Nitrile Oxides. VI. Some Novel Addition Reactions of Aromatic Nitrile Oxides[1]

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Contrary to earlier reports, aromatic nitrile oxides do add easily hydrogen halides, amines, and phenylhydrazine. Under proper conditions they react, too, with alcohols, mercaptans, organic acids, water, and sulfide, cyanide, thiocyanate, or azide ions. The study of these reactions has been facilitated by the use of the hindered stable nitrile oxides, *e.g.*, 2,4,6-trimethylbenzonitrile oxide. Most additions occur in the 1,3-position, but in a number of cases the initial products, hydroxamic acid derivatives, undergo further transformations.

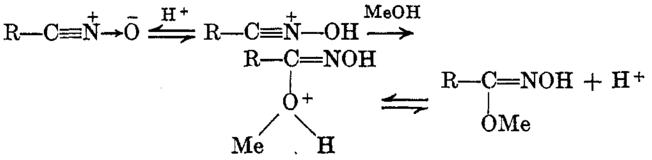
In the past, the study of the addition reactions of nitrile oxides has centered mainly on the 1,3 dipolar cycloadditions with unsaturated systems, such as olefins, acetylenes, carbonyl compounds, Schiff bases, and nitriles.[2] Only recently the addition of nitrile oxides (I, R—C≡N→O) to hydrogen halides, amines, and thiols has been described,[1,3] thus correcting erroneous statements in the literature.[4]

The study of addition reactions of nitrile oxides has been facilitated by the availability of sterically hindered stable nitrile oxides which do not dimerize to furoxans.[1,3b] This dimerization occurs so fast with most aliphatic and aromatic nitrile oxides that the investigation of other reactions proceeding at a considerably lower rate becomes difficult. Thus, this paper deals mostly with reactions of 2,4,6-trimethylbenzonitrile oxide (mesitonitrile oxide, Ia) and other stable nitrile oxides, but in several instances it was demonstrated that unstable nitrile oxides, *e.g.*, benzonitrile oxide, undergo the same transformations.

The reaction of I (R = C_6H_5) with ammonia or aniline gave benzamidoxime (II) and N-phenylbenzamidoxime (III) in excellent yields, while Ia reacted with dimethylamine or with cyclohexylamine to form the corresponding N,N-dimethyl- and N-cyclohexylmesitamidoximes (IV and V) (see Chart I). Thus, the reaction of aromatic nitrile oxides with primary and secondary amines is of a fairly general nature. The amidoximes II–V can easily be distinguished from the isomeric ureas VI by their basic nature; they dissolve in dilute mineral acids and are reprecipitated unchanged after neutralization. The complete absence of VI, ascertained in this manner, indicated that no Lossen rearrangement took place during the reaction of the nitrile oxides with the amines, if the addition was carried out in a solvent below 100°.

The aromatic nitrile oxides react easily with phenylhydrazine, but the picture is complicated by concomitant oxidation-reduction reactions between the nitrile oxide and the hydrazine, as established in the case of oxalobisnitrile oxide.[3c] Only in the reaction of benzonitrile oxide with phenyl hydrazine and subsequent oxidation with ferric chloride were we able to isolate a small amount of benzohydroxyimylphenyldiimide (VIII, R = C_6H_5), undoubtedly arising from the originally formed hydrazide oxime (VII, R = C_6H_5). The instability of VII, prepared by another route, has been observed previously.[5]

While aromatic nitrile oxides are inert toward aliphatic alcohols, at least below 100°, alkali catalyzed the addition of alkoxide ion to alkylhydroximic acids, a class of compounds hitherto arrived at with difficulty. Thus, when Ia reacted with methanol and sodium methoxide followed by neutralization with sulfuric acid, the methylmesitohydroximic acid (Xa) was obtained. With ethanol, the corresponding ethyl derivative Xb was formed analogously. The addition also occurred with dilute sulfuric acid as a catalyst. In this case the reaction probably involves the conjugate acid of the nitrile oxide.


$$R{-}C{\equiv}\overset{+}{N}{\rightarrow}\overset{-}{O} \xrightleftharpoons{H^+} R{-}C{\equiv}\overset{+}{N}{-}OH \xrightarrow{MeOH} \underset{\underset{Me\quad H}{\diagup\;\diagdown}}{\underset{O^+}{\underset{|}{R{-}C{=}NOH}}} \rightleftharpoons \underset{OMe}{\underset{|}{R{-}C{=}NOH}} + H^+$$

From methoxyamine and mesitoyl chloride there was obtained methyl mesitohydroxamate (XII), different from Xa. Both isomers Xa and XII were converted by further methylation with diazomethane into the same methyl methylmesitohydroximate (XI). XI was also obtained by the direct methylation of the free mesitohydroxamic acid (IX) with diazomethane.

As to be expected by their higher degree of nucleophilicity, mercaptans added easily to aromatic nitrile oxides without the aid of a catalyst[6]; thus, from Ia and ethanethiol, ethyl mesitothiohydroximic acid (XIII) was obtained.

The stable nitrile oxides could be recrystallized from hot acetic acid without change, but the addition of catalytic amounts of sulfuric acid converted Ia to the acetylmesitohydroximic acid (XIV), presumably by a mechanism analogous to that discussed above for the acid-catalyzed addition of alcohols. The structure XIV is supported by the strong red ferric chloride reaction of this substance, indicative of an acylhydroximic acid with a free =NOH group.[7] Acetic anhydride reacted with Ia at room temperature to give diacetylmesitohydroximic acid (XIVa); when concentrated sulfuric acid was added to the reaction mixture, XIVa underwent

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[1] Paper V: C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

[2] For a review, *cf.* R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963).

