discussed. Procedures are described for the determination of nickel after removal of large amounts of cobalt and of iron. The procedure given for the determination of nickel in nickel steels yields good results.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

# Some Alkamine Esters of Disubstituted Methylcarbamic Acids

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Most prominent among the various types of simple amines exhibiting local anesthetic properties are the benzohydrylamines. Amines of this type ($C_6H_5CH(NH_2)R$) were first found to be active local anesthetics by Ogata[1] and further study by Fourneau and his collaborators led to the development of a whole series of extremely active local anesthetics including numerous alkoxy-substituted benzohydrylamines.[2] Certain compounds of analogous structure have been studied in this Laboratory and found to be quite active although rather irritating. Experience has shown that in some cases[3] mixed, or aliphatic–aromatic, types are often more active than the diaryl or benzohydrylamine derivatives themselves. Hence typical examples of each of these classes were included in the present investigation.

It was thought possible that the introduction of groups on the nitrogen atom in compounds of this type might act to decrease the irritation produced in the test animals and among the groups considered for this purpose was the COOR group. The present paper describes the preparation of several types of disubstituted methylcarbamates in which R is an aminoalkyl group. It was thought that such compounds might combine the high activity of the benzohydrylamines with that of the amino alcohol carbamates, which are known to be local anesthetics.[4]

The compounds prepared were of the type $R_1R_2CHNHCOO(CH_2)_nNR_2$ where $R_1$ and $R_2$ are either aromatic or aliphatic radicals. Two methods of preparation have been worked out for the isocyanate intermediate in the synthesis of the type in which $R_1$ and $R_2$ are both aromatic. The first is based on a modification of the Curtius reaction of acid azides as developed by Naejeli.[5] This involves the reaction of an acid chloride with sodium azide in dilute acetone solution to give the isocyanate which is immediately treated with the appropriate amino alcohol to give a substituted carbamate. The second method, which was applied also to the aliphatic compounds, consists of the preparation of the isocyanate by the reaction of the alkyl bromide with silver isocyanate and treating this in turn with an amino alcohol. The compounds prepared are listed in Table I.

The pharmacological data will appear elsewhere[6]; it may be said here that the compounds are highly active local anesthetics of toxicity comparable to cocaine; they are somewhat irritating, however.

## Experimental

**Diphenylmethyl Isocyanate.**—Fifteen grams of diphenylmethyl bromide was placed in a flask equipped with a reflux condenser and a mechanical stirrer, care being taken to protect the mixture from moisture at all times. One hundred cc. of anhydrous ether was then added and 12 g. of silver cyanate introduced. The mixture was refluxed and stirred for three hours and refluxing continued overnight. After filtering from the silver bromide, the ether was removed and the product distilled. Diphenylmethyl isocyanate boils at 148° (4 mm.). The yield is 80% of the theoretical.

**Amino Alcohol Carbamates.**—A dry ether solution of the above isocyanate was treated with the calculated quantity of the desired amino alcohol. The solution was refluxed for three hours to ensure completion of the reaction. On passing dry hydrogen chloride into the cold reaction mixture the hydrochloride of the basic urethan precipitated in a fairly pure state. The products can be recrystallized from dry acetone. They are nicely crystalline salts soluble in water and somewhat hygroscopic.

**Amino Alcohol Carbamates from Diphenylacetyl Chloride.**—Twelve grams of diphenylacetyl chloride was dissolved in 80 cc. of acetone and the solution cooled to 0°.

(1) R. Ogata, *J. Pharm. Soc. Japan*, **456**, 81 (1920).

(2) M. Valette, *Bull. soc. chim.*, (4) **47**, 289 (1930); C. Torres, *ibid.*, (4) **37**, 1591 (1925); Y. Bonnard and J. M. Bulif, *ibid.*, (4) **49**, 1303 (1931).

(3) E. R. Bockstahler, private communication.

(4) A. D. Boese and R. T. Major, THIS JOURNAL, **57**, 175 (1935).

(5) C. Naejeli and A. Tyabji, *Helv. Chim. Acta*, **16**, 350 (1933).

