

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.07; H, 8.64. Found: C, 73.87, 74.20; H, 8.67, 8.82.

Summary

1. Neonicotine (β -pyridyl- α -piperidine) was separated from the products obtained in the author's sodium-pyridine-oxygen reaction. Nicotimine, isolated by Pictet and Rotschky from the nicotine alkaloids and tentatively identified by them as the same product, is probably different.

2. The reduction of γ, γ -, β, γ -, α, α - and β, β -dipyridyls by tin and hydrochloric acid results in varying yields of the corresponding pyridylpiperidines. The ease of reduction is probably greatest with γ, γ , diminishing in the order given, β, β being the least easily reduced.

3. Attempted synthesis of neonicotine from α, β -dipyridyl usually resulted in isoneonicotine but further study is to be made to accomplish this end successfully.

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

THE α, α' -DIMETHYLSUBERIC AND α, α' -DIBROMO- α, α' -DIMETHYLSUBERIC ACIDS

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Satisfactory methods for the preparation of tetramethylene bromide (1,4-dibromobutane) have not been available until recent years, with the result that, although several α, α' -dialkyl substituted adipic² and pimelic³ acids have been synthesized, the corresponding derivatives of suberic acid (1,6-hexane-dicarboxylic acid) are unknown. Perkin⁴ used a crude mixture of tetra- and pentamethylene bromides on the sodium salt of malonic ester, but obtained from the action of the tetramethylene bromide only the closed chain compound, ethyl 1,1-pentamethylene-dicarboxylate. In the preparation of the dialkyl acids, one molecular proportion of the bromide was condensed with one of the sodium salt of malonic ester to give two products; one was the ester of a closed chain acid⁵ and the other the ester of a straight chain tetracarboxylic acid.⁶ The latter results from the action of one mole of bromide on two moles of malonic ester.

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² Lean, *J. Chem. Soc.*, 65, 1004 (1894).

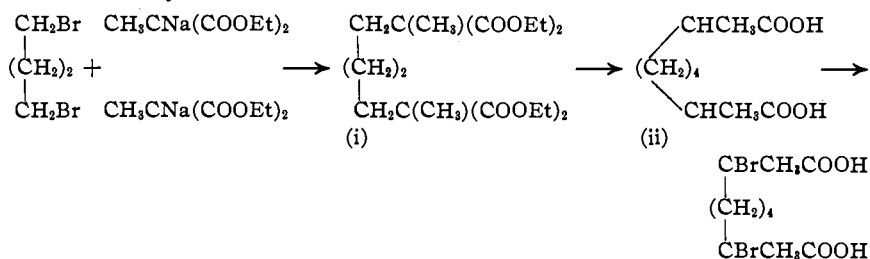
³ Perkin and Prentice, *ibid.*, 59, 829 (1891).

⁴ Perkin and Haworth, *ibid.*, 65, 88 (1894).

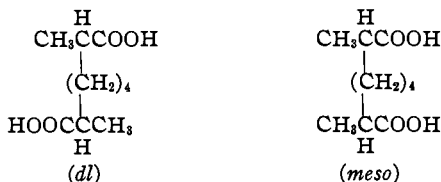
⁵ Ethyl trimethylene-dicarboxylate, Perkin, *ibid.*, 47, 807 (1885); ethyl tetramethylene-dicarboxylate, Perkin, *ibid.*, 51, 2 (1887).

⁶ Ethyl butane-tetracarboxylate, Perkin, *ibid.*, 51, 19 (1887); ethyl pentane-tetracarboxylate, Perkin, *ibid.*, 51, 241 (1887); Curtius, *J. prakt. Chem.*, [2] 94, 340 (1916).

The esters of the straight chain tetracarboxylic acids were then alkylated in the α, α' -positions by treating the disodium salt with an alkyl bromide.³ Hydrolysis of this product and heating to split off carbon dioxide gave the α, α' -substituted dibasic acids.^{2,3} A simpler method was used by Perkin⁷ in the preparation of α, α' -di-isobutylpimelic acid, in which he condensed trimethylene bromide with 2 moles of isobutylmalonic diethyl ester. The only other use made of this method in such syntheses was in the preparation of α, α' -dimethyladipic acid from ethylene bromide and monomethylmalonic diethyl ester.⁸



In the present investigation one molecular proportion of tetramethylene bromide was condensed with two of sodiomethylmalonic diethyl ester to give ethyl dimethylhexane-tetracarboxylate (i) in 40% yield. Hydrolysis of the ester gave the tetracarboxylic acid and on heating the latter to 240° α, α' -dimethylsuberic acid (ii) was obtained. This acid was found to exist in two isomeric forms, with melting points of 132–133° and 91–92°, respectively. One of these must be a racemic mixture (*dl*), and the other an internally compensated (or *meso*) form.



