Studies in the Chemistry of 1,2,5-Oxadiazole (II). Synthesis and Properties of Furazanodiazepines.

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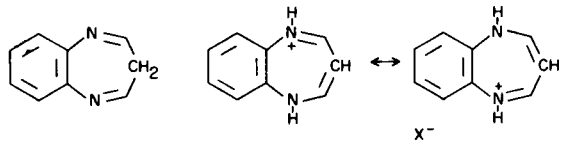
This paper describes the synthesis and the properties of some furazanodiazepine derivatives obtained by condensing the appropriate β-diketones with 3,4-diaminofurazan. On the basis of U.V., I.R. and N.M.R. evidence a mono-imino structure is suggested for the compounds obtained. Low temperature N.M.R. spectra suggest a rapid -NH-C(4)-C(8)-N= ⇌ =N-C(4)-C(8)-NH- tautomerism for the dimethyl derivative.

In a previous paper (1) we described some furazanopyrazine derivatives obtained by condensing 3,4-diaminofurazan (2) with α-diketones. We suggested that other reactions of the *o*-phenylendiamine could be applied to 3,4-diaminofurazan.

By condensing *o*-phenylendiamine with β-diketones, the 1,5-benzodiazepines were obtained (3). The structures of these compounds were studied by several authors (4,5) and it was demonstrated that the free colourless bases exist almost entirely in the angular di-imino form I, while the intense purple salts have a planar structure, the colour arising from the resonance canonical forms II.

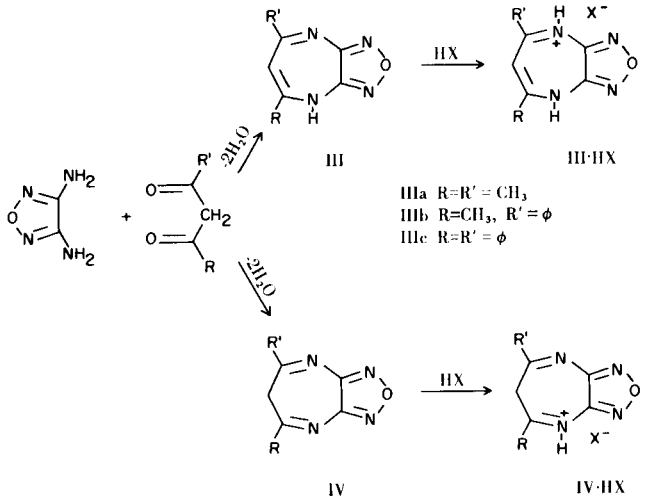


I II

Likewise, 3,4-diaminofurazan reacts with β-diketones affording the furazanodiazepines. The conditions required for the condensation are drastic compared with those required for the preparation of the corresponding 1,5-benzodiazepines.

In fact 5,7-dimethyl-4*H*-furazano[3,4-*b*][1,4]diazepine (IIIa R=R′=CH_3), and 5-methyl-7-phenyl-4*H*-furazano-[3,4-*b*][1,4]diazepine (IIIb R=CH_3, R′=φ), were obtained refluxing for 18 and 75 minutes, respectively, equimolecular amounts of acetylacetone and benzoylacetone with 3,4-diaminofurazan in a mixture of ethanol and acetic acid (3:1). Under analogous conditions the yield of 5,7-diphenyl-4*H*-furazano[3,4-*b*][1,4]diazepine (IIIc R=R′=φ) was very small; an improved yield was obtained refluxing equimolecular amounts of dibenzoylmethane and 3,4-diaminofurazan in acetic acid for 4 hours.

For the bases and their salts the structures III, III·HX, and IV, IV·HX are theoretically possible.



All furazanodiazepines are intensely coloured and this suggests a delocalized orbital system which implies a planar conformation (III) for the entire bicyclic skeleton. If the structure was angular, the resonance interaction between C=N bonds and the furazan ring would be small and consequently the compounds colourless. The structure III for the bases is also consistent with the I.R. spectra. The spectra of the dimethyl, methylphenyl and diphenylfurazanodiazepines in 1,2-dichloroethane and halocarbon show typical bands of NH absorption (see Experimental).

