[Contribution from the Baker Laboratory of Chemistry at Cornell University]

Many-Membered Carbon Rings. XV. Quinoxaline Derivatives of 1,2-Cyclononanedione[1]

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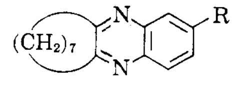
Several 6-substituted-2,3-heptamethylenequinoxalines have been prepared. Model considerations predicted that these compounds should be resolvable as a result of steric hindrance to the interconversion of dissymmetric conformations. Attempts at resolution failed to confirm this prediction. The spectral changes associated with the conversion of 6-amino-2,3-heptamethylenequinoxaline into its conjugate acid are recorded and discussed.

In connection with our interest in studying the rigidity of the nine-membered carbon ring[3] we have synthesized a series of 6-substituted-2,3-heptamethylenequinoxalines (I-V).



I, R = NO_2, II, R = NH_2, III, R = CN
IV, R = CO_2H, V, R = *o*-$NHCOC_6H_4CO_2H$

It was thought that with the nine-membered ring fused to an aromatic nucleus, such as the quinoxaline system, four adjacent carbon atoms of the ring would be required to be coplanar and the over-all flexibility of the nine-membered ring itself would be reduced. Inspection of Fischer-Hirschfelder-Taylor models showed that the five remaining carbon atoms of the ring must be disposed as a bridge either above or below the plane of the aromatic system as represented below (Fig. 1).

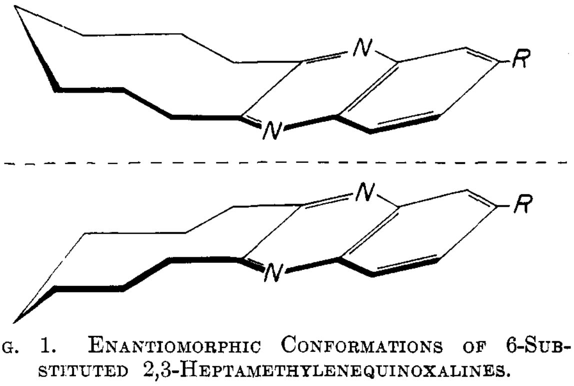
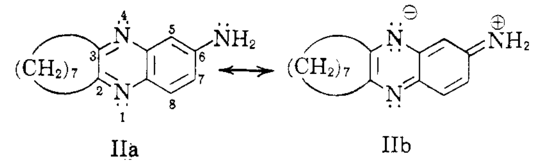


Fig. 1. Enantiomorphic Conformations of 6-Substituted 2,3-Heptamethylenequinoxalines.

Further, model considerations suggested that the two conformations would not be interconvertible without rupture of the nine-membered ring. With 6-substituted quinoxalines (I-V) these conformations are dissymmetric and hence might be expected to be resolvable.

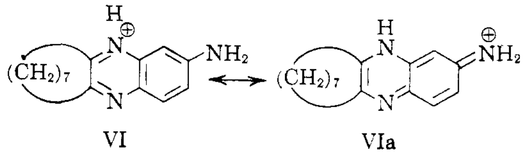
1,2-Cyclononanedione was treated with 4-nitro-1,2-phenylenediamine to give 6-nitro-2,3-heptamethylenequinoxaline (I). Reduction of the nitro compound I *via* catalytic hydrogenation gave the corresponding 6-aminoquinoxaline II. II was obtained as bright yellow needles, m.p. 171–172.5°, possessing an intense green fluorescence observable even in extremely dilute solutions. In acid solution it showed an intense red color. On treatment of II with (+)-camphor-10-sulfonic acid, a bright orange-red salt was obtained which decomposed in the range of 170–180°, depending on the rate of heating. The solution of this salt was too intense in color to allow observation of any rotation in the polarimeter.

In view of this surprising color effect, further consideration was given to the structure of the amine II. Both structures IIa and IIb, among others, are contributors to the resonance hybrid structure of the aminoquinoxaline II.

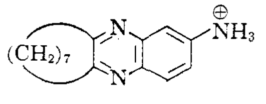


IIa IIb

In neutral or basic media the quinonoid structure IIb is not an important contributor since it involves charge separation and destruction of two aromatic nuclei. However, in acidic media, structure VI for the cation is preferred rather than VII because of the extra resonance energy contributed by forms such as VIa in which there is now no charge separation. In structure VII there is no pair of free



VI VIa



VII

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[1] For the preceding paper in this series see A. T. Blomquist and P. R. Taussig, *J. Am. Chem. Soc.*, **79**, 3505 (1957).

[2] Abstracted from part of the dissertation presented by Y. Chu (Meinwald) in September 1955 to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] A. T. Blomquist, E. S. Wheeler, and Y. Chu, *J. Am. Chem. Soc.*, **77**, 6307 (1955).

electrons on the nitrogen atom at position 6 and no resonance allowing the distribution of positive charge over two nitrogen atoms is possible.

