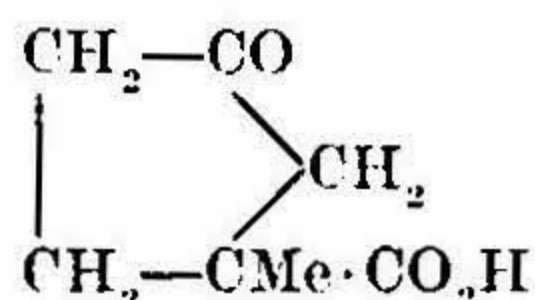


STUDIES IN BRIDGE FORMATION.

PART I. ATTEMPTS TO SYNTHESISE BICYCLIC TERPENE DERIVATIVES BY A NEW METHOD.*

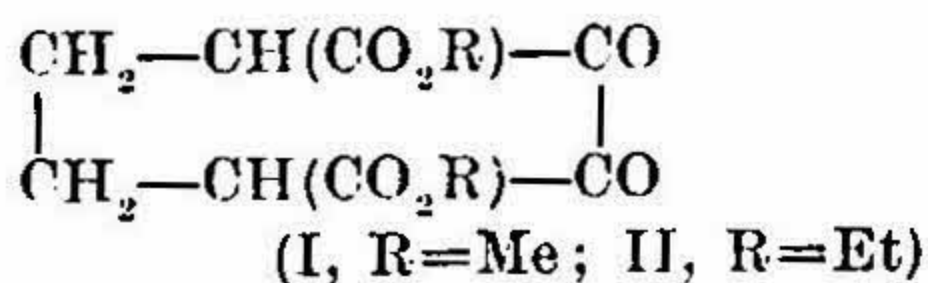
By P. P. Patel and P. C. Guha.

The factors in a synthesis of the bicyclic terpene derivatives camphor, fenchone and others, are the synthesis of *cyclopentane* derivatives by known methods, and the closing of the *cyclohexane* ring. Thus Komppa (*Ber.*, 1903, 36, 4332; *Annalen*, 1909, 368, 126; *ibid.*, 1909, 370, 209) and later Perkin and Thorpe (*J.C.S.*, 1906, 89, 795) synthesised camphoric acid, which through various stages they converted into camphor. Similarly Ruzicka (*Ber.*, 1917, 59, 1362), starting from laevulinic and bromoacetic ester prepared a *cyclopentane* derivative.



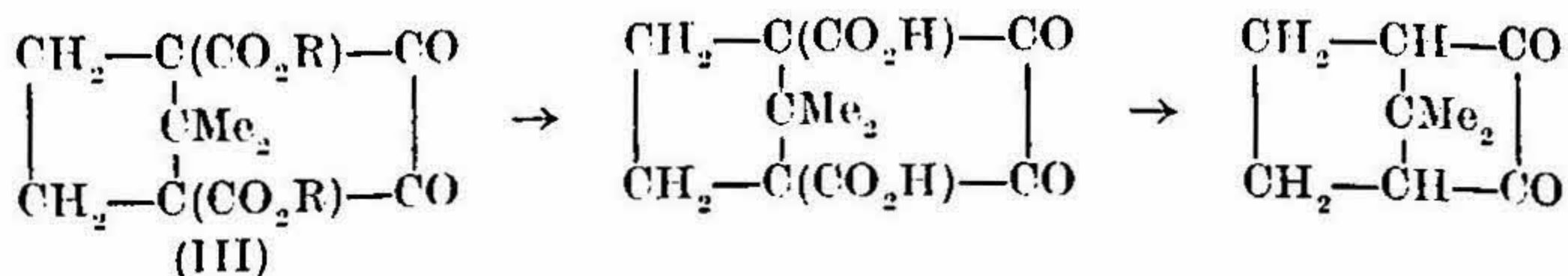
from which by condensing with another molecule of bromoacetic ester he obtained fenchone. Several similar processes are described in chemical literature, by which *cyclopentane* derivatives have been utilised for the formation of bicyclic terpene derivatives.

