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Selected Nitrophenols, Nitrophenol Ethers and Related Compounds of the Benzene Series together with Analogous Compounds in the Pyridine Series

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Selected Nitrophenols, Nitrophenol Ethers and Related Compounds of the Benzene Series together with Analogous Compounds in the Pyridine Series

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Table of Contents

INTRODUCTION

Substantial progress has been made toward completing the series of phenols and related compounds that were to be prepared in this laboratory. The compounds which have been made are listed in the Table of Contents.

Improved procedures for the preparation of 3,5-bis-(dimethylcarbamyloxy)-nitrobenzene and 3-hydroxy -5-dimethylcarbamyloxynitrobenzene are included in this report.

In addition, a start has been made on the preparation of pyridine analogues of the benzene derivatives previously made.

PREPARATION OF 3,5-bis-(DIMETHYLCARBAMYLOXY)-NITROBENZENE

Although the reaction of 5-nitroresorcinol with dimethylcarbamyl chloride has been described in previous reports, it has been carried out, during the period covered by this report, on a much larger scale. The details, therefore, are worth describing.

In a 2-liter flask equipped with a magnetic stirring bar, a reflux condenser, and a dropping funnel was combined 77.4g.(0.500 mole) of 5-nitroresorcinol and 1550 ml. of pyridine. When solution was complete, 146g. (1.36 moles) of dimethylcarbamyl chloride was added all at once. The temperature of the stirred reaction mixture rose spontaneously from 26° to 38° in twenty-five minutes. When the temperature remained constant, the reaction mixture was refluxed for one hour at 115°.

The hot reaction mixture was poured onto about 600 g. of crushed ice, and a white precipitate formed gradually as the ice melted. The solid was collected on a Büchner funnel and washed thoroughly with water. Evaporation of the reaction mother liquor yielded more crude product. After drying all of the isolated solid in a calcium chloride-charged desiccator, it was dissolved in 900 ml. of ethanol, treated with charcoal, and filtered. On cooling, the solution yielded 106g. of 3,5-bis-(dimethylcarbamyloxy)-nitrobenzene (m. p. 110-111°).

Distillation of the recrystallization mother liquor to about one-third of its volume yielded an additional 9.8g. of product. The total yield, therefore, was 116g which is 78% of the theoretical amount.

PREPARATION OF 3-HYDROXY-5- DIMETHYLCARBAMYLOXY-NITROBENZENE

In a 2-liter Erlenmeyer flask was combined 50 g. (0.168 mole) of 3, 5-bis-(dimethylcarbamyloxy)-nitrobenzene and 1000 ml. of absolute methanol. The mixture was warmed on a hot plate until solution was effected, and a solution consisting of 9.5 g. (0.170 mole) of potassium hydroxide pellets dissolved in 100 ml. of methanol was added rapidly with stirring. The reaction mixture was warmed until the first indications of refluxing occurred, and this stage was maintained for one hour. The solution turned from slightly yellow to dark red-orange during the course of the heating.

The reaction mixture was stripped of solvent by flash distillation under water pump vacuum, a dark red, gummy residue forming in the boiling flask. The solid was washed with five 100-ml. portions of water, and each portion was filtered. The white solid material which was collected in the funnel weighed 4.57g. and melted at 107-8° (starting material: 110-111°). This reduced the amount of starting material on which a yield may be based to 45.43g. (0.153 mole).

The dark red filtrate was acidified in the cold with concentrated hydrochloric acid. This resulted in the formation of a tan precipitate. After filtering the mixture, the solid was recrystallized from 50 ml. of ethanol. The dried precipitate weighed 23.7g. (68.5% based on recovered starting material) and melted at 152-3°.

PREPARATION OF 1-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-7- BROMOHEPTANE

To a 125-ml. Erleymeyer flask containing a magnetic stirring bar was added 5.00g. (0.0194 mole) of 1,7-dibromo-heptane. The flask was equipped with a parallel arm adapter, a reflux condenser, and a dropping funnel; and a combination heater-magnetic stirrer was used as the source of heat and stirring. A sodium ethoxide solution was prepared by adding 0.22g. (0.00970g-atom) of sodium metal to 50 ml. of absolute ethanol, and when the sodium had all reacted, 2.19g. (0.00970g-atom) of 3-nitro-5-dimethylcarbamyloxyphenol was added to form the alcohol soluble sodium salt.

After heating the 1,7-dibromoheptane to the point of reflux, the alcoholic solution of the sodium phenoxide was added dropwise and with stirring. Refluxing was continued for about four hours, during which time a precipitate formed. The reaction mixture was allowed to cool to room temperature, and then it was filtered. The filtrate was evaporated to dryness under water-pump vacuum, and a viscous oily residue was isolated. By adding portions of petroleum ether to the residue and refluxing the mixture for about one-half hour, a white crystalline solid was isolated on cooling the extracts in a refrigerator. In this manner a total of 3.5g of white solid was obtained. Methanolic recrystallization of the first extract yielded 0.7g of needles melting at 63.5-64.5°. Later extracts yielded a total of 1.5g of solid when recrystallized from methanol, but the melting range was 53-60°. A second recrystallization yielded 1.3g., m.p. 58-61°.

PREPARATION OF 1,7-bis(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-HEPTANE

In view of the fact that the commercial 1,7-dibromoheptane (Edcan Laboratories) was found to have a strong hydroxyl band as shown by infra red absorption, it was necessary to remove the alcohol impurity. Fractional distillation was not defeasible, but the following procedure gave good results.

The dihalide was treated with cold concentrated sulfuric acid in a separatory funnel. The cold heterogeneous mixture was vigorously mixed and allowed to settle. The lower layer, a light brown liquid which contains the acid soluble alcohol, was drawn off. The upper layer, a clear, colorless liquid, was washed with several portions of 5% sodium bicarbonate solution. The clear, colorless organic liquid (dihalide) was dissolved in ether and the ether layer washed several times with distilled water. The ether layer was dried for 24 hours over anhydrous magnesium carbonate.

The ether layer was separated from the magnesium carbonate by filtration and the bulk of the ether was evaporated under reduced pressure (aspirator). The clear colorless liquid was placed in a one-piece distilling unit containing a six inch Vigreux column. The liquid was distilled under reduced pressure (0.05 - 0.06 mm.). Only one fraction was noticed, distilling at 65-66° (oil bath 93-97°). An infra red spectrum showed no hydroxyl absorption in the region $2.4 - 3.2\mu$. The recovery of pure 1.7-dibromoheptane was 54%.

