# Reactions of 1,2-Dimethyl-5-nitroimidazole, Novel Methods of Conversion of the 2-Methyl Group to a Nitrile

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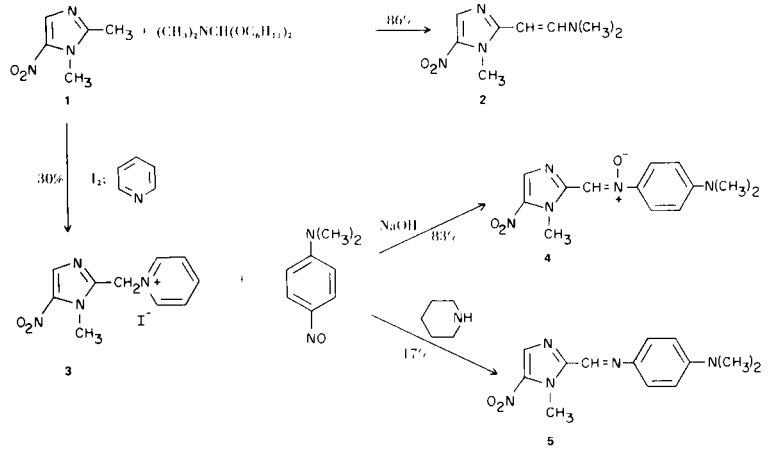
1,2-Dimethyl-5-nitroimidazole (**1**) and *N,N*-dimethylformamide dicyclohexylacetal gave the 2-(β-dimethylaminovinyl) analog **2** and with iodine and pyridine gave the 2-(1-pyridinium)methyl compound **3**. Benzoyl chloride-triethylamine and **1** led to benzoylation of the 2-methyl group to give ketone **9** as the enol benzoate. Nitrous acid or nitrosylsulfuric acid with **9** or its enol ester afforded the oximinoketone **10** which was cleaved with thionyl chloride to give 2-cyano-1-methyl-5-nitroimidazole (**11**) in high overall yield. 1-Ethyl-2-methylbenzimidazole (**22**) was converted to 2-cyano-1-ethylbenzimidazole (**25**) similarly. Reaction of **1** with ethyl oxalyl chloride and triethylamine afforded ethyl 1-methyl-5-nitro-2-imidazolepyruvate (**19**) as the enol oxalate. Nitrous acid and **19** gave the oximino pyruvate **20** which effervesced on mild heating to give 2-cyano-1-methyl-5-nitroimidazole (**11**). The preparation of 1-methyl-5-nitro-2-imidazoleacetonitrile (**39**) is reported.

The discovery that 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**13**) exhibited broad spectrum antibacterial and antiprotozoal activity (1) has led to the synthesis of numerous related compounds. We undertook synthetic studies which appeared to have potential for obtaining new intermediates useful in the preparation of additional heterocyclic analogs. 1,2-Dimethyl-5-nitroimidazole (**1**) was chosen for initial exploratory work since the 2-methyl group of **1** was theoretically amenable to modification.

Numerous attempts to oxidize the 2-methyl group or to substitute the 2-methyl group with halogen under a variety of conditions (2) were unsuccessful. Reaction of **1** with iodine and anhydrous potassium acetate in ethanol or in refluxing acetic acid as well as the reaction of **1** with iodine and pyridine in dimethyl sulfoxide at 100° was unsuccessful. Reaction of **1** with mercuric acetate in ethanol or in acetic acid was futile as were attempts to condense the 2-methyl group under basic conditions (potassium hydroxide in ethanol or *N,N*-diisopropylethylamine in dioxane) with nitroso derivatives (3) such as *N,N*-dimethyl-*p*-nitrosoaniline and isoamylnitrite. No oxidation of the 2-methyl group occurred on reaction of **1** with ceric ammonium nitrate in refluxing 90% acetic acid, although this procedure (4) has been used in the conversion of aromatic methyl groups to aldehydes. Acid-catalyzed formylation of **1** with ethyl orthoformate and 70% perchloric acid or ethyl orthoformate and acetic



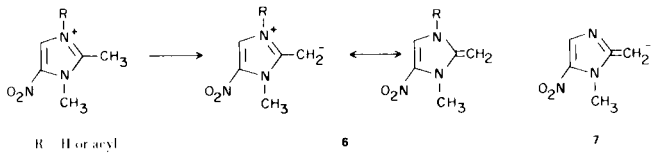
anhydride was also unsuccessful.

We discovered that 1,2-dimethyl-5-nitroimidazole (**1**) reacts with *N,N*-dimethylformamide dicyclohexylacetal (3a,5) at 140° to give the Vilsmeier-Haack product **2** in good yield. In addition, reaction of **1** with iodine and pyridine (Ortoleva-King reaction) (6,7) at 110-115° gave a moderate yield of the pyridinium compound **3**.

Pyridinium compounds of type **3** are useful intermediates (8) for they react with aromatic nitroso compounds under base catalysis to give either a nitrone or an aldinine derivative (9). In effect, the Ortoleva-King reaction followed by reaction with a nitroso derivative is a non-oxidative method for conversion of a methyl group to an aldehyde. Pyridinium derivative **3** and *N,N*-dimethyl-*p*-nitrosoaniline in aqueous ethanolic sodium hydroxide gave nitrone **4** (83%) while **3** with *N,N*-dimethyl-*p*-nitrosoaniline in ethanol under piperidine catalysis afforded **5** aldinine derivative (17%).

Vilsmeier product **2** is also a potentially useful intermediate for the preparation of 1-methyl-5-nitroimidazole-2-carboxaldehyde either through cuprous chloride oxygenation (10) or dye-sensitized photooxygenation of the double bond (11). However, oxygenation of enamine **2** with oxygen and cuprous chloride failed to affect the double bond. Other reagents reactive with typical enamines also failed to react with enamine **2**, as discussed later in this report.

