771. *Polynuclear Heterocyclic Systems. Part XIV.* Indoloquinoxalines.*

By G. M. Badger and P. J. Nelson.

Indolo[2,3-*b*]quinoxaline has been shown to exist predominantly in the form (II; R = H), but on methylation it gives a mixture of 5- and 6-methylquinoxalines. 5-Methylindolo[2,3-*b*]quinoxaline is protonated and methylated at the 11-position, and the 6-methyl isomer is protonated, and methylated, at the 5-position.

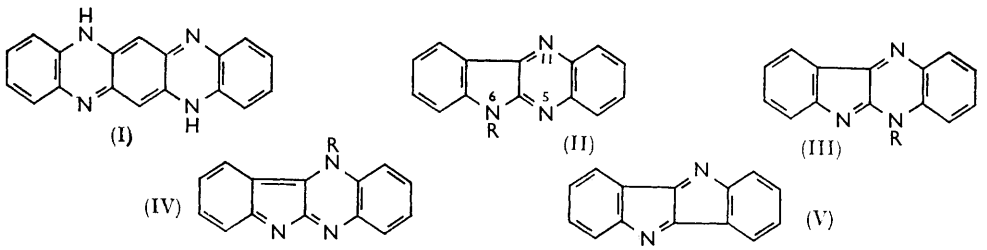
In previous papers in this series [1] it was shown that dihydro-polynuclear aza-hydrocarbons often exist as *p*-quinonoid-type structures, some of which are remarkably stable. The linear pentacyclic compound " homofluorindine " (5,12-dihydro-5,7,12,14-tetra-azapentacene), for example, has a stable structure of type (I), and the parent aromatic compound could not be prepared. It seemed of interest to determine whether the related conjugated system, $-N=C-C=N-$, is similarly stable, and the structure of indolo[2,3-*b*]quinoxaline has accordingly been examined.

Indoloquinoxaline has three theoretically possible tautomeric forms: the first (II, R = H) is generally regarded as being the most important; the second (III, R = H) has

* Part XIII, *J.*, 1958, 1179.

[1] Badger and Pettit, *J.*, 1951, 3211; 1952, 1874, 1877.

the conjugated system under discussion; but the third (IV, R = H) must be unimportant owing to its smaller resonance stabilisation. It is of interest that the –N=C–C=N– system also occurs in indolo[3,2-*b*]indole (dibenzodiazapentalene, V), which has recently been synthesised.[2]



The ultraviolet absorption spectrum of this indoloquinoxaline in ethanol is very similar to that of 6-methylindolo[2,3-*b*]quinoxaline (II; R = Me), but the spectrum of the 5-methyl isomer (III; R = Me) showed important differences, particularly at long wavelengths

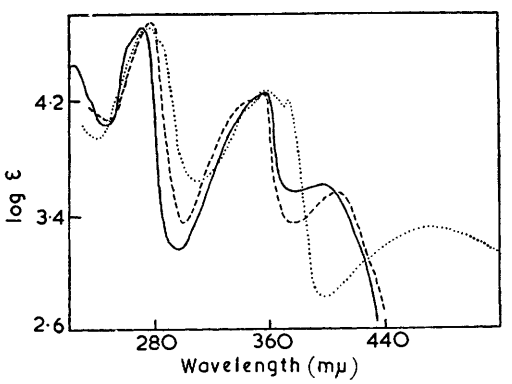


FIG. 1. Absorption spectra of indolo-[2,3-*b*]quinoxaline (——), of 6-methylindoloquinoxaline (– – – –) and of 5-methylindoloquinoxaline (. . . .), all in 95% ethanol.

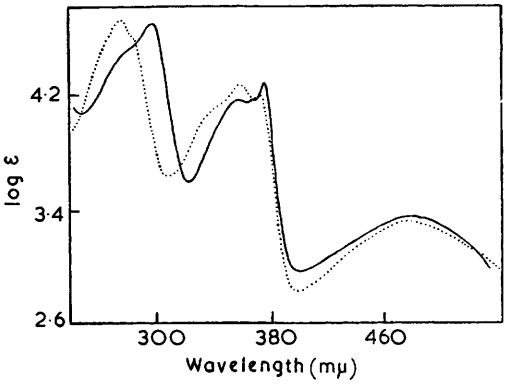


FIG. 2. Absorption spectra of indolo[2,3-*b*]-quinoxaline in 2N- sodium hydroxide (——) and of 5-methylindoloquinoxaline in 95% ethanol (. . . .).

