2. Based upon the similarity of behavior in fractional electrolysis experiments, diffusion experiments and experiments involving hydrogenation, oxidation, treatment with nitrous acid, tests of heat stability in acid, neutral and alkaline media and esterification, we conclude that the ability of these extracts to stimulate yeast growth is due to the presence of a single acid substance which appears to be of universal biological occurrence. We have tentatively designated it as "pantothenic" acid, the name being derived from the Greek, meaning *from everywhere.*

3. Pantothenic acid appears to have a molecular weight of about 150; to be a distinct acid without amphoteric properties, to have several hydroxyl groups in its structure, but no olefin double bond, aldehyde, ketone, sulfhydryl, basic nitrogen, aromatic or sugar group.

4. Pantothenic acid is synthesized by *Aspergillus niger.* The probability is suggested that it may be produced by microörganisms in the soil and may function very widely in nature as a growth catalyst. Several similarities suggest its close relationship to vitamin G(B_2).

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The Use of Gamma-Iodopropyl Chloride as a Synthetic Reagent. The Synthesis of Certain Alpha-Phenyl Dibasic Acids

BY FRANCIS H. CASE

γ-Iodopropyl chloride, prepared by Henry[1] from trimethylene chlorobromide and sodium iodide, may be conveniently prepared in large quantities by the action of phosphorus and iodine upon trimethylene chlorohydrin. A study of its reactions with sodium cyanide and the sodium derivatives of phenylacetonitrile, ethyl malonate and ethyl phenylmalonate is here reported.

In the reaction with an equimolar quantity of sodium cyanide the sole product is γ-iodobutyronitrile, the absence of chlorine being probably due to the interaction of the γ-chlorobutyronitrile, initially formed, with the sodium iodide produced in the primary reaction. Whether this is the true mechanism of the reaction could be ascertained by converting an unsymmetrically substituted chlorohydrin such as 3-chloro-1-phenylpropanol-1, $HOCH(C_6H_5)CH_2CH_2Cl$ (whose preparation is described), to the corresponding chloro-iodide, treating it with one mole of sodium cyanide, and identifying the acid formed by hydrolysis.

γ-Iodobutyronitrile reacts with the sodium derivative of ethyl phenylmalonate suspended in toluene to form an ester which on hydrolysis and

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[1] Henry, *Bull. soc. chim.*, [3] **17**, 93 (1897).

decarboxylation yields α-phenyladipic acid. Lower yields were obtained with these reagents in alcoholic solution, and from phenylacetonitrile with sodium amide.[2]

With the sodium derivative of ethyl malonate, γ-iodopropyl chloride yields ethyl γ-iodopropylmalonate as the main product, together with a small proportion of the corresponding chloro compound. The formation of the latter was suppressed by the addition of sodium iodide toward the end of the reaction. When treated with phenylacetonitrile and sodium amide in absolute ether, ethyl γ-iodopropylmalonate gives only a small yield of the cyano ester antecedent to α-phenylpimelic acid; the main product was ethyl cyclobutane-1,1-dicarboxylate. This same product was obtained by the reaction in toluene with the sodium derivative of ethyl phenylmalonate, which reappeared as ethyl phenylacetate. On the other hand, a satisfactory yield of α-ethyl-α'-phenylpimelic acid (in both forms) was obtained from ethyl ethyl-γ-iodopropylmalonate, in which the cyclization reaction was prevented by the substitution of the reactive hydrogen atom.

In the hope of finding a better method of preparing α-phenylpimelic acid, an attempt was made to synthesize ethyl γ-iodopropylphenylmalonate; however, the only condensation product that could be isolated was halogen free, and on hydrolysis yielded an acid of composition $C_{11}H_{12}O_2$. This same acid was obtained from γ-iodopropyl chloride and phenylacetonitrile with sodium amide; a high-boiling liquid, probably α,α'-diphenylpimelonitrile, was also formed, but gave no crystalline product on hydrolysis. The acid $C_{11}H_{12}O_2$ is almost certainly 1-phenylcyclobutane-1-carboxylic acid, since it is unchanged by the action of catalyzed hydrogen, the other possible isomers of this formula being unsaturated. Its formation from γ-iodopropyl chloride and ethyl phenylmalonate can be attributed to a partial breakdown[2] of the primary condensation product into ethyl α-phenyl-δ-iodovalerate, with subsequent cyclization. A better yield of the phenylcyclobutanecarboxylic acid can be obtained from trimethylene iodide and phenylacetonitrile in presence of two moles of sodium amide.

