Method B. Dehydrogenation with Sulfur.[7]—The diene (1.34 g., 0.01 mole) was mixed with sulfur (1 g., 0.03 mole) in a two-bulb distillation flask and the flask placed in a Wood's metal-bath at 200°. The temperature was gradually raised over a period of fifteen minutes to 240° and maintained at this temperature for fifteen minutes. The receiver was then cooled in a Dry Ice-acetone-bath and the mixture distilled under slight vacuum. Approximately 5 mg. of impure azulene was obtained. The tarry residue indicated that extensive polymerization had occurred.

Method C. Catalytic Liquid Phase Dehydrogenation.—The diene (1.5 g., 0.011 mole) dissolved in 1 ml. of β-methylnaphthalene was mixed with 200 mg. of 10% palladium-on-charcoal and refluxed in a carbon dioxide atmosphere for 48 hours. At the end of this time the reaction mixture was taken up in 50 ml. of 20–40° petroleum ether, filtered, and extracted with 5 ml. of cold 85% phosphoric acid. The acid solution was washed twice with 25-ml. portions of petroleum ether, diluted with 25 ml. of ice-water and the diluted acid extracted with 10 ml. of petroleum ether. The amount of azulene obtained on evaporation of the solvent was too small to measure.

Reaction of 1,2,3,4,5,6-Hexahydroazulene (VI) with N-Bromosuccinimide.—A solution of the diene (1.34 g., 0.01 mole) in 50 ml. of carbon tetrachloride was added to N-bromosuccinimide (5.34 g., 0.03 mole) in a 100-ml. round-bottom flask fitted with a condenser and drying tube. The mixture was refluxed on a steam-bath for one hour with intermittent irradiation with ultraviolet light. At the end of this time a test for active bromine was negative. The reaction mixture, which had become dark green and evolved hydrogen bromide, was placed in an ice-bath for one hour, the succinimide removed by filtration, 11 ml. of 2,4,6-collidine added to the filtrate and the solution refluxed for two hours. Excess collidine was precipitated as the hydrochloride by titration of the cooled solution with ethereal hydrogen chloride to the end-point (*p*H 4) of Butter Yellow and the collidine hydrohalides removed by filtration. The solvent was removed by distillation *in vacuo* at room temperature and the residue dissolved in petroleum ether. Extraction of this solution with phosphoric acid yielded no azulene. Chromatography of the petroleum ether solution on activated alumina gave, in addition to an unstable green oil, three different green crystalline fractions, each of which contained bromine and showed absorption in the ultraviolet similar to that of azulene compounds (Fig. 2). The quantities obtained were insufficient for analysis or further chemical studies.

Catalytic Vapor Phase Dehydrogenation of 4-Keto-1,2,3-4,5,6,7,8-octahydroazulene (IV).—The dehydrogenation of 3.0 g. (0.02 mole) of 4-keto-1,2,3,4,5,6,7,8-octahydroazulene was performed as described above (Method A) for the dehydrogenation of 1,2,3,4,5,6-hexahydroazulene. The crude product obtained was taken up in petroleum ether and chromatographed on an activated alumina column. The column was washed with petroleum ether until unchanged starting material and a faint band of azulene were eluted. The remaining red band, more strongly adsorbed, was eluted with methanol. Evaporation of the solvent from the red methanol solution in a stream of nitrogen at room temperature left a red oil which was somewhat unstable and could not be obtained analytically pure. The substance decomposed on standing alone or when adsorbed on the alumina column and also in alkaline solution. It reacted immediately with 1% aqueous ferric chloride to give a dark greenish-brown solution. A solution of the oil in 5% aqueous sodium hydroxide gave an immediate red coloration and a slight orange precipitate when treated with a solution of benzenediazonium chloride. A solution of the red oil in *n*-hexane showed absorption maxima in the ultraviolet at 248, 282, 304 and 331 mμ (Fig. 1). These properties indicated the compound to be a phenolic derivative of azulene and thus probably 4-hydroxyazulene (VIII).

A sample of the red oil was dissolved in 10 ml. of petroleum ether and the solution extracted with 2 ml. of 10% sodium hydroxide. The brown alkaline solution was shaken immediately with 0.2 ml. of benzoyl chloride for 15 minutes and the oil which separated extracted with 5 ml. of petroleum ether. The separated organic layer was concentrated by evaporation in a stream of air to 0.2 ml. and chromatographed on a column (9 × 30 mm.) filled with Florosil[16] (60/100 mesh). The column was washed with petroleum ether to elute the deep blue band of the **benzoate**. Some decomposition of the benzoate occurred on the column (on activated alumina decomposition took place rapidly) and the derivative, obtained as a blue oil, could not be obtained sufficiently pure for analysis. A solution of the product in *n*-hexane showed absorption maxima in the ultraviolet at 231, 274, 280 and 340 mμ (Fig. 1).

Summary

An improved synthesis of azulene in six steps and 5.8% over-all yield from decahydro-2-naphthol *via* the new 1,2,3,5,6,7-hexahydroazulene, and the preparation of a new, unstable azulene derivative, probably 4-hydroxyazulene for which the name 4-azulol is suggested, are reported.

[16] An activated magnesium silicate sold by the Floridin Company, Warren, Pennsylvania.

SEATTLE, WASHINGTON RECEIVED JULY 5, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Osage Orange Pigments. XII.[1] Synthesis of Dihydro-iso-osajin and of Dihydroisopomiferin[2]

BY M. L. WOLFROM AND BERNARD S. WILDI[3]

The classical method for establishing the structure of an organic compound requires that, as a final step, the formula assigned by degradative methods be verified by a synthesis effected by controlled reactions from intermediates of known structure. The work herein reported is concerned with such a synthetic verification of the structures assigned[1] to osajin (XXV) and pomiferin (XXVI), the isoflavone pigments of the fruit of the osage orange (*Maclura pomifera* Raf.).

It is known that dihydro-iso-osajin (XXIII)[4] and dihydro-isopomiferin (XXIV)[4] may be obtained readily from osajin and pomiferin, respectively, by treatment of the pigments with hydriodic acid.[1] Furthermore, the nature of this change is well established.[1] Therefore, through the synthesis of dihydro-iso-osajin and dihydro-isopomiferin to be described, conclusive evidence is obtained in support of the structures assigned to osajin and pomiferin by degradative methods.

For the synthesis of the two pigment derivatives XXIII and XXIV, there was required dihydro-iso-osajinol (V), the basic structure from which they could be formed by introduction of the isoflavone

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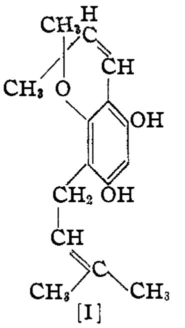
(1) Preceding communication in this series: M. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahan, S. M. Moffet and B. Wildi, THIS JOURNAL, **68**, 406 (1946).

