ured and compared with the corresponding diphenyltrichloroethanes. None of the dithienyltrichloroethanes showed any contact insecticidal action to the insects investigated comparable to the action of DDT and its derivatives.[13] The thienyltrichloroethanes, however, dehydrohalogenated in alkaline solution fully as readily as did the corresponding DDT derivatives.

(13) These compounds showed no appreciable fungicidal action against species of *Phytophthora*, *Dothiorella*, and *Macrosporium* in tests by Dr. George Zentmeyer, of this station.

RIVERSIDE, CALIFORNIA RECEIVED FEBRUARY 27, 1947

[CONTRIBUTION FROM THE BOYCE THOMPSON INSTITUTE FOR PLANT RESEARCH, INC.]

The Cleavage of Tetrahydropyran by Acid Chlorides in the Presence of Zinc Chloride. The Preparation of 5-Diethylaminopentanol-1

BY MARTIN E. SYNERHOLM

It is known that aliphatic ethers and ethylene oxide are cleaved by acid iodides[1] and by acid chlorides in the presence of zinc chloride.[2] The application of this reaction to the fission of other cyclic ethers has received very little attention. Paul[3] in 1939 concluded that tetrahydrofuran and tetrahydropyran rings could be cleaved by acetic anhydride only in the presence of zinc chloride and at 190° or higher. Wilson[4] described what he considered to be the best conditions for preparing 5-bromo-*n*-amyl acetate. His procedure consisted of allowing a mixture of tetrahydropyran and an acetic anhydride solution of hydrogen bromide to react over a period of six days. He did not report his yield, but stated that his product contained about 2.5 moles per cent. of pentamethylene dibromide.

The application of this reaction using tetrahydropyran and acid chlorides in the presence of zinc chloride is described here. An example of its usefulness in organic synthesis is illustrated in the preparation of 5-diethylaminopentanol-1. This preparation is shown in the following sequence of equations

$$4\text{H-pyran} \xrightarrow[ZnCl_2]{RCOCl} R{-}CO_2(CH_2)_5Cl \xrightarrow[2\ KOH]{1\ Et_2NH} HO{-}(CH_2)_5NEt_2$$

The paucity of references to 5-chloropentanol-1 or its derivatives is undoubtedly due, at least in part, to the fact that this material is not stable but reverts easily, with loss of hydrogen chloride, to tetrahydropyran. The acetate has been reported by Bennett and Heathcoat,[5] who prepared it in 41% yield by the action at 100° for eight days of acetyl chloride on pentamethylene glycol. This acetate has now been prepared in 85% yield by warming acetyl chloride and tetrahydropyran in the presence of zinc chloride. Benzoyl chloride reacts in an analogous fashion to give a comparable yield of the benzoate. Zinc chloride is necessary in the reaction; without it the starting materials are recovered unchanged. The product, on warming with diethylamine for twenty-four hours, gave the expected benzoate[5a] of 5-diethylaminopentanol-1 in 38% yield. Increasing the time of heating to seven days raised the yield to 77%. The benzoate was then saponified with a 68% recovery of 5-diethylaminopentanol-1. This amino alcohol was described in 1933 by Magidson and Strukow,[6] who prepared it in 26% yield by the Bouveault and Blanc reduction of ethyl δ-diethylaminovalerate.

(1) Gustus and Stevens, THIS JOURNAL, **55**, 378 (1933).
(2) Norris and Rigby, *ibid.*, **54**, 2088 (1932).
(3) Raymond Paul, *Compt. rend.*, **208**, 587 (1939).
(4) Christopher L. Wilson, *J. Chem. Soc.*, 48 (1945).
(5) Bennett and Heathcoat, *ibid.*, 268 (1929).

