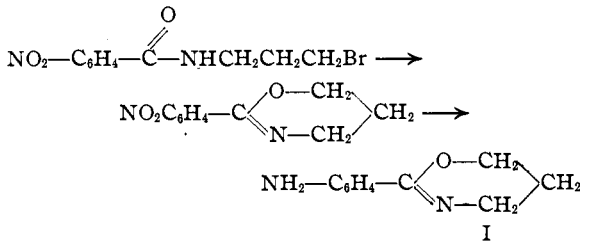
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Aminophenyl-2-pentoxazolines

BY A. NOVELLI AND ROGER ADAMS

The investigation that resulted in the discovery that aminophenyl-2-oxazolines are local anesthetics[1] has been extended to a study of aminophenyl-2-pentoxazolines (I).



I

These compounds also are local anesthetics. They have only slight solubility in water like the corresponding oxazolines and have a greater tendency to hydrolyze in acid solution. The bases, when tested pharmacologically in the usual way, show greater toxicity than procaine or the oxazolines.

Aminophenyl-2-pentoxazolines are conveniently prepared by synthesizing first the proper γ-bromopropyl nitrobenzamides and then treating with alcoholic potassium hydroxide and reducing.

Experimental

γ-Bromopropylamine Hydrobromide.—γ-Bromopropyl phthalimide was prepared by the method of Gabriel and Wenner[2] with the modification that the reaction mixture was heated for twelve hours at 180–200°. The dry mixture of diphthalimidopropane and γ-bromopropyl phthalimide was extracted with carbon bisulfide, which dissolves only the latter product. The conversion to γ-bromopropylamine hydrobromide was identical with that described by Gabriel.

γ-Bromopropyl Nitrobenzamides.—A solution of 4.4 g. of γ-bromopropylamine hydrobromide in 20 cc. of water was mixed with 20 cc. of *N* aqueous sodium hydroxide. After addition of a few drops of phenolphthalein as an indicator, it was shaken with a solution of 3.7 g. of pure nitrobenzoyl chloride in 20 cc. of benzene and then 25 cc. more of *N* aqueous sodium hydroxide was added. The reaction mixture was shaken for half an hour and kept alkaline, if necessary, by the addition of more sodium hydroxide. The product was filtered and purified as white crystals; yield 80–85%.

2-(Nitrophenyl) Pentoxazolines.—To a solution of 2.87 g. of γ-bromopropyl nitrobenzamide in 20 cc. of boiling alcohol was added with shaking 0.4 g. of sodium hydroxide in absolute alcohol. The shaking was continued for ten minutes at 60–65° and the reaction was then poured into ice water. The precipitate was filtered, suspended in water, and hydrochloric acid added dropwise until solution was complete. After filtering, the base was again set free by means of excess aqueous ammonia. The *m*- and *p*-compounds formed white crystals from alcohol. The ortho derivative was best extracted from the acidified solution with ether, dried and precipitated as the hydrobromide by means of dry hydrogen bromide.

TABLE I

γ-BROMOPROPYL NITROBENZAMIDES

	M. p., °C.	M. p. previously reported	Solvent	Anal. for $C_{10}H_{11}N_2O_3Br$ Calcd.	Found
p-Nitro	108.5–109.5	108[a]	Dil. alc.		
m-Nitro	89–90	89–90[b]	Alcohol		
o-Nitro	118–119	...	Alcohol	N, 9.74	N, 9.80

[a] Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 421 (1915).

[b] Elfredt, *Ber.*, **24**, 3218 (1891).

TABLE II

NITROPHENYL PENTOXAZOLINES

2-(Nitrophenyl)-pentoxazolines	M. p., °C.	M. p. previously reported	Anal. for $C_{10}H_{10}ON_2O_3$ Calcd.	Found
p-Nitro	145	...	N, 13.59	N, 13.46
m-Nitro	92–93	93–94[b]		
o-Nitro-hydrobromide	118–119	...	Br, 27.87	Br, 27.92

Aminophenyl Pentoxazolines.—As the pentoxazoline nucleus is sensitive to hydrolysis, the reduction of the nitro compounds must be carried out with particular care. The reduction of the *m*- and *p*-compounds with iron powder, water and a few drops of hydrochloric acid should not be allowed to become hot and cooling was required from time to time. After no more exothermic reaction took place the mixture was heated with stirring on a water bath at 70–80° for twenty minutes. The products were extracted with benzene and purified from ligroin as white crystals.

In the case of the *o*-nitrophenylpentoxazoline, the nitro base was reduced as described and the amino compound extracted with alcohol. It was purified by distillation *in vacuo*.

The dihydrochlorides were formed by passing dry hydrogen chloride into a dry ether solution.

***o*-Bromocyclohexanol Benzamide.**—White crystals from ethyl alcohol, m. p. 151–152°. *Anal.* Calcd. for $C_{13}H_{16}ONBr$: N, 4.95. Found: N, 5.31.

