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"PROTECTIVE AND THERAPEUTIC AGENTS FOR WAR GASES; THERAPEUTIC AGENTS FOR MUSTARD AND NITROGEN MUSTARDS II"

to

September 30, 1945

by

P.L. Salzberg, W.A. Lazier, B.W. Howk, A.A. Pavlic,
G.W. Rigby and W.H. Vinton
Chemical Department,
E. I. du Pont de Nemours and Company

Report OSRD No. 5979
Copy No. 40
Date: January 10, 1946

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"PROTECTIVE AND THERAPEUTIC AGENTS FOR WAR GASES; THERAPEUTIC AGENTS FOR MUSTARD AND NITROGEN MUSTARDS II"

Service Directive CWS-4

Endorsement (1) Dr. Homer Adkins, Member, Division 9, to Dr. Walter R. Kirner, Chief, Division 9.

Forwarding report and noting:

> "This report summarizes the chemical work in a search for an antidote for mustard and nitrogen mustards, as carried out by Drs. Paul L. Salzberg, W. A. Lazier, B. W. Howk, A. A. Pavlic, G. W. Rigby, and W. H. Vinton of the du Pont Company. The evaluation of the compounds for their effectiveness in decontamination and therapy of eyes and skin, and, to a considerable extent, the determination of the course of the investigation, was made by representatives of the Committee on Medical Research. Dr. Jonas S. Friedenwald of Johns Hopkins University was especially active in the evaluation of the possible value of the compounds in eye therapy, and he has been responsible in very considerable part for the emphasis given to the program under N.D.R.C. Many successes have been achieved by the du Pont group in carrying forward to a successful conclusion the chemical work on the synthesis of difficultly accessible compounds, particularly those related to o-aminobenzenethiol."

(2) from Walter R. Kirner, Chief, Division 9 to the Executive Secretary of the National Defense Research Committee.

Forwarding report with approval.

This is a progress report under Contract 9-274, OEMsr-377 with E. I. du Pont de Nemours and Company.

SECRET

TABLE OF CONTENTS

INTRODUCTION

The dramatic success of BAL as a therapeutic agent for Lewisite (L) has stimulated attempts to find a corresponding antidote for mustard gas (H) and the nitrogen mustards.

As H penetrates into the tissues, it appears to undergo a rapid and irreversible reaction with the tissue proteins. Preliminary work has seemed to indicate that the eye offers the most hopeful site for therapy, since H penetration and fixation are perhaps not as rapid there as elsewhere in the body. Of the several possible methods of chemical decontamination, removal of the beta-chlorine atoms of beta-dichloroethyl sulfide (H) by alkylation with compounds containing actual or potential sulfhydryl (SH) groups has given the greatest promise of success in eye therapy.

Previous work under this contract resulted in the preparation of over 100 compounds and their submission to collaborating groups in CMR for therapeutic evaluation. From this testing program there emerged two compounds of interest, o-aminobenzenethiol (NDR-159) and sodium diethyldithiocarbamate. NDR-159 was the most active decontaminant disclosed, but its irritancy and instability limited its usefulness. This report covers preparative work on derivatives and analogues of o-aminobenzenethiol which have been submitted to the CMR. A detailed discussion of the activity of these compounds is presented elsewhere.

Experimental work described in this report was carried out by Drs. A. A. Pavlic, G. W. Rigby, and W. H. Vinton under the direction of Drs. W. A. Lazier and B. W. Howk.

OBJECTIVES

The chief aim of this work has been the preparation of derivatives and analogs of o-aminobenzenethiol which bear substituents calculated to reduce the toxicity of the parent compound without loss of therapeutic efficiency. Another objective has been to supply quantities of these therapeutic agents as needed to the collaborating groups.

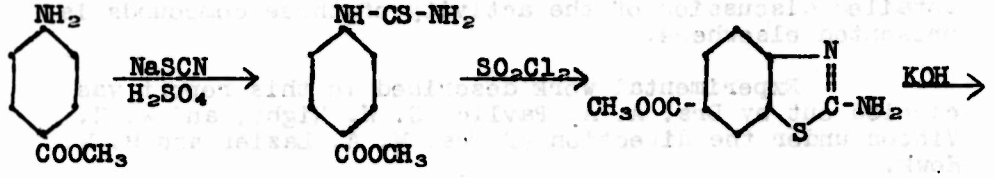
SUMMARY AND CONCLUSIONS

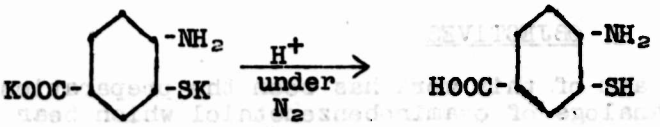
(1) Fourteen candidate compounds have been synthesized and submitted to CMR for evaluation. The great majority

of these were difficultly accessible derivatives of o-amino-benzenethiol. The modifying substituents present in the products include carboxylic acid, carbethoxy, carboxymethyl, methoxy, ethoxy, and sulfonamide groups. These groups were located in various unoccupied positions in the benzene nucleus, but emphasis was placed on derivatives bearing a substituent para to the amino group.

(2) Of the candidates submitted, 4-amino-3-mercapto-benzoic acid (NDR-602) and its ethyl ester hydrochloride (NDR-620) were reported to have decontaminating powers for splashes of H and the nitrogen mustards in the eyes of the test animals (rabbits).

(3) The synthesis of appropriately substituted o-aminobenzenethiols from the corresponding 2-aminobenzo-thiazoles has been shown to be a valuable synthetic tool. It has been used as a step in a widely applicable route ("the benzothiazole synthesis") to the desired compounds. This route consists of (1) thiocyanation of a primary aromatic amine to yield the corresponding thiourea, (2) ring closure of the thiourea by means of sulfuryl chloride to give the appropriate substituted aminobenzothiazole, (3) fission of the latter with 50% caustic, and (4) acidification of the caustic mixtures to give the o-aminobenzenethiol derivatives. The synthesis is illustrated here as applied to the formation of NDR-602.

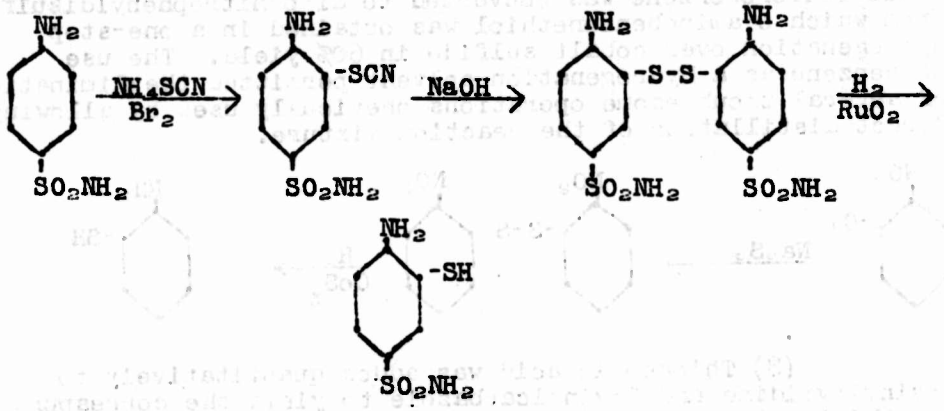




NDR-602

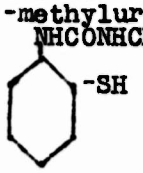
(4) After a number of unsuccessful attempts, 4-amino-3-mercaptobenzenesulfonamide (NDR-734) has been synthesized recently by a novel route starting with sulfanilamide. The compound has been submitted both as a crystalline solid and as a concentrated solution in dimethyl formamide for

evaluation by CMR. The first two steps of the synthesis (thiocyanation and hydrolysis) are described in the literature, but the hydrogenation as well as the final product are new.

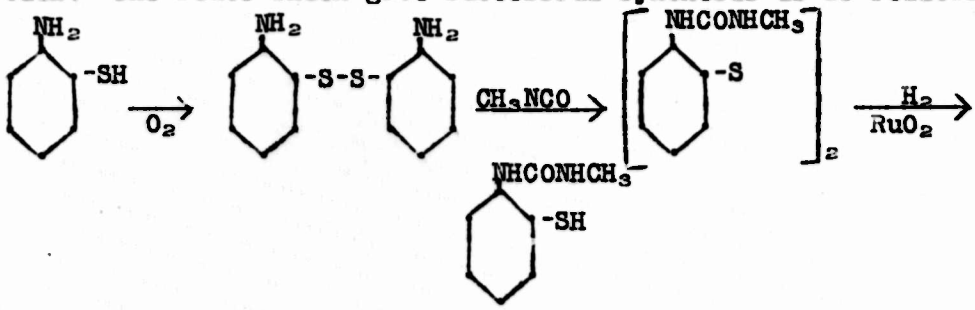


(5) A compound of unusual structure, dimercaptothiodiazole (NDR-610), has shown promise in preliminary screening tests, while the other candidates, aside from the three previously mentioned, though generally active, have exhibited a poorer therapeutic index.

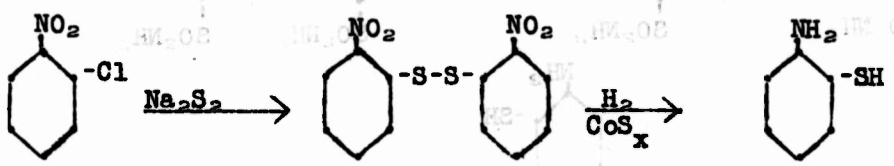
(6) Efforts directed toward the preparation of N-(2-mercaptophenyl)-N'-methylurea



have resulted in successful production of solutions of the desired material. Steps to isolate the desired solid, however, have led to rapid oxidation of the thiol to the disulfide. It might be possible to circumvent this difficulty by submitting filtered solutions directly obtained from hydrogenation. The route which gave successful synthesis is as follows:



(7) A simplified two-step process was uncovered for making o-aminobenzenethiol, an important intermediate. o-Nitrochlorobenzene was converted to di-o-nitrophenyldisulfide from which o-aminobenzenethiol was obtained in a one-step hydrogenation over cobalt sulfide in 60% yield. The use of benzene as a hydrogenation solvent permitted the elimination of several troublesome operations previously used by allowing direct distillation of the reaction mixture.



(8) Thioacetic acid was added quantitatively to 2-vinylpyridine and 9-vinylcarbazole to yield the corresponding thiolacetates, the former of which upon methanolysis gave 2-(beta-mercaptoethyl) pyridine, an interesting thiol which, though inactive in H therapy, may have other applications.

PROGRAM

With the issuance of this report, work on this phase of the therapeutic program has been brought to a close.

EXPERIMENTAL DETAILS

The experimental details on the synthesis of therapeutic agents for mustard and nitrogen mustards will be presented as shown in the following outline.

A. Application of the Benzothiazole Synthesis
   1. Preparation of 4-Amino-3-mercaptobenzoic Acid (NDR-602)
   2. Summary of 20 Preparations of NDR-602
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      b. Utilization
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2. S-(2-Aminophenyl)thiosulfuric Acid (NDR-672)
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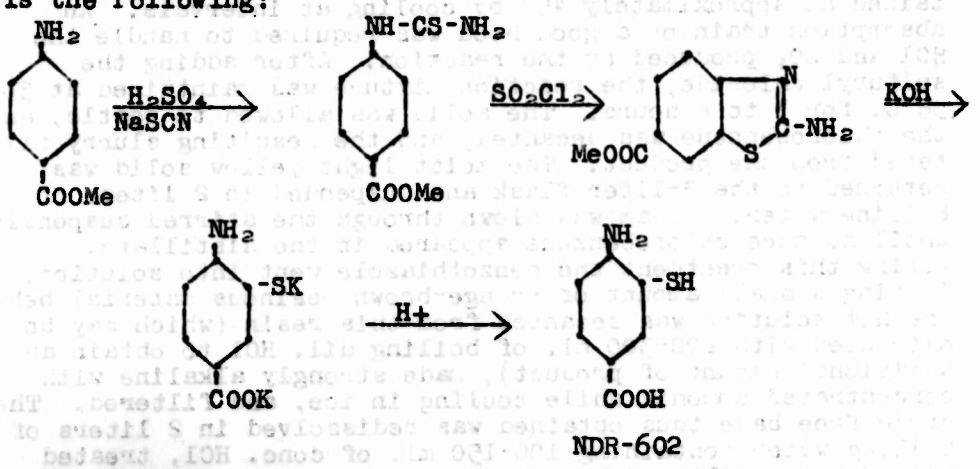
4. Early Attempts to Prepare 4-Amino-3-mercaptobenzenesulfonamide (NDR-734)
5. Attempts to Prepare 4-Amino-2-hydroxy-3-mercapto-5,6-dihydropyrindene
6. Attempted Alkylation of o-Aminobenzenethiol Derivatives

A. Application of the Benzothiazole Synthesis

The most useful route to aromatic o-aminothiols has been the "benzothiazole synthesis". This process was employed successfully to prepare seven difficultly accessible derivatives of o-aminobenzenethiol, the most important of which was 4-amino-3-mercaptobenzoic acid (NDR-602). The latter is considered the most promising therapeutic agent for H arising from this study. An example of the benzothiazole synthesis is the following:



NDR-602

1. Preparation of 4-Amino-3-mercaptobenzoic Acid (NDR-602)

Step I. Synthesis of Methyl 2-Amino-6-benzothiazolecarboxylate* (N.B. 5291-159)

A three-liter three-neck round bottom flask was fitted with a reflux condenser, Hershberg [Organic Syntheses, Collected Volume II Wiley 1943, p. 117] stirrer made of 20

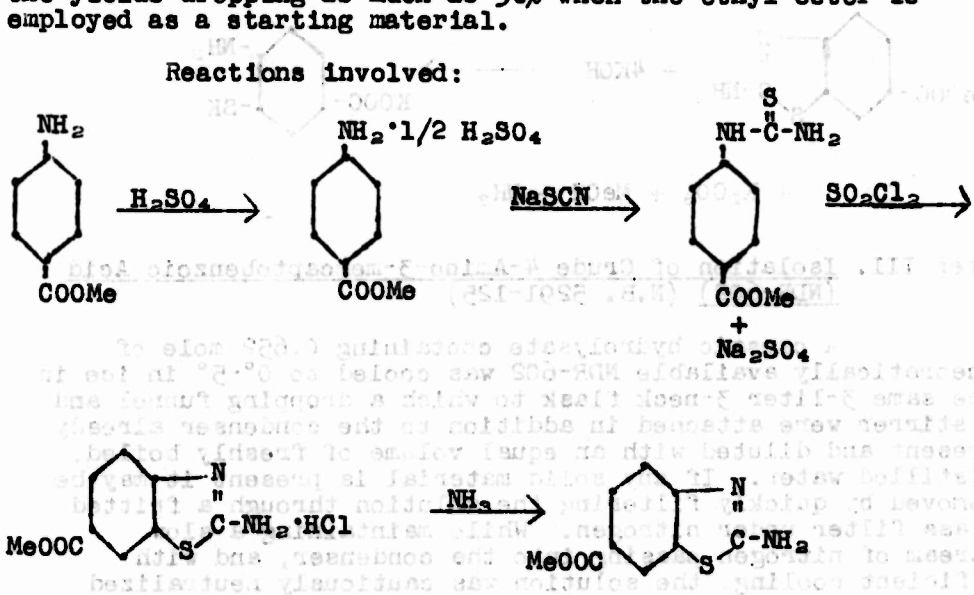
*An analogous synthesis has been reported by Allen and Van Allan, [Organic Syntheses, Volume 22 Wiley 1942, p. 167]

gauge Nichrome wire, thermometer, and dropping funnel. In it were placed 151.0 g. (1.00 mole) of methyl p-aminobenzoate, (Eastman redistilled) and 900 ml. of dry chlorobenzene. The mixture was warmed until the solid had completely dissolved; then 29.3 ml. (0.55 mole) of concentrated sulfuric acid was added dropwise to the well-stirred solution, causing the precipitation of finely divided sulfate and some evolution of heat. After the acid addition was complete, 89.1 g. (1.10 mole) of sodium thiocyanate was added and the mixture was heated with a Glas-Col heating mantle to an inside temperature of 100-105°C. for 4 to 5 hours with continued efficient stirring. During this time, sodium sulfate precipitated and the intermediate N-(p-carbomethoxyphenyl)thiourea was formed. (This can be isolated, if desired, by cooling and filtering the solid mixture, from which the sodium sulfate can be leached with 250 ml. of 60°C. water. The thiourea can then be recrystallized from chlorobenzene or ethanol). The hot chlorobenzene suspension was cooled with stirring to 35°-40°C., and a solution of 108 ml. (1.33 mole) of sulfuryl chloride was added dropwise thereto, while the temperature was maintained at approximately 45° by cooling at intervals. An absorption train or a good hood was required to handle the HCl and SO_2 produced by the reaction. After adding the sulfuryl chloride, the reaction mixture was maintained at 50°-55°C. for 3 to 4 hours. The solid was allowed to settle, and the chlorobenzene was decanted, and the resulting slurry filtered from the product. The moist light yellow solid was returned to the 3-liter flask and suspended in 2 liters of boiling water. Steam was blown through the stirred suspension until no more chlorobenzene appeared in the distillate. During this treatment the benzothiazole went into solution, leaving a small amount of orange-brown resinous material behind. The hot solution was decanted from this resin (which may be extracted with 200-300 ml. of boiling dil. HCl to obtain an additional amount of product), made strongly alkaline with concentrated ammonia while cooling in ice, and filtered. The crude free base thus obtained was redissolved in 2 liters of boiling water containing 100-150 ml. of conc. HCl, treated with Norite, filtered hot through a steam-jacketed Buchner funnel, and made alkaline with ammonia during cooling. The filtered product when dry weighed 158 g. (76% of theory), m.p. 223-224°C. (uncorr.)

