

Studies on the Syntheses of Spiro-dienone Compounds. III.¹⁾
Photolysis of 2-Halogeno-N-ethyl-4'-hydroxybenzanilide
in Aqueous Sodium Hydroxide

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Irradiation of 2-bromo-N-ethyl-4'-hydroxybenzanilide (Ia) in aqueous sodium hydroxide gave 2'-ethylspiro[cyclohexa-2,5-diene-1,1'-isoindoline]-3',4-dione (II), N-ethyl-4'-hydroxybiphenyl-2-carboxamide (III), and 4'-hydroxybenzanilide (IV). When the above photolysis was run in the presence of sodium borohydride, 2'-ethyl-4-hydroxyspiro[cyclohexa-2,5-diene-1,1'-isoindolin]-3'-one (V) was obtained in good yield. This dienol (V) was oxidized with manganese dioxide to give the spiro-dienone (II). On the other hand, irradiation of 2-chloro-N-ethyl-4'-hydroxybenzanilide (Ib) in aqueous sodium hydroxide gave almost the starting material. However, when the photolysis of Ib was run in the presence of sodium borohydride or sodium sulfite, the biphenyl (III) was obtained in good yield. The reaction processes of these reactions were discussed.

It is well known that the photolysis of halogenobenzene in benzene gives biphenyl compounds in good yield.³⁾ Matsuura and Omura⁴⁾ reported that the photolysis of *p*-halogenophenol in aqueous alkali gave 2,4'-dihydroxybiphenyl as major product. In this paper we describe the photolysis of 2-halogeno-N-ethyl-4'-hydroxybenzanilide (Ia and Ib) in aqueous sodium hydroxide and a new synthetic method of the spiro-dienone system *via* photochemical cyclization reaction.⁵⁾

Irradiation of the bromo compound (Ia) in aqueous sodium hydroxide with a 100 W high pressure mercury lamp for 7.5 hr gave 2'-ethylspiro[cyclohexa-2,5-diene-1,1'-isoindoline]-3',4-dione (II) (1%), N-ethyl-4'-hydroxybiphenyl-2-carboxamide (III) (25%), and 4'-hydroxybenzanilide (IV) (3%). These products were proved to be identical with authentic samples.

Because of the low yield of the spiro-dienone (II), we assumed that II was decomposed by oxidation with bromine and dissolved oxygen, and that II was unstable under light. At first, in order to prevent the oxidation, sodium nitrite^{6a)} and sodium sulfite⁶⁾ were added to the reaction mixture. The photolysis of Ia in the presence of sodium nitrite gave the spiro-dienone (II) in 5% yield. However, when the photolysis was run in the presence of sodium sulfite, the biphenyl (III) was obtained in 55% yield and II was not obtained. The photolysis of the spiro-dienone (II) in ethanol-aqueous sodium hydroxide in the presence of sodium sulfite gave the biphenyl (III) in 50% yield. Therefore, the photolysis of Ib in the presence

- 1) Part of this work was presented at The Third International Congress of Heterocyclic Chemistry, Sendai, August, 1971. Part I: Z. Horii, C. Iwata, S. Wakawa, and Y. Nakashita, *Chem. Commun.*, 1970, 1039. Part II: Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Letters*, 1971, 1167.
- 2) Location: 6-1-1, Toneyama, Toyonaka, Osaka.
- 3) R.K. Sharma and N. Kharasch, *Angew. Chem. Intern. Ed. Engl.*, 7, 36 (1968).
- 4) K. Omura and T. Matsuura, *Chem. Commun.*, 1969, 1394.
- 5) J.C. Anderson and C.B. Reese [*Tetrahedron Letters*, 1962, 1] reported that the photolysis of 2-chloro-4'-hydroxyacetophenone in ethanol gave ethyl *p*-hydroxyphenylacetate *via* spiro-dienone intermediate which was not isolated.
- 6) a) K. Erdmann, *Naturwissenschaften*, 41, 189 (1954); b) B.F. Procter, S.A. Goldblith, C.J. Bates, and O.A. Hammerle, *Food Technol.*, 6, 237 (1952).

