

182. *Lichen Acids. Part II. The Constitution of Evernic Acid and the Synthesis of Methyl Evernate.*

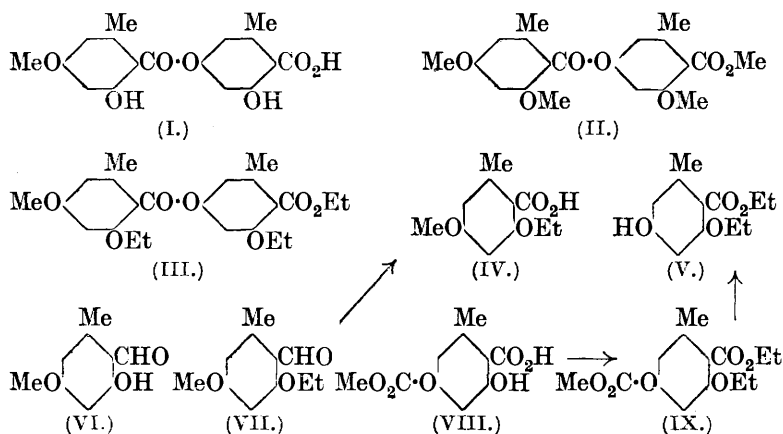
By ALEXANDER ROBERTSON and RICHARD JOHN STEPHENSON.

IN Part I (J., 1930, 313) we indicated that experiments on the synthesis of the depside barbatic acid were in progress. Several attempts to obtain this acid by methods analogous to those adopted by Fischer and Fischer (*Ber.*, 1913, 46, 1138) in their synthesis of lecanoric acid, *viz.*, the interaction of an *O*-acylrhizonoyl chloride with the disodium derivative of β -orcincarboxylic acid, were unsuccessful. Moreover, the preparation of the required intermediates in quantity is laborious and hence we were led to abandon this line of attack on the constitution of the acid. In any case as a means of determining the exact structure of the natural depsides their synthesis by Fischer's procedure of monoacylating polyhydric phenolic acids may lead to results of doubtful value, and require to be supplemented by experiments of another kind. Accordingly, in addition to synthetical experiments we resolved to investigate the problem of depside constitution by alkylation and subsequent hydrolysis of the products to their component acids. In dealing with depsides containing a methoxyl group, ethylation is to be preferred to methylation wherever it is possible.

The depside selected for study in the first instance by these methods was evernic acid. Fischer (*Ber.*, 1914, 47, 505) has shown that this substance is converted into methyl *O*-trimethyllecanorate by means of diazomethane and concludes that of the three formulæ proposed by Hesse (*J. pr. Chem.*, 1898, 57, 249), formula (I) only is in agreement with this result. Since according to Hesse (*loc. cit.*) evernic acid is isomeric with ramalic acid and both substances yield evernic acid on hydrolysis with baryta, it seemed desirable to place the constitution of the former compound beyond doubt.

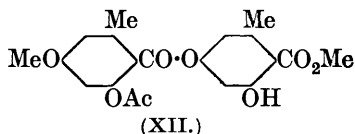
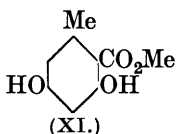
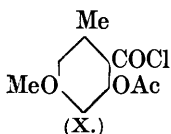
It has been found that methylation of evernic acid with methyl iodide and silver oxide in acetone affords the dimethyl ester (II) identical with methyl *O*-trimethyllecanorate (Fischer, *loc. cit.*). Ethylation with ethyl iodide in the same manner or with diazo-

ethane gave rise to *ethyl O-diethylevernate* (III), which on hydrolysis afforded a mixture of the acid (IV) and the ester (V). The conversion of everninaldehyde (VI) into 7-methoxy-5-methylcoumarin (Hoesch, *Ber.*, 1913, 46, 886) served to establish its constitution and consequently that of everninic acid; this result has been independently confirmed by Hirst (J., 1927, 2494). The structure of (IV) therefore follows from its formation from (VI) through the stage (VII). The constitution of the ester (V) is derived by its production from the *carbomethoxy*-derivative (IX), which was obtained from *p*-carbomethoxyorsellinic acid (Fischer and Hoesch, *Annalen*, 1912, 391, 347). Thus ethyl *O*-diethylevernate has formula (III) and the constitution (I) ascribed to evernic acid by Fischer is confirmed.



