

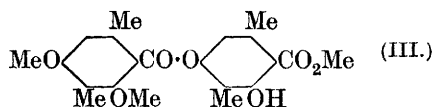
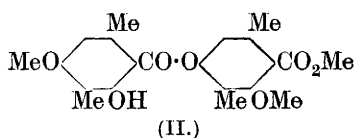
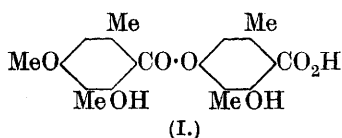
222. *Lichen Acids. Part III. The Constitution of Barbatic Acid and the Syntheses of isoRhizonic Acid and Methyl Barbatate.*

By ALEXANDER ROBERTSON and RICHARD JOHN STEPHENSON.

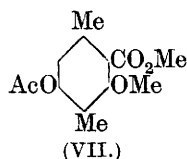
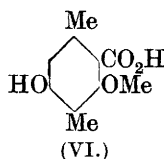
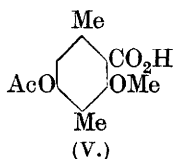
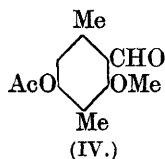
WHILE the depside evernic acid (Part II; this vol., p. 1388) is of rare occurrence, having been detected so far only in *Evernia prunastri* and *Ramalina pollinaria*, the homologous compound, barbatic acid, is present in the majority of lichens belonging to the genus *Usnea* as well as in *Alectoria ochroleuca* (for names of lichens and references, see Perkin and Everest, "Natural Organic Colouring Matters," 1918, pp. 530—542). On hydrolytic decomposition with warm baryta, this depside gives rise to rhizonic acid and β -orcinol (Hesse, *J. pr. Chem.*, 1903, **68**, 1, 13) and on prolonged boiling with alcohol forms ethyl rhizonate and β -orcinol (St. Pfau, *Helv. Chim. Acta*, 1928, **11**, 864). By analogy with evernic acid, St. Pfau (*loc. cit.*) concluded that of the three possible formulæ for the compound, formula (I) only was consistent with the properties of barbatic acid. Having failed to effect the synthesis of the acid (I) (compare Part II, *loc. cit.*), we decided to determine the constitution of the natural depside by means of alkylation experiments.

Barbatic acid was isolated from an ethereal extract of *Usnea barbata* by an improved method and the *methyl* and *ethyl* esters were prepared with the aid of ethereal diazomethane and diazoethane respectively. Hesse (*Ber.*, 1898, **31**, 663) and Zopf (*Annalen*, 1899, **306**, 298) claim to have obtained ethyl barbatate, m. p. 132°, by the action of ethyl iodide on the potassium derivative of barbatic acid in a sealed tube at 150°, but the properties of their compound (crystalline form, melting point, solubilities, and ferric chloride reaction) are entirely different from those of the authentic ester now described. It is almost certain that the drastic method employed by these authors would bring about the decomposition of the depside.

Unlike evernic acid (*loc. cit.*), barbatic acid on methylation with methyl iodide and silver oxide in boiling acetone gave rise to an amorphous product. This material, which was insoluble in 10% aqueous sodium hydroxide and did not give a ferric chloride reaction, had not the composition of methyl *O*-dimethylbarbatate (Found: OMe, 21.1%) (compare Asahina and Fuzikawa, *Ber.*, 1932, 65, 175). Prolonged treatment of the depside with ethereal diazomethane resulted in the formation of a crystalline methyl *O*-monomethylbarbatate instead of the expected *O*-dimethyl derivative. The amount of material available was insufficient to enable us to determine the constitution of this ether by hydrolysis and identification of the products, but the properties of the compound led us to believe that it had formula (II) rather than formula (III). This conclusion was confirmed by the synthesis of the ether (II).



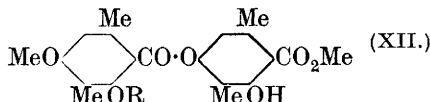
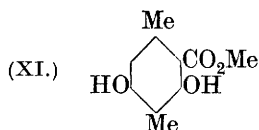
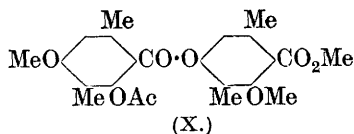
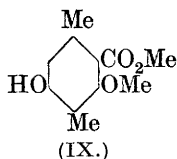
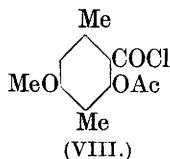
The mixture of aldehydes obtained from β -orcinol monomethyl ether by Gattermann's procedure contains only a small proportion (about 6%) of *isorhizonaldehyde* (St. Pfau, *loc. cit.*). In consequence this intermediate required for the synthesis of *isorhizonic acid* was prepared by the route described in Part I (J., 1930, 313) and the synthesis of the acid (VI) was then effected through the stages (IV) and (V). The properties of (VI) readily distinguish it from the isomeric rhizonic acid.