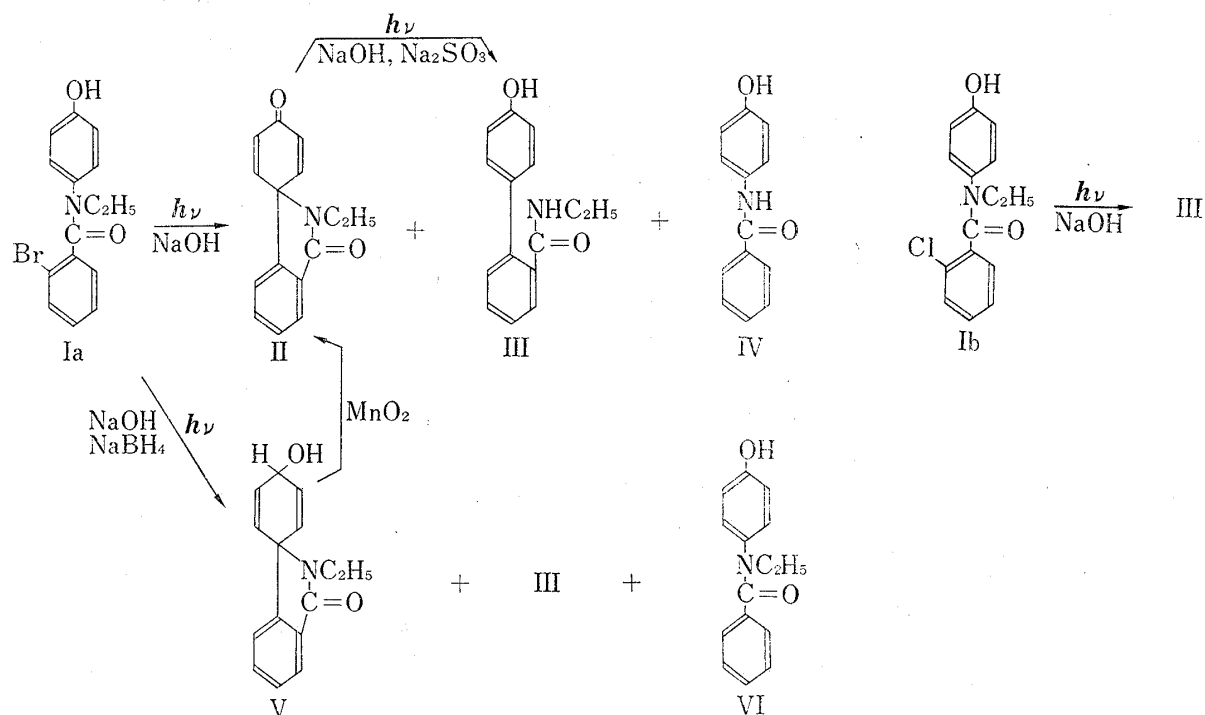


Chart 1

of sodium sulfite may partially proceed through II. No remarkable effect of diethylamine⁷⁾ and sodium thiosulfate⁸⁾ was observed for the photolysis of Ia.

Since the spiro-diene (V) may be more stable than the spiro-dienone (II)⁹⁾ under light, sodium borohydride was added to the reaction mixture. The photolysis of Ia in the presence of sodium borohydride gave 2'-ethyl-4-hydroxyspiro[cyclohexa-2,5-diene-1,1'-isoindolin]-3'-one (V) in 14% yield, accompanied by the biphenyl (III) and N-ethyl-4'-hydroxybenzanilide (VI) in 23% and 20% yield, respectively. These products were proved to be identical with authentic samples. When this reaction was stopped after 1.45 hr, the spiro-diene (V) was

TABLE I. Influence of Salts in the Photolysis of Ia (500 mg) in 0.12% Aqueous Sodium Hydroxide (250 ml)

Salts (g)	Duration of photolysis (hr)	Yields (%)					
		Ia	II	III	IV	V	VI
None	7.5	10	1	25	3	—	—
Na ₂ SO ₃	10	7	—	55	—	—	—
	1	3	8	34	3	—	—
	0.1	3	12	22	3	—	—
NaBH ₄	2	1.45	32	—	16	—	42 (62) ^{a)}
	2	3	—	—	26	—	14
	0.5	3	—	—	18	2	29
	0.1	3	13	—	14	12	13
NaNO ₂	10	6	5	6	—	—	—

a) Yield calculated on the basis of reacted Ia.

