40. *Lichen Acids. Part IV. Atranorin.*

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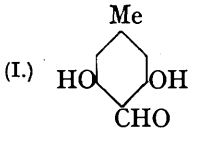
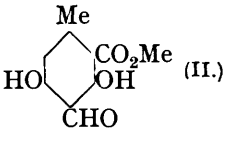
ATRANORIN, which appears to be one of the most widely distributed lichen products, having been obtained from about eighty species of lichen, was first isolated in 1877 by Paternò and Oglialoro (*Gazzetta*, **7**, 189), and has since been the subject of numerous investigations by various workers (for a complete list of references, see St. Pfau's memoir; *Helv. Chim. Acta*, 1926, **9**, 650). The earlier investigators showed that the substance was the methyl ester of a depside which on scission with hot alcohols furnished methyl β-orcincarboxylate and the esters of the unstable acid, hæmatommic acid. Further, the decomposition of both atranorin and ethyl hæmatommate was found to give rise to a phenolic compound, atranol, for which several formulæ were suggested. It was not until 1926, however, that the latter compound was shown by St. Pfau (*loc. cit.*) to be γ-orcylaldehyde. The synthesis by Robertson and Robinson (J., 1927, 2196) of *O*-dimethylatranol, which was identified by comparison with a natural specimen (J., 1931, 2697), confirmed the structure of atranol.

The structure assigned to esters of hæmatommic acid by St. Pfau (*loc. cit.*) has now been confirmed by the synthesis of methyl hæmatommate.



(I.)



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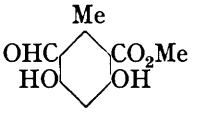


(III.)

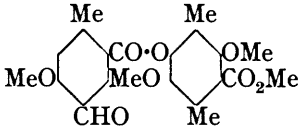
On condensation with hydrogen cyanide by Gattermann's method, methyl orsellinate gave rise to a mixture of two aldehydes, one of which was identical with a specimen of methyl hæmatommate derived from atranorin. Since atranol has formula (I), methyl hæmatommate and the isomeric *methyl* iso*hæmatommate* must have formulæ (II) and (III) respectively.

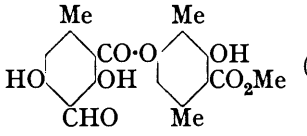
A quantity of atranorin was isolated from *Evernia prunastri* by a procedure similar to that described by Hesse (*J. pr. Chem.*, 1915, **92**, 431) involving the use of chloroform. Though the product appeared to be homogeneous and to have properties identical with those described by previous authors, it was found on analysis to contain chlorine. Further, a specimen of atranorin isolated and kindly supplied by Dr. St. Pfau was also found to contain chlorine; the two specimens gave the same analysis and appeared to be identical in every way. At first it appeared probable that the presence of halogen in our material was due to chloroform of crystallisation, but since it was unchanged after repeated crystallisation from different solvents before or after having been dried in a high vacuum, and since a chlorine-containing methylation product has been isolated, this view cannot be

maintained. On the other hand, the halogen-containing material may result from the decomposition of chloroform in the presence of moisture in the crude lichen extract. Subsequently a method was devised for the isolation and purification of atranorin which avoided the use of chloroform and furnished a halogen-free product. This substance was otherwise indistinguishable from the material which contained chlorine and on scission with hot 90% acetic acid according to St. Pfau's directions gave rise to atranol and methyl β-orcincarboxylate in almost theoretical yield. The analytical results obtained with halogen-free specimens, however, do not agree with the previously accepted empirical formula $C_{19}H_{18}O_8$; instead, they show conclusively that the depside has the composition $C_{19}H_{18}O_8,H_2O$. The compound did not lose weight when exposed to a high vacuum at 140—150° for 3 hours, but at higher temperatures underwent decomposition. In this connexion it may be noted that atranol hydrate is dehydrated with difficulty (compare St. Pfau, *loc. cit.*).

