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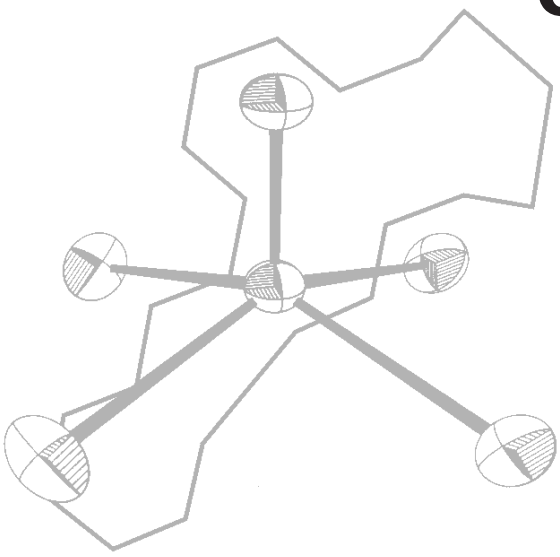

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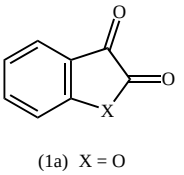
Fused Tetracyclic Quinoxalines from Reactions of *o*-Phenylenediamines in Polyphosphoric Acid

Leslie W. Deady and Anthony J. Kaye

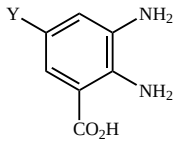
School of Chemistry, La Trobe University, Bundoora, Vic. 3083.

The condensation of 2,3-diaminobenzoic acid and the 5-chloro derivative with *o*-hydroxyphenylglyoxylic acid, isatin and benzothiophen-2,3-dione in polyphosphoric acid leads to the appropriate tetracycles. Isomeric products are formed from these unsymmetrical diamines, and methods of assigning particular structures are described.

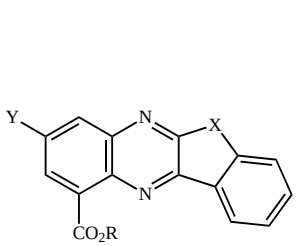
As part of continuing research into polycyclic nitrogen heterocycles as DNA-intercalating antitumour agents, we have prepared derivatives, namely compounds (3) and (4), of systems in which a five-membered ring containing O, S or NH is inserted into the phenazine system (Scheme 1). The basic tetracycles are known; the thia and aza examples have been prepared by reaction of a phenylene-1,2-diamine with the appropriate dicarbonyl compound, while the oxa analogue has been prepared by a quite different route.[1]

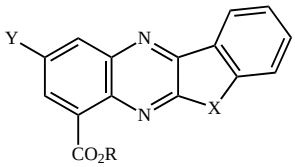


(1a) X = O
(1b) X = S
(1c) X = NH



(2a) Y = H
(2b) Y = Cl





	X	Y	R
(3a)	O	H	H
(3b)	O	Cl	H
(3c)	NH	H	H
(3d)	NH	H	Et
(3e)	NH	Cl	H
(3f)	NH	Cl	Et
(3g)	S	H	H

	X	Y	R
(4a)	O	H	H
(4b)	O	Cl	H
(4c)	NH	H	H
(4d)	NH	H	Et
(4e)	NH	Cl	H
(4f)	NH	Cl	Et
(4g)	S	H	H

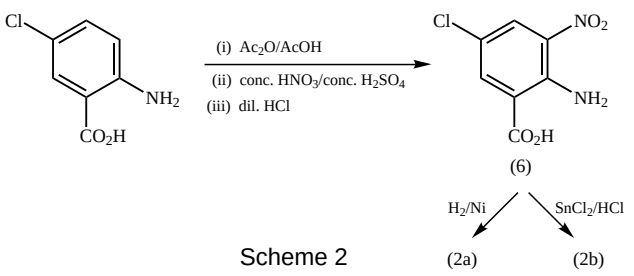
Scheme 1

We had a particular interest in the carboxy substituent, specifically in the position shown. This introduced some complexity into the reaction. Also, when the diamine is unsymmetrical, there is the task of assigning any product to the isomeric (3) or (4) series. This is an extension of a long-standing problem in quinoxaline chemistry. In the tetracyclic compounds, previous examples have either used a symmetrical diamine or have left the structures unresolved. This paper reports on our studies of a common path to all three hetero series (Scheme 1) and methods for establishing individual structures as (3) or (4).

