[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Antispasmodics. I. Basic Amides of Benzilic Acid

BY JOHN KRAPCHO, CHESTER F. TURK AND EDWARD J. PRIBYL

RECEIVED FEBRUARY 24, 1955

A series of basically-substituted benzilamides and their quaternary salts were prepared in order to establish some correlation between structure and activity of these compounds. Several of the quaternary salts exhibited over 50% of the activity of atropine with respect to their ability to control acetylcholine-induced spasms on the isolated rabbit ileum.

In a recent publication Phillips[1] described the preparation and pharmacological properties of four dialkylaminoethyl amides of benzilic acid and their quaternary salts. The most potent member of the series of compounds showed only 4% of the potency of atropine.

During the course of a similar investigation in these laboratories, in addition to N-(2-diethylaminoethyl)-benzilamide and the quaternary methobromide (compounds 1 and 2 in Table I),[1] we prepared N-(2-diethylaminoethyl)-N-methylbenzilamide and the quaternary methobromide (compounds 6 and 8). Since the replacement of the hydrogen by a methyl group on the amido linkage resulted in a fivefold increase in the potency of the hydrochloride and a tenfold increase in the activity of the quaternary methobromide salt, a series of compounds was prepared in order to determine the effect of modification of the N-alkyl group, the basic side chain and the quaternizing agent.

The basically-substituted benzilamides were usually obtained in 80–90% yield by the interaction of α-chlorodiphenylacetyl chloride with the appropriate diamines, followed by hydrolysis of the intermediate α-chloro amides. These products were converted to hydrochloride salts in quantitative yield by treatment of ethereal solutions of the bases with a slight excess of ethereal hydrogen chloride, or by addition of the calculated quantity of alcoholic hydrogen chloride to alcoholic solutions of the bases, followed by dilution with ether.

The quaternary salts were generally prepared in approximately 90% yield by addition of two equivalents of the appropriate quaternization agent to solutions of the bases in acetone and allowing the mixtures to stand overnight at room temperature; during this time the products precipitated from the reaction mixtures. Because the diisopropylaminoethyl group is difficult to quaternize, the reaction of N-(2-diisopropylaminoethyl)-N-methylbenzilamide with methyl bromide was carried out in a pressure bottle at 50–60° over a period of nine hours. Acetonitrile was utilized as a solvent in the preparation of the methochloride salt of N-(2-diethylaminoethyl)-N-methylbenzilamide (compound 7) since poor yields were obtained when the reaction was carried out in acetone or chloroform at room temperature.

Structure, Activity Relationships.—The activities of these compounds, with respect to their ability to control acetylcholine-induced spasms on the isolated rabbit ileum, are included in the table.[2] The most potent compounds (5, 7, 8 and 15) of the series are quaternary salts. These compounds contain a methyl group on the amido nitrogen and the latter is separated from the quaternary nitrogen by an ethylene linkage. The N-methyl group is optimum since the ethyl, propyl, isopropyl, allyl, benzyl and phenyl analogs are considerably less active. Replacement of the ethylene by the trimethylene linkage between the nitrogen atoms also resulted in less potent compounds. In general, variation of the substituents on the quaternary nitrogen did not produce marked changes in the activity of these compounds. One of these compounds, N-(2-diethylaminoethyl)-N-methylbenzilamide methochloride (Cotranul)[3] is being investigated clinically.

Acknowledgment.—The authors are indebted to Mr. W. A. Lott for his direction and encouragement throughout this investigation. Appreciation is extended to Dr. Byron B. Clark of Tufts College Medical School for the pharmacological data on these compounds. The microanalyses were carried out by Mr. Joseph Alicino and his associates.

