Department of Chemistry, University of Pennsylvania

5,8-Quinoxalinediones. IV.

Synthesis of Some *N*-Substituted 6-Amino-5,8-quinoxalinediones (1)

Kathleen Heidere Ford (2) and Madeleine M. Joullié

The interest in quinones and their chemistry has increased over the years, since they have been found to possess properties applicable to many aspects of research and industry. A group of ethyleneimino-substituted quinones prepared by Gauss and Petersen have shown antitumor activity (3a, b). The purpose of this work was to study the reactions and products of various amines with certain quinoxalinediones and to investigate the potential physiological activity of the aminoquinones. Although many aminoquinones have been prepared by the nucleophilic replacement of halogens (4) or alkoxy groups (5), primary and secondary amines are capable of forming 1,4-addition products with quinones. Theoretically, the reaction of a quinone with an amine should produce equal amounts of the substituted quinone and parent hydroquinone since electron-donating groups lower the oxidation potential of the systems. This results in the oxidation of the intermediate hydroquinone by the unsubstituted quinone. In the present work, the aminohydroquinones formed were immediately oxidized to the corresponding quinone. The parent 5,8-dihydroxyquinoxaline was also formed but only in some cases attempts were made to isolate this hydroquinone. The identification of this compound substantiated the fact that the oxidizing agent was the parent quinone. In general, the yields obtained were higher for secondary rather than primary amines. Since primary amines are weaker bases than secondary amines, nucleophilic attack on the quinone is slower and competing reactions can occur. The use of an aprotic solvent such as 1,2-dimethoxyethane is essential to the success of these 1,4-addition reactions.

The infrared spectra of the compounds prepared were examined in chloroform solution. The products derived from primary amines showed N-H stretching peaks around 3380-3360 cm^{-1}. All compounds showed split carbonyl peaks at around 1693-1683 cm^{-1} and 1640-1630 cm^{-1}. Ring stretching vibrations were observed in the 1600-1450 cm^{-1} region and C-N stretching vibrations were found around 1330 cm^{-1}.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The elemental analyses were carried out by Dr. A. Bernhardt, Max Planck Institute, 433 Mülheim (Ruhr), West Germany. Infrared spectra were recorded on a Perkin-Elmer double beam 521 recording spectrophotometer.

5,8-Quinoxalinediones.

Compounds I, II, and III were prepared by a five step synthesis described by Levy (6). Compound I was obtained in 47% yield, m.p. 193-196° dec. (lit. (6) m.p. 182° dec.). Infrared bands were observed at ν max ($CHCl_3$), 1688, 1678 (C=O), 1605, 1540 (ring stretching) 1440, 1390, 1355 (C-H deformation) and 1325 cm^{-1} (C-N stretching). Compound II was obtained in 57% yield, m.p. 171-177° dec. (lit. (7a) m.p. 155-160° dec.). Infrared bands were observed at ν max ($CHCl_3$), 1685 (C=O), 1603, 1530 (ring stretching), and 1313 cm^{-1} (C-N stretching). Compound III was obtained in 51% yield, m.p. 224-227° (lit. (7b) m.p. 230-232°). Infrared bands were observed at 1683 (C=O), 1600, 1513 (ring stretching), and 1325 cm^{-1} (C-N stretching).

A. Preparation of *N*-Substituted 6-Amino-5,8-quinoxalinediones from I, II, or III and Secondary Amines (Table I). 6-Morpholino-2,3-dimethyl-5,8-quinoxalinedione (VI). Typical Procedure.

This procedure was used to prepare compounds IV, V, XI and XIII. 2,3-Dimethyl-5,8-quinoxalinedione (I) (2 g., 0.0106 mole) was partially dissolved in 165 ml. of 1,2-dimethoxyethane in a 250 ml. three-necked, round-bottomed flask equipped with a reflux condenser, dropping funnel and a gas inlet tube.

A solution of 4 ml. of morpholine (3.99 g., 0.0450 mole) in 10 ml. of 1,2-dimethoxyethane was added dropwise to the quinone. Dry nitrogen was bubbled through the reaction mixture for 2 hours. The red precipitate was collected by filtration and air-dried. The filtrate produced an additional amount of product after standing for one week.

B. Preparation of *N*-Substituted 6-Amino-5,8-quinoxalinediones from I and Primary amines. (Table I). 6-(*p*-Toluidino-2,3-dimethyl-5,8-quinoxalinedione (X). Typical Procedure.

Compound I (1.5 g., 0.008 mole) was partially dissolved in 300 ml. of 1,2-dimethoxyethane in the same apparatus described in A. A solution of 2.6 g. (0.0265 mole) of *p*-toluidine in 20 ml. of 1,2-dimethoxyethane was added dropwise. Dry nitrogen gas was bubbled through the mixture for 18 hours while the reaction mixture was refluxed gently. The solution was evaporated to one-third of its original volume and a yellow precipitate was collected by filtration, m.p. 215-220°. This product was identified as 2,3-dimethyl-5,8-dihydroxyquinoxaline by comparing its physical properties to those of an authentic sample. After the filtrate stood for several days a black precipitate formed and was collected by filtration. Evaporation of the second filtrate yielded an additional amount of X.

Acknowledgment.

