Tetrahedron, 1965, Vol. 21, pp. 3531 to 3536. Pergamon Press Ltd. Printed in Northern Ireland

NEW REAGENTS FOR THE SYNTHESIS OF DEPSIDES[1,2]

METHYL EVERNATE, METHYL LECANORATE, EVERNIC ACID AND ATRANORIN*

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(*Received* 14 *June* 1965)

Abstract—Lichen depsides have now been synthesized by making use of two reagents, dicyclohexylcarbodiimide (DCC) and trifluoroacetic anhydride. Methyl evernate, methyl lecanorate and evernic acid have been prepared in satisfactory yields. Atranorin has been synthesized for the first time.

A LARGE number of compounds occurring in lichens belong to the group of depsides. Though they have essentially a phenyl benzoate structure (see formula VI), because of the substitution patterns of the component units the synthesis of these depsides is beset with difficulties. In almost all of them a hydroxyl and an alkyl group are present in the two positions *ortho* to the carboxyl group. This feature makes the preparation of the acid chloride and subsequent depside condensation difficult. Fischer and Fischer[3] were the first to solve these difficulties and develop satisfactory methods of depside synthesis. These were later improved by Asahina *et al.*[4] who successfully synthesized a number of natural depsides.

In both the above methods, the left half was always taken as an acid chloride and condensed with the phenolic part in the presence of aqueous alkali or pyridine. The preparation of the acid chloride involved the use of thionyl chloride, phosphorus pentachloride or oxalyl chloride but there was no simple and easy way of purifying and characterizing the product. Further, the preparation of the acid chloride required preliminary protection of all the free hydroxyl groups as the carbomethoxy, carbethoxy or acetyl derivatives. Consequently during the final removal of these protecting groups there was also a possibility of the fission of the depside linkage. In view of these difficulties there was need to look for an easy method for depside synthesis which could avoid the preparation of the acid chloride and use the required acid directly for the condensation. In the course of the present work this has been found possible by the use of N,N′-dicyclohexylcarbodiimide (DCC).

Substituted carbodiimides have been used in the past for the preparation of pyrophosphates[5] and peptides.[6] The isolation of the reaction product is simple since the urea which is the by-product of the reaction is insoluble in most of the solvents

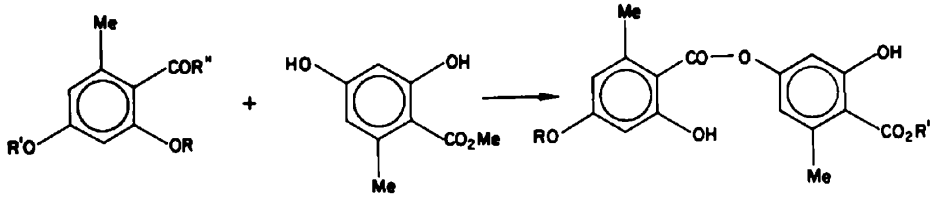
* For preliminary communications relating to this work, see Ref. 1 and 2.

[1] S. Neelakantan, R. Padmasani and T. R. Seshadri, *J. Sci. Industr. Res., India* **20B**, 510 (1961).
[2] S. Neelakantan, R. Padmasani and T. R. Seshadri, *Tetrahedron Letters* No. 7, 287 (1962).
[3] E. Fischer and H. Fischer, *Ber. Dtsch. Chem. Ges.* **46**, 1138 (1913).
[4] Y. Asahina and S. Shibata, *Chemistry of Lichen Substances*, Japan Society for the Promotion of Science, Tokyo, (1954).
[5] H. G. Khorana, *Chem. Rev.* **53**, 145 (1953).
[6] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.* **70**, 1067 (1955).

used for the condensation and separates out during the course of the reaction. The yield of the urea may be used to follow the progress of the reaction.

The use of DCC for the condensation of a hydroxy compound like a phenol or an alcohol with organic acids was first tested with simple examples. The reaction was carried out by taking equimolecular quantities of the reactants and condensing them in the presence of an equimolecular quantity of the carbodiimide. With benzoic acid and phenol, phenyl benzoate was obtained only in poor yields. Benzoic acid and *p*-nitrophenol on the other hand gave *p*-nitrophenyl benzoate in good yield. *p*-Hydroxybenzoic acid also gave the methyl and ethyl esters in good yield with the appropriate alcohols. Among the lichen depsides, the following were synthesized by making use of this reagent.