Results and Discussion

Precursors

Isatin (1c) was the aza dicarbonyl compound, and this was converted into *o*-hydroxyphenylglyoxylic acid (5).[2] This can be cyclized to benzofuran-2,3-dione (1a)[2,3] but we successfully used (5) itself in the condensation reaction. The sulfur compound (1b) was prepared from benzenethiol and oxalyl chloride.[4] A four-step preparation of 2,3-diaminobenzoic acid (2a) used an expensive starting material[5] and a more recent synthesis was also lengthy.[6] An alternative preparation, starting from the moderately priced 2-amino-5-chlorobenzoic acid, was devised (Scheme 2). By suitable choice of reducing agent in the final step, both the dechloro (2a) and chloro (2b) diamines were accessible.



Scheme 2

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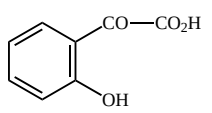
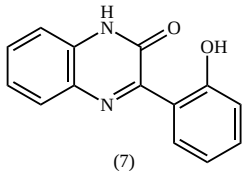
Condensations

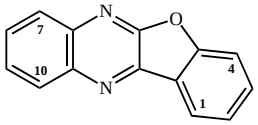
Previous reactions of benzofuran-2,3-dione (1a) with phenylene-1,2-diamine have resulted in the formation of compound (7) rather than the desired tetracycle.[7] We found that reaction in hot polyphosphoric acid was quite successful and (7) was only a minor component. As a model reaction, (8) was formed in 50% yield. A single product (4a) was formed from (2a). This result was exceptional, as inseparable isomeric mixtures were the norm in the present work. Thus, a 1 : 1 mixture of (4b) and (3b) was formed from (2b) (see below for the assignments). These results can be rationalized if, under these conditions, the 3-amino group of (2a) is the more nucleophilic and, in the preferred reaction, reacts with the more electophilic 3-carbonyl group of (1a) [or the ketone C=O of (5)]. In (2b), the chlorine *meta* to the 3-amino group reduces its nucleophilicity relative to the 2-amino group so that more of the other isomer is formed.



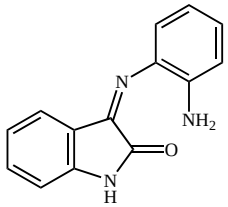
(5)



(7)



(8)



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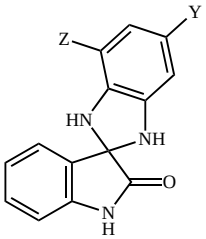
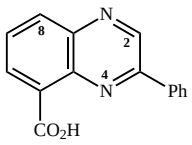


	Y	Z
(10a)	H	H
(10b)	Cl	CO_2H



(11)

The reaction of isatin with phenylene-1,2-diamine has received considerably more study. The reaction is complex and the Schiff base (9) and spiro compound (10a), as well as the indolo[2,3-*b*]quinoxaline, have been isolated, depending on the conditions.[8–10] In the present work, reaction with (2b) in aqueous acetic acid gave a good yield of the spiro compound (10b), but a change to hot polyphosphoric acid brought about the desired reaction, with only a trace of spiro contaminant. Isomeric mixtures [(4c)-to-(3c) ratio 4 : 1, (4e)-to-(3e) ratio 1 : 2] were obtained in both cases, with the chloro substituent favouring (3), relative to hydrogen, as in the furo analogues.

