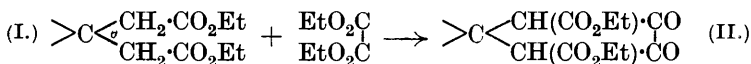


CCLXIX.—*Formation and Stability of spiro-Compounds.*
Part XIII. spiro-Compounds from the Substituted
Lævulic Acids.

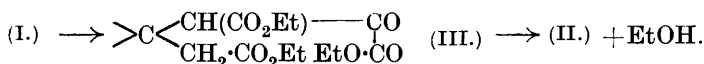
By EUGENE ROTHSTEIN and JOCELYN FIELD THORPE.

By condensing oxalic ester with various substituted glutaric acids (the Dieckmann-Komppa reaction) Dickens, Kon, and Thorpe

(J., 1922, **121**, 1496) obtained a series of cyclic diones whose general formula is (II).



It was shown that the reaction was not of a simple "box and lid" type, but that ring formation occurred in two stages. The first was the condensation of the glutaric acid with ethyl oxalate to give the oxalyl derivative (III). Next this eliminated alcohol to yield the cyclic dione (II).



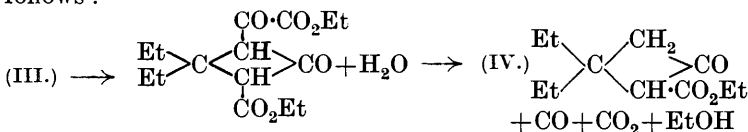
The yields obtained are in Table I.

TABLE I.

Oxalic ester with ester of	Angle θ .	Yield of <i>cyclo</i> -pentanedione.
Glutaric acid	115.3°	80%
β -Methylglutaric acid	112.5	Almost quantitative.
<i>cyclo</i> Pentanediacetic acid	109.5	60—70%
$\beta\beta$ -Dimethylglutaric acid	109.3	66%
$\beta\beta$ -Methylethylglutaric acid	?	20%
$\beta\beta$ -Diethylglutaric acid	?	Nil
<i>cyclo</i> Hexanediacetic acid	107.2	Nil

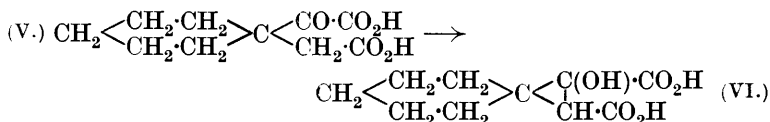
The greatest yield of dione is given by glutaric ester itself, the angle θ of which is far greater than that required to form a stable *cyclopentane* ring. The alteration of this angle must therefore have been caused by the presence of the oxalyl group on the α -carbon atom, and the ring itself stabilised by the 2 : 5-carbomethoxy-groups. The effect of further deflection of the angle θ by means of a *gem*-grouping, such as diethyl or the *cyclohexane* ring, would be to make the formation of the *cyclopentane* complex more difficult, and in some cases impossible.

This view was confirmed in the case of the diethyl compound by the formation of a small quantity of a four-membered cyclic compound (IV) the synthesis of which must be represented as follows :



It was of course expected that *cyclohexanediacetic* ester also would yield a four-membered cyclic compound, but Dickens, Kon, and Thorpe were unable to isolate it, a fact which they attributed to the experimental difficulties encountered in working with *cyclo*-

hexane compounds. There was no necessity, however, for such an assumption. It was shown subsequently (Lanfear and Thorpe, J., 1923, **123**, 2865) that α -ketocyclohexanedi-acetic acid (V) is completely converted into cyclohexanespirocyclopropan-2-ol-2 : 3-dicarboxylic acid (VI) when boiled with strong potassium hydroxide solution.



It follows, then, that in the cyclohexane series the carbethoxy-groups of the oxalyl derivative (III) deflected the angle θ even further than was necessary for the formation of the four-membered ring, and that as the conditions for the production of the spiro-cyclopropane ring were absent, no cyclic derivative could be isolated.

