700. *Researches on Acetylenic Compounds. Part LXV.* Synthesis of Odyssin A and Iso-odyssic Lactone.*

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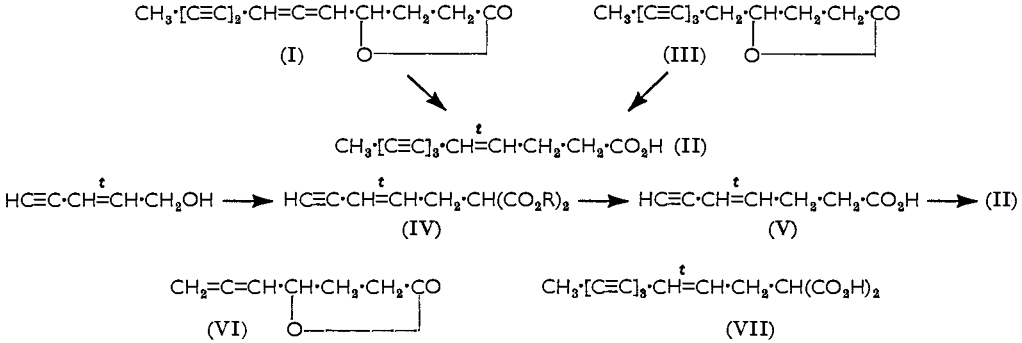
The structures assigned to odyssin and odyssic acid, metabolites of the wood-rotting fungus B. 841, have been confirmed by syntheses of two of their transformation products.

THE structures of odyssin and odyssic acid, produced by cultures of the Basidiomycete B. 841, have been established by Bu'Lock, Jones, and Leeming.[1] Odyssin (I) itself and iso-odyssic lactone (III) were found to undergo alkali-catalysed rearrangement to odyssin A (II).

Structure (II) was assigned to odyssin A on the basis of its ultraviolet and infrared absorption spectra, and its hydrogenation to dodecanoic acid. This structure has now been confirmed by the synthesis of *trans*-dodec-4-ene-6,8,10-triynoic acid (II) by the route shown below.



(I) $\mathrm{CH_3{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}}\underbrace{\mathrm{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO}}_{\mathrm{O}}$

(III) $\mathrm{CH_3{\cdot}[C{\equiv}C]_3{\cdot}CH_2{\cdot}}\underbrace{\mathrm{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO}}_{\mathrm{O}}$

$\mathrm{CH_3{\cdot}[C{\equiv}C]_3{\cdot}CH\overset{t}{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$ (II)

$\mathrm{HC{\equiv}C{\cdot}CH\overset{t}{=}CH{\cdot}CH_2OH} \longrightarrow \underset{\text{(IV)}}{\mathrm{HC{\equiv}C{\cdot}CH\overset{t}{=}CH{\cdot}CH_2{\cdot}CH(CO_2R)_2}} \longrightarrow \underset{\text{(V)}}{\mathrm{HC{\equiv}C{\cdot}CH\overset{t}{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}} \longrightarrow$ (II)

(VI) $\mathrm{CH_2{=}C{=}CH{\cdot}}\underbrace{\mathrm{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO}}_{\mathrm{O}}$

(VII) $\mathrm{CH_3{\cdot}[C{\equiv}C]_3{\cdot}CH\overset{t}{=}CH{\cdot}CH_2{\cdot}CH(CO_2H)_2}$

trans-Pent-2-en-4-yn-1-ol was converted into its bromide, which on treatment with diethyl malonate yielded (IV; R = Et). Hydrolysis afforded the dicarboxylic acid (IV; R = H), which was decarboxylated on distillation, giving *trans*-hept-4-en-6-ynoic

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* Part LXIV, preceding paper.

[1] Bu'Lock, Jones, and Leeming, *J.*, 1957, 1097.

acid (V). Oxidative coupling of this acid (V) with penta-1,3-diyne afforded *trans*-odyssin A, unfortunately in rather low yield. Methylation with diazomethane gave the methyl ester, identical with the naturally derived material.

