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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**), C₁₀H₉N₃O₂, 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 literature⁵⁾: 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-CH₃), 12.6 ppm (1H, broad, disappeared on addition of D₂O, 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

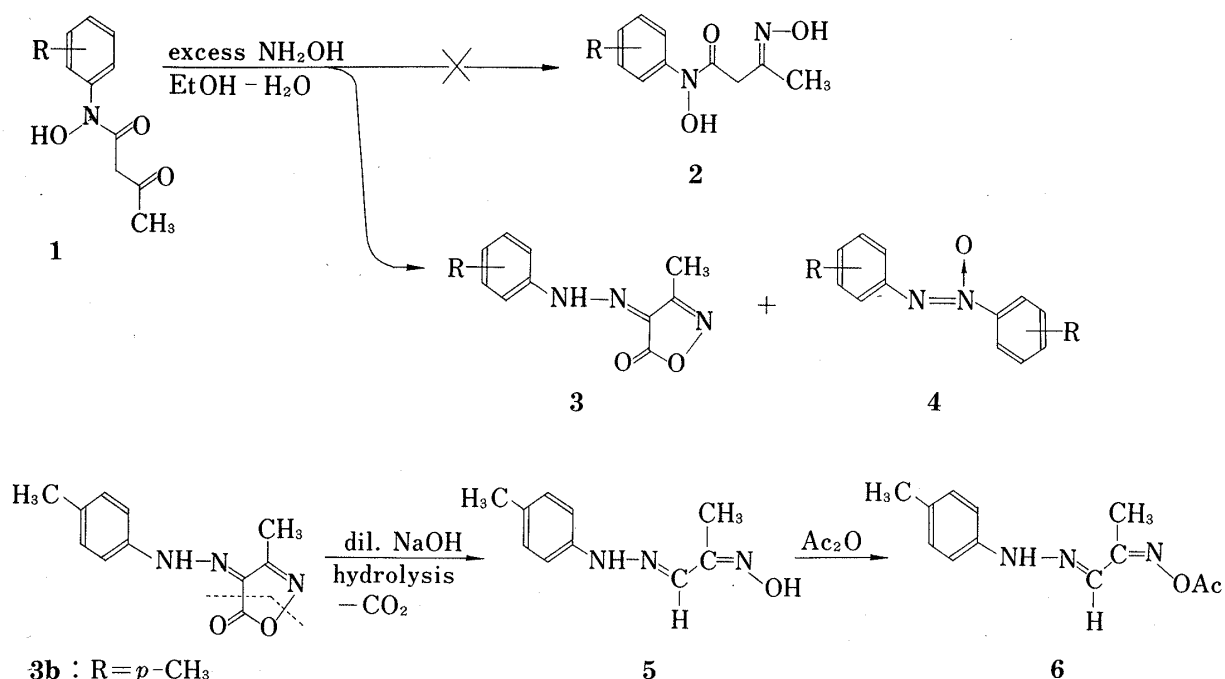


Chart 1

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

Compound 3b, $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$, derived from N-hydroxy-*p*-acetoacetotoluidide (1b, $\text{R} = p\text{-CH}_3$) was treated with 5% sodium hydroxide to give 1-(*p*-tolyl)hydrazono-2-hydroxyiminopropane (5), $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}$, 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, $=\text{C}-\text{CH}_3$), 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), $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$, 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

