Anal. *b*. Calcd. for $C_{18}H_{16}O_5NNa_2 \cdot 2H_2O$: C, 53.09; H, 4.70; Na, 11.29. Found: C, 53.09; H, 4.41; Na, 11.26.

***m*-Nitrobenzoylphenylalanine-N-acetic acid**, $NO_2C_6H_4CON(CH_2COOH)CH(CH_2C_6H_5)COOH \cdot 2H_2O$. was obtained in two different crystalline modifications, one of which (*a*) melts at 90–92° and decomposes with the evolution of a gas at 105°, while the other (*b*) remains unchanged until 105° when it decrepitates with the evolution of a gas, melting at 130–131° (dec.). Both substances were formed under the conditions described above except that potassium hydroxide was used in place of the sodium bicarbonate and it was found expedient to spread the addition of the *m*-nitrobenzoyl chloride and alkali over a period of thirty-six hours. Moreover, following the addition of hydrochloric acid, a gum was precipitated which crystallized on treatment with ether, yielding 3.81 g. of the product *a* in the form of thin creamy-white, glistening plates. Additional quantities obtained from the filtrate brought the percentage yield to approximately 65% of the theoretical value. The product was recrystallized from water (1 g. soluble in 50 cc. boiling and in 100 cc. at 20°).

The product *b*, isolated in small quantities during the process of recrystallizing *a*, has the same crystalline form but is more soluble in water.

Anal. Calcd. for $C_{18}H_{16}O_7N_2 \cdot 2H_2O$: C, 52.91; H, 4.94; N, 6.88. Found: *a*. C, 52.71; H, 4.79; N, 7.19. Found: *b*. C, 52.20; H, 5.02; N, 7.25.

Summary

Both dimethyl phenylureidophenylalanine-N-acetate and the corresponding acyclic dibasic acid undergo condensation, with the elimination of one molecule of methyl alcohol and one molecule of water, respectively, to form in each case only one of the two isomeric cyclic compounds which might be expected on the basis of purely theoretical considerations. These results agree with previous observations in showing that a marked difference exists between the reactivities of the two acid complexes present in certain unsymmetrical iminodibasic acids. Moreover, the configuration of the product, which has been definitely established in each case, indicates that in all instances so far reported ring closure always takes place in the same general sense.

New derivatives of N-3-phenyl-2-thiobenzalhydantoin and of ethyl N-3-phenylbenzalhydantoin-N-1-acetate are described, together with others obtained by the action of certain acyl chlorides upon phenylalanine-N-acetic acid and its dimethyl ester.

SOUTH HADLEY, MASS. RECEIVED APRIL 7, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF RICHMOND]

Local Anesthetics. I. β-Monoalkylaminoethyl Esters of Alkoxybenzoic Acids[1]

BY J. STANTON PIERCE, J. M. SALSBURY AND J. M. FREDERICKSEN

The majority of the synthetic local anesthetics are alkamine esters of the type $XC_6H_4COO(CH_2)_yNR_2$ in which X usually is the primary amino group, *y* is 2 or 3, and R is an alkyl group. Goldberg and Whitmore[2] have demonstrated that the tertiary amino group, above, can be replaced advantageously by a secondary amino group. Other investigators[3] have shown that in the above type formula, X can be an alkoxy group. This investigation takes up the preparation of alkamine esters of the type $ROC_6H_4COOCH_2CH_2NHR'$.

Most of the alkoxybenzoic acids reported in this work have been made by previous investigators.[4] For this investigation the alkoxybenzoic acids not obtainable from Eastman Kodak Co. were made from the methyl or ethyl ester of the phenolic acid, according to the method of Cohen and Dudley,[4a] by the alkylation of the ester with alkyl bromide and hydrolysis of the ester.

The alkoxybenzoyl chlorides were prepared from the alkoxybenzoic acids and phosphorus pentachloride in all but one case, that of *p*-allyloxybenzoic acid, when phosphorus trichloride was used.

