LXVII.—*The Preparation of cycloHeptane-1:1-diacetic Acid.*By JAMES NELSON EDMUND DAY, GEORGE ARMAND ROBERT KON,
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In two recent papers (Beesley, Ingold, and Thorpe, T., 1915, **107**, 1080; Ingold and Thorpe, T., 1919, **115**, 320), a comparison was made between derivatives of $\beta\beta$ -dimethylglutaric (I) and *cyclo*-

hexanediactic acid (II) with respect to the degree of ease with which a bond can be established between the two α -carbon atoms of the acid, and the stability of the trimethylene compounds so produced.

From the experimental data, it is argued that the forcing apart of two of the valencies of the quaternary carbon atom from $109^\circ 28'$ to 120° , consequent on the formation of a *cyclohexane* ring, has the effect of diminishing the angle between the other two valencies, thus bringing the two $\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ groups attached to the quaternary carbon atom into closer proximity. This facilitates the closing of a trimethylene ring, and, moreover, the

spiro-compound so produced is more stable than the corresponding trimethylene derivative, caronic acid (III).

It is obvious that this effect should be even more marked in the case of a compound in which two of the valencies of the quaternary carbon atom are forced still farther apart by participating in the formation of a seven- or eight-membered ring, the angle in these cases being, according to Baeyer's strain theory, $128^\circ 34'$ and 135° respectively.

The interest attaching to the question has led the present authors to study the best conditions for the preparation of *cyclo*-

heptanediacetic acid (IV), which would serve as the starting point in an investigation of the problem.

From analogy to similar acids containing five- or six-membered rings, it was thought that the desired acid could be readily obtained by condensing suberone with cyanoacetamide by Thole and Thorpe's method (T., 1911, **99**, 422) and hydrolysing the product, or with ethyl cyanoacetate and ammonia in alcoholic

solution by Guareschi's method (compare Kon and Thorpe, T.,

1919, **115**, 686), the latter product being also readily hydrolysed to the acid.

The necessary quantity of suberone was therefore prepared, but it was found that this ketone failed to react with cyanoacetamide under the conditions used by Thole and Thorpe in similar cases.

Guareschi's method was therefore adopted, but it was found that a yield of scarcely 15 per cent. of the theoretical was the best that could be obtained under the different conditions tried, and it generally amounted to about 10 per cent. only.

The reason of the unsatisfactory yields is at present without explanation. It may be due to the solubility of the ammonium salt of the dicyano-imide, which is not precipitated from the alcoholic solution, as is the case in other condensations of a similar nature; but it is also conceivable that the effect of a seven-membered ring may be to inhibit the closing of a piperidine ring, in the same way and for the same reason as it may be expected to facilitate the formation of a three-membered ring, that is, by reducing the angle between the two valencies of the quaternary carbon atom which do not take part in the formation of the seven-membered ring.

An examination of the mother liquor from the original condensation has led to the discovery, in addition to cyanoacetamide and unchanged ketone, of a compound apparently formed from one molecule of the former and two molecules of the latter by the

elimination of two molecules of water, doubtless in accordance with the following scheme:

although the experimental data are as yet insufficient to establish the constitution with certainty.

An examination of the main condensation product showed that it was formed in the usual manner from one molecule of the ketone reacting with two molecules of cyanoacetamide (see p. 640). It possessed the usual properties of such compounds, crystallised well, and gave on treatment with cold concentrated sulphuric acid the diamide,

On complete hydrolysis by means of boiling 85 per cent. sulphuric acid, a fair yield of *cycloheptanediacetic acid* was obtained from the imide.

The acid, which melts at 156—157°, greatly resembles its homologues, *cyclohexanediacetic acid* (Thole and Thorpe, *loc. cit.*, p. 445) and *cyclopentanediacetic acid* (Kon and Thorpe, *loc. cit.*, p. 700), and was characterised by the formation of its *anhydride* and *semianilide*, which crystallise very readily.

EXPERIMENTAL.

Preparation of Suberic Acid.

