Oenanthotoxin and Cicutoxin. Part II. The Synthesis of (±)-Cicutoxin and of Oenanthetol.*

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The structure of cicutoxin as (−)-heptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyne-1 : 14-diol is confirmed by synthesis of the (±)-isomer from a protected hepta-4 : 6-diyn-1-ol and deca-2 : 4 : 6-trienal. The natural and the synthetic compound have been oxidised to the same 1-hydroxyheptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyn-14-one.

Oenanthetol (heptadeca-*trans*-2 : 8 : 10-triene-4 : 6-diyn-1-ol), from *Oenanthe crocata*, has been synthesised by dehydrating heptadeca-2 : 8-diene-4 : 6-diyne-1 : 10-diol.

The water hemlock, *Cicuta virosa*, contains two triene-diynes, cicutoxin (I; R = OH) and cicutol, and the hemlock water dropwort, *Oenanthe crocata*, contains three ene-diyne-dienes, oenanthotoxin (II; R = OH), oenanthetol, and oenanthetone (Anet, Lythgoe, Silk, and Trippett, Part I *). Although complete degradative evidence was obtained for the structures allotted to the two toxins, those of cicutol and oenanthetol were assumed to be (I; R = H) and (II; R = H) respectively by analogy; the orientations of the unsaturated systems within their molecules (as distinct from their positions) were not directly determined. Synthetic work has been undertaken in order to confirm the postulated structures and this paper records syntheses of representatives of both groups of compounds, namely, (±)-cicutoxin and oenanthetol.

Cicutoxin appeared to be the most readily amenable of the five naturally occurring compounds to synthesis, since it contains a secondary allylic hydroxyl group and should be accessible by reaction of a Grignard derivative of a suitably protected hepta-4 : 6-diyn-1-ol

$$HO\cdot CH_2\cdot[CH_2]_2\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_3\cdot CHRPr^n \quad (I)$$

$$HO\cdot CH_2\cdot CH{=}CH\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_3\cdot[CH_2]_2\cdot CHRPr^n \quad (II)$$

(III)  $\cdot O\cdot CH_2\cdot[CH_2]_2\cdot[C{\equiv}C]_2\cdot H + OHC\cdot[CH{=}CH]_3\cdot R$ (IV)

↓

 $\cdot O\cdot CH_2\cdot[CH_2]_2\cdot[C{\equiv}C]_2\cdot CH(OH)\cdot[CH{=}CH]_3\cdot R$ (V)

↓

$$HO\cdot CH_2\cdot[CH_2]_2\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_3\cdot CHR\cdot OH \quad (VI)$$

$$CH_3\cdot[CH_2]_2\cdot CH{=}CH\cdot CHO + Li\cdot C{\equiv}C\cdot CH{=}CH\cdot OEt$$

↓

$$CH_3\cdot[CH_2]_2\cdot CH{=}CH\cdot CH(OH)\cdot C{\equiv}C\cdot CH{=}CH\cdot OEt \quad (VII)$$

↓

$$CH_3\cdot[CH_2]_2\cdot CH{=}CH\cdot CH(OH)\cdot[CH{=}CH]_2\cdot OEt \longrightarrow (IV;\ R = Pr^n)$$

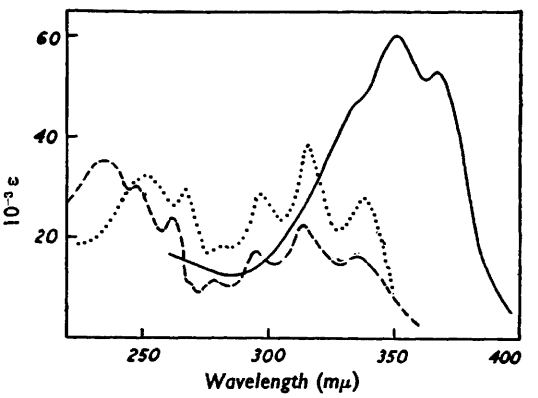
(*e.g.*, III) and deca-2 : 4:6-trienal (IV; R = Pr^n). The first of these components was readily obtained by reaction of 1-bromo-3-2′-tetrahydropyranyloxypropane with monosodiodiacetylene in liquid ammonia. As a means of testing the projected synthesis the magnesium bromide derivative from (III) was treated with octatrienal to give the alcohol (V; R = Me). Treatment with acid removed the protecting tetrahydropyranyl residue and

* Part I, *J.*, 1953, 309.

caused anionotropic rearrangement to the (±)-diol (VI; R = Me); this diol differs from cicutoxin only in its stereochemistry at $C_{(14)}$ and in having a methyl instead of a *n*-propyl group. Its infrared absorption spectrum showed that, as expected from its mode of synthesis, it had the all-*trans*-structure, and its ultraviolet absorption spectrum was very similar to that of cicutoxin. It absorbed 7 mols. of hydrogen in the presence of palladium, giving (±)-pentadecane-1 : 14-diol.