There is, however, a lack of information as to whether it is possible to synthesise such bicyclic compounds by bridging a proper *cyclohexane* derivative by suitable means. For example, *cyclohexane-2 : 3-dione-1 : 4-dicarboxylic ester*



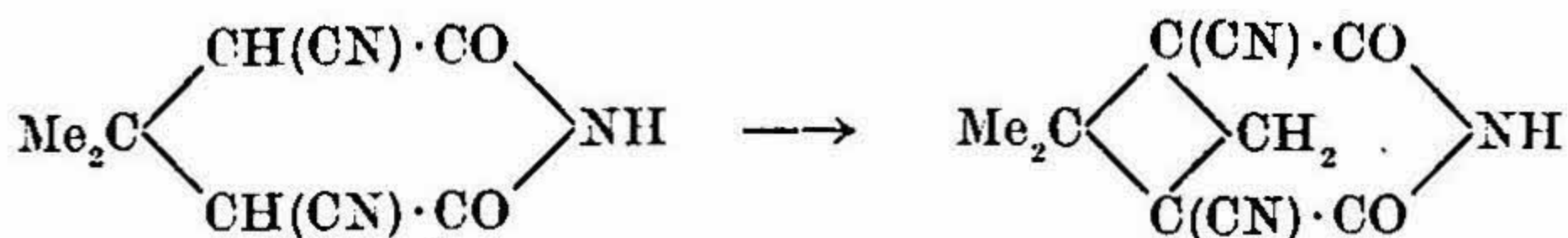
in which there are two hydrogen atoms replaceable by sodium, is expected to give bridged compounds on treatment of its disodium derivative with dihalogen compounds such as acetone dichloride, ethylene chloride; benzal chloride, benzophenone chloride, methylene iodide, carbonyl bromide, etc. In the case of bridging with acetone dichloride, the product was expected to give *apocamphorquinone* on hydrolysing the ester groups and subsequent decarboxylation thus:

* A preliminary report on this work has been published in the Proceedings of the Indian Science Congress (Chemistry Section, 1930, 177) and was communicated before 15th October 1929.

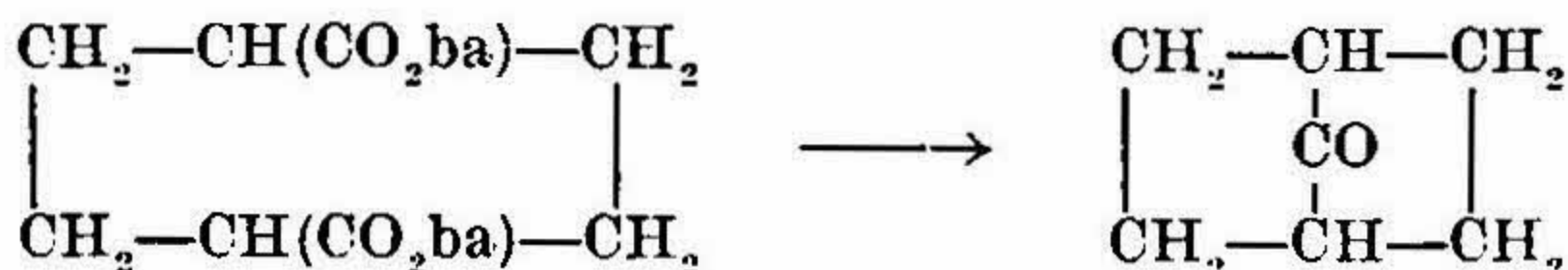


and with methylene iodide a series of derivatives of norcamphor.

cyclohexane-2:3-dione-1:4-dicarboxylic ester appears to be capable of enolisation in which form it might not lend itself to bridge formation. Recently, however, Kerr (*J. Amer. Chem. Soc.*, 1929, 51, 614) has succeeded in bridging Guareschi's imide, which is similarly constituted, by treating its disodium derivative with methylene iodide thus:

