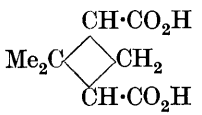
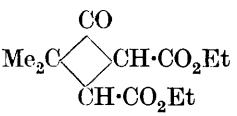
CCCXLV.—*Attempts to Synthesise Norpinic Acid.*

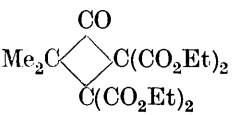
By GEORGE ROGER CLEMO and KENNETH NORMAN WELCH.

SINCE norpinic acid, one of the key compounds of terpene chemistry, was given the constitution (I) by Baeyer (*Ber.*, 1896, **29**, 1907), numerous unsuccessful attempts at its synthesis have been made. The claim of Ganguly (*J. Indian Inst. Sci.*, 1922, 23) must be included in this category, since, although it has only been possible to refer to an abstract of the paper, this states definitely that Ganguly's experiment cannot be regarded as successful. The following is a brief account of synthetic work designed to achieve this end, in which results of interest have been obtained although final success has not been reached. The continued inability to synthesise this acid is not easy to understand from Ingold's modification of the Baeyer strain theory (J., 1915, **107**, 197, 1082), in view of the fact that *cyclo*butane-1 : 3-dicarboxylic acid is easily prepared (Perkin and Simonsen, J., 1909, **95**, 1171).

The first synthetic method to be tried was to prepare (II) by condensing dimethylketen with maleic or fumaric ester. On hydrolysis, this should lose carbon dioxide, and the cyanohydrin of the resulting keto-acid by treatment with hydrobromic acid followed by the replacement of the bromine atom by hydrogen should yield (I).


(I.)


(II.)


(III.)

Only polymerised dimethylketen and unchanged ester, however, could be isolated from the reaction mixture, even when one or both of the reagents were produced *in situ*, and therefore presumably in an active phase, as by the action of a mixture of zinc and copper powder on an ethereal solution of α-bromo*iso*butyryl bromide and αβ-dibromosuccinic ester. Likewise, condensation could not be

effected between α-bromo*iso*butyryl bromide and sodioethanetetracarboxylic ester to give the compound (III).

The preparation of ethyl αα-dimethyltricarballylate,

$$CMe_2(CO_2Et)\cdot CH(CO_2Et)\cdot CH_2\cdot CO_2Et,$$

was then investigated with a view to carrying out the Dieckmann reaction on it to give (II). The corresponding acid has been obtained by the oxidation of pinic acid (Tiemann and Semmler, *Ber.*, 1895, **28**, 1349), of dihydroxycamphoceanic acid (Jagelki, *Ber.*, 1899, **32**, 1509), and of fenchone (Gardner and Cockburn, J., 1898, **73**, 708), and also synthetically from ethyl α-bromo*iso*butyrate and ethyl sodiocyanosuccinate, followed by hydrolysis. It was thought, however, that it might be easily prepared from the more accessible bromoacetic ester and sodio-αβ-dicyano*iso*valeric ester, which is readily obtained by the action of acetonecyanohydrin on sodium cyanoacetic ester (Higson and Thorpe, J., 1906, **89**, 1455). In spite of the fact, however, that a much improved method for the preparation of acetonecyanohydrin has been worked out, the poor yields of dimethyltricarballylic acid thus obtained render it impracticable to prepare thus the necessary amount for the full investigation of this synthetic method.

Attention was then directed to the action of formaldehyde and its derivatives on *iso*propylidenedimalonic ester, $CMe_2:[CH(CO_2Et)_2]_2$, which has been prepared from *iso*propylidenemalonic ester (Kötz, *J. pr. Chem.*, 1907, **75**, 494). The latter ester has been prepared by condensing acetone with malonic ester in the presence of acetic anhydride and zinc chloride (Meyenberg, *Ber.*, 1895, **28**, 786), and by modifying this method we have consistently obtained yields of 50%. It has not been found possible, however, to obtain the yields of *iso*propylidenedimalonic ester claimed by Kötz, whose method is inconvenient on a large scale; yields of 10% were obtained by forming the sodiomalonic ester and carrying out the condensation in alcoholic solution in sealed tubes, but the bulk of the *iso*propylidenemalonic ester was recovered unchanged. Eventually, however, 10 g. of *iso*propylidenedimalonic ester were accumulated, but when its sodio-derivative was treated with methylene iodide, *iso*propylidenemalonic ester and a higher-boiling compound, apparently methylenedimalonic ester, resulted instead of the expected *cyclo*butane derivative. These results can be explained on the assumption that the Michael reaction is reversible (Ingold and Powell, J., 1921, **119**, 1976).