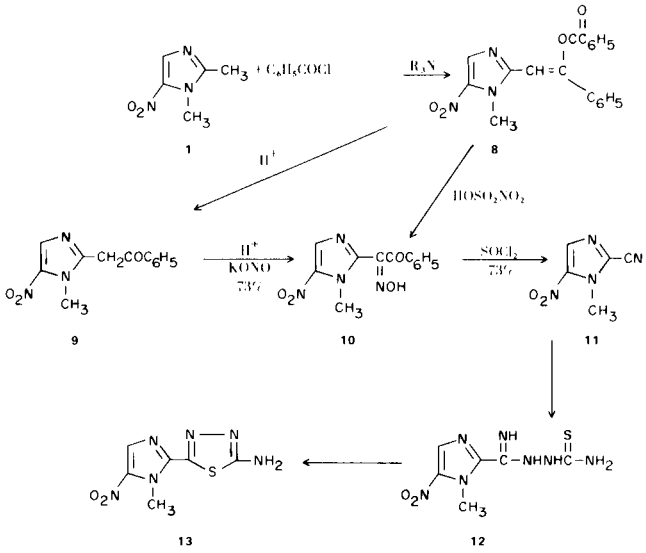
The successful results encountered in modifying the 2-methyl substituent of **1** encouraged us to explore further reagents and conditions for functionalizing the 2-methyl group of imidazole **1**. Mechanistically, acid catalysis should generate a reactive intermediate of type **6** and base catalysis should yield anion **7**. Both species would react with electrophiles at the 2-methyl function,



R = H or acyl 6 7

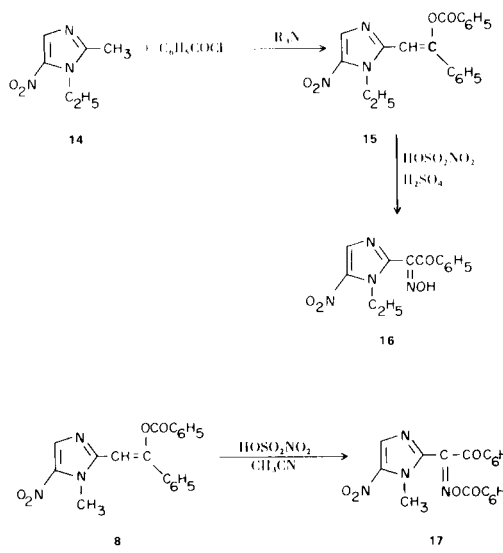
but the chemical experience discussed previously indicated that for reaction at the weakly activated methyl group it is necessary to generate such anions (preferably in low concentration to avoid decomposition) in the presence of a reactive substrate. Generation of anion **6** or **7** with a hindered tertiary base which would not interact with an acylating agent appeared to meet the criteria for successfully modifying the 2-methyl group; therefore, 1,2-dimethyl-5-nitroimidazole (**1**) was allowed to react with benzoyl chloride and *N,N*-diisopropylethylamine in refluxing dioxane. With a 2 to 3 molar excess of benzoyl chloride the yield of enol benzoate **8** was 80-90%. Subsequent studies showed that trimethylamine or triethylamine were also effective tertiary bases. This novel type of reaction with a heterocycle containing a weakly activated methyl group has been applied to other heterocycles (*vide infra*); however, its scope and limitations have not been thoroughly investigated.

Of immediate interest was the conversion of enol benzoate **8** to 2-cyano-1-methyl-5-nitroimidazole (**11**) which is a useful intermediate for the preparation of **13**. Acid hydrolysis of enol benzoate **8** afforded ketone **9** (75%) which was reacted with potassium nitrite in acetic acid (12) to give oximino ketone **10** (73%). Isoamyl-nitrite under acid (hydrochloric acid) or base (*N,N*-diisopropylethylamine) catalysis also converted ketone **9** to oximino ketone **10** but in very poor yields. Cleavage of **10** with thionyl chloride cleanly gave nitrile **11** (73%), while heating **10** at 210° afforded nitrile **11** in low yield. The fragmentation of oximino phenyl ketones to nitriles by heating above 200° or by reacting with reagents such as thionyl chloride is a known (13) but not widely used reaction in organic synthesis.



A direct conversion of enol benzoate **8** to oximino ketone **10** could be accomplished with potassium nitrite in sulfuric acid (nitrosylsulfuric acid) (14) in 78% yields. Thus, the overall conversion of 1,2-dimethyl-5-nitroimidazole (**1**) to 2-cyano-1-methyl-5-nitroimidazole **11** constitutes a practical preparation of 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**13**), since the conversion of **11** to **12** and ring closure to **13** in good yields has been established (15).

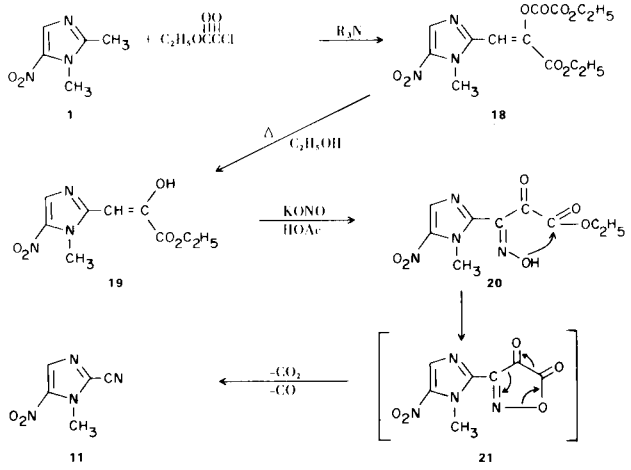
1-Ethyl-2-methyl-5-nitroimidazole (**14**) was allowed to react with benzoyl chloride and *N,N*-diisopropylethylamine in refluxing dioxane to give enol benzoate **15** (46%) which was directly converted to oximino ketone **16** (50%) with nitrosylsulfuric acid (14) in sulfuric acid.



A brief study of the reaction of enol benzoate **8** with nitrosylsulfuric acid in acetonitrile was carried out with the following results. A 25% molar excess of nitrosylsulfuric acid in acetonitrile gave incomplete reaction (*ca.* 20%) while a 1.5 molar excess afforded an 86% yield of solid which contained approximately 60% of product **17** and 40% of starting material **8** as evidenced by thin-layer chromatography. In attempts to drive the reaction to completion the enol benzoate **8** was stirred with a 4 molar excess of nitrosylsulfuric acid in acetonitrile for 67 hours; however, although no starting material was isolated, only a 21% yield of the oxime benzoate **17** was obtained.

Several aspects of the chemistry of the new intermediates require further discussion. For example, the enol benzoate **8** was hydrolyzed with ammonium hydroxide in aqueous tetrahydrofuran to the ketone **9** (43%) but a new compound with the empirical formula $C_{24}H_{21}N_5O_4$ (dimer minus the elements of $HNO_2$) was also isolated. The molecular weight and composition of the new product were established by analysis and high-resolution mass spectrometry. Neither the mass-spectral fragmentation nor the pmr spectrum provided enough definitive information for a structural assignment and the nature of this substrance remains unknown.

