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# Cyanoacetylation of indoles, pyrroles and amines, and synthetic uses of these products

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*To my family*

## Abstract

This thesis is based on an organic synthetic project aimed towards development of small molecules acting on the P2 receptor as well as development of synthetic methods to such molecules (primarily indoles and featuring isatogens in particular). The new methodology includes cyanoacetylation of indoles, pyrroles, amines, and enamines using cyanoacetic acid in acetic anhydride. The molecules obtained (e.g. 3-cyanoacetylindole) could be further functionalized by nitrosation followed by reduction.

Cyanoacetylated anilines carrying an appropriate substituent (e.g $NO_2$) could be cyclized to quinoxaline-N-oxides, a class of molecules which have been considered as analogues to isatogens. The molecule 2,2′-pyridylisatogen tosylate (PIT) is particularly interesting within this class because of its documented interaction with the P2 receptor.

**Keywords:** indole, pyrrole, reduction, oxidation, indoline, acylation, cyanoacetylation.

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***List of papers***

I. “Oxygenation of 2,3-dihydroindoles”

Slätt, J.; Bergman, J.

*Tetrahedron* **2002**, *58*, 9187-9191.

II. “Cyanoacetylation of indoles, pyrroles and aromatic amines with the combination cyanoacetic acid and acetic anhydride”

Slätt, J.; Romero, I.; Bergman, J.

*Synthesis* **2004**, 2670-2675.

III. ”Reinvestigation of a synthesis of quinoxaline-*N*-oxides”

Slätt, J.; Bergman, J.

Manuscript.

IV. “Synthetic applications of 3-(cyanoacetyl)indoles and related compounds”

Slätt, J.; Janosik, T.; Wahlström, N.; Bergman, J.

*J. Heterocyclic Chem*. **2004**, in press.

V. “Functionalizations of 3-(cyanoacetyl)indole and 2-(cyanoacetyl)pyrrole”

Slätt, J.; Beslic, S.; Stensland, B.; Bergman, J.

Manuscript.

# Introduction

This thesis is a result of a national program, *Principles in Drug Development*, sponsored by The Foundation for Strategic Research. My part of this drug development project has been performed in collaboration between Organic Chemistry, Karolinska Institute, Department of Cardiology, University of Lund Hospital, and Clinical Pharmacology (*in vitro*), Gothenburg University Hospital (*in vivo*). The work has been carried out at an organic chemistry department and focus has been put on organic chemistry, not only related to the P2 receptor, but also for development of new synthetic methods. This is reflected throughout the entire thesis, since the first half is primarily devoted to investigation of *N*-oxides, and the second half is focused on the development of new methods in organic chemistry.

## The P2 receptor

The discovery of the function of the extracellular P2 incurred in 1929, when ATP was found to decrease the heart rate and to dilate coronary blood vessels.[1] ATP was suggested as a neurotransmitter,[2] acting extracellularly on P2 receptors, which later were subdivided into P2X (ion channel) and P2Y (G-protein coupled) receptors, $P2X_{1,2,4,5}$ and $P2Y_{1,2,6,11,12}$.[3] In this study we have focused on some P2 receptors located in the cardiovascular system, $P2X_1$ and $P2Y_{1,12}$. P2 receptors are mediated by ATP or UTP. For more insight of the P2 receptors see Burnstock's[4] or Jacobson's[5] reviews, (the latter is more related to development of new ligands). Characterisation of P2 receptors is problematic since the closely related adenosine receptor,[6] mediated by adenosine, can be located in the same tissues.

## Drug design

This work has mainly been based on finding a new pharmacophore, which definition was, "a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity".[7] That definition has been unperturbed until Peter Gund formulated the following in 1977: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity".[8] Some of Lipinski's "The rule of five" has also been considered during the work with possible ligands

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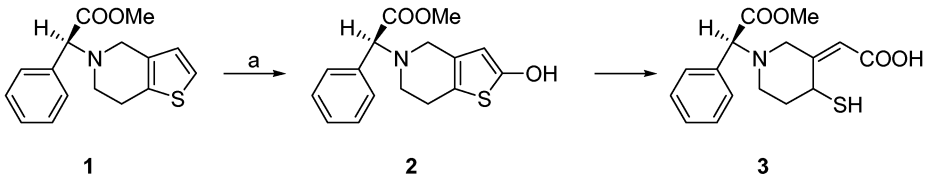
[1] Drury, A. N.; Szent-Györgyi, A. *J. Physiol. (London),* **1929**, *68*, 213-237.
[2] Burnstock, G. *Pharmacol. Rev.* **1972**, *24*, 509-581.
[3] Burnstock, G. *Gen. Pharmacol.* **1985**, *16*, 433-440.
[4] Burnstock, G. In: *The P2 nucleotide receptors*. Eds.; Turner, T. J.; Weisman, G. A.; Fredan, J. Human Press Inc, Totowa, New Jersey, 1998.
[5] Jacobson, K. A.; Jarvis, M. F.; Williams, M. *J. Med. Chem.* **2002**, *45*, 4057-4093.
[6] For a review, see: Ralevic, V.; Burnstock, G. *Pharmacol. Rev.* **1998**, *50*, 413-492.
[7] Ehrlich, P. *Chem. Ber*. **1909**, *42*, 17-47.
[8] Gund, P. Prog. Mol. Subcell. Biol. **1977**, *5*, 117-143.

for the P2 receptor, particularly those related to molecule weight (less then 500) and H-donors (not more then ten, expressed as the sum of Ns and Os).[9]
This study has mainly been focused on compounds bearing the indole skeleton, particularly those suggested as binding to ATP sites. ATP analogues were not considered in this project as this area has been previous explored.[5] Currently there is only one commercial drug available that is acting on P2 receptors namely Clopidogrel (SR25990C, PLAVIX) (**1**) which is a pro-drug that is metabolised to **2** in the liver by P4501A,[10] where the active metabolite **3**, eventually will form a disulfide bond to the P2Y12 receptor located on platelets.[11,12]




**Scheme 1.** a) CYP450A1.

## Indoles in nature and in drug development

Indole is an important heterocycle, both in Nature as well as for commercial drug development. The essential amino acid, tryptophan (**4**) and metabolites thereof, for example tryptamine (**5a**), serotonin (**5b**), melatonin (**6**), and indole-3-acetaldoxime (**7**) all contain the indole skeleton and participate in vital biological processes.

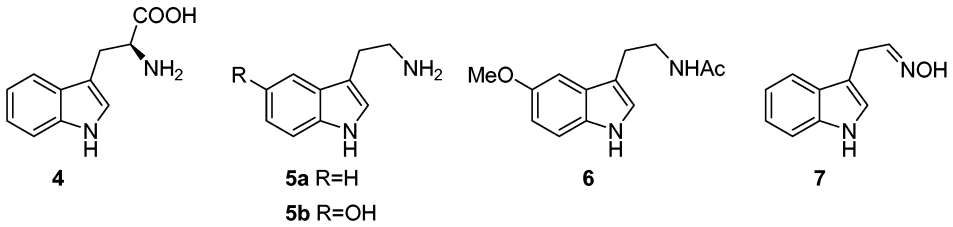



**Figure 1.**

[9] Lipinski, C. A. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25.
[10] Savi, P.; Combalbert, J.; Gaich, C.; Rouchon, M. C.; Maffrand, J. P.; Berger, Y. *Thromb. Haemostasis.* **1994**, *72*, 313-317.
[11] Hoessel, R.; Leclerc, S.; Endicott, J. A.; Noble, M. E.; Lawrie, A.; Tunnah, P.; Leost, M.; Damiens, E.; Marie, D.; Marko, D.; Niederberger, E.; Tang, W.; Eisenbrand, G.; Meijer, L. *Nat. Cell Biol.* **1999**, *1*, 60-67.
[12] Pereillo, J. M.; Maftouh, M.; Andrieu, A.; Uzabiaga, M. F.; Fedeli, O.; Savi, P.; Pascal, M.; Herbert, J. M.; Maffrand, J. P.; Picard, C. *Drug Metab. Dispos.* **2002**, *30*, 1288-1295.

Indole moieties are present in many drugs, for instance Sumatriptan (GlaxoSmithKline AB, migraine) (**8**), Zolmitriptan (AstraZeneca, migraine) (**9**), Indomethacin (Alpharma AB, anti-inflammatory) (**10**), and Tadalafil (Eli Lilly, erectile dysfunction) (**11**).

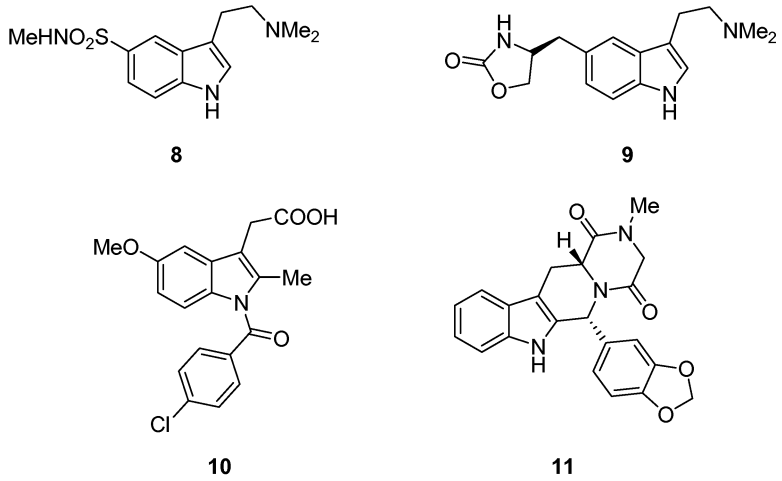



**Figure 2.**

Dimeric derivatives such as 2,2′- and 2,3′-bisindoles have been suggested to bind to ATP sites, particularly in kinases. 2,2′-Biindolyl (**12**), indigo (**13**) and in particular indirubin (**14a**) and indirubin-3′-monooxime (**14b**) have been investigated by several groups. Indirubin-3′-monooxime (**14b**) also takes part in the phosphorylation *in vitro* and *in vivo* in Alzheimer related diseases.[13] Furthermore indigo (**13**) and indirubin (**14a**) are ingredients in traditional Chinese anti-leukaemia formulations.[14]

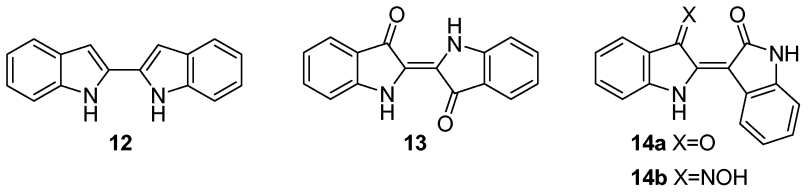
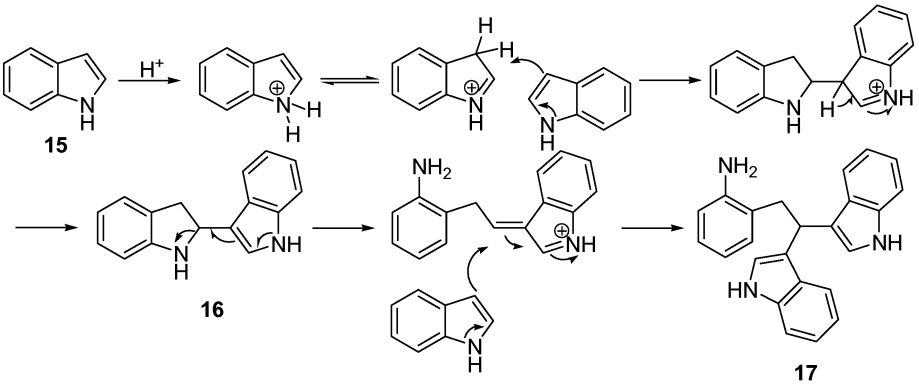



**Figure 3.**

[13] Leclerc, S.; Garnier, M.; Hoessel, R.; Marko, D.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Biernat, J.; Wu, Y. Mandelkow, E.; Eisenbrand, G.; Meijer, L. *J. Biol. Chem*. **2001**, *5*, 251-260.
[14] Damiens, E.; Barette, B.; Marie, D.; Eisenbrand, G.; Meijer, L. *Oncogen.* **2001**, *20*, 3786-3797.

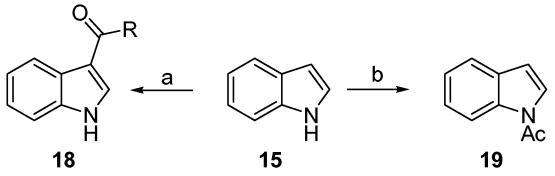
## Reactivity of indoles

Indole (**15**) is protonated by strong acids and will primarily form dimers **16** and trimers **17**. [15] Acylation of indole with activated carboxylic acid derivatives, like acid chlorides, gives 3-substituted indoles. The 2,3′-coupled dimer **16** can under certain conditions be rearranged to the corresponding 2,2′-coupled isomer. [16]




**Scheme 2.** Oligomerisation of indole induced by hydrochloric acid.

A general procedure to prepare acylated indoles is to activate an acid chloride with pyridine, [17] which will both increase the reactivity and scavenge the hydrochloric acid formed. Activating agents like Lewis acids are used for preparation of 3-acylindoles **18**.[18,19] *N*-Acylated indoles **19** are formed in the presence of bases like triethylamine or sodium hydride, or as minor products when indoles are reacted with ketenes. *N*-Acetylindole is relatively sensitive towards hydrolysis (e.g. by water alone).




