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An unusual hydrogen addition of indolo-2,3-quinodimethanes to dimethylindoles in the presence of 1,3-azoles

P T PERUMAL* and R NAGARAJAN
Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020
e-mail: ptperumal@hotmail.com

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Abstract. Indolo-2,3-quinodimethane generated *in situ* from *bis*-(bromomethyl)indole with NaI/DMF at 70°C was expected to undergo cycloaddition with 1,3-azoles to give carboline derivatives, which form the backbone of many indole alkaloids. However, the reaction did not give the anticipated product but proceeded via hydrogen addition to exocyclic methylene groups, furnishing dimethylindoles in good yields.

Keywords. Indolo-2,3-quinodimethane; *bis*-(bromomethyl)indole; 1,3-azoles; hydrogen addition; dimethylindoles.

1. Introduction

N-protected 2,3-disubstituted indoles are generally used as precursors for the *in situ* generation of indolo-2,3-quinodimethanes (**2a,b**) since, from a structural point of view, they are susceptible to selective 1,4-eliminations. Thus N-benzenesulphonyl and N-benzoylindolo-2,3-quinodimethanes (**2a,b**) can be generated easily from the N-substituted-2,3-*bis*(bromomethyl)indole (**1a,b**) by iodide-induced 1,4-eliminations.[1] The required dibromo compounds **1a,b**, have been synthesized from 2,3-dimethylindole by protection with appropriate acid chloride followed by bromination with NBS.[1]

Over the past twenty years, indolo-2,3-quinodimethanes and their stable analogues have been the focus of considerable interest.[2] Although indolo-2,3-quinodimethanes were earlier implicated by Bergman[3] and others[4,5] as intermediates in alkaloid synthesis and by Hofheinz[6] in alkaloid rearrangement, research by Marinelli[7] and especially by Magnus[8] has demonstrated the enormous utility of these intermediates in synthesis. Other research groups have described the generation and trapping of indolo-2,3-quinodimethanes.[9–12]

The heterocyclic diene reactivity of indolo-2,3-quinodimethane is primarily determined by the 2-aminobutadiene structural unit, MNDO calculations,[13] have also shown that the $[p^{4S} + p^{2S}]$-cycloaddition reactions with electron-poor dienophiles are HOMO diene–LUMO dienophile-controlled processes and that the peri- and regio selectivities found in numerous experimental syntheses can be predicted satisfactorily from the homo tropology of **1**.[14] Most reactions of indolo-2,3-quinodimethane and their applications in Diels–Alder reactions that are described are based on the well-known concepts of *o*-quinodimethane chemistry.[15]

Results available in the literature clearly demonstrate that, in comparison with other processes, the indolo-2,3-quinodimethane/Diels–Alder methodology represents the shortest and most elegant method for the preparation of selectively functionalized [*b*]-anelated indoles (including indole alkaloids and carbazoles). Dimerization of indolo-2,3-quinodimethanes is also reported.[12]

A convenient method for the synthesis of carbazoles involving the Diels–Alder reaction of an indolo-2,3-quinodimethane intermediate with suitable dienophile, furnishing carbazole derivatives has been reported.[1] We were interested in the synthesis of carboline derivatives by reaction of indolo-2,3-quinodimethane with compounds bearing the C=N moiety, the anticipated carboline derivative with the 1,3-azole moiety may be a potential DNA intercalating agent. However, the anticipated product was not obtained.