Formation of the thieno system is simplest[11] and there are no reports of other types of reaction products. This was also true in the present work, where both aqueous acetic acid and polyphosphoric acid were investigated as condensation media with contrasting results. Reaction of (1b) with (2a) gave good yields of tetracyclic products; (3g) (5 : 1) was favoured in aqueous acetic acid, while the change to polyphosphoric acid reversed the preference and (4g) (3 : 1) predominated.

Structural Assignment

It was not possible to assign structures to the (3) or (4) series from ^{1}H or ^{13}C n.m.r. spectra, but this could be done for the oxa and aza compounds from the chemical shifts produced by *N*-oxidation. We have recently applied this technique with ^{1}H and ^{13}C n.m.r. spectra[12,13] to solve similar problems.

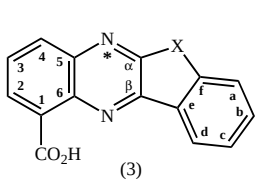
The systematic numbering of the tetracycles depends on the isomer and the heteroatom, and comparisons are therefore confusing. For the n.m.r. discussion, therefore, the system shown (Table 1) has been adopted. In this, numbers refer to the A-ring, starting at the acid-substituted position, letters apply to the D-ring, starting *ortho* to the heteroatom, and α and β refer to the 'inner' ring-junction carbons, with α being that between the two heteroatoms. The difference between (3) and (4) is therefore in the relative positions of α and β with respect to the numbered positions. This cannot be ascertained from the n.m.r. spectra although the atoms can be identified, and this was a necessary first step. The aza ethyl ester [later established as (4d)] was a conveniently soluble reference compound for the ^{1}H and ^{13}C n.m.r. experiments required to achieve this.

The ^{1}H, ^{13}C, $^1J_{C,H}$ HETCOR[14] and $^3J_{C,H}$ HMBC[15] spectra provided the data summarized in Table 1; these allow the atoms to be assigned without recourse to any reference spectra. For the carbons with attached protons, H 2 is the only one with $^3J_{C,H}$ coupling to the carbonyl carbon. There is also $^3J_{C,H}$ coupling to one other hydrogen-bound carbon, which must therefore be C 4. The remaining doublets for H a and H d can be distinguished by the extra $^3J_{C,H}$ coupling for the latter. The upfield triplet for H c is assigned from the $^3J_{C,H}$ coupling to C a. The close triplets for H b and H 3 can be distinguished by the $^3J_{C,H}$ coupling of the former to C d and the lack of $^3J_{C,H}$ coupling between H 3 and any other hydrogen-bound carbon. The quaternary carbons may be assigned from $^3J_{C,H}$ coupling to protons already identified. This allows distinction between C e ($^3J_{C,H}$ to H a and H c) and C f ($^3J_{C,H}$ to H b and H d), C 5 ($^3J_{C,H}$ only to H 3) and C 6 ($^3J_{C,H}$ to H 2 and H 4), and C β ($^3J_{C,H}$ only to H d) and C α (the only one with no $^3J_{C,H}$).

The remaining ^{1}H and ^{13}C n.m.r. assignments listed in Tables 2 and 3 were made by reference to those for (4d); these were aided by additional proton-coupled

Table 1. C,H coupling for compound (4d) in $(CD_3)_2SO$

∘ denotes $^1J_{C,H}$ (HETCOR); + denotes $^3J_{C,H}$ (HMBC)



Carbon		H c	H a	H b	H 3	H 2	H d	H 4
	7·37, t	7·55, d	7·72, t	7·74, t	8·00, d	8·35, d	8·38, d
CO	167·3					+		
C α	145·8							
C f	144·4			+			+	
C β	140·4						+	
C 5	138·3				+			
C 6	137·6					+		+
C 4	132·0					+		∘
C b	131·8			∘			+	
C 1	131·0				+			
C 2	128·5					∘		∘
C 3	125·0				∘			
C d	122·6			+			∘	
C c	121·0	∘	+					
C e	118·9	+	+					
C a	112·2	+	∘					