(2) A preliminary notice of this work appeared in *Abstracts Papers Am. Chem. Soc.*, **113**, 60L (1948).

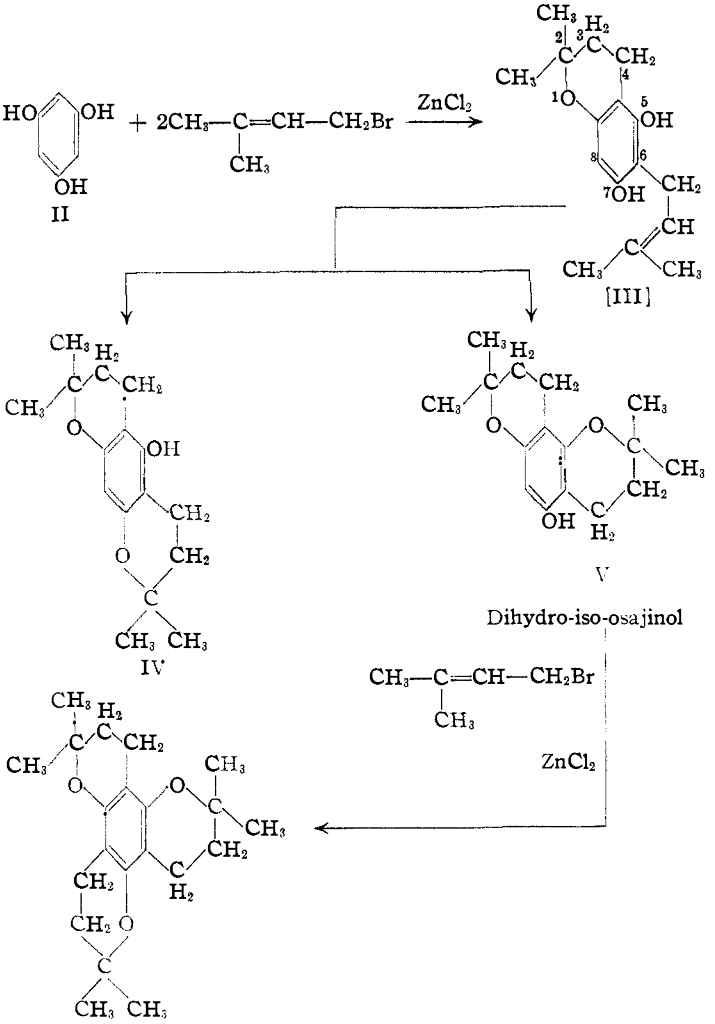
(3) Predoctoral Fellow of the American Chemical Society, 1946–1947.

(4) M. L. Wolfrom, F. L. Benton, A. S. Gregory, W. W. Hess, J. E. Mahan and P. W. Morgan, THIS JOURNAL, **63**, 422 (1941).



[I]

Osajinol



II

[III]

IV

V

Dihydro-iso-osajinol

VI

ring (the term osajinol denoting the hypothetical entity I).

Following the general method used by Karrer and co-worker[5] in their studies on the synthesis of the tocopherols, phloroglucinol (II) was allylated in the presence of zinc chloride with a 2 molar ratio (per mole of phloroglucinol) of γ,γ-dimethylallyl bromide. This led to the formation of three crystalline compounds isolated by chromatographic techniques. Evidence detailed below demonstrated that these were the desired dihydro-iso-osajinol (V), its isomer IV and the tetracyclic substance VI; the reaction leading to IV and V probably proceeded through the postulated intermediate [III]. Introduction of the side chain at position 8 of [III] would have led exclusively to V.

Structure VI was assigned on the basis of analysis; inertness toward: acetylation, alkaline permanganate, bromine in carbon tetrachloride; and insolubility at room temperature in aqueous sodium hydroxide and Claisen alkali (a mixture of equal volumes of 50% aqueous potassium hydroxide and absolute methanol). The absence of phenolic groups in VI was further demonstrated by negative colorations with alcoholic ferric chloride and ammonium phosphomolybdate (hindered phenol test[6,7]).

Substances IV and V exhibited positive phenol tests with ammonium phosphomolybdate and formed monoacetates on acetylation by either vigorous[8,9] (sodium acetate and acetic anhydride under reflux) or mild[8,9] (pyridine and acetic anhydride at 0°) conditions. Substance V, but not IV, was convertible to VI on further reaction with γ,γ-dimethylallyl bromide and zinc chloride. All of these reactions adequately establish the structures IV and V but further supporting evidence is cited below.

Reaction of 2,2-dimethyl-5,7-chromandiol[10] (VII; herein prepared directly from phloroglucinol) with β,β-dimethylacrylyl chloride in the presence of aluminum chloride yielded two products which were separated chromatographically and to which the structures X and XI were assigned. As with the previously described reaction with γ,γ-dimethylallyl bromide, the substance [VIII], analogous to [III], is a probable intermediate.

Substance XI was similar to VI in exhibiting a lack of phenolic properties but yielded a monoxime which formed peculiar helical-shaped crystals (Fig. 1). Clemmensen reduction of XI yielded VI. Substance X (m.p. 114–115°) yielded dihydro-iso-osajinol (V) on Clemmensen reduction. Compound IX was formed by a Hoesch[11] condensation of either β,β-dimethylacrylonitrile or β-hydroxyisovaleronitrile with 2,2-dimethyl-5,7-chromandiol (VII). Compound IX did not form an acetate

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[5] P. Karrer, H. Fritzsche, B. H. Ringier and H. Salomon, *Helv. Chim. Acta*, **21**, 520 (1938); P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. H. Ringier and H. Salomon, *ibid.*, **21**, 939 (1938); P. Karrer and H. Fritzsche, *ibid.*, **21**, 1234 (1938).

[6] G. H. Stillson, D. H. Sawyer and C. K. Hunt, This Journal, **67**, 303 (1945).

