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 $NH_2C_6H_4COO$-X- 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.

URBANA, ILLINOIS RECEIVED JULY 19, 1937

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

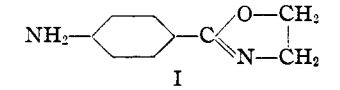
Aminophenyl-2-oxazolines as Local Anesthetics

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

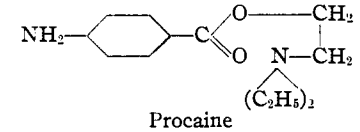
The general recognition and acceptance of procaine as a valuable local anesthetic has been accompanied by varied and extended search for still other promising anesthetics. It is a rather noticeable fact that the voluminous amount of research,[2] spent in this direction has led to the development of only 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.



I



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

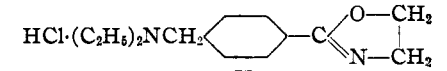
(1) Abstract of a thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in Chemistry.

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

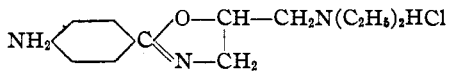
(3) Burnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **59**, 2248 (1937).

(4) Toxicity: rabbits intravenously.

and is of practically the same efficiency,[5] as demonstrated by tests with a 1% aqueous solution of the free base following the accepted procedure. The aqueous solutions of the aminophenyl oxazoline bases have the further advantage of exhibiting a *p*H of 7.5. From the practical standpoint there are several disadvantages to their use, namely, the low solubility of the free bases mentioned above, which is still further reduced by additional substituents in either the benzene or oxazoline ring; furthermore, the hydrochlorides of the aminophenyl oxazolines, although all very soluble in water, are too acidic (*p*H 4–5) and are unstable to boiling water, due to the gradual hydrolysis of the oxazoline ring. Salts of organic acids, *i. e.*, tartrates, mandelates, etc., do not form readily due to low basicity of the oxazoline nitrogen. The aqueous solutions of the bases, after many months of standing, also appear to undergo partial hydrolysis. The monohydrochlorides of *p*-diethylaminomethyl-phenyl-2-oxazoline (II) and 5-diethylaminomethyl-*p*-aminophenyl-2-oxazoline (III), are freely soluble in water and give solu-



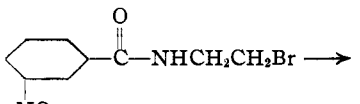
II



III

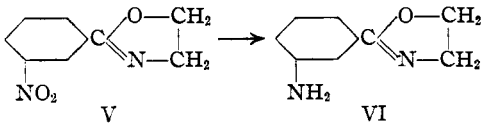
tions with *p*H 7 and 7.5, respectively. Compound II, however, is decidedly toxic and compound III does not possess an increased anesthesia parallel to the increased toxicity due to the additional $-CH_2N(C_2H_5)_2$ grouping.

Although phenyl oxazolines have long been known, no aminophenyl-2-oxazolines (VI) have been described previously. Two general procedures were used for their synthesis. One consisted in the conversion of β-bromoethyl nitrobenzamides (IV) to nitrophenyl oxazolines (V) by means of alcoholic sodium hydroxide, then reduction of the products. The nitrophenyl oxazoline also may be prepared by direct nitration of phenyloxazoline.



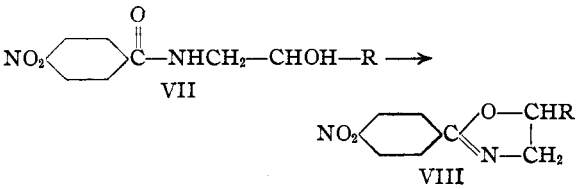
IV

(5) Efficiency: (a) frog sensory nerve; (b) intradermal wheal, guinea pigs. (These pharmacological results were kindly furnished by H. C. Spruth of the Abbott Laboratories.)



V VI

The second method was used in several cases, especially for certain 5-alkyl oxazolines. By condensing an aroyl chloride and a β-amino alcohol, a substituted β-hydroxyalkyl benzamide (VII) is produced, which is readily converted to an oxazoline (VIII) by means of sulfuric acid or thionyl chloride. The use of sulfuric acid as a reagent is particularly suitable if the hydroxyl group is attached to a tertiary carbon atom.



VII VIII

The aqueous solubility of aminophenyl oxazolines and their susceptibility to hydrolysis in hot dilute mineral acids have already been mentioned. By hydrolysis, the oxazoline ring is opened and the hydrochloride of a β-aminoethyl benzoate is formed.

For the preparation of the diethylamino compound (II), *p*-chloromethylphenyl-2-oxazoline from 2-bromoethyl-*p*-chloromethyl benzamide was condensed with diethylamine; for III, 3-diethylamino-2-hydroxy-*n*-propyl-*p*-nitrobenzamide was treated with thionyl chloride and then reduced.

