THE REACTIVITY OF 2-IMINOBENZO[a]QUINOLIZIDINES TOWARDS 2-MERCAPTOACETIC ACID

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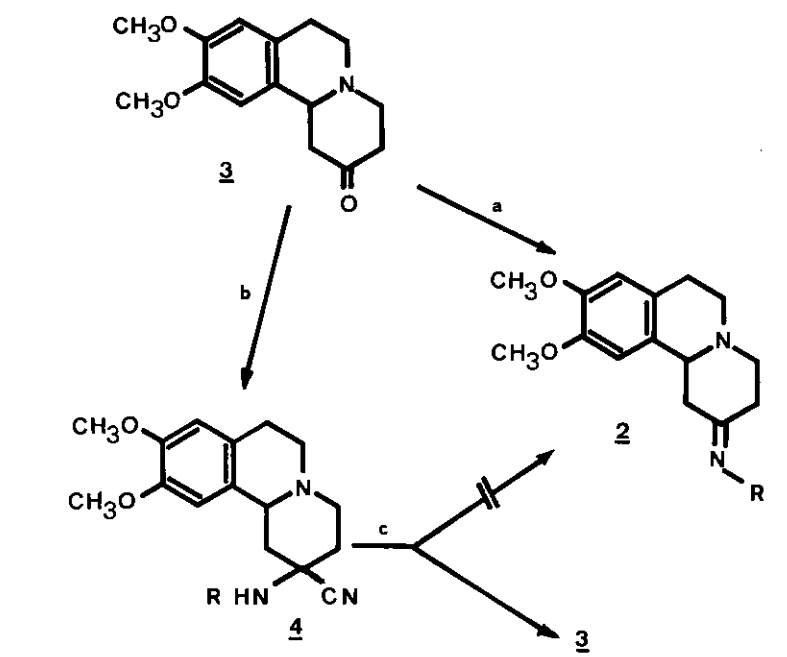
Abstract —The reaction between 2-iminobenzo[a]quinolizidines (2) and mercaptoacetic acid under a variety of conditions led to the thiazolo[2,3-a]isoquinoline derivative (5) instead of the expected spiro compound (1). The same result was obtained when the reaction was carried out on ketone (3). Modified reaction conditions allowed the preparation of an example of structure (1).

The benzo[a]quinolizidine ring system has been associated with interesting pharmacological properties, such as chemotherapeutic,[1] neuroleptic,[2] antihypertensive,[3] antiinflamatory,[4] and anticonvulsant activities,[5] among others. A recently discovered fact is the capacity of certain 2-substituted benzo[a]quinolizidines to antagonize α_2 adrenoceptors selectively.[6] The pharmacological interest of all these properties has prompted extensive studies on the chemistry of benzo[a]quinolizidines,[7] which have usually shown a considerable stability for the parent system and its derivatives. Thus, many benzo[a]quinolizidines have been shown to resist strongly acidic[8] and basic[9] media without alteration of the parent structure. We wish to report here an exception to such behaviour.

Within the scope of our research into 2-spiro derivatives of the benzo[a]quinolizidine system, the synthesis of spiro[benzo[a]quinolizidine-2,2'-1,3-thiazolidin]-4'-ones (1) was planned. An examination of review literature on 4-thiazolidinone synthesis[10] revealed the reaction between 2-imino derivatives of benzo[a]quinolizidine (2) and 2-mercaptoacetic acid as the most suitable procedure for the preparation of 1. Imines (2) were prepared (Scheme 1) by acid-catalyzed condensation of ketone (3)[11] with primary amines, while the attempted base-catalyzed elimination of hydrocyanic acid from aminonitriles (4)[12] under the conditions described by Walia[13] led only to the ketone (3).