Analysis: Calculated for $C_7H_{14}Br_2$: C 32.59, H 5.47, Br 61.95

Found: C 32.86, H 5.59, Br 61.75

In a 500 ml. 3-necked, round-bottomed flask fitted with a reflux condenser, (connected to a calcium chloride drying tube) dropping funnel, and a magnetic stirring egg, was placed 14.1g. (0.064 mole) of 3-dimethylcarbamyloxy-5-nitrophenol, 8.05g. (0.0314 mole) of purified 1,7-dibromoheptane and 150 ml. of commercial absolute ethanol. The mixture was stirred and warmed by means of a heating mantle until the mixture was homogeneous (light yellow green solution).

Reagent grade sodium (1.44g., 0.0624 g-atom), freshly cut, was dissolved in 150 ml. of absolute ethanol). The sodium ethoxide solution was filtered and added dropwise to the reaction mixture. During the addition of the sodium ethoxide solution (40 minutes) the reaction mixture turned deep red. It was refluxed for 30 hours. During the reflux time the solution gradually turned orange and the pH dropped to about 7.5.

The orange solution, which contained some metallic salt precipitate, was allowed to cool to room temperature. A small amount of heavy oil formed. The oil and metallic salts were separated by suction filtration. The filtrate was allowed to stand at room temperature for 2 hours. A large amount of solid formed. On addition of one liter of cold water more precipitate formed. The precipitate was collected by suction filtration and washed on the filter with water.

The precipitate was sucked dry overnight and dissolved in 500 ml. of hot anhydrous methanol. On cooling, a small amount of oil formed. The oil was separated by decantation and the methanol solution set aside, at room temperature, overnight. A precipitate formed slowly. The methanol solution was cooled in an ice bath and the precipitate collected by suction filtration. The solid which was dried at 78° and 0.05 mm. for 5 hours, melted at 93.5 - 95.5° with previous shrinking at 91°.

Four additional recrystallizations produced a soft rosette-like white crystal (6.8g.) which, when dried at 78° and 0.05 mm. for 24 hours, melted at 94.5 - 96° with previous shrinking at 94.0°. The rosette-like crystal structure was destroyed when the mother liquor was removed. Infra red showed a carbonyl absorption at 5.78μ, due to the carbamyl group.

Analysis: Calculated for $C_{25}H_{32}N_4O_{10}$: C 54.74, H 5.88, N 10.21

Found: Found: C 54.76, H 6.02, N 10.23

Consolidation of mother liquors produced 2.0g. of product which melted at 93-96°. The total yield of product melting over the range 93-96° was 8.8g. (52%). The impure product (2.0g) was used to prepare the hydrolysis product of the above compound.

PREPARATION OF 1.7-Bis(3-NITRO-5-HYDROXYPHENOXY)-HEPTANE

In a 500 ml. 3-necked round-bottomed flask was placed 5.3g. (0.011 mole) of 1,7-bis-(3-nitro-5-dimethylcarbamyloxyphenoxy)-heptane (m.p. 93-96°) and a solution containing 5.0 g. of potassium hydroxide (Baker Analyzed), 50 ml. of ethanol and 50 ml. of distilled water. The flask was fitted with a magnetic stirrer and reflux condenser, and the heterogeneous mixture was refluxed for 3 hours. The solution, which turned deep red as refluxing started, was homogeneous in about 30 minutes.

The homogeneous, red solution was allowed to cool to room temperature. To this solution was added 100 ml. of ice-cold water and the solution was filtered. The filtrate was cooled in an ice bath and neutralized with 30% hydrochloric acid. An orange oil first formed and then a yellow precipitate was noticed. The orange oil, which soon solidified, and the yellow precipitate were collected by suction filtration and washed on the filter with 200 ml. of distilled water.

Upon recrystallization from benzene and subsequent drying, the hydrolysis product weighed 3.9g. and melted at 99-102°. Four additional crystallizations from benzene and drying at 100° and 0.05 mm. for 40 hours gave 2.8g. (68%) of yellow hydrolysis product which melted at 112.5-114.0° with previous shrinking at 110°. An infra red spectrum showed no carbonyl absorption due to the carbamyl group. A hydroxyl peak at 3.0 μ was noticed.

Analysis: Calculated for $C_{19}H_{22}N_2O_8$; C 56.153, H 5.458, N 6.895;
Found: C 56.37 , H 5.35 , N 7.06 .

PREPARATION OF 1-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-8-BROMO-OCTANE

In a 500 ml. round-bottomed flask fitted with a reflux condenser (connected to a calcium chloride drying tube), dropping funnel, and a magnetic stirring egg was placed 14.1g. (0.0624 mole) of 3-nitro-5-dimethylcarbamyloxyphenol, 20.0g. (0.0735 mole) of 1,8-dibromooctane (Edcan, freshly distilled) and 200 ml. of absolute ethanol. To this refluxing solution was added dropwise a solution containing 1.40g. (0.0624g-atom) of reagent grade sodium (freshly cut) and 100 ml. of absolute ethanol. The first precipitate of metallic salts was noted in three hours. The solution was refluxed for nine hours until the pH was 7. The reaction mixture was allowed to cool to room temperature overnight. A large amount of white solid precipitated from the reaction mixture. The precipitate was collected by suction filtration and washed on the filter with 100 ml. of distilled water and then with 25 ml. of methanol. The precipitate was set aside.

The above filtrate (including the washings) was extracted with ether, the ether layer dried over anhydrous magnesium sulfate, and the ether allowed to evaporate. A yellow-brown viscous liquid remained as a residue. This liquid was dissolved in a small amount of hot methanol, filtered, and cooled in an ice-bath. A white precipitate slowly formed. The white precipitate, which was collected by suction filtration and recrystallized from methanol, weighed 4.9g. and melted over the range 56-60°. A qualitative test showed the presence of bromine.

