Indian Journal of Chemistry
Vol. 25B, July 1986, pp. 739-740

Displacement Reactions of 2,3-Dichloro-6-nitroquinoxaline: Synthesis of s-Triazolo[3,4-*a*]quinoxaline†

K NAGARAJAN‡, P C PARTHASARATHY*, S J SHENOY & L ANANDAN

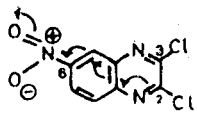
Hindustan CIBA-GEIGY Ltd., Research Centre, Goregaon East, Bombay 400 063

Received 9 *December* 1985; *accepted* 1 *January* 1986

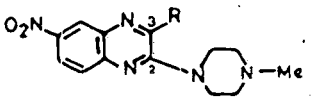
2,3-Dichloro-6-nitroquinoxaline (1) undergoes displacement reactions with 1-methylpiperazine in the hot to give the bis-derivative (2) and at 30°C selectively at position-2 to afford the mono-derivative (3). Structure-proof for the latter involves transformation of 3 through hydrazine derivative (4) to the traizoloquinoxaline (5) and its 1-phenyl derivative (6) and comparison of the chemical shifts of protons at C-9 in the pair.

In the course of our ongoing programme[1] to develop new amoebicides and discovery[2] of this activity in a series of condensed quinoxalines, we were attracted by a literature claim[3] of pronounced antiamoebic activity for 6-N,N-dimethylformamidino-2,3-*bis*-N-methylpiperazinoquinoxaline. We synthesised this by the reported procedure and found it to be inactive in our test systems. During this process, we observed that an early precursor, 2,3-dichloro-6-nitroquinoxaline (1) underwent selective displacement of one of the two reactive chlorine atoms to afford the product (3). We explored this finding to synthesize several new derivatives for biological evaluation. Further, by a series of manipulations ending with the triazoloquinoxalines (5) and (6), we were able to provide convincing structure proof for product (3).

The hydrazine derivative **4**, obtained from **3** by treatment with hydrazine, was transformed to **5** and **6**, respectively by reaction with triethyl orthoformate and benzoyl chloride. In the 90 MHz PMR spectrum of **5**, the C_9-H signal appeared at 8.95 as a doublet ($J = 2$ Hz; coupling with *meta*-placed C_7-H). The same signal in **6** appeared upfield at 8.20 while there were only minor differences in the location of other proton signals. The upfield shift is to be attributed to the shielding influence of the phenyl group at position-1 in **6**, which is twisted out of plane. If the monodisplacement product of **1** had the alternative structure (substituents at C-2 and C-3 are reversed in **3**), the resultant triazoles would be **7** and **8**. The signal due to



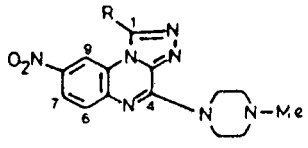
1



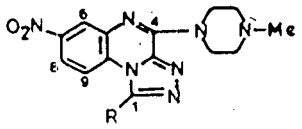
2 R = —N⟨⟩N—Me

3 R = Cl

4 R = $NH.NH_2$



5 R = H
6 R = C_6H_5



7 R = H
8 R = C_6H_5

C_9-H would have suffered an upfield movement going from **7** to **8** and this would be a doublet with a large *ortho* coupling (8 Hz). The structure of **3** and of all resultant products are thus secured. It is to be noted that this result would have been expected from electronic considerations as well. The arrows on **1** would require C-2 to be more electrophilic than C-3.

All melting points are uncorrected. PMR spectra were recorded in $CDCl_3$ on a Varian A 60 or Brucker WH 90 NMR spectrometer and mass spectra on a Varian Mat CH 7 spectrometer.

2,3-*Bis*(4-*methyl*-1-*piperazinyl*)-6-*nitroquinoxaline* (2)

A mixture of **1** (16 g) and N-methylpiperazine (20 g) in 2-methoxyethanol (150 ml) was stirred and heated under reflux for 16 hr. The mixture was then cooled in an ice-salt bath and filtered. The filtrate was evaporated *in vacuo* and the residue triturated with water and filtered. The product was crystallised from methylene chloride-ether to give **2** (14 g), m.p. 216-18° (Found: C, 58.1; H, 6.9; N, 26.1. $C_{18}H_{25}N_7O_2$ requires C, 58.2; H, 6.8; N, 26.4%), PMR: δ 2.37 ($N-CH_3$, *s*), 2.4-2.7 ($CH_2-N(CH_3)-CH_2$, t), 3.5-3.9 ($CH_2-N(Ar)-CH_2$, 2 overlapping *t*), 7.68 (C-8 *H*; *d*, $J = 10$ Hz), 8.17 (C-7 *H*, *dd*, $J = 10$, 2.5 Hz), 8.55 (C-5 *H*, *d*, $J = 2.5$ Hz).

