[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Alkyl Ethers of Basically-substituted 2-Amino-1-phenylethanol[1]

BY IRVING ALLAN KAYE AND IRVING C. KOGON[2]

The methyl ether of 2-amino-1-phenylethanol and a number of methyl and ethyl ethers of N-mono- and disubstituted 2-amino-1-phenylethanols were synthesized for pharmacological evaluation. The products were prepared either by the reaction of phenylmagnesium bromide with N-substituted aminoacetals at high temperatures or by treating an alkyl ether of 2-bromo-1-phenylethanol with a primary or secondary amine. The primary amino-ether was obtained by catalytic debenzylation of the methyl ether of 2-benzylamino-1-phenylethanol.

A series of compounds of general formula I were prepared as a consequence of the observation that the ethyl ether of 2-di-*n*-butylamino-1-phenylethanol hydrobromide displayed considerable potency in topical anesthesia.

$$C_6H_5—CH(OR)—CH_2—NR'R'' \qquad (I)$$

R = methyl or ethyl; R′ = hydrogen, alkyl, aralkyl, dialkylaminoalkyl or alkanol; R″ = R′ or hydrogen; $-NR'R''$ = piperidino or morpholino.

In the course of this work two methods were employed for the preparation of these compounds; a third (Method C) was used in preparing only one product. Method A is a modification of a procedure developed by Tschitschibabin, Jelgasin[3] and Späth.[4] Ethers of this type, lacking the basic substituent were prepared, by these investigators, by the reaction of phenylmagnesium bromide with acetal at an elevated temperature in the absence of solvent.[3,4]

Method A

$$C_6H_5MgBr + (RO)_2CH—CH_2NR'R'' \longrightarrow (I) + ROMgBr$$

Method B

$$C_6H_5CH(OR)CH_2Br + 2HNR'R'' \longrightarrow (I) + HNR'R''\cdot HBr$$

Method C

$$C_6H_5CH(OCH_3)CH_2NH(CH_2C_6H_5) + H_2 \xrightarrow{Pd\text{-}C} C_6H_5CH(OCH_3)CH_2NH_2 + C_6H_5CH_3$$

$$C_6H_5MgBr + CH_3—CH(OC_2H_5)_2 \longrightarrow C_6H_5—CH(OC_2H_5)CH_3 + C_2H_5OMgBr$$

As a general method for the preparation of ethers this procedure has not gained prominence primarily because of the unsatisfactory yields.[5] An attempt to prepare I (where R = ethyl and R′ = R″ = *n*-butyl) from phenylmagnesium bromide and di-*n*-butylaminoacetal, using the aforementioned experimental conditions,[3,4] gave rise to a reaction, initiated at about 135°, which quickly became so vigorous that an explosion occurred. It was found subsequently that the reaction could be moderated when conducted in xylene and that the expected amino ether could then be obtained in good yield (Method A). When used for the preparation of other members of this series, this mode of synthesis revealed some serious limitations as to yield and purity of product.

Houben and Führer[6] reported good yields of tertiary amino ethers by condensing β-chloro ethers with secondary amines. This seemed to be an alternative approach which might overcome these objections. Ammonia and primary amines were found to give mixtures of products.

$$R—CH(OC_2H_5)CH_2Cl + 2HNR'R'' \longrightarrow R—CH(OC_2H_5)CH_2NR'R'' + HNR'R''\cdot HCl$$

Swallen and Boord[7] also obtained mixtures in the reaction of aniline, a primary amine, with ethyl β-chloroethyl and ethyl β-chlorobutyl ethers.

This method (Method B) proved superior for the preparation of the tertiary amino ethers of formula I. Good yields of pure products were easily obtained by heating the ethyl or methyl ether of 2-bromo-1-phenylethanol with two or more equivalents of secondary amine. The products obtained in this fashion distilled over narrower temperature ranges; salts of these compounds had sharper, and often higher, melting points. Ammonia and methylamine yielded mixtures which were difficult to separate but other primary amines, contrary to expectations, gave good yields of secondary amino ethers. The primary amino ether (I, R′ = R″ = H) was prepared in good yield by catalytic debenzylation (Method C) of the methyl ether of 2-benzylamino-1-phenylethanol.