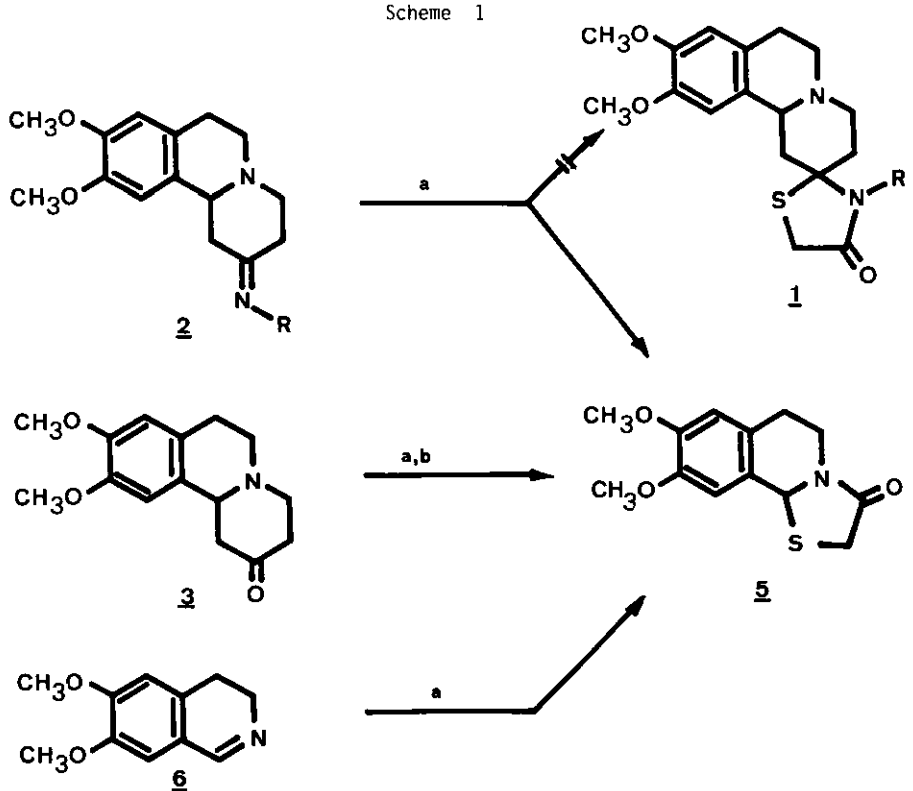
Treatment of (2) with 2-mercaptoacetic acid under the reaction conditions that had been previously tested on piperidine model compounds[12] (reflux in benzene, in the presence of toluenesulfonic acid and 4 Å molecular sieves) did not lead to the expected spiro derivatives (1). Instead, thiazolo[2,3-a]isoquinoline (5) was obtained in all cases; confirmation of this structure was achieved by spectroscopic means and by alternative synthesis from 9,10-dimethoxy-3,4-dihydroisoquinoline (6).[13]



Nr.	R
2a	$CH_2C_6H_5$
2b	C_6H_5
2c	4-Me-C_6H_4
2d	4-H_2NSO_2-C_6H_4

a. R-NH_2, TsOH, benzene or benzene-ethanol. Reflux, 6-24 h b. Ref. 10
c. KOH, MeOH, room temperature, 48 h.