Experimental

Diamines.—The preparations of the following intermediate diamines are reported in the literature: N,N,N′-trimethylethylenediamine,[4] N,N-diethyl-N′-methylethylenediamine,[5] 2-piperidinoethylmethylamine,[5] N,N-diethyl-N′-methyl-1,3-propanediamine,[4] N,N,N′-triethylethylenediamine,[5] N,N-diethyl-N′-propylethylenediamine,[5] N,N-diethyl-N′-isopropylethylenediamine,[5] N-benzyl-N′,N′-diethyl ethylenediamine[5] and N,N-dimethyl-N-phenylethylenediamine.[6]

N,N-Diisopropyl-N′-methylethylenediamine: prepared in 71% yield by the interaction of 2-diisopropylaminoethyl chloride hydrochloride[7] with excess methylamine according to the general procedure,[5] b.p. 84–85° (26 mm.).

Anal. Calcd. for $C_9H_{22}N_2$: N, 17.70. Found: N, 18.01.

2-(1-Pyrrolidyl)-ethylmethylamine.—Treatment of 2-(1-pyrrolidyl)-ethyl chloride hydrochloride with excess methylamine in the usual manner[5] resulted in a 59% yield of product, b.p. 93–95° (50 mm.).

Anal. Calcd. for $C_7H_{16}N_2$: N, 21.85. Found: N, 21.49.

N-Allyl-N′,N′-diethylethylenediamine.—A solution of 171 g. (3.0 moles) of allylamine in 450 ml. of absolute alcohol was stirred and treated portionwise with 172 g. (1.0 mole) of 2-diethylaminoethyl chloride hydrochloride, followed by 120 g. of potassium carbonate (pulverized). The mixture was allowed to stir at room temperature for one hour and then refluxed for two hours, cooled and diluted with a solution of 200 g. of sodium hydroxide in 800 ml. of water. The product was extracted with ether and dried over magnesium sulfate. After evaporation of the solvent, the residue was fractionated to give 87 g. (56%) of diamine, b.p. 85–87° (25 mm.).

(1) A. P. Phillips, THIS JOURNAL, **76**, 1955 (1954).

(2) Further pharmacology of compound 8 is described by R. Ursillo, R. Mitchell, F. Grace and B. B. Clark, *Federation Proc.*, **12**, 375 (1953).

(3) Registered Trade Mark.

(4) R. Damiens, *Ann. chim.*, **6**, 835 (1951).

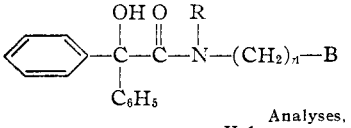
(5) W. O. Kermack and T. W. Wight, *J. Chem. Soc.*, 1421 (1935).

(6) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946).

(7) J. B. Wright, E. H. Lincoln, R. V. Heinzelmann and J. H. Hunter, *ibid.*, **72**, 3536 (1950).