All the amino ethers described in this publication are new, with the exception of the primary amine.[8]

Pharmacological Activity.—Three of the compounds (I; NR′R″ = piperidino or morpholino, R = ethyl; R′ = R″ = *n*-butyl, R = methyl) have shown no evidence of ability to retard the growth of sarcoma 180 in tests conducted under the supervision of Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research. The screening of the methiodide of one compound (I, NR′R″ = piperidino, R = ethyl), by Dr. Irwin H. Slater at the School of Medicine and Dentistry of the University of Rochester, revealed that the compound showed consistent curariform activity in cats in the dose of 5 mg./kg. This is about one-tenth the potency of *d*-tubocurarine. Most of the products tested thus far are convulsants. Evaluation of the local anesthetic activity of the products will be carried out at the laboratories of Endo Products, Inc. A complete report will be published elsewhere at a later date.

(1) From a thesis submitted by Irving C. Kogon to the Graduate Faculty of Brooklyn College, January 1951, in partial fulfillment of the requirements for the Master of Arts degree.

(2) Frederick G. Cottrell Research fellow.

(3) A. E. Tschitschibabin and S. A. Jelgasin, *Ber.*, **47**, 1843 (1914).

(4) E. Späth, (a) *ibid.*, **47**, 766 (1914); (b) *Monatsh.*, **35**, 319 (1914); (c) **36**, 1 (1915).

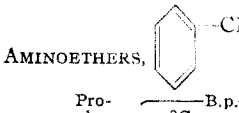
(5) J. Houben, "Die Methoden der Organische Chemie," Vol. III, George Thieme, Leipsig, Germany, 1930, p. 167.

(6) J. Houben and K. Führer, *Ber.*, **47**, 75 (1914).

(7) L. C. Swallen and C. E. Boord, THIS JOURNAL, **52**, 651 (1930).

(8) K. Rosenmund, *Ber.*, **46**, 1046 (1913). The methyl ether of 2-amino-1-phenylethanol was prepared by the reduction of the corresponding nitro compound. The hydrochloride was reported as melting at 158–159°.