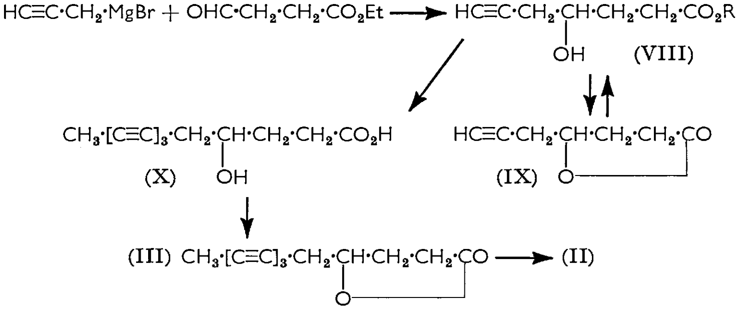
From the decarboxylation of the malonic acid (IV; R = H), a small amount of neutral material was obtained, whose infrared spectrum [$\nu_{max.}$ 1960 and 857 ($CH_2=C=CH$) and 1770 cm.$^{-1}$ (γ-lactone)] indicated structure (VI). This rearrangement, if general, could have been useful for the synthesis of odyssin (I).

Accordingly, penta-1,3-diyne was oxidatively coupled with hex-3-en-5-yne-1,1-dicarboxylic acid (IV; R = H) to give the acid (VII), from which on decarboxylation a mixture of odyssin and odyssin A might have been produced. However, on distillation, extensive decomposition occurred, and no product could be isolated.[2]

In order to synthesise iso-odyssic lactone (III), a route was developed which incidentally provided an alternative route to odyssin A.

The acetylenic hydroxy-ester (VIII; R = Et) prepared from propargylmagnesium bromide and ethyl β-formylpropionate always contained a small percentage of the lactone (IX), presumably formed by internal transesterification. In general, the contaminated ester was not purified, and the mixture was hydrolysed to the γ-hydroxy-acid (VIII; R = H), which on distillation with toluene-*p*-sulphonic acid yielded the pure lactone (IX).

Coupling[3] of 1-bromopenta-1,3-diyne with the lactone to give iso-odyssic lactone (III) could not be effected, even though a variety of conditions was tried. The use of primary amines[3] resulted in the formation of amides which then coupled normally, yielding the corresponding amides of iso-odyssic acid (X). No reaction occurred when pyridine was employed. The preparation of iso-odyssic acid (X) was finally accomplished by coupling 1-bromopenta-1,3-diyne with the potassium salt (VIII; R = K), the latter being prepared from the lactone (IX) with one equivalent of potassium hydroxide.



As iso-odyssic acid derived from the natural product was too unstable to be readily handled,[1] the synthetic acid was not purified but was converted directly into iso-odyssic lactone (III). The ultraviolet absorption confirmed the presence of the triyne chromophore, and the infrared spectra of both the naturally derived and the synthetic material were identical.

It was desirable to convert iso-odyssic lactone into odyssin A, as the final stage of the earlier synthesis gave only a low yield. The isomerisation of "natural" iso-odyssic lactone to odyssin A with 10% potassium carbonate[1] proceeded only in 20% yield, the main product being iso-odyssic acid. However, by using potassium t-pentyloxide a 70% conversion was achieved. Purification by countercurrent distribution afforded odyssin A as a mixture of *cis*- and *trans*-isomers, the *cis*-isomer being subsequently removed by crystallisation. This sample of the *trans*-form had m. p. 110—155° (decomp.), unchanged on repeated recrystallisation. A comparison with the "natural" and earlier synthetic acids, m. p.s 190° (decomp.), was unfortunately not possible, and it must be assumed that

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[2] Jones, Lee, and Whiting, unpublished work.
[3] Chodkiewicz, *Ann. Chim. (France)*, 1957, **2**, 852.

trans-odyssin A is dimorphous. Methylation of the *trans*-acid with diazomethane gave the methyl ester, identical with the naturally derived material.

The mother-liquors from the crystallisation of the *cis–trans*-acid mixture were re-examined in an attempt to isolate the *cis*-component, but only a concentrate of the latter could be obtained. Methylation of this gave an oil whose infrared absorption spectrum contained bands at 740 (*cis*-CH=CH) and 950 cm.$^{-1}$ (*trans*-CH=CH). On the basis of infrared absorption, it could be estimated that the pentyloxide-catalysed isomerisation of iso-odyssic lactone yielded *ca.* 90% of *trans*-odyssin A, compared with an estimated 75% of the *trans*-isomer produced by carbonate-isomerisation of both naturally derived odyssin and iso-odyssic lactone.[1]

EXPERIMENTAL

Ultraviolet absorption spectra were measured in ethanol on a Cary recording spectrophotometer model 14M, and infrared absorption spectra on a Perkin–Elmer spectrophotometer model 21. M. p.s were determined on a Kofler block and are corrected. Evaporations were carried out at 40° under reduced pressure. Light petroleum refers to material of b. p. 40—60°.

