SYNTHESIS OF CANTHARIDINE AND DESOXYCANTHARIDINE

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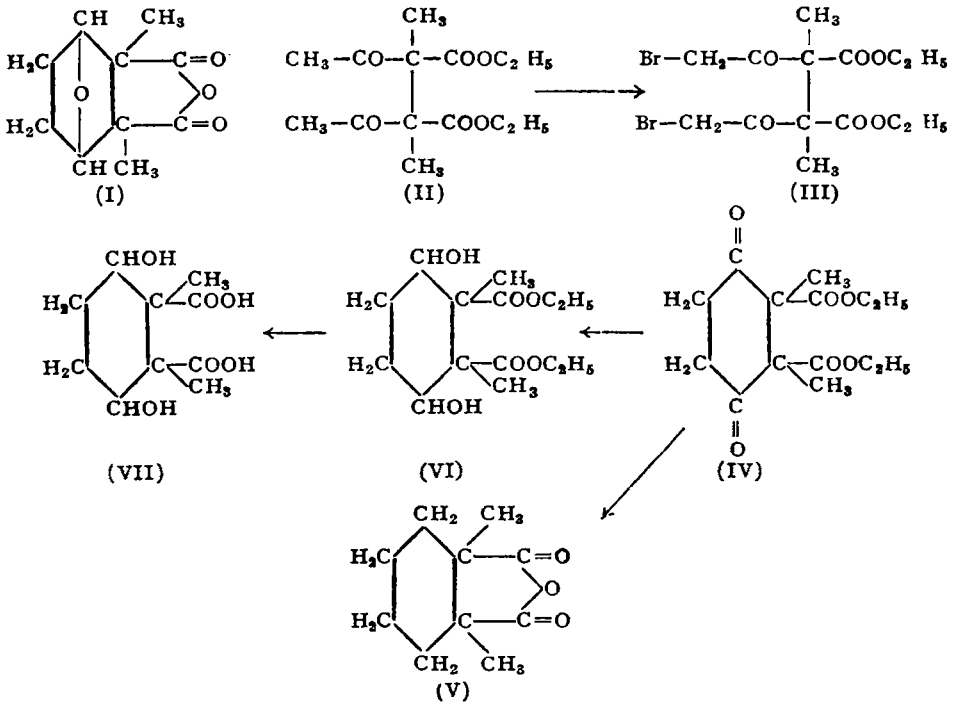
Cantharidine, the active principle of *Cantharis vesicatoria*[1] and of *Mylabris pustulata* Fb. India[2] has been assigned the structure (I) mainly on the basis of analytical evidence by Gadamer and others.[3] This structure has received further support by the observation of Bruchhausen and Bersch[4] that maleic anhydride is formed in the pyrolysis of cantharidine.

Various unsuccessful attempts at the synthesis of cantharidine have been made. Steele[5] attempted to prepare desoxycantharidine by debrominating $\alpha\alpha'$-dibromo-$\alpha\alpha'$-dimethyl suberic acid but the debromination could not be effected. Guha and Iyer[2] unsuccessfully attempted to replace bromine by cyanogen in 1-2-dibromo-1-2-dimethyl-cyclohexane. Pai and Guha[6] attempted to methylate 3-6-diketo-cyclohexane-1-2-dicarboxylate but no C methylation took place. The condensation of ethyl $\beta:\beta'$-diketo-tetrahydrofuran-$\alpha\alpha'$-dicarboxylate either with ethyl-α-bromo propionate or with alkylene bromides proved unsuccessful.[7] Diels and Alder[8] failed to add dimethyl maleic anhydride to furan although nor-cantharidine and iso-cantharidine were prepared by similar methods.

Recently Woodward and Loftfield[9] have reported the synthesis of desoxycantharidine by the reduction of the addition product obtained from butadiene and dimethyl maleic anhydride. Ziegler, Schenck, Krockow, Siebert, Wenz and Weber[10] have reported the synthesis of cantharidine and desoxycantharidine by a series of long and difficult reactions. The present paper describes the synthesis of these substances by a simpler method.

Sodio derivative of ethyl-α-methyl-acetoacetate when treated with iodine gave diethyl-$\alpha\alpha'$-diacetyl-$\alpha\alpha'$-dimethyl succinate (II). Bromination of (II) gave the dibromo-compound (III), which on treatment with finely divided silver was debrominated and cyclised to diethyl-3-6-diketo-1-2-dimethyl cyclohexane-1-2-dicarboxylate (IV). Clemmenson reduction of (IV) followed by hydrolysis and steam distillation gave desoxycantharidine (V). Reduction

of (IV) by aluminium isopropoxide gave (VI) which on hydrolysis gave the corresponding dihydroxy acid (VII). Treatment of crude (VI) with concentrated sulphuric acid at room temperature for 100 hours gave a black mass from which cantharidine was obtained by sublimation. The synthetic sample of cantharidine had m.p. 217° C. and did not depress the m.p. of an authentic sample kindly supplied by Dr. P. C. Guha, Indian Institute of Science, Bangalore, to whom our thanks are due.