Table 2. ^{1}H n.m.r. data in $(CD_3)_2SO$

Cpd	H 2	H 3	H 4	H a	H b	H c	H d
(4d)	8·00	7·74	8·38	7·55	7·72	7·37	8·35
(4a)	8·18	[A]	8·44	[A]	[A]	7·61	8·36
(4a)[B]	8·21	[A]	8·73	[A]	[A]	7·60	8·47
(3b)	8·15	—	8·35	[A]	[A]	7·61	8·34
(4b)	8·15	—	8·48	[A]	[A]	7·61	8·34
(4b)[B]	8·21	—	8·66	[A]	[A]	7·60	8·44
(3c)	8·37[C]	7·93	[D]	[D]	[D]	[D]	8·33[C]
(4c)	8·44	7·85	8·51	7·63	7·77	7·43	8·37
(4c)[B]	8·44	7·78	8·79	7·55	7·69	7·39	8·54
(3e)	8·23	—	8·52	7·61	7·77	7·42	8·35
(4e)	8·11	—	8·33	7·61	7·77	7·41	8·37
(4e)[B]	8·28	—	8·76	7·60	7·77	7·42	8·58
(3g)	8·32[C]	8·0	8·45	8·19	7·82	7·69	8·35[C]
(4g)	8·24	7·96	8·50	8·19	7·82	7·69	8·43

[A] Occurred as a multiplet at δ 7·8–7·9.
[B] The *N*-oxidation product.
[C] Peaks bearing this superscript within a row may be interchanged.
[D] Peaks are obscured by the signals of the corresponding protons of the major product (4c).

^{13}C and $^1J_{C,H}$ HETCOR experiments, and the effect of O relative to NH illustrated by spectra of dibenzofuran and carbazole.[16,17] Labelling as (3) or (4) required additional data from *N*-oxidation experiments.

By using quinoline[18,19] and our other work as examples,[12,13] *N*-oxidation results in *downfield* shifts in the ^{1}H n.m.r. spectrum for 'near' hydrogens, for example, H 4 and H d for reaction at N* in (4). In the ^{13}C spectra, on the other hand, *N*-oxidation causes marked *upfield* shifts for quaternary carbons next to the N–O function, while the more distant ring-junction carbons are hardly affected. In addition, quinoline *N*-oxidation is also accompanied by a substantial upfield shift for the *peri* carbon; C 4 is the equivalent in the tetracycles.

There are four possible structures for the *N*-oxide from a compound which could be either (3) or (4). However, in the present work, all *N*-oxides showed

Table 3. ^{13}C n.m.r. data in $(CD_3)_2SO$

Cpd	C 1	C 2	C 3	C 4	C 5	C 6	C α	C β	C a	C b	C c	C d	C e	C f	CO
(4d)	131·0	128·5	125·0	132·0	138·3	137·6	145·8	140·4	112·2	131·8	121·0	122·6	118·9	144·4	167·3
(4c)	132·7	132·2	125·5	133·3	138·0	137·2	144·3	141·7	112·5	132·2	121·7	122·6	118·9	144·2	166·4
(4c)[A]	133·7	133·2[B]	125·1	123·6	125·0[C]	139·8[D]	148·0	126·0[C]	111·9	131·3[B]	121·8	122·4	114·8	140·6[D]	166·5
(4a)	131·6	130·3	127·9	132·0	140·4	136·4	155·1	141·1	113·1	133·5	125·1	123·1	120·6	158·3	165·8
(4a)[A]	131·5	131·8[B]	127·0	120·4	135·6	138·1	158·1	124·8	111·6	131·6[B]	124·6	123·0	116·5	154·3	165·8

[A] The *N*-oxidation product.
[B,C,D] Resonances bearing the same capital superscript within a row may be interchanged.

appropriate shifts for C 4 and H 4. Thus, the steric effect of the 1-CO_2H group restricted oxidation to N*, so that the possibilities were now reduced to the two structures shown and the expectations from *N*-oxidation are as follows. For (4), upfield shifts are expected for C 4, C 5 and C α, whereas downfield shifts for H 4 and H d are expected. For (3), upfield shifts for C 4, C 5 and C β, and downfield shifts for H 4, are expected.

