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Quinoxalinediones. I. Synthesis of 6-Methyl-5,8-quinoxalinediones (1)

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Various synthetic routes were investigated as potential methods of preparation of 6-methyl-5, 8-quinoxalinediones which could be useful as antimetabolites of vitamin K. The preparation of 2,3-dimethyl-5,8-quinoxalinedione (II) was achieved by the condensation of 2,3-diamino-1,4-dimethoxybenzene with diacetyl. Demethylation was accomplished by the use of aluminum chloride in benzene and the resulting hydroquinone (I) was oxidized with dry silver oxide to the quinone (II). An analogous synthetic route could not be used to prepare 2,3,6-trimethyl-5,8-quinoxalinedione (VII). 6-Methyl-5,8-quinoxalinediones were prepared from 2,3-dinitro-4-methoxy-6-methylacetanilide (III) which was reduced and condensed with appropriate carbonyl compounds. Acid hydrolysis yielded aminophenols which were oxidized to (VII) and (VIII) with chromic acid. The ultraviolet and infrared spectra of the compounds prepared are recorded.

Vitamin K antagonists have been the subject of several investigations (2,3,4). Recent studies have shown that certain heterocyclic quinones may possess considerable physiological activity (5,6). Some quinoxalines have also proved to be physiologically active (7,8). Since quinoxalinediones contain both the quinoxaline ring system and the quinone grouping, one might reasonably expect these compounds to be of interest, possibly as vitamin K antagonists. Only a few quinoxalinediones have been reported in the literature (9,10). None of these have alkyl groups in the ring containing the quinone grouping. This type would bear some analogy to vitamin K and a synthetic route to these compounds was devised.

2,3-Dimethyl-5,8-quinoxalinedione (II) was obtained from the oxidation of 2,3-dimethyl-5,8-dihydroxyquinoxaline (I) with dry silver oxide in dioxane. Compound I was prepared by the demethylation (11) of 2,3-dimethyl-5,8-dimethoxyquinoxaline (9) with aluminum chloride. A similar route seemed the most promising to prepare quinoxalinediones having alkyl groups in the carbocyclic ring. However, the dinitration of 2,5-dimethoxytoluene could not be accomplished under a variety of conditions. Also the attempted nitration of 4-amino-2,5-dimethoxytoluene, with nitric acid in acetic anhydride, caused demethylation followed by oxidation to yield 4-acetamidotoluquinone instead of the expected nitro derivative. A synthetic route to 6-methyl-5,8-quinoxalinediones was finally devised as indicated in Flow Sheet I. When compound III was reduced and poured into concentrated hydrochloric acid, a product whose elemental analysis was in agreement with the values calculated for 2,5-dimethyl-6-methoxy-7-aminobenzimidazole dihydrochloride (IV) was obtained. When the solution resulting from the hydrogenation was poured into diacetyl, compound V was obtained. This compound was converted to the corresponding aminophenol (VI) by 70% sulfuric acid. Although aminophenols are most frequently converted to their respective quinones by the use of ferric chloride, VI could not be oxidized to a tractable product by either ferric chloride or silver oxide. Oxidation was finally accomplished with chromic acid by a procedure similar to the one used to prepare 6-methoxy-5,8-quinolinedione from 6-methoxy-5,8-diaminoquinoline (12). The overall yield of VIII by this procedure was much lower than that of VII presumably because of the greater sensitivity of VIII to acid reagents and also because of its greater solubility.