The synthesis of α-phenylundecane-α,α'-dicarboxylic acid, $HOOCCH-C_6H_5(CH_2)_{10}COOH$, proceeded smoothly when ethyl κ-iodoundecylate was treated with the sodium derivative of ethyl phenylmalonate in toluene.

An attempt to prepare α,α'-diphenyladipic acid by the action of ethylene iodide upon two moles of the sodium derivative of ethyl phenylmalonate in alcohol led, in spite of the low temperature adopted, to products which on hydrolysis yielded phenylacetic acid and the two forms of α,β-diphenylsuccinic acid, identified by mixed melting point with samples prepared by the method of Wren and Still.[3] This result was evidently due to the

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[2] Cope and McElvain [THIS JOURNAL, **54**, 4319 (1932)] have shown that ethyl diphenylmalonate is largely broken down to ethyl diphenylacetate in the presence of sodium ethoxide.

[3] Wren and Still, *J. Chem. Soc.*, **107**, 444 (1915).

liberation of iodine from the ethylene iodide. When benzene was employed in place of alcohol, no high boiling products were obtained, nor did alkylation result from the use of ethylene bromide.

The action of trimethylene iodide upon the sodium derivative of ethyl phenylmalonate in alcohol led to the formation of high-boiling products from which no crystals could be obtained after hydrolysis.

The author is indebted to Dr. E. P. Kohler for helpful suggestions in regard to the elucidation of the structure of the acid $C_{11}H_{12}O_2$.

Experimental

γ-Iodopropyl Chloride, $I(CH_2)_3Cl$.—To a cooled mixture of 15.6 g. of red phosphorus and 142 g. of trimethylene chlorohydrin, 192 g. of iodine was slowly added through a reflux condenser. After being allowed to stand for several hours at room temperature, the mixture was warmed for three hours on the steam-bath, cooled, and poured onto ice. The heavy oil was washed successively with sodium bicarbonate and sodium thiosulfate solutions, dried and distilled. The fraction boiling at 170–181°, on redistillation, yielded 178.5 g. (58.3%) of γ-iodopropyl chloride boiling at 169–173°.

γ-Iodobutyronitrile, $I(CH_2)_3CN$.—To a solution of 53 g. of sodium cyanide (96.3%) dissolved in 60 cc. of water, was added 250 cc. of alcohol and 188 g. of γ-iodopropyl chloride. After the mixture had been refluxed for three hours, most of the alcohol was evaporated off, and the residue poured into ice water. The oily layer separating was extracted with chloroform, washed with sodium thiosulfate solution, and dried. The residue after removal of the chloroform yielded, after two distillations, 74 g. of a liquid boiling at 101–116° (7 mm.) and containing only a trace of chlorine. This fraction was redistilled, and the part boiling at 113–116° (7 mm.) was found to be analytically pure.

Anal. Calcd. for C_4H_6NI: I, 65.11. Found: I, 65.25.

3-Chloro-1-phenylpropanol-1, $HOCH(C_6H_5)CH_2CH_2Cl$.—Sixteen and eight-tenths grams of β-chloropropiophenone[4] was dissolved in 100 cc. of glacial acetic acid and reduced by hydrogen in the presence of 0.3 g. of the Adams catalyst. The reaction was stopped after the absorption of one mole of hydrogen, which required about forty minutes. The acetic acid solutions from three such reductions were combined, diluted with water, and treated with solid sodium bicarbonate until only faintly acid. The solution was then extracted with ether, and the ether dried and evaporated. The residue on distillation yielded 11.7 g. of a liquid boiling at 130–132° (8 mm.). The lower boiling fraction from this distillation appeared to be unsaturated.

Anal. Calcd. for $C_9H_{11}OCl$: Cl, 20.79. Found: Cl, 20.14.

p-Nitrobenzoate, $O_2NC_6H_4COOCH(C_6H_5)CH_2CH_2Cl$.—This was prepared by the action of p-nitrobenzoyl chloride on 3-chloro-1-phenylpropanol-1 in pyridine. When crystallized from a mixture of benzene and petroleum ether it melts at 62–63°.