*For correspondence

2. Experimental section

2.1 *General*

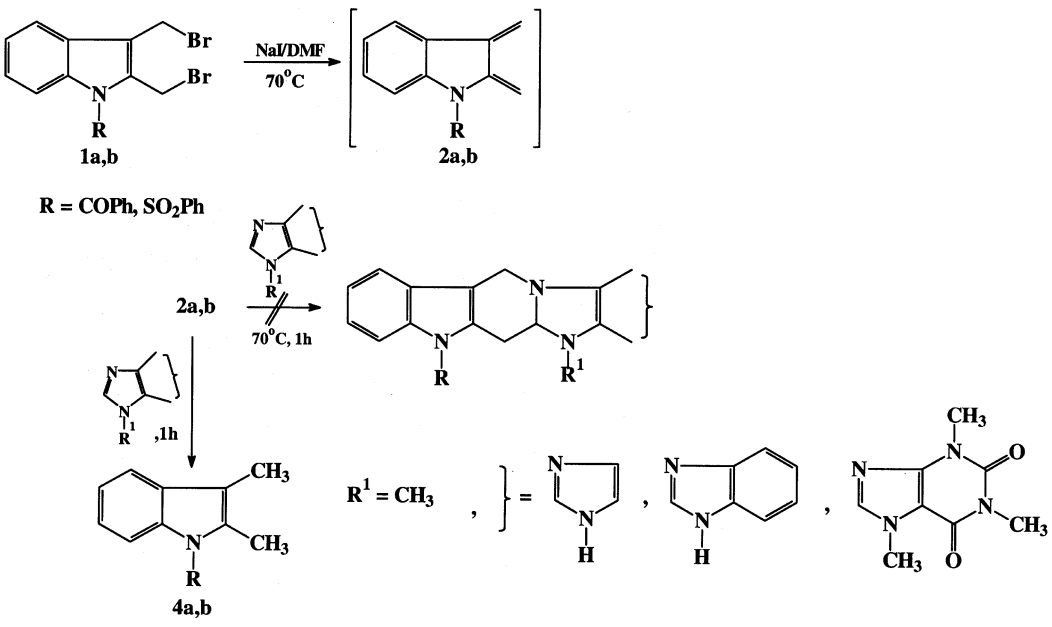
Melting points were measured in open capillaries and are uncorrected. Analytical thin layer chromatography was performed on precoated sheets of silica gel G of 0·25 mm thickness containing PF 254 indicator (Merck, Germany). Column chromatography was performed on silica gel (60–120 mesh: Sd fine, Boisar). IR spectra were recorded as KBr pellets on a Nicolot Impact-400 spectrometer, ^{1}H NMR spectra in $CDCl_3$ at 300 MHz on a Bruker spectrometer (chemical shifts in *d*, ppm) using TMS as internal standard, ^{13}C NMR spectra in $CDCl_3$ at 75 MHz and mass spectra using a VG 70-70H mass spectrometer at 70 ev. N-substituted 2,3-dimethylindoles are prepared by following known procedures[1].

2.2 *General procedure*

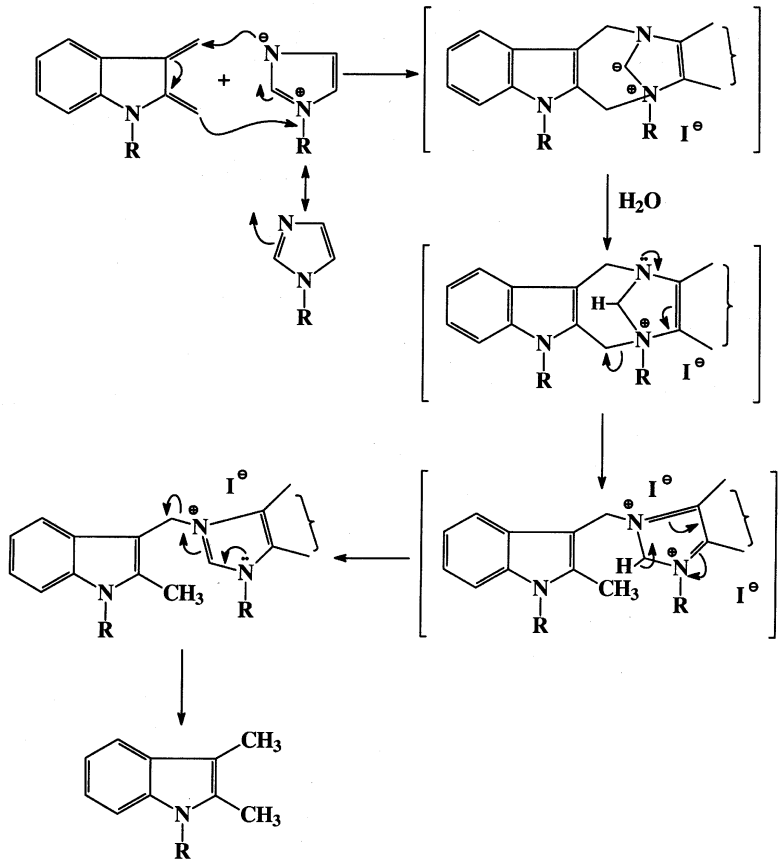
A mixture of dibromomethylindole (5 mmoles) and 1,3-azoles (25 mmoles) in DMF at 70°C is treated with NaI (25 mmoles). The reaction mixture becomes dark brown in colour due to iodine and is stirred for 1h at that temperature. The reaction mixture is poured onto a mixture of crushed ice and sodium thiosulphate (saturated, 10 ml), extracted with ethyl acetate (3×10 ml), dried over anhydrous Na_2SO_4 and the solvent distilled. The residue is subjected to a short column packed with silica gel and eluted with ethyl acetate–petroleum ether mixture (1 : 9) to afford pure dimethyl indoles.

