4-7-Benzimidazolediones. Reactions of 5,6-Dibromo-4,7-benzimidazoledione

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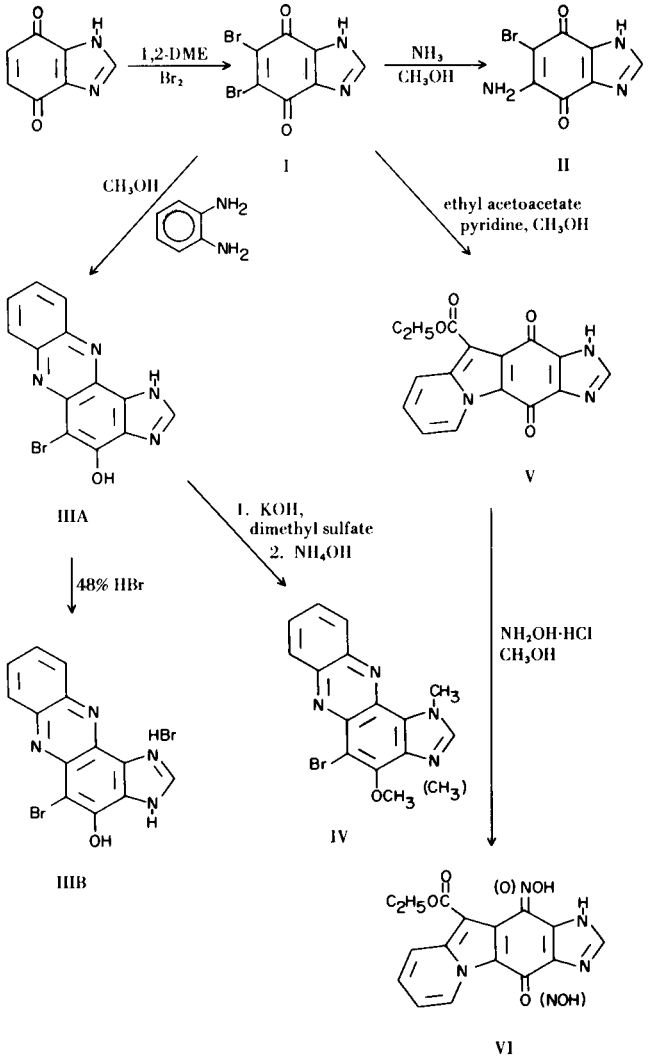
The reaction of 4,7-benzimidazoledione (2) with excess bromine in 1,2-dimethoxyethane resulted in the formation of 5,6-dibromo-4,7-benzimidazoledione (I). The structure of I was supported by its n.m.r. spectrum in deuterated dimethylsulfoxide which showed the presence of the proton at the 2 position at 8.23 δ. The infrared spectrum of I exhibited a carbonyl stretching frequency at 1675 cm^{-1}, typical of a quinone. The reaction of I with ammonia gas in methanol was found to cause the displacement of one of the bromine atoms to yield 5-amino-6-bromo-4,7-benzimidazoledione (II), which exhibited a carbonyl frequency at 1690 cm^{-1}.

It has been previously shown that mono- or dihalo-1,4-naphthoquinones react with *o*-phenylenediamine to yield 5-hydroxybenzo[*a*]phenazines which may or may not be halogenated, depending on the extent of substitution of the parent quinone (3,4,5). In the present study, when 5,6-dibromo-4,7-benzimidazoledione was treated with *o*-phenylenediamine in methanol, a red solid was formed. The infrared spectrum of the product did not exhibit a carbonyl frequency. This compound was shown to be 5-bromo-1*H*-imidazo[4,5-*a*]phenazin-4-ol (IIIA). The assignment was based on the infrared, ultraviolet, and n.m.r. spectra of IIIA and also on the fact that this product formed a dimethyl derivative (IV) when treated with dimethyl sulfate. The dimethyl derivative also did not exhibit a carbonyl frequency. This would indicate that methylation had occurred on the hydroxyl group and one of the nitrogen atoms of the imidazole ring. It was not determined on which of the imidazole nitrogen atoms methylation had occurred or whether a mixture of both isomers was formed. When 5-bromo-1*H*-imidazo[4,5-*a*]-phenazin-4-ol was recrystallized from 48% hydrobromic acid, a yellow hydrobromide salt was formed (IIIB).