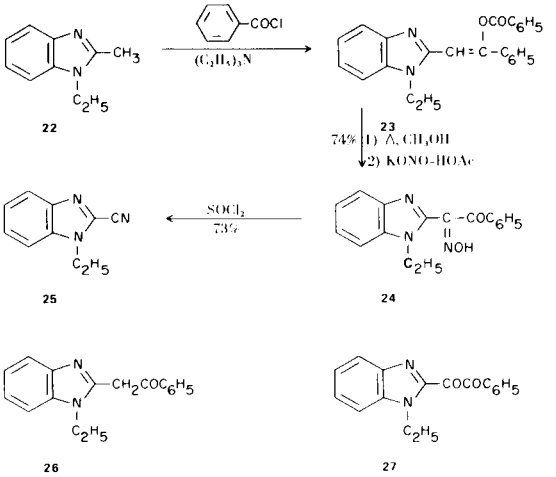
A second novel process for conversion of an activated methyl group to a nitrile was developed by reaction of 1,2-dimethyl-5-nitroimidazole (**1**) with ethyloxalyl chloride and triethylamine in toluene to give the enol ethyloxalyl derivative **18**. Heating **18** with ethanol readily removed the ethyloxalyl group to give **19** (50-55% overall yield from **1**), which exists completely in the enolic form as evidenced by its infrared and pmr spectra. Reaction of pyruvate derivative **19** with potassium nitrite in glacial acetic acid afforded the unstable oximino pyruvate **20** as an oil. This impure oil which showed a nitrile band in its infrared spectrum readily effervesced on warming on a steam bath to give crystalline nitrile **11** in 85% overall yield from **19**. A reasonable mechanistic pathway for



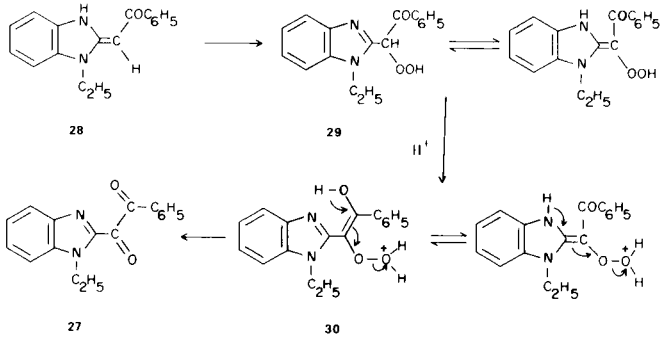
formation of the nitrile **11** from **19** involves the oximino pyruvate **20** (not characterized) which cyclizes to **21**. Loss of carbon dioxide and carbon monoxide from intermediate **21** then gives nitrile **11**. This sequence of reactions has not been completely investigated but nevertheless constitutes a new alternative procedure for converting an activated methyl group to a nitrile function. 1,2-Dimethyl-5-nitroimidazole (**1**) in the presence of a tertiary amine (triethylamine or *N,N*-diisopropylethylamine) was not acylated by acetic anhydride, acetyl chloride, ethyl chloroformate, trichloroacetyl chloride, *p*-toluenesulfonyl chloride or phenylisocyanate.

Application of the benzoyl chloride-triethylamine acylation procedure to different heterocycles containing weakly activated methyl groups was investigated. 2-Picoline, 2-methylquinoline and 2,4-dinitrotoluene failed to react. 1-Ethyl-2-methylbenzimidazole **22** gave the expected enol benzoate **23** in excellent yield (91%). Hydrolysis of the enol benzoate **23** by heating in methanol produced an oil (not purified) which was readily converted with potassium nitrite and glacial acetic acid to oximino ketone **24** (74%). Fragmentation of oximino ketone **24** afforded 2-cyano-1-ethylbenzimidazole (**25**) (73%).

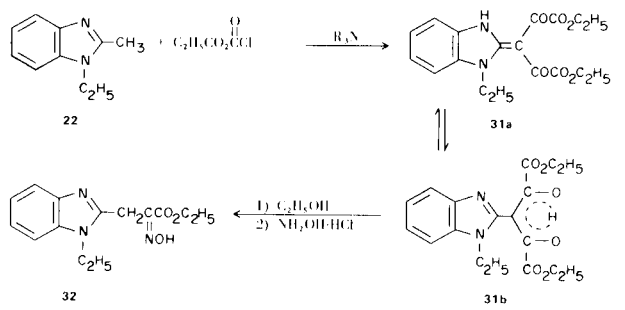
One attempt to purify intermediate ketone **26** by chromatography over silica gel with chloroform-ethanol as eluent led to the isolation of diketone **27**. The original oil **26** showed only trace impurities on thin-layer chromatography (tlc) while tlc of the fractions from the column showed new spots with the principle new component being **27**. Confirmation of diketone structure **27** rests on its analysis, ir and pmr spectra and on the mass spectrum which showed characteristic peaks at m/e 278 ($M^+$), 249 ($M^+$-$C_2H_5$), 173 ($M^+$-$C_6H_5CO$), 145 ($M^+$-$C_6H_5COCO$), 105 ($C_6H_5CO^+$). A possible mechanism



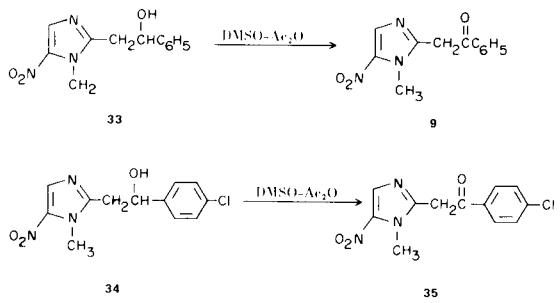
for formation of diketone **27** from **26** involves oxidation of tautomer **28**, which may be viewed as an enamine. Since enamines are known to react with oxygen or peroxides, a reasonable first step is the formation of peroxide **29** which undergoes conversion to α-diketone **27** by way of protonated intermediate **30**.



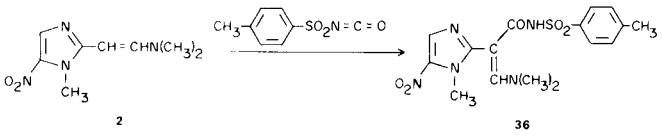
Straightforward acylation of 1-ethyl-2-methylbenzimidazole with ethyloxalyl chloride to give an enol ester was not observed; instead diacylation on carbon occurred to give **31**. Only one carbonyl (1742 $cm^{-1}$) was observed in its ir spectrum and the pmr spectrum showed a pair of methyl triplets at δ 1.10 (6H) and δ 1.40 (3H) and no vinyl proton. These data along with a broad peak at δ 14.33 and a negative ferric chloride test support a structure with equivalent ethyloxalyl moieties and indicate that tautomer **31a** is the structure rather than tautomer **31b**. Heating **31a** in ethanol apparently caused the loss of one of the ethyloxalyl groups (reverse aldol). After refluxing 30 hours in ethanol, deacylation was apparent from a strong ferric chloride test for enol and from formation of oximino derivative **32** with hydroxylamine. Since the α-keto ester plus several components were present, direct reaction of **31a** in aqueous ethanol with hydroxylamine hydrochloride was employed to produce oximino ester **32** (13%).