Diethyl trans-*Hex-3-en-5-yne-1,1-dicarboxylate* (IV; R = Et).—1-Bromopent-2-en-4-yne [4] (25 g.) was added during 1·5 hr. under reflux to a stirred suspension of ethyl sodiomalonate [from ethyl malonate (43·5 g.) and sodium (6 g.)] in absolute ethanol (115 c.c.). The mixture was then stirred overnight at 20° and poured into water. Extraction with ether, followed by distillation, afforded the *diethyl ester* (15·4 g.), b. p. 81—82°/0·05 mm., n_D^{27} 1·4625 (Found: C, 64·45; H, 7·1. $C_{12}H_{16}O_4$ requires C, 64·25; H, 7·2%).

trans-*Hex-3-en-5-yne-1,1-dicarboxylic acid* (IV; R = H).—The above diester (15 g.) was added to a solution of potassium hydroxide (10 g.) in ethanol (350 c.c.) and water (150 c.c.) and kept for 2 days at 5°. The mixture was evaporated to a small volume under reduced pressure, acidified, and extracted with ether. The ethereal extract was shaken with sodium hydrogen carbonate solution, and the acid again isolated with ether. The *acid* crystallised from benzene as needles (7·7 g.), m. p. 133—135° (decomp.) (Found: C, 56·9; H, 4·65. $C_8H_8O_4$ requires C, 57·15; H, 4·8%), $\lambda_{max.}$ 2240 Å (ε 13,400).

trans-*Hept-4-en-6-ynoic Acid* (V).—*trans*-Hex-3-en-5-yne-1,1-dicarboxylic acid (5·0 g.) was distilled at 140—150° (bath)/0·5 mm. The crystalline distillate was treated with potassium hydrogen carbonate solution, acidified, and extracted with ether. Recrystallisation of the product from light petroleum gave trans-*hept-4-en-6-ynoic acid* (0·53 g.) as long needles, m. p. 64—66° (Found: C, 67·6; H, 6·25. $C_7H_8O_2$ requires C, 67·75; H, 6·5%), $\lambda_{max.}$ 2220 Å (ε 14,000).

trans-*Dodec-4-ene-6,8,10-triynoic acid* (trans-*Odyssin A*) (II).—Penta-1,3-diyne [5] (500 mg.) and *trans*-hept-4-en-6-ynoic acid (210 mg.) were added to cuprous chloride (4 g.) and ammonium chloride (7 g.) in water (20 c.c.), and the mixture brought to pH 3 with concentrated hydrochloric acid. Hydrogen peroxide (7 c.c.) was added with stirring during 45 min., the temperature being kept below 5°. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The acidic product was purified by treatment with (*a*) sodium hydrogen carbonate solution, and (*b*) M/15-disodium hydrogen phosphate buffer solution. Ether-extraction of the acidified phosphate solution yielded *trans*-odyssin A, which separated from methylene chloride–light petroleum in small colourless plates (3 mg.), m. p. 190° (decomp.). Bu'Lock, Jones, and Leeming [1] give m. p. 185—195° (decomp.). For $\lambda_{max.}$ see Table.

Ultraviolet absorption spectra.

Compound	Absorption maxima (Å) and ε × 10^{-3} (in parentheses)								
Iso-odyssic lactone (III)	2080 (174)	2390 (0·29)	2520 (0·31)	2670 (0·35)	2850 (0·33)	3070 (0·27)			
N-Ethyliso-odyssamide	2100 (154)	2390 (0·19)	2530 (0·24)	2680 (0·33)	2860 (0·31)	3080 (0·16)			
trans-Odyssin A (II)	2100 (31)	2230 * (29·5)	2300 (71·0)	2420 (117)	2580 (3·4)	2725 (7·0)	2890 (13·3)	3080 (16·9)	3290 (12·0)
trans-Odyssin A methyl ester	2100 (33)	2230 * (33)	2300 (76·5)	2420 (135)	2570 (3·6)	2720 (8)	2880 (16)	3070 (21·3)	3290 (14·6)

* Inflexion

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[4] Henbest, Jones, and Walls, *J.*, 1950, 3646.

[5] Allan, Jones, and Whiting, *J.*, 1955, 1862.

The methyl ester was prepared with ethereal diazomethane and crystallised from pentane at −70° as needles, m. p. 57·5—61·5° (mixed m. p. 59·5—62·5° with naturally derived methyl *trans*-odyssin A, m. p. 61·5—64·5°) (for $\lambda_{max.}$ see Table), $\nu_{max.}$ (in CS_2) 1740 (ester C=O) and 950 cm.$^{-1}$ (*trans*-CH=CH). No band due to *cis*-CH=CH was present.

