The cinnamates are the most active of all studied, which is evidence of the favorable effect of a double bond in enhancing the anesthetic powers of compounds.

Summary

1. Esters of β-4-morpholinoethanol with benzoic, phenylacetic, β-phenylpropionic, cinnamic and tetraphydropyran-4-carboxylic acids; a second series of β-N-piperidinoethanol with these same acids; and a third series of β-menthylethylaminoethanol with benzoic and tetrahydropyran-4-carboxylic acids are described under the following heads: (a) preparation, (b) physical properties, (c) P_H values, (d) anesthetic activities, (e) surface tension.

2. The cinnamates are the most active physiologically of those studied.

3. No apparent relationship between surface tension and surface penetration was indicated.

4. The menthylethylamino derivatives differ from the others studied in the ease with which hydrogen chloride is lost.

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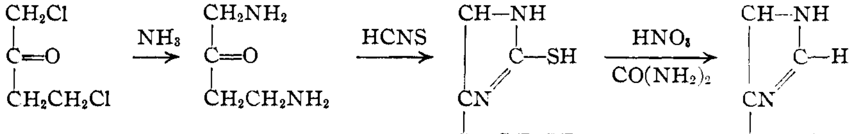
α′,β-Dichloromethylethyl Ketone (1,4-Dichlorobutanone-2)[1]

BY R. H. CARROLL AND G. B. L. SMITH

Introduction

The preparation of α′,β-dichloromethylethyl ketone is not recorded in the literature, and this relatively simple substance is important because of the possibility of using it as an intermediate in the synthesis of compounds of biological and pharmacological interest. For instance it might be employed in the synthesis of histamine, as follows[2]



The present paper describes two methods for the preparation of α′,β-dichloromethylethyl ketone.

The Nierenstein Reaction.—In 1915, Clibbens and Nierenstein[3] reported that acid chlorides react with diazomethane to produce α-chloro

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[1] This paper is constructed from part of the thesis submitted by Mr. Carroll to the faculty of the Polytechnic Institute of Brooklyn in June, 1932, in partial fulfilment of the requirements for the degree of Master of Science in Chemistry.

[2] Now being investigated in this laboratory.

[3] Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915).

ketones, but Bradley and Robinson[4] in employing this reaction obtained instead the diazo ketone. Bradley and Robinson[5] and Bradley and Schwarzenbach[6] found that when one molecular equivalent of an acid chloride is allowed to react with two molecular equivalents of diazomethane, the diazo ketone is obtained in excellent yields. Bradley and Schwarzenbach[6] were able to obtain the α-chlor ketone from the diazo ketone by treatment of the latter substance with dry hydrogen chloride.

α′,β-Dichloromethyl ethyl ketone was prepared through the Nierenstein reaction from diazomethane and β-chloropropionyl chloride and subsequent treatment of the product with dry hydrogen chloride. The α′,β-dichloromethylethyl ketone was identified by analysis and by the preparation of the hydrochloride of a new thiazole, 4-(β-chloroethyl)-2-aminothiazole. The ketone itself was a strong lachrymator. It distils at 65° at 3 mm. and changes from a colorless to a brown liquid on standing. Its specific gravity 20°/4° is 1.3295 (±0.0005).

Condensation of Ethylene and Chloroacetyl Chloride with Aluminum Chloride.—Lippmann[7] in 1864 prepared β-chloropropionyl chloride from ethylene and phosgene. This reaction suggested that if chloroacetyl chloride were used instead of phosgene, α′,β-dichloromethylethyl ketone might be formed. Various condensation agents such as mercuric sulfate, sulfuric acid, stannic chloride and aluminum chloride were used to bring about this reaction between chloroacetyl chloride dissolved in diethyl ether and ethylene, the ethylene being passed into the ethereal solution. These attempts were not successful.

