ether and acidified giving a tan oil, 0.92 g., 29% yield. Repeated recrystallizations from ethyl acetate afforded colorless **β-carbomethoxy-β-(8-methylperinaphthylidene-7)-propionic acid** (IV), m.p. 190–191°.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.54; H, 5.85; neut. equiv., 310.3. Found: C, 73.58; H, 5.95; neut. equiv., 310.6.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of III and IV in 95% ethanol were measured with a Model DU Beckman spectrophotometer. Maxima and (log ε) values are: III, 231 mμ (4.54) and 312 mμ (4.06); IV, 232 mμ (4.53) and 312 mμ (4.04).

LABORATORY OF ORGANIC CHEMISTRY
UNIVERSITY OF NEW MEXICO
ALBUQUERQUE, NEW MEXICO

Dialkylaminoethyl Amides of Benzilic Acid and their Quaternary Ammonium Salts as Antispasmodics

BY ARTHUR P. PHILLIPS

RECEIVED DECEMBER 21, 1953

In recent years considerable efforts in numerous laboratories have been directed toward the discovery of powerful new synthetic antispasmodic compounds. These should have, preferably, strong antispasmodic effects of both the atropine and papaverine type, while lacking the numerous undesirable side actions of the former drug.

Of the great variety of structures which have been investigated, many powerful antispasmodics have been found among the dialkylaminoalkyl esters of such acids as diphenylacetic, benzilic and others of similar structure. In only a very few instances[1] have some analogous dialkylaminoalkyl amides been made and tested. The amides reported were usually the diethylaminoethyl amides and they were stated as being less active than the corresponding diethylaminoethyl esters in most instances, at least in atropine-like activity. Miescher, Meisel and Hoffmann[2] have reported a number of dialkylaminoalkyl amides of various aliphatic aromatic acids, and they state that some of these approximate atropine in potency.

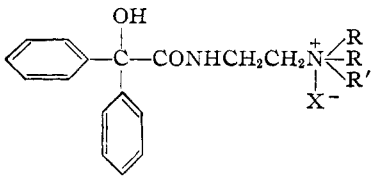
Since some recent work[3] from these laboratories has been concerned with various carboxylic acid aminoalkyl amides, it seemed worthwhile to prepare a series of substituted aminoethyl amides for antispasmodic testing. Benzilic acid was selected as the common acid component, since dialkylaminoalkyl esters of this acid frequently show strong activity, and because in the above-mentioned patent[2] one of the specific compounds claimed was the diethylaminoethyl amide of benzilic acid.

Benzilic acid methyl ester reacted with dimethylaminoethylamine, diethylaminoethylamine, morpholinoethylamine and with piperidinoethylamine to give the series of aminoalkyl amides shown in Table I. The individual tertiary aminoalkyl amides were quaternized with methyl iodide to give the methiodides, also in Table I.

The potency of these compounds as antispasmodics was compared with that of atropine by comparing the amounts of atropine and of compound needed to produce a 50% inhibition of the acetylcholine induced contraction in the isolated guinea pig ileum preparation. The diethylaminoethyl amide of benzilic acid was the most potent member of the present series and showed only 4% of the potency of atropine. The quaternary methiodide of this amide had only 1% of the potency of atropine in this test method, while the other compounds shown in Table I had 1% or less of the potency of atropine. Thus these compounds do not appear to offer any promise as useful antispasmodics. It is interesting to note that the quaternary salts were less potent than the tertiary amines while in the analogous ester series quaternization frequently enhanced activity.

TABLE I

DIALKYLAMINOETHYL AMIDES OF BENZILIC ACID AND SOME DERIVED SALTS



R	R′X	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	...	94–95	$C_{18}H_{22}N_2O_2$	72.4	72.2	7.4	7.1
CH_3	CH_3I	204–205	$C_{19}H_{25}IN_2O_2$	51.7	51.4	5.7	5.8
C_2H_5	...	104–105	$C_{20}H_{26}N_2O_2$	73.6	73.4	8.0	7.8
C_2H_5	CH_3I	189–190	$C_{21}H_{29}IN_2O_2$	53.9	53.8	6.2	6.4
$O(C_2H_4)_2$[b]	...	127–128	$C_{20}H_{24}N_2O_3$	70.6	70.4	7.1	6.9
$O(C_2H_4)_2$[b]	CH_3I	230–231	$C_{21}H_{27}IN_2O_3.H_2O$	50.3	50.4	5.9	5.7
$-(CH_2)_5-$[c]	HCl	201–202	$C_{21}H_{27}ClN_2O_2.H_2O$	64.2	64.6	7.4	7.6
$-(CH_2)_5-$[c]	CH_3I	171–172	$C_{22}H_{29}IN_2O_2.H_2O$	53.0	52.6	6.3	6.5