Experimental

3-Nitro-4-anisic Acid.—This acid and its acid chloride were prepared by the methods of King and Murch.[6]

***p*-Chloromethylbenzoic Acid.**—The procedure of Mellinghoff[7] gave a 70% yield of this acid which, purified by crystallization from alcohol, melted at 201–202°, the same as that observed by Case.[8] *p*-Chloromethylbenzoic acid was converted in the usual manner by thionyl chloride into *p*-chloromethylbenzoyl chloride, b. p. 126–128° (6 mm.).[9]

Preparation of Amino Alcohols

The 2-hydroxy-2-methylpropylamine used in this work was purchased from the Shell Development Company.

1-Amino-2-hydroxypropane.—A 1-liter autoclave containing a mixture of 250 cc. of concentrated aqueous ammonia, 116 g. (2 moles) of propylene oxide and 0.1 g. of solid sodium hydroxide, cooled to 0°, was closed tightly and allowed to stand at room temperature with occasional shaking for six hours. At the end of this time the contents were transferred to a modified Claisen distilling flask and

(6) King and Murch, *J. Chem. Soc.*, **127**, 2632 (1925).
(7) Mellinghoff, *Ber.*, **22**, 3207 (1889).
(8) Case, THIS JOURNAL, **47**, 3003 (1925).
(9) German Patent, 240,835 (1911).

the excess of ammonia and water removed under reduced pressure at a temperature below 35°. The residue was distilled *in vacuo*, collecting the fraction boiling at 45–140° (18 mm.), which consisted mainly of water, 1-amino-2-hydroxypropane, and higher polymers. This fraction was redistilled *in vacuo* using a modified Claisen flask with a six-inch (15-cm.) carborundum column. The 1-amino-2-hydroxypropane boiled at 62–65° (4 mm.); 156–158° (738 mm.), the values agreeing with those reported by Levene and Walti,[10] yield 37 g.

o-Aminocyclohexanol.—This compound was prepared as described by Godchot and Mousseron,[11] except that a little sodium hydroxide was added to the reaction mixture; yield 63%.

1-Phenyl-1-amino-2-ethanol.—To 70.0 g. of ethyl phenylaminoacetate in 250 cc. of freshly prepared absolute alcohol was added rapidly 74.4 g. of clean sodium.[12] Enough more absolute alcohol was added from time to time to react with all of the sodium. The reaction mixture was then refluxed vigorously in an oil-bath for four hours, cooled, and 400 cc. of water added to dissolve the sodium ethylate. The water and alcohol were removed carefully under reduced pressure, the residue diluted with water to a volume of 500 cc., and extracted continuously with ether for forty hours, using the apparatus described in "Organic Syntheses."[13] After distilling off the ether from the ether extract, the residue was distilled under reduced pressure in an atmosphere of nitrogen gas. The yield of 1-phenyl-1-amino-2-ethanol boiling at 125–127° (3 mm.), amounted to 14.5 g. (27%). Phenylaminoethanol gave a hydrochloride, m. p. 146–147°, and a benzamide, by treatment with one equivalent of benzoyl chloride, which melted at 149–150°. These constants check those previously reported by Kotz and Schneider[14] but the melting point of the hydrochloride does not agree with that reported by Gabriel and Colman,[15] m. p. 137–138°.

2-Amino-1-hexanol.—A solution of 91.5 g. of acetyl ethyl α-aminocaproate[16] (b. p. 133–134° at 2–3 mm.) in 250 cc. of absolute alcohol was reduced with 65 g. of sodium by the same procedure as outlined above in the preparation of 1-phenyl-1-amino-2-ethanol. A sixty-hour continuous ether extraction of a 300-cc. water solution yielded 20.5 g. (39%) of 2-amino-1-hexanol boiling at 111–113° (21 mm.), or 190–192° (740 mm.). Krassuski and Duda[17] reported the same boiling point but stated that the hydrochloride of 2-amino-1-hexanol was a sirup. It was found possible to isolate the hydrochloride as a colorless solid by adding an absolute alcoholic solution of hydrogen chloride to a dry ether solution of the free base. Two crystallizations from absolute alcohol gave colorless plates of 2-amino-1-hexanol hydrochloride, m. p. 93–94.5°.

Anal. Calcd. for $C_6H_{16}ONCl$: Cl, 23.11. Found: Cl, 23.16.