Methyl evernate (I) was synthesized earlier by Robertson and Stephenson[7] by condensing acetyleverninoyl chloride (II) and methyl orsellinate (III) in pyridine followed by deacetylation using sodium hydroxide. In the present work, everninic acid (IV) was directly condensed with methyl orsellinate (III) in the presence of DCC using dry ether as the solvent. The reaction was practically complete within 2 hr, and a good yield of methyl evernate (I) was obtained.



II, R=Ac; R'=Me; R"=Cl
IV, R=H; R'=Me; R"=OH
VII, R=R'=CO_2Et; R"=OH

III

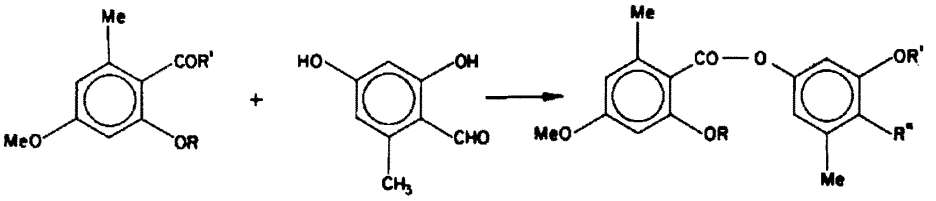
I, R=R'=Me
V, R=H; R=Me
VI, R=R'=H

Methyl lecanorate (V) is a slightly more complicated case since it has three free hydroxyl groups. It was earlier prepared by Asahina and Fuzikawa[8] by the esterification of lecanoric acid (VI) using diazomethane. During this reaction, there is a possibility of O-methylation but this was avoided in the present synthesis. The condensation of dicarbethoxyorsellinic acid (VII) and methyl orsellinate (III) in the presence of DCC was followed by decarbethoxylation. The dicarbethoxy derivative was used instead of orsellinic acid itself to avoid self condensation. Even though the yield of the initial condensation product was good the final product was obtained only in a poor yield due to loss by fission of the depside linkage during the subsequent removal of the carbethoxy groups.

Evernic acid (VIII) was first synthesized by Fuzikawa and Ishiguro[9] following Asahina's procedure. Carbethoxy-everninoyl chloride (IX) was condensed with orcylaldehyde (X) to give carbethoxyevernaldehyde (XI). This was converted into evernic acid (VIII) by further carbethoxylation, oxidation and decarbethoxylation. In the present work, everninic acid (IV) was directly condensed with orcylaldehyde (X)

[7] A. Robertson and R. J. Stephenson, *J. Chem. Soc.* 1388 (1932).
[8] Y. Asahina and F. Fuzikawa, *Ber. Dtsch. Chem. Ges.* **65**, 983 (1932).
[9] F. Fuzikawa and K. Ishiguro, *J. Pharm. Soc. Japan* **56**, 149 (1936).

to give evernaldehyde (XII). Later carbethoxylation gave the dicarbethoxy aldehyde (XIII) which underwent oxidation with potassium permanganate in acetone to dicarbethoxyevernic acid (XIV). Final decarbethoxylation was readily achieved, probably because the hydroxyl groups *ortho* to the carbonyl only are involved in this reaction, giving evernic acid (VIII) in good yield.

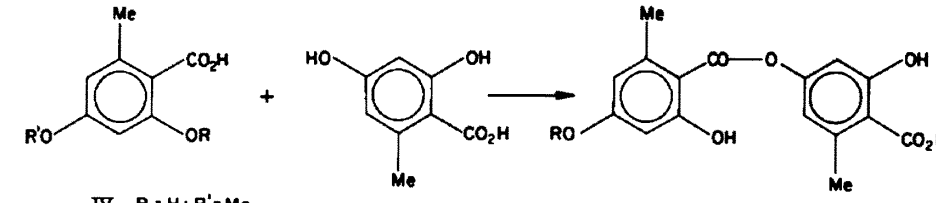


IX, R = CO_2Et; R' = Cl
IV, R = H; R' = OH

X

XI, R = CO_2Et; R' = H; R" = CHO
VIII, R = R' = H; R" = CO_2H
XII, R = R' = H; R" = CHO
XIII, R = R' = CO_2Et; R" = CHO
XIV, R = R' = CO_2Et; R" = CO_2H