Methylation of atranorin containing halogen has been found to give rise to a mixture of *O*-trimethylatranorin and a halogen-containing trimethyl ether. On scission, both products readily yielded methyl *iso*rhizonate (Robertson and Stephenson, J., 1932, 1675), but in spite of repeated attempts we were unable to isolate the methylated atranol residue either as *O*-dimethylatranol or as methyl *O*-dimethylhæmatommate.

(IV.)





(V.)

Nevertheless the formation of methyl *iso*rhizonate together with the synthesis of methyl hæmatommate in our opinion affords conclusive evidence that *O*-trimethylatranorin has formula (IV), and hence atranorin has formula (V).

With regard to the scission of depsides by means of boiling alcohol, we have observed that atranorin is unaffected by pure hot methyl or ethyl alcohol, but in the presence of a trace of alkali, however, the reaction proceeds rapidly. Stenhouse (*Annalen*, 1848, **138**, 63) has noted that evernic acid behaves in a similar manner. That other authors do not appear to have commented on this phenomenon may arise from the fact that alcohol distilled over lime or calcium is liable to contain traces of lime (Noyes, *J. Amer. Chem. Soc.*, 1923, **45**, 860).

Experimental.

Atranorin.—(A) An ethereal extract of the lichen *Evernia prunastri* (1·3 kg.) was evaporated, and the mixture twice extracted with boiling $CHCl_3$ (100 c.c. and 50 c.c.); the insol. fraction consisted of almost pure evernic acid. The combined $CHCl_3$ extracts, which contained atranorin, usnic acid, oils and waxes, and a small amount of chlorophyll, were evaporated and the residual mixture was agitated with acetone (100 c.c.). The insol. residue of almost pure atranorin was collected and crystallised from xylene (m. p. 195°) and then from $CHCl_3$ (2·1 g. in 40 c.c.), forming pale yellow prisms (1·7 g.), m. p. 196—197°, which gave positive tests for Cl (Found in material dried at 100° in a high vac. for 3 hr.: C, 58·2; H, 4·8%). Another specimen, purified in this manner, was found to be unchanged after repeated crystn. from C_6H_6 (Found in material dried in high vac. over P_2O_5 in presence of solid paraffin at room temp. for 3 days, and then at 100° for 2 hr.: C, 58·1; H, 4·9; Cl, 5·4; OMe, 7·9. Calc. for $C_{19}H_{18}O_8$: C, 60·9; H, 4·8; OMe, 8·3%. Calc. for $5C_{19}H_{18}O_8,CHCl_3$: C, 57·9; H, 4·6; Cl, 5·4; OMe, 7·8%). The Cl was not removed by dissolving the atranorin in an excess of boiling xylene and distilling the solvent until crystn. started or by dissolving it in cold aq. NaOH and repptg. with mineral acid. Treatment of the substance with a warm mixture of $PhNH_2$ and alc. KOH gave rise to the odour of phenylcarbylamine.

A specimen of atranorin isolated by St. Pfau gave positive reactions for chlorine (Found in dried material: C, 58·1; H, 4·8%).

(B) The residue obtained from the ethereal extract of the lichen (300 g.) was twice extracted with cold acetone (60 c.c. and 40 c.c.) and then agitated with warm saturated aq. $NaHCO_3$ (200 c.c. at 50°). The crude atranorin was collected, washed with much hot H_2O to remove sodium evernate (sparingly sol.), dried, and crystallised several times from C_6H_6. Halogen-

free atranorin (1 g.) thus obtained had m. p. 196—197°, alone or mixed with a specimen prepared by method A (Found in material dried at 110° in a high vac.: C, 58·3; H, 5·1. Calc. for $C_{19}H_{18}O_8,H_2O$: C, 58·2; H, 5·1%).

