A NEW HETEROCYCLIC RING SYSTEM: 13*H*-BENZIMIDAZO-[2',1':2,3][1,3]THIAZINO[6,5-*b*]QUINOLINE

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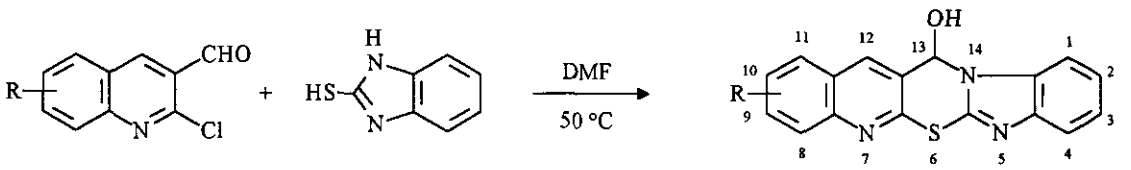
Abstract- 13*H*-Benzimidazo[2',1':2,3][1,3]thiazino[6,5-*b*]quinoline has been synthesised from 2-chloroquinoline-3-carboxaldehydes (**1**) and 2-mercapto-benzimidazole (**2**). Subsequent transformations of the corresponding 13-hydroxy derivatives are described.

2-Chloro-3-quinolinecarboxaldehydes[1] (**1**) are useful intermediates in the syntheses of various condensed heterocycles.[2-5] These new heterocyclic compounds are of biological interest because of their definite affinity to the benzodiazepine receptor.[6,7] In continuation of our studies in this field,[8,9] the reaction of 2-chloro-3-quinolinecarboxaldehydes (**1**) and carboxaldehyde acetals (**4**, **5**) with 2-mercaptobenzimidazole (**2**) was investigated.

Reaction of 2-chloro-3-quinolinecarboxaldehydes (**1**) with 2-mercaptobenzimidazole (**2**) in dry dimethylformamide (DMF) at 50 °C led to the formation of 13-hydroxy-13*H*-benzimidazo-[2',1':2,3][1,3]thiazino[6,5-*b*]quinolines (**3**) in good yield (Scheme 1, Table 1).



1 **2** **3**

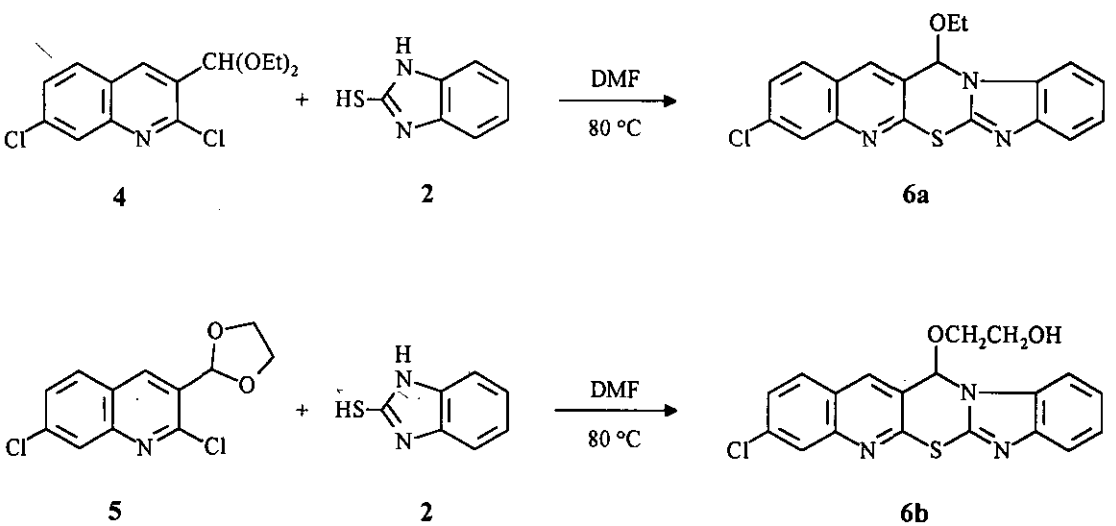
Scheme 1

Table 1. Yields and melting points of 13-hydroxy-13*H*-benzimidazo[2',1':2,3][1,3]thiazino[6,5-*b*]quinolines (**3a-f**).

Compound	R	Reaction time (h)	yield (%)	mp (°C)[a]
3a	H	5	86	254-257
3b	8-Me	22	69	272-274
3c	9-Me	7	66	249-252
3d	9-OMe	15	90	266-268
3e	9-Cl	4	88	276-279
3f	10-Me	8	80	284-286

[a] DMSO-ethanol. All the compounds melt with decomposition.