Markownikov's method (*Ber.*, 1894, **26**, 3089) was followed. One hundred kilos. of dilute nitric acid (D 1.25) were gradually added to 50 kilos. of castor oil contained in a large steam-jacketed pan; each addition of the acid caused considerable frothing, so that the operation occupied several days; the contents of the pan were finally heated for another day.

The aqueous layer was then syphoned out, and the gummy oil repeatedly extracted with boiling water. The combined aqueous solutions were evaporated to dryness, yielding about 5 kilos. of a dark solid still contaminated with oily matter.

The whole quantity was purified by dissolving it in water, boiling with animal charcoal (500 grams of crude acid, 750 c.c. of water, and 40 grams of animal charcoal), rapidly filtering, and allowing to crystallise. The solid so obtained was sandy in appearance and melted indefinitely between 110° and 130° ; the quantity was 3000 grams, which includes some recovered by extracting the charcoal with hot water.

Preliminary experiments showed that Markownikov's method of separating suberic and azelaic acids by means of ether (*loc. cit.*) was extremely tedious and unsatisfactory, and an attempt was made to find a simpler method. This was ultimately achieved, enabling sufficiently pure suberic acid to be produced in one operation.

Three hundred grams of mixed acids, purified as above, are suspended in 1500 c.c. of boiling benzene and brought into solution by adding absolute alcohol (about 390 c.c. were usually required). On cooling, almost pure suberic acid, melting at 136 — 138° , separates out, and can be used for the preparation of suberone without further purification.

A second crystallisation is sufficient to give pure, although still somewhat coloured, suberic acid, melting at 139 — 140° (Found: C=55.01; H=7.83. $C_8H_{14}O_4$ requires C=55.18; H=8.05 per cent.).

The separation of the acid was usually hastened by leaving the vessel in a cool place overnight, and it was found that the yield varied somewhat with the temperature, but was usually about 120 grams; if it was much higher, the quality of the product was inferior.

The mother liquors from the first crop of suberic acid were evaporated to half their bulk and allowed to crystallise again; from the solid which separated, more suberic acid could be obtained by repeating the process described above. The total amount of suberic acid produced in this way was 1500 grams.

The combined mother liquors on evaporation yielded a residue, from which, after removing the oily impurities by rubbing twice with dry ether and pressing on porous plates, azelaic acid could be obtained in a state of purity by repeated crystallisation from water (m. p. 106° ; Found: C=57.42; H=8.30. $C_9H_{16}O_4$ requires C=57.44; H=8.51 per cent.), but the quantity was rather small (200 grams).

Preparation of Suberone.

The catalytic process of the Farbenfabriken vorm. F. Bayer & Co. (D.R.-P. 256622), which was found to give such excellent

results in the case of adipic acid (Kon and Thorpe, *loc. cit.*), could not be applied to suberic acid, the latter distilling unchanged; the modification involving the use of iron filings instead of baryta as a catalyst was also unsatisfactory. The following method was finally adopted.

The suberic acid was converted through its ammonium salt into the calcium salt, using a 20 per cent. excess of lime. The salt was carefully dried at 100° and distilled in portions of not more than 28 grams at a time.

The best vessel for the purpose was found to be a 500 c.c. conical flask suspended in an iron saucepan serving as an air-bath, and provided with an asbestos cover perforated to allow the neck of the flask to protrude.

The flask was provided with a cork with two tubes passing through. One of these enabled a current of an inert gas to be circulated through the apparatus, whilst the other, which penetrated half way down into the flask and consisted of capillary tubing (compare Young, T., 1891, **59**, 621), served as a still-head, and was connected to the condenser. This arrangement minimises the decomposition, which is caused by the distillate dropping back on to the hot calcium salt in the flask.

Four such sets of apparatus enabled 1400 grams of suberic acid to be worked up in a few days.