The corresponding ethyl ester has a m.p. recorded in the literature of 240°C. (corrected). It was therefore synthesized by this route and its m.p. found to be 228.5-229 (uncorr.), a value considered to be in agreement with the literature. It should be noted that methyl p-aminobenzoate

is far superior to ethyl p-aminobenzoate in this synthesis; the yields dropping as much as 50% when the ethyl ester is employed as a starting material.

Reactions involved:

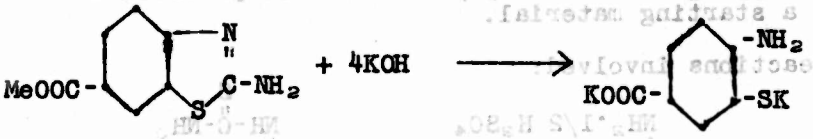


Step II. Caustic Fission of Methyl-2-amino-6-benzothiazole-carboxylate (N.B. 5760-5)

A similar reaction has been reported [Hofmann, Ber. 13, 20 (1880)].

A solution of 50% KOH was made up using freshly boiled, distilled water and analytical reagent grade KOH. One liter of this solution was placed in a three-liter round bottom three-neck flask (standard taper joints) fitted with condenser and having a slow stream of oxygen-free nitrogen passing through it. Then 310.0 g. (1.49 moles) of finely powdered methyl 2-amino-6-benzothiazolecarboxylate was added and the mixture refluxed for 30 hours. As the reaction proceeded, the solid gradually dissolved; ammonia was evolved, and the suspension gradually became a clear, light green solution. Aliquot samples (1 ml.) were removed from time to time and titrated in glacial HOAc with N/10 I_2 to determine the extent of the fission. The highest conversion reached was 83.9% after 30 hours. (This time may be shortened for smaller quantities of benzothiazole.) 1 ml. = 10.4 ml. N/10 I_2. Estimated theoretical amount. 12.4 ml. (based on volume of 1200 ml.).

Reaction involved:

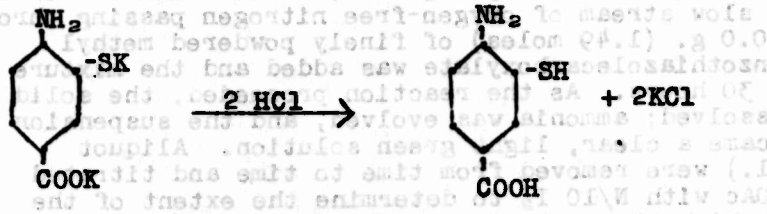


$+ K_2CO_3 + MeOH + NH_3$

Step III. Isolation of Crude 4-Amino-3-mercaptobenzoic Acid (NDR-602) (N.B. 5291-125)

A caustic hydrolysate containing 0.652 mole of theoretically available NDR-602 was cooled to 0°-5° in ice in the same 3-liter 3-neck flask to which a dropping funnel and a stirrer were attached in addition to the condenser already present and diluted with an equal volume of freshly boiled, distilled water. If any solid material is present it may be removed by quickly filtering the solution through a fritted glass filter under nitrogen. While maintaining a slow stream of nitrogen passing into the condenser, and with efficient cooling, the solution was cautiously neutralized with concentrated HCl; then brought to pH 3 by the addition of glacial acetic acid. During the neutralization a white solid precipitated and considerable quantities of CO_2 were liberated. Care is required to avoid excessive effervescence. The precipitate was filtered quickly under nitrogen, washed briefly with boiled water, transferred to a porcelain evaporating dish and dried under vacuum over P_2O_5 for two to three days. The crude faintly greenish solid contained large amounts of inorganic material but showed the presence of 0.620 mole of available NDR-602, (95% of theory).

Reaction:



Step IV. Extraction of NDR-602 (N.B. 5760-21)

An amount of crude material corresponding to 0.382 mole of NDR-602 was powdered finely under nitrogen, and

one-half of it was transferred to a 5-liter 3-neck flask (standard taper joints) fitted with a thermometer, reflux condenser, and mercury-seal stirrer. Two liters of deoxidized, dry chlorobenzene was added to the crude solid under a blanket of nitrogen. The slowly stirred suspension was heated nearly to boiling with a Glas-Col heating mantle, allowed to settle a few minutes; then the clear supernatent solution was forced under nitrogen pressure through an inverted U-tube of 10 mm. glass tubing, reaching nearly to the bottom of the flask and extending to an adjacent Buchner funnel attached to a 3-liter suction flask or its equivalent. (The filtration some times can be omitted.) The clear filtrate was chilled in ice water for two hours and the white to faint yellow-orange precipitate was quickly filtered under nitrogen, washed three times with petroleum ether, and dried at 1 mm. in a vacuum desiccator. The second half of the crude material was placed in the extractor with the residue from the first and the process repeated with an additional two liters of dry chlorobenzene. The combined yield of 64.0 g. of 4-amino-3-mercaptobenzoic acid represented 0.378 mole or 99% of theory. Occasionally the product is improved by recrystallization, utilizing the above technique. Great variation is encountered in Step IV, and oxygen must be rigidly excluded. NDR-602 exhibits the following properties: m.p. 194-197°C. (decomposition); fine needles from chlorobenzene; soluble in ethylene glycol, propylene glycol, ethyl acetate, dioxane, formamide, ethyl benzoate, hot chlorobenzene; sparingly soluble in acetone, ethanol, ether, acetic acid, benzene, xylene, isopropanol, and warm water; insoluble in chloroform and petroleum ether. It is reasonably stable toward oxidation when cold and dry; but like most thiols extremely prone to revert to the disulfide (yellow) in the presence of air and moisture.

In general it has not been found possible to improve the purity of NDR-602 as obtained by the initial extraction. A number of recrystallization procedures were attempted (N.B. 5760-61, 62, 66, 67, 68, 69) but in no case was a significant improvement noted, and in most attempts the thiol value dropped. A heightening of the yellow-orange color was noted when the material was recrystallized several times from hot chlorobenzene. The thiol value did not change significantly however, indicating perhaps a quinoid type of oxidation.

Analysis: Calc'd. for $C_7H_7O_2NS$: N, 8.28; S, 18.93; N.E. 84.5. Found N (Kjeldahl), 7.93, 7.80; S(SH), 18.7, 18.7; S (total), 18.57, 18.25; N.E. 86.0.

2. Summary of 20 Preparations of NDR-602

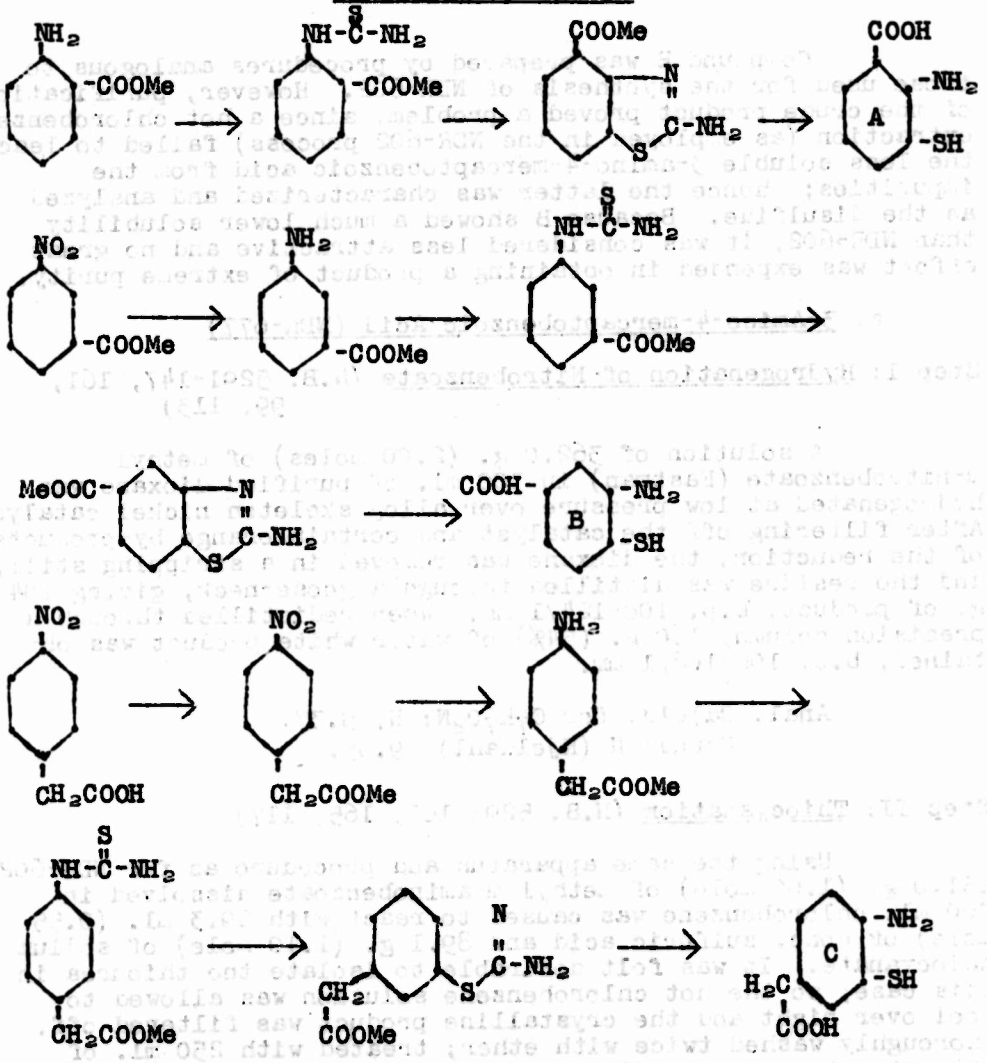
Appearing in the appendix is a table (Table I) showing the yields and variations in the 20 runs carried out to prepare NDR-602. It will be noted that these vary extremely for the several steps and in the purity of product. It is believed, however, that the above directions give the precautions essential for obtaining a satisfactory synthesis.

3. Properties of NDR-602

A graph (Graph I) has been placed in the appendix to illustrate the relation between the m.p. and the percentage of thiol present in various NDR-602 preparations. The melting point thus is a rather good criterion of purity. The appendix also carries a graph (Graph II) which illustrates the behavior of the pH of an alcohol solution of NDR-602 when titrated with N/10 sodium hydroxide. Alcoholic solutions of NDR-602 can be titrated conveniently with N/10 alkali using phenolphthalein as an indicator. Two equivalents of alkali are required.

4. Synthesis of Other Amino-mercapto-carboxylic Acids

In order to prepare certain position isomers and homologs of NDR-602, the following syntheses were attempted.



It was found possible to synthesize two of these three (B and C). Difficulty, however, arose in the initial step of the route to A; treatment of the sulfate salt of methyl anthranilate led to a high melting compound (m.p. >240°C.) of undetermined structure and varying analysis, which exhibited none of the properties of a thiourea, and produced only amorphous gums upon treatment with sulfuryl chloride. (N.B. 5291-132, 149, 150, 156, 158, 169).

Compound B was prepared by procedures analogous to those used for the synthesis of NDR-602. However, purification of the crude product proved a problem, since a hot chlorobenzene extraction (as employed in the NDR-602 process) failed to leach the less soluble 3-amino-4-mercaptobenzoic acid from the impurities; hence the latter was characterized and analyzed as the disulfide. Because B showed a much lower solubility than NDR-602, it was considered less attractive and no great effort was expended in obtaining a product of extreme purity.

a. 3-Amino-4-mercaptobenzoic Acid (NDR-677)

Step I: Hydrogenation of Nitrobenzoate (N.B. 5291-147, 161, 99, 113)

A solution of 362.0 g. (2.00 moles) of methyl m-nitrobenzoate (Eastman) in 300 ml. of purified dioxane was hydrogenated at low pressure over alloy skeleton nickel catalyst. After filtering off the catalyst and certain orange by-products of the reduction, the dioxane was removed in a stripping still, and the residue was distilled through a goose-neck, giving 184 g. of product, b.p. 108-124/1 mm. When redistilled through a precision column, 160 g. (54%) of water-white product was obtained, b.p. 106-108/1 mm.

Anal. Calc'd. for $C_7H_7O_2N$: N, 9.37.
Found: N (Kjeldahl), 9.35.

Step II: Thiocyanation (N.B. 5291-162, 165, 117)

Using the same apparatus and procedure as for NDR-602 151.0 g. (1.00 mole) of methyl m-aminobenzoate dissolved in 700 ml. chlorobenzene was caused to react with 29.3 ml. (0.55 mole) of conc. sulfuric acid and 89.1 g. (1.10 mole) of sodium thiocyanate. It was felt desirable to isolate the thiourea in this case; so the hot chlorobenzene solution was allowed to cool over night and the crystalline product was filtered off, thoroughly washed twice with ether; treated with 250 ml. of hot water to remove sodium sulfate and refiltered. The precipitate was refluxed with 500 ml. of ethanol (to remove a small amount of yellow gum), filtered and air dried; wt. 160 g. (76%), m.p. 170-175°. A sample when titrated slowly reacted with approximately the theoretical quantity of N/10 I_2.

Step III. Formation of Methyl 2-Amino-5-benzothiazolecarboxylate (N.B. 5291-167, 117)

The above thiourea (140 g. or 0.67 mole) was suspended in 700 ml. chlorobenzene and a mixture of 89 ml. sulfuryl

chloride and 80 ml. chlorobenzene was added as before with the temperature maintained just below 50°. The reaction was smoother than in the case of NDR-602; yield: 112 g. (80%) of pure white powder. Anal. Calc'd. for $C_9H_8O_2N_2S$: N, 13.46. Found, N, 13.46; 13.46. Here again it was found that the methyl ester gave a smoother reaction than the corresponding ethyl ester (5291-117).

Step IV. Caustic Fission (N.B. 5291-128, 173, 176)

Using a procedure similar to that employed for NDR-602, 8.45 g. (0.05 mole) of the above benzothiazolecarboxylic acid ester was refluxed 6 hours with 55 ml. of 50% KOH under N_2. Titration of an aliquot portion showed 0.0417 mole of thiol to be present (82.5% of theoretical). Acidification to pH 2.8-3.0, filtration under nitrogen and four washings with boiled cold water gave 6.5 g. of material showing 84.5% SH. This corresponded to 0.0325 mole of desired product (78% based on alkali thiol).

Step V. Extraction (N.B. 5291-135, 176)

The material was extracted with boiling chlorobenzene (350 ml.). Only 0.4 g. was extracted. M.P. 200°C. (decomp.). Ethanol extraction in a Soxhlet also gave a crystalline material which separated from the solvent. This product tended to oxidize to the disulfide even when nitrogen was employed during the extraction.

Anal. Calc'd. for $C_7H_7O_2NS$: N, 8.28; S, 18.93. Found, N(Kjeldahl) 8.37, 8.40; S (total), 18.89, 19.03; S(SH) 19.01.

b. 4-Amino-3-mercapto-α-toluic Acid (NDR-676)

The synthesis of the above compound, starting with methyl p-amino-alpha-toluate and utilized the same equipment as in the previous cases. The starting material was prepared from the corresponding nitro-acid by esterification and hydrogenation.