3-Amino-2-butanol.—Using the procedure and apparatus described in "Organic Syntheses"[13] (p. 519) for the preparation of trimethylene chlorohydrin, 2,3-butylene glycol was converted by gaseous hydrogen chloride into 2,3-butylene chlorohydrin. Dry hydrogen chloride was passed rapidly through a total amount of 50.0 g. of 2,3-butylene glycol heated to 135–140° in a Wood's metal bath maintained at 150–155°. These temperatures were found to be most favorable in reducing the amount of unreacted butylene glycol and the amount of pinacolone rearrangement to a minimum. The crude product, after removing the excess hydrogen chloride under reduced pressure, was dried over anhydrous magnesium sulfate and fractionally distilled. After three fractionations the portion boiling constantly at 137–139° (corr.) amounted to 18.5 g. (30%), $n^{20}D$ 1.4432, which agrees with that reported by Henry.[18]

A 350-cc. autoclave containing a mixture of 17.0 g. of 2,3-butylene chlorohydrin, 100 cc. of a saturated 50% alcoholic solution of ammonia, and 0.05 g. of solid sodium hydroxide was heated for two hours at 100–110°. To the light brown solution resulting from this treatment was added 10.0 g. of anhydrous sodium carbonate and the water carefully removed under reduced pressure at 35°. The sodium chloride thus formed was precipitated from the residue by the addition of 100 cc. of absolute alcohol, and the filtered solution distilled. The yield of 3-amino-2-butanol[19] boiling at 160–162° (742 mm.) (corr.) amounted to 6.7 g. (49%); $n^{20}D$ 1.4482.

Preparation of Aminoalkyl Halides

3-Chloro-2-hydroxypropylamine Hydrochloride.—The 3-chloro-2-hydroxypropylamine hydrochloride, m. p. 104.5–105.5°, was obtained by hydrolysis of N-γ-chloro-β-hydroxypropylphthalimide.[20]

***o*-Chlorocyclohexylamine Hydrochloride.**—This compound was prepared from the hydrochloride of *o*-aminocyclohexanol.[21]

2-Bromoethylamine Hydrobromide.—Monoethanolamine was converted into the hydrobromide salt by treatment with concentrated hydrobromic acid and removal of all of the water under reduced pressure. In a 500-cc., round-bottomed flask equipped with an extra long reflux condenser attached to an efficient gas-trap, was placed 142.0 g. (1 mole) of dry monoethanolamine hydrobromide and 135.0 g. (50% excess) of redistilled phosphorus tribromide. The reaction mixture was warmed with a free flame until a vigorous reaction set in and until the reddish-brown layer of the ethanolamine hydrobromide completely disappeared. After the reaction was complete, the excess of phosphorus tribromide was removed by warming under the vacuum of a water pump, the cooled solid residue washed thoroughly with dry ether, and recrystallized from absolute alcohol. The product obtained from one recrystallization amounted to 147 g. (72% based on the aminoethanol) and was sufficiently pure for further use. Three recrystallizations from absolute alcohol gave colorless plates of 2-bromoethylamine hydrobromide, m. p. 172–173°. Gabriel[22] reported the melting point as 172.5–173.5°.

(10) Levene and Walti, *J. Biol. Chem.*, **71**, 461 (1926).
(11) Godchot and Mousseron, *Bull. soc. chim.*, **51**, 1277 (1932).
(12) Karrer and co-workers, *Helv. Chim. Acta*, **4**, 76 (1921).
(13) "Organic Syntheses," Coll. Vol. I, p. 271.
(14) Kotz and Schneider, *J. prakt. Chem.*, **90**, 136 (1914).
(15) Gabriel and Colman, *Ber.*, **47**, 1866 (1914).
(16) Cherbuliez and Plattner, *Helv. Chim. Acta*, **12**, 317 (1929).
(17) Krassuski and Duda, *J. prakt. Chem.*, **77**, 84 (1908).
(18) Henry, *Compt. rend.*, **145**, 498 (1907).
(19) Henry, *Ber.*, **33**, 3169 (1900).
(20) Gabriel and Hohle, *ibid.*, **50**, 819 (1917).
(21) Osterberg and Kendall, THIS JOURNAL, **42**, 2616 (1920).
(22) Gabriel, *Ber.*, **50**, 826 (1917).

