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Synthesis of Some 11*H*-Indeno[1,2-*b*]quinoxalin-11-ones

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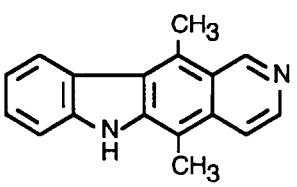
Abstract Condensation of substituted *o*-phenylene diamines and ninhydrins gave the title compounds The substituent orientation in the products was determined by ^{1}H NMR analysis of the chemical shifts brought about by N5-oxidation Reduction of the 8-nitro to 8-amino compound was achieved both with and without reduction of the carbonyl group Nitration of the 8-carboxylic acid occurred in the 2-position

INTRODUCTION

A number of polycyclic nitrogen heterocycles, for example, ellipticine (**1**) and batracylin (**2**) are of interest as anticancer compounds The title system is structurally similar to the latter and the parent compound is easily obtained by condensation of o-phenylenediamine (**3a**) and ninhydrin (**4a**) [1] Some other diamines have been investigated[2] but there is only one report[3] of a substituted o-phenylenediamine (the 3-methyl) being used to prepare a methyl substituted derivative



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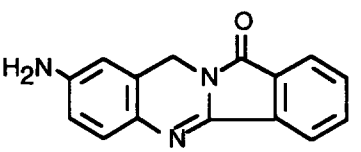

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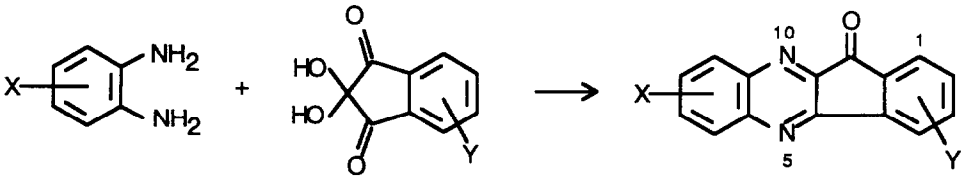
With a view to obtaining substituted analogs which might be further derivatized for anticancer testing, we report here an investigation of the condensation of other substituted o-phenylenediamines and ninhydrins When either the diamine or ninhydrin is unsymmetrically substituted, two isomers are possible Assignment of the product structures was a key requirement of the work, and a method to achieve this was devised

RESULTS AND DISCUSSION

Amino and carboxylic acid groups were the substituents of particular interest for further work Three relevant substituted phenylenediamines **3b-d** were available (Aldrich) and were each condensed with ninhydrin to give **5b, d, e** The complex aromatic signals in the 300 MHz ^{1}H NMR spectra could mostly be assigned and



3 **4** **5**

	X		Y
a	H	**a**	H
b	3-CH_3	**b**	5-CH_3
c	4-CO_2H		
d	4-NO_2		

	X	Y
a	H	H
b	6-CH_3	H
c	6-CO_2H	H
d	8-CO_2H	H
e	8-NO_2	H
f	8-NH_2	H
g	H	3-CH_3
h	H	3-CO_2H
i	8-CO_2H	2-NO_2
j	H	2-NO_2

in each case the spectrum was consistent with there being essentially one isomer produced Assignments were made by reference to the spectrum of 9-fluorenone,[4] with H4 shifted to lower field by the influence of N5 as seen in related compounds [5]

N-Oxidation was the key to assigning the isomeric structures This reaction had been reported for the parent compound **5a**[1] with the product presumed to be the N5-oxide[1] and there is some literature support for this orientation.[6] In our present work, NMR changes proved this orientation, N-oxidation produced a downfield shift of *c* 0 5 ppm for two one proton doublets, while the other signals were only slightly affected N5-Oxidation alone could account for this, the shifts being those for H4 and H6 N-Oxidation in quinoline, for example, results in a downfield shift of 0.7 ppm for the *peri* proton, H8 [7]

It is therefore reasonable to assume that N5-oxidation also occurs in the substituted tetracycles and so an analysis of the ^{1}H NMR shifts produced in the N-oxides allowed the isomer structure to be assigned For example, in the spectra of **5d** and its N5-oxide, the key difference was the downfield shifts of two doublets by *c* 0 4 ppm in the N-oxide These were the signals for H4 and H6 and, for H6 to be a doublet, the carboxyl must be attached to C8 The aromatic proton pattern in the ^{1}H NMR spectrum of the nitro compound **5e** was almost identical to that of **5d** and it was therefore concluded that this too was the 8-substituted compound

These orientations may be explained by a general mechanism where the first step is attack of the most nucleophilic amino group (in the two cases discussed above, the one *meta* to the electron withdrawing substituents) on the central (hydrated) carbonyl of the ninhydrin Cyclization then involves reaction of the other amino group with the more reactive 'outer' carbonyl of the ninhydrin moiety (both equivalent in unsubstituted ninhydrin) Thus the 8-carboxyl and 8-nitro compounds are the result.

