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Reaction of N-Hydroxyacetoacetanilide with Carbonyl Reagents[1,2]

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The reaction of N-hydroxyacetoacetanilide derivatives (**1a**—**g**) with hydroxylamine in aqueous ethanol gave 3-methyl-4-arylhydrazono-5-isoxazolones (**3a**—**g**). When ethanol or chloroform was used as the reaction medium, the reaction of N-hydroxyacetoacetanilide (**1a**) with carbonyl reagents gave N-phenylhydroxylamine derivatives and five-membered heterocycles such as 3-methyl-5-isoxazolone or 3-methyl-5-pyrazolone derivatives.

The mechanism of the formation of these products is discussed.

Keywords——N-hydroxyacetoacetanilide; carbonyl reagents; cyclization; elimination; 3-methyl-4-arylhydrazono-5-isoxazolone; 3-methyl-5-pyrazolone; 1-phenyl-3-methyl-5-pyrazolone

Reactions of 1,3-dicarbonyl compounds such as β-ketoesters or β-diketones with carbonyl reagents are widely used for the preparation of heterocyclic compounds such as pyrazolone and isoxazolone derivatives.[3] In connection with our continuing studies on acetoacetyl compounds, we have been interested in the synthetic utility of N-hydroxyacetoacetanilide as a 1,3-dicarbonyl substrate in the reaction with carbonyl reagents. The reason for this is that N-hydroxyacetoacetanilide has not only an acetoacetyl moiety but also an N-hydroxy group in its structure. The reaction of N-hydroxyacetoacetanilide derivatives with carbonyl reagents gave isoxazolone or pyrazolone derivatives through the oxime, hydrazone, or semicarbazone intermediates followed by cyclization and elimination of the N-phenylhydroxylamine moiety. The present paper describes these results in detail.

Following the procedure described in the literature,[4] N-hydroxyacetoacetanilide (**1a**, R=H) was allowed to react with a 3-fold molar excess of hydroxylamine in aqueous ethanol to give a yellow crystalline product (**3a**), $C_{10}H_9N_3O_2$, mp 189°, and azoxybenzene (**4a**) in 23.8 and 41.7% yields, respectively.

Compound **3a** was identified as 3-methyl-4-phenylhydrazono-5-isoxazolone by comparison of its spectral data with those of an authentic sample reported in the literature[5]: the infrared (IR) spectrum of **3a** showed characteristic bands at 3200 cm^{-1} (NH) and 1710 cm^{-1} (C=O). The nuclear magnetic resonance (NMR) spectrum of **3a** showed signals at 2.36 ppm (3H, singlet, 3-CH_3), 12.6 ppm (1H, broad, disappeared on addition of D_2O, NH) as well as aromatic proton signals at about 7.4 ppm (5H). The mass spectrum of **3a** showed its molecular ion peak at *m/e* 203.

Similarly, other N-hydroxyacetoacetanilide derivatives (**1b**—**g**) were allowed to react

