effect of the peptide linkage on dissociation, and other questions relating to these compounds, are briefly discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Dialkylaminoalkanol Esters of *p*-Aminobenzoic Acid

BY W. B. BURNETT,[1] R. L. JENKINS,[1] C. H. PEET,[1] E. E. DREGER,[1] AND ROGER ADAMS

From the time that Einhorn[2] described the preparation of diethylaminoethyl *p*-aminobenzoate and established its practical value as a local anesthetic, the study of analogous compounds with a modification of the alkyl groups on the tertiary nitrogen, of the character of the residue between the nitrogen and oxygen and of the position and kind of groups in the benzene nucleus has received much attention.

An investigation in this Laboratory on many of these compounds was started in 1917 and continued for five or six years thereafter, but the results were not published. In view of recent researches which have just been completed on anesthetic compounds of somewhat analogous structure in the oxazoline, thiazoline and related series, opportunity is taken here to record the accumulated data on the procaine homologs and to make a few general remarks on the deductions on pharmacological action and chemical constitution of these compounds.

Several series of compounds of the general formula, $H_2N-C_6H_4-C(=O)-O-X-NRR_1$ were prepared. They may be divided as follows:

(1) The grouping $NH_2C_6H_4COOCH_2CH_2-$ was kept constant and the $-NRR_1$ was varied. Compounds were synthesized in which the R and R_1 represented two methyls, ethyls, *n*-propyls, isopropyls, *n*-butyls, isobutyls, *s*-butyls, *n*-amyls, isoamyls, allyls, and in which R was allyl and R_1 was *n*-butyl.

(2) A series similar to (1) was prepared in which the grouping $NH_2C_6H_4COOCH_2CH_2CH_2-$ was kept constant. The compound with two cyclohexyl groups for the R and R_1 was included.

(3) The grouping $NH_2C_6H_4COOCH_2CH(CH_3)-$ was kept constant and the $-NRR_1$ was represented by diethylamine, di-*n*-butylamine and diallylamine.

(4) Three compounds of the general formula $NH_2C_6H_4COOCH_2CH(R)N(C_2H_5)_2$, where R was methyl, isobutyl and *n*-hexyl, were synthesized.

(5) The number of methylene groups between the oxygen and nitrogen was varied from two to five inclusive, maintaining in each case two ethyl groups on the nitrogen.

Pharmacological tests were made by Nielsen and Spruth of the Abbott Laboratories.[3] No attempt will be made here to give a detailed correlation, of anesthetic properties and chemical constitution; such would not be justified on the basis of the semiquantitative data available. General deductions, however, which are not without occasional exceptions, may be drawn.

With increase in size of the alkyl groups on the nitrogen, the toxicity increases. The anesthetic value also increases markedly, in fact more rapidly than the toxicity, especially in regard to duration of topical anesthesia. This statement applies in series (1), (2), and (3). A similar result is observed where alkyl groups are introduced on the carbons between the oxygen and the nitrogen as in series (4). Extending the distance between the oxygen and the nitrogen to four or five methylenes, results in increased toxicity, a gradual increase in anesthetic properties, more pronounced in case of topical anesthesia. It may be stated also that the compounds with iso or forked chain alkyls are generally less toxic and less anesthetic than the corresponding compounds with straight-chain alkyls. The majority of the compounds described had a more favorable ratio of M. L. D. to M. E. D. than procaine.

The di-*n*-butylaminopropyl *p*-aminobenzoate as the sulfate has found practical use as an anesthetic for topical anesthesia and is marketed under the name "Butyn."

The various anesthetics were prepared by two methods now well recognized as standard for such compounds: (1) condensation of *p*-nitrobenzoyl chloride with the proper aminoalkanol, and (2) condensation of a dialkylamine with an ω-halogen

(1) Submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry.

(2) Einhorn, *Ann.*, **371**, 162 (1909).

(3) Unpublished results.

