ATTEMPTS TOWARDS SYNTHESIS OF CANTHARIDIN

PART III

CONDENSATION OF ETHYL ββ'-DIKETOTETRAHYDROFURAN-αα'-DICARBOXYLATE WITH α-BROMO ESTERS*

By B H Iyer and P C Guha

Kirkpatrick (*Iowa State Coll J Sci*, 1936, **11**, 75, *Cf American Chemical Abstracts*, 1937, **31**, 1800^{2}) has observed that in physiological action furan resembles benzene The β-diethylaminoethyl esters of several furan acids are mild local anæsthetics A number of mixed ketones containing the furyl radical are hypnotics A group of furan derivatives of varied composition includes vesicants and lacrimators Further, Bruchhausen and Bersch (*Arch Pharm*, 1928, **266**, 697) have observed that when cantharidin is passed over palladised asbestos at 280° it is decomposed into furan and dimethylmaleic anhydride Therefore it would appear rational to employ a suitable furan compound as the starting material for the synthesis of cantharidin

Guha and Iyer (*J Indian Inst Sci*, 1938, **21 A**, 115) have shown that the condensation of ethyl ββ'-diketotetrahydrofuran-αα'-dicarboxylate and its thiophene analogue with alkylene bromides takes place only in the di-enolic phases of the two former esters As it is, however, possible that under certain conditions and with particular reactants these two esters might react in the diketo forms—as their nomenclatures indicate (*Cf* "*Organische Chemie*" by Richter-Anschutz, 1931 edition, pp. 18 and 19)—it was hoped to build up the cantharidin molecule according to the following scheme Condensation of one molecule of ethyl ββ'-diketotetrahydrofuran-αα'-dicarboxylate with two molecules of ethyl α-bromopropionate in

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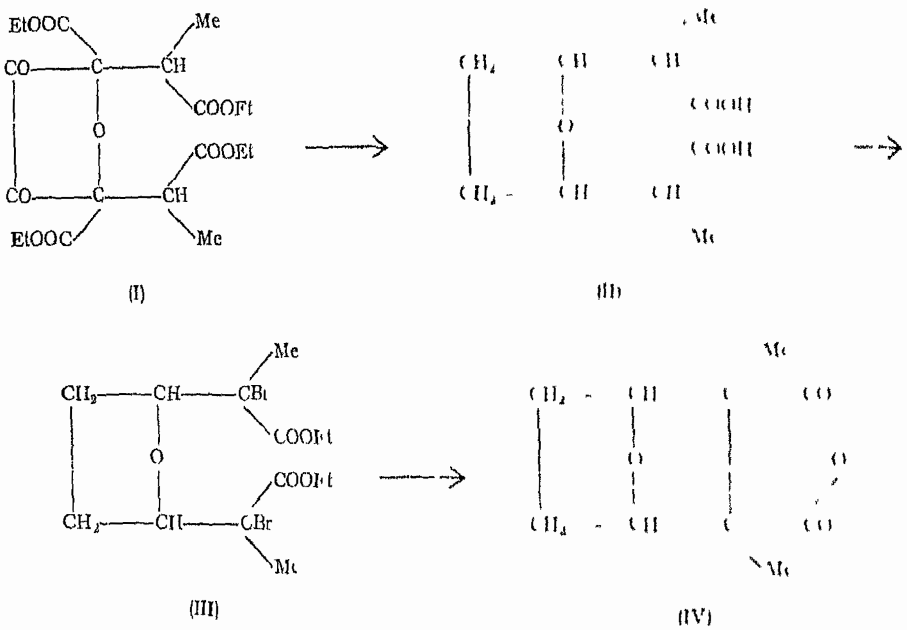
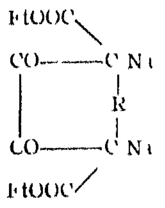
* Extracted from a thesis submitted by one of the authors (B H, I) for the Ph D Degree of the University of Bombay

presence of sodium ethylate was expected to give compound (I) which was to serve as a convenient starting material for the synthesis of cantharidin

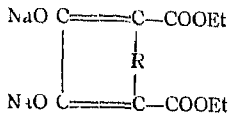

(I) (II) (III) (IV)

Clemmensen reduction of (I) with simultaneous hydrolysis and decarboxylation would then give the dicarboxylic acid (II) Bromination of the diacid chloride of (II) followed by esterification would then yield (III) The latter, on ring closure by removal of the two bromine atoms with zinc or silver and subsequent hydrolysis and dehydration would lead to cantharidin (IV)

