Synthesis of Novel Quino[2,3-*b*][1,5]benzodiazepin-12-ones [1]

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The synthesis of potentially biologically biologically active quino[2,3-*b*][1,5]benzodiazepin-12-ones has been reported for the first time by the reaction of 2-chloroquinoline-3-carboxylic acids with *o*-phenylenediamine.

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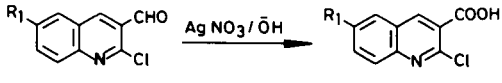
The dibenzodiazepinone ring system [2,3] is of importance in medicinal chemistry due to its antidepressant, antiallergic and neuroleptic actions [4-6], but quinoline fused benzodiazepinones have not been exploited so far. Hence, in continuation of our studies on the synthesis of quinoline fused novel heterocycles [7], an attempt has been made to synthesize the quino-fused benzodiazepinone **IV** by the reaction of 2-chloroquinoline-3-carboxylic acid **II** with a variety of *o*-phenylenediamines **III**.

A convenient method of synthesis has also been developed for the starting 2-chloroquinoline-3-carboxylic acids **II** by a facile oxidation of the corresponding aldehydes. 2-Chloroquinoline-3-carboxaldehydes **I** are oxidized with alkaline silver nitrate in ethanol at room temperature to give the corresponding acids **II** in 73-75% yield (Table 1). Other oxidizing agents like alkaline potassium permanganate were not effective under various conditions.

Scheme 1



The 2-chloroquinoline-3-carboxylic acids **II** upon reaction with *o*-phenylenediamine in xylene afforded the novel tetracyclic quino[2,3-*b*][1,5]benzodiazepin-12-ones **IV** (Table 2). The structure of these compounds is confirmed by ir, nmr, mass spectral data and elemental analysis.

Table 1

2-Chloroquinoline-3-carboxylic Acids **II**

No.	R_1	mp [a] °C	Yield (%)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
1	H	235	75	$C_{10}H_6ClNO_2$	57.85	2.91	6.75
					57.73	2.86	6.68
2	CH_3	224	73	$C_{11}H_8ClNO_2$	59.61	3.64	6.32
					59.62	3.58	6.20
3	OCH_3	196	75	$C_{11}H_8ClNO_3$	55.59	3.40	5.89
					55.48	3.33	5.81

[a] These compounds were recrystallized from methanol.

The yields of diazepinones **IV** vary with substituents and quino[2,3-*b*][1,5]benzodiazepin-12-one **IVa** is obtained up to 72%. But, the reaction of 4,5-dimethyl *o*-phenylenediamine with 2-chloroquinoline-3-carboxylic acids **II** has not yielded the expected diazepinones, instead 3-substituted benzimidazoles **V** are isolated in 60-70% yield.

These quinobenzodiazepinones **IV** have characteristic downfield singlets at 9-10.33 ppm and 8-9 ppm assigned to *H*N-C=O and N*H* protons, respectively (Table 3). The structure was also further confirmed by accurate mass measurement and by its fragmentation behaviour upon electron impact.

Table 2

Quino[2,3-*b*][1,5]benzodiazepin-12-ones **IV**

Product IV	R_1	R_2	R_3	mp [a] °C	Yield (%)	Molecular Formula (Accurate mass)	Analysis (%) Calcd./Found C	H	N
a	H	H	H	258-259 C	72	$C_{16}H_{11}N_3O$ (261.0906)	73.55	4.24	16.08
							73.38	4.18	16.16
b	CH_3	H	H	265-266 C	68	$C_{17}H_{13}N_3O$) (275.1067)	74.17	4.76	15.26
							74.12	4.74	15.23
c	OCH_3	H	H	255-256 C	70	$C_{17}H_{13}N_3O_2$ (291.1018)	70.09	4.50	14.42
							70.24	4.62	14.48
d	H	Cl	Cl	310 C/M	39	$C_{16}H_9Cl_2N_3O$ (329.0128)	58.20	2.75	12.73
							58.04	2.64	12.69
e	OCH_3	Cl	Cl	302 C/M	41	$C_{17}H_{11}Cl_2N_3O_2$ (359.0254)	56.69	3.08	11.67
							56.75	2.94	11.57

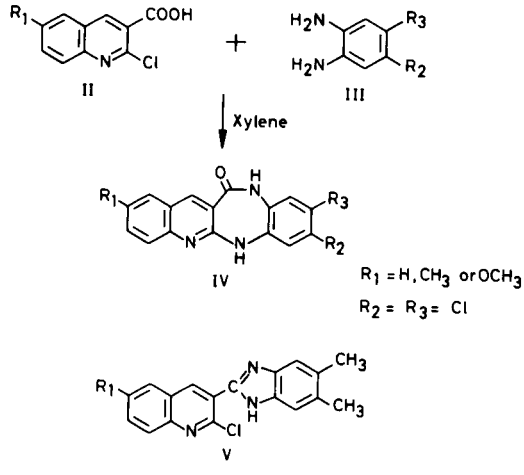
[a] Recrystallization solvent: Chloroform = C, Methanol = M.

