216. *Chemistry of the Higher Fungi. Part VII.* Odyssic Acid and Odyssin.*

By J. D. Bu'Lock, E. R. H. Jones, and P. R. Leeming.

Odyssic acid and odyssin, which accompany nemotinic acid and nemotin as fungus metabolites, are shown to be 4-hydroxydodeca-5 : 6-diene-8 : 10-diynoic acid (III) and the corresponding lactone (IV), respectively, *i.e.*, C_{12} homologues of the C_{11} compounds, nemotinic acid and nemotin.

The principal acetylenic constituents of the aqueous medium of cultures of the Basidiomycete B.841 are nemotinic acid and nemotin which have the structures (I) and (II), respectively.[1] In describing their purification by counter-current distribution we reported their separation from a pair of closely similar compounds; for these the names odyssic acid and odyssin were proposed. We now report the characterisation of these compounds

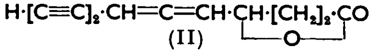
---

* Part VI, Bu'Lock, Jones, Leeming, and Thompson, *J.*, 1956, 3767.

[1] Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

as homologues of the constituents (I) and (II) in which the acetylenic $C_{(11)}$ hydrogen atom is replaced by a methyl group.

$H{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}CH(OH){\cdot}[CH_2]_2{\cdot}CO_2H$
(I)



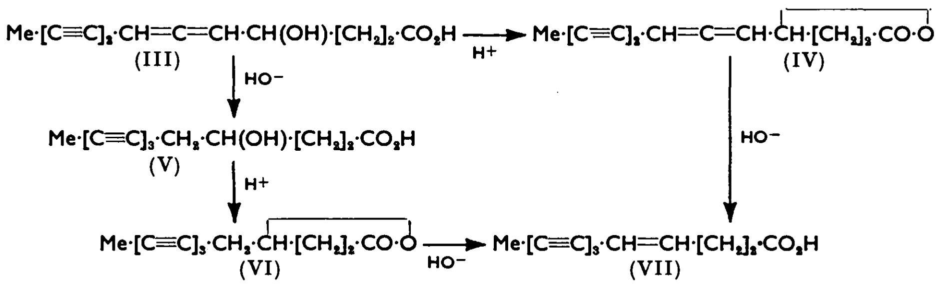
$H{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}CH{\cdot}[CH_2]_2{\cdot}CO{\cdot}O$
(II)

This structural difference presumably underlies our finding that odyssic acid, odyssin, and various derived compounds, although still very difficult to handle, are uniformly more stable than corresponding compounds of the nemotinic acid series already described; [1, 2] several compounds were obtained crystalline, and rather more significance could be attached to analytical data than in the earlier work. Nevertheless the techniques used in that work were retained, and, with the reservation that smaller amounts of material were available (particularly of odyssin [1]), the same reactions and interconversions were effected as in the nemotinic acid series, including the alkali-catalysed rearrangements,[2] in one of which the formation of stereoisomers has been observed.

Odyssic acid, obtained from the counter-current distribution of crude nemotinic acid [1] and purified by redistribution in the same solvent system, could be isolated only as a labile gum. Methylation gave a non-crystalline hydroxy-ester. Both are strongly dextrorotatory and give infrared spectra very similar to those of nemotinic acid (I) and its methyl ester, with the important difference that there is no band at 3300 cm.$^{-1}$, *i.e.*, no $\equiv$C—H group. This suggested that odyssic acid was an alkylated derivative of acid (I), a view substantiated by the ultraviolet absorption spectrum, which is very similar to that of acid (I) but with the bathochromic shift of some 20 Å to be expected on alkylation of the enediyne chromophore (cf. Table). Odyssic acid was converted by sulphuric acid–dioxan into a γ-lactone (carbonyl band at 1785 cm.$^{-1}$) which was also a labile gum. This lactone was identical with purified natural odyssin in its infrared and ultraviolet spectra and behaviour with aqueous alkali (see below). The spectroscopic properties of odyssin bear the same relation to those of odyssic acid as do those of nemotin to nemotinic acid.[1]

The rearrangement of nemotinic acid by aqueous alkali was shown in Part VI [2] to give the corresponding non-allenic triyne, *iso*nemotinic acid, in which the asymmetric centre at $C_{(4)}$ remained intact. On the other hand the rearrangement of the γ-lactone nemotin gives an ene-triyne acid, nemotin A, and in this reaction the lactone function disappears. The mechanism of this reaction requires that the lactone function (and therefore the hydroxyl group of the parent acid) should be adjacent to the allene group.

