

## Benzimidazolinetriones. Reactions of 2,5,6- and 2,4,7-Benzimidazolinetriones

Louis C. March and Madeleine M. Joullie

Department of Chemistry, University of Pennsylvania

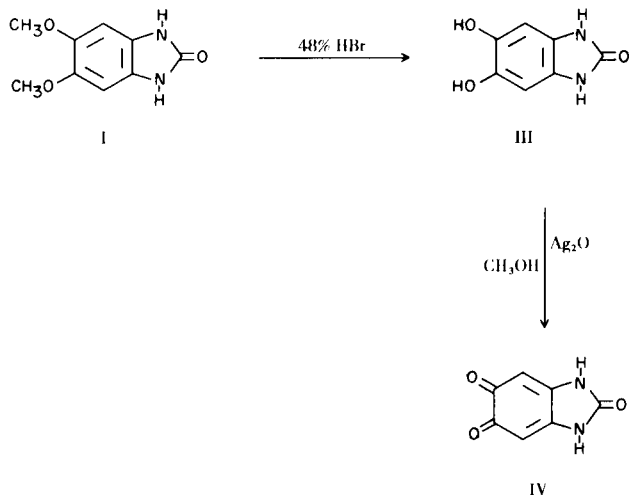
The condensation of 2,5,6-benzimidazolinetrione with ethylenediamine resulted in the formation of the 1,3-dihydro-2*H*-imidazo[4,5-*g*]quinoxalin-2-one ring system. The reaction of this trione with excess ethanethiol resulted in the isolation of three hydroquinones which were oxidized to the respective quinones. 2,4,7-Benzimidazolinetrione was shown to undergo a Diels-Alder reaction with isoprene and a mono-addition reaction with benzenethiol.

As a part of a general study (2-6) of the chemical and physical properties of various heterocyclic quinone systems, we are now reporting some reactions of benzimidazolinetriones.

2,5,6-Benzimidazolinetrione (IV) and 5,6-dihydroxy-2-benzimidazolinone (III) were first prepared by El'tsov and Efros (7). In their work, IV was prepared by the nitrous acid oxidation of 5,6-dimethoxy-2-benzimidazolinone (I) while III was prepared by the ascorbic acid reduction of IV.

In the present study, 5,6-dihydroxy-2-benzimidazolinone was prepared by the demethylation of I in 48% hydrobromic acid. 2,5,6-Benzimidazolinetrione was prepared by the ferric chloride oxidation of 5,6-benzimidazole diol hydrobromide or by the silver oxide oxidation of III.

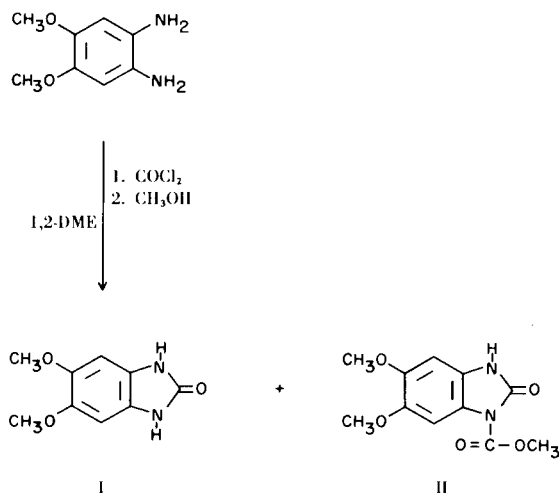
SCHEME 1



Other methods are available for the synthesis of 5,6-dimethoxy-2-benzimidazolinone (I) (8,9). In the present study, this compound was obtained by treating 4,5-diamino-1,2-dimethoxybenzene with phosgene in 1,2-dimethoxyethane. If an excess of methanol was added

to this reaction, a mixture of methyl 5,6-dimethoxy-2-oxo-1-benzimidazolinocarboxylate (II) and 5,6-dimethoxy-2-benzimidazolinone was isolated.

