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Synthesis of Indoles *via* Ring Closure of 2-Alkylnitroaniline Derivatives.

Jan Bergman* and Peter Sand
Royal Institute of Technology, Department of Organic Chemistry
S-100 44 Stockholm,SWEDEN.

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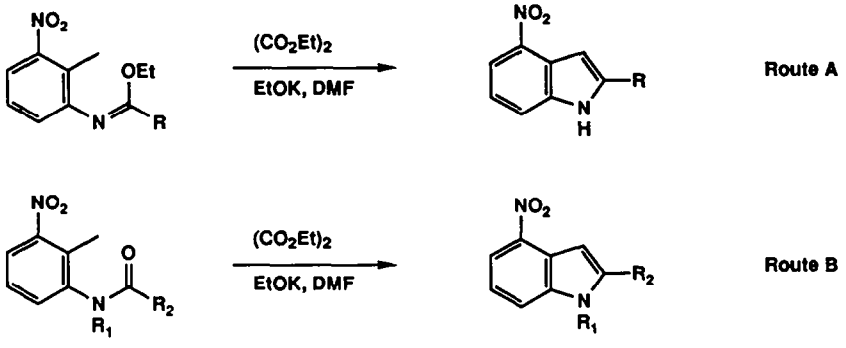
Abstract: A variety of nitroindoles have been prepared from imidate, amidine, and *sec*–anilide derivatives of 2-alkyl-3- or 5-nitroanilines by a base-induced cyclization promoted by dialkyl oxalates. It is shown that essentially the same procedure also can be used to synthesize the corresponding nitroindole-3-glyoxylates in one simple operation. The synthetic potential is discussed and a mechanism is proposed.

Introduction

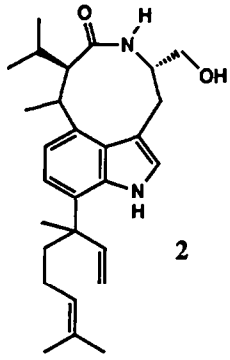
Alkyl-3-nitroaniline derivatives can readily be cyclized[1] (Scheme 1) to the corresponding 4-nitroindoles in a reaction promoted by dialkyl oxalates under basic conditions at room temperature.



Scheme 1

As the yields are high and the procedure is simple, this route is an interesting alternative to the Leimgruber-Batcho procedure[2-4] for the synthesis of 4-nitroindoles, which are of considerable interest as intermediates for the preparation of other simple 4-substituted indoles[5] and should (*cf* ref. 6) be useful precursors for more complex indoles such as chuongxinmycin (1), lyngbyatoxin (2), and the mitomycins (3).

1



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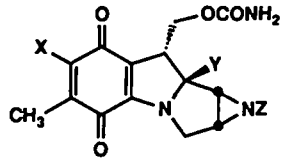
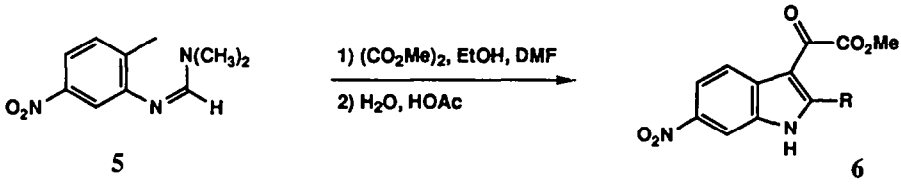


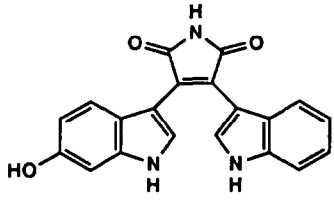
3

Indole-3-glyoxylates are, depending upon the oxalate concentration, formed as by-products in varying yields in most reactions and became particularly prominent when 3-methyl-5-nitroanilines are used as starting materials. In the latter case (Scheme 2) even an equimolar amount of oxalate resulted in a good yield of the glyoxylate (**6**), which is an interesting precursor[7] for the synthesis of certain unsymmetrically substituted alkaloids,[8,9] such as arcyriarubin B (**4**).



5 6

Scheme 2



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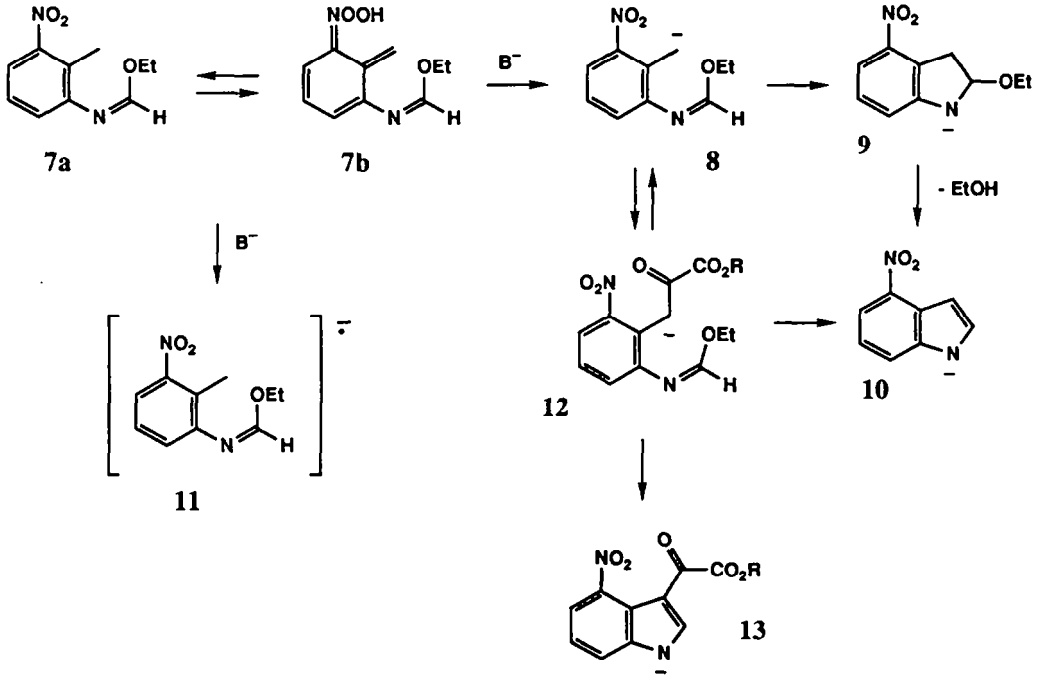
Results and Discussion

Obviously, the ring closure reactions shown in Scheme 1 and Table 1 can be considered as special cases of the Madelung reaction,[10] *ie* the intramolecular cyclization of 2-alkylanilides in the presence of bases like alkoxides and amides at elevated temperatures (200-400°C).[11] The smoothness (25°C) of the new procedure is due to the presence of the strongly electron

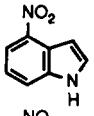
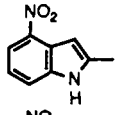
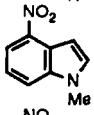
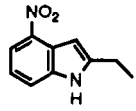
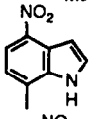
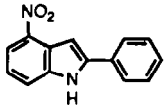
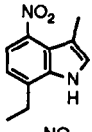
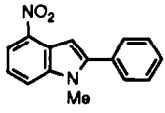
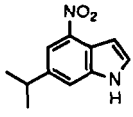
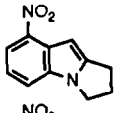
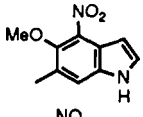
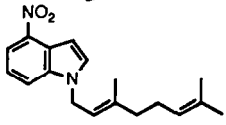
withdrawing nitro group as well as a reasonably good electrophile (imidate, *sec*-amide or amidine). Such a facilitating effect on the cyclization by a suitable electron withdrawing group has been known at least since 1950, when Robinson[12] cyclized 4,6-dinitro-2-nitromethylacetanilide to 2-methyl-3,5,7-trinitroindole by a short (5 minutes) reflux period in acetic anhydride. More recent examples are due to Reinhoudt,[13-15] who found that appropriate phenylacetonitriles, *eg* 4,5-dimethoxy-2-(2-oxo-1-piperidinyl)-phenylacetonitrile, could be cyclized to the corresponding indoles (in the example a 6,7,8,9-tetrahydropyrido[1,2-a]indole) with NaH in toluene. Further examples of the Madelung-type cyclizations relevant to the present study have been provided by Hirsch *et al*[16] who found that *eg* dimethyl 2-(2-nitrobenzylideneamino)-phenylmalonate could be cyclized to the corresponding indoline under mild conditions (25°C, t-BuOK in DMSO). Recently Makosza[17,18] showed that imidates of 2-aminobenzylarylsulfones can be cyclized to 3-arylsulfonylindoles by the interaction of sodium hydroxide in DMSO at room temperature.

Even moderately strong bases, such as alkoxides, should be able to abstract a benzylic proton from **7a** (or perhaps more likely[1] from the much more acidic[19] aci-nitro tautomer **7b**), yielding[20-24] the anion **8** (Scheme 3). A competing reaction would be the formation of the radical anion **11**. Now, if the imidate **7a** is treated with alkoxide in the absence of an oxalate, no indolization occurs. Instead, a complex mixture of so called Green compounds[25a] and reduced compounds[25b] is formed.



