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Formation of N-N Bonds by Thermolysis of 5-(2-Dimethylaminoethyl)-5*H*-indolo[2,3-*b*]quinoxaline

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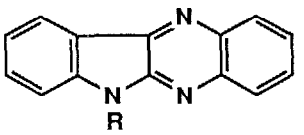
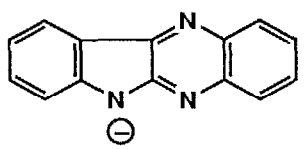
Abstract: Alkylation of the anion of indolo[2,3-*b*]quinoxaline with 2-(*N*,*N*-dimethylamino)-ethyl chloride gave a mixture of 6- and 5-isomers. Thermolysis of the 5-isomer resulted in the formation of 6-dimethylamino-6*H*-indolo[2,3-*b*]quinoxaline and ethylene rather than isomerization.

6-(2-Dimethylaminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline (**1b**) binds selectively[1] to DNA and some derivatives (like B-220) show interesting antiviral activity,[2,3] including high activity against CMV virus. In 1970 Knotz prepared[4] **1b** by *N*,*N*-dimethylaminoethylation of the ambident anion **2** in ethanol, but failed to discuss the expected co-formation of the isomer **3**. Repetition of this experiment yielded a mixture (4:1) of the isomers **1b** (light yellow) and **3** (red) respectivly, which could be separated by column cromatography (SiO_2, CH_2Cl_2-MeOH).[5]



1 a R=H
b R=$CH_2CH_2N(CH_3)_2$
c R=$N(CH_3)_2$



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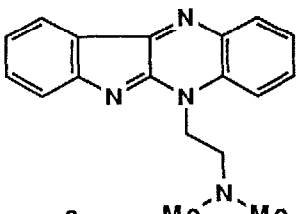

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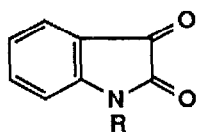
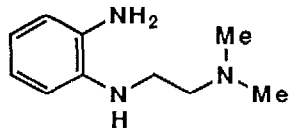


4 a R=H
b R=$N(CH_3)_2$



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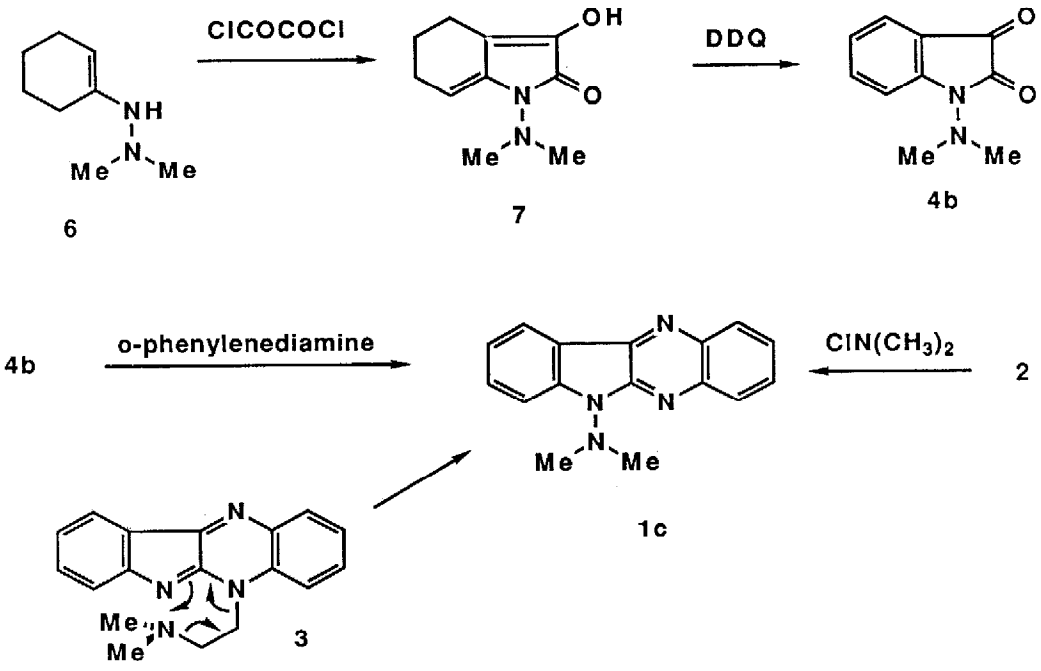
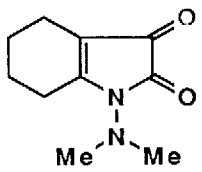


Scheme 1

The structure of the red isomer **3**, which does not show interesting antiviral activity, was proven by an independent condensation (*cf* ref. 5) starting with isatin (**4a**) and compound **5**.