Petroleum oils have been condensed[8] by the use of the addition compound of ethylene and aluminum chloride. Accordingly this ethylene–aluminum chloride addition compound was prepared in a dry petroleum ether solution and chloroacetyl chloride was added. α′,β-Dichloromethylethyl ketone was obtained in small yield and it was identified through the condensation product with thiourea.[9]

Experimental

Materials.—**Diazomethane** was prepared by the method of von Pechman[10] using nitrosomethyl urethan.[11] The ether was dried over sodium, distilled, dried over phosphoric anhydride and redistilled. **β-Chloropropionic acid** was prepared by the method given by Powell in "Organic Syntheses."[12] **β-Chloropropionyl chloride**[13] was prepared

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[4] Bradley and Robinson, *J. Chem. Soc.*, 1545 (1928).

[5] Ref. 4, p. 1310.

[6] Bradley and Schwarzenbach, *ibid.*, 2904 (1928).

[7] Lippmann, *Ann.*, **129**, 81 (1864).

[8] British Patent 345,334, Dec. 18, 1930; see *Chem. Abstracts*, **26**, 155 (1932).

[9] See Popp. *Ann.*, **250**, 274 (1889); Hantzsch, *ibid.*, **249**, 1, 7, 31 (1888); **250**, 257 (1889); Näf, *ibid.*, **265**, 108 (1891); Traumann, *ibid.*, **249**, 31 (1888).

[10] Houben-Weyl, "Methoden der organischen Chemie," G. Thieme, Leipzig, v. 3, 2d ed., 1922, p. 124.

[11] Purchased from the Eastman Kodak Company.

[12] "Organic Syntheses," John Wiley and Sons, Vol. VIII, 1928, p. 58.

[13] See Michael, *Ber.*, **34**, 4048 (1901), also Wolfenstein and Rolle, *ibid.*, **41**, 736 (1908).

by heating together a mixture of 15 g. of β-chloropropionic acid and 18 g. of thionyl chloride for ninety minutes. The mixture was fractionated at 5 mm.; 13 g. was collected at 44°, b. p. 144°.

α′,β,-Dichloromethylethyl Ketone (1,4-Dichlorobutanone-2) through the Nierenstein Reaction.—4.75 grams of β-chloropropionyl chloride was dissolved in 25 g. of absolute ether and the solution was cooled to $-5°$; 1.8 g.[14] of diazomethane was dissolved in 75 g. of absolute ether contained in a 500-ml. suction flask, cooled to $-5°$, and protected from moisture by a calcium chloride tube. This solution was treated with the ethereal solution of β-chloropropionyl chloride, taking about five minutes for the addition. The temperature was maintained at $-5°$ and the solution was allowed to stand for one hour, at the end of which period a second portion of 1.8 g. of diazomethane was added to the solution, nitrogen being again evolved. The solution was now placed in an ice box and allowed to stand for thirty-six hours. The yellow colored solution was treated with dry hydrogen chloride until the color was pale yellow and the evolution of nitrogen had ceased. During the treatment with hydrogen chloride the temperature was held below 10°. The ether was evaporated by a current of dry air and the residue was fractionated at reduced pressure. The portion distilling at 65° under a pressure of 3 mm. was collected; yield 3.2 g. The liquid had powerful lachrymatory properties and the density was 20°/4°, 1.3295. Refractive index $[n_D]$ 1.480 at 20°; molecular refraction calcd., 30.59; found, 30.10. This sample was two weeks old and a sample two months old gave a value $[n_D]$ 1.473 at 20°.

Anal. Calcd. for $C_4H_6OCl_2$: C, 34.04; H, 4.25. Found: C, 34.29; H, 4.09.

This preparation was repeated using 22 g. of β-chloropropionyl chloride and 14.4 g. of diazomethane; yield 18 g. at 65° and 3 mm. pressure.