Having thus established the constitution of evernic acid, we decided to attempt its synthesis. Fischer and Fischer (*loc. cit.*) in their synthesis of lecanoric acid employed the carbomethoxy-group to protect the hydroxyl groups of orsellinic acid in the preparation of the required acid chloride. We found that in the preparation of *O*-carbomethoxyeverninic acid by the oxidation of the corresponding aldehyde the yields were invariably poor, and the product was contaminated with everninic acid which was difficult to remove. Likewise the conversion of everninic acid into the carbomethoxy-compound was unsatisfactory. On the other hand, *acetyleverninaldehyde* is readily oxidised to the corresponding acid and, in agreement with the statement of Fischer regarding the ease of hydrolysis of acetates of this type, we found that acetyl-everninic acid was completely hydrolysed by *N*-sodium hydroxide at room temperature in 10 minutes. The interaction of the *acid chloride* (X) and orsellinic acid in alkaline aqueous acetone at -15°

resulted only in a mixture of the two original acids, and a solution of the compounds in a mixture of benzene (or acetylene tetrachloride) and pyridine (or dimethylaniline) gave rise to oily products which in contact with water reverted to the acids. Fischer (*Ber.*, 1913, **46**, 3265) has remarked that, although the yield in depside synthesis is generally good, it is sometimes considerably depressed by the formation of by-products of the anhydride type.



The use of methyl orsellinate (XI) in place of the acid itself, however, enabled us to effect a synthesis of *methyl evernate*. The interaction of (X) and (XI) in pyridine gave rise to the *acetate* (XII), which on deacetylation afforded the methyl ester identical with a specimen prepared from the natural acid.

Attention may be directed to the curious formation of methyl everninate by the hydrolysis of methyl evernate with aqueous-alcoholic potassium hydroxide. With aqueous potash a mixture of the expected compounds was obtained.

EXPERIMENTAL.

Acetyleverninaldehyde.—The following method proved convenient for the preparation of everninaldehyde in quantity (compare Hoesch, *loc. cit.*). A mixture of orcyaldehyde (25 g.), methyl iodide (12 c.c.), anhydrous potassium carbonate (25 g.), and acetone (175 c.c.) was refluxed for 1.5 hours; a further quantity of iodide (6 c.c.) was added after 1 hour. After isolation the aldehyde crystallised from 70% methyl alcohol in prisms (23 g.), m. p. 65°. Acetylation of the compound (10 g.) with acetic anhydride (75 c.c.) and sodium acetate (10 g.) on the steam-bath during 1 hour afforded the *acetate*, which separated from warm ligroin in slender prisms (12 g.), m. p. 84° (Found: C, 63.2; H, 5.7. $C_{11}H_{12}O_4$ requires C, 63.4; H, 5.8%). This derivative is readily soluble in alcohol, acetone or acetic acid and does not give a ferric chloride reaction.

O-Acetyleverninic Acid.—The foregoing acetate was dissolved in warm acetone (100 c.c. at 50°) and oxidised by the gradual addition of a solution of potassium permanganate (12 g.) and magnesium sulphate (12 g.) in water (200 c.c.). The reaction mixture was kept for 15 minutes, cooled to 0°, and cleared with sulphur dioxide. A solution of the solid in saturated aqueous sodium bicarbonate (100 c.c.) was filtered from traces of unchanged aldehyde, and on acidification with dilute hydrochloric acid gave

almost pure acetylevernic acid (9 g.). Crystallised from ethyl acetate–ligroin, it formed prisms, m. p. 117° (Found: C, 58.7; H, 5.7. Calc. for $C_{11}H_{12}O_5$: C, 58.9; H, 5.4%) (Hesse, *J. pr. Chem.*, 1915, **92**, 431, records m. p. 111° ; St. Pfau, *Ber.*, 1924, **57**, 468, m. p. 107 – 108°).

Hydrolysis of the acetate (2 g.) by means of 4% aqueous sodium hydroxide (25 c.c.) at room temperature during 10 minutes gave the acid, needles, m. p. 170° (rate of heating, 0.5° per second). The conversion of evernic acid (15 g.) into the acetate, m. p. and mixed m. p. 117° , is best effected by means of acetic anhydride (25 c.c.) and pyridine (45 c.c.) at 37° for 80 hours.