The assignment of this structure VI to the cation is also consistent with the color effect in acidic media. The electronic absorption spectra of the aminoquinoxaline II in neutral and acidic media are shown in Fig. 2. As pointed out by Steck and Ewing,[4] ordinary aromatic amines, *i.e.* α- and β-naphthylamines, show a hyposochromic shift in acid solution. On the other hand, quinoline shows a bathochromic shift in its ultraviolet absorption spectrum in acid solution, due to the addition of a proton to the ring nitrogen. This permits strengthening of the contributions of certain quinonoid forms of the quinolinium ion. The spectra of aminoquinolines and aminoacridines, in which similar conjugation between the two nitrogen atoms occurs, also show a bathochromic shift in acid solution. From these analogies, it can be concluded that the ring nitrogen of position 4 of the aminoquinoxaline II is the more basic nitrogen and therefore accepts the first proton.

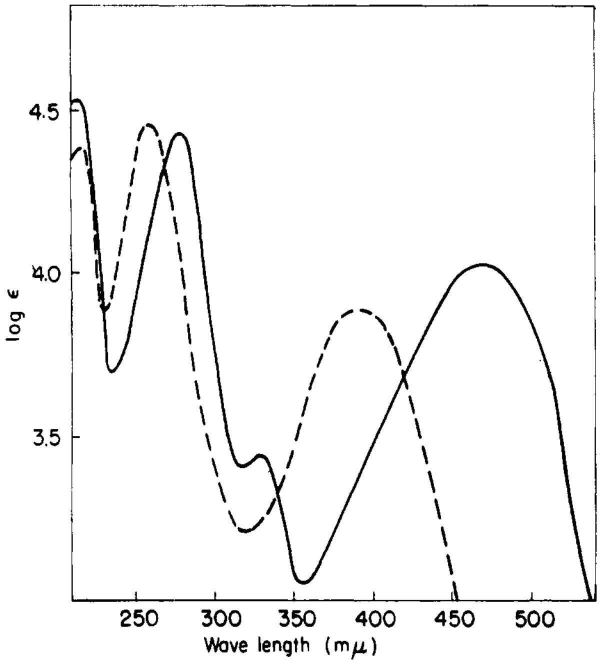

FIG. 2. ABSORPTION SPECTRA OF 6-AMINO-2,3-HEPTAMETHYLENEQUINOXALINE IN 95% ETHANOL.
- - -neutral
———acidic

In view of this complication, a route to the colorless acid IV was sought. II was diazotized and converted to the cyano compound III in low yield. Hydrolysis of III gave IV which proved to be identical with an authentic sample prepared by the direct condensation of 1,2-cyclononanedione and 3,4-diaminobenzoic acid.[5] Attempts to resolve IV by (+)-α-phenylethylamine and cinchonidine were both unsuccessful, although well characterized salts were obtained.

II was then treated with phthalic anhydride to give 6-acid phthalamido-2,3-heptamethylenequinoxaline V. The amide V was obtained from benzene as a colorless crystalline solid whereas from aqueous methanol it separated as a yellow crystalline monohydrate. The ultraviolet spectra of the two forms of V in 95% ethanol were identical. Fig. 3 shows the ultraviolet spectra of V in neutral, acidic, and basic media. It should be noted that there is no bathochromic effect in acid, reflecting the reduced electron mobility of the amide V compared to the amine II.

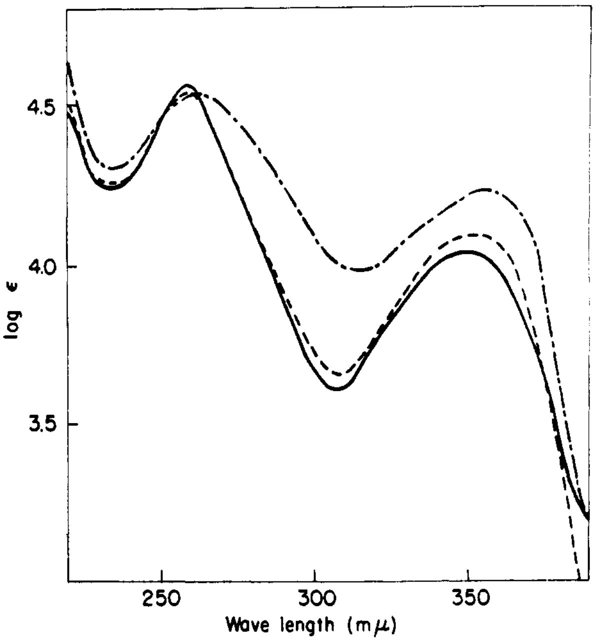

FIG. 3. ABSORPTION SPECTRA OF 6-ACID PHTHALAMIDO-2,3-HEPTAMETHYLENEQUINOXALINE IN 95% ETHANOL.
- - - - - neutral
———acidic
— — — — —basic

The amide V failed to form crystalline salts with (+)-α-phenylethylamine and brucine, but well characterized crystalline salts of cinchonidine and quinine were obtained. These highly purified salts gave inactive V after decomposition by hydrochloric acid at 0°.