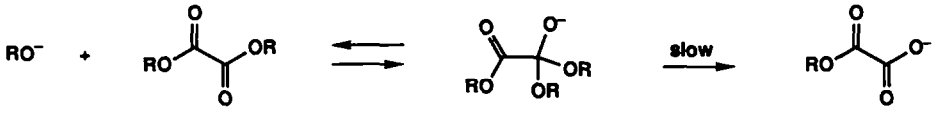
Scheme 3

Table 1

Compound	Mp (°C)	Yield (%)	Compound	Mp (°C)	Yield (%)
	204.5	71		192-4	40
	112-6	64		149-50	55
	161-5	51		203-6	75
	134-6	99+		126-7	69
	127-9	96		133-4	80
	70-4	89		oil	51
	194-5	95			

What then is the role of the oxalate? Initially[1] we believed that the anion **8** was captured by the oxalate yielding a glyoxylate anion, *ie* similar to the classical (but still unproven) mechanism of the Reissert reaction[26]. The anion **12** could be prepared independently and characterized as a potassium salt and cyclized to **10** in 70% yield (and with **13** as a side product) in dimethylformamide at 25°C. Hence, the route **8** → **12** → **10** is operative.In a separate experiment it was established that **13** does not undergo a base-induced cleavage[27] to the indole **10** under the relevant conditions. It is therefore suggested that a 4-center reaction is involved in the elimination of dialkyl oxalate during the transformation **12** → **10**. From the experiment just discussed it is obvious that at least part of the indolization takes place *via* **12**. However, one would expect a cyclization *via* **9** to be faster and some further experiments involving 3-nitro-2-ethylimidates (*vide infra*) which smoothly gave high yields of nitroindoles, rendered further

support for this view.The beneficial role played by the oxalate then seems to be as a quencher of the radical anion **11** in much the same way as the radical anion from 2-nitrotoluene is quenched by formaldehyde[23] as outlined in Scheme 5a. In Scheme 3, the base (which is added in the form of potassium ethoxide or *tert*-butoxide) is formulated as B^-, because the added base reacts rapidly with the oxalic ester present to establish the equilibrium shown in Scheme 4. At present, we do not know which of the two anions that abstracts the proton (Scheme 3) or if both do. The complex anion **14** slowly decomposes to monoalkyl oxalate salt as noted already by Adickes.[28]



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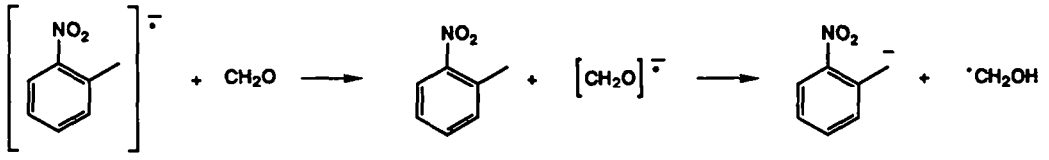
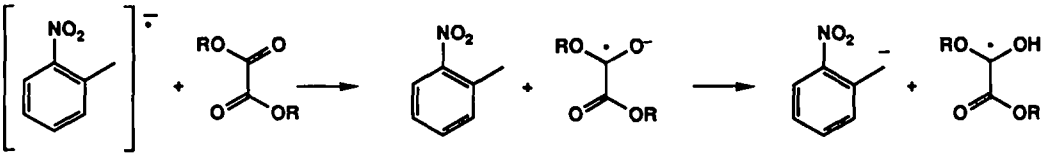
Scheme 4



Scheme 5a



Scheme 5b

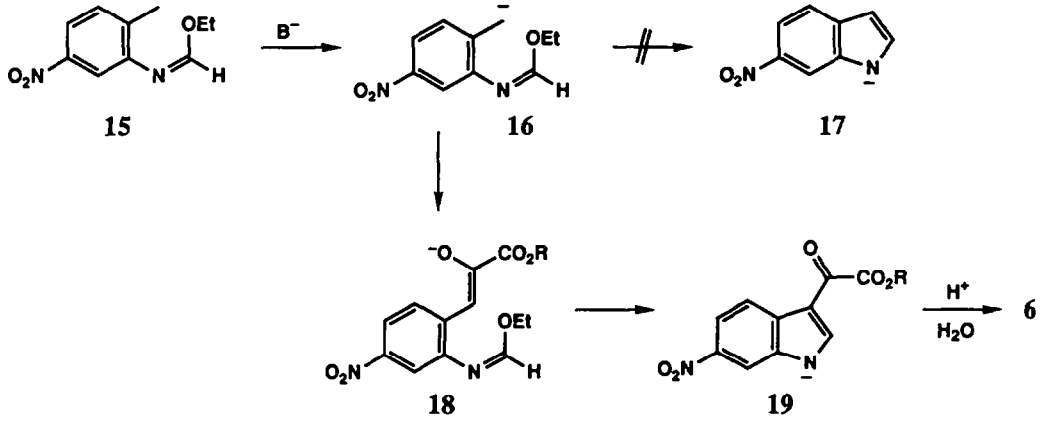
The failure to synthesize ethyl 1-methyl-4-nitroindole-2-carboxylate from ethyl *N*–methyl-*N*–(2-methyl-3-nitrophenyl)oxalmonoamide clearly demonstrates that the cyclization step is not an ordinary nucleophilic attack (if so, the oxalmonoamide should most certainly have been electrophilically powerful enough). Furthermore, this result cannot be explained by steric hindrance since even the benzimidate does cyclize.

Therefore the electrophilicity of the oxalamide group must change at some stage of the reaction. Such a change can occur in three ways: nucleophilic attack on the amide carbon (other than cyclization), on the ester carbon, or electron abstraction (1-electron reduction). The first two possibilities can be ruled out since they would have resulted in reaction products which never were observed.

In the light of the above mentioned observations it is tempting to explain the failure of the oxalamide to cyclize through an intramolecular quenching.

As discussed above the preferred reaction temperature is ca. 25°C. At higher temperatures side reactions such as the formation of bibenzyls are disturbing. Another side reaction observed at ca. 100°C, is oxalate induced alkylation of the indole anion.[29,30] This type of alkylation has been shown to be of preparative value in many systems.

The synthetic procedure can be further simplified by conducting the reactions in one pot without any significant decrease in yields. The aniline is heated with a slight excess of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid for ca 1h and the cyclization reagent is added to the imidate ester formed. The resultant red anion of the 4-nitroindole can then be titrated with the desired alkylating agent or quenched.

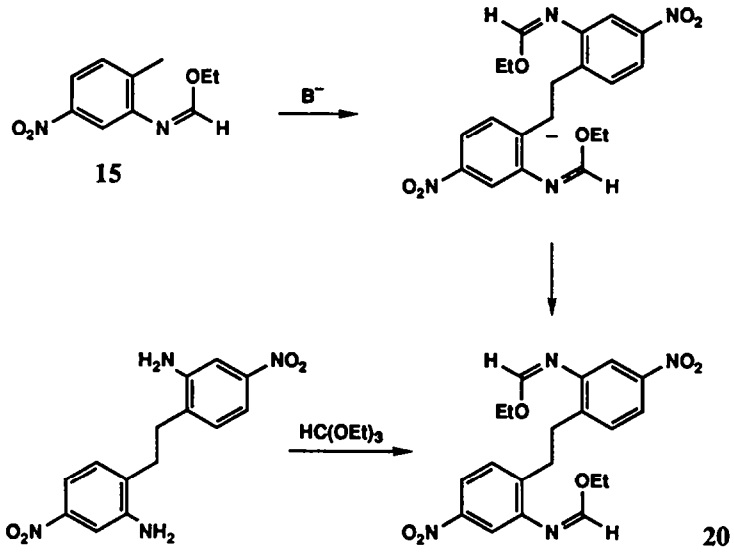


Scheme 6

After having completed the studies summarized in Table 1 we turned our attention to the possibility of preparing 6-nitroindoles in a similar way (As expected, neither 5- nor 7-nitroindoles could be synthesized using the title method). Thus, the imidate **15** was treated with alkoxide and oxalate at room temperature (Scheme 6). However, the anion **17** of 6-nitroindole, which also was prepared independently, was not formed.Instead the main product was the anion **18** which at higher temperatures cyclized to the anion **19**. The ready attack of oxalate on the anion **16** (as compared with the anion **8**) can be explained in terms of diminished steric hindrance. The inferred non-planarity of the *aci*-nitro tautomers of the *ortho*-substituted rings most likely plays a vital role in this context.[57] The anion **18** could be independently prepared and characterized but failed (in contrast to its isomer **12**) to cyclize to **17**.

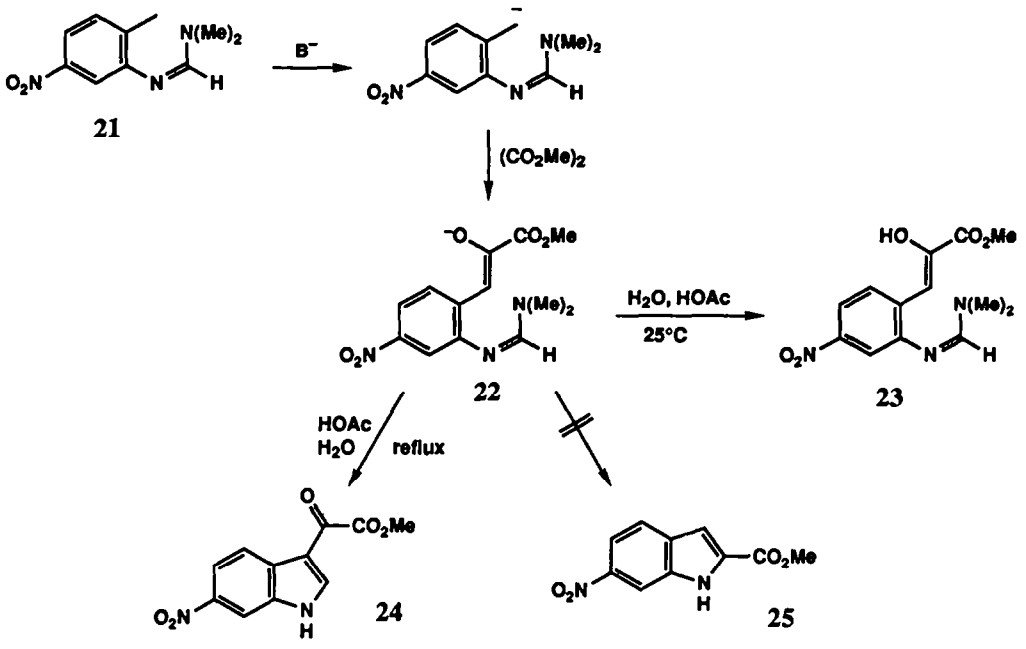
The diminished steric hindrance is also illustrated by the relatively high yield (ca. 15%) of the side product **20**, which is formed by a coupling reaction (Scheme 7).[21,31] The imidate groups in this compound are surprisingly insensitive to hydrolysis and survived the slightly acidic

(acetic acid) work-up. The structure of **20** was proven by an independent synthesis outlined in Scheme 7. 2,2'-Diamino-4,4'-dinitrobibenzyl was obtained by nitration of 2,2'-diaminobibenzyl which in turn was obtained in high purity and in a high yield by reduction of 2,2'-dinitrobibenzyl with hydrazine promoted[32-33] by FeOOH. During the preparation of 2,2'-dinitrobibenzyl by the classical Lapworth procedure[34] Yanagida's observations[3] that addition of sterically hindered oxalates or formates are beneficial for the yield, were confirmed. We believe that the esters, in this case too, act *via* quenching of the radical anions and the reaction of the anion with the esters is just an undesired side reaction (*cf* Scheme 3).