O-Diacetylevernic Acid.—Evernic acid was isolated from the lichen *Evernia prunastri* by extraction with ether, and separated from atranorin and usnic acid according to the directions of Hesse (*J. pr. Chem.*, 1915, **92**, 431). The substance was purified by crystallisation from warm acetone and obtained in tiny, colourless, prismatic needles, m. p. 170° ; yield, 65 g. from 1.3 kg. of lichen.

The acid (2 g.) was acetylated with acetic anhydride (4 c.c.) and pyridine (6 c.c.) at 37° for 120 hours. The mixture was poured into 3.5% hydrochloric acid (100 c.c.) and the diacetate was collected, washed, and crystallised from dilute acetone and then from ethyl acetate–ligroin, forming flat and almost rectangular prisms, m. p. 159° (without evolution of carbon dioxide) (Found: C, 60.7; H, 5.0. Calc. for $C_{21}H_{20}O_9$: C, 60.5; H, 4.9%). The compound dissolves in aqueous sodium bicarbonate with the evolution of carbon dioxide and does not give a ferric chloride reaction (Hesse, *J. pr. Chem.*, 1915, **92**, 431, describes the diacetate as a crystalline powder, m. p. 144° , which gives a faint brown ferric chloride reaction).

O-Ethyleverninaldehyde (VII).—Ethylation of everninaldehyde (2 g.) was effected with ethyl iodide (3 c.c.) and silver oxide (3 g.) in boiling acetone (20 c.c.) during 1 hour. The resulting ether crystallised from dilute alcohol in tiny irregular plates (2.1 g.), m. p. 64° (Found: C, 68.1; H, 7.5. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%). This compound does not give a ferric chloride reaction.

O-Ethylevernic Acid (IV).—The foregoing aldehyde (1.2 g.) was dissolved in warm acetone (10 c.c. at 50°) and oxidised by the addition of a warm 6% aqueous solution of potassium permanganate (25 c.c.). The reaction mixture was cleared with sulphur dioxide and the acid separated as an oil which gradually solidified. Crystallised from ethyl acetate–ligroin, *O-ethylevernic acid* formed pointed prisms, m. p. 87° (Found: C, 62.8; H, 6.9. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%). It is readily soluble in alcohol, benzene, acetone, or ethyl acetate and sparingly soluble in boiling water.

Ethyl 1-O-Ethylorsellinate (V).—*p*-Monocarbomethoxyorsellinic acid (Fischer and Hoesch, *loc. cit.*) (2 g.) was dissolved in acetone (30 c.c.) and ethylated by means of ethyl iodide (4 c.c.) and silver oxide (3 g.) during 1 hour on the water-bath; a sample then gave no ferric chloride reaction, thus showing that ethylation was complete. A solution of the product in 5% alcoholic potassium hydroxide (20 c.c.) was kept at room temperature for $\frac{1}{2}$ hour, diluted with water, and acidified with hydrochloric acid. The *ethyl ester*, which separated as an oil, solidified in the course of 12 hours, and on recrystallisation from light petroleum formed tufts of elongated slender prisms (0.8 g.), m. p. 89° (Found: C, 64.5; H, 7.0. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%). This compound is readily soluble in dilute sodium hydroxide solution, alcohol, acetone, or ethyl acetate, and sparingly soluble in boiling water. It does not give a ferric chloride reaction.

Methyl O-Dimethylevernate.—A mixture of evernic acid (1 g.), silver oxide (2 g.), methyl iodide (2 c.c.), and acetone (25 c.c.) was refluxed until a sample did not give a ferric chloride reaction (1 hour). After the removal of the silver salts by filtration (wash with acetone) the solvent was removed in a vacuum and the residual solid was crystallised from methyl alcohol. Methyl *O*-dimethylevernate formed aggregates of elongated flat prisms, m. p. 148° (compare Fischer, *loc. cit.*).

Ethyl O-Diethylevernate (III).—(A) The ethylation of evernic acid (10 g.) in boiling acetone (100 c.c.) with ethyl iodide (15 c.c.) and silver oxide (15 g.) was complete in 1 hour. After isolation, the *product* crystallised from alcohol in tiny, well-formed, rectangular prisms (10.5 g.), m. p. 123° (Found: C, 66.1; H, 6.7. $C_{23}H_{28}O_7$ requires C, 66.3; H, 6.8%). This substance is readily soluble in cold acetone, benzene or ethyl acetate and insoluble in aqueous sodium hydroxide. It does not give a ferric chloride reaction.

