[Chem. Pharm. Bull. 22(9)1990—1995(1974)]

UDC 547.543.04 : 547.556.8.04 : 547.555.04

Pyrazolines and Oxazolines. Reaction of Arylcarbonylethylthiosulfates with Hydrazines and Hydroxylamines

Mitsuru Furukawa, Takeshi Yuki, and Seigoro Hayashi

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

(Received October 20, 1973)

The reactions of arylcarbonylethylthiosulfates (I) with hydrazines and hydroxylamines were investigated. The compound I reacted with phenylhydrazine to give 1-phenyl-3-aryl-2-pyrazolines (II). The reaction of I with hydrazine, however, gave 1-β-arylcarbonylethyl-3-aryl-2-pyrazolines (III). On the other hand, in the reaction of I with N,N-dimethylhydrazine, demethylation occurred to afford 1-methyl-3-aryl-2-pyrazolines (IV). In the reaction of I with hydroxylamine, 3-aryl-2-isoxazolines (V) and β,β'-hydroxylamino-bis-propiophenones (VI) were obtained under refluxing conditions and at room temperature, respectively. Moreover, the reaction of I with phenylhydroxylamine gave N-arylcarbonylethylhydroxylamines (VIII).

We have recently found that β-carbonylethylthiosulfates readily react with amines to give β-carbonylethylamines.[2] The reaction is believed to proceed through the formation of vinylketone intermediates by the initial elimination of β-methylene hydrogen of the thiosulfates with amines, followed by the addition of further amines. If the elimination of the β-methylene hydrogen occurrs with hydrazines and hydroxylamines instead of amines to give the vinylketone intermediates, one-step syntheses of pyrazolines and oxazolines would be possible. A number of pyrazoline syntheses which proceed similarly to the assumed reaction mechanism have hitherto been known. For example, Scott[3] has reported that the reaction of Mannich bases with substituted hydrazines proceeds through the initial elimination reaction of the bases to yield vinylketone intermediates which then undergo hydrazone formation, followed by hydrazine intramolecular addition with cyclization to pyrazolines, though no details are described. Several synthetically valuable pyrazoline syntheses by the similar reaction of Mannich bases, in which β-carbonylethyl group is involved, with phenylhydrazine have also been known.[4] This paper deals with the reaction of arylcarbonylethylthiosulfates with hydrazines and hydroxylamines.

Reaction of Arylcarbonylethylthiosulfates with Hydrazines

When 2-arylcarbonylethylthiosulfates (I) were heated with two equivalent amounts of phenylhydrazine in water for 0.5—3 hours under reflux, 1-phenyl-3-aryl-2-pyrazolines (II) were yielded in 23—52% yields, as the only product isolated.

The structure of II was established by the infrared (IR) and mass spectra and elemental analyses. Further distinct evidence was provided by identification of 1,3-diphenyl-2-pyrazoline (IIa) with an authentic sample.[5]

The mechanism is proposed as follows: As the first step the abstruction of the β-methylene hydrogen of the thiosulfates (I) with phenylhydrazine forms the intermediate vinylketones

1) Location: *Oe-hon machi, Kumamoto, 862, Japan.*
2) M. Furukawa, T. Yuki, R. Kiyofuji, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 811 (1973).
3) F.L. Scott, S.A. Houlihan, and D.F. Fenton, *Tetrahedron Letters*, **1970**, 1991.
4) *a*) W. Wilson and Zu-Y. Kyi, *J. Chem. Soc.*, **1952**, 1321; *b*) S.G. Beech, J.H. Turnbull, and W. Wilson, *J. Chem. Soc.*, **1952**, 4686; *c*) G.F. Duffin and J.D. Kendall, *ibid.*, **1954**, 408; *d*) F.F. Blicke and J.H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).
5) W.G. Young and J.D. Roberts, *J. Am. Chem. Soc.*, **68**, 649 (1946).