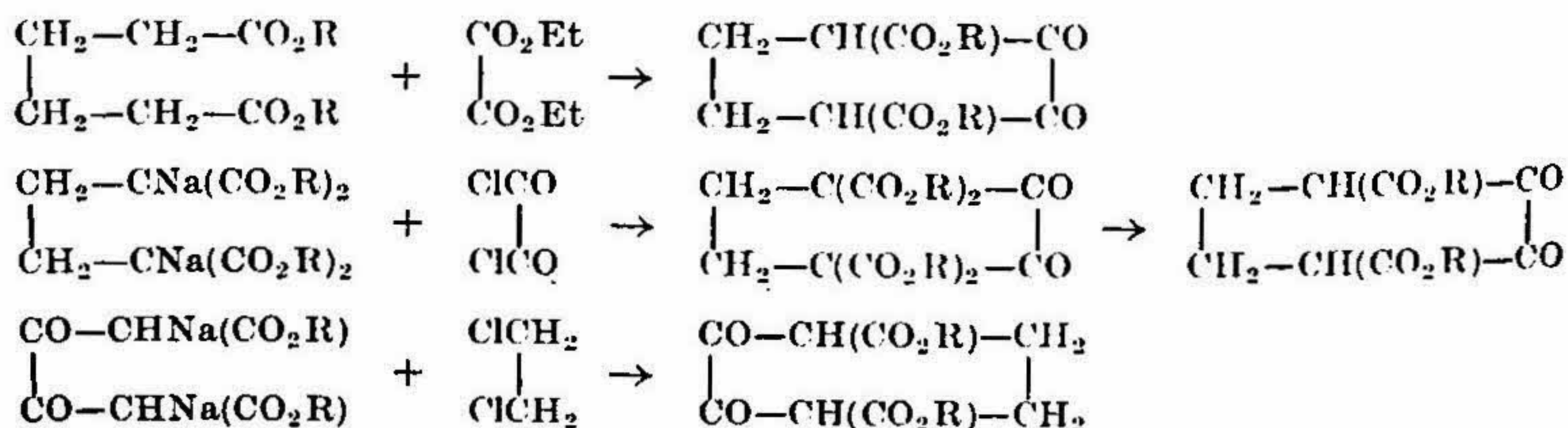


Though, in the case of Guareschi's imide the carbon atoms participating in bridge formation occupy the 1:3-position, there appears to be no reason why carbon atoms in the 1:4-position should not also take part in bridge formation and bridging of a *cyclohexane* derivative in the 1:4-position has been successful in the hands of Zelinsky (*Ber.*, 1901, 34, 380), who by heating the barium salt of hexahydroterephthalic acid with calcium carbonate obtained bicyclo (1:2:2)-heptanone-7, thus:



The object of the present investigation was based on the above expectations, the experimental verification of which necessitated in the first place, the preparation of compounds resembling ethyl *cyclohexane-2:3-dione-1:4-dicarboxylate*. Though the corresponding 1:3- and 1:4-analogues have been described, the required 1:2-diketone is unknown.

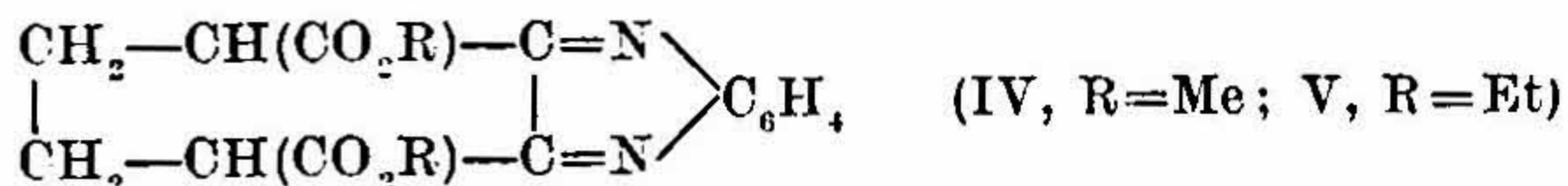
Three methods have been devised for the preparation of the desired diketonic ester: (1) condensation of oxalic ester with adipic ester, (2) interaction of oxalyl chloride with the disodium derivative of $\alpha\alpha\delta\delta$ -butanetetra-carboxylic ester, and (3) action of ethylene dichloride upon the disodium derivative of ketipic ester thus:



By analogy with the formation of ethyl ketipate from ethyl acetate and ethyl oxalate, Wislicenus and Schwanhauser (*Annalen*, 1897, 297, 98) attempted to prepare a cyclic diketone by the action of ethyl oxalate upon ethyl adipate, but they could isolate only an open chain compound, *viz.*, ethyl oxalo-adipate. Moreover, it is known that by the action of such dehydrating agents as metallic sodium, sodamide and phosphorus pentoxide, adipic ester is converted into ethyl *cyclopentanone-1-monocarboxylate-2*.

