[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Action of Heat on γ-Alkoxybutyryl Chlorides

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γ-Methoxybutyric acid (I) was heated with thionyl chloride on a steam-bath with the expectation that γ-methoxybutyryl chloride (II) would be formed. After removal of the excess thionyl chloride, a chlorine-containing liquid was isolated in 86% yield, but when the latter was poured into ammonia water there was no evidence of reaction and the material was recovered unchanged. We observed that the true acid chloride, which was obtained by treatment of the acid with thionyl chloride at a lower temperature,[4] reacted vigorously with ammonia water.

It was found that a product, identical with that obtained from the acid and thionyl chloride at steam-bath temperature, was formed in 84% yield when γ-methoxybutyryl chloride was heated for three hours on a steam-bath.

Eventually, it was discovered that the product was methyl γ-chlorobutyrate (III).

$$\begin{array}{rl} \text{(I)} & CH_3OCH_2CH_2CH_2COOH \\ \text{(II)} & CH_3OCH_2CH_2CH_2COCl \\ \text{(III)} & ClCH_2CH_2CH_2COOCH_3 \end{array}$$

We have found no reaction in the literature entirely similar to that mentioned above. However, a number of instances are known[5] in which an acid chloride, ether and zinc or ferric chloride interact to yield an ethyl ester and ethyl chloride. For example

$$CH_3COCl + C_2H_5OC_2H_5\ (+\ ZnCl_2) = CH_3COOC_2H_5 + C_2H_5Cl$$

Since γ-methoxybutyryl chloride is both an acid chloride and an ether, it seemed probable that methyl γ-chlorobutyrate was formed in the following manner

$$\underset{\text{II}}{2CH_3OCH_2CH_2CH_2COCl} \longrightarrow$$

$$\underset{\text{IV}}{CH_3OCH_2CH_2CH_2COOCH_3} + \underset{\text{V}}{ClCH_2CH_2CH_2COCl} \longrightarrow$$

$$\underset{\text{III}}{2ClCH_2CH_2CH_2COOCH_3}$$

Molecular equivalent amounts of compounds IV and V were heated at steam-bath temperature but we were unable to demonstrate that compound III had been produced.

Moreover, when α-ethyl-γ-methoxybutyric acid (ethyl-β-methoxyethylacetic acid), α-ethyl-γ-ethoxybutyric acid, α-ethyl-γ-butoxybutyric acid, α-(β′-phenylethyl)-γ-methoxybutyric acid (β-phenylethyl-β′-methoxyethylacetic acid), α-(β′-phenylethyl)-γ-ethoxybutyric acid or α-(β′-phenylethyl)-γ-butoxybutyric acid, dissolved in petroleum ether, was treated with thionyl chloride at ordinary temperature and the excess reagent removed under reduced pressure at approximately the same temperature, we found that the product, unquestionably the acid chloride, reacted vigorously with ammonia water to yield the acid amide.[6] However, after the acid chloride had been submitted to distillation under diminished pressure, the product then failed to react spontaneously with ammonia water. Undoubtedly, the chlorides of the acids mentioned above are transformed under the influence of heat into alkyl γ-chlorobutyrates.

γ-Ethoxy- and γ-butoxybutyric acid reacted with thionyl chloride at steam-bath temperature to yield ethyl and butyl γ-chlorobutyrate, respectively.

When β-methoxy- or β-ethoxypropionic acid and thionyl chloride were heated at 100° for six hours, no product other than β-methoxy- or β-ethoxypropionyl chloride could be isolated. Our experiments indicated also that methoxy- and ethoxyacetic acid are not converted into esters of chloro acids by thionyl chloride at 100°.

The manner in which the identity of methyl γ-chlorobutyrate was established is shown by the reaction scheme.

Experimental Part

γ-Methoxybutyryl Chloride.—To 35.4 g. of γ-methoxybutyric acid,[7] dissolved in 200 cc. of petroleum ether (30–40°), there was added 53.6 g. of practical thionyl chloride. After twelve hours at ordinary temperature, the solvent and excess thionyl chloride were removed under dimin-

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[1] This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by W. B. Wright, Jr., in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] Monsanto Chemical Company Fellow.