TABLE I

α-DIALKYLAMINO ACID ESTERS

α-Dialkylamino ethyl ester	Solvent	Time[a]	B. p. °C.	Mm.	*d*	n_D	Formula	Analyses, % N Calcd.	Found
Diethylaminopropionate[b]	Benzene 200 cc.	0 1	172–177		0.9985^{16}	1.4302^{16}	$C_9H_{19}O_2N$	8.09	7.99
Dibutylaminopropionate	Toluene 100 cc.	6 1	129–130	17	$.8770^{16}$	1.4388^{16}	$C_{13}H_{27}O_2N$	6.11	6.08
Diallylaminopropionate	...	0 1	148–150	123	$.9267^{20}$	1.4462^{20}	$C_{11}H_{19}O_2N$	7.11	6.97
Diethylaminoisobutyrate	...	48 6	136–139	45	....	....	$C_{10}H_{21}O_2N$	7.48	7.76
Diethylaminoheptoate	...	0 6	112–114	10	....	....	$C_{13}H_{27}O_2N$	6.11	6.66

[a] First figure gives number of hours mixture was allowed to stand before refluxing; second figure gives number of hours mixture was refluxed. [b] Von Braun, Leistner, and Munch, *Ber.*, **59**, 1950 (1926), report a b. p. of 85–88° (13 mm.).

alkyl ester of *p*-nitrobenzoic acid. Reduction of the nitro compounds gave the anesthetics.

The solubility in water of the hydrochlorides of those bases of higher molecular weight is much less than those of the lower molecular weight and consequently the use of a different salt for such compounds is necessary.

Among the various substances synthesized, three, γ-diisopropylaminopropyl *p*-nitrobenzoate hydrochloride, γ-diisopropylaminopropyl *p*-aminobenzoate hydrochloride, and γ-di-*n*-butylaminopropyl *p*-aminobenzoate hydrochloride, exhibited the phenomenon of double melting points. The lower melting forms were obtained in the preparations and, by holding at a temperature two or three degrees above the melting points, were converted to the higher melting forms. Solvents were found from which the higher melting forms could be recrystallized unchanged and others from which the lower melting forms separated. These substances are apparently dimorphous.

Experimental

The dialkyl amines were obtained from commercial sources or prepared by methods already described in the literature: diallylamine,[4] di-*n*-propylamine,[5] diisopropylamine,[6] di-*n*-butylamine,[7] di-*s*-butylamine,[6] di-*n*-amylamine,[6,8] and dicyclohexylamine.[9]

Butylallylamine.—To 190 g. of allylamine in a three-necked flask fitted with a mechanical stirrer, reflux condenser, and dropping funnel, was added during the course of nine and one-half hours, 270 g. of *n*-butyl bromide. The reaction mixture warmed, turned red, became viscous, and was almost solid at the end of the addition. The mixture was then warmed on a water-bath for one and one-half hours. An excess of hydrochloric acid was added and the mixture subjected to steam distillation. Less than 0.5 g. of butyl bromide was recovered. The residue was poured into a large flask immersed in an ice-bath, and to it was added an excess of concentrated sodium hydroxide. The amine layer was separated, dried over sodium hydroxide, and fractionated. This procedure yielded 128 g. (57%) of butylallylamine, b. p. 131–136°; and 37 g. of di-*n*-butylallylamine, b. p. 185–187.5°. Redistilled, the butylallylamine gave the following constants: b. p. 134.2–134.4° (744 mm.); $n^{20}D$ 1.4260; d^{20}_{20} 0.7717.

Anal. Calcd. for $C_7H_{15}N$: N, 12.39. Found: N, 12.07.

Ethyl Esters of α-Dialkylamino Acids.—The esters of α-bromo acids (1 mole) and secondary amines (4 moles) were condensed together, with or without a solvent. The amine hydrobromide was filtered and the filtrate acidified and extracted with ether to remove unchanged halogen ester; the amino esters were set free with alkali, extracted, dried and distilled. The yields were better than 80% in all cases except in the case of the ethyl diethylaminoisobutyrate.

The experimental conditions and physical constants of the products are given in Table I.