[3] (a) C. Grundmann, *ibid.*, **75**, 450 (1963); (b) C. Grundmann and J. M. Dean, *ibid.*, **76**, 682 (1964); (c) C. Grundmann, V. Mini, J. M. Dean, and H.-D. Frommeld, *Ann.*, **687**, 191 (1965); (d) G. Zinner and H. Günther, *Angew. Chem.*, **76**, 440 (1964); M. H. Benn, *Can. J. Chem.*, **42**, 2393 (1964).

[4] H. Wieland, *Ber.*, **40**, 1667 (1907).

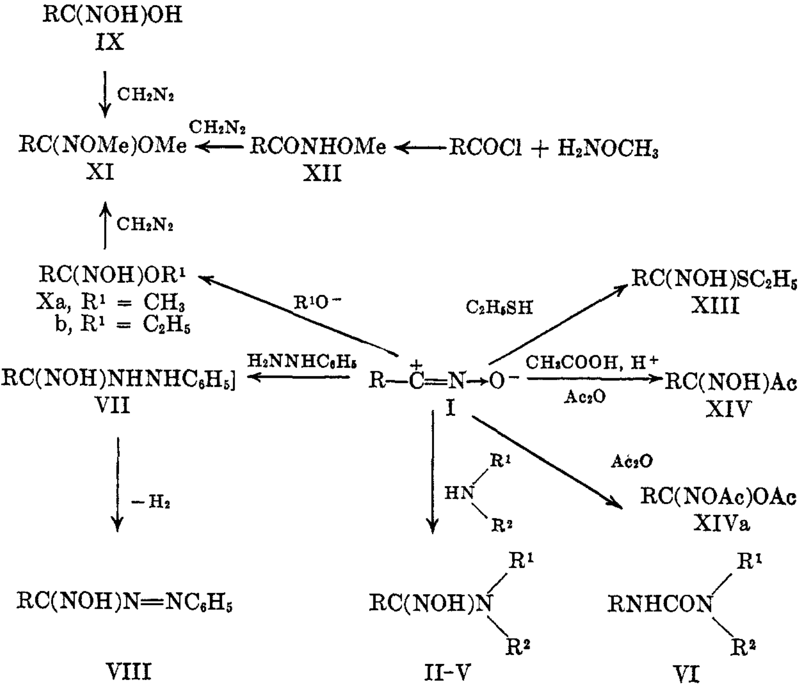
[5] H. Wieland, *ibid.*, **42**, 4199 (1909).

[6] While this work was in progress, the addition of thiols to some nitrile oxides has been reported.[3d]

[7] Benzoylbenzohydroximic acid, $C_6H_5COO(HON)CC_6H_5$, rearranges easily to the benzoylbenzohydroxamate $C_6H_5COONHCOC_6H_5$. The former gives a red $FeCl_3$ reaction; the latter does not. A. Werner and H. Buss, *Ber.*, **27**, 2198 (1894).

CHART I

ADDITION OF ORGANIC REAGENTS TO AROMATIC NITRILE OXIDES



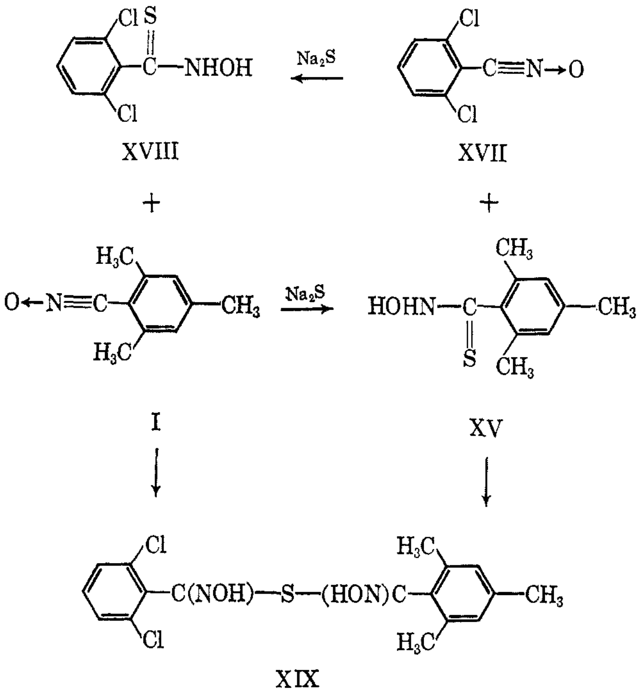
II, R = C_6H_5; R^1 = H; R^2 = H
III, R = C_6H_5; R^1 = C_6H_5; R^2 = H
IV, R = 2,4,6-$(CH_3)_3C_6H_2$; R^1 = CH_3; R^2 = CH_3
V, R = 2,4,6-$(CH_3)_3C_6H_2$; R^1 = C_6H_{11}; R^2 = H

Lossen rearrangement and the only identifiable product was N-acetylmesidine.

Generally, aromatic nitrile oxides are quite stable toward hydrolysis. In spite of much effort, the formation of the hydroxamic acids by the addition of hydroxide ion could not be achieved,; the action of alkali on nitrile oxides seems complicated and is not yet fully understood. Mineral acids, however, catalyzed the addition of water (see Chart II); Ia yielded mesitohydroxamic acid (IX); the mechanism may be analogous to that suggested above for the acid-catalyzed addition of methanol.

