[CONTRIBUTION FROM THE GAYLEY CHEMICAL LABORATORY OF LAFAYETTE COLLEGE AND THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Thiazolinephenols. 5-Methyl- and 5,5-Dimethylthiazolinephenols, By-Products and Derivatives[1]

BY WILLIAM F. HART AND JOSEPH B. NIEDERL

The rather unusual reaction between allyl mustard oil and phenols in the presence of a cationoid condensing agent (sulfuric acid) to yield 5-methylthiazolinephenols has been reported previously.[2]

R. Adams and co-workers have shown that aminophenyl-thiazolines, thiazines, oxazoles, thiazoles, oxazolines and pentoxazolines are local anesthetics some of which are comparable in effectiveness and low toxicity to procaine.[3]

It has been found that the thiazolinephenols possess a varying effectiveness as local anesthetics. In view of this fact, this work has been extended by the synthesis of other thiazolinephenols and their derivatives.

In an effort to improve the yields of these compounds, cationoid condensing agents other than sulfuric acid have been studied. It has been found that anhydrous aluminum chloride and dry hydrogen chloride may be used, the latter being greatly superior to any condensing agent yet studied. By the use of this procedure yields in the neighborhood of 50% are obtained as compared with 10–15% using concentrated sulfuric acid.

Allyl mustard oil, in addition to the previously reported compounds, was condensed with *o*-cresol, catechol and β-naphthol, yielding 5-methyl-2-(3′-methyl-4′-hydroxy)-phenylthiazoline (I), 5-methyl-2-(3′,4′-dihydroxy)-phenylthiazoline (II) and 5-methyl-2-(2′-hydroxy)-naphthylthiazoline (III), respectively. The hydrochlorides and picrates of these compounds were also prepared (Ia, Ib, IIa, IIb, IIIa, IIIb).

Derivatives of the previously reported 5-methyl-2-(2′-methyl-4′-hydroxy)-phenylthiazoline (IV) which have been prepared include the hydrochloride of the benzoate (IVa), the hydrochloride of the methyl ether (IVb), the *p*-nitrobenzoate (IVc), the corresponding hydrochloride (IVd), the *p*-aminobenzoate (IVe), and the corresponding dihydrochloride (IVf).

From the previously reported 5-methyl-2-(4′-hydroxy)-phenylthiazoline have been prepared the 3′-nitro derivative (Va), the corresponding hydrochloride (IVb), the 3′-amino derivative (Vc) and the corresponding dihydrochloride (Vd).

There has also been isolated from the condensation of allyl mustard oil and phenol a compound which appears to be a phenolic mustard oil β-(*p*-hydroxyphenyl)-propyl isothiocyanate (VI). This compound is formed by normal addition of the phenol to the ethylenic linkage in allyl isothiocyanate, *i. e.*

$$CH_2{=}CHCH_2NCS + C_6H_5OH \xrightarrow{H_2SO_4} SCNCH_2CH(CH_3)C_6H_4OH$$

By the condensation of methallyl mustard oil with phenol, *m*-cresol, and resorcinol, were prepared: 5,5-dimethyl-2-(4′-hydroxy)-phenylthiazoline (VII), 5,5-dimethyl-2-(2′-methyl-4′-hydroxy)-phenylthiazoline (VIII), and 5,5-dimethyl-2-(2′,4′-dihydroxy)-phenylthiazoline (IX), respectively, as well as the hydrochlorides and picrates (VIIa, VIIb, VIIIa, VIIIb, IXa and IXb).

From the reaction mixture of methallyl mustard oil and these phenols was also isolated 5,5-dimethyl-2-mercaptothiazoline (X). This compound was later identified by synthesis by Bruson and Eastes,[4] who found that it could be prepared by the action of concentrated sulfuric acid on methallyl mustard oil alone, and that the reaction seems to be a general one for β-γ-unsaturated isothiocyanates, in which the double bond carries a tertiary carbon atom. The formation of this compound substantiates further the reaction mechanism given in the first paper[2] and the most plausible explanation for its formation appears to be the following

$$2C_4H_7NCS + 2H_2O \xrightarrow{H_2SO_4} CO_2 + CH_2{=}C(CH_3)CH_2NH_2 + (CH_3)_2C(S)(CH_2{-}N{=}CSH)$$

From this compound were prepared *bis*-(5,5-dimethylthiazoline) 2,2-disulfide (Xa), the *p*-nitrobenzoate (Xb) and the hydrochloride of the *p*-aminobenzoate (Xc).

