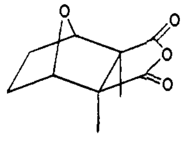
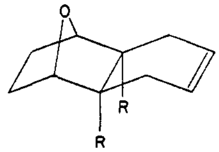
CANTHARIDIN. A STEREOSPECIFIC TOTAL SYNTHESIS

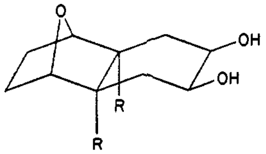
Sir:

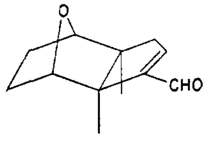
The active principle of cantharides was first obtained crystalline by Robiquet in 1810.[1] The extensive structural investigations that followed culminated in 1942 when Ziegler, Schenck, Krockow, Siebert, Wenz and Weber succeeded in effecting the total synthesis of cantharidin (I) by a route which included, however, an unsatisfactory last step, resulting in a complex mixture from which cantharidin was eventually isolated in a 2% yield.[2] Later efforts to render the synthesis stereospecific were unsuccessful.[3] We have now achieved a stereospecific synthesis of cantharidin:

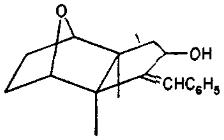

I

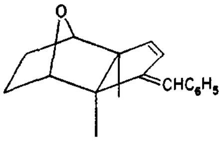

II–V

II, R = CO_2CH_3
III, R = CH_2OH
IV, R = $CH_2OSO_2CH_3$
V, R = $CH_2SC_2H_5$


VI, R = $CH_2SC_2H_5$
VII, R = CH_3


VIII


IX


X

Dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate was prepared by a modification of the method of Diels and Olsen[4] and condensed with butadiene in alcohol at 100° to give II, m.p. 78.5–79° (calcd. for $C_{14}H_{18}O_5$: C, 63.63; H, 6.10. Found: C, 63.36; H, 6.11). The butadiene adduct (II)[5] was reduced with lithium aluminum hydride to the corresponding glycol (III), m.p. 154–154.5° (calcd. for $C_{12}H_{18}O_3$: C, 68.53; H, 8.63. Found: C, 68.68; H, 8.60) which, with methanesulfonyl chloride, was transformed into the dimesylate (IV), m.p. also 154–154.5° (calcd. for $C_{14}H_{22}O_7S_2$: C, 45.88; H, 6.05. Found: C, 45.98; H, 5.76). Treatment of the dimesylate with potassium ethyl mercaptide in *t*-butyl alcohol gave the dithioethyl compound (V), b.p. (bath temp.) 145–150° (0.01 mm.), crude m.p. 41–43°. V on hydroxylation with osmium tetroxide yielded the corresponding dithioethyl glycol (VI), which was desulfurized directly with Raney nickel in boiling ethanol to VII, b.p. (bath temp.) 170–175° (0.3 mm.), m.p. 107–109° (calcd. for $C_{12}H_{20}O_3$: C, 67.88; H, 9.49. Found: C, 68.13; H, 9.51). This glycol (VII) was cleaved with aqueous periodic acid, and the resulting dialdehyde cyclized on heating in aqueous dioxane to the cyclopentene aldehyde (VIII), b.p. (bath temp.) 130–135° (0.4 mm.), m.p. 68–70°, $\lambda_{max.}$ 237–238 mμ (ϵ = 14,800),[6] characterized by its phenylhydrazone (orange prisms), m.p. 190–192° (calcd. for $C_{18}H_{22}ON_2$: C, 76.55; H, 7.85. Found: C, 76.24; H, 8.10). Reaction of the α,β-unsaturated cyclic aldehyde (VIII) with phenyllithium, followed by anionotropic rearrangement,[7] led to IX ($\lambda_{max.}$ 252 mμ, ϵ = 16,000), which was dehydrated to the desired diene (X) by thermal decomposition of its stearate. The liquid diene (X) was purified by chromatography and ozonized in ethyl acetate at −60°. Decomposition of the resulting ozonide with hydrogen peroxide gave directly cantharidin (I), crude m.p. 209–212°, which after recrystallization from acetone melted at 212–213° (sealed tube), alone or mixed with an authentic sample. The identity of the synthetic cantharidin was further established by comparison of its infrared spectrum and X-ray powder diffraction pattern with those of natural cantharidin.

A full account of this and related work will be published shortly.

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[1] M. Robiquet, *Ann. chim.*, [1] **76**, 302 (1810).

[2] K. Ziegler, G. Schenck, E. W. Krockow, A. Siebert, A. Wenz and H. Weber, *Ann.*, **551**, 1 (1942).

[3] K. Ziegler, W. Flaig and G. Velling, *ibid.*, **567**, 204 (1950).

[4] O. Diels and S. Olsen, *J. prakt. Chem.* [2] **156**, 286 (1940).

[5] The incorrect configuration for the corresponding diacid of this adduct was implied by Alder and Backendorf [*Ann.*, **535**, 101, 113 (1938)] and accepted by Ziegler, *et al.*[2]

[6] *Cf.* cyclopentene-1-aldehyde, $\lambda_{max.}$ 237–238 mμ, ϵ = 13,500 [J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3634 (1950)].

[7] *Cf.* E. A. Braude, E. R. H. Jones and E. S. Stern, *ibid.*, 1087 (1947).

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