TABLE I

AMINOETHERS, 

R	R′	R″	Procedure	B.p. °C.	B.p. Mm.	Yield, %	M.p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
CH_3	H	H	C	111–116	20	73	160–161[a,b]	$C_9H_{13}NO\cdot HCl$	7.46	7.46
C_6H_5	C_6H_5	H	B-2	129–130	8	62	109–110[a,c]	$C_{15}H_{19}NO\cdot HCl$	5.77	5.61
CH_3	*n*-C_4H_9	H	B-2	145.5–150	23	56	144.5–145[a,d]	$C_{13}H_{21}NO\cdot HCl$	5.73	5.70
C_2H_5	iso-C_4H_9	H	B-2	134–135	20	63	[e]	$C_{14}H_{23}NO$	6.30	6.10
CH_3	C_6H_{11}[f]	H	B-2	146–149	7	74	209.8–210.2[a,b]	$C_{15}H_{23}NO$	77.32[g]	77.38[g]
			A[i]	178–179	23	30			9.89[h]	9.87[h]
C_2H_5	C_6H_{11}[f]	H	B-2	151–158	8	54	174–175[a,b]	$C_{16}H_{25}NO$	77.79[g]	77.40[g]
			A[i]	179–180	23	20			10.11[h]	10.40[h]
CH_3	$CH_2C_6H_5$	H	B-2	196–202	21	78	197–197.5[a,b]	$C_{16}H_{19}NO\cdot HCl$	5.06	4.99
									69.45[g]	69.54[g]
									7.29[h]	7.42[h]
C_2H_5	$CH(C_6H_5)_2$	H	B-1	155–165	0.3	59	71–72[j,k]	$C_{20}H_{25}NO$	4.22	4.11
									83.37[g]	84.36[g]
									7.60[h]	7.40[h]
C_2H_5	$CH(C_6H_5)CH_2C_6H_5$	H	B-2	144–152	0.02	20	244.5–245.5[a,k]	$C_{24}H_{27}NO\cdot HCl$	3.67	3.87
C_2H_5	$HOCH_2CH_2$	H	B-1	170–176	18	57	[l]	$C_{12}H_{19}NO_2$	6.68	6.55
C_2H_5	$(CH_2)_2NC_4H_8O$[m]	H	B-1	169–171	4	64	131 (dec.)[a,b]	$C_{16}H_{26}N_2O_2\cdot 2HCl$	7.96	7.71
C_2H_5	$(CH_2)_3N(C_2H_5)_2$	H	B-1	148–151	4	79	[l]	$C_{17}H_{30}N_2O$	10.05	10.00
C_2H_5	$(CH_2)_3N(n\text{-}C_4H_9)_2$	H	B-1	143–144	2	62	[l]	$C_{21}H_{38}N_2O$	8.45	8.81
C_2H_5	CH_3	CH_3	B-3	115–123	20	59	150–151[a,n]	$C_{12}H_{19}NO\cdot HCl$	6.20	6.09
							148–149.5[o,p]			
CH_3	*n*-C_3H_7	*n*-C_3H_7	A	128–131	11	65[q]	144.5–145.5[a,d]	$C_{15}H_{25}NO$	76.66[g]	76.50[g]
			B-2	141–144	20	74			10.64[h]	10.10[h]
CH_3	*n*-C_4H_9	*n*-C_4H_9	A	162–166	16	78	143–144	$C_{17}H_{29}NO$	77.51[g]	77.74[g]
			B-2	160–167	18	71	126–126.5[r,s]		11.08[h]	11.10[h]
C_2H_5	*n*-C_4H_9	*n*-C_4H_9	A	167–181	11	80	87.5–88[t,u]	$C_{18}H_{31}NO$	5.05	5.09
			B-2	122–124	3	71[q]			78.00[g]	78.29[g]
									11.26[h]	11.22[h]
CH_3	C_6H_5	C_2H_5	A	118–121	10	68	152–153[a,d]	$C_{15}H_{21}NO$	6.05	5.70
CH_3	$C_5H_{10}N$[v]		A	145–160	17	41[q]	208–209[a,b]	$C_{14}H_{21}NO\cdot HCl$	5.47	5.47
			B-2	127–129	7	75	157–158[a,b]			
C_2H_5	$C_5H_{10}N$[v]		A	134–136	10	23[q]	151–152[a,b]	$C_{15}H_{23}NO\cdot HCl$	5.08	5.19
			B-2	153	19	78	166–167[o,d]		66.75[g]	66.45[g]
									8.96[h]	8.87[h]
CH_3	C_4H_8NO[w]		A	155–156	15	20	208.5–209[a,b]	$C_{13}H_{19}NO_2\cdot HCl$	5.43	5.39
			B-2	138–141	7	80	214–215[o,x]			
C_2H_5	C_4H_8NO[w]		A	135–147	9	62	208–209[a,b]	$C_{14}H_{21}NO_2$	71.55[g]	71.42[g]
			B-1	133–144	6	76			8.94[h]	9.17[h]
CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	A	128–130	0.03	80	192–192.5[a,b]	$C_{29}H_{29}NO\cdot HCl$	3.81	3.75
			B-1	145–150	0.09	66			82.71[g]	82.60[g]
									7.89[h]	7.53[h]
C_2H_5	$HOCH_2CH_2$	C_2H_5	B-1	120–130	5	56	[l]	$C_{14}H_{23}NO_2$	5.90	6.19
C_2H_5	$HOCH_2CH_2$	$HOCH_2CH_2$	B-1	178–182	4	34	[l]	$C_{14}H_{23}NO_2$	5.53	5.30
C_2H_5	$HOCH_2CH_2$	$CH_2CH(OC_2H_5)C_6H_5$	B-1[y]	161–170	0.2	59	[l]	$C_{22}H_{31}NO_3$	3.91	4.00
									357.4[z]	356.2[z]

[a] Hydrochloride. All salts were prepared by prevously described procedures.[10] [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from ethyl methyl ketone–ether. [d] Recrystallized from acetone. [e] Yielded only hygroscopic salts. [f] Cyclohexyl. [g] Carbon analysis, %. [h] Hydrogen analysis, %. [i] C. A. Blank, M.A. Thesis, Brooklyn College, 1949, p. 27. [j] Free base. [k] Recrystallized from methanol. Calcd. for $C_{24}H_{27}NO\cdot HCl$: Cl, 9.29. Found: Cl, 9.52. [l] The hydrochloride precipitated as an oil which failed to crystallize. Similar difficulty was experienced in attempts to prepare other crystalline salts. [m] 2-Morpholinoethyl. [n] Recrystallized from ethyl methyl ketone. [o] Methiodide. [p] Recrystallized from acetone–ether. [q] Yield of redistilled product. [r] Oxalate. [s] The compound was not recrystallized. [t] Hydrobromide. Calcd. for $C_{18}H_{31}NO\cdot HBr$: C, 60.32; H, 9.00; N, 3.91. Found: C, 60.18; H, 9.16; N, 3.98. [u] Recrystallized from isopropyl ether. [v] The piperidine radical replaces R′R″N–. [w] The morphlino radical replaces R′R″N–. [x] Recrystallized from acetonitrile. [y] The reactants were used in equimolecular amounts. [z] Neutralization equivalent.