The crude distillate was separated from the small amount of water and fractionated, the fractions obtained from the total amount of suberic acid being as follows:

(1).....	Below 100°	8 grams
(2).....	100—160°	15 "
(3).....	160—174	21 "
(4).....	174—183	362 "
(5).....	183—190	31 "
(6).....	190—200	26 "
(7).....	200—240	20 "

Fraction (4) was pure enough to condense with ethyl cyanoacetate. An attempt was made to purify fraction (5) through the semicarbazone, but this led to loss; the bisulphite method, however, proved very satisfactory, and a further 50 grams of pure suberone were obtained from the fractions of high and low boiling points.

Condensation of Suberone with Ethyl Cyanoacetate: ω-Imide of aa₁-Dicyanocycloheptane-1:1-diacetic Acid (V, p. 640).

As already mentioned in the introduction, only a very poor yield of the above condensation product could be obtained by the Guareschi method, and the ketone, which had failed to react, had to be recovered by a long and tedious process.

The best results were obtained as follows: 44 grams of suberone,

90 grams of ethyl cyanoacetate, and 200 c.c. of saturated alcoholic ammonia were mixed and kept in a stoppered bottle for three days. The mixture deposited a certain amount of cyanoacetamide and assumed a deep yellow colour. It was mixed with about 800 c.c. of water, and the aqueous layer twice extracted with ether and acidified, when 11 grams of a crystalline solid were precipitated, and 1.5 grams were recovered by evaporating the mother liquor to half its bulk.

On recrystallisation from dilute alcohol, the compound is obtained in colourless, sparkling plates melting at $203.5-204^{\circ}$:

0.1133 gave 0.2637 CO_2 and 0.0646 H_2O . $\text{C}=63.71$; $\text{H}=6.34$.

0.1045 „ 15.95 c.c. N_2 at 19.5° and 757.7 mm. $\text{N}=17.38$.

$\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}_3$ requires $\text{C}=63.64$; $\text{H}=6.17$; $\text{N}=17.14$ per cent.

ω -Imide of $\alpha\alpha_1$ -Dicarbamylcycloheptane-1:1-diacetic Acid
(VII, p. 641).

If the above dicyano-imide is dissolved in ten times its weight of cold concentrated sulphuric acid, and the solution, after remaining for twenty-four hours, is poured on ice, a crystalline solid is gradually deposited. It forms transparent prisms blackening at 295° and decomposing without melting at about 305° :

0.0914 gave 11.9 c.c. N_2 at 19.5° and 765.6 mm. $\text{N}=14.98$.

$\text{C}_{13}\text{H}_{19}\text{O}_4\text{N}_3$ requires $\text{N}=14.94$ per cent.

It is very sparingly soluble in all solvents, but can be recrystallised from a large quantity of acetic acid.

cycloHeptane-1:1-diacetic Acid (IV, p. 639).

Twenty grams of the dicyano-imide are dissolved in 70 c.c. of concentrated sulphuric acid, 15 c.c. of water are added, and the solution is gently heated on a sand-bath until a vigorous evolution of carbon dioxide begins; the temperature is then kept steady for about an hour until the reaction slackens, when the liquid is allowed to cool; 50 c.c. of water are then added, and the solution is boiled under reflux for five hours. When cold, the solution is diluted with water and repeatedly extracted with ether, the acid being removed from the ether by shaking with sodium carbonate solution; it is precipitated when the latter is acidified (13.5 grams).

The acid obtained in this way crystallises well from dilute alcohol in long, flattened needles, which melt at $156-157^{\circ}$. It is very sparingly soluble in water or benzene, differing in the latter property from the isomeric methylcyclohexanediactic acids, which are appreciably more readily soluble in benzene:

0.1282 gave 0.2902 CO_2 and 0.0980 H_2O . $\text{C}=61.73$; $\text{H}=8.49$.

$\text{C}_{11}\text{H}_{18}\text{O}_4$ requires $\text{C}=61.64$; $\text{H}=8.46$ per cent.

A neutral solution of the ammonium salt of the acid gives no precipitate with a normal solution of barium chloride. With calcium chloride, a precipitate is obtained on boiling the solution, and this does not redissolve on cooling or adding water.

