Lysine was isolated as the picrate which decomposed between 255 and 260°. *Anal.* Calcd. for $C_{12}H_{17}O_9N_5$: N, 18.7. Found[11]: N, 18.5 ± 0.1.

The dicarboxylic acids were separated from the monoamino acids by precipitation of their barium salts with alcohol.[13] Glutamic acid was then determined as the hydrochloride which decomposed sharply at 202–203°.

Anal. Calcd. for $C_5H_{10}O_4NCl$: N, 7.63. Found[11]: N, 7.65 ± 0.04.

(13) Jones and Moeller, *J. Biol. Chem.*, **79**, 429 (1928).

The Hopkins–Cole test for tryptophan was negative.

Summary

Cystine, histidine, arginine, lysine, tyrosine, glutamic acid, ammonia and humin were quantitatively determined in the previously described cottonseed allergenic fractions, CS-51R, CS-52R and CS-56H.

WASHINGTON, D. C. RECEIVED JULY 31, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Thiazoles. XXIV. Some Interesting Exchange Reactions between 6-Alkoxy-7-nitrobenzothiazoles and Alcohols

BY H. HERBERT FOX[1] AND MARSTON TAYLOR BOGERT

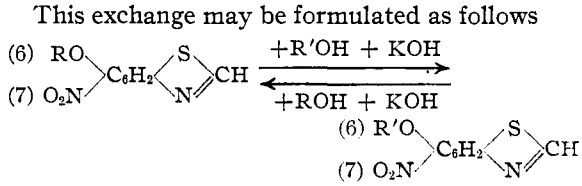
In the course of some experiments[2] to determine the location of the nitro group in what was subsequently proved to be the 6-methoxy-7-nitrobenzothiazole, attempts were made to break open the thiazole nucleus to the 2-amino-5-methoxy-6-nitrophenylmercaptan by fusion with potassium hydroxide,[3] and by the action of concentrated alcoholic potassium hydroxide solution.[4] In both cases, extensive decomposition resulted and no pure products could be isolated.

Recourse was had, therefore, to less drastic treatment, and an alcoholic solution of the nitro derivative, containing a small amount of potassium hydroxide, was heated for a short time on the steam-bath and the mixture, when cold, was poured into an excess of dilute hydrochloric acid. The product, on the basis of general appearance, solubilities, and melting point, obviously was neither the initial material nor the result of a scission of the thiazole nucleus, for it gave no tests for the presence of a primary amino, a mercapto, or a disulfide group, and an elementary analysis indicated an increase, and not a decrease, in carbon content. In short, the reaction had involved not the thiazole nucleus, but the methoxyl group, and the product was identified as the corresponding ethoxynitrobenzothiazole, evidently formed by an exchange between the methoxyl ions of the thiazole and the ethoxyl ions of the alcoholic alkali.

This reaction was reversible. When the ethoxy derivative so produced was subjected to the action of methanol containing a small quantity of potassium hydroxide, the original methoxy derivative was reformed.

The sensitivity of the alkoxyl group to alkali was shown by the saponification of the methoxy derivative with dilute aqueous alkali to the corresponding hydroxy derivative. All attempts to regenerate the alkoxy from the hydroxy derivative proved futile.

This exchange may be formulated as follows



In all cases, the other product of the reaction was the free hydroxy derivative, formed presumably by the direct action of the hydroxyl ions upon the ether.

As shown in Table A, such an exchange has been proved to take place with the following alcohols: methyl, ethyl, *n*- and *i*-propyl, *n*-butyl, β-phenylethyl, cyclohexyl, glycol, and ethanolamine. Glycol reacted with one and not with two moles of the thiazole, to give the β-hydroxyethyl, and not the dithiazylethylene derivative. Interestingly, the exchange reaction with ethanolamine did not require the addition of any alkali, the amino group apparently functioning similarly.

Isopropyl alcohol underwent the reaction more easily than the normal alcohol. It will be seen also from the table that the melting point of the ethers falls with increase in the molecular weight of the hydrocarbon radical, and that the isopropyl melts lower than the corresponding *n*-propyl

(1) Present address: Hoffmann-LaRoche Co., Nutley, N. J.
(2) Fox and Bogert, THIS JOURNAL, **61**, 2013 (1939).
(3) Hofmann, *Ber.*, **13**, 18 (1880).
(4) Mylius, *Chem. Zentr.*, **54**, 819 (1883).

derivative. The introduction of a phenyl group in position 2 did not prevent or impede the exchange.