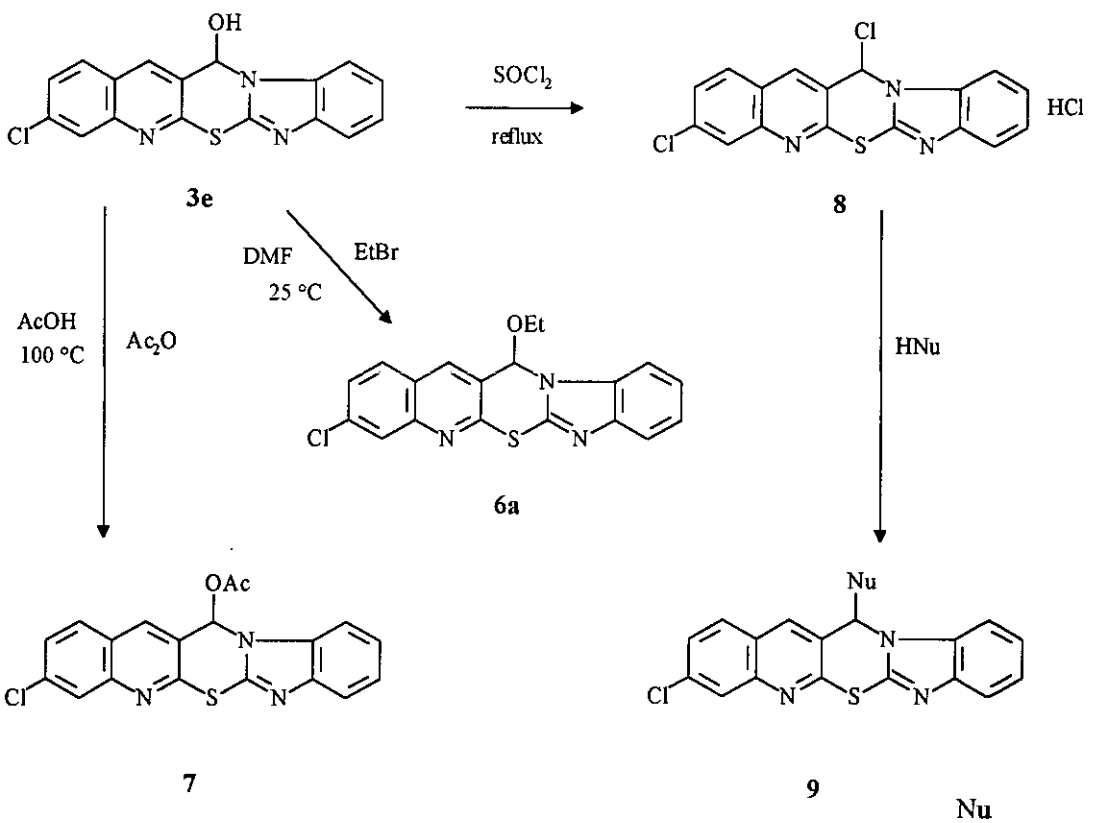
Similar cyclocondensation was observed when the diethyl- or ethylideneacetals of the 2-chloro-3-quinolinecarboxaldehydes[9,10] (**4**, **5**) were treated with 2-mercaptobenzimidazole (**2**) in dry DMF at 80 °C (Scheme 2, Table 2).



Scheme 2

The first step of the reaction presumably is the substitution of the 2-chloro group of **1**, **4**, or **5** by the thiol group of **2** followed by a cyclization similarly to that was observed in the formation of [1,2,4]triazolo[5',1':2,3][1,3]thiazino[6,5-*b*]quinolines.[9]

To investigate the reactivity of the 13-hydroxy group, transformation reactions of the 9-chloro-13-hydroxy-13*H*-benzimidazo[2',1':2,3][1,3]thiazino[6,5-*b*]quinoline (**3e**) have also been carried out (Scheme 3).



Scheme 3

Acetylation of **3e** with acetic anhydride (acetic acid, 100 °C) gave the 13-acetoxy derivative (**7**) in 73 % yield. Reaction of **3e** with ethyl bromide (DMF, room temperature) yielded **6a**. The 13-chloro derivative (**8**) was readily produced by the action of thionyl chloride on **3e**. Compound (**8**) was prepared as its hydrochloride salt. It was used in the next steps without purification. The 13-chloro group was replaced by n-butylamine, 2-mercaptoethanol, ethanol and ethylene glycol giving **9a**, **9b**, **6a**, and **6b**, respectively. These reactions were carried out without solvent at 25 °C. Compounds (**6a**) and (**6b**) were identical with that obtained by reaction of compounds **4** and **5** with **2**. (Tables 2-4).

Table 2. Yields and melting points of compounds (**6a** - **9b**).

