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N-CYANOINDOLES AND N-CYANOINDOLE-4,7-DIONES: CONSTRUCTION OF A BC RING SYNTHON FOR THE KINAMYCINS

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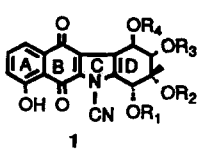
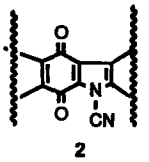
Abstract: N-Cyano-2,3-dialkylindoles, available by reaction of N-sodioindoles with phenyl cyanate, are substantially less reactive than N-acylindoles under electrophilic bromination conditions but readily yield side-chain brominated products under free radical conditions. Ceric ammonium nitrate oxidation of N-cyano-4,7-dimethoxy-2,3-disubstituted indoles yields the corresponding N-cyanoindole-4,7-diones which are potentially synthons for construction of kinamycins, **1**.

The kinamycin antibiotics[1], **1**, incorporate an unusual N-cyanoindoloquinone substructure, **2**, which is unique among natural products and appears to have no counterpart among synthetic indole derivatives [2]. Elegant applications of ^{13}C, ^{15}N and ^{2}H labelling and 2D NMR techniques have recently led to the elucidation of much of the biosynthetic route to these compounds.[6,7] No reports of the chemical synthesis of either the kinamycins, **1**, or simple analogs incorporating the part structure **2**, have appeared in the literature.

Figure 1



1
KINAMYCIN



2

	R1	R2	R3	R4
A	Ac	Ac	Ac	H
B	H	Ac	H	H
C	Ac	H	Ac	Ac
D	Ac	H	Ac	H
E	Ac	H	H	H
F	H	H	H	H
G	Ac	$COCHMe_2$	Ac	Ac
H	$COCHMe_2$	H	Ac	Ac

Disclosed herein are preliminary results of a study aimed at the synthesis of analogs of **1** designed to probe the structural basis for antimicrobial activity of the kinamycins. Our strategy in this area is centered around the construction of simple analogs, **3**, incorporating the BC rings of the kinamycin system. Comparison of the antimicrobial properties of such compounds will allow an assessment of the importance of ring A and D functionalities for biological activities. In addition, such analogs are intended to serve as templates for step-wise synthetic elaboration of rings A and D.

Since the most appropriate precursor to **3** was an N-cyano-4,7-dialkoxyindole, **4**, we became interested in the chemistry of N-cyano-indoles. Surprisingly, a search of the literature [2] failed to reveal any references to the preparation or the chemistry of N-cyanoindoles and hence, preliminary explorations of the synthesis and

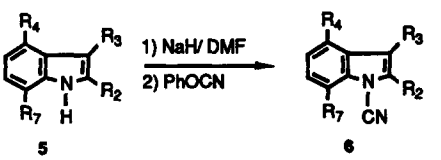
reactivity of simple N-cyanoindoles have been carried out.

Figure 2

3 4

After some experimentation [8], it was found that N-sodio-2,3-dialkylindoles react smoothly with phenyl cyanate [10] in DMF to yield the desired N-cyanoindoles in reasonable yields [11]. For the N-cyanoindoles generated in this study (**6a, 6b, 6c, 11, 13, 14**) the CN stretching frequency falls in the range 2237 to 2245 cm^{-1} (for chloroform solution infrared spectra) and the ^{13}C NMR signals due to the N-cyano group fall in the 105 to 108 ppm range ($CDCl_3$). By comparison, the ^{13}C NMR cyano resonance of N-cyanoaniline has been reported as 111.9 ppm.[6e]

Scheme 1

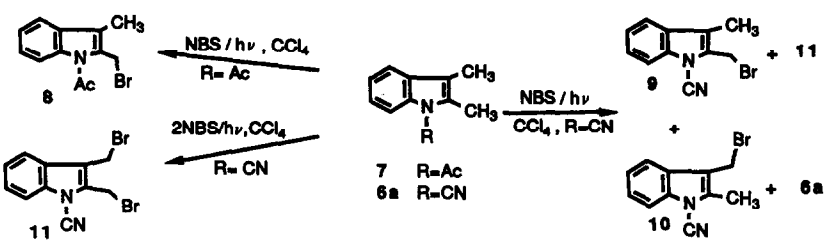


5 6

	R_2	R_3	R_4	R_7	% Yield
6a	CH_3	CH_3	H	H	80
6b	$-(CH_2)_4-$		H	H	64
6c	CH_3	CH_3	CH_3O	CH_3O	65

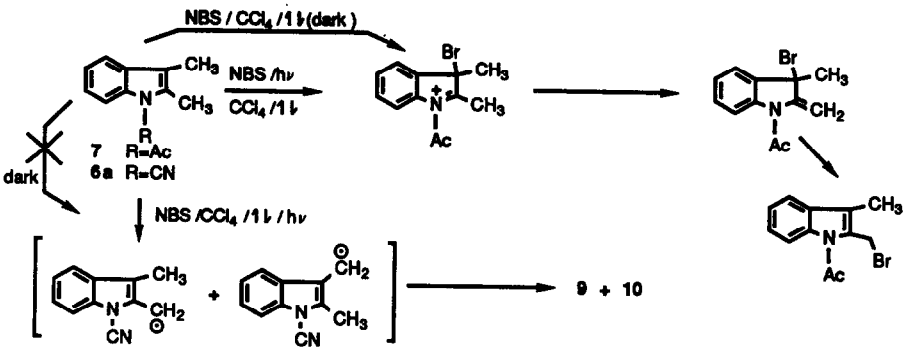
The reactivity of these N-cyanoindoles has been found to differ significantly from that observed for the corresponding N-acyl derivatives. For example, whereas N-acetyl-2,3-dimethylindole, **7**, reacts with NBS and light in refluxing carbon tetrachloride to yield the C-2 side-chain brominated product **8** exclusively [12], the N-cyano analog **6a** gives a mixture of the C-2 and C-3 side-chain substituted products **9** and **10** as well as some of the α,α'-dibromide **11** and unreacted **6a** (Scheme 2). N-cyanotetrahydrocarbazole **6b** behaves in a similar fashion yielding a mixture of 1- and 4-brominated products which are unstable with respect to elimination of HBr to yield the corresponding N-cyanodihydrocarbazoles.