**Scheme 3. a)** RCOCl, pyridine, toluene or dioxane.[17] b) $Et_3N$, $Ac_2O$.

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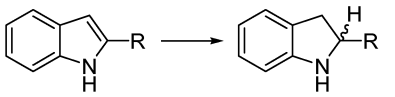
[15] Smith, G. F. *Adv. Heterocycl. Chem.* **1963**, *2*, 300-309.
[16] Ishii, H.; Murakami, K.; Murakami, Y.; Hosoya, K. *Chem. Pharm. Bull.* **1977**, *25*, 3122-3124.
[17] Bergman, J.; Bäckvall, J. E.; Lindström, J. O. *Tetrahedron* **1973**, *29*, 971-976.
[18] Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *17*, 6061-6066.
[19] Ottoni, O.; Neder, V. F.; Dias, A. K. B.; Cruz, R. P. A. Aquino L. B. *Org. Lett.* **2001**, *3*, 1005-1007.

## Reduction of indoles

Indole (**15**) and 2-methylindole (**20b**) are reduced to indoline derivatives by sodium cyanoborohydride in acetic acid.[20] The more resistant 2-phenylindole (**20c**) undergoes reduction with metals like iron or tin in hydrochloric acid.[21] In general, reduction of methyl indole-2-carboxylate (**20d**) is performed in dry hydrochloric acid in ethanol in a closed vessel,[22] or by reduction with magnesium in methanol.[23]



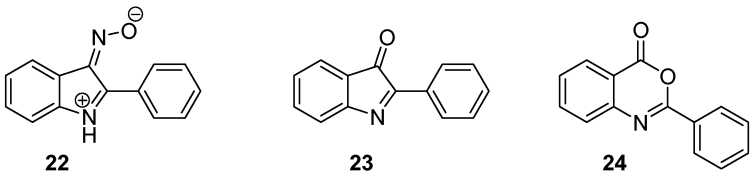
**15** R=H
**20b** R=Me
**20c** R=Ph
**20d** R=COOMe

**21a** R=H
**21b** R=Me
**21c** R=Ph
**21d** R=COOMe

**Scheme 4**. Reduction of indole to indoline derivatives.

## Nitrosation of indoles

2-Substituted indoles can be oxidized directly to indoxyls, but no practical procedures are currently available. Nitrosations of indoles with sodium nitrite in acetic acid are, with a few exceptions, often fast and high yielding.[24] The identity of nitrosated 2-phenylindole has aroused considerable controversy over the years, but Richman's and Hassner's zwitterionic species **22** is generally accepted.[25] Richman and Hassner also transformed this oxime to the indoxyl derivative **23**, which Kalb and Baeyer had first isolated in 1912 *via* oxidation of 3-aminoindole.[26] Attempts to convert **23** to the corresponding *N*-oxide (i.e. an isatogen) with *m*-CPBA failed, and the isolated product proved to be the ring expanded molecule, 2-phenyl-benz-3-oxazin-4-one (**24**).[25]



**22** **23** **24**

**Figure 4.**

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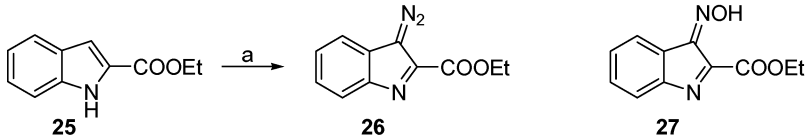
[20] Gribble, G. W.; Nutaitis, C. F., *Org. Prep. Proced. Int.* **1985**, *17* , 317-384.
[21] Bowden, B. F.; Read, R. W.; Richie, E.; Taylor, W. C. *Aust. J. Chem.* **1975**, *28*, 65-80.
[22] Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476-2488.
[23] Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409-2410.
[24] Büchi, G.; Lee, G. C. L.; Yang, D.; Tannenbaum, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 4115-4119.
[25] Richman, R. J.; Hassner, A. *J. Org. Chem.* **1968**, *33*, 2548-2551.
[26] Kalb, L.; Baeyer, A. *Chem. Ber.* **1912**, *45*, 2150-2162.

In connection with nitrosations, Tedder has suggested that the nitroso group can directly be converted to a diazo group.[27,28] Research workers at AstraZeneca have, in agreement with Tedder's proposal, shown that the diazoindole (**26**) is formed directly from **25** with an excess of sodium nitrite.[29] These results seem to rule out the previously suggested oxime derivative **27** as an intermediate.[30]




**Scheme 5. a**) THF, AcOH (10 eq.), $NaNO_2$ (10 eq.), 2 days.[29]

## Isatogens

2-Substituted-3*H*-indole-3-one-1-oxides, **28**, known as isatogens, were described more than 100 years ago.[31] These compounds have attracted interest due to their biological properties against a range of bacteria,[32] mycobacteria,[33] and fungi.[34] Some isatogens are also able to relax smooth muscle cells. Isatogens have also been suggested as spin traps and have been shown to give highly stable adducts with free radicals.[35] The chemistry of isatogens has been reviewed several times.[36,37]

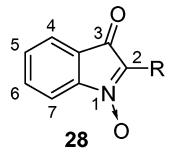



**Figure 5.** The skeleton of isatogen.

The suggestion[38] that isatogens provide examples of a quinoid system has later been confirmed by comparing the reduction potentials of isatogens with those of naphthoquinone (**30**) and 1,4-benzoquinone (**31**).[39]

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[27] Tedder, J. M.; Theaker, G. *J. Chem. Soc.* **1958**, 2573-2579.
[28] Tedder, J. M.; Theaker, G. *Tetrahedron* **1959**, *5*, 288-292.
[29] Kettle, J. G.; Faull, A. W.; Fillery, S. M.; Flynn, A. P.; Hoyle, M. A.; Hudson, J. A. *Tetrahedron Lett.* **2000**, *41*, 6905-6907.
[30] Monge, A.; Palop, J. A.; Recalde, I.; Martinez-Crespo, F.; Fernandez-Alvarez, E. *Anales. Quimica, ser C81*, **1985**, *3*, 267-270.
[31] Baeyer, A. *Chem. Ber.* **1881**, *14*, 1741-1746.
[32] Hooper, M.; Patterson, D. A.; Wibberley, D. G. *J. Pharm. Pharmacol.* **1965**, *17*, 734-741.
[33] Sahasrabudhe, A. B.; Kamath, H. V.; Bapat, B. V.; Kulkuarni, S. N. *Indian J. Chem.* **1980**, *19B*, 230-232.
[34] Hagen, H.; Kohler, R. D.; Pommer, E. H. *Eur. Pat.* 54147 (*Chem. Abstr.*, **1982**, *97*, 216 185).
[35] Nepveu, F.; Souchard, J. P.; Rolland, Y.; Dorey, G.; Spedding, M. *Biochem. Biophys. Res. Commun.* **1998**, *242*, 272-276.
[36] Prestion, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627-677.
[37] Hiremath, S. P.; Hooper, M. *Adv. Heterocycl. Chem.* **1978**, *22*, 123-181.
[38] Pfeiffer, P. *Justus Liebigs Ann. Chem.* **1916**, *411*, 72-158.

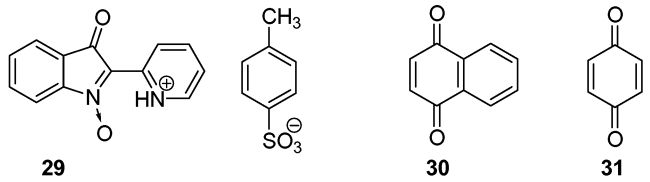
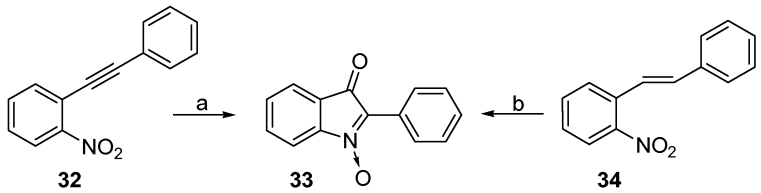


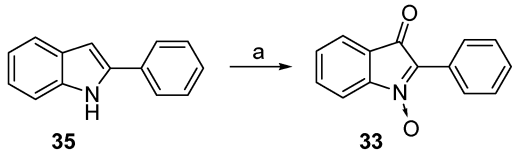

**Figure 6.**

Isatogens have been shown to possess oxidative capabilities comparable with some naturally occurring quinones. Upon treatment with isatogens, the amino acids leucine and valine will undergo oxidative deamination and decarboxylation giving aldehydes and reduction products of isatogen, a process which is suggested to proceed *via* a nucleophilic attack at C-2 of the isatogen.[40] The most commonly used procedures towards isatogens **33** start either from *o*-nitrotolan (**32**)[38,41,42] or *o*-nitrostilbene (**34**)[43] derivatives.




**Scheme 6.** a) Pyridine or nitrosobenzene in $CHCl_3$. b) hν, benzene.

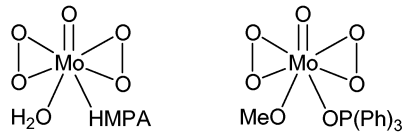
Direct oxidation of indoles **35** to isatogens **33**[44] with Mimoun's reagent ($MoO_5$·HMPA) (**36**)[45] is very convenient. Jimenez has suggested that the complex **37**, where the toxic HMPA had been substituted with triphenylphosphineoxide should have similar oxidzing properties.[46]




**Scheme 7**.a) $MoO_5$·HMPA (58%).[44]

[39] Bunney, J. E.; Hooper, M. *J. Chem. Soc. (B)*, **1970**, 1239-1241.
[40] Hooper, M.; Robertson, J. W. *Tetrahedron Lett.* **1971**, *12*, 2139-2140.
[41] Bond, C. C.; Hooper, M. *J. Chem. Soc.* **1969**, 2453-2460.
[42] Susvilo, I.; Brukstus, A.; Tumkevicius, S. *Synlett*, **2003**, *8*, 1151-1152.
[43] Splitter, J. S.; Calvin, M. *J. Org. Chem.* **1955**, *20*, 1086-1115.
[44] Chien, C.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 843-848.
[45] Mimoun, H.; De Roch, I. S.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, *5*, 1481-1492.
[46] Kiraz, C. I. A.; Emge, T. J.; Jimenez, L. S. *J. Org. Chem.* **2004**, 69, 2200-2202.

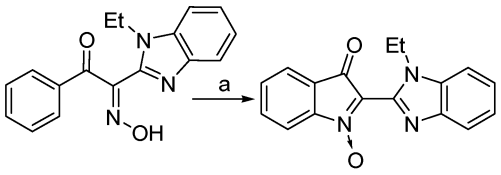
Attempted conversion of 2-phenylindole to 2-phenylisatogen with this HMPA-free reagent have however not been successful. The HMPA-complex has not been available to us.




**36** **37**

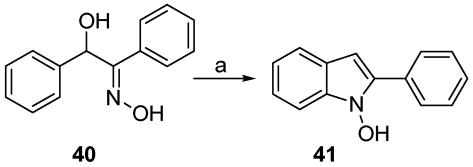
**Figure 7**. Mimoun's reagent **36** and Jimenez variant **37**.

Two different rearrangement reactions of oxime derivatives described a long time ago are still relatively unexplored and are yet to reveal their full potential. Thus Hagen[34] detected this rearrangement of the oxime derivative **38**, give isatogens **39**, this was later confirmed by Hooper.[49] A similar rearrangement is involved in the conversion of **40** to 1-hydroxy-2-phenylindole (**41**), a transformation discovered by Fischer as early as 1895.[47,48]




**38** **39**

**Scheme 8.** a) Phosphoric acid, $NaNO_2$ (65%)[34], (18%)[49].




**40** **41**

**Scheme 9.** a) $H_2SO_4$.

Oxidations of *o*-nitrostilbene derivatives (**34**) with BSA to generate **42** have been recently discussed as a possible route to isatogens **33**.[50]

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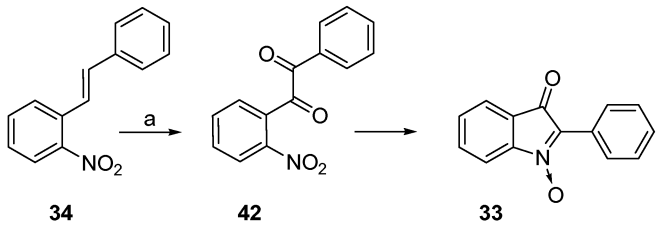
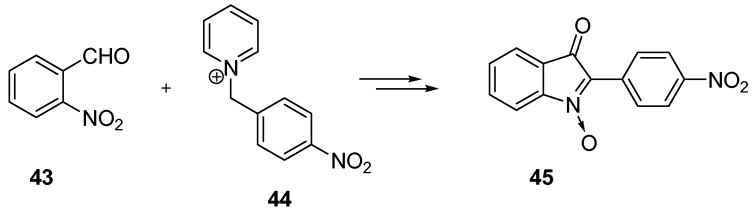
[47] Fischer, E.; Huetz, E. *Chem. Ber.* **1895**, *28*, 586-587.
[48] Fischer, E. *Chem. Ber.* **1896**, *29*, 1896-2063.
[49] Adams, D. B.; Hooper, M.; Morpeth, A. G. *J. Chem. Soc., Perkin Trans. 2* **1990**, *7*, 1269-1274.
[50] Boyer, J.; Bernardes-Génisson, V.; Nepveu, F. *J. Chem. Res. (S)*. **2003**, 507-508.