TABLE I

CONSTANTS OF SUBSTITUTED BENZAMIDES

No.	Benzamide	Method of prepn.	Yield, %	M. p., °C.	Form	Cryst. from	Prev. rep., m. p., °C.	Formula	N Analyses, % Calcd.	Found
1	2-Bromoethyl-*o*-nitro-	1	83	122.5–123.5	Colorless needles	Benzene	...	$C_9H_9O_3N_2Br$	10.26	10.53
2	2-Bromoethyl-*m*-nitro-[a]	1	85	116.5–117.5	Colorless needles	Benzene	116–117	$C_9H_9O_3N_2Br$	...	...
3	2-Bromoethyl-*p*-nitro-	1	91	121–122	Colorless needles	Benzene	...	$C_9H_9O_3N_2Br$	10.26	10.17
4	2-Bromoethyl-*m*-nitro-*p*-methoxy-	1	89	110–111	Colorless needles	Benzene	...	$C_{10}H_{11}O_4N_2Br$	9.24	9.49
5	2-Bromoethyl-*p*-chloromethyl-	1	89	117–118	Colorless needles	Ethyl acetate	...	$C_{10}H_{11}ONBrCl$	5.06	5.04
6	2-Bromopropyl-*o*-nitro-	1	84	104–105	Colorless needles	Benzene	104–105	$C_{10}H_{11}O_3N_2Br$	...	...
7	2-Bromopropyl-*m*-nitro-	1	89	84.5–85	Light yellow needles	Benzene	84–85	$C_{10}H_{11}O_3N_2Br$	...	...
8	2-Bromopropyl-*p*-nitro-	1	95	135.5–136	Colorless needles	Benzene	135	$C_{10}H_{11}O_3N_2Br$	...	...
9	2-Hydroxy-2-methyl-propyl-*m*-nitro-	2	79	129–129.5	Colorless plates	Ethyl acetate	...	$C_{11}H_{14}O_4N_2$	11.76	11.87
10	2-Hydroxy-2-methyl-propyl-*p*-nitro-	2	89	134.5–135.5	Greenish needles	Ethyl acetate	...	$C_{11}H_{14}O_4N_2$	11.76	11.57
11	2-Bromo-1-methyl-*n*-propyl-*p*-nitro-	1	..[b]							
12	1-Chloromethyl-*n*-amyl-*p*-nitro-	1	37	116.5–118	Colorless flakes	80% alcohol	...	$C_{13}H_{17}O_3N_2Cl$	9.84	9.76
13	1-Phenyl-2-chloroethyl-*p*-nitro-	1	92	132.5–133.5	Greenish needles	Benzene	...	$C_{15}H_{13}O_3N_2Cl$	9.19	8.96
14	3-Chloro-2-hydroxy-*n*-propyl-*p*-nitro-	2	86	110–111	Colorless needles	Benzene + ethyl acetate 3:1	110–112	$C_{10}H_{11}O_4N_2Cl$	10.83 (Cl)	10.85 (Cl)
15	3-Diethylamino-2-hydroxy-*n*-propyl-*p*-nitro- (hydrochloride)	3	66	163–164.5	Colorless spurs	Absolute alcohol	...	$C_{14}H_{22}O_4N_2Cl$	10.69	10.72
16	3-(Dibutylamino)-2-hydroxy-*n*-propyl-*p*-nitro-	3	65	83.5–84.5	Light yellow spurs	Benzene + high pet. ether 9:1	...	$C_{18}H_{29}O_4N_3$	11.96	12.12
17	2-Chlorocyclohexyl-*p*-nitro-	1	98	156–157	Pale greenish needles	Ethyl acetate	...	$C_{13}H_{15}O_3N_2Cl$	9.91	9.62
18	2-Hydroxycyclohexyl-*p*-nitro-	2	90	210.5–211.5	Colorless needles	95% alcohol	...	$C_{13}H_{16}O_4N_2$	10.60	10.60
19	2-Bromoethyl-*m*-nitrocinnamamide	1	82	107–108	Glistening colorless needles	Benzene	...	$C_{11}H_{11}O_3N_2Br$	9.34	9.32

[a] Prepared equally well by the nitration of 2-bromoethylbenzamide, as previously described. [b] 2-Bromo-1-methyl-*n*-propyl-*p*-nitrobenzamide was not isolated, due to the ease with which it lost hydrogen bromide. It was converted directly into the nitroöxazoline, No. 11, Table II.

1-Amino-2-Bromopropane Hydrobromide.—Using the same procedure outlined above for bromoethylamine hydrobromide, 1-amino-2-hydroxypropane was converted in 70% yield into 1-amino-2-bromopropane hydrobromide. Recrystallization from absolute alcohol gave somewhat hygroscopic colorless plates,[23] which, after careful drying in a vacuum desiccator, melted at 157–159°.

3-Bromo-2-aminobutane Hydrobromide.—This compound, prepared in the above manner with phosphorus tribromide, was not isolated, as the hydrobromide was a sirup.[24] The latter gave a picrate of m. p. 165–166°, which agrees with the melting point previously reported by Strauss.[24]

1-Phenyl-1-amino-2-chloroethane hydrochloride was prepared in 76% yield by the method of Gabriel and Colman.[15]

1-Chloro-2-aminohexane Hydrochloride.—Using the above procedure described by Gabriel for the preparation of phenylaminochloroethane, 19.6 g. of 2-amino-1-hexanol hydrochloride was converted into 1-chloro-2-aminohexane hydrochloride by treatment with a mixture of 129 g. (80 cc.) of phosphorus trichloride and 28 g. of phosphorus pentachloride. The product was found to be a sirup and could not be obtained in a solid state. It was converted, by treatment in alkaline solution with one equivalent of *p*-nitrobenzoyl chloride, into the *p*-nitrobenzoyl derivative of 2-amino-1-chlorohexane which, after three recrystallizations from 80% alcohol, gave colorless flakes, m. p. 116.5–118°.

Anal. Calcd. for $C_{13}H_{17}N_2O_3Cl$: N, 9.84. Found: N, 9.76.

