extraction with ether gave 582 mg. of strongly ferric chloride-positive material. The chromatogram on formamide-impregnated paper, using hexane-benzene (1 v.: 1 v.) as mobile phase, showed four spots with those at R_f 0.055 and 0.620 as the main components. The mixture was separated on a Celite-formamide column using hexane-benzene (1 v:1 v.) as elutant and collecting 100-cc. fractions. Fractions 17–20 gave 204 mg. of crystalline material, m.p. 169–170°, which was unchanged on crystallization from ether-hexane; $[\alpha]_D^{25}$ −41.2° (*c* 0.8); ultraviolet λ_{max} 269 mμ, log ε 3.95; in alkaline solution λ_{max} 315 mμ, log ε 3.79; infrared 2.92 (OH), 5.82 (OAc), 5.86 and 5.91 (C=O), 6.00, 6.14 (C=C—C=O); ferric chloride test strongly positive.

Anal. Calcd. for $C_{32}H_{46}O_8$: C, 68.79, H, 8.30; O, 22.91. Found: C, 68.37; H, 8.65; O, 22.72.

Fractions 22–26 eluted with benzene gave 43 mg. of material, m.p. 273–275°. This product was identical with diosphenol-III.

Diosphenol-III. To a solution of 1.1 g. of dihydrocucurbitacin B in 1.9 l. of 95% ethanol was added 100 cc. of 2*N* aqueous sodium hydroxide, and the mixture was allowed to stand for 22 hr. The ultraviolet absorption spectrum showed two strong bands at 272 mμ and 315 mμ. The solution was neutralized with acetic acid, concentrated at 60° under reduced pressure until a precipitate began to form, diluted with water, and extracted with ether. The combined product of three runs weighed 3.1 g. and gave a strong positive test with ferric chloride. It was chromatographed on a 1.5 × 60-cm. Celite-formamide column using hexane-benzene (1 v.:1 v.) as elutant and collecting 200-cc. fractions. Fractions 1–16 gave 370 mg. of amorphous products. Fractions 17–22 were eluted with benzene and gave 1.2 g. which, after crystallization from chloroform-hexane, weighed 700 mg., m.p. 271–273°. The analytical sample was recrystallized from methylene chloride-ether; m.p. 274–275°; $[\alpha]_D^{25}$ +35° (*c* 0.8); ultraviolet λ_{max} 270 mμ, log ε 4.27; in 0.02 *N* ethanolic sodium hydroxide λ_{max} 272 mμ, log ε 4.02 and λ_{max} 315 mμ, log ε 3.82; infrared 2.90 (OH), 5.87 and 5.89, (C=O), 5.99 and 6.13 (C=C—C=O).

Anal. Calcd. for $C_{32}H_{44}O_7$: C, 71.08; H, 8.20; O, 20.72. Found: C, 71.24; H, 8.09; O, 20.81.

A solution of diosphenol-III on further standing in 0.1*N* aqueous ethanolic solution showed no change in absorption in the ultraviolet. On the other hand diosphenol-II under the same conditions soon showed the appearance of a second maximum in the ultraviolet absorption spectrum at 272 mμ, the original diosphenol maximum at 315 mμ remaining unchanged. Isodihydrocucurbitacin B under these conditions after 3 hr. absorbed strongly at 315 mμ and after 22 hr. at both 272 mμ and 315 mμ.

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Improved Synthesis of Scopoletin

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Scopoletin has been prepared in 30% yield from commercial isovanillin. Reaction of isovanillin with peracetic acid provided a good yield of 3-hydroxy-4-methoxyphenyl formate which could be hydrolyzed to 2,4-dihydroxyanisole. Treatment of either the phenol or its formate with ethyl acetoacetate yielded 4-methylscopoletin, while use of the sodium derivative of diethyl oxalacetate gave ethyl scopoletin-4-carboxylate. Hydrolysis, and decarboxylation of the resulting acid, provided the desired coumarin.