Precisely analogous reactions were established for odyssic acid and odyssin. *iso*-Odyssic acid was obtained as a photosensitive crystalline solid by the alkali treatment of odyssic acid. The product was characterised as a 4-hydroxy-triynoic acid by conversion into its γ-lactone, a crystalline, optically active compound, polymorphic with m. p.s 64—66°, 73—74°, and 93—98°; this had, as expected, the ultraviolet absorption spectrum of a triyne and, in the infrared spectrum, a carbonyl band at 1796 cm.$^{-1}$ (γ-lactone) but no allene band.



---

[3] Bu'Lock, Jones, Leeming, and Thompson, *J.*, 1956, 3767.

Alkali-treatment of odyssin gave an acid, odyssin-A, with the ultraviolet absorption spectrum of a dialkyl-enetriyne (cf. Table; compare nemotin-A), and the infrared spectrum of its methyl ester confirms that there is no hydroxyl group, lactone ring, or allene group in the molecule. Material obtained by esterification of the total isomerisation product did not melt sharply and its infrared spectrum showed bands at both 950 (*trans*-C=C) and 740 cm.$^{-1}$ (*cis*-C=C), also present before esterification. However, the acid could be purified by crystallisation, and methylation of the crystallised acid gave an ester, m. p. 61·5—64·5°, which showed only the absorption band at 950 cm.$^{-1}$ and is therefore the *trans*-isomer; * methylation of material from the mother-liquors gave a concentrate of the *cis*-form. From infrared spectra of the mixed reaction products it may be concluded that isomerisation of odyssin gives about 75% of the *trans*-isomer, and re-examination of the infrared data for the whole product of the nemotin–nemotin-A isomerisation [2] indicates that this reaction too gives a mixture containing an appreciable proportion of the *cis*-isomer.

Ultraviolet absorption spectra.

Substance	Absorption max. (Å) and log ε (in parentheses)								
Odyssic acid (III)	2110	—	2380	2505	2650	2805			
	(4·78)	—	(3·77)	(4·02)	(4·18)	(4·09)			
Nemotinic acid (I) [1]	2090	—	2375	2495	2635	2785			
	(4·65)	—	(3·75)	(4·02)	(4·19)	(4·09)			
Odyssin (IV) (natural and from odyssic acid)	2100	—	2375	2500	2640	2800			
	(4·78)	—	(3·75)	(4·03)	(4·20)	(4·10)			
Nemotin (II) [1]	2085	—	2365	2490	2625	2780			
	(4·76)	—	(3·79)	(4·03)	(4·19)	(4·09)	—	—	—
*iso*Odyssic lactone (VI)	2095	—	2400	2530	2680	2860	3085		
	(5·21)	—	(2·18)	(2·32)	(2·43)	(2·40)	(2·19)		
*iso*Nemotinic lactone [2]	2060	—	2400	2530	2680	2850	3040		
	(5·11)	—	(2·16)	(2·28)	(2·42)	(2·41)	(2·20)		
Odyssin-A (VII) (from odyssin and from *iso*odyssic lactone)	2100	2240	2310	2425	2580	2730	2895	3085	3300
	(4·71)	(4·53)	(4·86)	(5·08)	(3·54)	(3·85)	(4·13)	(4·26)	(4·09)
Nemotin-A [2]	2115	2230 *	2300	2410	2580	2720	2885	3070	3280
	(4·37)	(4·47)	(4·77)	(4·93)	(3·44)	(3·78)	(4·07)	(4·19)	(4·04)
trans-Odyssin-A methyl ester	—	2240	2310	2430	2585	2735	2900	3090	3310
		(4·44)	(4·82)	(5·05)	(3·56)	(3·87)	(4·14)	(4·25)	(4·10)
Nemotin-A methyl ester [2]	2120	2230 *	2300	2410	2570	2720	2880	3070	3280
	—	—	—	—	—	—	—	—	—

* Inflexion.

As with nemotin-A, odyssin-A could also be obtained, in rather poor yield (<20%), by alkali treatment of the lactone from *iso*odyssic acid. The product was only characterised by its ultraviolet absorption spectrum, but in the similar reaction of *iso*nemotinic lactone,[2] re-examination of our infrared data again reveals that a mixture of *cis*- and *trans*-nemotin-A was produced.

These observations established the structure of the skeleton of odyssic acid as $C_n{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}CH(OH){\cdot}C{\cdot}C{\cdot}CO_2H$ and the chain length was settled by the hydrogenation of odyssin-A. The acid produced was converted directly into its *p*-toluidide, which depressed the m. p. of undecano- and tridecano-*p*-toluidides but not that of dodecano-*p*-toluidide.