Hydrochloride of 4-(β-Chloroethyl)-2-aminothiazole.—2.8 Grams of α′, β-dichloromethylethyl ketone was added to a solution of 1.4 g. of thiourea in 25 ml. of water and heated on the water-bath under reflux for thirty minutes. The mixture was frequently agitated and at the end of this period the insoluble layer of the ketone had entirely disappeared. The solution was evaporated under reduced pressure to 15 ml. and then made alkaline by adding 20 ml. of a solution of 0.1 *N* sodium hydroxide. It was then extracted with diethyl ether and the ethereal solution was dried with anhydrous sodium sulfate. The ether was evaporated and the residue crystallized; yield 1.4 g.; m. p. 60°. This base could not be recrystallized readily and accordingly the hydrochloride salt was prepared.

One-half gram of 4-(β-chloroethyl)-2-aminothiazole base was dissolved in 20 ml. of absolute ether and filtered; 20 ml. of absolute ether was saturated with dry hydrogen chloride and this was added to the solution of the base. The crystals which separated were filtered, washed with absolute ether, and dried *in vacuo* over calcium chloride and paraffin. The substance, m. p. 166°, started to melt at 144° but then solidified. The analyses were made on reprecipitated material.

Anal. Calcd. for $C_5H_8N_2SCl_2$: C, 30.15: H, 4.02; S, 16.08. Found: C, 31.01, 31.11; H, 4.56, 4.54; S, 16.62.

α′,β-Dichloromethylethyl Ketone from Ethylene and Chloroacetyl Chloride.—Two hundred and fifty ml. of dry petroleum ether (b. p. 40–60°) was placed in a three-necked flask fitted with a mechanical stirrer and a reflux condenser which was protected against moisture with a tube of calcium chloride, and 13.3 g. of powdered aluminum chloride (Akatos) was added. Ethylene was passed into the solution for two hours while the solution was maintained at the boiling temperature (47°) and most of the aluminum chloride dissolved; 11.3 grams of chloroacetyl chloride was added slowly through a separatory funnel and the mixture was boiled for thirty minutes after the addition of

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[14] Determined by titration by the *p*-nitrobenzoic acid method.

the chloroacetyl chloride. The mixture was poured into 600 ml. of ice water and stirred until the aluminum chloride had decomposed. The layer of petroleum ether was separated and the aqueous solution was extracted three times with a total volume of 300 ml. of diethyl ether. The combined extract was dried with anhydrous sodium sulfate, evaporated by a current of dry air and fractionated under reduced pressure. The fraction distilling at 63–65° under 3 mm. pressure was collected; yield 2.8 g.

0.14 Gram of this product and 0.076 g. of thiourea were dissolved in 4 ml. of water and heated for thirty minutes. The solution was made alkaline with a solution of sodium hydroxide and extracted with ether. The residue remaining after the evaporation of the ether melted at 60°. A mixed melting point determination of this material with the previously prepared thiazole base gave no depression. The hydrochloride of this substance was prepared as previously described, it melted at 166° and showed a tendency to fuse at 140° after which it solidified. This substance gave no depression in a mixed melting point determination with 4-(β-chloroethyl)-2-aminothiazole hydrochloride prepared from the larger sample of α′,β-dichloromethylethyl ketone. These facts are taken as positive proof that aluminum chloride can be used as a condensing agent for the preparation of this ketone.[15]

Summary

1. α′,β-Dichloromethylethyl ketone, 1,4-dichlorobutanone-2, has been prepared by the action of diazomethane on β-chloropropionyl chloride and subsequent treatment with dry hydrogen chloride.

2. α′,β-Dichloromethylethyl ketone has been prepared by the direct addition of ethylene to chloroacetyl chloride, using aluminum chloride as a condensing agent.

3. 4-(β-Chloroethyl)-2-aminothiazole has been prepared from α′,β-dichloromethylethyl ketone and thiourea. The hydrochloride of this base was identified by analysis.

4. Mixed melting point determinations have been used to identify the α′,β-dichloromethylethyl ketone prepared from ethylene and chloroacetyl chloride.

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[15] This reaction will be studied further in this Laboratory as a means of preparing chloro ketones.