

NOVEL FORMATION OF 11,12-DIHYDRO-6H-QUINO[2,3-b] [1,5] BENZODIAZEPINES :

REACTION OF 2-CHLOROQUINOLINE-3-CARBALDEHYDES WITH o-PHENYLENEDIAMINE

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Abstract - The reaction of 2-chloroquinoline-3-carbaldehydes with o-phenylenediamine gave 2-chloro-3-(2-benzimidazolyl)quinoline (VI), 6H-quin[2,3-b] [1,5]benzodiazepine (IV) and 11, 12-dihydro-6H-quin[2,3-b] [1,5]benzodiazepine (V). The latter (V) is assumed to be formed from (IV) by reduction with the benzimidazoline intermediate (III), a hydrogen donor.

In continuation of our studies on the synthesis of biologically active molecules¹, the synthesis of quinoline fused benzodiazepines was attempted for the first time, in a single step, by the reaction of 2-chloro-3-formylquinoline (I) with o-phenylenediamine (II) to study their pharmacological activity.

The reaction, however, gave 2-chloro-3-(2-benzimidazolyl)quinoline (VI) as a major product in the yields ranging from 50-55%. In addition to compound (VI), the reaction mixture showed on TLC, two separate products having close R_f values. The mass spectrum revealed it to be a mixture of two compounds having m/z 245 and m/z 247. The accurate mass measurement of these ions showed them to be having the molecular formulae $C_{16}H_{11}N_3$ (IV) and $C_{16}H_{13}N_3$ (V) respectively. Since attempts to separate these two compounds (IV & V) by chromatographic means were not successful, the mixture was subjected to reduction using sodium borohydride in methanol to get exclusively 11,12-dihydro-6H-quin[2,3-b] [1,5]benzodiazepine (V). The structure of this compound was confirmed by accurate mass and 1H NMR. Extension of this reaction to substituted quinoline aldehydes also gave similar products as shown in Table 1.

11,12-Dihydro-6H-quin[2,3-b] [1,5]benzodiazepines (V) might be formed by the reduction of 6H-quin[2,3-b] [1,5]benzodiazepines (IV) as follows.

The intermediate benzimidazoline derivative (III) is oxidised to 2-chloro-3-(2-benzimidazolyl)quinoline (VI), with simultaneous reduction of 6H-quin[2,3-b] [1,5]benzodiazepine (IV) to its 11,12-dihydro derivative (V). It is known that benzimidazoline derivatives reduce the isolated $C=N$ and $C=C^2$. These reactions are shown in the Scheme 1.

Scheme 1

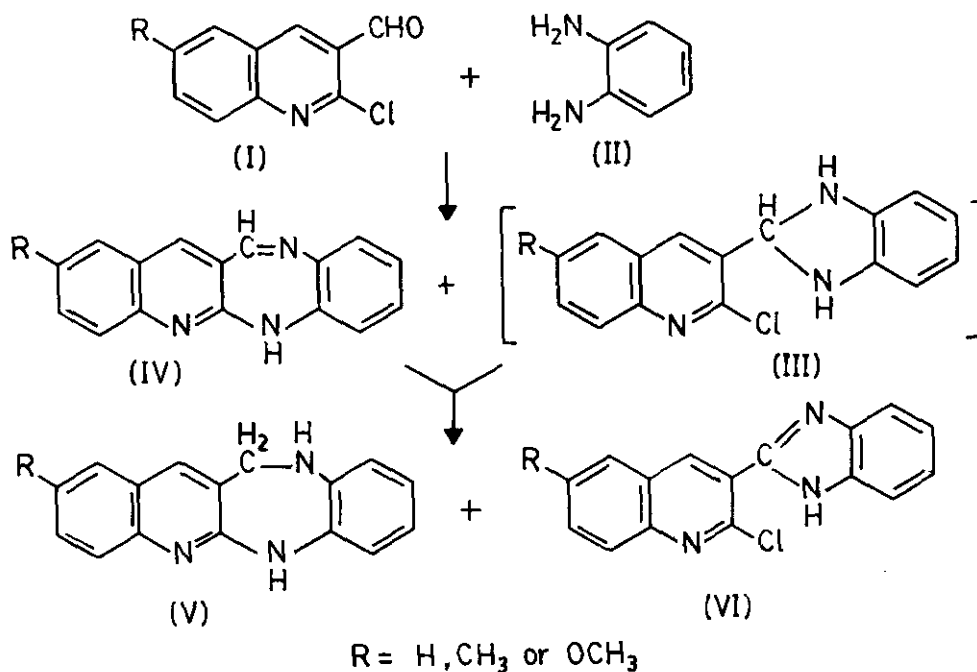


Table 1 - Products and other relevant data

No.	Product	Yield (%)	mp °C	Molecular formula (Accurate mass)	¹ H NMR (ppm) -CH ₂ -NH-
1	(V) R=H	14.5	235	C ₁₆ H ₁₃ N ₃ (247.1100)	4.3 (s)
2	(V) R=CH ₃	14.0	235-236	C ₁₇ H ₁₅ N ₃ (261.1254)	4.3 (s)
3	(V) R=OCH ₃	12.5	240-241	C ₁₇ H ₁₅ N ₃ O (277.1058)	4.35 (s)
4	(VI) R=H	52.0	200-201	C ₁₆ H ₁₀ N ₃ Cl (279.0561)	-
5	(VI) R=CH ₃	55.0	241-242	C ₁₇ H ₁₂ N ₃ Cl (293.0533)	-
6	(VI) R=OCH ₃	50.5	226-227	C ₁₇ H ₁₂ N ₃ OCl (309.0669)	-

EXPERIMENTAL

Melting points are uncorrected. Accurate mass measurements were carried out with VG Micromass 70-70H mass spectrometer at a resolution of 5000 with PFK as reference using the VG Data System. PMR spectra were recorded in CDCl_3 on JEOL FT FX-900 Spectrometer.

2-Chloro-3-formylquinolines were made as reported earlier³.

General procedure

a) 2-Chloro-3-formylquinoline (0.01 mole) and o-phenylenediamine (0.01 mole) were taken in ethanol⁴ (50 ml) and refluxed on a steam bath for 10 h. The reaction mixture was then concentrated and chromatographed on a column of silica gel (finer than 200 mesh) using mixtures of chloroform and methanol. Benzimidazole was eluted first, followed by benzodiazepines.

b) Procedure for the reduction of (IV)

To a mixture of benzodiazepines (150 mg) taken in (10 ml) methanol was added sodium borohydride (65 mg) in small portions. Then it was refluxed on the water bath for 2.5 h, concentrated and poured into water. The crude product was recrystallised from methanol.

REFERENCES AND NOTES

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- 4 Solvents of higher boiling points gave a considerable amount of polymeric material.

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