That the *o*-nitro group is largely responsible for the lability of the ether group in these reactions is borne out by the fact that similar exchanges have been observed with the 5-nitro isomer and will be communicated in a subsequent paper.

When, however, the nitro group was in position 4, *i. e.*, *meta* to the ether group, the behavior of the compound with alcoholic alkali was strikingly different. The relative labilities to alkali of the thiazole nucleus and its ether substituent were reversed. The ether group apparently was unattacked, while the thiazole nucleus was ruptured with production of the corresponding disulfide from the aminothiophenol first formed.

So far as antecedent investigations are concerned, Purdie[5] and Peters[6] studied the interchange of radicals between a number of esters and sodium alcoholates.

Gattermann and Ritschke,[7] in seeking to reduce *p*-nitrophenetole to the corresponding azoxy compound by means of sodium methylate in methyl alcohol, obtained instead azoxyanisole; and it has been shown that sodium hydroxide in methyl alcohol solution effects such a transformation with both *o*- and *p*-nitrophenetole. Similarly, *o*- and *p*-nitroanisole, when treated with alcoholic sodium hydroxide, give the corresponding azoxyphenetole.[7,8]

Blanksma[9] also found that the treatment of 2,4-dinitrophenetole with a methyl alcohol solution of sodium methylate yielded 2,4-dinitroanisole. Further, he reported that when 2,4-dinitroanisole was reduced with sodium sulfide and alcohol, a mixture of 2-amino-4-nitroanisole and 2-amino-4-nitrophenetole was obtained; that methyl picrate formed ethyl picrate under the influence of alcoholic sodium ethylate, and, conversely, that ethyl picrate could be reconverted into methyl picrate by treatment with sodium methylate in methyl alcohol.[10] The *n*-propyl, *i*-butyl, and *i*-amyl picrates have also been obtained from methyl picrate and the corresponding sodium alcoholates.[11]

(5) Purdie, *Ber.*, **20**, 1554 (1887).
(6) Peters, *Ann.*, **257**, 353 (1890).
(7) Gattermann and Ritschke, *Ber.*, **23**, 1738 (1890).
(8) Brend, *J. prakt. Chem.*, [2] **67**, 150 (1903).
(9) Blanksma, *Chem. Weekbl.*, **5**, 789 (1908).
(10) Blanksma, *ibid.*, **6**, 313 (1909).
(11) (a) Jackson and Boos, *Am. Chem. J.*, **20**, 453 (1894); (b) Jackson and Earle, *ibid.*, **29**, 104 (1903).

Researches also have been conducted on the action of sodium ethylate upon 2,3,4- and 2,3,5-trinitroanisoles.[10]

Preparatory to a similar series of studies, with the nitro group in the other possible *ortho* position to the methoxy, we have synthesized 6-methoxy-5-nitrobenzothiazole from *o*-nitro-*p*-anisidine (2-nitro-4-aminoanisole) in practically the same way as described in our previous paper[2] for the preparation of 6-methoxybenzothiazole from *p*-anisidine.

Acknowledgments.—We are indebted to the Carbide & Carbon Chemicals Corp., New York, for the monoethanolamine, and to E. I. du Pont de Nemours & Co., Inc., Wilmington, Del., for the *p*-anisidine used in this investigation, as well as to Mr. Saul Gottlieb, who carried out the analytical work reported herein.

Experimental

All melting points recorded, unless otherwise stated, are corrected and were taken while the temperature was being raised at the rate of 2–3° per minute.

The Roman numerals following the names of compounds correspond with those which appear in Tables A and B.

6-Ethoxy-7-nitrobenzothiazole (II).—To a solution of 2 g. of 6-methoxy-7-nitrobenzothiazole (XI) prepared as described by Fox and Bogert,[2] in 30 cc. of hot ethanol, there was added 1 g. of potassium hydroxide. As the potassium hydroxide dissolved, the solution turned dark red. After five minutes of heating on a steam-bath, the solution was poured into an excess of dilute hydrochloric acid. The copious pale yellow precipitate which separated was removed, washed with water, and crystallized first from 50% acetic acid, and then from 50% ethanol. The crystals were lustrous pale-yellow feathery plates or long flat needles.