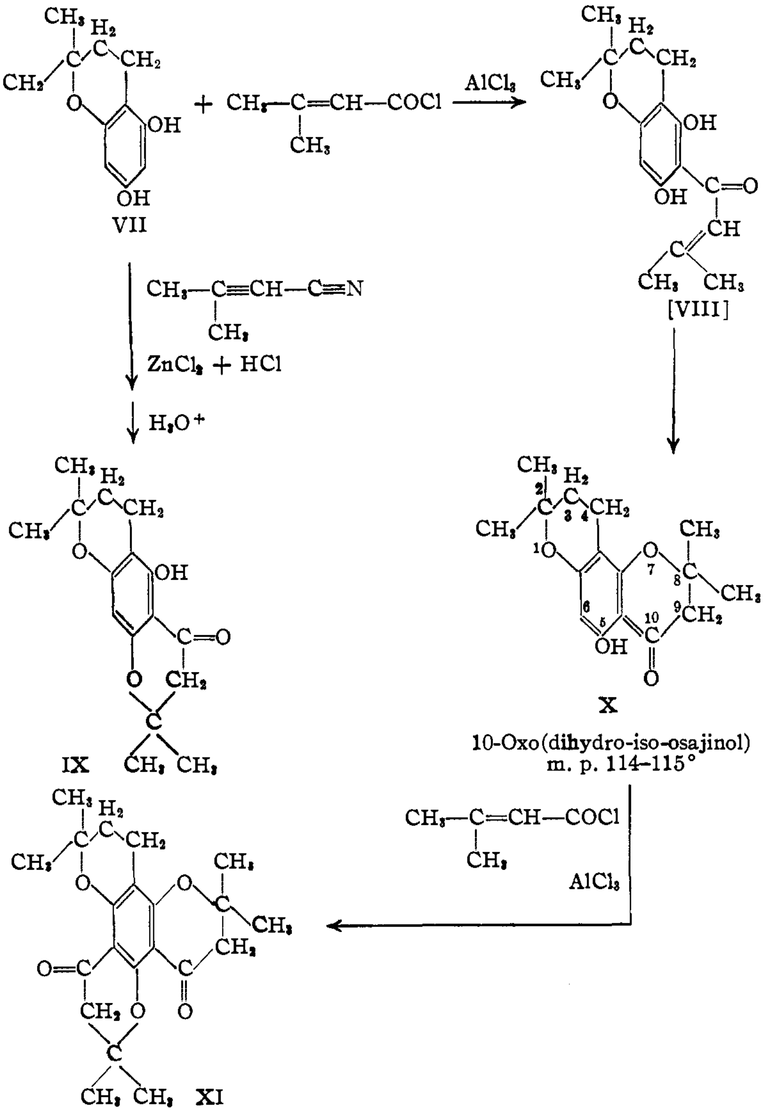
[7] V. M. Platkovskaya and S. G. Vatkina, *J. Applied Chem.* (*U. S. S. R.*), **10**, 202 (1937); *C. A.*, **31**, 4232 (1937).

[8] E. D. Walter, M. L. Wolfrom and W. W. Hess, This Journal, **60**, 574 (1938).

[9] M. L. Wolfrom, F. L. Benton, A. S. Gregory, W. W. Hess, J. E. Mahan and P. W. Morgan, *ibid.*, **61**, 2832 (1939).

[10] W. Bridge, R. G. Heyes and Alexander Robertson, *J. Chem. Soc.*, 279 (1937); W. Bridge, A. J. Crocker, T. Cubin and Alexander Robertson, *ibid.*, 1530 (1937).

[11] K. Hoesch, *Ber.*, **48**, 1122 (1915); *Org. Reactions*, **5**, 387 (1949).



VII

[VIII]

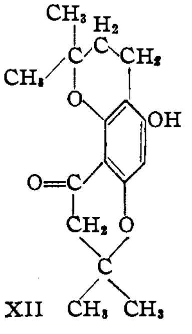
IX

X

10-Oxo(dihydro-iso-osajinol)
m. p. 114–115°

XI

when treated overnight at 0° with acetic anhydride and pyridine. This is characteristic of a diortho-substituted phenol *peri* to a carbonyl group.[1] Therefore the formula shown for IX was assigned to it rather than that of the isomeric structures X and XII, which contain no such hindered, by di-ortho substitution, phenolic group. Lack of material prevented IX from being subjected to a



XII

Clemmensen reduction. Formula XII is not thereby eliminated for the ketone of m. p. 114–115° since both X and XII would yield V on Clemmensen reduction. Substance XII would have to be formed from ring closure on a side-chain entering at position 8 of [VIII] (*cf.* III). Compound X may be designated 10-oxo(dihydro-iso-osajinol).

Dihydro-iso-osajinol (V, but not IV) underwent reaction under the Hoesch conditions with homoanisonitrile (XIII, *p*-methoxyphenylacetonitrile) to yield the ketimine hydrochloride [XV] which was hydrolyzed directly to the substance XVII isolated in 33% yield (based on V) and found to be identical with dihydro-iso-osajetin monomethyl ether[1] prepared from the natural pigment osajin; comparison was made by analysis, melting point, mixed melting point and ultraviolet absorption spectra. New data are reported for the latter property (Fig. 2). The parent substance dihydro-iso-osajetin is described for the first time.

Treatment of XVII with sodium and ethyl formate yielded dihydro-iso-osajin monomethyl ether (XIX) which was demethylated with hydrobromic acid and the resultant dihydro-iso-osajin was characterized as its monoacetate XXI,[1] identical in melting point and mixed melting point with the substance prepared from osajin. Conversion of the acetate to the parent dihydro-iso-osajin (XXIII) has been reported.[4] In an analogous manner, dihydro-iso-osajinol (V) was treated with homoveratronitrile (XIV, 3,4-dimethoxyphenylacetonitrile) and so converted through the intermediates [XVI], XVIII and XX to dihydro-isopomiferin diacetate (XXII), comparison with the products prepared from the natural pigment pomiferin being made with compounds XVIII and XXII. Likewise, conversion of the diacetate to dihydro-isopomiferin (XXIV) has been reported.[4]

Experimental[12]

Reaction of Phloroglucinol with γ,γ-Dimethylallyl Bromide to Produce Dihydro-iso-osajinol (V) and Compounds IV and VI.—Ten grams of anhydrous phloroglucinol, 18 g. of freshly fused and pulverized zinc chloride and 450 ml. of dry benzene (distilled from phosphorus pentoxide) were refluxed (moisture-guarded) for 30 minutes. An amount of 24 g. of freshly distilled γ,γ-dimethylallyl bromide[13] was then added dropwise under mechanical stirring, to the refluxing mixture over a period of 1 hour and reflux was maintained for 17 hours. The cooled benzene solution was decanted from the dark orange colored residue and washed successively with 100 ml. of water, 100 ml. of 5% aqueous sodium bicarbonate and 100 ml. of water. Colorless crystals were obtained on concentrating the dried benzene

