cluded for each bond-making step, the ratio calculated using Segal's surface decreases by less than 2%. A similar decrease is obtained using Bensons empirical estimates. No isotope effect is expected for the twixtyl.
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Destruction of Nitrosamines. Treatment of Nitrosamines with Various Acids and Halogens

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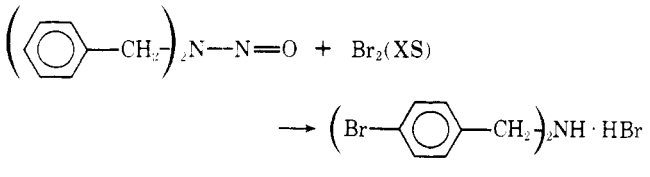
Received March 3, 1978

Several dinitroaniline compounds containing varying amounts of nitrosamines were treated with a variety of acids under different sets of conditions. Hydrogen chloride gas, hydrochloric acid, and hydrobromic acid were all effective at destroying the nitrosamines. Sulfuric acid efficiently removed nitrosamines without destruction, as the nitrosamines could be recovered from the neutralized acid extract. Other acids, e.g., ascorbic acid, phosphoric acid, *p*-toluenesulfonic acid, and oxalic acid, were either considerably less effective or ineffective at removing nitrosamines from dinitroaniline compounds. Additionally, molecular bromine, chlorine gas, and *N*-bromosuccinimide are quite effective in lowering the nitrosamine levels to about 1 ppm of the nitrosamine contaminant.

Nitrosamines, as a general class of organic compounds, have attracted an increasing amount of attention due to recent disclosures that many nitrosamine compounds are carcinogens in animals.[1] Recent innovations[2] in instrumentation have permitted definitive identification of nitrosamines even when present at very low levels (0.05 ppm).[3]

Since many literature references to the destruction of nitrosamines[4] deal with neat samples of the nitrosamines or materials containing relatively high amounts of the nitrosamines, we began a program to investigate the destruction of nitrosamines at the 1 → 500 ppm level. Various acids have been reported to reduce nitrosamine levels, e.g., sulfuric acid,[5] hydrogen chloride gas,[6] hydrochloric acid,[7] and hydrobromic acid.[8] However, we have found a large difference in the ability of various acids to reduce and destroy nitrosamines.

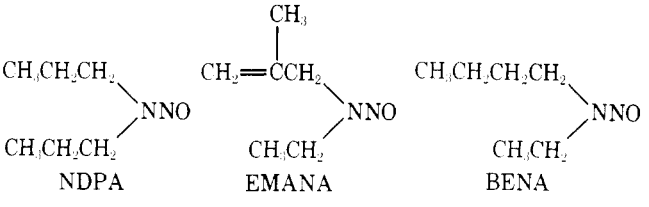
Literature also suggests that bromine[9] will react with nitrosamines. In the example cited, the author treated an aromatic *N*-nitroso compound with bromine as solvent and isolated a bromine-substituted product. This may suggest that the reactive reagent in this case is the hydrogen bromide[8] which is liberated during the electrophilic attack by bromine on the aromatic ring.



This paper details our observations that concentrated hydrochloric acid, hydrogen chloride gas, and hydrobromic acid effectively destroy low levels of nitrosamines, while sulfuric acid removes the nitrosamines by an extraction process.[10] Also, we have observed efficient destruction of nitrosamines by halogen reagents, including bromine, chlorine, and *N*-bromosuccinimide.

Results and Discussion

The specific nitrosamines analyzed for in this study were *N*-nitrosodipropylamine (NDPA), *N*-nitrosoethylmethallylamine (EMANA), and *N*-nitrosoethylbutylamine (BENA).[11] In most cases, the nitrosamines were contaminants at low levels (10–7400 ppm[10]) in various dinitroaniline solvents. The four specific dinitroanilines used include trifluralin,[12] benefin,[13] isopropalin,[14] and ethalfluralin.[15]



In the case of the acid reagents, normal reaction technique consisted of heating the dinitroaniline to approximately 70 °C (temperatures of 60–90 °C have been routinely used) and adding about 20% w/w of the desired acid relative to dinitroaniline. The reaction can be carried out neat or with an appropriate solvent (ethanol, chloroform, toluene, etc.). The reaction mixture is heated at the desired temperature for time periods of from 5 min to 3 h, with 15 min to 30 min being typical. Workup consisted of separating the aqueous and organic layers when applicable and then washing the organic layer with 10% sodium carbonate solution. Nitrosamine levels in the organic fraction were assayed by either gas chromatography,[16] combined gas chromatography–mass spectroscopy,[17] or by use of a thermal energy analyzer.[2]

Table I summarized the data generated. One can classify sulfuric acid, hydrochloric acid, hydrogen chloride gas, and hydrobromic acid as effective reagents in removing nitrosamines. In the case of hydrochloric acid, hydrogen chloride gas, and hydrobromic acid, the removal of the nitrosamine from the organic substrate is accompanied by destruction of the nitrosamine. For instance, when a sample of trifluralin containing 68 ppm of NDPA is vigorously stirred with concentrated hydrochloric acid and worked up in the usual manner, assay of the trifluralin shows <1 ppm NDPA, and assay of the methylene chloride extract of the neutralized hydrochloric acid layer shows <1 μg/mL of NDPA.