From the stable nitrile oxide Ia and sulfide ion there resulted two products: with Na_2S (pH >8) the sodium salt of the mesitothiohydroxamic acid (XV) was formed in excellent yield, while solutions of sodium hydrogen sulfide or—more slowly—hydrogen sulfide yielded a product resulting from the addition of 1 mole of H_2S to 2 moles of I. The same compound was obtained from the addition of 1 mole of Ia to the thiohydroxamic acid XV. For this adduct the open-chain structure of a mesitothiohydroximic acid thioanhydride (XVIa) was favored by the formation of a diacetyl derivative XVIb and by the n.m.r. spectrum, the signals for all six methyl groups being at the same place (τ 8.15 for the methyls in the 2,6-position, and τ 7.83 for the methyls in the 4-position).

Formula XVIa was finally established by the following reactions. 2,6-Dichlorobenzonitrile oxide (XVII) was converted into the thiohydroxamic acid XVIII and treated with I to give the mixed thiohydroximic acid thioanhydride XIX. Then the thiohydroxamic acid XV was added to XVII yielding an identical compound, thus proving the symmetrical thioanhydride structure of XIX and, by analogy, also of XVIa.

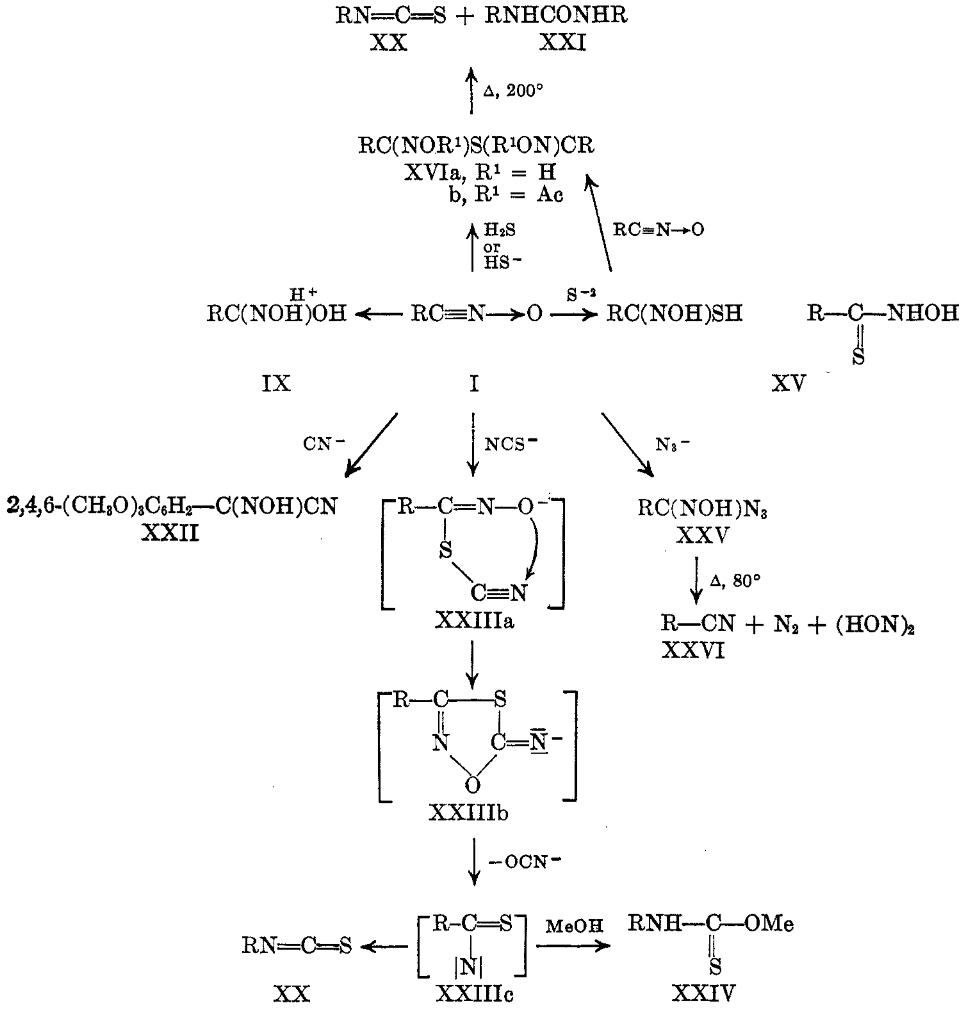


While 2,3,5,6-tetramethyl-benzonitrile oxide and 2,6-dichlorobenzonitrile oxide reacted with hydrosulfide ion to the corresponding thioanhydrides of the hydroximic acids, under the same conditions 2,4,6-trimethoxybenzonitrile oxide, however, was readily reduced to 2,4,6-trimethoxybenzonitrile. The electron-donating effect of the methoxy groups obviously increases the oxidation potential of the C≡N→O group.

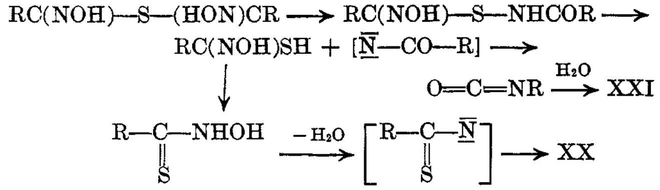
The thermal decomposition of XVIa at 200° gave an almost quantitative yield of 2,4,6-trimethylphenyl isothiocyanate (XX) and 42% of 1,3-di(2,4,6-trimethyl-

Chart II

Addition of Inorganic Reagents to Aromatic Nitrile Oxides



phenyl)urea (XXI). Since XVIa is a kind of acylated hydroximic acid, the mechanism of this transformation may involve first an acyl migration analogous to those observed in similar cases[7] followed by an α elimination of the acyl group, leaving a nitrene intermediate which stabilizes as the isocyanate. The eliminated thiohydroxamic acid will simultaneously undergo an analogous Lossen rearrangement to the isothiocyanate XX, while the water lost in this step converts the isocyanate in the known manner into the urea XXI.