(6) The authors are indebted to J. H. Weatherby and H. R. Hulpieu and the Pitman-Moore Company for carrying out the pharmacological tests.

TABLE I

SUBSTITUTED ALKAMINE METHYLCARBAMATES

| | M. p., °C. | Nitrogen, % Calcd. | Found |
|---|---|---|---|
| $(C_6H_5)_2CHNHCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl$ | 179 | 7.75 | 7.63 |
| $(C_6H_5)_2CHNHCOOCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$ | 183 | 7.45 | 7.26 |
| $(C_6H_5)_2CHNHCOOCH_2CH_2N(C_4H_9)_2HCl$ | 136 | 6.70 | 6.53 |
| $(C_6H_5)_2CHNHCOOCH_2CH_2N\langle CH_2CH_2 \rangle CH_2 \cdot HCl$ | 119 | Cl, 9.69 | 9.58 |
| $(C_6H_5)(CH_3)CHNHCOOCH_2CH_2N(C_2H_5)_2$ | B. 178 (5 mm.) | 8.60 | 8.82 |
| $(C_6H_5)(CH_3)CHNHCOOCH_2CH_2CH_2N(C_2H_5)_2$ | B. 164 (3 mm.) | 8.24 | 8.29 |
| $(CH_3)_2CHNHCOOCH_2CH_2N(C_2H_5)_2HCl$ | 114 | 11.76 | 11.65 |

To this was added a saturated aqueous solution of sodium azide and the mixture shaken and cooled in ice for one-half hour. An excess of cold water was then added and the solution extracted at once with ether; the ether extract, after drying briefly over calcium chloride, was filtered and treated with the calculated quantity of the desired amino alcohol. The solution was refluxed for two hours, the ether removed and the residue heated at 100° under diminished pressure to remove unchanged amino alcohol. The free base thus obtained was taken up in dry ether and a stream of dry hydrogen chloride passed into the solution. The hydrochloride precipitated at once and was filtered and recrystallized from acetone. The yield was 64% of the theoretical.

**Amino Alcohol Esters of α-Phenylethylcarbamic Acid.**—Eighteen grams of α-phenylethyl bromide dissolved in 100 cc. of anhydrous ether was stirred and refluxed with 15 g. of dry silver cyanate for six hours and refluxing continued overnight without stirring. At the end of this time the silver salts were filtered off and the ether evaporated. The residual oil could be distilled under reduced pressure; in this way 10.5 g. of phenylethyl isocyanate (72%) b. p. 96° (18 mm.) was obtained. This was converted to the amino alcohol carbamates by refluxing in ether solution with an amino alcohol as in the case of the diphenylmethyl isocyanate above. The esters so prepared gave hydrochlorides that were extremely hygroscopic and difficult to purify and hence these compounds were purified by distillation of the free bases. For purposes of pharmacological testing the light yellow oils thus obtained were suspended in water and the calculated amount of hydrochloric acid added to give a solution of the hydrochlorides.

**β-Diethylaminoethyl Ester of Isopropylcarbamic Acid.**—Twenty-four grams of isopropyl bromide in 200 cc. of anhydrous ether was refluxed for forty-eight hours with 30 g. of silver cyanate, after which time the appearance of the suspended salts seemed to have changed. Twenty grams of β-diethylaminoethanol was then added and the mixture refluxed for three hours longer. After filtering from the silver salts and removing the ether, the residue was fractionated *in vacuo*. There was obtained 10 g. of a colorless viscous oil, b. p. 123–125° (5 mm.), consisting of the pure amino alcohol carbamate. When this was treated in dry ether solution with hydrogen chloride there was obtained a crystalline hydrochloride which was purified by crystallization from acetone.

## Summary

1. A method has been described for the preparation of alkamine esters of the type $\frac{R_1}{R_2}$>CHNHCOOR.

2. A series of esters has been prepared in which $R_1$ and $R_2$ are phenyl or methyl groups and R is an amino alkyl group.

3. Those compounds in which $R_1$ and $R_2$ are both phenyl exhibit marked local anesthetic activity.

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