Our structure for the methyl compound **5b** is different from that reported in the literature It was suggested [3] that the absence of a lanthanide shift effect on the ^{1}H NMR spectrum was due to steric hindrance to complexing of the carbonyl oxygen by an adjacent 9-methyl group However, this methyl group would also exert a steric effect on the adjacent amino group in the starting **3b** and the other amino group would be the better nucleophile Then, the general mechanism leads to the 6-methyl product **5b** The ^{1}H NMR data on N-oxidation supports this assignment, where a downfield shift of 0 4 ppm was observed for only *one* doublet This would be the signal for H4 which is only compatible with the methyl group being in the 6-position

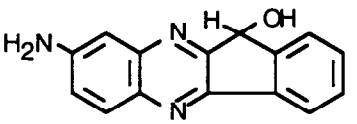
Many methods have been developed to synthesize ninhydrin[8] but adaptations to substituted compounds are multistep and not particularly attractive for preparing the derivatives of interest in this work We therefore limited this general approach to one compound, 5-methylninhydrin **4b** This was produced from 4-methylphthalic anhydride, converted through the diethyl ester by way of a Claisen condensation[9] to the indane-1,3-dione, which subsequently gave the ninhydrin by the method reported for 5-methoxyninhydrin,[10] in low overall yield Reaction of **4b** with o-phenylenediamine gave the one example of an isomeric product mixture, with the 2- and 3-methyl compounds being formed in a ratio of *c* 1 2 This result is explicable in terms of the general mechanism The 'outer' carbonyls in the intermediate are *meta* and *para* to the methyl substituent The *meta* carbonyl would be more electrophilic, leading to the preferred 3-methyl product. The difference in effect of *para* and *meta* methyl groups is not sufficient, however, to prevent formation of a significant amount of the isomeric 2-methyl product

N-Oxidation was again most helpful The H6 signal for each N-oxide was equally shifted downfield to appear as a multiplet but, similarly shifted and distinguishable were a singlet (major product, H4 of 3-methyl) and a doublet (minor product, H4 of 2-methyl) Recrystallization readily gave the pure 3-methyl isomer **5g**

For a nitro substituent in this ring, it was decided to nitrate a preformed tetracycle rather than prepare a nitroninhydrin Preliminary experiments on **5a** indicated that both benzenoid rings were of similar reactivity and a mixture of products resulted The 8-carboxy compound **5d**, however, did undergo nitration exclusively in the other ring and a good yield of the 2-nitrocompound **5i** was obtained (the 2- or 3-orientation was evident from ^{1}H NMR and the 2-product was assigned by analogy with nitration of 9-fluorenone[11]) Then, thermal decarboxylation of **5i** was achieved by way of the silver salt, though **5j** was obtained only in low yield

The methyl substituted compounds were prepared as entry points to carboxylic acids Various oxidations were investigated and a chromium acetate method[12] was successful and used without modification to prepare **5c** (62%) and **5h** (81%)

Nitro groups can be reduced in the presence of ketonic functions, as discussed for the nitroacetophenones [13] This proved to be difficult with the present compounds, probably because the first formed product was significantly more soluble than the reactant in all conditions, which aided further reduction to an aminoalcohol Thus, catalytic hydrogenation of **5e** over Adams' catalyst gave a good conversion to **6**



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An alternative hydrogenation[14] using 10% palladium/charcoal as catalyst in refluxing ethanol with cyclohexene as the hydrogen source produced an interesting result, and ultimate success A drawback of the method is the large amount of catalyst initially required but it was stated that the same catalyst could be reused a number of times With **5e**, it was found that reaction for 2h with fresh catalyst again produced **6** but subsequent runs reusing the same catalyst then gave the desired **5f** in good yield Some beneficial poisoning of the catalyst evidently occurs in the first use and the activity is reduced so that carbonyl reduction is significantly slowed relative to that of the nitro group Since preliminary anticancer screening of **5f**[15] showed very low activity, no reduction studies were carried out on **5j**