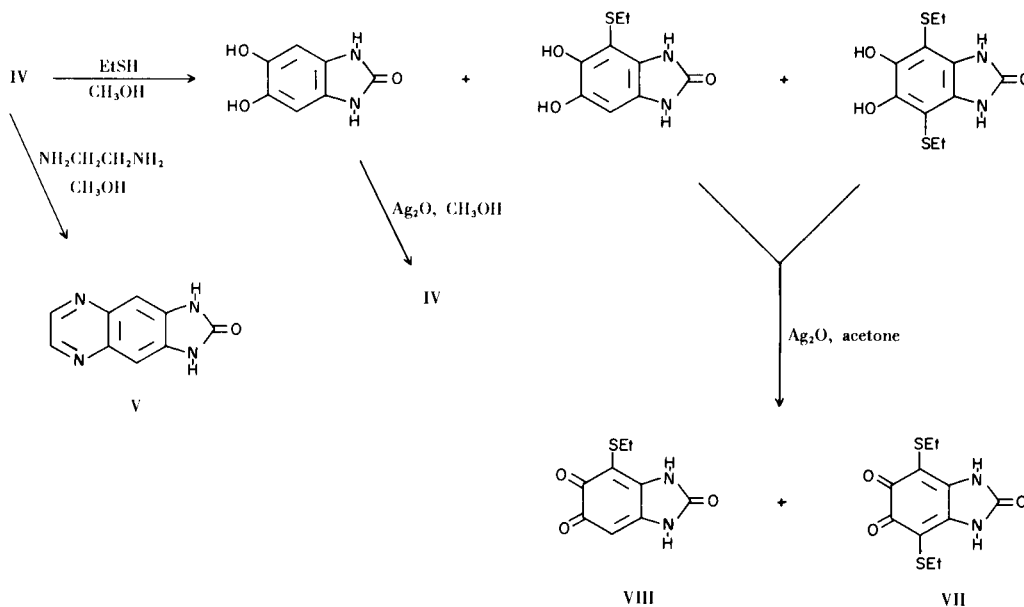
SCHEME 2



When 2,5,6-benzimidazolinetrione was treated with ethylenediamine, a sparingly soluble cream-colored solid was isolated. The infrared spectrum of this compound exhibited a carbonyl stretching frequency at 1721 cm<sup>-1</sup> and its nmr spectrum in trifluoroacetic acid solution indicated that a molecule of hydrogen had been lost during the reaction resulting in the formation of 1,3-dihydro-2*H*-imidazo[4,5-*g*]quinoxalin-2-one (V).

The addition of thiols to *o*-quinones was reported in 1964 and involved the reaction of 1-phenyl-5-mercaptotetrazole to *o*-benzoquinones (10). In the present study, 2,5,6-benzimidazolinetrione was treated with an excess of ethanethiol. After 14 hours, the nearly colorless reaction solution was found to contain air-sensitive hydroquinones, one of which was shown to be 5,6-dihydroxy-2-benzimidazolinone by oxidation to 2,5,6-benzimidazolinetrione.

SCHEME 3



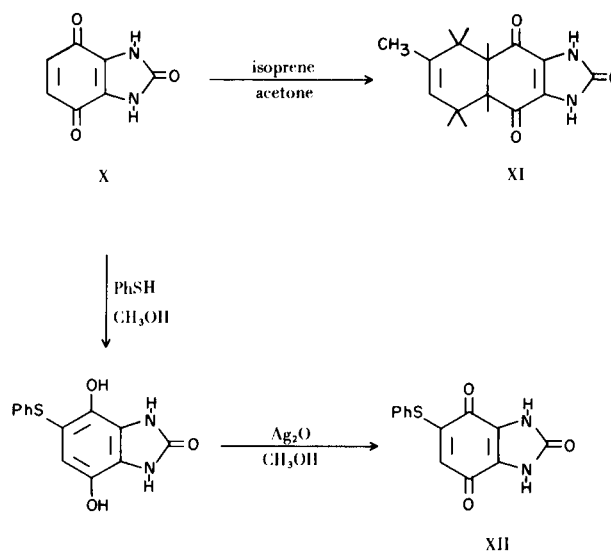
Since the remaining hydroquinones were air sensitive, they were oxidized without further attempt at purification to yield 4-(ethylthio)-2,5,6-benzimidazolinetrione (VIII) and 4,7-bis(ethylthio)-2,5,6-benzimidazolinetrione (VII). The formation of unsubstituted 5,6-dihydroxy-2-benzimidazolinone can be explained if one assumes that 2,5,6-benzimidazolinetrione enters into oxidation-reduction equilibrium with the intermediate thiosubstituted hydroquinone.