Most of the β-monoalkylaminoethanols were prepared by the reaction of an alkyl halide with a large excess of ethanolamine, without a solvent. Goldberg[5] recommends the use of approximately equimolar quantities of alkyl bromide and ethanolamine, in alcohol solution. This procedure was not found to be satisfactory for the formation of β-mono-*n*-butylaminoethanol, β-mono-*n*-propylaminoethanol, β-monoallylaminoethanol, and β-

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

(2) Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

(3) Wildman and Thorp, U. S. Patent 1,193,650 (1916); C. Rohmann and Scheurle, *Arch. Pharm.*, **274**, 110–126 (1936).

(4) (a) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1732–1751 (1910); (b) A. E. Bradfield and B. Jones, *ibid.*, 2660–2661 (1929); (c) B. Jones, *ibid.*, 1874 (1935); (d) Bennett and Jones, *ibid.*, 420 (1939); (e) Lauer, Sanders, Leekley and Ungnade, THIS JOURNAL, **61**, 3050 (1939).

(5) S. D. Goldberg, U. S. Patent 2,139,818 (1938).

mono-isopropylaminoethanol. β-Mono-isopropylaminoethanol and β-mono-*n*-dodecylaminoethanol were produced in poor yields when no solvent was used, but with dioxane as solvent (and with *n*-dodecyl iodide instead of bromide[6]), fair results were obtained. Allyl bromide reacted so vigorously with ethanolamine that it formed mainly diallylaminoethanol. Ethyl bromide gave a poor yield of β-monoethylaminoethanol when it reacted with ethanolamine. Therefore, β-monoallylaminoethanol and β-monoethylaminoethanol were prepared by the reaction of β-chloroethyl chlorocarbonate with the appropriate amine, followed by hydrolysis of the carbamate with alcoholic potash.[7]

The alkoxybenzoyl chlorides were condensed with hydrochlorides of β-monoalkylaminoethanols to form hydrochlorides of β-monoalkylaminoethyl alkoxybenzoates.

Pharmacological tests on these compounds are being made by Dr. H. B. Haag and Mr. I. L. Silverstein of the Medical College of Virginia. The results will be reported elsewhere.

Experimental

Alkoxybenzoic Acids.—In a typical experiment, 11.5 g. of sodium was dissolved in 175 ml. of absolute ethyl alcohol. To this alcoholate was added 0.5 mole of methyl- or ethylhydroxybenzoate and then 0.5 mole of alkyl bromide. The mixture was refluxed eight to twelve hours, cooled, and filtered from inorganic salts. About half of the alcohol was vacuum evaporated and the precipitated inorganic salt was filtered off. A solution of 1 g. of sodium hydroxide in 10 ml. of alcohol was added and the mixture was treated with 150 ml. of ether and 50 ml. of water. The ether layer and a second ether extract were combined. The ether was distilled off and the residue was vacuum distilled. The ether ester thus obtained was saponified by refluxing from 1.5 to 8 hours with aqueous sodium hydroxide or alcoholic potash. The alkaline solution was poured into from two to four volumes of water and the unchanged ester was extracted with ether. The *o*-alkoxybenzoic acids and the *m*-*n*-butoxybenzoic acid were isolated by acidification of the aqueous layer, ether extraction, and vacuum distillation. *m*-Ethoxybenzoic acid, *m*-*n*-amyloxybenzoic acid, and the *p*-alkoxybenzoic acids were isolated by acidification of the aqueous layer and filtration. The solid alkoxybenzoic acids were purified by recrystallization from ethyl alcohol and water.

Alkoxybenzoyl Chlorides.—In most cases, the alkoxybenzoyl chlorides were made by treating the corresponding alkoxybenzoic acid with 1.05 equivalents of phosphorus pentachloride and heating for one hour on a boiling water-bath. The phosphorus oxychloride formed was distilled off and the alkoxybenzoyl chloride was vacuum distilled. The alkoxybenzoyl chlorides which were decomposed by the above method were obtained in satisfactory yields by the following modification. A vacuum was applied as soon as the phosphorus pentachloride was added. When the initial vigorous reaction subsided, the phosphorus oxychloride was vacuum distilled from the reaction mixture and the alkoxybenzoyl chloride was vacuum distilled.