In Table I, N.M.R. data for the compounds obtained are reported.

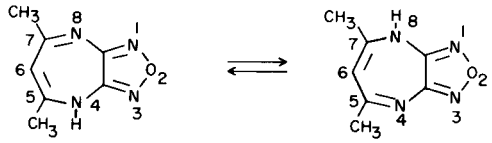
TABLE I

N.M.R. Data for the Furazanodiazepines

Compounds	δ (ppm) CH	CH_3	C_6H_5	Ratio CH/R+R'
IIIa (a)	4.53	1.86	–	1:6
(b)	5.11	2.35	–	1:6
IIIb (a)	5.05	1.93	7.55-8.10 (d)	1:8
(b)	5.50	2.45	7.66-8.18 (d)	1:8
IIIc (c)	5.73	–	8.00-8.45 (d)	1:10
(b)	5.91	–	7.33-8.66 (d)	1:10

(a) Spectrum recorded in chloroform solution with a drop of deuterodimethylsulfoxide, using tetramethylsilane as internal standard. (b) Spectrum recorded in trifluoroacetic acid solution, using tetramethylsilane as external standard. (c) Spectrum recorded in deuterodimethylsulfoxide solution, using tetramethylsilane as internal standard. (d) Peaks in the range reported.

The positions of the absorptions and the relative intensities agree with the previously suggested structures for the bases and their salts (III). In all recorded spectra we were unable to detect NH signals at room temperature. The structure suggested for the 5,7-dimethyl derivative is asymmetrical and two different signals for CH_3 groups would be expected in the spectrum. On the contrary only a singlet at 1.86 ppm is observed, which would imply a symmetrical molecule. This fact could be explained by a rapid tautomerism.



This tautomerism was confirmed by N.M.R. spectrum of IIIa at low temperature. In these conditions two separated peaks can be distinguished, the coalescence temperature being -29° (±2°). The existence of this tautomerism should be extended to compound IIIc, in which the study of the low temperature spectrum, for its complexity, would need a higher resolution instrument.

The low temperature spectrum of IIIb (at -60°) shows only one signal of the CH_3 group, broad and asymmetrical, which suggests a strong predominance of one tautomer. On the basis of presently available data, uncertainty surrounds the location of substituents and so IIIb may actually be a 5-methyl-7-phenyl-4*H*-furazano[3,4-*b*][1,4]-diazepine, or even a 5-phenyl-7-methyl-4*H*-furazano[3,4-*b*]-[1,4]diazepine.

Studies are in progress to investigate the pharmacological activity of these compounds.

EXPERIMENTAL

All melting points are uncorrected. Mass spectra were obtained on a Varian MAT CH7. N.M.R. spectra were determined using a Varian A 60 Mc/sec. spectrometer fitted with a Varian V 6040 temperature control and V 6031 variable temperature probe in which the sample was cooled by a stream of cold nitrogen. I.R. spectra were determined using a Perkin Elmer 257 spectrophotometer, and U.V. spectra were determined in ethanol solution, using a Perkin-Elmer model 350 spectrophotometer.

5,7-Dimethyl-4*H*-furazano[3,4-*b*][1,4]diazepine Hydrochloride (IIIa·HCl).

Acetylacetone (0.30 ml. = 3 mM) was added to a boiling solution of 3,4-diaminofurazan (0.30 g. = 3 mM) in 4 ml. of a mixture of ethanol (3 ml.) and acetic acid (1 ml.), and the resulting solution was gently refluxed for 18 minutes. Then ethanol was evaporated under reduced pressure and to the residue, cooled with a water-ice bath, was added 1 ml. of concentrated hydrochloric acid. The crude yellow material which separated was collected by filtration, dried and washed twice with anhydrous ether (yield 50%). The product was crystallized from ethanol-ether as a yellow powder, m.p. 196-197° dec.