Scheme 7

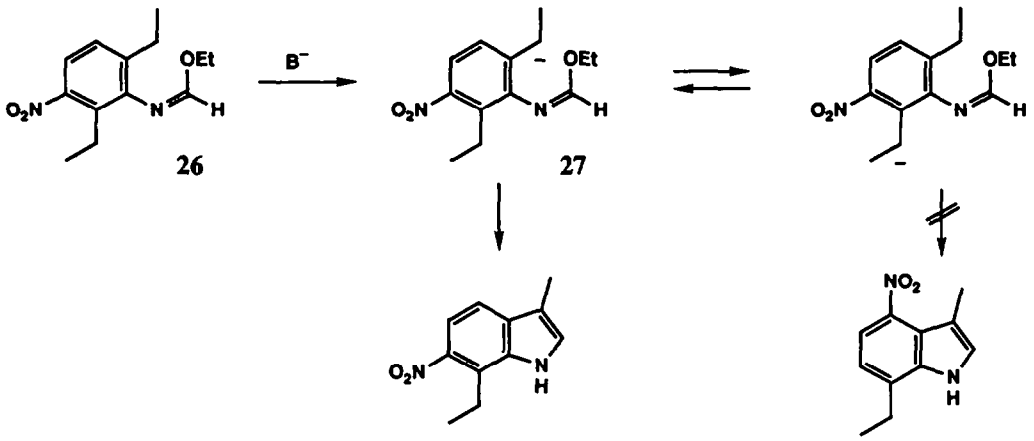
6-Nitroindole-3-glyoxylates are interesting starting materials for various alkaloids such as arcyriarubin B (**4**) but also for 6-azidoindole-3-acetic acid, which is of interest as a fluorescent photoaffinity labelling agent[35] which binds irreversibly to an auxin sensitive site. For this reason also the formamidine **21** (readily available from 5-nitro-2-methylaniline and DMF-$POCl_3$) was tried as a starting material.[36] Now the coupling reaction was greatly suppressed but the anion formed (**22**) did not cyclize (Scheme 8).



Scheme 8

The reaction mixture was therefore made acidic (aqueous acetic acid) and heated which resulted in direct precipitation of the desired compound (**24**) in high yield. In this procedure formation of methyl 6-nitroindole-2-carboxylate was not observed indicating that the isolable formamidine **23** is relatively stable towards hydrolysis. On the other hand when a reaction mixture containing imidate **18** was treated in the same way with hot aqueous acetic acid a mixture of methyl 6-nitroindole-3-glyoxylate (**24**) and methyl 6-nitroindole-2-carboxylate (**25**) was obtained. Similar results have previously been observed during cyclizations of 4-ethoxymethyleneamino-3-methoxy-pyridazinylpyruvate-1-oxides and some related compounds.[37] On heating (ca. 150°C) the red formamidine **23** cyclized, without melting and with evolution of dimethylamine, to methyl 6-nitroindole-3-glyoxylate (**24**).

6-Nitroindole-3-glyoxylates have previously been prepared[38,39] by nitration of indole-3-glyoxylates to give a mixture of 4- and 6-nitroindole-3-glyoxylates. This experiment has now been repeated and the mixture obtained has been separated. The pure isomers obtained agreed completely with those obtained with the new procedure. Hydrolysis of methyl 6-nitroindole-3-glyoxylate gave the corresponding acid which could readily be decarboxylated to 6-nitroindole-3-carboxaldehyde. 4-Nitro-3-carboxaldehyde could be similarly prepared.



Scheme 9

Steric factors at play are nicely illustrated by the example given in Scheme 9. In this case the sterically more hindered anion **27** (as compared to **16**) was not attacked by the oxalate and the anion of 7-ethyl-3-methyl-6-nitroindole was formed in excellent yield.[56] The isomer, 7–ethyl-3-methyl-4-nitroindole was not formed. Since the NMR data could not directly distinguish between the two isomers the structure was determined[40] by X-ray crystallography which showed (Figure 1) that the indole indeed has the nitro group in the 6-position.

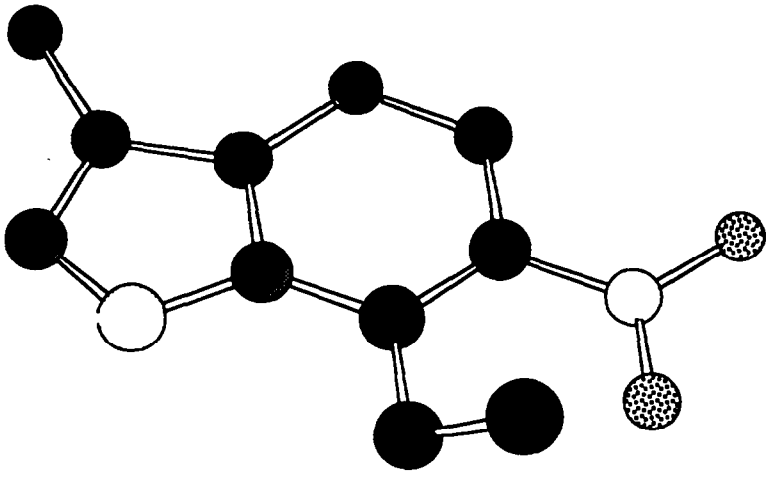
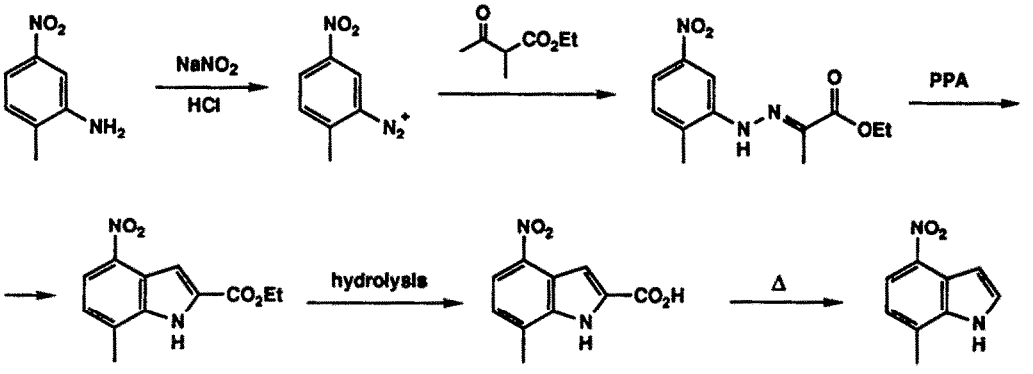


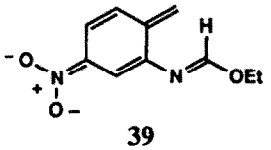
Figure 1 Chem3D drawing of 7-ethyl-3-methyl-6-nitroindole.

When an imidate prepared from 2,6-dimethyl-5-nitroaniline was used as starting material the yield was somewhat reduced as was the selectivity of the cyclization. The isomers 4-nitro-7-methylindole and 6-nitro-7-methylindole were obtained in the ratio 1:4. To distinguish between these two isomers the general approach[41] involving a Japp-Klingemann reaction given in Scheme 10 was utilized. After some investment in time and trouble 6-nitro-7-methylindole could be independently prepared (albeit in a low yield) and identified. The 4-nitro isomer had already been prepared by this route.[42,43] The final decarboxylation step was preferably performed with a neat melt as addition of solvents,such as quinoline, was detrimental to the yields.



Scheme 10

After having successfully prepared 7-ethyl-3-methyl-6-nitroindole and 6-nitro-7-methylindole we again turned our attention to the unsuccessful transformation **16** → **17** given in Scheme 6. However addition of sterically hindered oxalates such as diisopropyl oxalate as well as hindered formates to **16** under various basic conditions failed to give **17**. To account for this we suggest that the canonical resonance form (**39**) of the anion of **15** is relatively inert and hence dominant. The situation is completely different when a substituent is attached in the ortho position to the nitro group because now the nitro group in the anion is forced out of the plane of the phenyl ring.