In 1954, Pratt, Luckenbaugh, and Erickson (6) observed that 1-carbethoxy-2,3-phthaloylpyrrocoline was formed when 2,3-dichloro-1,4-naphthoquinone was treated with ethyl acetoacetate and pyridine in alcohol solution. In this investigation, a similar reaction was observed with 5,6-dibromo-4,7-benzimidazoledione, ethyl acetoacetate and pyridine in methanol solution. The product formed was ethyl 4,11-dihydro-4,11-dioxo-1*H*-indolizino[2,3-*f*]-benzimidazole-10-carboxylate (V). The infrared spectrum of V exhibited three bands in the carbonyl region at 1720, 1672 and 1640 cm^{-1}. Compound V formed a monoxime (VI) with hydroxylamine hydrochloride in methanol solution. It has previously been suggested (6) that the group farthest from the indolizine nitrogen reacts preferentially since it is less sterically hindered. In this investigation, no attempts were made to determine whether both of the possible isomeric oximes had been formed or which of the two isomeric structures predominated. The n.m.r. spectrum of VI in trifluoroacetic acid showed the presence

SCHEME I



of an ethyl group and the presence of a proton at the 2 position of the imidazole ring. This spectrum indicated the presence of the indolizine ring with splitting patterns and coupling constants characteristic of that ring system (7).

EXPERIMENTAL (8)

The yields, melting points, and analytical data for the compounds prepared are shown in Tables I and II.

5,6-Dibromo-4,7-benzimidazoledione (I).

4,7-Benzimidazoledione (2.94 g., 0.0199 mole) was suspended in 300 ml. of 1,2-dimethoxyethane. Bromine (10.0 ml., 0.183 mole) was added and the mixture was stirred for 2 hours during which time the dione dissolved. The solvent was concentrated to about 30 ml. on a steam bath under reduced pressure. Approximately 450 ml. of diethyl ether was added and the mixture was stirred overnight. The yellow solid which formed was collected by filtration and recrystallized first from methanol-diethyl ether using decolorizing carbon and then from methanol.

5-Amino-6-bromo-4,7-benzimidazoledione (II).

5,6-Dibromo-4,7-benzimidazoledione (1.98 g., 0.00647 mole) was dissolved in 500 ml. of methanol. The flask was fitted with a dry ice condenser and anhydrous ammonia gas was bubbled through the refluxing methanol solution for 0.5 hours. The solution turned red and was allowed to stand overnight. The solution was concentrated to approximately 20 ml. on a steam bath under reduced pressure. After standing for two days, the purple solid which formed was collected by filtration and recrystallized from methanol.

5-Bromo-1*H*-imidazo[4,5-*a*]phenazin-4-ol (IIIA).

5,6-Dibromo-4,7-benzimidazoledione (1.00 g., 0.00327 mole) was dissolved in 200 ml. of methanol and *o*-phenylenediamine (0.45 g., 0.00416 mole) was added to this solution. The solution turned red and was stirred for 2.25 hours. The dark red solid which separated was collected by filtration, washed with methanol and diethyl ether and recrystallized from methanol. A hydrobromide salt (IIIB) was formed when the compound (1.14 g., 0.00362 mole) was placed in 50 ml. of 48% hydrobromic acid, refluxed for 12 minutes and cooled.

5-Bromo-4-methoxy-(1 or 3)-methyl-1*H*-imidazo[4,5-*a*]phenazine (IV).

5-Bromo-1*H*-imidazo[4,5-*a*]phenazin-4-ol (1.011 g., 0.00321 mole) was placed in a solution of potassium hydroxide (0.378 g., 0.00674 mole in 50 ml. of water). The mixture was stirred for 10 minutes, dimethyl sulfate (5.0 ml., 0.0528 mole) was added and the reaction was stirred for 17.5 hours. Concentrated ammonium hydroxide was added dropwise with stirring until a gelatinous precipitate formed. This precipitate was collected by filtration and dissolved in glacial acetic acid to give a purple solution. The acetic acid solution was concentrated to a small volume under reduced pressure. Ethyl acetate was added and the solid which formed was collected and precipitated again from acetic acid-ethyl acetate. This gummy precipitate was recrystallized from methanol to give IV.

Ethyl 4,11-dihydro-4,11-dioxo-1*H*-indolizine[2,3-*f*]benzimidazole-10-carboxylate (V).