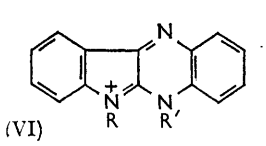
(Fig. 1). Even in solvents of greater dielectric constant (1 : 1 ethanol–water, or formamide), which might be expected to favour the tautomeric structure (III; R = H) for the indoloquinoxaline itself, the curves closely followed that for the 6-methyl derivative. It seems certain therefore that indolo[2,3-*b*]quinoxaline exists predominantly in the 6*H*-form (II; R = H).

On the other hand, the absorption spectrum of the indoloquinoxaline in sodium hydroxide was similar to that of its 5-methyl derivative (III; R = Me), so the indoloquinoxaline anion must have a significant proportion of the charge located at the 5-nitrogen atom (Fig. 2).

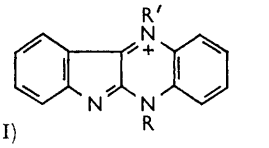
The methylation and the protonation of indoloquinoxaline and of 5- and 6-methylindoloquinoxalines have also been examined. Methylation of 6-methylindoloquinoxaline with methyl toluene-*p*-sulphonate, followed by exchange of the anion with perchlorate, gave a deep red salt. Its absorption spectrum (Fig. 3) showed a band in the visible region

[2] Treibs, *Naturwiss.*, 1961, **48**, 130; see also Kato and Ohta, *Bull. Soc. Chem. Japan*, 1961, **34**, 357.

at 480 mμ, and a conjugated system similar to that in 5-methylindoloquinoxaline (Fig. 1) may be confidently presumed. Methylation at the 6- or the 11-position would not give



(VI)



(VII)

the necessary conjugated structure, and the salt must therefore be 5,6-dimethylindoloquinoxalinium perchlorate (VI; R = R′ = Me). Its absorption spectrum was similar to that of the salt obtained by protonation of 6-methylindoloquinoxaline, as determined on a solution of 6-methylindoloquinoxaline in 5N-sulphuric acid (Fig. 3). The anion of this salt must therefore have the structure as in (VI; R = Me, R′ = H).

The absorption spectrum given by indolo[2,3-*b*]quinoxaline in 5N-sulphuric acid (Fig. 3) indicates that this compound also is protonated at the 5-position. With this salt, however, tautomerism is possible and both forms, (VI and VII; R = R′ = H), are probably present.

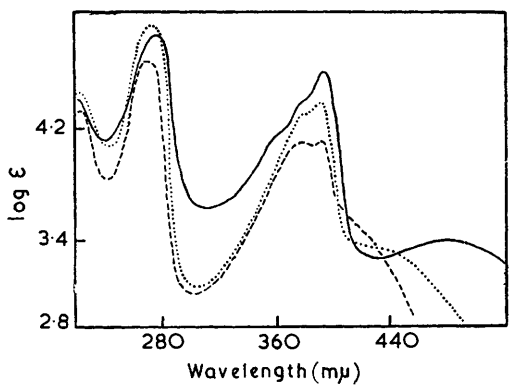


FIG. 3. Absorption spectra of 5,6-dimethylindolo[2,3-*b*]quinoxalinium perchlorate (VI; R = R′ = Me) in 95% ethanol (——), of 6-methylindoloquinoxaline in 5N-sulphuric acid (cf. VI; R = Me, R′ = H) (· · · ·), and of indoloquinoxaline in 5N-sulphuric acid (– – –).