Esterification was carried out in the usual fashion: 300 g. (1.66 mole) of p-nitro-alpha-toluic acid was dissolved in 1000 ml. of methanol and dry HCl was bubbled through the solution for 8 hours. The solution was refluxed 8 additional hours, cooled, and 309 g. (95.5%) of solid obtained, m.p. 52°-55°C. (reported m.p. 54°C.). The solid was dissolved in 150 ml. purified dioxane and hydrogenated over alloy-skeleton nickel catalyst at 75°C. The filtered solution was stripped

of dioxane, and distilled through a gooseneck yielding 185 g. (71.5%) of liquid boiling at 137-139°C./3 mm. (N.B. 5291-144, 146, 90, 96, 104)

In the fashion previously described the amine was converted to a thiourea, which was isolated. One mole (165.0 g.) of methyl p-amino-alpha-toluate yielded 169 g. (75.5%) of N-(p-carbomethoxymethylphenyl)thiourea, m.p. 122°. Anal. Calc'd. for $C_{10}H_{12}N_2O_2S$: N, 12.5; S, 14.30. Found: N(Kjeldahl) 11.90, 11.82; S, 14.54, 14.13. (N.B. 5291-152, 93, 108)

The thiourea was converted to methyl 2-amino-6-benzothiazoleacetate by treatment with sulfuryl chloride (N.B. 5291-166, 170, 93, 108) as previously discussed; 149 g. (0.73 mole) of the thiourea was treated in 700 ml. chlorobenzene with 68 g. of sulfuryl chloride in 60 ml. chlorobenzene. It was noted during neutralization of the acidic solution containing the benzothiazoleacetate that a white precipitate formed and again dissolved at pH 8-10; and only a small amount of ester was isolated. Recalling that acetic acid esters hydrolyze more readily than benzoic acid esters, it was felt and confirmed that the compound precipitated by bringing the solution to pH 6 was the 6-benzothiazoleacetic acid; yield: 13.5 g. of ester and 40 g. of the acid; 0.257 mole or 35% of theory. M.P. of ester 140-143°C.; m.p. of acid 248-252°C.

Anal. Calc'd. for $C_9H_8O_2N_2N_2S$: N, 13.46. Found, N(Dumas), 13.60, 13.61, 13.37.

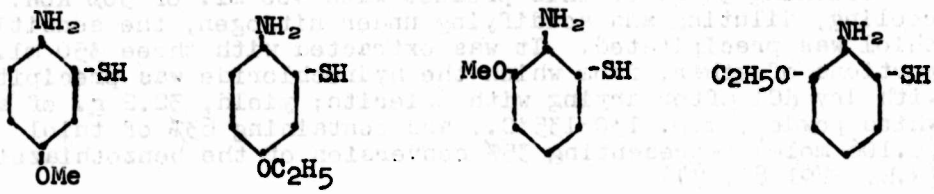
Anal. Calc'd. for $C_{10}H_{10}O_2N_2S$: N, 12.61. Found, N(Dumas), 12.83, 12.98.

As in previous caustic fissions, 10.5 g. (0.047 mole) of methyl 2-amino-6-benzothiazoleacetate was refluxed under nitrogen for 20 hours with 50% KOH, (90% conversion to thiol) diluted with an equal volume of water, cooled and acidified to pH 2.9. The resulting solid was filtered, washed, and dried. It was found to contain 0.042 mole (7.7 g.) of thiol (99% of recovery from alkali). Extraction with 1 liter of hot chlorobenzene gave, on cooling, 5.3 g. (0.029 mole) of 4-amino-3-mercapto-alpha-toluic acid (69%). M.P. 127-129°C. (N.B. 5291-172, 177, 178, 179, 186)

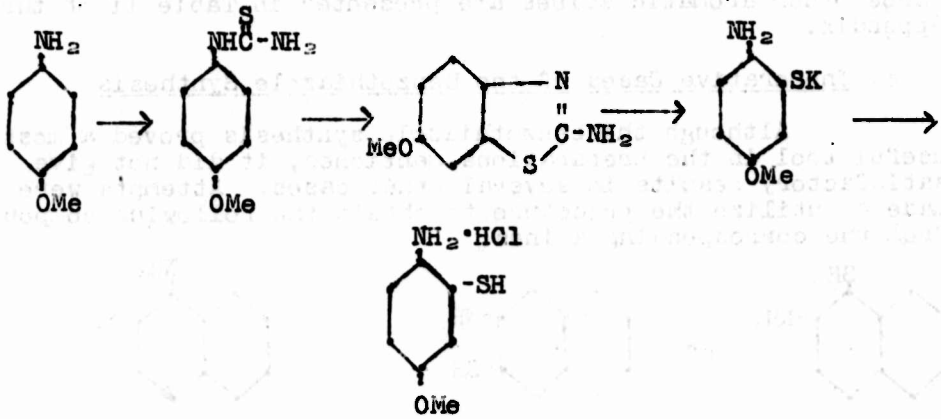
Anal. Calc'd. for $C_8H_9O_2NS$: N, 7.65; S, 17.49. Found: N(Dumas) 7.15; S (total) 16.72, S (SH) 17.2.

5. Synthesis of Ether-Substituted Aminobenzenethiols

Having demonstrated the value of the benzothiazole method in the synthesis of aromatic vicinal amino thiols, it was decided to apply it to the preparation of ether substituted derivatives of o-aminobenzenethiol. The following compounds were desired:



All were synthesized from the corresponding amines and isolated as the hydrochlorides. For example, the first of these was prepared from p-anisidine as follows:



All four compounds were extremely sensitive to oxidation; they could not be exposed to air in the form of the free bases. As the hydrochlorides, however, they were reasonably stable. The procedure followed for the carboxyl substituted compounds had to be modified somewhat to make allowance for this property. It was also found that the corresponding 2-aminobenzothiazoles were obtained in poorer yield than with the carbomethoxy analogues. The o-substituted amines were far inferior to the p-substituted compounds in this respect.

a. 2-Amino-5-methoxybenzenethiol Hydrochloride (NDR-618) (N.B. 5290-84, 73)

One mole (123 g.) of p-anisidine dissolved in 750 ml. chlorobenzene was caused to react with 29.3 ml. (0.55 mole) of

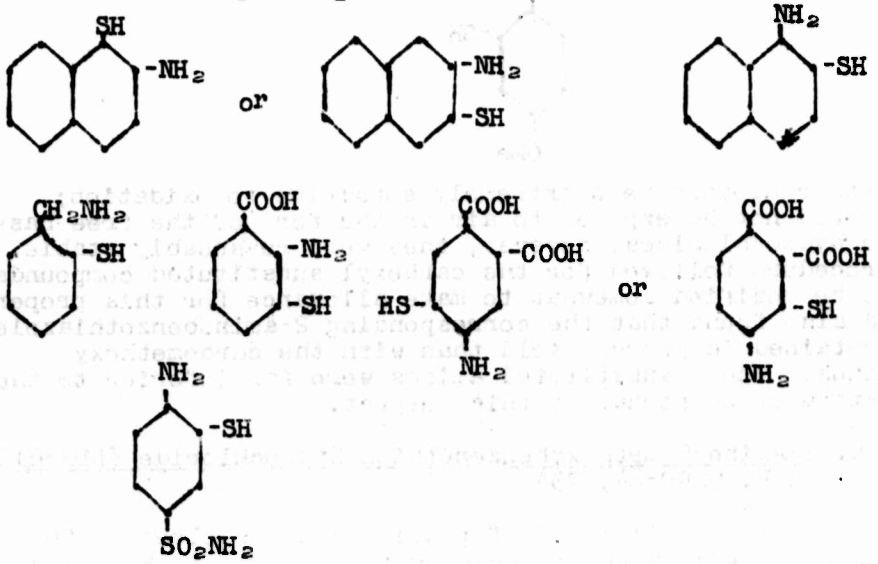
sulfuric acid and 89.1 g. (1.10 moles) of sodium thiocyanate by the procedure employed with NDR-602. A sample of the intermediate thiourea was removed (m.p. 204°). A solution of 108 moles of sulfuryl chloride in 100 ml. chlorobenzene was added slowly and the resulting 2-amino-6-methoxybenzothiazole was isolated as usual; yield 56 g. (0.311 mole) of 31% of theory. M.P. 145°-147°. The material is appreciably water soluble. By refluxing 54 g. of this product with 400 ml. of 50% KOH, cooling, diluting and acidifying under nitrogen, the sensitive thiol was precipitated. It was extracted with three 350 ml. portions of ether, from which the hydrochloride was precipitated with dry HCl after drying with Drierite; yield, 32.2 g. of a white powder, m.p. 130-135°C., and containing 63% of thiol (0.106 mole) representing 35% conversion of the benzothiazole. (N.B. 5291 87, 74)

b. Analogous Compounds

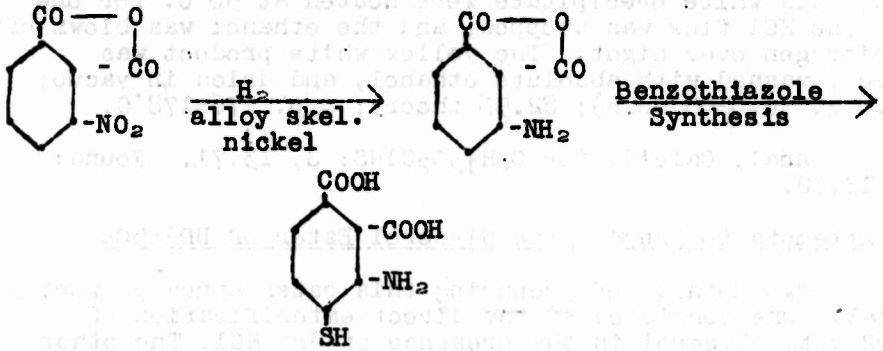
The results combined with those obtained from the three other aromatic amines are presented in Table II of the Appendix.

6. Inoperative Cases of the Benzothiazole Synthesis

Although the benzothiazole synthesis proved a most useful tool in the preparations mentioned, it did not give satisfactory results in several other cases. Attempts were made to utilize the procedure to obtain the following compounds from the corresponding amines.



In no case was more than a trace of aminobenzothiazole derivative isolated, and in many instances no thiourea formation took place. The reaction products were intractable, malodorous, orange gums. The results of these unsuccessful experiments are summarized in Table III of the appendix. In another scouting experiment the following was attempted.



However, hydrogenation of 3-nitrophthalic anhydride did not give the desired product and the route was abandoned. (N.B. 5291-142, 151, 184 and N.B. 5760-2)

B. Derivatives of NDR-602

It was felt desirable to attempt synthesis of certain derivatives of the parent compound by such procedures as esterifying the carboxylic acid group, acetylating the amino group or solubilizing the molecule by treatment with sodium formaldehyde sulfoxylate or ethylene oxide. It was recognized that these procedures would be difficult to carry out in view of the sensitivity of the compound toward oxidation and proneness to ring closures; see for example Jacobson, Ber. 20, 1895 (1887). The experimental results confirmed expectations, as it proved possible to prepare only one therapeutically active derivative, the ethyl ester hydrochloride of NDR-602. Other expedients such as temporary protection of the thiol group by converting it to the disulfide or to the benzyl thioether did not permit synthesis of the desired compounds.

1. Ethyl 4-Amino-3-mercaptobenzoate Hydrochloride (NDR-620) (N.B. 5291-91; N.B. 5760-15, 22, 75)

Care must be exercised in this preparation to prevent side reactions and oxidation. The temperature must never exceed 50°C. A 125 ml. stillpot having a side arm and a standard taper neck was fitted with a gas inlet tube and

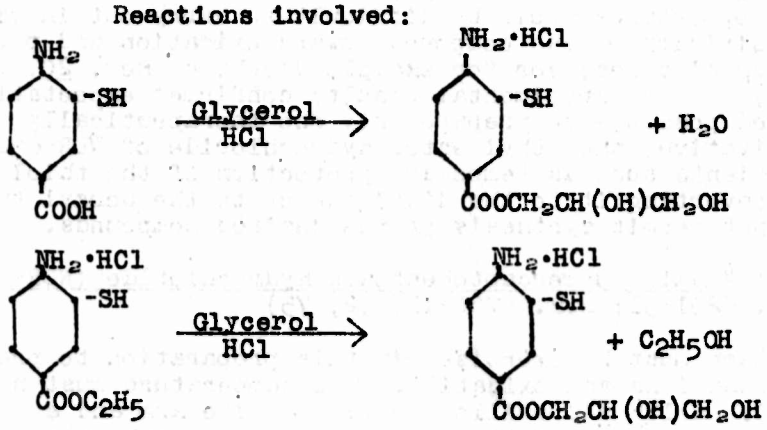
attached to a condenser holding a Drierite tube. Absolute ethanol (75 ml.) was placed in the pot and 4.22 g. (0.025 mole) NDR-602 was dissolved therein. A mixture of dry HCl and dry, deoxidized nitrogen was passed into the ice-cooled solution for one hour. Then the temperature was allowed to rise to about 25°C. and held there for four hours. Finally, the solution and its white precipitate were heated at 50°C. for one hour. The HCl flow was stopped, and the ethanol was blown off with nitrogen over night. The yellow white product was filtered, washed with absolute ethanol, and dried in vacuo; wt. 4.8 g. (0.0206 mole); 82.5% theory; m.p. 176-178°C.

Anal. Calc'd. for $C_9H_{12}O_2ClNS$: S, 13.71. Found: S(SH) 13.62.

2. Attempts to Prepare the Glycerol Ester of NDR-602

Two methods of preparing this ester appeared worthy of trial. One consisted of the direct esterification of NDR-602 with glycerol in the presence of dry HCl. The other involved ester interchange employing the ethyl ester hydrochloride of NDR-602 /NDR-620/ and glycerol. Both were tried, but neither gave evidence of clean cut reaction. Direct esterification (N.B. 5376-128) gave a thick yellow syrup. In attempting to purify this material (N.B. 5422-175), a water extraction was carried out. It revealed inhomogeneity of the mixture and provided evidence of failure to react. In another attempt (N.B. 5422-156), direct heating at 150°C. of the glycerol and NDR-602 hydrochloride produced a brittle, insoluble mass. Ester interchange (N.B. 5376-119) also produced an unpromising yellow plastic material.

Reactions involved:



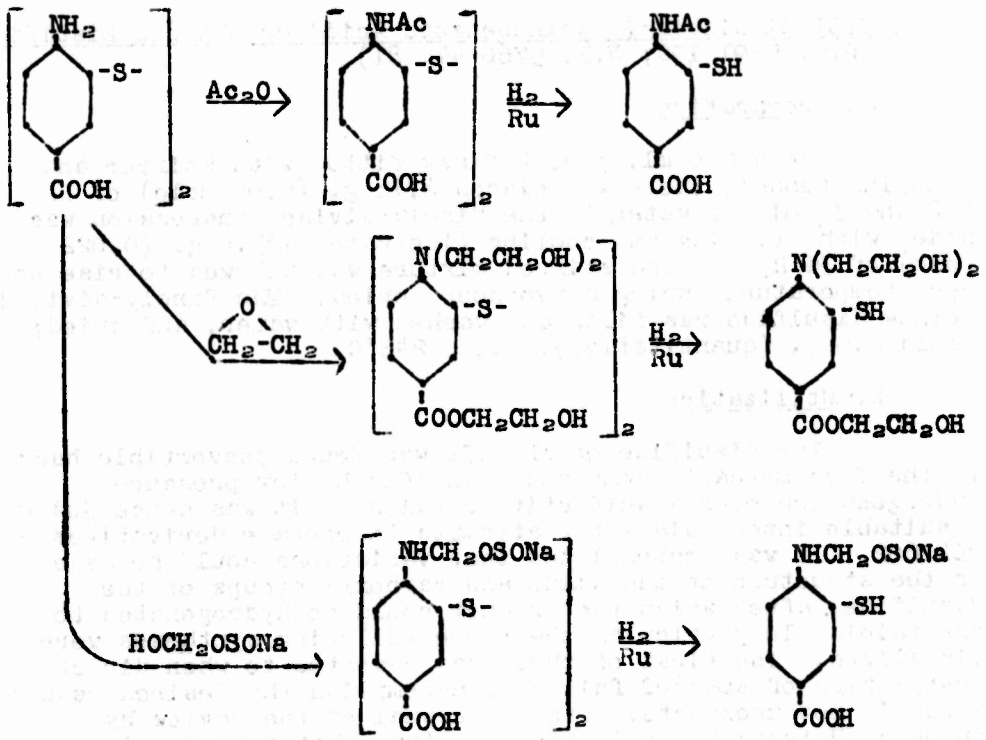
3. 3,3'-Dithiobis-(4-aminobenzoic Acid) or NDR-602 Disulfide (N.B. 5291-192; N.B. 5760-44, 81)

a. Preparation

In a 200 ml. 3-neck flask fitted with stirrer and dropping funnel, there was placed 6.76 g. (0.04 mole) of NDR-602 and 35 ml. of water. To the finely-divided suspension was added with stirring and cooling (ice water)25.0 g. (0.022 mole) of 3% H_2O_2. The stirred mixture was allowed to rise to room temperature during a two-hour period. The finely-divided yellow disulfide was filtered, washed with water, and dried; yield 6.6 g. (quantitative): m.p. 245°C.

b. Utilization

The disulfide of NDR-602 was found convertible back to the free mercapto compound (NDR-602) by low pressure hydrogenation over a sulfactive catalyst. It was hence judged a suitable intermediate for attempts to prepare derivatives of NDR-602. It was contemplated that variations could be made in the structure of the amino and carboxyl groups of the disulfide, after which the product could be hydrogenated to the thiol. In particular the three following syntheses were visualized. The first of these was resorted to when direct acetylation of NDR-602 failed to accomplish the desired result, a result not unexpected after a persual of the review by Burness /University of Illinois Seminar Abstracts for April 5, 1944 by Burness/.