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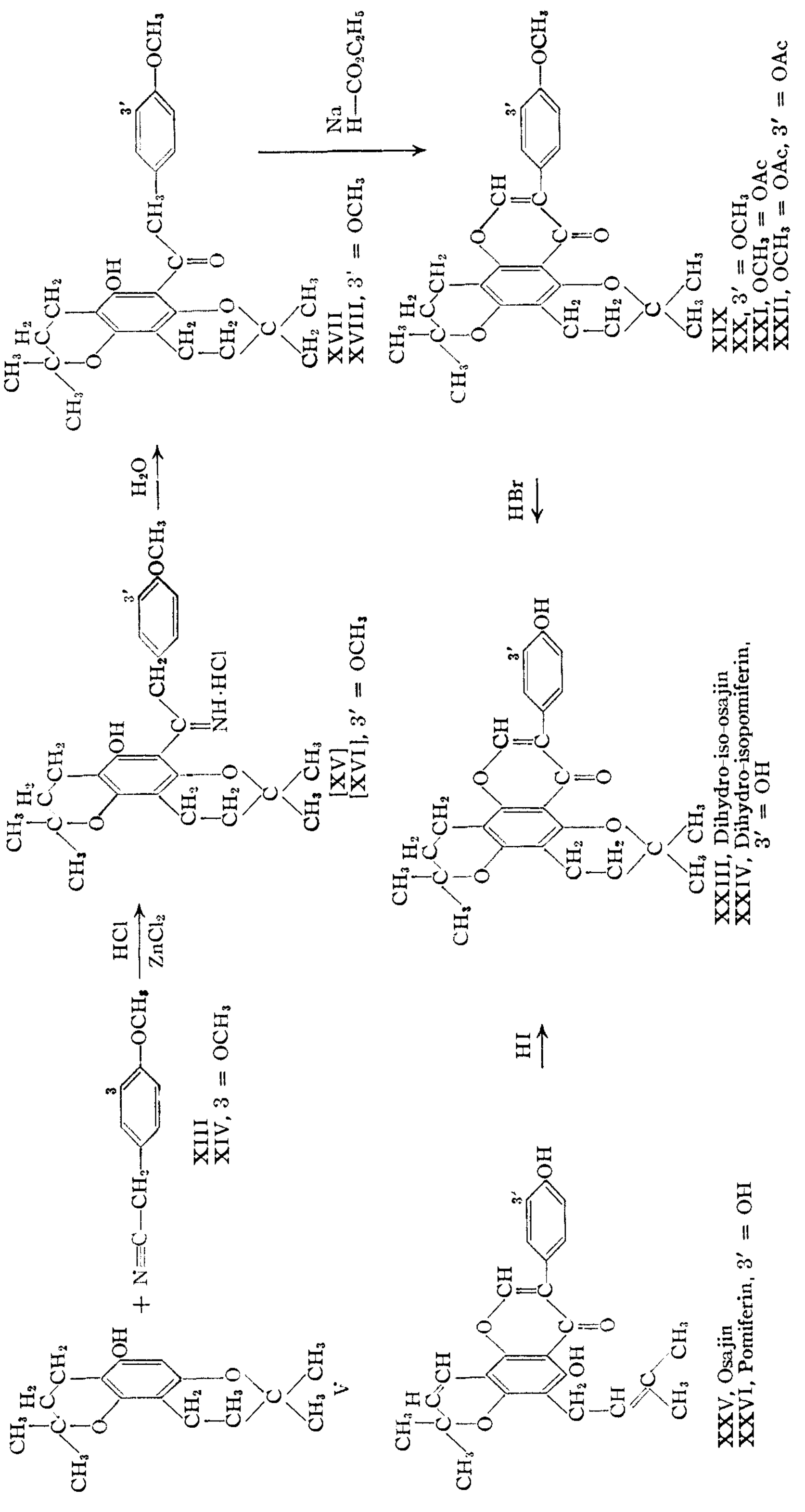
(12) All melting points are uncorrected centigrade readings; those below 195° were taken in a mineral-oil-bath on a 200° thermometer while those above 200° were taken on a modified Berl–Kullmann block as described by F. W. Bergstrom, *Ind. Eng. Chem., Anal. Ed.*, **9**, 340 (1937).

(13) H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).



solution to 10 ml.; yield 3.2 g., m.p. 90-91°. Pure material (VI) was obtained on further recrystallization from ethanol-water; m.p. 103.5-104.5°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.30; H, 9.15. Found: C, 76.13; H, 8.99.

Compound VI was insoluble in aqueous sodium hydroxide and in Claisen alkali. It did not decolorize neutral aqueous permanganate (1%, room temperature) or bromine in carbon tetrachloride. It was recovered unchanged on acetylation with hot acetic anhydride and sodium acetate. It exhibited negative phenol tests with alcoholic ferric chloride and ammonium phosphomolybdate.[6,7]

The residue obtained on solvent removal from the above-mentioned benzene mother liquor was suspended in 200 ml. of water made just acid with concentrated hydrochloric acid. The aqueous mixture was extracted with five 100-ml. portions of ether and the combined ether extracts were washed with five 100-ml. portions of water, followed by three 100-ml. portions of 5% aqueous sodium hydroxide. The aqueous sodium hydroxide extracts were set aside to be processed later. The combined ether extracts were evaporated to dryness and the residue was dissolved in 15 ml. of benzene and placed at the top of a 170 X 20 mm. (diam.) column (adsorbent dimensions) of Magnesol-Celite[14] (5:1 by wt.) and developed with 350 ml. of benzene-ethanol (100:1 by vol.). Colored polymeric material was retained at the top of the column and was removed by sectioning. Elution of the remainder of the column with 100 ml. of acetone and concentration yielded colorless, crystalline material; yield 2.1 g., m.p. 155-156°. Pure dihydro-iso-osajinol (V) was obtained on further recrystallization from benzene; yield 1.1 g., m.p. 157.5-158°, m.p. 130-142° on admixture with IV of m.p. 155-155.5°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.46. Found: C, 73.49; H, 8.32.

Dihydro-iso-osajinol does not give a coloration with dilute alcoholic ferric chloride solution but does give a positive hindered phenol test.[6,7] The material is only slowly soluble at room temperature in 5% aqueous sodium hydroxide but dissolves readily in Claisen alkali. It reacts with bromine in carbon tetrachloride with the evolution of hydrogen bromide and also slowly decolorizes 1% aqueous potassium permanganate.

The above-mentioned sodium hydroxide extracts were combined and acidified in the cold with concentrated hydrochloric acid. The precipitate formed was extracted with three 100-ml. portions of ether, which were combined and washed successively with one 100-ml. portion of water, 100 ml. of 5% aqueous sodium bicarbonate and two 100-ml. portions of water. The residue obtained on solvent removal from the dried ether solution was chromatographed on Magnesol-Celite as described above and the product was isolated in the same manner; yield 0.74 g., m.p. 151-152°. Pure material (IV) was obtained on further recrystallization from benzene; m.p. 155-155.5°, m.p. 130-142° on admixture with V of m.p. 157.5-158°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.46. Found: C, 73.31; H, 8.44.