A limited study of the oxidation of hydroxy derivative **33** (16) was carried out in order to determine whether this route would provide a convenient synthesis of **9**. Reaction with diethyl azodicarboxylate, NBS or manganese dioxide failed to give ketone **9** and starting material was recovered. Oxidation of **33** with phosphorus pentoxide-DMSO gave no isolable ketone **9**. Oxidation of hydroxy compound **34** with dimethylsulfoxide-acetic anhydride (17) afforded ketone **35** (46%).



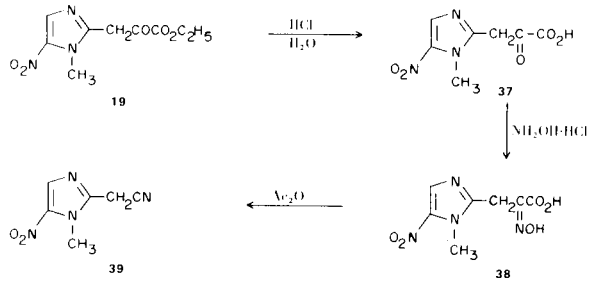
As mentioned in the earlier part of the discussion, Vilsmeier-Haack product **2**, a potentially useful enamine, was found to be essentially unreactive. The conjugation of the double bond of **2** with the electron-withdrawing nitro group lowers the otherwise high electron density at the carbon beta to the dimethylamino group and makes enamine **2** unreactive in typical electrophilic reactions. Acetyl chloride, benzoyl chloride, phenylisocyanate and diketene failed to react with **2** as did also tetrachloro-*o*-benzoquinone, benzofurazan oxide or sulfur and carbon



disulfide. However, the reactive *p*-toluenesulfonylisocyanate and enamine **2** in dichloromethane at room temperature afforded addition product **36**. Heating of **36** in ethanol or dimethyl sulfoxide caused partial loss of the sulfonylcarboxamide group to give back **2**.

The chain-extended nitrile **39** was prepared from pyruvate derivative **19** in the following manner. Acid

hydrolysis of **19** gave the α-ketoacid **37** which was converted to oxime **38**. Heating oximino acid **38** in acetic anhydride afforded nitrile **39**; however, the yields in a number of runs were generally low (*ca.* 10%). Modification of the usual conditions (hot acetic anhydride) for this type of reaction (18) by addition of a catalytic amount of pyridine led to nitrile **39** in approximately 30% yield.



## EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus and are corrected. Samples for analysis were dried *in vacuo* over phosphorus pentoxide at 70-90° for 16-24 hours. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined with a Varian A-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were determined with an A.E.I. MS-9 high resolution mass spectrometer.

2-(2-Dimethylaminovinyl)-1-methyl-5-nitroimidazole (**2**).

A mixture of 40 g. of *N,N*-dimethylformamide dicyclohexylacetal and 14.1 g. (0.10 mole) of 1,2-dimethyl-5-nitroimidazole (**1**) was heated under nitrogen at 138-145° in an oil bath for 3 hours. After standing overnight the mixture (containing crystals) was diluted with 50 ml. of ether and filtered. The red-violet crystals were washed with ether and air dried to yield 17.0 g. (85%) of **2**, m.p. 198-201°; pmr (deuteriochloroform + $d_6$-DMSO): δ 3.0 (s, 6, $N(CH_3)_2$), 3.78 (s, 3, $NCH_3$), 4.78 (d, 1, CH=C*H*N<), 7.65 (d, 1, J = 12.5, C*H*=CHN<), 7.90 (s, 1, >C=C<).

*Anal.* Calcd. for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.2; N, 28.6. Found: C, 48.9; H, 6.1; N, 28.8.

1-[(1-Methyl-5-nitro-2-imidazolyl)methyl]pyridinium Iodide (**3**).

A mixture of 28.2 g. (0.20 mole) of **1**, 51 g. (0.20 mole) of iodine and 40 g. (0.50 mole) of pyridine was heated and stirred at 115-120° (after *ca.* 15 minutes exothermic reaction appeared to occur). The mixture was heated for 2.5 hours and after standing overnight was diluted with 100 ml. of acetone. The crystals were filtered and washed with four 50-ml. portions of acetone to give 55 g. of brown solid. This solid was dissolved in 25 ml. of hot water; the solution was treated with activated charcoal and filtered and the filter cake was washed with three 5-ml. portions of hot water. Chilling the filtrate gave 20 g. of brown crystals (29%), m.p. 193-196° dec. A 10 g. portion of this solid was recrystallized with the aid of activated charcoal from 200 ml. of 90% ethanol to give 9.0 g. of **3** as tan crystals, m.p. 190-193° dec. From a similar run on a 0.020 mole scale, product of m.p. 194-196° dec., was obtained; pmr ($d_6$-DMSO): δ 4.03 (s, 3, $NCH_3$), 6.30 (s, 2, $-CH_2-$), 8.03 (s, 1, imidazole ring H), 8.28 (m, 2, pyridine-3,5-H's), 8.77 (m, 1, pyridine-4-H), 9.18 (m, 2, pyridine-2,6-H's).

*Anal.* Calcd. for $C_{10}H_{11}IN_4O_2$: C, 34.7; H, 3.2; N, 16.2. Found: C, 34.8; H, 3.2; N, 16.4.

2-[*N*-(*p*-Dimethylaminophenyl)formimidoyl]-1-methyl-5-nitroimidazole formimidoyl *N*-Oxide (**4**).

To a mixture of 3.4 g. (0.010 mole) of **3**, 1.65 g. (0.011 mole of *N,N*-dimethyl-*p*-nitrosoaniline, 15 ml. of water and 60 ml. of ethanol chilled to 3° was added dropwise with stirring 5 ml. of 2 *N* sodium hydroxide. The mixture was stirred at 3° for 1.5 hour and filtered to give 2.4 g. (83%) of reddish colored crystals, m.p. 187-190° dec. The solid was dissolved in 125 ml. of chloroform and 50 ml. of ethanol and the hot solution treated with activated charcoal. The mixture was filtered and the filtrate concentrated on a steam bath to 100 ml. The solution was diluted to 180 ml. with ethanol and chilled to give 2.2 g. (76%) of red-orange plates, m.p. 201-203° dec. Recrystallization was accomplished by dissolving the solid in 85 ml. of chloroform and 25 ml. of ethanol, concentrating the solution and diluting with ethanol. Chilling and filtering gave 1.7 g. (59%) of red-orange rectangular plates, m.p. 205-207° dec.; pmr ($d_6$-DMSO): δ 3.00 (s, 6, $N(CH_3)_2$), 3.90 (s, 3, $NCH_3$), 6.75 [d, 2, aromatic H ortho to $N(CH_3)_2$], 7.82 (d, 2, aromatic H meta to $N(CH_3)_2$], 8.22 (s, 1, $-CH=\overset{O^-}{\underset{|}{N^+}}-$), 8.48 (s, 1, imidazole ring H).