Though some signal overlap occurred in the ^{1}H n.m.r. spectra, the most downfield peaks, which included those for H 4 and H d, were always distinguishable. As an example, inspection of the results from Tables 2 and 3 for the single compound formed in the dechloro oxa case indicates *N*-oxidation shifts only compatible with this being (4a). This was true also for the aza analogue (4c).

This method of structure assignment could still be used where mixtures of the isomers (3) and (4) were present. It was beneficial in fact to have both isomers available for reaction under identical conditions, and only the isomer (4) reacted. So, for example, the mixture in the chloro oxa case after oxidation showed distinguishable peaks for the *N*-oxide of (4b) and unchanged (3b). This selectivity conforms with the knowledge that 2-methoxyquinoxaline undergoes oxidation at N 4.[20]

The *N*-oxidation approach failed for the sulfur case. While there are examples of *N*-oxidation in compounds with adjacent nitrogen- and sulfur-containing rings,[21] no success was achieved with the product [(3g) or (4g)] of the acetic acid condensation described above. Proton n.m.r. spectra were complex but always showed *upfield* shifts, which suggested breakdown of the ring system. An alternative approach made use of the ready desulfurization of many compounds, including dibenzothiophen, with Raney nickel.[22] The sulfur tetracycle, with deactivated catalyst and careful control of conditions (it over-reacted very easily), afforded a phenylquinoxalinecarboxylic acid. This was characterized by the appearance of the hetero-ring CH singlet in the ^{1}H n.m.r. spectrum, and the proton-coupled ^{13}C spectrum allowed it to be identified as (11). In particular, C 4a (138·3 ppm) and C 8a (140·8) were assigned by reference to quinoxalines.[23] The latter was a well resolved triplet ($^3J_{C,H2,7}$ 10·0 Hz), the former less so, and this multiplicity is incompatible with the alternative 2-phenyl isomer (C 8a should be a doublet). Thus the major tetracyclic product from the acetic acid condensation is (3g).

The work described in this paper shows that polyphosphoric acid is a convenient medium to bring about condensation of *o*-phenylenediamines with isatin and its oxa and thia analogues. In addition, a detailed n.m.r. analysis of the products provides a useful data base, and convenient methods have been found which enable isomeric structures of the resulting tetracycles to be determined.

Experimental

N.m.r. spectra were recorded on Brüker AM-300 (300·13 and 75·47 MHz for ^{1}H and ^{13}C, respectively) and Brüker DRX-400 (400·13 and 100·62 MHz) spectrometers, in $(CD_3)_2SO$ unless otherwise stated. The electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer by using a water/methanol/acetic acid (50 : 50 : 1) mobile phase. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

The (^{13}C–^{1}H) HETCOR experiment was performed by using the pulse sequence described by Bax and Morris.[14] The refocusing delay was optimized to 160 Hz (3·0 ms). The spectrum was acquired as 512×128 data points, zero-filled and subjected to both Fourier transforms to afford the 1024×1024 point data matrix. The number of transients per t_1 increment was 128. Spectral widths were 4761 Hz in F_1 (^{1}H) and 14705 Hz in F_2 (^{13}C). The 90° pulse widths were 14·0 (^{1}H) and 13·5 μs (^{13}C).

