α-methyl-β-ethyl-acrolein show practically no tendency toward cyclic acetal formation under the experimental conditions used.

3. The unsaturated aldehydes containing chlorine attached to the α-carbon atom, namely, α-monochlorocinnamic aldehyde and α-monochlorocrotonaldehyde, give a yield of about 22% of the corresponding cyclic acetal. The greater tendency of these aldehydes to form cyclic acetals is probably due to the activating influence exerted by the negative chlorine atom on the carbonyl group.

4. The saturated aldehydes, *viz.*, phenyldichloropropionaldehyde and dichlorobutyraldehyde, show the normal tendency of saturated aldehydes to form cyclic acetals, the yields being 37 and 50%, respectively.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

SYNTHESIS OF CYCLOBUTANE ACIDS. I. NORPINIC ACID

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It is remarkable that while *cis*-cyclobutane-1,3-dicarboxylic acid,[1] methylcyclobutane[2] and 1,2-dimethylcyclobutane-3,4-dicarboxylic acid[3] have been synthesized from open-chain compounds, all attempts to effect cyclobutane ring closure in carbon chains having the *gem.*-dimethyl group as substituent have failed. This is particularly evident from the repeated failures to synthesize the well-known norpinic acid or 2,2-dimethylcyclobutane-1,3-dicarboxylic acid, which is a key acid formed in the oxidation of α- and β-pinene and some other terpene compounds. In an attempt to synthesize norpinic acid, Ganguly[4] found that ethyl α,α′-dibromo-β,β-dimethylglutarate did not react with methylene iodide in the presence of sodium to give the expected cyclobutane compound, while Vogel[5] showed that the disodium derivative of ethyl-β,β-dimethyl-α-cyanopropane-α,α′,α′-tricarboxylate failed to give a ring compound when treated with methylene iodide. Clemo and Welch[6] failed to get a cyclic compound from an attempted condensation of maleic or fumaric ester and dimethylketene, and further showed that the disodium derivative of β,β-dimethylpropane-α,α,α′,α′-tetracarboxylic ester did not react with methylene iodide to give a cyclobutane compound, as expected. Prior to the publication of Clemo

[1] Bottomley and Perkin, *J. Chem. Soc.*, **77**, 298 (1900); Simonsen, *ibid.*, **93**, 1778 (1908).

[2] Perkin, *ibid.*, **53**, 201 (1888).

[3] Vogel, *ibid.*, **129**, 1986 (1927).

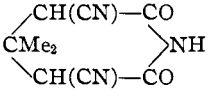
[4] Ganguly, *J. Ind. Inst. Science*, **5**, 23 (1922).

[5] Vogel, *J. Chem. Soc.*, **130**, 2010 (1928).

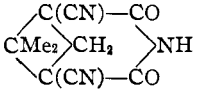
[6] Clemo and Welch, *ibid.*, **130**, 2621 (1928).

and Welch's experiments[6] the author had also failed to get ring closure between methylene iodide and the same disodium derivative used by these authors. In spite of the failure of Ganguly's experiment[4] with β,β-dimethyl-α,α-dibromoglutaric ester, it seemed probable that α,β,β-trimethyl-α,α'-dibromoglutaric ester, as a result of the position of its additional methyl group, might react with methylene iodide in the presence of sodium to give the ester of caryophyllenic acid or 2,2,1-trimethylcyclobutane-1,3-dicarboxylic ester, but the products of this reaction were unsaturated esters, with no evidence of ring formation.

In view of these discouraging results with open-chain compounds, it was thought that if an easily ruptured six-membered ring were first formed, the spacial configuration of the atoms might be more prone to the formation of four-membered rings, and this proved to be the case. The six-membered ring chosen was Guareschi's[7] imide, α,α'-dicyano-β,β-dimethylglutarimide (I) and it was found that the sodium derivative of this compound reacted with methylene iodide to give a 70% yield of the dicyclic imide (II). It



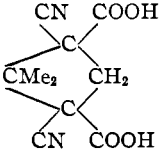
I



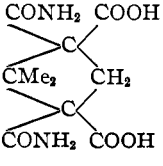
II

is interesting to note that in spite of the number of ways in which sodium derivatives of (I) might react with methylene iodide, cyclobutane ring formation took preference. The proof of the constitution of (II) was established by its hydrolysis to glutaric acid, by the formation of a mono-silver salt, and by determination of its molecular weight.