Since both IV and V appeared to be incapable of resolution, it may be concluded that the models used give an exaggerated picture of the rigidity of the medium size rings.

EXPERIMENTAL

6-Nitro-2,3-heptamethylenequinoxaline (I). A mixture of 38.6 g. (0.25 mole) of 1,2-cyclononanedione,[6] 38.6 g. (0.25 mole) of 4-nitro-2,3-phenylenediamine in 200 ml. of glacial acetic acid was refluxed for 1 hr. The reaction mixture was

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[4] E. H. Steck and G. W. Ewing, *J. Am. Chem. Soc.*, **70**, 3397 (1948).

[5] The authors are indebted to Mr. Peter W. Yu for the preparation of this acid.

[6] A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *J. Am. Chem. Soc.*, **74**, 3643 (1952).

cooled to about 70° and poured on to 350 ml. of chilled water with stirring. The light brown solid formed was filtered and washed thoroughly with ice water. The crude product weighed 69 g. (100%). Recrystallized from 95% ethanol it was obtained as pale yellow plates, m.p. 109.5–110.5°.

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.52; H, 6.29; N, 15.40.

A similar procedure was used to obtain the parent quinoxaline, 2,3-heptamethylenequinoxaline, m.p. 68.5–70° from ethanol.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.69; H, 8.08; N, 12.45.

6-Amino-2,3-heptamethylenequinoxaline (II). I (30 g., 0.11 mole) was reduced in a Parr hydrogenation apparatus with Raney Nickel as catalyst in 200 ml. of ethyl acetate. After completion of the reduction (2 hr.) and removal of the catalyst, the solution was decolorized and concentrated to a volume of 150 ml. A first crop of amine, 22 g., crystallized as bright yellow needles, m.p. 171–172.5°. From the mother liquor another 5 g. of the amine was obtained. The yield was quantitative.

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.80; H, 8.19; N, 17.63.

Treatment of II with (+)-camphor 10-sulfonic acid. To a solution of 1 g. of II in 15 ml. of anhydrous ethyl acetate was added a solution of 1 g. of (+)-camphor-10-sulfonic acid in 15 ml. of anhydrous ethyl acetate. A bright red precipitate formed instantly. The mixture was warmed on a hot plate for a few minutes and allowed to cool gradually to room temperature. A total of 1.9 g. of the red salt was obtained, m.p. 165–180° (dec.). It can be recrystallized from ethyl acetate–methanol (5:1) decompositon point 172–180°.

A sample of this salt after four recrystallizations was dissolved in water. Dilute sodium bicarbonate solution was added dropwise. The bright yellow regenerated amine showed a m.p. of 172.5–173°, $[\alpha]_D = 0$; mixed m.p. with starting amine II 171–173°.

6-Cyano-2,3-heptamethylenequinoxaline (III). II (2.41 g., 0.01 mole) was diazotized at 0–5° in a solution comprising 5 ml. of concentrated hydrochloric acid and 15 ml. of water, with an aqueous solution of 0.7 g. (0.01 mole) of sodium nitrite. The reaction mixture was kept cool with stirring for 2 hr. until the diazotization was completed. A small amount of orange solid material was removed by filtration. The clear red diazonium salt solution was added dropwise to a suspension of 2 g. of cuprous cyanide and 2 g. of potassium cyanide in 10 ml. of water at 0–5° with stirring for 2 hr. The reaction mixture was then heated at 70° for 3 hr. At the end of this period, the reaction mixture was cooled in ice and the dark brown solid was collected. The solid was extracted with boiling benzene thoroughly. From the benzene layer, a crude dark red solid, m.p. 130–166°, was obtained. The crude product was purified by recrystallizations from benzene-pentane and 95% ethanol respectively to give light yellow prisms, m.p. 169–171°; mixed m.p. with II 140–165°. The infrared spectrum of III showed a nitrile band at 4.55 μ.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.16; H, 6.83; N, 16.46.

2,3-Heptamethylenequinoxaline-6-carboxylic acid (IV). (1) A mixture of 100 mg. of III and 2 ml. each of acetic acid, sulfuric acid, and water was refluxed overnight. After the usual work up, the organic acid IV was obtained and recrystallized from ethanol, m.p. 238–240° (dec.).

(2). An equimolar mixture of 1,2-cyclononanedione and 3,4-diaminobenzoic acid was allowed to react as described for the preparaton of I. The product IV was obtained in 50% yield after recrystallization from 95% ethanol. It appeared as colorless needles, m.p. 238–240° (dec.) and crystallized as a monohydrate.