No attempt has yet been made to distinguish between the two forms.

The α, α' -disubstituted adipic acids exist in two forms;² of the corresponding pimelic series⁹ only α, α' -dimethoxypimelic acid has been separated, by crystallization of the amide.¹⁰ α, α' -Dibromosuberic acid,¹¹ prepared by the bromination of suberic acid, and α, α' -dimethoxysuberic acid¹¹ both exist in two forms, and α, α' -dimethoxyazelaic acid¹¹ was separated through the amides.

⁷ Perkin, *J. Chem. Soc.*, 59, 819 (1891).

⁸ Kitzing, *Ber.*, 27, 1578 (1894).

⁹ Perkin and Prentice, *J. Chem. Soc.*, 59, 820 (1891).

¹⁰ Hassell and Ingold, *ibid.*, 129, 1470 (1926).

¹¹ Goss and Ingold, *ibid.*, 129, 1473 (1926).

The fact that a dialkyl suberic acid also exists in two forms seems to indicate that the abnormality in the pimelic series is due to mechanical difficulty in separating the two isomers, and not to the existence of only one form of alkyl derivative, although it is surprising that six dialkyl derivatives, and the dibenzyl, dibenzal and dibromopimelic acids were all isolated as single compounds.

Bromination of α, α' -dimethylsuberic acid should result in an α, α' -dibromo- α, α' -dimethylsuberic acid. Treatment with red phosphorus and bromine, a method used successfully on suberic acid by Hell and Gantter,¹² surprisingly did not give the expected compound, but a mixture of partially brominated products, some of which were unsaturated. The dibromide, however, was obtained by the action of bromine on the acid chloride, as in the bromination of suberic acid by Ingold.¹¹

Both forms of α, α' -dimethylsuberic acid gave as the main product a dibromo acid, m. p. 200–210° *ex ethyl acetate* and although in both cases the crude mixture melted about 185°, a distinct crystalline second form was not obtained.

The original goal of this investigation was the preparation of *cis*-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride. This compound ought to be identical with deoxycantharidin, which is obtained from the naturally occurring drug cantharidin by the action of hydrogen bromide and subsequent reduction of this "dibromide" with zinc and acetic acid.¹³ Coffey¹⁴ prepared *cis*-cyclohexane-1,2-diacetic anhydride and *cis*-1,2-dimethylcyclohexane-4,5-dicarboxylic anhydride, these being the structures for deoxycantharidin derived from the other two possible formulas assigned to cantharidin. He found neither of these identical with the deoxycantharidin derived from the natural product but recorded no synthesis of the 1,2-dicarboxylic anhydride. In this work it was hoped to obtain it from dibromodimethylsuberic acid by the elimination of bromine and consequent formation of a cyclohexane ring, but treatment of both the bromo acid and its dimethyl ester with copper bronze or molecular silver met with no success.

Experimental Part

Preparation of Tetramethylene Bromide.—The simplest method recorded in the literature is that of Müller,¹⁵ who passed hydrogen bromide into tetramethylene glycol at 80°, using Böeseke's¹⁶ preparation of the latter by the reduction of diethyl succinate with sodium and alcohol. The glycol has been made in this Laboratory according to this method, with the modification that, after removal of the alcohol and toluene by distillation in steam, the residue was extracted continuously for forty-eight hours with

¹² Gantter and Hell, *Ber.*, **15**, 147 (1882).

¹³ Gadamer, *Arch. Pharm.*, **252**, 636 (1914); Rudolph, *ibid.*, **254**, 423 (1916).

¹⁴ Coffey, *Rec. trav. chim.*, **42**, 387, 1026 (1923).

¹⁵ Müller, *Monatsh.*, **49**, 27–30 (1928).

¹⁶ Böeseke, *Rec. trav. chim.*, **34**, 100 (1915).

ether and the glycol distilled, b. p. 148° (30 mm.). The bromination was carried out in a manner analogous to the preparation of trimethylene bromide¹⁷ except that the mixture was refluxed for eight hours instead of three. A 70% yield of distilled bromide was obtained, b. p. 106–110° (30 mm.).