Hydrolysis of the dicyclic imide (II) by sulfuric acid at temperatures ranging from 80 to 140° ruptured the cyclobutane ring with the formation of varying quantities of glutaric acid and of phorone, which was undoubtedly formed from acetone produced by the disruption of the ring and the addition of water. Treatment of (II) with 100% phosphoric acid or with nitrous acid failed to produce a nitrogen-free acid. On the other hand, dilute alkali produced about equal quantities of *sym.*-dicyanonorpinic acid (III) and *sym.*-dicarbamylnorpinic acid (IV) when boiled with the imide.



III

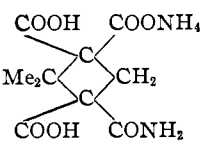


IV

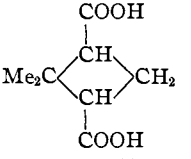
Although *sym.*-dicarbamylnorpinic acid can be heated with four molecular equivalents of sodium hydroxide without hydrolysis taking place, both (III) and (IV) are hydrolyzed to the corresponding 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid (V) by concentrated alkali. A

[7] Guareschi, *Atti. accad. sci. Torino*, **34**, 928 (1899).

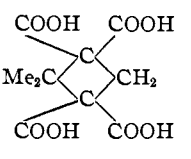
point of particular interest in regard to (IV) is the conversion of one of the carbamyl groupings to the corresponding ammonium salt by the addition of a molecule of water. Pure *sym.*-dicarbamylnorpinic acid, when dissolved in boiling water and the solution evaporated, leaves a white, crystalline water-soluble compound which has the structure represented by (VI).



VI



VII



V

An acidified aqueous solution of (VI) deposits crystals of a water-insoluble acid containing nitrogen, m. p. 236°, which gives 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid on boiling with concentrated alkali, and is probably 1-carbamyl-2,2-dimethylcyclobutane-1,3,3-tricarboxylic acid. This compound is still being studied with a view to proving its structure definitely.

When 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid (V) is heated at 200 to 205°, until no further evolution of carbon dioxide takes place, an oil remains which solidifies. This substance proved to be *trans*-norpinic acid (VII), described by Perkin and Simonsen,[8] who prepared it from the *cis* modification, which is an oxidation product of pinene. *Trans*-norpinic acid softened at 138° and melted at 146°, after repeated recrystallization from water. It is easily soluble in water, ether, alcohol and acetone, and separates in hard nodules from either aqueous solution or hydrochloric acid.

Now that a satisfactory method has been found for the formation of substituted cyclobutane acids in good yield, that is, by the condensation of substituted α,α'-dicyanoglutarimides with methylene iodide and hydrolysis of the resulting dicyclic compounds, the syntheses of other cyclobutane acids are under investigation, especially that of 2,2,1-trimethylcyclobutane-1,3-dicarboxylic acid, known as caryophyllenic acid and which is a key product in the oxidation of caryophyllene. Up to the present neither the structure of caryophyllenic acid nor of caryophyllene has been definitely determined.

Experimental

Ethyl α,α'-Dibromo-α,β,β-trimethylglutarate.—This was prepared by the method of Pandya and Thorpe.[9] Attempted condensation of the dibromo ester with methylene iodide in the presence of sodium failed, the product of the reaction being a mixture of unsaturated esters.

β,β-Dimethylpropane-$\alpha,\alpha,\alpha',\alpha'$-tetracarboxylic Ester.—On preparing this ester

[8] Perkin and Simonsen, *J. Chem. Soc.*, **95**, 1176 (1909).

[9] Pandya and Thorpe, *ibid.*, **123**, 2852 (1923).

according to the method of Kötz,[10] the high yields claimed by this author could not be attained. Using ether, benzene, toluene and methyl alcohol in turn as solvent, methylene iodide was allowed to react with the disodium derivative of β,β-dimethylpropane-α,α,α',α'-tetracarboxylic ester, but the product proved to be a mixture of malonic ester, *iso*propylidene malonic ester and a small undistillable residue.

β,β-Dimethyl-α,α'-dicyanoglutarimide was prepared according to the instructions of Kon and Thorpe,[11] but yields of only 60% of pure imide could be obtained, instead of 75%, as claimed by Kon and Thorpe.[11]

Condensation of β,β-Dimethyl-α,α'-dicyanoglutarimide with Methylene Iodide.—To a solution of 7.2 g. (6 atoms) of sodium in 100 cc. of methyl alcohol was added 20 g. of the imide and the whole refluxed on the steam-bath for one-half hour. Forty-four g. (3 moles) of methylene iodide was added through the condenser and refluxing continued for one and one-half hours, when all the methylene iodide had gone into solution. After standing overnight the mixture was again heated for one hour, cooled and the reaction mixture poured into 200 cc. of water containing 20 cc. of concd. nitric acid. Dicyanonorpinimide at once separated, was isolated by filtration and washed in the filter funnel several times with ether to remove the considerable quantity of methylene iodide which collects with the precipitate. When dried on a porous plate a yield of 15.5 g. was found and on recrystallization from glacial acetic acid 12 g. of pure dicyanonorpinimide separated in fine rhomboidal plates, m. p. 305–306° (decomp.). An attempt to purify dicyanonorpinimide by neutralizing with alkali and acidification by hydrochloric acid failed, only a small quantity of the imide being reprecipitated. Dicyanonorpinimide is slightly acid to litmus and is insoluble in all the common organic solvents and in water. It dissolves readily in alkali and in ammonium hydroxide.