*Anal.* Calcd. for $C_{13}H_{15}N_5O_3$: C, 54.0; H, 5.2; N, 24.2. Found: C, 53.7; H, 5.1; N, 24.4.

2-[*N*-(*p*-Dimethylaminophenyl)formimidoyl]-1-methyl-5-nitroimidazole (**5**).

A mixture of 3.4 g. (0.010 mole) of **3** and 1.50 g. (0.010 mole) of *N,N*-dimethyl-*p*-nitrosoaniline in 50 ml. of ethanol and 7 drops of piperidine was refluxed for 1 hour. The mixture was cooled to room temperature and diluted with 90 ml. of ether. The solid was filtered off and washed with ether. This 2.4 g. of reddish colored solid was washed with water and ether and then was heated with 200 ml. of hot acetone. The mixture contianing solid was chilled and filtered to give 0.48 g. (17%) of red-violet crystals, m.p. 190-194° dec. Recrystallization from 125 ml. of ethanol gave 0.30 g. (11%) of **5**, m.p. 210-214°; pmr ($d_6$-DMSO): δ 2.98 [s, 6, $N(CH_3)_2$], 4.38 (s, 3, $-NCH_3$), 6.77 [d, J = 9 Hz, 2, aromatic H ortho to $N(CH_3)_2$], 7.43 [d, J = 9 Hz, 2, aromatic H meta to $N(CH_3)_2$], 8.22 (s, 1, -CH=N-), 8.65 (s, 1, imidazole ring H).

*Anal.* Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.1; H, 5.5; N, 25.6. Found: C, 56.9; H, 5.4; N, 25.7.

1-Methyl-5-nitro-α-phenyl-2-imidazoleethenol Benzoate (**8**).

A mixture of 28.2 g. (0.20 mole) of **1**, 125 ml. of *N,N*-diisopropylethylamine, 75 ml. of dioxane and 70 ml. (84 g.) (0.60 mole) of benzoyl chloride was refluxed for 18 hours. After standing and cooling to room temperature, 300 ml. of ether was added to the crystalline mass. The solid was washed with two 100-ml. portions of water and with ether to give 59 g. (85%) of product, m.p. 194-198°. From a similar run a 5 g. sample was dissolved in a hot mixture of 400 ml. of ethanol, 100 ml. of chloroform and 150 ml. of tetrahydrofuran. Chilling and filtering gave 3.9 g. of yellow crystals, m.p. 205-207°; pmr ($d_6$-DMSO): δ 4.07 (s, 3, $NCH_3$), 7.27 (s, 1, -CH=C-), 7.97 (s, 1, imidazole ring H), 7.4-8.3 (m, 10 aromatic H's).

*Anal.* Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.3; H, 4.3; N, 12.0. Found: C, 65.4; H, 4.3; N, 12.1.

2-(1-Methyl-5-nitro-2-imidazolyl)acetophenone (**9**).

A mixture of 1.75 g. (0.0050 mole) of **8**, 10 ml. of water, 15 ml. of ethanol and 10 ml. of concentrated hydrochloric acid was refluxed for 18 hours. The solution was chilled, poured onto ice and the *p*H adjusted to 5 with 10 *N* sodium hydroxide. The solid was filtered and washed with water to give 0.9 g. (75%) of **9**, m.p. 137-141°. Recrystallization from ethanol gave yellow crystals, m.p. 148-149°.

*Anal.* Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.8; H, 4.5; N, 17.1. Found: C, 58.6; H, 4.5; N, 17.1.

Base Hydrolysis of 1-Methyl-5-nitro-α-phenyl-2-imidazoleethenol Benzoate (**8**).

To 59 g. of **8** suspended in 900 ml. of tetrahydrofuran was added 50 ml. of concentrated ammonium hydroxide. The mixture was stirred at room temperature for 18 hours and then concentrated *in vacuo* to near dryness. The residue was triturated with water, filtered and the solid washed with water to give 50 g. of brown product. This solid was dissolved in 2 liters of hot acetone. After standing overnight, the mixture was diluted with water, chilled and filtered to give 6.2 g. of yellow crystals, m.p. 207-209°. The filtrate was diluted with water and extracted with chloroform. The extracts were dried over magnesium sulfate, concentrated *in vacuo* and the residue triturated with ethanol to give 17.7 g. (43%) of ketone **9**. The first crop of crystals (6.2 g.) were recrystallized from ethanol-dimethyl sulfoxide to give 4.6 g. of yellow crystals, m.p. 208-210°; pmr ($d_6$-DMSO): δ 3.13 (s, 3, $NCH_3$), 3.45 (s, 3, $NCH_3$), 5.48, 5.60 (2), 6.38, 6.50 (1), 7.23-8.06 (m, 10, aromatic-H), 8.28 (s, 1, imidazole ring H).

*Anal.* Calcd. for $C_{24}H_{21}N_5O_4$: C, 65.0; H, 4.8; N, 15.8. Found: C, 64.6; H, 4.7; N, 15.5. MW Calcd. 443.45. Found: 443 by low resolution mass spectrum. High resolution mass spectrum confirmed $C_{24}H_{21}N_5O_4$ formula.

1-Oximino-1-(1-methyl-5-nitro-2-imidazolyl)-2-phenylglyoxal (**10**).

To a chilled mixture of 2.45 g. (0.010 mole) of **9** in 25 ml. of glacial acetic acid was added 1.3 g. (0.015 mole) of potassium nitrite. The mixture was stirred at 5-10° for 10 minutes and allowed to stand at room temperature for 1.5 hours. The mixture was chilled and filtered and the solid washed with 5 ml. of acetic acid. The solid was washed with water to give 2.0 g. (73%) of yellow crystals, m.p. 184-187°.

1-Oximino-1-(1-methyl-5-nitro-2-imidazolyl)-2-phenylglyoxal (**10**).

To 10.5 g. (0.030 mole) of **8** was added 30 ml. of concentrated sulfuric acid. To the solution was added 5.1 g. (0.060 mole) of potassium nitrite in three portions with occasional cooling. The mixture was stirred at room temperature for 45 minutes and poured onto ice. The mixture was diluted with water filtered and the solid washed thoroughly with water. The solid was recrystallized from ethanol to give 4.3 g. (52%) of yellow crystals, m.p. 187-189°; pmr ($d_6$-DMSO): δ 3.78 (s, 3, $NCH_3$), 7.63 and 7.97 (m, 5, aromatic H's), 8.18 (s, 1, imidazole ring H).

*Anal.* Calcd. for $C_{12}H_{10}N_4O_4$: C, 52.6; H, 3.7; N, 20.4. Found: C, 52.5; H, 3.7; N, 20.4.

In a similar smaller scale run containing glacial acetic acid as co-solvent, the crude yield of product, m.p. 173-179°, was 78%.

1-Oximino-1-(1-methyl-5-nitro-2-imidazolyl)-2-phenylglyoxal (**10**).