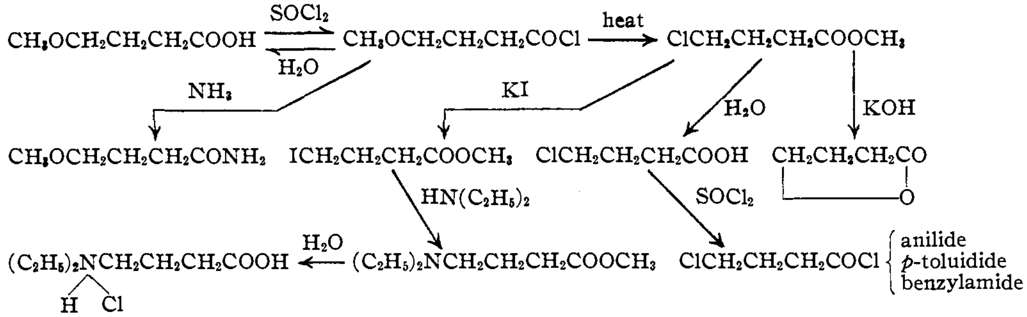
[3] Upjohn Company Fellow.

[4] Leimu, *Ber.*, **70**, 1051 (1937).

[5] (a) Descude, *Compt. rend.*, **132**, 1129 (1901). (b) Kyrides, THIS JOURNAL, **55**, 1209 (1933). (c) Kyrides and Dvornikoff, *ibid.*, **55**, 4630 (1933); see (b) for other articles.

[6] These amides, designated as amides of disubstituted acetic acids, will be described in a later publication.

[7] Palomaa and Kinetti, *Ber.*, **64**, 800 (1931).



ished pressure and the acid chloride distilled; yield 33 g. (81%); b. p. 46–47° (7 mm.).[8]

When a benzene solution of the acid chloride was treated with ammonia gas, the solvent removed and the residue extracted with acetone, γ-methoxybutyramide was obtained; m. p. 57°[9] after recrystallization from petroleum ether (30–40°).

A mixture of 33 g. of the acid chloride, 50 g. of potassium carbonate and 40 cc. of water was allowed to remain at room temperature for twelve hours, the solution evaporated to dryness, the residue made acid with hydrochloric acid, extracted with ether and the solvent removed from the extract. There was obtained 21 g. (74%) of γ-methoxybutyric acid; b. p. 112–114° (11 mm.).[10]

Methyl γ-Chlorobutyrate.—(a) Five grams of γ-methoxybutyric acid, which boiled at 103–104° (4 mm.),[10] and 5 g. of thionyl chloride (practical) were heated on a steam-bath for six hours and the mixture then distilled. The yield of methyl γ-chlorobutyrate was 5 g. (86%); b. p. 102–105° (58 mm.) or 172–174° (749 mm.).[11]

(b) After 27.3 g. of γ-methoxybutyryl chloride had been heated on a steam-bath for three hours the material was distilled. There was obtained 23 g. (84%) of methyl γ-chlorobutyrate; b. p. 172–174° (749 mm.).

γ-Butyrolactone was obtained in the following manner. A mixture of 20.0 g. of methyl γ-chlorobutyrate and 24.5 g. of potassium hydroxide, dissolved in 60 cc. of alcohol, was refluxed for forty-eight hours, practically all of the alcohol removed, the mixture acidified to congo red with hydrochloric acid, filtered, and the filtrate extracted with ether. From the dried ether solution there was obtained 8.5 g. (67.5%) of the lactone; b. p. 197–200° (735 mm.).[12]

When 58 g. of methyl γ-chlorobutyrate and 38 cc. of concd. hydrochloric acid were refluxed for six hours and the mixture extracted with ether, 16.5 g. (32%) of γ-chlorobutyric acid was obtained from the ether layer. The acid boiled at 111° (8 mm.) and melted at 13–14°.[13]

γ-Chlorobutyryl Chloride.—This compound was obtained in 82% yield when 16.5 g. of γ-chlorobutyric acid and 24.0 g. of thionyl chloride were heated for one hour on a steam-bath; b. p. 60–61° (12 mm.).[14]

The anilide of γ-chlorobutyric acid was formed when 1.4 g. of the acid chloride was mixed with 1.4 g. of aniline, dissolved in 50 cc. of benzene. The mixture was shaken with sodium carbonate solution, then washed with water and the benzene evaporated until crystals began to separate. After the addition of petroleum ether (30–40°) the precipitated anilide was filtered and recrystallized from a mixture of benzene and petroleum ether; m. p. 69–70°.[15]