Dialkylaminoalkanols.—These substances were prepared (a) by the reaction between a secondary amine and ethylene oxide; (b) by the reaction between a secondary amine and a polymethylene chlorohydrin; and (c) by the reduction of ethyl α-dialkylamino esters with sodium and alcohol.

In method (a) the amine (1 mole) and ethylene oxide (1 mole) together with a trace of water[10] were heated together at 100° in a sealed flask for a length of time depending upon the amine used. The resulting dialkylamino alcohol was then purified by fractional distillation. The yields varied from 70–95% except in the case of the dimethylamine and dicyclohexylamine, when the yields were considerably lower.

In method (b) the secondary amine (2 moles) and ethylene or trimethylene chlorohydrin (1 mole) were heated together with stirring. A temperature of 100° was used for dimethyl-, diethyl- and dipropylamine; a temperature of 120–130° for di-*n*-butyl-, di-*n*-amyl-, and diisoamylamine. The reaction mixture was then made alkaline with strong sodium hydroxide solution. The amine layer was separated, dried with solid sodium hydroxide, and fractionally distilled to obtain the pure dialkylamino alcohols.

In method (c) a mixture of powdered sodium (10–15 atoms equiv.) in dry toluene was prepared in a three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel. To the mixture was added rapidly (one minute) a solution of the ethyl ester of the α-dialkylamino acid (1 mol. equiv.) in absolute alcohol (20 g. in 30 cc.) and afterward enough absolute alcohol to cause

(4) "Organic Syntheses," Coll. Vol. I, 1932, p. 195.
(5) Mandl, *Monatsh.*, **7**, 99 (1886).
(6) Van der Zande, *Rec. trav. chim.*, **8**, 202 (1889).
(7) Reilly and Hickinbottom, *J. Chem. Soc.*, **113**, 99 (1918).
(8) Rupe, Metzger, and Vogler, *Helv. Chim. Acta*, **8**, 848 (1925); Adkins and Cramer, THIS JOURNAL, **52**, 4349 (1930).
(9) Voorhees and Adams, *ibid.*, **44**, 1397 (1922).
(10) Matthes, *Ann.*, **316**, 315 (1901).

TABLE II

DIALKYLAMINO ALKANOLS

Substance	B. p. °C.	Mm.	d^{20}_{20}	$n^{20}D$	Formula	N Analyses, % Calcd.	Found
β-Butylallylaminoethanol[a]	212–213	744	0.8848	1.4548	$C_9H_{19}ON$	8.92	8.94
β-Di-*n*-butylaminoethanol[b]	226–228	738	.8624	1.4444	$C_{10}H_{23}ON$	8.09	8.12
β-Di-*s*-butylaminoethanol[c]	224–226	745	.8780	1.4475	$C_{10}H_{23}ON$	8.09	8.23
γ-Di-*n*-propylaminopropanol	210–220	750	.8700	1.4440	$C_9H_{21}ON$	8.80	8.96
γ-Di-*n*-butylaminopropanol[d]	247–248	749	.8663	1.4448	$C_{11}H_{25}ON$	8.09	7.95
β-Diethylaminopropanol[e]	166–169	749	.8665	1.4305	$C_7H_{17}ON$		
β-Di-*n*-butylaminopropanol	112–114	20	.8533	1.4466	$C_{11}H_{25}ON$	7.49	7.59
β-Diallylaminopropanol	145–147	123	.9103	1.4466	$C_9H_{17}ON$	9.03	9.00
β-Diethylaminoisobutanol	132–135	45			$C_8H_{19}ON$	9.73	9.60
β-Diethylaminoheptanol	107–109	10	.8580	1.4412	$C_{11}H_{25}ON$	7.49	7.40

[a] Supniewski, *Rocznicki Chemji*, **7**, 163 (1927). [b] Adams, Kamm and Volwiler, U. S. Patent 1,358,750. [c] Adams, Jenkins and Volwiler, U. S. Patent 1,513,730. [d] Adams, Dreger and Volwiler, U. S. Patent 1,590,792. [e] Von Braun, Leistner and Munch, *Ber.*, **59**, 1950 (1926), report a b. p. of 78° (12 mm.). The density of this product was determined at 27° and the index of refraction at 24°.