(1) Presented before the Division of Medicinal Chemistry at the Baltimore meeting of the American Chemical Society, April, 1939.

(2) Niederl, Hart and Scudi, THIS JOURNAL, **58**, 707 (1936).

(3) R. Adams and co-workers, *ibid.*, **59**, 2252 (1937).

(4) Bruson and Eastes, *ibid.*, **59**, 2011 (1937).

TABLE I

No.	Compound	Formula	M. p., °C. (uncorr.)	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	5-Methyl-2-(3'-methyl-4'-hydroxy)-phenylthiazoline	$C_{11}H_{13}ONS$	134	63.71	6.32	6.76	63.18	6.26	6.94
(a)	Hydrochloride	$C_{11}H_{14}ONSCl$	220	54.18	5.79	5.24	54.03	5.70	5.68
(b)	Picrate	$C_{17}H_{16}O_8N_4S$	159			12.84			12.63
II	5-Methyl-2-(3',4'-dihydroxy)-phenylthiazoline	$C_{10}H_{11}O_2NS$	136	57.37	5.30	6.64	57.58	5.45	6.52
(a)	Hydrochloride	$C_{10}H_{12}O_2NSCl$	247			5.72			5.77
(b)	Picrate	$C_{16}H_{14}O_9N_4S$	188			12.78			12.70
III	5-Methyl-2-(2'-hydroxy)-naphthylthiazoline	$C_{14}H_{13}ONS$	65			5.76			5.62
(a)	Hydrochloride	$C_{14}H_{14}ONSCl$	220			5.08			5.18
(b)	Picrate	$C_{20}H_{16}O_8N_4S$	169			11.86			11.75
IV	5-Methyl-2-(2'-methyl-4'-hydroxy)-phenylthiazoline	$C_{11}H_{13}OSN$	131	63.71	6.32	6.76	63.90	6.45	6.71
(a)	Benzoate hydrochloride	$C_{18}H_{18}O_2NSCl$	185–186			4.27			4.48
(b)	Methyl ether hydrochloride	$C_{12}H_{16}ONSCl$	159–160			5.43			5.33
(c)	*p*-Nitrobenzoate	$C_{18}H_{16}O_4N_2S$	87–88			7.86			7.75
(d)	Hydrochloride	$C_{18}H_{17}O_4N_2SCl$	205	55.03	4.33	7.13	55.42	4.25	6.97
(e)	*p*-Aminobenzoate	$C_{18}H_{18}O_2N_2S$	142	66.20	5.56	8.58	65.63	5.29	8.47
(f)	Dihydrochloride	$C_{18}H_{20}O_2N_2SCl_2$	Above 250	54.11	5.05	7.01	54.28	4.90	6.81
V	5-Methyl-2-(4'-hydroxy)-phenylthiazoline	$C_{10}H_{11}ONS$	168	62.12	5.74	7.25	62.22	6.02	7.22
(a)	3'-Nitro deriv.	$C_{10}H_{10}O_3N_2S$	135	50.03	4.23	11.76	50.42	3.94	10.92
(b)	Hydrochloride	$C_{10}H_{11}O_3N_2SCl$	215			10.20			10.03
(c)	3'-Amino deriv.	$C_{10}H_{12}ON_2S$				13.46			13.26
(d)	Dihydrochloride	$C_{10}H_{14}ON_2SCl_2$	Above 250			9.96			9.82
VI	β-(4'-Hydroxy)-phenylpropyl isothiocyanate	$C_{10}H_{11}ONS$	150	62.12	5.74	7.25	61.85	5.38	7.15
VII	5,5-Dimethyl-2-(4'-hydroxy)-phenylthiazoline	$C_{11}H_{13}ONS$	181–182			6.76			6.62
(a)	Hydrochloride	$C_{11}H_{14}ONSCl$	240			5.74			6.08
(b)	Picrate	$C_{17}H_{16}O_8N_4S$	190			12.04			12.87
VIII	5,5-Dimethyl-2-(2'-methyl-4'-hydroxy)-phenylthiazoline	$C_{12}H_{15}ONS$	134			6.33			6.33
(a)	Hydrochloride	$C_{12}H_{16}ONSCl$	180–181	55.89	6.25	5.43	56.13	6.12	5.60
(b)	Picrate	$C_{18}H_{18}O_8N_4S$	186			12.44			12.46
IX	5,5-Dimethyl-2-(2',4'-dihydroxy)-phenylthiazoline	$C_{11}H_{13}O_2NS$	144–145			6.27			6.45
(a)	Hydrochloride	$C_{11}H_{14}O_2NSCl$	Above 270			5.39			5.20
(b)	Picrate	$C_{17}H_{16}O_9N_4S$	195			12.18			12.16
X	5,5-Dimethyl-2-mercaptothiazoline	$C_5H_9NS_2$	162	40.79	6.17	9.52	40.93	6.18	9.35
(a)	*bis*-(5,5-Dimethylthiazoline)-2,2-disulfide	$C_{10}H_{16}N_2S_4$	99			9.58			10.13
(b)	*p*-Nitrobenzoate	$C_{12}H_{12}O_2N_2S_2$	168	44.63	4.08	9.45	48.74	4.00	9.48
(c)	*p*-Aminobenzoate hydrochloride	$C_{12}H_{13}ON_2S_2Cl$	265			9.24			9.10