Phosphorus pentachloride decomposed *p*-allyloxybenzoic acid, so this compound was treated with 0.67 mole of phosphorus trichloride and was heated for two hours on a water-bath. The reaction mixture was extracted with anhydrous ether and the ether layer was filtered. The ether was removed by distillation and the *p*-allyloxybenzoyl chloride was vacuum distilled.

β-Monoalkylaminoethanols.—A typical experiment is given to illustrate the method used to form the β-monoalkylaminoethanols.

β-Mono-*n*-butylaminoethanol[8] was prepared by adding slowly 1 mole (137 g. of 93%) butyl bromide, over a period of about four hours, to 160 g. (2.54 moles) of vigorously stirred ethanolamine, in a water-bath at 50–60°. A solution of 112 g. (2 moles) of potassium hydroxide in 100 ml. of water was added and the mixture was stirred with a mechanical stirrer from five to fifteen minutes. The precipitated inorganic salt was filtered off with suction. If the filtrate did not separate into two layers, a hot concentrated solution of potassium carbonate was added until two layers were formed. The upper layer was treated in a continuous extractor with petroleum ether (preferably 65–110°) for from eight to sixteen hours. The petroleum ether was distilled off and the residue fractionated.

β-Mono-*n*-propylaminoethanol and β-mono-isobutylaminoethanol were prepared similarly. In the case of β-mono-*n*-heptylaminoethanol, it was found necessary to use several moles of ethanolamine to avoid dialkylation. β-Mono-*n*-dodecylaminoethanol was formed by heating *n*-dodecyl iodide with an excess of ethanolamine in dioxane solution for sixty hours at 102° or for sixteen hours at 140° in a sealed tube. Also, dioxane was used as solvent for the reaction of isopropyl bromide and ethanolamine. β-Mono-*n*-amylaminoethanol and the higher homologs were separated readily from excess aminoethanol by ether extraction.

The β-monoalkylaminoethanols were analyzed by titration with standard hydrochloric acid with methyl red as indicator.

Hydrochlorides of β-Monoalkylaminoethyl Alkoxybenzoates.—For the preparation of β-monoalkylaminoethyl alkoxybenzoates, an excess of hydrochloric acid was added to the amino alcohol and the solution was evaporated to dryness in a vacuum. An equimolar quantity of the alkoxybenzoyl chloride was added and the mixture was heated on a water-bath for about one hour under reduced pressure. The hydrochloride of the β-monoalkylaminoethyl alkoxybenzoate was taken up in water and this solu-

(6) Acknowledgment is made to Dr. Alfred Burger, of the Department of Chemistry of the University of Virginia, for suggesting the above change.

(7) J. S. Pierce, THIS JOURNAL, **50**, 241 (1928). Some β-monoallylaminoethanol prepared by the senior author fifteen years ago, as a possible intermediate for synthetic medicinals, had decomposed somewhat but, on vacuum distillation, yielded 85% of pure product.

(8) After most of this work was completed, β-monoethylaminoethanol and β-mono-*n*-butylaminoethanol appeared on the market.