For the preparation of deca-2 : 4 : 6-trienal (IV; R = Pr^n) hex-2-en-1-al was chosen as the starting material. It was obtained by reducing hex-2-enoic acid with lithium aluminium hydride to hex-2-en-1-ol which was oxidised with manganese dioxide to hex-2-enal. Reaction of the aldehyde with the lithium derivative of ethoxyvinylacetylene (cf. Inhoffen, Bohlmann, and Rummert, *Annalen*, 1950, **569**, 226) gave crude 1-ethoxydeca-1 : 6-dien-3-yn-5-ol (VII) which, after semihydrogenation with Lindlar's catalyst (*Helv. Chim. Acta*, 1952, **35**, 446) and subsequent treatment with acid, gave the trienal (IV; R = Pr^n), isolated as its semicarbazone.

The regenerated aldehyde was treated exactly as described for octatrienal and the final product purified chromatographically, giving (±)-cicutoxin (VI; R = Pr^n; *i.e.*, I; R = OH) with light absorption almost identical with that of natural (−)-cicutoxin. It had, as



Light absorption of (——) *1-hydroxyheptadeca-8 : 10 : 12-triene-4 : 6-diyn-14-one* (*in* CCl_4), (– – – –) *10-benzoyloxydeca-2 : 8-diene-4 : 6-diynal* (*in* EtOH), *and* (. . . .) *oenanthetol* (*in* EtOH).

expected from the mode of synthesis, an all-*trans*-structure, and the infrared absorption spectra of the natural and the synthetic material, compared in chloroform solutions, showed no discrepancies. That the two samples were identical in all save the stereochemistry at $C_{(14)}$ was shown chemically by oxidation with manganese dioxide to the same crystalline 1-hydroxyheptadeca-*trans*-8 : 10 : 12-triene-4 : 6-diyn-14-one, the light absorption of which is shown in the Figure. Dr. G. A. Mogey of the Department of Pharmacology, to whom we express our warm appreciation, tested the effect of the natural and the synthetic material on mice. The synthetic material was considerably more toxic, pointing to a considerably greater potency of the (+)-component than the natural isomer. This is of special interest in connection with our observation that natural oenanthotoxin, which has the (+)-configuration, is more toxic to mice than (−)-cicutoxin.

Attention was then turned to oenanthetol (II; R = H), whose synthesis was expected to present more problems than that of cicutoxin. Trideca-*trans*-3 : 5 : 11-triene-7 : 9-diyn-2-ol, which has the same unsaturated system as oenanthetol, was prepared (Part I, *loc. cit.*) by reaction of a Grignard derivative of hept-2-ene-4 : 6-diyne with sorbaldehyde followed by anionotropic rearrangement of the resulting alcohol, and, theoretically, the alcohol (VIII; R = $C_6H_{13}^n$; *n* = 1), accessible from trideca-5 : 7-diene-1 : 3-diyne and acraldehyde, should give oenanthetol by similar rearrangement. However, when such rearrangements displace only one ethylenic link in a system devoid of activating alkyl groups, they are known to proceed only with difficulty (Heilbron *et al.*, *J.*, 1945, 77, 84). The alcohol (VIII; R = Me; *n* = 1) should offer a suitable test substance; but the product from bromomagnesiohept-2-ene-4 : 6-diyne and acraldehyde could not be rearranged to an ene-diyn-ene, and this type of approach was abandoned.

An alternative appeared to lie in an oxidative coupling of the readily accessible pent-2-en-4-yn-1-ol with a dien-yne (IX). Such dien-ynes have not so far been prepared, but Eglinton and Whiting (*J.*, 1950, 3650) obtained pent-2-en-4-yne by the action of potassium hydroxide on the toluene-*p*-sulphonate of pent-4-yn-2-ol. Attempts to extend this method to hept-4-en-1-yn-3-ol gave discouraging results, nor could this alcohol be dehydrated directly by toluene-*p*-sulphonic acid without extensive destruction of the product. It seems likely, from results presented below, that this lability is caused by the terminal ethynyl group.

