[CONTRIBUTION FROM THE LABORATORY FOR PURE RESEARCH OF MERCK & CO., INC.]

Preparation and Properties of Dialkylaminoalkyl Esters of Phenyl-α-naphthylamine-N-carboxylate

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Probably the most generally accepted theory of narcotic action is the Meyer-Overton theory which states that drugs having narcotic properties exert their main action on the central nervous system because they are taken up by the fats and lipoids which abound there and so are held in contact with the cell structures.[1]

A recent investigation of the solubility of a number of amines in olive oil revealed the extraordinary solubility of phenyl-α-naphthylamine in this solvent. It was also found that it was only very slightly toxic. This raised the thought that some relatively simple derivatives of this amine might be good local anesthetics.

Recently the pharmacological action of a number of N-aryl urethans has been reported. A few of these compounds seem to be promising local anesthetics.[2] Also Fromherz[3] reported in 1914 that diethylaminoethyl diphenylamine-N-carboxylate had a strong local anesthetic action.

Accordingly, several urethans derived from phenyl-α-naphthylamine have been synthesized.

Phenyl-α-naphthylcarbamyl chloride was prepared by the action of phosgene on phenyl-α-naphthylamine according to the method described by Kym,[4] for the preparation of phenyl-β-naphthylcarbamyl chloride.

$$2C_6H_5(C_{10}H_7)NH + COCl_2 \longrightarrow C_6H_5(C_{10}H_7)COCl + C_6H_5(C_{10}H_7)NH\cdot HCl$$

The preparation of diethylaminoethyl diphenylamine-N-carboxylate by refluxing diphenylcarbamyl chloride with an excess of diethylaminoethanol has been described in the patent literature.[5]

We attempted to prepare diethylaminoethyl phenyl-α-naphthylamine-N-carboxylate in a similar manner. However, the chlorine atom in phenyl-α-naphthylcarbamyl chloride was quite unreactive under these conditions and no condensation took place. However, when phenyl-α-naphthylcarbamyl chloride was treated with a suspension of the sodium derivative of diethylaminoethyl alcohol in an inert high boiling solvent, such as xylene, an immediate reaction took place. Sodium chloride was formed and a good yield of diethylaminoethyl phenyl-α-naphthylamine-N-carboxylate was obtained.

$$C_6H_5(C_{10}H_7)NCOCl + NaOC_2H_4N(C_2H_5)_2 \longrightarrow C_6H_5(C_{10}H_7)NCOOC_2H_4N(C_2H_5)_2 + NaCl$$

1,3-Bis-diethylaminopropane-2 phenyl-α-naphthylamine-N-carboxylate and 1,3-bis-dimethylamine-2-ethyl-propane-2 phenyl-α-naphthylamine-N-carboxylate were prepared by similar reactions.

Experimental Part

Phenyl-α-naphthylcarbamyl Chloride.—To a solution of 50 g. of phenyl-α-naphthylamine in 300 cc. of dry chloroform at 10°, was added a cold solution of 25 g. of phosgene in 200 cc. of chloroform. The mixture stood in the cold for twenty-four hours during which time a precipitate of the hydrochloride of phenyl-α-naphthylamine formed. This was removed by filtration. When the filtrate was evaporated an oil remained which slowly crystallized. When this was recrystallized from alcohol colorless prisms were obtained, m. p. 105°; yield, 26 g.

Anal. Calcd. for $C_{17}H_{12}NOCl$: N, 4.97; Cl, 12.38. Found: N, 4.85; Cl, 12.24.

Preparation of Monohydrochloride of Dialkylaminoalkyl Phenyl-α-naphthylamine-N-carboxylate.—One-tenth of a mole of the required amino alcohol was added to exactly 0.1 mole of powdered sodium in 200 cc. of dry xylene contained in a flask with a reflux condenser. The mixture was refluxed for several hours until all the sodium had reacted. During the reaction, hydrogen was evolved and a slightly discolored gelatinous precipitate of the sodium derivative of the amino alcohol was formed. To the mixture was added a solution of 0.1 mole of phenyl-α-naphthylcarbamyl chloride in 75 cc. of hot xylene. An immediate precipitation of sodium chloride took place. The reaction mixture was refluxed for one hour, cooled and the sodium chloride removed by filtration. A stream of dry hydrogen chloride was passed through the filtrate; the hydrochloride of the reaction product precipitated as an oil which soon crystallized. Purification was effected by liberating the free base, reconverting to the hydrochloride with the calculated amount of hydrogen chloride in absolute alcohol and precipitating with dry ether. The hydrochlorides of diethylaminoethyl phenyl-α-naphthylamine-N-carboxylate and 1,3-bis-dimethylamino-2-ethylpropane-2 phenyl-α-naphthylamine-N-carboxylate were non-hygroscopic, colorless, microcrystalline compounds with definite melting points. The hydrochloride of 1,3-bis-diethylamino-pro-

(1) Bastedo, "Materia Medica, Pharmacology and Therapeutics," W. B. Saunders Co., Philadelphia and London, 1932, p. 348.

