Mol. wt.: subs., 0.0090; camphor, 0.0893; depression, 15°. Calcd. for $C_{20}H_{26}$: mol. wt., 264. Found: 263.

Dibenzyltetramethylethane is very soluble in ether, moderately soluble in alcohol and ethyl acetate. It is unaffected by treatment with sodium-potassium alloy in dioxane at 100°. On heating 0.133 g. of the substance with alloy in dioxane at the boiling point for ten minutes no color was developed and on working up the products over 90% of the ethane was recovered unchanged.

Summary

1. Sodium-potassium alloy was found to be without action on diphenyldimethylethane, diphenyldibutylethane, diphenyl-di-*iso*propylethane and diphenyl-di-*tert.*-butylethane. The last three hydrocarbons are new.

2. Propylstyrene and dimethylstyrene add sodium and potassium alloy and undergo condensation. By the action of carbon dioxide derivatives of adipic acid were formed. The action of water on the metallic compound from dimethylstyrene yielded a hexa-alkyl ethane (dibenzyltetramethylethane).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE SYNTHESIS OF α,β,γ-TRIMETHYLGLUTARIC ACID

BY FRANCIS EARL RAY

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Introduction

In 1913 Noyes and Littleton[1] studied the decomposition of the methyl ester of *iso*-aminocamphonanic acid with nitrous acid. The only product isolated was the *cis*-camphonololactone. Later Noyes and Skinner[2] studied the same reaction and fractionated the decomposition products under reduced pressure. The fraction boiling at 86–88° (21 mm.) contained unsaturated acids. It was saponified and submitted to oxidation with alkaline permanganate, giving an acid which lost carbon dioxide at its melting point and supposedly formed α,β,β-trimethylglutaric acid.

Dr. Friedrich Richter in revising Beilstein's "Handbuch" found that α,β,β-trimethylglutaric acid had been previously obtained by Balbiano[3] and synthesized by Perkin and Thorpe[4] and kindly called Professor Noyes' attention to the oversight. The α,β,β-trimethylglutaric acid had a melting point of 88–89°. In view of this discrepancy, it seems evident that the acid melting at 111° obtained by Noyes and Skinner was not the α,β,β-trimethylglutaric acid.

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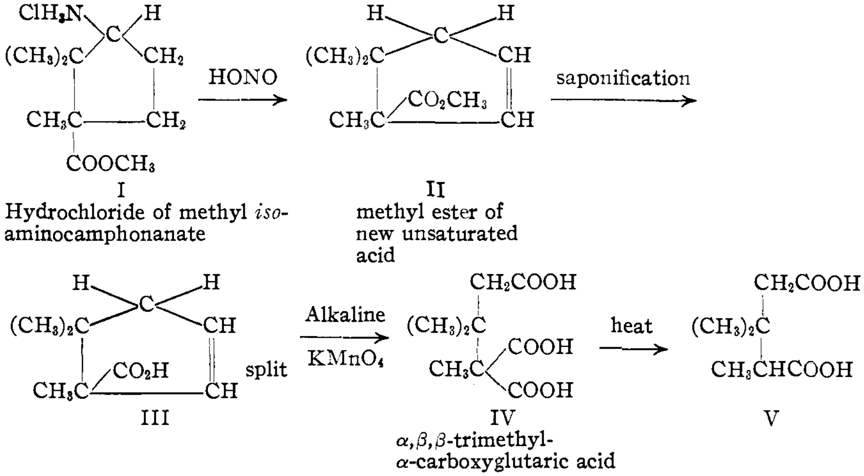
[1] Noyes and Littleton, THIS JOURNAL, **35**, 75 (1913).

[2] Noyes and Skinner, *ibid.*, **39**, 2692 (1917).

[3] Balbiano, *Ber.*, **27**, 2136 (1894); **28**, 1508 (1895).

[4] Perkin and Thorpe, *J. Chem. Soc.*, **75**, 65 (1899).