Mechanistically, hydrogen chloride gas and hydrochloric acid decomposition of nitrosamine is most probably initiated by electrophilic attack by the acid on the oxygen atom of the nitroso group,[18] a widely accepted reaction of nitrosamines.

We suggest, from preliminary data, that the chloride ion, stepwise or in a concerted fashion, attacks the nitrogen of the nitroso group resulting in nitrosyl chloride formation. This

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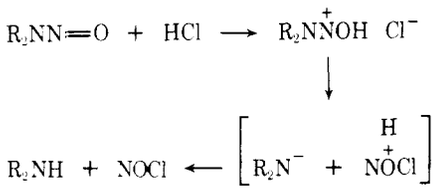
Table I. Removal of NDPA from Trifluralin by Different Acids[a]

acid	registry no.	NDPA,[e] ppm
50% sulfuric acid	7664-93-9	22
70% sulfuric acid		<1
85% sulfuric acid		<1
10% hydrochloric acid	7647-01-0	81
33% hydrochloric acid		<1
37% hydrochloric acid		<1
hydrogen chloride gas[b]		<1
50% formic acid	64-18-6	74
98% formic acid		58
70% acetic acid	64-19-7	58
oxalic acid[c]	144-62-7	<9
40% phosphoric acid	7664-38-2	90
48% hydrobromic acid	10035-10-6	<1
ascorbic acid[d]	50-81-7	85

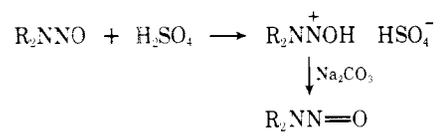
[a] Conditions for the treatments were: time, 20 min; temperature, 70 °C; and amount of acid used, 20% w/w of acid to trifluralin. Also untreated trifluralin contained 68 ppm of NDPA. [b] Hydrogen chloride gas flow was 35 mL/min. [c] Time, 2 h. [d] Time, 3 h. [e] Registry no., 621-64-7.



mechanism has been previously offered for other alkyl nitrosamine decompositions.[5]

In a test of the efficiency of hydrogen chloride gas to destroy nitrosamines, 100 μL of NDPA were added to 5 mL of carbon tetrachloride. Initial nitrosamine assay showed 18 400 μg/mL of NDPA. After 1 h of hydrogen chloride addition, assay of the carbon tetrachloride layer showed about 4 μg/mL of NDPA. Assay of dry ice trap contents and of the aqueous sodium carbonate wash layer shows only traces of NDPA. Destruction of NDPA by hydrogen chloride gas appears very rapid and efficient.

Sulfuric acid has also been utilized to "destroy" nitrosamines. In our hands, sulfuric acid (50–98%) treatment of dinitroanilines resulted in merely extraction of the nitrosamine into the acid layer. After layer separation, the aqueous layer



was neutralized with 10% sodium carbonate solution and immediate extraction with methylene chloride resulting in recovery of the nitrosamine intact in yields greater than 90%. These data suggest either that the hydrolysis of the bisulfate salt of the nitrosamine is very slow relative to the previous hydrochloride salt or that a resulting anion of greater nucleophilicity than bisulfate ion is necessary to attack the nitrogen of the nitroso group.

The other acids listed in Table I had little if any effect on the nitrosamine levels in the dinitroanilines tested at the specific relative amounts and conditions. Certain samples showed an increase in nitrosamine levels when treated with some reagents. These observations may be due, in part, to inherent assay variability and/or sampling techniques. Increases of nitrosamine levels due to alternate chemical reactions are possible.

In the use of halogen or halogen reagents, a general reaction

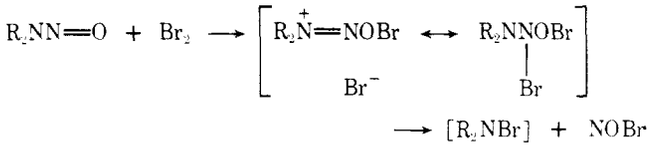
Table II. Removal of NDPA from Trifluralin Containing 68 ppm of NDPA[a]

	registry no.	no. of grams used	temp, °C	time, min	NDPA, ppm
bromine	7726-95-6	0.2	70	20	<1
bromine		0.1	90	15	<1
chlorine	7782-50-5	35 mL/min	70	30	16
chlorine		15 mL/min	110	120	~2
N-bromosuccinimide	128-08-5	0.5	70	30	1.7
iodine	7553-56-2	0.1	70	60	78