To test the truth of this deduction, it was decided to substitute hydrogen atoms for the two carbethoxy-groups. Under these conditions it was to be expected that the yield of the dimethylcyclopentane compound would be decreased, whereas the yield of the cyclohexanespirocyclopentane derivative should be increased. In the case of the compound (V), the formation of a cyclopropane ring would no longer be possible.

A series of cyclopentane compounds (VII) was prepared from the corresponding lævulic esters by direct ring closure through the action of dry sodium ethoxide in a manner analogous to that used by Vorländer in his synthesis of dihydroresorcinol from δ -ketobutyric ester (*Annalen*, 1896, **294**, 270).

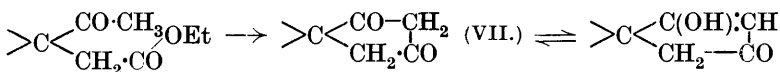


Table II shows that not only is the yield of the dione increased in the case of the cyclohexane compound, but that the order of stability given in Table I is reversed.

TABLE II.

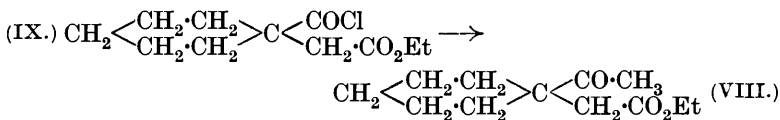
Ester used.	% Yield of cyclopentanedione.
$\beta\beta$ -Dimethyl-lævulic	20-25
$\beta\beta\beta$ -Trimethyl-lævulic	35 *
1-Acetylcyclohexane-1-acetic	48

* De Rosanbo, *Ann. Chim.*, 1923, [ix], **19**, 327.

Attempts made by De Rosanbo (*loc. cit.*) and by the authors to obtain cyclopentane-1 : 3-dione from lævulic acid itself failed owing to the tendency of the latter to form unsaturated lactonic compounds.

Trimethyl-lævulic acid gives a higher yield of the dione than the dimethyl compound (Table II). This is to be expected, since the introduction of another methyl group necessarily decreases the distance between the terminal carboxyl group and the terminal methyl group. The deflection caused by this group is not as great as in the case of the carbethoxyl or carboxyl group, as will become evident.

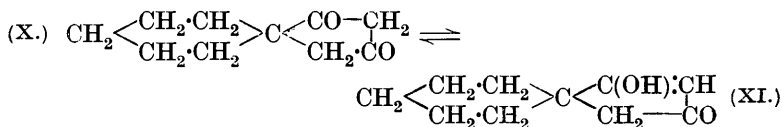
Ethyl 1-acetylcyclohexane-1-acetate (VIII) was prepared by the action of zinc methyl iodide on the acid chloride of ethyl 1-carboxycyclohexane-1-acetate (IX) (compare $\beta\beta$ -dimethyl-lævulic acid; Rothstein, Stevenson, and Thorpe, J., 1925, 127, 1072).



The acid obtained by its hydrolysis gave a theoretical yield of the *semicarbazone* and was extremely stable to reagents. It distilled without decomposition, and neither sulphuric acid (25%) nor potassium hydroxide solution (75%) had any action upon it. In the latter respect it differs markedly from α -ketocyclohexanedi-acetic acid (V), which is completely changed to *cyclohexanespirocyclopentan-2-ol-2 : 3-dicarboxylic acid*.

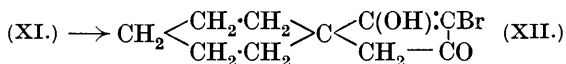
This difference in behaviour is only to be expected, since it is another illustration of the great deflection of the tetrahedral angle due to the carboxyl group. The substitution of an α -methyl group for the corresponding carboxyl group in α -ketocyclohexanedi-acetic acid increases the angle θ , and the α' and α -carbon atoms are no longer close enough for the closure of the *cyclopropane* ring to occur. The increase of the angle θ , however, separates the α -methyl group and the α' -carbon atom, thus introducing the possibility of the formation of the five-membered ring (VII).