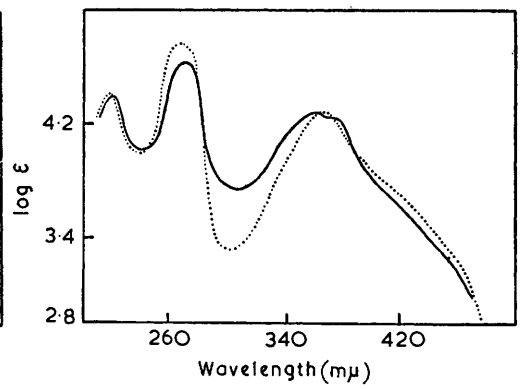
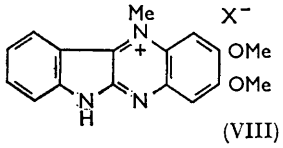


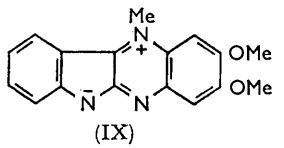
FIG. 4. Absorption spectra of 5,11-dimethylindolo[2,3-*b*]quinoxalinium perchlorate (VII; R = R′ = Me) in 95% ethanol (——), and of 5-methylindoloquinoxaline in 5N-sulphuric acid (· · ·) (cf. VII; R = Me, R′ = H).

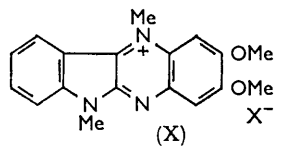
Methylation of indolo[2,3-*b*]quinoxaline was effected with methyl toluene-*p*-sulphonate; it gave 5-methyl-11*H*-indolo[2,3-*b*]quinoxalinium toluene-*p*-sulphonate (cf. VII; R = Me, R′ = H), the position of methylation being established by the isolation of 5-methylindoloquinoxaline on treatment of the salt with water. The same salt was also obtained from 5-methylindoloquinoxaline by treatment with toluene-*p*-sulphonic acid. In a similar fashion indolo[2,3-*b*]quinoxaline was treated with methyl iodide, to give the 5-methyl-11*H*-indoloquinoxalinium iodide (cf. VII; R = Me, R′ = H) identical with the salt obtained by treatment of 5-methylindoloquinoxaline with hydriodic acid. It may be noted, however, that the indoloquinoxaline with alkali and methyl iodide, or with alkali and dimethyl sulphate, gave a mixture of 5- and 6-methylindoloquinoxaline; the same compounds were obtained on use of diazomethane. 11-Methylindoloquinoxaline was never detected.

The location of the hydrogen atom in the above iodide (as VII; R = Me, R′ = H) may be inferred by comparison with the product obtained from 5-methylindoloquinoxaline

by treatment with methyl toluene-*p*-sulphonate and subsequent replacement of the anion with perchlorate (to facilitate isolation). This product was not identical with 5,6-dimethylindoloquinoxalinium perchlorate prepared as described above. The two methyl groups must therefore be located at the 5,11-positions, or both must be at the 5-position. The latter possibility was excluded by examination of the nuclear magnetic resonance spectrum which showed two absorption peaks for methyl protons (at 5·06 and 5·52τ) in trifluoroacetic acid solution. It must be concluded therefore that this salt is 5,11-dimethylindolo[2,3-*b*]quinoxalinium perchlorate (VII; R = R′ = Me). Its absorption spectrum (Fig. 4) was similar to that of 5-methylindoloquinoxaline (Fig. 1) except that the maximum at long wavelength had been reduced to a shoulder at a somewhat shorter wavelength. The absorption spectrum given by 5-methylindoloquinoxaline in 5N-sulphuric acid was very similar and is strong evidence for protonation at the 11-position to give (VII; R = Me, R′ = H).