Compound IV gave a pink coloration with dilute alcoholic ferric chloride and gave a positive hindered phenol test.[6,7] It was slowly soluble at room temperature in 5% aqueous

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[14] W. H. McNeely, W. W. Binkley and M. L. Wolfrom, This Journal, **67**, 527 (1945).

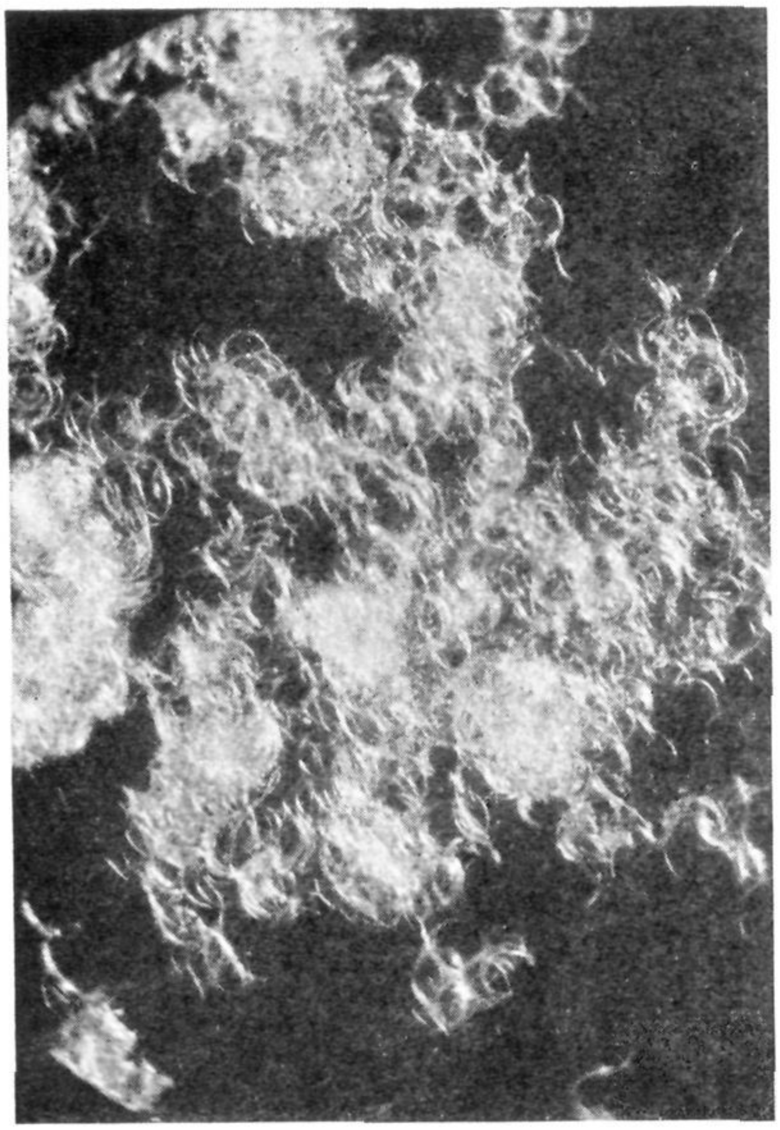

Fig. 1.—Crystals of the monoxime of XI.

sodium hydroxide and readily so in Claisen alkali. It did not decolorize bromine in carbon tetrachloride but slowly decolorized 1% aqueous potassium permanganate. The substance was treated with homoanisonitrile as described below for the synthesis of dihydro-iso-osajetin monomethyl ether from this nitrile and dihydro-iso-osajinol. The red oil which was obtained from the ether extract of the hydrolyzed reaction mixture was chromatographed directly without being separated into phenol and neutral fractions. No yellow band occurred in the position that dihydro-iso-osajetin monomethyl ether is known to occupy (see below) when chromatographed under the same conditions. Also, none of the bands on the column gave a green-black coloration when streaked with alcoholic ferric chloride as does dihydro-iso-osajetin monomethyl ether (XVII).

Dihydro-iso-osajinol Monoacetate.—Dihydro-iso-osajinol (200 mg.) was acetylated[8,9] with hot acetic anhydride and sodium acetate and the water-insoluble product was crystallized from ethanol-water; yield 126 mg. of colorless crystals, m.p. 116.5–117°.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95; mol. wt., 304. Found: C, 70.99; H, 8.09; mol. wt. (Rast), 310.

The same substance was obtained on acetylation[8,9] with pyridine and acetic anhydride at ice-box temperature overnight.

Monoacetate of IV.—Application of either of the above-cited two acetylation procedures to compound IV yielded a colorless, crystalline acetate; yield 81% (sodium acetate method), m.p. 91–92° (from ethanol-water).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95; mol. wt., 304. Found: C, 71.04; H, 8.12; mol. wt. (Rast), 280.

Conversion of Dihydro-iso-osajinol (V) to VI.—An amount of 262 mg. of dihydro-iso-osajinol, 0.5 g. of freshly fused and pulverized zinc chloride, and 6 ml. of dry benzene were heated (moisture-guarded) under reflux for 10 minutes with mechanical stirring. An amount of 0.3 ml. of γ,γ-dimethylallyl bromide was then added dropwise, after which the mixture was refluxed for one hour and then cooled. The benzene solution was decanted and washed successively with an equal volume of water, 5% aqueous sodium bicarbonate and finally with water. Crystalline material was obtained on solvent removal from the dried benzene solution; yield 73 mg. (on one recrystallization from 95% ethanol), m.p. 98–99°. Pure material (VI) was obtained on further crystallization from 95% ethanol; m.p. 103.5–104.5° unchanged on admixture with pure VI of like melting point prepared as described above.

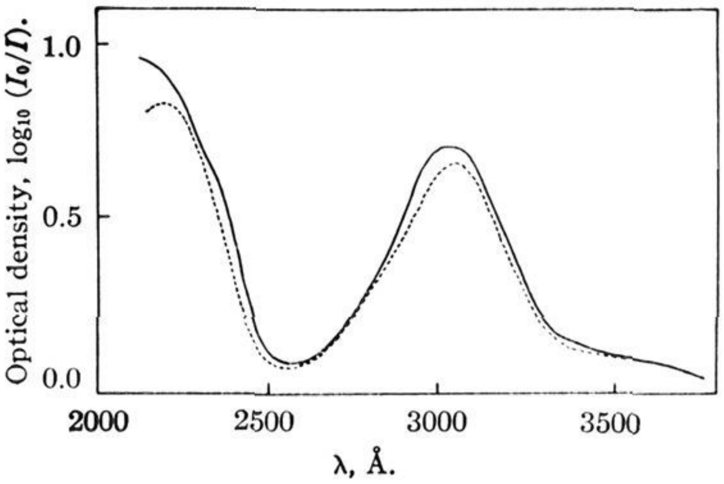

Fig. 2.—Absorption in absolute ethanol (2×10^{-6} molar) of dihydro-iso-osajetin monomethyl ether(---), $\epsilon_{max}(\log_{10})$ = 340,000 at 3030 Å., and dihydro-isopomiferitin dimethyl ether (—), $\epsilon_{max}(\log_{10})$ = 350,000 at 3020 Å.; cell length 1 cm., Beckman spectrophotometer, model DU. These data supersede those reported previously (ref. 1) but *do not* invalidate the conclusions therein drawn. The assistance of Mr. H. C. Weed in obtaining these data is acknowledged.