[a] Yields were all 90% or greater. The tertiary amino amides were recrystallized from mixtures of benzene and Skellysolve B. The methiodides and hydrochloride were recrystallized from mixtures of methanol and ether. [b] Morpholinoethyl amides. [c] Piperidinoethyl amides.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included and to A. E. Light for the pharmacological results which were briefly summarized.

(1) Meier and K. Hoffmann, *Helv. Med. Acta*, **7**, 106 (1941).

(2) K. Miescher, W. Meisel and K. Hoffmann, U. S. Patent 2,009,144 (July 23, 1935).

(3) A. P. Phillips, THIS JOURNAL, **73**, 5822 (1951); **74**, 4320 (1952).

Experimental

Preparation of Benzilic Acid Morpholinoethyl-Amide.—A solution of 7.3 g. (0.03 mole) of benzilic acid methyl ester and 6.5 g. (0.05 mole) of morpholinoethylamine in 100 cc. of methanol was refluxed for 24 hours on a steam-bath. After evaporating solvent the residual product was purified by crystallization from ethyl acetate; yield 9.5 g. (95%); m.p. 127–128°. This product was also recrystallized from water, ethyl acetate and from mixtures of ethyl acetate or benzene with Skellysolve B.

The other tertiaryamino amides of Table I were obtained by similar procedures. They were quaternized by refluxing with methyl iodide in methanol solution.

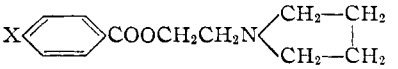
THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

β-Pyrrolidinoethyl *p*-Alkoxybenzoates[1]

BY J. STANTON PIERCE, MICHAEL J. FLETCHER AND SAMUEL L. COOKE, JR.

RECEIVED DECEMBER 15, 1953

In a recent survey of substituted aminoethyl benzoates with the same skeleton formula, X-C$_6$H$_4$-COOC-C-NRR', as in Einhorn's β-diethylaminoethyl-*p*-aminobenzoate,[2] out of over 450 compounds tabulated, only six are esters of β-pyrrolidinoethanol (A). The repeated use of diethylaminoethanol in the preparation of local anesthetics, the relationship of this compound to A and the present low cost of pyrrolidine suggest the desirability of the synthesis of a series of compounds of the structure,



with considerable variation in X. To date, esters have been prepared of A with benzoic acid,[3] *p*-nitrobenzoic and *p*-aminobenzoic acids,[4] *p*-*n*-butylaminobenzoic acid[5] and cinnamic acid.[5]

The β-pyrrolidinoethyl benzoates in the present study were prepared by condensation of the benzoyl chlorides with A, usually in benzene solution, and were isolated as the hydrochlorides. The pyrrolidinoethanol was prepared by the reaction of a methanol solution of pyrrolidine with ethylene oxide[3,6] at 45–60°.[7] The alkoxybenzoyl chlorides were prepared by the reactions[8]

p-HOC$_6$H$_4$COOC$_2$H$_5$ ⟶ *p*-ROC$_6$H$_4$COOC$_2$H$_5$ ⟶ *p*-ROC$_6$H$_4$COOH ⟶ *p*-ROC$_6$H$_4$COCl

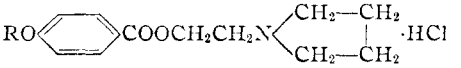
Experimental

β-Pyrrolidinoethyl-*p*-alkoxybenzoate Hydrochloride, *p*-ROC$_6$H$_4$COOCH$_2$CH$_2$N(CH$_2$—CH$_2$)$_2$·HCl.—In a typical run a solution of *p*-alkoxybenzoyl chloride, dissolved in approximately 2.0 volumes of benzene, was treated slowly with an equimolar quantity of A, in benzene. The mixture was refluxed for 0.5 hour and allowed to stand overnight. The crystalline product was filtered with suction, washed with anhydrous ether, dissolved in water and extracted with isopropyl ether, the ether being discarded. The aqueous solution was made basic with sodium carbonate solution and the oil which separated was dissolved in isopropyl ether. The isopropyl ether solution was filtered and treated with hydrogen chloride. The precipitate which formed was filtered with suction, washed with anhydrous ether, recrystallized from benzene, washed with absolute ether and recrystallized from absolute alcohol.