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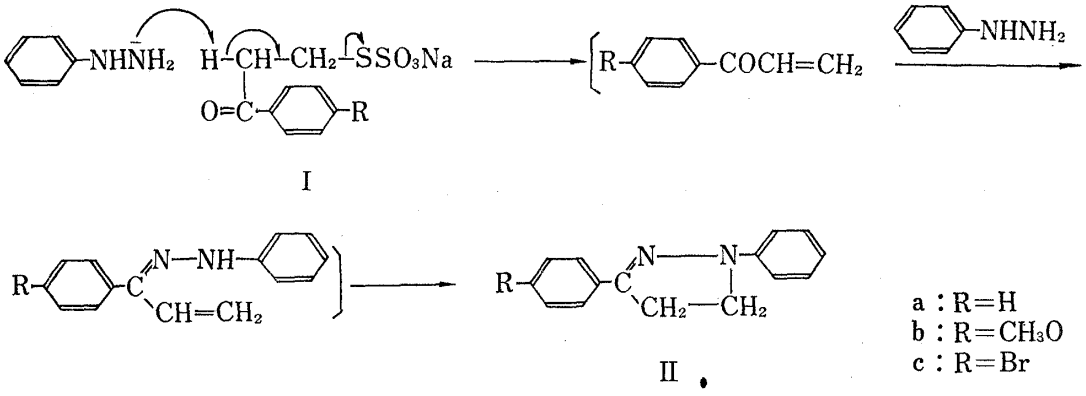
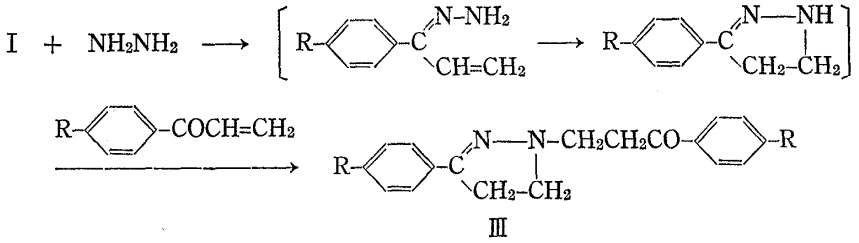


Chart 1

which then undergo hydrazone formation, followed by intramolecular cycloaddition to pyrazolines (II).

The thiosulfates (I) were also allowed to react with hydrazine hydrate. The reaction of hydrazine itself with α,β-unsaturated carbonyl compounds is more complex[6] and little has been known regarding the reaction with vinylketones. When I was treated with two equivalent amounts of hydrazine hydrate in water at room temperature, 1-β-arylcarbonylethyl-3-aryl-2-pyrazolines (III) were immediately isolated from the reaction mixture in 35—77% yields, no trace of any expected 3-aryl-2-pyrazolines being isolated. It is presumed that III would be formed by intramolecular cyclization of the hydrazone intermediates of vinylketones, followed by addition of further vinylketones.

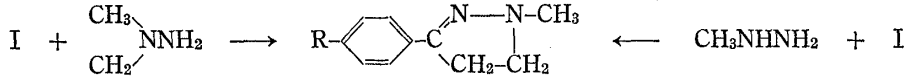


a: R=H, b: CH_3O, c: R=Br

Chart 2

All of the compounds III gave satisfactory elemental analyses and had mass spectra consistent with the structure, exhibiting the molecular ion peak as the most abundant peak. The IR absorption spectra showed the absorption assignable to the carbonyl group at 1675 cm^{-1} and the similar absorption pattern to those of II.

In the reaction of I with N,N-dimethylhydrazine, unexpectedly demethylation occurred, no trace of any anticipated N,N-dimethylhydrazones of vinylketones being isolated. When I was heated with two equivalent amounts of N,N-dimethylhydrazine in water for 7—10 hours under reflux, 1-methyl-3-aryl-2-pyrazolines (IV) which were formed through demethylation in the course of the reaction were obtained in low yields.



IVa : R=CH_3O
IVb : R=Br

Chart 3

6) A. Jacob and J. Madinaveitia, *J. Chem. Soc.*, 1937, 1929.

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The structure of IV was established by the IR, nuclear magnetic resonance (NMR) and mass spectra in which the molecular ion peak was observed as the most abundant peak and by satisfactory elemental analyses. Further evidence for the demethylation was provided by the fact that IV was formed by the reaction of I with methylhydrazine under the similar reaction conditions.