When a solution of 1 g. of this compound was dissolved in methyl alcohol (30 cc.) and 1 g. of potassium hydroxide was added, a deep red solution resulted, which was heated on the steam-bath for a few minutes and then poured into an excess of dilute hydrochloric acid. The precipitate was collected, washed with water, and crystallized from ethyl alcohol. It formed pale yellow plates, m. p. 202–203°. Mixed with a sample of authentic 6-methoxy-7-nitrobenzothiazole, the melting point was unchanged.

6-Hydroxy-7-nitrobenzothiazole (I and X).—When 0.5 g. of the 6-methoxy- or ethoxy-7-nitrobenzothiazole was refluxed for ten to fifteen minutes with 30–40 cc. of 10% aqueous sodium hydroxide, a deep red solution was formed. This solution was filtered hot, to free it from any unaltered initial material, and the filtrate was acidified with dilute hydrochloric acid. The flocculent yellow solid which separated was collected, washed with cold water and crystallized from boiling water. It formed long yellow needles, which were turned to bright red by caustic alkali or ammonium hydroxide, and dissolved in aqueous caustic alkali to an orange solution. It dissolved freely in alcohol, ether,

TABLE A

EXCHANGE REACTIONS BETWEEN 6-ALKYLOXY-7-NITROBENZOTHIAZOLES AND ALCOHOLS IN THE PRESENCE OF ALKALI (KOH)

	Gp. at 6	Alcohol used	Product	M. p., °C.	Appearance	Yield, %
I	OMe	HOH	ROH	156–157	Long yellow needles	
II	OMe	EtOH	ROEt	156	Feathery plates	79
III	OMe	*n*-PrOH	ROPr(*n*)	130–131	Large plates	40
IV	OMe	*n*-BuOH	ROBu(*n*)	126–127	Pale yellow plates	60
V	OMe	*i*-PrOH	ROPr(*i*)	123.5–124	Small tan flakes	60
VI	OMe	$PhCH_2CH_2OH$	$ROCH_2CH_2Ph$	117.5–118	Small yellow needles	70
VII	OMe	$HOCH_2CH_2OH$	$ROCH_2CH_2OH$	194–195	Feathery yellow flakes	97
VIII	OMe	$H_2NCH_2CH_2OH$	$ROCH_2CH_2NH_2$	206	Orange plates	62
IX	OMe	$C_6H_{11}OH$	ROC_6H_{11}	114–115	Yellow needles or plates	66
X	OEt	HOH	ROH	156–157	Long yellow needles	
XI	OEt	MeOH	ROMe	202–203	Pale yellow plates	
XII	OMe	EtOH	R'OEt	158–159	Fine yellow needles	70

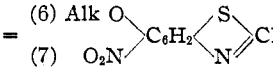
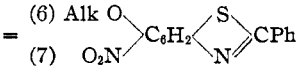
In the above table, R =  and R' = 

TABLE B

ANALYSES OF PRODUCTS RECORDED IN TABLE A

	Formula	Calcd. C	Calcd. H	Found C	Found H
I	$C_7H_4O_3N_2S$	42.9	2.1	43.1	2.2
II	$C_9H_8O_3N_2S$	48.2	3.5	48.3	3.5[a]
III	$C_{10}H_{10}O_3N_2S$	50.4	4.2	50.2	4.3
IV	$C_{11}H_{12}O_3N_2S$	52.4	4.8	52.4	4.9
V	$C_{10}H_{10}O_3N_2S$	50.4	4.2	50.6	4.4
VI	$C_{15}H_{12}O_3N_2S$	60.0	4.0	60.1	4.0
VII	$C_9H_8O_4N_2S$	45.0	3.4	45.0	3.4
VIII	$C_9H_9O_3N_3S$	45.2	3.8	45.1	4.0
IX	$C_{13}H_{14}O_3N_2S$	56.3	4.7	56.0	4.8
X	$C_7H_4O_3N_2S$	42.9	2.1		
XI	$C_8H_6O_3N_2S$	45.7	2.9	45.8	3.1
XII	$C_{16}H_{12}O_3N_2S$	60.0	4.0	60.2	4.0

[a] Calcd.: N, 12.5; S, 14.3. Found: N, 12.5; S, 14.1.

glacial acetic acid, benzene, or hot water, but was only slightly soluble in cold water. On long standing it appeared to give off a red sublimate.