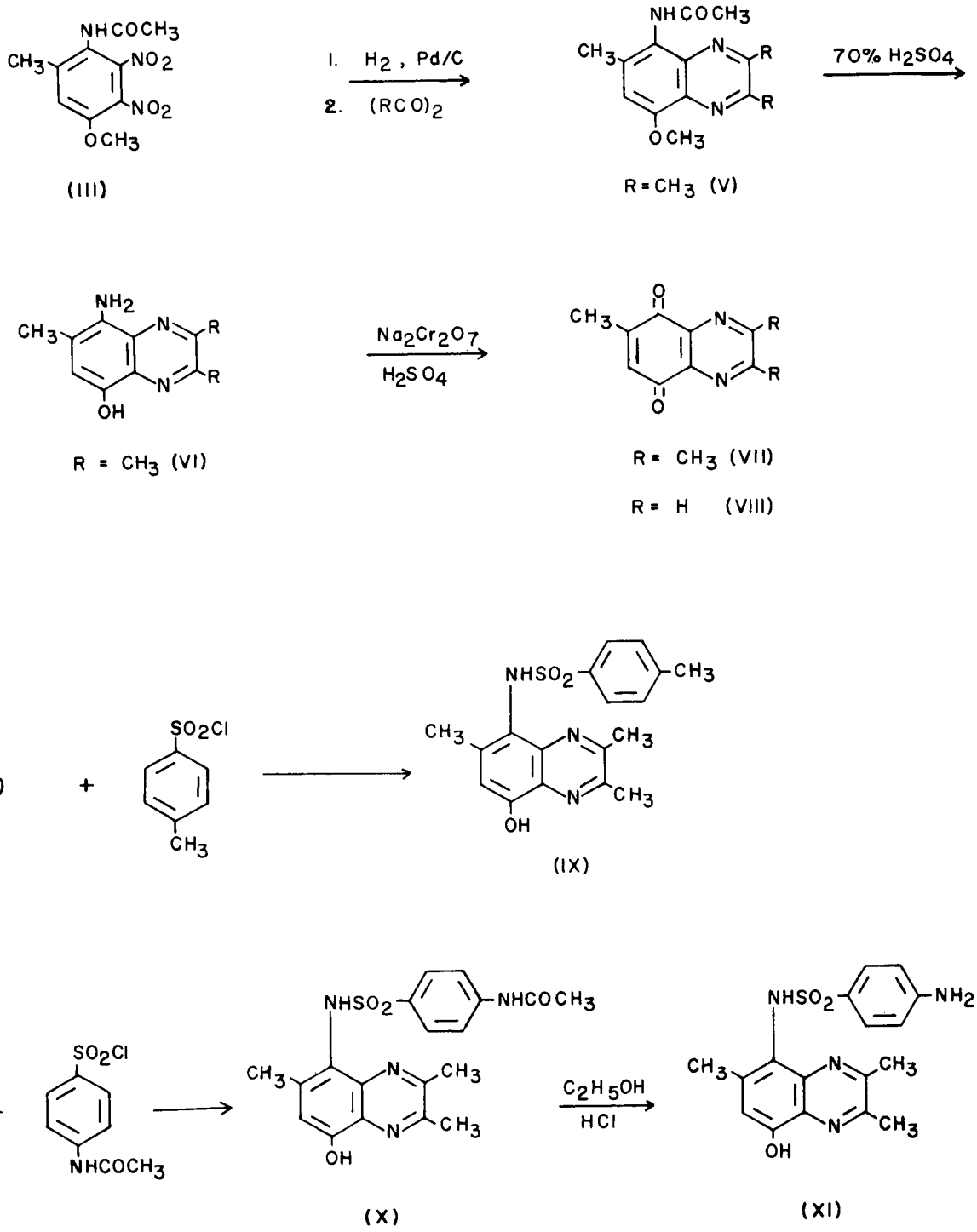
Compound VI is a quinoxaline analog of vitamin K_1 and as such may be of physiological interest. It reacted easily with substituted sulfonyl chlorides to form the corresponding sulfonamides.

The nuclear magnetic resonance spectrum of I, as a 15% solution in deuterochloroform, was examined. Tetramethylsilane was used as an internal reference. Resonance at approximately 164 cps was assigned to the ring methyl groups and resonance at approximately 421 cps, to the hydroxyl protons plus the two aromatic protons. Integral data indicated a ratio of 6:4 between the methyl protons and the remaining protons in the molecule. To confirm that the hydroxyl protons were contributing to low field resonance, a drop of D_2O was added. A loss of two protons was noted at approximately 420 cps in a second spectrum. The methyl protons did not exchange with deuterium indicating that no significant enolization involving the methyl groups on the quinoxaline ring occurred. The location of the OH proton resonance is typical of normal phenolic protons. This may be considered as some evidence against strong intramolecular hydrogen bonding between this group and the nitrogen atom of the quinoxaline ring.