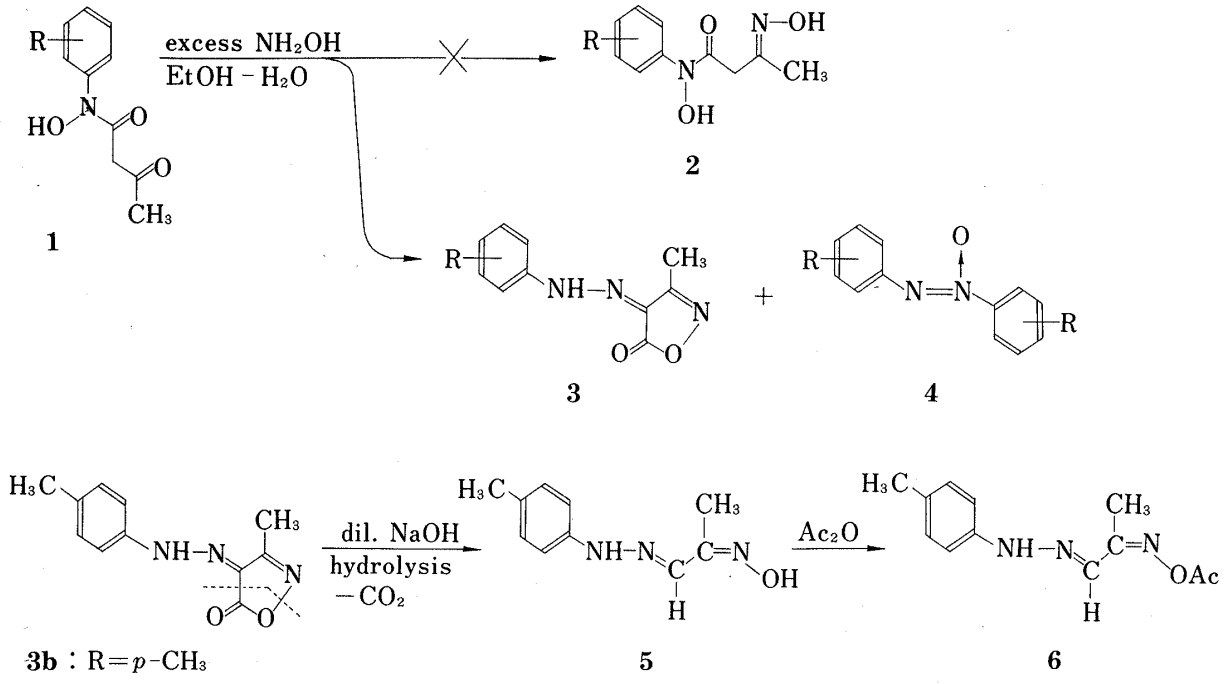


Chart 1

with an excess of hydroxylamine in aqueous ethanol to give yellow crystalline products (**3b**—**g**) in 14—38% yields. (Table I)

Compound **3b**, $C_{11}H_{11}N_3O_2$, derived from N-hydroxy-*p*-acetoacetotoluidide (**1b**, R=*p*-CH_3) was treated with 5% sodium hydroxide to give 1-(*p*-tolyl)hydrazono-2-hydroxyiminopropane (**5**), $C_{10}H_{13}N_3O$, mp 170°, in 55% yield. A carbonyl stretching band disappeared in the IR spectrum of compound **5** and an additional band appeared at 3300 cm^{-1} (OH). The NMR spectrum of **5** showed characteristic signals at 2.18 ppm (3H, s, tolyl-CH_3), 2.27 ppm (3H, s, =C-CH_3), 7.19 ppm (1H, s, olefinic H), and aromatic proton signals at 6.90 and 7.01 ppm (4H, AB-q), and 7.70 ppm (1H, broad, disappeared on addition of D_2O, active H). However, we could not detect a signal due to one proton.

Thus, compound **5** was acetylated with acetic anhydride to give the monoacetate (**6**), $C_{12}H_{15}N_3O_2$, mp 198°, in 80% yield. An active proton was seen in its NMR spectrum at 10.9 ppm (1H, s, disappeared on addition of D_2O, NH). These results are consistent with the structure of 1-(*p*-tolyl)hydrazono-2-hydroxyiminopropane (**5**) and 1-(*p*-tolyl)hydrazono-2-acetoxyiminopropane (**6**).

A possible mechanism for the formation of compound **3** is shown in Chart 2; *i.e.*, the first stage might well involve the formation of the oxime (**2**) as an intermediate, from which N-arylhydroxylamine (**7**) is eliminated to result in cyclization of the β-hydroxyiminoacetoacetyl moiety to 3-methyl-5-isoxazolone (**8**). The next stage involves oxidation of the arylhydroxylamine (**7**) to the nitrosobenzene derivative. This reacts with excess hydroxylamine to give the diazonium derivative which couples with isoxazolone (**8**) to afford the product (**3'**). It was already known that the 3-methyl-4-arylazo-5-isoxazolone derivative (**3'**) exists in a hydrazono form (**3**).[5b] The azoxybenzene derivative (**4**), on the other hand, is obtained by coupling of the nitrosobenzene intermediate with N-arylhydroxylamine (**7**). However, the oxime (**2**) was not detected even on the thin-layer chromatography.