As already established in other cases,[3c,8] hydrocyanic acid did not react with stable nitrile oxides, but cyanide ion added easily. Thus, from I [R = 2,4,6-$(CH_3O)_3$-C_6H_2] there was obtained 2,4,6-trimethoxybenzohydroximyl cyanide (XXII).

From the reaction of thiocyanate ion with I, a compound of the analogous structure R—C(NOH)SCN was expected. Refluxing Ia in methanol solution with potassium thiocyanate, however, resulted in an excellent yield of 2,4,6-trimethylphenylisothiocyanate (XX), while the same reaction at room temperature carried out over a longer period of time gave methyl 2,4,6-trimethylphenylthiocarbamate (XXIV). In the same manner, I [R = 2,3,5,6-$(CH_3)_4C_6H$] yielded methyl-2,3,5,6-tetramethylphenylthiocarbamate [XXIV, R = 2,3,5,6-$(CH_3)_4C_6H$]. The unexpected formation of XX instead of the hydroximyl thiocyanate may best be explained by assuming an initial nucleophilic attack of the nitrile oxide by the thiocyanate ion to XXIIIa followed by an electron shift to a 1,3,4-thiaoxazoline ion (XXIIIb). XXIIIb then decomposes into cyanate ion and the nitrene intermediate XXIIIc which stabilizes itself by rearrangement to the isothiocyanate XX. The expected amount of cyanate ion could be detected in the reaction mixture. Since the isothiocyanates once formed do not react with methanol under the prevailing conditions, one must assume that the addition of the solvent which finally leads to XXIV must occur in a concerted reaction during the decomposition or rearrangement of the intermediates XXIIIb or XXIIIc. At 25°, the lifetime of this intermediate is presumably long enough to allow this reaction to proceed to a major extent, while at 64° the decomposition is too fast, so that the isothiocyanate XX is the main product. The proposed mechanism is

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(8) R. Huisgen, W. Mack and E. Anneser, *Tetrahedron Letters*, 587 (1961).

consistent with the known reaction of aromatic nitrile oxides with thiocarbonyl compounds.[9]

Azide ion reacts with Ia by initial formation of the very unstable mesitohydroximyl azide (XXV) which, above room temperature, splits off nitrogen and hyponitrous acid with the quantitative formation of mesitonitrile (XXVI).[10]

Except for the acid-catalyzed additions of alcohols and water, the above described reactions are 1,3-additions to the nitrile oxide group reacting in the mesomeric form $-\overset{+}{C}{=}N{-}O^-$, all reactions resulting initially in derivatives of hydroxamic acids. These results, in connection with other recent observations,[1-8] correct the claims of the earlier literature about the relative inertness of nitrile oxides and establish this class of compounds among the most reactive in organic chemistry.

Experimental Section[11]

The nitrile oxides employed in the following experiments were prepared by the method recently described,[1] except for benzonitrile oxide which was prepared according to the literature[12] and used immediately after preparation.

Addition of Amines to Aromatic Nitrile Oxides.—The amidoximes II and IV were prepared by mixing ethereal solutions of the nitrile oxide (10 mmoles) with an excess of a saturated solution of ammonia or dimethylamine in methanol or ether. After standing overnight at 25°, the solvent was removed by evaporation under vacuum and the product was recrystallized from ether and petroleum ether (b.p. 30–50°). Thus were obtained **benzamidoxime** (II), m.p. 79° (82%), the melting point of which was not depressed by admixture of an authentic specimen,[13] and **N,N-dimethylmesitamidoxime** (IV), m.p. 134–135° (85%).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.86; H, 8.80; N, 13.58. Found: C, 69.58; H, 8.70; N, 13.35.

N-Phenylbenzamidoxime (III), m.p. 143° (68%), and **N-cyclohexylmesitamidoxime** (V), m.p. 160° (90%), were obtained by the procedure described previously.[1] III was identified by mixture melting point with an authentic specimen[14]; V yielded the required analytical values.

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.80; H, 9.29; N, 10.76. Found: C, 73.60; H, 8.94; N, 10.95.

Reaction of Phenylhydrazine with Aromatic Nitrile Oxides.—When equimolar amounts of phenylhydrazine and the nitrile oxide Ia were mixed in ethanol solution, the reaction mixture soon became purple-violet and later almost black with constant evolution of nitrogen. Only intractable resins were obtained from such runs. Adding gradually a benzene solution of mesitonitrile oxide to a refluxing solution of 1 equiv. of phenylhydrazine in benzene under a nitrogen atmosphere resulted in a yellow resin slowly evolving nitrogen. The reverse mode of addition gave essentially the same results. When an ethereal solution of benzonitrile oxide and phenylhydrazine after standing for 5 hr. at 25° (presumably containing VII among other products) was oxidized with an excess of an aqueous ferric chloride solution, was isolated from the ether layer by extraction with 2 *N* NaOH, neutralization with carbon dioxide, and subsequent recrystallization from a small amount of benzene **benzohydroximylphenyldiimide** (VIII), m.p. 134–135° dec., identical with an authentic sample,[15] yield 10–20%.