**Scheme 10.** a) Chlorobenzene, BSA 120°C, 140 h. (62%).

Kröhnke's procedure to prepare isatogens in the dark is convenient, but is however limited by the availability of *o*-nitrobenzaldehydes **43** and suitable pyridinium salts **44** (scheme 11).[51] The oxidation of 1-hydroxyindoles or 2-substituted indolines developed by Hooper is a more general procedure.[52,53]




**Scheme 11.**

## Oxygenation of 2,3-dihydroindoles (Paper 1)

The isatogen, (PIT) (**29**) has attracted much interest due to its biological properties (it interacts with P2 receptors and contracts smooth muscle cells). The quite related *N*-hydroxyindoles[54] also prevent platelet aggregation.[55] There is a possibility for formation of *N*-hydroxyindoles in nature since the *N*-hydroxylation of 2-phenylindole provides a minor metabolite, which has been suggested as a process for bio-activation.[56]

Biological studies of **KP-7** (**45**) gave increased contraction of blood vessels when ATP was administrated. The $P2X_1$ receptor was simultaneously relieved from desensitising. Since both **KP-7** and **PIT** have electron withdrawing groups in the 2-position, it has been suggested that the activity is related to the C-2 electron density. Thus by introducing several nitro groups,

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[51] Kröhnke, F.; Meyer-Delius, M. *Chem. Ber.* **1951**, *10*, 932-941.
[52] Bond, C. C.; Hooper, M. *Synthesis* **1974**, 443.
[53] Bristow, T. H. C.; Foster, H. E.; Hooper, M. *J. Chem. Soc., Chem. Commun.* **1974**, 677-678.
[54]For a review, see: Somei, M.; *Adv. Heterocycl. Chem.* **2002**, *82*, 101-155.
[55] Somei, M.; Yamada, K.; Hasegawa, M.; Tabata, M.; Nagahama, Y.; Morikawa, H.; Yamada, F. *Heterocycles* **1996**, *43*, 1855-1858.
[56] Jaccarini, A.; Felicie, M. A. The metabolism of pyrroles and indoles: ring nitrogen oxidation. In: *Biological oxidation of nitrogen*, Ed.; Gorrod, J. W, pp. 169-175, Elsevier/North-Holland 1978.

higher activity would be expected. To that end nitration of KP-7 with nitric acid gave (**46**) when the procedure used by Noland for nitration of 2-phenylisatogen was utilized.[57] Molecule **47** was obtained via Kröhnke's condensation of a pyridinum salt with 2,4-dinitrobenzaldehyde.

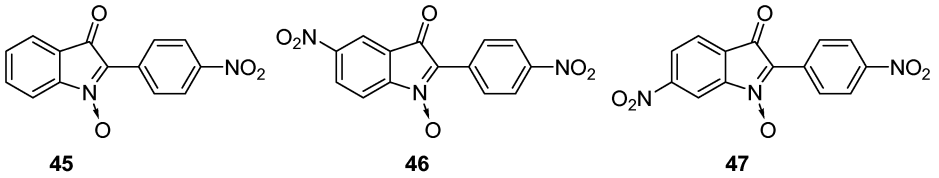
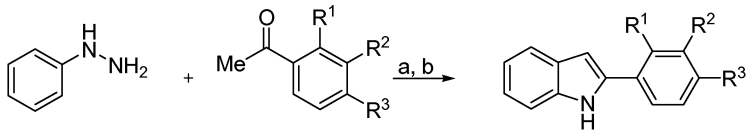



**Figure 8.**

Due to the relative unavailability of starting materials for Kröhnke's isatogen synthesis, an alternative route involving indole synthesis would provide higher flexibility. The Fischer indolisation[58] from the phenylhydrazine (**48**) and acetophenones **49a-f**, is an excellent procedure for generation of 2-phenylindoles **50a-f**. Preferably, the phenylhydrazone is generated in ethanol with acetic acid as catalyst.[59] This intermediate often crystallises when cooled and can then easily be added to a suitable acid such as PPA. When the aromatic ketone is substituted with amino, hydroxyl or thienyl groups, methanesulfonic acid is a useful reagent.[59] Preparation of indoles *via* the Fischer indole synthesis is an exotermic reaction and continuous measurement of the temperature is crucial in order to obtain the desired product in good yield.



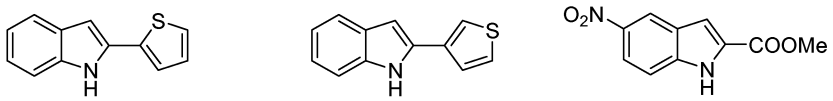

**48**

| | |
|---|---|
| **49a** $R^1$=H, $R^2$=OMe, $R^3$=OMe | **50a** $R^1$=H, $R^2$=OMe, $R^3$=OMe |
| **49b** $R^1$=H, $R^2$=H, $R^3$=OMe | **50b** $R^1$=H, $R^2$=H, $R^3$=OMe |
| **49c** $R^1$=OH, $R^2$=H, $R^3$=H | **50c** $R^1$=OH, $R^2$=H, $R^3$=H |
| **49d** $R^1$=H, $R^2$=OMe, $R^3$=H | **50d** $R^1$=H, $R^2$=OMe, $R^3$=H |
| **49e** $R^1$=H, $R^2$=H, $R^3$=H | **50e** $R^1$=H, $R^2$=H, $R^3$=H |
| **49f** $R^1$=H, $R^2$=H, $R^3$=Cl | **50f** $R^1$=H, $R^2$=H, $R^3$=Cl |

**Scheme 12.** a) EtOH, AcOH. b) PPA.

[57] Noland, W. E.; Rush, K, R.; Smith, L. *J. Org. Chem.* **1966**, *31*, 65-69.
[58]Robinson, B. In: *The Fischer Indole Synthesis*, Salisbury, Wiltshire, England, 1982.
[59]Billimoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *58*, 6777-6782.

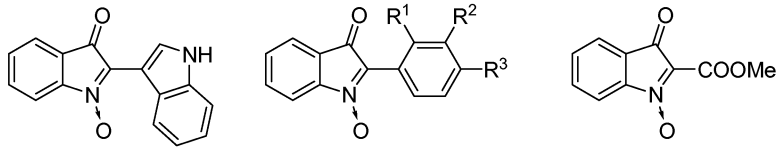
Attempts to reduce 2-thienylindoles **51** and **52** with tin in hydrochloric acid generated complex mixtures, as did attempted reduction of methyl 5-nitroindole-2-carboxylate (**53**) with magnesium in methanol.




**51** **52** **53**

**Figure 9**

The electron density at C-2 was initially believed to be related to the ascribed activity. Currently it is not clear how an optimal isatogen structure should be optimised. A series of isatogens possessing electron rich **54** C-2 to more average **55a-f** and electron deficient **45** and **56**, however no clear connection related to C-2 electron density could be stated. However it seems clear that the relative solubility, and hence the uptake, is important since 45 and 55d are relatively soluble and the only isatogens shown biological effects.[60]




**54**

**55a** $R^1$=H, $R^2$=OMe, $R^3$=OMe **56** R=H
**55b** $R^1$=H, $R^2$=H, $R^3$=OMe
**55c** $R^1$=OH, $R^2$=H, $R^3$=H
**55d** $R^1$=H, $R^2$=OMe, $R^3$=H
**55e** $R^1$=H, $R^2$=H, $R^3$=H
**55f** $R^1$=H, $R^2$=H, $R^3$=Cl
**45** $R^1$=H, $R^2$=H, $R^3$=$NO_2$

**Figure 10.**

All attempts to oxidise functionalized indoline derivatives like **57**[61] and **58a-b** generated complex mixtures.

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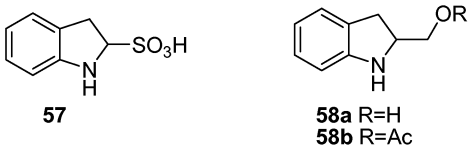
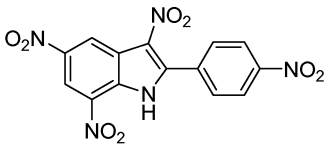
[60] Wihlborg, A. K.; Slätt, J.; Xiangyang, S.; Zhao, X. H.; Malmsjö, M.; Bergman, J. Hedner, T.; Erlinge, D. *Drug. Dev. Res*. **2003**, *59*, 82-87.
[61] Russel, H. F.; Harris, B. J.; Hood, H. D. B.; Thompson, E. G.; Watkins, A. D.; Williams, R. D. *Org. Prep. Proced. Int*. **1985**, *17*, 391-399.




**57** **58a** R=H
**58b** R=Ac

**Figure 11.**

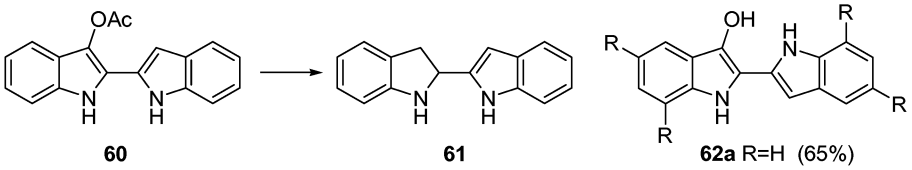
Since isatogens are sensitive to strong acids, attempts to introduce several nitro groups in 2-phenyindoline, gave simultaneously oxidation and nitration to yield 3,5,7-trinitro-2-(4-nitrophenyl)-1*H*-indole (**59**).




**59**

**Figure 12.**

During related studies on reduction of indole derivatives, Madelung reduced indigo with iron in hydrochloric acid and generated the structure of **60**, which was later confirmed by Bergman.[62,63] On the other hand, when Somei reduced indigo with zinc in acetic acid and acetic anhydride mixtures of **60** and **61** were obtained in varying ratios depending on temperature and amount of zinc used.[64,65] When Somei's experiment was repeated, only **60** could be isolated. Neither could Somei's statement that it was possible to transform **60** to **61** be verified. It was found however that both indigo and tetrabromoindigo readily underwent reduction to the functionalized 2,2′-biindolyl derivatives **62a-b**.




**60** **61** **62a** R=H (65%)
**62b** R=Br (68%)

**Figure 13.**

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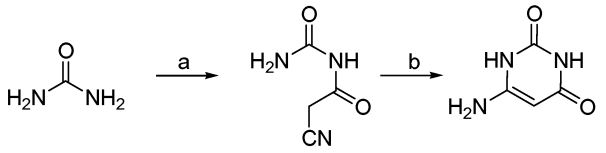
[62] Madelung, W.; Siegert, P. Chem. *Ber*. **1924**, *57*, 222-233.
[63] Bergman, J.; Eklund, N. *Chem. Scr.* **1982**, *19*, 193-204.
[64] Somei, M.; Hayashi, H.; Izumi, T.; Ohmoto, S. *Heterocycles* **1995**, *41*, 2161-2161.
[65] Somei, M.; Hayashi, H.; Ohmoto, S. *Heterocycles* **1997**, *44*, 169-176.

## Cyanoacetylation of indoles, pyrroles and aromatic amines (Paper 2)

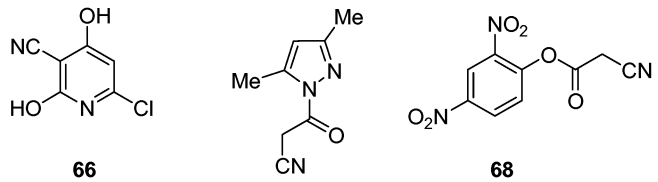
Heterocycles containing a cyanoacetyl group are relatively unexplored, most likely since previous preparations involved displacement of a halide in a haloacetyl substituted heterocycle with e.g. cyanide,[66] or from an alkyl carboxylate using acetonitrile in the presence of a strong base like sodium amide.[67] The cyanoacetylating reagent formed when acetic anhydride and cyanoacetic acid are mixed and heated has been used in the synthesis of uracils **65** *via* urea (**63**) or derivatives thereof,[68,69,70,71] and for the cyanoacetylation of enamines.[72] The acyl chloride itself is not particularly useful since it undergoes dimerization to **66**.[73]




**63** **64** **65**

**Scheme 13.** a) $NCCH_2COOH$, $Ac_2O$. b) NaOH.

Generation of the cyanoacetylation reagent from cyanoacetic acid and acetic anhydride has somehow been forgotten and instead other less convenient reagents like the pyrazole derivative **67** have been used.[74] The phenolic ester **68** of cyanoacetic acid is suggested to generate cyanoketene when heated.[75]



**66** **67** **68**

**Figure 14.**

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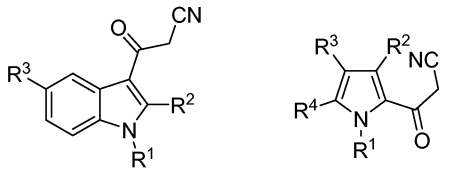
[66] Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647-1650.
[67] Eby, C. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 723-725.
[68] DE Patent 175415, Farbenfabriken vormals Freidrich Bayer & Co. (1905); *Chem. Abstr.*, **1**, 6240 (1905).
[69] Papesch, V.; Schroeder, E. *J. Org. Chem.* **1951**, *16*, 1879-1890.
[70] Muller, T.; Augustin, M.; Werchan, H. G. *Z. Chem.* **1989**, *29*, 281-283.
[71] Isobe, Y.; Tobe, M.; Inoue, Y.; Isobe, Y.; Tsuchiya, M.; Hayashi, H. *Biorg. Med. Chem.* **2003**, *11*, 4933-4940.
[72] Kappe, T.; Stelzel, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, *114*, 953-963.
[73] Schroeter, G.; Sidler, C.; Sulzbacher, M.; Kanitz, R. *Chem. Ber.* **1932**, *65*, 432-445.
[74] Stetinová, J.; Kada, R.; Lesko, J.; Zalibera, L.; Ilavský, D.; Bartovic, A. *Collect. Czech. Chem. C.* **1995**, *60*, 999-1008.
[75] Al-Lohedan, H.; Bunton, C. A. *J. Org. Chem.* **1981**, *46*, 3929-3930.

