methyldihydroxanthoxyletinic acid (2 g.) at 0° for 2 hours. After the removal of the solvent in a vacuum the product was hydrolysed with water (50 c.c.) at room temperature for 12 hours and then on the water-bath for 10 minutes; the resulting aldehyde was isolated with ether and converted into the semicarbazone, m. p. and mixed m. p. 215—216°, after purification from alcohol.

5 : 7-*Dimethoxy*-2 : 2-*dimethylchroman*-6-*carboxylic Acid* (XIV, R = Me; $R_1 = CO_2H$).—Oxidation of the foregoing aldehyde (1 g.), dissolved in acetone (20 c.c.), was effected at 60° with 3% aqueous potassium permanganate (50 c.c., added in the course of 1 hour). Next day the mixture was cleared with sulphur dioxide, and the *acid* (0·5 g.) precipitated with excess of dilute sulphuric acid and purified by crystallisation from dilute alcohol and then from dilute acetone, forming colourless needles, m. p. 142—143° (decomp.); a further quantity of the compound (0·2 g.) was isolated from the aqueous liquor with ether and separated from a little unchanged aldehyde by means of aqueous sodium bicarbonate [Found : C, 63·2; H, 7·1; OMe, 22·9. $C_{12}H_{12}O_3(OMe)_2$ requires C, 63·2; H, 6·8; OMe, 23·3%].

Decarboxylation of this acid (1 g.) at 144—145° in the course of 5 minutes yielded 5 : 7-dimethoxy-2 : 2-dimethylchroman (0·7 g.), which was purified by distillation in a high vacuum, b. p. 105°/0·05 mm. (Found : C, 70·4; H, 8·3%). On being submitted to the Gattermann reaction this material gave a rise to a good yield of 5 : 7-dimethoxy-8-formyl-2 : 2-dimethylchroman, which was characterised by conversion into the semicarbazone, m. p. 217—218°, identical with a specimen prepared from the authentic aldehyde (Found : C, 58·6; H, 6·7; N, 13·7; OMe, 21·0%). Similarly, the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 243—244° (Found : C, 56·0; H, 5·1; N, 12·9%).

Tetrahydroxanthoxyletin (XIX).—A mixture of dihydroxanthoxyletin (Part I, *loc. cit.*) (1 g.) and hot alcohol (20 c.c.), containing 20% aqueous sodium hydroxide (2 c.c.), was agitated until a clear solution was obtained and a test sample did not give a precipitate or opalescence on addition of water. After dilution with water (50 c.c.) the disodium derivative of dihydroxanthoxyletinic acid was hydrogenated with hydrogen (absorption, approx. theoretical) and an active palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 1 g. of charcoal), the catalyst removed by filtration, and the solution acidified (Congo-red) with 8% hydrochloric acid. On being heated in a vacuum at 180° 0·1 mm., the crystalline precipitate of tetrahydroxanthoxyletinic acid, needles, m. p. 150° (efferv.), which readily dissolved in aqueous sodium bicarbonate, was cyclised and the resulting *tetrahydroxanthoxyletin* simultaneously sublimed, forming colourless slender prisms. This compound separated from warm alcohol in tiny rhombic prisms, m. p. 121°, soluble in cold benzene and sparingly soluble in hot light petroleum (Found : C, 68·7; H, 6·8. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Mixed with dihydroxanthoxyletin, it melted at 115—117°.

Dihydroxanthoxyletin-3-*carboxylic Acid* (XX).—A mixture of 7-hydroxy-5-methoxy-6-formyl-2 : 2-dimethylchroman (1 g.), cyanoacetic acid (4 c.c. of a solution prepared by the method of Phelps and Tillotson, *loc. cit.*), and 20% aqueous sodium hydroxide (5 c.c.) was kept for 12 hours, diluted with water (20 c.c.), and acidified (Congo-red) with 8% hydrochloric acid. The precipitate was washed with water and boiled with 4% hydrochloric acid for 1½ hours. Recrystallisation of the resulting *coumarin*-3-*carboxylic acid* from alcohol gave elongated slender prisms (1·2 g.), m. p. 139—140°, readily soluble in aqueous sodium bicarbonate and giving a negative ferric reaction (Found : C, 63·1; H, 5·3. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%).

An intimate mixture of the acid (0·5 g.) and Kahlbaum's " Natur Kupfer " (0·5 g.) was heated at 190—195° for ½ hour; the resulting dihydroxanthoxyletin (XII), isolated from the reaction mixture by sublimation in a high vacuum, formed small, thick, rhombic prisms (0·3 g.). Purified from alcohol, it had m. p. and mixed m. p. 143° and was identical in every way with a natural specimen.

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