Search for methods of preparing dien-ynes such as (IX) was deferred since in the meantime it was observed that cicutoxin was readily dehydrated by toluene-*p*-sulphonic acid in

(VIII) $CH_2{=}CH{\cdot}CH(OH){\cdot}[C{\equiv}C]_2{\cdot}[CH{=}CH]_n{\cdot}R$ $\qquad$ $HC\,C{\cdot}[CH{=}CH]_2{\cdot}C_6H_{13}{}^n$ (IX)

(X) $RO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH \longrightarrow RO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CHO$ (XI) $\longrightarrow$

(XII) $HO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}C_6H_{13}{}^n \longrightarrow$ (II; R = H)

boiling benzene to give a product which, from its light absorption, was clearly heptadeca-4 : 6 : 8 : 10-tetraene-12 : 14-diyn-1-ol and appeared to be stable towards further action of the reagent. This opened the way to a synthesis of oenanthetol from the diol (XII).

As starting material, deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (X; R = H), readily available from oxidative Glaser coupling of pent-2-en-4-yn-1-ol (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586; Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998) was used. Its monobenzoate (X; R = Bz) was oxidised with manganese dioxide to the semi-aldehyde (XI; R = Bz), the ultraviolet absorption curve of which (see Figure) resembled that of oenanthetol. From the aldehyde the diol (XII) was obtained by reaction with an excess of *n*-heptylmagnesium bromide; dehydration with toluene-*p*-sulphonic acid in boiling toluene gave heptadeca-2 : 8 : 10-triene-4 : 6-dien-1-ol, whose all-*trans*-configuration was shown by its infrared absorption spectrum. Its identity with natural oenanthetol was established by direct comparison.

The ready availability of allylic alcohols such as (I; R = OH) and (XII), together with their easy dehydration, offer an attractive route to a variety of polyen-ynes. Experiments on the synthesis of cicutol and oenanthotoxin by this route are in progress.

Experimental

Operations with unsaturated compounds were carried out at low temperature under oxygen-free nitrogen. Light petroleum refers to the fraction, b. p. 40—60°. M. p.s are corrected.

1-Bromo-3-2′-tetrahydropyranyloxypropane.—2 : 3-Dihydropyran (28 g.) and trimethylene bromohydrin (42 g.) were mixed and, after the initial period when heat was evolved, were kept for 2 hr. at 20°, then diluted with ether (200 c.c.), and the solution was washed with aqueous sodium carbonate and then with water. Removal of the ether and distillation of the residue gave the *product* (62 g.) as a colourless liquid, b. p. 82—84°/0·3 mm. (Found: C, 43·1; H, 7·0. $C_8H_{15}O_2Br$ requires C, 43·1; H, 6·7%).

7-2′-Tetrahydropyranyloxyhepta-1 : 3-diyne.—To a solution of monosodiodiacetylene (Armitage, Jones, and Whiting, *J.*, 1952, 1993) prepared from 1 : 4-dichlorobut-2-yne (27 g.), ether (25 c.c.), and sodium (15·2 g.) in liquid ammonia (700 c.c.), the above bromo-compound (44·6 g.) in ether (25 c.c.) was added with stirring at —33°. Stirring was continued for 3 hr., then ether (300 c.c.) was added and the ammonia allowed to evaporate overnight in a current of nitrogen. The residue was extracted with ether (3 × 200 c.c.), and the solution washed with water, dried, and evaporated. Fractional distillation gave the *diyne* (10·2 g.) as an oil, b. p. (bath-temp.) 80—82°/10^{-4} mm., n_D^{20} 1·5010 (Found: 73·3; H, 8·6. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). Light absorption in EtOH: max. at 226, 237, and 250·5 mμ (ε 350, 370, and 238).