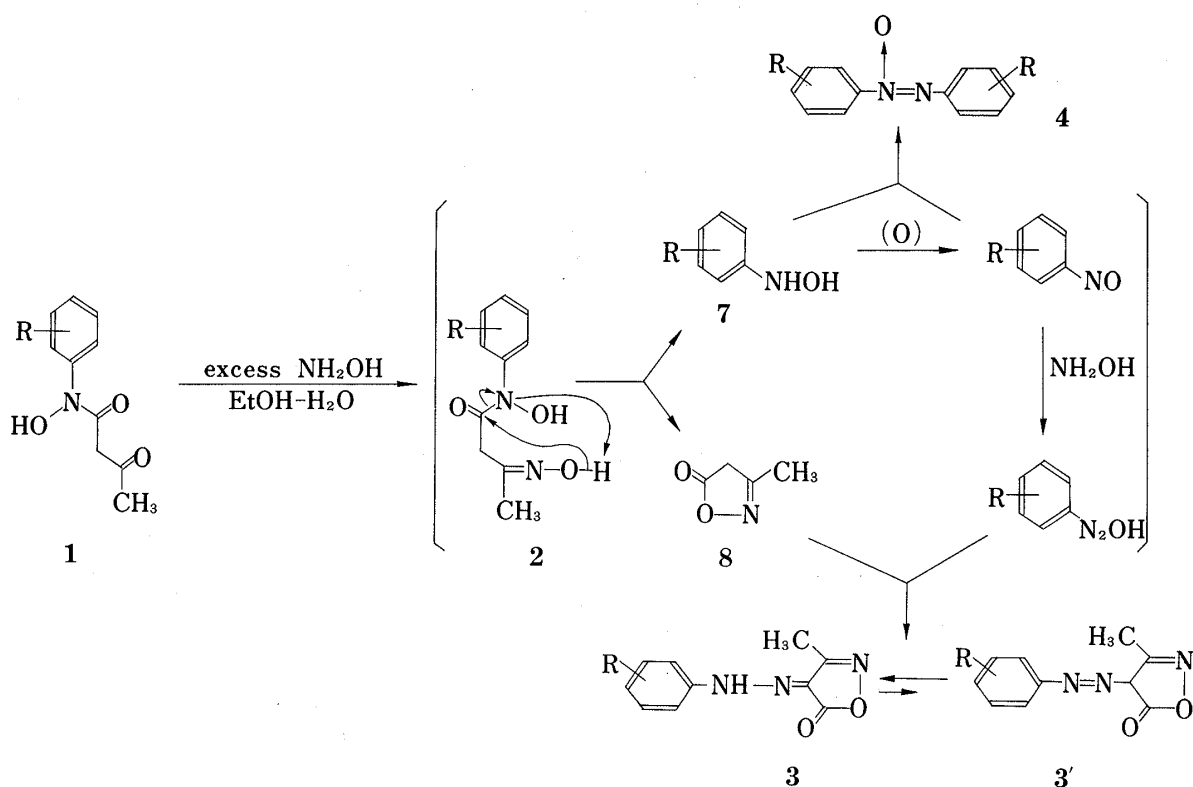


Chart 2

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-

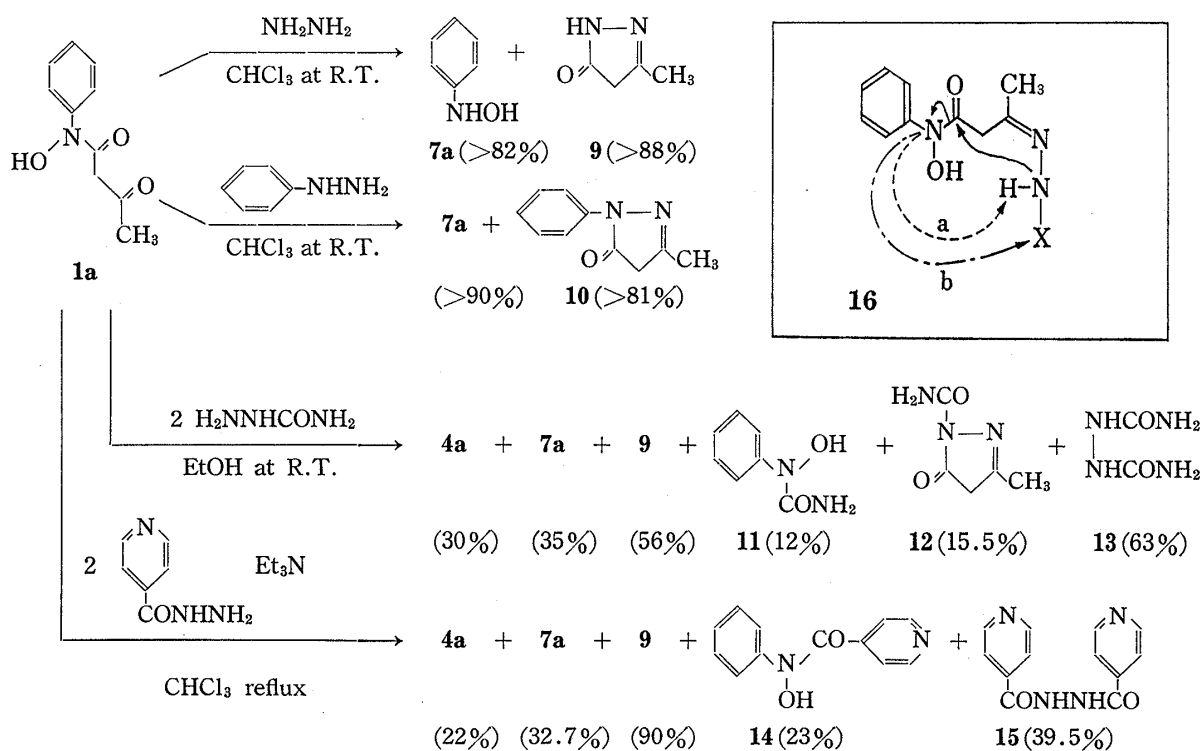


Chart 3

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 COHN₂) 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 NH₂OH·HCl (2.1 g, 0.03 mol) and Na₂CO₃ (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 CHCl₃. The CHCl₃ solution was washed with water, dried over Na₂SO₄, and evaporated to dryness to give a yellow residue, which was subjected to flash chromatography⁹⁾ on a silica gel column with CHCl₃ as an eluent to give 3-methyl-4-arylhydrazono-5-isoxazolone (3a—g) as yellow needles (recrystallized from EtOH or CHCl₃). 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	<i>p</i> -CH ₃	194	E	37.9	204
c	<i>m</i> -CH ₃	175	E	14.4	172
d	<i>p</i> -C ₂ H ₅	158	E	19.8	156
e	<i>p</i> -Cl	190	C	25.8	192
f	<i>m</i> -Cl	173	C	24.1	162
g	<i>p</i> -Br	202	E	25.5	194

a) C, CHCl₃; 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 NH₂OH·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 CHCl₃–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 Na₂SO₄, and concentrated. The resulting residue was subjected to flash chromatography on a silica gel column with CHCl₃ as an eluent to give 1-(*p*-tolyl)hydrazono-2-hydroxyiminopropane (5) (50 mg, 55%) as colorless needles (from CHCl₃), mp 170°. *Anal.* Calcd for C₁₀H₁₃N₃O: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.65; H, 7.00; N, 21.87. IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹): 3300, 3200, 1535, 1255. NMR δ (CDCl₃) (ppm): 2.18 (3H, s, tolyl-CH₃), 2.27 (3H, s, =C-CH₃), 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 D₂O, active proton). MS *m/e*: 191 (M⁺), 174, 149, 105.