The long-range proton-detected (three bond) (^{1}H–^{13}C) heteronuclear multiple bond correlation (HMBC) experiment used the pulse sequence described by Bax and Summers.[15] The low pass *J*-filter portion of the experiment was set for an average one-bond heteronuclear coupling of 150 Hz (3·3 ms). The long range delay utilized to excite the heteronuclear multiple-quantum coherence was set for 8·3 Hz (60 ms). The spectrum was acquired as 2 K×267 data points, zero-filled and subjected to both Fourier transforms to afford the 1024×1024 point data matrix. The number of transients per t_1 increment was 32. Spectral widths were 25062 Hz in F_1 (^{13}C) and 5841 Hz in F_2 (^{1}H). The 90° pulse widths were 9·33 (^{1}H) and 10·4 μs (^{13}C) and a 1 s interpulse delay was employed.

2-Amino-5-chloro-3-nitrobenzoic Acid (6)

2-Amino-5-chlorobenzoic acid (Maybridge Chemical Company; 5 g) was acetylated with a 1 : 1 mixture of acetic anhydride (10 ml) and glacial acetic acid (10 ml) (refluxed for 0·5 h and poured into water) and the resulting amide had a m.p. of 190–192°. Nitration was carried out by adding the amide (2·0 g) in small portions over 45 min to a solution of concentrated nitric acid (4 ml) and concentrated sulfuric acid (4 ml) at 0°, and the mixture was stirred for a further 1 h then poured into 100 ml of ice-water. With continued stirring, the initially sticky precipitate gave a yellow solid. This was filtered off to give the nitro amide as a pale yellow powder (2·0 g), m.p. 195–197°. Hydrolysis of the amide was carried out by heating with concentrated hydrochloric acid/water (1 : 4; 50 ml) for 1 h, during which time a solid separated. The cooled solution was filtered to give (6) as yellow *needles* (1·40 g), m.p. 238–240° [from light petroleum (b.p. 90–110°)/chloroform] (Found: C, 38·9; H, 2·4; N, 12·8. $C_7H_5ClN_2O_4$ requires C, 38·8; H, 2·3; N, 12·9%). ^{1}H n.m.r. [$(CD_3)_2SO$/$CDCl_3$] δ 8·10, s, 1H; 8·19, s, 1H.

2,3-Diamino-5-chlorobenzoic Acid (2b)

A mixture of compound (6) (2·3 g), stannous chloride dihydrate (9·0 g) and concentrated hydrochloric acid (30 ml) was stirred and heated at 100° until the clear solution was no longer yellow. The white precipitate which formed on cooling was collected by filtration to give a *hydrochloride salt* of the product (2b) (1·8 g), m.p. 244–246° (from hydrochloric acid) (Found: C, 37·8; H, 3·9; N, 12·7. $C_7H_7ClN_2O_2$.HCl requires C, 37·7; H, 3·6; N, 12·6%). ^{1}H n.m.r. δ 7·23, d, *J* 2·4 Hz, 1H; 7·47, d, *J* 2·4 Hz, 1H.

2,3-Diaminobenzoic Acid (2a)

A mixture of compound (2b) (0·5 g) and freshly prepared Raney nickel[24] (2 g of ethanol-wet material) in 0·2 M potassium hydroxide in ethanol (50 ml) was hydrogenated at atmospheric pressure. The catalyst was removed by filtration through Celite, the filtrate was concentrated to 5 ml, diluted to 30 ml with water and acidified to pH 2 with concentrated hydrochloric acid. The solvent was removed at reduced pressure to give the product (2a) as a hydrochloride salt in a mixture (1·6 g) with potassium chloride. ^{1}H n.m.r. (D_2O) δ 6·74, t, H 5; 7·40, d, J 7·9 Hz, H 4; 7·81, d, J 8·2 Hz, H 6. This mixture was used in the condensation reactions given below.

*Benzofuro[2,3-*b*]quinoxaline (8)*

Phenylene-1,2-diamine (0·5 g) was combined with *o*-hydroxyphenylglyoxylic acid[2] (0·5 g) and polyphosphoric acid (15 g). The mixture was stirred and heated at 110° for 5 h, then cooled to room temperature and thoroughly mixed with water (200 ml). The yellow solid which separated was collected by filtration and recrystallized from ethanol to give the product (8) (0·4 g, 50%), m.p. 169–170° (lit.[1] 171–172°). ^{1}H n.m.r. δ 7·59, t, H 2; 7·81–7·94, m, H 3,4,8,9; 8·14, d, H 7; 8·30, d, H 10; 8·35, d, H 1.

