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.

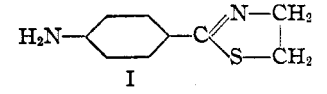
URBANA, ILLINOIS RECEIVED JULY 19, 1937

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

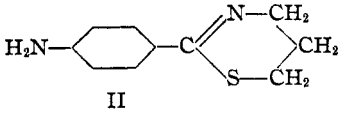
Aminophenyl Thiazolines and Thiazines

BY S. H. BABCOCK AND ROGER ADAMS

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



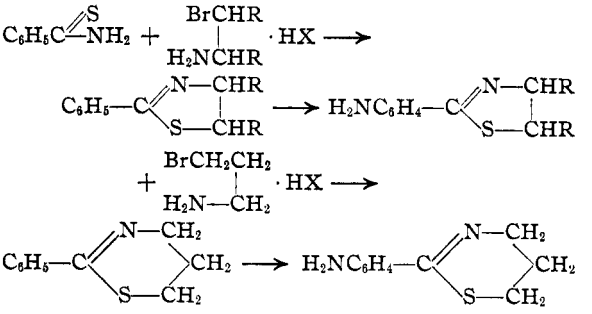
I



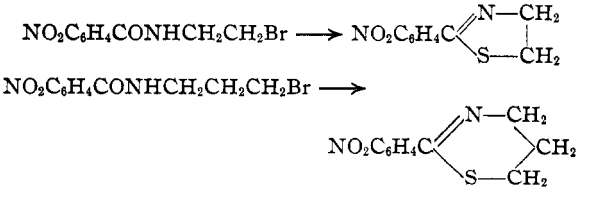
II

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).

TABLE I

NITROPHENYL THIOAZOLINES AND THIAZINES

Compound	Yield, %	M. p., °C. (corr.)	Mol. formula	Nitrogen, % Calcd.	Found
2-(*p*-Nitrophenyl)-thiazoline	91	156–157	$C_9H_8O_2N_2S$	13.46	13.72
2-(*p*-Nitrophenyl)-5-methylthiazoline	95	108–108.5	$C_{10}H_{10}O_2N_2S$	12.61	12.73
2-(*p*-Nitrophenyl)-5,5-dimethylthiazoline	34	117–118	$C_{11}H_{12}O_2N_2S$	11.87	11.48
2-(*m*-Nitrophenyl)-thiazoline	100	131–132	$C_9H_8O_2N_2S$	13.46	13.40
2-(*m*-Nitrophenyl)-5-methylthiazoline	50	70.5–71.5	$C_{10}H_{10}O_2N_2S$	12.61	12.92
2-(*p*-Nitrophenyl)-5,6-dihydro-1,3,4-thiazine	67	137–139	$C_{10}H_{10}O_2N_2S$	12.61	12.42
2-(*m*-Nitrophenyl)-5,6-dihydro-1,3,4-thiazine	52	90–91	$C_{10}H_{10}O_2N_2S$	12.61	12.81

TABLE II

AMINOPHENYL THIAZOLINES AND THIAZINES

Compound	Yield, %	M. p., °C.	Mol. formula	Nitrogen, % Calcd.	Found
2-(*p*-Aminophenyl)-thiazoline	71	163–164	$C_9H_{10}N_2S$	15.73	15.57
2-(*p*-Aminophenyl)-5-methylthiazoline	45	105–106	$C_{10}H_{12}N_2S$	14.58	14.56
2-(*p*-Aminophenyl)-5,5-dimethylthiazoline	57	141–142	$C_{11}H_{14}N_2S$	13.59	13.60
2-(*m*-Aminophenyl)-thiazoline	81	66–67	$C_9H_{10}N_2S$	15.73	15.61
2-(*m*-Aminophenyl)-5-methylthiazoline	69	58–59	$C_{10}H_{12}N_2S$	14.58	14.36
2-(*p*-Aminophenyl)-5,6-dihydro-1,3,4-thiazine	58	115–115.5	$C_{10}H_{12}N_2S$	14.58	14.95
2-(*m*-Aminophenyl)-5,6-dihydro-1,3,4-thiazine	70	75–76	$C_{10}H_{12}N_2S$	14.58	14.60

the minimum amount of benzene was added. The mixture was then shaken vigorously while being neutralized gradually with aqueous 10% sodium hydroxide solution. The shaking was continued for one hour longer, after which the precipitated N-(β-chloroisobutyl)-*p*-nitrobenzamide was collected on a Büchner funnel and recrystallized from benzene, m. p., 131–132° (yield 63%).