Scopoletin (6-methoxy-7-hydroxycoumarin) has been implicated widely in plant processes such as seed germination,[1] growth,[2] differentiation,[3] and disease.[4] The numerous methods reported for its synthesis involve extended series of reactions based on either a preformed coumarin[5] or 2,4-dihydroxyanisole (VI).[6,7] The phenol (VI) has been obtained from various substituted guaiacols through multistep sequences in which maximum yields have remained below 25%.[6-8] Repeated unsuccessful attempts in our laboratory to improve these procedures necessitated development of a more satisfactory route. Reaction of commercial isovanillin (3-hydroxy-4-methoxybenzaldehyde) (I) with a solution of peracetic acid in ethyl acetate provided 3-hydroxy-4-methoxyphenyl formate (II) in 74% yield (Chart I). Saponification of II gave a 72% yield of the desired phenol, while saponification without isolation of the intermediate formate provided a 66% yield of VI based on isovanillin.

Attempts to prepare scopoletin from VI by standard methods such as reaction with sodium ethyl formylacetate or malic acid and sulfuric acid were unsuccessful, although many variations in the reaction conditions were employed. Previous experience in this laboratory had indicated the utility of 85% phosphoric acid as a condensing agent in the Pechmann reaction, and, in this way, a quantitative yield of 4-methylscopoletin (VII) could be obtained easily from II and ethyl aceto-

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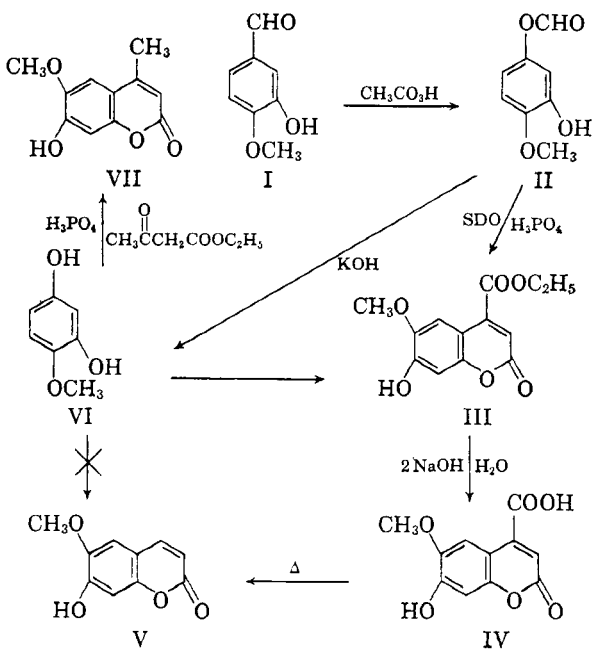
acetate. Condensation of VI with the sodium derivative of diethyl oxalacetate (SDO) similarly produced a 76% yield of ethyl scopoletin-4-carboxylate (III). Replacement of the phenol by its formate ester resulted in a less pure product and a lower yield.

Chart I



The ester III was resistant to hydrolysis with hydrochloric acid. However, hydrolysis at room temperature in the presence of exactly two equivalents of sodium hydroxide provided a 74% yield of scopoletin-4-carboxylic acid (IV) after twenty-four hours. Use of less than two equivalents of base did not permit complete hydrolysis, while three to six equivalents resulted only in the formation of dark tar. The odor of VI in the strongly alkaline hydrolyzate suggested that III undergoes alkaline degradation even more readily than does scopoletin itself.

The decarboxylation of IV to V could be carried out by pyrolysis in the presence of copper powder. However, a higher yield and purer product resulted when the reaction temperature was controlled by the use of a high boiling solvent such as quinoline. In either case, the course of the reaction could be followed by a change in the color of fluorescence under ultraviolet light from bright yellow to vivid blue.

Although no extensive search was made for optimum conditions and yields, the procedure described above permits the preparation of scopoletin in an overall yield of 30% based on isovanillin.