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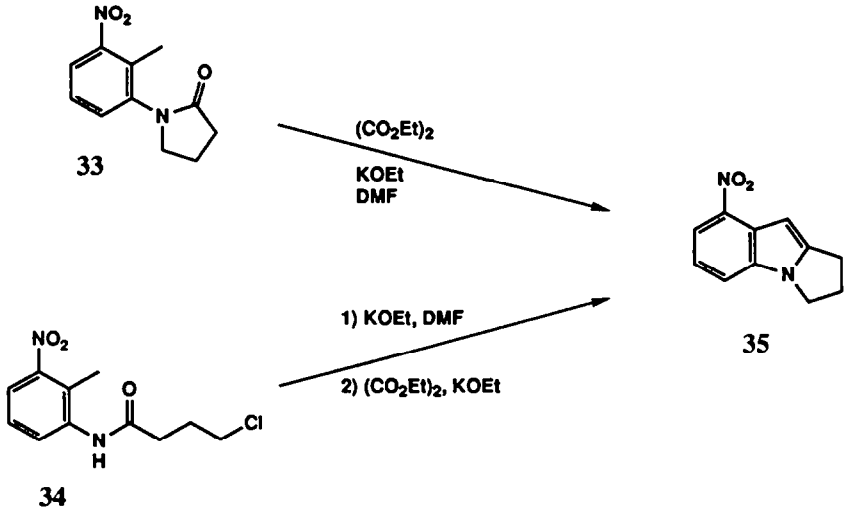
Further support for this steric effect includes the successful transformation of the 4,6-dibromo-derivative of **15** to the 5,7-dibromo-6-nitroindole in good yield. Also, 5,7-dibromo-4-nitroindole was prepared similarly in good yield. The latter two reactions also gave indications of the presence of a radical anion since, in both cases, small amounts of debrominated products

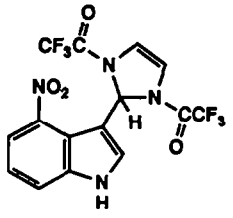
were found.At elevated temperatures the yields of debrominated products were comparable to the desired indoles. This hydrogen bromine exchange probably occurs *via* a bromide elimination of a brominated radical anion and the resulting phenyl radical abstracts a hydrogen atom from the solvent.

An interesting application of the new synthetic procedure is the cyclization of 1-(2-methyl-3-nitrophenyl)-2-pyrrolidone (**33**) to the pyrrolo[1,2-a]indole **35** depicted in Scheme 11. The reaction can also be conducted, with a slight reduction in yield, in one pot from the precursor of **35**, *ie* the nitroanilide **34**, thus providing a useful approach to synthesis of compounds in the mitomycin series (for other approaches see refs. 44-46).



Scheme 11

The 4-nitroindoles prepared were all surprisingly stable towards acids. Electrophilic reagents such as the Vilsmeier reagent[47,48] expectedly gave formylation in the 3-position in good yields. Even better yields were obtained by using a reagent composed of trifluoroacetic anhydride and imidazole for introduction of the one-carbon unit in the 3-position (*cf* ref 49). By the latter procedure compounds **36** and **37** were obtained in 92% and 99.8% yield respectively. Both compounds could readily be deprotected by alkaline hydrolysis. Reaction of 4-nitroindole with imidazole-acetic anhydride gave only *N*–acetyl-4-nitroindole. All indoles previously subjected[49] to these reaction conditions have given compounds of the type **38**. The outcome with 4-nitroindole is probably a consequence of the increased acidity of the proton in the 1-position. *N*–Acetyl-4-nitroindole underwent rapid hydrolysis even under mild alkaline conditions (*cf* ref. 50).



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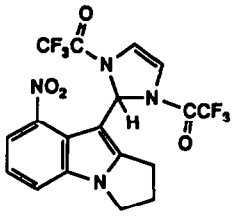
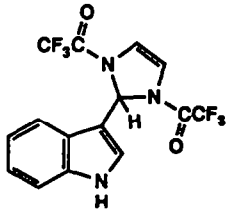


37



38

As mentioned above Robinson[12] cyclized 4,6-dinitromethylacetanilide to 2-methyl-3,5,7-trinitroindole by a short reflux period in acetic anhydride. However, all attempts to generate any kind of 4,6-dinitroindole from imidates or formamidines based on 3,5-dinitro-2-methylaniline, which is readily available by selective reduction[51] (Fe in AcOH) of 2,4,6-trinitrotoluene, failed. A possible explanation might be that the anions formed are relatively inert and that side reactions involving radical anions are totally dominating.

Finally, it should be noted that other means of preparation of nitroindoles, particularily 4-nitroindoles, *eg* the reductive cyclization of Somei *et al*[3] of a dinitrostyrene or the similar approach by Girgis *et al*,[52] are lengthy and/or involve tedious work-ups and above all, result in considerably lower yields.

Acknowledgements

We are indebted to Dr K. Törnroos for providing the X-ray crystallographic data and to Dr Lee Melhado, Urbana, Ill., for constructive discussions and for provision of information prior to publication. We also thank Hüls AG, Troisdorf, FRG and SSF Dottikon AG, Switzerland for generous gifts of orthoesters and nitroanilines respectively. The 2,4,6-trinitrotoluene was kindly provided by Dr L.Westfelt, Nobel Chemicals, Bofors, Sweden. The Swedish Natural Science Council is acknowledged for financial support (K-KU 1486-103).

Experimental

^{1}HNMR-spectra were obtained using a 60 MHz Varian EM360 or a Bruker 200MHz WP 200 spectrometer. IR spectra were obtained using a Pye-Unicam SP 1000 spectrometer. Mass spectra were recorded with an LKB 9000 mass spectrometer. The solvents used were dried over molecular sieves (4Å) for at least 4 days. Potassium ethoxide was purchased from Alfa Products, Inc. Other chemicals (except those stated in the acknowledgement) were purchased from Aldrich. Melting points are uncorrected. The limited availability of the necessary nitroanilines is a drawback of the procedure. To our knowledge only the parent compounds 2-methyl-3-nitroaniline and 2-methyl-5-nitroaniline are commercially available. We have therefore listed, in some cases improved, synthetic routes to nitroanilines (Scheme 11).

Ethyl 2-methyl-3-nitrophenylformimidate (**7a**).

2-Methyl-3-nitroaniline (15.2 g, 0.1 mol), triethyl orthoformate (20.0 g, 0.135 mol), and *p*–toluenesulfonic acid (0.172 g, 1 mmol) were heated together at 120°C until no more ethanol distilled off (ca. 1h). Vacuum distillation of the residue gave the imidate ester (19.6 g, 94%) as a light yellow, solidifying oil bp. 156-160°C/6 mm, mp. 57-58°C. ^{1}HNMR ($CDCl_3$) δ 1.40(3H, t, J=7.0Hz) 2.40(3H, s) 4.36(2H, q) 6.8-7.55(3H, m) 7.61(1H, s).

Ethyl 3-(2-ethoxymethyleneamino-6-nitrophenyl)-pyruvate potassium salt.

Potassium metal (0.47g, 12 mmol) was dissolved in absolute ethanol (3mL) under argon and excess ethanol was evaporated under reduced pressure and the residue dissolved in dry diethyl ether (70mL). After cooling of the solution to 10°C, diethyl oxalate (1.96 g, 20 mmol), and 30 seconds later ethyl 2-methyl-3-nitrophenyl-formimidate (2.08 g, 10mmol) in diethyl ether (30mL) were added. The solution turned deep red within 10 minutes of stirring and was then put in a refrigerator (<5°C) overnight. Filtration of the precipitate, still under argon, and several washings with dry ether gave dark red, highly hygroscopic crystals (2.22 g, 64%) mp. 170°C dec. IR (KBr) ν_{max} 2982(m), 1732(s), 1705(s), 1648(s), 1605(s), 1595(s), 1565(s), 1510(s), 1478(s), 1362(s), 1314(s), 1268(s), 1204(s), 1103(m), 1015(m), 939(m), 900(m), 857(m), 805(m), 773(m), 731(s) cm^{-1}. Efforts to obtain an ^{1}HNMR in $DMSO_{d6}$ resulted in a complex spectrum containing mainly the anions of 4-nitroindole and ethyl 4-nitroindole-3-glyoxylate. Attempts to isolate the conjugate acid of the title compound were unsuccessful.

Ethyl 2-methyl-5-nitrophenylformimidate

2-Methyl-5-nitroaniline (15.2 g, 0.1 mol), triethyl orthoformate (50.0 g, 0.34 mol), and *p*–toluenesulfonic acid (0.172 g, 1 mmol) were heated together at 130°C for 3h. Vacuum distillation gave the imidate ester fraction at 140-180°C/12mm as a light yellow, solidifying oil. Recrystallization from light petroleum gave white crystals (13.46 g, 65%) mp. 50-52°C. ^{1}HNMR ($CDCl_3$) δ 1.39(3H, t, J=7.5Hz) 2.27(3H, s) 4.30(2H, q) 7.18(1H, d, J=8.0Hz) 7.46(1H, d,

J=2.0Hz) 7.53(1H, s) 7.72(1H, dd).

Ethyl 3-(2-ethoxymethyleneamino-4-nitrophenyl)-pyruvate potassium salt.

The same procedure given above for the 6-nitroisomer was employed and resulted in a red, highly hygroscpoic powder (1.69 g, 49%) mp. 195°C dec. IR (KBr) ν_{max} 2980(m), 1728(m), 1640(s), 1610(s), 1519(m), 1346(m), 1313(m), 1180-1215(s), 1019(m), 900(m), 854(m), 835(m), 776(m), 741(m) cm^{-1}. Efforts to obtain an ^{1}HNMR in $DMSO_{d6}$ resulted in a complex spectrum whose components could not be identified. However no 6-nitroindole could be detected.

4-Nitroindole

Potassium ethoxide (8.4 g, 0.1 mol) was added under vigorous stirring and ice-cooling to a solution of diethyl oxalate (14.6 g, 0.1 mol) in 25 mL dry DMF. This solution was then poured into a solution of ethyl 2-methyl-3-nitrophenylformimidate (7a) (18.0 g, 87 mmol) in 80 mL dry DMF. The deep red solution was stirred for 2.5 h slightly above room temperature (30-40°C) and then poured into water. Filtration gave the crude product which was sublimed at 170°C/0.5 mm giving 10.8 g (77%) of yellow crystals, mp. 204-205°C (subl.). ^{1}HNMR ($DMSO_{d6}$) δ 3.18(1H, m) 6.6–6.75(1H, m) 6.95(1H, d, J=7 Hz) 7.25-7.75(3H, m).

1-Methyl-4-nitroindole.

2-Methyl-3-nitroaniline (1.52 g, 0.01 mol), trimethyl orthoformate (1.59 g, 0.015 mol), and *p*–toluenesulfonic acid (0.086 g, 0.5 mmol) in DMF (30mL) were heated at 100°C for 2h. A solution of dimethyl oxalate (1.77g, 0.015 mol) and potassium ethoxide (1.26g, 0.015 mol) in DMF (20mL) was then added and the reaction mixture was heated at reflux for 1h. It was then poured into water and the precipitate was collected giving the product (1.45 g, 76%) mp. 112-116°C. ^{1}HNMR ($CDCl_3$) δ 3.81(3H, s) 7.07-7.32(3H, m) 7.53(1H, d, J=7Hz) 8.07(1H, dd, J_1=7.5Hz, J_2=1Hz).

