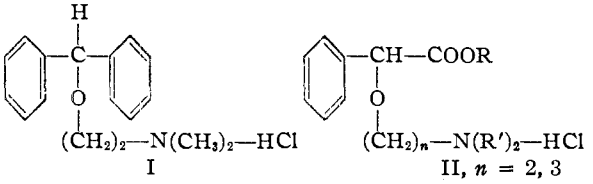
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Alkyl α-(2-Dialkylaminoalkoxy)-phenylacetates. I[1]

BY PRICE TRUITT, DEWEY MARK,[2] LOREN M. LONG[3] AND JACK JEANES[4]

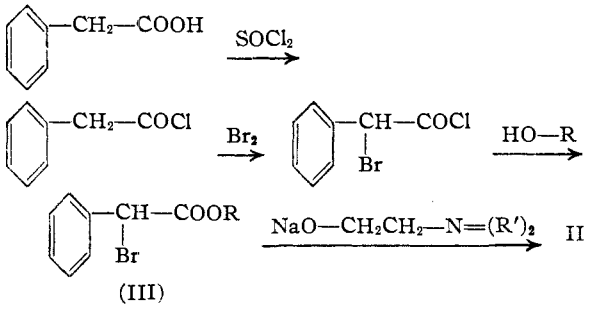
The success of Benadryl (I),[5] 2-dimethylaminoethyl benzhydryl ether hydrochloride, as a histamine antagonist[6] prompted the present investigation.

It was considered possible that, by replacing one of the benzene rings of the Benadryl molecule with various ester groups, and altering the structure of the dialkylaminoalkyl group, a compound might be found with desirable pharmacological properties. A comparison between the structure of Benadryl (I) and the general structure of the proposed compounds (II) is shown below

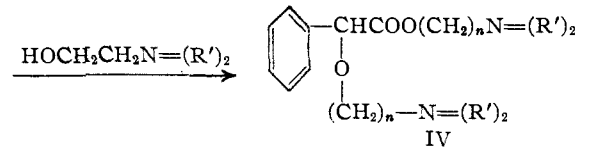


I II, n = 2, 3

The proposed method for preparing these esters, derivatives of phenylacetic acid, is shown by the following continuous equation



Attempts were made to use powdered potassium carbonate to bring about the condensation of the basic alcohol and the α-bromo ester (III); however, little of the desired product could be isolated from these reactions. In some instances the basic alcohol alone condensed satisfactorily to yield the hydrobromide of the desired ester, but in most preparations it was necessary to use the sodium or potassium salt of the aminoalcohol. The most serious competing reaction observed was that of ester exchange (see equation below). The fact that the compounds of type (IV) were formed was proved by comparison with compounds known to have this structure.[7] Attempts to isolate and purify the hydrobromides or hydrochlorides of the various basic products were often difficult or impossible due to the hydroscopic nature of the salts.



IV

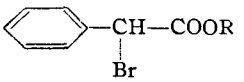
Experimental

Phenylacetyl Chloride.[8]—This compound was prepared in 95% yield by the action of 1.5 moles of thionyl chloride on one mole of phenylacetic acid without the use of a solvent. The mixture was refluxed until hydrogen chloride and sulfur dioxide ceased to be evolved. Distillation gave a product distilling from 94–96° at 12 mm.

α-Bromophenylacetyl Chloride.[9]—The phenylacetyl chloride was readily brominated by refluxing six hours with an equal molar amount of bromine with carbon tetrachloride as the solvent. If the product was not used immediately, it was distilled *in vacuo*, b. p. 125° (8 mm.).

Alkyl α-Bromophenylacetate (Table I).—These esters were prepared by adding one and one-tenth moles of anhydrous alcohol to a cooled solution of one mole of α-bromophenylacetyl chloride in carbon tetrachloride. The solutions were subsequently refluxed for one hour and the products purified by distillation *in vacuo*.

TABLE I

FORMULA III 

R	B. p., °C.	Mm.	Yield, %	Bromine, % Calcd.	Found
Methyl[10]	113	3	94	34.87	34.75
Ethyl[10]	127	3	79	32.88	32.80
Isopropyl	124	2	91	31.12	30.82
n-Hexyl	155	8	87	26.72	26.61
Benzyl	228	3	60	26.26	26.08

Alkyl α-(2-Dialkylaminoalkoxy)-phenylacetates (Table II).—One mole of potassium or sodium metal was added to one and one-tenth moles of dialkylaminoalkanol dissolved in dry benzene. When all of the metal had reacted, one mole of alkyl α-bromophenylacetate dissolved in benzene was added to the suspension of alkoxide. The mixture was refluxed with continuous stirring for twelve to forty-eight hours. The shorter time gave less reaction, while with longer refluxing ester exchange seriously cut down the yield of desired product in at least some instances. The structure of the dialkylaminoalkanol apparently affected the degree of ester exchange. Optimum time was twenty-four hours for most of the reactions.

(1) (a) The work described in this paper was made possible by a grant-in-aid from Parke, Davis and Company; (b) presented before the Medicinal Section at the Chicago meeting of American Chemical Society, April 21, 1948.

(2) Present address: Department of Chemistry, Indiana University, Bloomington, Indiana.