Thermolysis of **3**, which might *a priori* give rise to **1b** due to gain of aromaticity, was next studied as a means to rectify the mixture of isomers. However, heating (255°C, 30 min) of pure **3** yielded, except for some indophenazine (**1a**) due to cleavage of the side-chain, a new compound with the composition $C_{16}H_{14}N_4$ as the major product. No isomerization (**3** → **1b**) was observed.

The new compound could be assigned structure **1c**[6] as a result of an independent synthesis outlined in Scheme 1, where a possible mode of formation of **1c** from **3** is indicated. Compound **6** (prepared from cyclohexanone and 1,1-dimethylhydrazine) cyclized readily yielding **7**, a compound previously[7] incorrectly assigned the tautomeric structure **8**. The reassignment is based on IR- and NMR-spectroscopy. Dehydrogenation of **7** with DDQ gave the isatin derivative **4b**, previously prepared by Neber[8] using a lengthy procedure. In the final step **4b** was condensed with o-phenylenediamine yielding **1c**. Alternatively **1c** could be prepared from the anion **2** and dimethylchloroamine



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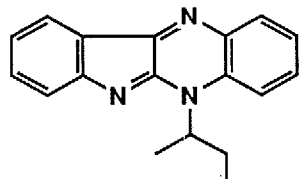

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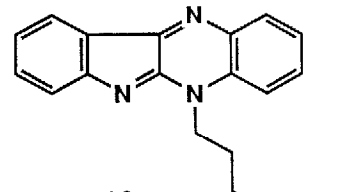

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To gain some further insight into the mechanism of the N-N bond formation the homologs **9** and **10** were prepared and thermolyzed (255°C, 30 min). Whereas **9** gave **1c** (and propene) in a good yield, compound **10** failed to give **1c**. Further experiments established that the indoloquinoxaline formed during the thermolysis of **9** (and **3**) is a secondary product due to N-N bond cleavage of **1c**. These facts render further support for the suggested mechanism.

REFERENCES AND NOTES

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5. 6-(2-Dimethylaminoethyl)-6H-indolo[2,3-b]-quinoxaline (**1b**), mp 88-90°C. IR (KBr): 3055, 2968, 2941, 2858, 2817, 2762, 1607, 1582, 1487, 1468, 1447, 1411, 1361, 1337, 1271, 1246, 1184, 762, 748 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 2.39(s,6H,NCH_3), 2.84(t,2H,NCH_2), 4.62(t,2H,NCH_2), 7.4-8.5(m,8H,aromatic H).

   5-(2-Dimethylaminoethyl)-5H-indolo[2,3-b]-quinoxaline (**3**), mp 109-110°C. ^{1}HNMR ($CDCl_3$): δ 2.42(s,6H,NCH_3), 2.91(t,2H,NCH_2), 4.96(t,2H,NCH_2), 7.2–8.3(m,8H,aromatic H). UV_{max} (EtOH): 475, 372, 354, 273 nm, log ε 3.27, 418, 4.21, 4.52, respectively. A very similar spectrum was reported by Badger and Nelson for 5-methyl-5*H*-indolo[2,3–b]-quinoxaline.[9]

6. 6-(Dimethylamino)-6H-indolo[2,3-b]-quinoxaline (**1c**), mp 164-165°C. MS (70eV): 262(20,M^+), 234(5), 219(100). IR (KBr): 3058, 2981, 2875, 1613, 1584, 1452, 1406, 1392, 1317, 1291, 1159, 1020, 773, 750 cm^{-1}.

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