***o*-Bromocyclohexanol-*p*-nitrobenzamide.**—White crystals from alcohol, m. p. 160–161°. *Anal.* Calcd. for $C_{13}H_{15}O_3N_2Br$: N, 8.56. Found: N, 8.48.

These products could not be converted by the procedure previously described to the corresponding pentoxazolines.

(1) Leffler and Adams, THIS JOURNAL, **59**, 2252 (1937).

(2) Gabriel and Wenner, *Ber.*, **21**, 2669 (1889).

TABLE III

AMINOPHENYL PENTOXAZOLINES

Aminophenyl pentoxazolines	M. p., °C.	Solvent for cryst.	Formula	Analyses, % Calcd.	Found
p-Amino	170–171	Ligroin	$C_{10}H_{12}ON_2$	N, 15.90	15.98
p-Amino di-HCl	192–193		$C_{10}H_{12}ON_2 \cdot 2HCl$	Cl, 28.51	28.37
m-Amino	139–139.5	Ligroin	$C_{10}H_{12}ON_2$	N, 15.90	15.85
m-Amino di-HCl	154–155		$C_{10}H_{12}ON_2 \cdot 2HCl$	Cl, 28.51	28.51
o-Amino	137/4 mm. (b. p.)		$C_{10}H_{12}ON_2$	N, 15.90	16.03
o-Amino di-HCl	128–131		$C_{10}H_{12}ON_2 \cdot 2HCl$	Cl, 28.51	28.10

Summary

o-, *m*- and *p*-aminophenyl pentoxazolines have been prepared and shown to be local anesthetics.

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

Aminophenyl Thiazolines and Thiazines

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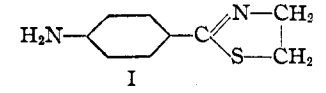
The synthesis of the sulfur analogs of the aminophenyl oxazolines[1] and pentoxazolines[2] described in previous papers has been accomplished. These compounds, illustrated by formulas I and II, are



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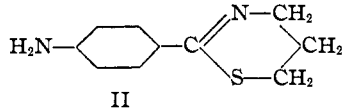
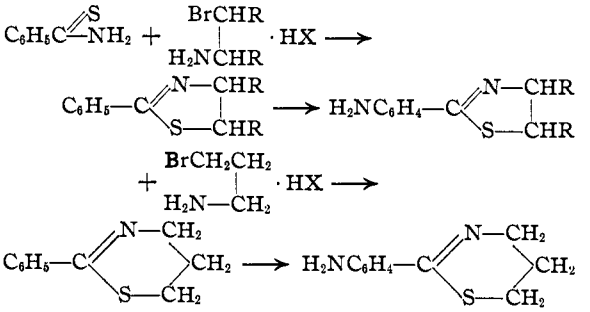


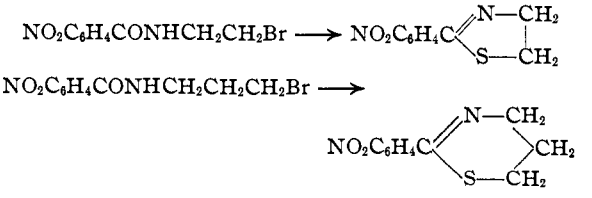
II

local anesthetics but are less soluble than the corresponding oxygen compounds and form hydrochlorides more acid in character. They were prepared by reduction of the nitrothiazolines or dihydrothiazines.

Two general methods proved satisfactory for preparing the nitro substituted products. (1) Aromatic thioamides condense smoothly with halogenated alkylamine salts to give aryl thiazolines. Certain substituents in the benzene ring of the aryl thioamides frequently hinder or prevent the reaction from taking place. This is especially true of the nitro substituted thiobenzamides. As a consequence the condensation mentioned was used merely for producing phenyl thiazolines, phenyl substituted thiazolines or the phenyl dihydrothiazines which were then converted to the corresponding nitro compounds. In each instance the nitro group enters the position *meta* to the thiazoline or dihydrothiazine ring as was demonstrated by preparing such compounds by another method which leaves no doubt as to the structure.



(2) A satisfactory procedure for preparing nitrophenyl thiazolines or dihydrothiazines with the nitro group in any desired position consists in condensing a β- or γ-halogenated alkyl nitrobenzamide with phosphorus pentasulfide.



Experimental

N - (β - Chloroisobutyl) - *p* - nitrobenzamide.—Twenty grams (0.225 mole) of isobutanolamine was neutralized with dilute hydrochloric acid. From this solution the dry hydrochloride was obtained by removing the water by distillation *in vacuo* followed by addition of benzene and subsequent distillation. To the dry salt was added 24 cc. (0.287 mole) of phosphorus trichloride. This mixture was warmed gently until it became homogeneous, after which it was cooled and dissolved in 100 cc. of water. To this solution 42 g. (0.225 mole) of *p*-nitrobenzoyl chloride in

(1) Leffler and Adams, THIS JOURNAL, **59**, 2252 (1937).

(2) Novelli and Adams, *ibid.*, **59**, 2259 (1937).