dines assigned the *cis–trans* relationship by Cromwell and his co-workers.[11,32] The ultraviolet spectra for IIa [$\lambda_{max}^{CH_3CN}$ 256 mμ (ϵ 14,000), 297 (sh); λ_{min} 225 mμ (ϵ 3300)] and IIb [$\lambda_{max}^{CH_3CN}$ 258 mμ (ϵ 12,000), ~300 (sh); λ_{min} 228 mμ (ϵ 4100)] appear to indicate lower energy electronic excitations than those for benzylacetophenone [$\lambda_{max}^{CH_3OH}$ 243 mμ (ϵ 13,300), 280 (100),[33,34]] and comparability in wave lengths, although not in extinction coefficients, of the maxima to those of the pair: *cis*-2-benzoyl-1-cyclohexyl-3-phenylaziridine, $\lambda_{max}^{CH_3OH}$ 247 mμ (ϵ 12,000), and *trans*-2-benzoyl-1-cyclohexyl-3-phenylaziridine, $\lambda_{max}^{CH_3OH}$ 253 mμ (ϵ 14,600).[33]

Our isolation of the aziridinium salts IIa and IIb and the determination of their *cis–trans* configurations by independent means support the postulate of the involvement of these aziridinium intermediates in the myriad reactions of the α-bromo-β-morpholinobenzylacetophenones Ia and Ib and are in full accord with earlier stereochemical assignments of intermediates and products.[6-9] We were also able to isolate an aziridinium intermediate from another "form A"[6-9] α-bromo-β-(tertiary amino) ketone. The product of the addition of piperidine to α-bromobenzalacetone,[5,35] *dl-threo-α*-bromo-β-piperidinobenzylacetone (III), was convertible to *dl-cis*-1-acetyl-2-phenyl-3-azoniaspiro[2.5]octane perchlorate (IV) by silver perchlorate in acetone at −40°. The AB doublet signals for the methine hydrogens in the n.m.r. spectra in trifluoroacetic acid and acetonitrile were found at τ 5.26 (C_6H_5CH) and 5.62 (CH_3COCH), and 5.20 and 5.50, respectively, with a coupling constant, $J = 9.7 \pm 0.3$ c.p.s., in the same range as for the *cis* isomer (IIa) of the pair described above. The corresponding aziridinium fluoborate (IV, BF_4^-) was obtained by treating III with silver fluoborate in acetone. The *dl-cis*-1-acetyl-2-phenyl-3-azoniaspiro-[2.5]octane salts were stable for at least 2 years when kept refrigerated under vacuum.

Experimental Section[37]

dl-cis-**1-Benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]octane Perchlorate (IIa).**—To a solution of 6.0 g. (16 mmoles) of *dl-threo*-α-bromo-β-morpholinobenzylacetophenone (form A) (Ia)[4,6,16-19,37] in 240 ml. of methylene chloride maintained at −40° was added 3.32 g. (16 mmoles) of silver perchlorate in 100 ml. of anhydrous acetone. The silver bromide was removed by filtration, and the filtrate was treated with absolute ether to yield an off-white precipitate. Recrystallization from methylene chloride gave 5.0 g. (79%) of colorless elongated prisms: m.p. 150°; ν_{max}^{Nujol} 1707 (s), 1596 (m), 1505 (w), 1283 (m), 1234 (m), 1221 (m), 1100 (s, broad), 966 (m), 950 (m), 874 (m), 790 (m),743 (m), 712 (m), 697 (m), 617 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.62; H, 5.19; N, 3.79.