Preparation of Substituted Benzamides

(1) **Condensation of Acid Chlorides with Aminoalkyl Halides.**—To an aqueous solution of 0.10 mole of the salt of an aminoalkyl halide in 150 cc. of distilled water was added a solution of 0.11 mole of the desired acid chloride in 50 cc. of warm benzene. The emulsion was shaken and cooled in running water during the gradual addition of a 5% aqueous solution of 0.23 mole of sodium hydroxide. The product precipitated out of the reaction mixture and usually solidified within a few minutes to an amorphous mass. The mixture was shaken mechanically for two hours, after which time the solid amide was filtered with suction and washed with dilute sodium carbonate solution. The amide was recrystallized from the solvent listed in Table I.

(2) **Condensation of Acid Chlorides with Amino Alcohols.**—This method differs from that just described for preparing aroyl aminoalkyl halides only in respect to the relative proportions of the reagents, a slight excess of the amino alcohol being employed in this case. A benzene solution of 0.27 mole of the desired acid chloride was added to an aqueous solution of 0.28 mole of amino alcohol, followed by the gradual addition of a 5% aqueous solution

(23) Elfeldt, *Ber.*, **24**, 3218 (1891).
(24) Strauss, *ibid.*, **33**, 2825 (1900).

of 0.28 mole of sodium hydroxide. The hydroxyamide formed in the reaction was recrystallized from the solvent indicated in Table I.

(3) **Condensation of 3-Chloro-2-hydroxypropyl-*p*-nitrobenzamide with Aliphatic Secondary Amines.**—A 250-cc. pressure bottle containing 10.0 g. of 3-chloro-2-hydroxypropyl-*p*-nitrobenzamide and 2 mole equivalents of the aliphatic secondary amine was heated on a steam cone from ten to twelve hours, the bottle being shaken frequently during this period. When the reaction was complete, the cooled pressure bottle was opened, and to the magma of amine hydrochloride and free base was added enough cold 10% hydrochloric acid to make the solution strongly acidic. Any unreacted amide was removed by extracting the acid solution with 50-cc. portions of ether. The water layer was then cooled to 10°, made alkaline with strong sodium hydroxide, and the mixture extracted three times with a solution of equal parts of benzene and ether. After drying the ether–benzene extract over solid potassium hydroxide, the solvents and excess of amine employed were removed by warming under diminished pressure. From this point the procedure was varied depending upon whether the aminobenzamide was in a solid or liquid state. In the case of a liquid derivative, it was dissolved in dry ether and completely precipitated with hydrogen chloride gas. If, on the other hand, the aminobenzamide was a solid, it was isolated by dissolving the residue in a small quantity of benzene, adding ether, and allowing the free base to crystallize from the cold solvent.

2-Bromoethyl-*m*-nitrobenzamide.—A solution of 5.0 g. of 2-bromoethylbenzamide in 15 cc. of concentrated sulfuric acid (sp. gr. 1.84) on treatment with a mixture of 2 cc. of concentrated nitric acid (sp. gr. 1.42) and 2 cc. of concentrated sulfuric acid for twenty minutes at 30–35° yielded 5.4 g. (91%) of 2-bromoethyl-*m*-nitrobenzamide, m. p. 115–117°. After one crystallization from benzene, it melted at 116–117° and showed no depression in melting point on being mixed with the substance prepared from *m*-nitrobenzoyl chloride.

Preparation of Substituted Phenyl-2-oxazolines

(1) **Alkaline Ring Closure.**—This procedure is a slight modification of that previously used by Elfeldt.[23] To a solution of 0.050 mole of a β-halogen substituted alkylbenzamide in 100 cc. of hot ethyl alcohol at 70–75° was added gradually with stirring a warm aqueous alcoholic (see Table II) solution of 0.051 mole of sodium hydroxide (except in the case of 4-phenyl-*p*-nitrophenyl-2-oxazoline where potassium hydroxide preferably may be used) made up to a 5% solution. After the addition of the alkaline condensing agent, the reaction mixture was maintained at the initial temperature for the length of time indicated in Table II. After pouring the reaction mixture rapidly, with stirring, into approximately 400 g. of ice water, the crude oxazoline was filtered with suction and was then dissolved in 15% cold hydrochloric acid (below 15° to prevent hydrolysis). The filtered acid solution was made alkaline with cold dilute aqueous ammonia or sodium carbonate solution. Sodium carbonate was used rather than ammonia if the product was a halogenated oxazoline.

(2) **Sulfuric Acid Ring Closure.**—To 0.15 mole of a β-hydroxyalkylbenzamide was added with stirring 100 cc. of concentrated sulfuric acid (sp. gr. 1.84). The reaction mixture was warmed slowly to 55–60° (with the exception of the 4,5-cyclohexano-*p*-nitrophenyl-2-oxazoline, which required a temperature of 100–110°) to dissolve the amide. Stirring was continued at this temperature for an additional ten minutes, the reaction mixture then cooled to 15° and poured into 600 g. of ice water. Insoluble material was filtered and the cold filtrate made ammoniacal with 10% aqueous ammonia (temperature below 20°). The oxazolines, which precipitated as colorless solids, were purified by recrystallization from the solvent indicated in Table II.