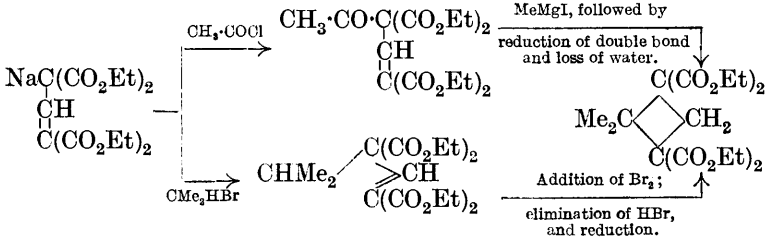
Acting on this basis, we attempted to condense methoxymethylmalonic ester with *iso*propylidenemalonic ester to give

$$CH(CO_2Et)_2\cdot CMe_2\cdot C(CO_2Et)_2\cdot CH_2\cdot OMe,$$

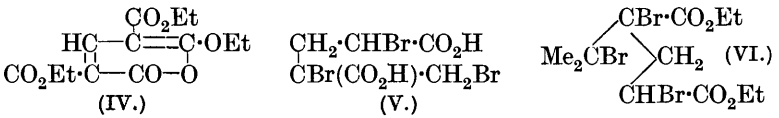
since if this ester were formed it could lose methyl alcohol with the

formation of the *cyclo*butane derivative and thus force the balanced Michael reaction to completion. No condensation, however, could be effected.

It was then decided to make sodio-$\alpha\gamma$-dicarbethoxyglutaconic ester (Conrad and Guthzeit, *Annalen*, 1884, **222**, 250) the starting point for the synthetic schemes :



The first method broke down, however, for the acetyl chloride reacted with the sodio-derivative in the enol phase, and the resulting *O*-acetyl compound then lost ethyl acetate to give ethyl ethoxy-α-pyrone-dicarboxylate (IV), a compound previously described by Guthzeit and Dressel (*Ber.*, 1889, **22**, 1415). Since the second part of this scheme was investigated, an account of a similar reaction with *iso*propyl iodide has been published by Hariharan, Menon, and Simonsen (this vol., p. 431), but as our results throw some light on this peculiar reaction they are worth mentioning. In addition to the trimesic ester obtained by these authors, it has been found that a considerable quantity of malonic ester is present in the reaction mixture. This result indicates hydrolysis at the double bond in the first instance, followed by the loss of carbon dioxide as sodium carbonate and subsequent formation of trimesic ester by the well-known reaction from formylacetic ester.



The last line of synthetic attack to be tried was based on the observation of Perkin and Simonsen (J., 1909, **95**, 1169), that a *cyclo*butane derivative resulted from the action of zinc and acetic acid on the compound (V). An attempt was made, therefore, to prepare (VI) from ethyl α-acetylglutarate by the action of magnesium methyl iodide, followed by the replacement of the hydroxyl group by bromine, and subsequent bromination. Acetylglutaric ester has now been prepared in good yield from β-chloropropionic ester and sodioacetoacetic ester. Magnesium methyl iodide reacts, however, with the enol phase of this ester with evolution of methane, and

α-acetylglutaric ester was recovered on acidification of the reaction mixture (compare Grignard, *Compt. rend.*, 1902, **134**, 849).

It was attempted to overcome this difficulty by preparing *ethyl α-bromo-α-acetylglutarate*, but the reaction with magnesium methyl iodide, in which iodine was eliminated, proved to be anomalous and resulted in the reduction of the bromo-ester to α-acetylglutaric ester.