dl-trans-**1-Benzoyl-2-phenyl-6-oxa-3-azoniaspiro[2.5]octane Perchlorate (IIb).**—*dl-erythro-α*-Bromo-β-morpholinobenzylacetophenone (form B) (Ib) was prepared by the method of Southwick and Walsh[20]: m.p. 137–139°, $\nu_{max}^{CHCl_3}$ 860 and 885 cm.$^{-1}$, a doublet distinguishing it from the *threo*, form A; n.m.r. signals ($CDCl_3$) at τ 1.8–2.7 (phenyl), 4.42 (α-CH), 4.96 (β-CH), an AB system with J = 11 c.p.s., 6.75 (CH_2OCH_2), and 7.55 (CH_2NCH_2). To a solution of 1.0 g. (2.67 mmoles) of this form B in 20 ml. of anhydrous methylene chloride chilled in Dry Ice was added a solution of 0.553 g. (2.67 mmoles) of anhydrous silver perchlorate in benzene. Silver bromide formed instantly, mixed with colorless aziridinium perchlorate. Within 5 min., the addition and reaction were complete, and the suspension was filtered immediately. The solid was washed rapidly with two portions of 10 ml. of benzene and rinsed with anhydrous ether. The aziridinium perchlorate was separated from silver bromide by dissolving in 50 ml. of anhydrous methylene chloride and filtering. The filtrate was concentrated under vacuum without heating. The colorless needles which formed were collected by rapid filtration, m.p. 146–148°, yield 0.5 g. (50%). A second crop with lower melting point but essentially identical infrared spectrum was obtained by adding ether to the filtrate: 0.4 g. (38%); ν_{max}^{Nujol} 1690 (s), 1602 (m), 1500 (w), 1281 (m), 1234 (m), 1100 (s, broad), 955 (m), 862 (m), 768 (m), 739 (m), 705 (m), 620 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.75; H, 5.20; N, 3.61.

dl-cis-**1-Acetyl-2-phenyl-3-azoniaspiro[2.5]octane Perchlorate (IV).**—To a solution of 2.0 g. (6.4 mmoles) of *dl-threo-α*-bromo-β-piperidinobenzylacetone (form A) (III)[5,35] in 200 ml. of anhydrous acetone maintained at −40° was added 1.34 g. (6.4 mmoles) of silver perchlorate in 100 ml. of anhydrous acetone. After filtration of the silver bromide, the filtrate was evaporated to dryness under vacuum and the remaining colorless residue was washed well with absolute ether. Recrystallization from anhydrous acetone yielded 1.05 g. (61%) of colorless crystals, m.p. 135–135.5°, ν_{max}^{Nujol} 1730 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{15}H_{20}ClNO_5$: C, 54.64; H, 6.10; N, 4.25. Found: C, 54.69; H, 6.25; N, 4.06.

The fluoroborate (IV, BF_4^-) was made in anhydrous acetone from III and silver fluoborate. Crystallization was induced by addition of ether to the filtered and concentrated acetone solution, yielding 84% of colorless crystals, m.p. 129–130°, ν_{max}^{Nujol} 1728 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{15}H_{20}BF_4NO$: C, 56.80; H, 6.36; N, 4.42. Found: C, 56.55; H, 6.60; N, 4.60.

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[32] N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

[33] N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, *J. Am. Chem. Soc.*, **82**, 4241 (1960). One must take into account the difference in solvents employed.

[34] N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

[35] N. H. Cromwell, *J. Am. Chem. Soc.*, **63**, 837 (1941).

[36] Melting points were determined in open capillary tubes and are uncorrected. We are indebted to Mr. Josef Nemeth and his staff for the microanalyses. The infrared spectra were determined with a Perkin-Elmer Model 521 grating spectrophotometer and the n.m.r. spectra with a Varian Associates Model A-60 spectrometer.

[37] We are grateful to Professor P. L. Southwick, Carnegie Institute of Technology, for identifying our synthesized material independently as form A on the basis of infrared spectrum (a single band present at *ca.* 875 cm.$^{-1}$ ($CHCl_3$) distinguishes form A from form B), crystal habit, and melting point (in order of decreasing usefulness).

The Acylation of Benzamidoximes

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Received April 27, 1965

The classical approach to the 1,2,4-oxadiazole ring is through the reaction of amidoximes with acid chlorides and anhydrides.[1,2] The intermediate in this reaction is generally accepted to be the O-acylamidoxime, although this assignment has been based solely on infrared and chemical properties.[1-3] In order to elucidate further the nature of the intermediate acylamidoxime, the reaction of benzamidoxime and benzoyl chloride has been studied.

The synthesis of O-benzoylbenzamidoxime 1 has now been accomplished in an unequivocal manner by the reaction of O-benzoylbenzhydroxamoyl chloride[4]

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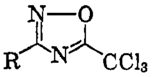
[1] E. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).