EXPERIMENTAL[9]

3-Hydroxy-4-methoxyphenyl formate (II). Commercial isovanillin[10] (194 g., 1.28 moles) was dissolved in 1 l. of 99% ethyl acetate and the solution was warmed to 40°. This temperature was maintained while 392 g. of peracetic acid (1.40 moles) (27.1% in ethyl acetate) was added over a period of 1 hr. Toward the end of addition, the reaction became exothermic and cooling was required. The mixture was maintained at 40° for an additional hour by continued cooling and then allowed to stand overnight. Ethyl acetate was removed by distillation, 500 ml. of ethylbenzene was added to the residue, and solvent again was removed by distillation. After another treatment with ethylbenzene, the residue was distilled. The colorless product, b.p. 111–115° (1 mm.), weighed 159 g. (74% yield). After 2 weeks at room temperature, the product solidified, and recrystallization from isopropyl ether gave colorless needles, m.p. 57–58°.

Anal. Calcd. for $C_8H_8O_4$: C, 57.1; H, 4.8. Found: C, 57.3; H, 4.7.

In a number of preparations, a semisolid crude product was obtained before distillation. Recrystallization of this material from ethanol afforded 3-hydroxy-4-methoxybenzoic acid, m.p. 255° (lit.[11] m.p. 251°).

2,4-Dihydroxyanisole (VI). The formate II (25 g., 0.15 mole) was mixed with 210 g. of a 10% solution of potassium hydroxide in 80% ethanol and boiled under reflux for 1 hr. The alcohol was removed by distillation, and the residue was acidified, extracted with ether, and the extracts dried. Distillation provided 15 g. (72% yield) of 2,4-dihydroxyanisole, b.p. 123–125° (1.5 mm.); the condenser was heated during distillation in order to prevent solidification of the product. Recrystallization from benzene-hexane provided white crystals, m.p. 70° (lit.[6] m.p. 72°).

In another experiment, 146 g. of isovanillin in 1 l. of 99% ethyl acetate was oxidized with 325 g. of a 24.7% solution of peracetic acid in ethyl acetate as described. After removal of ethyl acetate and treatment with three portions of ethylbenzene, the residue was saponified in 1340 g. of 10% potassium hydroxide in 80% aqueous ethanol to give 86 g. (66% yield) of colorless product, b.p. 115–116° (1 mm.).

4-Methylscopoletin (VII). The formate II (5.0 g., 0.03 mole) was mixed with ethyl acetoacetate (7.0 g., 0.05 mole), and 85% phosphoric acid (15 ml.) was added. After standing at room temperature overnight, the yellow semisolid was stirred with water, filtered, and the crystalline residue washed with water and air-dried. The crude yield of VII was 7.0 g. (100%), m.p. 212–214°, and recrystallization from ethanol gave pale yellow needles, m.p. 213–215° (lit.[8] m.p. 213–215°).

Ethyl scopoletin-4-carboxylate (III). (A) *From 3-hydroxy-4-methoxyphenyl formate.* The phenyl ester II (8.5 g., 0.05 mole), 15 g. (0.06 mole) of 92% sodium ethyl oxalacetate, and 20 ml. of 85% phosphoric acid were mixed and warmed on a steam bath for 30 min. with frequent stirring. The mixture was poured over several hundred grams of ice, and the precipitate was removed by filtration, washed with cold water, and sucked free of excess moisture. Recrystallization from a minimum amount of hot ethanol provided a 46% yield of yellow solid (6.0 g.) m.p. 169–171°. Infrared spectra and mixed m.p. indicated that the product was identical with that formed from 2,4-dihydroxyanisole in (B).

(B) *From 2,4-dihydroxyanisole.* The phenol VI (10 g., 0.07 mole) was melted with 20 g. (0.09 mole) of 92% sodium ethyl oxalacetate, and 85% phosphoric acid (40 ml.) was added. The mixture was heated on a steam bath for 1.5 hr. with frequent stirring, poured into 300 g. of ice, and stirred until a precipitate formed. The solid was isolated by filtration, washed with water, and air-dried to give 22 g. of orange-brown powder. This material was suspended in 100 ml. of ethyl ether, the suspension filtered, and the product washed with several additional portions of ether and air-dried. The yield of crude ester was 14 g. (76%), m.p. 162–165°; recrystallized from ethanol, its m.p. was 173–175°.