(3) **Thionyl Chloride Ring Closure.**—This method was employed only in the case of γ-dialkylamino-β-hydroxypropylbenzamides. To 0.01 mole of a γ-dialkyl-β-hydroxypropylbenzamide (the hydrochloride also may be used) in a 100-cc. round-bottomed flask was added a large excess of 33.4 g. (20 cc.) of redistilled thionyl chloride. The amide went into solution immediately with the evolution of heat and the reaction mixture was refluxed on a water-bath for one and one-half to two hours. After the solution had then been cooled to 5°, it was poured into 175 cc. of dry ether and allowed to stand at 5° overnight. The crystals of dihydrochloride which separated were filtered, washed with dry ether to remove excess thionyl chloride, and dissolved in 100 cc. of cold water. To the water solution, cooled in an ice–salt bath to below 5°, was added slowly, with stirring, a cold concentrated solution of sodium hydroxide, the temperature being kept below 5° during this neutralization. The free base usually came down as an oil which, however, soon solidified.

***m*-Nitrophenyl-2-oxazoline.**—A mixture of equal volumes of concentrated nitric and sulfuric acids (4.0 cc.) was added to a solution of 3.0 g. of phenyl-2-oxazoline in 12 cc. of concentrated sulfuric acid at 0°. The temperature was allowed to rise to 5–10° where it was held for twenty minutes. The acid solution was then poured into an excess of ice water and neutralized with cold, dilute aqueous ammonia. The nitrophenyloxazoline recrystallized from 75% alcohol and melting at 118–119°, amounted to 2.5 g. (64%).

Preparation of Aminophenyl-2-oxazolines

Iron-Water Reduction.—To a well-stirred mixture of 0.05 mole of nitroöxazoline and 0.75 mole of clean, fine iron turnings was added enough water to give a thin paste. A few drops of concentrated hydrochloric acid was added, and the mixture stirred for about twenty minutes until the initial heat of reduction had begun to diminish. After this treatment, a few drops of hydrochloric acid and a few grams of iron were added and the mixture warmed, with occasional stirring, on the steam-bath for about two hours, a little water being added from time to time. When the reaction was complete, the greater part of the water was allowed to evaporate, and the iron extracted completely with 100-cc. portions of benzene or ethyl acetate. The benzene was removed by vacuum evaporation.

***p*-Diethylaminomethylphenyl-2-oxazoline.**—A mixture of 7.0 g. of *p*-chloromethylphenyl-2-oxazoline (No. 5, Table II) and 5.3 g. (2 moles equiv.) of diethylamine was heated for seven hours on the steam cone in a pressure bottle. At the end of this time the cooled bottle was opened, the partially solid contents made strongly alkaline

TABLE II

CONSTANTS OF SUBSTITUTED OXAZOLINES

No.	Oxazoline	Method of prepn.	Alcohol, %	Time for react.	Yield, %	M. p., °C.	Form	Cryst. from aq. alcohol (% alc.)	Prev. rep., m. p., °C.	Formula	N Analyses, % Calcd.	Found
1	*o*-Nitrophenyl-2-	1	80	30 sec.	92	52–53	Colorless needles	50	...	$C_9H_8O_3N_2$	14.59	14.54
2	*m*-Nitrophenyl-2-	1[a]	80	30 sec.	82	118–119	Colorless plates	75	118–119	$C_9H_8O_3N_2$	...	...
3	*p*-Nitrophenyl-2-	1	80	30 sec.	72	178–178.5	Colorless needles	95	...	$C_9H_8O_3N_2$	14.59	14.32
4	*m*-Nitro-*p*-methoxyphenyl-2-	1	75	1 min.	91	122–123	Colorless needles	70	...	$C_{10}H_{10}O_4N_2$	12.61	12.77
5	*p*-Chloromethylphenyl-2-	1	25	30 sec.	93	70–71	Colorless needles	50	...	$C_{10}H_{10}ONCl$	7.16	7.21
6	5-Methyl-*o*-nitrophenyl-2- (hydrochloride)[b]	1	80	1 min.	83	119–120	...	100	119–120	$C_{10}H_{11}O_3N_2Cl$	...	...
7	5-Methyl-*m*-nitrophenyl-2-	1	80	1 min.	93	86–87	Colorless plates	95	85–86	$C_{10}H_{10}O_3N_2$	...	...
8	5-Methyl-*p*-nitrophenyl-2-	1	80	1 min.	91	134–135	...	95	...	$C_{10}H_{10}O_3N_2$	...	...
9	5,5-Dimethyl-*m*-nitrophenyl-2-	2	..	...	95	81–82	Colorless needles	70	...	$C_{11}H_{12}O_3N_2$	12.73	12.75
10	5,5-Dimethyl-*p*-nitrophenyl-2-	2	..	...	86	143–144	Colorless needles	70	...	$C_{11}H_{12}O_3N_2$	12.73	12.61
11	4,5-Dimethyl-*p*-nitrophenyl-2-	1	50	1 min.	74	122.5–123.5	Long colorless needles	80	...	$C_{11}H_{12}O_3N_2$	12.73	12.53
12	4-*n*-Butyl-*p*-nitrophenyl-2-	1	25	2 min.	43	46–47	Light yellow needles	80	...	$C_{13}H_{16}O_3N_2$	11.29	11.48
13	4-Phenyl-*p*-nitrophenyl-2-	1[c]	5	1 min.	86	108.5–109	Light yellow needles	95	...	$C_{15}H_{12}O_3N_2$	10.44	10.17
14	5-(Chloromethyl)-*p*-nitrophenyl-2-	3[d]	..	...	88	117–118	Hard spurs	Benzene	...	$C_{10}H_9O_3N_2Cl$	11.64	11.84
15	5-(Diethylaminomethyl)-*p*-nitrophenyl-2-	3[d]	..	...	86	57–57.5	Yellow needles	25	...	$C_{14}H_{19}O_3N_3$	15.15	14.82
16	5-(Dibutylaminomethyl)-*p*-nitrophenyl-2-	3	..	...	97	60.5–61	Colorless flakes	80	...	$C_{18}H_{27}O_3N_3$	12.61	12.44
17	4,5-Cyclohexano-*p*-nitrophenyl-2-	2[e]	..	...	38	129.5–130.5[f]	Glittering colorless needles	100	...	$C_{13}H_{14}O_3N_2$	11.38	11.44
18	*m*-Nitrostyryl-2-	1	80	1 min.	75	117–118	Glistening colorless needles	70	...	$C_{11}H_{10}O_3N_2$	12.84	12.91