Pentadeca-trans-8 : 10 : 12-triene-4 : 6-diyne-1 : 14-diol.—A solution of ethylmagnesium bromide, prepared from magnesium (1·41 g.), ethyl bromide (6·3 g.), and ether (100 c.c.), was stirred at 20° whilst the foregoing diyne (10·2 g.) in benzene (150 c.c.) was added. The mixture was stirred at 30° for 3 hr., then cooled to 0°, diluted with ether (100 c.c.), and treated dropwise with octatrienal (7·1 g.) in benzene (150 c.c.). Stirring was continued for a further 4 hr., and saturated aqueous ammonium chloride (200 c.c.) was added, the aqueous phase extracted with ether

(3 × 100 c.c.), and the combined benzene and ether phases were washed, dried, and evaporated. The crude product (20 g.) was shaken at 20° for 14 hr. with dioxan (120 c.c.), sulphuric acid (2·5 g.), and water (10 c.c.), the heterogeneous mixture diluted with ether (200 c.c.) and water (400 c.c.), and the ethereal layer dried and evaporated. Chromatography on morin–aluminium oxide as described for cicutoxin concentrates in Part I (*loc. cit.*) gave a red oily fraction (2·6 g.; purity 50%) containing the required diol, which was again chromatographed to give a fraction (900 mg.; purity 80%) which crystallised. Recrystallisation from benzene and finally from ether–light petroleum gave the (±)-*diol* as yellow crystals, m. p. 86° (Found: C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). Light absorption in EtOH: max. at 242, 251, 316·5, and 335·5 mμ, inflexion at 303 mμ ($10^{-3}\varepsilon$ 13·0, 21·5, 60·0, 59·7, and 35·0). The infrared spectrum (Nujol) showed *inter al.* bands at 3195 (s), 2208 (w), 2123 (w), 1600 (m), and 996 (v.s.) cm.$^{-1}$. Hydrogenation with palladium–charcoal (7·2 mols. of hydrogen) gave *pentadecane*-1 : 14-*diol* as crystals (from ether–light petroleum), m. p. 66° (Found: C, 72·6; H, 13·1. $C_{15}H_{32}O_2$ requires C, 73·6; H, 13·2%).

Hex-2-en-1-ol.—To a stirred solution of lithium aluminium hydride (16 g.) in ether (1 l.) hex-2-enoic acid (60 g.) in ether (500 c.c.) was added at a rate sufficient to maintain reflux of the ether, after which stirring was continued at room temperature for 2 hr. After addition of ethyl acetate excess of a concentrated aqueous solution of tartaric acid was added, and the ethereal layer was washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated. Distillation of the residue gave hex-2-en-1-ol (27·6 g.), b. p. 39°/0·15 mm. The *α-naphthylurethane* formed crystals, m. p. 73°, from light petroleum (Found: C, 75·7; H, 6·9. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

Hex-2-enal.—Hex-2-en-1-ol (27 g.), light petroleum (1500 c.c.), and manganese dioxide (270 g.) (Attenburrow *et al.*, *J.*, 1952, 1094) were shaken together for 16 hr., and the filtered solution was shaken for 2 hr. with excess of an alcoholic solution of semicarbazide acetate. The precipitated hex-2-enal semicarbazone (21 g.) had m. p. 175—176°. To regenerate the aldehyde the semicarbazone (58 g.) was heated with aqueous pyruvic acid in acetic acid (500 c.c.) for 15 min., the solution diluted with water, and the hexenal (35 g.) isolated with light petroleum and used directly for the next step.

1-*Ethoxydeca*-1 : 6-*dien*-3-*yn*-5-*ol.*—Ethoxyvinylacetylene (39·7 g.) in ether (250 c.c.) was treated with a solution of phenyl-lithium (from 5·74 g. of lithium) in ether (250 c.c.), and the solution heated under reflux for 45 min., cooled, and then stirred whilst hex-2-enal (35 g.) in light petroleum (200 c.c.) was added. Stirring was continued at 20° for 4 hr., then under reflux for 1 hr., then the mixture was cooled and decomposed with aqueous ammonium chloride, and the ethereal layer washed, dried, and evaporated. A solution of the residue in benzene was passed through a column of aluminium oxide; diphenyl was separated in the effluent. Elution with benzene–methanol (100 : 1) gave the crude *dienynol* which was purified by distillation, giving material (33·5 g.), b. p. 101—107°/0·2 mm. (Found: C, 74·4; H, 8·9. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