The reaction of compound **1a** with hydrazine in chloroform at room temperature yielded N-phenylhydroxylamine (**7a**) and 3-methyl-5-pyrazolone (**9**) in good yields.[6] On treatment of **1a** with phenylhydrazine, **7a** and 1-phenyl-3-methyl-5-pyrazolone (**10**) were obtained in good yields.[7] These reactions proceeded in the same way as in the reaction with

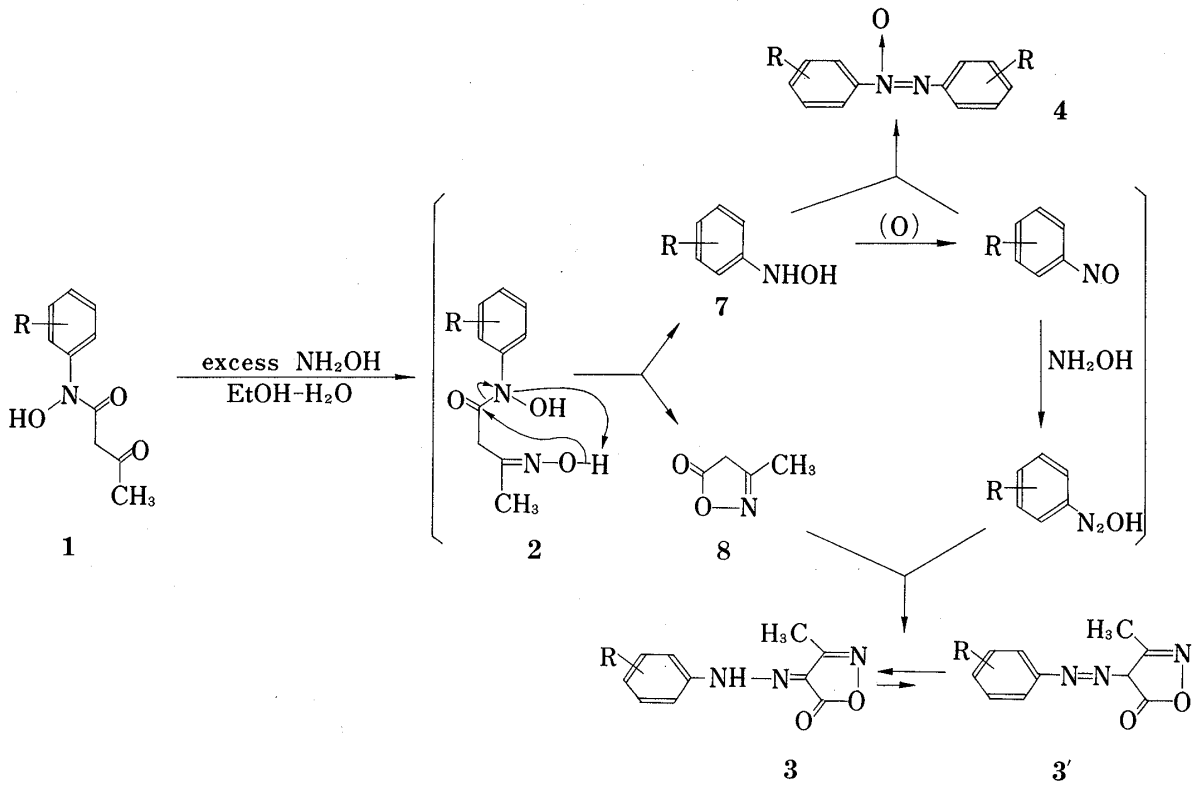


Chart 2

hydroxylamine, and gave the hydrazone intermediate (**16**, X=H or phenyl), which split into **7a** and a pyrazolone derivative (**9** or **10**) (path a).