[a] Prepared equally well by the nitration of phenyl-2-oxazoline. [b] The free base was an oil, and was extracted from the alkaline reaction mixture with ether. The hydrochloride was precipitated from the dried ether extract with dry gaseous hydrogen chloride. [c] Was soluble in 15% hydrochloric acid, but precipitated on dilution with water. [d] An unsuccessful attempt was made to convert No. 14 into No. 15 by means of diethylamine. The chlorine in this β-chloro-ether type was particularly unreactive, as no precipitate was obtained on prolonged boiling with alcoholic silver nitrate. A sodium fusion or copper wire gave a positive test for halogen. [e] This compound could not be prepared by method 1 on compound No. 17, Table I, as the starting material was completely recovered from the alkaline treatment. [f] Formed a hydrate melting at 99–100° on recrystallization from aqueous alcohol.

with cold concentrated sodium hydroxide (temperature being kept below 10°), and the oily mixture extracted three times with 75-cc. portions of ether. After drying the ether layer over solid potassium hydroxide for twelve hours, it was filtered from the alkali, the ether and excess diethylamine were removed by distillation and the residue distilled under reduced pressure. The yield of *p*-diethylaminomethylphenyl-2-oxazoline (No. 5, Table III) boiling at 152–154° (2–3 mm., uncorr.), amounted to 5.0 g. (60%). During the distillation the product solidified to spur-like needles which, however, melted below room temperature.

p-Amino-m,m-dibromophenyl-2-oxazoline.—The apparatus used in this preparation was adapted from that described in "Organic Syntheses."[25] A slow stream of bromine-laden air was drawn through a cold solution of 2.5 g. of *p*-aminophenyl-2-oxazoline (No. 3, Table III) in 30 cc. of 10% hydrochloric acid until the solution assumed a distinctly yellow color. The precipitate of crude product which separated was filtered, air dried, and recrystallized from 50% methanol, giving 4.0 g. (82%) of short colorless needles, m. p. 193–194° (with decomposition). The positions taken by the entering bromine atoms were established by refluxing 0.2 g. of the solid dibromo derivative in a mixture of 15 cc. of constant boiling hydrochloric acid and 5 cc. of alcohol for one hour. The reaction mixture, after dilution to a volume of 75 cc. with water, was filtered, the precipitate dissolved in dilute aqueous sodium hydroxide, and reprecipitated from the filtered solution by dilute hydrochloric acid. The 4-amino-3,5-dibromobenzoic acid so obtained was air dried and recrystallized from nitrobenzene in the form of light yellow needles, m. p. 328–329°. The melting point previously reported by Koopal[26] was 330°.

Preparation of Monohydrochlorides of Aminophenyl-2-oxazolines. General Procedure.—Monohydrochlorides were prepared by exact titration with aqueous hydro-

(25) *Organic Syntheses*, **13**, 96 (1933).

(26) Koopal, *Rev. trav. chim.*, **34**, 150 (1915).