Experimental

Benzoate of 5-Chloropentanol-1.—A mixture of 38 g. (0.27 mole) of redistilled benzoyl chloride, 30 g. (0.35 mole) of tetrahydropyran (dried over sodium hydroxide flakes and distilled) and 5 g. of freshly fused and coarsely ground zinc chloride was heated one hour on the steam-bath, cooled, diluted with 75 ml. of benzene and shaken, first with 50 ml. of cold water until the brown color had changed to yellow (about one minute), then with 50 ml. of a cold saturated solution of sodium bicarbonate until carbon dioxide was no longer evolved. The benzene layer, dried over anhydrous sodium sulfate, after fractionation boiled at 141–143° (2 mm.). The weight was 52 g. (yield 85%, based on the benzoyl chloride); $n^{20}D$ 1.5169; d^{20}_{20} 1.109; M_D calcd. 60.5; found 61.5.

Anal. Calcd. for $C_{12}H_{15}O_2Cl$: Cl, 15.63. Found: Cl (Parr bomb), 15.52.

Acetate of 5-Chloropentanol-1.—The acetate was prepared in 85% yield from acetyl chloride (25 g.), tetrahydropyran (30 g.) and zinc chloride (5 g.) under the conditions used in the preparation of the benzoate. The product boiled at 113–115° (34 mm.) or at 104° (18 mm.). This material is reported[5] to boil at 103° (18 mm.).

Benzoate of 5-Diethylaminopentanol-1.—A mixture of 100 g. (0.44 mole) of the benzoate of 5-chloropentanol-1 and 150 ml. of diethylamine (Sharples, dried over potassium hydroxide sticks and distilled) was heated in a pressure bottle at 75° for seven days, cooled, diluted with 100 ml. of benzene and evaporated *in vacuo* on a water-bath. The cooled mixture was diluted with 200 ml. of water and acidified with dilute hydrochloric acid (congo red), was extracted twice with 50-ml. portions of benzene. The combined benzene layers, after removal of the solvent, were found to contain about 15 g. of acid-insoluble material, of which about 5 g. consisted of unchanged 5-chloroamyl benzoate. The aqueous layer was neutralized carefully (in the presence of ice) with potassium carbonate, finally saturated with this reagent, and was extracted twice with 100-ml. portions of benzene. The combined

(5a) New compound.
(6) Magidson and Strukow, *Arch. Pharm.*, **271**, 569 (1933).

extracts were dried over anhydrous sodium sulfate and distilled. The product (light yellow) boiled sharply at 142–143° (1 mm.). The yield was 89 g. (77%), $n^{20}D$ 1.4971; d^{20}_{20} 0.980; M_D calcd. 78.1; found 78.0.

5-Diethylaminopentanol-1.—One hundred grams (0.38 mole) of the benzoate of 5-diethylaminopentanol-1, 200 ml. of water, 50 ml. of alcohol and 20 g. of potassium hydroxide were refluxed for four hours with vigorous stirring. The amino alcohol was salted out with potassium carbonate. After the addition of 50 ml. of benzene to the mixture, the potassium benzoate was filtered and washed with 50 ml. of benzene. The aqueous phase was extracted with a fresh 50-ml. portion of benzene. The combined benzene layers were dried over anhydrous potassium carbonate and distilled. The product, weighing 41 g. (68%), was collected at 125–130° (20 mm.). This material, on redistillation at 23 mm., boiled sharply at 130–131°; $n^{20}D$ 1.4544; lit.[6] b. p. 131° (23–24 mm.); $n^{20}D$ 1.4542.

Acknowledgment.—The author is grateful to E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware, for the sample of tetrahydropyran.

Summary

1. Acid chlorides react readily in the presence of zinc chloride to cleave the tetrahydropyran ring, forming 5-chloroamyl esters.

2. 5-Diethylaminopentanol-1 has been prepared in 44.5% over-all yield in three steps starting with benzoyl chloride and tetrahydropyran in the presence of zinc chloride, followed by replacement of the chlorine atom by a diethylamino group and hydrolysis.