Scheme 1

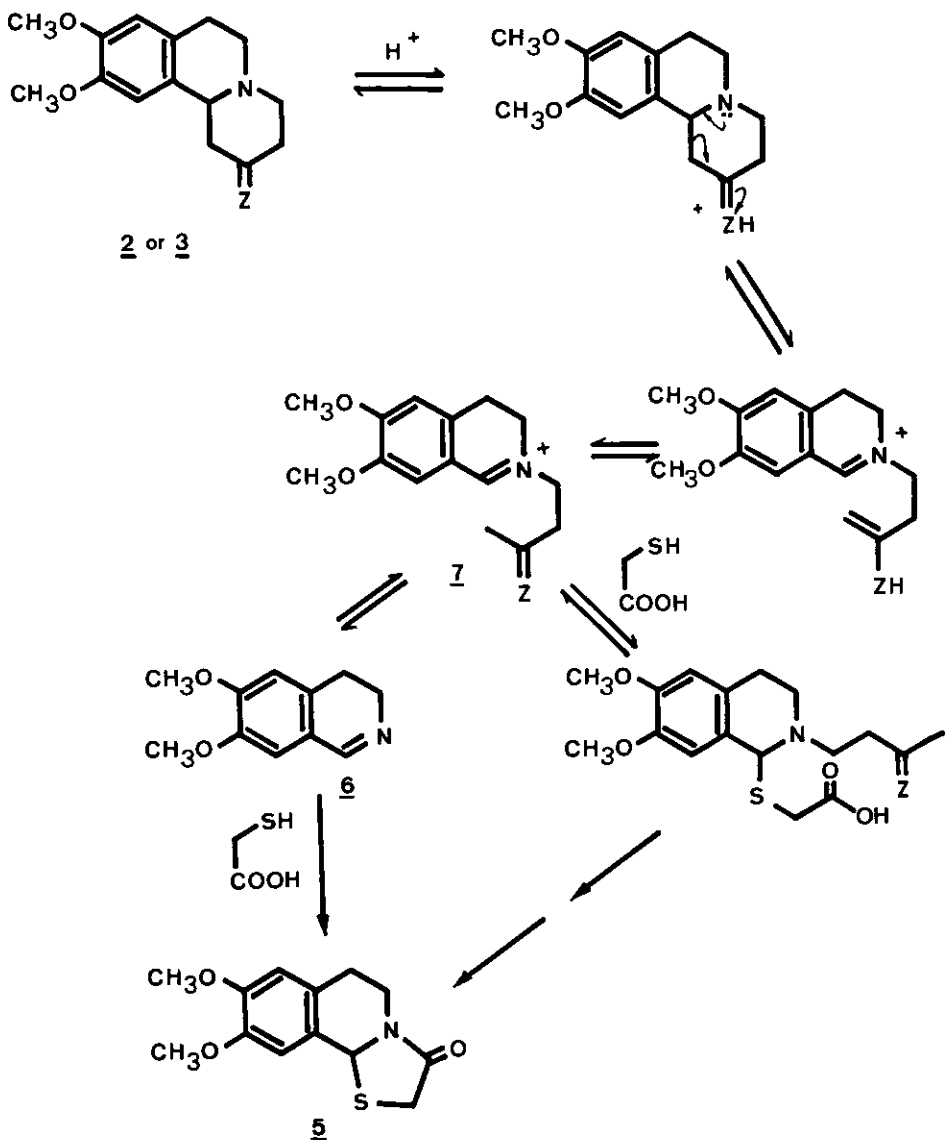


a. $HSCH_2CO_2H$, TsOH, 4 Å sieves, Benzene, reflux, 10-12 h
b. $HSCH_2CO_2H$, $(NH_4)_2CO_3$, TsOH, 4Å sieves, Benzene, reflux, 10 h.

Scheme 2

The same result was obtained when ketone (3) was treated with 2-mercaptoacetic acid under the same conditions, even in the presence of primary amines (Scheme 2).

These observations indicate that the benzo[*a*]quinolizidine derivatives (2) and (3) are not stable under the reaction conditions employed. A tentative explanation for the behaviuor described above that is consistent with all observed facts is summarized in Scheme 3. The transformation of 2 or 3 into 5 may be initiated as a series of acid-catalyzed equilibria that give rise to the immonium salt (7). The mechanism proposed is the opposite to the one that takes place during the synthesis of 3 from 5 and methyl vinyl ketone or a synthetic equivalent.[11,16] A retro-Michael process may then transform 7



Scheme 3

into 6, which, by reaction with the mercaptoacid, would yield the observed product (5). The feasibility of this ring opening is supported by literature data; thus, Bosch and coworkers[17] have detected the transformation of a derivative of an alkyl 1,1-dialkyl-2-oxobenzo[a]quinolizidine carboxylate into the corresponding 3,4-dihydroisoquinoline by heating in an acidic medium. However, the evidence available does not allow to rule out the alternative pathway in Scheme 3, in which mercaptoacid attack takes place prior to the retro-Michael reaction.

Some modifications have been introduced in the experimental conditions of the reaction between 2 and mercaptoacetic acid, affecting both the nature of the acid catalyst and the polarity of the reaction medium. Thus, the reaction in benzene and BF_3-Et_2O led also to 5 (47 %). If acetic acid was used as solvent instead, the reaction between 2a and 2-mercaptoacetic acid (3.5 equivalents) in the presence of BF_3-Et_2O and 4 Å molecular sieves led to the expected spiro compound (1) (R = CH_2-C_6H_5) as the major product, together with a small amount of 5, as shown by the ^{1}H-nmr spectrum of the crude reaction product. However, the complexity of the mixture of compounds obtained precluded the isolation of an analytical sample of 1.

EXPERIMENTAL

Melting points were obtained in a Büchi capillary apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometer and spectrometers: ir—Perkin Elmer 577. Mass—Hewlett-Packard 5995 CG-MS, using the DIP mode. ^{1}H-Nmr—Hitachi Perkin-Elmer R-24B (60 MHz). All chemical shifts are referred to TMS and all coupling constants are given in Hz. Elemental analyses were obtained using a Carlo Erba Elemental Analyzer model 1104.

General Procedure for the Synthesis of 2-Aryl (Arylalkyl)imino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizines 2. A solution of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizin-2-one (3) (3 g, 11.5 mmol) in anhydrous benzene (60 ml), or a 3:1 mixture of benzene-ethanol (60 ml) in the case of compound (2d), was treated with the suitable amine (13.8 mmol) and p-toluenesulfonic acid (100 mg), and refluxed for 6-24 h in a Dean-Stark apparatus placed in a 120 °C bath. The precipitated imino derivative was filtered from the cooled reaction mixture (compound 2d), or the benzene layer was washed with water (3 x 25 ml), dried over sodium sulfate and evaporated under reduced pressure to yield the compounds described in Table 1 as viscous oils, which were characterized by spectroscopic means and used without further purification.