Monomethylmalonic Diethyl Ester.—The action of either methyl iodide¹⁸ or methyl bromide¹⁹ on sodio-malonic ester gives a product which one cannot say with certainty is not contaminated with malonic or dimethylmalonic ester. Zane and Ingold²⁰ purified the product by hydrolysis, crystallization of the acid, and re-esterification. The method employed in this work was to convert ethyl α -bromopropionate to ethyl α -cyanopropionate, and to hydrolyze the nitrile. Zelinsky²¹ treated ethyl α -bromopropionate in absolute alcohol with potassium cyanide, heated and agitated the mixture with hot air for six hours and obtained a yield of 18% α -cyano ester; the main product of the reaction was dimethylcyanosuccinic ester. It was found by making a series of runs, using a steam-bath and a mechanical stirrer, that an optimum time existed for the yield of ethyl α -cyanopropionate and a correspondingly small amount of the succinic ester; the yield, based on the amount of α -bromo ester actually used in the reaction, was obtained as high as 43%.

To a boiling suspension of 144 g. of potassium cyanide in 195 g. of absolute alcohol was added, as rapidly as possible, 387 g. of ethyl α -bromopropionate (b. p. 158°), the mixture being mechanically stirred after about one-third of the ester had been added. Boiling was then continued for nine and a half hours, the mixture was cooled, filtered and the filtrate and washings poured into 2 liters of water. The oily product was washed and distilled under atmospheric pressure with the use of a 25–30 cm. fractionating column, when the following fractions were obtained

155–170°	Unreacted α -bromo ester	154 g.
170–185°	Intermediate fraction	10 g.
195–205°	Ethyl α -cyanopropionate	70.5 g.

A second distillation of the cyano ester gave a boiling range of 197–198°, the residue being succinic ester.

Hydrolysis and esterification of the nitrile were accomplished in one operation.²² A cold, thoroughly agitated solution of 127 g. of ethyl α -cyanopropionate in 196 g. of 95% ethyl alcohol was treated gradually with 196 g. of concd. sulfuric acid, then gently refluxed for seven hours, cooled and poured into 2 liters of water. The oily layer was washed with dilute sodium carbonate solution, and on distillation gave 118 g. (93%), b. p. 104–105° (27 mm.).

Ethyl Dimethylhexane-tetracarboxylate.—23.8 g. of metallic sodium was added to a solution of 180.5 g. of monomethylmalonic diethyl ester in 1 liter of absolute alcohol (magnesium dried) contained in a 3-liter, 3-necked flask fitted with a mechanical stirrer, condenser and dropping funnel. The mixture was warmed until a clear solution was obtained,²³ then treated with 112 g. of tetramethylene bromide, and refluxed for eighteen

¹⁷ Kamm and Marvel, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1921, Vol. I, p. 8.

¹⁸ Conrad, *Ann.*, **204**, 134 (1889).

¹⁹ Lucas and Young, *THIS JOURNAL*, **51**, 2536 (1929).

²⁰ Zane and Ingold, *J. Chem. Soc.*, **129**, 14 (1926).

²¹ Zelinsky, *Ber.*, **21**, 3162 (1888).

²² Compare conversion of benzoyl cyanide to ethyl phenyl acetate, Adams and Thal, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1922, Vol. II, p. 27.

²³ The sodium salt of methylmalonic diethyl ester is practically insoluble in toluene, so the use of this solvent, which was tried first, was discontinued.

hours. The alcoholic solution, decanted from the sodium bromide, and the washings were distilled to remove most of the alcohol; the residue, poured into water, gave an oil which, after being washed with water, was separated into the following fractions by distillation

90–125° (30 mm.)	35 g. water and unchanged ester
150–160° (6 mm.)	61.5 g. (a)
210–217° (6 mm.)	83 g. (b)

(a) is 3-butenyl monomethylmalonic diethyl ester,²⁴ and (b) is the required dimethylhexane-tetracarboxylate (40% yield).

Anal. Calcd. for $C_{20}H_{34}O_8$: C, 59.7; H, 8.45. Found: C, 59.53; H, 8.37.