(9) All melting points were measured in a Vanderkamp block and are corrected.

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Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.1; H, 4.6. Found: C, 58.8; H, 4.7.

Scopoletin-4-carboxylic acid (IV). Crude ester III (3.77 g., 14.3 moles) was slurried in 50 ml. of water and 2.5*M* sodium hydroxide solution (11.5 ml.) was added. After 24 hr. at room temperature, the deep red solution was acidified, the precipitate was removed by filtration, washed with cold water, and air-dried to give 2.50 g. (74% crude yield) of red powder, m.p. 292–293° dec. Trituration with a small amount of cold ethanol provided a yellow-orange powder, m.p. 297–299° dec., while recrystallization from ethanol gave bright yellow needles, m.p. 300–301° dec.

Anal. Calcd. for $C_{11}H_8O_6$: C, 55.9; H, 3.4. Found: C, 55.9; H, 3.5.

Scopoletin (V). The crude acid IV (300 mg.) was mixed with 12 g. of quinoline and 500 mg. of copper powder and boiled under reflux until carbon dioxide evolution ceased (about 30 min.). The cooled mixture was diluted with 100 ml. of chloroform, filtered, and extracted with 10% sulfuric acid. After washing further with water, the chloroform solution was dried, decolorized, and the solvent evaporated under nitrogen. The solid residue was triturated with a few drops of ethanol and filtered. The yield of crystalline scopoletin, m.p. 201–202°, was 200 mg. (82%). The melting point of a mixture with authentic scopoletin (m.p. 203–204°) was undepressed, and infrared spectra and chromatographic properties of the two were identical.

Another portion of IV (300 mg.) was thoroughly mixed with 500 mg. of copper powder and warmed over a small flame. As decomposition proceeded, a yellow solid sublimed onto the walls of the tube. When gas evolution had ceased, the tube was cooled and the contents extracted repeatedly with hot ethanol until extracts no longer were appreciably fluorescent. The combined extracts were filtered, ethanol removed under nitrogen, and the residue recrystallized from glacial acetic acid. The yield of scopoletin, m.p. 198–200°, was 150 mg. (60%).

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Bitter Principles of the Simaroubaceae. I. Chaparrin from *Castela Nicholsoni*

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A bitter lactone, chaparrin, has been isolated from *Castela Nicholsoni*, and converted into a bis-dehydration product, chaparrol, also a lactone. The uncharacterized crystalline material accompanying chaparrin yielded glaucanol on treatment with acid, suggesting the presence in *Castela Nicholsoni* of glaucarubol.

Castela Nicholsoni Hook ("Chaparro amargosa") is a bitter shrub of the family Simaroubaceae, native of Mexico. Like a number of species of other genera of this family (*Simarouba, Brucea, Ailanthus, Quassia*), *Castela Nicholsoni* has found extensive use in folk medicine:[2] most of these drugs are used as amoebicides in the treatment of dysentery,[3–12] and several of them have yielded crystalline principles that have been found to be highly effective amoebicidal agents.

C. Nicholsoni has been examined chemically and pharmacologically by numerous investigators. Bosman[13] reported the isolation of three crystalline compounds: castelin, a glycoside; castelagenin, its aglycon; and castelamarin. To the latter, a bitter lactone giving a blue color with concentrated sulfuric acid (characteristic of many of the compounds of this group), was assigned the unlikely structure of the lactone of 2-hydroxy-3-methoxycyclohexaneacetic acid. The synthesis of a compound with this structure was reported by Paranjape *et al.*,[14] and found not to be identical with the natural lactone.

In 1944, Alles and Saunders[15] re-examined "chaparro amargosa" and succeeded in isolating two substances. One of these, m.p. 286–288°, gave a blue coloration with concentrated sulfuric acid; the other, m.p. 280–287°, gave no color with sulfuric acid. Their study was terminated before adequate purification of these materials could be carried out.

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