2,6-Dimethyl-3-nitroaniline.

2,6-Xylidine (12.1g, 0.1mol) was dissolved in conc. sulfuric acid (80mL). Fuming nitric acid (6.6g, 0.11 mol) was added dropwise keeping the temperature below 15°C. The reaction mixture was stirred for 10 minutes at room temperature and then poured into ice-water and neutralized with sodium hydroxide without exceeding 25°C. The precipitate was collected and recrystallized from methanol to give yellow crystals (11.0g, 66%) mp. 77-78°C. ^{1}HNMR ($CDCl_3$) δ 2.17(3H, s) 2.23(3H, s) 3.8(2H, s) 6.85(1H, d, J=8Hz) 7.07(1H, d).

Methyl *N*–(2,6-dimethyl-3-nitrophenyl)-formimidate.

2,6-Dimethyl-3-nitroaniline (8.4g, 0.05 mol) was dissolved in trimethyl orthoformate (180mL) after which a catalytic amount of *p*–toluenesulfonic acid was added. The reaction

mixture was heated at reflux for 30 minutes and then the solvent was removed under vacuum. Recrystallization of the residue from light petroleum gave the title product (8.3g, 80%) mp. 46-47°C. ^{1}HNMR ($CDCl_3$) δ 2.18(3H, s) 2.27(3H, s) 3.97(3H, s) 7.04(1H, d, J=8Hz) 7.44(1H, s) 7.47(1H, d).

7-Methyl-4-nitroindole and 7-methyl-6-nitroindole.

Potassium metal (0.56 g, 14 mmol) was dissolved in absolute ethanol (3.0 g, 65 mmol) and excess solvent was removed under vacuum. To this was added a solution of diethyl oxalate (2.19 g, 15 mmol) in dry DMF (20 mL). This solution was rapidly added to a solution of methyl *N*–(2,6-dimethyl-3-nitrophenyl)-formimidate (2.08g, 10mmol) in dry DMF (30 mL) and the reaction mixture was stirred at room temperature for 12 h and then poured onto water, filtered and dried. The crude product was chromatographed on silica (hexane/ethyl acetate 80/20) to give 7-methyl-4-nitroindole (0.89g, 51%) mp 173.5-174°C. ^{1}HNMR ($CDCl_3$) δ 2.61(3H, s) 7.07(1H, d, J=8Hz) 7.33(1H, m) 7.47(1H, m) 8.09(1H, d) 8.51(1H, br. s) and 7-methyl-6-nitroindole (0.22g, 13%) mp 170-171°C. ^{1}HNMR ($CDCl_3$) δ 2.79(3H, s) 6.65(1H, m) 7.48(1H, m) 7.53(1H, d, J=9Hz) 7.85(1H, d) 8.5(1H, br. s).

Ethyl *N*–(2-methyl-3-nitrophenyl)-acetimidate.

2-Methyl-3-nitroaniline (3.04g, 20mmol), triethyl orthoacetate (16.2g, 100mmol) and *p*–toluenesulfonic acid (0.172g, 1 mmol) were heated at ca. 120°C so that the ethanol formed distilled off (ca. 1h). The reaction mixture was then reduced under vacuum and the residue was recrystallized from light petroleum at -50°C to give the yellowish white acetimidate (3.26g, 73%) mp. 15-25°C. ^{1}HNMR ($CHCl_3$) δ 1.33(3H) t, J=7 Hz) 1.76(3H, s) 2.22(3H, s) 4.26(2H, q) 6.87(1H, dd, J_1=2Hz) 7.20(1H, dd, J_1=8Hz, J_2=7Hz) 7.50(1H, dd).

2-Methyl-4-nitroindole

Potassium metal (0.56 g, 14 mmol) was dissolved in absolute ethanol (3.0 g, 65 mmol) and excess solvent was removed under vacuum. To this was added a solution of diethyl oxalate (2.19 g, 15 mmol) in dry DMF (20 mL) and then a solution of ethyl *N*–(2-methyl-3-nitrophenyl)-acetimidate (2.22g, 10mmol) in dry DMF (20 mL) and after 36h at room temperature the reaction mixure was poured onto ice, filtered and sublimed at 150°C/0.1mm to give the title compound (0.47 g, 27 %) mp. 197-198 °C. ^{1}HNMR ($DMSO_{d6}$) δ 2.60(3H, s) 6.84(1H, s) 7.21(1H, dd) 7.77(1H, d, J=7Hz) 8.03(1H, d, J=8Hz).

Ethyl *N*–(2-methyl-3-nitrophenyl)propionimidate.

2-Methyl-3-nitroaniline (3.04g, 20mmol), triethyl orthopropionate (17.6g, 100mmol) and *p*–toluenesulfonic acid (0.172g, 1 mmol) were heated at ca. 120°C so that the ethanol formed distilled off (ca. 1h). The reaction mixture was then reduced under vacuum and the residue was recrystallized from light petroleum to give the grey-white propionimidate (4.22g, 89%) mp.

41–45°C. ^{1}HNMR $CHCl_3$) δ 1.06(3H, t, J=8 Hz) 1.34(3H, t, J=7 Hz) 2.04(2H, q) 2.23(3H, s) 4.22(2H, q) 6.79(1H, dd, J_1=7 Hz) 7.13(1H, dd) 7.42(1H, dd, J_1=7.5 Hz, J_2=2 Hz).

2-Ethyl-4-nitroindole.

Potassium metal (0.56 g, 14 mmol) was dissolved in absolute ethanol (3.0 g, 65 mmol) whereupon excess solvent was removed under vacuum. To this was added a solution of diethyloxalate (2.19 g, 15 mmol) in 20 mL dry DMF (20mL) and then a solution of ethyl *N*–(2-methyl-3-nitrophenyl)propionimidate (2.36g, 0.01mol) in dry DMF (20mL). After ca. 20h at room temperature the reaction mixure was poured onto ice, filtered and recrystallized from ethanol. A first crop gave ethyl 2-ethyl-4-nitroindol-3-glyoxylate (0.78g, 24%) mp. 151-153°C. ^{1}HNMR ($DMSO_{d6}$) δ 1.23(3H, t, J=8Hz) 1.32(3H, t, J=7Hz) 2.94(2H, q) 4.17(2H, q) 7.33(1H, dd) 7.87(1H, br. d, J=8Hz) 7.93(1H, br. d, J=8Hz). The mother liquor was filtered through silica (CH_2Cl_2) to give the yellow title compound (0.54g, 28 %) mp. 140-143°C. ^{1}HNMR ($DMSO_{d6}$) δ 1.36(3H, t, J=7Hz) 2.82(2H, q) 6.82(1H, br. s) 7.14(1H, dd) 7.73(1H, d, J=8Hz) 7.97(1H, d, J=8Hz).

4,6-Dibromo-2-methyl-3-nitroaniline.

Bromine (32g, 0.2 mol) was added to 2-methyl-3-nitroaniline (15.2g, 0.1mol) dissolved in acetic acid (150mL) and the reaction mixture was heated on a steam bath for 1h and then poured into water (500 mL). Filtration and recrystallization from methanol gave light yellow crystals (26g, 84%) mp. 101.5-102°C. ^{1}HNMR ($CDCl_3$) δ 2.08(3H, s) 4.3(2H, br. s) 7.39(1H, s).

Methyl *N*–(4,6-dibromo-2-methyl-3-nitrophenyl)formimidate.

4,6-Dibromo-2-methyl-3-nitroaniline (3.10g, 0.01mol) and *p*–toluenesulfonic acid (0.08g, 0.5mmol) were dissolved in triethyl orthoformate (30mL) and heated at 100°C for 20 minutes and then evaporated to dryness. Recrystallization of the residue from light petroleum/diethyl ether gave the formimidate (3.32g, 94%) mp. 101-102°C. ^{1}HNMR ($CDCl_3$) δ 2.12(3H, s) 4.01(3H, s) 7.53(1H, s) 7.68(1H, s).

5,7-Dibromo-4-nitroindole.

Potassium metal (0.56 g, 14 mmol) was dissolved in absolute ethanol (3.0 g, 65 mmol) whereupon excess solvent was removed under vacuum. To this was added a solution of diethyloxalate (2.19 g, 15 mmol) in 20 mL dry DMF and then a solution of methyl (2,4-dibromo-6-methyl-5-nitrophenyl)-formimidate (3.52 g, 10 mmol) in 20 mL dry DMF and the solution was stirred at room temperature for 24 h. The reaction mixure was then poured onto ice, filtered and recrystallized from ethanol to give the indole as light yellow crystals (2.99 g, 93 %) mp. 195-197 °C. ^{1}HNMR ($DMSO_{d6}$) δ 6.68(1H, d, J=3Hz) 7.67(1H, d) 7.82(1H, s).

2-Ethyl-5-nitroaniline.

2-Ethyl aniline (12.1g, 100mmol) was dissolved in concentrated sulfuric acid (50mL) and cooled to 0°C. Fuming nitric acid (9.3g, 150mmol) was added dropwise without exceeding 5°C. After the addition the reaction mixture was stirred 30 min. at room temperature and then poured onto ice water, carefully neutralized with sodium hydroxide and filtered. The crude product was recrystallized from light petroleum to give 10g (60%) yellow needles mp. 59-60°C. ^{1}HNMR ($CDCl_3$) δ 1.28(3H, t, J=7Hz) 2.56 (2H, q) 4.00(1H, br. s) 7.15(1H, d, J=8Hz) 7.47(1H, d, J=2Hz) 7.55(1H, dd).

Methyl *N*–(6-ethyl-3-nitrophenyl)-formimidate.