TABLE III

DIALKYLAMINOALKYL-*p*-NITROBENZOATE HYDROCHLORIDES

Dialkyl(amino)*alkyl* *p*-nitrobenzoate hydrochloride	Method	M. p., °C.	Solvent	Formula	Analyses, % Calcd.	Found
β-Dimethyl ( ) ethyl[a,d]	1	58		$C_{17}H_{14}O_4N_2$		
β-Di-*n*-propyl ( ) ethyl	1	133.5–134.5	EtOAc	$C_{15}H_{23}O_4N_2Cl$	N 8.47	8.33
					Cl 10.74	10.67
β-Diisopropyl ( ) ethyl[a]	1	162.5	$(CH_3)_2CO$	$C_{15}H_{23}O_4N_2Cl$	Cl 10.74	10.48
β-Butylallyl ( ) ethyl	1	117.5–118.5	EtOH–EtOAc	$C_{16}H_{23}O_4N_2Cl$		
β-Di-*n*-butyl ( ) ethyl[b]	1	92.5–93.5	EtOH–EtOAc	$C_{17}H_{27}O_4N_4Cl$	Cl 9.90	9.95
β-Diisobutyl ( ) ethyl[a]	1	160–161		$C_{17}H_{27}O_4N_2Cl$		
β-Di-*s*-butyl ( ) ethyl[d]	1	51–51.5		$C_{17}H_{26}O_4N_2$	N 8.69	9.03
β-Diisoamyl ( ) ethyl[a]	1	123–124		$C_{19}H_{31}O_4N_2Cl$		
γ-Dimethyl ( ) propyl[c]	1	161		$C_{12}H_{17}O_4N_2Cl$	Cl 12.30	11.82
γ-Diethyl ( ) propyl[c]	1	189–190		$C_{14}H_{21}O_4N_2Cl$		
γ- Di-*n*-propyl ( ) propyl[c]	1 and 2	147–148		$C_{16}H_{25}O_4N_2Cl$	N 8.13	8.53
					Cl 10.30	10.28
γ-Diisopropyl ( ) propyl[b,c]	2	140 and 160		$C_{16}H_{25}O_4N_2Cl$		
γ-Di-*n*-butyl ( ) propyl	1	127.5–128.5	H_2O	$C_{18}H_{29}O_4N_2Cl$	Cl 9.54	9.54
γ-Diisobutyl ( ) propyl[b,d]	2	40.5–41.5		$C_{18}H_{28}O_4N_2$	N 8.33	8.46
β-Diethyl ( ) propyl	1	155.6	Abs. EtOH	$C_{14}H_{21}O_4N_2Cl$	Cl 8.85	8.81
δ-Diethyl ( ) butyl	2	159–160	Bz-EtOH	$C_{15}H_{23}O_4N_2Cl$	Cl 10.74	10.81
ε-Diethyl ( ) amyl	2	142.3	Bz-EtOH	$C_{16}H_{25}O_4N_2Cl$	Cl 10.25	10.69

[a] Einhorn, *Ann.*, **371**, 162 (1909). [b] Kamm, Adams and Volwiler, U. S. Patent 1,358,750. [c] Kamm, THIS JOURNAL, **42**, 1030 (1920). [d] Data obtained on free base instead of hydrochloride. [e] See Table V.

all the sodium to dissolve. After refluxing for one-half hour, the solution was concentrated, acidified, covered with ether, made alkaline with sodium carbonate, and extracted with ether. The ether extract was dried with potassium carbonate and fractionally distilled to obtain the desired dialkylamino alcohol.

The constants of the dialkylamino alkanols are given in Table II.

