# CLXIV.—*Hydroxy-carbonyl Compounds. Part I. A Synthesis of Scopoletin.*

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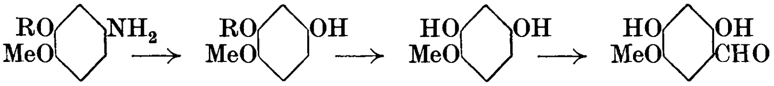
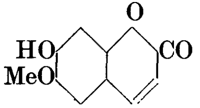
THE results of the investigations of Takahashi (*Chem. Zentr.*, 1888, **19**, 1364), Henschki (*Arch. Pharm.*, 1888, **226**, 203), and Schmidt (*Arch. Pharm.*, 1897, **236**, 324) show that scopoletin is an ether of æsculetin which is isomeric with the monomethyl ether prepared by Tiemann and Will (*Ber.*, 1882, **15**, 2072). Moore (J., 1911, **99**, 1043) degraded the coumarin to the parent phenol, which he concluded to be 2 : 4-dihydroxyanisole (III) since it was isomeric and not identical with methoxyquinol, and in consequence considered that scopoletin had formula (V). It is of interest to note that, whereas Tiemann and Will prepared 7-*O*-methylæsculetin by the partial methylation of æsculetin with methyl iodide and alkali, Glaser (*Arch. Pharm.*, 1928, **266**, 573), using methyl sulphate, obtained scopoletin. The orientation ascribed to Tiemann and Will's ether by Bargellini and Monti (*Gazzetta*, 1915, **45**, 90) has been confirmed by synthesis (J., 1930, 2434), but a direct synthesis of scopoletin from 2 : 4-dihydroxyanisole does not appear to have been described.



(I.) (II.) (III.) (IV.)

[R = $C_6H_4Me{\cdot}SO_2{\cdot}$]



(V.)

In order to overcome the difficulties encountered in unsuccessful attempts to prepare 2 : 4-dihydroxyanisole directly from 5-nitroguaiacol it was considered necessary to protect the hydroxyl group of the nitro-compound. Moreover, it was essential that the protecting group employed must be stable during the stages of reduction, diazotisation, and decomposition of the diazonium salt and still be capable of being finally removed to give the required phenol (III). Thus, although *2-benzyloxy-*p*-anisidine* was readily obtained, decomposition of the corresponding diazonium sulphate resulted in simultaneous debenzylation and only a small amount of highly impure dihydroxyanisole was isolated. The *p*-toluenesulphonate of 5-nitroguaiacol, however, proved a convenient starting material and enabled the preparation of (III) to be readily effected through the stages (I) and (II).

The orientation of the *aldehyde* (IV) follows from its methylation to asarylaldehyde, and on vigorous acetylation by the method of Perkin it gave 7-acetoxy-6-methoxycoumarin. Removal of the acetyl group gave 7-hydroxy-6-methoxycoumarin (scopoletin) the properties of which are identical with those of the natural product. The synthetic compound has m. p. 204° (acetate, m. p. 177°) in agreement with that of the natural compound given by Power and Moore (J., 1909, **95**, 243), Moore (J., 1910, **97**, 2223; 1911, **99**, 1043), and Edwards and Rogerson (*Biochem. J.*, 1927, **21**, 1010) (Glaser, *loc. cit.*, gives m. p. 199°).

The properties of 2 : 4-dihydroxyanisole, m. p. 72°, closely resemble those of the compound, m. p. 66—67°, obtained by the alkali fusion of a sulphonic acid of guaiacol (D.R.-P. 109,289). This is in agreement with the suggestion of Herzig and Pollak (*Monatsh.*, 1904, **25**, 808).

## EXPERIMENTAL.

2-*Benzyloxy*-p-*anisidine*.—4-Nitro-2-benzyloxyanisole, obtained from 5-nitroguaiacol (Pollecoff and Robinson, J., 1918, **113**, 648) by the action of benzyl chloride and potassium carbonate in boiling acetone, crystallised from benzene–ligroin in pale yellow prisms, m. p. 91—92°, which in contact with the solvent changed to the form of m. p. 98° (Allan and Robinson, J., 1926, 376).