[a] Each reaction used 30 g of trifluralin.

procedure included heating the dinitroaniline compound to between 70 and 120 °C and adding the solid, liquid, or gaseous halogen reagent in such a manner as to minimize volatilization. Workup may include a wash with sodium carbonate solution and drying of the organic layer. Table II summarizes our results. Molecular bromine appears more effective than chlorine gas based upon temperature, time, and resulting nitrosamine levels. This observation may be due, in part, to bromine's ready solubility in the organic medium. Also, this coincides with the general reactivity trend of the halogen family which rationalizes iodine's inability to destroy nitrosamines under normal conditions.

From a mechanistic viewpoint, one can suggest several reasonable mechanisms, all of which appear possible. We suggest that the halogen (e.g., molecular bromine) initiates an electrophilic attack on the nitrosamine, resulting in the formation of nitrosyl bromide and the corresponding bromoamine.[4] This bromoamine, being unstable to the reaction



conditions, potentially undergoes free-radical decomposition to several possible products. Nitrosyl bromide has been tentatively detected in the reaction mixture but not definitively isolated and/or identified. No other products (e.g., from the free-radical decomposition of the postulated bromoamine) have been isolated or detected.

In summary, one can remove trace to large amounts (10 to 7400 ppm) of various nitrosamines from multifunctional molecules by the use of certain acids and halogen reagents. Acid reagents, such as hydrochloric acid, hydrogen chloride gas, and hydrobromic acid, remove and destroy nitrosamines from organic compounds to less than 1 ppm of nitrosamine. Sulfuric acid merely extracts the nitrosamine from its organic carrier into the aqueous layer. Care must be taken to destroy the nitrosamines contained in the aqueous acid layer when sulfuric acid is used.

Halogen reagents, such as molecular bromine, chlorine gas, and *N*-bromosuccinimide, are also exceptionally effective at destroying trace amounts of nitrosamine contaminants in various organic solvents.

Experimental Section

Three methods of analysis for nitrosamines were employed.[19] The first method utilized a gas chromatograph equipped with a flame ionization detector and a glass coil column, 4 ft. × 1/8 in. i.d., packed with 3% Carbowax 20M on 100/120 mesh AW DMCS Chromosorb G, at 100 °C. The second method uses a thermal energy analyzer as previously described.[2] In a third method the nitrosamine content in a sample was measured on a LKB-9000 gas chromatograph–mass spectrometer equipped with a 5% Carbowax 20M column.

CAUTION: Appropriate care should be exercised when handling nitrosamines. Rubber gloves may not be adequate protection.[20]

Nitrosamine Removal from Trifluralin with Hydrochloric Acid. Trifluralin (30 g), containing 68 ppm of NDPA, was stirred with 6 mL of concentrated hydrochloric acid at 70 °C for 30 min. Then, the layers were separated and the organic fraction was washed with 10 mL of 10% sodium carbonate solution. The organic fraction was assayed for NDPA by the gas chromatograph method and <1 ppm was detected.

Also, the aqueous acid layer was neutralized with cold 20% sodium hydroxide solution and extracted with 6 mL of methylene chloride. Assay of the methylene chloride layer for NDPA showed <1 ppm.

Nitrosamine Removal from Ethalfluralin with Hydrogen Chloride Gas. Ethalfluralin (100 g), containing 65 ppm of EMANA, was heated to 70 °C. Then hydrogen chloride gas was bubbled through the reaction mixture at a rate of 90 mL/min. Samples were removed periodically and washed with 10% sodium carbonate solution, dried, and analyzed for EMANA. After 30 min of hydrogen chloride gas treatment, less than 1 ppm of EMANA was detected.

Nitrosamine Removal from Trifluralin with Sulfuric Acid. Trifluralin (100 g), containing 68 ppm of NDPA, was heated to 70 °C and 20 mL of 85% sulfuric acid was added. The reaction mixture was stirred vigorously for 30 min and then the layers were separated. The organic layer was washed with 10% sodium carbonate solution and analysis for NDPA showed <1 ppm. The aqueous acid layer was neutralized with 20% sodium hydroxide solution and extracted with 20 mL of methylene chloride. Analysis of the methylene chloride layer for NDPA showed 73 ppm.

Destruction of NDPA in Carbon Tetrachloride. One-hundred microliters of NDPA were dissolved in 5 mL of carbon tetrachloride contained in a 10-mL reaction flask equipped with a gas inlet adapter, magnetic stirrer, and a condenser attached to a dry ice–alcohol cold trap containing 5 mL of carbon tetrachloride. Hydrogen chloride gas was added at a rate of 12 mL/min subsurface at 50 °C. Samples were removed at various intervals and after 75 min of reaction time, 5 mL of 10% sodium carbonate solution was added.