On the other hand, the reaction of **1a** with an excess of semicarbazide in ethanol at room temperature gave several products; **4a**, **7a**, **9**, N-hydroxy-N-phenylurea (**11**), 1-carbamoyl-3-

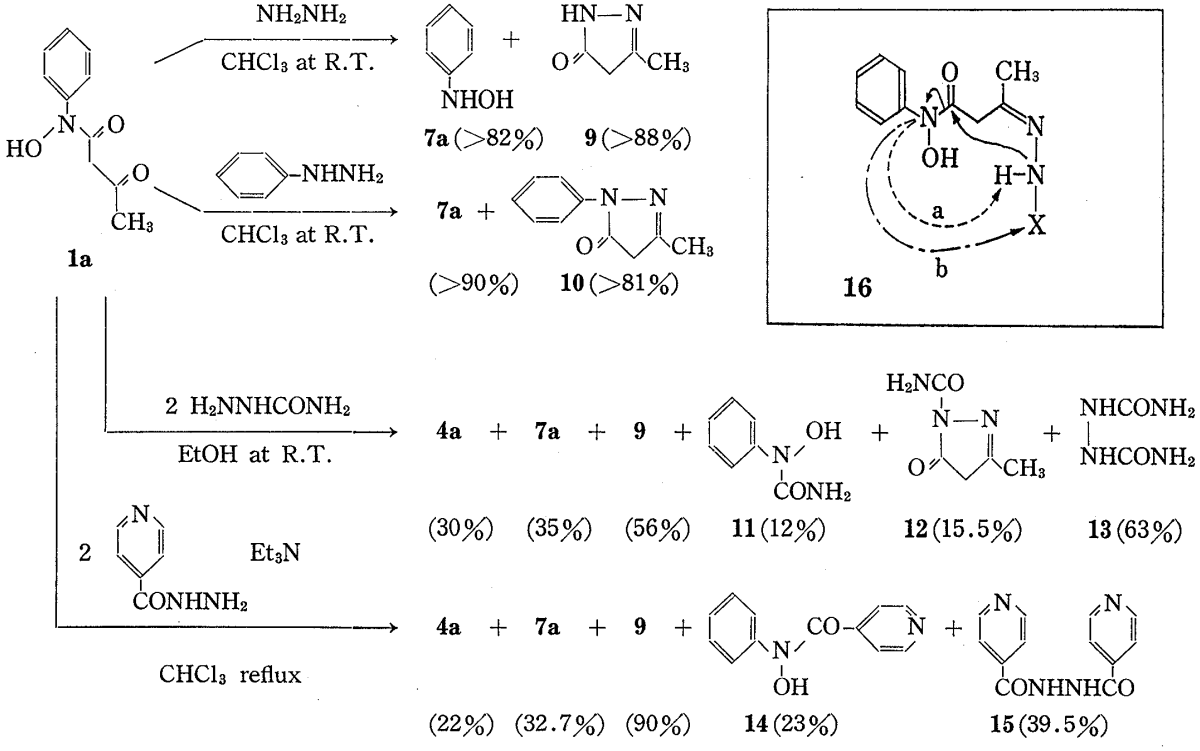


Chart 3

methyl-5-pyrazolone (**12**),[8] and 1,2-dicarbamoylhydrazine (**13**) in 30, 35, 58, 12, 15.5, and 63% yields, respectively.

Similarly, the reaction of **1a** with an excess of isonicotinoylhydrazine in the presence of a catalytic amount of triethylamine afforded **4a**, **7a**, **9**, N-hydroxy-N-phenylisonicotinamide (**14**), and 1,2-diisonicotinoylhydrazine (**15**) in 22, 32.7, 90, 23, and 39.5% yields, respectively.

In the reaction with semicarbazide, the formation of **7a** and **12** can be explained along the above lines, while the formation of **9** and **11** suggests that the fission of the intermediate **16** (where X is $COHN_2$) follows path b.