In all the above condensations, the phenolic unit did not contain free carboxyl group but instead an ester or an aldehyde group. The direct condensation of two acids was tried in order to simplify the synthesis further. This method was attempted for the following condensations: (i) dicarbethoxy-orsellinic acid (VII) and orsellinic acid (XV); (ii) self condensation of orsellinic acid (XV) and (iii) everninic acid (IV) and orsellinic acid (XV) to give the corresponding depside acids in one stage. In (i) unchanged orsellinic acid could be recovered and the desired depside, *viz.*, lecanoric acid (VI) was obtained only after decarbethoxylation in a poor yield. In the other condensations, dicyclohexylurea separated out almost quantitatively but the yields of the desired depsides, *viz.*, lecanoric acid (VI) and evernic acid (VIII) were low. Although DCC was reacting the low yield of the depsides seems to be due to anhydride formation which is the major reaction here.



IV, R = H; R' = Me
XV, R = R' = H
VII, R = R' = CO_2Et

XV

VI, R = H
VIII, R = Me

Atranorin (XVI), one of the most widely distributed lichen depsides, was first isolated by Paterno and Oglialoro[10] and the correct structure was assigned to it by St. Pfau.[11] This substance belongs to the β-orcinol series of depsides and contains an aldehydic group in 3-position in the acid part (A). Although its structure was proposed long ago its synthesis has not so far been reported because the earlier procedures[3,4] are not suitable on account of the presence of the aldehyde group.

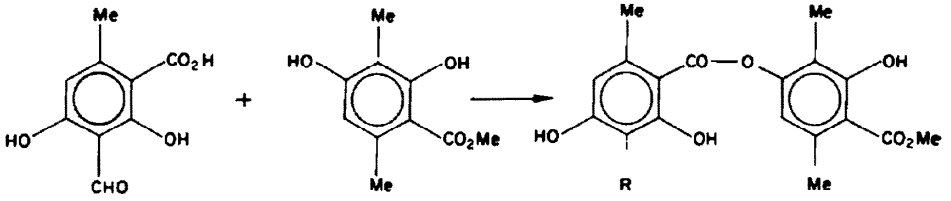
The direct condensation of haematommic acid (XVII) and methyl β-orcinol

[10] E. Paterno and A. Oglialoro, *Gazz. Chim. Ital.* **7**, 189 (1877).
[11] A. St. Pfau, *Helv. Chim. Acta* **9**, 650 (1926).

carboxylate (XVIII) using DCC as a condensing agent was first applied during the present work. Though in the reaction the urea separated in quantitative yield, atranorin could be isolated only in a poor yield which could not be improved by changing the conditions of the reaction. Condensation was also repeated using dicarbethoxyhaematommic acid and methyl β-orcinol carboxylate. In this case there was considerable difficulty in the selective removal of the carbethoxy groups without affecting the depside linkage. Hence it was not possible to synthesize atranorin satisfactorily by this method and there was need for a better reagent.

Bourne *et al.*[12] reported the use of trifluoroacetic anhydride for the preparation of phenolic as well as alcoholic esters of both aliphatic and aromatic carboxylic acids and as the reagent may also be used as a solvent, it enables the components to react directly under mild conditions. While we were preparing depsides using this reagent, Brown *et al.*[13] reported the preparation by this method of a depside intermediate, needed in the synthesis of diploicin. Taub *et al.*[14] have subsequently used it for the condensation of acids with phenols to yield ketones and they have reported the formation of esters as by-products. In the course of the present work, no ketone could be isolated. The difference in the two results may probably be due to the difference in the temperature of the reaction. In the present study, excess of acid component has been avoided in order to simplify the purification procedure and a slight excess of the anhydride used to dissolve the reactants completely.