(VIII)

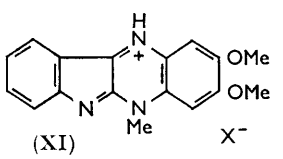

(IX)

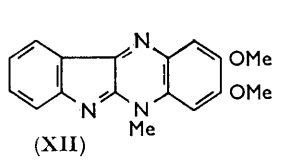

(X)

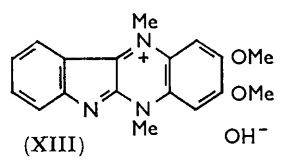
The indolo[2,3-*b*]quinoxaline used in this work was readily obtained from isatin and *o*-phenylenediamine;[3] 6-methylindoloquinoxaline was similarly obtained from *N*-methylisatin and *o*-phenylenediamine.[4] 5-Methylindoloquinoxaline was prepared from isatin and *N*-methyl-*o*-phenylenediamine,[4] but, as this synthesis is not unambiguous, the compound was also prepared by cyclisation of an authentic sample of 3-*o*-aminophenyl-1,2-dihydro-1-methyl-2-oxoquinoxaline.[5]

Armit and Robinson, in 1925,[6] methylated 2,3-dimethoxyindoloquinoxaline to give a product which they regarded as the 11-methyl derivative (VIII); on treatment with potassium hydroxide in aqueous ethanol, this gave a substance which they regarded as the anhydronium base (IX). This substance was obtained as scarlet needles, and it is also significant that addition of acid to a dilute aqueous solution resulted in a change from orange to yellow. Methylation of the supposed anhydronium base with dimethyl sulphate and subsequent treatment with aqueous potassium hydroxide gave a salt regarded as (X).

It is unlikely that the two methoxy-groups would affect the position of methylation, and the above structures (which were supported only by analytical data) may now be revised. On the basis of the work now reported the quaternisation of 2,3-dimethoxyindolo[2,3-*b*]quinoxaline would be expected to give the salt (XI) which on treatment with


(XI)


(XII)


(XIII)

alkali would give 2,3-dimethoxy-5-methylindoloquinoxaline (XII). The properties of this compound (formerly believed to be IX) are in fact very similar to those of 5-methylindoloquinoxaline. Methylation of this base, and treatment with alkali, would then give

[3] Schunck and Marchlewski, *Ber.*, 1895, **28**, 2528; see also Bednarczyk and Marchlewski, *Biochem. Z.*, 1938, **300**, 46.
[4] Buraczewski and Marchlewski, *Ber.*, 1901, **34**, 4011.
[5] Clark-Lewis, *J.*, 1957, 439.
[6] Armit and Robinson, *J.*, 1925, **127**, 1608.

2,3-dimethoxy-5,11-dimethylindoloquinoxalinium hydroxide (XIII) which was obtained as orange-yellow needles. The 5,11-dimethylindoloquinoxalinium perchlorate obtained in the present work was likewise obtained as orange-yellow needles.

Experimental

Indolo[2,3-*b*]*quinoxaline*.—This was prepared by Schunck and Marchlewski's [3] method. After recrystallisation from ethanol it formed yellow needles, m. p. 295—296°.

6-*Methylindolo*[2,3-*b*]*quinoxaline*.—*o*-Phenylenediamine (2 g.) in 1 : 1 aqueous acetic acid (20 ml.) was added to a hot solution of *N*-methylisatin (2 g.) in 1 : 1 aqueous acetic acid (20 ml.), and the mixture was heated for 30 min. The cooled mixture was poured into water, and the product collected, and purified by chromatography in light petroleum (b. p. 60—80°) on alumina, followed by recrystallisation from light petroleum. 6-Methylindoloquinoxaline formed yellow needles, m. p. 148—149° (lit.,[4] 148°).

5-*Methylindolo*[2,3-*b*]*quinoxaline*.—(i) Condensation of *N*-methyl-*o*-phenylenediamine with isatin by Buraczewski and Marchlewski's method [4] gave 5-methylindoloquinoxaline as red needles, m. p. 177—178° (from aqueous ethanol) (lit., 175—176°).

(ii) A mixture of 3-*o*-aminophenyl-1,2-dihydro-1-methyl-2-oxoquinoxaline [5] (50 mg.) and polyphosphoric acid (1 g.) was heated at 150° for 2 hr. Water was added dropwise to the cooled mixture which was then made alkaline with 10% aqueous sodium hydroxide. The product was collected and recrystallised from aqueous ethanol, to give 5-methylindoloquinoxaline (41 mg., 88%) as red needles, m. p. 177—178° alone or mixed with a specimen prepared as above.