Nagakubo has reported that compound **13** is derived from **12** by the nucleophilic attack of semicarbazide on the carbamoyl moiety of compound **12** (*loc. cit.*). Reaction of **1a** with isonicotinoylhydrazine proceeded similarly to give **14** and **15**, which corresponds to **13**. However, 1-isonicotinoyl-3-methyl-5-pyrazolone, the intermediate corresponding to compound **12**, was not detected in the present experiment. Reaction of **1a** with *p*-toluensulfonylhydrazine, on the other hand, resulted in recovery of the starting materials.

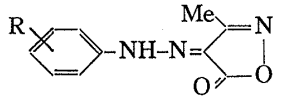
Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer. NMR spectra were recorded on a JEOL PS-100 spectrometer at 100 MHz with TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-7 mass spectrometer.

The starting materials, N-hydroxyacetoacetanilide derivatives (**1a—g**), were prepared from N-phenylhydroxylamine derivatives and diketene.

3-Methyl-4-arylhydrazono-5-isoxazolone (**3a—g**)——A mixture of $NH_2OH \cdot HCl$ (2.1 g, 0.03 mol) and Na_2CO_3 (1.6 g, 0.015 mol) in water (50 ml) was added to a stirred solution of an N-hydroxyacetoacetanilide derivative (**1a—g**) (0.01 mol) in EtOH (50—80 ml), and the mixture was stirred for 3—6 hr at 80—85°. After removal of the solvent by evaporation, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated to dryness to give a yellow residue, which was subjected to flash chromatography[9] on a silica gel column with $CHCl_3$ as an eluent to give 3-methyl-4-arylhydrazono-5-isoxazolone (**3a—g**) as yellow needles (recrystallized from EtOH or $CHCl_3$). The mps and yields are listed in Table I.

Table I. 3-Methyl-4-arylhydrazono-5-isoxazolones



3	R	Mp (°C)	Recryst.[a] solvent	Yield	lit. mp[b] (°C)
a	H	189	C	23.8%	190
b	*p*-CH_3	194	E	37.9	204
c	*m*-CH_3	175	E	14.4	172
d	*p*-C_2H_5	158	E	19.8	156
e	*p*-Cl	190	C	25.8	192
f	*m*-Cl	173	C	24.1	162
g	*p*-Br	202	E	25.5	194

a) C, $CHCl_3$; E, EtOH.
b) L. A. Summers *et. al.*, *J. Chem. Soc.*, **1965**, 3312.

Reaction of N-Hydroxyacetoacetanilide (1a) with Hydroxylamine in Absolute Ethanol——A mixture of $NH_2OH \cdot HCl$ (70 mg, 1 mmol) and NaOEt (70 mg, 1 mmol) in abs. EtOH (30 ml) was added to a solution of N-hydroxyacetoacetanilide (**1a**) (190 mg, 1 mmol) in abs. EtOH (30 ml) and the mixture was stirred for 6 hr at room temperature under an argon atmosphere. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column with $CHCl_3$–EtOAc (4: 1) mixture as an eluent to give N-phenylhydroxylamine (**7a**) (97 mg, 91%, mp 82°) and 3-methyl-5-isoxazolone (**8**) (92 mg, 92.7%).

Hydrolysis of 3-Methyl-4-(*p*-tolyl)hydrazono-5-isoxazolone (3b)——A mixture of 3-methyl-4-(*p*-tolyl)-hydrazono-5-isoxazolone (**3b**) (105 mg, 0.5 mmol) and 5% NaOH (10 ml) was stirred for 2 hr under reflux. The reaction mixture was extracted with EtOAc. The EtOAc solution was washed with water, dried over Na_2SO_4, and concentrated. The resulting residue was subjected to flash chromatography on a silica gel column with $CHCl_3$ as an eluent to give 1-(*p*-tolyl)hydrazono-2-hydroxyiminopropane (**5**) (50 mg, 55%) as colorless needles (from $CHCl_3$), mp 170°. *Anal.* Calcd for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.65; H, 7.00; N, 21.87. IR ν_{max}^{KBr} (cm^{-1}): 3300, 3200, 1535, 1255. NMR δ ($CDCl_3$) (ppm): 2.18 (3H, s, tolyl-CH_3), 2.27 (3H, s, =C–CH_3), 6.90 and 7.01 (4H, AB-q, $J=7$ Hz, aromatic H), 7.19 (1H, s, =CH), 7.70 (1H, b, disappeared on addition of D_2O, active proton). MS *m/e*: 191 (M^+), 174, 149, 105.