Anal. Calcd. for $C_{16}H_{14}O_4NCl$: Cl, 11.10. Found: Cl, 11.26.

Alpha-phenyladipic Acid, $HOOCCHC_6H_5(CH_2)_3COOH$.—To 7.7 g. of sodium shot suspended in 400 cc. of toluene, was added 79 g. of ethyl phenylmalonate. After refluxing for several hours until all the sodium had been converted into the salt of the ester, the cooled mixture was treated with 65 g. of γ-iodobutyronitrile, and refluxed in an oil-bath for ten hours. After cooling, water was added, sufficient to dissolve the precipitated sodium iodide, and the toluene layer separated and dried. The toluene was removed in a vacuum on the water-bath, and the residue distilled in a vacuum. The distillate was divided into two parts; A, that boiling from 118–190° (3 mm.) (weight 19 g.),

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(4) Hale and Britton, THIS JOURNAL, **41**, 845 (1919).

and B, that boiling from 190–211° (3 mm.) (weight 40 g.). Both fractions were hydrolyzed by alcoholic potash, and heated for two hours at 210°. From the hydrolysate of Fraction A, 2 g. of phenylacetic acid was extracted by means of petroleum ether, and 3 g. of phenyladipic acid was crystallized from benzene and ether. The hydrolyzed product from fraction B yielded 28.5 g. of phenyladipic acid melting at 132–133°; total yield, 31.5 g., or 43%.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.83; H, 6.35. Found: C, 64.86; H, 6.59.

Ethyl γ-Iodopropylmalonate, $ICH_2CH_2CH_2CH(COOC_2H_5)_2$.—This was prepared by refluxing molar quantities of the sodium derivative of ethyl malonate and γ-iodopropyl chloride in absolute alcohol, 20 g. of sodium iodide being added toward the end of the reaction; yield 125 g., b. p. 164–168° (8 mm.).

Anal. Calcd. for $C_{10}H_{17}O_4I$: I, 38.68. Found: I, 38.80.

Action of Ethyl Phenylmalonate on Ethyl γ-Iodopropylmalonate.—Two-tenths molar quantities of sodium ethyl phenylmalonate and ethyl γ-iodopropylmalonate refluxed in toluene yielded 18.5 g. of a liquid, b. p. 114–116° (12 mm.) (Fraction A) and 18.5 g. of a liquid boiling at 163–167° (12 mm.) (Fraction B), but no high boiling fraction. On hydrolysis with alcoholic potash and decarboxylation A yielded cyclobutane-1,1-dicarboxylic acid, m. p. 156–157°, and B yielded phenylacetic acid, m. p. 77–78°.

α-Phenylpimelic Acid, $HOOCCH(C_6H_5)(CH_2)_4COOH$.—From the reaction of 0.3 molar quantities of the monosodium derivative of phenylacetonitrile and ethyl γ-iodopropylmalonate in absolute ether solution an oil was obtained yielding on distillation 29.5 g. of a liquid boiling at 113–117° (14 mm.) (Fraction A); and 20 g. of a liquid boiling at 200–232° (6 mm.) (Fraction B). On hydrolysis with alcoholic potash and decarboxylation Fraction A yielded an acid which melted unchanged with the cyclobutane-1,1-dicarboxylic acid obtained by the action of ethyl phenylmalonate on ethyl γ-iodopropylmalonate. Fraction B, weighing 20 g., after hydrolysis and decarboxylation, yielded an oil which after several weeks standing in a vacuum desiccator afforded 10.5 g. of crude acid. Repeated recrystallization from a mixture of ether and petroleum ether yielded 1 g. of pure acid which melted at 92–93°, and crystallized in prisms.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.06; H, 6.83. Found: C, 65.93; H, 7.02.