3-*Chloro*-2-(4-*Methyl*-1-*piperazinyl*)-6-*nitroquinoxaline* (3)

A solution of **1** (13.4 g) in methylene chloride (150 ml) was stirred at room temperature (30 C) and

†Contribution No. 759 from Research Centre

‡Present address: Searle (India) Ltd, R&D Centre, Thane-Belapur Road, Thane 400 601.

treated dropwise with 1-methylpiperazine (11 g). After being left overnight, the solvent was evaporated off. The residue was triturated with water and filtered. The product was crystallised from methylene chloride-hexane to give **3** (12.5 g) m.p. 128-30° (Found: C, 50.9; H, 4.7; N, 22.9. $C_{13}H_{14}ClN_5O_2$ requires C, 50.7; H, 4.6; N, 22.8%); MS: M^+ (^{35}Cl) 307, (^{37}Cl) 309; PMR: δ 2.37 ($N-CH_3$, *s*), 2.60 ($CH_2-N(CH_3)-CH_2$, *t*), 3.77 ($CH_2-N(Ar)-CH_2$), 7.77 (C-8 *H*, *d*, $J=10$ Hz); 8.33 (C-7 *H*, *dd*, $J=10$, 2.5 Hz), 8.63 (C-5 *H*, $J=2.5$ Hz).

3-Hydrazino-2-(4-methyl-1-piperazinyl)-6-nitroquinoxaline (**4**)

Compound (**3**, 5 g) hydrazine hydrate (6 g) and ethanol (100 ml) were refluxed on a water-bath for 2 hr. A dark yellow crystalline solid separated from the reaction mixture on cooling. This was filtered off and the residue (3 g) recrystallised from chloroform to give **4**, m.p. 245° (Found: C, 51.2; H, 5.8. $C_{13}H_{17}N_7O_2$ requires C, 51.5; H, 5.7%).

4-(4-Methyl-1-piperazinyl)-8-nitro-s-triazolo [3,4-a]quinoxaline (**5**)

Compound (**4**, 0.6 g) and triethyl orthoformate (5 ml) were heated at 120-40° under reflux for 4 hr. The solid that separated was filtered off and recrystallised from methanol (0.2 g, m.p. 225°) (Found: C, 53.5; H, 5.2. $C_{14}H_{15}N_7O_2$ requires C, 53.7; H, 4.9%); MS: M^+ at *m/z* 313; PMR: δ 2.32 ($N-CH_3$, *s*) 2.57 [$CH_2-N(CH_3)-CH_2$, *m*], 4.43 [$Ar-N(CH_2)_2$, *m*), 7.40 (C-6 *H*, *d*, $J=8$ Hz), 8.07 (C-7 *H*, *dd*, $J=2$, 8 Hz), 8.95 (C-9 *H*, *d*, $J=2$ Hz), 10.07 (C-1 *H*, *s*).

1-Phenyl-4-(4-methyl-1-piperazinyl)-8-nitro-s-triazolo[3,4-*a*]*quinoxaline* (**6**)

Compound (**4**, 0.6 g) was added with stirring to a well-cooled solution of pyridine (6 ml) admixed with benzoyl chloride (0.3 g). The mixture was warmed on a steambath until it was clear, heated under reflux at 100° for 1 hr, cooled, poured over crushed ice and left overnight. The solid that separated was filtered off, washed with water and crystallised from methanol to yield **6** (0.4 g) m.p. 195° (Found: C, 61.1; H, 5.1. $C_{20}H_{19}N_7O_2$ requires C, 61.6; H, 4.9); PMR: δ 2.40 ($N-CH_3$, *s*), 2.67 [$CH_2-N(CH_3)-CH_2$, *m*], 4.62 [$Ar-N(CH_2)_2$, *m*], 7.22 (C-6 *H*, *d*, $J=8$ Hz), 8.17 (C-7 *H*, *dd*, $J=2$, 8 Hz), 8.20 (C-9 *H*, *d*, $J=2$ Hz), 7.70 (C_6H_5 at C-1).

References

1 Nagarajan K, Arya V P, George T, Nair M D, Sudarsan V, Ray D K & Srivastava V B, *Indian J Chem*, **23B** (1984) 342.

2 Parthasarathy P C, Joshi B S, Chaphekar M R, Gawad D H, Anandan Lalitha, Likhate M A, Hendi Mukta, Mudaliar Sheela, Iyer Suresh, Ray D K & Srivastava V B, *Indian J Chem*, **22B** (1983) 1250.

3 Fabio P F, Lang Jr S A, Lin Yang-i & Tomcufcik A S, *J mednl Chem*, **23** (1980) 201.