Prepared in the same manner with the aid of *p*-toluidine and benzylamine, respectively, the *p*-toluidide melted at 95°[16] and the benzylamide at 67°.[17]

γ-Diethylaminobutyric Acid Hydrochloride.—A mixture of 4.8 g. (0.035 mole) of methyl γ-chlorobutyrate, 8.0 g. (0.053 mole) of sodium iodide and 30 cc. of acetone was refluxed for eight hours, the acetone removed, the residue extracted with ether and the ether extract shaken with sodium thiosulfate solution. The ether layer was dried over fused sodium sulfate and the solvent removed. The methyl γ-iodobutyrate weighed 4.6 g.; b. p. 80–83° (11 mm.).[18]

The iodo ester, 30 cc. of benzene and 5 g. of diethylamine were heated in a magnesium citrate bottle for three hours at 60° and the precipitated diethylamine hydriodide filtered. From the filtrate there was obtained 2.6 g. (74%) of methyl γ-diethylaminobutyrate; b. p. 61–63° (3 mm.).

The basic ester was dissolved in ether and treated with hydrogen chloride. The precipitated hydrochloride was recrystallized from a mixture of acetone and ether; m. p. 102°.

Anal. Calcd. for $C_9H_{20}O_2NCl$: Cl, 16.91. Found: Cl, 16.99.

Methyl γ-diethylaminobutyrate was heated for one hour on a steam-bath with three times its volume of 18% hydrochloric acid and the mixture then concentrated until crystals began to appear. Acetone was added and the precipitated γ-diethylaminobutyric acid hydrochloride was recrystallized from a mixture of alcohol and ether; m. p. 166°.[19]

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[8] The same boiling point has been reported (ref. 4).

[9] Prepared by a different method, Kilpi, *Z. physik. Chem.*, **80**, 185 (1912), found 59.1°.

[10] Ref. 7, b. p. 107–109° (8 mm.).

[11] Obtained from γ-methoxybutyronitrile, hydrogen chloride and methyl alcohol, Henry, *Bull. soc. chim.*, (2) **46**, 341 (1886), found 173–174° and Campbell and Campbell, THIS JOURNAL, **60**, 1375 (1938), reported 90° (45 mm.).

[12] Bentley, Haworth and Perkins, *J. Chem. Soc.*, **69**, 168 (1896), reported 204–206°.

[13] Cloves, *Ann.*, **319**, 362 (1901), found the boiling point to be 115–115.5° (13 mm.) and the melting point to be 16°.

[14] Lipp and Caspers, *Ber.*, **58**, 1013 (1925), found 59–60° (11 mm.).

[15] The same melting point has been reported (ref. 14, p. 1013).

[16] Wolffenstein and Rolle, *Ber.*, **41**, 737 (1908), found the same melting point.

[17] Hanford and Adams, THIS JOURNAL, **57**, 924 (1935), reported 68°.

[18] Henry, *Compt. rend.*, **102**, 369 (1886), found 198–200°.

[19] Wohlgemuth, *Ann. chim.*, (9) **2**, 317 (1914), found the same melting point.

Ethyl γ-Chlorobutyrate.—Thirty-five grams (77%) of this product was obtained when 40 g. of γ-ethoxybutyric acid, which boiled at 114–116° (7 mm.),[20] and 54 g. of thionyl chloride were heated on a steam-bath for four hours. The ethyl γ-chlorobutyrate boiled at 70–71° (10 mm.).[21]

When 30 g. of the ester was heated for six hours on a steam-bath with 18 cc. of concd. hydrochloric acid and the mixture extracted with ether, 8 g. of γ-chlorobutyric acid, b. p. 104–109° (6 mm.), and 18 g. of unchanged ester were obtained. Upon further fractionation, 4 g. of the acid was found to boil at 107–108° (6 mm.); m. p. 13°.[22]

The following compounds were prepared in the manner described above. Ethyl iodobutyrate was obtained in 67% yield; b. p. 69–71° (3 mm.).[23]

Ethyl γ-diethylaminobutyrate was prepared in 78% yield; b. p. 73–75° (4 mm.).[24] The hydrochloride, after recrystallization from a mixture of acetone and ether, melted at 113°.

Anal. Calcd. for $C_{10}H_{22}O_2NCl$: Cl, 15.84. Found: Cl, 15.85.

Upon hydrolysis of the ester with concd. hydrochloric acid, γ-diethylaminobutyric acid hydrochloride was produced; m. p. 166–167°.