Acetylation of Compound 5——A mixture of **5** (96 mg, 0.5 mmol) and Ac_2O (0.2—0.3 ml) was stirred for 30 min at 70—80° and then diluted with $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed with 5% $NaHCO_3$ and water, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column with $CHCl_3$ as an eluent to give 1-(*p*-tolyl)hydrazono-2-acetoxyiminopropane (**6**) (93 mg, 80%) as colorless needles (from $CHCl_3$), mp 198°. *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.02. Found: C, 61.82; H, 6.50; N, 18.19. IR ν_{max}^{KBr} (cm^{-1}): 3300, 1750, 1540, 1262. NMR δ ($CDCl_3$) (ppm): 2.15 (3H, s, tolyl-CH_3), 2.20 (3H, s, acetyl CH_3), 2.29 (3H, s, =C–CH_3), 6.93 and 7.00 (4H, AB-q, $J=7$ Hz, aromatic H), 7.46 (1H, s, =CH), 10.9 (1H, s, disappeared on addition of D_2O, active H). MS *m/e*: 233 (M^+), 173, 105.

Reaction of 1a with Hydrazine——A mixture of **1a** (483 mg, 2.5 mmol) and NH_2NH_2 (80 mg, 2.5 mmol) in $CHCl_3$ (25 ml) was stirred for 1.5 hr at room temperature under an argon atmosphere. The colorless crystals that precipitated were collected and recrystallized from EtOAc to give 3-methyl-5-pyrazolone (**9**) (215 mg, 88%, mp 218°). The filtrate was concentrated *in vacuo* and the residue was subjected to flash chromatography on a silica gel column with hexane–EtOAc (3: 1) mixture as an eluent to give N-phenylhydroxylamine (**7a**) (223 mg, 81.8%, mp 82°).

Reaction of 1a with Phenylhydrazine——A mixture of **1a** (970 mg, 5 mmol) and phenylhydrazine (540 mg, 5 mmol) in $CHCl_3$ (50 ml) was stirred for 3 hr at room temperature under an argon atmosphere. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column with hexane–EtOAc (3: 1) mixture as an eluent to give **7a** (490 mg, 90%) and 1-phenyl-3-methyl-5-pyrazolone (**10**) (705 mg, 81%, mp 131°).

Reaction of 1a with Semicarbazide——A mixture of semicarbazide hydrochloride (1.115 g, 10 mmol) and Na_2CO_3 (530 mg, 5 mmol) in 50% EtOH (40 ml) was added to a solution of **1a** (970 mg, 5 mmol) in EtOH (20 ml). The mixture was stirred for 24 hr at room temperature under an argon atmosphere. After removal of the solvent by evaporation *in vacuo*, the resulting residue was diluted with EtOAc, and the solution was extracted with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash chromatography on a silica gel column with hexane–EtOAc (2: 1, 1: 1, 1: 2, and then 1: 3, each 200 ml) mixture as an eluent to give **4a** (156 mg, 30%), **7a** (190 mg, 35%), N-hydroxy-N-phenylurea (**11**) (66 mg, 8.6%, mp 96°), 1-carbamoyl-3-methyl-5-pyrazolone (**12**) (25 mg, 3.5%, mp 192°), and 1,2-dicarbamoylhydrazine (**13**) (7.3 mg, 1.2%, mp 244°). The aqueous solution was concentrated *in vacuo* and the resulting residue was subjected to gel filtration on a Sephadex G-10 column with water as an eluent to give **13** (406 mg, 61.8%), **9** (277 mg, 58%), **12** (85 mg, 6.9%), and **11** (24 mg, 3.4%) in that order. The total yields of **11**, **12**, and **13** were 12, 15.5, and 63%, respectively.