The ultraviolet spectra of the quinoxalines in methanol are shown in Table I.

An interesting observation was made in the case of I. If the ultraviolet spectrum of this compound

FLOW SHEET I


NHCOCH3
CH3
NO2
NO2
OCH3
(III)
1. H2 , Pd/C
2. (RCO)2
NHCOCH3
CH3
N
R
R
N
OCH3
R=CH3 (V)
70% H2SO4
NH2
CH3
N
R
R
N
OH
R = CH3 (VI)
Na2Cr2O7
H2SO4
O
CH3
N
R
R
N
O
R= CH3 (VII)
R= H (VIII)
(VI)
+
SO2Cl
CH3
NHSO2
CH3
CH3
N
CH3
N
CH3
OH
(IX)
(VI)
+
SO2Cl
NHCOCH3
NHSO2
NHCOCH3
CH3
N
CH3
N
CH3
OH
(X)
C2H5OH
HCl
NHSO2
NH2
CH3
N
CH3
N
CH3
OH
(XI)

was determined immediately after the solution was made up the values shown in Table I were obtained. However, if the solution was allowed to stand for a few days, the values changed to 282 mμ (shoulder) (4.16); 269 mμ (4.18). Evaporation of the alcohol solution yielded a solid which although darker than the original compound still retained the same melting point. The infrared spectra of the two products did not show any differences although this evidence is not conclusive. The ultraviolet spectrum of a mixture of compound I and its corresponding quinone, in methanol, when run immediately showed the following bands: 360 mμ (shoulder) (2.92); 264 mμ (4.42). After standing several days the bands were at 282 mμ (4.16); 269 mμ (4.19). Similar results were obtained in ethanol. This behavior suggests that oxidation and quinhydrone formation may be occurring when compound I is allowed to stand in alcohol solution and any determination in this solvent must be carried out immediately after the sample has been dissolved.

Although it is reported (13) that solutions of *p*-benzoquinones in water or alcohols are unstable, the quinones studied showed no noticeable changes in absorption after their solutions had stood for several days. All of the compounds studied had a high intensity band (log $\epsilon \sim 4.00$) around 260 mμ, comparable to the band found in *p*-benzoquinone in ethanol, at 242 mμ (log $\epsilon = 4.23$).

The infrared spectra of the substituted quinoxalines studied showed a stronger band around 1610 cm^{-1} and a weaker band around 1570-1550 cm^{-1}. A band around 1480 cm^{-1} was found in the spectra of all the quinoxaline derivatives but was absent in the spectra of the quinones. These bands appear to be ring-stretching bands. Strong bands at 1460 cm^{-1} and 1380 cm^{-1}, due to the symmetric and asymmetric deformations of the methyl groups, were always present. Aromatic ether groups gave rise to bands around 1250 cm^{-1} and 1050 cm^{-1} and CH out-of-plane bending modes gave rise to bands between 800-850 cm^{-1}.

All of the sulfonamides prepared showed two strong bands, one near 1310 cm^{-1} probably due to the asymmetric stretching of the SO_2 group and C-N deformation. The other band due to the symmetric stretching of the SO_2 group was found near 1150 cm^{-1}. The carbonyl stretching frequencies of the quinones prepared were 1667 cm^{-1} for II, 1669 cm^{-1} for VII, and 1669 cm^{-1} for VIII. The two vicinal hydrogen atoms of II give rise to a strong band at 860 cm^{-1}. Compound VII showed two sharp bands at 910 and 930 cm^{-1} and VIII showed bands at 870 cm^{-1}, 920 cm^{-1} and 944 cm^{-1}. These bands are out-of-plane CH deformation bands.