2,4,7-Benzimidazolinetrione (X) has previously been synthesized by El'tsov, Kuznetsov, and Efros (11). In the present study, a mixture of 2,3-diamino-1,4-dimethoxybenzene and 2,5-diamino-1,4-dimethoxybenzene was treated with phosgene in 1,2-dimethoxyethane to give 4,7-dimethoxy-2-benzimidazolinone. Demethylation in 48% hydrobromic acid followed by recrystallization from 48% hydrobromic acid gave 4,7-dihydroxy-2-benzimidazolinone which was oxidized to X without further attempt at purification.

The Diels-Alder reaction of 2,4,7-benzimidazolinetrione with excess isoprene in acetone solution led to the formation of 4a, 5, 8, 8a-tetrahydro-6-methylnaphth[2,3-*d*]imidazole-2,4,9-trione (XI).

The reaction of excess benzenethiol with 2,4,7-benzimidazolinetrione in methanol solution resulted in the formation of a mono-addition compound. This reaction apparently proceeds in a typical 1,4 manner since one could observe after the removal of solvent an air sensitive hydroquinone which was oxidized without further purification. The resulting red solid was shown to be 5-phenylthio-2,4,7-benzimidazolinetrione (XII).

SCHEME 4



## EXPERIMENTAL (12)

## 5,6-Dimethoxy-2-benzimidazolinone (I).

4,5-Diamino-1,2-dimethoxybenzene dihydrochloride (13) was dissolved in a minimum amount of water and a saturated aqueous sodium hydroxide solution was added to this solution. The free diamine which separated was collected and dried *in vacuo*. The diamine (23.2 g., 0.138 mole) was suspended in 500 ml. of 1,2-dimethoxyethane. The reaction flask was fitted with a dry ice condenser and a calcium chloride drying tube. Phosgene gas was bubbled through the mixture for 45 minutes while stirring. The stirring was continued for 17 hours after which the mixture was

heated to reflux and the insoluble solid was removed by filtration. The filtrate was concentrated to a small volume under reduced pressure and the light colored solid which formed was collected and recrystallized from 1,2-dimethoxyethane. The yield was 12.61 g. (47%), m.p. 251-254° (lit. (9) m.p. 246°);  $\lambda$  max (methanol), 225  $\mu$  shoulder, 302  $\mu$  ( $\log \epsilon$  3.99);  $\nu$  C=O (potassium bromide) 1734  $\text{cm}^{-1}$ ; nmr (DMSO- $d_6$ )  $\delta$  10.35 s ( $H_1, H_3$ ), 6.63 s ( $H_4, H_7$ ), and 3.68 s (6  $\text{CH}_3$  protons).

*Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3$ : C, 55.67; H, 5.19; N, 14.43. Found: C, 55.71; H, 5.35; N, 14.33.

Methyl 5,6-dimethoxy-2-oxo-1-benzimidazolinocarboxylate (II).

4,5-Diamino-1,2-dimethoxybenzene (8.23 g., 0.049 mole) was placed in 600 ml. of 1,2-dimethoxyethane and treated with phosgene as previously described. Methanol (200 ml.) was added to the resulting filtrate and the solution was concentrated to an oil under reduced pressure. The oil was dissolved in methanol and precipitated with ether. The gummy precipitate slowly solidified and weighed 3.35 g. On standing, the methanol-ether filtrate afforded additional white solid (0.29 g.) which was shown to be II. Repeated fractional recrystallization of the main product first from methanol and then from 1,2-dimethoxyethane gave 5,6-dimethoxy-2-benzimidazolinone, 1.21 g. (13%) and methyl 5,6-dimethoxy-2-oxo-1-benzimidazolinocarboxylate, 0.755 g. (6%), m.p. 234-235°;  $\lambda$  max (methanol), 207  $\mu$  ( $\log \epsilon$  4.52), 252  $\mu$  ( $\log \epsilon$  3.72), 298  $\mu$  ( $\log \epsilon$  3.90);  $\nu$  C=O (potassium bromide), 1784, 1720  $\text{cm}^{-1}$ ; nmr (DMSO- $d_6$ )  $\delta$  10.97 broad s ( $H_3$ ), 7.43 s ( $H_7$ ), 6.66 s ( $H_4$ ), 3.92 s (3  $\text{CH}_3$  protons of ester group) and 3.75 s (6  $\text{CH}_3\text{O}$ -protons).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_5$ : C, 52.38; H, 4.80; N, 11.11. Found: C, 52.59; H, 4.89; N, 11.22.