[2] L. C. Behr, "1,2,4-Oxadiazoles," "Heterocyclic Compound," R. W. Wiley, Ed., Vol. 17, Interscience Publishers, Inc., New York, N. Y., 1962, p. 245 ff.

[3] F. Eloy, R. Lenaers, and C. Moussebois, *Helv. Chim. Acta*, **45**, 437 (1962).

[4] Prepared by the method of H. Wieland and Z. Kitasato, *Ber.*, **62**, 1253 (1929). The intermediate benzhydroxamoyl chloride was prepared by the method of G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Am. Chem. Soc.*, **79**, 646 (1957).

TABLE I



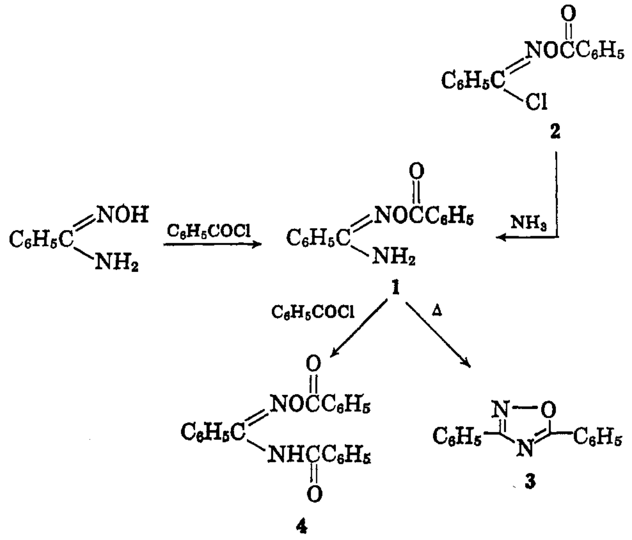
1,2,4-OXADIAZOLES FROM SUBSTITUTED AMIDOXIMES AND TRICHLOROACETIC ANHYDRIDE

			Analysis, %					
			Carbon		Hydrogen		Nitrogen	
R	M.p., °C.	Yield, %	Calcd.	Found	Calcd.	Found	Calcd.	Found
4-$CH_3C_6H_4$–	70–70.5	53	43.27	42.93	2.54	2.90	10.10	9.65
4-$NO_2C_6H_4$–	107–107.5	45	35.11	35.14	1.30	0.97	13.68	13.54
3-$NO_2C_6H_4$–	125	84	35.11	34.93	1.30	1.01	13.68	13.53
C_6H_5–	25–26[a]	69						

[a] R. Lenaers and F. Eloy [*Helv. Chim. Acta*, 46, 1067 (1963)] reported m.p. 26.5°.

(2) with ammonia.[5–7] Comparison of this material by mixture melting point and infrared spectra with the benzoyl benzamidoxime prepared by reaction of benzamidoxime with benzoyl chloride in pyridine[8] or in toluene at room temperature showed the materials to be identical.[7] In none of these cases was 3,5-diphenyl-1,2,4-oxadiazole (**3**) observed as might be predicted had N benzoylation occurred.[6]

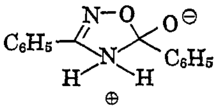
Cyclization of **1** to the oxadiazole **3** could be effected either by heating at the melting point[9] or more slowly (20 hr.) in refluxing toluene. When the latter conditions were employed with the addition of 1 equiv. of benzoyl chloride, the major product was the dibenzoyl compound **4** with small amounts of **3** being formed. Reaction of benzamidoxime with 1 equiv. of benzoyl chloride in refluxing toluene gave predominantly **3** with a small amount of **4**.



Evidence supporting the intermediacy of O-acylarylamidoximes was also found in the reactions of various arylamidoximes with trichloroacetic anhydride (Table I). The reaction proceeded in the expected manner in all cases except that of 4-methoxybenzamidoxime, from which the only product isolated was 1-(4-methoxyphenyl)-3-trichloroacetylurea. The structural assignment was based on elemental analysis and independent synthesis from 4-methoxyphenyl isocyanate and trichloroacetamide. Reaction of 4-methoxybenzamidoxime with acetic anhydride under similar conditions gave only the expected oxidazole.