*Benzofuro[2,3-*b*]quinoxaline-7-carboxylic Acid (4a)*

A mixture (1·6 g) of 2,3-diaminobenzoic acid/potassium chloride [from 0·5 g of (6)] and *o*-hydroxyphenylglyoxylic acid[2] (0·5 g) in polyphosphoric acid (15 g) was stirred and heated at 110° for 5 h, then cooled to room temperature and thoroughly mixed with water (100 ml). The green solid (0·39 g) which separated was filtered off, washed with water and recrystallized from acetonitrile to give the product (4a) (0·2 g). For microanalysis, a sample was stirred with acetic acid/water (1 : 1), which removed the small amount of (7), filtered and again recrystallized from acetonitrile to give the *acid* (4a), m.p. *c.* 270° (after shrinking and darkening) (Found: C, 68·1; H, 2·9; N, 10·6. $C_{15}H_8N_2O_3$ requires C, 68·2; H, 3·1; N, 10·6%).

*8-Chlorobenzofuro[2,3-*b*]quinoxaline-10-carboxylic Acid (3b) and 9-Chlorobenzofuro[2,3-*b*]quinoxaline-7-carboxylic Acid (4b)*

The hydrochloride (0·44 g) of the diamine (2b) and *o*-hydroxyphenylglyoxylic acid[2] (0·5 g) in polyphosphoric acid (15 g) were reacted as for (4a) to give a light green solid (0·24 g, 27%), m.p. 237–240° (from acetonitrile). This was shown by ^{1}H n.m.r. to be a *c.* 1 : 1 mixture of (3b) and (4b), containing a trace of the ring-opened product which could not be removed. Electrospray mass spectrum: *m/z* 299 (100%), 300 (16), 301 (36); all (M+1).

*6*H*-Indolo[2,3-*b*]quinoxaline-4-carboxylic Acid (4c)*

2,3-Diaminobenzoic acid/potassium chloride (1·6 g) [from 0·5 g of (6)] was combined with isatin (0·6 g) and polyphosphoric acid (15 g). The mixture was stirred and heated at 140° for 5 h, then cooled to room temperature and thoroughly mixed with water (200 ml). The solid which separated was filtered off and washed thoroughly with water, to give a black glass (0·75 g). This was treated with 1 M sodium hydroxide (50 ml), filtered, and the filtrate acidified to pH 2 with concentrated hydrochloric acid. The product was collected by filtration to give 0·6 g of a dark solid. ^{1}H n.m.r. analysis suggested that this was largely product but it could be further purified by Soxhlet extraction with tetrahydrofuran to give a yellow solid, m.p. >300°. This contained the title compound (4c) and the isomeric (3c) in a 4 : 1 ratio, with trace impurities.

For microanalysis, a sample of the dark solid (0·35 g) in ethanol (12 ml) and concentrated sulfuric acid (2 ml) was heated under reflux for 2·5 h, then cooled, and the insoluble material was removed by filtration. The filtrate was concentrated at reduced pressure to 4 ml, diluted with water to 30 ml and the pH adjusted to 3 with 10% sodium hydroxide. The solid which separated was filtered off to give the *ethyl esters* (4d) and (3d) (>19 : 1 by ^{1}H n.m.r.) (0·22 g), m.p. 228–230° (from ethanol) (Found: C, 70·2; H, 4·2; N, 14·2. $C_{17}H_{13}N_3O_2$ requires C, 70·1; H, 4·5; N, 14·4%).