Dimethylhexane-tetracarboxylic Acid and α, α' -Dimethylsuberic Acid.—Eighty-two grams of the ester [(b) above] was hydrolyzed by boiling with 90 g. of potassium hydroxide in 1 liter of 95% alcohol for fifteen hours with mechanical stirring. The solution, diluted with water, was taken to dryness in an evaporating dish, the residue taken up in the minimum amount of water, and refluxed for four hours with 180 cc. of concd. hydrochloric acid. Dilution with water and evaporation to dryness gave a mixture of potassium chloride and the tetrabasic acid, 58 g. (calcd. 60 g.) of the latter being isolated by five extractions with ether. It was not purified further, but heated in a metal-bath at 240° for twenty minutes (or until all the carbon dioxide was expelled), giving 38 g. (calcd. 41 g.) of crude dibasic acid.

The Two Isomeric Forms of Dimethylsuberic Acid.—The following method of separating the isomers was adopted. The dibasic acid was extracted five times with boiling water, the aqueous solutions decanted off the dark, oily material, and filtered hot through ordinary filter paper. The first fractions which separated had melting points in the range 100–118° (18 g. of crude) and these on five recrystallizations from boiling water gave small, colorless plates with constant m. p. 132–133° (first form). Second fractions from the original extracts gave similarly an additional 1 g.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.91. Found: C, 59.34; H, 8.79.

The other isomer was isolated from the fractions melting below 100° by first washing out oily material with cold ligroin, then dissolving in boiling ligroin and filtering from any insoluble material. The solution on cooling deposited crystals which on two recrystallizations gave 3.5 g. of small, glistening prisms, m. p. 91–92° (second form).

Anal. Calcd. for $C_{10}H_{18}O_4$: neut. equiv., 101. Found: 102.4.

Dimethylsuberic Diethyl Ester.—Forty grams of the crude acid was esterified in the usual manner; 43 g. of the diethyl ester was obtained (84%), b. p. 178–185° (25 mm.).

Bromination of α, α' -Dimethylsuberic Acid, First Form.—(a) An intimate mixture of 5 g. of acid (m. p. 132–133°) and 0.5 g. of red phosphorus was allowed to stand overnight with 6 cc. of bromine, then warmed gently and air blown through to remove excess bromine. On addition of water and warming to decompose the acid halide, partial carbonization took place and no pure compound was isolated.

(b) Eleven grams of the acid, 1.2 g. of red phosphorus and 12 cc. of bromine were allowed to stand overnight, then treated slowly with methyl alcohol; the solution was poured into a large volume of water, and extracted with ether. On distillation, the following fractions were obtained

²⁴ Compare the allyl compounds obtained by Kipping and Perkin, *J. Chem. Soc.*, 57, 32 (1890), and Perkin, *ibid.*, 59, 819 (1891).

(i) 4.2 g. 156–160° (30 mm.)	<i>Anal.</i> Found by Stepanov method: Br, 12.87
(ii) 4.3 g. 175–185° (30 mm.)	<i>Anal.</i> Found by Stepanov method: Br, 24.88
(iii) 1.3 g. 180–188° (12 mm.)	(Copious evolution of fumes)
Calcd. for $C_{12}H_{20}O_4Br_2$: dibromo acid:	Br, 41.18
Calcd. for $C_{12}H_{21}O_4Br$: monobromo saturated acid:	Br, 25.24
Calcd. for $C_{12}H_{18}O_4Br$: monobromo unsaturated acid:	Br, 26.05

(i) and (ii) did not decolorize permanganate immediately, but were oxidized by it on standing. (iii) decolorized permanganate immediately.

(c) α, α' -Dibromo- α, α' -dimethylsuberic Dimethyl Ester.—Thirteen grams of the acid of m. p. 132–133° was warmed with 11.2 cc. of thionyl chloride in a flask fitted with a ground-in water condenser until there was no further reaction; 10.4 cc. of bromine was then added gradually, the mixture kept hot on the steam-bath for eight hours, then cooled and treated with absolute methyl alcohol. On distillation 19.5 g. of ester was obtained (78%), b. p. 216–219° (30 mm.). It was colorless when freshly distilled, but turned brown on exposure to air.

(d) α, α' -Dibromo- α, α' -dimethylsuberic Acid.—Three grams of acid of m. p. 132–133° was treated as above with thionyl chloride and bromine. After standing overnight it was warmed with about 50 cc. of water until all the sirup had decomposed to a hard, crystalline mass. This was filtered off and washed with water: yield, 3.8 g., m. p. 177–193° with decomposition.

Anal. Calcd. for $C_{10}H_{16}O_4Br_2$: Br, 44.4. Found for crude acid: Br, 46.9.