EXPERIMENTAL

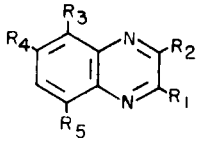
General Information.

The microanalyses for all compounds were performed by Galbraith Laboratories. The melting points were determined in a Thomas-Hoover capillary melting-point apparatus and are uncorrected. All infrared spectra were recorded on a Perkin-Elmer 421 spectrophotometer.

Table I

Ultraviolet Spectra

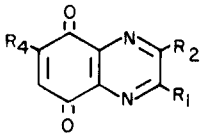
Substituted Quinoxalines



Substituents

R_1	R_2	R_3	R_4	R_5	λ max (CH_3OH) mμ (log ε)
CH_3	CH_3	OCH_3	H	OCH_3	360(3.23); 308(3.48); 265(4.58)
CH_3	CH_3	OH	H	OH	380(3.04); 310(3.11); 266(4.62)
CH_3	CH_3	NH_2	CH_3	OH	400(3.15); 310(3.46); 272(4.55)
H	H	NH_2	CH_3	OH	420(2.99); 310(3.11); 271(4.68)

Substituted 5, 8-Quinoxalinediones



CH_3	CH_3	----	H	----	257(4.16)
CH_3	CH_3	----	CH_3	----	264(4.26)
H	H	----	CH_3	----	264(4.03)

Ultraviolet spectra were determined with a Beckmann DU spectrophotometer equipped with a recorder model RS-3 from Process and Instruments Co. The nuclear magnetic resonance spectral analysis was carried out by Varian Associates.

2,3-Dimethyl-5, 8-dihydroxyquinoxaline (I).

This compound was first prepared by the demethylation of 2,3-dimethyl-5, 8-dimethoxyquinoxaline with aluminum chloride in chlorobenzene (11). This procedure required steam distillation of the solvent and isolation of the product as its hydrochloride. A useful modification (10) was to reflux the methylated compound (7.0 g., 0.032 mole) with powdered anhydrous aluminum chloride (50 g.) in 250 ml. of dry benzene for nine hrs. The reaction mixture was poured into 500 ml. of ice water, the precipitate obtained removed by filtration, washed thoroughly with water and recrystallized from ethyl acetate. The yield was 77%, m.p. 228.5-230° (lit. (11) m.p. 224-227°). Compound I gave a positive test with ceric nitrate and also with a solution of ferric chloride in chloroform.

2,3-Dimethyl-5, 8-quinoxalinedione (II).

Fisher purified silver oxide (3.0 g., 0.01 mole) was added to a solution of 2 g. (0.01 mole) of 2,3-dimethyl-5,8-dihydroxyquinoxaline in 40 ml. of dioxane and the reaction mixture refluxed for four hrs. After the addition of more dioxane, the colloidal silver was removed by filtration and the filtrate evaporated to yield the desired product. The dione was recrystallized from an ethanol-ethyl acetate mixture, yield 87%, m.p. 182°. Compound II gave a positive Craven test (14).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.53; H, 4.19; N, 14.59.

2,4-Dimethyl-7-amino-6-methoxybenzimidazole dihydrochloride (IV).

This compound was prepared from 2,3-dinitro-4-methoxy-6-methylacetanilide (III) obtained by the dinitration of 2-methyl-4-methoxyacetanilide according to the procedure of MacMillan (15), yield 24%, m.p. 249-251° (lit. (15) m.p. 249-251°). This compound (6.6 g., 0.038 mole) was reduced in 100 ml. of methanol with 200 mg. of platinum dioxide in a Parr hydrogenator. After removal of the catalyst, the solution was received in 20 ml. of concentrated hydrochloric acid and saturated with hydrogen chloride. The crystals formed were removed by filtration and dried, yield 67%.

Anal. Calcd. for $C_{10}H_{15}N_3OCl_2$: C, 45.47; H, 5.72; N, 15.53; Cl, 26.84. Found: C, 45.53; H, 5.67; N, 15.70; Cl, 26.94.