*2-Chloro-6*H*-indolo[2,3-*b*]quinoxaline-4-carboxylic Acid (4e) and 3-Chloro-6*H*-indolo[2,3-*b*]quinoxaline-1-carboxylic Acid (3e)*

Reaction of the hydrochloride of the diamine (2b) (0·5 g) with isatin (0·6 g) and polyphosphoric acid (15 g) as for (4c) gave 0·6 g of a dark solid, which contained a 2 : 1 mixture of (3e) and (4e), after the same base/acid treatment. Extraction with hot tetrahydrofuran gave a yellow solid (0·22 g), m.p. >300°, with the same composition.

This was esterified as for (4c) to give a mixture of the *ethyl esters* as a tan solid, m.p. 220–225° (from ethanol/water) (Found: C, 62·4; H, 3·5; N, 12·7. $C_{17}H_{12}ClN_3O_2$ requires C, 62·7; H, 3·7; N, 12·9%).

*[1]Benzothieno[2,3-*b*]quinoxaline-10-carboxylic Acid (3g) and [1]Benzothieno[2,3-*b*]quinoxaline-7-carboxylic Acid (4g)*

(A) A warm solution of 2,3-diaminobenzoic acid/potassium chloride (1·6 g) in acetic acid/water (1 : 1; 10 ml) was added, with stirring, to a hot solution of benzothiophen-2,3-dione[4] (0·52 g) in glacial acetic acid (20 ml). The reaction mixture was warmed and stirred for 15 min and the resultant precipitate was filtered off to yield a khaki *solid* (0·34 g, 38%). ^{1}H n.m.r. analysis showed this to contain (3g) and (4g) (5 : 1), with m.p. range of 240–261° after recrystallization from ethanol (Found: C, 64·4; H, 3·1; N, 10·3. $C_{15}H_8N_2O_2S$ requires C, 64·3; H, 2·9; N, 10·0%).

(B) The conditions in polyphosphoric acid were as for (4a) and gave a 75% yield of a mixture of (4g) and (3g) (3 : 1) as a green solid, m.p. 237–240°.

3-Phenylquinoxaline-5-carboxylic Acid

A mixture of (3g) and (4g) [5 : 1; from the acetic acid preparation (A) above] (0·05 g), sodium carbonate (0·1 g) and deactivated Raney nickel[25] (5 g, acetone-wet) in water (4 ml) was stirred vigorously and heated at 70° for 3 h. The catalyst was removed by filtration through Celite, the filtrate was acidified to pH 2 with concentrated hydrochloric acid and the solid which formed was filtered off. This was recrystallized from ethanol to give a little of the unchanged tetracycle, and removal of the ethanol from the filtrate gave the title product (0·015 g) as pale yellow needles, m.p. 206–208° (from methanol). ^{1}H n.m.r. δ 7·65–7·69, m, 4H; 7·97, t, 1H; 8·31–8·38, m, 4H; 9·74, s, H 2. ^{13}C n.m.r. δ 127·5, CH; 129·1, CH; 129·3, CH; 130·9, CH; 132·7, CH; 134·7, C; 138·3, C; 140·8, C; 144·4, CH; 150·1, C; 165·9, C. Electrospray mass spectrum: *m/z* 251 (M+1).

N-*Oxidation Procedure*

A sample of the acid (*c.* 0·08 g) was dissolved in hot glacial acetic acid (4 ml). Hydrogen peroxide solution (30% v/v; 1·25 ml) was added and the reaction mixture was heated under reflux for the time indicated below, when substantial separation of solid had occurred. The mixture was cooled, and the solid filtered off and analysed by n.m.r. The following results were obtained:

Acid	Time	Products
(3c)/(4c)	2 h	Mixture of the *N*-oxide of (4c) and unchanged (3c)
(3e)/(4e)	2 h	Mixture of the *N*-oxide of (4e) and unchanged (3e)
(4a)	2 h	*N*-oxide of (4a) as yellow needles, m.p. 269–270°
(3b)/(4b)	48 h	Mixture of the *N*-oxide of (4b) and unchanged (3b)

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