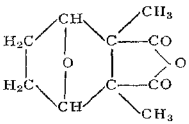
ATTEMPTS TOWARDS THE SYNTHESIS OF CANTHARIDIN, PART II.

By P. C. Guha and B. H. Iyer.

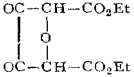
Since the isolation of cantharidin from a variety of local blister beetles (Iyer and Guha, *J. Indian Inst. Sci.*, 1931, **14A**, 31) several attempts have been made in this laboratory towards its synthesis, and the results published from time to time (Iyer and Guha, *loc. cit.*; Pai and Guha, *J. Indian Chem. Soc.*, 1934, 11, 231). The following attempts have now been made towards the synthesis of cantharidin for which the present accepted formula is (I).



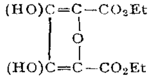
(I)

The earlier attempts (Iyer and Guha; Pai and Guha, *loc. cit.*) starting from *cyclo*hexane compounds having the necessary *ortho*-substituents, with a view to building up the deoxycantharidin structure having proved unsuccessful, attention was directed to methods involving the use of suitable furane compounds.

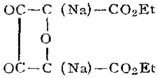
Diethyl diglycollate condenses with diethyl oxalate in presence of sodium ethylate to give oxalodiglycollic ester (diethyl 3:4-dioxyfuran-2:5-dicarboxylate) (II) (Johnson and Johns, *Am.*, 1906, **36**, 290; *cf.* Hinsberg, *Ber.*, 1912, **45**, 2416). Although an alternative formula (III) with a di-enolic structure has been suggested for the product, the formation of a disodium derivative of the structure (IV) and also the formation of a condensation product with *o*-phenylene diamine indicated that under conditions unfavourable to enolisation the furan derivative can behave in the diketo-form (II).



(II)

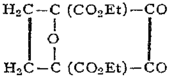


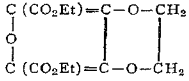
(III)



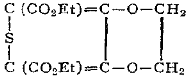
(IV)

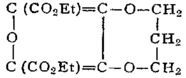
Based on this assumption the disodium derivative (IV) was condensed with ethylene bromide with a view to obtaining a product of structure (V) that might form a useful starting material for the synthesis of cantharidin. The alkali-insoluble product, m.p. 174–75°, in alcoholic solution gave no coloration with aqueous ferric chloride, the combustion data tallied with the empirical formula for (V), but its failure to yield a semicarbazone created doubt as to the correctness of structure (V). The substance on being subjected to hydrolysis gave a dicarboxylic acid melting with decomposition at 316°. All attempts to decarboxylate this hydrolysed product were unsuccessful. Similar failures to decarboxylate β-ketonic esters having no free H-atom attached to the α-carbon atom have already been observed (*cf.* Guha, *Curr. Sci.*, 1936, **5**, 19, Bredt, *J. pr. Chem.*, 1937, (ii), **148**, 221). This resistance to decarboxylation evidently makes the compound of structure (V) unsuitable for employment as a starting material for the synthesis of cantharidin. Non-formation of a semicarbazone of the ester ruled out the formula (V) for the condensation product leaving the alternative formula (VI).


(V)

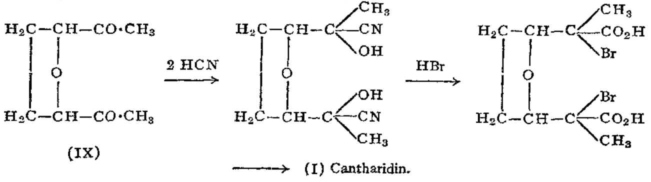

(VI)

In this compound a furan ring is fused with a dioxane ring and as such a further study is likely to lead to interesting results. The corresponding thio-analogue (VII) of compound (VI) was prepared from oxalothio-diglycollic ester and ethylene bromide, and the higher homologue (VIII) with trimethylene bromide. The condensation of ethylene bromide with the disodium derivative of cyclic-*o*-diketonic esters has been shown to proceed in the enolic phase of the ester leading to the formation of similar compounds (*cf.* Guha and Ranganathan, *Ber.*, 1936, **69**, 1195).


(VII)


(VIII)

Work was undertaken to prepare diacetylfuran and diacetyltetrahydrofuran (IX) from the corresponding di-acid chlorides, so that the cantharidin molecule could be built up according to the following scheme:



For want of mucic acid, the starting material in the present scheme, the work is suspended for some time, and it seems desirable to keep on record the results obtained so far.

EXPERIMENTAL.

Diethyl 3:4-dioxyfuran-2:5-dicarboxylate (II) was prepared by condensing diethyl diglycollate with diethyl oxalate in presence of sodium ethylate. Johnson and Johns' method (*loc. cit*) of carrying out this condensation in an ethereal medium occupied an unnecessarily long period and also required the use of a very volatile solvent. A trial experiment conducted solely in absolute alcohol showed that the yield of the product was as good in this case as in Johnson and Johns' with the added advantage of avoiding ether. A typical experiment is detailed below.