2,3,7-Trimethyl-5-methoxy-8-acetamidoquinoxaline (V).

Compound III (18.9 g., 0.07 mole) was reduced in 120 ml. of ethyl cellosolve with 0.7 g. of 10% palladium on charcoal, at 70°, in a Parr hydrogenator. The catalyst was removed by filtration and the solution poured into diacetyl (10 ml., 0.11 mole). The product was recrystallized from a mixture of benzene and cyclohexane, yield 53.5%, m.p. 221-222°.

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.74; H, 6.70; N, 16.20.

2,3,7-Trimethyl-5-hydroxy-8-aminoquinoxaline (VI).

Compound V (5.01 g., 0.019 mole) was dissolved in 25 ml. of 70% sulfuric acid and the mixture refluxed for one to two min. The solution was cooled and neutralized to *p*H 7.5 with sodium bicarbonate. The crystals formed were collected, dried and recrystallized from benzene to yield brick-red crystals, yield 78%, m.p. 197-198.5°.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.22; H, 6.51; N, 20.52.

The free base was converted to its hydrochloride by treatment with concentrated hydrochloric acid.

Anal. Calcd. for $C_{11}H_{14}N_3OCl$: C, 55.12; H, 5.89; N, 17.53; Cl, 14.79. Found: C, 55.23; H, 5.92; N, 17.26; Cl, 14.53.

2,3,6-Trimethyl-5,8-quinoxalinedione (VII).

A solution containing 2.19 g. (0.01 mole) of VI, 4.5 ml. of 12 N sulfuric acid and 67 ml. of water was cooled to 20° and treated, with stirring, with a 10% sodium dichromate solution (26.2 ml.) and 12 N sulfuric acid (7.0 ml.), in small portions over a period of two min. at a maximum temperature of 25°. Chloroform (50 ml.) was added to the reaction mixture and stirring was maintained for ten more min. The organic layer was withdrawn, washed with a saturated sodium chloride solution and dried with anhydrous calcium sulfate. The chloroform solution was reduced to about half of its original volume, the product precipitated by addition of a large volume of low boiling petroleum ether (30-60°) and recrystallized from cyclohexane, yield 45%, m.p. 181-182°. This compound gave a positive Craven test (14).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.08; H, 5.04; N, 13.63.

6-Methyl-5,8-quinoxalinedione (VIII).

This compound was prepared from compound IV by a procedure similar to that used to prepare VII. No analytical data was obtained for the intermediate products. However, the ultraviolet spectrum of 5-amino-6-methyl-8-hydroxyquinoxaline was very similar to the spectrum of VI. Compound VIII was obtained in low yield, 5%, m.p. 171°.

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 26.08. Found: C, 61.98; H, 3.40; N, 15.98.

Sulfonamide derivatives of VI.

Compound VI was found to react easily with substituted sulfonyl chlorides by refluxing it with these compounds in pyridine for one hr. and isolating the sulfonamides in the usual manner. *p*-Toluenesulfonyl chloride yielded IX by this method, yield 61%, m.p. 220-221°.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 60.48; H, 5.36; N, 11.78; S, 8.97. Found: C, 60.57; H, 5.52; N, 11.57; S, 8.82.

N-Acetylsulfanilyl chloride formed X, yield 66.5%, m.p. 265.5-267°.

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.98; H, 5.06; N, 13.99; S, 8.01. Found: C, 56.87; H, 5.17; N, 13.96; S, 7.94.

The amide grouping was hydrolyzed with ethanolic hydrochloric acid to yield XI, yield 81%, m.p. 210°.

Anal. Calcd. for $C_{17}H_{16}N_4O_3S$: C, 56.96; H, 5.06; N, 15.64; S, 8.95. Found: C, 57.02; H, 5.20; N, 15.52; S, 8.98.

Acknowledgment.

The authors wish to thank Mr. Wilson Gum for his assistance in the spectral studies. This work was supported in part by a grant (AM 07684-01) from the National Institutes of Health, Public Health Service.

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Received May 18, 1964 Philadelphia, Pa.