In fact, the formation of *cyclohexanespirocyclopentane-2 : 4-dione* (X) proceeded quite easily. The compound was a crystalline solid giving a deep crimson colour with alcoholic ferric chloride. Its

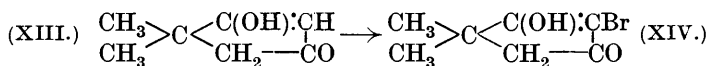


constitution was shown by oxidation with alkaline sodium hypochlorite, 1-carboxycyclohexane-1-acetic acid being produced. When

treated with the theoretical quantity of bromine, it gave a quantitative yield of the *bromide* (XII).



1 : 1-Dimethylcyclopentane-2 : 4-dione (or 1 : 1-dimethyl- Δ^2 -cyclopenten-2-ol-4-one; XIII) could not be isolated from the syrupy products formed by the action of sodium ethoxide on ethyl $\beta\beta$ -dimethyl-lævulate. The yield was therefore estimated by titration with bromine (compare experimental portion). A solid *bromide* (XIV) was isolated in an 18% yield.



EXPERIMENTAL.

Anhydride of 1-Carboxycyclohexane-1-acetic Acid.—In the preparation of 1-carboxycyclohexane-1-acetic acid by Lapworth and McRae's method (J., 1922, **121**, 2754) it was found better to hydrolyse the dicyano-ester, $\text{C}_5\text{H}_{10} \cdot \text{C}(\text{CN}) \cdot \text{CH}(\text{CN}) \cdot \text{CO}_2\text{Et}$, with 75% sulphuric acid instead of fuming hydrochloric acid as described. The hydrolysis product was distilled in steam to remove traces of unchanged nitrogen compounds. An acid was obtained which after recrystallisation from benzene and petroleum melted at 134° and not 132° as given in the above paper (Found : C, 58.4; H, 7.7. Calc. : C, 58.0; H, 7.5%).

The anhydride was best obtained by distilling the acid under reduced pressure through a wide air condenser. It volatilised with the steam produced and it was necessary to take precautions to prevent the pump being blocked. The anhydride separated from petroleum (b. p. $40\text{--}60^\circ$) in shimmering leaflets, m. p. 55° (yield 76%) (Found : C, 64.6; H, 7.3. Calc. : C, 64.3; H, 7.1%).

Ethyl 1-Acetylcyclohexane-1-acetate (VIII).—A solution of sodium (8.9 g.) in absolute ethyl alcohol (100 c.c.) was added slowly with shaking to the pure recrystallised anhydride (65 g.), also dissolved in absolute ethyl alcohol (50 c.c.). The alcohol was removed in a vacuum, and after acidification the heavy oil was extracted with ether. The ethereal extract yielded a thick, almost colourless syrup, which subsequent treatment showed to be almost entirely ethyl 1-carboxycyclohexane-1-acetate, b. p. $175\text{--}180^\circ/11$ mm. (yield 70 g.).

The crude acid ester (60 g.) was converted into the acid chloride with thionyl chloride (30 c.c.) in the usual way. The crude chloride,

diluted with an equal bulk of benzene, was added during 45 minutes to zinc methyl iodide, methyl acetate being used instead of ethyl acetate in the preparation of the latter compound. (Unless these precautions were taken, the yield was reduced to a negligible quantity.) The product, after standing an hour, was worked up in the usual way; b. p. 144—154°/14 mm. (yield 20—30 g.).

1-Acetylcyclohexane-1-acetic Acid.—The above ester was boiled under reflux with potassium hydroxide (50%) and an equal bulk of ethyl alcohol. The sticky solid obtained on acidification became crystalline after being rubbed with petroleum-ether.

The crude acid (9.5 g.) yielded 10 g. of a *semicarbazone*, m. p. 212° after recrystallisation from ethyl alcohol and water (Found: C, 55.0; H, 8.0; N, 17.2. $C_{11}H_{19}O_3N_3$ requires C, 54.8; H, 7.9; N, 17.4%). From the aqueous filtrate, ether extracted 4.7 g. of *1-carboxycyclohexane-1-acetic acid*.