Table 3
Selected Spectral Data for Subsituted Quino[2.3-*b*][1,5]benzodiazepin-12-ones **IV**

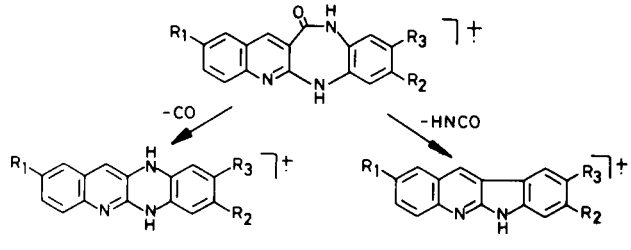
Product IV	IR (KBr) cm-1	^{1}H NMR (DMSO-d_6) NN–C(=O)	^{1}H NMR (DMSO-d_6) NH	Mass spectral Fragments: m./z (Relative intensities)
a	3310, 3190, 3020, 1660	9.36	7.96	261 (100), 233 (35), 232 (30), 218 (20)
b	3320, 3190, 3030, 1670	9.66	8.26	275 (100), 247 (25), 246 (20), 232 (18)
c	3320, 3180, 3020, 1660	10.21	8.68	291 (100), 276 (50), 248 (33), 220 (21)
d	3200, 3120, 3040, 1680	10.23	9.10	329 (100), 294 (40), 286 (46), 259 (40)
e	3200, 3120, 3040, 1660	10.25	9.32	359 (100), 344 (70), 331 (40), 316 (50)

The mass spectra of these compounds show an intense molecular ion (base peak) and two other important fragment ions, one due to the loss of CO and the other due to elimination of HNCO from the molecular ion (Table 3).

Scheme 2



Scheme 3



Thus, this reaction opens up a very facile synthesis of new tetracyclic quinobenzodiazepinones.

EXPERIMENTAL

Mass spectra were recorded on VG micromass 70-70H mass spectrometer. The pmr spectra were recorded on JEOL FT FX-90Q spectrometer. The ir spectra were recorded on Perkin-Elmer Model 283B spectrometer. 2-Chloroquinoline-3-carboxaldehydes **I** were made according to the procedure reported earlier [8].

General Procedure for the Oxidation of 2-Chloroquinoline-3-carboxaldehydes **I**.

To a solution of 2-chloroquinoline-3-carboxaldehyde (0.025 mole) in ethanol (200 ml) was added silver nitrate (0.04 mole) in ethanol (100 ml) with stirring at room temperature. After addition of the oxidant, sodium hydroxide (0.125 mole) in 80% ethanol (100 ml) was added to the reaction mixture in small portions and it was stirred for 4 hours. It was filtered and concentrated to dryness. It was dissolved in water and acidified with dilute hydrochloric acid (5*N*). Yields of the acids were in the range of 73-75%.

General Procedure for the Synthesis of Quino[2,3-*b*][1,5]benzodiazepin-12-ones **IV**.

A mixture of *o*-phenylenediamine (0.01 mole) and 2-chloroquinoline-3-carboxylic acid (**II**, 0.01 mole) was heated in xylene (15 ml) at 130-135° for 2 hours. Later, it was cooled, washed with 10% sodium hydrogen carbonate solution and the solvent was removed by steam distillation. The crude product was purified by chromatography on a column of silica gel using a mixture of chloroform and methanol (9:1 v/v) as eluent to give the title compounds (Table 2).

However, in the case of dimethylphenylenediamine, benzimidazole **V** was obtained. These were characterized from their mass spectral data and elemental analysis.

Compound **Vi** (R_1 = H) had mp 189-190° (chloroform) 60%.

Anal. Calcd. for $C_{18}H_{14}ClN_3$: C, 70.25; H, 4.58; N, 13.65. Found: C, 70.48; H, 4.55; N, 13.61.

Compound **Vii** (R_1 = CH_3) had mp 166-167° (chloroform) 61%.

Anal. Calcd. for $C_{19}H_{16}ClN_3$: C, 70.92; H, 5.01; N, 13.06. Found: C, 70.84; H, 4.98; N, 12.86.

Compound **Viii** (R_1 = OCH_3) had mp 134-135° (chloroform) 68%.

Anal. Calcd. for $C_{19}H_{16}ClN_3O$: C, 67.56; H, 4.78; N, 12.44. Found: C, 67.74; H, 4.82; N, 12.66.

REFERENCES AND NOTES

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