As a model experiment, ethyl bromacetate was first condensed with the disodium derivative (V or VI, R=O) of ethyl ββ'-diketotetrahydrofuran-αα'-dicarboxylate when a fine crystalline substance (m.p 65°) was obtained The corresponding compound (m.p 50°) from the disodium derivative (V or VI, R=S) of ethyl ββ'-diketotetrahydrothiophene-αα'-dicarboxylate was also prepared The results of elementary analyses and a study of the products of hydrolyses showed that two molecules of the bromo ester combined with one each of the furan and thiophene esters. Therefore the products of condensation might be represented by either of the two formulæ (VII) and (VIII) (R O or S)



(V)



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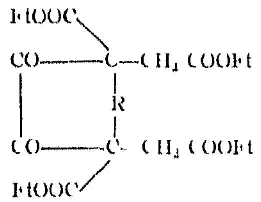
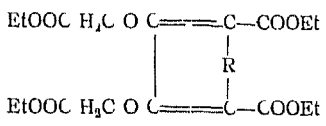


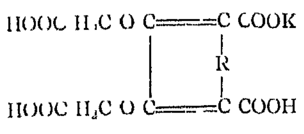
(VII)



(VIII)

From their failure to give any indication of the presence of ketonic groups when tried with semicarbazide hydrochloride, phenylhydrazine and 2 4-dinitrophenylhydrazine, from their insolubility in alkali and from their tendency to decompose on heating with dilute hydrochloric acid, the structure (VIII) has been suggested as the more probable one than (VII) for these two products They may be called (1) ethyl αα′-dicarbethoxy-furan-ββ′-dioxydiacetate (VIII, R=O) and (2) ethyl αα′-dicarbethoxythiophene-ββ′-dioxydiacetate (VIII, R=S) Efforts to brominate them were not successful

On hydrolysis with alcoholic potash, the products yielded the mono-potassium salt (IX, R-O or S) of the corresponding tetracarboxylic acid instead of the acid itself

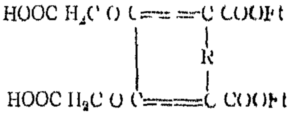


(IX)

This is proved by the determination of the equivalent of the potassium salts

When the hydrolysis was effected by refluxing with dilut hydrochloric acid, decomposition occurred and no product could be isolated Here it should be mentioned that the dicarboxylic acids corresponding to ββ'-diketotetrahydrofuran (and thiophene)-αα'-dicarboxylates have not so far been isolated Perhaps from the very nature of their configuration viz, ββ'-diketonic di-acids with oxygen or sulphur as members of the ring, they are incapable of stable existence

However, hydrolysis of the condensation products (VIII) with concentrated hydrochloric acid in the cold readily yielded the two corresponding diester-di-acids viz, αα' dicarbethoxyfuran-ββ' dioxydiacetic acid (X, R=O) and αα'-dicarbethoxythiophene ββ' dioxydiacetic acid (X, R=S)



(X)

Equivalents and the results of analyses afford additional support to the above structures

A systematic study of the hydrolysis of these products will be interesting because it looks as though a stepwise hydrolysis can be effected by varying the experimental conditions The aim of the present investigation being different, a further study of the hydrolysis has not been made

Because of the occurrence of decomposition on heating with hydrochloric acid, Clemmensen reduction of the condensation products could not be carried out successfully

It is clear from our experiments that these condensations proceed only with the di-enolic phases of the furan and thiophene esters, (*Cf* Hoehn, *Iowa State Coll J Sci*, 1936, **11**, 66; *Cf American Chemical Abstracts*, 1937, **31**, 1800^7)

When ethyl α-bromopropionate and ethyl bromomalonate were condensed with the disodium derivative of the furan ester in alcoholic medium, no reaction took place, the reactants were totally recovered Experiments using magnesium instead of sodium were also unsuccessful The dry disodium derivative, on being refluxed with a large excess of the bromo ester, yielded oily products which could not be further worked out and characterised owing to poor yields

EXPERIMENTAL

Ethyl-ββ'-diketotetrahydrofuran-αα'-dicarboxylate was prepared by condensing ethyl diglycollate with ethyl oxalate in presence of sodium ethylate (*Cf* Guha and Iyer, *loc cit*)