Deca-2 : 4 : 6-*trienal.*—The above dienynol (33·5 g.) was hydrogenated at 20° in ethanol in presence of Lindlar's catalyst (50 mg.; *loc. cit.*). After 5 hr. 3·92 l. of hydrogen (0·95 mol.) had been absorbed, the catalyst was removed, and the filtrate treated with alcohol (50 c.c.) and 20% aqueous sulphuric acid (10 c.c.) and kept overnight at 20°. Dilution with water and extraction with light petroleum gave the crude aldehyde from which *deca*-2 : 4 : 6-*trienal semicarbazone* (26·8 g.) was obtained as plates, m. p. 215° (decomp.), from 2-methoxyethanol (Found: N, 20·2. $C_{11}H_{17}ON_3$ requires N, 20·3%). Light absorption in alcohol: max. at 308, 321, and 337 mμ ($10^{-3}\varepsilon$ 41, 58, and 55). The infrared absorption spectrum showed *inter al.* bands at 1667 (s), 1592 (s), and 997 (s) cm.$^{-1}$. The aldehyde (yield 55%) regenerated by pyruvic acid treatment of the semicarbazone was sufficiently pure for use in the next step.

(±)-*Cicutoxin.*—The magnesium bromide derivative from 7-2′-tetrahydropyranyloxyhepta-1 : 3-diyne was prepared as described above from the diyne (7·0 g.) in ether (450 c.c.) and benzene (450 c.c.), and the mixture was cooled to 0° and stirred during the addition (1 hr.) of deca-2 : 4 : 6-trienal (6 g.) in benzene (100 c.c.). Stirring was continued at 0° for a further 4 hr., the mixture was finally decomposed with saturated aqueous ammonium chloride, and the product (12 g.) isolated in the usual way. Its solution in acetone (120 c.c.) containing concentrated sulphuric acid (2·5 g.) and water (10 c.c.) was kept at 20° for 18 hr., then diluted with water (400 c.c.), and the red oily product (13 g.) isolated with ether. Chromatography on morin–aluminium oxide (Part I, *loc. cit.*) gave a crude oily cicutoxin fraction (5·65 g.) estimated spectrometrically to contain 1·32 g. of cicutoxin. This was again chromatographed, giving as the purest fraction material (625 mg.; purity 50%) which crystallised at 0°. Recrystallisation of the crude

crystalline material from benzene and finally from ether–light petroleum gave (±)-*cicutoxin* (50 mg.) as colourless crystals, m. p. 67° (Found: C, 79·1; H, 8·7. $C_{17}H_{22}O_3$ requires C, 79·0; H, 8·6%). Light absorption in alcohol: max. at 242, 252, 318·5, and 335·5 mμ, inflection at 303 mμ ($10^{-3}\varepsilon$ 14·6, 21·6, 50·6, 60·3, and 37·0). The infrared absorption spectra of (±)-cicutoxin and natural (−)-cicutoxin measured in 10% solutions in chloroform were identical. In alcohol with palladium–charcoal (±)-cicutoxin absorbed 7·2 mols. of hydrogen.

1-*Hydroxyheptadeca*-trans-8 : 10 : 12-*triene*-4 : 6-*diyn*-14-one.—(−)-Cicutoxin (60 mg.), acetone (50 c.c.), and manganese dioxide (1·5 g.) were shaken together for 2 hr. and the solution was filtered and evaporated. The product crystallised from ether–light petroleum, giving 1-*hydroxyheptadeca*-trans-8 : 10 : 12-*triene*-4 : 6-*diyn*-14-*one*, m. p. 84° (Found: C, 79·7; H, 8·3. $C_{17}H_{20}O_3$ requires C, 79·6; H, 7·8%). Light absorption in carbon tetrachloride: max. at 351 and 367 mμ, inflexion at 334 mμ ($10^{-3}\varepsilon$ 53·5, 60·5, and 46·5). The infrared absorption spectrum (Nujol) showed bands *inter al.* at 3145 (w), 2237 (m), 1681 (s), 1603 (s), and 1002 (s) cm.$^{-1}$.

Material identical in all respects was obtained by similar treatment of (±)-cicutoxin.

Dehydration of (±)-*Cicutoxin*.—A solution of the toxin (2 mg.) in benzene (110 c.c.) containing toluene-*p*-sulphonic acid (50 mg.) was boiled and aliquot portions of 1 c.c. were withdrawn for spectroscopic examination at intervals of 2½, 5, and 7½ min. In the first portion the absorption bands of cicutoxin had disappeared completely and new bands with max. (alcohol) at 255, 331, 347, and 367 mμ ($10^{-3}\varepsilon$ 55, 49, 73, and 75) had appeared. No further change was observed in the samples removed after 5 and 7½ min.