Butyl γ-Chlorobutyrate.—When 32 g. of γ-butoxybutyric acid, which boiled at 120–125° (4 mm.),[25] and 30 g. of thionyl chloride were heated for four hours on a steam-bath, there was obtained 32 g. (90%) of butyl γ-chlorobutyrate; b. p. 93–96° (8 mm.).

Anal. Calcd. for $C_8H_{15}O_2Cl$: Cl, 19.85. Found: Cl, 19.93.

Butyl γ-iodobutyrate was obtained in 65% yield; b. p. 100–103° (4 mm.).

Butyl γ-diethylaminobutyrate was prepared in 74% yield; b. p. 105–107° (5 mm.). Upon acid hydrolysis of the ester the hydrochloride of γ-diethylaminobutyric acid was isolated; m. p. 166°.

When β-methoxypropionic acid was heated on a steam-bath with thionyl chloride, β-methoxypropionyl chloride was obtained; b. p. 34–36° (6 mm.).[26]

To a cooled mixture of 9.8 g. of the acid chloride, 7 cc. of methyl alcohol and 7 cc. of water, sodium hydroxide pellets were added, gradually, until the mixture was slightly alkaline. The alcoholic layer yielded 5.6 g. of methyl β-methoxypropionate; b. p. 145–147° (746 mm.).[27]

β-Ethoxypropionic acid and thionyl chloride yielded β-ethoxypropionyl chloride; b. p. 34–35° (5 mm.).[28] Ethyl β-ethoxypropionate, obtained from the acid chloride in 74% yield, boiled at 49–50° (6 mm.).[29]

Summary

γ-Methoxy-, γ-ethoxy- and γ-butoxybutyryl chloride are transformed, under the influence of heat, into methyl, ethyl and butyl γ-chlorobutyrates, respectively. Certain α-substituted γ-alkoxybutyryl chlorides seem to behave in a similar manner but β-alkoxypropionyl chlorides apparently are unaffected by heat under the same conditions.

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[20] Ref. 7, b. p. 116.5–117° (8 mm.).

[21] Ref. 19, p. 307, b. p. 77° (16 mm.).

[22] Cloves, ref. 13, found that the acid boiled at 115° (13 mm.) and melted at 16°.

[23] Fuson, Arnold and Cooke, THIS JOURNAL, **60**, 2273 (1938), found 84–85° (4 mm.).

[24] Ref. 19, b. p. 98° (13 mm.).

[25] Ref. 7, b. p. 122.5–123° (4 mm.).

[26] Ref. 4, b. p. 27–27.5° (3 mm.).

[27] Palomaa and Kilpi, *Chem. Zentr.*, **81**, II, 1453 (1910), found 143.4–143.6° (750 mm.).

[28] Ref. 4, b. p. 28–28.5° (2 mm.).

[29] Ref. 27, b. p. 49.5–49.8° (7 mm.).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Certain Reactions of *p*-Bromocinnamic Acid

BY MARIE REIMER AND ELISE TOBIN

In the course of a study of *p*-bromobenzalpyruvic acid,[1] it became of interest to have for comparison certain derivatives of *p*-bromocinnamic acid. This acid and several related compounds have, therefore, been prepared.

p-Bromocinnamic acid has been obtained previously by the usual methods[2] and also by vacuum distillation of brominated truxillic acids[3] and, unexpectedly, as a by-product in the Friedel–Crafts reaction with the acid chloride of cinnamic acid dibromide.[4] The acid used in this study was the product of hydrogen peroxide oxidation of *p*-bromobenzalpyruvic acid. This method of preparation of various cinnamic acids has been used repeatedly in this Laboratory and found to give far better yields than those noted by other procedures.

The dibromide of *p*-bromocinnamic acid, like that of cinnamic acid, readily loses bromine as well as hydrogen bromide on heating. By treatment of the dibromide with potassium hydroxide in methanol solution, however, it has been found

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[1] Reimer and Tobin, THIS JOURNAL, **62**, 2515 (1940).

[2] Knoevenagel, *Ber.*, **31**, 2604 (1898); Gabriel, *ibid.*, **15**, 2501 (1882); Perkin's synthesis.[1]

[3] Kraus, *ibid.*, **35**, 2932 (1902); **37**, 223 (1904).

[4] Kohler, Heritage and Burnley, *Am. Chem. J.*, **44**, 60 (1910).