The original precipitate which was previously set aside was stirred vigorously with 500 ml. of a warm 95% petroleum ether -5% benzene solution. This heterogeneous mixture was filtered and the resulting insoluble white solid (m.p. range 75-90), weighed 4g. The petroleum ether-benzene solution was heated on a stem bath until the volume decreased to about 10 ml. Some white precipitate was noticed on cooling this solution. The entire contents were dissolved in a small amount of hot methanol. Upon cooling a white precipitate formed. The white precipitate which was collected by suction filtration and air dried overnight, melted at 59-61°.

The two low melting white precipitates (m.p. 56-60° and 59-61°) were combined and recrystallized from methanol. The resulting white needle crystals weighed 6.4g. (25%) and melted at 61-62°. Two additional crystallizations from methanol gave white needle crystals melting at 61-62°.

Analysis: calculated for $C_{17}H_{25}BrN_2O_5$:

C 48.93, H 6.04, Br 19.16

Found: C 49.15, H 6.02, Br 19.05

The higher melting product (m.p. 75-90°) is probably the crude di- substituted product 1,8-bis(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-OCTANE.

PREPARATION OF 1,8-bis(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-OCTANE

In a one-liter, 3-necked, round-bottomed flask fitted with a reflux condenser (connected to a calcium chloride drying tube), dropping funnel, and a magnetic stirring egg, was placed 28.2g. (0.125 mole) of 3-nitro-5-dimethylcarbamyloxy phenol, 17.1g. (0.0628 mole) of 1,8-dibromooctane (Edcan Laboratories - freshly distilled at 78° and 0.05 mm.) and 300 ml. of commercial absolute ethanol. To this heterogeneous mixture at room temperature was added dropwise a clear solution of 2.87g. (0.125g-atom) of reagent grade sodium (freshly cut) in 150 ml. of absolute ethanol. The contents of the flask became homogeneous (red solution) after approximately half of the sodium ethoxide solution was added.

The solution was refluxed for fifty hours. During the reflux time the color of the solution turned light orange, a precipitate (metallic salts) was noted, and the pH dropped to approximately 7. When the solution was allowed to cool to room temperature overnight a copious precipitate formed. The precipitate was collected by suction filtration and washed on the filter with 200 ml. of distilled water.

The precipitate was vigorously stirred with 200 ml. of 2% KOH solution to remove any unreacted starting material. The precipitate was again collected by suction filtration and washed on the filter with distilled water. The crude precipitate, which was air dried overnight, weighed 24.7g. and melted over the range 63-80°.

The product was recrystallized six times from methanol and three times from benzene. When benzene is the final crystallization solvent the product is a light yellow coarse crystal which, when dried at 64° and 0.05 mm., melts at 94.0-95.5. When methanol is the final crystallization solvent the product is a white crystal which, when dried at 64° and 0.05 mm. for 150 hours, melts at 86-88°. The yield was 17g. (55%).

A possible reason for the difference in the melting points is the formation of methanol of crystallization when methanol is used as the crystallizing solvent since the melting points are interconvertible when the proper solvent is used. In order to determine qualitatively whether any methanol is present as a solvate of crystallization in the product melting at 86-88° a test was devised to detect the odor of methyl salicylate (oil of wintergreen). The result of this test was a qualified yes. The odor of the decomposition products of the 1,8-bis(3-nitro-5-dimethylcarbamyloxyphenoxy)-octane partially masked the odor of wintergreen. However, a very slight wintergreen odor was present.

Analysis: Calculated for $C_{26}H_{34}N_4O_{10}$ (unsolvated): C 55.51, H 6.09, N 9.96

Found (1) Cry. Fr. MeOH: C 55.61, H 6.08, N 9.83

(2) Cry. Fr. Bz. C 55.67, H 5.90, N10.06

Note: Calculated for $C_{26}H_{34}N_4O_{10}.CH_3OH$ (Methanol solvate 1:1 molar)

C 54.54, H 6.44, N 9.42

While the analytical results do not correspond to one mole of methanol to one mole of dicarbamate, we have no basis for limiting consideration to a 1:1 ratio. It might be 5:1 or 10:1. We considered the compound is sufficiently pure to be used.

PREPARATION OF 1,8-bis (3-NITRO-5-HYDROXYPHENOXY)-OCTANE

In a one-liter round-bottomed flask fitted with a reflux condenser and a magnetic stirring egg was placed 9.80g. (0.0164 mole) 1,8-bis-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-OCTANE, 100 ml. 95% ethanol, 100 ml. distilled water and 10.0g. of potassium hydroxide. The flask was warmed by a heating mantle to reflux temperature and the heterogeneous mixture became homogeneous in 3.5 hours. The red, homogeneous solution was refluxed for 10 more hours.

The clear, deep-red homogeneous solution was cooled to 0° and slowly acidified with 30% hydrochloric acid. The fine, yellow precipitate which formed was collected by suction filtration and washed on the filter with distilled water. The yellow product which was dried in a vacuum desiccator weighed 7.2g. and melted at 150-153°C.

The yellow precipitate was recrystallized three times from anyhdrous methyl alcohol to give 6.7g. (91%) of fine yellow crystals which when dried at 115° and 0.05 mm. melted at 154-155°.

Analysis: calculated for $C_{20}H_{24}N_2O_8$; C 57.15, H 5.75, N 6.67

Found: C 57.40, H 6.02, N 7.03

PREPARATION OF 1-(3 NITROPHENOXY)-4-BROMOBUTANE

In a 500 ml. round-bottomed flask fitted with a magnetic stirring egg was placed 40.3g. (0.250 mole) of the sodium salt of m-nitrophenol (prepared from m-nitrophenol and sodium methoxide in methanol), 304g. (1.41 mole) of 1,4-dibromobutane (Matheson, freshly distilled, B.P. 56-58° at 4 mm.) and 25 ml. of dimethylformamide. The heterogeneous, reddish mixture was warmed to 90-100°. In 20 minutes the reddish color of the nitrophenoxide ion had disappeared leaving a pale orange solution. Considerable precipitated sodium bromide was noticed..

The pale orange solution was allowed to cool to room temperature and the sodium bromide was removed by suction filtration. The pale orange filtrate was dissolved in about 1.5 liter of ether and the ethereal solution was washed with 5% potassium hydroxide and with distilled water until the ether washings were neutral to pH paper. The ether layer was dried briefly over anhydrous magnesium sulfate, decolorized with a small amount of Norit, and filtered. The ether was allowed to evaporate leaving a pale yellowish oil.