The oxidation of the carbomethoxy-derivative of *isorhizonaldehyde* (Part I, *loc. cit.*) in aqueous acetone with potassium permanganate gave only a poor yield of the corresponding acid. This fact necessitated the longer route in the synthesis of (VI) indicated above.

Methyl *isorhizonate* (IX) was obtained from (V) through the stage (VII) and on treatment with *O*-acetylrhizonoyl chloride (VIII) in presence of pyridine gave rise to the acetate (X), which on deacetyl-

ation afforded (II) identical in every way with the compound derived from the natural depside.



In a similar way the synthesis of methyl barbatate (XII, R = H) was effected by the interaction of (VIII) and (XI) and subsequent hydrolysis of the acetate (XII, R = Ac). The synthetic ester was identical in all respects with the natural derivative.

EXPERIMENTAL.

Acetylisorhizonaldehyde (IV).—*isoRhizonaldehyde* was prepared by the route described in Part I (J., 1930, 320) and crystallised from dilute methyl alcohol in needles, m. p. 151° (Found: C, 63.3; H, 6.5. Calc. for $C_{10}H_{12}O_3$: C, 66.6; H, 6.7%). Acetylation of this compound (4 g.) with acetic anhydride (25 c.c.) and sodium acetate (4 g.) on the steam-bath for 1 hour gave the *acetate*, which separated from dilute acetone in tiny rectangular prisms (4 g.), m. p. 67° (Found: C, 65.0; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.8; H, 6.4%). The substance is readily soluble in cold alcohol, acetone, or benzene.

Acetylisorhizonic Acid (V).—A mixture of potassium permanganate (4.5 g.) and magnesium sulphate (4 g.) was dissolved in water (75 c.c.) and gradually added to a solution of the foregoing acetate (3.5 g.) in acetone (35 c.c.) maintained at 55° . The reaction mixture was kept for 10 minutes, cooled to 0° , and cleared with sulphur dioxide and on slow evaporation of the acetone the product gradually separated. After 2 days the solid was collected and dissolved in aqueous sodium bicarbonate and the solution was filtered from traces of the unchanged aldehyde. Acidification with dilute hydrochloric acid gave *acetylisorhizonic acid*, which crystallised from ethyl acetate–ligroin in small rhombic prisms (2.5 g.), m. p. 160° (Found: C, 60.4; H, 5.9. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

isoRhizonic Acid (VI).—Hydrolysis of the acetate (0.4 g.) was effected by means of 4% aqueous sodium hydroxide (5 c.c.). On isolation the acid crystallised from benzene in colourless slender needles (0.25 g.), m. p. 156 – 157° with evolution of carbon dioxide

(Found: C, 61.3; H, 6.3. Calc. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2%) (Asahina and Fuzikawa, *Ber.*, 1932, 65, 175, record m. p. 154°). The compound is readily soluble in cold acetone, alcohol, or ethyl acetate, and sparingly soluble in boiling ligroin, and gives a yellow coloration with calcium hypochlorite. Unlike rhizonic acid, it does not give a ferric chloride reaction and is decomposed by boiling water. On being boiled with methyl or ethyl alcohol, this acid is not esterified.

Acetylisorhizonic acid (0.6 g.), dissolved in ether (20 c.c.), gave after addition of an excess of diazomethane and evaporation of the solvent a pale yellow syrup, which was dissolved in 4% methyl-alcoholic potassium hydroxide (7 c.c.) and kept at room temperature for 3 hours; the solution was then diluted with water (20 c.c.) and acidified with dilute hydrochloric acid. The methyl ester thus obtained crystallised from dilute methyl alcohol in rhombic prisms, or from ligroin in needles, m. p. 142°, which remained constant on repeated crystallisation (Asahina and Fuzikawa, *loc. cit.*, give m. p. 146°) (Found: C, 62.5; H, 6.9. Calc. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7%). The compound is easily soluble in alcohol or hot benzene and insoluble in aqueous sodium bicarbonate. It does not give a coloration with alcoholic ferric chloride or with aqueous calcium hypochlorite.