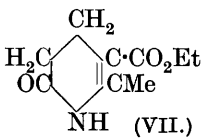
α-Acetyl-α-methylglutaric ester was then prepared in the hope that the methyl group would prevent both enolisation and reduction, but on treatment with the Grignard reagent the acetyl group was eliminated to give α-methylglutaric ester (compare Grignard, *loc. cit.*).

In the course of some of the above reactions it became necessary to prove the presence of α-acetylglutaric ester as an end product, and accordingly a search was made for crystalline derivatives for the purpose of characterisation. When the ester is heated with aniline, diphenylcarbamide results, whilst treatment with gaseous ammonia in the cold in the presence of a trace of iodine gives *ethyl α-(α′-aminoethylidene)-glutarate*,

$$CH_3{\cdot}C(NH_2){:}C(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et,$$

which on heating loses alcohol and forms the lactam (VII) (Emery, *J. Amer. Chem. Soc.*, 1891, **13**, 352).

The action of benzenediazonium chloride on α-acetylglutaric ester under the conditions of the Japp–Klingemann reaction gave *α-carboxypentane-γδ-dione-γ-phenylhydrazone* (VIII), whereas treatment of the ester with phenylhydrazine gave the *pyrazolone* (IX).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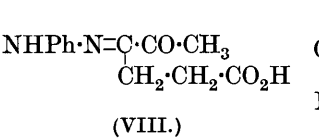
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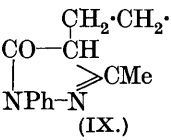
(IX.)

EXPERIMENTAL.

αα-Dimethyltricarballylic Acid.—Acetonecyanohydrin (10 g.) (see note, this vol., p. 2629) was condensed with sodiocyanoacetic ester (from cyanoacetic ester, 12 g.) in the manner of Higson and Thorpe (*loc. cit.*). The sodio-αβ-dicyano*iso*valeric ester thus formed was refluxed with bromoacetic ester (20 g.) until neutral. Water was then added, the oil extracted with ether, the extract separated, dried, and fractionated, a considerable proportion of αβ-dicyano*iso*valeric ester being recovered unchanged, together with 2 g. of material, b. p. above 160°/14 mm. This fraction was hydrolysed by refluxing with concentrated hydrochloric acid; the solution was evaporated and the acid extracted with ether, and on evaporation of the ether

a syrup remained which partly crystallised on standing to give αα-dimethyltricarballylic acid, m. p. 149°.

iso*Propylidenemalonic Ester*.—Malonic ester (130 g.), acetic anhydride (120 g.), and a solution of zinc chloride (8 g.) in acetone (110 g.) were heated in thick sealed bulb-tubes in the water-bath for 80 hours. The reaction mixture was added to an equal volume of water and left for 24 hours with occasional shaking to decompose unchanged acetic anhydride. The ester was then separated, the aqueous layer extracted with ether, the extract added to the ester, and dried over sodium sulphate. After removal of the ether the residue was fractionated four times, giving 90 g. of *iso*propylidenemalonic ester, b. p. 116—120°/14 mm. (Found: C, 59·8; H, 8·0. Calc.: C, 60·0; H, 8·0%).

iso*Propylidenedimalonic Ester*.—*iso*Propylidenemalonic ester (20 g.) was heated in alcoholic solution with an equivalent of sodiomalonic ester in a sealed tube in a water-bath for 24 hours. The alcohol was then removed, dilute sulphuric acid added, and the separated oil extracted with ether and distilled. The distillate, b. p. above 160°/14 mm., was refractionated, yielding 3 g. of *iso*propylidenedimalonic ester, b. p. 155°/1 mm. This was refluxed until neutral with two equivalents of sodium ethoxide and excess of methylene iodide in alcoholic solution, the product poured into water, extracted with ether and fractionated; *iso*propylidenemalonic ester passed over at 100—120°/14 mm., and a small quantity of methylenedimalonic ester above 160°/14 mm., as proved by hydrolysis to an acid, m. p. 97° (glutaric acid has m. p. 97·5°).