Substance VI was not obtained when IV was substituted for dihydro-iso-osajinol in the above procedure.

Preparation of 2,2-Dimethyl-5,7-chromandiol (VII).—Anhydrous phloroglucinol (10 g.) was treated with γ,γ-dimethylallyl bromide as described above except that heating was maintained for only 1 hour after the addition of the bromide. The benzene solution was decanted and the residue was suspended in water, made alkaline with 5% aqueous sodium hydroxide and filtered. The precipitate that formed on acidification of the filtrate with 6 *N* hydrochloric acid was added to the benzene decantate. Crystalline material separated on concentration to 20 ml.; yield 5.2 g. (11%, phloroglucinol basis), m.p. 151–152.5°. Material of good purity was obtained on further crystallization from benzene; m.p. 157.5–158.5° unchanged on admixture with an authentic sample (m.p. 160–160.5°[1]) of 2,2-dimethyl-5,7-chromandiol.

Robertson and co-workers[10] record the m.p. 162–163° for this substance.

Reaction of 2,2-Dimethyl-5,7-chromandiol (VII) with β,β-Dimethylacrylyl Chloride to Produce Compounds X and XI.—β,β-Dimethylacrylyl chloride, prepared with phosphorus pentachloride in ether from 25 g. of β,β-dimethylacrylic acid,[15] was added dropwise with stirring to a mixture (moisture-guarded) of 7.5 g. of 2,2-dimethyl-5,7-chromandiol (m.p. 158–159°), 250 ml. of dry nitrobenzene and 10 g. of anhydrous aluminum chloride (Hooker Electrochemical Co.). The mixture was stirred at room temperature for 2 days, 2 g. of aluminum chloride being added each day, and was then poured into 1 liter of ice and water containing 50 ml. of 6 *N* hydrochloric acid. The nitrobenzene was steam distilled from the solution and the resulting aqueous acid suspension was extracted with six 100-ml. portions of ether. The combined ether extracts were washed successively with 100 ml. of water, 100 ml. of 5% aqueous sodium bicarbonate and 100 ml. of a saturated sodium chloride aqueous solution. The ether was removed, leaving an oil which crystallized only very slowly. The oil was dissolved in a minimum of benzene and placed on a 160 × 20 mm. (diam.) column containing 12.5 g. of a 5:1 mixture of Magnesol–Celite and developed with 60 ml. of benzene–ethanol (100:1 by vol.). The light yellow band near the middle of the column was eluted with acetone to yield a light yellow solid which was

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[15] P. Barbier and G. Leser, *Bull. soc. chim.*, [3] **33**, 815 (1905); *Org. Syntheses*, **23**, 27 (1943).

triturated with a small amount of low boiling petroleum ether to remove the coloring matter. The white solid was crystallized from 95% ethanol; yield 0.7 g. of colorless crystals (XI), m.p. 214-215°, m.p. 214.5-215.5° after sublimation at 200° at 1 mm., mixed m.p. 95-170° with anhydrous phloroglucinol of m.p. 215-216°.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.36; H, 7.31. Found: C, 70.55; H, 7.40.

Compound XI exhibited a negative hindered phenol test[6,7] and gave no coloration with dilute alcoholic ferric chloride. It was insoluble at room temperature in both 5% aqueous sodium hydroxide and Claisen alkali. It did not react with 1% aqueous neutral potassium permanganate at room temperature.

On repeating the above-described reaction using 5 g. of β,β-dimethylacrylyl chloride, 4 g. of 2,2-dimethyl-5,7-chromandiol, 4 g. of aluminum chloride and 150 ml. of dry nitrobenzene, there was obtained from the residue by ether extraction after steam distillation, 1.70 g. of very dark colored material. This product was recrystallized from methanol-water (1:1 by vol.) after preliminary treatment with Magnesol-Celite (5:1 by wt.) after the fashion with decolorizing charcoal; yield 816 mg. (X), m.p. 114-115° unchanged on steam distillation at 150-175° or on sublimation at 85-95° at 1 mm.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.48; H, 6.90.

Compound X gave a dark wine coloration with dilute alcoholic ferric chloride and was readily soluble at room temperature in 5% aqueous sodium hydroxide.

Monoxime of XI.—An amount of 300 mg. of compound XI, 0.4 g. of hydroxylamine hydrochloride and 2 g. of potassium hydroxide were dissolved in 10 ml. of 95% ethanol. The mixture was refluxed for three hours, poured into 75 ml. of water, acidified with 8 ml. of concentrated hydrochloric acid and then placed in the ice-box overnight. The solid cream colored material which crystallized was recrystallized from ethanol (decolorizing charcoal); yield 14 mg. of helical shaped crystals (Fig. 1), m.p. 243-244° (dec.) raised to 252-254° (dec.) on two further crystallizations from ethanol and a sublimation at 1 mm. Lack of material allowed only a single combustion analysis.

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.28. Found: C, 67.27; H, 7.31.

Conversion of the Diketone XI to Compound VI.—Amalgamated mossy zinc[16] (60 g.) was placed in 75 ml. of water and to this was added 150 mg. of compound XI (m.p. 214.5-215.5°) dissolved in a mixture of 25 ml. of ethanol and 5 ml. of glacial acetic acid, followed by 25 ml. of concentrated hydrochloric acid. The mixture was refluxed for 25 hours, during which time 150 ml. of concentrated hydrochloric acid was added in 15-ml. portions. The cooled mixture was neutralized with solid sodium bicarbonate and extracted with four 50-ml. portions of ether. The combined ether extracts were washed with 50 ml. of water and 50 ml. of 5% aqueous sodium bicarbonate. The residue obtained on solvent removal from the dried ether solution was crystallized from ethanol (decolorizing charcoal); yield 52 mg., m.p. 103.5-104.5° unchanged on admixture with compound VI of like melting point.