With the aid of diazoethane the *ethyl* ester was prepared by the same procedure; it crystallised from dilute ethyl alcohol in slender prisms, m. p. 103° (Found: C, 64.5; H, 7.4. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%), and from warm ligroin in fern-like clusters of tiny prisms.

Barbatic Acid.—The dried lichen, *Usnea barbata* * (1 kg. in 2 portions), was extracted in a Soxhlet apparatus with pure dry ether (5 l.) for 15 hours. Twelve hours later the ethereal extract was decanted from the usnic acid which had separated and the solvent was evaporated. The greenish residue was agitated with benzene (40 c.c.), collected, washed with a further portion of benzene (15 c.c.), and dried. A suspension of the pale green powder (consisting mainly of barbatic acid and usnic acid) in 15% aqueous potassium bicarbonate (100 c.c.) was agitated for 2 hours to convert the barbatic acid into the sparingly soluble potassium salt. The solid was then collected, washed with water (50 c.c.), and dried, and the usnic acid removed by boiling the mixture twice with benzene (200 c.c. and 100 c.c.), leaving a residue of crude potassium barbatate (3 g.). Agitation of this salt with cold 10% hydrochloric acid (50 c.c.) for 15 minutes liberated the depside, which was collected, washed, and

* This lichen was collected in the woods of Aberdeenshire and Elgin, Scotland.

dissolved in warm acetic acid, and hot water added until a faint turbidity appeared; on cooling, almost pure barbatic acid (1.8 g.) separated, m. p. 180° . Recrystallisation from benzene gave the pure compound in minute colourless prisms (1.5 g.), m. p. 186° (Found in dried material: C, 63.4; H, 5.6. Calc. for $C_{19}H_{20}O_7$: C, 63.3; H, 5.6%). The characteristic ferric chloride reaction (intense violet) and other properties of the acid were identical with those described by previous authors.

Esters of Barbatic Acid.—A solution of diazomethane [prepared from nitrosomethylurethane (1 c.c.)] in ether (15 c.c.) was added to a suspension of barbatic acid (0.5 g.) in ether (10 c.c.). The methyl ester, which separated immediately, crystallised from boiling acetone or methyl alcohol in colourless slender prisms, m. p. 170° (Found: C, 64.0; H, 6.1. $C_{20}H_{22}O_7$ requires C, 64.1; H, 5.9%). The compound is sparingly soluble in cold alcohol or hot ligroin and readily soluble in cold ethyl acetate or hot benzene. With alcoholic ferric chloride it gives a light purple-brown coloration.

The ethyl ester, prepared from the acid (0.5 g.) by the action of diazoethane (from 1 c.c. of nitrosoethylurethane), crystallised from hot benzene in colourless cubes (0.4 g.), m. p. 189° (Found: C, 64.9; H, 6.3. $C_{21}H_{24}O_7$ requires C, 64.9; H, 6.2%). This ester is considerably less soluble in organic solvents than the methyl ester and owing to its slight solubility in alcohol the ferric chloride reaction is almost imperceptible.

Methyl O-Methylbarbatate (II).—Barbatic acid (0.5 g.) was suspended in ether (20 c.c.) and treated with an excess of diazomethane (nitrosomethylurethane, 4 c.c.) in ether (80 c.c.); the acid quickly dissolved and a part of the methyl ester then separated. The mixture gradually cleared and after 3 days the ether and excess of diazomethane were removed in a vacuum, leaving a crystalline residue. Recrystallised from 80% methyl alcohol, the compound formed voluminous tufts of slender needles, m. p. 123° [Found: C, 65.1; H, 6.4; OMe, 23.5. $C_{18}H_{15}O_4(OMe)_3$ requires C, 64.9; H, 6.2; OMe, 24.0%]. It is readily soluble in acetone, benzene or ethyl acetate and gives a faint brown coloration with alcoholic ferric chloride. The substance appears to be almost insoluble in cold dilute aqueous sodium hydroxide, but the addition of an excess of 1% aqueous sodium hydroxide to a cold alcoholic solution of the compound does not give a precipitate. If, however, water is used as the diluent, the substance is immediately precipitated. Acidification of the alkaline alcoholic solution with acetic acid immediately gives a precipitate of unchanged material.