Dialkylaminoalkyl *p*-Nitrobenzoate Hydrochlorides.—To prepare these substances two methods were employed:

(1) A dialkylamino alcohol was added to an equimolecular amount of *p*-nitrobenzoyl chloride dissolved in benzene. The solution was then refluxed for one hour during which time the greater part of the resulting dialkylaminoalkyl *p*-nitrobenzoate hydrochloride separated either as an oil or as a solid. In the former case no further purification was attempted, and the crude nitro compound was reduced directly to the amine. In the latter case it was purified by boiling a water solution of the hydrochloride with norite, filtering, making alkaline with sodium carbonate and extracting the free amine with benzene. The benzene extract was then dried, filtered, and treated with dry hydrogen chloride until no more hydrochloride precipitated. The precipitate was collected and recrystallized from a suitable solvent.

(2) Twice the theoretical amount of a secondary amine was refluxed with an ω-bromoalkyl *p*-nitrobenzoate. Two to five hours usually sufficed, but the reaction between diisopropylamine and γ-bromopropyl *p*-nitrobenzoate required fifty-five hours. After the reflux period the mixture was dissolved in benzene. After first removing the secondary amine hydrobromide formed as a by-product, the dialkylaminoalkyl *p*-nitrobenzoate was extracted with dilute hydrochloric acid. The water solution of the hydrochloride thus formed was then treated as in the first method.

The yields by both methods were practically quantitative. The constants of the solid products are given in Table III.

The hydrochlorides of the β-di-(*n*)-amylaminoethyl, γ-di-(*s*)-butylaminopropyl, γ-di-(*n*)-amylaminopropyl, γ-diisoamylaminopropyl, γ-dicyclohexylaminopropyl, γ-butylallylaminopropyl, β-di-(*n*)-butylaminopropyl, β-diallylaminopropyl, β-diethylaminoisobutyl, and β-diethylaminoheptyl *p*-nitrobenzoate hydrochlorides were obtained only as non-crystallizing oils.

Dialkylaminoalkyl *p*-Aminobenzoate Hydrochlorides (Procaine Homologs).—Each of these substances was prepared by the reduction of the corresponding dialkylaminoalkyl *p*-nitrobenzoate hydrochloride. The latter was mixed with an excess of pure iron powder in a beaker and stirred to a thick paste with water. The reaction commenced at once and generated heat. The temperature of the reaction mixture was prevented from rising above about 50° by immersing occasionally in an ice-bath. Hydrolysis was thus prevented. The reduction was considered complete when, after a period of continued vigorous stirring, the temperature no longer rose. The mixture was then repeatedly extracted with benzene. The benzene solution was evaporated to dryness, and the residual base dissolved in alcohol and titrated with alcoholic hydrogen chloride. The alcohol was evaporated and the dialkylaminoalkyl *p*-aminobenzoate hydrochloride recrystallized from a suitable solvent (Table IV).

Double Melting Points.—The substances γ-diisopropylaminopropyl *p*-nitrobenzoate hydrochloride (I), γ-diisopropylaminopropyl *p*-aminobenzoate hydrochloride (II), and γ-di-*n*-butylaminopropyl *p*-aminobenzoate hydrochloride (III) each possessed two melting points. In each case the lower-melting (α) form was obtained in the process

