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

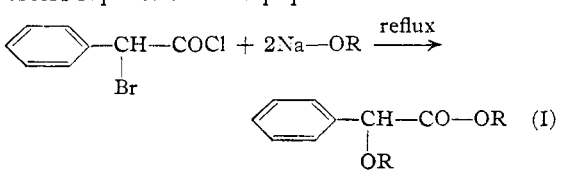
2-Dialkylaminoalkyl α-(2-Dialkylaminoalkoxy)-phenylacetates and Related Amides. II[1]

BY PRICE TRUITT, E. E. RICHARDSON,[2] LOREN M. LONG[3] AND WILLIAM J. MIDDLETON[4]

In the first paper of this series[5] a number of compounds structurally related to 2-dimethylaminoethyl benzhydryl ether hydrochloride, Benadryl,[6] were reported. These compounds were alkyl esters of α-(2-dialkylaminoalkoxy)-phenylacetic acid. Although this substitution of the alkyl carboxyl group for one of the phenyl groups of Benadryl completely eliminated the antihistaminic activity, some antispasmodic activity was noted.[7]

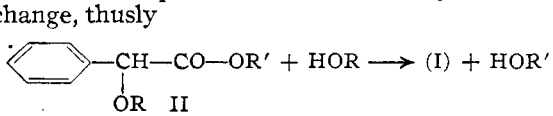
Since numerous reports of physiologically active compounds containing the dialkylaminoalkyl ester linkage have been recorded,[8] we deemed it worthwhile to prepare some 2-dialkylaminoalkyl esters of the α-2-dialkylaminoalkoxy)-phenylacetic acids in order to compare their physiological activity with that of the previously reported alkyl α-(2-dialkylaminoalkoxy)-phenylacetates.[5] Also to obtain a still broader view of the effect of changes in structure on physiological activity, the preparation of several amide derivatives of the α-(2-dialkylamino-alkoxy)-phenylacetic acids was desirable.

The reactions utilized in the preparation of the esters reported in this paper are



R = 2-dialkylaminoalkyl, 2-piperidinoethyl, 2-morpholinoethyl

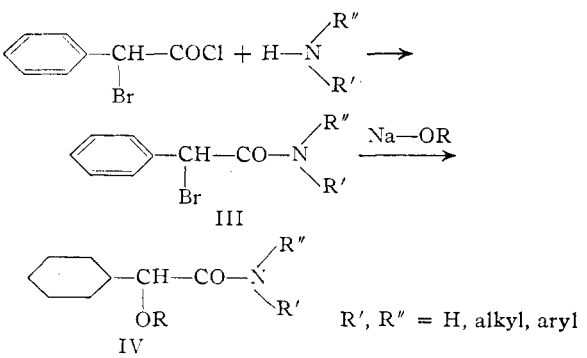
In the preceding paper mention was made of the fact that compound I was formed by ester exchange, thusly



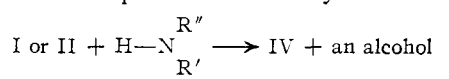
R′ = alkyl, R = as above

The latter method will give a satisfactory yield (60–80%) of I but it is not a useful method of preparation since compound II is obtained in poor yield in two steps from bromophenylacetyl chloride. The method utilized for the synthesis of the esters reported in this paper involves only one step in addition to the preparation of α-bromophenylacetyl chloride.

The amides corresponding to the above esters were obtained via the reactions



Attempts to prepare compound IV by the following reaction were not satisfactory. The yields of desired products were very low.



None of the compounds reported in this paper exhibited anti-histaminic activity; however, all of those tested showed some antispasmodic action.

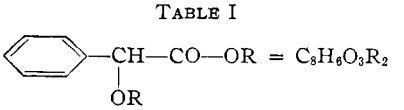
Experimental

The dialkylaminoalkanols used in these experiments were obtained from Eastman Kodak Company and distilled before use.

The α-bromophenylacetyl chloride was prepared as previously reported.[5]

2-Dialkylaminoalkyl α-(2-Dialkylaminoalkoxy)-phenylacetates (Table I).—Two moles of potassium metal was added to 2.2 moles of dialkylaminoalkanol dissolved in

TABLE I



R	Yield, %	B. p., °C.	Mm.	$n^{20}D$	Nitrogen, % Calcd.	Found	Anti-spas.[c] 1	2
$(CH_3)_2NC_2H_4$	77	215	20	1.5011	9.49	9.36	12	5
$(C_2H_5)_2NC_2H_4$	75	200	12	1.4943	8.60	8.80	8	20
$C_4H_8NOC_2H_4$[a]	38	155	3	1.5170	7.22	6.94	10	5
$(C_2H_5)_2NC_3H_6$	71	145	3	1.4948	7.41	7.46		
$C_5H_{10}NC_2H_4$[b]	73	160	6	....	7.48	7.31		
n-$(C_4H_9)_2NC_2H_4$	43	230	5	....	6.06	6.27		

[a] 2-Morpholinoethyl. [b] 2-Piperidinoethyl. [c] Anti-spasmodic action on (1) the rabbit, (2) the guinea pig as % of that of papaverine.

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(4) Research Fellow 1947–1948, Faculty Research Grant.

(5) Truitt, Mark, Long and Jeanes, THIS JOURNAL, **70**, 4214 (1948).

(6) Rieveschl and Huber, Paper 41, Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, 1946.

(7) Recent tests indicate that one of these compounds, benzyl α-(2-diethylaminoethoxy)-phenylacetate had an antispasmodic activity of 200% of papaverine with barium chloride induced spasms and 300% with acetylcholine.