The excess 1,4-dibromobutane was removed by vacuum distillation through a nine inch Vigreux column, the major portion distilling at 48-56° (4 mm.). The residue, a light orange oil, was distilled _in vacuum_. A clear, yellowish liquid (41.0g.) was collected (b.p. 152-154° at 0.01-0.025 mm.)

The yellowish liquid was dissolved in about 200 ml. of anhydrous methanol, decolorized with a small amount of Norit, and filtered. Upon cooling in a freezer white plate crystals slowly formed. The white crystals of 1-(3-NITROPHENOXY)-4-BROMOBUTANE (35g.) were dried on the filter for one hour (m.p. 33-34°). AAfter drying for 48 hours at room temperature and 0.05 mm. the white crystals weighed 35g. (52%) and melted at 34-35°.

Analysis: Calculated for $C_{10}H_{12}O_3NBr$; C 43.80, H 4.41, Br 29.15

Found: C 44.34, H 4.47, Br 29.25

PREPARATION OF 1-(3-NITROPHENOXY)-4-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-BUTANE

In a 500 ml. round-bottomed flask fitted with a reflux condenser and a magnetic stirring egg was placed 19.2g. (0.070 mole) of 1-(3-nitrophenoxy)-4-bromobutane (m.p. 34-35°) and 50 ml. of absolute ethanol. The mixture was warmed slightly to effect solution. To this clear, homogeneous solution was added a clear, reddish solution containing 13.5g. (0.060 mole) of monocarbamate of 5-nitroresorcinol and 300 ml. of a sodium ethoxide solution prepared by dissolving 1.38g. (0.060 g-atom) of freshly cut sodium in 300 ml. of absolute ethanol. The contents were magnetically stirred and refluxed for 8 hours, at which time the solution was neutral to litmus. Precipitated sodium bromide was noticed after 30 minutes.

The slightly orange solution was allowed to cool to room temperature at which time an additional precipitate was observed. The contents were added to one liter of ice-cold water containing 2g. of potassium hydroxide. Additional precipitate formed. The contents were thoroughly mixed and the white precipitate was collected by suction filtration. The white precipitate was crystallized from 80% methanol-20% benzene. The resulting white product (20.0g., 80%) which was dried for one hour at 115° and 0.05 mm. melted at 121.5-122°.

Since this compound was prepared before, no analysis was performed.

PREPARATION OF 1-(3-NITROPHENOXY)-4-(3-NITRO-5-HYDROXYPHENOXY)-BUTANE

In a 500 ml. round-bottomed flask fitted with a magnetic stirring egg and reflux condenser was placed 20.0g. of 1-(3-nitrophenoxy)-4-(3-nitro-5-dimethylcarbamyloxyphenoxy)-butane (m.p. 121.5-122°), 150 ml. of 95% ethanol, and 200 ml. of a solution containing 200 ml. of water and 15g. of potassium hydroxide. The heterogeneous mixture was refluxed for 8 hours at which time a red, homogeneous solution resulted. This solution was cooled to about 50° and acidified with 10% hydrochloric acid. A tan precipitate formed immediately. The tan precipitate was recrystallized several times from benzene and from methanol. When recrystallized from benzene the resulting solvated yellow nugget crystals were desolvated to a yellow product at room temperature (m.p. 139-140°). When the product was recrystallized from methanol yellow solvated crystals formed which were desolvated at 115° and 0.025 mm. (m.p. 138-139°). The final crystallization from 90% benzene-10% methanol gave 11.5g. (70%) of desolvated crystals (desolvated at 115° and 0.025 mm.) which melted at 139.5-141°.

Analysis: Calculated for $C_{16}H_{16}O_7N_2$: C 55.16, H 4.63, N 8.04

Found: C 55.40, H 4.85, N 8.00

PREPARATION OF 1-(3-NITROPHENOXY)-6-BROMOHEXANE

In a 300 ml. round-bottomed flask fitted with a magnetic stirring egg was placed 32.2g. (0.20 mole) of the sodium salt of m-nitrophenol (prepared from m-nitrophenol and sodium methoxide in methanol), 170g. (0.70 mole) of 1,6-dibromohexane (Aldrich Co., freshly distilled, b.p. 68-70° at 0.05 mm.), and 20 ml. of dimethylformamide. The heterogeneous reddish mixture was warmed to 95-100° for 30 minutes. The reddish color of sodium salt of m-nitrophenol disappeared and considerable sodium bromide was noted after 15 minutes.

The slightly yellow solution was allowed to cool to room temperature and the sodium bromide was removed by suction filtration. The pale yellow filtrate was dissolved in 1.5 liters of ether and washed with 5% potassium hydroxide solution and with distilled water until the washings were neutral to litmus. The ether layer was dried with anhydrous sodium sulfate, decolorized with a small amount of Norit, and filtered. The ether was allowed to evaporate, leaving 152g. of a light yellow oil.

The 1,6-dibromohexane was removed by vacuum distillation through a nine inch Vigreux column, the major portion distilling at 55-65°C (0.025 mm.; oil bath 110-115°). The residue, a light orange oil, was vacuum distilled through a nine inch Vigreux column. The product distilled at 165-167° and 0.025-0.035 mm. A light yellow liquid (24g), was collected (oil bath 235-245°). The yellow oil was dissolved in ca. 200 ml. of anhydrous methanol and allowed to crystallize in the freezer. The resulting clear plate crystals of 1-(3-NITROPHENOXY)-6-BROMOHEXANE weighed 22.3g. (38%) and melted at 28-29.

Analysis: Calculated for $C_{12}H_{16}O_3NBr$: C 47.69, H 5.34, Br 26.45

Found: C 47.77, H 5.42, Br 26.52

PREPARATION OF 1-(3-NITROPHENOXY)-6-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-HEXANE

In a 250 ml. round-bottomed flask was placed 20.0g (0.067 mole) of 1-(3-nitrophenoxy)-6-bromohexane (m.p. 28-29°) and 50 ml. of absolute ethanol. The mixture was warmed slightly to effect solution. To this clear, homogeneous solution was added a clear, reddish solution containing 15.1g. (0.067 mole) of monocarbamate of 5-nitroresorcinol and 100 ml. of a sodium ethoxide solution prepared by dissolving 1.54g. (0.067g-atom) of sodium (freshly cut) in 100 ml. of absolute ethanol. The contents were magnetically stirred and refluxed for 20 hours. Precipitated sodium bromide was noticed in 30 minutes.