(B) An excess of diazoethane (prepared from nitrosoethylurethane, 14 c.c.) in ether (170 c.c.) was added to a suspension of evernic acid (1.5 g.) in the same solvent; a brisk evolution of nitrogen followed and the solid quickly dissolved. Next day the ether and excess of diazoethane were removed in a vacuum, and a solution of the residue in boiling alcohol (30 c.c.) was filtered from a small amount of insoluble material. On cooling, small rectangular prisms (0.9 g.) of ethyl *O*-diethylevernate separated, m. p. and mixed m. p. 123°.

Hydrolysis of Ethyl O-Diethylevernate.—A suspension of the foregoing ester (5 g.) in 2.5% alcoholic potassium hydroxide (100 c.c.) was maintained at 40–50° with frequent shaking. The solid gradually dissolved and after 8 hours the solution was diluted with water (500 c.c.) and the resulting turbid mixture was cleared

by means of charcoal and acidified with hydrochloric acid. Next day the semi-solid product was extracted with warm saturated aqueous sodium bicarbonate (100 c.c. at 50°), and on acidification the extract gave *O*-ethylevernic acid, which crystallised from ethyl acetate-ligroin in pointed prisms (1.6 g.), m. p. and mixed m. p. 87°, and was identical with a synthetical specimen (Found : C, 62.9; H, 7.0%). The residue which was insoluble in sodium bicarbonate solution consisted of almost pure ethyl 1-*O*-ethylorsellinate. It crystallised from light petroleum in tufts of long slender prisms (2.1 g.), m. p. and mixed m. p. 89° (Found : C, 64.1; H, 7.3%).

Ethyl *O*-diethylevernate was unaffected by treatment with methyl-alcoholic ammonia during 24 hours.

O-Acetyleverninoyl Chloride (X).—Phosphorus pentachloride (11 g.) was gradually added to a solution of acetylevernic acid (10 g.) in chloroform (65 c.c.). After the evolution of hydrogen chloride had almost ceased the mixture was kept at 50° for 5 minutes and the chloroform and phosphorus oxychloride were distilled in a vacuum at 45–50°. To remove the last traces of phosphorus oxychloride the residue was dissolved in dry chloroform (100 c.c.), and the solution evaporated in a vacuum; repetition of this procedure finally left a pale yellow syrup which gradually solidified. To a solution of the crude solid in chloroform (20 c.c.), light petroleum was added until a faint turbidity appeared; the *chloride* then slowly separated in clusters of colourless prisms, m. p. 68° (Found : Cl, 14.8. $C_{11}H_{11}O_4Cl$ requires Cl, 14.6%). This compound is readily soluble in acetone, benzene or carbon tetrachloride and decomposes in moist air with the formation of acetylevernic acid.

The acid chloride (2 g.) was mixed with well-cooled aniline (4 c.c.) and after 12 hours the excess of the base was removed with 10% acetic acid (50 c.c.). An ethereal solution of the oily product was washed with aqueous sodium bicarbonate to remove acetylevernic acid, dried, and concentrated. The solid which separated gave a marked ferric chloride reaction and appeared to be a mixture of everninanilide and its acetate. On treatment with 4% aqueous sodium hydroxide (agitate) it quickly dissolved and after 10 minutes the solution was filtered from a trace of insoluble material and acidified. Everninanilide thus precipitated crystallised from 60% acetone in colourless plates (0.4 g.), m. p. 178° (Found : C, 69.8; H, 5.9. Calc. for $C_{15}H_{15}O_3N$: C, 70.0; H, 5.9%) (Asahina and Ihara, *Ber.*, 1929, **62**, 1197, describe this substance as a reddish-coloured crystalline powder, m. p. 175°). With alcoholic ferric chloride the compound gives an intense reddish-brown coloration.

Methyl Orsellinate.—A solution of dicarbomethoxyorsellinic acid

(7 g.) and methyl iodide (6 c.c.) in acetone (100 c.c.) was refluxed with silver oxide (5 g.) for 1 hour. After filtration from silver salts the acetone was evaporated and a solution of the residue in 10% methyl-alcoholic potassium hydroxide (55 c.c.) was kept at room temperature for $\frac{1}{2}$ hour, diluted with water (100 c.c.), and acidified with hydrochloric acid. The ester was collected, washed with water, and crystallised from dilute methyl alcohol, forming long slender prisms, m. p. 142°.