2-Ethyl-5-nitroaniline (1.66g, 10mmol) was added to a solution of *p*–toluenesulfonic acid (0.08g, 0.5mmol) in trimethyl orthoformate (30 mL). After 5 min. at room temperature excess orthoformate and the methanol formed was evaporated under vacuum giving a yellow oil that solidified upon cooling with ice. Yield: 2.1g (99$^+$%), mp. 54.5-55°C. ^{1}HNMR ($CDCl_3$) δ 1.25(3H, t, J=7.5Hz) 2.70(2H, q) 3.91(3H, s) 7.22(1H, d, J=8Hz) 7.53(1H, d, J=2.5Hz) 7.69(1H, s) 7.81(1H, dd).

3-Methyl-6-nitroindole

Potassium metal (0.56 g, 14 mmol) was dissolved in absolute ethanol (4 mL). To this was added a solution of diethyl oxalate (2.19 g, 15 mmol) in dry DMF (20mL) and then a solution of methyl *N*–(6-ethyl-3-nitrophenyl)-formimidate (2.08g, 10 mmol) in dry DMF (30mL). After 5h at room temperature the reaction mixture was poured onto ice, filtered, dried, and chromatographed on silica to yield the indole (0.46g, 26%) mp. 147–148°C. ^{1}HNMR ($CDCl_3$) δ 2.36(3H, s) 7.28(1H, m) 7.60(1H, d, J=9Hz) 8.01(1H, dd) 8.33(1H, d, J=2Hz) 8.50(1H, br. s).

2,4-Dibromo-6-ethyl-3-nitroaniline.

Bromine (6.4g, 40mmol) was added to 2-ethyl-5-nitroaniline (3.32g, 20mmol) dissolved in acetic acid (50mL) and the reaction mixture was heated on a steam bath for 1h and then poured into water (200 mL). Recrystallization of the crude product from ethanol gave yellow crystals (5.7g, 90%) mp. 100-103°C. ^{1}HNMR ($CDCl_3$) δ 1.26(3H, t, J=7Hz) 2.52(2H, q) 4.58(2H, br. s) 7.22(1H, s).

Methyl *N*–(2,4-dibromo-6-ethyl-3-nitrophenyl)-formimidate.

2,4-Dibromo-6-ethyl-3-nitroaniline (3.24g, 10mmol) was added to a solution of *p*–toluenesulfonic acid (0.08g, 0.5mmol) in trimethyl orthoformate (50 mL). After 5 min. at room temperature excess orthoformate and the methanol formed was evaporated under vacuum giving a brownish oil that solidified upon cooling with ice. Yield: 3.7g (99$^+$%), mp. 55-60°C. ^{1}HNMR ($CDCl_3$) δ 1.14(3H, t, J=7Hz) 2.52(2H, q) 3.98(3H, s) 7.39(1H, s) 7.60(1H, s).

5,7-Dibromo-6-nitro-3-methylindole.

Potassium metal (0.11 g, 2.8 mmol) was dissolved in absolute ethanol (2 mL). To this was added a solution of diethyl oxalate (0.44 g, 3 mmol) in dry DMF (10mL) and then a solution of methyl *N*–(2,4-dibromo-6-ethyl-3-nitrophenyl)-formimidate (736 mg, 2 mmol) in dry DMF (5mL). After 10h at room temperature the reaction mixure was poured onto ice, filtered, dried, and chromatographed on silica to yield the indole (376mg, 56%) mp. 166-167°C. ^{1}HNMR ($DMSO_{d6}$) δ 2.28(3H, br. s) 7.50(1H, br. s) 7.97(1H, s).

2,5-Dimethyl-4,6-dinitroanisole.

2,5-Dimethyl-4-nitroanisole (10g, 0.0055 mol) was added to fuming nitric acid (30mL) without exceeding 10°C. After standing at room temperature for 2h the reaction mixture was poured into ice-water (400mL). Filtration and recrystallization from ethanol gave the product (8g, 65%) as white needles mp. 60°C. ^{1}HNMR ($CDCl_3$) δ 2.42(6H, s) 3.90(3H, s) 7.77(1H, s).

2,5-Dimethyl-4-methoxy-3-nitroaniline.

2,5-Dimethyl-4,6-dinitroanisole (2.26g, 0.01 mol) was added to refluxing water (30mL). To this slurry, a solution of monoclinic sulfur (0.64g, 0.02 mol) and sodium sulfide hydrate (4.8g, 0.02 mol) in water (15mL) was added dropwise during 1h after which the mixture was refluxed for an additional 1h. Upon cooling an orange-yellow solid deposited, which was collected and recrystallized from ethanol giving the product (1.05g, 54%) as yellow needles mp. 96-96.5°C. ^{1}HNMR ($CDCl_3$) δ 2.00(3H, s) 2.20(3H, s) 3.49(2H, br. s) 3.73(3H, s) 6.52(1H, s).

5-Methoxy-6-methyl-4-nitroindole.

2,5-Dimethyl-4-methoxy-3-nitroaniline (1.96g, 0.01 mol), triethyl orthoformate (2.96g, 0.02 mol) and *p*–toluenesulfonic acid (0.172g, 0.001 mol) in dry DMF (25mL) were stirred at room temperature for 24h and then at 100°C for 20 minutes. The solution was then poured into ice-water (200mL) and the greasy precipitate was filtered off and dried giving 2.27g (90%) of ethyl *N*–(2,5-dimethyl-4-methoxy-3-nitrophenyl)-formimidate. ^{1}HNMR ($CDCl_3$) δ 1.33(3H, t, J=6.5Hz) 1.97(3H, s) 2.26(3H, s) 3.78(3H, s) 4.19(2H, q) 6.53(1H, s). This formimidate was not further purified but dissolved in DMF (20mL). A solution of diethyl oxalate (2.19g, 0.015 mol) and potassium ethoxide (1.26g, 0.015 mol) in DMF (20mL) were then added and the resulting brownish red solution was stirred at room temperature for 3h. Then, water (200mL) was added and the mixture was extracted with diethyl ether and the resultant oil from the ether extracts was recrystallized from acetonitrile to give the desired indole (1.20g, 65%) as yellow needles mp. 70-74°C. ^{1}HNMR ($CDCl_3$) δ 2.39(3H, s) 3.90 (3H, s) 6.64-6.80(1H, m) 7.14-7.28(1H, m) 7.33(1H, s) 8.6(1H, br. NH).

7-Ethyl-3-methyl-6-nitroindole.

2,6-Diethylaniline (14.9g, 0.1 mol) was dissolved in concentrated sulfuric acid (50 mL).

Fuming nitric acic (6.6g, 0.11 mol) was added dropwise keeping the temperature below 10°C. After the addition the reaction mixture was stirred at room temperature for 30 minutes and then poured into water (500 mL) and neutralized with potassium hydroxide maintaining a temperature below 25°C. Extraction with diethyl ether (2x50mL) and evaporation of the solvent gave 2,6-diethyl-3-nitroaniline (**26**) (16.3g, 84%) as a yellow oil. ^{1}HNMR ($CDCl_3$) δ 1.28(6H, br. t, J=7.5 Hz) 2.51(2H, q) 2.64(2H, q) 3.90(2H, br. s) 6.93(1H, d, J=8Hz) 7.12(1H, d).

The nitroaniline **26** (1.94g, 0.01 mol), triethyl orthoformate (2.96g, 0.02 mol) and *p*–toluenesulfonic acid (0.172g, 0.001 mol) were heated on a steam bath for 1h whereafter a solution of diethyl oxalate (2.19g, 0.015 mol) and potassium ethoxide (1.26g, 0.015 mol) in DMF (50mL) was added and the resulting mixture was stirred at 45°C for 1h, poured into water, filtered, and the resulting yellow crystals were recrysallized from ethanol to give 7-ethyl-3-methyl-6-nitroindole (2.0g, 98%) mp. 135-136°C. ^{1}HNMR ($CDCl_3$) δ 1.38(3H, t, J=7Hz) 2.30(3H, s) 3.10(2H, q) 7.17(1H, m) 7.38(1H, d, J=9Hz) 7.76(1H, d) 8.35(1H, br. s).

4-Nitro-2-phenylindole.

2-Methyl-3-nitroaniline (1.52 g, 0.01 mol), triethyl orthobenzoate (2.24g, 0.01 mol), and *p*–toluenesulfonic acid (0.86 g, 0.5 mmol) in DMF (30mL) were heated at 50°C for 8h and then poured into ice-water (100mL) giving a yellowish precipitate (2.8g, 99%) mainly (>90% pure) consisting of ethyl *N*–(2-methyl-3-nitrophenyl)-benzimidate. ^{1}HNMR ($CDCl_3$) δ 1.37(3H, t, J=7Hz) 2.32(3H, s) 4.36(2H, q) 6.4-7.35(8H, aromatic).

Without further purification the benzimidate was dissolved in DMF (40 mL) and to this was added a solution of diethyl oxalate (1.46g, 0.01 mol) and potassium ethoxide (0.84g, 0.01mol) in DMF (20 mL), and the resultant reaction mixture was stirred at 50°C for 8h. The crude product from precipitation in water was recrystallized from acetonitrile to give yellow needles (1.52g, 65%) mp. 203-206°C. ^{1}HNMR ($DMSO_{d6}$) δ 3.12(1H, br. s) 6.87-7.29(5H, aromatic m) 7.50-7.86(4H, aromatic m).

1-Methyl-4-nitro-2-phenylindole.