The orange solution, which was slightly basic to litmus was allowed to cool to room temperature and added to a solution of 500 ml. of ice water and 3g. of potassium hydroxide pellets. A light tan solid formed (26.5g). Recrystallization from a solution containing 1.1 liters of methanol and 150 ml. of benzene gave 24.4g. (81%) of a white powder which melted at 108-110°. An additional recrystallization from a 90% methanol-10% benzene solution gave a white product which melted at 109-110°. Infra-red shows two peaks in the carbonyl absorption region at 5.7 and 5.8μ. It is suggested that the splitting of the carbonyl absorption into two distinctive peaks is due to a group frequency shift.

The analytical sample which was recrystallized four times from 95% methanol -5% benzene solution and dried at 100° and 0.05 mm. melted at 109.5-110°.

Analysis: Calculated for $C_{21}H_{25}O_8N_3$: C 56.37, H 5.63, N 9.39

Found: C 56.80, H 5.72, N 9.25

PREPARATION OF 1-(3-NITROPHENOXY)-6-(3-NITRO-5-HYDROXYPHENOXY)-HEXANE

In a 500 ml. round-bottomed flask fitted with a magnetic stirring egg and reflux condenser was placed 16.0g. (0.0358 mole) of 1-(3-nitrophenoxy)-6-(3-nitro-5-dimethylcarbamyloxyphenoxy)-hexane (m.p. 109-110°), 100 ml. of 95% ethanol, and a solution containing 150 ml. of water and 8g. of potassium hydroxide.. The heterogeneous mixture was refluxed for 9 hours at which time a red, homogeneous solution was obtained. This solution was cooled to about 50° and acidified with 10% hydrochloric acid. A light yellow precipitate formed immediately. The yellow precipitate was collected by suction filtration and crystallized from about 250 ml. of benzene. When dried at 0.5 mm. and 100° for 4 hours the resulting yellow product weighed 10.8g. (80%) and melted at 134-134.5°.

The analytical sample which was recrystallized from benzene and dried at 100° and 0.5 mm., melted at 134.5-135°.

Analysis: Calculated for $C_{18}H_{20}O_7N_2$: C 57.44, H 5.36, N 7.44

Found: C 57.59, H 5.33, N 7.78

PREPARATION OF 1-(3-NITROPHENOXY)-8-BROMOOCTANE

In a 250 ml. round-bottomed flask fitted with a magnetic stirring egg was placed 25.8g. (0.16 mole) of sodium salt of m-nitrophenol, (freshly prepared from m-nitrophenol and sodium methoxide), 190g. (0.70 mole) of 1,8-dibromooctane (freshly distilled, b.p. 78° at 0.05 mm), and 20 ml. of dimethylformamide. The heterogeneous mixture became a red homogeneous solution in 15 minutes and the solution temperature was maintained at 90-100°. In 35 minutes the solution was light yellow and considerable sodium bromide was noticed.

The solution was allowed to cool to room temperature and the sodium bromide was removed by suction filtration. The pale yellow liquid was dissolved in 1.5 liters of ether and the ether layer was washed with 5% potassium hydroxide and with distilled water until the aqueous layer was neutral to litmus. The ether layer was dried with anhydrous magnesium sulfate, decolorized with a small amount of Norit, and filtered. The ether was allowed to evaporate leaving a light-yellow oil residue.

The 1,8-dibromooctane was removed by vacuum distillation, 150g. of a clear, colorless liquid being collected at 0.05-0.20 mm. and 97-106°. The residue, a brownish-black viscous liquid, was dissolved in 700 ml. of methanol, decolorized with a small amount of Norit, and filtered. Upon cooling in a freezer, a light tan solid (35g) formed. The tan solid was stirred, at room temperature, with 150 ml. of methanol. The resulting mixture, which contained some solid (disubstituted product) was filtered and the solid material set aside. The filtrate was recrystallized twice more as described above. The resulting white, crystalline 1-(3-nitrophenoxy)-8-bromooctane weighed 14.8g. and melted at 26.5-27.6°. This compound was not analyzed.

PREPARATION OF 1-(3-NITROPHENOXY)-8-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-OCTANE

In a 250 ml. round-bottomed flask was placed 14.8g. (0.045 mole) of 1-(3-nitrophenoxy)-8-bromooctane and 50 ml. of absolute ethanol. To this clear, homogeneous solution was added a clear, reddish solution containing 10.2g. (0.045 mole) of monocarbamate of 5-nitroresorcinol and 100 ml. of a sodium ethoxide solution prepared by dissolving 1.03g. (0.045g-atom) of sodium (freshly cut) in 100 ml. of absolute ethanol. The contents were magnetically stirred and refluxed for 24 hours. The resulting orange solution was slightly basic to litmus.

The solution was allowed to cool to room temperature and slowly added to ice-water. A tan precipitate formed. The tan precipitate was dissolved in 500 ml. of methanol, decolorized with a small amount of Norit and filtered. The clear solution was cooled. A white solid, which weighed 20.2g, and melted at 50-51° formed. Drying at room temperature and 0.05 mm. for 24 hours failed to improve the melting point. The white solid was dissolved in 1 liter of hot methanol, filtered, and allowed to stand at room temperature. White needle crystals formed slowly (about 8 hours). The white crystals were collected by suction filtration, washed on the filter with a small amount of methanol and dried in a desiccater (over anhydrous calcium chloride). The white needle crystals weighed 12.5g (60%) and melted at 62.5-63°.

The analytical sample which was recrystallized four times from methanol and dried at room temperature and 0.25 mm. for 10 hours, melted at 62.8-63.2°.

