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Synthesis of Some New *o*-Substituted Arylcarbamates and Related Compounds

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Seven new 2-substituted-5-*N*′, *N*′-dimethylaminophenyl *N*,*N*-dimethylcarbamates and three other compounds of similar structures have been synthesized aiming at obtaining potent anti-ChE agents. It has been found that the 2-substituents, regardless of their character, decrease the biological activity of the carbamates.

Many efforts had been made in the past to synthesize anticholinesterase agents (anti-ChE), e.g., carbamates, and to study the structure–activity relationship. Until 1945 most of the work had been directed toward the development of toxic agents. Later on, some compounds of that class, e.g., arylcarbamates, had found therapeutic applications, including the treatment of several serious diseases (*1*). Structure–activity studies indicated the importance of the presence of two alkyl groups at the carbamate nitrogen atom and a substituted amino group at the other part of the molecule (*2–4*). Effects of additional substituents, e.g., at the benzene ring in phenyl carbamates, had not yet been fully recognized.

Therefore, the main goal of this work was to synthesize the new 2-substituted-5-*N*′,*N*′-dimethylaminophenyl *N*,*N*-dimethylcarbamates, **2b–8b**, and some other compounds **9b–11b**, with allosteric substitution in the known 3-*N*′,*N*′-dimethylaminophenyl *N*,*N*-dimethylcarbamate **1b** (Scheme 1), to search for more satisfactory anti-ChE agents. Actually, compound **5b** has already been described (*5*) as a by-product from the neostigmine bromide degradation. It had been assumed by us that a substituent in the 2 position (*ortho* to the carbamate oxygen atom) would affect activity of the compounds to a greater extent. This assumption can be supported by the observation that, in a number of cases, anomalously enhanced transmissibility of electronic effects from substituents at the benzene ring to the carbamyl moiety had been observed (so called ''the positive bridge effect''). In addition, effects of 2-substituents, in contrast to 3- or 4-substituents (*6*), due to steric interactions, are rather unpredictable. Therefore, a synthetic work seemed to be necessary.

RESULTS AND DISCUSSION

Compounds **2b–8b** were obtained in a reaction of *N*,*N*-dimethylcarbamyl chloride with appropriately 2-substituted-5-*N*,*N*-dimethylaminophenols in the presence of bases. All attempts to use triethylamine in the reaction have failed. Even at elevated

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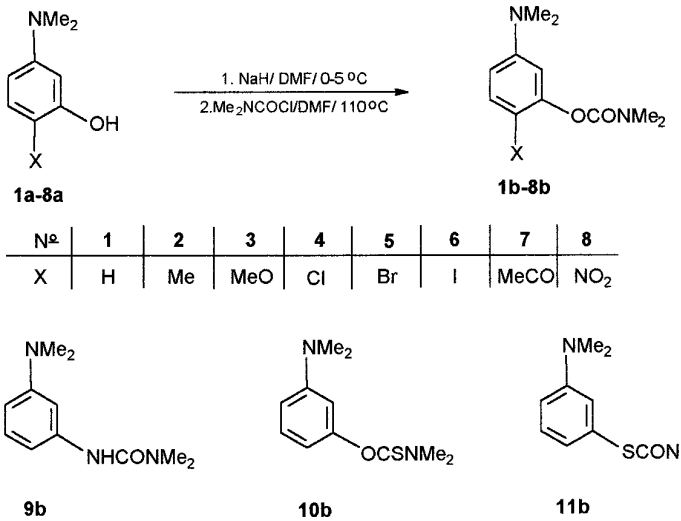

SCHEME 1

temperature (120°C) starting aminophenols have been recovered. The use of sodium salts, prepared from the dimethylaminophenols **1a–8a** by treating them with sodium hydroxide, led to the formation of the desired aryl carbamates, however, in low yields. Good results (yields 58–83%) were obtained when the sodium salts, prepared *in situ* by means of sodium hydride (*6*), were treated with dimethylcarbamyl chloride in anhydrous dimethylformamide at 110°C for ca. 3 h.

Products **1b–5b** and **7b**, separated from postreaction mixtures by extraction off unreacted dimethylaminophenols and residue distillation under reduced pressure, were practially pure. The iodo-derivative **6b** required column chromatography purification and the nitroderivative **8b** was precipitated by dilution of the postreaction solution with aqueous potassium hydroxide.

N′-(3-dimethylaminophenyl)-*N*,*N*-dimethylurea **9b**, allosteric with **1a**, was prepared by carbamylation of the corresponding amine **9a** according to the method of Michler and Escherich (*7*) known for a synthesis of, e.g., *N′*-phenyl-*N*,*N*-dimethylurea. The reaction of **1a** (formerly treated with sodium hydride) with *N*,*N*-dimethylthiocarbamyl chloride yielded a crude product which required troublesome purification to obtain the expected **10b** in 33%. Thermal rearrangement of **10b** gave known **11b**, though in a lower yield than reported earlier (*7*).

Structures of all new compounds were proved by elemental analyses, IR and ^{1}H NMR spectra. Elemental analysis data were in accordance with calculated ones within a range of 0.1% for C, 0.2% for H, and 0.1% for N. Basic physical constants and yields of the synthesized compounds are given in the experimental part. ^{1}H NMR data are disclosed in Table 1.

We have undertaken several attempts to correlate the protons chemical shifts