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INDOLE-2,3-QUINODIMETHANES: GENERATION, REACTIVITY AND REGIOSELECTIVE CONTROL OF INTERMOLECULAR DIELS-ALDER REACTIONS

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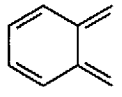
Abstract: N-acylindole-2,3-quinodimethanes generated at low temperature from the N-acyl-2,3-bis (bromomethyl)indoles undergo a variety of cycloadditions including the reversible chelotropic reaction with sulphur dioxide to yield the unreported 1,3-dihydrothieno[3,4-b]indole-2,2-dioxide 9. Successful attempts to control the regioselectivity of reactions with unsymmetrical dienophiles are described.

There has been recently a considerable increase in the number of reports describing generation procedures and the reactivity of heterocycle analogues of *o*-xylenes **1**[1,2,3]. The high synthetic value of these transient systems, which accounts for the interest in this area, has been best illustrated by Magnus and coworkers who have widely explored the utility of the indole analogue of **1** in several syntheses of complex indole alkaloids [4]. The strategy developed by these researchers involved the generation of a suitably substituted indole-2,3-quinodimethane **2** which was subsequently trapped *in situ* in an intramolecular Diels-Alder reaction.

Except for the pioneering work of Plieninger [5] and the successful intermolecular Diels-Alder reaction reported by Marinelli [6], no further progress has been described towards the potential application of intermolecular cycloaddition reactions of indole-2,3-quinodimethanes. Thus we would like to disclose the results of our studies aimed at extending the scope of the chemistry of these intermediates and our efforts directed towards achieving complete control of the regioselectivity of intermolecular cycloadditions of these dienes with unsymmetrical dienophiles.



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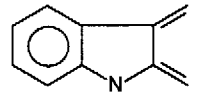

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Previous work in this laboratory [7a] in the area of side chain functionalization methods of 2,3-dialkylindoles provided a convenient procedure for the synthesis of 2,3-bis(bromomethyl)indoles **3**, which were recognized as potential precursors of **2** (scheme1). As we reported earlier[7b], the indole-2,3-quinodimethanes **2** can in fact be generated upon treatment of **3** with an excess of sodium iodide in acetone at low temperature (-30 °C)[8] in a related procedure to that used by Cava and coworkers [9] to generate *o*-quinodimethanes **1** from α, α'-dibromoxylenes. A spectroscopic study carried out in acetone at low temperature, allowed the detection and characterization of the indole-2,3-quinodimethane **2**, which was seen to derive from the transient bis(iodomethyl)indole **4** in a 1,4-elimination process induced by an excess of sodium iodide. Upon warming, and in the absence of a dienophile, **2** dimerizes to give the adduct **5** the structure of which , initially deduced on the basis of ^{1}H and ^{13}C nmr spectra, was further confirmed by a single crystal X-ray diffraction study. In the

presence of dienophiles, **2** gave the corresponding Diels-Alder adducts in good yields (table I).

Scheme 1

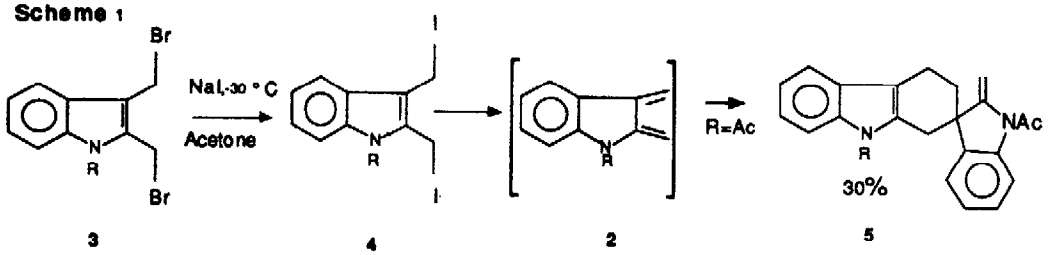
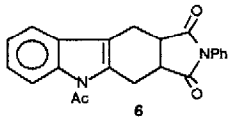
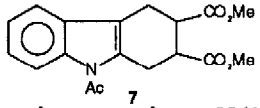
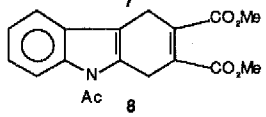
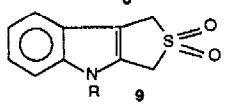


Table I

Diels-Alder Trapping Experiments of Indole-2,3-quinodimethanes with Symmetrical Dienophiles