Reaction of Arylcarbonylethylthiosulfates with Hydroxylamines

The reaction of I with hydroxylamine indicated quite different behaviors depending upon the reaction temperature. When heated with four equivalent amounts of hydroxylamine in water in the presence of sodium hydroxide under reflux for 3 hours, 3-aryl-2-isoxazolines (V) were expectedly obtained in comparatively low yields. On the other hand, when treated at room temperature, β,β'-hydroxylamino-bis-propiophenones (VI) were the only product isolated, no formation of V anticipated being observed by thin-layer chromatograph (TLC). The structures of V and VI were established by the IR and mass spectra and by elemental analyses. In both cases, base condition was essential and no reaction occurred in the absence of alkali, different from the case of hydrazines. These results suggest that hydroxylamine does not act as an effective drawing reagent for the elimination of β-methylene hydrogen of I to form vinylketones and probably VI is the intermediate of V.

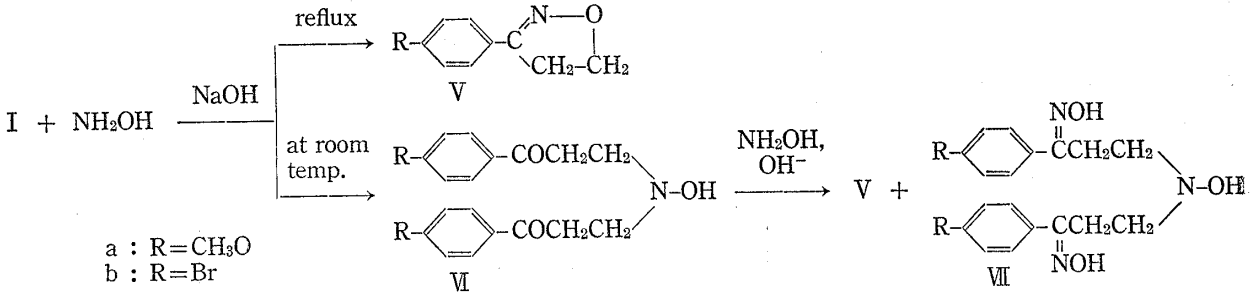

Chart 4

Regarding the conversion of a certain Mannich base oxime, β-dimethylaminopropiophenone oxime, to isoxazoline, Scott[7] has reported that this cyclization does not proceed through a vinyl or related intermediate. However, Barnes[8] has shown that the formation of isoxazoline by the condensation of benzalacetophenone with hydroxylamine is achieved through β,β'-hydroxylamino-bis-(β-phenylpropiophenone) intermediate. On the basis of this fact, in order to elucidate that the conversion to V proceeds through VI, VI was heated with hydroxylamine in water in the presence of sodium hydroxide for 17 hours under reflux.

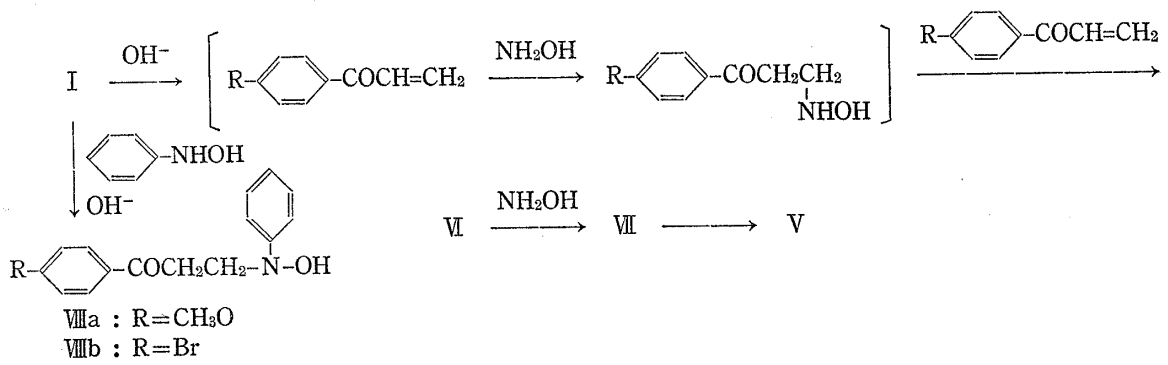

Chart 5

7) *a*) F.L. Scott, J.C. Riordan, and A.F. Hegarty, *Tetrahedron Letters*, **1963**, 537; *b*) F.L. Scott and J. McConaill, *ibid.*, **1967**, 3685.
8) R.P. Barnes, G.E. Pinkney, and G.M. Philips, *J. Am. Chem. Soc.*, **76**, 276 (1954).