Then, assay of the separated reaction mixture showed <1 μg/mL of NDPA. The sodium carbonate layer showed also <1 μg/mL of NDPA. Assay of the carbon tetrachloride layer from the cold trap showed 11 μg/mL of NDPA.

Treatment of Trifluralin with Iodine. To 30 g of trifluralin containing 68 ppm of NDPA was added 0.1 g of iodine. The reaction was heated at 70 °C for 1 h. Then air was passed through the mixture to remove excess iodine. A sample was analyzed for NDPA and showed 78 ppm.

Removal of BENA from Benefin. To 30 g of benefin containing 20 ppm of BENA was added 0.1 g of molecular bromine at 70 °C. The reaction mixture was stirred for 1 h. Then, 10 mL of 5% sodium carbonate solution was added. The layers were separated and the organic layer showed 1 ppm of BENA upon analysis.

Nitrosamine Removal from Trifluralin with Molecular Bromine. Trifluralin (30 g), having an average nitrosamine assay of 68 ppm, was heated to 70 °C and 0.2 g of molecular bromine was added at the surface interface. The reaction mixture was allowed to stir at 70 °C for 20 min. Then the trifluralin sample was washed with 10 mL of 10% sodium carbonate solution and the organic layer was isolated. A sample was sent for gas chromatographic assay of NDPA and less than 1 ppm of NDPA was detected.

Removal of NDPA from Trifluralin with *N*-Bromosuccinimide. Trifluralin (30 g), with an average assay of 68 ppm NDPA, was heated to 70 °C and 0.5 g of *N*-bromosuccinimide was added. The reaction mixture was stirred at 70 °C for 30 min. A sample was analyzed by gas chromatography and showed 1.7 ppm of NDPA.

Removal of NDPA from Trifluralin with Chlorine Gas. A 30-g portion of trifluralin (68 ppm of NDPA) was heated to 110 °C and chlorine was bubbled through the reaction mixture at a rate of 15 mL/min. Samples were taken periodically and assayed for NDPA. After 2 h, approximately 1.2 ppm of NDPA was detected.

Registry No.—Trifluralin, 1582-09-8; ethalfluralin, 55283-68-6; benefin, 1861-40-1; EMANA, 68630-39-7; BENA, 4549-44-4.

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(10) While this paper was being reviewed, a paper by Swern and co-workers described macro denitrozation results using methanol and hydrogen chloride gas. See: S. K. Vohra, G. W. Harrington, and D. Swern, *J. Org. Chem.*, **43**, 1671 (1978).
(11) Our thanks to Dr. Herschel D. Porter and Mr. Kenneth H. Fuhr of Eli Lilly and Co. for the synthesis of nitrosamine standards.
(12) 2,6-Dinitro-*N,N*-dipropyl-4-(trifluoromethyl)benzenamine.
(13) *N*-Butyl-*N*-ethyl-2,6-dinitro(trifluoromethyl)benzenamine.
(14) 4-(1-Methylethyl)-2,6-dinitro-*N,N*-dipropylbenzenamine.
(15) *N*-Ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine.
(16) See Experimental Section.
(17) See Experimental Section.
(18) U. Klement and A. Schmidpeter, *Angew. Chem.*, **80**, 444 (1968).
(19) Our thanks to Dr. Ed Day for analysis of some samples by the Thermal Energy Analyzer technique.
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Synthesis of α-Methylene-γ-butyrolactones by Rearrangements of Cyclopropylcarbinyl Substrates

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Received October 23, 1978

α-Methylene-γ-butyrolactones can be viewed as derivatives of homoallylic alcohols, potentially obtainable from rearrangements of cyclopropylcarbinyl derivatives. In order to test this concept, the cyclopropylcarbinyl derivatives **3a–7a** were prepared. Acid-catalyzed rearrangements of **3a** and **4a**, solvolytic rearrangements of **5a**, and $AgClO_4$-induced rearrangements of **6a** and **7a** gave the α-methylene-γ-butyrolactone **10** in good yields. The unsaturated substrates **3b–6b** were similarly prepared and shown to rearrange to α-methylene lactone **16**, showing that a suitably placed double bond can direct the regiochemistry of these rearrangements. Lactone **16** has a double bond in a position characteristic of many naturally occurring lactones.

The α-methylene-γ-butyrolactone ring is present in a wide variety of sesquiterpenes and other naturally occurring compounds.[2] Many of these compounds have biological activity; some have been shown to have tumor-inhibiting activity.[3] The α-methylene-γ-butyrolactone ring has been suggested to be of central importance to the biological activities of these compounds. Thus, considerable research activity has been directed toward the synthesis of α-meth-

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