To 5 ml. of cooled sulfuric acid (98%) was added 1.74 g. (0.0071 mole) of **9** followed by 0.64 g. (0.0075 mole) of potassium nitrite. The mixture was allowed to stand at room temperature (heat liberature on warming above 10°) for 40 minutes. The mixture was poured onto ice, diluted with water and filtered. The solid was washed with water and air dried to give 1.56 g. (80%) of **10** as yellow crystals, m.p. 175-180°.

2-Cyano-1-methyl-5-nitroimidazole (**11**).

To 1.37 g. (0.0050 mole) of **10** was added 5 ml. of thionyl chloride. The mixture was warmed on a steam bath until thionyl chloride began to boil. After standing 2 hours at room temperature the mixture was concentrated *in vacuo*. The oily residue was poured onto ice and made slightly basic with concentrated ammonium hydroxide. The mixture was extracted with ether and the extracts dried over magnesium sulfate and concentrated *in vacuo*. Trituration with methanol gave 0.30 g. (39%) of **11**, m.p. 81-84°. From the mother liquors an additional 0.26 g. (34%) of **11**, m.p. 80-84° was obtained. Compound **11** had identical ir spectrum with authentic sample (19).

1-Ethyl-5-nitro-α-phenyl-2-imidazoleethenol Benzoate (**15**).

A mixture of 7.75 g. (0.050 mole) of **14**, 25 ml. of *N,N*-diisopropylethylamine, 15 ml. of dioxane and 21.1 g. (0.15 mole) of benzoyl chloride was refluxed for 19.5 hours. The mixture was chilled, diluted with 125 ml. of ether and filtered. The solid was washed with ether, with water and with ethanol to give 7.0 g. (38%) of yellow crystals, m.p. 147-149°. An additional 1.5 g. (8%) of product was recovered from the mother liquors. Recrystallization of a 7.7 g. sample from ethanol gave 5.4 g. of yellow needles, m.p. 150-151°; pmr ($d_6$-DMSO): δ 1.38 (t, 3, $CH_2CH_3$), 4.62 (q, 2, $CH_2CH_3$), 7.23 (s, 1, -CH=C<), 7.96 (s, 1, imidazole ring H), 7.3-8.3 (m, 10, aromatic H's).

*Anal.* Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.1; H, 4.7; N, 11.6. Found: C, 66.2; H, 4.9; N, 11.7.

1-Oximino-1-(1-ethyl-5-nitro-2-imidazolyl)-2-phenylglyoxal (**16**).

To 10 ml. of concentrated sulfuric acid (97%) was added 6.0 g. of a solution containing 54% nitrosyl sulfuric acid in 104% oleum (0.024 mole of nitrosylsulfuric acid). The solution was diluted with 5 ml. of acetic acid and 7.27 g. (0.020 mole) of **15** was added. The mixture was stirred (chilled occasionally) for ½ hour and poured onto ice. The mixture was filtered and the solid washed thoroughly with water to give 4.0 g. (69%) of crystals, m.p. 155-165°. Recrystallization from ethanol with the aid of activated charcoal gave 2.9 g. (50%) of **16** as tan crystals, m.p. 165-167°; pmr ($d_6$-DMSO): δ 1.33 (t, 3, $CH_2CH_3$), 4.23 (q, 2, $CH_2CH_3$), 7.65 and 8.0 (m, 5, aromatic H's), 8.23 (s, 1, imidazole ring H), 13.8 (s, 1, OH).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.2; H, 4.2; N, 19.4. Found: C, 53.9; H, 4.2; N, 19.4.

1-(1-Methyl-5-nitro-2-imidazolyl)-2-phenylglyoxal 1-(*O*-Benzoyloxime) (**17**).

To a mixture of 40 ml. of dry acetonitrile, 7.0 g. (0.020 mole) of **8** chilled in an ice bath was added 12.7 g. (0.10 mole) of nitrosylsulfuric acid. The mixture under nitrogen was stirred at room temperature for 67 hours and poured onto ice. A saturated sodium bicarbonate solution was added until the mixture was basic. The solid was filtered off and washed with water to give 1.6 g. (21%) yellow-brown crystals. Recrystallization from benzene with the aid of activated charcoal gave 1.1 g. (14%) of pale yellow crystals, m.p. 148-151°.

*Anal.* Calcd. for $C_{19}H_{14}N_4O_5$: C, 60.3; H, 3.7; N, 14.8. Found: C, 60.4; H, 3.8; N, 15.0.

In a similar run with 7.0 g. (0.020 mole) of enol benzoate and 7.36 g. (0.050 mole) of nitrosylsulfuric acid which was stirred 17 hours, there was obtained 6.6 g. of a mixture of starting material and product. Thin-layer chromatography indicated that the mixture contained *ca.* 60% of product.

Ethyl 1-Methyl-5-nitro-2-imidazolepyruvate (**19**).

To a mixture of 28.2 g. (0.20 mole) of 1,2-dimethyl-5-nitroimidazole (**1**), 175 ml. of toluene, and 80.9 g. (0.80 mole) of

triethylamine was added (with occasional cooling) 75 g. (0.55 mole) of ethyl oxalyl chloride. The mixture was stirred for 22 hours, diluted with 100 ml. of ether and chilled. The mixture was filtered and the solid washed with three 100-ml. portions of ether and with four 100-ml. portions of water to give 37 g. (54%) of ethyl 1-carboethoxy-2-(1-methyl-5-nitro-2-imidazolyl)-vinyloxalate (**18**). Thirty g. of the solid was recrystallized from ethanol to give 20.7 g. (43%) of **19** as orange crystals, m.p. 138-141°; pmr (deuteriochloroform): δ 1.20 (t, 3, $CH_2CH_3$), 4.00 (s, 3, $NCH_3$), 4.37 (q, 2, $CH_2CH_3$), 6.45 (s, 1, C=C-H), 8.02 (s, 1, imidazole ring H), 11.87 (s, broad 1, OH of enol).

*Anal.* Calcd. for $C_9H_{11}N_3O_5$: C, 44.8; H, 4.6; N, 17.4. Found: C, 44.8; H, 4.6; N, 17.4.

Ethyl 1-Methyl-5-nitro-α,β-dioxo-2-imidazolepropionate β-Oxime (**20**) and Conversion to 2-Cyano-1-methyl-5-nitroimidazole (**11**).

To a suspension of 1.2 g. (0.0050 mole) of **19** in 15 ml. of glacial acetic acid was added 0.8 g. (0.0095 mole) of potassium nitrite. The mixture was stirred at room temperature for 20 minutes and the solvent concentrated *in vacuo*. The residual oil was dissolved in water and the *p*H adjusted to 7 with 10 *N* sodium hydroxide. The mixture was extracted with chloroform and the extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residual oil was heated on a steam bath for 15 minutes (gas evolution) to give 0.65 g. (85%) of **11** as off-white crystals, m.p. 73-77°.

