BENZODIAZINES

# XII. QUINOXALONES BEARING METHYL GROUPS IN THE BENZENE RING*

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Quinoxalones bearing methyl groups in the benzene and pyrazine rings have been synthesized. Methyl groups in the 6- and 7-positions cause a shift in the $\nu_{C=O}$ absorption band to lower frequencies, and reduce the reactivity of a methyl group in the 3-position.

Since the presence of two ortho-methyl groups in the isoalloxazine moiety of the vitamin $B_2$ molecule and two such groups in the benzimidazole moiety of the vitamin $B_{12}$ molecule have a considerable effect on the physiological activity of these compounds [2, 3], it has been suggested that, as a result of steric hindrance from the adjacent methyl groups, the external or internal valence angles in the benzene ring are somewhat increased, and that this is important for the specific conversion of the methyl groups in the organism [3]. In addition, we must take into account their electron-donor influence, which is probably propagated through the benzene ring to the fused heterocyclic system.

To test this hypothesis on model compounds, we synthesized 6,7-dimethyl- and 3,6,7-trimethylquinoxalones (III and VII), which may be considered as simplified fragments of vitamin $B_2$. For the properties of the other quinoxalones I, II, IV, V, and VI, see Table 1.

I, II, and III were obtained in good yields from the corresponding ortho-phenylenediamines by reaction with chloroacetic acid in the presence of solid NaOH, followed by oxidation of the resulting tetrahydroquinoxalines with hydrogen peroxide. Better yields were obtained by this method than those obtained in [4], in which zinc dust was used as the condensing agent. Also our method avoids the use of the unstable glyoxylic acid which is normally used in such reactions [5].

IV and VII, in which the methyl group is located in the heterocycle, were obtained in high yields by a slight modification of the method used in [6], by heating an aqueous solution of the corresponding ortho-p phenylenediamine and acetylenedicarboxylic acid. The reaction between 4-methyl-1,2-phenylenediamine and acetylenedicarboxylic acid gives two isomers, 3,6- and 3,7-dimethyl-2-quinoxalones (V and VI), which were separated by taking advantange of their different solubilities in water, and purified by sublimation. These compounds were identical with those described in the literature [7, 8], which were obtained by other methods.

We see from the results given in Table 1, that the IR spectra of all the compounds show very strong, broad carbonyl stretching bands. The introduction of one and two methyl groups results in a shift of $\nu_{C=O}$ toward lower $cm^{-1}$ values, indicating an increase in the basicity of the carbonyl group caused by the electron-donor influence of these substituents, the effect of a 7-methyl group being greater than that of a 6-methyl group. It is interesting to recall for comparison, that a methyl group in the 7-position in vitamin $B_{12}$ results in higher activity than one in the 6-position, with the result that riboflavin is able to form dimers. This methyl group can be oxidized to the acid, and under appropriate conditions it condenses with p-chlorobenzaldehyde [3].

*For part XI, see [1].

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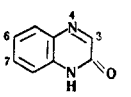
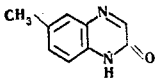
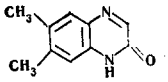
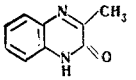
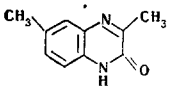
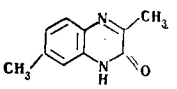
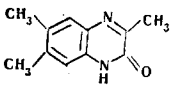
TABLE 1. Some Absorption Frequencies of Quinoxalones, Reciprocal Centimeters

| Compound | Formula | $\nu_{C=O}$ | $\nu_{CH\ arom}$ | C=N |
|---|---|---|---|---|
| I |  | 1699 } v strong, 1682 } broad | 1642 strong, sharp | 1615 } weak 1582 } |
| II |  | 1682 v strong | 1692 strong, sharp | 1546 medium |
| III |  | 1679 v strong | 1626 medium | 1543 weak |
| IV |  | 1671 medium, broad | 1611 weak | 1570 medium, sharp |
| V |  | 1673 v strong, broad | 1624 medium | 1568 medium, sharp |
| VI |  | 1665 v strong, broad | 1624 medium | 1561 medium, sharp |
| VII |  | 1660 v strong, broad | 1628 medium, broad | 1558 strong, sharp |

The influence of the methyl groups in the benzene ring attached to the heterocycle is also manifested in a reduction in the reactivity of the methyl group in the 3-position. This is apparently due to a reduction in the electron-acceptor properties of the heterocycle, and to $\sigma,\pi$-conjugation of the group ($N_{(4)} = C_{(3)}$-$CH_3$), which is observed in the reaction with diazonium salts. While IV reacts smoothly with phenyldiazonium chloride to give an azo dye [8], VII reacts with the more reactive p-nitrophenyldiazonium chloride to give the corresponding hydrazone.