5,6-Dihydroxy-2-benzimidazolinone (III).

Compound I (12.61 g., 0.065 mole) was placed in 100 ml. of 48% hydrobromic acid and refluxed for 1 hour. When the reaction mixture was cooled in ice water, the white solid which formed was collected and recrystallized 4 times from 48% hydrobromic acid. This solid was shown to contain approximately 1/2 mole of hydrogen bromide. The yield of this product was 80%. This compound lost hydrogen bromide when recrystallized three times from acetone to give III, m.p. 388-393° dec. (Lit. (7)  $> 300^\circ$ ). The ultraviolet spectrum of this product was identical to that of 2,5,6-benzimidazolinetrione indicating that air oxidation had occurred in methanol,  $\nu$  C=O (potassium bromide), 1700  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_7\text{H}_6\text{N}_2\text{O}_3$ : C, 50.61; H, 3.64; N, 16.86. Found: C, 50.44; H, 3.81; N, 16.72.

2,5,6-Benzimidazolinetrione (IV).

5,6-Dihydroxy-2-benzimidazolinone containing 1/2 mole of hydrogen bromide (1.78 g., 0.00862 mole) was dissolved in 1 liter of refluxing methanol. Silver oxide (5.00 g., 0.0216 mole) was added and the mixture was refluxed for 1 hour. The insoluble solid was removed by filtration and the filtrate was concentrated to approximately 50 ml. under reduced pressure and cooled. The dark red solid was collected and gave 0.996 g. (71%) of IV, m.p.  $> 300^\circ$  dec. (Lit. (7)  $> 300^\circ$ ). The compound could also be prepared by dissolving 5,6-benzimidazolediol hydrobromide (4.00 g., 0.0173 mole) in 60 ml. of water and adding this solution to a solution of ferric chloride hexahydrate (14.0 g., 0.052 mole) in 100 ml. of water. The reaction turned dark blue and was stirred for 1/2 hour after which the rust colored solid that formed was collected and recrystallized from methanol to yield 0.67 g. (24%) of IV,  $\lambda$  max (methanol), 229  $\mu$  shoulder, 242  $\mu$  shoulder, 320  $\mu$  ( $\log \epsilon$  4.13);  $\nu$  C=O (potassium bromide), 1772, 1755, 1643

$\text{cm}^{-1}$ ; nmr spectrum at 100 MHz. (DMSO- $d_6$ )  $\delta$  11.34 broad s ( $H_1, H_3$ ), 5.55 s ( $H_4, H_7$ ).

*Anal.* Calcd. for  $\text{C}_4\text{H}_7\text{N}_2\text{O}_3$ : C, 51.23; H, 2.46; N, 17.07. Found: C, 51.20; H, 2.47; N, 17.06.

1,3-Dihydro-2H-imidazo[4,5-g]quinoxalin-2-one (V).

Compound IV (0.80 g., 0.00488 mole) was dissolved in 1250 ml. of refluxing methanol. Ethylenediamine (1.0 ml., 0.015 mole) was added and the solution turned dark blue. The solution was refluxed for 5 minutes and stirred for 100 minutes during which time a precipitate formed. The solid which formed was collected and afforded 0.83 g. (91%) of V. Recrystallization from glacial acetic acid gave a cream colored solid which decomposed gradually above 300°;  $\lambda$  max (methanol), 245  $\mu$  ( $\log \epsilon$  4.31), 247  $\mu$  shoulder, 356  $\mu$  ( $\log \epsilon$  4.23);  $\nu$  C=O (potassium bromide), 1721  $\text{cm}^{-1}$ ; nmr spectrum (trifluoroacetic acid)  $\delta$  10.45 s ( $H_1, H_3$ ), 9.37 s ( $H_6, H_7$ ) and 8.50 s ( $H_4, H_9$ ).