The structure of the reactive species formed when cyanoacetic acid and acetic anhydride are mixed has been assigned as a ketene or a mixed anhydride. Ketene intermediates have also been suggested when cyanoacetic acid or diethylphosphonic acid are reacted with DCC, and trapped as esters.[76] Wentrup has generated high yields of cyanoketene with FVT from derivatives of Meldrum's acid or (**79**) (Scheme 14).[77] Kreher cyanoacetylated indoles and pyrroles with a reagent generated from the methanesulfonate-cyanoacetic acid, and noted that 2-phenylindole was not cyanoacetylated.[78]

Bergman has investigated the reaction between indole and diketene, and it was concluded that mixtures of 1- and 3-acetoacetyl indoles were formed. A selectivity favouring the 3-substituted isomer was generated when a temperature maintained higher than 100 °C.[79] Cyanoacetic acid in acetic anhydride has been used by us to cyanoacetylate indoles and pyrroles. All products but **70a** gave precipitates upon cooling of the reaction mixtures in good yields (75-98%), thus the procedure is both quick and convenient. 2-Phenylindoles are somewhat less reactive and two equivalents of cyanoacetic acid had to be used. Formation of *N*-cyanoacetylated indoles or pyrroles was never observed during these experiments.



**69a** $R^1$=H, $R^2$=H, $R^3$=H
**69b** $R^1$=Me, $R^2$=H, $R^3$=H
**69c** $R^1$=H, $R^2$=Me, $R^3$=H
**69d** $R^1$=H, $R^2$=H, $R^3$=OMe
**69e** $R^1$=H, $R^2$=Ph, $R^3$=H
**69f** $R^1$=Me, $R^2$=Ph, $R^3$=H

**70a** $R^1$=H, $R^2$=H, $R^3$=H, $R^4$=H
**70b** $R^1$=Me, $R^2$=H, $R^3$=H, $R^4$=H
**70c** $R^1$=H, $R^2$=Me, $R^3$=H, $R^4$=Me
**70d** $R^1$=H, $R^2$=Et, $R^3$=Me, $R^4$=Me

**Figure 15.**

Carbazole and tetrahydrocarbazole do not react as fast as indole and an excess of cyanoacetic acid and prolonged reaction times were used to drive the reaction to completion. Other substituted acetic acids reacted similarly, i.e., reaction of indole with methanesulfonylacetic acid gave molecule **72**. Interestingly acetylated indoles substituted in the 1- and 3-postions, that contain phosphorus , such as **73a**, have been considered as derivatives of some natural

[76] Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975-8982.
[77] Moloney, W. J.; Wong, M. W.; Flammand, R.; Wentrup, C. *J. Org. Chem.* **1997**, *62*, 4240-4247.
[78] Kreher, R.; Wagner, P. H. *Chem. Ber.* **1980**, *113*, 3675-3677.
[79] Bergman, J. *Acta. Chem. Scand.* **1968**, *22*, 1063-1066.

metabolites, which had previously been obtained from 3-chloroacetylindoles with triethyl phosphite *via* the Arbuzov reaction.[80]

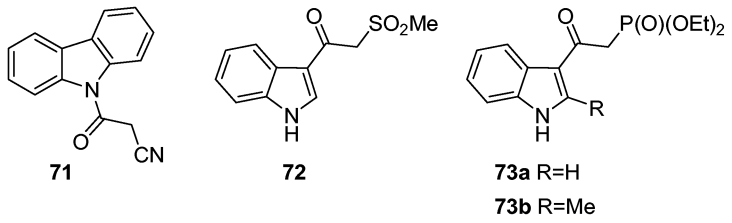



**Figure 16.**

A synthesis of cyanoacetylated 2,2′-bindolyl **74** has previously been described by Somei using a lengthy procedure starting from indigo (**13**).[81] The same product **74** could now be prepared from the readily available 2,2′-biindolyl (**12**)[82] within a few minutes in 90% yield. A related derivative of **74** can be converted to an analogue of the marine alkaloid **75**[83] in a few steps.[84] Derivatives like (**76c-d**) have been suggested as intermediates when *o*-aminobenzonitrile reacted with ethyl cyanoacetate in the presence of methoxide.[85] Low yielding reactions where *o*-nitroaniline was heated in ethyl cyanoacetate can be avoided by using cyanoacetic acid in acetic anhydride. Even weak enamines, for instance **77**, react with this reagent giving **78**, which is in agreement with results reported by Russian workers.[86]

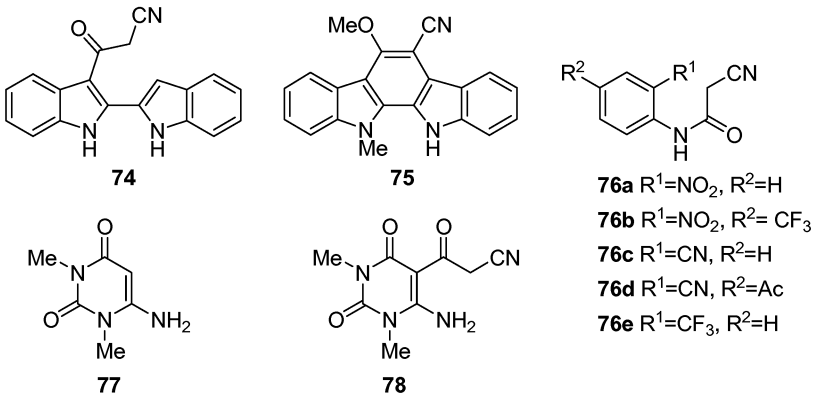



**Figure 17.**

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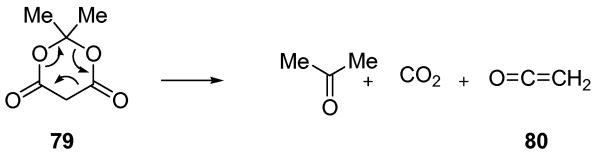
[80] Gurevich, P. A.; Yaroshevskaya, V. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2000**, *36*, 1361-1401.
[81] Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647-1650.
[82] Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631-5642.
[83] Knübel, G.; Larsen, L. K.; Moore, R. E. *J. Antibiot.* **1990**, *43*, 1236-1239.
[84] Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293-2295.
[85] Schäfer, H.; Sattler, K.; Gewald, K. *J. Prakt. Chem.* **1979**, *321*, 695-698.
[86] Smirnova, N. M.; Cherdantseva, N. M.; Burova O. A.; Nesterov, V. M.; Safonova, T. S. *Chem. Heterocycl. Compd.* **1990**, 811-815.

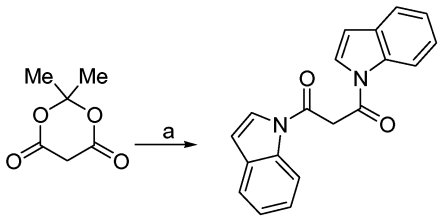
Meldrum's acid (**79**) forms the ketene **80** under mild conditions in solution (e.g refluxing toluene) whereas pyrolysis of Meldrum's acid requires temperatures higher than 200 °C in a condensed phase, suggested as a retro-Diels-Alder cleavage (scheme 14).[87]




**79** **80**

**Scheme 14.** Formation of ketene from Meldrum's acid.

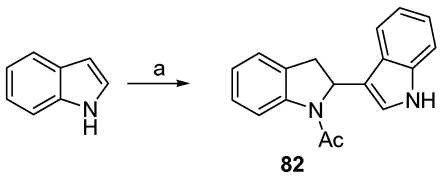
Derivatives of Meldrum's acid also form ketenes under FVP conditions.[88] However this type of ketenes has never been generated in the presence of an indole. When indole itself was reacted with Meldrum's acid the dimeric indole **81** derivative could be isolated. This indicates that Meldrum's acid (**79**) reacted similarly to diethyl malonate and thus not as a ketene.




**79** **81**

**Scheme 15.** a) indole in AcOH or toluene, reflux.

All attempts to use potassium ethyl malonic acid or nitroacetic acid[89] combined with acetic anhydride generated complex mixtures. Nitroacetic acid is a strong acid which will protonate indole, generateing complex mixtures of oligomers (c.f. Scheme 2). Attempts to use fumaric acid (also a relatively strong acid) induced dimerisation of indole, followed by acetylation to provide compound **82**.



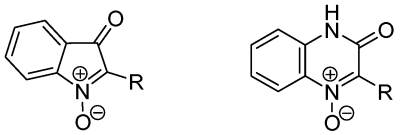

**82**

**Scheme 16.** a) Fumaric acid, $Ac_2O$, 100 °C.

[87] Gaber, A. E.; McNab, H. *Synthesis* **2001**, 2059-2074.
[88] Gaber, A. E.; Hunter, G. A.; McNab, H. *J. Chem. Soc., Perkin Trans 1*. **2002**, 548-554.
[89] Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1976**, 55, 77.

## Quinoxaline-*N*-oxides (Paper 3)

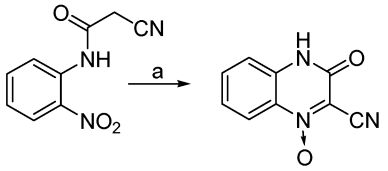
There are some interesting similarities in the reactivity of isatogens **28**,[90,91,92] and quinoxaline-3(4*H*)-one (**83**).[93,94,95] Thus both molecules can participate as 1,3-dipoles in cycloaddition reactions. Quinoxaline-3(4*H*)-ones **83** are also of interest as they have been considered as pharmacological analogues to isatogens **28**.[96]



**28** **83**

**Figure 18.**

A comprehensive monograph by Brown covering quinoxaline and its *N*-oxides has been released recently.[97] Quinoxaline-*N*-oxides **83** can be prepared from *o*-nitroanilines, which are first acylated with acetic acid derivatives containing an activated α-methylene group. The intermediate **76a** formed will directly condense intramolecularly with the nitro group present giving the corresponding *N*-oxide **84a** in the presence of base (scheme 17).[98,99]



**76a** **84a**

**Scheme 17.** a) $Ba(OH)_2$ or pyridine and NaOH.

As previously described (schemes 8 and 9) oximes can undergo rearrangement to form isatogens or 1-hydroxyindoles, but also quinoxaline-*N*-oxides. A related rearrangement is

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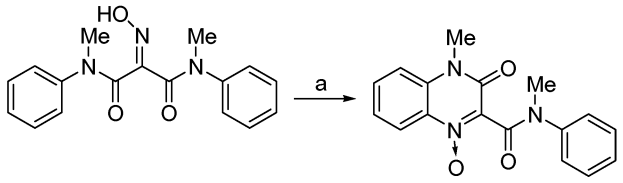
[90] Seidel, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, *102*, 904-914.
[91] Huisgen, R.; Hauck, H.; Seidl, H.; Burger, M. *Chem. Ber.* **1969**, *102*, 1117-1128.
[92] Tommasi, G.; Bruni, P.; Greci, L.; Sgarabotto, P.; Roghi, L. *J. Chem. Soc., Perkin Trans. 1* **1999**, *6*, 681-686.
[93] Mason, J. C.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1972**, 218-219.
[94] Ungureanu, M.; Zugaravescu, D. I. Stiin. *Univ. Al. I. Cuza Iasi, Sect. 1c.* **1974**, *20*, 29-34.
[95] Fusco, R.; Rossi, S. *Gazz. Chim. Ital.* **1969**, *94*, 3-30.
[96] Puhl, R. J., Ph. D. Thesis, University of Minnesota, 1971.
[97] Brown, D. J, In: *Quinoxalines,* John Wiley & Sons, New Jersey, 2004.
[98] Loudon, J. D.; Wellings, I. *J. Chem. Soc.* **1960**, 3462-3466.
[99] Loudon, J. D.; Tennant, G. *J. Chem. Soc.* **1960**, 3466-3470.

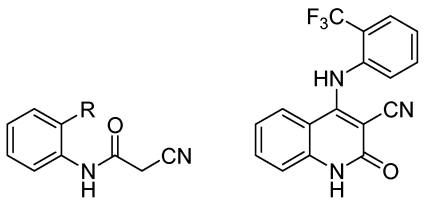
demonstrated by the conversion of the oxime derivative **85** to the quinoxaline-*N*-oxide **86** in sulfuric acid.[100]




**85** **86**

**Scheme 18.** a) $H_2SO_4$.

Cyanoacetylated aromatic amines like **76c**, **e** have been discussed as intermediates in cyclisation reactions where the active methylene group will condense with an *o*-substituent. The cyanoacetylated derivative **76c** was suggested as an intermediate in a quinolinone synthesis.[101] The *o*-trifluoroaniline derivative **76e** has been suggested as intermediate in formation of **87**.[102] Thus the suggested intermediate **76e** was prepared by cyanoacetylation, however it did not react at all even when treated with potassium *tert*-butoxide.