Analysis: Calculated for $C_{23}H_{29}O_8N_3$: C 58.08, H 6.15, N 8.85

Found: C 58.00, H 5.90, N 8.62

PREPARATION OF 1-(3-NITROPHENOXY)-8-(3-NITRO-5-HYDROXY PHENOXY)-OCTANE

In a 500 ml. round-bottomed flask fitted with a magnetic stirring egg and reflux condenser was placed 6.3g. (0.013 mole) of 1-(3-nitrophenoxy)-8-(3-nitro-5-dimethylcarbamyloxyphenoxy)-octane (m.p. 62-63°) and a solution containing 200 ml. of methanol and 5g. of potassium hydroxide. The contents of the flask became a light red homogeneous solution as the mixture was warmed. Two milliliters of water was added to the clear light red solution. The homogeneous solution was refluxed for two hours. When 200 ml. of water was added to the light red solution, the contents of the flask remained homogeneous.

The contents were added to a 600 ml. beaker and the methanol was allowed to evaporate while the solution was magnetically stirred and heated on a hot plate. The resulting clear, red, homogeneous solution was acidified warm with 10% hydrochloric acid. An oil, which soon solidified, formed immediately. The resulting yellow solid which was broken up and collected by suction filtration weighed 5.1g. and melted at 105-108°. Crystallization from 100 ml. of benzene gave 4.5g. (85%) of small yellow needle crystals which melted at 106-107.5°.

The analytical sample, which was recrystallized several times from benzene and dried at 100° and 0.25 mm., melted at 107-108°.

Analysis: Calculated for $C_{20}H_{24}O_7N_2$: C 59.40, H 5.98, N 6.93

Found: C 59.04, H 5.81, N 6.76

PREPARATION OF 1-(3-NITROPHENOXY)-10-BROMODECANE

The sodium salt of m-nitrophenol was prepared from 22.1g. (0.160 mole) of m-nitrophenol (Eastman) and a solution of sodium ethoxide, freshly prepared from 3.68g. (0.160 g-atom) of reagent grade sodium (freshly cut) and 100 ml. of absolute ethanol. The m-nitrophenol was dissolved in 100 ml. of anhydrous methanol (Merck Reagent) and the sodium ethoxide solution was added slowly with constant stirring. The solvents were allowed to evaporate at room temperature and the resulting bright orange sodium salt dried for 3 days in an evacuated desiccator (over anhydrous calcium chloride).

1,10-Dibromodecane (Eastman, m.p. 24.5-26°) was freshly distilled from a vacuum distillation apparatus containing a one-foot Vigreux column. A clear, colorless liquid (b.p. 103.5-107 at 0.05-0.10 mm.) was collected (oil bath 156-165°).

In a 250 ml. round-bottomed flask fitted with a magnetic stirring egg was placed 25.8g. (0.16 mole) of the sodium salt of m-nitrophenol, 145g. (0.48 mole) of 1,10-dibromodecane (freshly distilled) and 50 ml. of dimethylformamide (Matheson, Coleman and Bell, used as received). The contents were magnetically stirred and soon became a deep red, homogeneous solution. The flask was heated by means of a Variac-controlled heating mantle and the solution temperature maintained at 90°. In 20 minutes a large amount of precipitate (sodium bromide) was noticed and the solution was yellow-orange. In 30 minutes the solution, a pale yellow-green liquid, was neutral to pH paper. [Note: when dimethylformamide was not used as a solvent, the reaction took 4 hours for completion.]

The solution was allowed to cool to room temperature and the sodium bromide was removed by filtration. The pale yellow-green liquid was dissolved in 1.5 liters of ether and the ether layer was washed with 5% potassium hydroxide solution and with distilled water until the aqueous layer was neutral to litmus. The ether layer was dried with anhydrous magnesium sulfate, decolorized with a small amount of Norit, and filtered. The ether was allowed to evaporate leaving a light yellow oil.

The 1,10 dibromodecane was removed by vacuum distillation, 90g. of a clear colorless liquid (dihalide) being collected at 97-104° (0.25-0.5 mm.). The residue in the flask, a dark brown oil, weighed 29g. The oil was dissolved in 1 liter of hot, anhydrous methanol, stirred with a small amount of Norit and filtered. Upon cooling in a freezer, a white crystalline precipitate formed. The white precipitate was recrystallized several times from methanol. After each crystallization from methanol the product was stirred with about 150 ml. of methanol at room temperature. The insoluble white product 1,10-bis(3-nitrophenoxy) -decane, m.p. 82°) was removed by filtration. The desired bromodecane dissolved, and was recovered by cooling in the freezer. The final product weighed 22g. (40%) and melted at 27.4-27.6. A qualitative test showed the presence of bromine. This compound was not further analyzed.

PREPARATION OF 1-(3-NITROPHENOXY)-10-(3-NITRO-5-DIMETHYLCARBAMYLOXYPHENOXY)-DECANE

In a 250 ml. round-bottomed flask was placed 21.0g. (0.060 mole) of 1-(3-nitrophenoxy)-10-bromodecane and 100 ml. of absolute ehtanol. To this clear, homogeneous solution was added a clear, reddish solution containing 13.6g. (0.060 mole) of the monocarbamate of 5-nitroresorcinol and 100 ml. of a sodium ethoxide solution prepared by dissolving 1.38g. (0.060 g-atom) of sodium (freshly cut) in 100 ml. of absolute ethanol. The contents were magnetically stirred and refluxed for 27 hours. A precipitate of sodium bromide was noted in 30 minutes. During the course of the reaction the original deep red solution gradually changed to a light orange red solution. The solution was still slightly basic to litmus after 27 hours.

The solution was allowed to cool to room temperature. The oil which formed soon solidified. To the cool solution was added 1g. of potassium hydroxide in 500 ml. of water. The contents were thoroughly mixed and filtered. The precipitate was washed on the filter with distilled water. The resulting light tan precipitate which was air-dried overnight weighed 28.2g. and melted at 54-57°.

Recrystallization from anhydrous methanol produced 24.0g. (80%) of white product which melted at 58.5-59.5°. An additional recrystallization from methanol and drying at 0.05 mm. and room temperature produced a white product which melted at 60.5-61.5°. Considerable product was lost on recrystallization.

The analytical sample, which was recrystallized four times from methanol and dried at 0.05 mm. for 24 hours, melted at 60.7-61.7°.