(1) Acetylation: 3,3'-Dithiobis-(4-acetylamino-benzoic Acid) N.B. 5760-81

To a suspension of 16.8 g. (0.05 mole) NDR-602 disulfide suspended in 60 ml. of glacial acetic acid there was added with stirring 30.6 g. (0.30 mole) of acetic anhydride. The mixture was maintained at 40° for 2 hours, cooled, and filtered, thoroughly washed with water and dried, yield, 20 g. (95%) of product; m.p. >240°.

Experiments on the reduction of this compound led only to the formation of benzothiazoles; hence this route was investigated no further.

(2). Other Attempts

The action of ethylene oxide on NDR-602 disulfide was investigated briefly. Starting material only was recovered from a mixture of the disulfide and refluxing ethylene oxide. (N.B. 5760-73, 74). When "sodium formaldehydesulfoxylate" ($HO-CH_2OSONa$) was allowed to act on the disulfide, only unpromising plastic masses were obtained (N.B. 5760-53).

4. Attempted N-Acetylation (N.B. 5290-157, 168, 187; N.B. 5760-65, 72)

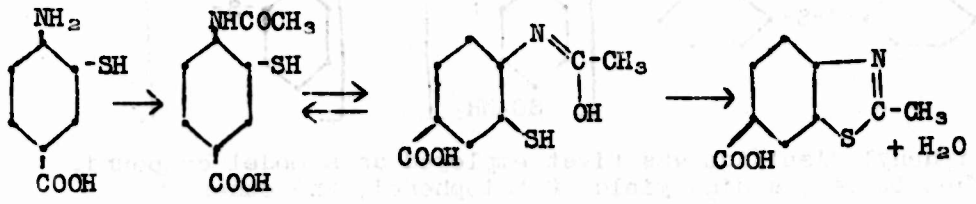
As might be expected, attempts to monoacetylate NDR-602 on the amino group led to mixtures of which the chief component appeared to be 2-methyl-6-benzothiazolecarboxylic acid. Even the mildest conditions (low temperatures and operation in very dilute solution) led to extensive ring closure. The results are tabulated below:

Chart I

Attempts to Monoacetylate NDR-602

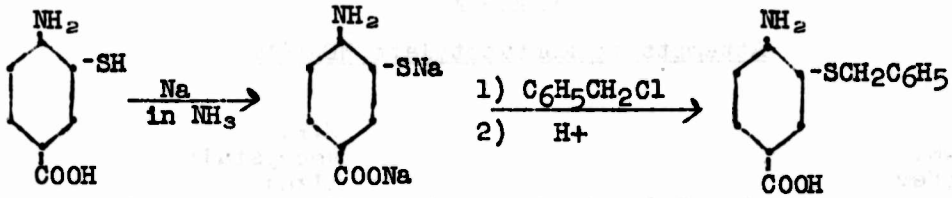
N.B. Reference	Reagents	Solvent	Temperature	M.P. Recrystallized Product	Analysis
5290-157	Ac_2O+Zn (trace)	None	Spontaneous to 80-100	208-220 decomp.	N, 6.57; S(total) 14.37; S(SH) 0
5290-187	Ac_2O+Zn	HOAc	30-35°	230-240	S(SH) 0
5290-65	AcSH	None	Room	207-212 decomp.	C, 55.1; H, 4.27; S(total), 15.0; S(SH), 0; N.E. 173
5760-73	AcSH	Ether	Room	No reaction	

The properties of the product correspond to those calculated for 2-methyl-6-benzothiazolecarboxylic acid, the by-product whose formation may be explained by the following series of reactions.



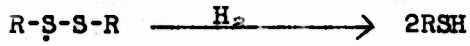
5. Attempted Benzylation (N.B. 5760-45, 47, 51)

Since the benzyl group is reportedly easily attached to a thiol group and also easily removed by treatment with sodium in liquid ammonia [Wood and du Vigneaud, J. Biol. Chem. 131, 267 (1939)], it has occurred to us that this might be utilized to advantage in protecting the thiol group of NDR-602 while operating on the amino or carboxyl groups. Accordingly attempts were made to carry out the benzylation using the standard method of treating the disodium salt of the mercapto-carboxylic acid in liquid NH_3 with one mole of benzyl chloride, viz.



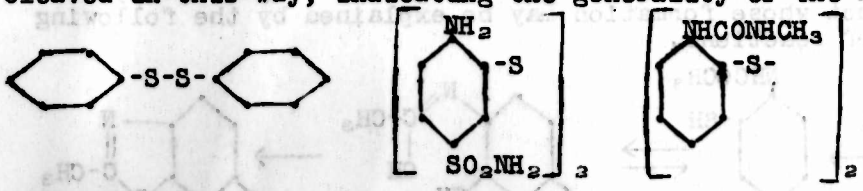
In no case was anything but a plastic mass obtained. To determine whether 2-mercaptobenzoic acid could be protected in this fashion, similar experiments were carried out (N.B. 5760-41, 48, 52, 55), but the same type of product was obtained. Thiophenol, however, undergoes benzylation smoothly. (5760-49).

C. Aromatic Thiols by Reduction of Disulfide Linkages



1. Introduction

When the desired disulfides could be synthesized readily, this method proved to be extremely valuable; especially when it was discovered that the reduction could be performed catalytically in the presence of ruthenium at low temperatures and pressures. During the course of the work three following widely-differing aromatic disulfides were cleaved in this way, indicating the generality of the method.

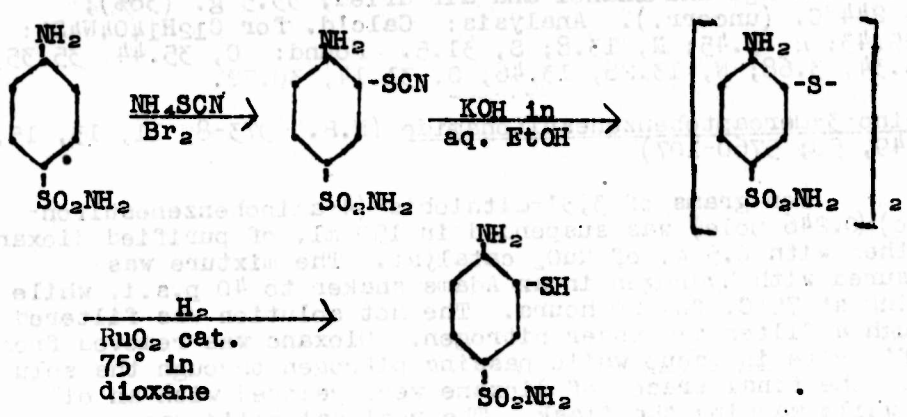


Diphenyl disulfide was first employed as a model compound. When it gave a high yield of thiophenol, the other two

disulfides were reduced under similar conditions, and both cleaved smoothly at 60°-75°C. in dioxane under a hydrogen pressure of 2-3 atmospheres. One of the compounds most desired under this program was 4-amino-3-mercaptobenzenesulfonamide (3-mercaptosulfanilamide), hence a considerable effort was made to synthesize this sulfanilamide derivative. All of the efforts failed (including a catalytic hydrogenation of the corresponding disulfide over cobalt sulfide), until the catalytic method with ruthenium was tested.

2. Synthesis of 4-Amino-3-mercaptobenzenesulfonamide (NDR-634)

The entire synthesis from sulfanilamide is accomplished in three steps as shown below:



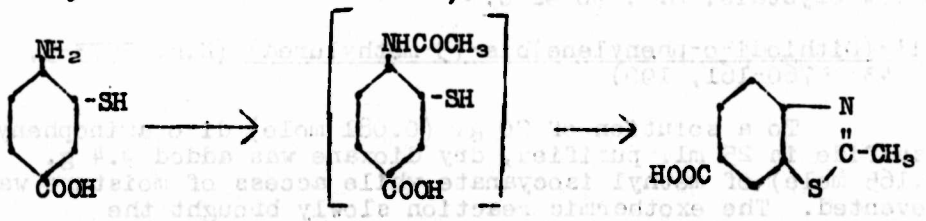
NDR-734

The preparation is described in detail in the following:

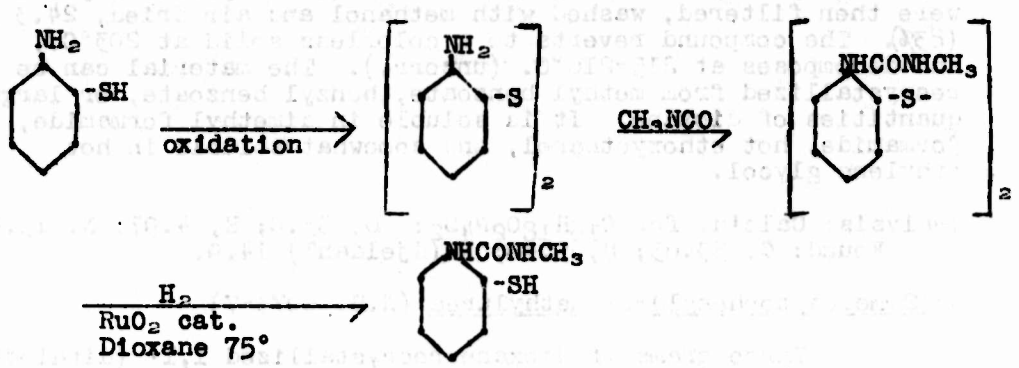
4-Amino-3-thiocyanobenzenesulfonamide (N.B. 5973-28, 29, 30; 5760-87, 93-98)

This is a procedure reported by Kaufmann and Bückmann /Arch. Pharm. 279, 202 (1941)/. To a solution cooled to 5°C. of 25 g. (0.145 mole) sulfanilamide and 40.0 g. (0.525 mole) ammonium thiocyanate in 450 ml. of methanol, there was added dropwise (during three hours) with stirring and cooling a solution of 30.0 g. (0.188 mole) of Br_2 in 75 ml. of methanol. Stirring was continued for 1/2 hour; the solution was then slowly diluted with 5 l. of H_2O. The fine white needles thus formed were filtered, washed with H_2O and dried; 20.5 g. (61.6%); m.p. 161-2°. The product can be recrystallized from aqueous methanol, but appears quite labile when in solution;

lessened. It appeared that substitution in the amino group might confer the desired properties, however, this substitution must at the same time not enhance the chances for ring closure (which occurs with extreme ease in the case of the acetyl derivative of NDR-602).



The formation of a ureide seemed to offer a possible solution to the problem, and the following synthesis was attempted:



The first two steps were carried out smoothly and in high yield; in the hydrogenation step using the conditions previously found effective, a theoretical absorption of hydrogen was observed. However, in the isolation of the solid thiol from the dioxane reaction medium, it was observed that the desired product was extremely sensitive to oxidation and isolation as such did not seem feasible. The utilization of filtered solutions as obtained from hydrogenation remains a possibility. With this end in view carefully purified samples of the disulfides of the ureide and of the disulfide of NDR-734 were sent to Dr. Friedenwald to determine whether they exhibited any unusual toxicity.

Di-o-aminophenyl Disulfide (N.B. 5973-37)

To a solution of 46 g. (0.368 mole) o-aminobenzenethiol in 30 ml. ethanol and 10 ml. H_2O was added 0.1 g. ferric

chloride and air was bubbled through the solution over night. The solid present was taken up in 150 ml. hot ethanol, treated with Darco G-60, diluted with H_2O at the boiling point until the solution was hazy. Slow cooling gave 40 g. (87%) of yellow crystals; m.p. 90-92°C.

1,1'-(Dithiodi-o-phenylene)bis-(3-methylurea) (N.B. 5973-5, 42, 43; 5760-161, 190)

To a solution of 20 g. (0.081 mole) di-o-aminophenyl disulfide in 25 ml. purified, dry dioxane was added 9.4 g. (0.165 mole) of methyl isocyanate while access of moisture was prevented. The exothermic reaction slowly brought the temperature to 50°C., at which point the rise was checked with cooling in ice. The material was allowed to stand for 2-3 hours protected with a Drierite tube; the yellow crystals were then filtered, washed with methanol and air dried, 24.3 g. (83%). The compound reverts to a colorless solid at 203°C., and decomposes at 215-216°C. (uncorr.). The material can be recrystallized from methyl benzoate, benzyl benzoate, or large quantities of dioxane. It is soluble in dimethyl formamide, formamide, hot ethoxyethanol, and somewhat soluble in hot ethylene glycol.

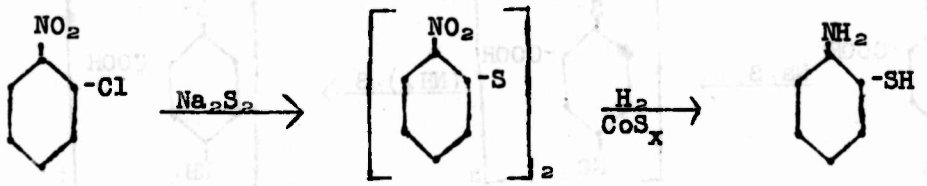
Analysis: Calc'd. for $C_{16}H_{18}O_2N_4S_2$: C, 53.0; H, 4.97; N, 15.48.
Found: C, 53.63; H, 5.40; N (Kjeldahl) 14.9.

N-(2-Mercaptophenyl)-N'-methylurea (N.B. 5973-7)

Three grams of dioxane-recrystallized 1,1'-(dithiodi-o-phenylene)bis-(3-methylurea) was suspended in 100 ml. purified dioxane with 0.5 g. RuO_2 catalyst. The mixture was shaken for 6 hours in an Adams' shaker at 65°C. under 40 p.s.i. H_2 pressure. The hot solution was filtered under nitrogen to remove catalyst and a 1 ml. sample removed for titration with N/10 I_2. Showed 41.5% of the theoretical thiol value. On cooling yellow needles appeared and were tentatively identified as starting material, (m.p. 225°C.). The filtrate from these needles was concentrated to dryness under nitrogen, but the residual material no longer showed any thiol content indicating sensitivity to oxidation.

4. o-Aminobenzenethiol (N.B. 5760-160, 162-5; 5973-12, 17-25)

During the course of this work there was need for o-aminobenzenethiol both as an intermediate and as potential therapeutic agent. While preparing the compound according to directions in ESP-43-303, it was discovered that this latter procedure could be shortened considerably by conducting the hydrogenation in benzene solution. The reactions involved are as follows:



The first step is conducted as described in Organic Syntheses, Coll. Vol. I, p. 220.