Addition of Alcohols to Aromatic Nitrile Oxides. A. Base Catalyzed.—Mesitonitrile oxide (0.290 g., 1.8 mmoles) was dissolved in methanol (60 ml.) and cooled to 0°, whereby part of the nitrile oxide crystallized. With efficient stirring 3.6 ml. of a 1.1 *N* solution of sodium methylate in methanol was then added gradually. The reaction mixture was stirred for 4 hr. at 0° and for 1 hr. more at 25°. The colorless and homogeneous solution was diluted with 125 ml. of water, acidified with 1 *N* H_2SO_4, and extracted four times with 50-ml. portions of ether. The combined ether extracts, dried over sodium sulfate, yielded after evaporation 0.63 g. (83%) of crystalline **methylmesitohydroximic acid (Xa)**, m.p. 110–116°. After four recrystallizations from ether–petroleum ether, a pure sample, m.p. 141–142°, was obtained.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25; mol. wt., 193. Found: C, 68.25; H, 7.63; N, 7.51; mol. wt., 197.

In an analogous manner **ethylmesitohydroximic acid** (**Xb**), m.p. 107° after recrystallization from ether–petroleum ether was obtained in 71% yield.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.35; N, 6.67.

B. Acid Catalyzed.—Mesitonitrile oxide (0.290 g., 1.8 mmoles) was suspended in methanol (20 ml.), a mixture of concentrated H_2SO_4 (5 ml.) and water (5 ml.) was added, and the reaction mixture stirred at 25° for 4 hr., whereby finally a clear solution was obtained. After neutralization of most of the sulfuric acid with 2 *N* NaOH, the still acidic reaction mixture was extracted three times with 50-ml. portions of ether. The combined ether extracts, after drying over sodium sulfate, were evaporated under vacuum yielding 0.335 g. of crude acid (m.p. 125–133°, 96%). Three recrystallizations from ether–petroleum ether yielded 79% of pure **methylmesitohydroximic acid** (**Xa**), m.p. 141–142°, identical with the above-described product. In the same manner **ethylmesitohydroximic acid** (**Xb**), m.p. 106–107, was obtained in 81% yield.

Methyl Mesitohydroxamate (**XII**).—A solution of methoxyamine (3.0 g.) in benzene (25 ml.) was added at 0° to a solution of 2,4,6-trimethylbenzoyl chloride (3.67 g.) in benzene (25 ml.). After standing for 24 hr. at 25°, the precipitate of methoxyamine hydrochloride was removed by filtration and the filtrate was evaporated under vacuum leaving a crystalline residue (3.53 g.) of crude XII. After four recrystallizations from aqueous methanol or ether–petroleum ether, 2.05 g. of XII (53%), m.p. 150–151°, was obtained.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.59; N, 7.32.

Methyl Methylmesitohydroximate (**XI**).—To methyl mesitohydroxamate (XII, 2.78 g.) dissolved in methanol (60 ml.) an ethereal solution of diazomethane was added gradually until the yellow color remained unchanged for 2 hr. After removal of the solvent, the remaining oil was distilled *in vacuo:* b.p. 98–100° (0.5 mm.), $n^{25}D$ 1.5215, yield 74%. After storage for several weeks in the refrigerator, XI crystallized; after drying on porous clay, it had m.p. 43–44°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76; mol. wt., 2.07. Found: C, 69.22; H, 8.11; N, 6.84; mol. wt., 2.01.

Methyl methylmesitohydroximate was also obtained by the reaction of mesitohydroxamic acid (IX) or of methyl mesitohydroximic acid (Xa) with diazomethane under the conditions described above. Samples of all three modes of preparation were identical in boiling point, melting point, and refraction index and they had superimposable infrared spectra.

Ethylmesitothiohydroximic Acid (**XIII**).—Mesitonitrile oxide (1.77 g.) was suspended in ether (10 ml.) and ethanethiol (2 ml.) was added. On occasional shaking the reaction mixture became homogeneous within 2 hr. After standing for 24 hr., solvent and excess mercaptan were evaporated at the water pump leaving behind almost analytically pure XIII. After one recrystallization from ether–petroleum ether, a 92% yield of XIII, m.p. 142–143°, was obtained.

Anal. Calcd. for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.70; H, 7.77; N, 6.45; S, 14.19.

Acetylmesitohydroximic Acid (**XIV**).—Mesitonitrile oxide (0.200 g., 1.24 mmoles) was dissolved at room temperature in

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[9] R. Huisgen, W. Mack, and E. Anneser, *Angew. Chem.*, **73**, 656 (1961). The 1,3,4-thiaoxazolines formed in this reaction as isolable intermediates decompose—depending on the nature of the substituents in 5-position—between room temperature and 150° into the isothiocyanate and the corresponding carbonyl compound.

[10] For the analogous decomposition of benzohydroximyl azide, *cf.* ref. 5. For the structure of hydroximyl azides, *cf.* F. Eloy, *J. Org. Chem.*, **26**, 952 (1961); the ease of decomposition of benzohydroximyl azide and XXV, however, refute this author's claim about the unusual stability of this type of azides.

[11] All melting points were determined with the Fisher-Johns melting point apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular weights were determined by the osmometric method in acetone or chloroform.

[12] A. Quilico and G. Speroni, *Gazz. chim. ital.*, **76**, 148 (1946).

[13] F. Tiemann and P. Krüger, *Ber.*, **17**, 1685 (1884).