1-Ethyl-α-phenyl-2-benzimidazoleethenol Benzoate (**23**).

To a chilled mixture of 16.0 g. (0.10 mole) of 1-ethyl-2-methylbenzimidazole (**22**), 200 ml. of toluene and 40 ml. of dry triethylamine was added 30 ml. (0.25 mole) of benzoyl chloride. The mixture was stirred and chilled occasionally for 15 minutes and allowed to stir at room temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue triturated with 300 ml. of ether, filtered and the solid washed with 200 ml. of ether. The solid was washed with water to give 27.4 g. (74%) of **23** as off-white crystals, m.p. 126-129°. The ether filtrate and ether washings were concentrated *in vacuo* and the solid triturated with ether, filtered and washed with water to give 5.9 g. (16%) of off-white crystals, m.p. 125-128°. Recrystallization of this crop of crystals by dissolving in benzene and diluting with ether gave 5.25 g. of **23**, m.p. 127-129°; pmr ($d_6$-DMSO): δ 1.35 (t, 3, $CH_2CH_3$), 4.50 (q, 2, $CH_2CH_3$), 7.03-8.40 (m, 15, aromatic + -CH=C).

*Anal.* Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.2; H, 5.5; N, 7.60. Found: C, 78.3; H, 5.6; N, 7.37.

1-Oximino-1-(1-ethyl-2-benzimidazolyl)-2-phenylglyoxal (**24**).

A mixture of 3.68 g. (0.010 mole) of **23** and 50 ml. of methanol was refluxed for 2 hours. The solvent was removed *in vacuo* and the oil dissolved in 15 ml. of glacial acetic acid. To this solution was added 1.01 g. (0.0120 mole) of potassium nitrite. After stirring for 45 minutes at room temperature, the mixture was chilled and the solid filtered off and washed with glacial acetic acid. There was obtained 2.18 g. (74%) of whtie crystals, m.p. 205-210°. Recrystallization from ethanol gave 1.34 g. (45%) of white crystals, m.p. 211-213°; pmr ($d_6$-DMSO): δ 1.35 (t, 3, $CH_2CH_3$), 4.18 (q, 2, $CH_2CH_3$), 7.01-8.17 (m, 9, aromatic), 13.53 (s-broad, 1, NOH).

*Anal.* Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.6; H, 5.2; N, 14.3. Found: C, 69.3; H, 5.2; N, 14.4.

2-Cyano-1-ethylbenzimidazole (**25**).

A mixture of 3.9 g. (0.0133 mole) of **24**, 25 ml. of dichloromethane and 5 ml. of thionyl chloride was refluxed for 15 minutes. The solvent was removed *in vacuo*. To the residue was added ice and water and the *p*H periodically adjusted to **7** by dropwise addition of dilute sodium hydroxide. After stirring 45 minutes chloroform was added and the *p*H adjusted to **7**. After one hour the chloroform layer was separated, dried over magnesium sulfate and concentrated *in vacuo*. The solid was triturated with methanol and the solvent removed *in vacuo*. The residue was tirutrated with ethanol and filtered to give in two crops 2.29 g. (73%) of white crystals, m.p. 85-88°; pmr ($d_6$-DMSO): δ 1.48 (t, 3, $CH_2CH_3$), 4.53 (q, 2, $CH_2CH_3$), 7.3-7.9 (m, 4, aromatic H).

*Anal.* Calcd. for $C_{10}H_9N_3$: C, 70.2; H, 5.3; N, 24.6. Found: C, 70.0; H, 5.3; N, 24.3.

2-(1-Ethyl-2-benzimidazolyl)acetophenone (**26**).

A mixture of 3.0 g. of **23** and 50 ml. of ethanol was heated with 50 ml. of ethanol and the solvent removed *in vacuo*. The residual oil was chromatographed over 100 g. of silica gel with chloroform-ethanol (99.5:0.5). After the first 600 ml. of eluent was collected, the next 250 ml. (50 ml. cuts) was concentrated *in vacuo* to a gum. Crystals formed on standing and trituration with ether and filtration gave 0.20 g. of white crystals, m.p. 120-123°. A second crop (0.12 g.) was obtained from the filtrate. The first crop was recrystallized from ether to give 0.08 g. of **27** as white crystals, m.p. 125-126°; pmr (deuteriochloroform): δ 1.53 (t, 3, $CH_2CH_3$), 4.75 (q, 2, $CH_2CH_3$), 7.2-8.2 (m, 9, aromatic H), mass spectrum (m/e), 278 ($M^+$), 249 ($M^+$-$C_2H_5$), 173 ($M^+$-$C_6H_5CO$), 145 ($M^+$-$C_6H_5COCO$), 105 ($C_6H_5CO^+$).

*Anal.* Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.4; H, 5.1; N, 10.1.

Diethyl 3-(1-Ethyl-2-benzimidazolinylidene-2,4-dioxoglutarate (**31**).

To a mixture of 6.41 g. (0.040 mole) of 1-ethyl-2-methylbenzimidazole (**22**) in 50 ml. of toluene and 22 ml. of triethylamine chilled in an ice bath was added 18 g. (0.13 mole) of ethyl oxalyl chloride. The mixture was stirred at room temperature for 18 hours, diluted with ether and filtered. The solid was washed with ether and then with ice-water to give 14.2 g. (98%) of yellow crystals. Recrystallization from 50 ml. of ethanol gave 8.5 g. (82%) of **31a** as yellow crystals, m.p. 167-170° (with previous sintering); pmr ($d_6$-DMSO): δ 1.10 (t, 6, $OCH_2CH_3$), 1.40 (t, 3, $NCH_2CH_3$), 4.10 (q, 4, $OCH_2CH_3$), 4.30 (q, 2, $NCH_2CH_3$), 7.4-8.2 (m, 4, -aromatic H), 14.33 (s-broad, 1, NH); ν max (potassium bromide): 1742 $cm^{-1}$.

*Anal.* Calcd. for $C_{18}H_{20}N_2O_6$: C, 60.0; H, 5.6; N, 7.8. Found: C, 59.8; H, 5.5; N, 7.7.

Ethyl 1-Ethyl-2-benzimidazolepyruvate Oxime (**32**).

A mixture of 1.82 g. (0.0050 mole) of **31**, 0.41 g. (0.0060 mole) of hydroxylamine hydrochloride in 25 ml. of ethanol and 5 ml. of water was heated on a steam bath for 10 minutes and allowed to stand at room temperature for 17 hours. The solvent was removed *in vacuo* and the residual crystals triturated with water, filtered and washed with water. The filtrate was brought to *p*H 7 with ammonium hydroxide and the crystals filtered. Recrystallization from ethanol gave 0.18 g. (13%) of **32** as off-white crystals, m.p. 210-212° (with previous sintering); pmr ($d_6$-DMSO): δ 1.18 (t, 3, $OCH_2CH_3$), 1.33 (t, 3, $NCH_2CH_3$), 4.13 (s, 2, $-CH_2-$), 4.19 (q, 2, $OCH_2CH_3$), 4.31 (q, 2, $NCH_2CH_3$), 7.1-7.8 (m, 4, aromatic), 12.52 (s, 1, NOH).