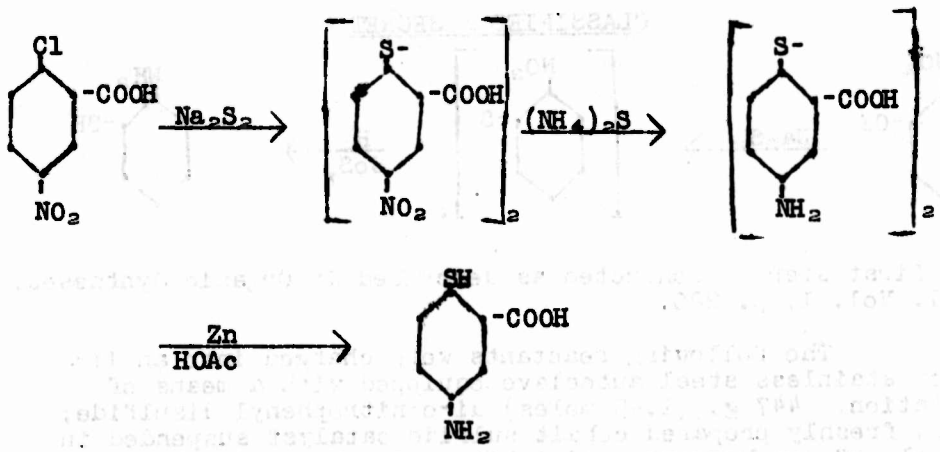
The following reactants were charged into an 11-liter stainless steel autoclave equipped with a means of agitation: 447 g. (1.45 moles) di-o-nitrophenyl disulfide; 50 g. freshly prepared cobalt sulfide catalyst suspended in 150 ml. of dry benzene; and 3 liters dry benzene. The autoclave was pressured with 100 p.s.i. of H_2, and a 50 p.s.i. pressure drop was observed. The temperature was slowly raised and between 125°-135°C. H_2 was absorbed at 1000 p.s.i. producing a pressure drop of 270 p.s.i. The total represents 98.5% of the theoretical H_2 uptake. The autoclave was cooled to 5°C.; the solution filtered under nitrogen to remove catalyst and stripped (also under nitrogen) to remove most of the benzene and water. Distillation of the residual liquid was carried out under nitrogen through a 3' column packed with glass helices. After a foreshot of benzene and aniline was collected, 210 g. (58%) of pure o-aminobenzenethiol was obtained; b.p. 95°C./4 mm.; sp. gr. 25/4, 1.1667; n_D^{25} 1.6450.

Analysis: Calc'd. for C_6H_7NS: C, 57.5; H, 5.60; S, 25.60
Found: C, 58.00; H, 5.89; S (SH) 25.6.

About 100.5 g. residue remained in the stillpot, and was identified as being chiefly the disulfide. It should be mentioned that an attempt to reduce di-o-nitrophenyl disulfide with RuO_2 at 75°C. under 40 p.s.i. of H_2 gave no reduction whatsoever.

5. 5-Amino-2-mercaptobenzoic Acid (NDR-645)

The preparation of this compound was one of the first undertaken in the period covered by this report. It will be noted that the amine and thiol groups are not ortho to each other; however, it was the aim of this preparation to learn (a) whether the reduction of aromatic disulfide linkages offerod an attractive method for the synthesis of the desired type of thiols and (b) whether active H decontaminants were obtained in compounds in which the amino and mercapto groups were not vicinal. The route employed was as follows:



From the results of later discoveries utilizing RuO_2-catalyzed hydrogenations, it is now indicated that the process described below could be materially simplified with accompanying increase in yield and purity of product by cleavage of the aminodisulfide with H_2 over RuO_2. An even more abbreviated process (patterned after the o-aminobenzenethiol synthesis, hence on sound experimental basis) would involve the cobalt sulfide catalyzed hydrogenation of the nitrodisulfide. Since the product did not show therapeutic promise, these latter routes were not investigated. The preparation also served to indicate that chemical reduction is not an attractive route to amino thiols. It suffers from contamination of the final product and difficulty in the isolation of the latter.

2,2'-Dithiobis-(5-nitrobenzoic) Acid (N.B. 5291-31, 32, 10, 11, 44)

This step was patterned on the procedure of Bogart and Stull (Organic Syntheses, Collective Volume I, Wiley 1941, p. 220) for preparing o-dinitrophenyl disulfide. A solution of 36.0 g. (0.15 mole) of sodium sulfide nonahydrate was stirred while 4.8 g. (0.15 mole) of sulfur powder was added, and refluxed until the sulfur dissolved. This solution was added during a 5-10 minute period to a stirred solution of 40.3 g. (0.20 mole) of recrystallized 2-chloro-5-nitrobenzoic acid dissolved in 90 ml. of water containing 8.0 g. (0.20 mole) of NaOH and 100 ml. of ethanol. The solution turned to a dark color and was refluxed for two hours. On standing over night in the cold, 37 g. of red solid was obtained by filtration. This represented 0.168 mole of product (84% of theory). It was dissolved in 120 ml. hot water, treated with Norite, filtered, and the free acid was precipitated by dil.

HCl, washed with water and then ethanol; overall yield 24 g. (60%).

Analysis: Calc'd. for $C_{14}H_8O_8N_2S_2$: N, 7.08; S, 16.4; N.E. 198
Found: N(Kjeldahl) 6.63; S (total) 16.35; N.E. 196.5.

2,2'-Dithiobis-(5-aminobenzoic Acid) (N.B. 5291-33, 45)

To 100 ml. of 6N ammonia there was added 19.8 g. (0.05 mole) of the previous product; the suspension was diluted with 30 ml. water, and was saturated with H_2S in an ice-bath during a period of 3 hours. The solution was boiled for two hours during which time the color changed from dark brown to light yellow, and free sulfur was deposited. The sulfur was filtered, and to the filtrate was added 12 ml. glacial acetic acid. After cooling, the light yellow precipitate was filtered, washed with water and dried. It was completely soluble in dilute warm HCl, m.p. 240°C. Yield: 16 g. (95%). This ammonium sulfide reduction is based on the process of Robertson (Organic Syntheses, Collective Volume I, Wiley 1941, p. 52).

5-Amino-2-mercaptobenzoic Acid (NDR-645) (N.B. 5291-46,35)

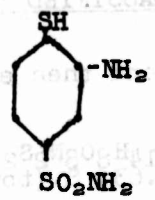
This reduction was based on the method of Allen and MacKay (Organic Syntheses, Collective Volume II, Wiley 1943, p. 580).

To 30 ml. of glacial acetic acid containing 3.0 g. of Zn dust was added 16 g. (0.0475 mole) of the previous product, and the mixture was refluxed with stirring for 4 hours. The solution was filtered hot, and the cake extracted twice with hot acetic acid. The filtrate and extracts were combined, partially neutralized with ammonia (until a portion had precipitated) and filtered quickly under nitrogen. The filtrate was carefully treated with dilute ammonia under nitrogen until no more precipitate formed. The white solid was quickly filtered, washed with a little boiled water and dried in vacuo. Yield: 7.7 g. or 0.0455 mole (48%).

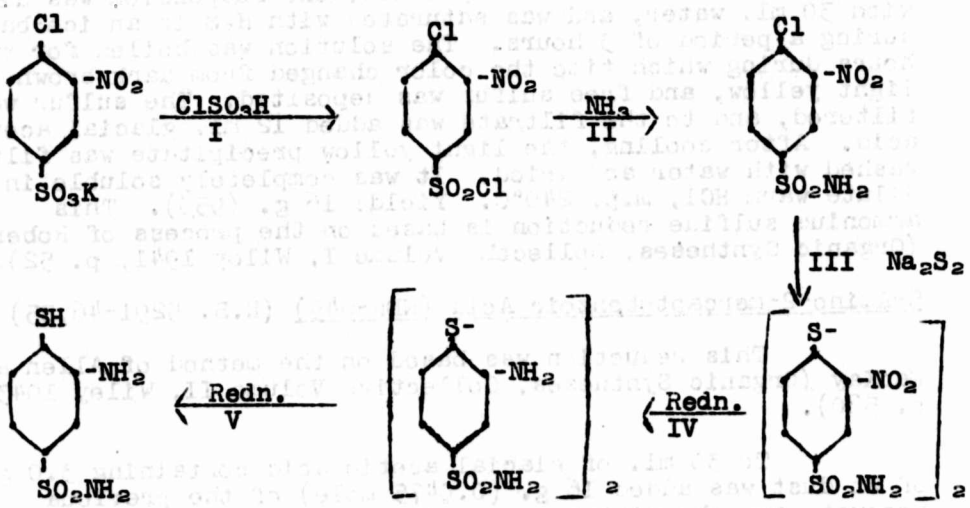
Analysis: Calc'd. for $C_7H_7O_2NS$: S, 18.93; Found: S(SH), 17.1.

6. Attempted Preparation of 3-Amino-4-mercaptobenzenesulfonamide

It was felt desirable to try to synthesize the isomer of 3-mercaptosulfanilamide in which the sulfonamide group was para to the mercapto substituent, i.e.



It seemed possible that the above compound might be made using a disulfide intermediate according to the following scheme.



Steps I, II, and III were accomplished in nearly quantitative yield, but step IV gave a product of unchanged nature. It seems likely in the light of recent discoveries that catalytic techniques with sulfactive catalysts might bring about the desired reduction smoothly.

4-Chloro-3-nitrobenzenesulfonylchloride (N.B. 5760-31,32,58)

In a 300 ml. 3-neck flask with ground glass joints was placed 90 ml. of distilled chlorosulfonic acid; the flask was cooled with ice water and to it was slowly added 55.0 g. (0.20 mole) of recrystallized powdered 3-nitro-4-chlorobenzenesulfonic acid (potassium salt). A small reflux condenser was attached and the mixture was heated at 80° for 14 hours. The cooled light-brown solution was poured onto two liters of chipped ice. The low-melting, white solid was used

without further purification in the next step. The yield was 52 g. (quantitative) of dry product.

4-Chloro-3-nitrobenzenesulfonamide (N.B. 5760-33, 34)

The previous product was slowly added to a well stirred solution of conc. ammonia (250 ml.). The temperature of the ammonia was raised to about 50°C. and stirring was continued to 2 hours. The mixture was cooled thoroughly and filtered, yielding 41.7 g. (88% of theory). The product was recrystallized from 2B ethanol (100 ml.); yield, 38.3 g. of m.p. 173-175°.

Analysis: Calc'd. for $C_6H_5N_2O_4ClS$: N, 11.83, S, 13.5.
Found: N, 11.60, 11.30; S, 13.87, 13.76.

4,4'-Dithiobis-(3-nitrobenzenesulfonamide)(N.B. 5760-40, 42)

An alcohol solution of Na_2S_2 was made up from 29.0 g. (0.12 mole) of $Na_2S \cdot 9H_2O$, 3.9 g. (0.12 mole) of sulfur and 120 ml. of 2B ethanol. The recrystallized product from the preceding preparation (38.3 g., 0.162 mole) was dissolved in 280 ml. of 2B ethanol (warm). The Na_2S_2 solution was added fairly rapidly to the sulfonamide; an immediate darkening took place accompanied by the separation of a whitish solid. After refluxing for three hours, the chilled mixture was filtered, and the yellow solid treated with 250 ml. of H_2O, filtered and washed thoroughly with water. The dry product weighed 30 g. (0.064 mole) representing a 79% yield.

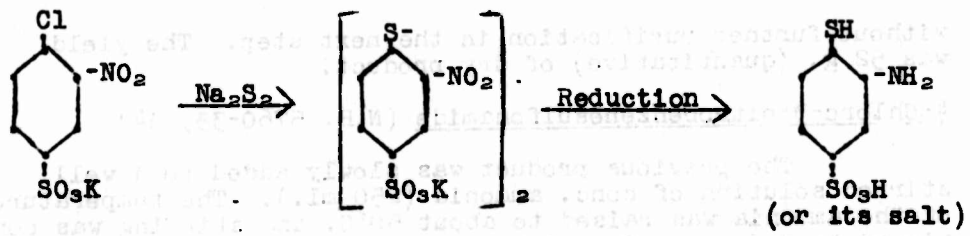
Analysis: Calc'd. for $C_{12}H_{10}N_4O_8S_4$: S, 27.3.
Found: S (total) 27.21.

Attempted Reduction of 4,4'-Dithiobis-(3-nitrobenzenesulfonamide)(N.B. 5760-50)

The reduction of this compound was attempted with four different chemical reducing agent systems: Zn + dil. HCl; Zn + NaOH; Zn + othanol; and Zn + glacial HOAc. In no case was the amino compound isolated.

7. Attempted Synthesis of 3-Amino-4-mercaptobenzenesulfonic Acid

In a series of reactions analogous to those described above, the synthesis of a sulfonic acid analogue of NDR-602 was tried, with the object of producing an amino thiol more soluble in water than NDR-602.



The first step was carried out successfully, but no pure product would be isolated from the reduction step. Evidence of the formation of an aromatic mercaptosulfonic acid was provided by (1) the isolation of an S-benzylthiouronium salt derivative differing from the corresponding derivative of the starting material and (2) the reaction of the crude solution with N/10 iodine solution.

4,4'-Dithiobis-(3-nitrobenzenesulfonic Acid), Potassium Salt (N.B. 5760-25, 27, 36, 60)

A solution of Na_2S_2 was prepared from 400 ml. 2B ethanol, 90 g. $Na_2S \cdot 9H_2O$ (0.375 mole) and 12 g. of sulfur (0.375 mole). It was added with stirring to a suspension of 137.8 g. of recrystallized 4-chloro-3-nitrobenzenesulfonic acid (potassium salt) in 500 ml. of 2B ethanol. The resulting black mixture was refluxed for 4 hours with stirring, and allowed to stand over night. The alcohol was decanted from the yellow-orange precipitate; the latter was extracted with one liter of hot water, leaving behind 13 g. of a water-insoluble yellow powder. The solution which contained the above-named compound was used without further purification.

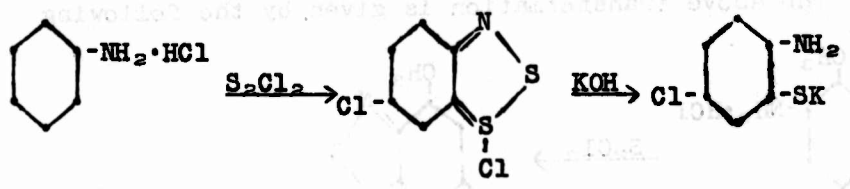
Attempted Reduction of the Above Disulfide (N.B. 5760-26,27,36)

The solution obtained above was treated with 230 ml. of 50% KOH and 193 g. of zinc dust by heating and stirring on the steam bath for 16 hours. After filtering off the unreacted zinc, a 5 ml. aliquot was removed and found to react with 8.5 ml. N/10 I_2. The solution was made weakly acid with glacial acetic acid and the zinc was removed by precipitation with hydrogen sulfide. A sample of the clear filtrate reacted with S-benzylthiouronium chloride to give a solid derivative, m.p. 147-149°C., but no pure 3-amino-4-mercaptosulfonic acid could be isolated.

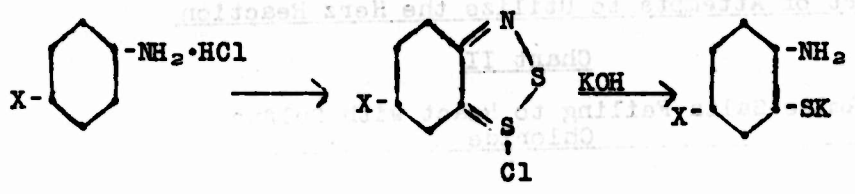
D. Application of the Herz Reaction to o-Aminobenzenethiols

1. Introduction and Model Example

The Herz reaction is illustrated as follows:



or



Hence where X = a halogen atom it, like the benzothiazole synthesis, would appear to offer an attractive path to a large number of substituted o-aminobenzenethiols. However, the benzothiazole synthesis proved to be of more general applicability, and the Herz reaction was tried only in those cases where the former route failed. To verify the technique before applying it to unreported synthesis, a preparation according to the patent literature (Herz. German Patents 360,690; 364,822; 367,346; 367,493 (1914)) was carried out. It gave an excellent yield of product showing correct analytical figures, but when the Herz reaction was extended to three amine salts of interest in this program, no reaction took place, and the amine salts were recovered unchanged.