[14] A. Werner and T. Herberger, *ibid.*, **32**, 2690 (1899).

[15] E. Bamberger and L. Frei, *ibid.*, **35**, 1091 (1902).

acetic acid (5 ml.) and 4 drops of concentrated sulfuric acid was added. After 1 hr. at 25°, the mixture was held for another hour at 35°, and then diluted with 50 ml. of water and extracted four times with 50-ml. portions of ether. The combined ether extracts were evaporated *in vacuo* and the residue was dried in a vacuum desiccator over KOH until the adhering acetic acid was completely removed. The crude product yielded, after one recrystallization from ether–petroleum ether, 0.246 g. (89%) of XIV, m.p. 136–138° dec. A methanolic solution of XIV gave with ferric chloride solution an intense burgundy red color reaction.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.92; H, 6.64; N, 6.49.

Diacetylmesitohydroximic Acid (XIVa).—A solution of mesitonitrile oxide (0.35 g.) in acetic anhydride (5 ml.) was kept for 48 hr. at 25°. The reaction mixture was then concentrated *in vacuo* to approximately 1 ml., 20 ml. of water was added, and the mixture was heated for 1 min. to 40° and then cooled in ice whereby XIVa crystallized. The crystals were dried *in vacuo* over KOH and phosphorus pentoxide until the last traces of acetic acid were removed, yielding 0.54 g. (95%) of XIVa, melting after one recrystallization from ether–petroleum ether at 65°.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.09; H, 6.60; N, 5.54.

Mesitohydroxamic Acid (IX).—Mesitonitrile oxide (1.00 g.) was dissolved in acetone (20 ml.) and, after addition of 2 *N* H_2SO_4 (20 ml.), stirred at 35° for 6 hr. The now homogeneous reaction mixture was extracted five times with 50-ml. portions of ether. The combined extracts, after drying with sodium sulfate, left after evaporation of the solvent 0.98 g. of IX (88%), m.p. 165–166° after one recrystallization from ether–petroleum ether.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31; N, 7.82; mol. wt., 179. Found: C, 66.97; H, 7.31; N, 7.74; mol. wt., 178.

Addition of Sulfide Ion to Aromatic Nitrile Oxides. Mesitothiohydroxamic acid (XV) was obtained in 92% yield when mesitonitrile oxide (0.60 g.), dissolved in ether (50 ml.), was stirred with a solution of sodium sulfide ($Na_2S \cdot 10H_2O$, 5.6 g.) in water (50 ml.) for 5 hr. at 25°. After acidification with diluted sulfuric acid, the ethereal layer was separated and the aqueous phase was extracted twice with 50-ml. portions of ether. Evaporation of the combined ether extracts left a mixture of sulfur and crude XV, from which the latter was isolated by extraction with petroleum ether. After evaporation of the solvent, pure XV, m.p. 91–92°, remained.

Anal. Calcd. for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.19; S, 16.42; mol. wt., 195. Found: C, 61.69; H, 6.71; N, 6.92; S, 16.51; mol. wt., 201.

Mesitothiohydroximic Acid Thioanhydride (XVIa).—A solution of mesitonitrile oxide (0.32 g.) in ether (20 ml.) was stirred at room temperature with a solution of sodium sulfide (2.4 g.) in water (10 ml.) after adjusting the pH to 8–7 by addition of 2 *N* H_2SO_4. A few minutes later XVIa, which is only slightly soluble in ether, started to separate. After 5 hr. the reaction mixture was acidified with 20 ml. of 2 *N* H_2SO_4, and crude XVIa (0.33 g., 92%) was filtered and recrystallized from acetone or dimethylformamide by addition of water: m.p. 194° dec., resolidifying ~200° and not melting again to 300°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86; S, 8.99; mol. wt., 356. Found: C, 67.19; H, 6.57; N, 7.64; S, 9.17; mol. wt., 360.

XVIa was also obtained in 84% yield when a solution of mesitonitrile oxide (1.08 g.) in ether (50 ml.) and water (10 ml.) was saturated with hydrogen sulfide and left for 24 hr. at 25°. From a solution of mesitonitrile oxide (0.31 g.) and mesitothiohydroxamic acid (XV) (0.38 g.) in methanol (20 ml.), XVIa crystallized in 74% yield after standing for 24 hr. at 25°.

Diacetylmesitothiohydroximic acid thioanhydride (XVIb) was obtained by acetylation of XVIa (0.20 g.) in pyridine (5 ml.) with acetic anhydride (1 ml. at 25°). After standing 24 hr., pyridine and excess acetic anhydride were removed under vacuum. Upon addition of water XVIb crystallized (0.24 g., 97%) and was obtained analytically pure after one recrystallization from ether–petroleum ether, m.p. 175–176°.

Anal. Calcd. for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36; S, 7.28; mol. wt., 440. Found: C, 65.71; H, 6.40; N, 6.30; S, 7.17; mol. wt., 428.

2,3,5,6-Tetramethylbenzothiohydroximic acid thioanhydride [**XVIa, R** = 2,3,5,6-$(CH_3)_4C_6H$] was obtained as described for XVIa above from 2,3,5,6-tetramethylbenzonitrile oxide and sodium sulfide in 67% yield, m.p. 163–164° dec.

Anal. Calcd. for $C_{22}H_{28}N_2O_2S$: C, 68.71; H, 7.34; N, 7.29; S, 8.37; mol. wt., 385. Found: C, 69.04; H, 7.50; N, 7.12; S, 8.17; mol. wt., 388.