Ethyl-αα'-dicarbethoxyfuran-ββ'-dioxydiacetate (VIII,R=O) —To a hot solution of ethyl ββ'-diketotetrahydrofuran-αα'-dicarboxylate (24 6 g) in absolute alcohol (400 c c), a solution of sodium (4 6 g) in absolute alcohol (100 c.c) was gradually added and refluxed for about one hour The white disodium derivative immediately separated out This was cooled and excess of ethyl bromacetate (40 g) was added There was no immediate visible reaction The contents of the flask were refluxed on a water bath for nearly 20 hours when the white disodium derivative gradually acquired a yellow colour The resulting clear solution was acidic to litmus and a small quantity of sodium bromide had separated This was filtered out, alcohol was removed from the filtrate and the residual oily mass was subjected to steam distillation to remove the excess of ethyl bromacetate On treating the resulting pasty product with 2 N sodium hydroxide, a solid separated out This was collected on filter paper, washed successively with water, dilute acid and water and finally crystallised from alcohol, m p 65° It is soluble in most of the organic solvents but insoluble in petrol Alcoholic solution does not give any coloration with ferric chloride whereas the furan ester gives a characteristic coloration (Found C, 51 64, H, 6 16, $C_{18}H_{24}O_{11}$ requires C, 51 92, H, 5 76 per cent)

The alkaline filtrate from the reaction product yielded unchanged furan ester on acidification

Alkali hydrolysis of the above ester (VIII, R=O) Formation of the mono-potassium salt (IX, R=O) —To an alcoholic solution of the ester (2 g) an alcoholic solution of potassium hydroxide (1 5 g) was added At once a solid separated out The mixture was refluxed on a water bath for 15 minutes, alcohol removed and the residue dissolved in water The filtered alkaline solution yielded a fine white precipitate on acidification with hydrochloric acid This was collected on filter paper, washed with ice cold water and crystallised from boiling water It does not melt but gets darkened on long heating at 110° and chars above 250° The aqueous solution of the inorganic residue obtained on incineration, is alkaline in reaction The product dissolves with effervescence in cold 2 N sodium bicarbonate and is insoluble in organic solvents

A warm aqueous solution of 0 0744 g of the mono-potassium salt (IX, R=O) required 13 45 c c of 0 0186 N sodium hydroxide for neutralisation (phenolphthalein) (Found equivalent, 113 9, $C_{10}H_7O_{11}K$ requires equivalent 114)

0 2030 g of the mono-potassium salt gave 0 0510 g of K_2SO_4 (Found K, 11 27, $C_{10}H_7O_{11}K$ requires K, 11 10 per cent)

Silver salt—0 5 g of the mono-potassium salt was treated with 8 to 10 c c. of ammonium hydroxide and evaporated to dryness To the filtered aqueous solution of the residue, was added, an aqueous solution of silver nitrate (1 3 g) when a white heavy precipitate resulted This was collected on filter paper, washed with water and alcohol and dried in a steam oven (1.5 g) A correct estimation of silver was not possible owing to the sudden decomposition of the salt on heating in a crucible

Acid hydrolysis of [VIII, R-O]—*(a) with dilute hydrochloric acid* (1 1)—The ester (4 g) was refluxed with 10 c c of (1 1) dilute hydrochloric acid Within about 15 minutes the contents of the flask got dark and lot of frothing occurred The ill-looking filtrate left only a tarry residue on evaporation from which nothing definite could be isolated

(*b*) *With concentrated hydrochloric acid Formation of αα'-dicarbethoxyfuran-ββ'-dioxydiacetic acid* (*X*, *R O*)—The ester (2 g) was mixed in the cold with concentrated hydrochloric acid

(20 c c) in a conical flask, warmed on the water bath for a minute, corked and shaken well with simultaneous cooling under the water tap After shaking for about 5 minutes, a clear solution resulted This was left at ordinary temperature for about 15 to 18 hours At the end of the period, the resulting solution was diluted with water, cooled in ice and filtered The acidic filtrate was repeatedly (6 times) extracted with ether, the combined ethereal solution washed with iced water, dried ($MgSO_4$) and the product recovered It was dried in a desiccator, m p. 221-225° (decomp), yield 1 g Soluble in alcohol, acetone, chloroform, and methyl alcohol, insoluble in benzene Effervesces with and dissolves in sodium bicarbonate solution Elementary analysis and equivalent weight determination show that it contains one molecule of water of crystallisation Separate estimation of the water of crystallisation was not possible owing to the decomposition occurring when the substance was heated (Found C, 44 39, H, 5 34, $C_{14}H_{16}O_{11}$, H_2O requires C, 44 44, H, 4 76 per cent)

A warm aqueous solution of (a) 0 1188 g of the above hydrolysed product required 13 c c and (b) 0 0785 g required 8 55 c c of 0 0486 N Sodium hydroxide for neutralisation (phenolphthalein) [Found equivalent, (a) 188 1 and (b) 188 9, $C_{14}H_{16}O_{11}$, H_2O requires equivalent 189]