Hence odyssic acid and odyssin are, respectively, 4-hydroxydodeca-5 : 6-diene-8 : 10-diynoic acid (III) and the corresponding lactone (IV), the C_{12} homologues of the C_{11} compounds, nemotinic acid and nemotin. *iso*Odyssic acid is (V), its lactone (VI), and odyssin-A is (VII). The ultraviolet absorption spectra of these compounds are summarised in the Table; comparison with the data for corresponding compounds of the C_{11} series

---

* The structure and configuration assigned to *trans*-odyssin-A have now been confirmed by comparison of its methyl ester with synthetic methyl *trans*-dodec-4-ene-6 : 8 : 10-triynoate (Jones, Skatteböl, and Whiting, unpublished work).

shows in each case the bathochromic shift of *ca.* 15—20 Å due to alkylation of the chromophore.

It is unusual in studies of natural products to encounter a compound occurring together with a *C*-methyl derivative. In the present instance there are at least three possible biogenetic explanations. Odyssic acid might be formed by a route similar to, but largely independent of, the biosynthesis of the lower homologue. Or both compounds might be formed from a single closely-related precursor, for example in a scheme such as:

$$\text{(reduction) } R{\cdot}CH_3 \longleftarrow R{\cdot}CO_2H \longrightarrow R{\cdot}H \text{ (decarboxylation)}$$

A third possibility is the direct transfer of a methyl group as such from an " active methyl " donor to nemotinic acid. Studies on this and other aspects of the biosynthesis are in progress; meanwhile it may be observed that the present instance of the co-occurrence of C_{11} and C_{12} compounds emphasises the fact that, though many natural acetylene derivatives belong in a formal sense to the series of unsaturated fatty acids, the polyacetylenes in general do not show that preponderance of even-numbered carbon chains so characteristic of the natural fats.

EXPERIMENTAL

The general experimental techniques were similar to those outlined in earlier papers.[1, 2]

Odyssic Acid (III).—The acid was separated from nemotinic acid by counter-current distribution as described previously [1] and purified by redistribution in the same benzene–water system (60 transfers in 40 tubes). Spectroscopic assay indicated a yield of purified odyssic acid of *ca.* 30 mg./l. of culture medium; the acid had $[\alpha]_D^{20}$ +300° (*c*, 0·25); pK_a (in water) 4·90; ultraviolet absorption, cf. Table; infrared absorption, bands at 3520 and 3600 (O—H), 2300—3500 (CO·O—H), 2230 (C≡C), 1960 (C=C=C), and 1710 cm.$^{-1}$ (HO·C=O); no band at 3300 cm.$^{-1}$ (no ≡C—H). Evaporation of solutions of the acid gave a labile gum. Esterification with diazomethane gave methyl odyssate, a labile oil; ultraviolet absorption, cf. Table; infrared absorption bands at 1740 (MeO·C=O) and 3470 and 3620 cm.$^{-1}$ (O—H).

Odyssin (IV).—Separated from nemotin as previously described [1] and purified by redistribution in the same system (*n*-heptane–aqueous ethanol), natural odyssin (*ca.* 80% pure) was obtained only in small amounts (*ca.* 5 mg./l. of culture-medium on spectroscopic assay) and identified by comparison of its infrared spectrum with that of the lactone from odyssic acid (see below); $[\alpha]_D^{20}$ +360° (*c*, 0·2); ultraviolet absorption spectrum (qualitative only), cf. Table.

Odyssin from Odyssic Acid.—A solution of the acid (300 mg.) in pure dry dioxan (300 c.c.) was treated with sulphuric acid (9 c.c.), and the solution left for 4 days in the dark at 20°, after which water (50 c.c.) was added followed by sodium hydrogen carbonate solution to bring the solution to pH 4. Sodium sulphate was filtered off and washed with ether, and the combined filtrate and washings evaporated to 80 c.c. Water (3·5 l.) was added and the solution extracted with ether (2 × 350 c.c.). The combined extracts, when washed with water (2 × 200 c.c.) and dried, contained *ca.* 160 mg. of neutral polyacetylenes. Of this 100 mg. were purified by counter-current distribution between 32% aqueous ethanol and *cyclo*hexane. The purified odyssin (76 mg.) was a labile oil; $[\alpha]_D^{20}$ +345° (*c*, 0·24); ultraviolet absorption, cf. Table; infrared absorption identical with natural odyssin, with band at 1785 cm.$^{-1}$ (γ-lactone).

iso*Odyssic Acid* (V).—A solution of odyssic acid (100 mg.) in ether was shaken with 0·1N-sodium hydroxide (2 × 100 c.c.) and the combined aqueous extracts were kept for 2 hr. at 20°, the ultraviolet absorption spectrum then showing no further change; a small amount of enetriyne had been formed. The solution was acidified and extracted with ether (2 × 150 c.c.), and the extracts combined, dried, and evaporated. The residue of *iso*odyssic acid, recrystallised from ether–pentane at −40°, formed persistently yellow needles, m. p. 128—130°, still containing some enetriyne as shown by the ultraviolet absorption spectrum. The compound was therefore purified by counter-current distribution between ether and M/15-disodium hydrogen phosphate solution, and the purified material converted into its lactone (see below).