TABLE I

ALKOXYBENZOIC ACID DERIVATIVES

Substituent	Alkoxybenzoates B. p. range, °C.	Mm.	Yield, %	Alkoxybenzoic acids B. p. range, °C.	Mm.	M. p., °C., uncor.	Yield, %	Alkoxybenzoyl chlorides B. p. range, °C.	Mm.	Yield, %
p-Methoxy								161–168[g]	38	93
p-Ethoxy								170–171[d]	35	90
p-*n*-Propoxy	189–191[a]	40	81			139–142[d,f,g]	99	175–178[d,f]	30	70
p-*n*-Butoxy	196–197.5[a]	31	77			145.5–147[f,g]	99	191–193[f]	33	75
p-*n*-Amyloxy	207–208[a,b]	30	69			118–121[h,i]	94	198–200	30	86
p-*n*-Hexyloxy	217–218[a]	30	79			105–106[h,i]	98	213–214	30	87
p-*n*-Heptyloxy	228–229[a]	30	86			90–92[h]	99	226–227	30	83
p-*n*-Dodecyloxy	290–301[a]	45	59			137[j]	85	251–261	2.5	95
p-*iso*-Propoxy	171–177[a]	30	70			163–165[d]	94	177–181[f]	47	90
p-*iso*-Butoxy	192–198[a]	34	38			137–138[f,i,k]	90	181–187[f]	30	61
p-2-Octyloxy	226–229[a]	35	61	203–213[l,m]	2		62	224–229	40	87
p-Allyloxy	188–191[a]	37	72			160–162[d,f]	92	186–191	45	57
o-Ethoxy	167–179[c,d]	47	93	216–229[d]	90		63	172–184[d]	50	82
o-*n*-Propoxy	165–170[c,d,e]	40	64	205–207[d]	40		88	182–192[d]	50	85
o-*n*-Butoxy	184–190[c,e]	40	63	211–221[n]	35		82	189–205	47	91
o-*n*-Dodecyloxy	211–216[c]	2.5	64	234–242[o,p]	2.5		57	202–212	3	92
o-*iso*-Propoxy	182–190[c,d]	95	34	216–227[d]	93		81	174–189[d]	47	91
o-*iso*-Amyloxy	184–194[c,d]	40	50	239–246[d]	95		68	200–213[d]	50	89
m-Ethoxy	171–181[a,d]	37	65			131–135[d]	90	150–159[d]	30	97
m-*n*-Butoxy	192–198[a]	38	59			59– 61[q]	95	153–163	4	87
m-*n*-Amyloxy	200–206[a]	30	53			70– 71[r]	76	186–189	28	91

[a] Ethyl ester. [b] This crystallized as long needles, m. p. 29–33°, without further purification. [c] Methyl ester. [d] Also prepared by Cohen and Dudley, *J. Chem. Soc.*, 1732–1751 (1910). [e] Acknowledgment is made to Henry Heller and Henry Nakdimen for their assistance in the preparation of this compound. [f] Also prepared by Rohman and Scheurle, *Arch. Pharm.*, **274**, 110–116 (1936). [g] Also prepared by Bradfield and Jones, *J. Chem. Soc.*, 2660 (1929). [h] Also prepared by Jones, *ibid.*, 1874 (1935). [i] Also prepared by Lauer, Sanders, Leekley and Ungnade, THIS JOURNAL, **61**, 3050 (1939). [j] Also prepared by Bennett and Jones, *J. Chem. Soc.*, 420 (1939). [k] Also prepared by Bradfield and Jones, *ibid.*, 3073–3081 (1928). [l] This product, after one recrystallization from ethanol–water, melted at 58–62°. [m] Calcd. for $C_{15}H_{22}O_3$: neut. eq., 250.3. Found: neut. eq., 248.4, 247.4. [n] Calcd. for $C_{11}H_{14}O_3$: neut. eq., 194.2. Found: neut. eq., 190.4, 190.8. [o] This crystallized as fine needles, m. p. 43–47°, without further purification. [p] Calcd. for $C_{19}H_{30}O_3$: neut. eq., 306.4. Found: neut. eq., 319.5, 317.9. [q] Calcd. for $C_{11}H_{14}O_3$: neut. eq., 194.2. Found: neut. eq., 194.3, 194.2. [r] Calcd. for $C_{12}H_{16}O_3$: neut. eq., 208.2. Found: neut. eq., 208.0, 208.8. [s] Also prepared by Rossel, *Ann.*, **151**, 31 (1869).