7) J. Nasielski, A. K-Demesmaeker, P. Kirsch, and R. N-Hinkens, *Chem. Commun.*, **1970**, 302.

8) Sodium thiosulfate was used to trap liberated bromine, which slowed the reaction appreciably if allowed to accumulate.

9) cf. O.L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

obtained in 62% yield. The oxidation of V with manganese dioxide in chloroform at room temperature for 12 hr gave II in 59% yield. This photochemical reaction could be used as a new synthetic method of the spiro-dienone compound.¹⁰⁾

In order to examine the influence of salt concentration, the photolysis of Ia was carried out under three different conditions (Table I). It was found that the reaction was accelerated

TABLE II. Influence of Salts in the Photolysis of Ib (500 mg) in 0.12% Aqueous Sodium Hydroxide (250 ml)

Salts (g)	Duration of photolysis (hr)	Yields (%)	
		Ib	III
None	6	70	5
NaBH ₄ (2)	6	4	45(47) ^{a)}
Na ₂ SO ₃ (10)	6	15	49(57) ^{a)}

a) Yield calculated on the basis of reacted Ib.

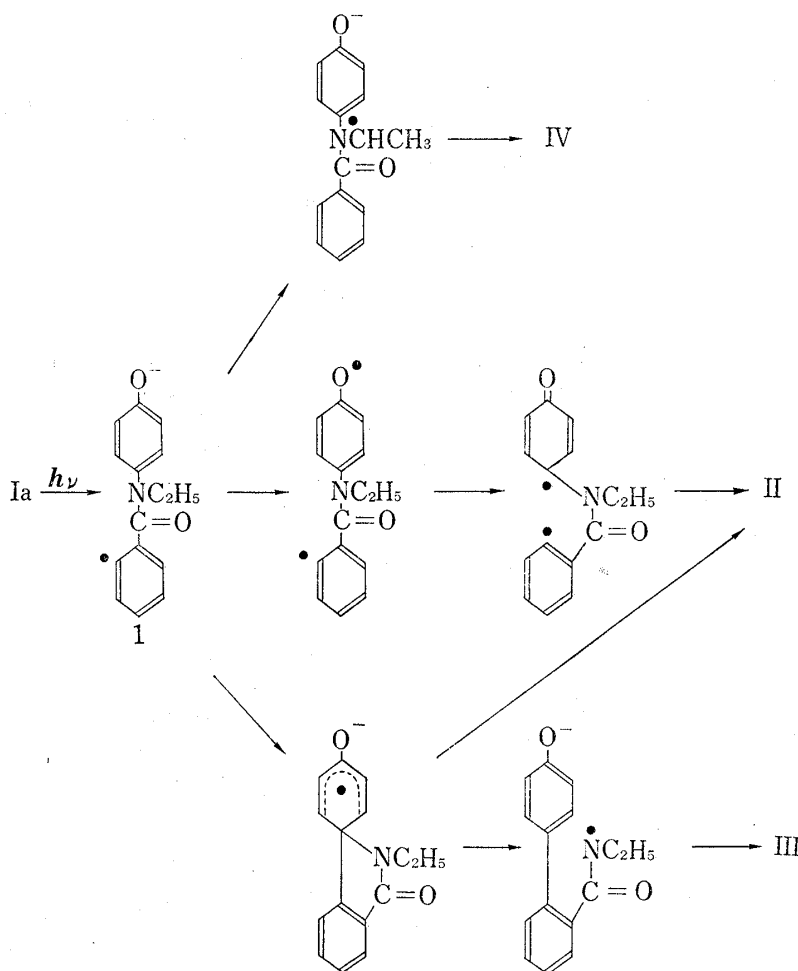


Chart 2

10) After our preliminary communications¹⁾ appeared, similar photochemical cyclization reaction have been reported on the following papers: D.H. Hey, G.H. Jones, and M.J. Perkins, *Chem. Commun.*, **1971**, 47; T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *ibid.*, **1971**, 724; T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *ibid.*, **1971**, 774; T. Kametani and T. Kohno, *Tetrahedron Letters*, **1971**, 3155; T. Kametani, H. Nemoto, T. Nakano, S. Shibuya, and K. Fukumoto, *Chem. Ind. (London)*, **1971**, 788; T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *ibid.*, **1971**, 818; R.J. Spangler and D.C. Boop, *Tetrahedron Letters*, **1971**, 4851.

by adding the salts and the influence of the salts increased with their concentration.

The photolysis of the chloro compound (Ib) in aqueous sodium hydroxide for 6 hr gave the biphenyl (III) in 5% yield and the starting material (Ib) was recovered in 70% yield. When the photolysis of Ib was run in the presence of sodium borohydride and sodium sulfite for 3 hr, the biphenyl (III) was obtained in 45% and 49% yield, respectively.