Action of Phenylacetonitrile on γ-Iodopropyl Chloride.—From the reaction of 0.7 molar quantities of the monosodium derivative of phenylacetonitrile and γ-iodopropyl chloride in absolute ether an oil was obtained which on distillation yielded 19 g. of a liquid A boiling at 115–120° (5 mm.) and 20 g. of a liquid B boiling at 210–270° (5 mm.), both practically halogen free. After hydrolysis the acid from B could not be made to crystallize; from A, 6 g. was obtained of an acid crystallizing from petroleum ether in large prisms and melting at 106–107°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87. Found: C, 74.82; H, 7.00.

This acid was unreduced during two hours in the catalytic reduction apparatus under conditions which brought about the complete reduction of an equimolar amount of maleic acid in fifteen minutes.

Action of Ethyl Phenylmalonate on γ-Iodopropyl Chloride.—Half-molar quantities of sodium ethyl phenylmalonate and γ-iodopropyl chloride were allowed to react in absolute alcohol. Although none of the expected ethyl γ-iodopropylphenylmalonate could be isolated from the reaction product, 13.5 g. of a halogen-free liquid boiling at 135–145° (3 mm.) was obtained, which yielded on hydrolysis an acid melting unchanged with the 1-phenylcyclobutane-1-carboxylic acid described in the preceding experiment.

Preparation of 1-Phenylcyclobutane-1-carboxylic Acid, $HOOC\overline{C(C_6H_5)(CH_2)_3}$.—One-third molar quantities of the disodium derivative of phenylacetonitrile and of trimethylene iodide were allowed to react in absolute ether. From the reaction mixture 20.5 g. of a liquid boiling at 90–122° (4 mm.) was obtained. On hydrolysis this yielded 8.5 g. of 1-phenylcyclobutane-1-carboxylic acid, m. p. 106–107°.

Ethyl γ-Iodopropylethylmalonate.—This was prepared by the action of half-molar quantities of sodium ethyl ethylmalonate and γ-iodopropyl chloride in alcohol. A yield of 83 g. was obtained, b. p. 162–167° (9 mm.). This product, though impure, was successfully used in subsequent synthesis.

α-Phenyl-α'-ethylpimelic Acid, $HOOCCH(C_2H_5)(CH_2)_3CH(C_6H_5)COOH$.—From the reaction of three-tenths molar quantities of sodium ethyl phenylmalonate and ethyl γ-iodopropylethylmalonate in toluene a liquid was obtained boiling at 200–238° (3 mm.) (64.5 g.). On hydrolysis it yielded 8 g. of a white solid crystallizing from a mixture of ether and petroleum ether and melting at 149–150° (β-form).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.14; H, 7.63. Found: C, 67.93; H, 7.72.

From the filtrate from the above crystallization 4 g. of a solid crystallizing from the same solvent and melting at 138–139° (α-form) was obtained.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.14; H, 7.63. Found: C, 68.15; H, 7.84.

Ethyl κ-Iodoundecylate, $I(CH_2)_{10}COOC_2H_5$.—κ-Bromoundecylic acid was prepared from undecylenic acid by the method of Perkins and Cruz.[5] Its ethyl ester was converted by refluxing with sodium iodide in alcohol solution to the iodo ester, b. p. 175–179° (6 mm.). Although redistilled it was not obtained completely pure.

Anal. Calcd. for $C_{13}H_{25}O_2I$: I, 37.32. Found: I, 36.17.

α-Phenylundecane-α,α'-dicarboxylic Acid, $HOOCCH(C_6H_5)(CH_2)_{10}COOH$.—The action of 0.2 molar quantities of sodium ethyl phenylmalonate and ethyl κ-iodoundecylate in toluene yielded 25 g. of a liquid boiling at 200–252° (3 mm.). On hydrolysis and decarboxylation, 13 g. of an acid was obtained crystallizing from a mixture of ethyl acetate and petroleum ether, and melting at 87–88°.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.20; H, 8.81. Found: C, 70.98; H, 8.99.

Action of Ethylene Diiodide on Ethyl Phenylmalonate.—A solution of 0.3 mole of sodium ethyl phenylmalonate and 0.15 mole of ethylene diiodide in absolute alcohol was stirred for two hours at room temperature, and allowed to stand overnight. It was then stirred for five hours at 50–55° and refluxed for six hours. The resulting product yielded on distillation two fractions: A, b. p. 130–195° (5 mm.) (19 g.), and B, 195–222° (5 mm.) (19 g.). On hydrolysis and decarboxylation A yielded phenylacetic acid and B yielded 1.5 g. of an acid melting at 183–184°, and unchanged when mixed with a sample of the α-form of α,β-diphenylsuccinic acid prepared by the method of Wren and Still.