TABLE III

SUBSTITUTED AMINOPHENYLOXAZOLINES

No.	Oxazoline	Yield, %[a]	M. p., °C.	Form	Cryst. from	M. p., °C. of monohydrochloride	Form from abs. alcohol	Formula for base or hydrochloride	N Analyses, % Calcd.	Found
1	*o*-Aminophenyl-2-	83	55–56	Colorless needles	Low petr. ether	...	...	$C_9H_{10}ON_2$	17.28	17.24
2	*m*-Aminophenyl-2-[b]	84	125–126	Colorless needles	Water or ethyl acetate	...	...	$C_9H_{10}ON_2$	17.28	17.14
3	*p*-Aminophenyl-2-[b]	93	160–161	Colorless needles	Benzene	254–255 (dec.)	Colorless needles	$C_9H_{10}ON_2$	17.28	17.19
4	*m*-Amino-*p*-methoxyphenyl-2-	87	126.5–127.5	Colorless needles	Ethyl acetate	...	...	$C_{10}H_{12}O_2N_2$	14.59	14.87
5	*p*-(Diethylaminomethyl)-phenyl-2-	60	(B. p.) 152–154 (2 mm.)	...	...	150.5–151	Colorless flakes	$C_{14}H_{21}ON_2Cl$	Cl, 13.20	13.28
6	5-Methyl-*o*-aminophenyl-2-	56	41.5–42	Colorless spurs	Low petr. ether	...	...	$C_{10}H_{12}ON_2$	15.90	15.77
7	5-Methyl-*m*-aminophenyl-2-	68	115–116	Colorless needles	Benzene + Low petr. ether 3:1	...	...	$C_{10}H_{12}ON_2$	15.90	15.56
8	5-Methyl-*p*-aminophenyl-2-	94	128.5–129.5	Colorless needles	Benzene	213–214	Colorless spurs	$C_{10}H_{12}ON_2$	15.90	16.02
9	5,5-Dimethyl-*m*-aminophenyl-2-	94	122–123	Monoclinic prisms	Ethyl acetate	...	...	$C_{11}H_{14}ON_2$	14.74	14.81
10	5,5-Dimethyl-*p*-aminophenyl-2-	91	145–146	Colorless needles	Ethyl acetate	...	...	$C_{11}H_{14}ON_2$	14.74	14.47
11	4,5-Dimethyl-*p*-aminophenyl-2-	95	211–212	Colorless needles	Ethyl acetate	...	...	$C_{11}H_{14}ON_2$	14.74	14.84
12	4-*n*-Butyl-*p*-aminophenyl-2-	95	Oil	...	...	197–197.5	Colorless flakes	$C_{13}H_{19}ON_2Cl$	Cl, 13.93	14.06
13	4-Phenyl-*p*-aminophenyl-2-	96	150–150.5	Colorless prisms	Ethyl acetate	239–240 (dec.)	Colorless prisms	$C_{15}H_{14}ON_2$	11.76	12.02
14	5-(Diethylaminomethyl)-*p*-aminophenyl-2-	92	(B. p.) 205–206 (2.5 mm.)	...	...	190–191 (dec.)	Colorless spurs	$C_{14}H_{22}ON_3Cl$	Cl, 12.53	12.59
15	5-(Dibutylaminomethyl)-*p*-aminophenyl-2-	84	Oil	...	...	204–205[c] (dec.)	Colorless prisms	$C_{18}H_{30}ON_3Cl$	Cl, 10.44	10.60
16	4,5-Cyclohexano-*p*-aminophenyl-2-	91	155–156	Colorless prisms	Ethyl acetate	...	...	$C_{12}H_{16}ON_2$	12.95	12.80
17	*p*-Amino-*m*,*m*-dibromophenyl-2-	82	193–194	Colorless needles	50% methanol	...	...	$C_9H_8ON_2Br_2$	9.04	8.81
18	*m*-Aminostyryl-2-	78	144–145	Yellow needles	Ethyl acetate	...	...	$C_{11}H_{12}ON_2$	14.90	14.91

[a] The yields reported for all primary amino derivatives are based on method 1. [b] Was also conveniently prepared in 76–80% yields by catalytic reduction of the corresponding nitro compound in 95% ethyl alcohol solution, using platinum oxide and hydrogen under 2 to 3 atmospheres. It was found necessary to add a drop of glacial acetic acid to the alcohol solution to prevent the reduction from stopping at the intermediate azo compound. The compounds, as prepared by this method, were a little more difficult to purify than those produced by the iron–water reduction, method 1, since alcohol solutions tend to become colored. [c] The melting point tube was placed in the bath at 197°.

chloric acid of a known amount of free base in absolute methanol, with subsequent vacuum evaporation of solvent, or by titrating a solution of 0.01 mole of aminophenyl-2-oxazoline in 150 cc. of dry ether with the equivalent amount of standard solution of absolute alcoholic hydrogen chloride. The mixture was allowed to stand at 5° overnight, the hydrochloride salt filtered, and recrystallized from absolute alcohol.

Summary

Various aminophenyl-2-oxazolines have been prepared. They are local anesthetics. The *m*-amino-2-oxazoline is one-third as toxic and of about the same anesthetic effectiveness as procaine.

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