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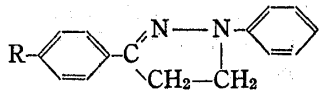
As expected, V and β,β'-hydroxylamino-bis(propiophenone oxime) (VII) were obtained in low yields. By this result, it is reasonable to conclude that V is formed according to the following scheme. The conversion of thiosulfates to vinyl compounds by hydroxide ion has already been known.[9]

The reaction of I with two equivalent amounts of phenylhydroxylamine in water in the presence of sodium hydroxide at ordinary temperature gave N-arylcarbonylethylhydroxylamines (VIII) in comparatively good yields. The reaction occurred immediately after adding sodium hydroxide into a solution of I and phenylhydroxylamine in water to give a crystalline product of VIII, though no reaction occurred in the absence of alkali. The IR absorption spectra of VIII exhibited the absorption assignable to the hydroxy and carbonyl groups near 3400 cm^{-1} and 1670 cm^{-1}, respectively. The mass spectra showed the molecular ion peak as the most abundant peak.

Experimental

1-Phenyl-3-aryl-2-pyrazoline (II)——General Procedure: A solution of 0.01 mole of sodium 2-arylcarbonylethylthiosulfate and 0.02 mole of phenylhydrazine in 20 ml of H_2O was heated for 0.5—3 hr under reflux. After cooling, the precipitates deposited were collected by filtration, washed with H_2O and recrystallized from a suitable solvent. Detailed data were summarized in Table I. These compounds exhibited the molecular ion peak as the most abundant peak.

Table I. 1-Phenyl-3-aryl-2-pyrazoline (II)



Compd. No.	R	mp (°C)	Yield (%)	React. time (hr)	Appearance (Recryst. solv.)	Formula	Analysis % Found (Calcd.) C	H	N
IIa	H	151—152	23	0.5	yellow needles (pet. ether)	$C_{15}H_{14}N_2$	80.97 (81.05)	6.44 (6.35)	12.19 (12.60)
IIb	CH_3O	138—140	52	1	yellow leaflets (MeOH)	$C_{16}H_{16}ON_2$	76.38 (76.16)	6.09 (6.39)	10.81 (11.10)
IIc	Br	123—124	33	3	yellow powder (EtOH)	$C_{15}H_{13}N_2Br$	59.62 (59.81)	4.09 (4.35)	9.09 (9.31)

1-β-Arylcarbonylethyl-3-aryl-2-pyrazoline (III)——General Procedure: To a solution of 0.005 mole of sodium 2-arylcarbonylethylthiosulfate in 20 ml of H_2O was added with stirring 0.01 mole of hydrazine hydrate at room temperature. The precipitates deposited immediately were collected by filtration and washed with H_2O. Recrystallization from a suitable solvent gave light yellow crystals. Detailed data were summarized in Table II. These compounds exhibited the molecular ion peak and fragment ion peak corresponding to the elimination of arylcarbonyl group as the most abundant peak.

1-Methyl-3-*p*-methoxyphenyl-2-pyrazoline (IVa)——a) A solution of 1.5 g (0.005 mole) of sodium 2-*p*-anisoylethylthiosulfate and 0.6 g (0.01 mole) of N,N-dimethylhydrazine in 20 ml of H_2O was heated for 7 hr under reflux. After cooling, the solution was repeatedly extracted with ether and the combined extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from pet. ether gave 0.1 g (12%) of light yellow leaflets melting at 68—70°. *Anal.* Calcd. for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.80; H, 7.45; N, 14.85. IR ν_{max}^{KBr} cm^{-1}: 1250 (OCH_3). Mass Spectrum *m/e*: 190 (M^+); 175 (M^+-CH_3).

b) To a solution of 1.5 g (0.005 mole) of sodium 2-*p*-anisoylethylthiosulfate and 1.5 g (0.01 mole) of methylhydrazine sulfate in 30 ml of H_2O was added with stirring 2 ml (0.01 mole) of 20% NaOH aqueous solution and the mixture was heated for 4 hr under reflux. After cooling, the precipitates deposited were collected by filtration, washed with H_2O and recrystallized from pet. ether to give 0.4 g (48%) of light yellow

9) H. Distler, *Angew. Chem.*, **79**, 520 (1967).