The *silver* salt is obtained as a curdy precipitate on adding a solution of silver nitrate to a neutral solution of the ammonium salt. It is very sparingly soluble:

0.3025 gave 0.1515 Ag. $\text{Ag} = 50.08$.

$\text{C}_{11}\text{H}_{17}\text{O}_4\text{Ag}$ requires $\text{Ag} = 50.42$ per cent.

The *anhydride* is readily formed by the action of boiling acetyl chloride on the acid, and crystallises in large laminae as the reagent evaporates. It separates from light petroleum (b. p. $60-80^\circ$) in iridescent plates melting at $75-76^\circ$, and is slowly reconverted to the acid on boiling with water:

0.1189 gave 0.2940 CO_2 and 0.0883 H_2O . $\text{C} = 67.41$; $\text{H} = 8.25$.

$\text{C}_{11}\text{H}_{16}\text{O}_3$ requires $\text{C} = 67.35$; $\text{H} = 8.22$ per cent.

The *semianilide* is prepared by boiling a benzene solution of the anhydride with aniline for a few minutes. It crystallises on evaporating off the benzene, and can be purified by recrystallisation from dilute alcohol. It forms small plates melting at $139.5-140^\circ$:

0.1321 gave 0.3409 CO_2 and 0.0957 H_2O . $\text{C} = 70.37$; $\text{H} = 8.05$.

$\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$ requires $\text{C} = 70.53$; $\text{H} = 8.01$ per cent.

The *imide* of cycloheptanediactic acid,

is formed as a by-product in the hydrolysis of the dicyano-imide, and can be obtained by evaporating the ether used for extracting the acid after the latter has been removed by means of sodium carbonate solution. The solid residue crystallises extremely well from benzene, and is obtained in large, iridescent plates melting at $177-178.5^\circ$:

0.1202 gave 8.0 c.c. N_2 at 20.0° and 757.1 mm. $\text{N} = 7.55$.

$\text{C}_{11}\text{H}_{17}\text{O}_2\text{N}$ requires $\text{N} = 7.18$ per cent.

*Examination of the Mother Liquors from the Original
Condensation (Compound VI, p. 641).*

The ethereal extract containing unchanged suberone is reduced to a small bulk by distillation on a steam-bath, using an efficient fractionating column to prevent loss of ketone. The residue in the flask is treated with a concentrated solution of sodium hydrogen sulphite, which rapidly combines with the ketone; the solid compound is isolated by filtration, purified by grinding with ether, and

yields, on decomposition with alkali, the ketone in a state of purity; about one-fifth to a quarter of the original amount is recovered in this way.

The ethereal washings are added to the filtrate from the hydrogen sulphite compound, which contains mainly cyanoacetamide, in addition to oily impurities. On prolonged keeping, a small quantity of a very sparingly soluble solid separates, and can be purified by recrystallisation from much alcohol, separating from this solvent in prisms melting at 187° :

0.1367 gave 0.3745 CO_2 and 0.1078 H_2O . $\text{C}=74.71$; $\text{H}=8.76$.

0.1581 „ 14.8 c.c. N_2 at 22.0° and 748.8 mm. $\text{N}=10.40$.

$\text{C}_{17}\text{H}_{24}\text{ON}_2$ requires $\text{C}=74.94$; $\text{H}=8.89$; $\text{N}=10.29$ per cent.

On boiling for ten minutes with concentrated hydrochloric acid, this compound is transformed into a semi-solid mass which solidifies on cooling. On crystallisation from dilute alcohol, this is obtained in small plates melting sharply at 137° . It is much more readily soluble in alcohol than the former compound, with which it is isomeric:

0.1482 gave 0.4973 CO_2 and 0.1159 H_2O . $\text{C}=74.94$; $\text{H}=8.69$.

0.1606 „ 14.6 c.c. N_2 at 21.3° and 775.2 mm. $\text{N}=10.46$.

These compounds are still under investigation.

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