TABLE I

SALTS OF BASIC AMIDES OF BENZILIC ACID



Compd. no.	R	n	B	Salt[a]	M.p., °C. (uncor.)	Formula	Analyses, % Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found	Activity[b] Atropine=100
1	H	2	$N(C_4H_8)_2$	HCl	176–178[c]	$C_{20}H_{27}ClN_2O_2$			7.72	7.70	3.2
2	.....	..	.....	CH_3Br	188–189[d]	$C_{21}H_{29}BrN_2O_2$	18.97	18.63	6.65	6.44	4.5
3	CH_3	2	$N(CH_3)_2$[e]	HCl	252–253[e]	$C_{19}H_{25}ClN_2O_2$	10.16	9.87	8.03	7.91	3[f]
4	.....	..	.....	CH_3Br	200–201[e]	$C_{20}H_{27}BrN_2O_2 \cdot C_2H_5OH$[h]	17.63	17.77	6.18	6.33	45
5	.....	..	.....	C_2H_5Br	134–136[e]	$C_{21}H_{29}BrN_2O_2 \cdot H_2O$	18.19	18.29	6.38	6.27	53
6	CH_3	2	$N(C_2H_5)_2$	HCl	157–158	$C_{21}H_{29}ClN_2O_2$	9.41	9.74	7.44	7.11	17
7	.....	..	.....	CH_3Cl	191–192[e]	$C_{22}H_{31}ClN_2O_2$	9.07	9.00	7.17	7.13	50
8	.....	..	.....	CH_3Br	186–187	$C_{22}H_{31}BrN_2O_2$	18.36	18.25	6.44	6.36	59
9	.....	..	.....	$(CH_3)_2SO_4$	85–86[e]	$C_{23}H_{34}N_2O_6S \cdot {}^1/_2H_2O$		[i]	5.89	5.64	30[f]
10	.....	..	.....	C_2H_5I	207[e]	$C_{23}H_{33}IN_2O_2$	25.57	25.48	5.64	5.88	30[f]
11	.....	..	.....	$C_7H_8BrNO_2$[j]	195–196[e]	$C_{28}H_{34}BrN_3O_4$	14.36	14.39	7.55	7.84	3[f]
12	CH_3	2	$N[CH(CH_3)_2]_2$	HCl	230–231[e]	$C_{23}H_{33}ClN_2O_2$	8.76	8.83	6.92	7.03	21
13	.....	..	.....	CH_3Br	164–165[e]	$C_{24}H_{35}BrN_2O_2$	17.24	17.02	6.05	5.78	13
14	CH_3	2	NC_4H_8[k]	HCl	229–230[e]	$C_{21}H_{27}ClN_2O_2$	9.45	9.15	7.47	7.56	4.7
15	.....	..	.....	CH_3Br	165–166	$C_{22}H_{29}BrN_2O_2$	18.44	18.57	6.47	6.67	71
16	CH_3	2	NC_5H_{10}[l]	HCl	212–214	$C_{23}H_{29}ClN_2O_2$	9.12	9.39	7.20	7.53	2.4
17	.....	..	.....	CH_3Br	202–204	$C_{23}H_{31}BrN_2O_2$	17.86	18.30	6.26	5.80	0.8
18	CH_3	3	$N(CH_3)_2$	HCl	202–203[d]	$C_{20}H_{27}ClN_2O_2$	9.77	10.07	7.72	7.44	1[f]
19	.....	..	.....	CH_3Br	238–239	$C_{21}H_{29}BrN_2O_2$	18.97	18.79	6.65	6.62	1.1
20	.....	..	.....	C_2H_5Br	210–212	$C_{22}H_{31}BrN_2O_2$	18.36	18.46	6.44	6.36	6.0
21	CH_3	3	$N(C_2H_5)_2$	HCl	144–146	$C_{22}H_{31}ClN_2O_2$	9.07	9.02	7.17	7.12	6[f]
22	.....	..	.....	CH_3Br	192–193	$C_{23}H_{33}BrN_2O_2$	17.78	17.69	6.23	6.20	3.3
23	C_2H_5	2	$N(C_2H_5)_2$	HCl	158–159	$C_{23}H_{31}ClN_2O_2$	9.07	9.07	7.17	6.94	10
24	.....	..	.....	CH_3Br	186–187	$C_{23}H_{33}BrN_2O_2$	17.78	17.73	6.23	5.94	9.6
25	$CH_2CH_2CH_3$	2	$N(C_2H_5)_2$	HCl	187–188	$C_{23}H_{33}ClN_2O_2$	8.76	8.41	6.92	6.60	0.2[f]
26	.....	..	.....	CH_3Br	193–194	$C_{24}H_{35}BrN_2O_2$	17.24	17.05	6.05	5.95	0.2[f]
27	$CH(CH_3)_2$	2	$N(C_2H_5)_2$	HCl	174–176	$C_{23}H_{33}ClN_2O_2$	8.76	8.66	6.92	7.21	0.4[f]
28	.....	..	.....	CH_3Br	192–193	$C_{24}H_{35}BrN_2O_2$	17.24	17.43	6.05	6.11	3.0
29	$CH_2CH=CH_2$	2	$N(C_2H_5)_2$	HCl	198–200	$C_{23}H_{31}ClN_2O_2$	8.80	8.77	6.95	6.82	9.5
30	.....	..	.....	CH_3Br	168–170	$C_{24}H_{33}BrN_2O_2$	17.32	17.07	6.07	5.94	7.4
31	$CH_2C_6H_5$	2	$N(C_2H_5)_2$	HCl	214–215	$C_{27}H_{33}ClN_2O_2$	7.83	7.34	6.19	5.91	0.2[f]
32	.....	..	.....	CH_3Br	190–192	$C_{28}H_{35}BrN_2O_2$	15.60	15.56	5.48	5.38	0.1[f]
33	C_6H_5	2	$N(CH_3)_2$	HCl	230–231[e]	$C_{24}H_{27}ClN_2O_2$	8.63	8.80	6.82	7.02	0.1[f]
34	.....	..	.....	CH_3Br	218–220[e]	$C_{25}H_{29}BrN_2O_2$	17.03	17.12	5.97	6.22	0.1[f]