Condensation of Sodio-αγ-dicarbethoxyglutaconic Ester with Acetyl Chloride. Ethyl Ethoxy-α-pyronedicarboxylate (IV).—Sodiodicarbethoxyglutaconic ester (6 g.; vacuum-dried over sulphuric acid), anhydrous ether (20 c.c.), and redistilled acetyl chloride (2 g.) were introduced into a small flask, the neck of which was immediately sealed, and allowed to stand for 5 days with occasional shaking. The ethereal solution was then filtered from sodium chloride and evaporated on the water-bath. As the last traces of ether were being removed a distinct smell of ethyl acetate was noticed. When an attempt was made to distil the residue in a vacuum, decomposition occurred and the distillate, b. p. 180—200°/3 mm., partly solidified in the receiver. The compound crystallised from benzene–light petroleum in colourless needles, m. p. 94°, not depressed by admixture with an authentic specimen of the pyrone (IV).

Action of iso*Propyl Bromide on Sodiodicarbethoxyglutaconic Ester*.—Sodiodicarbethoxyglutaconic ester (6 g.), alcohol (20 c.c.), and *iso*propyl bromide (1·8 g.) were heated in a sealed tube at 150° for 12 hours. When the tube was opened an inflammable gas (? propyl-

ene) was evolved, and when the alcoholic solution was decanted from the mixture of sodium bromide and carbonate, and a small volume of water was added, a solid separated. This having been collected, more water was added to the filtrate. The resulting oil was extracted with ether and fractionated, giving 2 g. up to 100°/3 mm., 0·5 g. from 100—180°/3 mm., and 1 g. above 180°/3 mm. The last fraction partly solidified and, together with the solid collected initially, was recrystallised from alcohol and found to be trimesic ester, m. p. 131° (Found : C, 61·4; H, 6·1. Calc. for $C_{15}H_{18}O_6$: C, 61·2; H, 6·1%). On redistillation, the first fraction boiled at 80°/14 mm., and on treatment with aqueous-alcoholic ammonia gave malonamide, m. p. 171°, mixed m. p. with an authentic specimen 171°.

α-Acetylglutaric Ester.—To a cooled solution of sodium (6 g.) in alcohol (150 c.c.), acetoacetic ester (33 g.) was added, followed, after cooling, by β-chloropropionic ester (35 g.), and the mixture was refluxed for 3 hours on the water-bath. The excess of alcohol was then removed, water added to the residue, and the oil extracted with ether and fractionated; after a small quantity of acetoacetic ester had passed over, ethyl α-acetylglutarate (40 g.; 70%), b. p. 145—147°/12 mm., was obtained (Found : C, 57·5; H, 8·1. Calc. for $C_{11}H_{18}O_5$: C, 57·4; H, 7·8%), giving a deep blue coloration with ferric chloride. In addition, a small higher-boiling fraction of ethyl γ-acetylpentane-αγε-tricarboxylate passed over finally.

Action of Magnesium Methyl Iodide on α-Acetylglutaric Ester.—The Grignard reagent from 5 g. of methyl iodide was dropped into α-acetylglutaric ester (7 g.) in ether (50 c.c.), and the mixture kept over-night. Dilute sulphuric acid was then added, and the ethereal layer distilled, but the ester was recovered unchanged.

α-Bromo-α-acetylglutaric Ester.—As a result of many experiments the following method was adopted as the only one to give satisfactory yields of the bromo-ester : α-Acetylglutaric ester (11·5 g.) was shaken with water (15 c.c.) and calcium carbonate (2·5 g.), and bromine was added drop by drop; the first 0·5 c.c. was rapidly absorbed, presumably by the enol phase of the ester, but further quantities of 0·5 c.c. reacted slowly, the mixture being kept cool and stirred, and the reaction appeared to be complete when 2·7 c.c. had been absorbed during the course of a week. The mixture was then extracted with ether and fractionated, the *bromo*-compound (13 g.) passing over at 162—165°/14 mm. (Found : C, 42·2; H, 5·7. $C_{11}H_{17}O_5Br$ requires C, 42·7; H, 5·5%). The compound gives no coloration with ferric chloride.