*Anal.* Calcd. for  $\text{C}_9\text{H}_6\text{N}_4\text{O}$ : C, 58.06; H, 3.23; N, 30.09. Found: C, 58.09; H, 3.48; N, 29.84.

1,3-Dihydro-2H-imidazo[4,5-g]quinoxalin-2-one Hydrochloride (VI).

Compound V (0.79 g., 0.00425 mole) was dissolved in 675 ml. of refluxing concentrated hydrochloric acid. The yellow solution stood overnight and the yellow crystals which formed were collected by filtration. After the filtrate stood for three days, additional product was collected. The total yield was 0.81 g. (86%). The compound was recrystallized from concentrated hydrochloric acid since it was unstable in ordinary solvents. The compound turned white above 280° and decomposed gradually above 450°,  $\nu$  C=O (potassium bromide), 1720, 1706  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_9\text{H}_7\text{ClN}_4\text{O}$ : C, 48.55; H, 3.17; Cl, 15.92; N, 25.17. Found: C, 48.59; H, 3.21; Cl, 16.00; N, 25.02.

4,7-Bis(ethylthio)-2,5,6-benzimidazolinetrione (VII) and 4-Ethylthio-2,5,6-benzimidazolinetrione (VIII).

Compound IV (1.721 g., 0.0105 mole) was suspended in 525 ml. of methanol. Ethanethiol (7.5 ml., 0.101 mole) was added and the mixture was stirred for 14 hours. The solution was evaporated to dryness under reduced pressure and a small volume of acetone was added. Insoluble 5,6-dihydroxy-2-benzimidazolinone (0.376 g., 22%) was collected. When this solid was recrystallized from methanol, it turned red, indicating air oxidation. This solid was oxidized with silver oxide in methanol solution and the red solid which was obtained was shown to be IV from its physical properties and infrared spectrum. The acetone filtrate was turning purple from air oxidation. Therefore, it was diluted to 600 ml. with acetone and treated with silver oxide (4.65 g., 0.0201 mole). The mixture was stirred for 4.5 hours, the insoluble material was removed and the purple filtrate was evaporated to dryness under reduced pressure. The residue was treated with 300 ml. of chloroform and the insoluble solid which remained was collected and recrystallized from acetone. The yield of VIII was 0.421 g. (18%), m.p. 267-269° dec.;  $\lambda$  max (methanol) 212  $\mu$  ( $\log \epsilon$  4.19), 258  $\mu$  ( $\log \epsilon$  4.00), 321  $\mu$  ( $\log \epsilon$  4.06);  $\nu$  C=O (potassium bromide), 1760, 1633  $\text{cm}^{-1}$ ; nmr spectrum (DMSO- $d_6$ )  $\delta$  11.35 broad s ( $H_1, H_3$ ), 5.62 s ( $H_7$ ), 2.92, 2.80, 2.68 q (the fourth peak was masked by a solvent peak at 2.55) (2  $\text{CH}_2$  protons), 1.28, 1.17, 1.05 t (3  $\text{CH}_3$  protons).

*Anal.* Calcd. for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_3\text{S}$ : C, 48.21; H, 3.59; N, 12.49; S, 14.30. Found: C, 48.41; H, 3.71; N, 12.31; S, 14.13.

The purple chloroform filtrate from above was concentrated to a small volume under reduced pressure. After the solution was cooled, 1.218 g. (41%) of dark purple crystalline VII was collected,

m.p. 246-248° dec. An analytical sample was recrystallized from chloroform,  $\lambda$  max (methanol), 220  $m\mu$  ( $\log \epsilon$  4.27), 273  $m\mu$  ( $\log \epsilon$  4.20), 318  $m\mu$  ( $\log \epsilon$  3.97);  $\nu$  C=O (potassium bromide), 1749, 1660  $cm^{-1}$ ; nmr spectrum (DMSO- $d_6$ )  $\delta$  11.48 s ( $H_1, H_3$ ), 2.93, 2.80, 2.68 q (the fourth peak was masked by a solvent peak at 2.52) (4  $CH_2$  protons), 1.28, 1.15, 1.03 t (6  $CH_3$  protons). A nmr spectrum in deuterated acetone showed  $\delta$  3.03, 2.90, 2.77, 2.65 q (4  $CH_2$  protons), 1.35, 1.22, 1.12 t (6  $CH_3$  protons).