Sodium (16 g.) was dissolved in anhydrous alcohol (400 c.c.) taken in an one litre three-necked flask fitted with a reflux condenser. To this cooled alcoholic solution of sodium ethylate was added gradually, a mixture of diethyl diglycollate (60 g.) and diethyl oxalate (46 g.), and the whole refluxed on water-bath for two hours, the disodium derivative of the reaction product separating out gradually. After the refluxing was over, alcohol was distilled off, the residue in the reaction vessel dissolved in water and the product was precipitated with sulphuric acid (1:1) under cooling. The filtered precipitate was washed with water till free from mineral acid and crystallised from dilute alcohol, m.p. 189°. Yield, 50 per cent. of theory.

Diethyl diglycollate was prepared from monochloracetic acid (Lossen and Eichloff, *Ann.*, 1905, **342**, 121).

Condensation of the disodium derivative of diethyl oxalo-diglycollate with (a) ethylene bromide and (b) trimethylene bromide: Formation of (VI) and (VIII).—(*a*) An alcoholic solution of sodium ethylate prepared from sodium (4.6 g.) and anhydrous alcohol (150 c.c.) was gradually added to a boiling solution of the furan diester (24.6 g.) in anhydrous alcohol (400 c.c.). On refluxing for about an hour the insoluble disodium derivative separated. This was filtered quickly through a covered Buchner funnel taking particular care to avoid atmospheric moisture, washed with anhydrous ether and dried in a flask on boiling water-bath under a vacuum of 30 mm. The dried sodium derivative (30 g.) taken in a round-bottomed flask fitted with a reflux condenser was mixed with a large excess of ethylene bromide (300 g.) and refluxed on an oil-bath at 130–40° for over fifty hours. At this stage the reaction mixture had assumed a tarry appearance. After cooling, the contents of the flask were subjected to steam distillation when all the unchanged ethylene bromide was recovered. The granular precipitate (VI) remaining in the flask was filtered, treated several times with dilute caustic soda, washed with water and crystallised from dilute alcohol, m.p. 174–75°; yield, 10 g. (Found: C, 53.68, 53.02; H, 5.43, 4.71. $C_{12}H_{14}O_7$ requires C, 53.33; H, 5.18 per cent.)

(*b*) Condensation with trimethylene bromide was carried out in a similar way, keeping the oil-bath at 160–70°.

After steaming, an oil remained in the flask which, on cooling, set into a pasty mass. The insoluble precipitate (VIII) obtained on treating this with dilute caustic soda was filtered, washed and crystallished from dilute alcohol, m.p. 139°; yield very poor. (Found: C, 55.11; H, 6.02. $C_{13}H_{16}O_7$ requires C, 54.93; H, 5.63 per cent.)

Hydrolysis of compound (*VI*).—Compound (VI) (7 g.) dissolved in the minimum quantity of alcohol was treated with a solution of potassium hydroxide (3.5 g.) in alcohol and refluxed for 15 minutes on a water-bath. Alcohol was distilled off, the residue being dissolved in water and filtered. The filtrate on acidification with hydrochloric acid yielded a precipitate which, when crystallised from water, melted at 316° (decomp.). This dissolves with effervescence in sodium bicarbonate solution. It is only slightly soluble in alcohol and ether. (Found: C, 44.51; H, 3.34. $C_8H_6O_7$ requires C, 44.86; H, 2.8 per cent.)

Diethyl oxalothiodiglycollate was prepared in a manner similar to that described above for the furan derivative by condensing diethyl thioglycollate with diethyl oxalate in presence of sodium ethylate (*cf.* Johnson and Johns, *loc. cit.*; Hinsberg, *Ber.*, 1910, **43**, 903).

Condensation of ethylene bromide with disodium derivative of diethyl oxalothiodiglycollate: *Formation of compound* (*VII*) *with ethylene bromide.*—The dry disodium derivative of diethyl 3:4-dioxythiophen-2:5-dicarboxylate (26 g.) was treated with excess of ethylene bromide in the same manner as described above.

On treating the tarry mass obtained after steaming the reaction mixture, a dark powdery product resulted. This (VII) was treated with dilute alkali, washed with water and crystallised from alcohol after refluxing with animal charcoal, m.p. 148–50°; yield very poor, 3 g. (Found: C, 50.11; H, 5.28. $C_{12}H_{14}O_6S$ requires C, 50.35; H, 4.89 per cent.)

For want of sufficient material, hydrolysis experiments could not be carried out in the latter two cases.

Department of Organic Chemistry,
Indian Institute of Science,
Bangalore.

[Received. 10–6–1938.]

976-38 Printed at The Bangalore Press, Bangalore City, by G. Srinivasa Rao, Superintendent.