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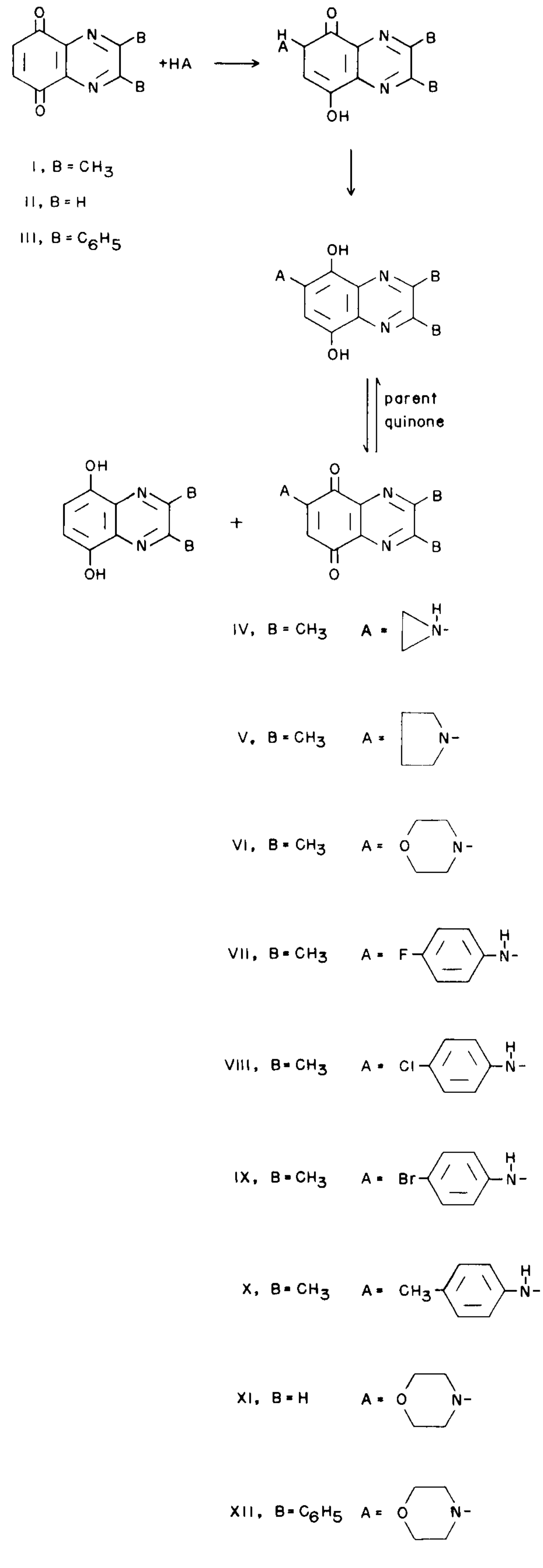
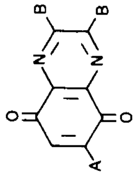


TABLE I

N-Substituted 6-Amino-5,8-quinoxalinedione



Compound No.	Yield, % (a)	M.p., °C	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Main Infrared Bands ν max ($CHCl_3$), cm^{-1}
IV	45 (b)	193.5	$C_{13}H_{13}N_3O_2$	64.19	64.07	5.39	5.60	17.27	17.20	3380, 1683, 1630, 1595, 1535, 1495
V	79 (b)	184-189	$C_{14}H_{15}N_3O_2$	65.36	65.29	5.88	6.04	16.33	16.25	1685, 1615, 1565, 1535, 1473
VI	83 (b)	199-202	$C_{14}H_{15}N_3O_3$	61.53	61.48	5.53	5.70	15.38	15.32	1688, 1635, 1575, 1543
VII	63 (c)	258-260	$C_{16}H_{12}N_3O_2F$ (d)	64.63	64.44	4.07	4.18	14.14	14.24	3350, 1683, 1630, 1600, 1590, 1503, 1327
VIII	47 (c)	260-262	$C_{16}H_{12}N_3O_2Cl$ (e)	61.25	61.46	3.86	3.88	13.39	13.23	3355, 1693, 1640, 1610, 1590, 1505, 1490, 1332
IX	44 (c)	264-266	$C_{16}H_{12}N_3O_2Br$ (f)	53.65	53.72	3.38	3.52	11.73	11.56	3350, 1690, 1638, 1605, 1585, 1505, 1485, 1330
X	51 (c)	224-230	$C_{17}H_{15}N_3O_2$	69.61	69.79	5.15	5.22	14.33	14.27	3360, 1693, 1635, 1615, 1600, 1515, 1333
XI	89 (b)	220-222	$C_{12}H_{11}N_3O_3$	58.77	58.82	4.52	5.70	17.13	17.04	1693, 1640, 1578, 1550
XII	65 (b)	226	$C_{24}H_{19}N_3O_3$	72.53	72.31	4.82	4.77	10.57	10.64	1690, 1635, 1568, 1515

(a) Yields are of recrystallized products. All compounds were recrystallized from 1,2-dimethoxyethane. (b) Red crystals. (c) Black crystals. (d) Calcd. F, %: 6.39. Found: 6.22. (e) Calcd. Cl, %: 11.30. Found: 11.14. (f) Calcd. Br, %: 22.31. Found: 22.27.

(2) Abstracted from the M.S. thesis of K. H. Ford, University of Pennsylvania, 1966.

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