On two recrystallizations from ethyl acetate the acid had the constant m. p. 200–201°. The original mother liquor, when taken to dryness, gave 1 g. of partially crystalline material which could not be recrystallized from any of the ordinary solvents.

Second Form. Bromination of Second Form of Dimethylsuberic Acid.—Two and one-half grams (m. p. 91–92°) was brominated in the manner outlined above. The crude product consisted of 3.9 g. of m. p. 194–196°, and on recrystallization from ethyl acetate 2 g. was obtained, m. p. 200–201°; this gave a mixed melting point with the acid melting at 200–201° from (d) of 200–201°. The initial mother liquors gave 1.2 g. of sirupy material on evaporation to dryness.

Anal. Calcd. for $C_{10}H_{16}O_4Br_2$: Br, 44.4. Found for pure acid: Br, 44.4.

Attempts at Ring Closure.—(a) A mixture of 10 g. of copper bronze and 18.6 g. of ester on heating to 140° appeared to boil suddenly and evolved copious fumes. When the mass was cooled, extracted with alcohol and distilled, only low-boiling fractions were obtained and no definite compound was isolated.

(b) When a suspension of copper bronze in a solution of 2 g. of the acid in nitrobenzene was heated to 160°, the liquid darkened and the copper lost its luster. Heating was continued at this temperature for an hour, with addition of more copper at intervals, the mixture cooled, filtered and most of the solvent removed by distillation. Precipitation from the residue with petroleum ether (b. p. 40–60°) gave a sirupy product which could not be induced to crystallize.

(c) A solution of 2 g. of the acid in 35 cc. of acetone was shaken for twenty-four hours with 1.6 g. of molecular silver, then filtered and the filtrate taken to dryness. On one recrystallization from ethyl acetate, the material had the melting point 200–201°, gave a positive test for bromine, and a mixed melting point with the starting material (m. p. 200–201°) was exactly the same.

The author wishes to record her indebtedness and thanks to Professor Roger Adams, at whose suggestion this work was undertaken, and with whose help and criticism it was carried out.

Summary

1. Tetramethylene bromide was prepared by the action of a solution of hydrobromic acid and sulfuric acid on tetramethylene glycol. Mono-methylmalonic diethyl ester was prepared from ethyl α -cyanopropionate, and the conditions for the maximum yield of the latter product from α -bromopropionate were elaborated.

2. Methylmalonic ester and tetramethylene bromide were condensed to give ethyl dimethylhexane-tetracarboxylate, which on hydrolysis and decomposition at 240° gave α, α' -dimethylsuberic acid.

3. α, α' -Dimethylsuberic acid exists in two isomeric forms, both of which were isolated pure. Bromination of either acid gave as the principal product one and the same α, α' -dibromo- α, α' -dimethylsuberic acid.

4. Attempts to form a cyclohexane ring by removal of bromine with copper bronze and molecular silver were unsuccessful.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

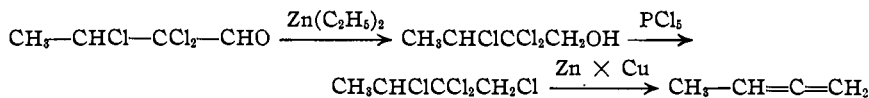
SYNTHESIS AND PYROLYSIS OF METHYLALLENE AND ETHYLACETYLENE¹

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The only previous mention of methylallene in the literature is its synthesis in 1888 by Norton and Noyes.⁴ They listed its boiling point at 19° and prepared its tetrabromide. The synthesis was effected through "butyric chloral" by the following steps



Since that time a few general methods of synthesis for allenes have been developed, none of which, however, has received application in the synthesis of methylallene. Bouis' general method⁵ seemed to possess definite advantages and was therefore selected.

Crotonaldehyde was the starting point in the synthesis. It was reduced

¹ This paper contains results obtained in an investigation on "The Pyrolysis of Pure Hydrocarbons" listed as Project No. 18 of American Petroleum Institute Research. Financial assistance in this work has been received from a research fund of the American Petroleum Institute donated by the Universal Oil Products Company. This fund is being administered by the Institute with the coöperation of the Central Petroleum Committee of the National Research Council.

² Director of Project No. 18.

³ American Petroleum Institute Junior Research Fellow.

⁴ Norton and Noyes, *Am. Chem. J.*, 10, 430 (1888).

⁵ Bouis, *Compt. rend.*, 182, 788 (1926); 183, 133 (1926).