Experimental[9]

Intermediates.—The preparation of the N-substituted aminoacetals was described in a previous publication.[10] Benzhydryl- and 1,2-diphenylethylamines were prepared by Mr. Chester L. Parris by the Leuckart reaction in an investigation supported by the U. S. Public Health Service and to be published later. The methyl and ethyl ethers of 2-bromo-1-phenylethanol were obtained by previously described procedures.[11,12] Decomposition of the magnesium complex with a saturated aqueous solution of ammonium chloride[13] gave improved yields. The ethyl and methyl ethers of 1,2-dibromomethanol were prepared by the method of Swallen and Boord.[7] However, the ethyl ether of 1,2-dibromoethanol was prepared more conveniently and in better yield by bromination of vinyl ethyl ether.[14,15] The use of ethylene dichloride as solvent led to a 92% yield of product, b.p. 81–83° (21 mm.).

Method A.—To an ethereal solution of the Grignard reagent, prepared from 0.8 mole each of bromobenzene and magnesium, was added 0.4 mole of the N-substituted aminoacetal. The solution was heated with stirring while removing most of the ether by distillation. Three hundred and fifty ml. of xylene (technical grade, b.p. 135–140°) was added and distillation was continued until the temperature of the reaction mixture reached 135–140°; it was then re-

(9) All melting points are corrected; boiling points are not.

(10) I. A. Kaye and I. Minsky, THIS JOURNAL, **71**, 2272 (1949).

(11) W. M. Lauer and M. A. Spielman, *ibid.*, **53**, 1533 (1931).

(12) W. M. Lauer and M. A. Spielman, *ibid.*, **55**, 4923 (1933).

(13) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 410.

(14) A sample of vinyl ethyl ether was generously contributed by the General Aniline and Film Corp.

(15) (a) A. E. Favorskii and M. F. Shostakovskii, *J. Gen. Chem.* (*U. S. S. R.*), **13**, 1 (1943) [*C. A.*, **38**, 330 (1944)]; (b) A. E. Favorskii and M. N. Shchukina, *ibid.*, **15**, 385 (1945) [*C. A.*, **40**, 4347 (1946)].

fluxed with stirring for four hours. A white precipitate appeared during this reflux period. Hydrolysis was effected by the addition of 120 ml. of a saturated aqueous ammonium chloride solution.[12] The bulky magnesium salts were removed by filtration and washed well with xylene. After removal of the solvent, the product was isolated by distillation at reduced pressure.

Method B.—A mixture consisting of 0.15 mole of the ethyl or methyl ether of 2-bromo-1-phenylethanol and 0.30 mole of the amine was heated under reflux in an oil-bath until an exothermic reaction occurred (Method B-1). When the reaction had abated somewhat, the mixture was then refluxed from one-half to 23 hours. The length of the heating period depended upon the amount of visible decomposition. In some cases the two reactants were refluxed in 100 ml. of benzene or toluene for 16–40 hours (Method B-2). In the reaction with dimethylamine, the gaseous base was bubbled into the bromo ether over a three-hour period while the latter was heated at a bath temperature of 120° (Method B-3). After cooling, ether was added (in Methods B-1 and B-3) and the hydrobromide of the excess starting amine was separated by filtration and washed well with ether. The solvents were removed and the residue was distilled *in vacuo*. In several preparations where the amine hydrobromide separated as an oil or hygroscopic solid, the salt was dissolved in water and the product separated from the aqueous solution of the salt by extraction several times with ether. After drying over anhydrous potassium carbonate and removing the solvent, the product was obtained by distillation *in vacuo*.