Experimental

Condensation Method.—One mol of allyl mustard oil was added to one mol of phenol, and the solution was saturated at room temperature with dry hydrogen chloride gas. The condensation was allowed to stand in a stoppered flask at room temperature and was saturated repeatedly with dry hydrogen chloride gas at intervals of one or two days. After a period (varying according to the phenol) of from one week to one month crystallization of the thiazolinephenol hydrochloride usually set in and within a few days the reaction mixture was filled with crystals. The crystals were filtered off using a fritted glass Büchner funnel. The viscous filtrate was collected and resaturated with dry hydrogen chloride gas. In this way three or four crops of the crystalline hydrochloride were obtained before finally working up the entire reaction material. The crystals were further purified by washing them with warm dry acetone until no more coloring matter could be removed. The crystals were then dissolved in water treated with decolorizing carbon at room temperature and the solution evaporated to dryness on a steam-bath. The hydrochlorides were finally recrystallized from 95% ethyl alcohol.

In some cases the condensation became very viscous after prolonged saturation with hydrogen chloride gas but failed to crystallize. In these cases and in the case of condensations where a further crop of crystals failed to form after having removed several crops, the reaction material was taken up in excess dry acetone whereupon a crop of crystalline hydrochloride usually precipitated out. The acetone was distilled off. The residue was taken up in an excess of water and if necessary made distinctly acid with hydrochloric acid. The water suspension was stirred while heating on a steam-bath for half an hour, cooled to room temperature and then treated with decolorizing carbon. The filtered solution was evaporated to dryness on a steam-bath. The combined yields of purified hydrochlorides usually averaged about 50% of the theoretical.

The free bases were prepared by making a solution of the hydrochloride just alkaline with sodium carbonate, extracting these solutions with ether, and evaporating the ether solution. The free thiazolinephenols were recrystallized from ethyl alcohol, with the use of a small amount of decolorizing carbon, if necessary.

The picrates were made by adding filtered, saturated picric acid solution to an equal volume of filtered solution of the hydrochloride. The picrates were recrystallized once from ethyl alcohol.

The phenolic mustard oil (VI) was obtained using the sulfuric acid process by fractional distillation *in vacuo* (160–170° at 2 mm.) of the alkali soluble, but acid insoluble portion of the reaction material.

Esterifications. Benzoates, *p*-Nitrobenzoates, *p*-Aminobenzoates.—Due to the amphoteric nature of the thiazo-

linephenols esterification cannot be carried out by the Schotten–Baumann method, or the more usual modifications. A perfectly anhydrous reaction medium is necessary for successful esterification. One gram of *m*-cresolthiazoline (IV) was dissolved in a sodium methylate solution containing one equivalent of sodium (0.0716 g.) in a 250-cc. distilling flask fitted with a dropping funnel, Liebig condenser, and a suction flask as receiver, which was connected to a water pump, with an intervening trap and calcium chloride tube. The methanol was distilled from a water-bath using a slight vacuum. Benzene (dried over sodium) was dropped into the flask and distilled to remove the last traces of methanol. One equivalent of benzoyl chloride (0.394 g.) dissolved in dry benzene was added, and the mixture refluxed at such a rate that the benzene slowly distilled over, employing a slight vacuum. More benzene was added from time to time; the reaction was complete in an hour. The benzene solution was filtered to remove the sodium chloride and then saturated with dry hydrogen chloride gas, whereupon the hydrochloride precipitated out in pure form. This was washed with dry acetone and recrystallized from 95% alcohol (IVa).