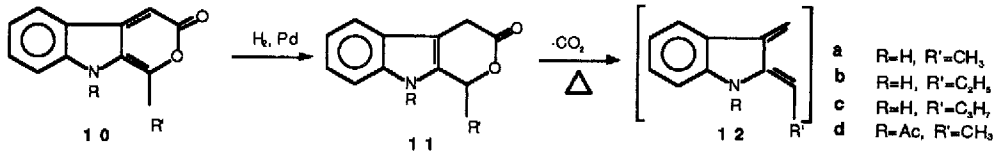
Diene	Dienophile	Adduct	Yield (%)
2	Phenylmaleimide	 **6**	80
2	Dimethyl fumarate	 **7**	77
2	Dimethyl acetylene dicarboxylate	 **8**	85
2	Sulphur dioxide	 **9**	a R= Ac 48 b R= t-BOC 75

The previously unreported 1,3-dihydrothieno[3,4-b]indole-2,2-dioxide **9** could also be easily prepared by passing gaseous SO_2 through a solution of **2** at -30° C followed by warming to room temperature. This procedure is thus similar to the well known concerted addition of sulphur dioxide to 1,3-dienes to give 2,5-dihydrothiophene-1,1-dioxides [10]. The interest and potential value of **9** as a masked stable equivalent of **2** have been previously pointed out [4]. These indole-sulphones upon heating at 80-110° C were able to undergo a retro Diels-Alder reaction with simultaneous extrusion of sulphur dioxide to regenerate **2** which, except for the case of the unprotected sulphone **9c** (R=H, prepared in 80% yield by deacylation of **9a** under basic conditions), could be trapped with dienophiles to give the corresponding adducts (e. g. **8**, with dimethyl acetylenedicarboxylate, in 85% yield).

Cycloadditions of the indole-2,3-quinodimethane **2** and **12a** (scheme 2) with unsymmetrical dienophiles were then investigated. The precursor of **12a** (R=CH_3), the hitherto unreported 1-methyl-1,4-dihydropyrano[3,4-b]indol-3-one **11a** was prepared by hydrogenation of the 1-methylpyrano[3,4-b]indol-3-one **10a** [5] in 61% yield, in a similar procedure to that described for the preparation of **11b** and **11c** , precursors of **12b** and **12c** first generated by Plieninger.

When **2** , generated either by thermolysis of **9** or at low temperature from the dibromide precursor **3**, was

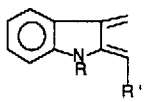
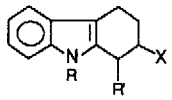
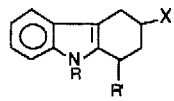
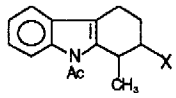
Scheme 2



trapped *in situ* with methyl vinyl ketone or methyl acrylate, mixtures of the two possible regioisomers **13** and **14** were obtained (table II), (e.g. **a**,X= $COCH_3$, 85% , X= CO_2CH_3, 82%, combined yields). The structural assignment of the major and minor adducts was inferred upon comparison of both the ^1H nmr spectra and HPLC of an authentic sample of the N-acetylated derivative of the 3-carbomethoxy-1,2,3,4-tetrahydrocarbazole which was obtained by an alternative synthesis[11] and found to be identical to the minor regioisomer **14a**.

Table II

Diels-Alder Reactions of Indole-2,3-quinodimethanes with Unsymmetrical Dienophiles

Diene	Dienophile	Adducts		ratio
				
2a R=$COCH_3$ R'=H	methyl acrylate or methyl vinyl ketone	**13a** R=$COCH_3$ R'=H X=CO_2CH_3 X=$COCH_3$	**14a** R=$COCH_3$ R'=H	70 : 30[a]
2b R=SO_2CF_3 R'=H	"	**13b** R=SO_2CF_3 R'=H X= CO_2CH_3	**14b** R=SO_2CF_3 R'=H	71 : 29[a]
2c R=$OCOC(CH_3)_3$ R'=H	"	**13c** R=$OCOC(CH_3)_3$ R'=H X= CO_2CH_3	**14c** R=$OCOC(CH_3)_3$ R'=H	66 : 34[a, b]
2d R=$COCF_3$ R'=H	"	**13d** R=$COCF_3$ R'=H X= CO_2CH_3	**14d** R=$COCF_3$ R'=H	75 : 25[a]
12a R=H R'=CH_3	methyl vinyl ketone	**15** (cis + trans) R=H R'=CH_3 X= $COCH_3$	**16** (cis + trans) R=H R'=CH_3	72 : 28[c]
12d R= $COCH_3$ R'=CH_3	methyl vinyl ketone	**17** (cis + trans) X= $COCH_3$		99 : 1[c]