Anal. Calcd. for $C_{16}H_{18}O_2N_2 \cdot H_2O$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.57; H, 6.85; N, 9.52.

Attempted resolution of IV. An equimolar mixture of IV and the optically active base was warmed in acetone until the solution became clear. The solution was filtered whenever necessary and allowed to cool slowly to room temperature. The crystalline salt was collected and recrystallized three more times after it showed constant melting point and rotation.

The (+)-α-phenylethylamine salt of IV appeared as soft needles from acetone, m.p. 156–158°, $[\alpha]_D = +23°$ (c = 5, in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{29}O_2N_3$: C, 73.62; H, 7.47; N, 10.73. Found: C, 73.88; H, 7.64; N, 10.94.

The cinchonidine salt of IV appeared as soft needles from ethanol, m.p. 232° (dec.), $[\alpha]_D = -47.5°$ (c = 1, in $CHCl_3$).

Anal. Calcd. for $C_{35}H_{40}O_3N_4$: C, 74.44; H, 7.14; N, 9.92. Found: C, 74.71; H, 7.08; N, 9.70.

The salts were decomposed by treating with dilute hydrochloric acid in chloroform solution. The resulting acid showed m.p. 238–240° (dec.) and zero rotation.

6-Acid phthalamido-2,3-heptamethylenequinoxaline (V). A solution of 3 g. (0.02 mole) of phthalic anhydride in 20 ml. of benzene was added to a solution of 4.82 g. (0.02 mole) of II in 25 ml. of benzene. The solution turned deep red and became warm immediately. After the initial reaction had subsided, the mixture was heated to boiling for two minutes, during which time the reaction mixture gradually turned light yellow and a white solid started to precipitate. The mixture was left at room temperature until precipitation was complete. The white crude product, m.p. 134–135°, weighed 7.6 g. (quantitative yield).

A small portion of the crude product was recrystallized from 60% ethanol. The solution turned orange and a yellow crystalline product, the monohydrate, was obtained, m.p. 131–135°. This monohydrate can be reconverted to the anhydrous form by boiling in benzene.

Anal. Calcd. for $C_{23}H_{23}O_3N_3$: C, 70.93; H, 5.95; N, 10.79. Found: (white form) C, 71.19; H, 6.16; H, 10.62.

Anal. Calcd. for $C_{23}H_{23}O_3N_3 \cdot H_2O$ or $C_{23}H_{25}O_4N_3$: C, 67.79; H, 6.18; N, 10.31. Found (yellow form): C, 67.68; H, 6.21; N, 10.47.

Treatment of V with optically active bases. An equimolar mixture of the acid V and an optically active base was warmed in acetone until the solution became clear. The solution was decolorized and filtered whenever necessary, and allowed to cool slowly to room temperature. With brucine or (+)-α-phenylethylamine no solid salt was obtained. In both cases when the solvent was finally evaporated, a glassy residue, which failed to crystallize, was obtained.

With cinchonidine as the base, a quantitative yield of the salt of V was obtained after standing at room temperature for two days; m.p. 139–141°, $[\alpha]_D = -72.3°$ (c = 1.4 in $CHCl_3$). This salt was recrystallized from acetone (60 ml./g.) five times, m.p. 140–142° $[\alpha]_D = -79.1°$ (c = 2.5, in $CHCl_3$), $[\alpha]_D + 11.7°$ (c = 2, in EtOH).

Anal. Calcd. for $C_{42}H_{45}O_4N_5$: C, 73.77; H, 6.63; N, 10.24. Found: C, 73.53; H, 6.76; N, 10.25.

The salt was decomposed by dissolving in chloroform and shaking thoroughly with 10% hydrochloric acid and water. The light yellow chloroform layer was directly transferred into a polarimeter tube. The observed rotation was zero.

The quinine salt was prepared in the same manner. The salt crystallized from acetone as very fine needles; m.p. 188–189°, $[\alpha]_D = -143°$ (c = 1, in $CHCl_3$).

Anal. Calcd. for $C_{43}H_{47}O_5N_5$: C, 72.35; H, 6.70; N, 9.81. Found: C, 72.25; H, 6.42; N, 9.61.

From methanol long crystalline needles, m.p. 141–143° $[\alpha]_D = -144°$ (c = 2, in $CHCl_3$) were obtained.

Anal. Calcd. for $C_{43}H_{47}O_5N_5$: C, 72.35; H, 6.70; N, 9.81. Found: C, 72.38; H, 6.48; N, 9.48.

A sample (0.5 g.) of the quinine salt, which was crystallized seven times, was decomposed in the same manner as described before. The chloroform solution of the regenerated free acid showed zero rotation.

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