The formation of the spiro compound as predominant product in the photolysis of Ia differs from the photolysis of Ib in which the biphenyl compound is the major product. The difference of the major product from the photolysis of Ia and Ib suggests a different mechanism is operative in each case. In general,²⁾ aryl bromides are known to be easily cleaved photochemically, whereas the corresponding aryl chlorides are more stable under the same conditions. The photolysis of the bromo compound (Ia) may proceed through the aryl radical intermediate 1 by photochemical homolysis of the carbon-bromine bond as shown in Chart 2.

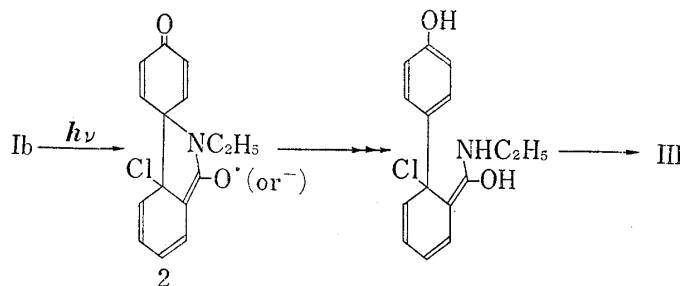


Chart 3

On the other hand, the photolysis of the chloro compound (Ib) may proceed through the cyclic intermediate 2¹¹⁾ as shown in Chart 3.

Further works on the mechanism of these photochemical reactions and extension of these reactions to the syntheses of natural products are in progress.

Experimental¹²⁾

Photolysis of 2-Bromo-N-ethyl-4'-hydroxybenzanilide (Ia)—A) Absence of Salt: A water-cooled mixture of 500 mg of Ia, 300 mg of NaOH and 250 ml of H₂O was irradiated with 100 W high pressure mercury lamp for 7.5 hr. The reaction mixture was acidified with conc. HCl under ice cooling and extracted with CHCl₃ and AcOEt, successively. The CHCl₃ extract was washed with satd. NaHCO₃ and H₂O, and dried. After the solvent was removed under reduced pressure, the residue (240 mg) was chromatographed on silica gel with CHCl₃. The first elution gave 5 mg (1%) of (C=C). This compound was identified with II as pale yellow crystals, mp 137–138° (from petr. ether). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1685 (C=O), 1670 (C=O), 1632 authentic sample¹³⁾ by mixed mp and the comparison of the IR spectra. The second elution gave 50 mg (10%) of Ia. The third elution gave 93 mg (25%) of III as colorless needles, mp 191–192° (from aq. EtOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3275 and 3040 (OH and NH), 1613 (C=O). Anal. Calcd. for C₁₅H₁₅O₂N: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.50; H, 6.30; N, 5.90. This compound was identified with authentic sample¹³⁾ by mixed mp and the comparison of the IR spectra.

