Regioselective Synthesis of the Kinamycin ABCD ring system

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Abstract The new bromoquinone-enamine annulation was successfully extended to acyclic enamino ketones resulting in a new synthesis of the ABC framework 6 of kinamycins and when applied to cyclic enamino ketones 8a-c the first synthesis of their ABCD (ing system. Smooth aromatisation of compounds 4b,d to 9a,b respectively was effected with DDQ.

The kinamycin family of antibiotics 1^{1a-d} possess a novel benzolb]tetrahydrocarbazole framework Biosynthetic investigation has shown they are polyketide in origin 2a-g Their N-cyano indole moiety is unique among natural products Recently Dmitrienko has synthesised N-cyano benzolf]indoloquinone 2, the N-cyano ABC ring fragment of the kinamycins 3^{-4} Rapoport 5^{-4} and Murayamia 6^{-6} have seperately synthesised the benzolf]indoloquinone ABC ring fragment in their preparation of mitomycin congeners

			D	D	
	1	<u>nı</u> <u>n</u> 2	п3	ru	11 Prekinamycin
1a 1b 1c 1d 1f 1g 1h	Kinamyoin A Kinamyoin B Kinamyoin C Kinamyoin D Kinamyoin E Kinamyoin F Kinamyoin G Kinamyoin H	Ас Ас Н Ас Ас Н Ас Н Ас Н Н Н Ас СОСНМи СОСНМе ₂ Н	Ac H Ac H H e ₂ Ac	H H H H Ac Ac	$ \begin{array}{c} $

Figure 1

Recently in this laboratory we developed a new bromoquinone enamine annulation methodology for the regiospecific preparation of the 47-indologuinone nucleus 3 (figure 2) and applied this to the synthesis of 7-methoxymitosene 7

We now wish to report the application of this methodology to a new regiospecific synthesis of the kinamycin ABC ring framework and to the first synthesis of the kinamycin tetrahydrobenzo[b]carbazole-1,6,11-trione ring framework 4



2-Bromonaphthoquinone **5a** ($\mathbf{R} = \mathbf{H}$) ⁸ and 3-bromojugione **5b** ($\mathbf{R} = \mathbf{OH}$) ⁹ were prepared by the literature procedures Enamino ketone **6** was readily accessible by direct methods ¹⁰ The annulation of bromonaphthoquinones **5** and the acyclic N-benzyl enamino ketone **6** to the ABC kinamycin ring framework proceeded smoothly under the conditions we had reported previously *viz* copper (II) bromide / potassium carbonate in acetonitrile (figure 3)⁷ and the tricyclic products **7a,b** were readily isolable although in low yield



Encouraged by these results we considered the direct synthesis of the ABCD ring system by involving the cyclic analogue **8**, of enamino ketone **6**. The enamino ketones **8a-c** were easily prepared from 1,3-cyclohexadiones.¹⁰ The desired annulation of bromonaphthoquinones **5** and the cyclic N-benzyl enamino ketones **8a-c** to the ABCD kinamycin ring framework proceeded albeit in modest yield (36-50%) with regrospecific formation of the tetrahydrobenzo[b]carbazole-1,6.11-triones **4a-d** (see figure 4.) There was no evidence for formation of the regroisomeric annulation product Furthermore, none of the tetracycle **4b** was formed when simple unsubstituted naphthoquinone was treated with enamino ketone **6b** under the same conditions



Aromatisation of ring D of **4b** and **4d** occurred smoothly in refluxing dioxane in the presence of DDQ to give the benzo[b]carbazoles **9a** and **9b** The latter has a carbon framework and substitution pattern identical to prekinamycin 11^{2g}



This work represents the first regospecific synthesis of the kinamycin tetrahydrobenzo[b]carbazole ring system in the future we intend to convert benzo[b]carbazole 7b to prekinamycin li by employing a suitably substituted indole and subsequent N-cyanation. In addition compound 7b is undergoing investigation as an entry point to the synthesis of the more challenging kinamycins A-H, which have multiple chiral centres.

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- Enamino ketones 6, 8a-c were prepared by refluxing the corresponding 1, 3-dione, benzylamine and a catalytic amount of <u>p</u>-toluenesulphonic acid in chloroform in a Dean Stark apparatus Removal of solvent <u>in vacuo</u> gave crude enamino ketone Compound 6 was purified by distillation, whereas compounds 8a-c were purified by recrystallisation from ethyl acetate

Deducated to Prof H C Brown on the occasion of his eightieth birthday

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