Attempts to reconvert this hydroxyl derivative into the original alkoxy derivative by the action of alcoholic (methyl or ethyl) caustic alkali, yielded only the alkali salt of the hydroxy derivative.

Potassium Salt.—Because of the apparent instability of the free hydroxy compound, the potassium salt was prepared by dissolving it in a methyl alcohol solution of potassium hydroxide. The solution was concentrated and on cooling, deep red plates precipitated, which were crystallized from a mixture of methyl alcohol and benzene.

Anal. Calcd. for $C_7H_3O_3N_2SK$: C, 35.9; H, 1.3. Found: C, 35.9; H, 1.6.

Unless otherwise stated, the compounds which follow were prepared in essentially the same way as the ethoxy derivative (II), and were crystallized from ethanol. They are listed, together with their analyses, in Tables A and B. Some additional details follow the tables.

6-*n*-Propoxy-7-nitrobenzothiazole (III).—Initial materials: 0.9 g. of the 6-methoxy-7-nitrobenzothiazole, 0.7 g. of potassium hydroxide and 30 cc. of *n*-propyl alcohol.

6-*n*-Butoxy-7-nitrobenzothiazole (IV).—Initial materials: 0.9 g. of the methoxy compound, 0.7 g. of potassium hydroxide and 30 cc. of *n*-butanol. The reaction mixture was precipitated by pouring it into 30% ethyl alcohol.

6-*i*-Propoxy-7-nitrobenzothiazole (V).—Initial materials: 0.6 g. of the methoxy compound, 0.17 g. of potassium hydroxide and 40 cc. of isopropyl alcohol; duration of heating, one minute.

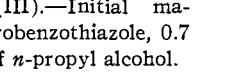
6-β-Phenylethoxy-7-nitrobenzothiazole (VI).—Initial materials: 0.6 g. of the methoxy compound, 0.34 g. of potassium hydroxide and 7 cc. of β-phenylethyl alcohol; duration of heating, five minutes. The mixture was then poured into a dilute (50%) aqueous solution of ethylene glycol containing a slight excess of hydrochloric acid. The emulsion which formed was boiled until the solution cleared. As this solution cooled, an oil separated which finally congealed and was crystallized first from dilute acetic acid and then from dilute ethyl alcohol.

6-β-Hydroxyethoxy-7-nitrobenzothiazole (VII).—Initial materials: 1 g. of the methoxy compound, 0.5 g. of potassium hydroxide and 30 cc. of ethylene glycol.

6-β-Aminoethoxy-7-nitrobenzothiazole (VIII).—A solution of 0.7 g. of the methoxy compound in 15 cc. of monoethanolamine was heated at 100° for three minutes and then poured into water. The orange precipitate was filtered out, washed with dilute potassium hydroxide and crystallized from alcohol containing an excess of aqueous hydrochloric acid. The crystallized product was washed again with dilute potassium hydroxide, then with water, recrystallized several times from water and finally from ethyl alcohol.

6-Cyclohexyloxy-7-nitrobenzothiazole (IX).—To a solution of 0.17 g. of potassium hydroxide in 15 cc. of cyclohexanol, there was added 0.7 g. of the methoxy compound. The mixture was heated to effect solution and, after standing for two minutes, was poured into a very large volume of water, which precipitated the desired product.

2-Phenyl-6-ethoxy-7-nitrobenzothiazole (XII).—Initial materials: 1 g. of the 2-phenyl-6-methoxy compound, 1.4 g. of potassium hydroxide and 30 cc. of ethyl alcohol.



2,2'-Diamino-3,3'-dinitro-5,5'-dimethoxydiphenyl Disulfide.—A mixture of 0.5 g. of 6-methoxy-4-nitrobenzothiazole, 0.5 g. of potassium

hydroxide and 30 cc. of ethyl alcohol was carried through the same process as described above for the 7-nitro isomer. The orange red crude product, crystallized from dilute ethyl alcohol, yielded red needles, insoluble in aqueous caustic alkali and melting at 171°. Mixed with a sample of authentic disulfide,[2] the melting point was unchanged.

6-Methoxy-5-nitrobenzothiazole.—To a cold solution of 69 g. of 2-nitro-4-aminoanisole (m. p. 57–57.5°) in 420 g. of glacial acetic acid, there was added 350 g. of well cooled sulfur monochloride, and the mixture was heated at 75° for about five hours, with constant stirring. The crude product amounted to 105 g.