iso*Odyssic Lactone* (VI).—A solution of *iso*odyssic acid (80 mg.) and sulphuric acid (3 c.c.) in pure dry dioxan (100 c.c.) was kept in the dark at 20° for 4 days. The solution was then neutralised with sodium hydrogen carbonate solution and the precipitated sodium sulphate filtered off and washed with ether. The combined filtrate and washings were evaporated to 30 c.c. and poured into water (800 c.c.); the solution was extracted with ether (2 × 200 c.c.), and the ether extracts washed with water (3 × 200 c.c.), dried, and concentrated to 100 c.c. The pale yellow solution was decolorised with a little charcoal, evaporated, and iso*odyssic lactone* crystallised from methylene chloride–pentane forming trimorphic plates, m. p.s 64°, 73—74°, and 93—98°, stable for several days at −40° in the dark (Found: C, 76·9; H, 5·5. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%); $[\alpha]^{20}_{D}$ −2° (*c*, 0·5); ultraviolet absorption, cf. Table; infrared absorption with band at 1795 cm.$^{-1}$ (γ-lactone) and no allene band.

Odyssin-A from Odyssin.—Odyssin (from odyssic acid) (180 mg.) in ether (450 c.c.) was added to 0·1N-sodium hydroxide (500 c.c.), and the ether evaporated; after 2 hr. the solution was acidified and extracted with ether (2 × 300 c.c.). The yellow extracts were added to M/15-disodium hydrogen phosphate (300 c.c.), the ether was evaporated, and the aqueous solution then extracted with ether (5 × 300 c.c.), giving a colourless solution (methylation of the dissolved material and measurement of the infrared spectrum of the product showed this to be a mixture of *cis*- and *trans*-isomers). Evaporation of the solution and recrystallisation of the residue from methylene chloride–pentane at −80° gave trans-*odyssin-A* (yield *ca.* 60%) as rhombs, becoming slowly yellow in light, decomp. at 185—195° (Found: C, 77·2; H, 5·7%; equiv., 179. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%; equiv., 186); ultraviolet absorption, cf. Table; infrared absorption, band at 1710 cm.$^{-1}$ (HO•C=O), no allene or hydroxyl bands.

Methyl Esters of Odyssin-A.—Methylation with distilled diazomethane of the total reaction product (above) gave material which did not melt sharply and had infrared absorption bands at 740 (*cis*-CH=CH) and 950 cm.$^{-1}$ (*trans*-CH=CH). Methylation of recrystallised odyssin-A in the same way gave methyl *trans*-odyssin-A, which crystallised from *n*-pentane at −70° as needles, m. p. 61·5—64·5°, mixed m. p. 59·5—62·5° with synthetic material (cf. footnote, p. 1099) (m. p. 57·5—61·5°), ultraviolet (cf. Table) and infrared absorption identical with synthetic material, the latter showing bands at 1740 (MeO•C=O) and 950 cm.$^{-1}$ (*trans*-CH=CH) and no allene, hydroxyl, or *cis*-CH=CH bands. Similar methylation of material from the liquors remaining after crystallisation of *trans*-odyssin-A gave an oil, shown by its infrared absorption spectrum to contain *ca.* 60% of methyl *cis*-odyssin-A and *ca.* 40% of the *trans*-ester.

Odyssin-A from iso*Odyssic Lactone.*—The lactone (6 mg.) in dioxan (13 c.c.) and 10% aq. potassium carbonate (13 c.c.) was left at 20°; the ultraviolet absorption spectrum (cf. Table) indicated a fairly rapid reaction affording about 20% of odyssin-A.

Hydrogenation of Odyssin-A.—The acid (45 mg.) in ethanol (25 c.c.) over platinum (from 50 mg. of oxide) rapidly took up 6·9 mol. of hydrogen; filtration and evaporation of the solution gave *n*-dodecanoic acid (50 mg.) identified by conversion into the *p*-toluidide, m. p. 84—85°, and comparison with authentic material. Mixed m. p. with dodecano-*p*-toluidide (m. p. 85·5—86·5°), 84—86°, with undecano-*p*-toluidide (m. p. 78·5—79·5°), 76·5—78·5°, with tridecano-*p*-toluidide (m. p. 88·0—88·5°) 81—84°.

The authors are indebted to the Rockefeller Foundation for financial assistance and to Glaxo Laboratories Ltd. for a maintenance grant (to P. R. L.). They are also grateful to Miss E. F. Leadbeater who prepared the fungus cultures, to Dr. G. D. Meakins for advice on infrared spectra, and to Mr. E. S. Morton and Miss W. Peadon for microanalyses and spectrographic measurements, respectively.

THE UNIVERSITY, MANCHESTER, 13.
DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

[*Received, October 30th, 1956.*]