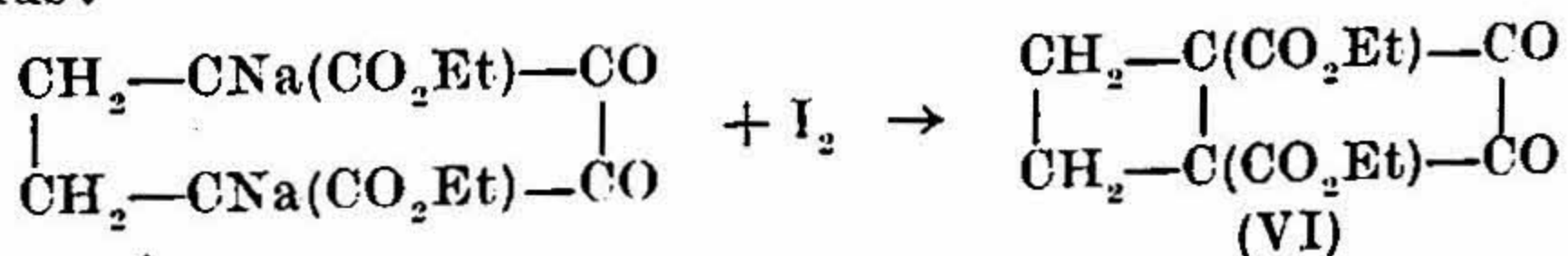
Though these facts were against the probability of formation of the required diketonic ester, it was hoped that under suitable conditions and with excess of dry sodium alcoholate the desired product might yet be formed. Freshly prepared methyl oxalate on being condensed with dry methyl adipate, employing an excess of dry sodium methoxide as condensing agent, has now according to expectation yielded methyl *cyclohexane-2:3-dione-1:4-dicarboxylate* (I), besides methyl *cyclopentanone-1-monocarboxylate-2* and two more oils boiling at different temperatures which appeared in all probability to be dimethyl carbonate and methyl oxalo-adipate respectively, but could not be definitely identified owing to poor yield. The corresponding diethyl ester (II) of *cyclohexanedione* has been prepared from ethyl adipate. *cycloHexanedionedicarboxylic ester* dissolves readily in dilute alkalis, gives a dark violet coloration with ferric chloride and a mono-semicarbazone.

With *o*-phenylenediamine both the methyl and ethyl esters give phenazine derivatives (IV and V).