**76c** R=CN
**76e** R=CF3

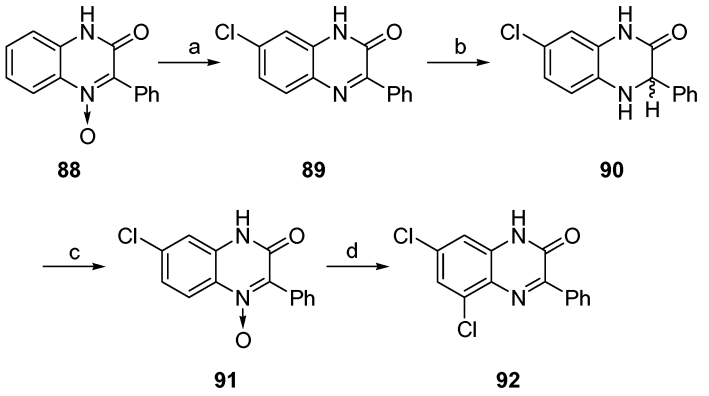
**87**

**Figure 19.**

Condensations between active methylene groups and nitro groups can be initiated by bases, such as pyridine, sodium hydroxide or barium hydroxide. Expectedly these bases also cause hydrolysis, a problem which has been discussed,[103] but no feasible solutions have been suggested. 2-Phenylquinoxaline-*N*-oxides **88** undergo chlorination in the 6-position in a mixture of hydrochloric acid and acetic acid. It has also been stated that when the 6-position is blocked, for instance with a chlorine atom, no further chlorination would occur.[104] The suggested compound **91** was prepared, and it became clear that an additional chlorine atom

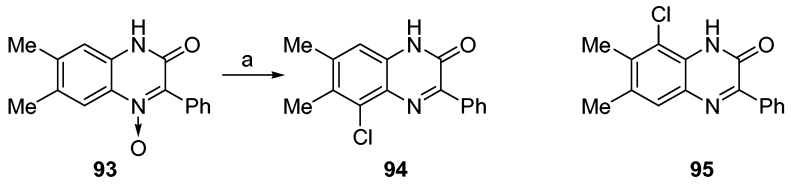
[100] Usherwood, E. H.; Whiteley, M. A. *J. Chem. Soc.* **1923**, 1069-1089.
[101] Cabrera, G.; Márquez, C. *Acta. Cient. Venez.* **1996**, *47*, 219-222.
[102] Bylov, I. E.; Bilokin, Y. V.; Kovalenko, S. M. *Heterocycl. Commun.* **1999**, *5*, 281-284.
[103] Tennant, G. *J. Chem. Soc.* **1964**, 2666-2673.
[104] Ahmad, Y.; Habib, M. S.; Iqbal, M. S.; Qureshi, M. I.; Ziauddin. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1659-1663.

does add predominantly in the 8-position. Preparation of **91** by direct oxidation with *m*-CPBA of **89** did not proceed in analogy with similar types of oxidations.[105]




**Scheme 19.** a) HCl, AcOH, reflux. b) $NaCNBH_3$, AcOH, 25 °C. c) *m*-CPBA, MeOH. d) HCl, AcOH, reflux.

However reduction of **89** followed by oxidation with *m*-CPBA gave compound **91** with the same melting point as Ahmad′s **91**. Chlorination of **91** in the 8-position can be performed with hydrochloric acid in acetic acid, however thionyl chloride is preferable since it gives higher yields. To verify these conclusions the known compound **93**[106] with both the 6- and 7-positions blocked with methyl groups, was prepared. Chlorination gave only one product with the suggested structure **94**, although the isomer **95** cannot be excluded rigorously.

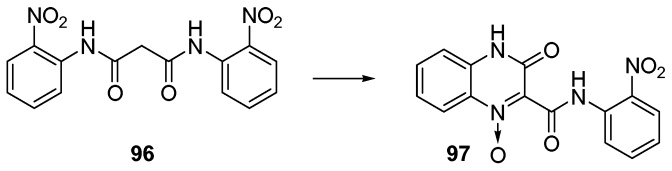



**Scheme 20.**

It has been reported that heating *o*-nitroaniline with diethyl malonate gave the dimeric product **96** in a poor yield (7%), which could be verified.[103] However, the same product has now been obtained in excellent yields (96%) from the reaction of *o*-nitroaniline with Meldrum's acid in acetic anhydride. The cyclisation of **96** was performed using potassium *tert*-butoxide in DMF to generate the quinoxaline derivative **97** in an acceptable yield (45%). All previous cyclization attempts had led to hydrolysis.[103]

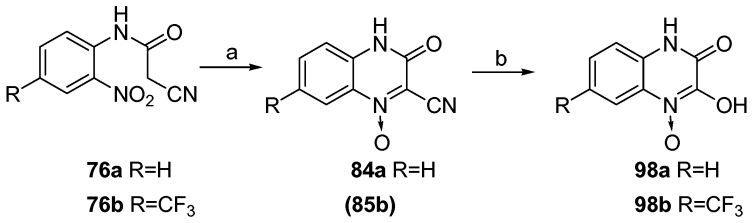
---

[105] Yoshida, K.; Otomasu, H. *Chem. Pharm. Bull.* **1984**, *32*, 3361-3365.
[106] Gazit, A.; App, H.; McMahon, G.; Chen, J.; Levitzki, A.; Bohmer, F. D. *J. Med. Chem.* **1996**, *39*, 2170-2177.



**Scheme 21.**

This is probably why preparation of 2-cyano-quinoxaline-*N*-oxides has been problematic for some researchers, particularly when various hydroxides have been used. Ahmad demonstrated that substitution of the nitrile with hydroxide is possible, albeit when boiled in aniline the *N*-oxide function was lost.[107] Both these findings are in agreement with those of Ahmad, however when **76d** was cyclised, compound **85b**, could not be isolated probably due to the electron withdrawing group, which promotes the substitution of the nitrile to generate **98b**.



**Scheme 22.** a) 1M NaOH, Pyridine or Potassium *tert*-butoxide, DMF. b) NaOH, EtOH, reflux.

Both these findings are in agreement with those of Ahmad, and the product from aniline **99** displayed a molecule ion at *m/z* 237, and quite complex NMR spectra. However a crystallographic study confirmed the previous conclusions.

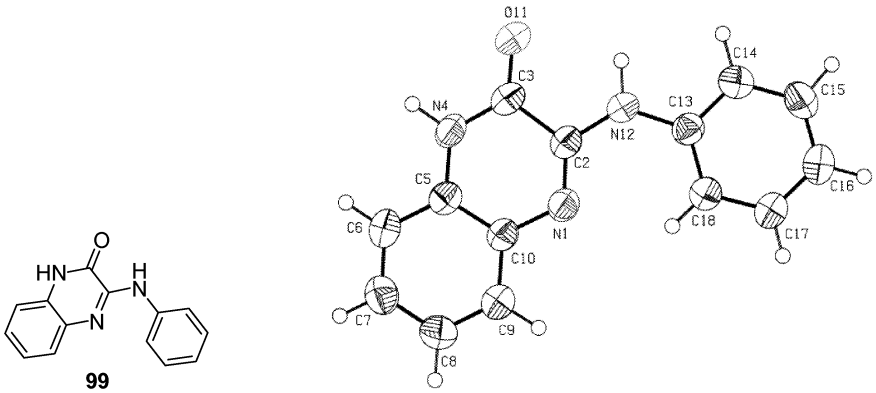
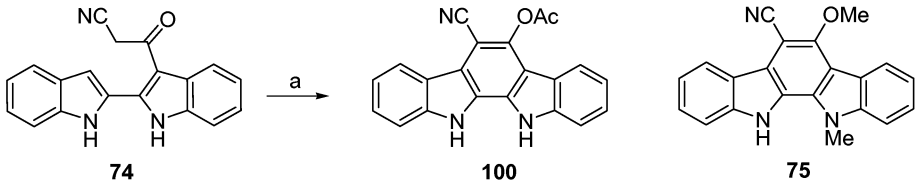


**Figure 20.** Structure of **99**, and the X-Ray structure of **99**.

[107] Ahmad, Y.; Habib, M. S.; Iqbal M. Ziauddin. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 562-565.

## 3-(Cyanoacetyl)indole as a synthetic intermediate (Papers 4 and 5)

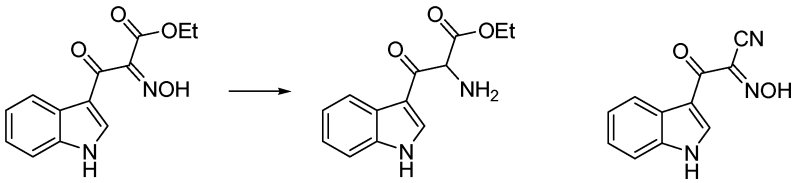
The relatively low occurrence of cyanoacetylated heterocycles prompted us to explore some synthetic applications of these compounds. One example illustrating the utility of the cyanoacetyl groups was demonstrated by Somei, who used cyanoacetylated 2,2′-biindolyl (**74**) to make an analogue (**100**) and the marine alkaloid **75**.[81]




**74** **100** **75**

**Scheme 23.** a) $Ac_2O$, AcOH, 10% Pd/C (35%).[81]

A synthesis of the oxime **101** was already suggested by Baker,[108,109] and has briefly been described by a Russian group, who also developed a procedure to reduce the generated oxime **101** to **102** in fair yield.[110] Nitrosation of cyanoacetylindole (**69a**) with sodium nitrite in acetic acid gave the oxime **103a**.



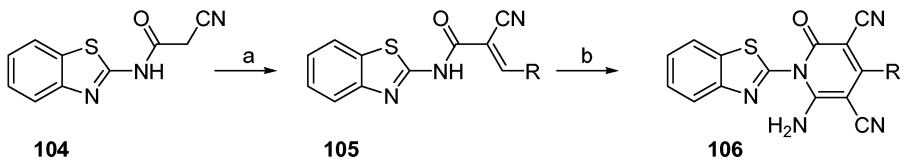

**101** **102** **103a**

**Scheme 24.**

One example how cyanoacetylated derivatives can be used is provided by the transformation of *N*-(2-benzothiazolyl)-cyanoacetamide (**104**), which is condensed with aldehydes **105**, and finally cyclised to **106**.[75]

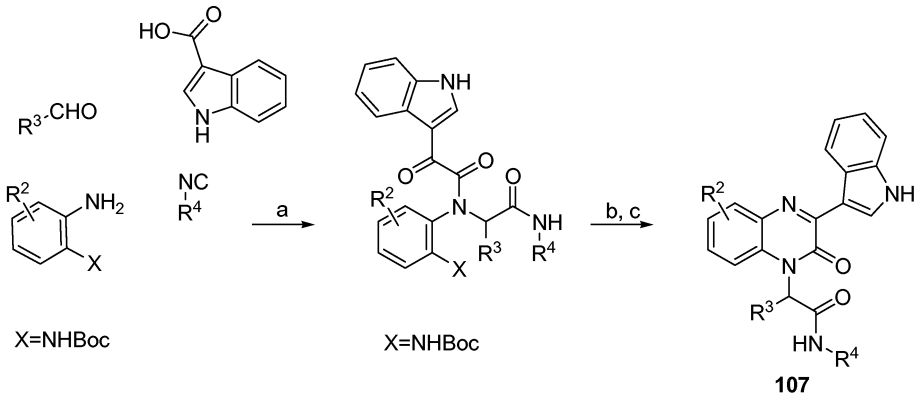
---

[108] Baker, J. W. *J. Chem. Soc.* **1940**, 458-460.
[109] Baker, J. W. *J. Chem. Soc.* **1946**, 461-463.
[110] Vinograd, L. K.; Sorokina, N. P.; Turchin, K. F.; Dubiskii, R. A.; Suvorov, N. N. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 2222-2226.



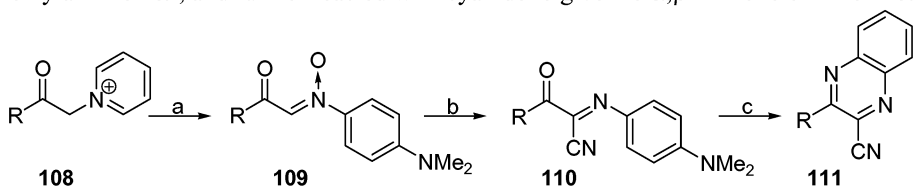

**Scheme 25.** a) R-CHO, $K_2CO_3$, AcOH, reflux 3 h.(77-95%) b) $NCCH_2CN$, piperidine, EtOH, reflux 6 h. (17-33%)[75]

Only a few examples of quinoxalines bearing indolic substituents are known for instance compound **107**, which has been prepared using a rather complex technique (Scheme 26).[111]




**Scheme 26.** a) MeOH, rt, 36 h. b) polystyrene-tosylhydrazine (3 equiv.), THF:$CH_2Cl_2$, 1:1 24 h. c) 10% TFA/$CH_2Cl_2$, 18 h.

Synthetic methodology based upon α,β-diketo nitriles has proven to be versatile in reactions with *o*-phenylenediamine to yield quinoxalines.[112] Kröhnke prepared α,β-iminoketonitriles **110** from King's pyridinium salts **108**,[113] which were condensed with *p*-nitroso-*N,N'*-dimethylaniline **109**, and further reacted with cyanide to give the α,β-iminoketonitrile **110**.




**Scheme 27.** a) *p*-nitroso-*N,N'*-dimethylaniline b) NaCN c) *o*-phenylenediamine, AcOH reflux.

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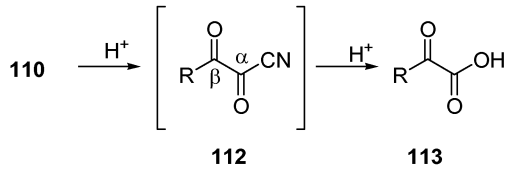
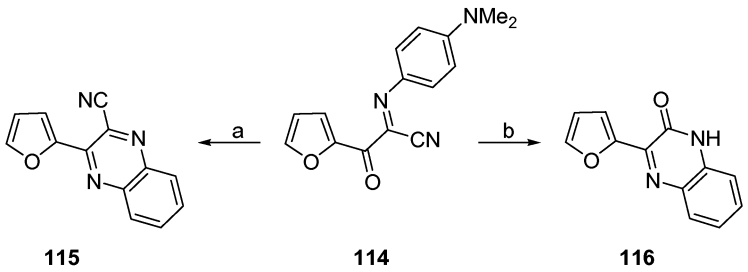
[111] Nixey, T.; Tempest, P.; Humle, C. *Tetrahedron Lett.* **2002**, *43*, 1637-1639.
[112] Sachs, F.; Barschall, H. *Chem. Ber.* **1901**, *34*, 3047-3054.
[113] King, C. *J. Am. Chem. Soc.* **1944**, *66*, 894-895.

