

SYNTHESIS OF QUINO[2,3-b]7/1,5]BENZOXAZEPINES:
A NOVEL TETRACYCLIC RING SYSTEM

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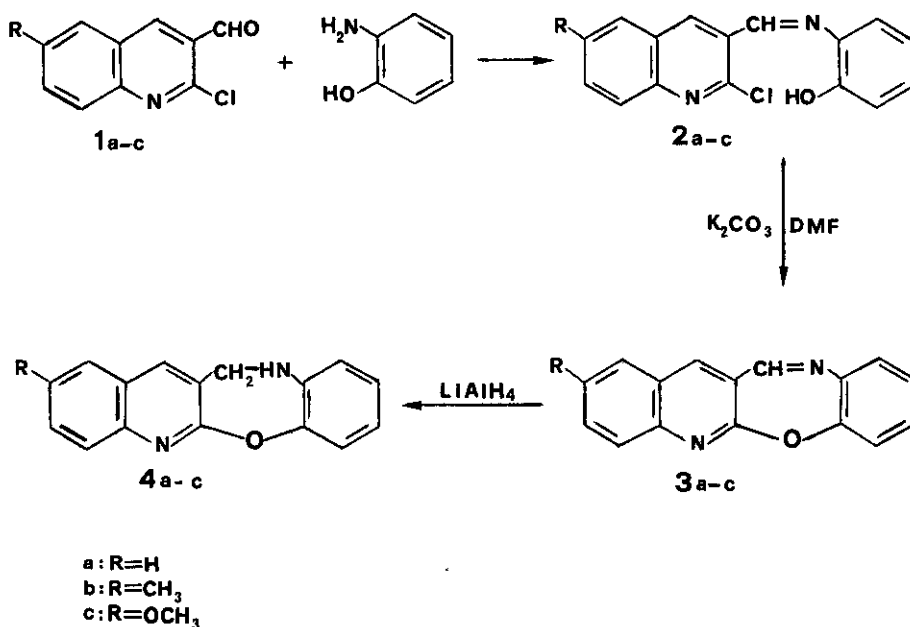
Abstract - The one-pot synthesis of quino[2,3-b]7/1,5]benzoxazepines 3a-c from 2-chloroquinoline-3-carbaldehydes 1a-c and *ortho*-aminophenol is described. Reduction of 3a-c with lithium aluminum hydride afforded 11,12-dihydroquino[2,3-b]7/1,5]benzoxazepines 4a-c in high yields.

Although condensed seven membered heterocycles have been the subject of many synthetic studies in view of their pharmacological properties, little work has been carried out on the preparation of tetracyclic derivatives. Recently the formation of 6H-quino[2,3-b]7/1,5]benzodiazepine and its 11,12-dihydro derivative was observed by Bhanumathi and coworkers¹, when a 2-chloroquinoline-3-carbaldehyde was treated with *o*-phenylenediamine. However a benzimidazole derivative was the main reaction product.

In this paper we report a facile one-pot synthesis of quino[2,3-b]7/1,5]benzoxazepines 3a-c and the reduction to the corresponding 11,12-dihydro derivatives 4a-c.

2-Chloro-3-formylquinolines 1a-c were condensed with *o*-aminophenol to give quantitatively the intermediate imines 2a-c, which were then cyclized in high yields to 1,5-benzoxazepines 3a-c, using anhydrous potassium carbonate under the conditions adopted by Nielsen and Pedersen².

The structure of tetracyclic derivatives 3a-c was inferred from analytical and spectroscopic data. A characteristic feature of the ¹H nmr spectra of these 1,5-benzoxazepines is the higher field resonance of iminic and C-13 protons relative to that shown by the corresponding Schiff bases (CH=N and 4-H in compounds 2a-c). Compounds 3a-c were then smoothly reduced by lithium aluminum hydride to the 11,12-dihydrobenzoxazepines 4a-c in high yields.



In the ¹H nmr spectra of 4a-c the presence of a singlet at $\delta = 4.55$ ppm assigned to CH₂-NH protons, together with the lack of iminic signal, provided evidence for the structure of these reduction products.

Table 1. Physical and analytical data of aldimines 2a-c

compound	mp, °C crystallization solvent	$\overline{[a]_D^{25}}$	formula	analyses %			
				calcd./found		Cl	N
2a ~	193-194 EA		C ₁₆ H ₁₁ ClN ₂ O	67.97 68.04	3.92 4.03	12.54 12.81	9.91 9.92
2b ~	186-187 EA-E		C ₁₇ H ₁₃ ClN ₂ O	68.80 68.84	4.42 4.48	11.95 12.10	9.44 9.29
2c ~	182-183 EA		C ₁₇ H ₁₃ ClN ₂ O ₂	65.28 65.34	4.19 4.21	11.34 11.81	8.96 8.86

$\overline{[a]_D^{25}}$ All the compounds melt with decomposition. $\underline{[b]_D^{25}}$ EA = ethyl acetate; E = ether.