The suitability of this method was first examined by preparing phenyl benzoate using equimolecular quantities of benzoic acid and phenol when the ester was obtained in good yield. Similarly everninic acid (IV) and methyl orsellinate (III) were condensed to produce methyl evernate (I). Finally by condensing haematommic acid (XVII) and methyl β-orcinol carboxylate (XVIII) in the presence of a slight excess of trifluoroacetic anhydride and purifying the reaction product on a column of silicic acid, pure atranorin (XVI) was obtained in satisfactory yield. The synthetic depside was characterized by its m.p. and mixed m.p. with an authentic sample, colour reactions and reduction[15] to methyl nor-barbatate (XIX).



XVII XVIII XVI, R = CHO
XIX, R = CH_3

EXPERIMENTAL

Use of DCC

Phenyl benzoate. To a solution of benzoic acid (0·25 g) and phenol (0·19 g) in dry ether (50 ml) DCC (0·43 g) was added and the solution stirred for 6 hr at room temp. After leaving overnight the solvent was evaporated and the solid residue macerated with cold acetone. The acetone-insoluble

[12] E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.* 2976 (1949).
[13] C. J. Brown, D. E. Clark, W. D. Ollis and P. L. Veal, *Proc. Chem. Soc.* 393 (1960).
[14] D. Taub, C. H. Kuo and N. L. Wendler, *J. Org. Chem.* **28**, 2752 and 3344 (1963).
[15] Y. Asahina and T. Tukamoto, *Ber. Dtsch. Chem. Ges.* **66**, 897 (1933).

portion melted at 225–227°, identified as dicyclohexylurea.[16] The acetone-soluble fraction was treated with pet. ether and the pet. ether-soluble fraction on crystallization from EtOH gave phenyl benzoate (0·05 g) as colourless needles m.p. 70–71°.

Methyl p-*hydroxybenzoate*. *p*-Hydroxybenzoic acid (0·5 g) and MeOH (0·3 ml) were dissolved in dry ether (50 ml) and DCC (0·8 g) added. After stirring the solution for 6 hr the product was isolated and purified by washing with 2% $NaHCO_3$aq. The ester (0·25 g) crystallized from benzene–pet. ether as colourless stout rods and prisms m.p. 127–128°. Ethyl *p*-hydroxybenzoate was also prepared by a similar procedure using EtOH instead of MeOH.

p-*Nitrophenyl benzoate*. *p*-Nitrophenol (0·6 g) and benzoic acid (0·4 g) in dry ether solution (100 ml) were condensed using DCC (0·74 g). The product crystallized from EtOH as fine needles m.p. 138–139°.

Methyl evernate (I). Everninic acid (IV) required for this was prepared by partial methylation of III using dimethyl sulphate, K_2CO_3 and acetone and hydrolysing the resulting methyl everninate with 10% methanolic KOH.

Everninic acid (IV; 0·18 g), III (0·18 g) and DCC (0·21 g) were dissolved in dry ether (50 ml) and stirred for 2 hr. The solid which separated (dicyclohexylurea) was filtered off and washed with ether. The filtrate on evaporation yielded I (0·35 g) which crystallized from ethyl acetate as colourless stout prisms m.p. and mixed m.p. 141–142°. (Found: C, 62·6; H, 5·5. $C_{18}H_{18}O_7$ requires: C, 62·4; H, 5·2%.) $\nu_{max}^{CHCl_3}$ 1666 (s), 1613 (s), 1575 (m), 1492 (w), 1439 (m), 1408 (m), 1352 (w), 1307 (m), 1243 (s), 1191 (m), 1156 (s), 1136 (s), 1111 (w), 1075 (m), 1064 (m), 1030 (m), 995 (w) cm^{-1}. The IR spectra of the natural and synthetic samples were identical.

Methyl evernate (I) (*by esterification of evernic acid*). Evernic acid (VIII; 0·2 g), dry acetone (10 ml), anhydrous $NaHCO_3$ (0·6 g) and dimethyl sulphate (0·2 ml) were refluxed gently for 9 hr. The product crystallized from ethyl acetate as colourless stout prisms (0·18 g) m.p. 141–142°.

