The Synthesis of Aryloxycarbamates

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Certain carbamic acid esters are widely used as sedatives and muscle relaxants.[1] In this communication, we describe the synthesis of nine aryloxycarbamates, the first examples of carbamates carrying the novel aryloxy substituent (Table I).

TABLE I

Carbamate	Mp, °C	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ethyl phenoxy	58–59	Hexane–benzene	$C_9H_{11}NO_3$	59.66	6.12	7.73	59.38	5.96	7.74
Benzyl phenoxy	111–112	Acetone	$C_{14}H_{13}NO_3$	69.14	5.39	5.76	68.88	5.31	5.42
n-Butyl phenoxy	40–41	Hexane–ether	$C_{11}H_{15}NO_3$	63.16	7.18	6.70	62.99	7.60	6.73
Phenyl phenoxy	122–123	Ether	$C_{13}H_{11}NO_3$	68.12	4.80	6.11	67.72	5.09	6.33
Allyl phenoxy	71–72	Hexane	$C_{10}H_9NO_3$	62.16	5.74	7.25	62.22	5.90	7.27
Phenyl *m*-trifluoromethylphenoxy	70–76	Hexane	$C_{14}H_{10}F_3NO_3$[a]	56.57	3.37	4.71	56.41	3.50	5.01
Phenyl *p*-tolyloxy	104–108	Benzene	$C_{14}H_{13}NO_3$	69.14	5.39	5.76	69.29	5.22	5.82
Phenyl *m*-chlorophenoxy	101–102	Hexane–benzene	$C_{13}H_{10}ClNO_3$[b]	59.20	3.80	5.31	59.17	4.22	5.23

[a] *Anal.* Calcd: F, 19.19. Found: F, 19.16. [b] *Anal.* Calcd: Cl, 13.47. Found: Cl, 13.62.

The aryloxycarbamates were prepared by the reaction of an aryloxyamine and a chloroformate ester. Aryloxycarbamates with an N–H proton are acidic compounds soluble in dilute aqueous sodium carbonate and can be alkylated with an alkyl halide under basic conditions.

Experimental Section[2]

***m*-Trifluoromethylphenoxyamine Hydrochloride.**—The method described by Baumgardner and Lilly[3] for phenoxyamine was employed. A mixture of 100 g (0.60 mole) of *m*-hydroxybenzotrifluoride, 33.6 g (0.6 mole) of KOH, 420 ml of water, and 200 ml of methylcyclohexane was heated under reflux with stirring, and a solution of 17.0 g (0.15 mole) of hydroxylamine-O-sulfonic acid in 40 ml of water was added. After 10 min, the mixture was cooled, the layers were separated, and the aqueous phase was extracted with ether. The combined organic solutions were washed with 1 *N* NaOH and water and were dried ($MgSO_4$). The solution was acidified with ethanolic HCl. The solid which separated was collected and recrystallized from isopropyl alcohol–ether to provide 2.1 g (6.5%) of colorless plates, mp 150–151° dec.

Aryloxycarbamates.—A mixture of 0.01 mole of an aryloxyamine hydrochloride[3,4] and 10 ml of 1 *N* NaOH was extracted with ether, and the ether solution was dried briefly (K_2CO_3). Then, 0.01 mole of a chloroformate ester was added. A colorless solid gradually separated, and after 2 hr was collected; in each case it was identified as the aryloxyamine hydrochloride. The filtrate was concentrated, and the residue was crystallized from the indicated solvent.

Ethyl N-Methyl-N-phenoxycarbamate.—A solution of 0.23 g (0.011 g-atom) of Na in 10 ml of anhydrous ethanol was prepared, and 1.81 g (0.01 mole) of ethyl phenoxycarbamate was added. After 15 min, 1 ml of CH_3I was added, and the solution was stirred at room temperature for 18 hr. The solvent was distilled, and the residue was taken up in water. The mixture was extracted with ether, and the ether phase was dried (K_2CO_3) and concentrated to an oil. Distillation gave 1.53 g (79%) of a colorless liquid, bp 64–65° (0.04 mm).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 62.03; H, 7.11; N, 7.24.

(1) W. C. Cutting, "Handbook of Pharmacology," Appleton-Century-Crofts, New York, N. Y., 1964, pp 538, 569.

(2) Melting points were determined in a Hershberg apparatus and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff.

(3) C. L. Baumgardner and R. L. Lilly, *Chem. Ind.* (London), 550 (1962).

(4) V. J. Bauer and H. P. Dalalian, *J. Med. Chem.*, **8**, 886 (1965).

Book Review

The Salicylates. A Critical Bibliographical Review. Edited by M. J. H. SMITH and P. K. SMITH. Interscience Publishers–John Wiley and Sons, Inc., New York, N. Y. 1966. xiv + 313 pp. 16.5 × 24.5 cm. $10.00.

After a century of wide-spread clinical use of the salicylates, their mode of action on the molecular level is still unknown. The chemical structure of the salicylates is so simple, and their biological and therapeutic action so varied, that thousands of investigators have tried to unravel this mystery. A review of all the facets of metabolism, interaction at the molecular and tissue level, and the analgetic–antipyretic and toxicological effects is both timely and welcome.

The orientation of this book is biochemical wherever possible. In the study of the effects of a drug on enzymes and on substrates, one would probably start looking for information in the simplest cell systems, especially if the drug affects microorganisms as in the case of the salicylate ion. Indeed, a fair amount of salicylic acid is manufactured for use in the inhibition of microbial floras. It is therefore disturbing that the present "critical review" nowhere even mentions or lists this extensive area of research and practical uses. This broad omission, for which no excuse is offered, shakes one's faith in the critical attitude of the whole volume. Nevertheless, the pharmacological and clinical manifestations of the salicylates are well treated and documented. The descriptions of the interactions of the drugs with endocrine systems, and their analgetic and antiinflammatory actions will fill a real need in the assessment of these confused fields. The chapter on toxicity is excellent and should form the basis for an evaluation of excessive claims as they are found in the news media.

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