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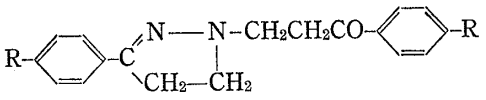
Table II. 1-Arylcarbonylethyl-3-aryl-2-pyrazoline (III)



Compd. No.	R	mp (°C)	Yield (%)	Appearance (Recrys. solv.)	Formula	Analysis % Found (Calcd.) C	H	N	IR cm^{-1} (CO)
IIIa	H	105—106	67	yellow needles (pet. ether)	$C_{18}H_{18}ON_2$	77.83 (77.67)	6.48 (6.52)	10.27 (10.07)	1677
IIIb	CH_3O	142—143	35	yellow leaflets (MeOH)	$C_{20}H_{22}O_3N_2$	71.25 (70.98)	6.65 (6.55)	8.45 (8.28)	1670
IIIc	Br	136—138	77	yellow leaflets (EtOH)	$C_{18}H_{16}ON_2Br_2$	49.64 (49.56)	3.64 (3.70)	6.12 (6.43)	1674

leaflets melting at 68—70°, which was identified with an authentic sample prepared by the procedure a) by mixed melting point determination and comparison of the IR spectrum.

1-Methyl-3-*p*-bromophenyl-2-pyrazoline (IVb)——A solution of 1.7 g (0.005 mole) of sodium 2-*p*-bromobenzoylethylthiosulfate and 0.6 g (0.01 mole) of N,N-dimethylhydrazine in 20 ml of H_2O was heated for 10 hr under reflux. The solution was treated by the same procedure as described above. Recrystallization from pet. ether gave 0.3 g (25%) of light yellow plates melting at 68—69°. *Anal.* Calcd. for $C_{10}H_{11}N_2Br$: C, 50.23; H, 4.64; N, 11.72. Found: C, 50.72; H, 4.52; N, 11.43. Mass Spectrum *m/e*: 239 (M^+).

3-*p*-Methoxyphenyl-2-isoxazoline (Va)——To a solution of 1.5 g (0.005 mole) of sodium 2-*p*-anisoylethylthiosulfate and 1.4 g (0.02 mole) of hydroxylamine HCl in 20 ml of H_2O was added a 20% aqueous solution of 1.2 g (0.03 mole) of NaOH. The mixture was heated for 3.5 hr under reflux and after cooling the solution was repeatedly extracted with benzene. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from MeOH to give 0.3 g (33%) of light yellow needles melting at 78—79°. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.79; H, 6.09; N, 7.75. IR ν_{max}^{KBr} cm^{-1}: 1250 (OCH_3). Mass Spectrum *m/e*: 177 (M^+).

3-*p*-Bromophenyl-2-isoxazoline (Vb)——To a solution of 1.7 g (0.005 mole) of sodium 2-*p*-bromobenzoylethylthiosulfate and 1.4 g (0.02 mole) of hydroxylamine HCl in 20 ml of H_2O was added a 20% aqueous solution of 1.2 g (0.03 mole) of NaOH and then 20 ml of EtOH. The mixture was heated for 3 hr under reflux. The precipitates deposited after cooling were collected by filtration, washed with H_2O and recrystallized from EtOH to give 0.1 g (9%) of white needles melting at 137—139°. *Anal.* Calcd. for C_9H_8ONBr: C, 47.81; H, 3.57; N, 6.20. Found: C, 47.94; H, 3.39; N, 6.45.