EXPERIMENTAL

^{1}H NMR spectra were recorded at 300 MHz, in $(CD_3)_2SO$ unless otherwise stated

5-Methylninhydrin (4b). Pyridine (3 3 g) was added to a solution of 5-methylindan-1,3-dione[9] (2 2 g) in dioxan (80 ml) at <15°C and then bromine (4 8 g) was slowly added whilst maintaining the temperature at <15°C The mixture was then stirred at room temperature for 2h and poured onto ice to give 2,2-dibromo-5-methylindan-1,3-dione (3 3 g, 75%), m p. 170°C

Dimethyl sulfoxide (24 ml) was added to a solution of this compound (2.8 g) in toluene (20 ml) at 100°C and the solution was kept at 100°C for 3h Water was added to the cooled solution which was then extracted with light petroleum (b p 40-70°C) (2 x 20 ml) The aqueous material was extracted with ethyl acetate (3 x 20 ml) and the combined extracts were washed with a little water, dried and the solvent removed to give the ninhydrin as an off-white solid (1 1 g, 65%) m p 170-172°C (turns red at 120-140°C) ^{1}H NMR (90 MHz, $CDCl_3$) δ 2 58, s, CH_3, 7 8, d, *J* 8 Hz, H-6, 7 86, s, H 4, 8 0, d, H-7

11*H*-indeno[1,2-*b*]quinoxalin-11-one (5a). Prepared according to the literature[1] in 85% yield as green needles, m p 217-219°C (lit[1] m p 218-219°C) ^{1}H NMR δ 7 80, t, *J* 7 5 Hz, H-2, 7 90-8 04, m, H-1,3,7,8, 8.15-8 28, d+d+d, H-4,6,9

11*H*-11-Oxoindeno[1,2-*b*]quinoxaline-8-carboxylic acid (5d) 3,4-Diaminobenzoic acid (0 85 g) and ninhydrin (1 0 g), each dissolved in warm acetic acid/water (4 1, 5 ml), were mixed, and the solution was heated and stirred for 5 min., then cooled and the solid which formed was filtered off and recrystallized from ethanol to give the product as yellow needles (1 3 g, 84%), m p >320°C ^{1}H NMR δ 7 76, t, *J* 7.1 Hz, H-2, 7 88-7 93, m, H-1,3, 8 13, d, *J* 7 2 Hz, H-4, 8 22, d, *J* 8 6 Hz, H-6, 8 35, dd, *J* 8 6,1 8 Hz, H-7, 8 64, d, *J* 1 8 Hz, H-9 Found C, 69 3, H, 3 2, N, 10 3% Calcd for $C_{16}H_8N_2O_3$ C, 69 5, H, 2 9, N, 10 2%

11*H*-6-Methylindeno[1,2-*b*]quinoxalin-11-one (5b) This was prepared in 75% yield from 2,3-diaminotoluene and ninhydrin, as for **5d**, but with ethanol as the reaction solvent, and had m.p 222-224°C (from acetone) (lit.[3]—assigned as the 9-methyl isomer—m p 224-224 5°C) ^{1}H NMR δ 2 86, s, CH_3, 7 68-7 80, m, 3H, 7 85-7 90, m, 2H, 7 99+8 08, d+d, *J* 8 1 Hz, H-4,9

11*H*-3-Methylindeno[1,2-*b*]quinoxalin-11-one (5g) This was prepared from o-phenylenediamine and 5-methylninhydrin, as for **5d**, but with ethanol as the reaction solvent. The crude product (81%) was a mixture of 2- and 3-methyl isomers Recrystallization from acetone gave the 3-methyl compound, m p 260-262°C ^{1}H NMR δ 2 54, s, CH_3, 7 63, d, *J* 7 5 Hz, H-2, 7 89, d, *J* 7 5 Hz, H-1, 7 92-8 05, m, H-7,8, 8 04, s, H-4, 8 23+8 28, d+d, *J* 7 8 Hz, H-6,9 Found C, 77 7, H, 4 2, N, 11 3% Calcd for $C_{16}H_8N_2O_3$ C, 78 0, H, 4 1, N, 11 4%