A mixture of the nitro-compound (50 g.), hydrated sodium sulphide (100 g.), and water (400 c.c.) was refluxed for 21 hours. The cooled reaction mixture was extracted with chloroform and the gradual addition of sulphuric acid to the dried chloroform solution precipitated the sulphate (45 g.), which crystallised from hot water in needles. This salt is sparingly soluble in cold water. Decomposition of the sulphate with excess of 10% aqueous sodium hydroxide gave the *amine*, which separated from dilute methyl alcohol in colourless needles, m. p. 100—101° (Found: C, 73·4; H, 7·0. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6%). The compound is easily soluble in benzene or alcohol and sparingly soluble in ligroin or water. It gives with alcoholic ferric chloride a pale green coloration rapidly changing to purple and finally to blue, which persists after dilution with water. The *acetyl* derivative crystallised from dilute methyl alcohol in colourless needles, m. p. 135° (Found: C, 70·8; H, 6·5. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3%).

5-*Amino*-2-*methoxyphenyl* p-*Toluenesulphonate* (I).—The *p*-toluenesulphonate of 5-nitroguaiacol was prepared by heating a mixture of 5-nitroguaiacol (30 g.), *p*-toluenesulphonyl chloride (48 g.), and pyridine (30 c.c.) on the steam-bath for 1 hour. It crystallised from acetone in prisms, m. p. 149°, identical with a specimen prepared by the procedure of Reverdin and Crépieux (*Ber.*, 1903, **36**, 2258). These authors give m. p. 145°.

The nitro-compound (40 g.) was gradually added to a hot solution of stannous chloride (100 g., anhydrous) in a mixture of acetic acid (100 c.c.) and concentrated hydrochloric acid (100 c.c.), and the reduction completed by heating on the steam-bath for 1 hour. The cooled reaction mixture was poured into 28% potassium hydroxide solution (600 c.c.) at 0°, and the suspension collected, washed with water, and extracted with boiling alcohol. After filtration, the greater part of the solvent was distilled, and the *amine* (29 g.) precipitated with water. Crystallised from methyl alcohol (charcoal), it formed colourless prisms, m. p. 151° (Found: C, 57·6; H, 5·2. $C_{14}H_{15}O_4NS$ requires C, 57·3; H, 5·1%). The compound is easily soluble in benzene and sparingly soluble in water or ligroin. The ferric chloride reaction in alcohol is reddish-brown, changing to wine-red on dilution with water. The *acetyl* derivative crystallised from 50% methyl alcohol in rhombic plates, m. p. 138—139° (Found: C, 57·3; H, 5·2. $C_{16}H_{17}O_5NS$ requires C, 57·3; H, 5·1%). On addition of sulphuric acid to a chloroform solution of the base the sulphate was obtained, which crystallised from water in sparingly soluble needles.

*5-Hydroxy-2-methoxyphenyl* p-*Toluenesulphonate* (II).—The foregoing sulphate was suspended in water (400 c.c.) and concentrated sulphuric acid (22 c.c.) cooled to below 0° and diazotised by the addition of sodium nitrite (8·5 g.) (agitate). After 3 hours the diazonium solution was gradually added to a boiling solution of copper sulphate (400 g.) in water (400 c.c.). After cooling, the reaction mixture was extracted three times with ether and the combined extracts were washed with sodium bicarbonate solution and dried. The residue left on removal of the solvent crystallised from warm 50% methyl alcohol (charcoal) in yellow prisms (11 g.). On recrystallisation, the *phenol* formed colourless squat prisms, m. p. 124° (Found: C, 57·3; H, 5·0. $C_{14}H_{14}O_5S$ requires C, 57·1; H, 4·8%). The substance is easily soluble in alcohol, moderately easily soluble in benzene, and almost insoluble in water. It gives with alcoholic ferric chloride a pale green coloration which deepens on dilution with water.