*Anal.* Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.1; H, 6.2; N, 15.3. Found: C, 61.0; H, 6.2; N, 15.3.

A mixture of 4.0 g. of **31** and 100 ml. of ethanol was refluxed for 30 hours. The solvent was removed *in vacuo* and the residue triturated with ether. The solid (0.5 g.) was filtered off and the

filtrate concentrated *in vacuo* to give 3.3 g. of an oil (strong purple color with ethanolic ferric chloride). Treatment of a small portion of the oil with hydroxylamine hydrochloride in ethanol-water for 5 days gave crystals of oximino ester **32**.

*p*-Chloro-2-(1-methyl-5-nitro-2-imidazolyl)acetophenone (**35**).

A mixture of 1.41 g. (0.0050 mole) of 1-*p*-chlorophenyl-2-(1-methyl-5-nitro-2-imidazolyl)ethanol (**34**), 4 ml. of dry dimethyl sulfoxide and 1.9 ml. (0.020 mole) of acetic anhydride was stirred at room temperature for 20 hours. The mixture containing solid was poured onto ice and allowed to stand for 2 hours. Filtration gave 1.3 g. of yellow-orange crystals, m.p. 145-157° after washing thoroughly with water. The solid was recrystallized from ethanol to give 0.76 g. of yellow crystals. Chromatography over silica gel with solvent tetrahydrofuran gave in the first peak after removal of the solvent and trituration of the residue with ethanol, 0.65 g. (46%) of yellow crystals, m.p. 165-172° with previous sintering. The pmr spectrum shows the presence of three components (A, B, C) – the unenolized ketone-A (37%) and two enolic forms (B-46% and C-17%); pmr ($d_6$-DMSO): δ 3.87 (s, $NCH_3$ of A), 4.01 (s, $NCH_3$ of B), 4.07 (s, $NCH_3$ of C), 4.86 (s, $CH_2C$ of A), 6.54 (s, CH=C- of B), 7.20 (s, CH=C- of C), 7.30-8.40 (aromatic + imidazole ring H's).

α-(Dimethylaminomethylene)-1-methyl-5-nitro-*N*-*p*-tolylsulfonyl-2-imidazoleacetamide (**36**).

A mixture of 1.96 g. (0.010 mole) of 2-(2-dimethylamino-vinyl)-1-methyl-5-nitroimidazole (**2**), 1.3 g. (0.0066 mole) of *p*-toluenesulfonyl isocyanate and 10 ml. of dichloromethane was stirred at room temperature for 1.5 hours. The mixture was filtered and the solid washed with dichloromethane and with ether to give 3.2 g. of yellow crystals, m.p. 165-169° dec. The solid was triturated with 50 ml. of acetone and the insoluble solid (0.14 g.) filtered off. The filtrate was chilled and the insoluble solid (0.85 g.) removed. The acetone solution was diluted with water (50 ml.) to give 1.5 g. of yellow crystals, m.p. 149-151° dec. Recrystallization twice from ethanol gave 0.35 g. of **36** as yellow crystals, m.p. 159-161°.

*Anal.* Calcd. for $C_{16}H_{19}N_5O_5S$: C, 48.8; H, 4.9; N, 17.8; S, 8.2. Found: C, 48.9; H, 4.8; N, 17.5; S, 8.0.

1-Methyl-5-nitro-2-imidazolepyruvic Acid (**37**).

A mixture of 30 g. of **19**, 150 ml. of water and 100 ml. of concentrated hydrochloric acid was heated on a steam bath for 1.5 hours. The mixture was chilled for 20 hours and filtered to give 28.2 g. of brown crystals (after air drying), m.p. 200-201° dec.

1-Methyl-5-nitro-2-imidazoleacetonitrile (**39**).

A mixture of 0.73 g. (0.0034 mole) of **37** and 0.278 g. (0.0040 mole) of hydroxylamine hydrochloride in 10 ml. of ethanol and 1 ml. of water was heated on a steam bath for 15 minutes. The solvent was removed *in vacuo*, ethanol was added and the solvent removed *in vacuo*. To the residual glass was added 5 ml. of acetic anhydride and the mixture heated on a steam bath for 5-10 minutes. The mixture was poured onto ice and the *p*H adjusted to 6.5 with 10 *N* sodium hydroxide. After standing overnight the mixture was extracted with chloroform and the extracts dried over magnesium sulfate. Concentration of the chloroform *in vacuo* gave a gummy residue which was triturated with ether to give 0.20 g. (35%) of tan crystals, m.p. 104-108°.

On a large scale 18.12 g. (0.085 mole) of pyruvate, 6.26 g. (0.090 mole) of hydroxylamine hydrochloride, 200 ml. of ethanol and 25 ml. of water was heated on a steam bath for 30 minutes. The solvent was removed *in vacuo* and the residue heated on a steam bath with 60 ml. of acetic anhydride. Pouring onto ice and working-up as above gave a red oil which was dissolved in benzene. Chilling gave 1.73 g. (12%) of crystals which were recrystallized from ethanol with the aid of activated charcoal to give 1.1 g. (7.8%) of tan crystals, m.p. 120-122°; pmr ($d_6$-DMSO): δ 3.98 (s, 3, $NCH_3$), 4.25 (s, 2, $CH_2$), 7.93 (s, 1, imidazole ring H).

*Anal.* Calcd. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.3; H, 3.6; N, 33.8.

In numerous runs poor yields (5-10%) were obtained. The following modified procedure using pyridine catalysis was developed. To a stirred mixture of 39 g. of 1-methyl-5-nitro-2-imidazolepyruvic acid oxime (**38**) and 200 ml. of acetic anhydride was added dropwise 14 ml. of pyridine over a period of 6 minutes. The mixture was chilled to keep the temperature at 50-60°. After 10 minutes the mixture was poured onto ice and brought to *p*H 7 with concentrated ammonium hydroxide while chilling. Crystals separated from the mixture (*ca.* 1200 ml.) and filtration gave 3.8 g. (13.4%) of dull red crystals, m.p. 117-121°. The filtrate was extracted with chloroform and the extracts were washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The solid (6.4 g.) was dissolved in chloroform-methanol (9:1) and filtered through silica gel which was washed with chloroform-methanol (9:1). Concentration of the filtrate *in vacuo* and trituration of the residue with ether-ethanol (99:1) gave 3.85 g. (13.5%) of crystals, m.p. 119-123°.

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