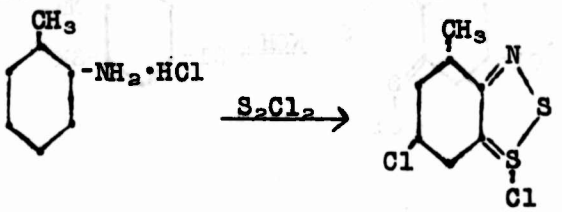
4-Methyl-6-Chlorobenzothiazthionium Chloride (N.B. 5291-13-17)

Sulfur monochloride (150 g.) was placed in a 500 ml. 3-neck flask fitted with a mercury-seal stirrer, reflux condenser, and thermometer. With stirring 25 g. (0.175 mole) of o-toluidine hydrochloride was added slowly, and then the temperature was carefully raised to 50° and held there for 4 hours. The product was stirred with dry benzene, filtered and washed until all S_2Cl_2 had been removed. There was obtained 28 g. (0.118 mole) of a red powder which was sensitive to moisture (68% of theory).

Analysis: Calc'd. for $C_7H_5NS_2Cl_2$: C, 35.3; H, 2.1; N, 5.87; S, 26.95; Cl, 29.8.

Found: C, 35.05; H, 2.57; N (Kjeldahl) 5.46; S (total) 27.90; Cl, 27.45.

The above transformation is given by the following equation:



2. Chart of Attempts to Utilize the Herz Reaction

Chart II

Amine Salts Failing to React with Sulfur Chloride

N.B. Reference	Amine	Maximum Temp.	Catalyst	Comment
5291-36,37	Methyl p-Amino-benzoate	31°	None	No sulfur in product.
5291-42	"	70°	$ZnCl_2$	22 hr.; apparently amine HCl.
5760-35	Dimethyl 4-Amino-phthalate	70°	None	Starting material recovered.
5760-37	"	80°	$ZnCl_2$	"
5760-38	p-Aminobenzene-sulfonamide	90°	None	"
5760-43	"	90°	None	"

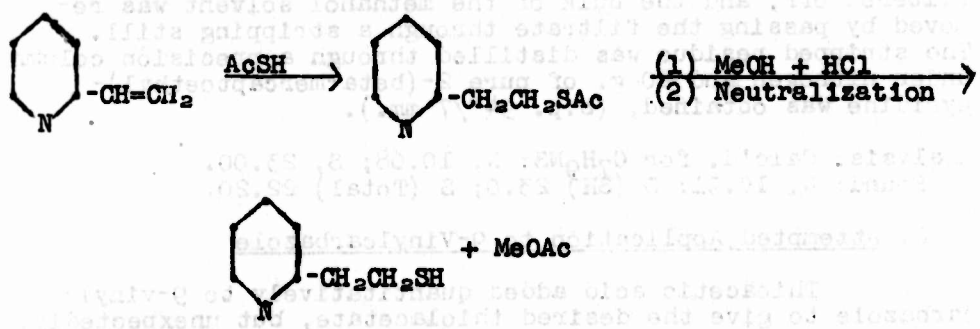
E. Thiols by Methanolysis of Thiolacetates

A convenient synthesis of thiols (when the proper intermediates are available) involves the methanolysis of thiolacetates. The latter are frequently obtained by the addition of thioacetic acid to properly constituted unsaturated compounds.

$$RCH{=}CH_2 \xrightarrow{AcSH} RCH_2CH_2\text{-}SAc \xrightarrow[HCl]{MeOH} RCH_2CH_2SH + MeOAc$$

1. Synthesis of 2-(beta-Mercaptoethyl)pyridine (NDR-671)

These reactions were effectively applied to 2-vinylpyridine as follows:



Step I. 2-(beta-(Acetylmercapto)ethyl)pyridine (N.B. 5291-120, 143; N.B. 5290-116)

A 500 ml. three-neck flask was fitted with an anchor stirrer, dropping funnel and low temperature thermometer. In it was placed 114 g. (1.50 moles) of thioacetic acid, and the latter was chilled to -40°C. By means of the dropping funnel, 157.5 g. (1.50 moles) of freshly distilled 2-vinylpyridine was added rapidly to the well-stirred thioacetic acid. The heat from the highly exothermic reaction was dissipated by cooling with a dry ice-acetone mixture. The temperature was allowed to rise gradually to 20°C. at which point it was maintained until addition was complete. An iodine titration of an aliquot portion dissolved in alcohol showed that 96% of the thioacetic acid had reacted. The product was transferred to a still pot and fractionated under nitrogen in a precision still. After a small forerun of lower boiling material, the bulk of the product was collected at 95-97°/1 mm. The yield was 247.5 g. (91.3% of theory).

Analysis: Calc'd. for $C_9H_{11}NOS$: C, 59.6; H, 6.08; N, 7.75; S, 17.7.
Found: C, 60.62, 60.82; H, 6.31, 6.47; N, 8.54, 8.85; S, 16.97, 16.81.

Step II. 2-(beta-Mercaptoethyl)pyridine (NDR-671)

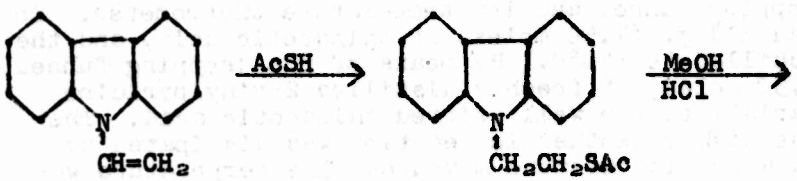
To a solution of dry HCl (1.45 moles) in 770 ml. of methanol there was added slowly with cooling 106.2 g. (0.585 mole) of 2-[beta-(acetylmercapto)ethyl]pyridine. A mild evolution of heat occurred and the temperature reached 45°C. After standing for 20 minutes a 1 ml. aliquot portion was titrated with iodine and showed that 66% of the free thiol had been liberated. The solution was allowed to stand overnight, and then 1.45 moles of sodium methylate was added with

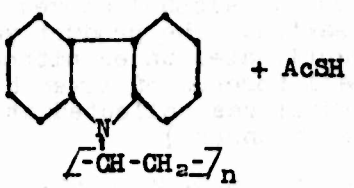
stirring. The resulting sodium chloride precipitate was filtered off, and the bulk of the methanol solvent was removed by passing the filtrate through a stripping still. The stripped residue was distilled through a precision column under nitrogen and 20 g. of pure 2-(beta-mercaptoethyl)-pyridine was obtained, (b.p. 94°/7 mm.).

Analysis: Calc'd. for C_7H_9NS: N, 10.08; S, 23.00.
Found: N, 10.91; S (SH) 23.0; S (Total) 22.20.

2. Attempted Application to 9-Vinylcarbazole

Thioacetic acid added quantitatively to 9-vinylcarbazole to give the desired thiolacetate, but unexpectedly, the latter split out thioacetic acid when subjected to methanolysis conditions. Several attempts were made to conduct the methanolysis in such a way as to avoid the split but none was successful. The reactions involved are:





9-/beta-(Acetylmercapto)ethyl/carbazole (N.B. 5760-82, 84)

A 500 ml. round bottom 3-neck flask was fitted with a stirrer and low temperature thermometer and in it was placed 76 g. (1.00 mole) of thioacetic acid. The contents were chilled to -10°C., and finally powdered 9-vinylcarbazole was added in 1 to 2 g. portions. The temperature rose gradually to 40°C. where it was maintained by cooling. The reaction mixture began to thicken when the carbazole addition was nearly complete. When 171 g. (0.89 mole) of 9-vinyl carbazole

had been added, the entire mixture became virtually solid. At this point, 250 ml. of 2B ethanol was added; the reaction mixture was heated to reflux, and filtered hot through a steam-jacketed Buchner funnel. The filtrate was cooled in tap water with agitation. After standing overnight in the cold, the solid product was filtered and washed three times with 2B ethanol. The product, which was carefully dried over a mixture of soda lime and caustic in a vacuum desiccator, weighed 235 g. (98.6% of theory) and melted at 83-93°C.

Analysis: Calc'd. for $C_{16}H_{15}ONS$: N, 5.58;
Found: N, 5.85, 6.05 (Dumas).

The attempts at methanolysis are described in N.B. 5760-91.

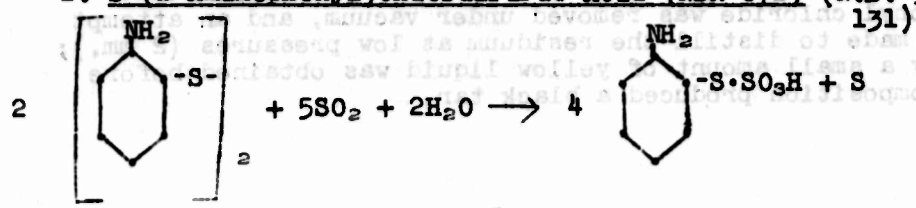
F. Miscellaneous Sulfhydryl Preparations

1. Dimercaptothiodiazole (NDR-610) (N.B. 5321-175)

The directions of Dubsky and Okac [Zeit. Anal. Chem., 96, 268 (1934)] were modified slightly to permit the substitution of hydrazine hydrate for the sulfate in this preparation. Thirty-five grams of 85% hydrazine hydrate, 60 g. of carbon disulfide, 300 cc. of water and 100 cc. of ethanol were mixed in a 1-liter, round-bottomed flask. A solution of 20 g. of sodium hydroxide in 80 cc. of water was added carefully to the stirred solution, some heat being generated during this addition. The reaction mixture which consisted of two layers, was refluxed carefully for about three hours after the lower layer had disappeared. At the end of this time, the solution was cooled and acidified with a large excess of conc. HCl. A white, voluminous precipitate separated. The dried solid, 30 g. which had turned slightly yellow upon standing, was recrystallized from ethyl acetate to yield 11 g. of large, yellow crystals, m.p. 163°C. with decomposition.

Analysis: Calc'd. for $C_2H_2N_2S_3$: S, 64.22; S(H), 42.7; C, 15.99; H, 1.4, 1.34; N, 18.65.
Found: S, 64.73; S(H), 43.0; C, 16.14, 16.06; H, 1.18, 1.59; N, 18.35.

2. S-(2-Aminophenyl)thiosulfuric Acid (NDR-672) (N.B. 5422-131)

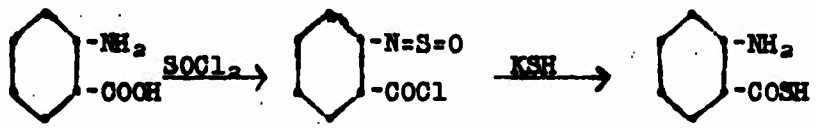


This preparation was adapted from the patent literature /Clayton Aniline Co., German Patent 120,5047 wherein 20 g. of bis-(2-aminophenyl)disulfide was suspended in 200 cc. of water and the solution was then saturated with sulfur dioxide. Most of the solid dissolved, and the remaining suspended matter was filtered while the solution was still warm as a result of the slightly exothermic reaction. Upon cooling, yellow flakes or needles separated (18 g.). The product was purified by extracting the dried crude crystals with methanol and precipitating the acid by the addition of ether. Twelve grams of white silky needles of indefinite melting point was recovered.

Analysis: Calc'd. for $C_6H_7O_2NS_2$: S, 31.21; N, 6.82.
Found: S, 29.12, 29.03; N, 6.56.

3. 2-Aminothiolbenzoic Acid - Attempted Synthesis

It was felt that the above compound might be therapeutically active; the following synthesis was proposed:



The intermediate had been prepared by Graf and Langer (J. prakt. Chem. 148, 161 (1937)). Difficulty was encountered in obtaining the yields reported, and the small amount of o-(thionamino)benzoyl chloride obtained reacted almost explosively with KSH to yield a solid compound devoid of N. (N.B. 5291-114)

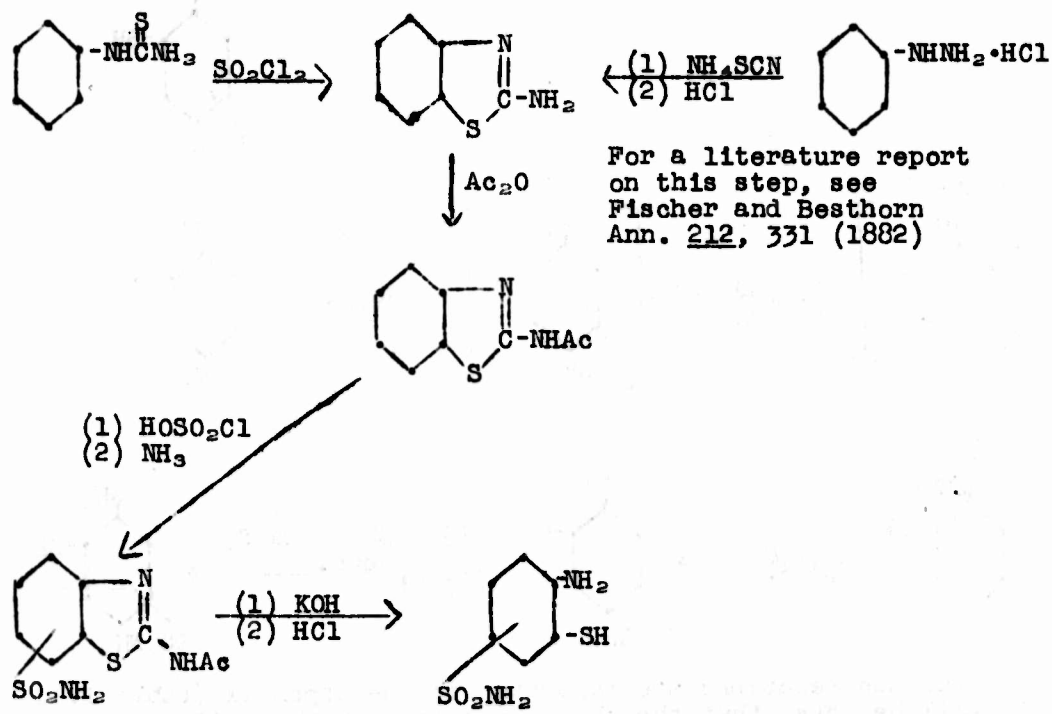
o-(Thionamino)benzoyl Chloride (N.B. 5290-105, 106)

Finely powdered anthranilic acid (50.0 g.) and 350 ml. thionyl chloride were mixed in a 1-liter still pot attached to a ground glass joint condenser carrying an efficient stirrer. The reactants were heated on the steam bath with stirring, causing the evolution of much HCl and SO_2. After 30 minutes refluxing, the solid was completely dissolved and the condenser was replaced by a still head. Thionyl chloride was removed under vacuum, and an attempt was made to distill the residuum at low pressures (2 mm.); only a small amount of yellow liquid was obtained before decomposition produced a black tar.

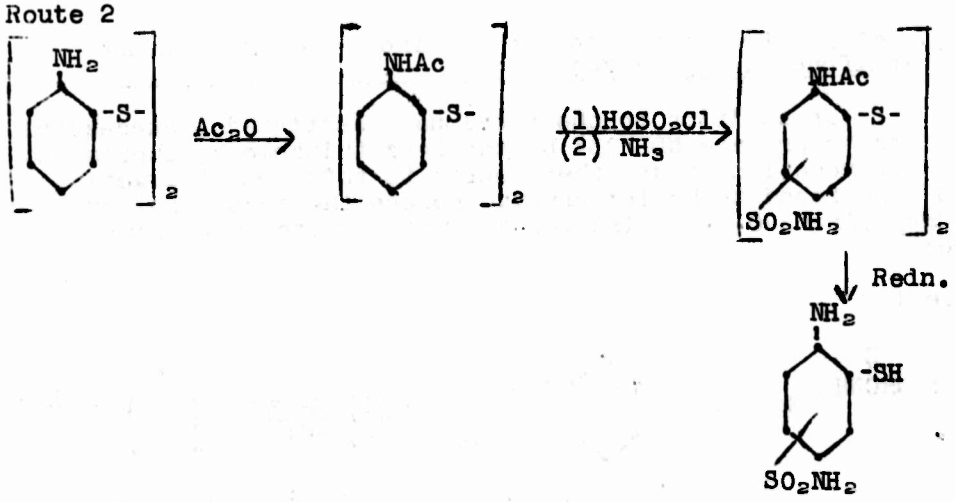
4. Early Attempts to Prepare 4-Amino-3-mercaptobenzenesulfonamide (NDR-734)

In addition to the previously mentioned unsuccessful attempts to prepare NDR-734 by the benzothiazole synthesis and the Herz reaction, four other routes to this compound were tried and found to be inoperative before the successful procedure using RuO_2 was discovered. These routes are shown here:

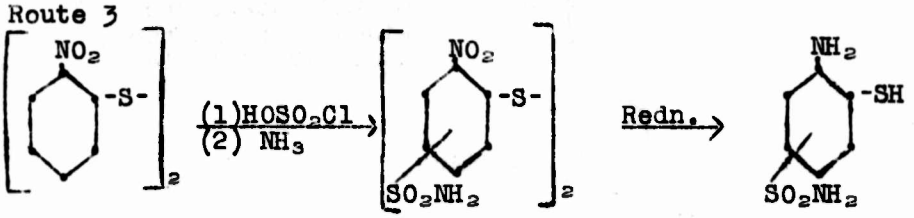
Route 1



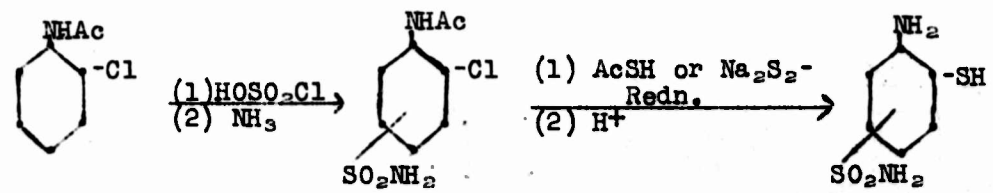
Route 2



Route 3



Route 4



The various reactions are tabulated in the appendix (Table IV). It will be noted that the above reaction schemes failed at the following steps: Route I was invalidated in the final step where the sulfonamide was hydrolyzed by the 50% caustic. Route II failed in the treatment with ammonia, while III and IV both failed to chlorosulfonate smoothly.