The *p*-nitrobenzoate hydrochloride was prepared in exactly similar manner (IVd).

The free ester (IVc) was prepared by making a suspension of the hydrochloride in water alkaline with ammonium hydroxide, extracting with ether, evaporating to dryness, and recrystallizing it from 95% ethyl alcohol.

The *p*-nitrobenzoate hydrochloride (IVd) was reduced with stannous chloride and hydrochloric acid in glacial acetic acid solution at 100° in the usual manner. The reaction was complete in one hour. The solution was taken up in water, and carefully neutralized with sodium hydroxide solution keeping the temperature below 50°. The resulting suspension was extracted with ether, the ether solution dried over anhydrous sodium sulfate and then saturated with dry hydrogen chloride gas. The resulting salt, which precipitated out, was washed with dry acetone, and recrystallized from 95% alcohol, in which it is slightly soluble; very insoluble in water (IVf).

The free ester (IVe) was prepared by evaporating to dryness the ether extract prepared as above, and recrystallizing the residue from 95% ethyl alcohol.

Ether Formation.—Two and seven-tenths grams of thiazoline-*m*-cresol was dissolved in sodium methylate containing one equivalent of sodium (0.3014 g.). The methanol was evaporated off on a steam-bath, the last traces being removed by evaporating it with dry benzene. The sodium salt was taken up in dry benzene, and one equivalent (1.65 g.) of dimethyl sulfate added. The resulting suspension was boiled for one-half hour, and sufficient water was added to dissolve the solid present. The solution was then heated on a steam-bath until all the benzene had evaporated. The suspension which was found to be slightly acid was made strongly alkaline with 10% sodium hydroxide solution and extracted with ether. From the alkaline solution 0.85 g. of unreacted *m*-cresolthiazoline was recovered by acidification, filtration, and subsequent neutralization with sodium carbonate. The ether solution was dried over anhydrous sodium sulfate and saturated with dry hydrogen chloride gas. The hydrochloride which separated out as an oil was dissolved in 95% alcohol, evaporated to dryness and crystallized by the addition of dry acetone. The hydrochloride is readily soluble in water and gives no color reaction with ferric chloride (IVb).

Nitration, Aminization.—Thiazolinephenol was nitrated by the procedure of Babcock and Adams[5] used in the nitration of phenylthiazolines and phenyldihydrothiazines. Upon pouring the nitration mixture into ice water, much of the nitrated product separated out as an insoluble salt. Without separating this, the solution was made alkaline with sodium carbonate and the free thiazolinenitrophenol filtered off. The yield was practically quantitative. The air-dried product was dissolved in dry benzene, filtered from a small amount of insoluble impurity and the solution saturated with dry hydrogen chloride gas. The precipitated hydrochloride was washed with dry acetone. It cannot be recrystallized from water or alcohol, in which it is very soluble, as upon evaporation it is hydrolyzed to the free base (Vb). The free base was prepared by evaporating an aqueous solution of the hydrochloride on a steam-bath. Golden yellow crystals formed (Va).

The hydrochloride of the nitro derivative was reduced in aqueous solution with stannous chloride and hydrochloric acid at 100° in the usual manner. The reaction was carried on for two hours, and was not quite complete at the end of that time. The reaction mixture was made alkaline with sodium carbonate and the resulting suspension extracted with ether. The ether extract was dried over anhydrous sodium sulfate and saturated with dry hydrogen chloride. The resulting dihydrochloride was recrystallized from absolute ethyl alcohol. The compound is readily soluble in water (Xd).

The free amino derivative was prepared by neutralizing a solution of the dihydrochloride with sodium carbonate, extraction with ether, evaporation of the ether, and recrystallization from 95% alcohol (Vc).

5,5-Dimethyl-2-mercaptothiazoline and Derivatives.—This compound is formed in condensations of methallyl mustard oil with phenols, using concentrated sulfuric acid as condensing agent. It was precipitated from the alkali-soluble fraction upon acidification, partially in crystalline form, and partly as an oil. The crystalline material was filtered from the oil, and the oil repeatedly extracted with boiling water from which it crystallized on cooling. This compound was purified by dissolving in 10% sodium hydroxide solution, adding some decolorizing carbon, heating on the steam-bath for half an hour, filtering and acidifying the solution with hydrochloric acid. The precipitated mercaptothiazoline was recrystallized once from boiling water (X).