Conversion of X to Dihydro-iso-osajinol (V).—To 30 g. of amalgamated zinc powder, 20 ml. of water and 10 ml. of concentrated hydrochloric acid was added a solution of 398 mg. of the ketone X (m.p. 114-115°) in a mixture of 25 ml. of ethanol and 5 ml. of glacial acetic acid. The mixture was kept at room temperature for 2 days during which time 50 ml. of 6 *N* hydrochloric acid was added; it was then refluxed for 4 hours with addition of 50 ml. of 6 *N* hydrochloric acid. The cooled aqueous decantate was extracted with seven 50-ml. portions of ether. The combined ether extracts were washed successively with 50 ml. of water, 50 ml. of 5% aqueous sodium bicarbonate and 100 ml. of a saturated aqueous sodium chloride solution. The residue obtained on solvent removal from the dried ether solution was crystallized from benzene-petroleum ether; yield 50 mg., m.p. 157.5-158° unchanged on admixture with dihydro-iso-osajinol (V; prepared above) of like melting point.

The mother liquor from the above crystallization was concentrated to 5 ml. and chromatographed on a 140 × 20 mm. (diam.) column of Magnesol-Celite (5:1 by wt.) using 90 ml. of benzene-ethanol (500:1 by vol.) as developer. The acetone eluate material from the bottom third of the extruded column was dissolved in 10 ml. of benzene and rechromatographed on a 165 × 20 mm. (diam.) column of Magnesol-Celite (5:1 by wt.) using 80 ml. of benzene-ethanol (100:1 by vol.) as developer. A light yellow band located at 60-88 mm. from the column top was eluted with acetone from the extruded column and the eluate material was recrystallized from benzene; yield 20 mg., m.p. 157.5-158° unchanged on admixture with dihydro-iso-osajinol (prepared above) of like melting point.

Synthesis of Compound IX from 2,2-Dimethyl-5,7-chromandiol (VII) by the Hoesch Reaction.—Five grams of 2,2-dimethyl-5,7-chromandiol (m.p. 158-159°), 40 ml. of anhydrous ether and 2 g. of freshly fused and pulverized zinc chloride were cooled in an ice-salt-bath and 4.7 g. of β,β-dimethylacrylonitrile (b.p. 138-140°) was added. Anhydrous hydrogen chloride gas was passed rapidly into the flask for 2 hours. The stoppered flask was held in the ice-box overnight and the dark red ether solution was then cautiously poured with vigorous stirring into 200 ml. of ice and water. The mixture was extracted quickly with a 75-ml. portion of ether to separate any of the reactants present from the separated ketimine hydrochloride. Fifty ml. of concentrated sulfuric acid was added to the ketimine hydrochloride solution, which was refluxed for one hour. Colorless needles separated on cooling; yield 170 mg., m.p. 121.5-127.5°. Pure material (IX) was obtained on further crystallization from 50% ethanol and this was unchanged in melting point on crystallization from acetone-water; m.p. 131.0-131.5°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.47; H, 7.03.

Compound IX was very soluble in 5% aqueous alkali and gave a wine-red coloration with dilute alcoholic ferric chloride. It was recovered unchanged on overnight treatment at 0° with acetic anhydride and pyridine.

Unchanged 2,2-dimethyl-5,7-chromandiol was obtained from the above mother liquor by concentration and recrystallization from ethanol-water; yield 2 g., m.p. 158-159°, mixed melting point unchanged.

The above procedure was repeated except that the β,β-dimethylacrylonitrile was replaced by an equivalent amount of β-hydroxyisovaleronitrile[17] (b.p. 60-62° at 2 mm.). The residue obtained on ether removal was triturated with benzene and the benzene solution was placed at the top of a 170 × 20 mm. (diam.) column of Magnesol-Celite (5:1 by wt.) and developed with 60 ml. of benzene-ethanol (100:1 by vol.). The effluent material was a light yellow oil that was crystallized from ethanol-water (decolorizing charcoal); yield 125 mg., m.p. 131° (IX).

A like amount (2 g.) of the original 2,2-dimethyl-5,7-chromandiol was recovered by ethanol-water crystallization, from the above residue from the benzene trituration.

Dihydro-iso-osajetin Monomethyl Ether (XVII) from Dihydro-iso-osajinol (V).—Dihydro-iso-osajinol (400 mg.) and 1 ml. of homoanisonitrile[18] were dissolved in 10 ml. of anhydrous ether and saturated at 0° with dry hydrogen chloride gas. Freshly fused and pulverized zinc chloride (1 g.) and 0.3 g. of anhydrous aluminum chloride were added cautiously and then dry hydrogen chloride gas was passed in for 30 minutes. The reaction was maintained overnight at ice-box temperature followed by 1 day at room temperature. An equal volume of anhydrous ether was then added. Two layers formed, the lower of which was separated, washed with anhydrous ether and treated with 100 ml. of water and 4 ml. of concentrated sulfuric acid under reflux for 2 hours. The cooled solution was extracted with ether. The ether extracts were washed with 5% aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. On ether removal there was obtained a dark oil which was dissolved in a minimum of benzene and chromatographed on a 165 × 20 mm. (diam.) column of Magnesol-Celite (5:1 by wt.) using 125 ml. of benzene-ethanol (100:1 by vol.) as developer. The material in the yellow band located 52-119 mm. from the column top was obtained by acetone elution from the extruded and sectioned column. It was crystallized from ethanol-water; yield 199 mg. (33%) of light yellow crystals, m.p. 111-112.5°. Pure

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[16] *Org. Reactions*, **1**, 163 (1942).

[17] J. Lemaire, *Rec. trav. chim.*, **29**, 57 (1910).

[18] R. L. Shriner and R. W. Stephenson, THIS JOURNAL, **64**, 2737 (1942).

material was obtained on further crystallization from ethanol-water; m.p. 115-116° unchanged on admixture with a specimen of dihydro-iso-osajetin monomethyl ether[1] of like melting point prepared from the natural pigment osajin. The lemon yellow color of the crystals, the wine-red coloration with ferric chloride (alcohol) and ultraviolet absorption spectrum (Fig. 2) were identical for the preparations from the two sources.

Anal. Calcd. for $C_{25}H_{30}O_5$: C, 73.14; H, 7.36. Found: C, 73.16; H, 7.62.

Dihydro-iso-osajin Monomethyl Ether (XIX) from Dihydro-iso-osajetin Monomethyl Ether (XVII).—Dihydro-iso-osajetin monomethyl ether (188 mg.) was dissolved in 10 ml. of freshly distilled ethyl formate, cooled to 0°, and the solution slowly poured on 0.5 g. of thinly sliced sodium under a nitrogen atmosphere. After standing overnight at ice-box temperature, the mixture was poured into 200 ml. of an ice-water mixture and allowed to stand for 12 hours. The precipitated gum was filtered and dissolved in ethanol. The ethanol solution was treated with Magnesol (in the manner used for decolorizing charcoal), filtered and concentrated to about 5 ml. Water was added to incipient opalescence and the solution was set aside to crystallize; yield 50 mg., m.p. 191-192°. Pure material was obtained on further crystallization from ethanol-water; m.p. 197-198° unchanged on admixture with dihydro-iso-osajin monomethyl ether[1] of like melting point prepared from osajin.