Action of Magnesium Methyl Iodide on α-Bromo-α-acetylglutaric Ester.—The Grignard reagent from methyl iodide (5·6 g.) was dropped

into α-bromo-α-acetylglutaric ester (10 g.) in ether (100 c.c.); a pale brown solid separated and the mixture was left over-night and then decomposed by adding ammonium chloride solution. The ethereal layer, which on evaporation in the cold gave no coloration with ferric chloride, was dried, the ether removed, and the residue distilled in a vacuum; iodine was evolved, and the distillate after treatment with caustic soda solution was proved to be α-acetylglutaric ester by the ferric chloride colour reaction, and by conversion into the amino-derivative (see below).

α-Acetyl-α-methylglutaric Ester.—This ester was prepared in 60% yield by the condensation of β-chloropropionic ester and methylacetoacetic ester as described above for α-acetylglutaric ester.

Action of Magnesium Methyl Iodide on α-Acetyl-α-methylglutaric Ester.—The Grignard reagent from methyl iodide (3·5 g.) was dropped into α-acetyl-α-methylglutaric ester (6 g.) in ether (15 c.c.) and refluxed for 7 hours. On being worked up in the usual manner, the main fraction boiled at 120—140°/15 mm. and redistilled at 122—125°/15 mm., and was therefore ethyl α-methylglutarate (Found: C, 59·4; H, 8·6. Calc.: C, 59·4; H, 8·9%).

Ethyl α-(α'-Aminoethylidene)glutarate.—Gaseous ammonia was passed into α-acetylglutaric ester (5 g.), containing a little iodine, for 4 days. Water separated, and on cooling, the product solidified. It was collected, dried on porous plate, and when crystallised from light petroleum (b. p. 40—60°) by spontaneous evaporation gave large colourless prisms, m. p. 37° (Found: C, 57·8; H, 8·1. $C_{11}H_{19}O_4N$ requires C, 57·7; H, 8·3%). When this compound was heated to 190—220°, alcohol was eliminated and the lactam (VIII) formed, m. p. 156° (Found: C, 58·9; H, 6·9. Calc. for $C_9H_{13}O_3N$: C, 59·9; H, 7·1%).

Action of Aniline on α-Acetylglutaric Ester.—Aniline (1 g.), α-acetylglutaric ester (2·5 g.), and a trace of iodine were heated on an oil-bath at 140—160° for 4 hours. On cooling, the product solidified, and after recrystallisation from methyl alcohol gave slightly brown needles, m. p. 238°, not depressed by admixture with a pure specimen of *s*-diphenylcarbamide.

α-Carboxypentane-γδ-dione-γ-phenylhydrazone (γδ-Diketohexoic Acid γ-Phenylhydrazone).—α-Acetylglutaric ester (4·7 g.), dissolved in a solution of caustic potash (2·4 g.) in water (9 c.c.), was kept for 24 hours in a corked flask. Water (30 c.c.), acetic acid (3 c.c.), and ice were then added, the solution was vigorously stirred, and benzenediazonium chloride (from aniline, 2 g.), together with an excess of sodium acetate, added immediately. Carbon dioxide was evolved and a flesh-coloured solid separated, which after standing over-night was collected, dissolved in sodium carbonate solution,

and boiled with charcoal. The *phenylhydrazone* was reprecipitated by the addition of hydrochloric acid, and crystallised from alcohol, giving pale yellow needles, m. p. 178° (yield 80%) (Found : C, 61·6; H, 6·0. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%); the highly crystalline *sodium* salt is sparingly soluble in cold water.

Ethyl 1-*Phenyl*-3-*methyl*-5-*pyrazolone*-4-β-*propionate*.—α-Acetylglutaric ester (10 g.), phenylhydrazine (4 g.), and acetic acid (1 drop) were mixed and allowed to stand for 3 hours. Ether was then added and the solution dried with sodium sulphate. The ether was removed and the residue heated on the water-bath for 10 hours and then distilled, giving the *pyrazolone* as a pale yellow oil, b. p. 215°/3 mm. (Found: C, 65·7; H, 6·55. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6%).

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