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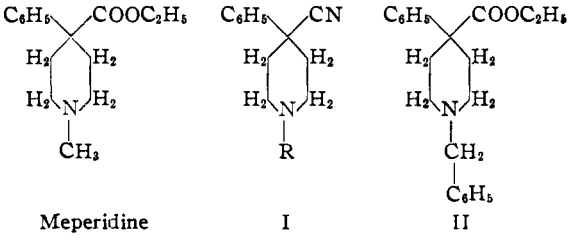
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Substituted 4-Aminomethylpiperidines and their Straight Chain Analogs[1]

BY CHARLES E. KWARTLER AND PHILIP LUCAS[2]

There are many references in the literature to the preparation[3] and pharmacological properties[4] of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride (meperidine, isonipecaine, Demerol,[5] Dolantin, Dolantal, Pethidine). The various pharmacological reports on meperidine hydrochloride emphasize its properties as an analgesic and spasmolytic agent. It appeared to be desirable, therefore, to institute a research program for the purpose of preparing compounds structurally similar to meperidine hydrochloride, or to incorporate into the meperidine nucleus various groupings which might result in compounds of significant pharmacological activity.



Meperidine I II

a, R = benzyl
b, R = methyl

During the synthesis of meperidine hydrochloride, several intermediates are prepared which readily lend themselves to further synthetic work. Among these compounds are 1-benzyl-4-cyano-4-phenylpiperidine (Ia), 1-methyl-4-cyano-4-phenylpiperidine (Ib) and ethyl 1-benzyl-4-phenylpiperidine-4-carboxylate (II).

The following series of catalytic reductions beginning with 1-benzyl-4-cyano-4-phenylpiperidine (Ia) has been carried out

By a procedure similar to that shown in Diagram I, 1-methyl-4-cyano-4-phenylpiperidine (Ib) is reduced with Raney nickel in the presence of an excess of ammonia[5a] to form 1-methyl-4-aminomethyl-4-phenylpiperidine. The reduction of ethyl 1-benzyl-4-phenylpiperidine-4-carboxylate (II) in the presence of palladium sponge resulted in the formation of ethyl 4-phenylpiperidine-4-carboxylate. Table I furnishes a summary of the amines prepared and studied in this paper. Some of the compounds reported in the present paper include the ureides, guanidino derivatives and urethans of the amines described in Table I.

In order to prepare the urea derivatives, nitrourea was used according to the method of Davis and Blanchard.[6]

As indicated in Diagram II, compounds VI, VII or VIII were obtained depending upon whether R was benzyl, methyl or hydrogen. By a procedure similar to that shown in Diagram II, ethyl 4-phenylpiperidine-4-carboxylate was converted to ethyl 1-carbamyl-4-phenylpiperidine-4-carboxylate. Table II furnishes a summary of the

(1) This paper was presented before the Medicinal Chemistry Division at the Chicago meeting of the American Chemical Society, September, 1946.

(2) Present address: Massengill Chemical Co., Bristol, Tennessee.

(3) (a) Eisleb, U. S. Patent 2,167,351 (1939); (b) Eisleb, *Ber.*, **74B**, 1433 (1941); (c) Bergel, Morrison and Rinderknecht, *J. Chem. Soc.*, 265–269 (1944).

(4) (a) Eisleb and Schaumann, *Deut. med. Wochschr.*, **65**, 967–968 (1939); (b) Schaumann, *Arch. exptl. Path. Pharmakol.*, **196**, 109–136 (1940); (c) Gruber, Hart and Gruber, *J. Pharmacol. Exptl. Therap.*, **73**, 319 (1941); (d) Barlow, Climenko and Homburger, *Proc. Soc. Exptl. Biol. Med.*, **49**, 11 (1942); (e) Climenko, *Federation Proc.*, [Pt. 11] **1**, 15 (1942); (f) Batterman, *Arch. Int. Med.*, **71**, 345 (1943); (g) Batterman and Himmelsbach, *J. Am. Med. Assoc.*, **122**, 222 (1943).

(5) Registered mark of the Winthrop Chemical Company, Inc.

(5a) Huber, THIS JOURNAL, **66**, 876 (1944).

(6) Davis and Blanchard, *ibid.*, **51**, 1790 (1929).