Analysis: Calculated for $C_{25}H_{33}O_8N_3$: C 59.64, H 6.61, N 8.36

Found: C 59.96, H 6.81, N 8.55

PREPARATION OF 1-(3-NITROPHENOXY)-10-(3-NITRO-5-HYDROXYPHENOXY)-DECANE

In a 300 ml. round-bottomed flask was placed 12.0g. (0.0238 mole) of 1-(3-nitrophenoxy)-10-(3-nitro-5-dimethylcarbamyloxyphenoxy)-decane (m.p. 58.5-59.5°), 75 ml. of 95% ethanol, and a solution containing 100 ml. of water and 10g. of potassium hydroxide. The heterogeneous mixture was stirred and refluxed. The heterogeneous solution became orange after 3 hours. A total of 22 hours of refluxing was necessary before the contents of the flask appeared homogeneous. (Although the solution appeared homogeneous after 22 hours, the difficulty in purifying the hydrolysis product suggests that homogeneity was not obtained.)

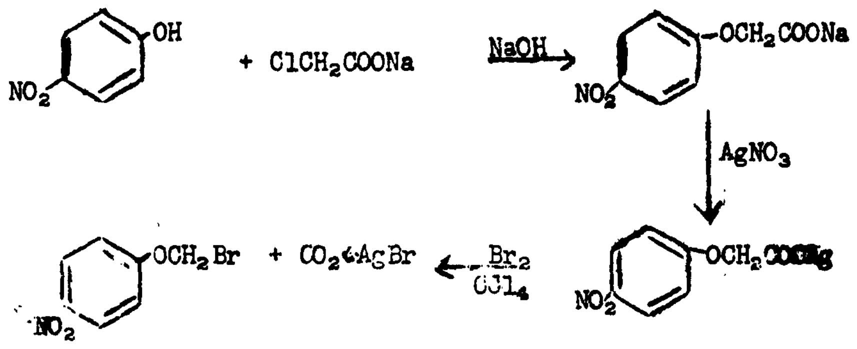
The deep-red homogeneous-appearing solution was cooled to 10° and acidified with 10% hydrochloric acid. A tan precipitate formed immediately.

The tan product was decolorized with Norit and recrystallized three times from benzene and four times from methanol to give 1.8g. (17%) of yellow crystals which melted at 84-86°.

Analysis: Calculated for $C_{22}H_{28}O_7N_2$: C 61.09, H 6.52, N 6.48

Found: C 61.22, H 6.47, N 6.97

ATTEMPTED PREPARATION OF 4-NITROPHENOXYMETHYL BROMIDE



A possible route to α-bromo ethers by the Hunsdiecker reaction was considered. In anticipation of preparing 3-nitrophenoxymethyl bromide later, a forerun using the less expensive 4-nitrophenol was attempted. Considerable (80g.) 4-nitrophenoxyacetic acid was prepared and converted to its silver salt. The silver salt was thoroughly dried in a drying oven at 130° for 48 hours. Carbon tetrachloride (Reagent grade) and bromine were dried for 24 hours over phosphorus pentoxide.

The silver salt of 4-nitrophenoxyacetic acid and an equimolar quantity of dry bromine were mechanically stirred through a mercury seal and refluxed in dry carbon tetrachloride for 48 hours. No carbon dioxide appeared to evolve from the refluxing, heterogeneous mixture. The top of the condenser was protected by a calcium chloride tube leading into a mercury (U-tube) seal. The other arm of the U-tube was connected by glass tubing to another U-tube filled with a clear, saturated barium hydroxide solution protected from atmospheric carbon dioxide by an ascarite guard. No barium carbonate precipitated.

The stirred, heterogeneous mixture was irradiated with ultraviolet light (G.E.Sunlamp) for 48 hours. No carbon dioxide was formed. The heterogeneous mixture was filtered and the unreacted silver salt held aside. The filtrate was allowed to evaporate at room temperature. A small amount of viscous red oil remained. The small quantity of residue did not justify spending time in further investigation.

Because of the lack of success with the silver salt of 4-nitrophenoxyacetic acid, it was decided not to carry out the above series of reactions using 3-nitrophenol.

PREPARATION OF 1,7-DIBROMOHEPTANE

$$\begin{tikzcd}
HOOC(CH_2)_7COOH \arrow[r, "NaOH"] & NaOOC(CH_2)_7COONa \arrow[d, "AgNO_3"] \\
Br(CH_2)_7Br + CO_2 + AgBr & AgOOC(CH_2)_7COOAg \arrow[l, "Br_2"', "CCl_4"]
\end{tikzcd}$$

A synthesis of 1,7-dibromoheptane from azelaic acid has been carried out. A 35% yield of slightly impure 1,7-dibromoheptane was obtained.

In a large flask was placed 103g. (0.548 mole) of commercial grade azelaic acid and 500 ml. of an aqueous solution containing 44.8g. of 97.8% reagent grade sodium hydroxide (equivalent to 43.8g. pure sodium hydroxide; 1.10 mole). The mixture was warmed to approximately 40° to effect solution. The solution was cooled to room temperature and filtered. To this clear, light yellow solution was added a 3% aqeous solution containing 206g. (10% excess) of reagent grade silver nitrate. A white precipitate formed immediately. The white precipitate was collected by suction filtration and washed on the filter with large quantities of water. The white precipitate was sucked dry on the filter overnight and dried in an oven at 130° for 48 hours. the resulting white precipitate weighed 170g. (80%). The loss of silver salt due to handling was large because of the nature of the precipitate.

In a 2-liter,3-necked, round-bottomed flask equipped with a reflux condenser protected on the top by a calcium chloride tube, a magnetic stirring egg, and a large dropping funnel, was placed 170g. (0.423 mole) of silver azelate and 600 ml. of dry carbon tetrachloride. The heterogeneous mixture was refluxed gently as a solution containing 135g. (0.846 mole) of bromine in 150 ml. of dry carbon tetrachloride was added dropwise. A vigorous evolution of carbon dioxide and an exothermic reaction were noticed immediately. The heating mantle was removed and the flask was cooled in an ice-bath periodically to control the extent of refluxing. The total time for the addition of the bromine solution was approximately 1.5 hours. After all the bromine solution was added, the mixture was stirred and refluxed until no evolution of carbon dioxide was noticed [30 minutes].

The precipitated silver bromide was removed by suction filtration and the resulting red-brown filtrate was placed in a large beaker to allow the bulk of the carbon tetrachloride to evaporate at room temperature. The resulting dark brown liquid was filtered free of a small amount of solid and distilled under vacuum. The clear, colorless liquid (dihalide) which was collected at 86-89° and 0.5 mm. (36g., 35%) soon discolored. This product has been held aside for further purification.