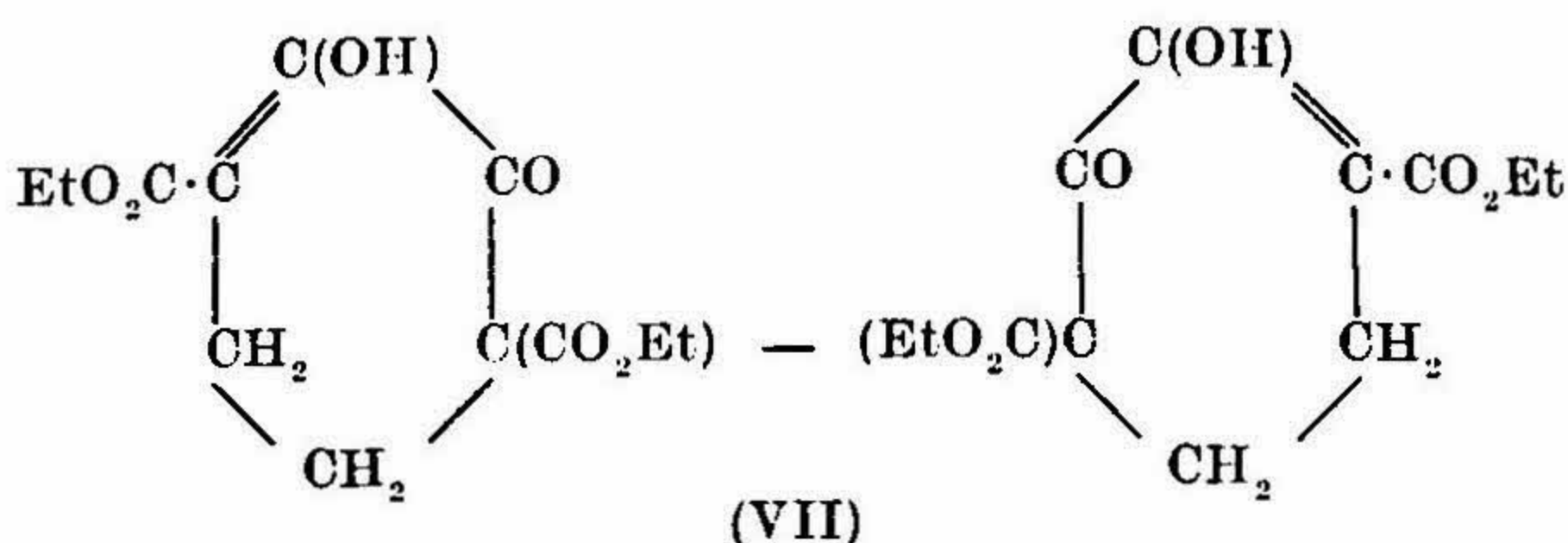


The first experiment on bridge formation was carried out with acetone dichloride by boiling a mixture of the halide, the disodium derivative of (II) and anhydrous benzene continuously, without result. In another attempt, the disodium derivative was heated in a sealed bottle with acetone dichloride in presence of anhydrous xylene, between 135-140° for 6-8 hours, but again the diketo-ester was recovered unchanged. Ethylene chloride, benzal chloride and benzophenone chloride have also been found not to react.

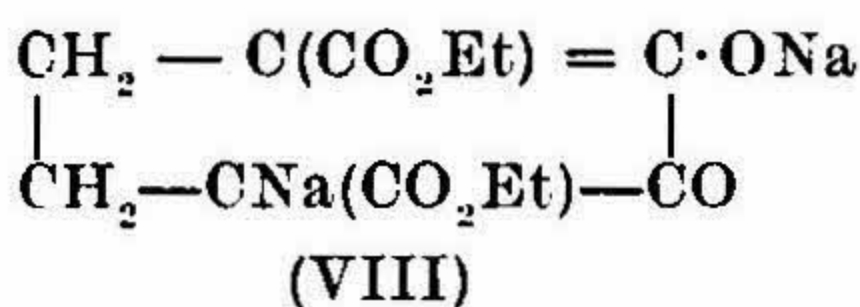
Noting the inertness of the above dihalogen compounds it was thought worth while to study the behaviour of iodine towards the disodium derivative of (II) when the bridged compound (VI) was expected to be formed thus:



The product melted at 90°, gave a deep green coloration with ferric chloride and dissolved readily in dilute alkali, but a compound of formula (VI) cannot behave as an enol; and as it is not the original di-ester the formula (VII) is ascribed to it.



Non-formation of the bridged compound (VI) is probably due to the disodium derivative existing in the mono-enolic form (VIII) though the formation of the phenazine derivatives (NL. IV) suggests a diketonic structure for the parent di-ester.



Experimental.

Methyl cyclohexane-2:3-dione-1:4-dicarboxylate (I).—To dry sodium methoxide obtained from 15 grams of sodium was added dry methyl oxalate (40 g.) and the mixture shaken very vigorously with occasional cooling by immersion in ice-water to prevent too rapid rise of temperature. After addition of anhydrous ether (150 c.c.) an ethereal solution of methyl adipate (12 g.) was slowly added and shaken vigorously for 30 minutes, when the mixture became yellow, and was left overnight at ordinary temperature well protected from moisture. It was then heated in an oil-bath to remove ether followed by dimethyl carbonate at 100°, after which the temperature was maintained at 140° during 12 hours. On acidifying with cold dilute sulphuric acid, a small quantity of thick oil separated which was washed several times with cold water and shaken with a small quantity of cold ethyl alcohol (95 per cent.) liberating a solid crystallising from ethyl alcohol in shining plates m.p. 111-112° (yield about 15 per cent. of theoretical). The diketo-ester is slightly yellowish, gives in alcoholic solution a dark violet coloration with ferric chloride and dissolves readily in cold alkali forming a yellow solution which on acidification loses colour and regenerates the diketo-ester (Found: C, 52.05; H, 6.0. C₁₀H₁₂O₆ requires C, 52.6; H, 5.3 per cent.).

Mono-semicarbazone of the diketo-ester.—An alcoholic solution of the diketo-ester (0.5 g.) was added to a cold saturated solution of semicarbazide hydrochloride and sodium acetate and the mixture thoroughly shaken and cooled in ice for five minutes; the solid product was crystallised from alcohol, m.p. 170° (decomp.) (Found: N, 14.98. C₁₁H₁₅O₆N₃ requires N, 14.74 per cent.).