Anal. Calcd. for $C_7H_8N_4O$.HCl: C, 41.90; H, 4.52; N, 27.92; Cl, 17.67. Found: C, 41.85; H, 4.53; N, 27.96; Cl, 17.50.

5,7-Dimethyl-4*H*-furazano[3,4-*b*][1,4]diazepine (IIIa).

Sodium acetate (0.15 g.) dissolved in a small amount of water was added to an aqueous solution of 0.30 g. of IIIa·HCl. The resulting yellow precipitate was collected and dried. It crystallized from benzene as a yellow powder (yield 58%) m.p. 201-202° dec.; U.V. and visible absorption peaks (all peaks are broad), 308 mμ, log ε = 3.41; 412 mμ, log ε = 3.30; I.R. absorption bands, 2.97 μ in 1,2-dichloroethane, 3.08-3.17 μ in halocarbon; mass spectrum (70 eV, 110°), parent peak m/e 164.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.15. Found: C, 51.35; H, 4.87; N, 34.43.

5-Methyl-7-phenyl-4*H*-furazano[3,4-*b*][1,4]diazepine Hydrochloride (IIIb·HCl).

Benzoylacetone (0.48 g. = 3 mM) was added to a boiling solution of 3,4-diaminofurazan (0.30 g. = 3 mM) in 4 ml. of a mixture of ethanol (3 ml.) and acetic acid (1 ml.) and the resulting solution was gently refluxed for 75 minutes and then worked up as described for the preparation of IIIa·HCl. The crude hydrochloride, washed twice with anhydrous ether (yield 86%), was crystallized from absolute alcohol-ether as a red powder m.p. 181-182° dec.

Anal. Calcd. for $C_{12}H_{10}N_4O$·HCl: C, 54.86; H, 4.24; N, 21.33; Cl, 13.49. Found: C, 54.96; H, 4.19; N, 21.30; Cl, 13.50.

5-Methyl-7-phenyl-4*H*-furazano[3,4-*b*][1,4]diazepine (IIIb).

A suspension of 0.40 g. of IIIb·HCl in 8 ml. of water was carefully basified with diluted ammonia. The orange material was collected by filtration, dried and crystallized from benzene (yield 75%) as an orange-red powder, m.p. 154-155° dec.; U.V. and visible absorption peaks (all peaks are broad), 280 mμ, log ε = 4.27, shoulder 320 mμ, 435 mμ, log ε = 3.28; I.R. absorption bands, 2.97 μ in 1,2-dichloroethane, 3.05-3.14 μ in halocarbon; mass spectrum (70 eV, 150°), parent peak m/e 226.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.42; H, 4.48; N, 24.81.

5,7-Diphenyl-4*H*-furazano[3,4-*b*][1,4]diazepine (IIIc).

Equimolecular amounts of dibenzoylmethane (0.67 g. = 3 mM) and of 3,4-diaminofurazan (0.30 g. = 3 mM) were heated in refluxing acetic acid (2 ml.) for 4 hours. Then to the solution cooled at room temperature was added 1 ml. of concentrated hydrochloric acid. The material which separated was collected, dried and washed several times with anhydrous ether, dissolved in absolute alcohol and precipitated with ether as a red powder. Five tenths g. of this material in 10 ml. of water was worked up as described for IIIb. The red material was crystallized from benzene (yield 15%) as red needles, m.p. 221-222°. U.V. and visible absorption peaks (all peaks are broad), 278 mμ, log ε = 4.45, shoulder 320 mμ, 452 mμ, log ε = 3.40; I.R. absorption bands, 2.98 μ in 1,2-dichloroethane, 3.05-3.12 μ in halocarbon; mass spectrum (70 eV, 180°), parent peak m/e 288.

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 71.04; H, 4.30; N, 19.61.

All efforts to obtain a pure analytical sample of IIIc·HCl failed because of a partial decomposition of the salt during the crystallization.

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