11*H*-8-Nitroindeno[1,2-*b*]quinoxalin-11-one (5e) This was prepared in 61% yield from 4-nitro-o-phenylenediamine and ninhydrin as red needles, m p 220-221°C (from ethane-1,2-diol) ^{1}H NMR δ 7 80, t, *J* 7 5 Hz, H-2, 7 91-8 00, m, H-1,3, 8 19, d, *J* 8 1 Hz, H-4, 8 34, d, *J* 8 8 Hz, H-6, 8 60, dd, *J* 8 8,2 0 Hz, H-7, 8 96, d, *J* 2 0 Hz, H-9 Found C, 65 0, H, 2 7, N, 15.7% Calcd for $C_{15}H_7N_3O_3$ C, 65 0, H, 2 6, N, 15 2%

11*H*-11-Oxoindeno[1,2-*b*]quinoxaline-6-carboxylic acid (5c) Concentrated sulfuric acid (3 ml) was added, dropwise and with stirring, to a mixture of compound **5b** (0 13 g), acetic anhydride (3 ml) and acetic acid

(10 ml) Chromium trioxide (1 0 g) was added and the mixture was stirred at room temperature for 0 5h and then poured onto ice The solid which formed was filtered off, recrystallized from ethane-1,2-diol and washed with ether to give the acid (0 1 g, 69%) as yellow needles, m p. >300°C. ^{1}H NMR δ 7.74, t, *J* 7 3 Hz, H-2, 7 85-7 95, m, H-1,3,8, 8 09, d, *J* 7.9 Hz, H-4(9), 8 16, d, *J* 8 0 Hz, H-9(4), 8 28, d, *J* 8 3 Hz, H-7 Found C, 69 6, H, 3.0, N, 10 2% Calcd for $C_{16}H_8N_2O_3$ C, 69 5, H, 2 9, N, 10 1%

11*H*-11-Oxoindeno[1,2-*b*]quinoxaline-3-carboxylic acid (5h) This was prepared in 75% yield by oxidation of **5g** as for **5c** and obtained as yellow needles, m p >300°C (from ethanol/water) ^{1}H NMR δ 7 95-8 13, m, 3H, 8 25-8 38, m, 3H, 8.59, s, H-4 Found C, 65 8, H, 3 8, N, 9 4% Calcd for $C_{16}H_8N_2O_3$ H_2O C, 65 3, H, 3 4, N, 9 5%

11*H*-2-Nitro-11-oxoindeno[1,2-*b*]quinoxaline-8-carboxylic acid (5i) Compound **5d** (0 2 g) was carefully added, with stirring, to a cooled mixture of concentrated nitric (1 ml) and sulfuric (2 ml) acids and the whole was heated at 50°C for 12h, then poured onto ice The solid which formed was filtered off, washed with water, dried and recrystallized from toluene to give the product (0 08 g, 34%) as yellow needles, m p >300°C(dec) ^{1}H NMR δ 8 28-8 43, m, 3H, 8 53, d, *J* 1 8 Hz, H-1, 8 65-8 72, m, H-3,9 Found C, 60 1, H, 2 2, N, 13 1% Calcd for $C_{16}H_7N_3O_5$ C, 59 8, H, 2 2, N, 13 1%

Reduction of 11*H*-8-Nitroindeno[1,2-*b*]quinoxalin-11-one (5e) A mixture of **5e** (0 25 g), palladium on carbon (0 5 g, 10%), cyclohexene (0 4 g) and ethanol (20 ml) was refluxed vigorously for 2h, filtered while hot and the solvent removed from the filtrate under vacuum to give the crude product as a yellow fluorescent solid (0 17 g, 76%) This was recrystallized from ethanol to give needles of **11*H*-8-amino indeno[1,2-*b*]quinoxalin-11-ol (6)**, m p 265-266°C. ^{1}H NMR δ 5 63, d, *J* 8.3 Hz, CHOH, 6 15, s, NH_2, 6 30, d, *J* 8 3 Hz, CHOH, 7 12, d, *J* 2 1 Hz, H-9, 7 30, dd, *J* 8 3,2 1 Hz, H-7, 7 58-7 63, m, H-1,2, 7 82, m, H-3, 7 88, d, *J* 8 3 Hz, H-6, 8 02, m, H-4 IR (KBr) complex 3500-3000 cm^{-1}, no C=O Found C, 67 3, H, 4 8, N, 15 7% Calcd for $C_{15}H_{11}N_3O$ H_2O C, 67 4, H, 4 9, N, 15 7%