Method C. Methyl Ether of 2-Amino-1-phenylethanol.[8]—A solution of 18.9 g. of the methyl ether of 2-benzylamino-1-phenylethanol in 200 ml. of absolute ethanol was hydrogenated at an initial pressure of 58 lb. in the presence of 3.2 g. of 10% palladium-on-charcoal catalyst.[16] The calculated amount of hydrogen was absorbed in 24 hours. The catalyst was removed by filtration, washed well with ethanol, and the solvent removed from the filtrate by distillation. The product, collected at 111–116° (20 mm.), weighed 8.7 g. (73%).

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(16) Purchased from Baker and Co., Inc., Newark, N. J.

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Anticonvulsants. I. An Investigation of N-R-α-R$_1$-α-Phenylsuccinimides

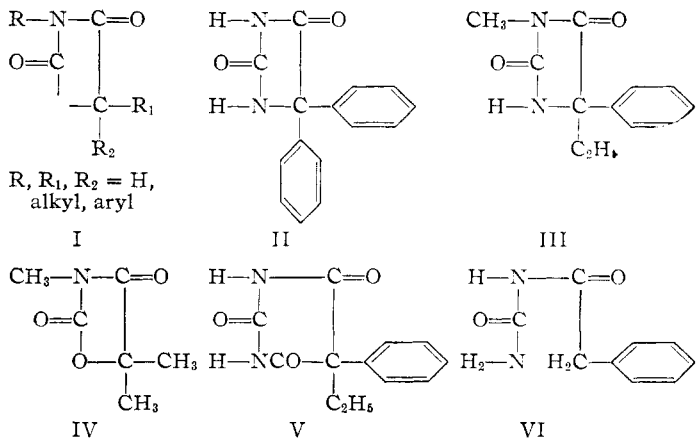
BY C. A. MILLER AND LOREN M. LONG[1]

A series of substituted succinimides has been prepared and tested for anticonvulsant properties. Many of the derivatives exhibit appreciable activity against metrazol and/or electrically-induced convulsions. Several of these have proved effective in clinical studies of petit mal epilepsy.

Since the discovery of the usefulness of 5,5-diphenylhydantoin[2] (Dilantin)[3] in the treatment of grand mal epilepsy, much effort has been expended in the search for new agents which might suppress convulsive seizures in man. The field of hydantoin derivatives has been examined rather thoroughly. Although many of these exhibit activity against electrically-induced convulsions,[4] none has shown any particular advantage over Dilantin in the treatment of grand mal epilepsy.[5]

Anticonvulsants which are effective against grand mal seizures usually do not show a similar activity against petit mal epilepsy. Indeed, until the introduction of 3,5,5-trimethyloxazolidinedione[6,7] (Tridione)[8] there was no drug known which could be employed with any appreciable success against the lesser convulsive seizures. However, because of certain side effects, the use of this drug demands unusual care.[9a,b,10] Therefore, a more effective agent devoid of toxic properties remains an important objective. This paper is a report on the results obtained in a study of a series of succinimide derivatives, including certain members which show promise of proving useful in the treatment of this type of epilepsy.

It has been observed that group I occurs in many of the effective anticonvulsants as well as sedatives and hypnotics.



Among these may be cited Dilantin (II), Mesantoin

(1) Address inquiries to L. M. L.

(2) H. H. Merritt and T. J. Putnam, *J. Am. Med. Assoc.*, **111**, 1068 (1938).

(3) Parke, Davis & Co. registered trademark for 5,5-diphenylhydantoin.

(4) H. H. Merritt and T. J. Putnam, *Epilepsia*, **3**, 51 (1945).

(5) J. A. Abbott and R. S. Schwab, *New Engl. J. Med.*, **242**, 943 (1950).

(6) M. A. Spielman, THIS JOURNAL, **66**, 1244 (1944).

(7) (a) G. M. Everett and R. K. Richards, *J. Pharmacol. Exp. Therap.*, **81**, 402 (1944); (b) W. G. Lennox, *J. Am. Med. Assoc.*, **129**, 1069 (1945).

(8) Abbott Laboratories registered trademark for 3,5,5-trimethyloxazolidinedione.

(9) (a) J. N. Briggs and J. L. Emery, *Lancet*, **1**, 59 (1949); (b) H. S. Mustard, S. C. Anderson and S. Livingston, *J. Pediat.*, **35**, 540 (1949).

(10) S. E. Leard, W. E. R. Greer and I. C. Kaufman, *New Engl. J. Med.*, **240**, 962 (1949).