Determination of the pK_a *Values*.—(i) *Acid* pK_a. pH Determinations were carried out on a Pye Universal pH meter which was standardised at pH 9·18 with 0·05M-sodium borate at 20°. A Hilger Uvispek spectrophotometer was used for optical-density measurements of 2×10^{-5}M-solutions of indoloquinoxaline in 1 : 1 ethanol–water at 295 mμ. Measurements were made on solutions which had pH values in the range 12·8—13·3. The acid pK_a found for indoloquinoxaline was $13{\cdot}6 \pm 0{\cdot}1$.

(ii) *Base* pK_a. The pH meter was standardised at pH 3·97 (0·05M-potassium hydrogen phthalate solution) at 20°. Optical-density measurements were made for 2×10^{-5}M-solutions in 1 : 1 ethanol–water at 381 and 272 mμ. Measurements were made on solutions which had pH values in the range 0·6—1·44. The base pK_a found for indoloquinoxaline was $\sim 0{\cdot}3$.

Methylation of Indoloquinoxaline.—(i) A mixture of indoloquinoxaline (2·2 g., 0·01 mole), sodium hydroxide (0·4 g., 0·01 mole), methyl iodide (1·5 g., 0·01 mole), and absolute ethanol (100 ml.) was heated under reflux for 24 hr. and poured into water. The solid was collected, recrystallised from aqueous ethanol, and extracted with boiling hexane. The insoluble fraction (0·70 g.) was indoloquinoxaline. The hexane solution was chromatographed on alumina (100 g.). Elution with hexane gave 6-methylindoloquinoxaline (0·92 g., 40%), m. p. 146—147°, followed by 5-methylindoloquinoxaline (0·27 g., 12%), m. p. 176—177°.

(ii) A solution of indoloquinoxaline (2·5 g., 0·012 mole) in ethanol (100 ml.) and 5% aqueous sodium hydroxide (100 ml.) was heated on a steam-bath, and dimethyl sulphate (6 ml., 0·06 mole) was added dropwise. The mixture was left overnight and the solid (2·4 g.) then collected. Chromatography on alumina (100 g.) in hexane gave 6-methylindoloquinoxaline (1·9 g., 70%), m. p. 146—147°, followed by 5-methylindoloquinoxaline (0·4 g., 15%), m. p. 176—177°.

(iii) An ethereal solution of diazomethane (*ca.* 4 g.) was added to a suspension of indoloquinoxaline (2·2 g.) in acetone (250 ml.) at 0°. After 2 hr. the mixture was left at room temperature overnight. The solvent was removed and the solid extracted with hexane, to give an insoluble fraction (indoloquinoxaline, 0·32 g.) and a soluble fraction. The latter was chromatographed on alumina with hexane as eluant. The first fraction gave an unknown colourless compound (0·59 g.) which could not be purified by recrystallisation or by chromatography on alumina or acetylated cellulose. After repeated recrystallisation it formed colourless needles, m. p. 202—203° after sintering; analysis indicated that it contained oxygen. The second fraction was an intractable mixture (0·46 g.) of 6-methylindoloquinoxaline and the colourless material. The third fraction (0·43 g.) consisted of essentially pure 6-methylindoloquinoxaline, m. p. 146—148°, and further elution gave 5-methylindoloquinoxaline (0·36 g.) as red needles, m. p. 176—177°.

*5-Methyl-*11H*-indolo*[2,3-*b*]*quinoxalinium Toluene*-p-*sulphonate*.—(i) A mixture of indoloquinoxaline (2 g., 0·008 mole), methyl toluene-*p*-sulphonate (2 g., 0·012 mole), and ethanol (5 ml.) was heated at 120° for 2 hr. The resulting solid was extracted with chloroform (20 ml.), to give the product as a residue (1 g.), m. p. 244—245°, and a further yield (0·4 g.) was obtained by concentration of the extract. After recrystallisation from ethanol the *toluene*-p-*sulphonate* formed yellow needles, m. p. 247—248° (decomp.) (Found: C, 65·0; H, 4·8; N, 10·4. $C_{22}H_{19}N_3O_3S$ requires C, 65·2; H, 4·7; N, 10·4%), $\lambda_{max.}$ (in EtOH) 220 (log ε 4·41), 274 (4·65), shoulder 340 (4·10), 355 (4·23), 371 (4·18), and 417 mμ (3·33); $\nu_{max.}$ 8·66, 8·93, 9·71, and 9·92 μ (toluene-*p*-sulphonate [7]). A solution of this material (100 mg.) in ethanol (30 ml.) was poured into water. Recrystallisation of the product from aqueous ethanol gave 5-methylindoloquinoxaline as red needles, m. p. and mixed m. p. 177—178°.