2-Methyl-3-nitroaniline (15.2g, 0.1 mol) was added to a solution of benzoyl chloride (14.1g, 0.1 mol) in dry pyridine (100mL). The reaction mixture was stirred for 30 minutes at room temperature and then poured into water. The precipitate was collected and dried giving *N*–(2-methyl-3-nitrophenyl)-benzamide (20.1g, 78%) as an off-white solid mp. 167-168°C. ^{1}HNMR ($DMSO_{d6}$) δ 2.15(3H, s) 7.07-7.9(8H, aromatic m) 10.1(1H, br. s). This benzamide (2.56g, 0.01 mol) and dimethyl sulfate (2.52g, 0.02 mol) were dissolved in DMF (50mL) and cooled to 0°C. Potassium ethoxide (1.68g, 0.02 mol) was then added at a rate keeping the temperature below 25°C. After the addition, the mixture was stirred for 1h at room temperature after which a solution of diethyl oxalate (1.46g, 0.01 mol) and potassium ethoxide (0.84g, 0.01 mol) in DMF (15mL) was added and the resultant deep red solution was stirred for 30 minutes at 50°C. The reaction mixture was then partitioned between water and diethyl ether, the ether extract was

evaporated and the crude product was recrystallized from acetonitrile giving 1.74g (69%) of yellow crystals mp. 126-7°C. ^{1}HNMR ($CDCl_3$) δ 3.80(3H, s) 7.15-7.50 (7H, aromatic m) 7.58(1H, dd, J_1=1Hz, J_2=8Hz) 8.09(1H, J_3=1Hz, J_4=7Hz).

4,6-Dibromo-2-methyl-5-nitroaniline.

2-Methyl-5-nitroaniline (15.2 g, 0.1 mol) was dissolved in 100 mL acetic acid and to this bromine (32.0 g, 0.22mol) was added and after heating at 100°C for 1h the reaction mixture was poured into ice-water, filtered and recrystallized from ethanol to yield yellow crystals (25.3 g, 92%) mp. 102-104 °C. ^{1}HNMR ($CDCl_3$) δ 2.20(3H, s) 4.16(2H, br. s) 7.17(1H, s).

Methyl *N*–(4,6-dibromo-2-methyl-5-nitrophenyl)-formimidate.

4,6-Dibromo-2-methyl-5-nitroaniline (15.5g, 0.05mol) and *p*–toluenesulfonic acid (0.08g, 0.5mmol) were dissolved in trimethyl orthoformate (150mL) and heated at 100°C for 20 minutes and then evaporated to dryness. Recrystallization of the residue from light petroleum gave the formimidate (17.2g, 98%) mp. 88-90°C. ^{1}HNMR ($CDCl_3$) δ 2.19(3H, s) 3.98(3H, s) 7.36(1H, s) 7.57(1H, s).

5,7-Dibromo-6-nitroindole.

Sodium metal (0.32 g, 14 mmol) was dissolved in absolute ethanol (3.0 g, 65 mmol). To this was added a cooled (0°C) solution of diethyl oxalate (2.19 g, 15 mmol) in 20 mL dry DMF and then a solution of methyl (2,4-dibromo-6-methyl-3-nitrophenyl)-formimidate (3.52 g, 10 mmol) in 20 mL dry DMF whereupon the solution turned deep red. After 12 h at r. t. the reaction mixture was poured onto ice, filtered and recrystallized from ethanol to give light yellow crystals (2.98 g, 93 %) mp. 195-195.5°C. ^{1}HNMR ($CDCl_3$) δ 6.65(1H, dd) 7.46(1H, dd) 7.83(1H, d, J=0.6 Hz) 8.68(1H, br. s).

N–(2-methyl-3-nitrophenyl) formamide.

2-Methyl-3-nitroaniline (15.2g, 0.1 mol) was dissolved in formic acid (60 mL) and the solution was heated (100°C) for 3h and then poured into water, filtered, and dried to yield (17.8g, 99%) of a white solid product mp. 134.5-136°C. ^{1}HNMR ($DMSO_{d6}$) δ 2.27(3H, s) 7.33-8.00(3H, m) 8.33(1H, s) 10.0(1H, br. NH).

1-Geranyl-4-nitroindole

N–(2-methyl-3-nitrophenyl) formamide prepared as described above (1.8 g, 10 mmol) was dissolved in dry dimethyl sulfoxide (50mL) and cooled to 0°C. Potassium ethoxide (0.92 g, 11 mmol) was added and the purple solution thus formed was titrated with geranyl bromide (ca. 2.5 g, 12 mmol). After stirring for 10 minutes at room temperatures a solution of diethyl oxalate (1.46 g, 10 mmol) and potassium ethoxide (0.8 g, 10 mmol) in dry DMF (40 mL) was added and the reaction mixture was stirred for 2h at room temperature. Partitioning between water and light

petroleum and repeated washings of the organic layer with 2 N sodium hydroxide, 1 N hydrochloric acid and water gave the crude product as a brownish-yellow oil. The product was eluated with chloroform on silica gel giving a yellow oil, 1.52 g (52%). ^{1}HNMR ($CDCl_3$) δ 1.45-1.80(9H, m) 1.97-2.14(4H, m) 4.66(2H, d, J=7Hz) 4.8-5.1(1H, m) 5.30(1H, br. t) 6.9-7.3(3H, m) 7.53(1H, br. dd, J_1=8Hz, J_2<1Hz) 8.02(1H, dd, J_3=7Hz, J_4=1Hz).

N'-(2-Methyl-5-nitrophenyl)-*N,N*-dimethylformamidine(**5**).

2-Methyl-5-nitroaniline (15.2g, 0.1 mol) was added to a stirred solution of phosphorus oxychloride (10.3mL, 0.11 mol) in DMF (120mL) at 25°C, whereupon the solution was heated on a steam bath for 2h. The reaction mixture was then allowed to cool and poured into ice/water (600mL) under stirring. The solution was made alkaline with aqueous potassium hydroxide (25%) without exceeding 15°C and the precipitate formed was collected, washed with water and recrystallized from ethanol to yield 6.5g (80%) mp. 89-90°C. ^{1}HNMR ($CDCl_3$) δ 2.31(3H, s) 3.03(6H, s) 7.12(1H, d, J=8.8Hz) 7.45(1H, s) 7.54(1H, d, J=1.5Hz) 7.64(1H, dd).

The following compounds were similarly prepared:

N'-(2-Methyl-3-nitrophenyl)-*N,N*-dimethylformamidine

Yield:80% bp. 145-150°C/0.03 mm. ^{1}HNMR (CCl_4) δ 2.25(3H, s) 2.86(6H, s) 6.6-7.3(4H, m, arom. + N=CH).

N'-(3,5-Dinitro-2-methylphenyl)-*N,N*-dimethylformamidine

Yield:85% mp. 128-130°C. ^{1}HNMR ($CDCl_3$) δ 2.48(3H, s) 3.10(6H, s) 7.5(1H, s) 7.65(1H, d, J=1.8Hz) 8.18(1H, d). IR (KBr) ν_{max} 3085, 2930, 1644, 1601, 1518, 1373, 1351, 1264, 1116, 821 cm^{-1}.

N'-(2,4-Dimethyl-3-nitrophenyl)-*N,N*-dimethylformamidine

Yield:70%, mp. 80-82°C.

2,2'-Diaminobibenzyl.

Hydrazine monohydrate (15 mL) dissolved in methanol (30mL) was added dropwise during 3h to a refluxing mixture of FeOOH (350 mg) and 2,2'-dinitrobibenzyl[53] (10.88g, 0.04 mol) in methanol (100mL) and dimethylacetamide (35 mL). After completed addition the reflux was continued for 3h and then filtered, concentrated and poured into water. The colourless oil solidified within 2 minutes to yield 8.02g (95%), mp. 65-67°C(lit.[33b,54] 65-66°C, 66-67°C).

2,2'-Diamino-4,4'-dinitrobibenzyl.

2,2'-Diaminobibenzyl (4.24g, 0.02 mol) was dissolved in a stirred mixture of fuming nitric acid (1.8 mL) and concentrated sulfuric acid (30 mL) at 10°C. After 2h at this temperature the mixture was poured into ice-water and neutralized with sodium hydroxide. The yellow-brown percipitate formed was recrystallized from dimethylacetamide-acetonitrile to give the desired product (4.5g, 73%), mp. 232-234°C. ^{1}HNMR ($DMSO_{d6}$) δ 2.88(4H, s) 6.15(4H, s) 7.1-7.8(6H, m).

2,2'-Bis-(ethoxymethyleneamino)-4,4'-dinitrobibenzyl (**20**).

Method A:

Ethyl *N*–(2-methyl-5-nitrophenyl)formimidate (**15**) (4.16g, 0.02 mol) dissolved in DMF (25 mL) was added to a solution of diethyl oxalate (5.88g, 0.04 mol) and potassium *tert*–butoxide (3.36g, 0.03 mol) in DMF (40 mL) at 35°C. After 45 minutes of stirring the mixture was poured into water. The solid formed was collected and recrystallized from dimethylacetamide to give **20** (0.75g, 18%), mp. 214-218°C. IR (KBr) ν_{max} 3092(w), 3075(w), 2986(m), 2941(w), 2897(w), 1643(s), 1612(m), 1516(s), 1345(s), 1308(m), 1267(m), 1218(s), 1175(s), 1010(m), 1075(m), 982(m), 850(s), 832(m), 733(m) cm^{-1}. MS *m/z* 414(2, M^+), 414(42), 383(100), 327(85), 299(73), 253(71), 206(40).

Method B:

2,2'-Diamino-4,4'-dinitrobibenzyl (3.02g, 0.01 mol) was refluxed in triethyl orthoformate (10 mL) and dimethylacetamide (5 mL) for 2h, whereupon the excess of formate was distilled off and the residue crystallized from dimethylacetamide to give **20** (3.60g, 86%) mp. 214-218°C in all respects identical with the material synthesized by method A.

Methyl 3-(4-nitro-2-dimethylaminomethyleneaminophenyl)-pyruvate (**23**).

The formamidine **5** (10.35g, 0.05 mol) dissolved in DMF (50mL) was added to a stirred solution of dimethyl oxalate (5.90g, 0.05 mol) and potassium *tert*–butoxide (5.60g, 0.05 mol) in DMF at room temperature. After 45 minutes on a steam bath the reaction mixture was poured into water (400mL) and neutralized with acetic acid. The red-brown precipitate was collected and dried to yield **23** (9.5g, 65%). The analytical sample was recrystallized from chloroform. ^{1}HNMR ($CDCl_3$) δ 3.14(6H, s) 3.80(3H, s) 6.57(iH, s) 7.22(1H, d, J=7.5Hz) 7.51(1H, s) 7.61(1H, d, J=1.5Hz) 7.79(1H, dd). IR (KBr) ν_{max} 3220, 2955, 1729, 1665, 1638, 1620, 1488, 1442, 1339, 1264, 1133, 775 cm^{-1}.