Methyl O-Acetylevernate (XII).—A mixture of *O*-acetyleverninoyl chloride (2 g.), methyl orsellinate (0.75 g.), and pyridine (5 c.c.) was kept at room temperature for 3 days and poured into 6% acetic acid (100 c.c.). The mixture was thrice extracted with ether and the combined extracts were washed with water and then with aqueous sodium bicarbonate to remove acetylevernic acid. After the removal of the ether, the residue was dissolved in warm methyl alcohol, and water added until a faint turbidity appeared. In the course of several days the *acetate* of methyl evernate separated in tufts of slender prisms (0.75 g.), m. p. 119° after repeated crystallisation from 80% methyl alcohol (Found: C, 61.8; H, 5.2. $C_{20}H_{20}O_8$ requires C, 61.8; H, 5.2%). The compound is easily soluble in acetone, ethyl acetate or benzene. With alcoholic ferric chloride it gives a light brown coloration which fades on dilution with water.

Methyl Evernate.—(A) An ethereal solution of diazomethane (prepared from nitrosomethylurethane, 10 c.c.) was gradually added to a suspension of an excess of powdered evernic acid (10 g.) in ether (100 c.c.). After the evolution of nitrogen had ceased, the solvent was removed in a vacuum and the residue agitated with aqueous sodium bicarbonate to convert the unchanged acid into the sparingly soluble sodium salt. Extraction of the mixture with hot water left the *ester*, which crystallised from warm acetone in short thick prisms (5 g.), m. p. 148° (Found: C, 62.4; H, 5.2. $C_{13}H_{18}O_7$ requires C, 62.4; H, 5.2%). The compound is moderately easily soluble in benzene or ethyl acetate and sparingly soluble in hot ligroin. In alcohol the ferric chloride reaction is red with a tinge of purple and changes to an intense reddish-brown on dilution with water. This ester was also prepared in poor yield by the refluxing of a mixture of potassium evernate, methyl iodide and acetone and by warming a suspension of silver evernate in a mixture of benzene and methyl iodide.

(B) A solution of the synthetic monoacetate (1 g.) in 4% aqueous sodium hydroxide (10 c.c.) was kept at room temperature for 20 minutes and then acidified with dilute hydrochloric acid. The precipitate of methyl evernate (0.8 g.) was collected, washed with water to remove mineral acid, and dissolved in warm methyl alcohol.

On cooling, the ester separated in colourless prisms, m. p. 148° alone, or mixed with a specimen prepared from the natural acid (Found: C, 62.3; H, 5.3%). The properties of the synthetic compound were identical with those of the natural derivative.

Ethyl Evernate.—The preparation of the *ethyl* ester from evernic acid by means of diazoethane and its subsequent purification were effected by the procedure described for the preparation of the methyl ester. Crystallised from ethyl alcohol, it formed colourless tiny prisms, m. p. 152° (Found: C, 63.5; H, 5.7. $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.7%). The compound separates from warm 90% acetone in tufts of needles which in the course of an hour change into short colourless prisms. With alcoholic ferric chloride this ester gives a reddish-purple coloration which changes to pale brown on dilution with water.

Hydrolysis of Methyl Evernate.—A solution of the ester (1 g.) in a mixture of methyl alcohol (5 c.c.), water (15 c.c.), and potassium hydroxide (0.8 g.) was maintained at 45° for 3 hours, cooled, diluted with water (20 c.c.), and saturated with carbon dioxide. The methyl everninate (sparassol) (0.45 g.) thus precipitated was purified by crystallisation from dilute methyl alcohol, forming needles, m. p. and mixed m. p. 67° . Acidification of the aqueous filtrate left after the removal of the methyl everninate gave a mixture of acids (0.15 g.), m. p. 160° (decomp.). Hydrolysis of the ester (5 g.) by means of 4% aqueous potassium hydroxide (100 c.c.) at room temperature for 12 hours gave rise to methyl orsellinate (1.5 g.), m. p. 142° , and a mixture of orsellinic and evernic acids (2.8 g.).

The authors are indebted to the Chemical Society for grants in aid of this investigation.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE,

UNIVERSITY OF LONDON.

[Received, February 27th, 1932.]
