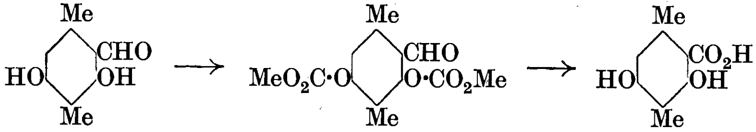
XLVII.—*Lichen Acids. Part I. Derivatives of β-Orcinol.*

By ALEXANDER ROBERTSON and RICHARD JOHN STEPHENSON.

ALTHOUGH β-orcinol, the homologue of orcinol, was isolated in 1848 by Stenhouse (*Annalen*, **68**, 104) as a product of the action of lime-water on impure usnic acid from *Usnea ceratina*, it was not until 1880 that Stenhouse and Groves (J., **37**, 405) were able to show that the phenol was derived from barbatic acid, which they obtained from *U. barbata.* This acid has since been isolated from a number of lichens, in which it invariably occurs along with usnic acid (for references, see Perkin and Everest, "Natural Organic Colouring Matters," 1918, pp. 530—542). Hesse (*Ber.*, 1898, **31**, 664; *J. pr. Chem.*, 1898, **58**, 526; 1903, **68**, 14) found that barbatic acid on hydrolysis gave rhizonic acid in addition to β-orcinol; rhizonic acid he believed to be the monomethyl ether of β-orcinolcarboxylic acid, and the depside to be derived from β-orcinolcarboxylic acid and rhizonic acid. The β-orcinol nucleus has since been found to occur in a number of depsides—atranorin (Hesse, *Ber.*, 1897, **30**, 358; *J. pr. Chem.*, 1898, **57**, 280), dirhizonic acid (Hesse, *ibid.*, 1898, **58**, 531; 1906, **73**, 120), soloric acid (Zopf, *Annalen*, 1909, **364**, 307; Hesse, *J. pr. Chem.*, 1915, **92**, 425), and armoric acid (Hesse, *ibid.*, 1907, **76**, 7).

In a study of the constitution of these depsides by synthetical means, it was essential first to devise a method for the preparation of β-orcinol in quantity, Kostanecki's process (*Ber.*, 1886, **19**, 2323) having been found unsuitable. Reduction of 2 : 6-dinitro-*p*-xylene (prepared from *p*-xylidine by Sonn's method; *Ber.*, 1916, **49**, 621) by ammonia and hydrogen sulphide invariably gave poor yields of 6-nitro-*p*-2-xylidine, but reduction by sodium disulphide in aqueous-acetone solution proved effective. The nitroxylidine was converted into 6-nitro-*p*-2-xylenol (compare D.R.-PP. 95,359 and 97,012), the reduction of which to 6-*amino*-p-2-*xylenol* was conveniently effected in alcoholic solution by iron (compare West, J., 1925, **127**, 494). Attempts to prepare β-orcinolcarboxylic acid by the method adopted by one of us (A. R.) and Robinson (J., 1927, 2196) for the preparation of *p*-orsellinic acid failed (compare Kostanecki, *loc. cit.*).

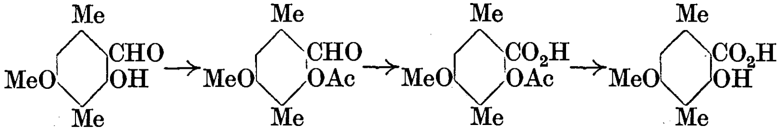
β-Orcylaldehyde (I) was prepared by Gattermann's method (compare St. Pfau, *Helv. Chim. Acta*, 1928, **11**, 864): the *dicarbomethoxy*-derivative (II) on oxidation with potassium permanganate in acetone solution and hydrolysis of the product, gave β-*orcinolcarboxylic acid* (III).



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

The synthetic acid is identical with a specimen obtained by hydrolysis of the methyl ester prepared from atranorin by St. Pfau's method (*Helv. Chim. Acta*, 1926, **9**, 650): the instability of the acid and its salts in warm aqueous solution may account for the inability of previous workers to isolate it by hydrolysis of the ester or of barbatic acid. The silver salt rapidly decomposed on exposure to light and was unsuitable for the preparation of esters. These, however, were readily formed in warm alcoholic solutions of the acid. The methyl ester thus obtained was identical with a specimen from atranorin. This ester has also been isolated from oak moss oil by Rosenthal and Walbaum (*Ber.*, 1924, **57**, 770). Its reaction with ferric chloride depends on the concentration of the alcoholic solution —a fact which may account for the divergent results recorded by previous authors.