O-Acetyl-rhizonoyl Chloride (VIII).—To a solution of O-acetyl-rhizonic acid (Robertson and Stephenson, *loc. cit.*) (4 g.) in chloro-

form (20 c.c.), phosphorus pentachloride (4 g.) was added in several portions. A mild reaction ensued and hydrogen chloride was slowly evolved, and after 1 hour the chloroform and phosphorus oxychloride were removed in a vacuum at 40°. The residue was dissolved in dry chloroform, and the solution evaporated under diminished pressure. Repetition of this procedure removed the last traces of phosphorus compounds and left the *chloride* as a pale yellow syrup. Light petroleum was added to a solution of this syrup in chloroform until a faint turbidity appeared and after a time the compound separated in tiny prisms (3 g.), m. p. 84° (Found: Cl, 13.3. $C_{12}H_{13}O_4Cl$ requires Cl, 13.8%). In moist air this substance quickly decomposes with the formation of acetylrrhizonic acid.

O-Acetylrrhizonanilide.—Aniline (4 c.c.) was mixed with a solution of the foregoing chloride (1 g.) in chloroform (3 c.c.) and next day 3% hydrochloric acid (30 c.c.) was added and the chloroform removed in a vacuum. The solid was agitated with 4% aqueous sodium hydroxide to remove a small amount of deacetylated anilide and the insoluble residue was collected, washed, and crystallised from 50% acetone. The *anilide* formed colourless, minute, slender prisms (0.7 g.), m. p. 179°, readily soluble in cold acetone or ethyl acetate (Found: C, 68.7; H, 6.3. $C_{18}H_{19}O_4N$ requires C, 69.0; H, 6.1%). The compound crystallised from warm benzene in slender needles and did not give a ferric chloride reaction.

The deacetylated compound was precipitated from its aqueous alkaline solution by means of carbon dioxide and crystallised from 80% acetone, forming colourless slender prisms (0.2 g.), m. p. 179°. It gave a very dark purple coloration with alcoholic ferric chloride.

Synthesis of Methyl O-Methylbarbatate.—The interaction of *O*-acetylrrhizonoyl chloride (0.75 g.) and methyl isorhizonate (0.5 g.) in the presence of pyridine was allowed to proceed at room temperature for 3 days. 6% Acetic acid (80 c.c.) was then added, and the resulting solution extracted three times with ether (25 c.c.). The combined ethereal extracts were washed with water (50 c.c.) and then with sodium bicarbonate solution (15 c.c.) and the solvent was evaporated. A solution of the residue in 3.3% alcoholic sodium hydroxide (6 c.c.) was kept at room temperature for 15 minutes and on the addition of 0.5% aqueous sodium bicarbonate (100 c.c.) methyl *O*-methylbarbatate slowly separated. Crystallised from 80% methyl alcohol, it formed tufts of fine needles (0.4 g.), m. p. and mixed m. p. 123° (Found: C, 65.1; H, 6.3%). The ferric chloride reaction and the solubilities of the synthetic compound were identical with those of the ether prepared from barbatate acid.

Synthesis of Methyl Barbatate (XII, R = H).—A mixture of

O-acetyl rhizonoyl chloride (1.25 g.), methyl β -orcincarboxylate (J., 1930, 317) (1 g.), and pyridine (5 c.c.) was kept at room temperature for 3 days and then poured into 6% acetic acid (100 c.c.). The solution was extracted three times with ether and the combined ethereal extracts (90 c.c.) were washed with water (50 c.c.) and then with saturated aqueous sodium bicarbonate (25 c.c.) to remove acetyl rhizonic acid. The crude acetate (XII, R = Ac) left on the evaporation of the ether was dissolved in 5% methyl-alcoholic sodium hydroxide (12 c.c.) and after 15 minutes the mixture was poured into 1% aqueous sodium bicarbonate (120 c.c.). Methyl barbatate gradually separated, leaving the excess of methyl β -orcincarboxylate in solution, and, on crystallisation from acetone, formed slender rhombic prisms (0.5 g.), m. p. 170° (Found: C, 64.2; H, 6.1%). The properties of the synthetic ester were identical with those of the natural substance and a mixture of the two specimens gave an undepressed melting point.

Our thanks are due to Dr. M. M. Robertson, who kindly assisted us in collecting and sorting quantities of the lichen *Usnea barbata*. We are also indebted to the Chemical Society for grants which have in part defrayed the cost of this investigation.

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