The formation of the urea derivative is most likely the result of an initial O acylation followed by a Beckmann-type rearrangement. The analogous reaction has been reported for O-sulfonylamidoximes.[10] The present example is apparently the first one involving an acylamidoxime and is explicable because of the high migratory tendency of the 4-methoxyphenyl group coupled with the stability of the trichloroacetate anion.

The results from the reaction of benzoyl chloride or trichloroacetic anhydride with arylamidoximes suggest that the predominant initial product is the O-acyl compound. This may eliminate water to form an oxidiazole, react further with acylating agent to form an O,N-diacyl compound, or, depending upon substituents, undergo a Beckmann rearrangement. No evidence was found for an O to N benzoyl migration in O-benzoylbenzamidoxime (**1**). Such a rearrangement would involve the intermediate **5** which would also be intermediate in the cyclization of **1** to **3**.



5

Experimental Section

The infrared studies were carried out in 1% potassium bromide plaques using a Perkin-Elmer Mdel 21 spectrophotometer; n.m.r. spectra were obtained using a Varian A-60 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

O-Benzoylbenzamidoxime (1) from O-Benzoylbenzhydroxamoyl Chloride and Ammonia.—To a solution of 5.2 g. (0.02 mole) of **2** in 20 ml. of methylene chloride was added, at room temperature, dropwise with stirring 3.8 ml. (equivalent to 0.042 mole of NH_3) of ethanolic ammonia. No heat evolution was noted, but a solid began to separate quite rapidly. After 30 min. at room temperature an additional 1 ml. of ethanolic ammonia was added, and after 30 min. the mixture was filtered to give, after drying, 0.87 g. of white solid, shown by infrared studies to be NH_4Cl (theory of NH_4Cl is 1.04 g.). An additional 3.8 ml. of ethanolic ammonia was then added; since after 20 min. no more solid had formed, the liquid was concentrated by evaporation under a

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(5) R. Boyle [*Helv. Chim. Acta*, **46**, 1073 (1964)] isolated only 1-phenylurea and benzamidoxime from the ammonolysis of O-(phenylcarbamoyl)-benzhydroxamoyl chloride.

(6) Recent efforts to prepare the analogous N-benzoylbenzamidoxime by reaction of hydroxylamine with ethyl N-benzoyliminobenzoate gave only 3,5-diphenyl-1,2,4-oxadiazole (**3**); the intermediate N-benzoylbenzamidoxime was presumably too unstable to isolate [F. Eloy, R. Lenaers, and R. Buyle, *Bull. soc. chim. Belges*, **73**, 518 (1964)].

(7) The n.m.r. and infrared spectra of **1** are in agreement with data presented for similar compounds by C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **29**, 2873 (1965). Further agreement is found with the infrared data for a series of O-acylamidoximes in ref. 6.

(8) F. Tiemann and P. Kruger, *Ber.*, **17**, 1694 (1884).

(9) F. Tiemann and P. Kruger, *ibid.*, **17**, 1685 (1884).

(10) See ref. 1, p. 180.

stream of dry nitrogen. The residue was triturated with 40 ml. of water, then 10 ml. of petroleum ether (30–60°) was added, and the mixture was stirred for 15 min. Filtration gave ultimately 2.07 g. whitish solid.

This solid was dissolved with heating in 20 ml. of ethanol, filtrated while hot, and allowed to crystallize with chilling. There was obtained by filtration 0.7 g. of crystals, m.p. 142–143°, shown by infrared studies and mixture melting point (144–145.5°) to be identical with **1**.[11] The residue from this fraction (0.55 g.) obtained by evaporation in a dry nitrogen stream was shown by infrared studies to be impure **1** giving a crude yield of 26% and a purified yield of 14% of **1**. An infrared spectrum showed the following bands, 5.75 (C=O) and 3.02 and 6.19 μ (NH_2), while an n.m.r. spectrum (deuterated dimethylformamide, tetramethylsilane internal standard) showed complex multiplets centered at 7.55, 7.95, and 8.29 p.p.m. (10 H, aromatic) and a broad singlet at 7.2 p.p.m. (2 H, NH_2); the latter shifted by addition of hydrogen chloride vapors.