(ii) Toluene-*p*-sulphonic acid in acetone was added dropwise to 5-methylindoloquinoxaline in acetone until the mixture became yellow, ether was added, and the mixture was cooled. The product which separated was recrystallised from ether–acetone, and the resulting 5-methyl-11*H*-indoloquinoxalinium toluene-*p*-sulphonate formed yellow needles, m. p. 247—248° (decomp.) alone or admixed with a specimen prepared as above. Its infrared spectrum was also identical with that from the material above.

*5-Methyl-*11H*-indolo*[2,3-*b*]*quinoxalinium Iodide*.—(i) A mixture of indoloquinoxaline (1 g.), methyl iodide (10 ml.), and ethanol (10 ml.) was heated under reflux for 60 hr. The resulting precipitate was collected and recrystallised from ethanol, to give the *iodide* (0·75 g., 47%) as orange-yellow needles, m. p. 255—256° (decomp.) (Found: C, 49·7; H, 3·7; N, 11·5. $C_{15}H_{12}IN_3$ requires C, 49·9; H, 3·4; N, 11·6%). $\lambda_{max.}$ (in EtOH) 219 (log ε 4·56), 273 (4·83), shoulder 340 (4·16), 355 (4·30), 371 (4·23), and 417 mμ (3·38).

(ii) Hydriodic acid was added dropwise to 5-methylindoloquinoxaline until the solution became permanently yellow. Ether was added, the solution cooled, and the resulting solid recrystallised from ether–acetone to give the iodide as orange-yellow needles, m. p. and mixed m. p. 255—256° (decomp.).

5,6-Dimethylindolo[2,3-*b*]*quinoxalinium Perchlorate*.—A mixture of 6-methylindoloquinoxaline (1 g., 0·004 mole), methyl toluene-*p*-sulphonate (1·1 g., 0·006 mole), and ethanol (3 ml.) was heated at 120° for 1 hr. The resulting solid was dissolved in ethanol, and the solution acidified with perchloric acid and then poured into water. After recrystallisation from ethanol the *5,6-dimethylindoloquinoxalinium perchlorate* (1·4 g., 93%) formed red needles, m. p. 273—274° (decomp.) (Found: C, 55·3; H, 4·2; N, 12·0. $C_{16}H_{14}ClN_3O_4$ requires C, 55·3; H, 4·1; N, 12·1%).

5,11-Dimethylindolo[2,3-*b*]*quinoxalinium Perchlorate*.—Methylation of 5-methylindoloquinoxaline was effected as for the 6-methyl derivative. After recrystallisation from ethanol the *5,11-dimethylindoloquinoxalinium perchlorate* (0·61 g., 41%) formed orange-yellow needles, m. p. 308—309° (decomp.) (Found: C, 55·0; H, 4·2; N, 12·2%).

Absorption Spectra.—Unless otherwise stated all spectra were determined in 95% ethanol by using an Optica recording spectrophotometer.

We are indebted to Dr. J. W. Clark-Lewis for helpful discussions and for a gift of 3-*o*-aminophenyl-1,2-dihydro-1-methyl-2-oxoquinoxaline, to Dr. T. M. Spotswood for the nuclear magnetic resonance spectrum, and to a Referee for useful criticism and for suggestions which proved helpful in establishing some of the structures.

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[7] Weisenborn and Burn, *J. Amer. Chem. Soc.*, 1953, **75**, 259.