The crude mixture (which, as shown above, contained 80% of the *keto-acid*) was distilled; b. p. 140—200°/20 mm. The distillate was extracted with saturated sodium hydrogen carbonate solution, and the extract on acidification yielded the pure ketonic acid which, after two crystallisations from benzene and petroleum, melted at 82° (Found: C, 65.2; H, 8.8. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.7%).

The ketonic acid is remarkably stable, resisting attack by phosphorus pentabromide, phosphorus trichloride, acetyl chloride, and phenylcarbimide.

The *ethyl ester*, b. p. 155°/15 mm., was prepared from the pure acid by Phelps and Tillotson's alcohol vapour method (yield 94%). It gave neither a *semicarbazone* nor any derivative with acetyl chloride or phenylcarbimide.

cycloHexanespirocyclopentane-2 : 4-dione (X).—Ethyl 1-acetylcyclohexane-1-acetate (13 g.) was treated with dry sodium ethoxide in ethereal solution by a method similar to that used by De Rosanbo (*loc. cit.*) in the preparation of 1 : 1 : 3-trimethylcyclopentane-2 : 4-dione from $\beta\beta\delta$ -trimethyl-lævulic acid. The product was rubbed with dry ether and recrystallised from ethyl alcohol and water; m. p. 180° (yield 48%) (Found: C, 72.3; H, 8.1. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.4%). The compound decolorised cold alkaline potassium permanganate and was unchanged by boiling 50% potassium hydroxide solution.

Oxidation with sodium hypochlorite. The *spiro*-compound (1 g.) dissolved in a small quantity of potassium hydroxide solution was added cautiously to 25% sodium hypochlorite solution (15 c.c.), cooled in ice. After being shaken, the mixture was kept for 30 minutes, acidified, and extracted with ether. The extract yielded

1-carboxycyclohexane-1-acetic acid, m. p. 130—131°, from which the anhydride was prepared.

Enol content. Titration with bromine by Meyer and Kapelheir's method (*Ber.*, 1911, **44**, 2718) showed a 69·4% enolisation of both keto-groups.

cycloHexanespiro-3-bromo- Δ^2 -cyclopenten-2-ol-4-one (XII).—The spiro-compound (2 g.), suspended in chloroform, dissolved on addition of a chloroform solution of bromine (2 g.). The solution was evaporated on the steam-bath; the solid obtained was recrystallised from ethyl alcohol and water; m. p. 238° (Found: C, 48·5; H, 5·2. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·3%). The compound was strongly acidic, decomposing sodium hydrogen carbonate. An alcoholic solution gave an intense crimson colour with neutral ferric chloride.

1 : 1-Dimethylcyclopentane-2 : 4-dione (1 : 1-Dimethyl- Δ^2 -cyclopenten-2-ol-4-one) (XIII).—Ethyl $\beta\beta$ -dimethyl-lævulate was treated with sodium ethoxide in the same way as the cyclohexane ester. A syrup was obtained which did not solidify. As this compound had been isolated before (Farmer, Ingold, and Thorpe, J., 1922, **121**, 128), the purification was not proceeded with, but the yield was estimated by means of bromine titrations. Although it could not be estimated exactly, it was considered that the amount of enolisation would probably be equal to that of the cyclohexanespiro-compound. Assuming this, it was found that the yield was between 20% and 25%. This figure was confirmed by the formation of 3-bromo-1 : 1-dimethyl- Δ^2 -cyclopenten-2-ol-4-one (XIV), which was obtained by the action of a chloroform solution of bromine (0·9 g.) on a solution of the syrup (1·3 g.) in chloroform. After evaporation, a gummy residue was obtained which partly solidified. The adhering syrup was removed by rubbing with chloroform-petroleum; the solid then crystallised from ethyl alcohol and water in clusters of prisms, m. p. 203° (yield 18%) (Found: C, 40·8; H, 4·0. $C_7H_9O_2Br$ requires C, 41·0; H, 4·3%). The bromide is insoluble in benzene, is strongly acidic, and gives a blood-red colour with alcoholic ferric chloride.

We are indebted to the Chemical Society for a grant which has partly defrayed the cost of the materials required for the investigation.