The formation and constitution of the compound obtained by Noyes and Skinner was explained by the following reactions



I
Hydrochloride of methyl *iso*-aminocamphonanate

II
methyl ester of new unsaturated acid

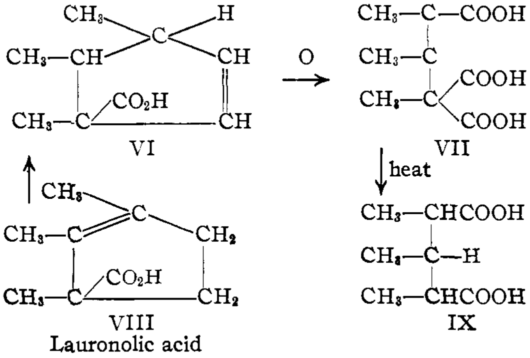
III

IV
α,β,β-trimethyl-α-carboxyglutaric acid

V

Discussion

It was thought possible, therefore, that the reaction involved a rearrangement similar to the shift of the methyl group observed in the formation of lauronolic acid, which was also obtained in this decomposition and isolated in a higher-boiling fraction. If a migration of one of the gem methyl groups to the adjacent primary carbon atom occurs during the decomposition with nitrous acid, the compound VI might be formed. On this assumption oxidation would give α,β,γ-trimethyl-α-carboxyglutaric acid, VII, which would split off carbon dioxide and give α,β,γ-trimethylglutaric acid, IX. A shift of the double bond in lauronolic acid, VIII, might also give VI.



VI

VII

VIII
Lauronolic acid

IX

A search of the literature failed to reveal the previous synthesis of α,β,γ-trimethylglutaric acid and its preparation was accordingly undertaken.

An attempt was made to prepare it by the Knoevenagel[5] reaction, which involved condensing 1 mole of acetaldehyde with 2 moles of malonic ester and then methylating the product in the α and γ positions. On hydrolysis with 1–1 hydrochloric acid, α,β,γ-trimethyl-α,γ-dicarboxyglutaric acid was obtained. This melted at 190° with decomposition. The liquid obtained by heating to split off carbon dioxide did not solidify and seemed by the wide range of its boiling point to be a mixture.

Other condensations tried were acetaldehyde and cyano-acetic ester, acetaldehyde and aceto-acetic ester, ethylidene chloride and cyano-acetic ester and ethylidene malonic ester and malonic ester. From all of these the tetracarboxylic acid was obtained but on decomposition the desired glutaric acid could not be isolated.

It was thought that the symmetrical character of the molecule militated against its successful decomposition. Accordingly, the attempt was made to prepare a derivative of an unsymmetrical nature. It might be supposed that such an acid would melt (with evolution of carbon dioxide) at a lower temperature than the tetracarboxylic acid and so avoid the profound change that seemed to take place when an attempt was made to split off carbon dioxide from the tetrabasic acid.

The synthesis adopted was as follows: ethylmethylacetic acid was prepared from malonic ester in the usual manner. This was brominated, and esterified and then unsaturated by boiling with quinoline. Cyano-acetic or malonic ester was condensed with this unsaturated ester by means of sodium ethylate. The product so obtained was methylated and hydrolyzed by prolonged boiling with potash. The α,β,γ-trimethyl-α-carboxyglutaric acid so obtained melted with evolution of carbon dioxide at 144° and the α,β,γ-trimethylglutaric acid, after repeated recrystallization, melted at 134°. A mixed melting point determination with Dr. Skinner's acid melted at 95–100°.

It seems, therefore, that the acid obtained by Noyes and Skinner was not α,β,γ-trimethylglutaric acid.

Dr. Richter has also called attention to an α,α,β-trimethylglutaric acid prepared by Perkin and Thorpe,[6] which has a melting point of 112°. The supposed α,β,β acid of Noyes and Skinner melted at 111°. The similarity of melting points suggested the preparation of the α,α,β compound. The acid obtained was not fully purified but on comparison with the compound supplied by Dr. Skinner by a mixed melting point, the two were found to be identical. Dr. Skinner in a private communication has expressed the opinion that during the decomposition of the α,β,β-trimethyl-α-carboxyglutaric acid, one of the β methyl groups migrates to the α position, forming α,α,β-trimethylglutaric acid.

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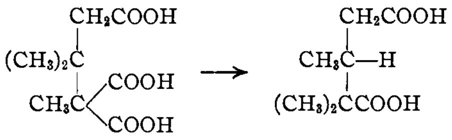
[5] Knoevenagel, *Ber.*, **27**, 2345 (1894); *Ann.*, **281**, 104 (1894).

[6] Perkin and Thorpe, *J. Chem. Soc.*, **71**, 1185 (1897).