Experimental

Diethyl-αα'-diacetyl-αα'-dimethyl succinate (II).—To finely pulverised sodium (4·6 gm.) suspended in dry benzene (50 c.c.) was added ethyl-α-methyl-acetoacetate (28·8 gm.). It was then refluxed for three hours and iodine (25·4 gm.) was then added and refluxing continued till the colour of iodine disappeared. It was then treated with ice and dilute sulphuric acid. The benzene layer was separated, washed with water and dried and benzene was removed. The residue could not be purified by distillation under reduced pressure and was therefore used to prepare the bromo-compound as described below.

Diethyl-αα'-di-(ω-bromoacetyl)-αα'-dimethyl succinate (III).—To a solution of the above ester (II) (28·6 gm.) in carbon disulphide (50 c.c.) was

added bromine (32 gm.) dissolved in the same solvent (50 c.c.), a trace of anhydrous aluminium chloride being used as a catalyst. Vigorous evolution of hydrobromic acid took place. The residue after removal of carbon disulphide was crystallised from benzene and had m.p. 55° C.

[Found: Br, 36·4; $C_{14}H_{20}O_6Br_2$ requires Br, 36·0 %.]

Diethyl-3-6-*diketo*-1-2-*dimethyl-cyclohexane*-1-2-*dicarboxylate* (*IV*).—Diethyl-$\alpha\alpha'$-di-(ω-bromoacetyl)-$\alpha\alpha'$-dimethyl succinate (III) (22 gm.) and molecular silver (10·8 gm.) were heated together on an oil-bath at 120° C. for three hours and then at 150° C. for half an hour. The product recovered by ether extraction was a viscous liquid which could not be distilled without decomposition. It was characterised by its di-*p*-nitrophenyl hydrazone, m.p. 143° C.

[Found: C, 56·2; H, 5·4; N, 15·6. $C_{26}H_{30}N_6O_8$ requires C, 56·3; H, 5·4; N, 15·2%.]

1-2-*Dimethylcyclohexane*-1-2-*dicarboxylic anhydride* (*V*).—Diethyl-3-6-diketo-1-2-dimethylcyclohexane-1-2-dicarboxylate (IV) (5 gm.) was reduced by zinc amalgam by Clemmenson's method. The product recovered by ether extraction was hydrolysed by alkali and the product obtained after acidification was steam-distilled. The steam volatile product was identified as desoxycantharidine, m.p. 128°. The steam-non-volatile product crystallised from alcohol when it had m.p. 165°. It was therefore 1-2-dimethyl cyclohexane dicarboxylic acid.

[Found: C, 60·3%; H, 8·0% and Eq. wt. 100·4. $C_{10}H_{16}O_4$ requires C, 60·0%; H, 8·0%; Eq. wt. 100.] Woodward and Loftfield[9] give m.p. 129° for desoxycantharidine and m.p. 166° for desoxycantharic acid.

3-6-*Dihydroxy*-1-2-*dimethylcyclohexane*-1-2-*dicarboxylic acid* (*VII*).—Diethyl 3-6-diketo-1-2-dimethylcyclohexane 1-2-dicarboxylate (IV) (15·2 gm.) was reduced by aluminium isopropoxide (from aluminium 0·8 gm. and isopropyl alcohol 34 c.c.) following the method of Lund.[11] The recovered product (VI) was directly hydrolysed by alkali and the acid obtained when crystallised from petrol, had m.p. 99°.

[Found: C, 51·92%; H, 7% and Eq. wt. 116·2. $C_{10}H_{16}O_6$ requires C, 51·72%; H, 6·89% and Eq. wt. 116.] It was soluble in all organic solvents except chloroform.

3-6-*Oxido*-1-2-*dimethyl-cyclohexane*-1-2-*dicarboxylic anhydride* (*Cantharidine*) (*I*).—Crude diethyl-1-3-6-dihydroxy-1-2-dimethyl-cyclohexane 1-2-dicarboxylate (VI) (10 gm.) obtained in the above experiment, was mixed with concentrated sulphuric acid (100 gm.) and the mixture was kept at room

temperature for 100 hours. It was then poured into water and the product recovered by ether extraction was hydrolysed by alkali. It was then acidified and extracted with chloroform. The product obtained after removal of chloroform was sublimed preferably with a drop of concentrated sulphuric acid when cantharidine was obtained in colourless needles, m.p. 217° and did not depress the m.p. of an authentic specimen. It gave all the colour reactions of cantharidine (yield 10% calculated on ethyl acetoacetate used).

[Found: C, 61·3%; H, 6·1%. $C_{10}H_{12}O_4$ requires C, 61·2%; H, 6·1%.] It formed a mono-phenyl-hydrazone, m.p. 193 (*cf.* Spiegel[12]).

Summary

A new and simple method for the synthesis of cantharidine and desoxy-cantharidine has been described.

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