TABLE II

β-MONOALKYLAMINOETHANOLS: $RNHCH_2CH_2OH$

R	B. p. range, °C., uncor.	Yield, %	Formula	Nitrogen, % Calcd.	Found
Ethyl[a]	164–169	35	$C_4H_{11}ON$	15.72	15.79
n-Propyl[a]	178–185	38	$C_5H_{13}ON$	13.58	13.24
n-Butyl[a]	195–205	53	$C_6H_{15}ON$	11.94	11.76
n-Amyl[a]	215–220	41	$C_7H_{17}ON$	10.68	10.51
n-Heptyl	248–251	42	$C_9H_{21}ON$	8.79	8.62
n-Dodecyl	188–198 (4.5 mm.)	16	$C_{14}H_{31}ON$	6.11	6.15
Isopropyl	172–174	23	$C_5H_{13}ON$	13.58	13.52
Isobutyl[a]	185–189	43	$C_6H_{15}ON$	11.95	11.92
Allyl[b]	89– 94 (3.5 mm.)	49	$C_5H_{11}ON$	13.85	13.66

[a] Also prepared by Goldberg and Whitmore, THIS JOURNAL, **59**, 2288 (1937). [b] Also prepared by Pierce, *ibid.*, **50**, 241 (1928).

tion was extracted with isopropyl ether or was filtered to remove acid insoluble material. The aqueous solution was made basic and was extracted with isopropyl ether. Hydrogen chloride was passed into this extract to precipitate the hydrochloride of the amino ester. Most of these compounds were purified by recrystallization. Table III lists these hydrochlorides.

Some of the β-monoalkylaminoethyl alkoxybenzoate hydrochlorides, on attempted recrystallization, came out of solution as gels. Others did not form crystalline products. Therefore, some of these products were not obtained in a pure condition. These hydrochlorides are listed below. They have the formula $ROC_6H_4COOCH_2CH_2NHR'\cdot HCl$, where R and R′ are, respectively, *p*-ethyl

TABLE III

β-MONOALKYLAMINOETHYL ALKOXYBENZOATE HYDROCHLORIDES: $ROC_6H_4COOCH_2CH_2NHR'\cdot HCl$

R	R′	M. p., °C. uncor.	Yield,[a] %	Formula	Chlorine, % Calcd.	Found
p-Methyl	*n*-Butyl[b]	127.5–129	36	$C_{14}H_{22}O_3NCl$	12.32	12.23
p-Ethyl	*n*-Butyl[b]	138 –140	41	$C_{15}H_{24}O_3NCl$	11.75	11.61
p-*n*-Propyl	*n*-Butyl[b]	136 –138	67	$C_{16}H_{26}O_3NCl$	11.23	11.27
p-*n*-Butyl	Ethyl[b]	135 –136	61	$C_{15}H_{24}O_3NCl$	11.75	11.80
p-*n*-Butyl	*n*-Propyl[c]	110.5–111.5	34	$C_{16}H_{26}O_3NCl$	11.23	11.08
p-*n*-Butyl	*n*-Butyl[b]	128 –130	61	$C_{17}H_{28}O_3NCl$	10.75	10.56
p-*n*-Butyl	*n*-Amyl[b]	123 –125	59	$C_{18}H_{30}O_3NCl$	10.31	10.23
p-*n*-Butyl	Isopropyl[b]	168 –170	40	$C_{16}H_{26}O_3NCl$	11.23	10.95
p-*n*-Butyl	Isobutyl[d]	171.5–172.5	52	$C_{17}H_{28}O_3NCl$	10.75	10.81
p-*n*-Butyl	Allyl[e]	94 – 97	44	$C_{16}H_{24}O_3NCl$	11.30	11.60
p-*n*-Amyl	*n*-Butyl[b]	124 –126	26	$C_{18}H_{30}O_3NCl$	10.31	10.18
p-*n*-Hexyl	Ethyl[b]	128 –129	54	$C_{17}H_{28}O_3NCl$	10.75	10.29
p-*n*-Hexyl	*n*-Butyl[b]	120 –123	17	$C_{19}H_{32}O_3NCl$	9.91	9.57
p-*n*-Heptyl	*n*-Butyl[c]	129.5–130.5	62	$C_{20}H_{34}O_3NCl$	9.53	9.60
p-*n*-Dodecyl	*n*-Butyl[b]	142 –143	50	$C_{25}H_{44}O_3NCl$	8.02	8.09
p-*iso*-Propyl	*n*-Butyl[e]	118 –120	54	$C_{16}H_{26}O_3NCl$	11.23	10.78
p-*iso*-Butyl	*n*-Butyl[b]	150 –152	67	$C_{17}H_{28}O_3NCl$	10.75	10.78
o-*n*-Propyl	*n*-Butyl[e]	135 –138	91	$C_{16}H_{26}O_3NCl$	11.23	11.44
o-*n*-Butyl	*n*-Butyl[e]	85.5– 87	39	$C_{17}H_{28}O_3NCl$	10.75	10.68
o-*n*-Butyl	Isopropyl[b]	107 –109	34	$C_{16}H_{26}O_3NCl$	11.23	11.25
o-*n*-Butyl	Isobutyl[c]	76 – 77	32	$C_{17}H_{28}O_3NCl$	10.75	11.05
o-*n*-Dodecyl	*n*-Butyl[b]	97 – 99	13	$C_{25}H_{44}O_3NCl$	8.02	8.00
m-*n*-Butyl	*n*-Butyl[e]	109 –110	46	$C_{17}H_{28}O_3NCl$	10.75	10.43