If crystallization did not occur in the original reaction mixture, the benzene solution was extracted with approximately 4 volumes of 0.5 *N* hydrochloric acid and the aqueous layer was made basic with sodium hydroxide solution. The oil which separated was dissolved in isopropyl ether and converted to the hydrochloride as above. If the hydrochloride did not crystallize readily it was converted into a crystalline solid by trituration with dry ether or absolute alcohol.

TABLE I

β-PYRROLIDINOETHYL *p*-ALKOXYBENZOATE HYDROCHLORIDES[a,b,c]



R	M.p. (uncor.), °C.	Yield, % crude	Chlorine, % Calcd.	Found
Ethyl	174–174.5	74	11.83	11.36
n-Propyl	147–148	47	11.29	11.43
n-Butyl	157–158	48	10.81	10.74
n-Amyl	136–137	90	10.37	10.32
n-Hexyl	132.5–133	36	9.96	9.65
Cycloamyl	141.5–143	45	10.43	10.52
Cyclohexyl	158.5–160	49	10.02	10.00

[a] β-Pyrrolidinoethyl *p*-chlorobenzoate hydrochloride, m.p. 194–196°, was prepared from *p*-chlorobenzoyl chloride purchased from Distillation Products Industries. *Anal.* Calcd. for $C_{13}H_{17}O_2NCl_2$: Cl (ionized), 12.22. Found: Cl, 12.36. [b] β-Pyrrolidinoethyl *p*-amyloxycinnamate hydrochloride, m.p. 160–160.5°, was prepared from *p*-amyloxycinnamoyl chloride, which was prepared from *p*-hydroxybenzaldehyde by way of *p*-amyloxycinnamic acid.[9] *Anal.* Calcd. for $C_{21}H_{30}O_3NCl$; Cl, 9.65. Found: Cl, 9.64. [c] The activities of these compounds as local anesthetics are being determined by Dr. Harvey B. Haag of the Medical College of Virginia.

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Advisor to the Chemistry Department of the University of Richmond, for his advice in this work.

(2) A. Einhorn and E. Uhlfelder, *Ann.*, **371**, 131 (1909).

(3) J. von Braun, O. Braunsdorf and K. Räth, *Ber.*, **55B**, 1666 (1922).

(4) J. Supniewski, *Roczniki Chem.*, **7**, 163 (1927); *C. A.*, **22**, 666 (1928).

(5) R. O. Clinton, U. J. Salvador, S. C. Laskowski and J. S. Buck, THIS JOURNAL, **72**, 1331 (1950).

(6) New Products Bulletin No. 28, E. I. du Pont de Nemours and Co., Inc.

(7) For a similar preparation of diethylaminoethanol, see W. H. Horne and R. L. Shriner, THIS JOURNAL, **54**, 2025 (1932).

(8) J. Stanton Pierce, J. M. Salsbury and J. M. Fredericksen, *ibid.*, **4**, 1691 (1942).

(9) J. S. Pierce, R. D. Gano and J. M. Lukeman, *ibid.*, **70**, 255 (1948).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF RICHMOND
RICHMOND, VIRGINIA

Elimination Reactions on 1,4-Systems. II. Use of Metals to Prepare 1,3-Butadiene and Derivatives[1]

BY W. M. SCHUBERT AND WAYNE A. LANKA

RECEIVED DECEMBER 9, 1953

In an earlier report on the possible extent of the general reaction 1 in which $n > 0$, it was shown that 1,4-dibromo-2-butyne and 1-bromo-4-phenoxy-2-butyne yielded butatriene when treated with zinc in the solvent diethylene glycol–diethyl ether or acetonitrile.[2] Other examples of the reaction 1 in which $n > 0$ include: the preparation of 1,3-buta-

(1) Supported in part by a Cottrell grant of the Research Corporation.

(2) W. M. Schubert, T. H. Liddicoet and W. A. Lanka, THIS JOURNAL, **76**, 1929 (1954).