The results show that, in these compounds, the electron-donor effect of the methyl group is transmitted through the benzene ring to the heterocyclic system. This suggests that this effect, together with the possible effects of the ortho-methyl groups, should be taken into account in the reactions of vitamins $B_2$ and $B_{12}$ with a substrate.

## EXPERIMENTAL

6,7-Dimethyl-2-quinoxalone (III). A mixture of 2.07 g (0.015 mole) of 4,5-diamino-o-xylene, 1.5 g (0.015 mole) of chloroacetic acid, and 1.2 g (0.03 mole) of solid NaOH was ground thoroughly in a mortar. The mixture was placed in a flask and heated gently until the reaction commenced. Heat was liberated and foaming occurred, and after 10 min, the mixture solidified. The melt was treated with 20 ml of hot alcohol with the addition of activated charcoal, filtered, and cooled. The precipitate of 6,7-dimethyltetrahydro-2-quinoxalone (yellow plates, mp 173-175° C, 1.6 g) was filtered off and placed in a flask. To this were added 10 ml of 2-N NaOH and 1.5 ml of 30% hydrogen peroxide, and the mixture was heated on a water bath for 1 hr. After cooling, 2-N HCl was added to pH 4, and precipitated III was filtered off to give 1.3 g of product (50% calculated on starting diamine). Purification by sublimation gave almost colorless, long needles, mp 291-292° C (lit [10], mp 292-293° C). Found, %: C 69.06; H 5.74; N 16.55. Calculated for $C_{10}H_{10}N_2O$, %: C 68.95; H 5.79; N 16.08.

3,6-Dimethyl-2-quinoxalone (V) and 3,7-Dimethyl-2-quinoxalone (VI). To 13.3 g (0.1 mole) of 3,4-diaminotoluene dissolved in 20 ml of hot water was added at 85-90° C a solution of 11.4 g (0.1 mole) of acetylenedicarboxylic acid in 50 ml of water. A vigorous evolution of $CO_2$ took place, and a copius precipitate separated. After boiling for 30 min, the hot mixture was filtered, and the solid (V) was washed with a small amount of hot water to give 12.5 g (63.7%), mp 205-208° C. Purification by sublimation gave color-

less needles, with a constant mp of 209-210° C (reference [7] gives a mp of 220° C, referring to a mixture of isomers). Found, %: C 69.11; H 6.01; N 16.40. Calculated for $C_{10}H_{10}N_2O$, %: C 68.95; H 5.79; N 16.08.

The filtrate, after separation of V, was extracted with chloroform. The chloroform extract was treated with 2-N NaOH, the alkaline layer was separated and cooled, and the solid which separated was filtered off (0.5 g), mp 225-230° C (mixture of V and VI). The filtrate was acidified to pH 4, and the precipitate of VI was filtered off, washed with water, dried, and purified by sublimation giving 0.6 g of nearly colorless needles, mp 238-239° C (literature [8] mp 238° C). Over all yield 69%. Found, %: C 68.56; H 5.84; N 16.23. Calculated for $C_{10}H_{10}N_2O$, %: C 68.95; H 5.79; N 16.08.

3,6,7-Trimethyl-2-quinoxalone (VII). To 13.8 g (0.1 mole) of 4,5-diamino-o-xylene dissolved in 400 ml of hot water was added at 80-85° C an equimolecular amount of acetylenedicarboxylic acid in 30 ml of water. The reaction mixture foamed, $CO_2$ being evolved, and a solid separated, it was filtered off after boiling for 30 min, washed with water, and dried to give 15 g (80%), mp 278-279° C, colorless needles from dimethylformamide. Found, %: C 70.46; H 6.56; N 15.04. Calculated for $C_{11}H_{12}N_2O$, %: C 70.24; H 6.43; N 14.98.

6,7-Dimethyl-2-quinoxalone-3-aldehyde p-Nitrophenylhydrazone (VIII). A 0.57-g (0.003 mole) quantity of VII was dissolved in 40 ml of glacial acetic acid, and p-nitrophenyldiazonium chloride, obtained in the usual way from 0.42 g (0.003 mole) of p-nitroaniline, was added with cooling. After the mixture had been allowed to stand overnight in the refrigerator, it was filtered, and the solid was washed with water and recrystallized from a large volume of dimethylformamide to give 0.8 g (77%) of orange needles, mp above 350° C. Found, %: C 60.72; H 4.64; N 20.95. Calculated for $C_{17}H_{15}N_5O_3$, %: C 60.53; H 4.51; N 20.76.

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