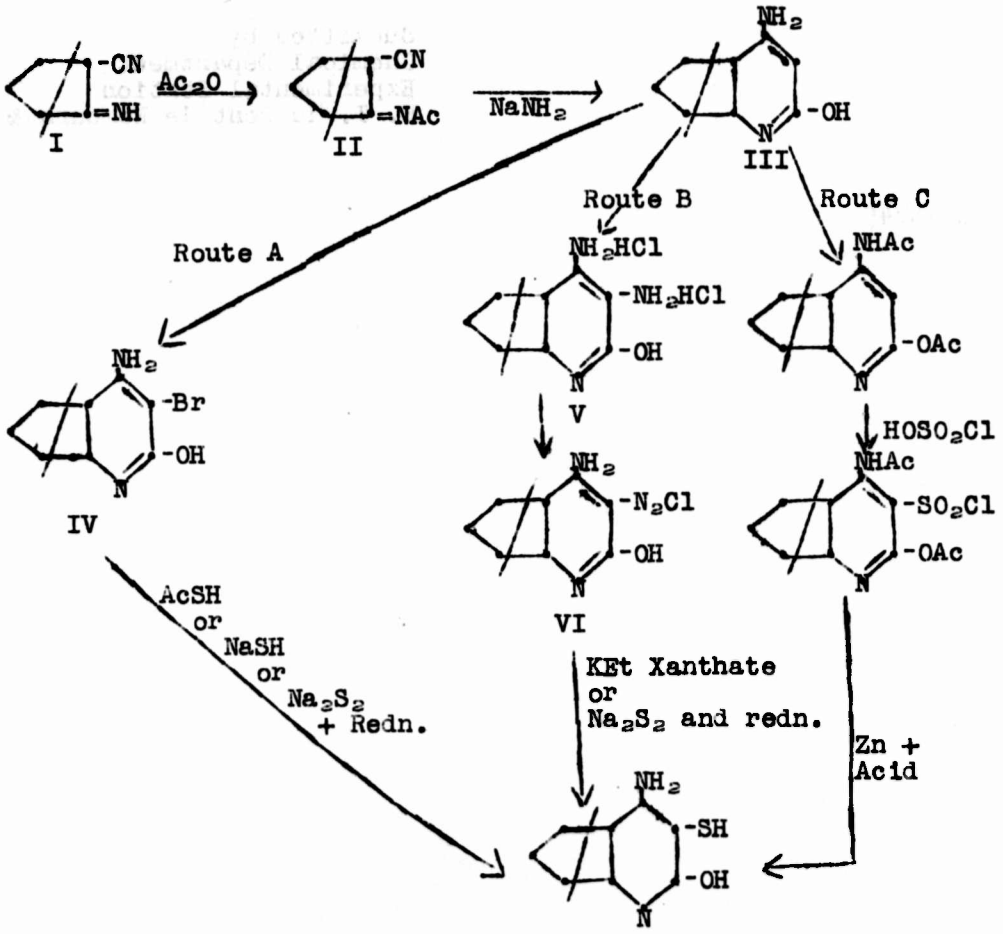
5. Attempts to Prepare 4-Amino-2-hydroxy-3-mercapto-5,6-dihydropyrindene

It was felt that this vicinal aminothiol might be obtained by clean-cut reactions from 1-imino-2-cyanocyclopentane. In the following syntheses, route A was thoroughly

explored and found to be inoperative, since sulfur was not introduced by any of the reagents tested. Other more elaborate routes (B) and (C) also failed to accomplish the desired result. Compounds I-VII are all previously known, and their preparation will not be described. (N.B. 5376-101 to 130).

Chart III

Routes to 4-Amino-2-hydroxy-3-mercapto-5,6-dihydropyrindene



A summary of the various unsuccessful thionations and acetylations will be found in Table V of the appendix.

6. Attempted Alkylation of o-Aminobenzenethiol Derivatives

It was considered theoretically important at one stage of the work to prepare an N-alkylated o-aminobenzenethiol. Several efforts were made in this direction but no products of interest were isolated. The outcome of these runs is presented in Table VI of the appendix.

Submitted by
Chemical Department
Experimental Station
E. I. du Pont de Nemours & Co.

10/3/45

Index of Compounds

An index of all aromatic aminothiol candidate compounds and intermediates synthesized during the period from July 21, 1943 to September 1, 1945, has been prepared and is to be found in the appendix. All those which have been submitted to CMR investigators for evaluation have been designed by their NDR code number, and the date of transmittal has been indicated.

The classes of compounds are as follows:

1. Aromatic Aminothiols
2. Benzothiazole Derivatives
3. Thiourea Derivatives
4. Aromatic Amines
5. Nitroesters
6. Nitrodisulfides
7. Aminodisulfides
8. Thiolacetates
9. Pyrindene Intermediates
10. Miscellaneous Compounds

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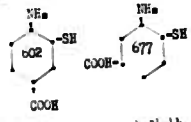
INDEX OF COMPOUNDS SYNTHESIZED

1. Aromatic Thiols



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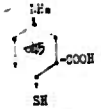
12-15-43
4-14-44
5-8-44

4-14-44



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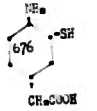

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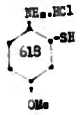

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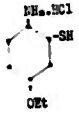

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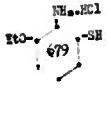

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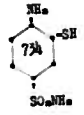

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8-3-45

6-6-45

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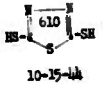

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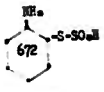

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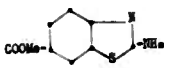
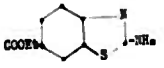
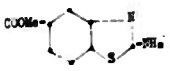
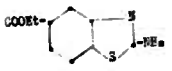
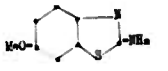
2. Benzothiazoles

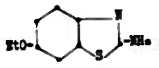


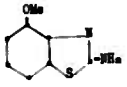


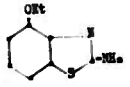


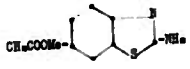


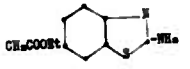


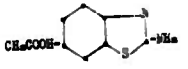


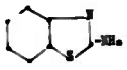


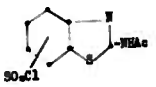












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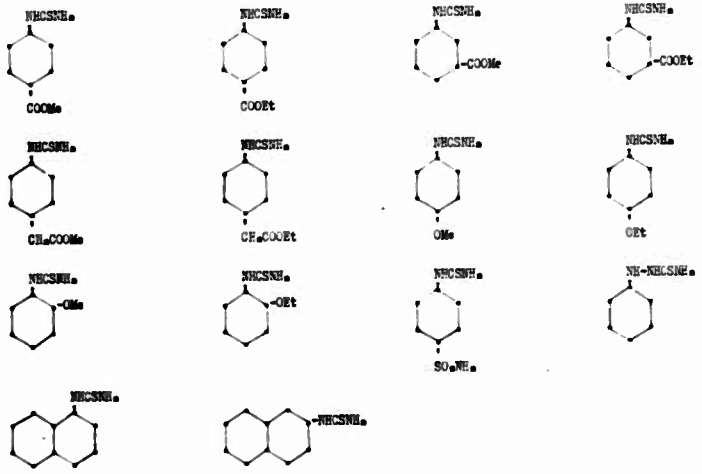
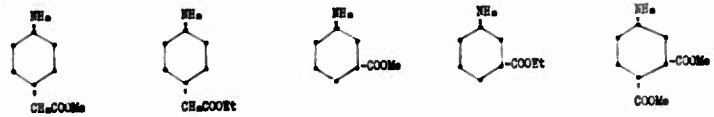
3. Thiourea Derivatives



4. Amines

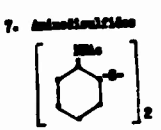
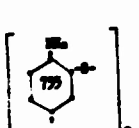


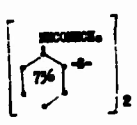
5. Nitroesters

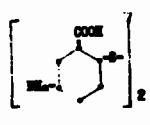
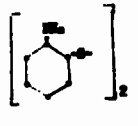
6. Nitrodisulfides

INDEX OF COMPOUNDS SYNTHESIZED CONT'D.

7. Aminothiolides



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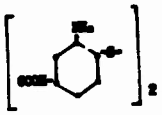
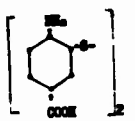
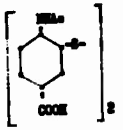
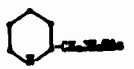
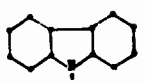




8. Thiaindenes

9. Pyridone Intermediates

10. Miscellaneous Compounds

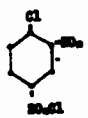
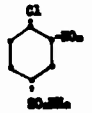
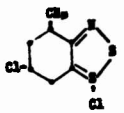




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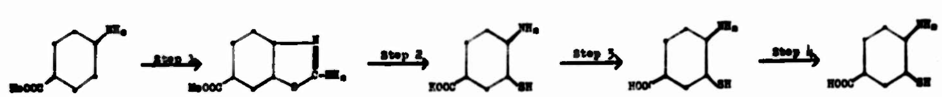
TABLE I

DETAILS ON TWENTY PREPARATIONS OF MDR-602

Notebook Reference	Moles of Starting Material	Moles of Benzo-thiazole	% Yield for Step 1	Moles of 602 after Step 2	% Yield for Step 2	Moles of 602 after Step 3	% Yield for Step 3	Moles of 602 after Step 4	% Yield for Step 4	Purity of 602 (Thiol Titration)	Melting Point (uncorr.)	Overall Yield (Steps 1-4)	Comments
5291-50, 52	0.63	0.180	28	0.162	90	-	-	0.038	25*	93	191-4	6	Ethyl ester used. Low step 1 because H_2O extraction insufficient. Wet Cl extraction
" -58	1.00	0.210	27	-	-	0.140	67*	0.112	80	99.5	193-6	11	Ethyl ester used. Low step 1 because H_2O extraction insufficient. Soxhlet used (Step 4)
" -109, 113	2.00	0.716	56	-	-	0.027	4*	0.0	0	-	-	0	Ethyl ester used. Extensive loss by oxidation.
" -116, 119	2.00	0.630	32	0.219	35	-	-	0.156	62*	99	-	7	Ethyl ester used. Filtered at pH 6 in Step 2.
" -122, 133	1.00	0.374	37	0.252	68	0.240	95	0.165	69	99	-	17	Ethyl ester used. Filtered at pH 12 in Step 2. Combined with 5291-123 after Step 2.
" -123, 133	1.00	0.373	57	0.400	74	0.380	95	0.263	69	99	-	26	
" -140, 180	1.00	0.338	34	0.750	73	0.305	41	0.168	55	99	192-6	13	Gum formed in Step 1. Combined with 5291-159 after Step 1.
" -159, 180	1.00	0.760	76										
5760-4, 11	2.00	1.491	75	1.250	84	1.020	82	0.339	33	95	189-93	17	
" -8, 12	1.00	-	-	0.440	44*	0.407	33	0.300	74	93	187-91	30	
" -9, 14	1.00	0.300	30	-	-	0.148	30 *	0.140	95	87	182-187	8	Ethyl ester used. Combined with 5760-10 after Step 1.
" -10, 14	1.00	0.200	20	-	-								
" -18	1.00	0.520	52	0.266	51	0.216	81	0.173	80	78	-	17	Methyl ester HCl used (Impure).
" -19	1.00	0.453	45	0.220	49	0.166	76	0.122	74	51	-	12	Methyl ester HCl used.
" -20	1.00	0.582	58	0.370	64	0.266	72	0.248	93	85	177-85	25	Methyl ester HCl used.
" -21	1.00	0.675	68	0.415	62	0.383	93	0.382	99	80	-	38	Methyl ester HCl used.
" -63	1.00	-	-	0.480	48*	0.376	79	0.274	73	87	-	27	
" -76	1.00	0.650	65	-	-	0.320	49*	0.169	53	95	193-5	17	Lost consid[redacted]le in Step 3 by spilling.
" -79	-	-	-	-	-	0.080	-	0.046	57	92	191-3	-	2-Amino-6-b[redacted]thiazo[redacted]acid used.
" -80	1.00	-	-	-	-	0.370	57*	0.176	51	92	192-4	18	

* Indicates yield calculated over more than one step.



(Crude) (MDR-602)

MDV:md
10/3/44

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TABLE II

SYNTHESIS OF ETHER-SUBSTITUTED VICINAL AMINOTHIOLS

Notebook References	Amine Used	Melting Point of Thiourea	Yield of Benzothiazole	Melting Point of Benzothiazole	Conversion of Benzothiazole to Thiol Hydrochloride	Purity of Crude Thiol Hydrochloride	Comments
5290-84, 87 (also 73, 74)	p-Anisidine	204	31%	145-150	35%	63%	Analyzed benzothiazole; checked (N.B. 5291-63).
5290-69, 95 (also 61-4, 70, 83, 86, 92)	p-Phenetidine	164	49%	152-154	44%	54%	
5290-71, 85, 88 (also 53, 94, 60, 69)	o-Anisidine	150-152	11%	135-140	12%	34%	
5290-100, 112, 174	o-Phenetidine	118-122	8%	Not taken	59%	77%	Analyzed benzothiazole; fair check (N.B. 5291-112)

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TABLE II

SYNTHESIS OF ETHER-SUBSTITUTED VICINAL AMINOTHIOLS

Notebook References	Amine Used	Melting Point of Thiourea	Yield of Benzothiazole	Melting Point of Benzothiazole	Conversion of Benzothiazole to Thiol Hydrochloride	Purity of Crude Thiol Hydrochloride	Comments
5290-84, 87 (also 75, 74)	p-Anisidine	204	31%	145-150	35%	63%	
5290-69, 95 (also 61-4, 70, 85, 96, 92)	p-Phenetidine	164	49%	152-154	44%	54%	Analysed benzothiazole; checked (N.B. 5291-63).
5290-71, 85, 88 (also 53, 94, 60, 69)	o-Anisidine	150-152	11%	135-140	12%	34%	
5290-100, 112, 174	o-Phenetidine	118-122	8%	Not taken	59%	77%	Analysed benzothiazole; fair check (N.B. 5291-112)

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TABLE III

BENZOTHIAZOLE SYNTHESIS: INOPERATIVE AMINES

Notebook Reference	Starting Material (A)	Ultimate Objective	Behavior of Sulfuric Acid (A)	Behavior of (B) with Sodium Thiocyanate	Melting Point of Thiourea (C)	Behavior of (C) with Sulfuryl Chloride	Comments
5291-75	α-Naphthylamine	1-Amino-2-naphthalenethiol	Formed crystalline sulfate (B)	Smooth reaction to (C) thiourea	186°	Formed orange resin	No benzothiazole obtained.
5291-77	β-Naphthylamine	2-Amino-3-naphthalenethiol	" " "	Apparently smooth reaction	195-210	" " "	" " "
5291-127	Benzylamine	2-Aminomethylbenzenethiol	" " "	No evidence of reaction	-	Had polymeric mass	" " "
5291-132	Ethyl Anthranilate	2-Amino-3-mercaptobenzoic Acid	" " "	Formed unknown product	>240° (not a thiourea)	Yellow plastic material	No benzothiazole obtained on extracting plastic mass with H_2O. Methyl anthranilate odor.
5291-149, 150, 156	Methyl "	" "	" " "	" " "	>240° (" " ")	" " "	No benzothiazole. Anthranilate odor. Sample of acetone extracted solid analyzed. No light cast on product.
5291-158	" "	" "	" " "	" " "	>240° (" " ")	Not tested.	Sample of (B) analyzed. High in both N,S for thiourea.
5291-169	" "	" "	" " "	" " "	>240°		Sample of (B) analyzed. High in N, low in S; 43% Ash. (Probably sulfate salt).
5291-154	Dimethyl-4-Aminophthalate	4-Amino-5-mercaptophthalic Acid	Formed amorphous mass	Had oil formed	-	Not tested	
5760-7	" "	" "	" white gum	Yellow plastic mass	-	" "	
5760-24	" "	" "	The crystalline hydrochloride was prepared	" " "	-	" "	
5291-79, 80	p-Aminobenzenesulfonamide	4-Amino-3-mercaptobenzene-sulfonamide	Crystalline ppt.	White crystalline material	198°	No apparent reaction	No benzothiazole formed. (B) may have been impure sulfate salt of A, or the thiourea.
5291-185, 190	"	"	Dil. H_2SO_4 --> Sulfate m.p. 225-7	" " "	210-214	" " "	No benzothiazole formed. No heat effect with SO_2Cl_2. White product m.p. 208-209. Impure C perhaps.
5760-39, 46, 56	"	"	" " " "	" " "	>240	" " "	No benzothiazole formed. Material C definitely not sulfanilamide. Analysis checks for thiourea.