Anal. Calcd. for $C_{10}H_9O_2N_3$: C, 59.1; H, 4.4; N, 20.7. Found: C, 58.5; H, 4.6; N, 20.4. *Mol. wt.* Calcd.: 203. Found: 203, 209.

Silver Salt of Dicyanonorpinimide.—When ammoniacal silver nitrate is added to a solution of the imide in ammonium hydroxide, the mono silver salt separates slowly.

Anal. Calcd. for $C_{10}H_8O_2N_3Ag$: Ag, 34.8. Found: Ag, 34.2.

Action of Sulfuric Acid on Dicyanonorpinimide.—3.6 g. of dicyanonorpinimide was added to 5.4 cc. of sulfuric acid and then 1 cc. of water. After heating on a sand-bath at 135° until all evolution of carbon dioxide had ceased, 1.8 cc. of water was added and heating continued at 140° for one hour. The cooled mixture was diluted with water and by extraction with ether six times an oil resulted which soon crystallized. This on recrystallization from hot benzene melted at 98–99° and was proved to be glutaric acid from a mixed melting point and analysis.

Anal. Calcd. for $C_5H_8O_4$: C, 45.5; H, 6.1. Found: C, 45.3; H, 6.3.

In the hope of obtaining norpinic acid, the imide was hydrolyzed as above by sulfuric acid, but the temperature was maintained at 100° throughout. Glutaric acid was again formed. At 80° sulfuric acid produces a very small yield of an acid containing nitrogen which was not identified. From the action of alkaline hydrogen peroxide on the imide no definite products could be isolated.

Preparation of *Sym.*-dicyanonorpinic Acid and *Sym.*-dicarbamylnorpinic Acid.—Dicyanonorpinimide on treatment with dilute alkali gives both *sym.*-dicyanonorpinic acid and *sym.*-dicarbamylnorpinic acid, the yield of the latter increasing with prolonged heating of the reaction mixture. The yellow solution obtained by dissolving 10 g. (1 mole) of dicyanonorpinimide in 180 cc. of 2.15% sodium hydroxide (slight excess over 2 moles) on heating gives off ammonia. At the end of two hours the solution was con-

[10] Kötz, *J. prakt. Chem.*, [2] **75**, 498 (1907).

[11] Kon and Thorpe, *J. Chem. Soc.*, **119**, 818 (1919).

centrated to half its bulk, acidified with sulfuric acid and 25 cc. of concentrated sodium sulfate solution was added. A white, crystalline solid separated from solution in flat plates, which when filtered, washed well with ice cold water and dried had a m. p. of 190° (decomp.). This was pure *sym.*-dicarbamylnorpinic acid; yield, 5.0 g.

Anal. Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.5; H, 5.4; N, 10.85. Found: C, 46.8; H, 5.5; N, 10.75. Equivalent (by Ag salt method): 127.5. Calcd. equivalent: 129.

The acid filtrate above was extracted six times with ether and on concentrating the dried ethereal extracts a solid separated. This can be crystallized from glacial acetic acid but separates from this solvent with one molecule of acetic acid attached. It is best recrystallized from a mixture of ether and petroleum ether (40–60°) and separates in small, hard nodules, m. p. 225–226° (decomp.). This was *sym.*-dicyanonorpinic acid; yield, 4.0 g.

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.0; H, 4.5; N, 12.6. Found: C, 53.9; H, 4.6; N, 12.5. Calcd. equivalent, 111. Found: equivalent (from silver salt): 111.

The dimethyl ester of *sym.*-dicyanonorpinic acid can be prepared by refluxing the dried silver salt of the acid with excess of methyl iodide in ether solution for twelve hours. The ether solution on filtration and concentration gives the solid dimethyl ester, which may be purified by recrystallization from ether and separates in short prisms, m. p. 139–140°.

Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.6; H, 5.6. Found: C, 57.8; H, 5.7.