The procedure was repeated with four further batches of **5e**, reusing the same catalyst each time, to give a total of 0 71g (80 %) of **11*H*-8-aminoindeno[1,2-*b*] quinoxalin-11-one (5f)** as a red-brown solid, m p 264-266°C (from toluene) Satisfactory microanalysis figures were not obtained ^{1}H NMR δ 6 37, s, NH_2, 7 12, d, *J* 2 5 Hz, H-9, 7 37, dd, *J* 8 9,2 5 Hz, H-7, 7 65, t, *J* 7 4 Hz, H-2, 7 84-7 91, m, H-1,3,6, 7 97, d, *J* 7 9 Hz, H-4 IR (KBr) 1725 (C=O) cm^{-1}

11*H*-2-Nitroindeno[1,2-*b*]quinoxalin-11-one (5j) The nitroacid **5i** (1 3 g) was dissolved in warm aqueous ammonia (15 ml 30% ammonia and 30 ml water) and to this was added a solution of silver nitrate (1 4 g) in water (30 ml) The silver salt which precipitated out was filtered off, washed with water and dried at 170°C This salt (1 6 g) was stirred and refluxed with diphenyl ether (15 ml) for 36 h, cooled, diluted with light petroleum, and the solid which separated was filtered off This was extracted (Sohxlet) with ethanol and the ethanol evaporated to give 0 2 g of crude product Column chromatography [silica, ethyl acetate/light petroleum (b p 60-80°C) (1 3)] gave the yellow product (0 11 g, 10%), R_f = 0 4, m p 266-268°C (from ethyl acetate) ^{1}H NMR δ 7 83-7 95, m, H-7,8, 8 20, dd, *J* 8 5,1 3 Hz, H-6(9), 8 28-8 34, m, H-4,9(6), 8 64, dd, *J* 8 2,2 2 Hz, H-3, 8 72, d, *J* 2 0 Hz, H-1 Found C, 64 8, H, 2 4, N, 14 9% Calcd for $C_{15}H_7N_3O_3$ C, 65 0, H, 2 6, N, 15 2%

Preparation of N5-oxides. A suspension of the heterocycle (0.1 g) in acetic acid (5 ml) and 30% hydrogen peroxide (1 5 ml) was heated and stirred under the conditions listed below The solid present in the cooled mixture was filtered off and washed with water Further purification was not undertaken and the ^{1}H NMR

spectra were recorded on these samples

5a N5-oxide (60°C, 18h), orange needles, m p 268-271°C(dec) [lit.[1] m p 271°C(dec)] ^{1}H NMR δ 7 80, t, *J* 7 8 Hz, H-2, 7 95-8 08, m, H-1,3,7,8, 8 38, m, H-9, 8 62-8 66, m, H-4,6

5b N5-oxide. (80°C, 48h with more hydrogen peroxide added every 12h) The solution was brought to pH 5-6 to liberate the product as gold needles, m p 226-230°C. ^{1}H NMR δ 2 87, s, CH_3, 7 75-7 81, m, H-2,7, 7 89-7 97, m, H-1,3,8, 8 14, d, *J* 7 6 Hz, H-9, 8 39, d, *J* 8 5 Hz, H-4

5d N5-oxide (100°C, 96h with more hydrogen peroxide added every 12h.), orange needles, m p >300°C ^{1}H NMR δ 7 72, t, *J* 7 5 Hz, H-2, 7 85-7 95, m, H-1,3, 8 35, d, *J* 8 9 Hz, H-7, 8 55, d, *J* 7 5 Hz, H-4, 8 60, d, *J* 8 9 Hz, H-6, 8 66, s, H-9

5g N5-oxide (c 2 1 mixture with the 2-methyl isomer) (80°C, 48h with more hydrogen peroxide added every 12h), orange needles, m.p 214-218°C ^{1}H NMR δ 2 54, s, CH_3(both), 7.58, d, *J* 7 8 Hz, H-2(3-Me), 7 72, d, *J* 7 8 Hz, H-3(2-Me), 7 80, s, H-1(2-Me), 7 85, d, *J* 7 8 Hz, H-1(3-Me), 7 98-8 05, m, H-7,8(both), 8 32-8 37, m, H-9(both), 8 42, s, H-4(3-Me), 8 46, d, *J* 7 8 Hz, H-4(2-Me), 8 55-8 61, m, H-6(both).

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