Ethyl β-*Formylpropionate.*[6]—Ethyl α-formylsuccinate (50 g., prepared by the method of Wislicenus, Böklen, and Reuthe[6]) and M/15-phosphate buffer solution[7] (150 c.c.; pH 7) were heated in an autoclave at 140—145° for 1 hr. with stirring, then saturated with salt, and extracted with ether (2 × 75 c.c.), and the ethereal solution was washed with water (2 × 50 c.c.). Evaporation of the ether was carried out under reduced pressure *via* a 10″ Dufton column. Fractionation of the residue afforded ethyl β-formylpropionate (18 g.), b. p. 72°/10 mm., n_D^{19} 1·4230 (lit.,[8] b. p. 70—72°/10 mm., n_D^{23} 1·4218).

Ethyl 4-*Hydroxyhept*-6-*ynoate* (VIII; R = Et).—Propargylmagnesium bromide was prepared under nitrogen from propargyl bromide (5·95 g.), magnesium (1·15 g.), and dry ether (50 c.c.) as described by Prévost, Gaudemar, and Honigberg.[9] The Grignard solution was added dropwise at 0° during 45 min., with stirring under nitrogen, to freshly distilled ethyl β-formylpropionate (7·15 g.) in dry ether (100 c.c.). Then the suspension was stirred for a further 15 min. at 0° and the complex decomposed with saturated ammonium chloride solution (50 c.c.). The ethereal layer was separated and the aqueous layer extracted further with ether (2 × 50 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated. Distillation gave a fraction (4·8 g.), b. p. 70—100°/0·1 mm., which was shown to contain 5—10% of the lactone (IX) by the intensity of an infrared band at 1785 cm.$^{-1}$. Careful redistillation afforded the *ethyl ester* (4·2 g.), b. p. 75—76°/0·1 mm., n_D^{17} 1·4600 (Found: C, 63·55; H, 8·25. $C_9H_{14}O_3$ requires C, 63·55; H, 8·3%), $\nu_{max.}$ (in CCl_4) 3510 and 3400 (OH), 3270 (≡CH), 2105 (C≡C), and 1727 cm.$^{-1}$ (ester C=O).

Lactone of 4-*Hydroxyhept*-6-*ynoic Acid* (IX).—The above ester (before separation of the lactone) (8·5 g.) was kept with potassium hydroxide (8·5 g.) in 50% aqueous ethanol (400 c.c.) overnight at 20°. The solution was evaporated (to 100 c.c.), made just acid to litmus with N-hydrochloric acid, and extracted continuously with ether for 24 hr. Drying and evaporation gave the hydroxy-acid (VIII; R = H) as a viscous yellow oil (7·7 g.). Distillation of a portion (4·05 g.) with a crystal of toluene-*p*-sulphonic acid gave the *lactone* (2·9 g.), b. p. 72°/0·05 mm., n_D^{16} 1·4764 (Found: C, 67·65; H, 6·4. $C_7H_8O_2$ requires C, 67·75; H, 6·5%), $\nu_{max.}$ (in CCl_4) 3280 (≡CH), 2110 (C≡C), and 1785 cm.$^{-1}$ (γ-lactone).

N-*Ethyliso-odyssamide.*—The above lactone (0·62 g.) was added with stirring under nitrogen to 33% aqueous ethylamine (1·4 c.c.), cuprous chloride (0·01 g.), and a crystal of hydroxylamine hydrochloride. 1-Bromopenta-1,3-diyne[3] [from penta-1,3-diyne[5] (0·35 g., 1·1 mol.)] in methanol (1 c.c.) was then added during 5 min. at 30°. After being stirred for a further 10 min., the mixture was poured into N-hydrochloric acid and extracted with ether (2 × 50 c.c.). Evaporation gave a white solid (400 mg.) which was washed with light petroleum to remove hydrocarbon impurities and recrystallised from methylene chloride–light petroleum, the *ethylamide* separating as a microcrystalline solid (250 mg.), m. p. 89° (Found: C, 72·0; H, 7·2; N, 6·45. $C_{14}H_{17}O_2N$ requires C, 72·65; H, 7·4; N, 6·1%) ($\lambda_{max.}$ see Table), $\nu_{max.}$ (in CCl_4) 3430 (OH), 3280 (NH), 2233 (C≡C), 1656 (amide CO-I), and 1532 cm.$^{-1}$ (amide CO-II).