TABLE IV

EFFORTS TO OBTAIN AN AMINO-MERCAPTO-BENZENESULFONAMIDE

Notebook Reference	Starting Material	Quantity	Reagents	Quantity	Solvent	Temperature	Time	Objective	Results
5422-161	N-Phenylthiourea	0.735 mols	Sulfuryl chloride	0.93 mols	Chlorobenzene	50	2 hrs.	2-Aminobenzothiazole	0.35 mols desired of product; m.p. 102-110°.
5422-173	Phenylhydrazine·HCl	2.88 mols	Ammonium thiocyanate	5.50 mols	MeOH	Reflux	12 hrs.	Phenyl Thiosemiarbazide	1.43 mols of desired product.
5422-175	Phenylthiosemicarbazide	1.43 mols	Conc. HCl	600 ml.	None	"	12 hrs.	2-Aminobenzothiazole	89 g. obtained. m.p. 126-7°
5422-179, 165	2-Aminobenzothiazole	89 g.	Acetic anhydride (H_2SO_4 catalyst)	300 ml.	None	"	1-1/2 h.	2-(Acetylamino)benzothiazole	90 g. of MeOH-recrystallized product obtained. m.p. 188°.
5422-167	2-(Acetylamino)benzothiazole	14 g.	Chlorosulfonic Acid	52 g.	None	70°	"	Chlorosulfonation	Reaction took place. HCl evolved. Pouring on ice gave white solid.
5422-167	Chlorosulfonated product	-	Ammonia (conc.)	100 ml.	None	25°	1/2 hr.	2-(Acetylamino)-6-benzothiazole sulfonamide	Obtained product or its isomer. Analysis checked.
5422-171	Previous product	4.8 g.	50% KOH	25 ml.	None	Reflux	5 hrs.	4-Amino-3-mercaptobenzene sulfonamide	Acidification gave no -SH containing ppt.
5422-162	2-Aminobenzothiazole	10 g.	Dilute H_2SO_4	175 ml.	None	80	30 min.	Sulfate salt	Obtained sulfate on cooling soln. 11 g. mp 189°.
5422-164	2-Aminobenzothiazole sulfate	10 g.	Chlorosulfonic acid	27 g.	None	50°	2 hrs.	To obtain sulfonylchloride	Obtained a solid on pouring on ice, but only a gum when treated with alcoholic ammonia. Not satisfactory.
5422-137	2,2'-Dithiobisaniline	6.2 g.	Acetic anhydride	6.0 g.	None	60°	15 min.	2,2'-Dithiobis(acetanilide)	5.5 g. of desired derivative, m.p 155-160.
5422-140	2,2'-Dithiobis(acetanilide)	33.2 g.	Chlorosulfonic acid	220 g.	None	60°	1 hr.	To obtain sulfonylchloride	29 g. of green powder. Failed to give a sulfonamide with NH_3.
5422-151	2,2'-Dithiobis(nitrobenzene)	5 g.	" "	35 ml.	None	25°	2 hrs.	" "	Failed to chlorosulfonate.
5422-139, 135	o-Chloroacetanilide	10 g.	" "	50 ml.	None	115°	1 hr.	" "	Obtained gummy unpromising mass; which gave little or no sulfonamide. Failed to react at 70°.

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TABLE V

ATTEMPTS TO PREPARE 4-AMINO-2-HYDROXY-3-MERCAPTO-5,6-DIHYDROPYRIMIDINE

Notebook Reference	Starting Material	Thionating Agent	Solvent	Temperature	Time	Result
5376-107	4-Amino-3-bromo-2-hydroxy-5,6-dihydropyrimidine	Thioacetic acid	HOAc	90° briefly	4 de. at 25°	White crystals; m.p. 191°C. Contained no S.
-109	"	" "	"	"	"	
-111	"	" "	"	25	24 hrs.	Crystals. These were neutralized with NH_3. Resulting product on methanolysis contained no S.
-113	"	" "	"	100	4 "	Methanolysis of product yielded ppd. containing no S.
-102	"	Thioacetic acid + pyridine	Dioxane	25	7 days	No sulfur in product.
-106	"	" " "	"	25	2 "	Solid ppt'd. Neutralized with NH_3. Resulting product on methanolysis contained no S.
-124	"	" " "	HOAc	25	28 hrs.	Needles containing no sulfur.
5422-138		NaSH	Absolute ethanol	90	2 "	No sulfur introduced
-132	4-Acetylamino-2-acetoxy-5,6-dihydropyrimidene	Na_2S_2	Water	50	1/4 hr.	No reaction
-132	"	Ac_2O (to acetylate before thionating)	None	50	"	Starting material recovered unchanged
-132	"	Ac_2O + H_2SO_4 (cat.)	"	50	"	" " " "
-132	"	Ac_2O & H_3PO_4 (cat.)	"	50	"	" " " "
-132	"	Ac_2O	AcOH	100	1 hr.	" " " "
-153	4-Amino-2-hydroxy-5,6-dihydro-4-pyrimidene diazonium chloride	Ac_2O	AcOH	100	6 hrs.	Yellow gum formed. Treatment of gum with hot KOH yielded no thiol.
		Potassium ethyl xanthate	Water	25	1/2 hr.	Infusible, insoluble mass. High (36%) S; low (4%) N; reduced with Zn + HOAc; no thiol.
-146, 147	"	Na_2S_2	Dilute HCl	5	"	Brown, friable mass.
-155	"	"	" "	-10	2 hrs.	A water-soluble salt formed. Treated with Zn + H_2SO_4. No thiol formed.
-158	4-Acetylamino-2-acetoxy-5,6-dihydropyrimidene	Chlorosulfonic acid	None	60	"	

TABLE VI

ALKYLATIONS OF o-AMINOBENZENETHIOL DERIVATIVES

Notebook Reference	Starting Material and Quantity	Alkylating Agent and Quantity	Quantity of NaOH Used	Temperature	Solvent	Result
5422-143	2,2'-Dithiobisanilino 0.01 mole	Diethyl sulfate 0.06 mole	0.04 mole	60°	None	Titration indicated that some alkylation had occurred. No pure product isolated.
-145	" "	Methyl Iodide 0.04 "	0.04 "	25 (sealed tube)	"	Dark gum formed. Cleavage of S-S indicated.
-166	" 0.10 mole	Methyl chloride 30 p.s.i.	0.40 "	65	80 ml. xylene 80 ml. H_2O	No evidence of alkylation.

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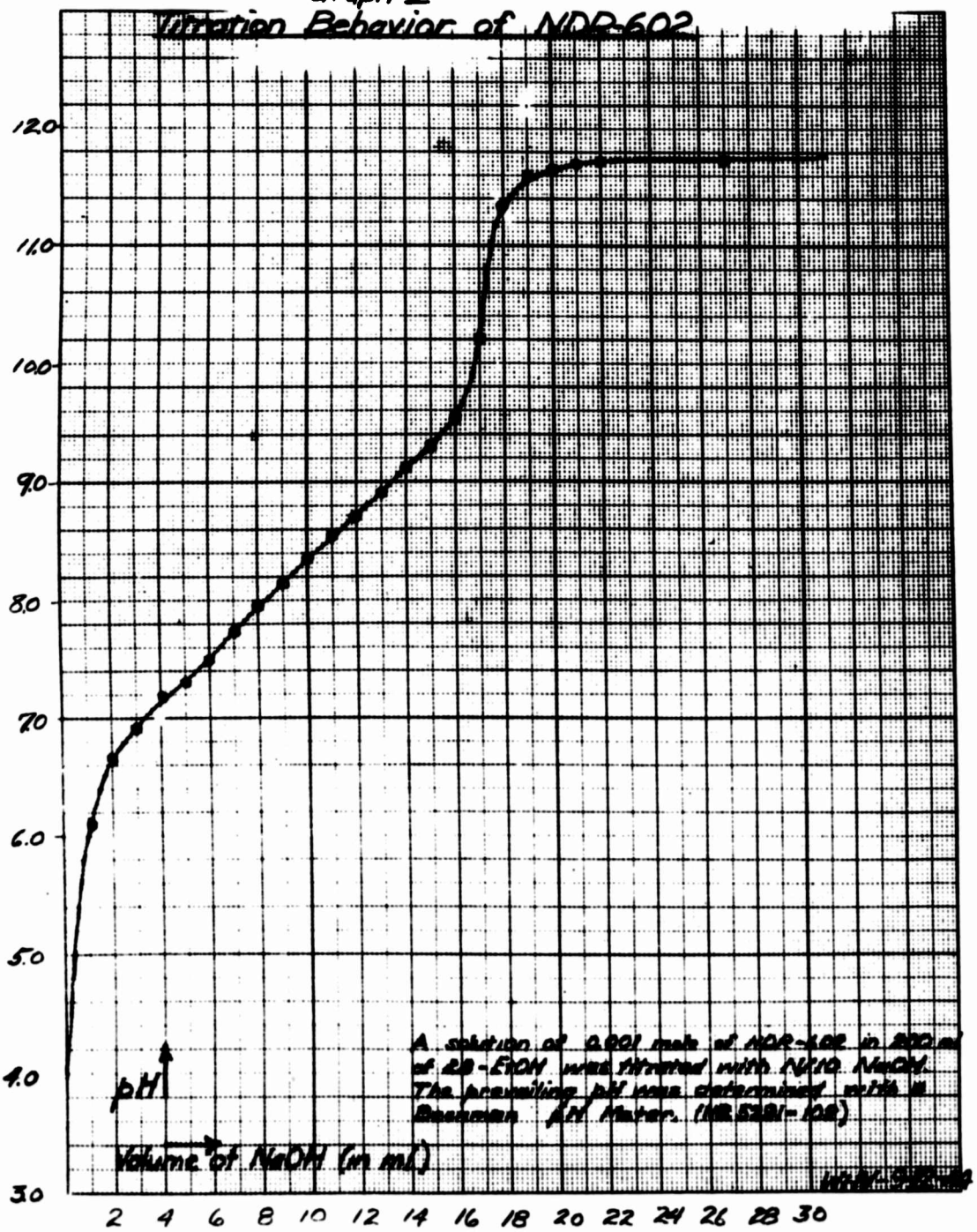
Graph I

Titration Behavior of NDR-602



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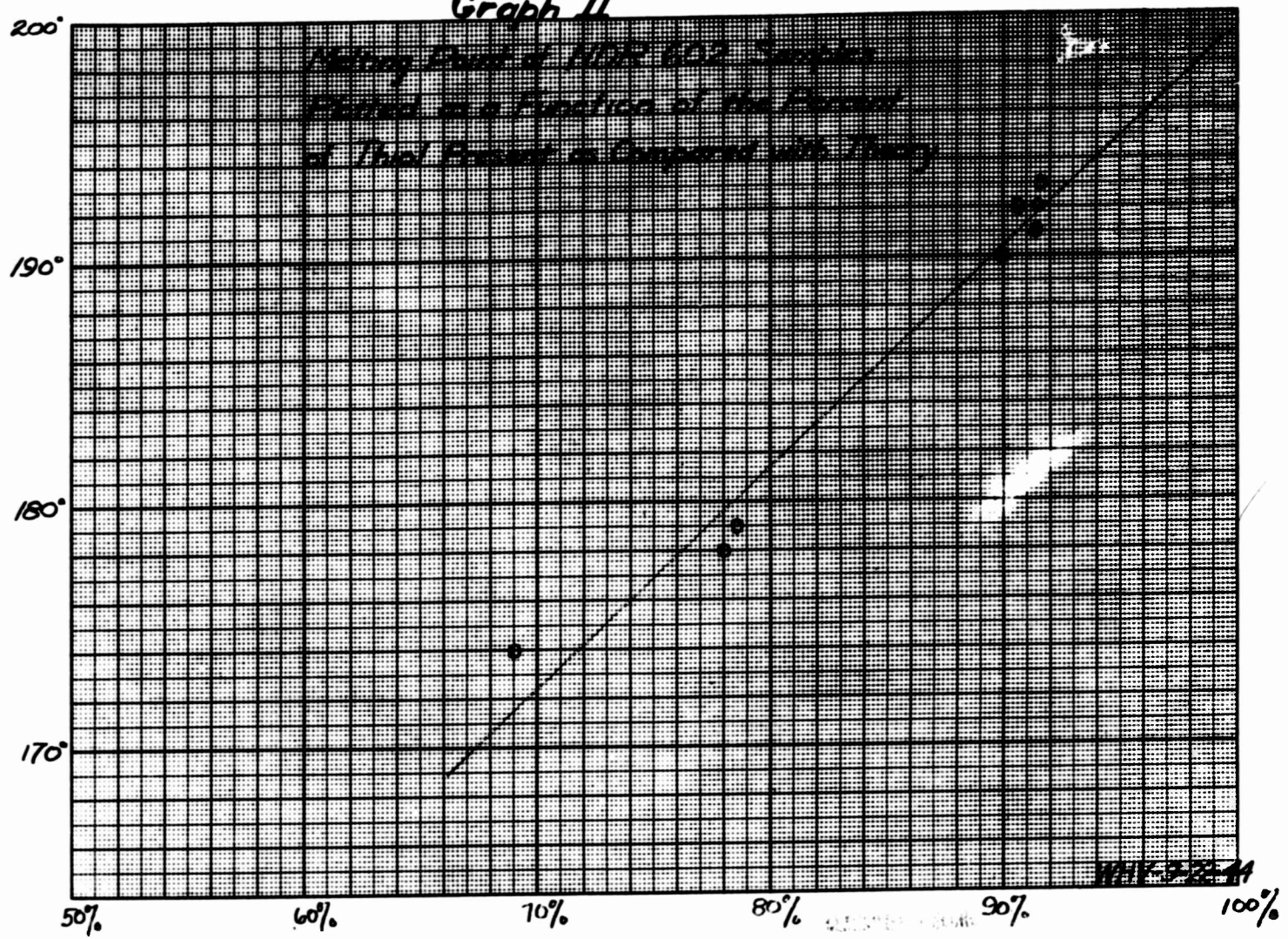
Graph II



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ABSTRACT:

Work was done on the preparation of derivatives and analogues of o-aminobenzenethiol which bear substituents calculated to reduce the toxicity of the parent compound without loss of therapeutic efficiency. Fourteen candidate compounds were synthesized to CMR for evaluation; the majority of these were difficultly accessible derivatives of o-aminobenzenethiol. Of the candidates submitted, 4-amino-3-mercaptobenzoic acid and its ethyl ester hydrochloride were reported to have decontaminating powers for splashes of mustard gas and the nitrogen mustards in the eyes of test animals (rabbits). The synthesis of appropriately substituted aminobenzenethiols from the corresponding 2-aminobenzothiazoles has been shown to be a valuable synthetic tool.

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