Disulfide.—One gram of the above mercaptothiazoline was dissolved in the least amount of acetone and to it was added an excess of 3% hydrogen peroxide. The solution turns dark yellow and on evaporation at room temperature a yellow solid remains. This was treated with boiling water to remove any unoxidized mercaptothiazoline, and the residue was recrystallized from alcohol, with the use of decolorizing carbon; yellow crystals (Xa).

Esters.—The *p*-nitrobenzoate was prepared by the reaction of the sodium salt with *p*-nitrobenzoyl chloride in

(5) Babcock and Adams, THIS JOURNAL, **59**, 2260 (1937).

dry benzene, in the manner described for preparation of esters of thiazoline phenols, although in this case elaborate precautions against hydrolysis are not necessary. The filtered benzene solution was evaporated to dryness and the product extracted with boiling water to remove any unreacted mercaptothiazoline, then with 10% sodium carbonate solution to remove any *p*-nitrobenzoic acid, and finally again with water. The compound was crystallized from benzene in large lemon-yellow crystals or from 95% ethyl alcohol in fine yellow needles (Xb).

The 4-nitrobenzoyl ester was reduced by the method of Babcock and Adams using iron powder and concentrated hydrochloric acid. The benzene extracts of the reduction mixture were combined, dried, filtered, and saturated with dry hydrogen chloride gas. The precipitated hydrochloride was purified by extraction with boiling water, with the use of decolorizing carbon, as white crystals, soluble in hot water, less soluble in cold water (Xc).

Physiological Properties.—Some of the thiazolinephenols thus far prepared were examined for physiological action. It was found that these thiazolinephenols, the hydrochlorides of which are all water soluble, are not toxic and have little bactericidal action, their phenol coefficients being less than one. Then it was found that these sulfur–nitrogen–heterocyclic phenols possess local anesthetic action some to a higher and others to a lesser degree. The best thus far found is the 5-methylthiazoline-*m*-cresol. Little difference in local anesthetic action was found between a 1% cocaine solution and a solution of this compound of equal strength. The toxicity of this compound as compared with cocaine was found to be as shown in the table.

	5-Methylthiazoline-*m*-cresol		Cocaine	
Dose, mg. per kg. body weight	No. of mice	% dead	No. of mice	% dead
50	5	0	15	0
100	5	0	15	87
200	5	0	15	100
300	20	5		
400	20	15	(1% solution injected	
500	10	60	intraperitoneally)	

The methyl ether of this compound is about 2–3 times as effective as either cocaine or procaine, but all the compounds, tested as hydrochlorides, upon parenteral injection or topical application, produced severe irritations lasting for more than twenty-four hours. The tartrates, however, are non-irritating.

The above physiological tests were carried out by the Merck Institute of Therapeutic Research.

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Summary

Several new 5-methyl- and 5,5-dimethylthiazolinephenols have been described, together with a number of derivatives. Physiological tests have been conducted upon several of these compounds, indicating local anesthetic properties and a relatively low toxicity.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Ketones Derived from Tetrahydrobenzo[b]naphtho[2,3-d]furan[1]

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In previous communications[3] we have described the synthesis of amino alcohols of the type $R\text{-}CHOHCH_2NR_2$ derived from dibenzofuran and tetrahydrodibenzofuran, respectively. These amino alcohols proved to be slightly more analgesic than the corresponding compounds of the phenanthrene series.[4] Since the most potent synthetic analgesics were found among amino alcohols having the hydroxyl and the nitrogen-containing group directly attached to a hydrogenated benzene nucleus of phenanthrene[5] as indicated in formula I, it appeared desirable to prepare analogous amino alcohols derived from dibenzofuran. We expected that from ketones of formula III or IV such compounds should be obtainable through the series of reactions used for the synthesis of the above mentioned "cyclic amino alcohols" of the phenanthrene series.

When γ-[2-dibenzofuryl]-*n*-butyric acid was cyclized by means of phosphoric acid, a mixture of III and IV was obtained in nearly quantitative yield. Its separation was effected by fractional crystallization, whereby ketone III was isolated

(1) (a) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan. (b) This communication includes also the description of experiments pertaining to a previous note entitled "Amino Alcohols Derived from 1,2,3,4-Tetrahydrodibenzofuran."[3b]

(2) Merck Fellow in Alkaloid Chemistry 1935–1936.

(3) (a) Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935); (b) *ibid.*, **58**, 688 (1936).

(4) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, pp. 99, 102 (Washington, D. C., 1938).

(5) (a) See pp. 88, 90 of ref. 4; (b) Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935).