*Anal.* Calcd. for  $C_{11}H_{12}N_2O_3S_2$ : C, 46.46; H, 4.25; N, 9.85, S, 22.55. Found: C, 46.62; H, 4.19; N, 10.02; S, 22.43.

#### 4,7-Dimethoxy-2-benzimidazolinone (IX).

2,3-Diamino-1,4-dimethoxybenzene dihydrochloride was placed in saturated sodium hydroxide solution. The mixture was stirred for 15 minutes and the white solid which remained was collected and washed with a small amount of ice water and dried. 2,3-Diamino-1,4-dimethoxybenzene (21.27 g., 0.126 mole) was placed in 600 ml. of 1,2-dimethoxyethane. Phosgene gas was bubbled through the mixture for 1/2 hour while stirring. The mixture was stirred for an additional 15 hours and the insoluble solid which remained was removed by filtration. The brown filtrate was treated with activated carbon. After removal of the carbon, the filtrate was concentrated to approximately 100 ml. under reduced pressure. The light colored solid was collected to give 13.55 g. (56%) of IX. An analytical sample was recrystallized from 1,2-dimethoxyethane using activated carbon, m.p. 250-252° (Lit. (7) m.p. 252°),  $\lambda$  max (methanol), 212  $m\mu$  ( $\log \epsilon$  4.60), 234  $m\mu$  shoulder, 269  $m\mu$  ( $\log \epsilon$  3.10);  $\nu$  C=O 1679  $cm^{-1}$ .

*Anal.* Calcd. for  $C_9H_{10}N_2O_3$ : C, 55.67; H, 5.19; N, 14.43. Found: C, 55.82; H, 5.34; N, 14.32.

#### 2,4,7-Benzimidazolinetrione (X).

Compound IX (5.33 g., 0.0275 mole) was refluxed in 50 ml. of 48% hydrobromic acid for one hour. The reaction was cooled and the pink solid which formed was collected, washed with ether and dried. This solid appeared to be 4,7-dihydroxy-2-benzimidazolinone containing approximately 1/2 mole of hydrogen bromide. This hydroquinone hydrobromide (5.77 g., 0.028 mole) was dissolved in 500 ml. of methanol and treated with silver oxide (14.43 g., 0.0622 mole). The mixture was refluxed for 75 minutes. The insoluble material was removed and concentration of the filtrate under reduced pressure afforded 3.18 g. (69%) of X. The trione was recrystallized from methanol and also from acetone, m.p. > 200° dec. (Lit. (7) > 240° dec.);  $\lambda$  max (methanol), 214  $m\mu$  ( $\log \epsilon$  4.27), 255  $m\mu$  ( $\log \epsilon$  3.88), 305  $m\mu$  ( $\log \epsilon$  3.40);  $\nu$  C=O (potassium bromide), 1706, 1653  $cm^{-1}$ ; nmr spectrum (DMSO- $d_6$ )  $\delta$  11.50 s ( $H_1, H_3$ ), 6.57 s ( $H_5, H_6$ ).

*Anal.* Calcd. for  $C_7H_4N_2O_3$ : C, 51.23; H, 2.46; N, 17.07. Found: C, 51.43; H, 2.61; N, 16.88.

#### 4a, 5, 8, 8a-Tetrahydro-6-methylnaphth[2,3-d]imidazoline-2,4,9-trione (XI).

Compound X (0.533 g., 0.00325 mole) was dissolved in 500 ml. of refluxing acetone. The flask was fitted with a dry ice condenser and 2-methyl-1,3-butadiene (10.0 ml., 0.10 mole) was added. The solution was refluxed for 1 hour, an additional 10.0 ml. (0.10 mole) of 2-methyl-1,3-butadiene was added to it and the mixture was stirred for 64 hours. The colorless precipitate which formed was collected. Concentration of the filtrate afforded additional solid, total yield, 0.721 g. (96%). The product was recrystallized from acetone, m.p. 346-350° dec.;  $\lambda$  max (methanol); 209  $m\mu$  ( $\log \epsilon$  4.20), 225  $m\mu$  shoulder, 274  $m\mu$  shoulder, 283  $m\mu$