***β,β'*-Hydroxylamino-bis(*p*-methoxypropiophenone) (VIa)**——To an aqueous solution of hydroxylamine prepared by dissolving 0.6 g (0.015 mole) of NaOH into a solution of 0.7 g (0.01 mole) of hydroxylamine HCl in 20 ml of H_2O was added with stirring 1.5 g (0.005 mole) of sodium 2-*p*-anisoylethylthiosulfate at room temperature. After stirring was continued for additional 0.5 hr, the precipitates deposited were collected by filtration, washed with H_2O and recrystallized from MeOH to give 0.3 g (33%) of white leaflets melting at 134—135.5°. *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.02; H, 6.48; N, 4.13. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH, broad); 1668 (CO). NMR ($CDCl_3$) τ: 6.77 (6H, s, CH_3O); 6.15 (8H, s, $2CH_2CH_2$); 4.40 (1H, broad s, OH); 3.10 (4H, d, J=9 Hz, aromatic hydrogens); 2.07 (4H, d, J=9 Hz, aromatic hydrogens).

***β,β'*-Hydroxylamino-bis(*p*-bromopropiophenone) (VIb)**——To an aqueous solution of hydroxylamine prepared by dissolving 0.6 g (0.015 mole) of NaOH into a solution of 0.7 g (0.01 mole) of hydroxylamine HCl in 20 ml of H_2O was added with stirring 1.7 g (0.005 mole) of sodium 2-*p*-bromobenzoylethylthiosulfate at room temperature. After stirring was continued for additional 0.5 hr, the precipitates deposited were collected by filtration, washed with H_2O and recrystallized from MeOH to give 0.4 g (25%) of white leaflets melting at 185—187°. *Anal.* Calcd. for $C_{18}H_{17}O_3NBr_2$: C, 47.54; H, 3.77; N, 3.08. Found: C, 47.81; H, 3.63; N, 3.13. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH, broad); 1675 (CO).

Reaction of *β,β'*-Hydroxylamino-bis(*p*-bromopropiophenone) with Hydroxylamine——A solution of 0.3 g (0.001 mole) of *β,β'*-hydroxylamino-bis(*p*-bromopropiophenone), 0.1 g (0.0015 mole) of hydroxylamine HCl and 1 ml of 10% NaOH aqueous solution in 30 ml of 50% EtOH was heated for 17 hr under reflux and then allowed to stand at room temperature overnight. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.1 g (22%) of white leaflets of *β,β'*-hydroxylamino-bis(*p*-bromopropiophenone oxime) melting at 194—195°. *Anal.* Calcd. for $C_{18}H_{19}O_3N_3Br_2$: C, 44.60; H, 3.95; N, 8.67. Found: C, 45.03; H, 3.67; N, 8.74. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH, broad). The filtrate was allowed to stand for 1 week. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.02 g

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(7%) of white needles of 3-*p*-bromophenyl-2-isoxazoline melting at 137—139°, which was identified with an authentic sample by mixed melting point determination and comparison of the IR spectrum.

N-Phenyl-N-*p*-anisoylethylhydroxylamine (VIIIa)——To a solution of 3 g (0.01 mole) of sodium 2-*p*-anisoylethylthiosulfate and 2.2 g (0.02 mole) of N-phenylhydroxylamine in 30 ml of H_2O was added with stirring 0.1 g (0.0025 mole) of NaOH. The precipitates immediately deposited were collected by filtration and recrystallized from EtOH to give 2.5 g (93%) of light yellow leaflets melting at 152—154°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.98; H, 6.03; N, 4.88. IR ν_{max}^{KBr} cm^{-1}: 3405 (OH); 1669 (CO); 1260 (OCH_3). Mass Spectrum *m/e*: 271 (M^+).

N-Phenyl-N-*p*-bromobenzoylethylhydroxylamine (VIIIb)——To a solution of 1.7 g (0.005 mole) of sodium 2-*p*-bromobenzoylethylthiosulfate and 1.1 g (0.01 mole) of N-phenylhydroxylamine in 30 ml of H_2O was added with stirring 0.1 g (0.0025 mole) of NaOH. The precipitates immediately deposited were collected by filtration and recrystallized from EtOH to give 0.6 g (37.5%) of light yellow leaflets melting at 152—155°. *Anal.* Calcd. for $C_{15}H_{14}O_2NBr$: C, 56.26; H, 4.41; N, 4.38. Found: C, 56.40; H, 4.28; N, 4.08. IR ν_{max}^{KBr} cm^{-1}: 3395 (OH); 1668 (CO).

Acknowledgement We are grateful to Mr. K. Takeda for measurements of NMR and mass spectra and to Miss M. Sato for IR data. We also thank Mrs. K. Shiraki for microanalytical data.

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