8,9-Dimethoxy-2,5,6,10b-tetrahydrothiazolo[2,3-a]isoquinolin-3-one 5. Method A. 5 Mmol of any of the imino derivatives (2) or ketone (3) were mixed with 2-mercaptoacetic acid (0.53 g, 5 mmol), p-toluenesulfonic acid (0.2 g) or BF_3-Et_2O complex (0.2 ml) and 4 Å molecular sieves (0.2 g), and dry benzene (50 ml) was added. The reaction mixture was refluxed for 10-12 h, with simultaneous removal of water (Dean-Stark). The benzene layer was decanted from the tarry material formed during the

reaction, washed with water (3 x 15 ml), dried (sodium sulfate) and evaporated *in vacuo*. The residue obtained was washed with boiling petroleum ether (3 x 15 ml) and triturated with a small amount of ethanol, yielding 40-60 % of crystalline 5. The use of excess mercaptoacetic acid did not affect this result. Method B. Ketone (3) (1 g, 3.8 mmol), 2-mercaptoacetic acid (0.41 g, 3.8 mmol), ammonium carbonate (1 g), *p*-toluenesulfonic acid (0.2 g), and 4 Å molecular sieves (0.2 g) in dry benzene (20 ml) were refluxed for 10 h in a Dean-Stark apparatus. The benzene layer was decanted, washed with water (5 x 50 ml), dried (sodium sulfate) and evaporated to yield 0.45 g (44 %) of 5. mp 173-174 °C (ethanol). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 55.86; H, 5.66; N, 5.28 Found: C, 59.07; H, 5.77; N, 4.91. Ir (KBr): 1690 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 6.60 (s, 2H, C_7-H and C_{10}-H), 6.05 (s, 1H, C_{10b}-H), 4,45 (q, J = 9 Hz, 2H, C_2-H), 3.80 (s, 6H, 2 OMe), 3.40-2.50 (m, 4H, C_6-H and C_7-H). Ms, m/z (%): 265 (M^+, 65), 234 (11), 192 (14), 191 (37), 190 (100), 176 (31), 146 (10), 133 (9), 104 (11), 91 (9), 77 (13), 46 (24), 42 (6).

3-Benzyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[*a*]quinolizine-2,2'-thiazolidin]-2'-one 1a. Compound (2a) (0.4 g, 1.2 mmol), 2-mercaptoacetic acid (0.43 g, 4 mmol), freshly distilled BF_3-Et_2O complex (1 ml) and 4 Å molecular sieves (0.2 g) in glacial acetic acid (25 ml) were stirred for 3 h at 100 °C, and then at room temperature for 14 h. The cooled reacion mixture was filtered, basified with 20 % ammonium hydroxide, filtered again and extracted with chloroform (3 x 100 ml). The combined chloroform layers were dried (sodium sulfate) and evaporated. Addition of ethanol (5 ml) to the residue caused the precipitation of 50 mg of 5 (16 %). Evaporation of the ethanolic solution left 0.25 g of crude 1a as a thick syrup which could not be further purified. Ir (NaCl): 1660 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 7.20 (s, 5H, $CH_2C_6H_5$), 6.60 and 6.50 (2s, 2H, C_8-H and C_{11}-H), 4.30 (d, J = 7.5 Hz, 2H, $CH_2C_6H_5$), 3.75 (s, 6H, 2 OMe), 3.60 (s, 2H, C_5-H), 3.40-1.50 (m, 11H).

Compd No.	Reaction time/h	Yield/%	Ir: ν C=N/cm^{-1}	^{1}H-nmr ($CDCl_3$, 60 MHz) δ		
				C_8-H + C_{11}-H	OMe	R
2a[18]	6	92	1665	6.70 (s, 1H)	3.75 (s, 6H)	7.40-7.10 (m, 5H)
				6.55 (s, 1H)		3.60 (s, 2H)
2b	24	90	1660	6.60 (s, 1H)	3.75 (s, 6H)	7.30-7.00 (m, 2H)
				6.50 (s, 1H)		6.80-6.50 (m, 3H)
2c	24	85	1660	6.70 (s, 1H)	3.80 (s, 6H)	7.15 (d, J=9 Hz, 2H)
				6.60 (s, 1H)		6.65 (d, J=9 Hz, 2H)
						2.30 (s, 3H)
2d[19]	24	46	1665	6.70 (s, 1H)	3.70 (s, 6H)	6.70 (m, 2H)
				6.60 (s, 1H)		7.50 (m, 2H)

Table 1

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18. Mass spectrum, m/z (%): 350 (M^+, 3.8), 260 (18), 245 (100), 230 (17), 218 (32), 205 (19), 192 (14), 191 (22), 190 (22), 176 (14), 91 (52), 77 (9).
19. mp 218-220 °C (ethanol). Anal. Calcd for $C_{21}H_{25}N_3O_4S$: C, 60.72; H, 6.02; N, 10.12. Found : C, 60.51; H, 5.93; N, 10.35.

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