(8) Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

dry toluene. When all of the potassium had reacted, 1 mole of freshly distilled α-bromophenylacetyl chloride dissolved in an equal volume of dry toluene was added dropwise with constant stirring. When the initial reaction had subsided, the mixture was refluxed with continuous stirring for four to ten hours. Apparently little reaction occurred after the four hours heating period but no decrease in yield was noted when the longer reflux time was used.

The reaction mixture was filtered to remove the precipitated sodium salts and the toluene was subsequently distilled under a water-pump vacuum. The residual liquid was distilled *in vacuo* and further purified by two fractional distillations. The hydrochlorides of these esters were too hydroscopic to handle conveniently.

α-Bromophenylacetamide.—A concentrated solution of 2 moles of ammonium hydroxide was cooled to −10°. This solution was stirred vigorously while 1 mole of α-bromophenylacetyl chloride was added dropwise. Care was taken to keep the temperature of the reaction mass below 0°. After stirring for two hours at this temperature the reaction was allowed to warm to room temperature. The crystals which had formed were collected and recrystallized from alcohol to give glistening white crystals of α-bromophenylacetamide.

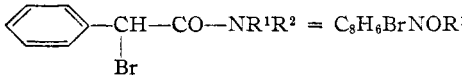
N,N-Diethyl α-Bromophenylacetamide.—A solution of 1 mole of α-bromophenylacetyl chloride in an equal volume of carbon tetrachloride was cooled to −10° and a solution of 2 moles of diethylamine in carbon tetrachloride added dropwise with constant stirring so as to keep the temperature below 0°. After stirring for two hours at this temperature, water was added to dissolve the diethylamine hydrochloride. The organic layer was separated, dried and the carbon tetrachloride distilled *in vacuo*. The liquid residue was fractionated at reduced pressure to give N,N-diethyl-α-bromophenylacetamide.

The remaining amides were prepared in an analogous manner. Data for all of the amides are given in Table II.

α-(2-Piperidinoethoxy)-phenylacetamide.—One mole of α-bromophenylacetamide was refluxed with 1 mole potassium 2-piperidinoethoxide suspended in xylene for two hours. The product was extracted from the xylene with 5% hydrochloric acid. Neutralization of this acid extract gave a white precipitate. Recrystallization from alcohol gave white flakes of the expected α-(2-piperidinoethoxy)-phenylacetamide.

Other amides were prepared in the same manner and data concerning these are given in Table III. N,N-Diphenyl-α-bromophenylacetamide failed to give the expected product. The yields in all other cases were approximately 50%.

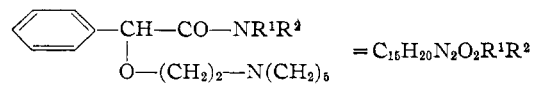
TABLE II



R¹	R²	Yield, %	M. p.,[a] °C.	% Bromine Calcd.	% Bromine Found	% Nitrogen Calcd.	% Nitrogen Found
H	H	92	148[b]	37.34	37.49	6.55	6.54
C_2H_5	C_2H_5	49	155–160[c]	29.59	29.68	5.18	5.22
H	C_6H_5	40	123	27.53	27.65	4.83	4.90
C_6H_5	C_6H_5	32	140	21.82	21.95	3.82	3.87
H	CH_3	68	74	35.07	35.17	6.15	6.23

[a] Corrected. [b] First prepared by Darapsky, *J. prakt. Chem.*, **96**, 285 (1917). [c] B. p. at 6 mm.

TABLE III



R¹	R²	Yield, %	M. p.,[a] °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Antispas.[b] 1	Antispas.[b] 2
H	H	165–167	155–157	10.69	10.77	20	80
CH_3	H	51	133–134	10.15	10.26	15	10
C_6H_5	H	43	171–172	6.39	6.48		
C_2H_5	C_2H_5	47	[c]	8.80	8.91		

[a] Corrected. [b] Tests as given in Table I. [c] An oily solid that melted slightly above room temperature.

Summary

Six dialkylaminoalkyl α-(2-dialkylaminoalkoxy)-phenylacetates have been prepared and characterized. In addition six N- and N,N-disubstituted α-bromophenylacetamides have been synthesized and four of these converted to the corresponding N- and N,N-substituted α-(2-piperidinoethoxy)-phenylacetamides. A partial evaluation of the physiological properties for some of these compounds is given.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of Certain 2-Alkoxyethyl Phenyl Ketones[1]

BY ROBERT EDWARD LESLIE[2] AND HENRY R. HENZE

In connection with another problem, certain alkoxyethyl ketones, especially the 2-propoxyethyl phenyl and 2-(1-methylethoxy)-ethyl phenyl ketones, were needed. Initially, it was visualized that these ketones might be prepared from interaction of Grignard reagents and appropriately substituted alkoxypropionitriles. Attempts to develop this method were not successful, but the desired substances were obtained as a result of reactions between diphenylcadmium and certain β-alkoxypropionyl chlorides. The latter were synthesized through the following sequence: (a) addition of appropriate alcohols to acrylonitrile[3] forming β-alkoxynitriles; (b) hydrolysis of the latter to the corresponding β-alkoxypropionic acids; (c) subsequent conversion into β-alkoxypropionyl chlorides.

Preparation of the ketones was tried first by the method of Cason,[4] namely, addition of the acyl halide to the solution of diphenylcadmium, but the reaction complexes formed very heavy precipitates. Before reaction was complete, agglutination of the suspended matter made stirring practically impossible and thus homogenization of the reaction mixtures was not attained. However, by reversing the sequence of addition of reactants, clumping of the addition products was avoided and

(1) From the M.A. thesis of R. E. Leslie, June, 1948.

(2) Present address: Guatemala City, Guatemala, C. A.

(3) Utermohlen, THIS JOURNAL, **67**, 1505 (1945).

(4) Cason, *ibid.*, **68**, 2078 (1946)