[a] Yields are based on one recrystallization. [b] Recrystallized from anhydrous acetone. [c] Recrystallized from anhydrous acetone–petroleum ether (b. p. 65–110°). [d] Recrystallized from anhydrous acetone–absolute ethanol. [e] Recrystallized from anhydrous acetone–anhydrous ether.

and *n*-heptyl, *p*-*n*-butyl and *n*-dodecyl, *p*-allyl and *n*-butyl, *p*-2-octyl and *n*-butyl, *o*-ethyl and *n*-butyl,[9] *o*-*n*-butyl and ethyl, *o*-*n*-butyl and *n*-propyl, *o*-*n*-butyl and *n*-dodecyl, *o*-isopropyl and *n*-butyl, *o*-isoamyl and *n*-butyl, *m*-ethyl and *n*-butyl, *m*-*n*-butyl and *n*-propyl, *m*-*n*-butyl and isobutyl, and *m*-*n*-amyl and *n*-butyl.

Since some of the monoalkylamino esters of alkoxybenzoates have been found to have high local anesthetic action, the work is being continued in this Laboratory with alkoxycinnamates and alkoxynaphthoates to see the effect of the variation of the aromatic nucleus on the anesthetic action.

Since Donleavy and English[10] found dialkylaminoethyl alkylthiobenzoates to have anesthetic action and to have low irritation, two β-monoalkylaminoethyl alkylthiobenzoates were prepared and tested for corneal anesthesia on a rabbit's eye. *o*-*n*-Butylthiobenzoyl chloride was prepared[11] as described by Donleavy and English.[10] This acid chloride was condensed with the hydrochlorides of β-mono-*n*-butylaminoethanol and β-mono-isobutylaminoethanol, as were the alkoxybenzoyl chlorides described in this paper. The butylaminoethyl *o*-*n*-butylthiobenzoates were isolated by the usual procedure and were recrystallized from anhydrous acetone.

β-Mono-*n*-butylaminoethyl *o*-butylthiobenzoate hydrochloride, m. p. 123.5–126°, was obtained in a 50% yield. Calcd. for $C_{17}H_{28}O_2NClS$: Cl, 10.27. Found: Cl, 9.97.

β-Mono-isobutylaminoethyl *o*-butylthiobenzoate hydrochloride, m. p. 83–84°, was obtained in an 82% yield. Calcd. for $C_{17}H_{28}O_2NClS$: Cl, 10.27. Found: Cl, 10.20.

Both of these products, in 1% aqueous solution, had a slight anesthetic action on a rabbit's cornea but were irritating.

(9) First prepared by David H. Miller.

(10) Donleavy and English, THIS JOURNAL, **62**, 220–222 (1940).

(11) Acknowledgment is made to Kenneth Garrison and O. G. Gilbert, Jr., for assistance in the preparation of *o*-*n*-butylthiobenzoic acid.

Summary

The hydrochlorides of a series of β-monoalkylaminoethyl alkoxybenzoates have been prepared and described.

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