The *phenazine* derivative (IV).—An alcoholic solution of the diketo-ester (0.25 g.), *o*-phenylenediamine (0.15 g.) and sodium acetate (0.3 g.) were heated under reflux for one hour when the solution became orange. On

concentration and cooling a solid separated which crystallised from 95 per cent. alcohol in deep yellow feathery needles, m.p. 175° (Found: N, 9.25. $C_{16}H_{16}O_4N_2$ requires N, 9.33 per cent.).

Methyl *cyclopentanone-1-monocarboxylate-2*.—The acidic aqueous solution left from the diketo-ester was extracted thrice with ether, the ethereal solution washed successively with dilute sodium carbonate solution and water, and dried. After removing ether, a brown, sweet-smelling oil remained and for the most part distilled under 17 mm. at $106-108^{\circ}$; Bouveault and Locquin (*Compt. rend.*, 1908, 146, 138) give $105^{\circ}/19$ mm. as the boiling point (Found: C, 58.64; H, 6.53. $C_7H_{10}O_3$ requires C, 59.1; H, 7.00 per cent.).

The *semicarbazone* of methyl *cyclopentanone-2-carboxylate* was prepared in the usual manner and crystallised from 95 per cent. alcohol, m.p. 176° (Found: N, 20.8. $C_8H_{13}O_3N_3$ requires N, 21.1 per cent.).

Ethyl cyclohexane-2:3-dione-1:4-dicarboxylate (II) was prepared as above using ethyl adipate in place of methyl adipate; the resulting oil partially solidified in an ice-chamber during 24 hours. On being washed with a small quantity of cold dilute alcohol pale yellow shining plates, m.p. 56° , were obtained (Found: C, 56.51; H, 6.91. $C_{12}H_{16}O_6$ requires C, 56.25; H, 6.25 per cent.).

The *phenazine* derivative (V) crystallised from alcohol in orange coloured needles, m.p. 101° (Found: N, 8.81. $C_{18}H_{20}O_4N_2$ requires N, 8.5 per cent.).

Disodium derivative (VIII) of the diketo-ester (II).—An anhydrous ethereal solution of the diketo-ester (11 g.) was added to an absolute alcoholic solution of sodium (2 g.) and the yellow powdery product washed with anhydrous ether (Found: Na, 14.9. $C_{12}H_{14}O_6Na_2$ requires Na, 15.3 per cent.).

Chloracetol (acetone dichloride), prepared according to the method of Friedel and Landenberg (*Annalen*, 1867, 142, 315), could be obtained pure only after a large number of fractional distillations, and boiled at $68-70^{\circ}/686$ mm.

Attempts to prepare compound (V) by bridging the diketo-ester (II) with chloracetol.—The disodium derivative (7 g.), anhydrous benzene (50 c.c.) and chloracetol (7 g.) were heated together in absence of moisture on a water-bath under reflux for 8–9 hours, when the red solution was alkaline. The thick red semi-solid left after removing benzene by distillation was dissolved in cold water and extracted with ether, the residue from which on distillation was negligible. The aqueous solution on being acidified with dilute sulphuric acid gave an oil which on cooling partly solidified; when crystallised from 93 per cent. alcohol the product melted at $55-56^{\circ}$ and was identified with the original di-ester (II). The same experiment conducted in presence of xylene at $135-140^{\circ}$ in a sealed bottle gave no better results.

Action of iodine upon the disodium derivative of (II): Formation of compound (VII).—To an alcoholic suspension of the disodium derivative

obtained from the diketo-ester (5.5 g.) and sodium (1 g.) was added portionwise a solution of iodine (2.5 g.) in absolute alcohol; after two hours on a water-bath the residue from alcohol gave on neutralisation a thick brown oil which in contact overnight with a small quantity of 93 per cent. alcohol yielded a solid. This crystallised readily from alcohol, m.p. 90° ; it is soluble in alkali and gives a deep green coloration with ferric chloride (Found: C, 56.08; H, 5.31. $C_{24}H_{30}O_{12}$ requires C, 56.47; H, 5.88 per cent.).

The action of different hydrolysing agents, methylene iodide, and di-acid halides upon the di-ester (I) is under investigation.

[Accepted, 21-11-32.]

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