Partial methylation of β-orcylaldehyde (I) by the methyl iodide–acetone method (Robertson and Robinson, J., 1928, 1455) proved convenient for the preparation of rhizonaldehyde (IV). Sonn (*Ber.*, 1916, **49**, 2589), who prepared this aldehyde from β-orcinol monomethyl ether by the Gattermann method, believed it to be represented by the constitution (X) (*iso*rhizonaldehyde).

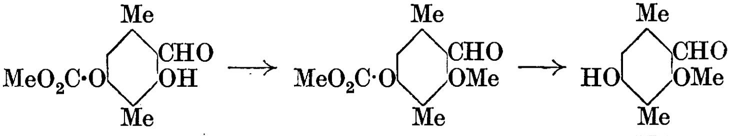


(IV.) (V.) (VI.) (VII.)

The orientation of the ether (IV) determined by St. Pfau (*Helv. Chim. Acta*, 1928, **11**, 864) has been confirmed, the condensation of (IV) with ω-methoxyacetoveratrone giving 3 : 7 : 3′ : 4′-*tetramethoxy*-5 : 8-*dimethylflavylium chloride*. Oxidation of the *acetyl* derivative (V) gave *acetylrhizonic acid* (VI), which on deacetylation yielded rhizonic acid (VII). This acid (VII) has the properties attributed to it by St. Pfau (compare Sonn, *loc. cit.*).

Attempts to methylate the *carbomethoxy*-derivative (VIII) with diazomethane in ethereal solution failed, and when a mixture of nitrobenzene and ether was used a resinous product was obtained.

Agitation of an acetone solution of (VIII) containing methyl iodide and active silver oxide gave only a trace of (IX), but this was obtained when a methyl iodide solution of (VIII) was refluxed in presence of silver oxide. On hydrolysis, it gave *iso*rhizonaldehyde (X) identical with that prepared by St. Pfau from β-orcinol monomethyl ether. As might be expected, the aldehyde (X) did not condense with ω-methoxyacetoveratrone to give a flavylium salt. The production of (X) from (VIII) determines the orientation of the latter substance.



(VIII.) (IX.) (X.)

Experiments on the synthesis of barbatic acid and its ethyl ester are in progress.

EXPERIMENTAL.

6-*Nitro*-p-2-*xylidine*.—A solution of sodium disulphide, prepared by refluxing a mixture of sulphur (16·5 g.), hydrated sodium sulphide (120 g.), and water (400 c.c.), was added in four portions to 2 : 6-dinitro-*p*-xylene (100 g.), dissolved in acetone (600 c.c.). When the vigorous reaction had ceased, the mixture was refluxed for 3 hours and poured into water (2 l.). After 12 hours, the solid was extracted three times with warm 10% hydrochloric acid, and on addition of aqueous ammonia to the combined extracts (1·5 l.) the nitroamine (68 g.) was obtained as a yellow solid, which crystallised from ligroin in orange-yellow needles, m. p. 96°.

6-*Nitro*-p-2-*xylenol*.—A solution of the nitroamine (50 g.) in a mixture of concentrated sulphuric acid (100 c.c.) and water (200 c.c.) was poured on ice (300 g.) to ensure the separation of the sulphate in small crystals. Sodium nitrite (20·7 g.), dissolved in water (100 c.c.), was then introduced, and the mixture stirred for 1·5 hours. The filtered diazo-solution was gradually added to boiling 30% sulphuric acid (300 c.c.); on cooling, the nitroxylenol separated. Crystallisation from water and then from ligroin gave the product (37 g.) in orange-yellow plates, m. p. 91°. The crude nitroxylenol, which could not be employed for the next stage, can be purified by distillation under diminished pressure, b. p. 185—187°/20 mm.; the warm residue in the flask is, however, liable to explode.