Ethyl $\beta\beta'$-diketotetrahydrothiophene-$\alpha\alpha'$-dicarboxylate was prepared from ethyl thiodiglycollate and ethyl oxalate in a manner similar to that employed for its furan analogue (*Cf* Guha and Iyer, *loc cit*)

Ethyl $\alpha\alpha'$-dicarbethoxythiophene-$\beta\beta'$-dioxydiacetate (*VIII, R=S*)—To the thiophene ester (26 g) dissolved in hot absolute alcohol (300 c c) was added a solution of sodium (4 6 g) in absolute alcohol (100 c c) To the warm disodium derivative thus obtained, excess of ethyl bromacetate (80 g) was added and the mixture refluxed on a water bath After some time a solution resulted This was refluxed for 10 hours Then alcohol was distilled out and the residue subjected to steaming when the excess of the bromo-ester was removed The steamed residue was treated with 2 N. NaOH when the alkali insoluble reaction product separated out as a solid. This was filtered out, washed with water and crystallised from dilute alcohol, m.p. 50°, yield 18.6 g. Soluble in ether, benzene, acetone, chloroform and carbon tetrachloride, insoluble in petrol. Alcoholic solution does not give any coloration with ferric chloride whereas the thiophene ester gives a distinct coloration. (Found: C, 49.78; H, 5.71. $C_{18}H_{21}O_{10}S$ requires C, 50.00; H, 5.56 per cent.)

Alkali hydrolysis. Formation of the mono-potassium salt (*IX, R=S*).—An alcoholic solution of the ester (2 g.) was hydrolysed with an alcoholic solution of KOH (1.5 g.). The product was worked out and purified as in the analogous experiment described before, yield 1.2 g. Does not dissolve in organic solvents, effervesces and dissolves in sodium bicarbonate, leaves residue on incineration.

A warm aqueous solution of (a) 0.1804 g. of the mono-potassium salt required 31.25 c.c. and (b) 0.0940 g. required 16.30 c.c. of 0.0486 N NaOH for neutralisation. [Found: equivalent (a) 118.8 and (b) 119.1. $C_{10}H_7O_{10}SK$ requires equivalent, 119.33]

0.2120 g. of the mono-potassium salt gave 0.0511 g. of K_2SO_4. (Found: K, 10.87. $C_{10}H_7O_{10}SK$ requires K, 10.89 per cent.)

Silver salt.—This was prepared from 0.5 g. of the mono-potassium salt as detailed in the former case, yield 1.2 g. Silver could not be estimated as swelling and sudden decomposition occurred on heating.

· *Acid Hydrolysis* (*a*) *with* (1 : 1) *dilute hydrochloric acid.*—When the hydrolysis was conducted with dilute HCl under refluxing decomposition and charring occurred as in the case of the furan analogue. No product could be isolated.

(b) *with concentrated hydrochloric acid. Formation of αα'-dicarbethoxythiophene-ββ'-dioxydiacetic acid* (*X, R=S*).—Ester (2g. of VIII, R=S) was mixed in the cold with 20 c.c. of concentrated hydrochloric acid in a small flask, warmed for a minute on the water bath, corked and well shaken with simultaneous cooling under the water tap. The resulting solution soon solidified. This was left at room temperature for over 15 hours. Then added water, filtered out the solid, washed it with ice-cold water and dried on porous plate (1 5 g) It was then dissolved in 2 N NaOH and filtered to remove any unchanged ester The alkaline filtrate was acidified and the product taken up in ether by repeated extractions The washed and dried ethereal solution yielded the diesterdiacid (X, R=S) m p 225–227° (decom) When the molten substance is raised to higher temperature, vigorous evolution of gas followed by charring takes place It is soluble in acetone, chloroform, ethyl acetate, alcohol and boiling water , sparingly soluble in benzene and insoluble in carbon tetrachloride and petrol (Found C, 44 22 , H, 4 08 , $C_{14}H_{16}O_{10}S$ requires C, 44 68 , H, 4 26 per cent)

A warm aqueous solution of 0 0723 g of the above hydrolysed product required 7 90 c c of 0 0486 N NaOH for neutralisation (Found equivalent, 188 3 , $C_{11}H_{10}O_{10}S$ requires, equivalent 188)

SUMMARY

Ethyl $\beta\beta'$-diketotetrahydro- (1) furan- and (2) thiophene-$\alpha\alpha'$-dicarboxylates condensed with ethyl bromacetate to give ethyl $\alpha\alpha'$-dicarbethoxy- (1) furan- and (2) thiophene-$\beta\beta'$-dioxydiacetates Alkali and acid hydrolyses of these two products have been studied The condensations always proceeded in the enolic phases of the furan and thiophene esters

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