In another identical experiment the high boiling fraction (197–210°) (3 mm.) (15 g.) yielded 1.5 g. of an acid melting at 230–232°, and unchanged when mixed with a sample of the β-form of α,β-diphenylsuccinic acid prepared by the method of Wren and Still.

Action of Ethylene Dibromide on Ethyl Phenylmalonate.—The procedure was the same as above, except that an equimolar quantity of ethylene dibromide was substituted for the ethylene diiodide. The only product obtained was ethyl phenylacetate (45 g.), b. p. 224–228°.

Action of Trimethylene Iodide on Ethyl Phenylmalonate.—From the action of one-third mole of sodium ethyl phenylmalonate and one-sixth mole of trimethylene iodide in absolute alcohol an oil was obtained which yielded on distillation two fractions: A, 155–200° (4 mm.) (24 g.), and B 200–255° (4 mm.) (22 g.). Fraction A yielded, after hydrolysis and decarboxylation, phenylacetic acid. The acid from B would not solidify.

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[5] Perkins and Cruz, THIS JOURNAL, **49**, 1070 (1927).

Summary

1. A convenient method is described for the preparation of γ-iodopropyl chloride in considerable quantity.

2. Its reactions with sodium cyanide and the sodium derivatives of ethyl malonate, ethyl phenylmalonate and phenylacetonitrile have been studied.

3. The following acids have been prepared: α-phenyladipic, α-phenylpimelic, α-phenylundecane-α,α'-dicarboxylic, α-ethyl-α'-phenylpimelic (both forms) and 1-phenylcyclobutane-1-carboxylic acid.

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Reactions of Triphenylmethylmagnesium Bromide. II

BY W. E. BACHMANN AND R. F. COCKERILL

In a previous paper it was shown that triphenylmethylmagnesium bromide reacts with aromatic ketones and with benzils[1] in an unusual manner. The MgBr group of the Grignard reagent adds to the oxygen atom of the C=O group of the ketone but the triphenylmethyl group does not join to the carbon atom; instead, it remains free as the radical. On the other hand, the Grignard reagent reacts normally with carbon dioxide[2] and gives a nearly quantitative yield of triphenylacetic acid; likewise it couples in normal fashion with diarylmethyl halides[3] and gives penta-arylethanes. We have now investigated the reactions of triphenylmethylmagnesium bromide with a variety of reagents in order to ascertain the extent of its irregular behavior and in order to determine the practical application of the Grignard reagent in introducing the triphenylmethyl group into molecules.

Reaction with Oxygen and with Sulfur.—Contrary to the statement of Schmidlin[4] and of others[5] that the Grignard reagent is converted readily into triphenylmethyl peroxide by the oxygen of the air, only a small amount of triphenylmethyl peroxide is formed when air is passed through a solution of the Grignard reagent; the chief product is the salt of triphenylcarbinol $(C_6H_5)_3COMgBr$ when the reaction is carried out at room temperature or at the boiling point of the solution.

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(1) Bachmann, THIS JOURNAL, **53,** 2758 (1931).

(2) Gomberg and Bachmann, *ibid.*, **52,** 2455 (1930); see also Schmidlin, *Ber.*, **39,** 634 (1906) and Gilman and Zoellner, THIS JOURNAL, **51,** 3493 (1929).

(3) Bachmann, *ibid.*, **55,** 2135 (1933).

(4) Schmidlin, "Das Triphenylmethyl," Ferdinand Enke, Stuttgart, 1914, p. 127.

(5) Kinney and Mayhue [THIS JOURNAL, **53,** 193 (1931)] report an almost quantitative yield of triphenylmethyl peroxide but they give no experimental details. Gilman and Fothergill [*ibid.*, **51,** 3152 (1929)] intimate a similar reaction and offer it as support for the dissociation of the Grignard reagent but give no details. Our results make it appear unlikely that there is any appreciable dissociation of the Grignard reagent into triphenylmethyl and magnesious halide as has been postulated by these investigators.