Reaction of 1a with Isonicotinoylhydrazine——A solution of **1a** (485 mg, 2.5 mmol) and isonicotinoylhydrazine (685 mg, 5 mmol) in $CHCl_3$ (50 ml) was stirred for 24 hr under reflux in the presence of Et_3N as a catalyst (0.2—0.3 ml). The colorless crystals that precipitated were collected and washed with water. The insoluble residue was dried and recrystallized from EtOH to give 1,2-diisonicotinoylhydrazine (**15**) (605 mg, 39.5%, mp 267°).

The washing was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give **9** (220 mg, 90%).

The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash chromatography on a silica gel column with hexane–EtOAc (3: 1) mixture as an eluent to give **4a** (55 mg, 22%), **7a** (90 mg, 32.7%), and N-hydroxy-N-phenylisonicotinamide (**14**) (123 mg, 23%, mp 255°) successively.

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References and Notes

1) This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan (April 1980, Tokyo).
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6) The structure of **9** is shown in the CH-form herein. The tautomerism of **9** was discussed in detail by Katritzky *et al.*; A.R. Katritzky, F.W. Maine, and S. Golding, *Tetrahedron*, **21**, 1693 (1965).
7) Compound **10** exists in the CH-form under most conditions in nonpolar media; A.R. Katritzky and F.W. Maine, *Tetrahedron*, **20**, 299 (1964).
8) From the IR data (1700 and 1650 cm^{-1}), it is considered that **12** exists in the CH-form in the crystalline state.
9) Flash chromatography was carried out on a Kimura Kagaku flash chromatography apparatus with Kieselgel 60 (Merck, 230—400 mesh) under the elution conditions described in the literature; W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

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The Chemistry of Indoles. XII.[1] A Facile Route to 5-Nitroisocoumarins and Methyl Indole-4-carboxylate

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A convenient synthesis of 5-substituted isocoumarin derivatives, such as 5-nitroisocoumarin (**2**), 5-aminoisocoumarin (**8**), 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), and 5-amino-3,4-dihydro-3-methoxyisocoumarin (**10**), from 2-methyl-3-nitrobenzoic acid (**1**) is reported. Several synthetic routes to methyl indole-4-carboxylate (**9**) from methyl 2-methyl-3-nitrobenzoate (**4**) directly or *via* these isocoumarins (**8** and **10**) are also presented.

Keywords——5-nitroisocoumarin; 5-aminoisocoumarin; 3,4-dihydro-3-methoxy-5-nitroisocoumarin; 5-amino-3,4-dihydro-3-methoxyisocoumarin; methyl indole-4-carboxylate; 2-methyl-3-nitrobenzoic acid; titanium (III) chloride; ring transformation

Formylation of activated methyl groups on aromatics and heteroaromatics with dimethylformamide acetal is well established[2] and the reaction was successfully applied in the synthesis of substituted indoles.[3] Examination of the reaction of dimethylformamide dimethylacetal (DMFDMA) with 2-methyl-3-nitrobenzoic acid (**1**) has led us to find a novel route to 5-nitroisocoumarin (**2**) and 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), which are not readily available[4] as yet, but are suitable synthetic equivalents[5] for 4-substituted indoles. In this paper, we describe a facile synthesis of **2** and **3**, together with their conversion into methyl indole-4-carboxylate (**9**).

Refluxing of 2-methyl-3-nitrobenzoic acid (**1**) in abs. dimethylformamide (DMF) in the presence of DMFDMA resulted in the formation of 5-nitroisocoumarin (**2**), 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), and methyl 2-methyl-3-nitrobenzoate (**4**) in yields of 30.2%, 20.8%, and 1.6%, respectively (Chart 1). The structure of **2** was assigned from the nuclear magnetic resonance (NMR) spectrum, which showed characteristic protons on C-3 and C-4 of isocoumarin as two sets of doublets at δ 7.23 and 7.38 ($J=6$ Hz), and the infrared spectrum, which indicated the presence of both lactone carbonyl (1730 cm^{-1}) and nitro groups (1518 and 1350 cm^{-1}). The final confirmation of the structure (**2**) was provided by the following