The AcOEt extract was washed with satd. NaHCO₃ and H₂O, and dried. After the solvent was removed under reduced pressure, the residue (40 mg) was treated with a small amount of CHCl₃ to give a solid, which was recrystallized from aq. EtOH to give 10 mg (3%) of IV as colorless needles, mp 220–221°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3345 (shoulder) and 3260 (OH and NH). Anal. Calcd. for C₁₃H₁₁O₂N: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.87; H, 5.15; N, 6.66. This compound was identified with authentic sample¹⁴⁾ by mixed mp and the comparison of the IR spectra.

B) In the Presence of Na₂SO₃: A water-cooled mixture of 500 mg of Ia, 300 mg of NaOH, 1 g of Na₂SO₃ and 250 ml of H₂O was irradiated for 6 hr. The reaction mixture was worked up as described above, giving 204 mg of the CHCl₃ extract and 15 mg of the AcOEt extract. The CHCl₃ extract was treated with a small amount of CHCl₃ to give a pale yellow solid, which was washed with CHCl₃. This solid was recrystallized from aq. EtOH to give 121 mg (32%) of III as colorless needles, mp 191–192°. The CHCl₃ washings

11) cf. W.A. Henderson, Jr. and A. Zweig, *J. Am. Chem. Soc.*, **89**, 6778 (1967); M.P. Cava, M.J. Mitchell, S.C. Havlicek, A. Lindert, and R.J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).

12) All melting points were uncorrected. Eikosha PIH-100 (100 watt high pressure mercury lamp) from Eikosha Co., Osaka, was used as light source for the photochemical reactions. Organic extracts were dried over anhyd. Na₂SO₄.

13) D.H. Hey, J.A. Leonard, T.M. Moynahan, and C.W. Rees, *J. Chem. Soc.*, **1961**; 232.

14) K. Takatori, *Yakugaku Zasshi*, **73**, 548 (1953).

were condensed under reduced pressure and chromatographed on silica gel with CHCl_3 . The first elution gave 40 mg (8%) of Ia. The second elution gave 8 mg (2%) of III.

The AcOEt extract was recrystallized from aq. EtOH to give 9 mg (3%) of IV as colorless needles, mp 220—221°.

C) In the Presence of NaNO_2 : A water-cooled mixture of 500 mg of Ia, 300 mg of NaOH, 10 g of NaNO_2 and 250 ml of H_2O was irradiated for 6 hr. Excess of CO_2 gas was bubbled through the reaction mixture and the resulting solution was extracted with CHCl_3 and AcOEt, successively. The CHCl_3 extract (133 mg) was chromatographed on silica gel with CHCl_3 . The first elution gave 17 mg (5%) of II as pale yellow crystals, mp 137—138°. The second elution gave 32 mg (6%) of Ia. The third elution gave 23 mg (6%) of III as colorless needles, mp 191—192°.

The AcOEt extract gave no pure products.

D) In the Presence of NaBH_4 : A water-cooled mixture of 500 mg of Ia, 300 mg of NaOH, 500 mg of NaBH_4 and 250 ml of H_2O was irradiated for 3 hr. The reaction mixture was worked up as described above A), giving 346 mg of the CHCl_3 extract and 5 mg of the AcOEt extract. The CHCl_3 extract was treated with a small amount of CHCl_3 to give a pale yellow solid, which was washed with CHCl_3 . The solid was recrystallized from EtOH to give 57 mg (15%) of III as colorless needles, mp 191—192°. The CHCl_3 washings were condensed under reduced pressure and chromatographed on silica gel with CHCl_3 . The first elution gave 57 mg of VI as colorless needles, mp 162—163° (from aq. EtOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3100 (OH), 1620 (C=O). Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.75; H, 6.43; N, 5.82. The second elution gave 3 mg of IV as colorless needles, 220—221°. The third elution gave 12 mg (3%) of III as colorless needles, mp 191—192°. The fourth elution gave 109 mg (29%) of V as colorless needles, mp 198—201° (from aq. EtOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3390 and 3275 (OH), 1670 (C=O). Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.42; H, 6.23; N, 5.78.