Compound	yield (%)	mp (°C)	(solvent)
6a	66[a]	193-195	(DMSO-ethanol)
6b	42[b]	179-182	(DMSO-acetone)
7	73	227-229	(DMSO-ethanol)
8	96	[c]	-
9a	41	167-169	(DMSO-ethanol)
9b	64	229-231	(DMSO-ethanol)

[a] From the reaction of compound (**8**) with ethanol. [b] From the reaction of compound (**8**) with ethylene glycol. [c] Decomposition without melting.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ^{1}H-Nmr spectra were recorded on a Varian Gemini-200 instrument at 200 MHz using TMS as internal standard and chemical shifts are expressed in ppm. DMSO-d_6 was used as solvent in every case. Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70 eV.

Table 3. ^{1}H-Nmr and mass spectral data of compounds (**3-9**).

Compound	^{1}H-Nmr δ (ppm), J (Hz)	Ms m/z (%)
3a	7.35(m, 3H); 7.62(m, 3H); 7.83(m, 2H); 8.00(d, J=8, 1H); 8.12(d, J=8, 1H); 8.69(s, 1H)	305(M^+, 93); 289(50); 276(100); 244(38)
3b	2.71(s, 3H); 7.35(m, 3H); 7.54(m, 2H); 7.68(m, 2H); 7.83(m, 1H); 7.95(d, J=8, 1H); 8.64(s, 1H)	319(M^+, 97); 317(80); 303(67); 290(100);
3c	2.53(s, 3H); 7.32(m, 3H); 7.52(m, 2H); 7.63(m, 1H); 7.81(m, 2H); 8.01(d, J=7.5, 1H); 8.61(s, 1H)	319(M^+, 87); 302(76); 290(100); 258(32)
3d	3.93(s, 3H); 7.31(m, 5H); 7.50(m, 1H); 7.63(m, 1H); 7.82(m, 1H); 8.02(d, J=8, 1H); 8.58(s, 1H)	335(M^+, 32); 333(40); 318(100); 306(23)
3e	7.35(m, 3H); 7.65(m, 3H); 7.82(m, 1H); 8.08(d, J=1.5, 1H); 8.20(d, J=8.5, 1H); 8.72(s, 1H)	339(M^+, 45); 337(100); 323(43); 309(10)
3f	2.52(s, 3H); 7.32(m, 3H); 7.53(m, 1H); 7.65(m, 2H); 7.87(m, 3H); 8.58(s, 1H)	319(M^+, 57); 317(100); 302(84); 290(47)
6a	0.97(t, J=7, 3H); 3.48(m, 2H); 7.35(m, 2H); 7.47(s, 1H); 7.69(m, 2H); 7.93(m, 1H); 8.10(d, J=1.5, 1H); 8.22(d, J=8.5, 1H); 8.79(s, 1H)	367(M^+, 27); 338(7); 322(100); 287(13)
6b	3.45(m, 4H); 3.9-4.2(broad, 1H); 7.33(m, 2H); 7.48(s 1H); 7.69(m, 2H); 7.93(m, 1H); 8.08(d, J=1.5, 1H); 8.20(d, J=8.5, 1H); 8.78(s, 1H)	383(M^+, 3); 367(6); 322(21); 45(100)
7	1.96(s, 3H); 7.37(m, 2H); 7.72(m, 3H); 8.12(m, 1H); 8.22(m, 1H); 8.63(s, 1H); 8.84(s, 1H)	381(M^+, 10); 338(15); 322(100)
8	7.42(m, 3H); 7.71(m, 2H); 7.98(m, 1H); 8.11(d, J=1.5, 1H); 8.23(d, J=8.5, 1H); 8.79(s, 1H); 10.0-10.5(broad)	-
9a	0.62(t, J=7, 3H); 1.13(m, 4H); 2.29(m, 2H); 3.48(m, 1H); 6.97(d, J=7, 1H); 7.30(m, 2H); 7.64(m, 2H); 7.91(m, 1H); 8.06(d, J=1.5, 1H); 8.18(d, J=8.5, 1H); 8.65(s, 1H)	394(M^+, 28); 351(13); 337(100); 322(27)
9b	2.63(m, 2H); 3.42(t, J=7, 2H); 4.82-5.08(broad, 1H); 7.35(m, 2H); 7.69(m, 2H); 7.80(s, 1H); 7.90(m, 1H); 8.10(d, J=1.5, 1H); 8.20(d, J=8.5, 1H); 8.65(s, 1H)	399(M^+, 3); 322(100); 287(15)

13-Hydroxy-13H-benzimidazo[2',1':2,3][1,3]thiazino[6,5-b]quinolines (3a-f). General procedure.
The mixture of the corresponding 2-chloro-3-quinolinecarboxaldehyde (**1**) (10 mmol) and 2-mercaptobenzimidazole (**2**) (1.65 g, 11 mmol) in DMF (20 ml) was stirred at 50 °C. The reaction times are given in the Table 1. The reaction mixture was diluted with water (50 ml), the product was filtered off, washed with water, dried, and crystallized from DMSO-ethanol mixture.