2 : 4-*Dihydroxyanisole* (III).—A solution of the foregoing *p*-toluenesulphonate (35 g.) in 12% aqueous potassium hydroxide was refluxed for 4 hours, cooled, and neutralised with hydrochloric acid. The mixture was saturated with ammonium sulphate, and 2 : 4-dihydroxyanisole isolated by eight extractions with ether. The semi-solid, dark red product was distilled under diminished pressure; the pale yellow distillate (11 g.), b. p. 175—178°/25 mm., which

solidified, crystallised from benzene or benzene–ligroin in colourless hygroscopic plates, m. p. 72° (Found : C, 60·2; H, 6·1. Calc. for $C_7H_8O_3$ : C, 60·0 ; H, 5·7%). (Moore, *loc. cit.*, gives m. p. 66—68°.) In alcohol the ferric chloride reaction is grass-green, changing to orange-yellow on dilution with water. The phenol dissolves in concentrated sulphuric acid to a light brown solution and, after 5 minutes, on addition of a little water, an intense crimson colour is produced, changing to pale blue on further dilution. On addition of an excess of alkali, the blue colour changes to reddish-orange, but returns on acidification with mineral acid.

Acetylation with pyridine and acetic anhydride gave the diacetate, m. p. 63° (Moore, *loc. cit.*, gives m. p. 62—64°).

2 : 4-*Dihydroxy*-5-*methoxybenzaldehyde* (IV).—The condensation of 2 : 4-dihydroxyanisole (10 g.) and hydrogen cyanide (10 c.c.) in ethereal solution was effected by means of zinc cyanide (5 g.) and excess of hydrogen chloride. On hydrolysis of the aldimine–zinc chloride compound at 80°, the *aldehyde* separated as a brown solid (10 g.). Crystallised from dilute methyl alcohol (charcoal), it formed pale straw-coloured, elongated prisms, m. p. 152° (Found : C, 57·5; H, 5·1. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). With alcoholic ferric chloride the substance gives a dark green coloration which changes to pale green on dilution with water. The aldehyde was acetylated (0·5 g.) by means of acetic anhydride (3 c.c.) and pyridine (2 c.c.) at 37° during 24 hours; the resulting *diacetate* crystallised from alcohol in colourless needles, m. p. 119°, which did not give a ferric chloride reaction (Found: C, 57·3; H, 5·1. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%).

Methylation of this aldehyde by means of methyl iodide and potassium carbonate in boiling acetone gave a quantitative yield of asarylaldehyde, which crystallised from dilute alcohol in colourless needles, m. p. 114° alone or mixed with an authentic specimen.

*Scopoletin* (V).—A mixture of the foregoing aldehyde (3 g.), sodium acetate (6 g.), and acetic anhydride (15 c.c.) was heated on the steam-bath for 2 hours and then at 180° for 14 hours. After the addition of warm water (80 c.c.) to the reaction mixture, the liquid was decanted from the brown gum which separated and, on cooling, *O*-acetylscopoletin (1 g.) crystallised. Purified, it separated from alcohol or acetic anhydride in colourless rectangular plates, m. p. 177° (Found: C, 61·7; H, 4·3. Calc. for $C_{12}H_{10}O_5$ : C, 61·7; H, 4·6%).

A suspension of the acetate (0·7 g.) in a mixture of methyl alcohol (15 c.c.) and hydrochloric acid (10 c.c.) was refluxed for 5 minutes. On cooling, the dark bluish solution deposited scopoletin in pale yellow needles (0·45 g.). Recrystallised from alcohol, it formed colourless needles, m. p. 204° (Found : C, 62·4 ; H, 4·5. Calc. for $C_{10}H_8O_4$ : C, 62·5 ; H, 4·2%).

An alcoholic or aqueous-alcoholic solution of the synthetic material exhibits the blue fluorescence characteristic of the natural substance. The ferric chloride reaction is green and the potassium permanganate reaction is identical with that described by Kunz-Krause (*Arch. Pharm.*, 1885, **223**, 721).

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