Table 2. Selected spectral data for aldimines $\underline{2a-c}$

compound	^1H nmr (δ , ppm) <u>[a]</u>			ir (ν , cm^{-1})
	CH=N	4-H	6-R	
$\underline{2a}$ ~	9.24	8.97		1612, 1329
$\underline{2b}$ ~	9.15	8.79	2.51 (CH_3)	1615, 1336
$\underline{2c}$ ~	9.18	8.81	3.93 (OCH_3)	1614, 1338

[a] All the reported signals appear as singlets.

 Table 3. Physical and analytical data of quino[2,3-b]7[1,5]benzoxazepines $\underline{3a-c}$ and their 11,12-dihydro derivatives $\underline{4a-c}$

compound	yield % <u>[a]</u>	mp, $^\circ\text{C}$ <u>[b]</u>	formula	analyses %		
				calcd./found	C	H
$\underline{3a}$ ~	100	168-170	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}$	78.03 77.76	4.09 4.07	11.38 11.31
$\underline{3b}$ ~	93	156-157	$\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}$	78.44 78.55	4.65 4.75	10.76 11.07
$\underline{3c}$ ~	92	143-143.5	$\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2$	73.90 74.04	4.38 4.47	10.14 10.08
$\underline{4a}$ ~	91	190-191	$\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}$	77.40 77.22	4.87 4.92	11.28 11.17
$\underline{4b}$ ~	81	201.5-202	$\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$	77.84 77.71	5.38 5.43	10.68 10.48
$\underline{4c}$ ~	85	202-202.5	$\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$	73.36 73.24	5.07 5.16	10.07 9.93

[a] Yields from weights of homogeneous chromatographic fractions. [b] All the compounds were crystallized from ethyl acetate.

Table 4. Selected spectral data for quino/2,3-b/1,5/benzoxazepines 3a-c and their 11,12-dihydro derivatives 4a-c

compound	¹ H nmr (δ, ppm) /a/				ir (ν, cm ⁻¹)
	CH=N	13-H	CH ₂ -NH	2-R	
3a	8.53	8.14			1612, 1479
3b	8.50	8.00		2.43 (CH ₃)	1615, 1500
3c	8.48	7.94		3.83 (OCH ₃)	1631, 1600, 1499
4a		8.00/b/	4.55		3418, 1496
4b		7.91/b/	4.55	2.49 (CH ₃)	3418, 1501
4c		7.91/b/	4.55	3.91 (OCH ₃)	3415, 1501

/a/ All the reported signals appear as singlets. /b/ Superimposed on another aromatic.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus and are uncorrected. Ir spectra (KBr) were recorded with a Perkin-Elmer 983 spectrophotometer. The ¹H nmr spectra were measured with a Varian EM-390 (90 MHz) spectrometer, using deuteriochloroform as the solvent (tetramethylsilane as internal standard). Merck silica gel 60 (230-400 mesh) was used for column chromatography. The drying agent was sodium sulphate. Dry tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were used.

General Procedure for the Synthesis of Quino/2,3-b/1,5/benzoxazepines 3a-c

A solution of 2-chloroquinoline-3-carbaldehyde³ 1a-c (0.5 mmol) and o-aminophenol (0.5 mmol) in 2.5 ml of THF was stirred at room temperature for 2 h (3 h in the case of 1c) and evaporated under vacuum. To the yellow homogeneous (nmr) residue⁴ DMF (5 ml) and dry potassium carbonate (0.25 g) were added. After stirring at 85-90 °C for 3 h, the mixture was cooled and partitioned between ethyl acetate and water. The organic phases were dried and evaporated to give a solid residue, which was chromatographed on a column of silica (1:40). Elution with dichloromethane and dichloromethane-ether (95:5) afforded pure title compounds 3a-c,

Reduction of Quino/2,3-b/1,5/benzoxazepines 3a-c

To a stirred solution of 3a-c (0.5 mmol) in THF (5 ml), cooled at 0 °C, lithium aluminum hydride (1 mmol) was carefully added. After stirring at room temperature for 30 min the excess of hydride was decomposed with the minimum amount of ethyl

acetate and ice, cooling at 0 °C. The organic solution was separated by filtration, washing the solid residue with ethyl acetate. The filtered organic solution was washed with water, dried and evaporated. The residue was chromatographed on a silica column (1:20), eluting with dichloromethane-n-hexane (9:1) and dichloromethane, to afford pure 11,12-dihydroquino[2,3-b7/[1,5]benzoxazepines 4a-c.

REFERENCES AND NOTE

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2. F.E. Nielsen and E.B. Pedersen, Chem. Scr., 1986, 26, 343.
3. O. Meth-Cohn, B. Narine, and B. Tarnowski, J. Chem. Soc., Perkin Trans. I, 1981, 1520.
4. The intermediate imines were also isolated and characterized (Tables 1 and 2). Cyclization of pure imine 2b afforded benzoxazepine 3b in higher yield (97%) than that arising from one-pot procedure (93%).

Received, 11th May, 1987