Deca-2 : 8-*diene*-4 : 6-*diyne*-1 : 10-*diol Monobenzoate*.—To a cooled and stirred solution of deca-2 : 8-diene-4 : 6-diyne-1 : 10-diol (45 g.) in pyridine (90 c.c.), benzoyl chloride (39 g.) in pyridine (45 c.c.) was added dropwise (3 hr.), and the mixture was kept overnight and then decomposed with ice and 20% sulphuric acid. Addition of ether precipitated some dibenzoate (m. p. 96°) which was removed. The ethereal solution was washed repeatedly with ice-cold 15% sulphuric acid and then dried, and kept at −40°, then more dibenzoate separated and was removed. Evaporation of the filtrate gave an oil which was treated with benzene whereupon unchanged diol, m. p. 154—155°, remained undissolved and was removed. The benzene solution was passed through a column of neutral alumina, development with benzene giving in the first portion of the effluent more dibenzoate. This was followed by monobenzoate, elution of which was completed by benzene–methanol (100 : 1). Finally, elution with methanol gave more unchanged diol. Crystallisation of the middle fraction from benzene–light petroleum gave the *monobenzoate* (22 g.), m. p. 65—65·5° (Found: C, 76·7; H, 5·3. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). Diol (6 g.) and its dibenzoate (15·2 g.) were obtained by recrystallisation of the appropriate fractions.

10-*Benzoyloxydeca*-2 : 8-*triene*-4 : 6-*diynal*.—The above monobenzoate (1·75 g.) was oxidised in the usual way with manganese dioxide (17·5 g.) in acetone (175 c.c.) for 4½ hr. and gave the required *aldehyde* as pale yellow crystals (from ether at −20°), m. p. 91—91·5° (Found: C, 77·0; H, 4·8. $C_{17}H_{12}O_3$ requires C, 77·3; H, 4·5%). Light absorption in alcohol: max. at 235, 248, 262, 278, 295, 314, and 335·5 mμ ($10^{-3}\varepsilon$ 35·0, 30·3, 24·1, 11·6, 17·8, 22·5, and 16·2). The semicarbazone was very unstable, and became blue in air or when heated.

Heptadeca-trans-2 : 8 : 10-*triene*-4 : 6-*diyn*-1-*ol*.—To a solution of *n*-heptylmagnesium bromide (from 3·8 g. of magnesium and 28·4 g. of *n*-heptyl bromide) in ether (100 c.c.) the above aldehyde (6·9 g.) in benzene (200 c.c.) was added during ½ hr. at room temperature with stirring. Stirring was continued for 5½ hr. after which ammonium chloride (18 g.) in water (200 c.c.) was added and the crude product (16·2 g.) isolated in the usual manner. Its solution in toluene (50 c.c.) was added to a boiling solution of toluene-*p*-sulphonic acid (1·62 g.) in toluene (750 c.c.) from which toluene was distilled rapidly. After 15 min. the mixture was cooled, washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated. The residual oil (17·4 g.) was chromatographed on morin–aluminium oxide. The product with the required light absorption (yield, 50%) was eluted with benzene–methanol (100 : 1) and collected in fractions; some of the fractions crystallised, and recrystallisation from light petroleum gave the *triene-diynol* as plates, m. p. 71—71·5° (Found: C, 84·5; H, 9·4. Calc. for $C_{17}H_{22}O$: C, 84·3; H, 9·1%). Light absorption in alcohol: max. at 213, 251, 267, 281, 297, 316, and 338 mμ ($10^{-3}\varepsilon$ 24·3, 32·2, 30·0, 18·3, 29·0, 38·2, and 27·8). A mixture with natural oenanthetol showed no depression of m. p., and the infrared spectra (Nujol) of natural and synthetic materials were identical. In alcohol with palladium–charcoal the synthetic compound absorbed 7·1 mols. of hydrogen.

Toxicity Tests.—Albino mice (30—60 g.) were treated by intraperitoneal injection of suspensions of cicutoxin in lecithin–normal saline. Of 5 mice which received 5 mg. of (−)-cicutoxin

per kg., all died within 30—35 min.; of 5 which received 3·5 mg./kg. only 1 died (100 min.). Of 5 which received 2·5 mg. of (±)-cicutoxin per kg., 4 died (30—37 min.), and of 5 which received 1·8 mg./kg. all survived. The racemic material is thus about twice as active as the natural material.

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