Attempted melting point determination of the product revealed decomposition at ca. 140°C (evolution of dimethylamine) and a colour change from red to pale yellow forming methyl 6-nitroindole-3-glyoxylate (**6**) in a quantitative yield. In fact, heating of **23** for a short period at 150°C can advantageously be used for the preparation of **6**.

Methyl 6-nitroindole-3-glyoxylate (**6**).

The amidine **23** (5.86g, 0.02 mol) was heated at reflux for 30 minutes in ethanol (100mL) containing acetic acid (3mL). The crude precipitate of **6** formed was collected from the cooled solution and washed with cold ethanol giving **6** (4.62g, 93%) mp. >260°C.

The following compounds were similarly prepared:

Ethyl 6-nitroindole-3-glyoxylate

Yield:75%, mp. 287-288°C (lit.[37] 284-286°C).

Ethyl 4-nitroindole-3-glyoxylate,

Yield:68%, mp. 187-188°C (lit.[37] 184-186°C).

Alternative method for the preparation of **6**

The synthesis of **23**, described above was repeated with the exception that the precipitate was not collected. Instead, the whole reaction mixture was heated at reflux for 10 minutes whereupon **6** was formed in 90% yield.

6-Nitroindole-3-glyoxylic acid,

Methyl 6-nitroindole-3-glyoxylate (4.98g, 0.02 mol) was heated at reflux for 90 minutes in a solution of ethanol (80mL), water (10mL) and potassium hydroxide (3.5g). Upon cooling, a reddish-brown potassium salt of 6-nitroindole-3-glyoxylic acid precipitated. Enough water was then added to give a clear solution, which was then acidified with concentrated hydrochloric acid. The precipitate was collected and dried to give 6-nitroindole-3-glyoxylic acid (4.50g, 96%) mp. 259°C dec. (lit.[37] 250°C dec.).

4-Nitroindole-3-glyoxylic acid could be similarly prepared giving an 85% yield, mp. 190°C dec (lit.[38] 177°C dec).

Independent synthesis of 4-Nitro-7-methylindole.

The procedure given by Hiremath and Siddappa was used starting from 2-methyl-5-nitroaniline (Scheme 10) to give a 5% yield, mp. 170-173°C (lit.[42] 200°C). This compound was identical to one of the two isomeric products formed by cyclization of *N*–(2,6-dimethyl-3-nitrophenyl)-formimidate. Since our two melting points agree well we conclude that the one cited above is in error.

Independent synthesis of 6-Nitro-7-methylindole.

The procedure given above was followed starting from 2-methyl-3-nitroaniline to give a 7% yield mp. 174-175°C. The compound was identical to one of the two isomeric products formed by cyclization of *N*–(2,6-dimethyl-3-nitrophenyl)-formimidate.

N–(2-methyl-3-nitrophenyl)-pyrrolidone-2 (**33**).

2-Methyl-3-nitroaniline (15.2g, 0.1 mol) and dry pyridine (24g, 0.3 mol) were dissolved in diethyl ether (700mL). To this, 4-chlorobutyryl chloride (14.4g, 0.1 mol) was added dropwise under stirring. After 3h the white solid deposited was collected and dried giving 4-chloro-*N*–(2-methyl-3-nitrophenyl)-butyramide (**34**) (22g, 86%) mp. 97-98.5°C. ^{1}HNMR ($CDCl_3$) δ 2.0-2.7 (7H, m) 3.65(2H, t, J=6Hz) 6.94-7.25(1H, m) 7.38-7.67(2H, m) 8.0(1H, br. s). This anilide (2.57 g, 0.01 mol) was dissolved in DMF (25mL) and this solution was added dropwise to a sodium hydroxide solution (200mL, 10M) at room temperature with stirring. After 1h the precipitate was collected, washed with water and recrystallized from ethanol to give the pyrrolidone (1.7 g, 77%)

as colourless prisms mp. 78-79°C. ^{1}HNMR ($CDCl_3$) δ 2.2-2.75(7H, m) 3.72(2H, t, J=6Hz) 7.21-7.45(2H, m) 7.60-7.86(1H, m).

1-*H*-2,3-Dihydro-8-nitropyrrolo-[1,2-a]-indole (**35**).

The pyrrolidone **33** (1.1g, 0.005 mol) was dissolved in DMF (25 mL) and a solution of diethyl oxalate (0.73g, 0.005 mol) and potassium ethoxide (0.42g, 0.005 mol) in DMF (25mL) was added and the reaction mixture was heated on a steambath for 2h. Addition of water and extraction with diethyl ether gave, after recrystallization from methanol, greenish yellow flakes (0.8g, 80%) mp. 113-114°C. ^{1}HNMR ($CDCl_3$) δ 2.48-2.87(2H, m) 2.80-3.22(2H, m) 4.11(2H, br. t, J=6Hz) 6.79(1H, s) 6.85-7.20(1H, m) 7.40(1H, d, J=7Hz) 7.97 (1H, d, J=8Hz). IR (KBr) ν_{max} 1622(w), 1560(m), 1522(s), 1504(s), 1478(s), 1418(m), 1363(s), 1321(s) cm^{-1}.

Compound **35** can also be synthesized *in situ* from the anilide **34** dissolved in DMF through an initial addition of one equivalent of potassium ethoxide to create the pyrrolidone (**33**). Using this procedure the yield decreased to 55%.

1,3-Bis-(trifluoroacetyl)-2-(1H-2,3-dihydro-8-nitropyrrolo[1,2–a]indol-9-yl)-4-imidazole (**37**).

The nitroindole **35** (2.02g, 0.01 mol) was added to a solution of imidazole (0.74g, 0.011 mol) and trifluoroacetic anhydride (2.5 mL) in acetonitrile (10 mL) and the reaction mixture was heated at reflux for 2h. Solvents were removed, the residue was treated with water (25mL) and the resulting solid was boiled in ethanol and filtered hot. Yield: 4.57g, 99%. mp. 238-240°C. IR (KBr) ν_{max} 3060(w), 1725(s), 1706(s), 1525(w), 1436(s), 1342(s), 1235(s), 1150(s), 856(m) cm^{-1}.

1H-2,3-Dihydro-9-formyl-8-nitropyrrolo[1,2-a]indole.

The imidazole **37** (0.6g, 0.003mol) was heated at reflux for 30 min. in a solution of potasium hydroxide (1.65g, 0.03 mol) in ethanol (15mL) and water (6mL). The reaction mixture was concentrated to *ca* 6mL and acidified with acetic acid. The solid formed was collected and recrystallized from methanol giving greenish-yellow plates (0.63g, 92%) mp. 215-216°C. ^{1}HNMR ($CDCl_3$) δ 2.5-2.97(2H, m) 3.22-3.57(2H, t, J=7Hz) 7.03-7.30(1H, m) 7.51(1H, dd, J_1=8Hz, J_2=1Hz) 7.97(1H, dd, J_3=7Hz, J_4=1Hz) 10.40(1H, s).

The compound could also be synthesized from **35** (0.6g, 0.003 mol) in DMF (20mL) and phosphorus oxychloride-DMF complex (0.004 mol) (Vilsmeier procedure) giving 0.51g (74%).

1,3-Bis(trifluoroacetyl)-2-(4-nitro-3-indolyl)-4-imidazoline (**36**).

4-Nitroindole (3.24g, 0.02 mol) was added to a solution of imidazole (1.47g, 0.022 mol) and trifluoroacetic anhydride (5.0 mL) in acetonitrile (20 mL) and the reaction mixture was heated at reflux for 2h, evaporated under vacuum and treated with water (50mL). The solid formed was collected and purified by boiling in ethanol, filtered hot, and the product was collected as yellow crystals (7.74g, 92%) m. p. 257-259°C. IR (KBr) ν_{max} 3340(s), 3155(w), 1716(s), 1681(s),

1512(s), 1448(s) cm^{-1}. MS *m/z* 422(12, M^+), 405(38), 309(24), 308(68), 306(81), 293(20), 292(100), 291(38), 211(27), 210(31), 209(35), 195(95).

3-Formyl-4-nitroindole.

Method A:

Freshly distilled phosphorus oxychloride (5.5 mL) was added dropwise to DMF (10 mL) maintaining the temperature below 5°C. The solution was allowed to warm to room temperature and was then added dropwise to a solution of 4-nitroindole (8.1g, 0.05 mol) in DMF (30 mL) at 100°C. The reaction mixture was stirred at this temperature another 2h after the completion of the addition and then poured into 2M sodium hydroxide (100 mL). The resultant slurry was stirred for 15 minutes, acidified with hydrochloric acid and the product (7.3g, 77%) was collected as a brownish solid m.p. 189-192°C (lit.[55a,b] 191-192°C). ^{1}HNMR ($DMSO_{d6}$) δ 7.17(1H, dd, J_1=J_2=8Hz) 7.68(1H, dd, J_3=1Hz) 7.81(1H, dd, J_4=1Hz) 8.10(1H, s) 10.12(1H, s).

Method B:

The imidazole **36** (422mg, 1mmol) was heated under reflux in a solution of potassium hydroxide (500mg) in ethanol (5mL) and water (2mL). Reduction of the volume to *ca* 2 mL and acidification with acetic acid gave 226 mg (85%) of 3–formyl-4-nitroindole.

Method C:

4–Nitroindole-3-glyoxylic acid (4.68g, 0.02mol) was heated to 185°C in quinoline for 2h under nitrogen after which the solvent was distilled off and the residue treated with 10% hydrochloric acid (15 mL). The solid obtained was washed with water and recrystallized from acetone/water. Yield:2.95g (77%) mp. 190-191°C.

3-Formyl-6-nitroindole.

Method A described above for the 4-isomer but starting from 6-nitroindole yields 95%, mp. 302-304°C(lit.[37] 302-304°C). Method C was also applied and gave an identical product in 80% yield.

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