TABLE IV

DIALKYLAMINO *p*-AMINOBENZOATE HYDROCHLORIDES

Dialkyl(amino)*alkyl* *p*-aminobenzoate hydrochloride	M. p., °C.	Solvent	Formula	Analyses, % Calcd.	Found
β-Dimethyl ( ) ethyl[a]	185	Abs. EtOH	$C_{11}H_{17}O_2N_2Cl$		
β-Di-*n*-propyl ( ) ethyl	201–202	Abs. EtOH	$C_{15}H_{25}O_2N_2Cl$	Cl 11.80	11.81
β-Diisopropyl ( ) ethyl[a]	166–167	Abs. EtOH	$C_{15}H_{25}O_2N_2Cl$	Cl 11.80	11.72
β-Butylallyl ( ) ethyl	181–182	EtOH-EtOAc	$C_{16}H_{25}O_2N_2Cl$	Cl 11.34	11.39
β-Di-*n*-butyl ( ) ethyl[b]	169.5–170.5	EtOH-EtOAc	$C_{17}H_{29}O_2N_2Cl$	Cl 10.80	10.75
β-Diisobutyl ( ) ethyl[a]	198–199	EtOH-EtOAc	$C_{17}H_{29}O_2N_2Cl$		
β-Di-*s*-butyl ( ) ethyl	188.5–190.5	BuOH	$C_{17}H_{29}O_2N_2Cl$	Cl 10.80	10.91
β-Di-*n*-amyl ( ) ethyl	154	Abs. EtOH	$C_{19}H_{33}O_2N_2Cl$		
β-Diisoamyl ( ) ethyl[a]	152–152.5	Abs. EtOH	$C_{19}H_{33}O_2N_2Cl$		
γ-Dimethyl ( ) propyl[b]	164.5	Abs. EtOH	$C_{12}H_{19}O_2N_2Cl$	Cl 13.73	13.91
γ-Diethyl ( ) propyl[c]	161–162	BuOH	$C_{14}H_{23}O_2N_2Cl$		
γ-Di-*n*-propyl ( ) propyl	181–182	Abs. EtOH	$C_{16}H_{27}O_2N_2Cl$	Cl 11.27	11.20
γ-Diisopropyl ( ) propyl[b,d]	163.5	BuOH	$C_{16}H_{27}O_2N_2Cl$	N 8.90	9.04
				Cl 11.27	11.28
γ-Butylallyl ( ) propyl	143.5–144.5	EtOH-EtOAc	$C_{17}H_{27}O_2N_2Cl$	Cl 10.85	10.86
γ-Di-*n*-butyl ( ) propyl[b,d]	124–126	Abs. EtOH	$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.27
γ-Diisobutyl ( ) propyl[b]	208–209	EtOH-EtOAc	$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.32
γ-Di-*s*-butyl ( ) propyl	164.5–165.5	Abs. EtOH-EtOAc	$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.28
γ-Di-*n*-amyl ( ) propyl	137	EtOH-EtOAc	$C_{20}H_{35}O_2N_2Cl$	Cl 9.58	9.73
γ-Diisoamyl ( ) propyl[b]	172–172.5	EtOH	$C_{20}H_{35}O_2N_2Cl$	Cl 9.58	9.77
γ-Dicyclohexyl ( ) propyl	dec. 270–280	EtOH	$C_{22}H_{35}O_2N_2Cl$	Cl 9.04	9.18
β-Diethyl ( ) propyl	159–160	Abs. EtOH	$C_{14}H_{23}O_2N_2Cl$	Cl 12.34	12.35
β-Di-*n*-butyl ( ) propyl	200	Abs. EtOH	$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.37
β-Diallyl ( ) propyl	182.3	Abs. EtOH	$C_{16}H_{23}O_2N_2Cl$	Cl 11.43	11.51
δ-Diethyl ( ) butyl	155–156	EtOH-EtOAc	$C_{15}H_{25}O_2N_2Cl$	Cl 11.80	11.99
ε-Diethyl ( ) amyl	133–134	Abs. EtOH	$C_{16}H_{27}O_2N_2Cl$	Cl 11.27	11.25
β-Diethyl ( ) isobutyl	171–172	EtOAc-EtOH	$C_{15}H_{25}O_2N_2Cl$	Cl 11.80	11.75
β-Diethyl ( ) heptyl	118–119	EtOAc	$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.42

[a] Einhorn, *Ann.*, **371**, 162 (1909). [b] Kamm, Adams and Volwiler, U. S. Patent 1,358,750; 1,358,751. [c] Kamm, THIS JOURNAL, **42**, 1030 (1930). [d] See Table V.