[a] These salts were crystallized from absolute alcohol except 1 and 27 (butanone); 3 (water); 7, 8, 9, 21, 23, 24, 25, 26, 28, 30, 32 (isopropyl alcohol); 10 (methanol); 13 (butanone-absolute alcohol) and 15 (acetonitrile). [b] Activity against acetylcholine induced spasms on the rabbit ileum; Trasentin, 0.5. [c] K. Miescher, W. Meisel and K. Hoffman (U. S. Patent 2,009,144) report 178–179° (cor.). [d] The base was crystallized from hexane; m.p. 96–97° (uncor.). *Anal.* Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 72.76; H, 7.55; N, 8.78. [e] Melts with decomposition. [f] Approximate value obtained from screening data. [g] Material softens at 130°. [h] *Anal.* Calcd.: C, 58.27; H, 7.56. Found: C, 58.05; H, 7.09. [i] *Anal.* Calcd.: C, 58.08; H, 7.21. Found: C, 58.23; H, 7.23. [j] *p*-Nitrobenzyl. The melting point was taken after immersion at 175°. [k] Pyrrolidyl. [l] Piperidyl.

Anal. Calcd. for $C_9H_{20}N_2$: neut. equiv., 78.1. Found: neut. equiv., 79.2.

The **picrate** of this material, after crystallization from absolute alcohol, melted at 129–130° (uncor.)

Anal. Calcd. for $C_9H_{20}N_2 \cdot C_6H_3N_3O_7$: N, 18.17. Found: N, 18.15.

A second fraction, **N″-allyl-N,N,N′,N′-tetraethyldiethylenetriamine**, weighed 25 g. (20%), b.p. 125–127° (7 mm.).

Anal. Calcd. for $C_{15}H_{33}N_3$: N, 16.49. Found: N, 16.36.

N,N,N′-Trimethyl-1,3-propanediamine. (a) **N,N-Dimethyl-N′-formyl-1,3-propanediamine.**—To 250 g. (4.0 moles) of formic acid (98–100%) was added portionwise 153 g. (1.5 moles) of 3-dimethylaminopropylamine and the resulting solution refluxed for 16 hours. The excess acid was removed under reduced pressure, the residue was cooled and treated with a cold solution of 60 g. of sodium hydroxide in 120 ml. of water. The product was extracted with ether containing a small quantity of chloroform and the extract dried over magnesium sulfate. After evaporation of the solvent, the residue was fractionated to give 52 g. (27%) of colorless product, b.p. 118–119° (6 mm.).

Anal. Calcd. for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.16; H, 10.76; N, 21.32.