Action of Water on *Sym.*-dicarbamylnorpinic Acid.—Although this substance is quite insoluble in cold water, it was found that it readily dissolves on heating, but the substance recovered by evaporation of the solvent was found to be a totally different compound, being soluble in water and chlorohydrin and giving off ammonia in the cold on grinding with sodium hydroxide, whereas the dicarbamylnorpinic acid has none of these properties. That one of the dicarbamyl groups passed over to the corresponding ammonium salt was shown by analysis of the compound and the existence of two equivalents.

Anal. Calcd. for $C_{10}H_{16}O_7N_2$: N, 10.15. Found: N, 10.21. Calcd. equivalent (by silver salt): 92; by titration with potash: 138. Found equivalent: 92; by titration with potash: 138.

On acidification of an aqueous solution of this mono-ammonium salt with dilute sulfuric acid, a precipitate of a water-insoluble acid comes down slowly. This acid is soluble in ether and, though not definitely identified, is most probably 1-carbamyl-2,2-dimethylcyclobutane-1,3,3-tricarboxylic acid, since it also gives 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid on further hydrolysis with concentrated alkali.

Preparation of 2,2-Dimethylcyclobutane-1,1,3,3-tetracarboxylic Acid.—When 0.75 g. (1 mole) of *sym.*-dicarbamylnorpinic acid was heated with 0.52 g. (4.5 moles) of sodium hydroxide under reflux for one and a half hours and then acidified, a precipitate at once was formed. This when washed well with water and dried had a melting point of 185–190° and was unchanged dicarbamylnorpinic acid; yield, 0.5 g. However, when 3.7 g. of *sym.*-dicarbamylnorpinic acid was refluxed with 50 cc. of 10% sodium hydroxide solution for nine hours, acidified with sulfuric acid and extracted five times with ether, an oil was found which slowly solidified. The solid was partially purified by filtering its aqueous solution and boiling down the filtrate to dryness. It can be purified by recrystallization from a mixture of acetone and benzene, being very soluble in the former. When pure, 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid melts at 200° and is very soluble in water, acetone and alcohol, but insoluble in benzene, chloroform and petroleum ether. The equivalent of this acid is difficult to determine, as a very indefinite end-point is experienced on direct titration with alkali and the silver salt tends

to be explosive on heating. By mixing the silver salt with a little pure cane sugar before heating, an equivalent was found.

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.15; H, 4.6. Found: C, 46.4; H, 4.7. Calcd. equivalent: 65. Found: 66.

Tetramethyl Ester of 2,2-Dimethylcyclobutane-1,1,3,3-tetracarboxylic Acid.—This ester can be made by refluxing the silver salt of the acid with excess of methyl iodide in ether solution for twelve hours. The filtered ether solution gave an uncrystallizable oil which distilled with slight decomposition at 100° (25 mm.).

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.1; H, 6.3. Found: C, 53.4; H, 6.4.

The Action of Alkali on *Sym.*-dicyanonorpinic Acid.—When heated for six hours under reflux a solution of 2.0 g. of dicyanonorpinic acid in 25 cc. of 20% caustic soda ceased to evolve ammonia. The mixture was acidified with sulfuric acid and extracted six times with ether; by concentrating the dried ether extracts an oil remained which solidified. This on purification gave a melting point of 200° and was proved to be 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid by a mixed melting-point determination; yield, 1.2 g.

Preparation of *Trans*-norpinic Acid.—When 3.5 g. of 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid was maintained at 200–205° for half an hour, all evolution of carbon dioxide ceased. On cooling, the dark yellow oil solidified. This was dissolved in water, filtered and concentrated to small bulk on the water-bath. Crystals which softened at 132° and melted at 140° separated, and these after two further recrystallizations from aqueous solution yielded a substance which softened at 138° and melted at 146°. This is without doubt *trans*-norpinic acid, described by Perkin and Simonsen,[8] who prepared it from *cis*-norpinic acid by heating with hydrochloric acid, and who record that it softens at 137 and melts at 144°. In agreement with Perkin and Simonsen it was found that *trans*-norpinic acid separates in hard nodules from concd. hydrochloric acid.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.8; H, 6.9. Found: C, 56.0; H, 6.9.

This opportunity is taken to express thanks to Professor M. Gomberg, who not only granted every facility for this research, but also gave the benefit of his very wide experience in the experimental problems which arose in this investigation. To the Commonwealth Fund the author is also indebted for a Fellowship during the tenure of which this work was carried out.

Summary

1. The syntheses of *trans*-norpinic acid, dicyanonorpinic acid, dicarbamylnorpinic acid and 2,2-dimethylcyclobutane-1,1,3,3-tetracarboxylic acid are described.

2. The synthesis of a new type of bicyclic imide, dicyanonorpinimide, is described.

3. A method capable of general application has been found for the synthesis of substituted cyclobutanedicarboxylic acids.

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