6-*Amino*-p-2-*xylenol*.—A mixture of the nitroxylenol (50 g.), iron powder (50 g.), alcohol (300 c.c.), and concentrated hydrochloric acid (5 c.c.) was refluxed for 6 hours, a test then showing that the reduction was complete. The filtered solution was concentrated to 75 c.c., saturated with hydrogen chloride, and kept at 0° for some hours. The hydrochloride was collected and washed with 96% alcohol saturated with hydrogen chloride. The salt crystallised in colourless elongated prisms (38 g.). Saturated sodium bicarbonate solution liberated *6-amino-*p*-2-xylenol,* which crystallised from water in fern-like clusters of colourless plates, m. p. 155° (Found : C, 70·1; H, 8·3. $C_8H_{11}ON$ requires C, 70·0; H, 8·1%). The amine is readily soluble in alcohol and in acetone.

2 : 6-*Dihydroxy-*p*-xylene* (β-*Orcinol*).—The aminoxylenol hydrochloride (20 g.) was dissolved below 0° in a mixture of concentrated sulphuric acid (55 c.c.) and ice and water (800 c.c.). Sodium nitrite (8 g.), dissolved in water (100 c.c.), was then introduced, and the mixture stirred for 45 minutes. The diazonium salt solution was heated on the steam-bath until the evolution of nitrogen had almost ceased and was then boiled for 5 minutes. A little charcoal was added and the solution was filtered, cooled, and saturated with ammonium sulphate. Part of the β-orcinol crystallised; the remainder was isolated by three extractions with ether. The product (12 g.) crystallised from benzene in pink stellate aggregates of prisms, m. p. 163°; distillation gave a colourless specimen, b. p. 277—280°.

β-*Orcylaldehyde* (I).—A mixture of β-orcinol (20 g.), anhydrous hydrogen cyanide (15 c.c.), and ether (300 c.c.) was saturated with hydrogen chloride. The aldimine hydrochloride, which separated in almost colourless prisms in 2 hours, was collected after 12 hours, washed with ether, and dissolved in cold water (400 c.c.). The solution was heated on the steam-bath for 2 hours; a part of the aldehyde crystallised and the remainder separated on cooling. Recrystallisation from 30% alcohol gave a hydrate (22 g.) in colourless needles, m. p. 168° (Found : C, 61·9; H, 6·5. Calc. for

$$C_9H_{10}O_3,0{\cdot}5H_2O:$$

C, 61·7; H, 6·3%. Found in a specimen dried at 105—110° for 6 hours : C, 65·1; H, 6·1. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%) (St. Pfau, *loc. cit.*, gives m. p. 163—164°). The ferric chloride reaction in alcohol is reddish-violet and addition of the aldehyde to aqueous calcium hypochlorite gives an intense yellow coloration. Acetylation with acetic anhydride and potassium carbonate gave a product which could not be purified.

2 : 4 - *Dimethylcarbonato* - 3 : 6 - *dimethylbenzaldehyde* (II).—8% Aqueous sodium hydroxide (62·5 c.c.) was gradually added with vigorous agitation to a solution of β-orcylaldehyde (8·8 g.) in a mixture of acetone (80 c.c.) and methyl chloroformate (14·5 g.). After ½ hour, saturated sodium bicarbonate solution (50 c.c.) was introduced and on dilution with water (300 c.c.) the *dicarbomethoxy-*

derivative separated as an oil which solidified on being scratched. The substance crystallised from ligroin in tufts of colourless slender needles (13 g.), m. p. 91° (Found: C, 55·4; H, 5·2. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). This carbonate is readily soluble in acetone and moderately readily soluble in cold alcohols. It does not give a ferric chloride reaction.