Methylation of Atranorin.—(A) A mixture of atranorin (2 g., containing Cl), MeI (2 c.c.), Ag_2CO_3 (4 g.), and acetone (25 c.c.) was agitated for 16 hr., the filtered solution evaporated in a vac., and the yellow viscous residue refluxed with MeI (20 c.c.) and Ag_2CO_3 (4 g.) until a sample failed to give a reaction with $FeCl_3$ (1·5—4 hr.). On isolation the gummy product was dissolved in AcOEt; after the addition of warm light petroleum until a faint turbidity appeared, *O-trimethylatranorin* gradually separated in colourless prisms (1·1 g.), m. p. 108—112°. Cryst. twice from MeOH, it formed stellate aggregates of rhombic prisms, m. p. 123° [Found: C, 63·2; H, 5·9; OMe, 29·6. $C_{18}H_{12}O_4(OMe)_4$ requires C, 63·4; H, 5·8; OMe, 29·8%]. The compound is readily sol. in C_6H_6, AcOEt, or acetone and insol. in dil. aq. NaOH.

In one expt. a compound was isolated which crystallised from AcOEt–ligroin (1 : 6) in tiny colourless prisms, m. p. 136°, and appeared to be a *dimethyl* ether of atranorin [Found: OMe, 22·6. $C_{18}H_{13}O_5(OMe)_3$ requires OMe, 23·1%]. This ether, which gave a light brown coloration with alc. $FeCl_3$ and was insol. in aq. NaOH, dissolved in aq.-alc. NaOH, forming a yellow solution. On methylation with MeI and Ag_2CO_3 in boiling acetone it gave rise to *O*-trimethylatranorin, m. p. and mixed m. p. 122°.

After the isolation of *O*-trimethylatranorin the combined AcOEt–light petroleum mother-liquors from several expts. were concentrated and in the course of several months a second product separated in tufts of colourless needles. Recryst. from xylene, then from MeOH, and finally twice from AcOEt–ligroin, it formed clusters of silky needles, m. p. 106—107°, which contained chlorine [Found: C, 59·2, 59·2, 59·1, 59·2; H, 5·5, 5·4, 5·4, 5·4; Cl, 7·6, 7·6; OMe, 26·8. Calc. for $C_{18}H_{11}O_4Cl)OMe)_4$: C, 58·6; H, 5·1; Cl, 7·9; OMe, 27·5%. Calc. for $3C_{18}H_{12}O_4(OMe)_4,CHCl_3$: C, 58·9; H, 5·3; Cl, 7·8; OMe, 27·3%]. This material was insol. in aq. NaOH, did not give a reaction with $FeCl_3$, and reduced ammoniacal $AgNO_3$ (mirror). Prepared in the usual manner, the semicarbazone separated from the reaction mixture in short needles, m. p. 208°, which were sparingly sol. in org. solvents and contained Cl (Found: N, 8·2; Cl, 7·1. Calc. for $C_{23}H_{26}O_8N_3Cl$: N, 8·3; Cl, 7·0. Calc. for $3C_{23}H_{27}O_8N_3,CHCl_3$: N, 8·2; Cl, 6·9%).

The semi-solid residues left after the removal of the compound, m. p. 106—107°, were ground with a little MeOH, drained on a filter, and washed with MeOH. The resulting white solid, m. p. 98—99°, consisted mainly of the halogen-containing trimethyl ether, m. p. 106—107° after crystn. from xylene. Evaporation of the MeOH filtrate left a gum, from which a solid compound could not be isolated. A solution of this material in 10% methyl-alc. KOH was refluxed for ½ hr., cooled, diluted with H_2O, and acidified with dil. H_2SO_4, and the cryst. ppt. of methyl *iso*rhizonate which gradually separated was collected after 12 hr. Extraction of the aq. filtrate with Et_2O gave a yellow gum, which did not contain alkali-sol. material and did not crystallise alone or on inoculation with *O*-dimethylatranol.