( $\log \epsilon$  3.35), 332  $m\mu$  ( $\log \epsilon$  3.79);  $\nu$  C=O (potassium bromide), 1737, 1670, 1652  $cm^{-1}$ ; nmr spectrum (DMSO- $d_6$ )  $\delta$  11.42 s ( $H_1, H_3$ ), 5.33 s ( $H_7$ ), 2.22 broad s (4  $CH_2$  protons at the 5 and 8 positions), 1.62 s (3  $CH_3$  protons), (the ring junction protons were masked by the solvent peak at 3.28).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_3$ : C, 62.06; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.42; N, 11.91.

#### 5-Phenylthio-2,4,7-benzimidazolinetrione (XII).

Compound X (2.57 g., 0.0157 mole) was placed in 200 ml. of methanol. Benzenethiol (5.0 ml., 0.0486 mole) was added and the mixture was stirred for 21 hours. The solution was evaporated to dryness under reduced pressure and the residue treated with methanol (200 ml.). Silver oxide (7.42 g., 0.032 mole) was added to this solution and the mixture was refluxed for 2 hours. The insoluble solid was removed and the filtrate was cooled. The red crystals which separated were collected to give 1.57 (37%) of XII. The compound was recrystallized from acetone, m.p. 269-273° dec.;  $\lambda$  max (methanol), 210  $m\mu$  shoulder, 223  $m\mu$  ( $\log \epsilon$  4.51);  $\nu$  C=O (potassium bromide), 1720, 1707, 1643  $cm^{-1}$ ; nmr spectrum (DMSO- $d_6$ )  $\delta$  11.57 s ( $H_1, H_3$ ), 7.57 s (5 phenyl protons), 5.27 s ( $H_6$ ).

*Anal.* Calcd. for  $C_{13}H_8N_2O_3S$ : C, 57.34; H, 2.96; N, 10.29; S, 11.79. Found: C, 57.42; H, 2.92; N, 10.09; S, 11.84.

#### REFERENCES

- (1) Abstracted in part from the Ph.D. thesis of L. C. March, University of Pennsylvania, 1967.
- (2) P. K. Joseph and M. M. Joullié, *J. Med. Chem.*, **7**, 801 (1964).
- (3) M. R. W. Levy and M. M. Joullié, *J. Heterocyclic Chem.*, **1**, 171 (1964).
- (4) W. F. Gum, Jr. and M. M. Joullié, *J. Org. Chem.*, **30**, 2583 (1965).
- (5) J. F. Munshi and M. M. Joullié, *J. Heterocyclic Chem.*, **4**, 133 (1967).
- (6) P. K. Joseph and M. M. Joullié, *ibid.*, **7**, 000 (1970).
- (7) A. V. El'tsov and L. S. Efros, *J. Gen. Chem. (U.S.S.R.)*, **30**, 3319-3324 (1960).
- (8) R. Clark and A. Pessolano, *J. Am. Chem. Soc.*, **80**, 1657 (1958).
- (9) A. V. El'tsov and L. S. Efros, *J. Gen. Chem. (U.S.S.R.)*, **29**, 3699 (1959).
- (10) R. F. Porter, W. W. Rees, E. Frauenglass, H. S. Wilgus, III, G. H. Nawn, P. P. Chiesa and J. W. Gates, Jr., *J. Org. Chem.*, **29**, 588 (1964).
- (11) A. V. El'tsov, V. S. Kuznetsov, and L. S. Efros, *J. Gen. Chem. (U.S.S.R.)*, **33**, 3965 (1963).
- (12) Melting points were taken either on a Thomas-Hoover or an Mel-Temp melting point apparatus. The infrared spectra were determined on a Perkin-Elmer 521 recording spectrophotometer as potassium bromide pellets. The ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer. Microanalyses were carried out by Dr. A. Bernhardt, Max Planck Institute, 433 Mülheim (Ruhr), West Germany. The nmr spectra were determined at 60 MHz on a Varian Associates Model HR-60 spectrometer unless otherwise specified.
- (13) L. Weinberger and A. R. Day, *J. Org. Chem.*, **24**, 1451 (1959).

Received September 4, 1969

Philadelphia, Pa. 19104