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

Physiologically Active Compounds. I. Hydrochlorides of β-Aminoethyl Esters of Methyl-substituted Benzilic Acids

HILTON A. SMITH, C. A. BUEHLER, AND K. V. NAYAK

Received June 18, 1956

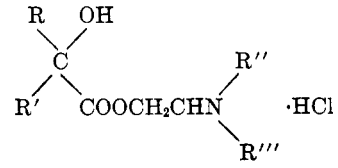
Twenty-five hydrochlorides of β-aminoethyl esters of methyl-substituted benzilic acids have been prepared. Three of these compounds are more active in experimental animals than atropine in preventing mortality from an anticholinesterase compound and of the two potent antispasmodics, one appears to be worthy of additional study.

The salts of β-aminoethyl esters of benzilic and glycolic acids have long been known as compounds of physiological activity. Well-known examples are hydrochloride of β-diethylaminoethyl ester of benzilic acid, a common antispasmodic known as "diphenamin," and the methyl bromide of β-diethylaminoethyl ester of phenylcyclohexylglycolic acid, a common anticholinergic known as "antrenyl." Since a variety of methyl-substituted benzilic acids were available from previous research,[1] it was of interest to prepare the hydrochlorides of the β-aminoethyl esters, as listed in Table I, for testing.

The tests were made in the Pharmacology Branch of the Chemical Corps Medical Laboratories in the Army Chemical Center by Drs. Gerald Groblewski and J. H. Wills, to whom we are greatly

TABLE I

ESTER HYDROCHLORIDES OF SUBSTITUTED BENZILIC ACIDS



No.	R	R'	R''	R'''	Yield, %	Melting Point, °C.	Analyses Calculated C	Calculated H	Found C	Found H
1	C_6H_5	2-$CH_3C_6H_4$	C_2H_5	C_2H_5	71.9	180–181	66.74	7.47	66.53	7.53
2	C_6H_5	3-$CH_3C_6H_4$	C_2H_5	C_2H_5	83.2	173–174	66.74	7.47	66.91	7.57
3	C_6H_5	4-$CH_3C_6H_4$	C_2H_5	C_2H_5	80.7	175–176	66.74	7.47	66.48	7.06
4	C_6H_5	2,3-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	77.9	191–192.5	67.41	7.72	67.52	7.89
5	C_6H_5	2,4-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	50.1	168.5–170	67.41	7.72	67.52	7.89
6	C_6H_5	2,5-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	[a]	165.5–166.5	67.41	7.72	67.64	7.65
7	C_6H_5	2,6-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	82.5	214.5–215.5 (dec.)	67.41	7.72	67.41	7.71
8	C_6H_5	3,4-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	89.8	193–194	67.41	7.72	67.39	7.76
9	C_6H_5	3,5-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	69.7	185–186	67.41	7.72	67.27	7.47
10	C_6H_5	2,3,4-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	77.9	192.5–193.5	68.04	7.94	68.24	8.08
11	C_6H_5	2,3,5-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	71.9	189.5–191	68.04	7.94	67.95	8.14
12	C_6H_5	2,3,6-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	[a,b]	221.5–223 (dec.)	68.04	7.94	68.01	7.77
13	C_6H_5	2,4,5-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	[a]	183–184.5	68.04	7.94	67.88	8.03
14	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	93.4	213–214 (dec.)	68.04	7.94	68.12	8.03
15	C_6H_5	3,4,5-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	67.4	204.5–205.5	68.04	7.94	68.02	8.05
16	C_6H_5	2,3,4,5-$(CH_3)_4C_6H$	C_2H_5	C_2H_5	70.6	207–208 (dec.)	68.63	8.16	68.42	8.12
17	C_6H_5	2,3,4,6-$(CH_3)_4C_6H$	C_2H_5	C_2H_5	86.9	225–226 (dec.)	68.63	8.16	68.86	8.19
18	C_6H_5	2,3,5,6-$(CH_3)_4C_6H$	C_2H_5	C_2H_5	84.7	214–215 (dec.)	68.63	8.16	68.52	8.36
19	C_6H_5	2,3,4,5,6-$(CH_3)_5C_6$	C_2H_5	C_2H_5	50.5	225–226 (dec.)	69.18	8.36	69.18	8.24
20	2-$CH_2C_6H_4$	2-$CH_3C_6H_4$	C_2H_5	C_2H_5	73.6	175.5–176.5	67.41	7.72	67.19	7.78
21	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	CH_2—CH_2 / CH_2—CH_2	CH_2	47.0[c]	170–171	68.38	7.49	68.62	7.65
22	3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	C_2H_5	C_2H_5	75.5	190–191	67.41	7.72	67.48	7.76
23	3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	CH_2—CH_2 / CH_2—CH_2	CH_2	58.0[c]	195–196	68.38	7.49	68.12	7.65
24	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	C_2H_5	C_2H_5	83.4	172–173[d]	67.41	7.72	67.35	7.92
25	3,5-$(CH_3)_2C_6H_3$	3,5-$(CH_3)_2C_6H_3$	C_2H_5	C_2H_5	89.2	199–200	68.63	8.16	68.85	8.31

[a] Produced from uncrystallizable oil of Shacklett and Smith, reference 1. [b] Crystallized from methanol. [c] Prepared by Dan M. Glenn of this laboratory. [d] U. S. Patent 2,394,770 gives m.p. 185–190°.