Anal. Calcd. for $C_{11}H_{23}O_3N_2Cl$: N, 10.92. Found: N, 11.32.

2-(*p*-Nitrophenyl)-5,5-dimethylthiazoline.—An intimate mixture of 25.6 g. of N-(β-chloroisobutyl)-*p*-nitrobenzamide and 4.5 g. of phosphorus pentasulfide was placed in a large stoppered test-tube equipped with an inlet tube and an outlet tube, and then heated at 100–110° for two hours in an atmosphere of nitrogen. The mixture slowly melted to form a tarry mixture of salts of 2-(*p*-nitrophenyl)-5,5-dimethylthiazoline. At the end of two hours the heating was discontinued and a mixture of aqueous 10% sodium hydroxide solution and acetone added. Shaking was continued until homogeneity was effected. Upon dilution with water, 9 g. of the crude thiazoline precipitated. After several recrystallizations from ethyl alcohol it melted at 115.4–115.5°.

In exactly the same manner 2-(*p*-nitrophenyl)-thiazoline, 2-(*p*-nitrophenyl-5-methylthiazoline and 2-(*p*-nitrophenyl)-5,6-dihydro-1,3,4-thiazine were prepared from N-(β-bromoethyl)-*p*-nitrobenzamide,[1] N-(β-bromo-*n*-propyl)-*p*-nitrobenzamide,[3] N-(β-bromoethyl)-*o*-nitrobenzamide,[1] and N-(γ-bromopropyl)-*p*-nitrobenzamide,[4] respectively. The experimental and analytical data concerning these substances are collected in Table I.

2-(*m*-Nitrophenyl)-thiazoline, 2-(*m*-Nitrophenyl)-5-methylthiazoline and 2-(*m*-Nitrophenyl)-5,6-dihydro-1,3,4-thiazine.—These substances were prepared by the nitration of 2-phenylthiazoline,[5] 2-phenyl-5-methylthiazoline[5] and 2-phenyl-5,6-dihydro-1,3,4-thiazine[6] according to the directions for the nitration of acetophenone given in "Organic Syntheses," Vol. X, p. 74. Since these substances are bases, they remained in solution when the nitration mixture was poured onto ice, were then precipitated with strong alkali and afterward purified by several crystallizations from alcohol. The experimental and analytical data for these substances are given in Table I.

Aminophenyl Thiazolines and Dihydrothiazines.—These compounds were prepared by the reduction of the nitro compounds listed in Table I. In each case the nitro compound was mixed with iron powder in the ratio of five grams to eight and stirred to a thick paste with water. A drop of concentrated hydrochloric acid was then added and the mixture stirred, with occasional cooling by immersing in a bath of ice water, until the temperature no longer rose above that of the room. It was next warmed on a steam-bath for one hour and then repeatedly extracted with benzene. Upon evaporation, the crude aminophenyl thiazoline separated from the benzene solution. It was purified by recrystallization from a mixture of benzene and petroleum ether. The experimental data and analyses for these compounds are collected in Table II.

Summary

Aminophenyl thiazolines and dihydrothiazines which have local anesthetic action were prepared from the corresponding nitro derivatives. Two methods for preparing the nitro compounds consist in (1) nitration of the phenyl thiazoline or dihydrothiazine under which conditions the nitro group enters the meta position, or (2) condensation of halogenated alkyl nitrobenzamides with phosphorus pentasulfide.

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(3) Vedinck, *Ber.*, **32**, 967 (1899).

(4) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 421 (1915).

(5) Gabriel and Hirsch, *Ber.*, **29**, 2610 (1896).

(6) Pinkus, *ibid.*, **26**, 1077 (1893).