In a subsequent experiment, a 79% yield of this product was obtained by treatment of a chloroform solution of 3-dimethylaminopropylamine with chloral.[8]

(b) **N,N,N′-Trimethyl-1,3-propanediamine.**—A solution of 50.4 g. (0.38 mole) of the above formyl compound in 50 ml. of ether was added dropwise to a cooled suspension of 25.0 g. (0.66 mole) of lithium aluminum hydride in 900 ml. of ether. After completion of the addition, the mixture was refluxed for four hours, cooled and treated dropwise with 40 ml. of water. The mixture was treated with a solution of 8 g. of sodium hydroxide in 120 ml. of water, stirred for two hours and filtered through a sintered glass funnel. The solid was washed well with ether and the filtrate dried over magnesium sulfate. After evaporation of the solvent, the residue was fractionated to give 29 g. (65%) of product, b.p. 140–142°.

Anal. Calcd. for $C_6H_{16}N_2$: N, 24.11. Found: N, 24.05.

Amides

N-(2-Diethylaminoethyl)-N-methylbenzilamide.—A solution of 450 g. (1.7 moles) of α-chlorodiphenylacetyl chloride[9] in a mixture of 1200 ml. of hexane and 800 ml. of benzene was maintained at 20–30° during the dropwise addition (30 minutes) of a solution of 216 g. (1.66 moles) of N,N-diethyl-N′-methylethylenediamine[5] in 200 ml. of benzene. A heavy precipitate of N-(2-diethylaminoethyl)-N-methyl-α-chlorodiphenylacetamide hydrochloride separated from the mixture. After completion of the addition, the mixture was stirred for one hour at room temperature, refluxed for one hour, cooled and treated with 700 ml. of water. After this mixture had stirred for about 30 minutes, the precipitate

(8) According to a general procedure described by F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, **74**, 3933 (1952).

(9) F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

was dissolved completely, and the aqueous layer separated. The organic phase was extracted with a solution of 150 ml. of concentrated hydrochloric acid in 800 ml. of water (in two portions). The aqueous layers were combined, extracted once with about 300 ml. of ether to remove any non-basic material and then heated on a steam-bath at 70–80° for 30 minutes to complete the hydrolysis of the α-chloro to the α-hydroxy amide. After cooling, the solution was treated portionwise with a solution of 240 g. of sodium hydroxide in 400 ml. of water. The liberated base was extracted with 1.6 l. of ether (in two portions). The organic layers were combined, washed with 500 ml. of water and dried over magnesium sulfate. After standing overnight, the solution was treated with Darco, filtered, and the solvent evaporated to yield 514 g. (91%) of a pale red sirupy liquid. This material was suitable, without further purification, for conversion to the compounds 6, 7, 8, 9, 10 and 11 of Table I.

N-(2-Diethylaminoethyl)-N-methylbenzilamide Methochloride.—A solution of 656 g. (1.9 moles) of the above N-(2-diethylaminoethyl)-N-methylbenzilamide in 2 l. of acetonitrile was cooled and treated with 300 g. (5.9 moles) of methyl chloride gas. The product slowly crystallized from the reaction mixture. After standing for four days at room temperature, the colorless product was filtered and dried; weight 610 g. Concentration of the filtrate to about one-half the volume, followed by cooling, yielded an additional 57 g. (total yield 89%) of pure material.

A similar yield of product was obtained when a methanol solution of the base and methyl chloride was heated at 100° in a closed vessel for six hours.

NEW BRUNSWICK, N. J.

[CONTRIBUTION NO. 937 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Reactions of Certain Fluorinated and Chlorinated Acetic Acids with Phenyllithium in Refluxing Ether[1]

BY THOMAS F. McGRATH[2] AND ROBERT LEVINE

RECEIVED OCTOBER 26, 1954

The addition of trifluoroacetic acid to two or more equivalents of phenyllithium in refluxing ether gave none of the expected trifluoroacetophenone. Instead, some or all of the following cleavage products were obtained: benzoic acid, benzophenone, triphenylmethane and tetraphenylethylene. It is suggested that the trifluoroacetic acid is cleaved by phenyllithium to carbon dioxide and fluoroform and these compounds react with phenyllithium to give the observed products. Evidence in support of this scheme is given. The same products are obtained when trichloroacetic acid is treated with phenyllithium, while a mixture of benzophenone and 1,1-diphenylethanediol (49%) is obtained from the reaction of chloroacetic acid and phenyllithium.