(1) Shacklett and Smith, *J. Am. Chem. Soc.*, 75, 2654 (1953).

indebted. These tests were: (1) ability to prevent mortality from a standard dose of an anticholinesterase compound; (2) ability to block blood pressure fall produced by a standard dose of acetylcholine; (3) ability to block blood pressure fall by a standard dose of histamine; (4) ability to block stimulation of gut and decrease in tracheal air exchange [done with (2) and (3)]; (5) ability to produce changes in diameter of the eye pupil; and (6) ability to produce anesthesia of the cornea. The results of these tests on most of the compounds synthesized are found in Tables II, III, and IV in which the numbers are those of the compounds listed in Table I. An examination of these tables shows that:

TABLE II

ANTICHOLINESTERASE SCREENING (Test 1)
(Tests on rabbits with standard 2.0 mg./kg. unless otherwise indicated)

Compared to Atropine			
More Active	Equally as Active		Less Active
1[a]	2[b]	11[b]	12[c]
20[b]	4[a]	13[c]	14[b]
22[b]	5[a]	15	18[b]
	6[c]	16	19[c]
	7[b]	17[b]	21[c]
	8[b]	23	25[b]
	9	24	
	10[d]		

Notes: Compound 3 was too toxic for standard screening dose; compound 21 produced tonic, clonic convulsions with opisthotonus with a standard dose.

[a] Test on rats and rabbits. [b] Test on rats. [c] Had to be tested at dose of 1.0 mg./kg. [d] Had to be tested at dose of 0.5 mg./kg.

TABLE IV

EYE EFFECTS (Tests 5, 6)

Mydriasis					
Active	Moderately active	Least active	No definite effect	Local Irritation Active	
4	2	3	1	2	15
20	5	8	11	5	16
	7	14	15	8	17
	9		16	9	18
				11	20
				14	25

No compound produced miosis or local anesthesia.

methylbenzilic acids, are the most potent antispasmodics. Of the two, the 4-methylbenzilic acid ester appears to offer sufficient promise to justify more thorough study.

3. Two compounds, the diethyl ester hydrochlorides of 2,3-dimethylbenzilic and 2,2′-dimethylbenzilic acids, are effective in dilating the pupil of the eye, but the latter produces irritation.

EXPERIMENTAL[2]

β-Aminoethyl chlorides. β-Diethylaminoethyl chloride was obtained from the corresponding alcohol which was first converted into the β-diethylaminoethyl chloride hydrochloride by the method of Slotta and Behnisch[3] and then into the free base by the method of Gilman and Shirley.[4] β-N-Piperidinoethyl chloride was prepared from ethylene chlorohydrin by conversion first into β-N-piperidinoethyl alcohol, then to the chloride hydrochloride, and finally to the free base by the method of Hazard, Cheymol, Chabrier, Corteggiani, and Nicolas.[5] In each case dimerization was prevented by keeping the chloride in solution in dry xylene (1:1) in a cold room.

β-Aminoethyl ester hydrochlorides of substituted benzilic acids. Both the diethyl and piperidino esters were prepared by the method of Blicke and Grier.[6] For the diethyl esters,

TABLE III

BLOOD PRESSURE, GUT, AND RESPIRATION EFFECTS (Tests 2, 3, 4)

No.	Dose mg./kg.	Effect on B.P. Fall in % after Acetylcholine (2.5γ)	Histamine (1.5γ)	Effect of Compound on Gut	B.P.	Respiration
1	4.0	−62	−47	None	None	−Rate
3	1.8	−25	−41	−100%	−5%	−Depth, +rate
4	1.0	−49	0		None	+Depth, −rate
5	2.0	−50	−17	None	None	+Depth, −rate
9	3.5	−27	−33	None	−15%	Apneusis
15	7.5	−27	−4	−100%	−24%	−Depth, +rate
16	4.0	−25	None	−100%	−30%	Apneusis
22	2.5	−24	+9			
	5.0	−16	+10	None	None	None
	7.0	−55	+5			

1. Three compounds, the diethyl ester hydrochlorides of 2-methylbenzilic, 2,2′-dimethylbenzilic, and 3,3′-dimethylbenzilic acids, are more active than atropine in preventing mortality from an anticholinesterase compound. Of the three, the 2,2′-dimethylbenzilic acid ester appears to be the best.

2. Two compounds, the diethyl ester hydrochlorides of 4-methylbenzilic and 2,3,4,5-tetra-

(2) Melting points were determined on a Fisher-Johns melting point apparatus.

(3) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(4) Gilman and Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944).

(5) Hazard, Cheymol, Chabrier, Corteggiani, and Nicolas, *Bull. soc. chim. France*, 209 (1951).

(6) Blicke and Grier, *J. Am. Chem. Soc.*, **65**, 1725 (1943).

the substituted benzilic acid and β-diethylaminoethyl chloride in equimolecular proportions in pure, dry isopropyl alcohol (5 l. per mole of acid) were refluxed for 12 hours. Cooling produced a solid which was removed by filtration and dissolved in the minimum amount of boiling absolute ethanol. On cooling, dry ether was added and the mixture was allowed to crystallize. The solid removed by filtration was washed with dry ether, dried, and analyzed. Table I gives a summary of the ester hydrochlorides thus prepared.

Acknowledgment. This investigation was supported by a research grant, B-652, from the National Institutes of Health, Public Health Service, to which organization our sincere thanks are due.

KNOXVILLE, TENNESSEE