A modification of the above procedure in which the silver salt will be added to the carbon tetrachloride-bromine solution will be tried. It is thus hoped to increase the Hunsdiecker reaction (with a corresponding increase in yield of dihalide) and decrease the competing Simonini reaction.

PREPARATION OF SODIUM NITROMALONALDEHYDE

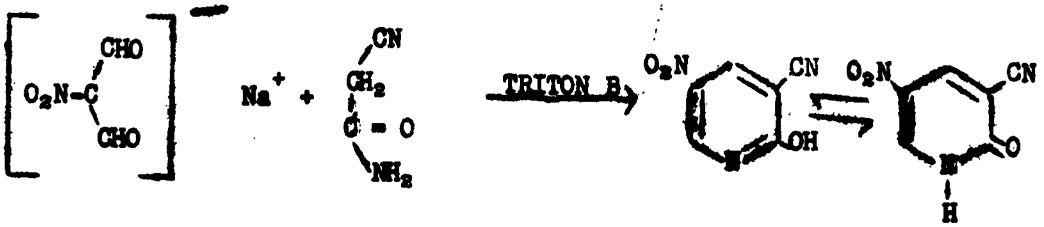
$$\overset{\mathrm{Br}}{\underset{\mathrm{CHO}}{\mathrm{C}}}=\overset{\mathrm{Br}}{\mathrm{C}}\mathrm{-COOH}+\mathrm{NaNO_2}\xrightarrow{54^\circ}\mathrm{Na}^+\,[\mathrm{C(CHO)_2NO_2}]^-\cdot\mathrm{H_2O}$$

The following procedure was adapted from Fanta, Org. Syn., 32, 95

In a 1-liter, 3-necked, round-bottomed flask was placed 100g. (1.45 moles) of sodium nitrite and 100 ml. of water. The mixture was warmed slightly to effect solution. To this clear solution was added a solution of 100g. (0.386 mole) of mucobromic acid in 100 ml. of warm 95% ethanol dropwise such that the temperature was maintained at 54° ± 1°. The reaction is mildly exothermic. After the addition of the acid was completed (90 minutes), the reddish solution was stirred for 10 minutes at 54°. The reaction mixture was cooled to 0-5° in an ice-bath. Light brown crystals soon formed. The light brown crystals were collected by suction filtration on a previously chilled Büchner funnel. The moist cake was recrystallized from a solution containing 160 ml. of 95% ethanol and 40 ml. of water. The resulting light brown crystals, which were air-dried overnight weighed 30g. and decomposed with evolution of gas at 101-104°.

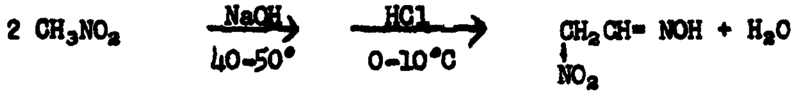
The above reaction was repeated on a small scale using the less expensive mucochloric acid in lieu of mucobromic acid. Some sodium nitromalonaldehyde was isolated but optimum conditions have not been obtained as yet. Further work is underway on this synthesis.

PREPARATION OF 2-HYDROXY-3-CYANO-5-NITROPYRIDINE



In anticipation of preparing 2-hydroxy-3,5-dinitropyridine from nitroacetamide and sodium nitromalonaldehyde, suitable conditions were sought. Fanta and Stein [J. Am. Chem. Soc., 77, 1045, (1955)] condensed α-cyanoacetamide with sodium nitromalonaldehyde and recovered a 93% yield of 2-hydroxy-3-cyano-5-nitropyridine. This synthesis was successfully repeated in our laboratory. It is hoped that nitroacetamide and sodium nitromalonaldehyde will condense to 2-hydroxy-3,5-dinitropyridine under similar or slightly altered conditions.

PREPARATION OF NITROACETALDOXIME



$$2\ CH_3NO_2 \xrightarrow[40\text{-}50°]{NaOH} \xrightarrow[0\text{-}10°C]{HCl} \underset{NO_2}{CH_2}CH{=}NOH + H_2O$$

For the synthesis of nitroacetamide (cf. preceding synthesis) considerable quantities of nitroacetaldoxime are necessary. It has been established in this laboratory that "pure" nitroacetaldoxime can be stored in a cold place without decomposition. Impure nitroacetaldoxime containing traces of acid or solvent readily decomposes at room temperature.

The procedure followed was that of Steinkopf [Ber., 42, 2031, (1909)] with modifications. In a large beaker was placed 82g. (2.0 moles) of 98% sodium hydroxide pellets and 100 ml. of water. When the temperature of the solution dropped to 45°, 80g. (1.3 moles) of nitromethane (used as received) was added, dropwise, with constant stirring, to the sodium hydroxide solution. The temperature of the reaction mixture was maintained at 40-50° during the addition of the nitromethane (approximately 45 minutes) by the use of an ice bath. A white precipitate and a red-brown solution were soon noted. Near the end of the reaction, the temperature of the solution was allowed to be raised to 55° for a minute. Small chips of ice were used to prevent the temperature from exceeding 55°. The solution was allowed to cool to room temperature, and then cooled to 0° in an ice-salt bath. Considerable solid formed during this cooling.

The temperature of the mixture was maintained at 0-10° while the sodium hydroxide was neutralized with 160 ml. (2.0 moles) of concentrated hydrochloric acid (sp. gr. 1.19, 37.7%). A white precipitate (slightly yellow with solvent) was formed. The precipitate was separated by suction filtration on a chilled Büchner funnel. The precipitate was pressed on the filter to remove as much solvent as possible. The slightly moist, light yellow cake was stirred vigorously with 500 ml. of ether. Considerable solid did not dissolve. The ether solution was filtered free of solid material, decolorized with a small amount of Norit,

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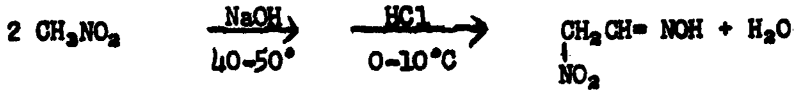

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It should be noted in this experiment that higher yields were sacrificed in order to obtain high purity.