2 : 4-*Dihydroxy*-3 : 6-*dimethylbenzoic Acid* (β-*Orcinolcarboxylic Acid*) (III).—(A) Potassium permanganate (5 g.), dissolved in water (80 c.c.), was gradually added to a solution of 2 : 4-dimethylcarbonato-3 : 6-dimethylbenzaldehyde (3 g.) in acetone (50 c.c.) maintained at 50—55°. After 15 minutes, the reaction mixture, cooled to 0°, was cleared with sulphur dioxide, and on slow evaporation of the acetone a colourless solid separated. A solution of the solid, collected after 3 days, in 4% aqueous sodium hydroxide (15 c.c.) was kept at room temperature for ½ hour, then cooled to 0°, and acidified with 10% hydrochloric acid (10 c.c.). The precipitate was dissolved in saturated aqueous sodium bicarbonate (75 c.c.), and the solution filtered from traces of β-orcylaldehyde. Acidification with 10% hydrochloric acid gave almost pure β-*orcinolcarboxylic acid* (1 g.). Warm water was added to a solution of the substance in warm acetone until a faint turbidity appeared; the cooled solution gave the acid in elongated silky needles, m. p. 184° (decomp. to β-orcinol and carbon dioxide) (Found: C, 59·3; H, 5·7. $C_9H_{10}O_4$ requires C, 59·4; H, 5·5%). The acid is readily soluble in alcohol and in acetone and sparingly soluble in cold water. It decomposes in boiling water to β-orcinol and carbon dioxide. The ferric chloride reaction in alcoholic solution is intense bluish-violet. Addition of the acid to aqueous calcium hypochlorite solution gives a transient blood-red coloration.

A solution of the acid (0·8 g.) in absolute methyl alcohol (20 c.c.) was refluxed for 4 hours, and the methyl ester precipitated from the cooled solution by means of 1% aqueous sodium bicarbonate (50 c.c.). The ester crystallised from 50% methyl alcohol in colourless, elongated, slender prisms, m. p. 143° alone or mixed with a natural specimen prepared from atranorin (Found: C, 61·1; H, 6·1. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%). Ferric chloride added to a dilute alcoholic solution gives a greenish-brown coloration, which becomes brownish-purple on addition of water. A concentrated alcoholic solution gives a brownish-purple colour, unchanged by dilution with alcohol or by addition of water. The calcium hypochlorite coloration is a transient orange.

The *ethyl* ester was isolated from a solution of the acid (0·8 g.) in absolute alcohol (20 c.c.) which had been maintained at 75° for 6 hours. Crystallisation from 50% alcohol gave colourless slender needles, m. p. 129° (Found : C, 62·8; H, 6·9. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%). The ferric chloride coloration is purple, and the calcium hypochlorite an intense orange which rapidly fades.

(B) A solution of methyl β-orcinolcarboxylate (from atranorin) 5 g.) in 10% aqueous potassium hydroxide solution was kept in a tightly stoppered vessel at room temperature for 50 hours. The reddish-brown solution, cooled to 0°, was acidified with 10% hydrochloric acid. After ½ hour, the cream-coloured precipitate was collected and extracted with cold saturated sodium bicarbonate solution (100 c.c.). Addition of 10% hydrochloric acid to the solution, filtered from traces of unchanged ester, gave the acid (III) (3 g.), which crystallised from acetone–water in elongated silky needles, m. p. 184° (decomp.) alone or mixed with a synthetic specimen (Found : C, 59·2; H, 5·7%). The colour reactions are identical with those given by the synthetic acid.

2-Acetoxy-4-methoxy-3 : 6-dimethylbenzaldehyde (*Acetylrhizonaldehyde*) (V).—A mixture of β-orcylaldehyde (10 g.), methyl iodide (8·2 g.), potassium carbonate (10 g.), and acetone (75 c.c.) was refluxed for 1¼ hours; a further quantity of iodide (4·1 g.) was added after 45 minutes. After removal of the potassium salts and acidification with acetic acid, the mixture deposited rhizonaldehyde (IV) (7 g.); a further quantity (3 g.) was obtained by evaporation of the acetone residue, and by dissolving the potassium salts in 50% acetic acid. The substance crystallised from 50% alcohol in colourless prisms, m. p. 136° (Found : C, 66·6; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%). The ferric chloride reaction is reddish-brown. This aldehyde does not give a coloration with calcium hypochlorite.

Rhizonaldehyde (10 g.), on treatment with acetic anhydride (75 c.c.) and sodium acetate (10 g.) during 3 hours on the steam-bath, gave the *acetyl* derivative (V) (11 g.), which crystallised from 40% alcohol in colourless needles, m. p. 71° (Found : C, 64·9; H, 6·6. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). The substance is easily soluble in alcohol and acetone and does not give a ferric chloride reaction.

4% Aqueous sodium hydroxide solution (8 c.c.) was added to a mixture of rhizonaldehyde (1 g.), methyl chloroformate (1 g.), and acetone (25 c.c.) cooled to 0° (agitation). The carbomethoxy-derivative separated on addition of dilute sodium bicarbonate solution (40 c.c.) and was collected after 3 hours. It crystallised from light petroleum in clusters of prisms, m. p. 90°, which gave a faint brown ferric chloride coloration.