Hydrolysis of the α,β-iminoketonitrile **110** with mineral acids readily generated the α-keto acids **113** (scheme 28).[114,115,116] When the α,β-iminoketo nitrile **110** was heated in acetic acid, it was suggested to form α,β-diketonitrile **112**, an intermediate where the α-keto group was considered more reactive than the β-carbonyl (scheme 28).[117]




**Scheme 28.** a) Hydrolysis of α,β-iminoketo nitrile with $H_2SO_4$.

A slightly modified version gave either the cyano quinoxaline **115** or the quinoxalin-one derivative **116** (scheme 29).[118] Recently Wasserman utilised similar technique; however the diketo derivatives were generated by ozonolysis of phosphoranylideneacetonitriles.[119]

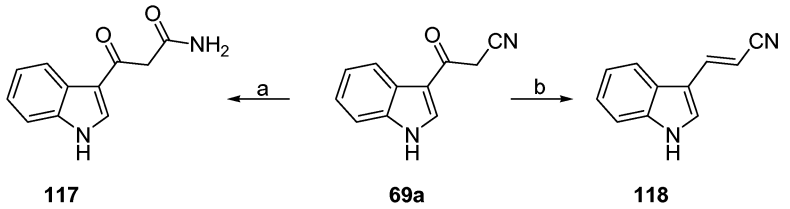



**Scheme 29.** a) *o*-phenylenediamine, AcOH, reflux. b) *o*-phenylenediamine, EtOH, cat. $H_2SO_4$, reflux.

Hydrolysis of the nitrile functionality of **69a** in PPA gave the amide **117**. Surprisingly, both diketo compounds, **103a** and **117** were relatively unreactive towards reducing agents like $NaBH_4$ or $NaCNBH_3$ in EtOH or AcOH. 3-Cyanoacetylindole itself was easily reduced with $NaBH_4$ in EtOH giving the corresponding alcohol, which underwent elimination during acidic workup giving *E*-cyanovinylindole (**118**). A mixture of isomers was generated when cyanoacetic acid was condensed with 3-formylindole followed by decarboxylation.[120]

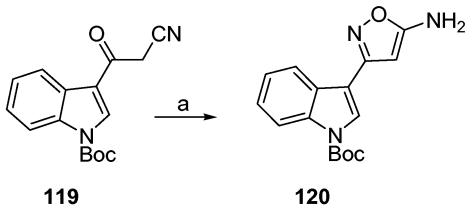
---

[114] Kröhnke, F. *Chem. Ber.* **1947**, *80*, 298-311.
[115] Balenovic, K.; Cerar, D.; Bregant, N. *Croat. Chim. Acta.* **1956**, *28*, 279-235.
[116] Michalsky, J. *J. Pract. Chem.* **1959**, *4*, 186-198.
[117] Pfeiffer, F. R.; Case, F. H. *J. Org. Chem.* **1966**, *31*, 3384-3390.
[118] Saldabol, N. O.; Alekseeva, L. N.; Brizga, B. A.; Zile, A. Ya.; Kruzmetra, L. V.; Medne, K. K. *Pharm. Chem. J. (Engl. Transl.)*, **1968**,*10* ,541-544.
[119] Wasserman, H. H.; Long, Y. O.; Parr, J. *Tetrahedron Lett.* **2003**, *44*, 361-363.
[120] Scapini, G.; Tornetta, B.; Pappalardo, G.; Bernardini, A. *Boll. Sedute Accad. Gioenia Sci. Natur. Catania.* **1968**, *9*, 497-506.




**Scheme 30.** a) PPA 100 °C, 2h, $H_2O$ (98 %). b) EtOH, $NaBH_4$, reflux, HCl.

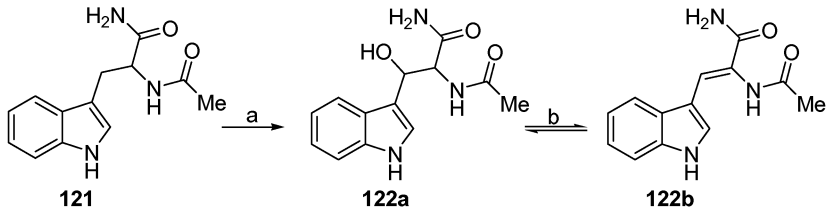
The carbonyl group of compound **69a** was relatively unreactive, but introduction of a Boc group on the indole nitrogen to give **119**, and subsequent reaction with hydroxylamine gave the isoxazole **120**. Such reactions do not normally occur without the presence of the protecting and activating group.




**Scheme 31.** a) $H_2NOH{\cdot}HCl$, NaOAc, $CH_2Cl_2$, MeOH.

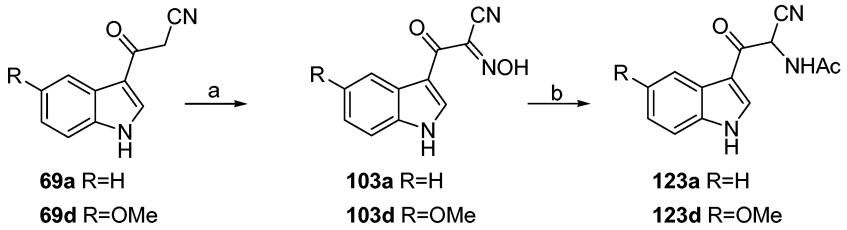
Some metabolites of tryptophan isolated from *Pseudomonas*, have been tentatively referred to as "tryptophan-side chain α,β-oxidase" (scheme 32). These species have been shown to catalyze the oxidation of various tryptophan containing peptides.[121,122] This type of oxidation also occurs by lignin isozymes from the white rot fungus *Phanerochaete chrysosporium*. The oxidation product forms an equilibrium between **122a** and **122b** dependent upon the presence of water.[123] A related antibiotic peptide containing several related oxidised tryptophan derivatives **122a,b** is telomycin.[124]

[121] Noda, Y.; Takai, K.; Tokuyama, T.; Narumiya, S.; Ushiro, H.; Hayaishi, O. *J. Biol. Chem.* **1977**, *12*, 4413-4415.
[122] Noda, Y.; Takai, K.; Tokuyama, T.; Narumiya, S.; Ushiro, H.; Hayaishi, O. *J. Biol. Chem.* **1978**, *14*, 4819-4822.
[123] Blodig, W.; Doyle, W. A.; Smith, A. T.; Winterhalter, K.; Choinowski, T.; Piontek, K. *Biochemistry* **1998**, *37*, 8832-8838.
[124] Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462-470.




**Scheme 32.** a) *Pseudomonas*. b) $-H_2O$.

Nitrosation of **69a,d** was first performed with sodium nitrite in acetic acid, which generated complex mixtures when **69d** were nitrosated. However a procedure based on *iso*-pentyl nitrite in ethanol/ethoxide gave the desired products in excellent yields regardless the nature of the ring substituent used. All attempts to reduce the oxime to the corresponding amine have failed. The acetylated amine, however, could be obtained in good yields. For reduction of the oxime to the corresponding amine, the oxygen atom in the oxime group was first acetylated and this material was treated with AcOH, $Ac_2O$ and zinc powder at room temperature giving **122a,d**.




**Scheme 33.** a) *iso*-pentyl nitrite, NaOEt, EtOH. b) Zn, $Ac_2O$, AcOH.

The tryptophan derivatives **123a,d** may possibly display biological activities related to tryptophan, melatonin, serotonin, and biological studies would therefore be of considerable interest. 3-Cyanoacetylindole does undergo condensation with aldehydes, thus for example 3-formylindole gave the dimeric indole derivative **124**. *o*-Salicaldehyde, similarly generated the coumarine derivative **125a**. The intermediate **126**, (an analogue of **124**), was not isolated due to quick intramolecular cyclisation followed by hydrolysis of the imidate derivative **125b**.

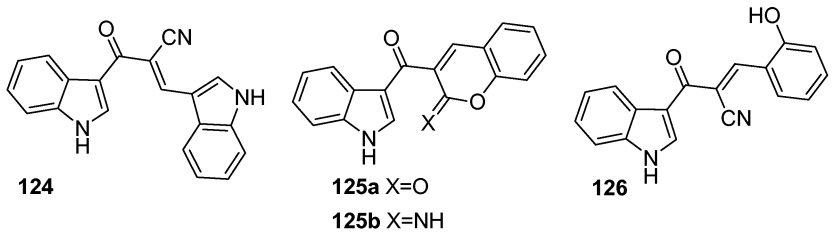
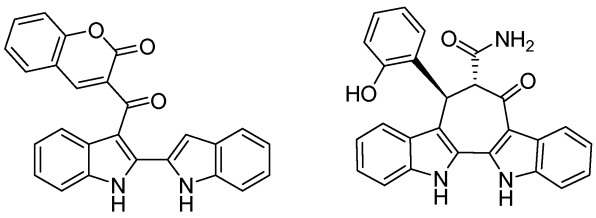



**Figure 21.**

When the same methodology as for preparation of **125a** was adapted to cyanoacylated-2,2′-biindolyl (**71**), the coumarine derivative **127** was not observed, rather a fused 7-membered

ring **128** was formed. This is due to the nucleophilicity of the second indole ring which reacts in a Michael fashion which will create the new 7-membered ring.



**127** **128**

**Figure 22.**

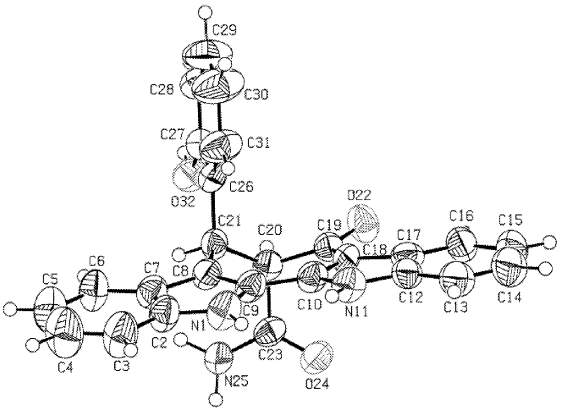



**Figure 23.** X-ray structure of **128.**

When DMF/DMA was reacted with 3-cyanoacetyl-2,2′-biindolyl (**71**) in DMF the similarly fused azepine derivative[125] **129** (bound 1,3 to the 2,2′-biindolyl system) was obtained. The isomeric (3,3) related structure **130** could be excluded primarily due to the presence of a characteristic 3-H indolic signal (at 7.91 ppm in the NMR spectrum). In analogy with the indole case **125a**, 2-thienylindole gave the coumarine derivative **131**.

[125] For a review see: Pietra, F. *Chem. Rev.* **1973**, *73*, 293-358.

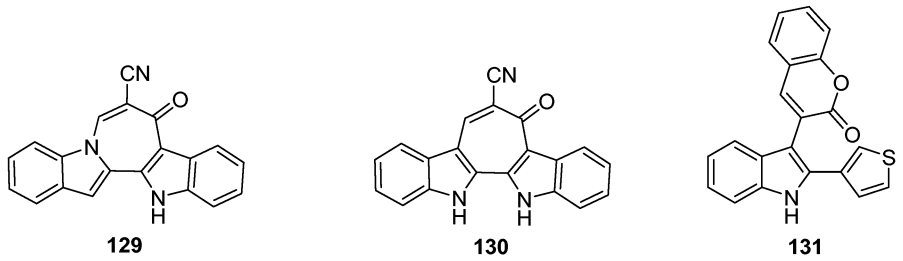
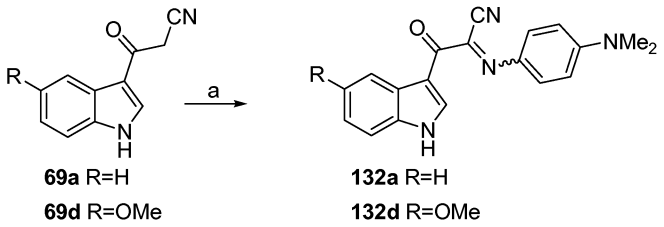


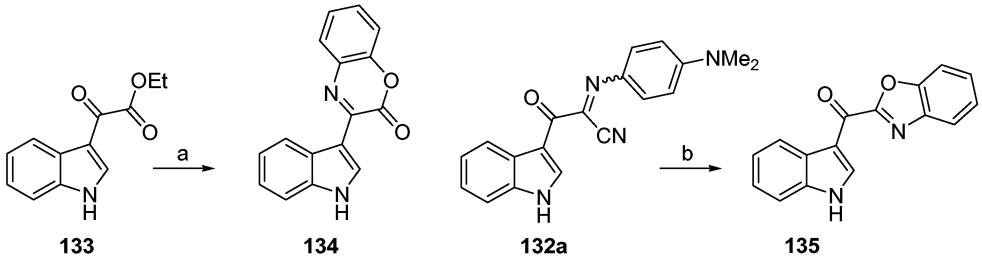

**Figure 24.**

Condensation of **69a,d** with nitroso compounds gave the α,β-iminoketo nitriles **132a,d**.