Reaction of 2-chloro-3-quinolinecarboxaldehyde acetals (4, 5) with 2-mercaptobenzimidazole (2).
The corresponding acetal (**4** or **5**) (5 mmol) and 2-mercaptobenzimidazole (**2**) (0.825 g, 5.5 mmol) was dissolved in dry DMF (15 ml) and the solution was stirred at 80 °C for 14 h. The mixture was poured into water (30 ml), the precipitated product was collected, washed with water, dried, and crystallized from DMSO-ethanol and DMSO-acetone mixture, respectively, to give **6a** (1.2 g, 65 %) and **6b** (1.3 g, 68 %).

Alkylation of 9-chloro-13-hydroxy-13H-benzimidazo[2',1':2,3][1,3]thiazino[6,5-b]quinoline (3e) with ethyl bromide.
Compound (**3e**) (1.12 g, 3.3 mmol), ethyl bromide (0.72 g, 6.6 mmol) and K_2CO_3 (0.46 g, 3.3 mmol) were suspended in DMF (15 ml). The suspension was stirred at room temperature for 6 h. The reaction mixture was worked up in a manner similar to that described for the preparation of compounds (**3a-f**). The yield of **6a** was 0.64 g, 53 %.

13-Acetoxy-9-chloro-13H-benzimidazo[2',1':2,3][1,3]thiazino[6,5-b]quinoline (7).
Compound (**3e**) (1.12 g, 3.3 mmol) was suspended in glacial acetic acid (10 ml). Acetic anhydride (5 ml, 53 mmol) was added and the suspension was heated at 100 °C for 2 h. The solid material has gone to solution. The reaction mixture was cooled to room temperature and diluted with water (30 ml). The crude product was filtered off, washed with water, dried and crystallized from DMSO-ethanol. Yield: 0.92 g, 73 %.

9,13-Dichloro-13H-benzimidazo[2',1':2,3][1,3]thiazino[6,5-b]quinoline hydrochloride (8).
Compound (**3e**) (3.39 g, 10 mmol) was treated with thionyl chloride (30 ml, 413 mmol) at reflux temperature for 3 h. After cooling to room temperature, the solution was diluted with chloroform (30 ml), the crystalline hydrochloride salt was filtered off, washed with chloroform and dried. It was used without further purification. Yield: 3.79 g, 96 %.

Transformations of 9,13-dichloro-13H-benzimidazo[2',1':2,3][1,3]thiazino[6,5-b]quinoline hydrochloride (8). General procedure.

Hydrochloride salt (**8**) (0.99 g, 2.5 mmol) was stirred in 15 ml of the corresponding nucleophile (butylamine: 151 mmol; ethanol: 258 mmol; ethylene glycol: 269 mmol; 2-mercaptoethanol: 214 mmol) at room temperature for 5 h. Work-up:

9a: The reaction mixture was evaporated and the residue was crystallized from DMSO-ethanol mixture.

6a: The solution was poured into water (30 ml), neutralized with 15 % aq. ammonia solution, the solid material was collected, washed with water, dried and crystallized from DMSO-ethanol mixture.

6b, 9b: The reaction mixture was worked up in a manner similar to that described for the preparation of **3a-f**.

Table 4. Analytical data for compounds (**3-9**) synthesised.

Compound	Formula	Elemental Analysis (%)					
		Calculated			Found		
		C	H	N	C	H	N
3a	$C_{17}H_{11}N_3OS$	66.86	3.64	13.76	66.73	3.60	13.87
3b	$C_{18}H_{13}N_3OS$	67.68	4.11	13.16	67.60	4.14	13.22
3c	$C_{18}H_{13}N_3OS$	67.68	4.11	13.16	67.57	4.16	13.09
3d	$C_{18}H_{13}N_3O_2S$	64.45	3.92	12.53	64.59	3.85	12.51
3e	$C_{17}H_{10}N_3OClS$	60.08	2.97	12.37	60.00	2.91	12.43
3f	$C_{18}H_{13}N_3OS$	67.68	4.11	13.16	67.84	4.20	13.20
6a	$C_{19}H_{14}N_3OClS$	62.03	3.84	11.43	62.19	3.82	11.37
6b	$C_{19}H_{14}N_3O_2ClS$	59.45	3.68	10.95	59.41	3.68	10.85
7	$C_{19}H_{12}N_3O_2ClS$	59.76	3.17	11.01	59.85	3.14	11.12
9a	$C_{21}H_{19}N_4ClS$	63.86	4.86	14.19	63.84	4.90	14.18
9b	$C_{19}H_{14}N_3OClS_2$	57.06	3.54	10.51	57.22	3.55	10.55

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