X XI

Experimental Part

Ethylidene Dimalonic Ester.—One hundred and sixty g. of malonic ester and 22 g. of acetaldehyde, both freshly distilled, were mixed and cooled to 0°. Five g. of diethylamine was added slowly with stirring and the mixture allowed to stand overnight. It was heated for five to six hours and then twice distilled; b. p. 200–210° (20 mm.), 170–175° (1 mm.), yield 18–20 g.

α,β,γ-Trimethyl-α,γ-dicarboxyglutaric Ester.—The above-mentioned product was added to 2.6 g. of sodium dissolved in 28 cc. of absolute alcohol and then treated with 16 g. of methyl iodide. After heating for three to four hours on the water-bath the alcohol was distilled off and the ester extracted and distilled; b. p. 190–195° (2–3 mm.), yield about 5 g. Considerable tar always remained in the flask after the distillation.

α,β,γ-Trimethyl-α,γ-dicarboxyglutaric Acid.—Five g. of the ester was boiled over the free flame with 25 cc. of 1–1 hydrochloric acid for twenty-four hours. The tar was removed by filtration and the filtrate on concentration deposited the crystalline acid. After one recrystallization from alcohol it melted sharply at 190°.

Anal. Subs., 0.0414: 6.34 cc. of 0.1 N alkali. Calcd. for $C_{10}H_{14}O_8$: 6.34 cc. Subs., 0.0933: CO_2, 0.1585; H_2O, 0.0541. Calcd. for $C_{10}H_{14}O_8$: H, 5.38; C, 45.79. Found: H, 5.4; C, 46.3.

0.8662 g. of this tetracarboxylic acid was heated to 190–200° and the products were aspirated through calcium chloride and soda lime. After twenty-five minutes the weight of the carbon dioxide bulb became constant and showed a gain of 0.2750 g. or 31.75%; theoretical, 33.6%.

The liquid residue was boiled with a few drops of 1–1 hydrochloric acid to destroy any anhydride formed but no crystals were obtained on evaporation of the ether extract. On distillation the product boiled over a range of 142–180°. It was evidently a mixture of various products.

Bromo-ethylmethylacetic Acid.—Ethylmethylacetic acid was prepared from malonic ester in the usual manner. Fifty g. was obtained. One hundred and twenty g. of phosphorus pentachloride and 80 g. of bromine were used to brominate the acid. It was then esterified, washed and distilled. Ninety g. boiling at 75–80° (25 mm.) was obtained.

Tiglic Ester.—The bromo ester was boiled with 65 g. of quinoline for two hours and allowed to stand overnight. The unsaturated tiglic ester was decanted and distilled; yield, 35 g. boiling at 100° (30 mm.).

Condensation of Tiglic Ester and Cyano-acetic Ester.—Ten g. of tiglic ester and 15 g. of cyano-acetic ester were boiled with 0.25 g. of sodium in 4 cc. of absolute alcohol for eight hours. The mass was then poured into ice-cold, acidulated water, extracted, dried and distilled; yield 8 g. boiling at 150–170° (30 mm.).

Methylation of β,γ-Dimethyl-α-cyanoglutaric Ester.—This product was methylated by 0.7 g. of sodium dissolved in 15 cc. of absolute alcohol and 5 g. of methyl iodide. After extraction and distillation 6 g. of α,β,γ-trimethyl-α-cyanoglutaric ester was obtained boiling at 140–150° (1–2 mm.).

α,β,γ-Trimethyl-α-carboxyglutaric Acid.—The ester was hydrolyzed with 10 g. of potash dissolved in 10 cc. of water. It was heated on the water-bath and the evolved ammonia collected in acid. After forty-eight hours only about 50% of the theoretical amount of ammonia had been evolved. It was then boiled over a small flame for sixteen hours until over 90% of the calculated ammonia had been collected and no further appreciable amount was given off. Two methods of isolating the free acid were used with about equal success. The first consisted in acidifying and extracting with ether and the second in preparing the barium salt by adding a concentrated solution of barium chloride to the alkaline solution of the acid. The barium salt, which is less soluble in hot than in cold solution, was washed with hot water, acidified with hydrochloric acid, dried and extracted with alcohol. The extracts from both procedures on spontaneous evaporation were clear, colorless sirups which crystallized after standing for several days. It was difficult to find a suitable solvent for recrystallization. After many experiments a mixture of benzene and acetone was used. It was generally necessary to allow the solution to stand overnight before crystals were deposited. After several recrystallizations the acid melted at 144–145° with decomposition.