Acetylation of Compound 5—A mixture of 5 (96 mg, 0.5 mmol) and Ac₂O (0.2–0.3 ml) was stirred for 30 min at 70–80° and then diluted with CHCl₃ (50 ml). The CHCl₃ solution was washed with 5% NaHCO₃ and water, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column with CHCl₃ as an eluent to give 1-(*p*-tolyl)hydrazono-2-acetoximinopropane (6) (93 mg, 80%) as colorless needles (from CHCl₃), mp 198°. *Anal.* Calcd for C₁₂H₁₅N₃O₂: C, 61.78; H, 6.48; N, 18.02. Found: C, 61.82; H, 6.50; N, 18.19. IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹): 3300, 1750, 1540, 1262. NMR δ (CDCl₃) (ppm): 2.15 (3H, s, tolyl-CH₃), 2.20 (3H, s, acetyl CH₃), 2.29 (3H, s, =C-CH₃), 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 D₂O, active H). MS *m/e*: 233 (M⁺), 173, 105.

Reaction of 1a with Hydrazine—A mixture of 1a (483 mg, 2.5 mmol) and NH₂NH₂ (80 mg, 2.5 mmol) in CHCl₃ (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 CHCl₃ (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 Na₂CO₃ (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 Na₂SO₄ 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 CHCl₃ (50 ml) was stirred for 24 hr under reflux in the presence of Et₃N 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 CHCl₃ layer was dried over Na₂SO₄ 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).
- 2) This paper forms Part III of "Reaction of γ -Bromoacetoacetyl Bromide with N-Phenylhydroxylamine Derivatives." Part II: K. Tabei, E. Kawashima, and T. Kato, *Chem. Pharm. Bull.*, **28**, 330 (1980).

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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 established²⁾ 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 available⁴⁾ as yet, but are suitable synthetic equivalents⁵⁾ 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