(B) A mixture of atranorin (2 g.), well-ground K_2CO_3 (4 g.), MeI (4 c.c.), and acetone (30 c.c.) was refluxed for 100 hr.; after 50 hr., more MeI (2 c.c.) was added; methylation was complete when the original yellow colour of the solution had disappeared and a sample did not give a reaction with $FeCl_3$. On isolation in the usual manner *O*-trimethylatranorin gradually separated from hot AcOEt–ligroin in clusters of prisms, which on recrystn. from MeOH formed rhombic prisms (0·3 g.), m. p. 123°, identical with a specimen prepared by method (A).

Treatment of atranorin with diazomethane gave an intractable resinous product.

Hydrolysis of O-Trimethylatranorin.—The trimethyl ether (5 g.) dissolved in 10% methyl-alc. KOH (70 c.c.) at room temp. in the course of 16 hr. (agitate), and 2 hr. later the solution was diluted with H_2O (1 l.) and acidified with HCl aq. (Congo-red). Methyl *iso*rhizonate slowly separated in slender needles (2·1 g.); after 20 hr. it was collected and recryst. from 30% aq. MeOH, forming rhomboidal prisms, m. p. 142°, identical with an authentic specimen (Found: C, 62·6; H, 6·8. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%).

O-Trimethylatranorin was not decomposed by boiling 90% AcOH.

After the removal of the methyl *iso*rhizonate, the aq. liquor was saturated with $(NH_4)_2SO_4$ and extracted with Et_2O. Evaporation of the combined extracts left a viscous liquid, from which a small amount of methyl *iso*rhizonate was isolated, but a definite compound could not be obtained from the residue.

Well-ground trimethylatranorin (containing halogen; m. p. 106—107°) (1·5 g.) dissolved in 20% methyl-alc. KOH (50 c.c.) in the course of 36 hr. 12 Hr. later the mixture was acidified

with dil. H_2SO_4 and extracted several times with Et_2O. The combined extracts were agitated with aq. $NaHCO_3$ and then with aq. NaOH, dried, and evaporated, leaving no appreciable residue.

Acidification of the aq. NaOH washings gave methyl *iso*rhizonate (0·6 g.), m. p. 142° after purification.

From the acidified aq. $NaHCO_3$ washings by means of Et_2O a small amount of an oil was isolated which partially solidified, but owing to lack of material this solid was not investigated.

Methyl Hæmatommate.—(A) A mixture of powdered atranorin (2 g.) and MeOH (200 c.c.) containing NaOH (20 mg.) was refluxed for 3 hr., the resulting clear solution acidified with dil. H_2SO_4, the MeOH evaporated, and the mixture of methyl β-orcincarboxylate and methyl hæmatommate distilled with steam and separated by fractional crystn. from MeOH. The less sol. methyl hæmatommate formed elongated slender needles, m. p. 146°.

(B) Powdered anhydrous $ZnCl_2$ was suspended in a solution of methyl orsellinate (J., 1932, 1388) (10 g.) in Et_2O (300 c.c.), anhyd. HCN (10 c.c.) added, and the mixture saturated with HCl. 4 Hr. later the cryst. solid was collected, washed with Et_2O, and dissolved in H_2O (100 c.c.), and the solution heated on the steam-bath for ¾ hr. After cooling, the product was collected and distilled in steam: almost pure methyl hæmatommate separated from the distillate in needles; recryst. from MeOH, it melted at 146° alone or mixed with a natural specimen (Found: C, 57·4; H, 5·0. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). The $FeCl_3$ reaction (reddish-brown) and the coloration in aq. Na_2CO_3 (canary-yellow) of the synthetical material were identical with those of the natural compound.

The residue (0·3 g.) non-volatile in steam consisted mainly of *methyl* iso*hæmatommate*, which crystallised from hot H_2O in almost colourless, elongated, rectangular prisms, m. p. 130° (Found: C, 57·5; H, 5·1%). This aldehyde gave a brown coloration with alc. $FeCl_3$ and a colourless solution in dil. aq. NaOH. It formed a bisulphite compound which on cautious treatment with warm dil. H_2SO_4 yielded the original compound.

Evaporation of the ethereal filtrate and washings from the mixed aldimines gave unchanged methyl orsellinate (6·5 g.).

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