The AcOEt extract was condensed under reduced pressure, the residue was recrystallized from aq. EtOH to give 2 mg (1%) of IV, mp 220—221°.

Photolysis of 2-Chloro-N-ethyl-4'-hydroxybenzanilide (Ib)—A) Absence of Salt: A water-cooled mixture of 500 mg of Ib, 300 mg of NaOH and 250 ml of H_2O was irradiated for 6 hr. The reaction mixture was worked up as described above, giving 410 mg of the CHCl_3 extract. The CHCl_3 extract was chromatographed on silica gel with CHCl_3 to give 352 mg (70%) of Ib and 22 mg (5%) of III as colorless needles, mp 191—192°.

B) In the Presence of NaBH_4 : A water-cooled mixture of 500 mg of Ib, 300 mg of NaOH, 12 g of NaBH_4 and 250 ml of H_2O was irradiated for 6 hr. The reaction mixture was worked up as described above, giving 420 mg of the CHCl_3 extract. The CHCl_3 extract was chromatographed on silica gel with CHCl_3 to give 20 mg (4%) of Ib and 196 mg (45%) of III as colorless needles, mp 191—192°.

C) In the Presence of Na_2SO_3 : A water-cooled mixture of 500 mg of Ib, 300 mg of NaOH, 10 g of Na_2SO_3 and 250 ml of H_2O was irradiated for 6 hr. The reaction mixture was worked up as described above, giving 415 mg of the CHCl_3 extract. The CHCl_3 extract was chromatographed on silica gel with CHCl_3 to give 73 mg (15%) and 212 mg (49%) of III as colorless needles, mp 191—192°.

Photolysis of 2'-Ethylspiro[cyclohexa-2,5-diene-1,1'-isoindoline]-3',4-dione (II)—A water-cooled mixture of 100 mg of II, 300 mg of NaOH, 10 g of Na_2SO_3 , 80 ml of EtOH and 170 ml of H_2O was irradiated for 6 hr. The reaction mixture was worked up as described above, giving 75 mg of the CHCl_3 extract and 10 mg of the AcOEt extract. The CHCl_3 extract was chromatographed on silica gel with CHCl_3 to give 51 mg (51%) of III as colorless needles, mp 191—192°. The AcOEt extract gave uncharacterizable products.

2'-Ethylspiro[cyclohexa-2,5-diene-1,1'-isoindoline]-3',4-dione (II)—A mixture of 110 mg of V, 2 g of MnO_2 and 25 ml of CHCl_3 was stirred at room temperature for 9 hr. The reaction mixture was filtered and the residue was washed with CHCl_3 repeatedly. The filtrate and washings were combined and condensed under reduced pressure. The residue was recrystallized from petr. ether to give 65 mg (59%) of II as pale yellow crystals, mp 137—138°.

2-Chloro-4'-hydroxy-N-ethylbenzanilide (Ib)—2-Chlorobenzoyl chloride, prepared from 12.5 g of 2-chlorobenzoic acid, in 50 ml of anhyd. ether was slowly added to a stirred suspension of 8.1 g of *p*-ethylaminophenol in 40 ml of anhyd. pyridine and 50 ml of anhyd. ether. After 10 hr, the mixture was poured into dil. HCl and extracted with CHCl_3 . The CHCl_3 extract was further washed with dil. HCl and then H_2O . The solvent was removed and the residue was boiled with 150 ml of 10% NaOH under reflux for 5 hr. The alkaline solution was acidified and extracted with CHCl_3 . The CHCl_3 extract was washed with satd. NaHCO_3 and then 10% NaOH. Acidification of the aq. NaOH solution gave a brown solid which was recrystallized from aq. EtOH to give 6.5 g (40%) of Ib as colorless needles, mp 252—253°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3110 (OH), 1614 (C=O). Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{NCl}$: C, 65.34; H, 5.11; N, 5.01. Found: C, 65.14; H, 5.10; N, 4.94.