Under the same conditions 2,6-dichlorobenzonitrile oxide (1.12 g.) dissolved in methanol (10 ml.) and ether (25 ml.) reacted with sodium sulfide (10 g. in 50 ml. of water) to a semicrystalline product, which was extracted with carbon disulfide (5 ml., extract A). The residue was recrystallized from acetone–petroleum ether and then extracted with a little boiling ether, yielding 46% of **2,6-dichlorobenzothiohydroximic acid thioanhydride (XVIa, R** = 2,6-$Cl_2C_6H_3$), m.p. 192–195° dec.

Anal. Calcd. for $C_{14}H_8Cl_4N_2O_2S$: C, 41.00; H, 1.97; Cl, 34.58; N, 6.83; S, 7.80. Found: C, 41.07; H, 2.00; Cl, 34.35; N, 6.94; S, 7.65.

2,6-Dichlorobenzohydroximyl-2′,4′,6′-trimethylbenzohydroximyl Sulfide (XIX). A. From 2,6-Dichlorobenzothiohydroxamic Acid (XVIII) and Mesitonitrile Oxide.—The above-obtained carbon disulfide extract A was evaporated, leaving behind a mixture of sulfur and XVIII (0.95 g.) from which XVIII was extracted with methanol (10 ml.). After evaporation of the solvent under vacuum, XVIII (0.62 g., 47%) remained as a yellowish oil which showed no tendency to crystallize. Therefore, this product was dissolved together with mesitonitrile oxide (0.50 g.) in methanol (25 ml.) whereupon crystals of XIX started to separate immediately. After 24 hr. at 25°, 0.76 g. was collected. The mother liquor yielded, after concentration and cooling to 0°, another crop (0.25 g.): total yield 94%. XIX was recrystallized from methanol, m.p. 165–166° dec.

B. From Mesitothiohydroxamic Acid (XV) and 2,6-Dichlorobenzonitrile Oxide.—XV (0.52 g.) and 2,6-dichlorobenzonitrile oxide (0.50 g.) were dissolved in 20 ml. of ether and the separated crystals of XIX (0.88 g.) were collected after standing for 24 hr. at 25° and subsequent cooling to 0°. From the mother liquor 0.14 g. more of XIX was obtained. One recrystallization from methanol yielded pure XIX (0.92 g., 90%), m.p. 165–166° dec. The mixture melting point of the samples prepared by the routes A and B, above, was without depression; the infrared spectra were superimposable.

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2S$: C, 53.27; H, 4.21; Cl, 18.50; N, 7.35; S, 8.36. Found: C, 53.18; H, 4.39; Cl, 18.31; N, 7.16; S, 8.33.

2,4,6-Trimethoxybenzonitrile from 2,4,6-Trimethoxybenzonitrile Oxide.—A solution of sodium sulfide (2.4 g.) in water (10 ml.) was adjusted to pH 8 by addition of 1 *N* sulfuric acid, a suspension of 2,4,6-trimethoxybenzonitrile oxide (0.21 g.) in ether (100 ml.) was added, and the reaction mixture was stirred for 5 hr. After acidification with 2 *N* H_2SO_4 (20 ml.), the ethereal layer was separated and the aqueous phase was extracted twice with 20-ml. portions of ether. The combined ether extracts were evaporated; the residue was washed with carbon disulfide to remove sulfur and recrystallized from methanol, yielding 2,4,6-trimethoxybenzonitrile (0.16 g., 83%), m.p. 138–140°, identified by mixture melting point with an authentic sample.[16]

Thermal Decomposition of Mesitothiohydroximic Acid Thioanhydride (XVIa).—In a cold-finger microsublimation apparatus 568 mg. of XVIa were heated to 220° under 0.3-mm. pressure for 4 hr. resulting in a charred residue of 43 mg. and a crystalline sublimate (484 mg.), consisting of a mixture of XX and XXI. Extraction with methanol (10 ml.) left behind 100 mg. (42%) of **1,3-di(2,4,6-trimethylphenyl)urea (XXI)**, not melting to 360° and soluble only with difficulty in most organic solvents.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.13; H, 8.18; N, 9.26.

The methanol extract of the sublimate was evaporated *in vacuo* and a little more XXI separated from the residue on dissolving it in a few milliliters of ether. The ethereal filtrate was evaporated again and the residue was recrystallized from aqueous methanol yielding 270 mg. (95%) of **2,4,6-trimethylphenyl isothiocyanate (XX)**, m.p. 61–62°, identical with an authentic sample.[17]

Anal. Calcd. for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90; S, 18.09. Found: C, 67.60; H, 6.23; N, 7.91; S, 18.19.

2,4,6-Trimethoxybenzohydroximyl Cyanide (XXII).—2,4,6-Trimethoxybenzonitrile oxide (0.51 g.) and potassium cyanide

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(16) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **30**, 2077 (1965).

(17) J. Eisenberg, *Ber.*, **15**, 1012 (1882).

(0.5 g.) were dissolved on the steam bath in a mixture of ethanol (30 ml.) and water (5 ml.). After 10 min. the ethanol was evaporated into the water pump at a bath temperature of 50°; the remainder was diluted with 10 ml. of water and acidified with concentrated HCl, whereby a dark oil precipitated which soon crystallized: yield 92%, m.p. 130–136°. The crude adduct was recrystallized from benzene with charcoal yielding XXII in almost colorless thick platelets, m.p. 148–149° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.09; H, 5.02; N, 11.71.