Methyl lecanorate (V). To a solution of VII[17] (0·2 g) and III (0·12 g) in dry ether (50 ml) DCC (0·12 g) was added and the mixture stirred for 6 hr. The urea was filtered off and the ether filtrate on evaporation gave a sticky solid which was directly hydrolysed with a solution of 1N NaOHaq (10 ml) and acetone (10 ml) at 35° for 3 hr in an H_2 atm. The solution was filtered and the filtrate acidified with ice-cold dil HCl. The separated solid (0·05 g) crystallized from EtOH as colourless needles m.p. 144–146°. (Found: C, 61·5; H, 4·9. $C_{17}H_{16}O_7$ requires: C, 61·4; H, 4·8%.) $\nu_{max}^{CHCl_3}$ 3690 (m), 3031 (m), 2381 (w), 1666 (s), 1613 (m), 1504 (w), 1439 (m), 1360 (w), 1307 (s), 1250 (s), 1198 (s), 1169 (m), 1143 (s), 1111 (w), 1075 (s) cm^{-1}. The IR spectra of the above synthetic sample and the one obtained by esterification of lecanoric acid[8] were identical. The aqueous acetone filtrate on concentration under red. press. yielded unchanged methyl orsellinate.

Evernaldehyde (XII). To a solution of IV (1·0 g) and X (0·84 g) in dry ether (50 ml) DCC (1·13 g) was added and the solution stirred for 6 hr. Evernaldehyde (0·3 g) crystallized from benzene as colourless silky needles m.p. 154–155°. (Found: C, 64·2; H, 5·3. $C_{17}H_{16}O_6$ requires: C, 64·6; H, 5·1%.) It gave a violet colour with alc. $FeCl_3$ and formed a 2,4-dinitrophenylhydrazone m.p. 192–193°.

Evernic acid (VIII). To an ice-cold solution of evernaldehyde (0·2 g), dissolved in dry pyridine (5 ml), ethyl chlorocarbonate (0·5 ml) was added dropwise with shaking. The solution was left at room temp for 2 hr, acidified with ice-cold dil HCl. The dicarbethoxy derivative (XIII; 0·27 g) crystallized from pet. ether as colourless silky needles m.p. 88–89°. (Found: C, 60·6; H, 5·6. $C_{23}H_{24}O_{10}$ requires: C, 60·0; H, 5·2%.) It did not give any colour with alc. $FeCl_3$.

The above dicarbethoxyevernaldehyde (XIII; 0·25 g) was dissolved in warm acetone (30 ml) and maintained at 40–50°. Powdered $KMnO_4$ (0·15 g) was added with stirring over a period of 35 min. The mixture was cooled and treated with SO_2 and XIV (0·25 g) was filtered m.p. 135–136° (lit.[9] m.p. 135°). The acid (XIV; 0·25 g) was decarbethoxylated by dissolving in acetone (8 ml) and 1N NaOHaq (7 ml) and allowing the solution to stand in an H_2 atm for 1 hr at room temp. On acidification, a thick colourless solid separated which was purified by treatment with 2% $NaHCO_3$aq. The bicarbonate-soluble fraction gave VIII (0·13 g) which crystallized from EtOH as colourless prisms m.p. and mixed m.p. 172–173°. (Found: C, 61·5; H, 5·2. $C_{17}H_{16}O_7$ requires: C, 61·4; H, 4·8%.) It gave a reddish violet colour with alc. $FeCl_3$. ν_{max}^{nujol} 1656 (s), 1613 (m), 1575 (m), 1504 (m), 1460 (s), 1419 (m), 1379 (m), 1307 (m), 1266 (m), 1220 (m), 1191 (m), 1162 (s), 1080 (w), 1058 (w), 1026 (m), 1000 (w) cm^{-1}. The IR spectra of natural and synthetic samples of evernic acid were identical.

[16] F. Zetsche and A. Fredrich, *Ber. Dtsch. Chem. Ges.* **72**, 1477 (1936).

[17] K. Hoesch, *Ber. Dtsch. Chem. Ges.* **46**, 887 (1913).