Anal. Subs., 0.0063: Ag, 0.0038. Calcd. for silver salt: 60.1. Found: 60.3. Subs., 0.0222: 2.55 cc. of 0.1 *N* alkali. Calcd. for $C_8H_{14}O_4$: 2.54.

α,β,γ-Trimethylglutaric Acid.—The α-carboxy acid, in a test-tube immersed in an oil-bath, was heated at 150–160° for twenty minutes to split off carbon dioxide. On cooling the mass solidified and after ten recrystallizations from benzene the melting point was raised from 107 to 134°.

Condensation of Tiglic Ester with Malonic Ester.—In a manner precisely similar to the foregoing 20 g. of tiglic ester was condensed with 30 g. of malonic ester and the product methylated; boiling point 181° (25 mm.).

Anal. Subs., 0.1093: H_2O, 0.0870; CO_2, 0.2412. Calcd. for $C_{15}H_{26}O_6$: H, 8.61; C, 60.0. Found: H, 8.83; C, 60.1.

The ester was hydrolyzed with concentrated potash but the acid did not crystallize. It was distilled to split off carbon dioxide and the anhydride so formed was hydrolyzed by warming with a few drops of dilute hydrochloric acid. On evaporation α,β,γ-trimethylglutaric acid melting at 134° was obtained.

α,α,β-Trimethylglutaric Acid.—This acid was prepared according to the methods given by Perkin and Thorpe.[4] The acid after twelve recrystallizations melted at 103–104°. Lack of material prevented its further purification. A mixture of approximately equal amounts of this α,α,β-trimethylglutaric acid and of Dr. Skinner's acid melted at 105°.

Conclusion

It seems probable that α,α,β-trimethylglutaric acid is formed from α,β,β-trimethyl-α-carboxyglutaric acid by a shift of one of the β-methyl groups to the α position upon loss of carbon dioxide, as Dr. Skinner suggests.

The writer wishes to express his sincere appreciation to Professor W. A. Noyes for the help and encouragement received during the progress of this investigation which was conducted in the latter's laboratory at Urbana, Illinois.

Summary

The decomposition of the methyl ester of *iso*-aminocamphonanic acid with nitrous acid gives a fraction boiling at 86–88° (21 mm.), which consists of unsaturated acids. On saponification and oxidation of this ma-

terial with alkaline permanganate and loss of carbon dioxide an acid was obtained by Noyes and Skinner which was thought to be α,β,β-trimethylglutaric acid.

The possibility of this acid being α,β,γ-trimethylglutaric acid has been eliminated by the synthesis of this compound and direct comparison with a sample of the original acid. The α,β,γ- is a new acid and completes the trimethylglutaric acid series.

It has been shown also that the compound obtained by Noyes and Skinner is α,α,β-trimethylglutaric acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

LOCAL ANESTHETICS DERIVED FROM β-PIPERIDYL CARBINOL

BY L. T. SANDBORN[1] WITH C. S. MARVEL

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Some of the molecular structures which produce local anesthetic action are very well known. Numerous compounds have been prepared in the attempt to find the best combination of high anesthetic value and low toxicity which is desirable for this type of drug. The earlier synthetic substitutes for cocaine were usually esters of cyclic amino alcohols; then with the discovery of novocaine the esters of open chain amino alcohols became more important. Recently McElvain[2] has shown that in a series with very closely related structures the closed ring derivatives are much more efficient in anesthetic action.

In connection with some other researches, a method for the preparation of β-piperidyl carbinol (II) was developed. The fact that it was a cyclic amino alcohol at once suggested its use for the synthesis of a compound which should have local anesthetic action. The very favorable properties which were shown by this substance led to a more complete study of the derivatives of β-piperidyl carbinol with a view to producing a drug that might have properties better than any of those now available. β-Piperidyl carbinol was obtained in about 43% yields by the reduction of ethyl nicotinate (I) with sodium and absolute alcohol. It was also obtained in 50% yields by a similar reduction of ethyl nipecotate, but the difficulties involved in the preparation of nipecotic ester make the former method more practical. It has the properties that would be expected of an amino alcohol of this type.

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[1] This communication is an abstract of a thesis submitted by L. T. Sandborn in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] McElvain, THIS JOURNAL, **46**, 1721 (1924).