The Reaction of Benzamidoxime and Benzoyl Chloride in Toluene. A. O-Benzoylbenzamidoxime (1).—To a suspension of 2.72 g. (0.02 mole) of benzamidoxime in 70 ml. of toluene was added in one portion with stirring 2.62 g. (0.02 mole) of benzoyl chloride. A fine white solid began to form. The reaction mixture was stirred at room temperature overnight and filtered to give, when dry, 4 g. of solid. Recrystallization from ethanol gave white crystals, m.p. 135–140°. A small portion crystallized a second time from ethanol had m.p. 147–148°. A mixture melting point with known material was undepressed.[11] Infrared comparison with known material[11] and that from the preceding run showed the three materials to be identical.

B. 3,5-Diphenyl-1,2,4-oxadiazole (3) and O,N-Dibenzoylbenzamidoxime (4).—A mixture of 13.6 g. (0.1 mole) of benzamidoxime and 14 g. (0.1 mole) of benzoyl chloride in 400 ml. of toluene was refluxed for 20 hr. when the theoretical amount of water had separated. A small amount of insoluble tar remained in the reaction flask. The hot toluene solution was decanted from this. Upon cooling, light yellow crystals separated and were collected. From the toluene solution was isolated, by concentration to 40 ml., 15 g. (65% yield) of 3,5-diphenyl-1,2,4-oxadiazole (**3**), m.p. 104.5–106°. Recrystallization from hexane gave 13 g. of material, m.p. 106–107°.[12]

The lemon yellow crystalline material was triturated with 10% sodium hydroxide, filtered, washed with water, and finally recrystallized from ethanol to give a white crystalline material, m.p. 193–193.5°. A similar experiment using xylene as a solvent gave this same material for a combined yield of 2.5 g. Recrystallization from ethanol followed by drying under vacuum gave **4**, m.p. 200–201°, identical with **4** prepared in the following experiments. An infrared spectrum showed C=O bands at 5.72 and 6.0 with an NH band at 3.08 μ.

Anal. Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.21; H, 4.70; N, 8.26.

Reaction of O-Benzoylbenzamidoxime (1) with Benzoyl Chloride in Refluxing Toluene.—A mixture of 7.2 g. (0.03 mole) of **1** and 4.2 g. (0.03 mole) of benzoyl chloride in 65 ml. of toluene was heated at reflux. Complete solution occurred, but, after about 20 min., a solid began to separate. The reflux was continued for 3.5 hr. when the reaction mixture was cooled to room temperature. The solid (A) was collected and dried. The toluene filtrate was evaporated with a nitrogen stream to residue B. Solid A (7.51 g.) was recrystallized from 1 l. of ethanol. There was obtained 4.5 g. (44% yield) of material, m.p. 193–194°, shown by infrared comparison to be identical with **4** from the preceding and subsequent experiments.

The residue (B) from the toluene evaporation was triturated with 10% sodium hydroxide solution to remove acidic material, and the insoluble material was extracted with five 20-ml. portions of petroleum ether (b.p. 60–75°). These extracts were filtered through a mixture of charcoal and potassium carbonate on a filter bed, and the filtrate was evaporated to about 15 ml. Chilling and filtration gave 0.25 g. of **3**, m.p. 106–108°,[12] confirmed by infrared studies.

O,N-Dibenzoylbenzamidoxime (4).—This material was prepared in a manner analogous to benzoylbenzamidoxime **1**, except that 3.1 g. (0.025 mole) of benzamidoxime, 7.0 g. (0.05 mole) of benzoyl chloride, and 40 ml. of pyridine were employed.[11] There was obtained 4 g. (48% yield) of a white crystalline material melting at 198.5–200° dec. This material was identical (by infrared comparison and mixture melting point) with **4** isolated in the preceding experiments.