In 1933, Gilman and VanEss[3] reported that ketones can be prepared by treating the lithium salts of carboxylic acids with alkyl- and aryl lithium compounds. Thus, the reaction of lithium *n*-butyrate with phenyllithium gives *n*-butyrophenone

$$n\text{-}C_3H_7CO_2Li + C_6H_6Li \longrightarrow C_6H_5COC_3H_7\text{-}n$$

in 62% yield. This reaction has been extended by several other workers[4–6] and it has been found that ketones may be prepared in good yields by the reaction of carboxylic acids with at least two equivalents of an organolithium compound.

It seemed that the Gilman–VanEss[3] method might be used to synthesize a series of alkyl and aryl perfluoroalkyl ketones. However, when lithium trifluoroacetate was added to an equivalent of phenyllithium in refluxing ether, none of the desired trifluoroacetophenone was obtained. Instead, a mixture of benzoic acid and benzophenone was isolated.

Therefore, the course of the reaction between trifluoroacetic acid and phenyllithium was investigated. The addition of trifluoroacetic acid to one equivalent of an ether solution of phenyllithium gave, on hydrolysis, a mixture of benzene and the trifluoroacetic acid–water azeotrope. However, when the molar ratio of base to acid was 2:1 or greater a mixture of some or all of the following products was obtained: benzoic acid, benzophenone, triphenylmethane, tetraphenylethylene, benzene and biphenyl. These results are summarized in Table I.

TABLE I

REACTIONS OF TRIFLUORO- AND TRICHLOROACETIC ACID WITH PHENYLLITHIUM IN REFLUXING ETHER

Moles of base/acid	Products, mole[a]					
	RCO_2H	RCOR	R_3CH	$R_2C{=}CR_2$	RH	RR
1	0	0	0	0	0.86[b]	0
2	.16	.16	.06	.02	[c]	.02
3	.08	.19	.06	.02	[c]	.04
4	0	.52	.08	.04	[c]	.16
	0[d]	.18[d]	.09[d]	.03[d]	[c]	.05[d]
5	0	.52	.09	.06	[c]	.18
	0[d]	.24[d]	.13[d]	.04[d]	[c]	.08[d]
7	0	.36	.21	.06	[c]	.20

[a] R = C_6H_5; data based on one mole of halogenated acid. [b] CF_3CO_2H–H_2O azeotrope also isolated. [c] RH not isolated quantitatively. [d] CCl_3CO_2H used; in all other runs CF_3CO_2H was used.

The reaction cannot be explained by a simple scheme involving the cleavage of trifluoroacetophenone by phenyllithium since this scheme does not account for the formation of benzoic acid and since an authentic sample of trifluoroacetophenone[7] gives diphenyltrifluoromethylcarbinol in 93% yield on treatment with phenyllithium. Furthermore, the cleavage of phenyl trityl ketone,[8] conceivably formed from trifluoroacetic acid *via* lithium triphenylacetate, cannot be involved since this ketone is neither formed when triphenylacetic

(1) Part of this work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) Monsanto Chemical Company Fellow, 1953–1954.

(3) H. Gilman and P. R. VanEss, THIS JOURNAL, **55**, 1258 (1933).

(4) J. F. Arens and D. A. van Dorp, *Rec. trav. chim.*, **65**, 338 (1946).

(5) M. S. Newman and T. S. Bye, THIS JOURNAL, **74**, 905 (1952).

(6) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(7) J. H. Simons and E. O. Ramler, THIS JOURNAL, **65**, 389 (1947).

(8) H. L. Bradlow and C. A. VanderWerf, *ibid.*, **69**, 1254 (1948).