3 : 7 : 3′ : *4′-Tetramethoxy-*5 : *8-dimethylflavylium Ferrichloride*.—Dark red needles with a green reflex separated when hydrogen chloride was passed into a solution of rhizonaldehyde (0·75 g.) and

ω-methoxyacetoveratrone (0·5 g.) in ethyl acetate (40 c.c.). After 3 days, the chloride was collected and converted into the *ferrichloride*, which crystallised from a mixture of formic and acetic acids (equal vols.) in dark red needles, m. p. 240—245° after sintering at 236° (Found : C, 45·6; H, 4·4. $C_{21}H_{23}O_5Cl_4Fe$ requires C, 45·4; H, 4·2%).

2-*Acetoxy*-4-*methoxy*-3 : 6-*dimethylbenzoic Acid* (*Acetylrhizonic Acid*) (VI).—Potassium permanganate (5 g.), dissolved in water (80 c.c.), was gradually added to a solution of acetylrhizonaldehyde (4 g.) in acetone (50 c.c.) maintained at 50°. The solution, cooled to 0°, was cleared with sulphur dioxide, and on slow evaporation of the acetone *acetylrhizonic acid*, mixed with a trace of unchanged aldehyde, crystallised. The acid (purified by solution in aqueous sodium bicarbonate as described for β-orcinolcarboxylic acid) crystallised from acetone–water (equal vols.) in rectangular plates, m. p. 146° (decomp.) (Found : C, 60·7; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). It is readily soluble in acetone and alcohol and sparingly soluble in warm water, from which it separates in small plates.

A solution of the acetyl derivative (2 g.) in 4% aqueous sodium hydroxide solution was kept at room temperature for 3 hours. Acidification of the solution with dilute hydrochloric acid then gave rhizonic acid (VII), which crystallised from acetone–water in hexagonal plates, m. p. 232° (Found in a specimen dried at 100° : C, 61·1; H, 6·4. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%). Addition of ferric chloride to an alcoholic solution gives a brown coloration, which becomes intense blue-violet on addition of water. The calcium hypochlorite coloration is yellow.

2-*Hydroxy*-4-*methylcarbonato*-3 : 6-*dimethylbenzaldehyde* (VIII).—4% Aqueous sodium hydroxide solution (25 c.c.) was gradually added to a mixture of β-orcylaldehyde (4 g.), acetone (40 c.c.), and methyl chloroformate (2·4 g.) cooled to 0° (agitation). After ½ hour, aqueous sodium bicarbonate (200 c.c.) was introduced, and after 2 hours the *carbomethoxy*-derivative was isolated; it crystallised from 70% acetone in masses of colourless slender needles, m. p. 110° (Found : C, 58·7; H, 5·6. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). The substance is easily soluble in acetone and in alcohol and insoluble in water. It crystallises from light petroleum in tiny prisms. The ferric chloride coloration is red-brown.

2-*Methoxy*-4-*methylcarbonato*-3 : 6-*dimethylbenzaldehyde* (IX).—Active silver oxide was added to a solution of the foregoing carbomethoxy-derivative (5 g.) in methyl iodide (30 c.c.), and the mixture refluxed until a sample did not give a ferric chloride reaction. The silver oxide was removed by filtration and washed with acetone

(150 c.c.). Evaporation of the combined filtrates gave a semi-solid product, which was extracted with boiling ligroin. The extract, decanted from the insoluble residue and cooled, gave the *ether* (IX) in tufts of colourless elongated prisms (4 g.), m. p. 74—75° (Found : C, 60·6; H, 6·2. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). The substance is readily soluble in alcohol and acetone and sparingly soluble in light petroleum.

A solution of the foregoing ether (0·6 g.) in 4% methyl-alcoholic sodium hydroxide (5 c.c.) was kept at room temperature for ½ hour, then acidified with 50% acetic acid, and diluted with water (40 c.c.); *iso*rhizonaldehyde (X), thus precipitated, crystallised from 25% methyl alcohol in slender needles, m. p. 151°. This aldehyde does not give a ferric chloride reaction.

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