Of this crude 1-chloro-5-nitro-6-methoxyisobenzo-1,2,3-dithiazole, 100 g. was stirred into 2–3 liters of cold water. There resulted a yellow flocculent precipitate, presumably the corresponding hydroxy dithiazole. After allowing the mixture to stand overnight, to complete this primary hydrolysis, an excess of aqueous sodium hydroxide was poured in and the color of the solution changed to a blood-red. To the filtered solution, there was added 200 cc. of mixed formic–acetic anhydride and the reaction mixture was stirred vigorously for about ten minutes. The gummy precipitate was removed and crystallized from alcohol in the presence of Norit; yield, 11 g. Recrystallized from alcohol, it gave long fine pale yellow needles, m. p. 184–184.5°.

Anal. Calcd. for $C_8H_6O_3N_2S$: C, 45.7; H, 2.9. Found: C, 46.0; H, 2.9.

Since this compound is quite different from the 4- and 7-nitro isomers in melting point and other respects, it must be the other possible *bz*-nitro derivative, *viz.*, the 5-nitro derivative.

Summary

1. 6-Alkoxy-7-nitrobenzothiazoles, in the presence of various alcohols and small amounts of dilute caustic alkali, exchange their alkyls for the radicals of the alcohols used.

2. The melting points of the thiazyl ethers so produced sink with increasing molecular weight of the alcohol radical thus introduced, and the normal melts higher than the isopropyl ether.

3. A nitro group in position 7 on the 6-alkoxybenzothiazole nucleus appears to labilize the alkoxy group and stabilize the thiazole nucleus toward alkali. When the nitro group, however, is in position 4, the reverse is true; the alkoxy group remains intact and the thiazole ring is broken open, with formation of the corresponding *o*-aminothiophenol, or its disulfide.

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[CONTRIBUTION FROM THE HAYDEN MEMORIAL LABORATORIES, NORTHEASTERN UNIVERSITY]

The Preparation of Some Alkane-α,ω-disulfonic Acids

BY SAVERIO ZUFFANTI AND RUDOLPH HENDRICKSON

Introduction

The method used for the preparation of monosulfonic acids of the alkane series,[1] must be modified slightly due to the decreased solubility of the disulfonic acids in the ether used as a suspension medium for the sodium salts.

Gilbert C. Stone[2] has outlined a satisfactory method of preparing the sodium salts of the α,ω-disulfonic acids of the alkane series. This method was used for the preparation of the sodium salts of α,ω-disulfoethane, -propane, -butane, -pentane, -hexane, and -decane.

Experimental

Preparation of the Anhydrous α,ω-Decamethylenedisulfonic Acid.—55.9 grams of the purified and dried sodium salt was suspended in 400 cc. of absolute methanol. Dry hydrogen chloride gas was introduced to decompose the sodium salt. The suspended salt changes in appearance from glossy flakes to a granular residue of sodium chloride that tends to settle quickly, thus affording a means of following the decomposition which, in this case, seemed to be complete in eighteen hours. The residue was filtered off into a sintered glass funnel and the weight of the dried residue indicated that the decomposition was not quantitative. The filtrate was allowed to evaporate (at room temperature) in a vacuum desiccator, leaving a clear oily liquid that was soluble in water but insoluble in ether. This material failed to crystallize while kept under vacuum in the desiccator over a period of two weeks. Accidentally breaking the vacuum too quickly caused the liquid to be splashed onto the walls of the desiccator with immediate crystallization taking place. It was subsequently discovered that if a stream of dry air is allowed to spread the oily liquid into a thin layer it shortly crystallizes to a pasty solid. Washing with ether leaves a white crystalline solid on the sintered glass funnel, yield 46.3 g. The yields varied between 80 and 95% except for the α,ω-hexamethylene-disulfonic acid where the yield was but 68%.

The acids were purified by redissolving them in a minimum of absolute methanol and saturating the solutions with dry hydrogen chloride. This procedure carried the reaction further to completion as evidenced by the precipitation of sodium chloride. After filtration, the acids were recovered as previously indicated and recrystallized several times from absolute methanol. Table I summarizes the data obtained on the purified acids.

(1) Zuffanti, THIS JOURNAL, **62**, 1044 (1940).
(2) Stone, *ibid.*, **58**, 488 (1936).