TABLE V

CONSTANTS OF COMPOUNDS SHOWING DOUBLE MELTING POINTS

Compound	Melting point α-Form	Melting point β-Form	Solvent β → α	Solvent Crys. of β-form	Formula	Analyses, % Calcd.	Found α	Found β
I	140	160	H_2O	BuOH or abs. EtOH	$C_{16}H_{25}O_4N_2Cl$	N 8.13	8.32	8.38
						Cl 10.30	10.23	10.30
II	163.5	180–181	BuOH, or abs. EtOH or EtOAc	Chloroform or water or chlorobenzene	$C_{16}H_{27}O_2N_2Cl$	N 8.90	9.04	9.02
						Cl 11.27	11.28	11.27
III	124–126	149–150.5	Water or abs. EtOH		$C_{18}H_{31}O_2N_2Cl$	Cl 10.36	10.27	10.31

by which the substance was made. When held at a temperature two or three degrees above its melting point, the α-form was converted to the higher-melting (β) form, which first solidified and then remelted sharply at a higher temperature. Solvents from which the β-forms recrystallized unchanged, and another set in which the β-forms were converted to the corresponding α-forms are given in Table V. Heat was the only agent found which would effect the transformation of the α to the β-forms. Analytical data showed that the two forms were of identical composition. They are probably dimorphs.

Summary

1. Several series of local anesthetics of the procaine type are described. Modifications of the general formula, $NH_2C_6H_4COO\text{-}X\text{-}NR_1R_2$, were synthesized in which (a) the alkyl groups on the nitrogen were varied while several nuclei of the type $NH_2C_6H_4COO\text{-}X\text{-}$ were held constant; (b) the X was a forked residue with only two carbons between the oxygen and nitrogen; (c) the X was a straight-chain residue consisting of 2, 3, 4 and 5 methylenes. In (b) and (c) the $-N(C_2H_5)_2$ group represented $-NRR_1$ in each case.

In general terms, it may be said that increasing the molecular weight of the molecule in any of the ways indicated, resulted in compounds of increased toxicity and increased anesthetic effect, especially in respect to topical anesthesia.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

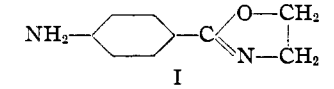
Aminophenyl-2-oxazolines as Local Anesthetics

BY M. T. LEFFLER[1] AND ROGER ADAMS

The general recognition and acceptance of procaine as a valuable local anesthetic has been accompanied by varied and extended search for still other promising anesthetics. It is a rather noticeable fact that the voluminous amount of research,[2] spent in this direction has led to the development of only a very few new types of anesthetics and has consisted for the most part merely in variations of the general type of which procaine is the most important member. The present investigation was undertaken in the hope of finding a local anesthetic which might have a favorable ratio between minimum lethal and minimum effective dose and at the same time have a lower toxicity than procaine.

Local anesthetics of the procaine type have been discussed in a previous paper,[3] and the general conclusion can be drawn that an increase in molecular weight over that of procaine itself, regardless of the point of substitution, almost invariably leads to molecules of higher toxicity. To be sure, the anesthetic effectiveness of these compounds also increases, especially for topical anesthesia, and many of them have a more favorable ratio between minimum effective and minimum lethal dose than procaine. A molecule of lower molecular weight, however, might well be expected to have a lower toxicity than procaine. The anesthetic value probably might be decreased also, but possibly not to the same relative degree.

It is known that the dimethylamino homolog of procaine causes only a very slight anesthesia and so the molecular weight must be lowered by means other than mere omission of methylene groups. This has been attempted by the preparation of aminophenyl oxazolines, the simplest member of which is shown in Formula I.



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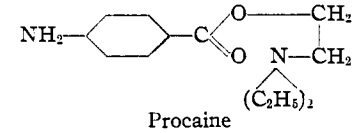

Procaine

Such a molecule retains the $-O-CH_2-CH_2-N=$ linkage but eliminates the oxygen of the carbonyl and the two ethyl groups on the nitrogen, thus reducing the molecular weight by about 31%. The product (I) is a local anesthetic but its low water solubility of less than 0.5% makes an accurate comparison with procaine difficult. The *m*-amino derivative corresponding to I, however, is soluble to the extent of 1% in water at 30° and is the most soluble member in the series. This product is only one-third as toxic[4] as procaine

(1) Abstract of a thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in Chemistry.

(2) Lee Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932), and many original articles.

(3) Burnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **59**, 2248 (1937).

(4) Toxicity: rabbits intravenously.