Scheme 2



The difference in regioselectivity of the bromination of **7** and **6a** appears to result from a difference in mechanism of the two processes. Although conditions conducive to free radical reactions are employed, the NBS bromination of **7** appears to be an ionic process (Scheme 3) which occurs equally well in the dark. Bromination of **6a** with NBS on the other hand, is suppressed in the dark and is likely a free radical process.

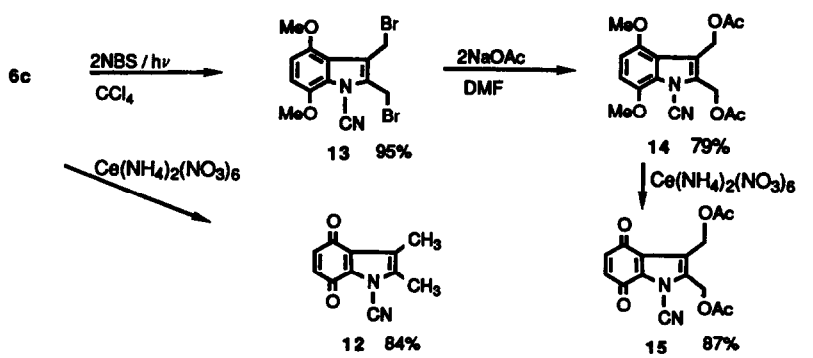
Scheme 3



A competition experiment employing one equivalent of molecular bromine and a mixture of one equivalent of each of **7** and **6a** leads to exclusive formation of **8** consistent with the strong electron-withdrawing properties of the cyano group.[13]

The N-cyanoindole-4,7-dione system was readily prepared by cyanation of the known indole **5c** [14] (Scheme 4) followed by oxidation with ceric ammonium nitrate [15], to give **12**. Halogenation of **6c** with two equivalents of NBS gave the side-chain bis-brominated derivative **13** which reacted readily with sodium acetate in DMF to give the diacetate **14**. Ceric ammonium nitrate oxidation of **14** yielded the corresponding indole-4,7-dione **15**.[16]

Scheme 4



Studies of the biological activity of this simplified kinamycin analogue are in progress. Preliminary experiments indicate that construction of ring A and ring D employing **12** or **15** as templates is feasible and, thus, a rational exploration of the structural basis for biological activity of the kinamycins by synthetic elaboration of simple 2,3-disubstituted-N-cyanoindole-4,7-diones of the type described herein should now be possible. Results of these studies will be reported in detail elsewhere.

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References and Notes

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2. Indole-4,7-diones have been the subject of intensive investigation in the context of the mitomycin antibiotic-antitumour agents.[3] However, a search of the review literature concerning indole chemistry[4] as well as Chemical Abstracts has revealed no reference to the synthesis of either N-cyanoindoles or the corresponding 4,7-diones. By contrast, the C-cyanation of indoles has been well-studied.[5]
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7. K. Ajisaka, H. Takeshima, S. Omura, J. Chem. Soc. Chem. Comm. 1976, 581. This paper reported the use of an i.r. spectroscopic analysis to determine the biosynthetic origin of the cyanamide carbon of kinamycin D but the validity of these results has since been questioned.[6c]
8. Initial experiments employing cyanogen bromide in the place of phenyl cyanate gave poor yields of the N-cyanoindoles accompanied by highly coloured products reminiscent of the decomposition products of brominated 2,3-dialkylindoles.[9]
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11. In a typical preparation, the indole was added to a suspension of sodium hydride (1.1 equivalents) in DMF (10 mL/g of indole) at room temperature in a dry nitrogen atmosphere. Phenyl cyanate (1.1 equivalents) was added dropwise with stirring and the mixture was stirred at room temperature for 1.5 h. Aqueous workup with extraction by ethyl acetate, drying and evaporation of the organic extract followed by recrystallization of the crude product gave the desired N-cyano-indole. Cyanation of **5c**, on the other hand, was very sluggish under those conditions. The use of DMSO in place of DMF and the use of an excess of phenyl cyanate (2 equivalents) with **5c** dramatically accelerated this reaction. All new compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, uv and low resolution m.s. and combustion analysis and/or high resolution mass spectrometry.
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16. The cyano group resonance in the ^{13}C NMR spectra of the kinamycins has escaped detection by ^{13}C-NMR until very recently. It has been identified during the course of biosynthetic studies which have led to the surprising observation of a very weak N-cyano signal at 78.5 ppm, some 30 ppm upfield of the value expected based on comparison with model compounds such as N-cyanoaniline.[6c] As a result, the ^{13}C-NMR spectra of N-cyano-indole-4,7-diones are of interest in that some light may be shed on the structural basis for the anomalous N-cyano resonance of the kinamycins. The ^{13}C-NMR N-cyano resonances for the simple N-cyanoindole-4,7-diones **12** and **15** occur at 104.7 and 103.6 ppm respectively and hence the anomaly in the N-cyano resonance for the kinamycins cannot be simply ascribed to the N-cyano-indole-dione ring system. A study of the ^{13}C-NMR characteristics of other related model systems aimed at exploring this phenomenon further is in progress.

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