**Scheme 34.** a) *N,N'*-dimethyl-*p*-nitrosoaniline, $Na_2CO_3$, EtOH.

Moffett has reacted ethyl indole-3-glyoxylate (**133**) with *o*-aminophenol and obtained **134**.[126,127] When the related compound **132a** was reacted with *o*-aminophenol in acetic acid it was anticipated that the same type of compound i.e. 2-cyano-3-indolyl quinoxaline (**136)** , would be formed (c.f. Scheme 29). However, the compound obtained was verified by crystallographic studies which established the structure as the benzoxazole **135**. This is in agreement with the suggested reactivity of the intermediate of **132a** (scheme 28).




**Scheme 35. a)** *o*-aminophenol, DMF. b) *o*-aminophenol, AcOH reflux.

[126] GB Patent 1022037, Upjohn Co. (1966); *Chem. Abstr.* **64**, 84611 (1966).
[127] Moffett, R. B. *J. Med. Chem.* **1966**, *9*, 475-478.

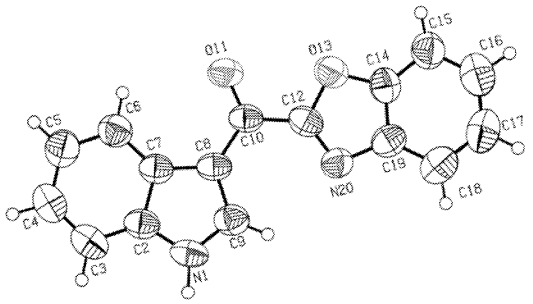
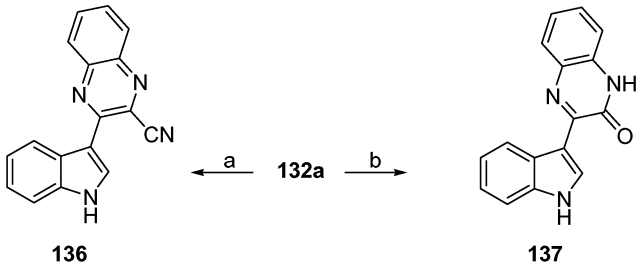


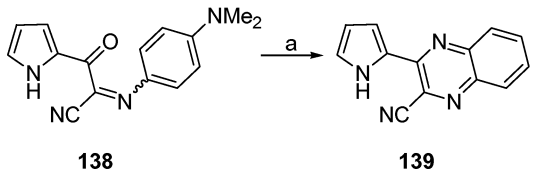

**Figure 25.** X-ray structure of the benzoxazole derivative **135.**

The indolyl α,β-iminoketo nitrile **132a** was reacted with *o*-phenylenediamine in acetic acid and the quinoxaline **136** was formed. In analogy with literature precedents compound **137** was obtained when stronger acid (sulfuric acid dissolved in ethanol) was used as the reaction medium.[118]




**Scheme 36.** a) *o*-phenylenediamine, AcOH, reflux. b) *o*-phenylenediamine, EtOH, $H_2SO_4$, reflux.

In analogy (c.f. scheme 34) the active methylene group of 2-(cyanoacetyl)pyrrole (**70a**) could be condensed with *N,N'*-dimethyl-*p*-nitrosoaniline to generate **138**, which underwent transformation to the quinoxaline derivative **139** with *o*-phenylenediamine in acetic acid. Attempts to similarly prepare compounds (such as the indole derivative **135**) with *o*-aminophenol and **138** were not successful.




**Scheme 37.** a) *o*-phenylenediamine, AcOH, reflux.

## Conclusions

Acylation with derivatives of acetic acid such as, cyanoacetic acid, methanesulfonic acetic acid, and diethylphosphonoacetic acid in combination with acetic anhydride constitutes a convenient method of preparing acylated pyrroles, indoles, amines and enamines. Meldrum's acid forms dimeric amides with indole or *o*-nitroaniline.

Cyanoacetylated amines bearing *o*-substituents like, nitro or cyano functions can undergo intramolecular cyclisation to quinoxaline-*N*-oxide or quinoline derivatives. 2-Phenylquinoxaline-*N*-oxides can be chlorinated in either 6- or 8-position with hydrochloric acid in acetic acid to yield halogen containing deoxygenated quinoxaline.

2-Phenylindoles was reduced with tin in hydrochloric acid and ethanol to give 2-phenylindoline, which was oxidised to 2-phenylisatogen with *m*-CPBA.

The methylene of cyanoacetyl derivatives was used for condensation reactions with aldehydes (with salicylaldehyde to form coumarine derivatives). Condensations of aldehydes with cyanoacetylated 2,2′-biindolyl produced derivatives containing 7-membered rings. These methylenes can also be condensed with *N,N*′-dimethyl-*p*-nitroso-aniline, these α,β-iminoketo nitriles reacted with *o*-phenylenediamine in acetic acid gives quinoxalines.

The methylene was nitrosated preferably with *iso*-pentyl nitrite instead of acetic acid and sodium nitrite. These nitrosated derivatives were reduced with zinc in mixtures of acetic anhydride and acetic acid to give acetylated amines.

## Abbreviations

| | |
|---|---|
| AcOH | acetic acid |
| $Ac_2O$ | acetic anhydride |
| ATP | adenosine triphosphate |
| ADP | adenosine diphosphate |
| AMP | adenosine monophosphate |
| BSA | benzeneseleninic anhydride |
| DCC | dicyclohexylcarbodiimide |
| DMF | *N,N*-dimethylformamide |
| DMFDMA | dimethylformamide dimethyl acetal |
| FVT | flash vacuum thermolysis |
| HMPA | hexamethylphosphoramide |
| *m*-CPBA | meta-chloroperbenzoic acid |
| PIT | 2,2′-pyridylisatogen tosylate |
| SAR | structure activity relationship |
| TFA | trifluroacetic acid |
| THF | tetrahydrofuran |
| PPA | polyphosphoric acid |

## Acknowledgements

Först av allt vill jag tacka min handledare Professor Jan Bergman, som låtit mig härja fritt på lab, ibland kanske lite väl yvigt. Tack för ditt förtroende du har visat mig under dessa år.

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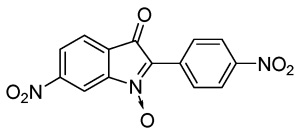
Jag vill även tacka alla mina syskon, Mica, Lotten och Robin för att ni alltid finns där.

Jag vill tacka Annica för all kärlek och värme.

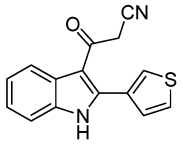
## Appendix: Supplementary material




YY

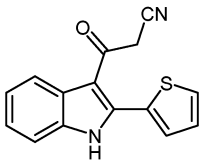
Compond **47**

2,4-dinitrobenzaldehyde (2.1 g, 11 mmol) was added to a mixture of **44** (2.0g, 7.1 mmol), $Ac_2O$ (40 mL), AcOH (1.5 mL) and KOAc (0.33g, 3.4 mmol) and heated at 75 °C 17 h. The precipitate formed was collected by filtration and dried to give **47** (1.2, g 54%)
mp 262-263 °C.
ir (neat) 1711, 1592, 1544, 1514, 1481, 1384, 1352, 1314, 866, 837, 736, 687 $cm^{-1}$.
$^1H$ NMR (DMSO-$d_6$): 8.00-8.02 (m, 1H), 8.31-8.32 (m, 1H), 8.39-8.40 (m, 2H), 8.53-8.56 (m, 1H), 8.72-8.74 (m, 2H) ppm.




3-oxo-3-(2-(thiophen-3-yl)-1*H*-indol-3-yl)propanenitrile

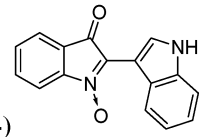
2-(thiophen-3-yl)-1*H*-indole (**52**) (2.3 g, 12 mmol) was added to a solution of cyanoacetic acid (2.0 g, 24 mmol) in acetic anhydride (30 mL), and heated at 85 °C for 30 minutes. The mixture was which was cooled and then poured into water and left for 2 h. Evaporation of the solvent gave a solid, collected by filtration and washed with water and dried to give 3-oxo-3-(2-(thiophen-3-yl)-1*H*-indol-3-yl)propanenitrile (2.9g, 92%).
mp 184-185 °C.
ir (neat) 3260, 2210, 1615, 1440, 1175, 1099, 750 $cm^{-1}$.
$^1H$ NMR (DMSO-$d_6$) 4.12 (s, 2H), 7.22-7.30 (m, 2H), 7.45-7.51 (m, 2H), 7.78-7.81 (m, 1H), 8.09-8.13 (m, 2H), 12.35 (bs, 1H) ppm.
$^{13}C$ NMR (DMSO-$d_6$) 31.9, 111.9, 112.0, 116.1, 121.2, 122.4, 123.4, 126.6, 127.1, 128.2, 129.0, 131.6, 135.4, 140.8, 183.7 ppm.




3-Oxo-3-(2-thiophen-3-yl-1*H*-indol-3-yl)-propionitrile

Compound was prepared as described for 3-oxo-3-(2-(thiophen-3-yl)-1*H*-indol-3-yl)propanenitrile.
Yield: 76 %; mp 156-157 °C.
ir (neat) 3261, 2225, 1644, 1626, 1434, 1363, 1306, 1175, 1096, 889, 852, 744, 695 $cm^{-1}$.
$^1H$ NMR (DMSO-$d_6$) 4.31 (s, 2H), 7.22-7.31 (m, 3H), 7.48-7.53 (m, 1H), 7.75-7.76 (m, 1H), 7.87-7.89 (m, 1H), 8.02-8.05 (m, 1H), 12.47 (bs, 1H) ppm.

$^{13}$C NMR (DMSO-$d_6$) 32.3, 112.0, 112.2, 116.1, 121.1, 122.4, 123.7, 126.2, 127.6, 130.1, 131.1, 131.4, 135.6, 138.1, 183.8 ppm.



2-(3-indolyl)-indolon-*N*-oxide (**54**)

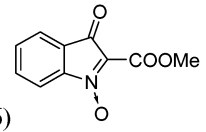
Prepared as compound **56** in 67% yield.

mp 198-199 °C.

ir (neat) 3240, 1718, 1600, 1542, 1473, 1459, 1425, 1391, 1283, 1226, 1183, 1093, 739 cm$^{-1}$.

$^{1}$H NMR (DMSO-$d_6$) 7.15-7.26 (m, 2H), 7.50-7.64 (m, 4H), 7.72-7.77 (m,1H), 8.55-8.58 (m, 1H), 8.92-8.94 (m, 1H), 12.01 (bs, 1H) ppm.

$^{13}$C NMR (DMSO-$d_6$) 102.6, 112.1, 112.9, 120.6, 121.4, 122.7, 122.9, 123.6, 124.1, 130.0, 130.5, 132.7, 135.2, 136.2, 147.8, 186.7 ppm.



Compund (**56**)

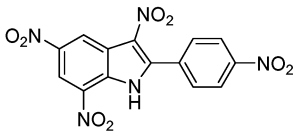
*m*-CPBA 50-55% (15.0 g) was added to a solution of **21d** (2.0 g, mmol) in MeOH (60 mL) and left for 3 h. The precipitate formed was collected by filtration and dried to give 65 (2.1 g, 81 %).

mp °C 208-209 °C.

ir (neat) 1705, 1500, 1446, 1397, 1233, 1142, 1075, 984, 967, 885, 859, 768, 750, 657 cm$^{-1}$.

$^{1}$H NMR (DMSO-$d_6$) 3.81 (s, 3H), 7.73-7.82 (m, 4H) ppm.

$^{13}$C NMR (DMSO-$d_6$) 51.9, 114.9, 121.9, 122.3, 126.5, 133.7, 135.2, 146.9, 157.3, 182.3 ppm.



3,5,7-trinitro-2-(4-nitrophenyl)-1*H*-indole (**59**)

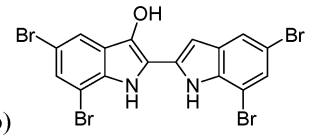
1-(2-phenylindolin-1-yl) ethanone (0.5 g, 2.1 mmol) was added in small portions to a (ice bath cold) nitric acid (5 mL d=1.52) and left for 30 minutes, whereupon the mixture was poured on ice to and the precipitate formed, which was recrystallized from EtOH gave **59** (0.2 g 25%) as a yellowish solid.

mp 199-200 °C.

ir (neat) 3374, 3104, 1710, 1540, 1516, 1502, 1475, 1341, 1315, 1293, 1221, 1159, 1112, 1062, 855, 829, 739, 699 cm$^{-1}$.

$^{1}$H NMR (DMSO-$d_6$) 8.04 (d, *J*=8.5 Hz, 2H), 8.42 (d, J=8.5, 2H), 8.92-8.94 (m, 1H), 9.28-9.29 (m, 1H), 13.91 (bs, 1H) ppm.

$^{13}$C NMR (DMSO-d6) 116.2, 122.2, 122.9, 124.1, 127.4, 128.8, 132.2, 133.5, 132.5, 134.6, 142.6, 145.0, 148.6 ppm.



5,7-dibromo-2-(5,7-dibromo-1*H*-indol-2-yl)-1*H*-indol-3-ol (**62b**)

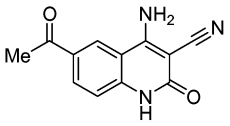
Tin chloride (10.0 g, 44.3 mmol) was added to a mixture of tetrabromoindigo (5.0 g, 8.65 mmol) in hydrochloric acid (50 mL) and ethanol (30 mL), and heated at 100°C for 8 h. The precipitate formed was collected by filtration and dried to give **62b** (3.3 g, 68%) as a grey solid.

mp 286 °C (dec).

ir (neat) 3426, 3174, 1610, 1593, 1532, 1454, 1443, 1312, 1150 $cm^{-1}$.