Cyclization of O-Benzoylbenzamidoxime (1) in Refluxing Toluene.—A suspension of 2 g. (0.08 mole) of **1** in 20 ml. of toluene was heated at reflux (complete solution occurred) and held there about 20 hr. The cooled solution was filtered, and the filtrate was evaporated leaving 1.84 g. (100% yield) of **3**, m.p. 105–106°.[12]

General Procedure for the 1,2,4-Oxadiazoles in Table I.—To 61 g. (0.2 mole) of trichloroacetic anhydride in a 250-ml. erlenmeyer flask protected with a calcium chloride drying tube was added portionwise, with stirring, at room temperature over 20 min., 0.1 mole of the required amidoxime. When addition was complete, the mixture was heated at 90–120° for 75 min., and the hot mixture was then poured, with stirring, into ice–water. The resulting solid was recrystallized from a solvent such as hexane or isopropyl ether to give the products shown in Table I.

1-(4-Methoxyphenyl)-3-trichloroacetylurea. A. From Methoxybenzamidoxime and Trichloroacetic Anhydride.—The preceding procedure was applied to 4-methoxybenzamidoxime. The solid which separated upon water quenching was collected on a filter and dissolved, with heating, in a mixture of 200 ml. of water and 450 ml. of ethanol; the solution was filtered through charcoal and cooled at room temperature. The solid was collected and air dried (m.p. 124–131°), then dried in a 40° vacuum oven, and recrystallized from 500 ml. of isopropyl ether to give 9 g. (31% yield) of white shiny crystals, m.p. 131–133°. An infrared spectrum showed the following bands: 3.04 (NH), 5.8 (C=O), 8.15 (C—O), and 12 μ (1,4-disubstituted phenyl).

Anal. Calcd. for $C_{10}H_9Cl_3N_2O_3$: C, 38.55; H, 2.90; N, 8.99. Found: C, 38.40, 38.28; H, 2.75, 3.08; N, 8.99, 9.06.

B. From 4-Methoxyphenyl Isocyanate and Trichloroacetamide.—A mixture of 21 g. (0.13 mole) of 4-methoxyphenyl isocyanate and 16.3 g. (0.1 mole) of trichloroacetamide in 125 ml. of xylene was refluxed for 20 hr., during which time complete solution took place. The reaction mixture was then cooled at room temperature for 24 hr., and the solid which formed was collected and air dried. There was isolated 17 g. of solid material which, upon extraction with 200 ml. of boiling isopropyl ether, partially dissolved. The isopropyl ether solution, after charcoal treatment and cooling, gave 3 g. of white crystals, m.p. 131.5–133.5°. The isopropyl ether insoluble material was crystallized from 50 ml. of boiling toluene to give 7.5 g. of white crystals, m.p. 130–131.5°. The total yield of the urea was 10.5 g. (34% yield). Infrared comparison showed it to be identical with the product from 4-methoxybenzamidoxime and trichloroacetic acid anhydride.

3-(4-Methoxyphenyl)-5-methyl-1,2,4-oxadiazole.—To 20 g. of acetic anhydride was added to room temperature, portionwise, and stirring 8 g. (0.048 mole) of 4-methoxybenzamidoxime. When addition was complete, the mixture was refluxed for 1 hr. and then poured over ice with stirring to give a white solid (7.5 g.). Recrystallization from ethanol–water gave 6 g. (66% yield) of product, m.p. 58–59°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.88; H, 5.41; N, 14.73.

4-Methoxybenzamidoxime.—Using the general procedure of Miller[13] a solution of 17 g. (0.25 mole) of hydroxylamine hydrochloride, 10.6 g. (0.1 mole) of sodium carbonate, and 13.3 g. (0.1 mole) of 4-methoxybenzonitrile in 100 ml. of water and enough ethanol (~100 ml.) to give a clear solution was allowed to react at 70° for 24 hr. The mixture was concentrated under vacuum until solid separated, and after chilling, this solid was collected and air dried. Recrystallization from toluene with azeotropic drying gave 10 g. of white crystals, m.p. 102–117°. A second recrystallization gave a product with m.p. 121–124°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: N, 16.86. Found: 16.72.

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(11) Lit.[8] m.p. 148–9.5° (from ethanol). Calcd. for $C_{14}H_{12}N_2O_2$: N, 11.66; mol. wt., 248. Found: N, 11.24, mol. wt. (ebullioscopic), 248.

(12) Infrared comparison with a material (m.p. 108°) prepared from **1** after the method of ref. 8, p. 1685, showed the materials to be identical.

(13) J. A. Miller, *Ber.*, **22**, 2791 (1889).