(2) Rider, THIS JOURNAL, **52**, 2115 (1930); Knoefel, *J. Pharmacol.*, **47**, 69-78 (1933).

(3) Fromherz, *Arch Exptl. Path. Pharmacol.*, **76**, 257 (1914).

(4) Kym, *Ber.*, **23**, 425 (1890).

(5) German Patent 272,529.

TABLE I

ANALYTICAL AND OTHER DATA

	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
$C_6H_5(C_{10}H_7)NCOOC_2H_4N(C_2H_5)_2 \cdot HCl$	66	214–216	7.02	6.87	8.90	9.01
$C_6H_5(C_{10}H_7)NCOOCH(CH_2N(C_2H_5)_2)_2 \cdot HCl$	71	90 (dec.)	..	..	7.34	7.30
$C_6H_5(C_{10}H_7)NCOOC.C_2H_5(CH_2N(CH_3)_2)_2 \cdot HCl$	61	165–167	9.22	9.30	7.78	7 90

pane-2 phenyl-α-naphthylamine-N-carboxylate was a hygroscopic substance. When heated above 80° it gradually softened and decomposed.

Free Base of Diethylaminoethyl Phenyl-α-naphthylamine-N-carboxylate.—Diethylaminoethyl phenyl-α-naphthylamine-N-carboxylate which was first formed as an oil, crystallized after standing for several weeks. When it was recrystallized from light petroleum ether it occurred as colorless prisms which melted at 60–61°.

Anal. Calcd. for $C_{23}H_{26}O_2N_2$: N, 7.73. Found: N, 7.72.

Preparation of Acid Citrate of Diethylaminoethyl Phenyl-α-naphthylamine-N-carboxylate.—To a solution of diethylaminoethyl phenyl-α-naphthylamine-N-carboxylate in dry ether was added exactly one molecular equivalent of anhydrous citric acid, dissolved in a small amount of absolute alcohol. The precipitate which formed was collected on a filter, washed with dry ether and dried *in vacuo* over calcium chloride. It occurred as a colorless, microcrystalline, hygroscopic substance. When it was heated in a melting point tube, it gradually softened and decomposed with effervescence between 50 and 80°.

Anal. Calcd. for $C_{29}H_{34}O_9N_2$: N, 5.02. Found: N, 5.04.

We are indebted to Dr. Hans Molitor of the Merck Institute of Therapeutic Research for a pharmacological investigation of the new compounds. The results of his investigation will be reported in detail elsewhere. However it may be said that all of the new compounds were powerful local anesthetics. For terminal and bloc anesthesia the anesthetic action could be compared with that of a procaine solution of equal strength, whereas the action upon the eye and mucous membrane was somewhat stronger than that of procaine. Test animals tolerated a subcutaneous dose up to 25 mg. per kilo without any marked toxic symptoms. The toxicity by intravenous injection was very high. The new compounds had very marked penetrating powers. When an ointment containing from 5 to 20% of the anesthetic was rubbed into the intact skin of rabbits or guinea pigs, there was induced a degree of anesthesia sufficient to permit major surgical operations (as opening the abdomen or exposing the sciatic nerve). Unfortunately the penetrating action through the human skin was much lower.

Summary

1. Phenyl-α-naphthylcarbamyl chloride has been prepared.

2. Several dialkylaminoalkyl esters of phenyl α-naphthylamine-N-carboxylic acid have been prepared by the condensation of phenyl-α-naphthylcarbamyl chloride and the sodium derivative of the corresponding dialkylaminoalkyl alcohol.

3. The new urethans had a marked local anesthetic action.

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1-Xenyl-2-aminopropanol

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Xenylaminopropanol, an analog of norephedrine, has been synthesized with the expectation that it should have a pressor activity of sufficient magnitude to be of pharmacological interest. The synthesis of this substance was easily accomplished as follows: biphenyl was converted to 4-propionylbiphenyl from which the corresponding α-isonitroso derivative was prepared; the latter was then reduced to the desired 1-xenyl-2-aminopropanol which was isolated in the form of its hydrochloride. This salt appears to be stable for an indefinite period although the free base is oxidized immediately by air with the formation of colored products. The 4-propionylbiphenyl was obtained by the interaction of biphenyl with propionyl chloride in the presence of aluminum chloride, a reaction erroneously claimed by Willgerodt and Scholtz[1] to yield 3-propionylbiphenyl. The remaining steps of the synthesis require no comment as the methods employed were essentially those devised by Hartung and Munch[2] for the synthesis of norephedrine and its derivatives.

Through the couresty of Drs. Co Tui and Frank Calderone of the University and Bellevue Medical

(1) Willgerodt and Scholtz, *J. prakt. Chem.*, [2] **81**, 396 (1910).
(2) Hartung and Munch, THIS JOURNAL, **51**, 2262 (1929).