a-Calculated by ^1H nmr and hplc. b-see reference 12. c-Calculated by ^1H nmr

Thermolysis of **11a** in refluxing chlorobenzene and in the presence of an excess of methyl vinyl ketone afforded a mixture of the 4 possible adducts (**15** and **16** cis and trans). Preparative thin layer chromatography gave a major adduct which was identified as **15** (*cis*, 35% yield)[13] and a mixture of the remaining three isomers in 25% yield in which it was possible to locate the important ^1H nmr signals for **15** *trans* (C_1CH_3 and C_2H). The overall regioselectivity of **15** versus **16** as established from the ^1H nmr

integration of the C_1CH_3 doublets in the crude mixture, (at δ = 1.15 ppm (cis) and δ= 1.24 for **15** (trans) and between δ=1.30-1.35 ppm for both isomers **16**) was 72 : 28, thus very similar to that obtained with the N-acetyl-2,3-quinodimethanes.

The high degree of regioselectivity of these reactions suggested that formation of only one adduct might result from cycloadditions involving indole-2,3-quinodimethanes such as **12d** (R= $COCH_3$, R'= CH_3), if the effects of N-protection and $C_{2\alpha}$ substitution were to combine in an additive fashion.

Different routes have been explored to prepare a precursor for the diene **12d**. It was quite disappointing to find that this precursor could not be obtained by procedures such as those depicted in schemes 1 and 2 [14]. Efforts to alkylate selectively the sulphone **9a** were also unsuccessful. While a satisfactory synthetic route is still unavailable, it was possible to isolate the acetylated indole-lactone **11d** [15] from direct acylation of **11a** with NaH/acetic anhydride (5% yield, after chromatographic separation).

Reaction of the indole-2,3-quinodimethane **12d**, generated upon thermolysis of **11d**, with a large excess of methyl vinyl ketone was in fact highly regioselective, confirming the influence of the combined effect of both N-acetyl and $C_{2\alpha}$ alkyl substituents on the diene. The ^1H nmr analysis of the crude product obtained showed exclusively, within the limits of 400 MHz detection, the 2-substituted tetrahydrocarbazole **17** as a mixture of *cis* and *trans* stereoisomers. Although the stereochemistry of the major adduct cannot be unambiguously determined just on the basis of the C_1H and C_2H coupling constants, the stereoselectivity of this cycloaddition was estimated as 1 : 1.3.

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11-This route is based in the known Diels-Alder reaction[16] of 2-trimethylsilyloxybutadiene with methyl acrylate followed by aqueous acid treatment to give the 4-carbomethoxycyclohexanone which in turn is reacted with phenylhydrazine hydrochloride. The 3-carbomethoxy-1,2,3,4,-tetrahydrocarbazole thus obtained is then acetylated.

12-Essentially the same regioselectivity was obtained by Marinelli[6] in the reaction of **2c** with methylacrylate.

13-The stereochemistry was assigned on the basis of the analysis of the ^1H nmr spectra and decoupling experiments jH_1,H_2(cis isomer) = 5.2Hz ; $j\,H_1,H_2$ (trans isomer) = 9.7 Hz approximate values obtained upon irradiation of the C_1CH_3 doublet, which removes the H_1,CH_3 coupling of 7.2 Hz.

14-The 2,3-dibromo-2-ethyl-3-methyl precursor similar to **3** was not the product of the dibromination of the N-acetyl-2-ethyl-3-methylindole and the N-acylpyrone **10d** resisted to different hydrogenation conditions used for its conversion into the lactone precursor **11d** .

15-Some spectroscopic parameters for **10d**: m. p.=157-159° C,δ_H : 2.62 (s, 3, C_1 CH_3), 2.79 (s, 3, N-$COCH_3$), 5.55 (s, 1, C_4H), 7.40-8.03 (m, 4, Ar-H); **11d**- δ_H: 1.73 (d,J = 6.4 Hz, 3, C_1CH_3), 2.84 (s, 3, $COCH_3$) 3.65-4.00 (m, 2H, C_4H_α and C_4H_β). 6.26-6.29 (m, 1, C_1H) 7.31-7.50 (m, 3, C_5,C_6, C_7H), 7.69-7.72 (d, J = 8.9Hz,1, C_8H).

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