Iso-odyssic Lactone (III).—The lactone of 4-hydroxyhept-6-ynoic acid (0·62 g.) with potassium hydroxide (0·28 g., 1 mol.) in 30% aqueous ethanol (1·5 c.c.) was kept overnight at 20°. The solution was then added to a mixture of 33% aqueous ethylamine (1·4 c.c.), cuprous chloride (0·01 g.), and a crystal of hydroxylamine hydrochloride. The mixture was stirred in nitrogen at 30° and 1-bromopenta-1,3-diyne[3] [from penta-1,3-diyne[5] (0·35 g., 1·1 mol.)] in 80% aqueous methanol (1·5 c.c.) added dropwise during 10 min. After being stirred for a further 10 min., the solution was poured into N-hydrochloric acid (50 c.c.), and extracted with ether (3 × 25 c.c.). The ethereal solution was extracted with N-sodium hydroxide (2 × 50 c.c.), and the combined aqueous phases were washed with ether. After acidification with 2N-hydrochloric acid, crude iso-odyssic acid was isolated *via* ether as a pale yellow solid (0·45 g.).

The crude iso-odyssic acid was immediately mixed with dry dioxan (97 c.c.) and concentrated sulphuric acid (3 c.c.) and kept in the dark at 20° for 4 days. Water (1 l.) was then

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[6] Cf. Wislicenus, Böklen, and Reuthe, *Annalen*, 1908, **363**, 347; Sugasawa, *J. Pharm. Soc. Japan*, 1926, **46**, 65.

[7] Sörensen, *Biochem. Z.*, 1909, **21**, 131.

[8] Stoll and Bolle, *Helv. Chim. Acta*, 1938, **21**, 1547.

[9] Prévost, Gaudemar, and Honigberg, *Compt. rend.*, 1950, **230**, 1186.

added and the yellow solid obtained by isolation with ether was decolorised with charcoal in methylene chloride solution. Recrystallisation from methylene chloride–ether–pentane gave iso-odyssic lactone as needles (0·27 g.), m. p. 97° (Bu'Lock, Jones, and Leeming[1] found the optically active, naturally derived, material to be polymorphic with m. p.s 64°, 73—74°, and 93—98°) ($\lambda_{max.}$ see Table), $\nu_{max.}$ (in CS_2) 2215 ($C\equiv C$), and 1793 cm.$^{-1}$ (γ-lactone).

trans-*Odyssin A* (II).—Potassium (42 mg., 1·1 equiv.) was dissolved in dry t-pentyl alcohol (5 c.c.) under reflux, and the cooled solution added to iso-odyssic lactone (180 mg.) in dry t-pentyl alcohol (100 c.c.). After 5 min. at 20°, potassium hydroxide (6 g.) in water (100 c.c.) was added and the mixture was made homogeneous with ethanol and kept overnight at 20° (hydrolysis of esters). Water (500 c.c.) was added and the solution extracted with methylene chloride (3 × 150 c.c.). The aqueous phase was then acidified (Congo Red) with 5N-hydrochloric acid and extracted with ether (3 × 100 c.c.). The combined ethereal extracts were evaporated to 40 c.c.. and the mixture of odyssin A and iso-odyssic acid was resolved by counter-current distribution between ether and M/15-disodium hydrogen phosphate. Evaporation of the ethereal odyssin A fractions afforded a solid (125 mg.) which on crystallisation from methylene chloride–pentane at −40° gave *trans*-odyssin A as needles (80 mg.), m. p. 110—155° (slow decomp.) ($\lambda_{max.}$ see Table), $\nu_{max.}$ (in CCl_4) 2220 ($C\equiv C$), 1715 (C=O), and 950 cm.$^{-1}$ (*trans*-CH=CH).

Treatment of *trans*-odyssin A (35 mg.) with ethereal diazomethane gave the methyl ester, which separated from pentane at −40° in needles (26 mg.), m. p. 62—63° (Bu'Lock, Jones, and Leeming[1] give m. p. 61·5—64·5°) (Found: C, 78·15; H, 5·9. Calc. for $C_{13}H_{12}O_2$: C, 77·95; H, 6·05%), $\lambda_{max.}$ and $\nu_{max.}$ identical with values quoted previously.

Grateful acknowledgment is made for the award of a Royal Norwegian Council for Scientific and Industrial Research Fellowship (to L. S.) and and I.C.I. Fellowship (to J. B. J.).

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