(3) Research Chemist, Parke, Davis and Company, Detroit, Mich.

(4) Parke, Davis Fellow, 1947–1948.

(5) Rieveschl and Huber, Paper 41, Division of Medicinal Chemistry, The American Chemical Society meeting, Atlantic City, 1946.

(6) Loew, Kaiser and Moore. *J. Pharmacol. Exptl. Therap.*, **83**, 120 (1945).

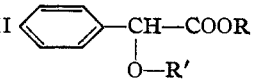
(7) The preparation of these compounds will be given in the next paper of this series.

(8) Stecker, *Ann.*, **113**, 68 (1860).

(9) Wieland and Fisher, *ibid.*, **446**, 65 (1925).

(10) Hell and Weinzweig, *Ber.*, **28**, 2446 (1895).

TABLE II

FORMULA II 

R	R′	Yield, %	B. p., °C.	Mm.	Reflux time, hours	Empirical formula	Nitrogen, % Calcd.	Found
Methyl	2-Dimethylaminoethyl·HBr	39	201.5[a]		48	$C_{13}H_{20}BrNO_3$	4.58	4.49
Methyl	2-Diethylaminoethyl	18	160–165	4	18	$C_{15}H_{23}NO_3$	5.27	5.40
Methyl	2-Morpholinoethyl	10	168–170	4	24	$C_{15}H_{21}NO_4$	5.03	5.25
Ethyl	2-Dimethylaminoethyl	17	145–146	3	24	$C_{14}H_{21}NO_3$	5.58	5.55
Ethyl	2-Diethylaminoethyl	18	148–150	2	20	$C_{16}H_{25}NO_3$	5.02	5.27
Ethyl	2-Piperidinoethyl	11	178–182	2	48[7]	$C_{17}H_{25}NO_3$	4.82	5.10
Ethyl	2-Morpholinoethyl	5	177–179	3	36[7]	$C_{16}H_{23}NO_4$	4.78	4.83
Isopropyl	2-Dimethylaminoethyl	12	129–133	2	20	$C_{15}H_{23}NO_3$	5.28	5.03
Isopropyl	2-Diethylaminoethyl	14	150–155	3	24	$C_{17}H_{23}NO_3$	4.81	4.61
Isopropyl	2-Piperidinoethyl	21	140–144	4	24	$C_{18}H_{27}NO_3$	5.38	5.28
Isopropyl	2-Dimethylaminopropyl	19	138–140	2	18	$C_{16}H_{25}NO_3$	5.02	5.09
Isopropyl	2-Dibutylaminoethyl	7	170–173	4	36[7]	$C_{21}H_{35}NO_3$	4.01	4.03
n-Hexyl	2-Dimethylaminoethyl	11	140–144	4	20	$C_{18}H_{29}NO_3$	4.61	4.80
n-Hexyl	2-Di-*n*-butylaminoethyl	9	130–135	4	24[7]	$C_{24}H_{41}NO_3$	3.59	3.65
n-Hexyl	2-Morpholinoethyl	9	155–159	3	18[7]	$C_{20}H_{31}NO_4$	4.38	4.42
n-Hexyl	2-Diethylaminoethyl	10	160–163	1	12	$C_{20}H_{33}NO_3$	4.14	4.16
n-Hexyl	2-Diethylaminopropyl	15	190–193	7	12	$C_{21}H_{35}NO_3$	4.07	4.19
Benzyl	2-Dimethylaminoethyl·HBr	17	212–213[a]		12	$C_{19}H_{24}BrNO_3$	3.81	3.75
Benzyl	2-Piperidinoethyl·HBr	8	229–230[a]		36	$C_{22}H_{27}BrNO_3$	3.40	3.26
Benzyl	2-Diethylaminoethyl	24	195–199	3	24	$C_{21}H_{27}NO_3$	4.11	4.30
Benzyl	2-Di-*n*-butylaminoethyl	23	200–205	3	24	$C_{25}H_{35}NO_3$	3.52	3.95

[a] Melting point, °C. cor.

The product was isolated by washing the reaction mixture with water to remove the bromides and any unreacted aminoalcohol. The benzene layer was extracted with 10% hydrochloric acid and this extract washed with ether. When the acid extract was made alkaline by the addition of sodium bicarbonate, an oil separated which was taken up in ether, dried and the ether evaporated. The oily residue was purified by at least two fractional distillations.

Most of the compounds described in this paper have been found to exhibit no antihistaminic activity.

TABLE III

Compound	Antispasmodic action % of papaverine Rabbit	Guinea pig
1	1	4
3	6	10
6	15	25
7	10	8
18	1	1
19	12	20

In addition, several of the compounds were tested for antispasmodic activity. The results are collected in Table III. The number of the compound refers to Table II.

The physiological activity of these compounds did not warrant further testing at this time.

Summary

Five alkyl α-bromophenylacetates have been prepared; three are new to the literature. These esters have been converted to the corresponding alkyl α-(2-dialkylaminoalkoxy)-phenylacetates by condensing with dialkylaminoalkanols. Twenty-one compounds of this structure have been prepared. All are new to the literature. Some of these compounds were found to exhibit a slight antispasmodic activity but no antihistamine activity.

DENTON, TEXAS RECEIVED SEPTEMBER 3, 1948