Condensation of dicarbethoxyorsellinic acid (VII) *and orsellinic acid* (XV). To an ice-cold solution of VII (0·3 g) in dry ether (50 ml) DCC (0·2 g) was added. After a few min, a solution of XV[17] (0·16 g) in dry ether (25 ml) was added and the solution stirred for 6 hr at −4°. After 15 hr, the urea was filtered, the residue obtained after removal of ether was directly decarbethoxylated with 1N NaOHaq (10 ml) in acetone (4 ml) at 20° in an H_2 atm. for 2 hr. The solution was acidified and the solid was purified by repeatedly boiling with water to remove any orsellinic acid and then crystallized from aqueous acetone as colourless needles (0·015 g) m.p. 168–169°. It was identified as lecanoric acid by comparison with an authentic sample (mixed m.p. and paper chromatography).

Similar condensations were also carried out with evernic acid and orsellinic acid, and also with orsellinic acid itself. Small quantities of evernic acid and lecanoric acid were obtained.

Atranorin (XVI). Haematommic acid (XVII; 0·34 g) and XVIII (0·34 g) in dry ether (100 ml) were condensed in the presence of DCC (0·35 g) at room temp. The separated urea was filtered after 15 hr. Atranorin (XVI; 0·02 g) was obtained from the ether filtrate as the sodium carbonate-insoluble fraction and it crystallized from chloroform as small colourless prisms m.p. and mixed m.p. 196–197°. The sodium carbonate-soluble portion of the ether solution contained XVII m.p. and mixed m.p. 176–177° and XVIII m.p. and mixed m.p. 142–143°.

Use of trifluoroacetic anhydride

Phenyl benzoate. A mixture of benzoic acid (0·13 g), phenol (0·1 g) and trifluoroacetic anhydride (0·4 ml) was warmed at 60° for 30 min, cooled and poured into water. The solid obtained on leaving overnight was macerated with a solution of $NaHCO_3$ to remove any free acid. Crystallization of the residue from pet. ether gave phenyl benzoate (0·19 g) m.p. 70–71°.

Methyl evernate (I). A mixture of IV (0·2 g) and III (0·18 g) was treated with trifluoroacetic anhydride (0·3 ml) at 65° for 1 hr. The product was worked up as in the above experiment and the sodium carbonate-insoluble fraction (0·25 g) crystallized from ethyl acetate as colourless prisms m.p. and mixed m.p. 142–144°.

Atranorin (XVI). A mixture of XVII (0·2 g), XVIII (0·2 g) and trifluoroacetic anhydride (0·6 ml) was heated at 65° for 2 hr. The mixture was allowed to stand at room temp for 24 hr, diluted with water and extracted with ether. The ether extract was washed with 2% $NaHCO_3$aq (100 ml). The product obtained on removal of ether was purified by passing through a column of silicic acid using chloroform as the solvent. The first fraction gave atranorin (0·125 g) which crystallized from chloroform as stout prisms m.p. and mixed m.p. 196–197°. (Found: C, 60·3; H, 5·1. $C_{19}H_{18}O_8$ requires: C, 60·9; H, 4·8%.) It gave a wine red colour with alc. $FeCl_3$ and formed a 2,4-dinitrophenylhydrazone derivative. ν_{max}^{nujol} 3702 (m), 1666 (s), 1563 (m), 1538 (w), 1515 (w), 1450 (s), 1387 (s), 1282 (m), 1198 (w), 1162 (m), 1111 (s), 1075 (m) cm^{-1}. The IR spectra of the synthetic and the natural samples were identical.

Methyl norbarbatate (XIX). This depside (XIX) was earlier prepared by Asahina and Tukamoto[16] by carrying out the catalytic reduction of atranorin using PdC and glacial acetic acid at 100°. The following procedure is more convenient.

Atranorin (XVI; 0·15 g) was dissolved in ethyl acetate (45 ml) and 5% PdC (0·3 g) was added and the mixture stirred in an H_2 atm at room temp. After the absorption of H_2 was complete the catalyst was filtered off and the filtrate on evaporation yielded XIX (0·13 g) which crystallized from pet. ether as colourless prisms m.p. 133–134°. (Found: C, 62·9; H, 5·9. $C_{19}H_{20}O_7$ requires: C, 63·3; H, 5·9%.) It gave a pink colour with alc. $FeCl_3$ and the test for aldehyde group was negative.

Acknowledgment—The authors thank the Council of Scientific and Industrial Research, New Delhi, for the award of a Research Fellowship to one of them (R. P.).