$^{1}$HNMR (DMSO-$d_6$) 7.24 (m, 1H), 7.45 (d, *J*=1.6, 1H), 7.49 (d, *J*=1.6, 1H), 7.80 (d, *J*=1.5, 1H), 7.93 (d, *J*=1.5, 1H), 9.84 (bs, 1H), 11.11 (bs, 1H), 11.43 (bs, 1H) ppm.

$^{13}$C NMR (DMSO-$d_6$) 101.1, 104.2, 105.2, 110.4, 111.9, 115.0, 119.8, 121.5, 122.6, 125.2, 126.3, 130.7, 131.5, 131.9, 133.3, 135.4 ppm.



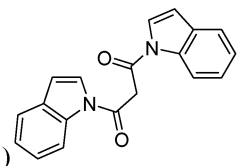
6-Acetyl-4-amino-2-oxo-1,2-dihydro-quinoline-3-carbonitrile

Potassium *tert*-butoxide (1.46 g, 13 mmol ) was added to a solution of **76d** (1.0 g, 4.4 mmol) in DMF (10 mL), and heated at 100 °C for 30 min. The reaction mixture was cooled and poured into 2M hydrochloric acid and the precipitate formed, was collected by filtration and dried to give 6-acetyl-4-amino-1,2-dihydro-2-oxoquinoline-3-carbonitrile (0.94 g 94%) yield % mp >400 °C.

ir (neat) 3359, 3229, 2215, 1671, 1642, 1614, 1590, 1507, 1476, 1400, 1359, 1252, 980, 699, 688 $cm^{-1}$

$^{1}$H NMR (DMSO-$d_6$) 2.60 (3H, s), 7.30 (d, *J*=8.7, 1H), 8.06 (d, *J*=8.7, 1H), 8.13 (2H, bs), 8.79 (1H, s), 11.57 (1H, bs) ppm.

$^{13}$C NMR (DMSO-$d_6$) 26.6, 77.7, 110.8, 116.4, 116.5, 126.0, 130.5, 131.7, 142.7, 158.4, 160.8, 196.4 ppm.



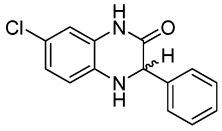
1,3-di(1*H*-indol-1-yl)propane-1,3-dione (**81**)

Indole (**15**) (1.1 g, 9.4 mmol) was added to a mixture of Meldrum′s acid (**79**) (0.65 g, 4.3 mmol) in acetic anhydride(20 mL), at 70 °C during 2 h. Evaporation gave a semisolid, which was treated with diethyl ether and the precipitate formed, was collected by filtration and dried to give **81** (0.3g 21%) as a yellow solid.

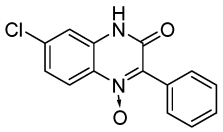
mp 201-202 °C.

ir (neat): 3150, 3054, 2990, 2951, 1695, 1676, 1541, 1471, 1449, 1381, 1348, 1284, 1206, 1151, 1106, 923, 742, 700, 622 $cm^{-1}$.

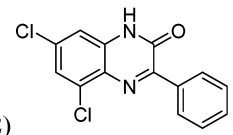
$^{1}$H NMR (DMSO-$d_6$): 5.02 (s, 2H), 6.81 (d, 2H, J=3.8), 7.28-7.38 (m, 4H), 7.64-7.66 (m, 2H), 7.97 (d, 2H, J=3.8), 8.33-8.35 (m, 2H) ppm.
$^{13}$C NMR (DMSO-$d_6$): 44.8, 109.0, 115.9, 121.0, 123.9, 124.9, 127.2, 130.5, 135.0, 166.0 ppm.



7-chloro-3,4-dihydro-3-phenylquinoxalin-2(1*H*)-one (**90**)
Sodium cyano borohydride (0.5 g, 8.0 mmol) was added to a solution of (**89**) (1.8 g, 7.0 mmol) in acetic acid (50 mL), and left overnight. Evaporation gave a solid which was treated with sodium carbonate and the precipitate formed was collected by filtration and dried to give **90** (1.78g 98%) as a white solid.
mp 212-213 °C.
ir (neat) 3304, 2962, 1669, 1596, 1497, 1380, 1338, 1303, 1240, 860, 805, 750, 701, 645 cm$^{-1}$.
$^{1}$H NMR (DMSO-$d_6$) 4.96 (s, 1H), 6.74-6.86 (m, 4H), 7.27-7.33 (m, 5H), 10.56 (s, 1H) ppm.
$^{13}$C NMR (DMSO-$d_6$) 59.1, 114.2, 114.3, 120.8, 122.4, 126.6, 126.9, 127.8, 128.4, 132.9, 140.0, 165.8 ppm.

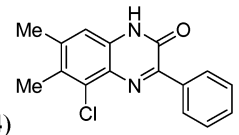


Compound (**91**)
*m*-CPBA (50-55%) (2.4 g) was added to a solution of 7-chloro-3,4-dihydro-3-phenylquinoxalin-2(1*H*)-one (**90**) (0.9 g, 3.5 mmol) in methanol (25 mL), after 30 min the yellow precipitate formed was collected by filtration and dried to give **91** (0.84 g 89%) as a yellow solid.
mp 315-316 °C.
ir (neat) 2812, 1639, 1611, 1477, 1360, 1307, 1250, 1217, 1163, 1117, 1083, 1051, 1021, 941, 854, 828, 771, 688, 589 cm.
$^{1}$H NMR (DMSO-$d_6$) 7.35-7.38 (m, 2H), 7.45-7.50 (m, 3H), 7.67-7.70 (m, 2H), 8.15-8.19 (m, 1H), 12.54 (s, 1H) ppm.
$^{13}$C NMR (DMSO-$d_6$) 115.1, 121.9, 123.2, 127.4, 128.5, 129.2, 129.4, 130.6, 133.0, 136.3, 138.7, 156.5 ppm.

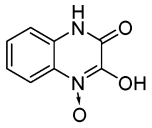


5,7-dichloro-3-phenylquinoxalin-2(1*H*)-one (**92**)
(**91**) (140 mg, 0.5 mmol) was dissolved in $SOCl_2$ (3 mL) and heated for 2 h. Evaporation gave a precipitate which was collected by filtration and washed with cold ethanol to give **92** (110 mg, 67%) as a yellow solid.
mp 283-284 °C.

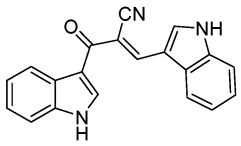
ir (neat) 2835, 1655, 1579, 1530, 1444, 1259, 1179, 1091, 1014, 896, 836, 758, 677, 650, 578 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 7.24-7.25 (m, 1H), 7.47-7.55 (m, 4H), 8.35-8.38 (m, 2H), 12.76 (s, 1H) ppm.
$^{13}C$ NMR (DMSO-$d_6$) 113.6, 123.3, 127.3, 128.0, 129.4, 130.8, 133.6, 134.0, 134.2, 135.1, 154.2, 154.4 ppm.




5-chloro-6,7-dimethyl-3-phenylquinoxalin-2(1*H*)-one (**94**)
Preparation of **94** was performed from 1,2-dihydro-2-keto-3-phenyl-6,7-dimethylquinoxaline-4-N-oxide[106] using same procedure as for **92** in 82 % yield.
mp 272-273 °C.
ir (neat) 2900, 1649, 1615, 1443, 1258, 1021, 917, 804, 761, 685, 635 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 2.38 (s, 3H), 2.41 (s, 3H), 7.48-7.56 (m, 3H), 7.66 (s, 1H), 8.26-8.29 (m, 2H), 11.87 (s, 1H) ppm.




Compound **98a**
**84a** (1.0g, 5.34 mmol) was added to 20 % potassium hydroxide (15 mL) and heated at reflux for 2 h. The mixture was cold and poured was 2M hydrochloric acid the precipitate formed was collected by filtration and dried to give **98**a (8.6 g 90%)
mp 289-290 °C (Lit.[128] 290-292 °C) .
ir (neat) 3470, 2853, 2421, 1667, 1602, 1498, 1386, 1330, 1046, 939, 887, 748, 717 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 7.19-7.22 (m, 3H), 7.44-7.47 (m, 1H), 11.68 (bs, 1H), 12.14 (bs, 1H) ppm.
$^{13}C$ NMR (DMSO-$d_6$) 112.8, 115.2, 123.3, 123.4, 124.1, 127.4, 127.4, 151.7, 154.9 ppm.




Compound **124**

3-Cyanoacetylindole (**69a**) (2.0 g,10.9 mmol) was added to a mixture of 3-formylindole (1.58 g, 12 mmol), sodium carbonate (14 g, 49 mmol) in ethanol (140 mL), and the mixture was heated at reflux for 6 h. The reaction mixture was cooled and then poured into water, the precipitate formed was collected by filtration and dried to give **124** (2.87 g, 85%).

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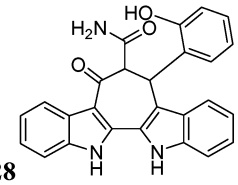
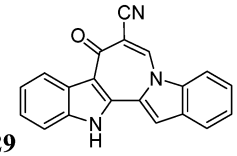
[128] Ahmad, Y.; Habib, M. S.; Ziauddin. *Tetrahedron* **1964**, *20*, 1107-1112.

mp 263 °C (dec).
ir (neat) 3256, 2200, 1609, 1456, 1493, 1435, 1372, 1332, 1228, 1183, 1141, 1007, 901, 733, 705, 633 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 7.19-7.29 (m, 4H), 7.57-7.61 (m, 2H), 7.89-7.92 (m, 1H), 8.24-8.27 (m, 1H), 8.51 (s, 1H), 8.65-8.67 (m, 2H), 11.47 (bs, 2H) ppm.



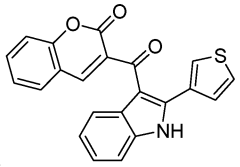

Compound **128**

**74** (1.0 g, 3.3 mmol) was added to a solution of salicylaldehyde (0.4 g, 3.4 mmol), piperidine (10 dr.) in EtOH (40 mL). The mixture was left at 25 °C for 16 h and then added to 2 M HCl and a precipitate formed was collected by filtration and dried to give **128** (0.7 g 49%).
mp 308-309 °C.
ir (neat) 3308, 3186, 1663, 1564, 1435, 1339, 1259, 1228, 1148, 740 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 4.22 (d, J=4.3 Hz, 1H), 5.48 (d, J=4.3 Hz, 1H), 6.32-6.34 (m, 1H), 6.41-6.44 (m, 1H), 6.83-7.22 (m, 8H), 7.46-7.54 (m, 3H), 8.13-8.16 (m, 1H), 9.83 (bs, 1H), 11.31 (bs, 1H), 11.86 (bs, 1H) ppm.
$^{13}C$ NMR (DMSO-$d_6$) 33.2, 61.4, 111.5, 111.6, 113.2, 115.3, 117.5, 118.6, 119.2, 119.7, 121.8, 122.1, 123.3, 123.6, 125.2, 127.3, 127.5, 127.7, 127.9, 128.0, 135.7, 136.4, 136.6, 154.8, 170.5, 191.3 ppm.




Compound **129**

DMFDMA (110 mg, 0.9 mmol) was added to a solution of **74** (200 mg , 0.7 mmol) in DMF (10 mL) and heated at 60 °C for 30 min, and then left at room temperature (25 °C) over night. A precipitate formed as yellow needles, which were collected by filtration and dried to give 129 (145 mg 70%).
mp 375 °C (dec).
ir (neat)3245, 2225, 1625, 1464, 1423, 1404, 1382, 1323, 1233, 1095, 808, 744, 730 $cm^{-1}$.
$^{1}H$ NMR (DMSO-$d_6$) 7.28-7.30 (m, 1H), 7.37-7.39 (m, 1H), 7.47-7.57 (m, 3H), 7.86-7.87 (m, 1H), 7.91 (s, 1H), 8.39-8.40 (m, 1H), 8.47-8.48 (m, 1H), 9.14 (s, 1H), 12.6 (bs, 1H) ppm.
$^{13}C$ NMR (DMSO-$d_6$) 99.0, 108.3, 111.2, 112.1, 113.6, 117.5, 121.1, 122.3, 122.4, 124.8, 125.0, 125.1, 126.4, 127.4, 130.0, 132.7, 136.8, 137.2, 137.6,176.7 ppm.




Compound **131**

3-oxo-3-(2-(thiophen-3-yl)-1*H*-indol-3-yl)propanenitrile (0.3 g, 1.2 mmol) was added to a solution of salicyaldehyde (0.14 g, 1.1 mmol) and sodium piperidine (10 dr.) in EtOH (25 mL) and stirred at 25 °C 20 h. Dilution with 2M HCl and the precipitate formed was collected by filtration and dried to give **131** (0.23 g 56%).

mp 292-293 °C.

ir (neat) 3298, 3092, 2971, 1710, 1626, 1599, 1430, 1192, 1165, 953, 896, 804, 741, 674 $cm^{-1}$.

$^{1}H$ NMR (DMSO-$d_6$) 7.13-7.21 (m, 1H), 7.22-7.34 (m, 4H), 7.38-7.40 (m, 1H), 7.45-7.54 (m, 1H), 7.59-7.64 (m, 2H), 7.70-7.72 (m, 1H), 8.05 (s, 1H), 8.11-8.14 (m, 1H), 12.37 (bs, 1H)

$^{13}C$ NMR (DMSO-$d_6$) 111.9, 113.1, 115.9, 118.2, 121.0, 122.3, 123.4, 126.5, 127.3, 127.4, 128.6, 128.7, 129.3, 131.7, 132.8, 135.6, 141.8, 142.9, 153.5, 157.9, 185.7 ppm.