4,6-Dibromo-4,7-benzimidazoledione (2.00 g., 0.00654 mole) was dissolved in 300 ml. of methanol and ethyl acetoacetate (3.0 ml., 0.0236 mole) was added to the solution with stirring. Pyridine (4.0 ml., 0.0497 mole) was added and the mixture was warmed to 45°. The solution was stirred for 20 hours at room temperature. The precipitate which formed was collected by filtration and the filtrate was concentrated to a small volume under reduced pressure. Additional red solid was collected by cooling the solution. This solid was recrystallized from methanol.

Ethyl 4,11-dihydro-4,11-dioxo-1*H*-indolizino[2,3-*f*]benzimidazole-10-carboxylate (4 or 11)-oxime (VI).

Ethyl 4,11-dihydro-4,11-dioxo-1*H*-indolizino[2,3-*f*]benzimidazole-10-carboxylate (0.943 g., 0.00305 mole) was dissolved in 500 ml. of refluxing methanol. Hydroxylamine hydrochloride (0.71

TABLE I

Compound No.	Yield %	M.p. °C	Formula	Calcd., % C	H	N	Br	Found, % C	H	N	Br
I	79	275-279d	$C_7H_2N_2O_2Br_2$	27.48	0.66	9.16	52.24	27.66	0.81	9.19	52.06
II	54	>300d	$C_7H_4N_3O_2Br$	34.74	1.67	17.36	33.01	34.99	1.81	17.23	32.93
IIIA (a)	52	>300d	$C_{13}H_7N_4OBr$	49.55	2.24	17.78	25.36	49.39	2.38	17.62	25.56
IIIB	–	365-368d	$C_{13}H_8N_4OBr_2$	39.43	2.04	14.15	40.35	39.28	2.19	13.99	40.55
IV (b)	10	297-299d	$C_{15}H_{11}N_4OBr$	52.50	3.23	16.33	23.28	52.47	3.30	16.48	23.26
V	35	310-311d	$C_{16}H_{11}N_3O_4$	62.14	3.58	13.59	0.00	62.02	3.72	13.44	0.00
VI (c)	56	312-313d	$C_{16}H_{12}N_4O_4$	59.26	3.73	17.28		59.03	3.87	17.39	

(a) The n.m.r. spectrum in trifluoroacetic acid showed a singlet at 9.67 δ (1H), a multiplet at 8.67 δ (2H), and a multiplet at 8.47 δ (2H). (b) The n.m.r. spectrum was obtained in deuterated trifluoroacetic acid and showed a singlet at 9.38 δ (1H), a multiplet at 8.67 δ (2H), a multiplet at 8.47 δ (2H), a singlet at 4.92 δ (3H), and a singlet at 4.63 δ (3H). (c) The n.m.r. spectrum in trifluoroacetic acid showed a doublet with peaks at 10.08 and 9.98 δ (1H), a singlet at 9.24 δ (1H), a doublet with peaks at 8.77 and 8.61 δ (1H), a triplet with peaks at 8.07, 7.95 and 7.81 δ (1H), a triplet with peaks at 7.66, 7.55 and 7.43 δ (1H), a quartet with peaks at 4.97, 4.84, 4.73 and 4.61 δ (2H) and a triplet with peaks at 1.77, 1.66 and 1.53 δ (3H).

g., 0.0102 mole) was added and the solution was refluxed for 4.5 hours. The reaction mixture stood overnight and the red-orange solid which formed was collected by filtration and recrystallized from acetic acid.

TABLE II

Ultraviolet Spectra (8)

Compound No.	λ max (CH_3OH) mμ (log ε)
I	218(4.22), 296(4.16).
II	207(4.12), 233(4.22), 306(4.13).
IIIA	212(4.37), 241(4.34), 280(4.66), 297(sh).
V	217(4.24), 244(4.45), 284(4.24), 315(3.89), 326(3.96).

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(8) All melting points were taken on a Thomas-Hoover or Mel-temp capillary melting point apparatus and are uncorrected. The infrared spectra were determined on a Perkin-Elmer 521 spectrophotometer as potassium bromide pellets. The ultraviolet spectra were obtained in methanol solution on a Cary Model 14 recording spectrophotometer. Microanalyses were carried out by Dr. A. Bernhardt, Max Planck Institute, 433 Mulheim (Ruhr), West Germany. The n.m.r. spectra were determined at 60 MHz on a Varian Associates n.m.r. spectrometer (Model HR-60).

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