Anal. Calcd. for $C_{25}H_{25}O_4(OCH_3)$: C, 74.26; H, 6.71; OCH_3, 7.38. Found: C, 74.39; H, 6.61; OCH_3, 7.49.

Dihydro-iso-osajin Monoacetate (XXI) from Dihydro-iso-osajin Monomethyl Ether (XIX).—Dihydro-iso-osajin monomethyl ether (250 mg.) was dissolved in 15 ml. of acetic anhydride and 4 ml. of 40% hydrobromic acid was added cautiously while heating on the water-bath. Heating was continued for 6 hours whereupon the solution was poured into 200 ml. of ice and water. The crude product was removed by filtration and crystallized from acetone-water; yield 300 mg., m.p. 254-255° (dec.). An amount of 100 mg. of this material was acetylated overnight at ice-box temperature with acetic anhydride (15 ml.) and pyridine (5 ml.). The product obtained on pouring the solution into 150 ml. of ice and water was crystallized from ethanol (Magnesol); yield 68 mg. of colorless crystals, m.p. 222-223° raised to 235-236° on grinding in a mortar which latter melting point was unchanged on admixture with a specimen of dihydro-iso-osajin monoacetate of like melting point prepared from osajin. This polymorphous behavior is characteristic of this substance.[1]

Anal. Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.27; H, 6.39.

Dihydro-isopomiferitin Dimethyl Ether (XVIII) from Dihydro-iso-osajinol (V).—Dihydro-iso-osajinol (400 mg.) was treated as described above for dihydro-iso-osajetin monomethyl ether except that 1 g. of homoveratronitrile (m.p. 63-63.5°) was substituted for the homoanisonitrile. The crude product was isolated and chromatographed in the same manner; yield 210 mg. (33%), m.p. 112-113°. Pure material was obtained on recrystallization from benzene; m.p. 113.5-114° unchanged on admixture with a specimen of dihydro-isopomiferitin dimethyl ether[1] of like melting point prepared from the natural pigment pomiferin. The light buff color of the crystals, the coloration with ferric chloride (alcohol) and ultraviolet absorption spectrum (Fig. 2) were identical for the preparations from the two sources.

Anal. Calcd. for $C_{24}H_{26}O_4(OCH_3)_2$: C, 70.88; H, 7.32; OCH_3, 14.09. Found: C, 70.78; H, 7.04; OCH_3, 13.96.

Dihydro-isopomiferin Dimethyl Ether (XX) from Dihydro-isopomiferitin Dimethyl Ether (XVIII).—Dihydro-isopomiferitin dimethyl ether (400 mg.) was treated with ethyl formate and sodium as described above for the corresponding osajetin derivative and the product was isolated in the same manner; yield 295 mg., m.p. 202-205°. Further crystallization from ethanol-water yielded pure material; m.p. 207.5-209° unchanged on admixture with dihydro-isopomiferin dimethyl ether[1] of like melting point prepared from pomiferin.

Anal. Calcd. for $C_{25}H_{24}O_4(OCH_3)_2$: C, 71.97; H, 6.71; OCH_3, 13.78. Found: C, 72.06; H, 6.55; OCH_3, 13.98.

Dihydro-isopomiferin Diacetate (XXII) from Dihydro-isopomiferin Dimethyl Ether (XX).—Dihydro-isopomiferin dimethyl ether (300 mg.) was demethylated with hydrobromic acid as described above for the corresponding osajin derivative and the product was isolated in the same manner; yield 300 mg., m.p. 205-209° (dec.). Pure material was obtained on further crystallization from acetone-water; m.p. 238-239° (dec.). The m.p. 221-222° has been previously recorded[1] for dihydro-isopomiferin. An amount of 100 mg. of this material was acetylated as described above for the corresponding osajin derivative and the product was isolated in the same manner; yield 70 mg. of colorless crystals, m.p. 204-207°. Further crystallization from ethanol yielded pure material; m.p. 221.5-222° unchanged on admixture with a specimen of dihydro-isopomiferin diacetate of like melting point[1] prepared from pomiferin.

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 68.77; H, 5.97. Found: C, 68.48; H, 6.15.

Dihydro-iso-osajetin.—Dihydro-iso-osajin[1,4] (300 mg., m.p. 287-288°, dec.) was dissolved in 10 ml. of 95% ethanol and added slowly to a boiling solution consisting of 12 ml. of 95% ethanol and 18 ml. of 20% aqueous sodium hydroxide. After the addition was completed the solution was refluxed for 20 minutes, cooled and acidified with phosphoric acid. The aqueous acid solution was extracted with four 25-ml. portions of ether. The ether extracts were combined and washed with 5% aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. On removal of the ether a yellowish-red oil was obtained which was crystallized from ethanol; yield 127 mg. of light yellow crystals, m.p. 171.5-172.5°. The substance gave a green-brown coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{24}H_{28}O_5$: C, 72.69; H, 7.12. Found: C, 72.77; H, 7.24.

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Summary

Reaction of phloroglucinol with 3-methyl-2-butenyl bromide led to the synthesis of dihydro-iso-osajinol (V), its isomer IV and the tetracyclic derivative VI (IV and V characterized as monoacetates). Compound V was also obtained by reduction of the ketone X synthesized from 2,2-dimethyl-5,7-chromandiol (VII) and β,β-dimethylacrylyl chloride, the tetracyclic diketone XI (characterized as its monoxime) being formed in the latter reaction and yielding VI on reduction. A compound IX, isomeric with X, was obtained on condensation of β,β-dimethylacrylonitrile (or β-hydroxyisovaleronitrile) with VII.

Condensations of dihydro-iso-osajinol (V) with homoanisonitrile (XIII) and with homoveratronitrile (XIV) led to the synthesis of dihydro-iso-osajetin monomethyl ether (XVII) and dihydro-isopomiferitin dimethyl ether (XVIII), respectively, identical with specimens prepared from the natural pigments osajin and pomiferin (corrected ultraviolet spectra are presented for XVII and XVIII; dihydro-iso-osajetin is described). Compounds XVII and XVIII were converted to dihydro-iso-osajin monomethyl ether (XIX) and dihydro-isopomiferin dimethyl ether (XX), respectively, and these on demethylation produced dihydro-iso-osajin (XXIII) and dihydro-isopomiferin (XXIV).

These syntheses verify the structures assigned to XXIII and XXIV by degradative methods and also verify those assigned to the natural pigments osajin (XXV) and pomiferin (XXVI), since the reactions leading to the conversion of these into their dihydro-iso derivatives are well established.

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