2.2a *N-Benzoyl-2,3-dimethylindole:* Prepared by the hydrogen addition of indolo-2,3-quinodimethane **2a** generated *in situ* from dibromomethylindole (**1a**, 0·407 g, 1 mmol) with caffeine (0·485 g, 2·5 mmol) and NaI (0·6 g, 4 mmol). The crude product was chromatographed using petroleum ether: ethyl acetate (90 : 10) to afford **4a** as colourless solid in 86% yield. IR (KBr): 2919, 1679, 1456, 1357, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *d* 7·73 (*d*, 1H, *J* = 1·2 Hz), 7·73–6·78 (*m*, 8H), 2·39 (*s* 3H), 2·16 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *d* 169·7, 139·6, 137·4, 136·9, 134·0, 132·7, 129·4, 128·9, 128·8, 128·3, 127·4, 124·1, 123·7, 130·0, 118·4, 29·7, 21·3; Mass *m/z* 249 (M^+); Anal. Calcd. For $C_{17}H_{15}NO$; C, 81·90; H, 6·06; N 5·62%; Found, C, 81·75; H, 5·81; N, 5·76%.

2.2b *N-Phenylsulphonyl-2,3-dimethylindole:* Prepared from indoloquinodimethane **2b** generated *in situ* from dibromomethylindole (**1b**, 0·443 g, 1 mmol) with caffeine. The crude product was chromatographed from petroleum ether : ethyl acetate (90 : 10) to afford **4b** as colourless solid in 90% yield. IR (KBr): 2922, 1445, 1369, 765 cm^{-1}; ^{1}H NMR



Scheme 1.



Scheme 2.

Table 1. Synthesis of dimethylindoles.

Dienes	1,3-Azoles	Yield of the product (%)
2a	Benzimidazole	80
	Caffeine	90
2b	Benzimidazole	68
	Caffeine	86

(300 MHz, $CDCl_3$) *d* 8·20 (*d*, 1H, *J* = 8·2 Hz), 7.74 (*d*, 2H, *J* = 7·7 Hz), 7·47–7·23 (*m*, 6H), 2·52 (*s*, 3H), 2·11 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *d* 139·2, 136·2, 133·4, 132·2, 131·2, 129·1, 126·2, 123·9, 123·3, 118·2, 116·1, 114·4, 12·7, 8·8; Mass *m*/*z* 285 (M^+); Anal. Calcd. for $C_{16}H_{15}NO_2S$; C, 67·34; H, 5·30, N, 4·91%; found, C, 67·04; H, 5·41; N, 5·24%.

3. Results and discussion

A mixture of N-phenylsulphonyl dibromomethylindole and caffeine in DMF at 70°C is treated with NaI. The reaction mixture becomes dark brown in colour and is stirred for 1 h at that temperature. Then the reaction mixture is poured onto a mixture of crushed ice and sodium thiosulphate, extracted with ethylacetate, dried over anhydrous Na_2SO_4 and distilled. The residue is subjected to column chromatography and spectral data clearly show that the product formed is not a carboline. Careful examination of the spectral data reveals that the product obtained is N-phenylsulphonyl 2,3-dimethylindole (scheme 1).

The results are surprising because indolo-2,3-quinodimethane is an unstable compound, that either undergoes cycloaddition with dienophile or dimerises in the absence of the dienophile. The reaction works well with benzimidazole and not with imidazole. Good yields of the dimethylindoles obtained show that some mechanism which greatly suppresses the dimerization, must be operating. The reaction proceeds only in the presence of 1,3-azoles, and no indoles were isolated when the reactions were carried out in the presence of benzoxazole and benzothiazole, which shows that 1,3-nitrogen atoms play some role during the reaction. Similar cycloaddition of 1,3-azoles is also carried out with the *o*-quinodimethane derived from *o*-xylenyl dibromide leads to red-coloured poly-

meric product. Based on the above results we have proposed a plausible mechanism that accounts for the formation of dimethylindoles (scheme 2).

4 Conclusion

In conclusion, we have shown that indolo-2,3-quinodimethane gives unusual products in the presence of 1,3-azoles. The formation of dimethylindoles from indole-2,3-quinodimethane in the presence of 1,3-azoles is found to be novel, and to the best of our knowledge, is a new result in the field of quinodimethane chemistry.

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