Reaction of Potassium Thiocyanate with Nitrile Oxides.—Mesitonitrile oxide (0.190 g., 1.18 mmoles) dissolved in methanol (20 ml.) was refluxed for 1 hr. with a solution of potassium thiocyanate (0.115 g., 1.18 mmoles) in methanol (10 ml.) and concentrated to 10 ml., 50 ml. of ether was added, and the solution was extracted twice with 20-ml. portions of water. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated yielding almost pure **2,4,6-trimethylphenyl isothiocyanate (XX)**. After one recrystallization from aqueous methanol, 0.202 g. of XX (96%), m.p. 62.5–63°, was obtained, which did not depress the melting point of an authentic sample.[17] In the above-obtained aqueous extracts, potassium cyanate was identified by the known conversion into urea (0.6 g., 84%).

When the same reaction was carried out at 25–30° over a period of 7 days, a 93% yield of **methyl 2,4,6-trimethylphenylisothiocarbamate (XXIV)** resulted. After one recrystallization from aqueous methanol, XXIV melted at 94°.

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32; mol. wt., 209. Found: C, 63.05; H, 7.13; N, 6.40; S, 14.87; mol. wt., 210.

In the same manner 2,3,5,6-tetramethylbenzonitrile oxide was converted into **methyl 2,3,5,6-tetramethylphenylisothiocarbamate** (93%), m.p. 145° after recrystallization from aqueous methanol.

Anal. Calcd. for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N, 6.27; S, 14.36; mol. wt., 223. Found: C, 64.66; H, 7.48; N, 6.19; S, 14.57; mol. wt., 228.

Mesitohydroximyl Azide (XXV).—Mesitonitrile oxide (1.34 g.) and sodium azide (0.65 g.) were suspended in ice-cold methanol (25 ml.) and stirred at 0° for 2 hr. The homogeneous reaction mixture was neutralized with 1 *N* H_2SO_4, diluted with 50 ml. of water, and extracted twice with 50-ml. portions of ether. The combined ethereal extracts were washed with water, dried over sodium sulfate, and evaporated without heating at the water pump, leaving a crystalline residue (1.65 g., 97%) of the azide XXV. The azide was dissolved at room temperature in a little ether and a large excess of petroleum ether was added, whereupon XXV crystallized on cooling to −10°, (1.44 g.), m.p. 88–89° dec. This product was dried *in vacuo* over P_2O_5 at 0° and then stored in Dry Ice until analyzed.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.44. Found: C, 59.18; H, 6.13; N, 27.67.

The azide XXV decomposed spontaneously after standing for several hours at 25–30° with evolution of nitrogen and nitrogen oxides. The residue crystallized again, melting then at 47–48°, and proved to be almost pure **2,4,6-trimethylbenzonitrile (XXVI)**. After recrystallization from petroleum ether, a product melting at 50–51° was obtained, which did not depress the melting point of an authentic specimen.[16] Decomposition of XXV into XXVI occurred momentarily on contact with nitrogen dioxide or hydrogen chloride.

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1,2-Benzothiazines. III. The Preparation of 2H-1,2-Benzothiazin-4(3H)-one 1,1-Dioxide by the Acid-Catalyzed Deacetylation of β-Diketone

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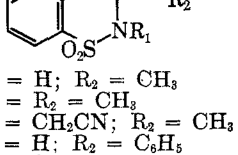
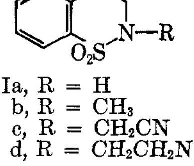
The acid-catalyzed reaction of 3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Ia) with ethylene glycol resulted in deacetylation to give IIa which was hydrolyzed to the ketone IIIa. The reaction did not take place with Ib, Ic, or Id; it did not take place with Ia when ethylene glycol was replaced by monoalcohols. Base-catalyzed condensations of IIIa with aldehydes as well as the conversion of IIa to 2-alkyl, 4-hydroxy, and 4-amino analogs are described.

The preparation of 3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Ia) was described in our previous publication.[1] Continuing our studies in the 1,2-benzothiazine series, we have obtained the ketal IIa in 67% yield by refluxing Ia with ethylene glycol and *p*-toluenesulfonic acid in benzene for 120 hr.; in addition there was isolated 13% of unreacted Ia. This reaction is of particular interest in that it represents an example of the deacylation of a β-diketone under acidic conditions. Although such reactions have been described by Adkins, *et al.*,[2] they do not appear to have enjoyed the widespread application of the classical base-catalyzed procedures.



Ia, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_2CN$; $R_2 = CH_3$
d, $R_1 = H$; $R_2 = C_6H_5$
e, $R_1 = CH_3$; $R_2 = C_6H_5$



IIa, R = H
b, R = CH_3
c, R = CH_2CN
d, R = $CH_2CH_2N(C_2H_5)_2$

It is evident that the reaction has fairly specific structural requirements since the N-substituted compounds Ib and Ic as well as the N-unsubstituted phenyl analog Id were recovered unchanged when subjected to the same reaction conditions. The lack of reactivity of Id is in accord with the observation of Adkins, *et al.*,[2] that dibenzoylmethane is unaffected by the same treatment with ethanolic hydrogen chloride which readily deacetylates benzoylacetone.

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[1] H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 2241 (1965).

[2] (a) H. Adkins, W. Kutz, and D. D. Coffman, *J. Am. Chem. Soc.*, **52**, 3212 (1930); (b) W. M. Kutz and H. Adkins, *ibid.*, **52**, 4036 (1930). These workers observed the hydrogen chloride catalyzed ethanolysis of a series of simple β-diketones and determined some of the structural parameters affecting the reaction rate.