SYNTHESIS OF 5,1-BENZOTHIAZOCINES AND THEIR HOMOLOGUES[1a,b]

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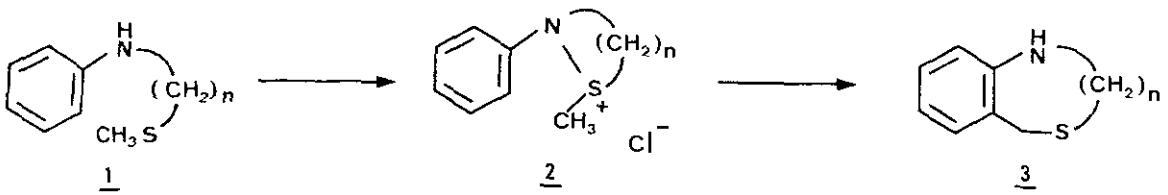
Abstract - A facile one pot synthesis of 5,1-benzothiazocines and their homologues from acyclic aniline derivatives has been achieved by the effective synthetic control via aza-sulfonium intermediates.

The problem of constructing medium and/or macrocyclic compounds has long exercised synthetic chemists. Our interest in the chemistry and biological properties of the heterocyclic medium rings, for which less studies have been accumulated, led to the developement of a facile one pot synthesis of 5,1-benzothiazocines and their homologues from acyclic compounds by the effective synthetic control via aza-sulfonium templates as follows.[2]

Treatment of N-(3-methylthiopropyl)aniline (1b), which was readily available from aniline,[3] with N-chlorosuccinimide in methylene chloride below 0°C for 30 min and subsequent addition of sodium methoxide gave 5,1-benzothiazocine (3b)[4,5] in high yield. The reaction intermediate, aza-sulfonium salt (2b)[6], could be isolated quantitatively as a crystalline solid by removal of the solvent at the first stage of the reaction and converted to the benzothiazocine by the base addition. Thus, the process is apparently based on the formation of the aza-sulfonium salt and subsequent 2,3-sigmatropic rearrangement of the ylide formed from the sulfonium salt.

The homologous novel heterocycles with 9-11 membered ring were obtained by the similar way in the yield shown in Table 1, which suggested that susceptibility to form aza-sulfonium intermediates seemed crucial for these reactions.[7]

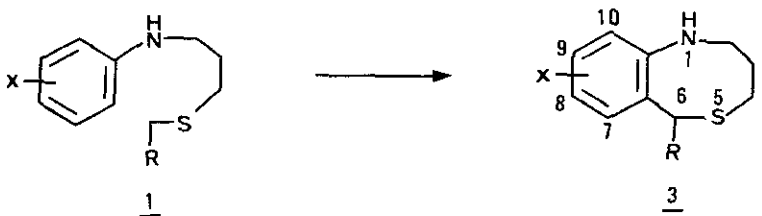


1 2 3

Table 1

		Yield of 3	mp, °C
a	n=2	0%	-
b	3	82	77-79
c	4	87	91-93
d	5	40	oil
e	6	6	oil
f	11	0	-

Synthesis of the substituted benzothiazocines was accomplished in the same manner as shown below (Table 2).



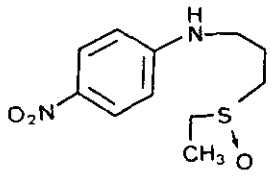
1 3

Table 2

	X	R	Base[a]	mp, °C	Yield %		X	R	Base	mp, °C	Yield %
3g	8-CH_3	H	A	197[b]	87	3p	8-F	CH_3	B	220[b]	55
3h	8-Cl	H	A	54-55	80	3q	H	CH_3	B	72-74	65
			B		90	3r	8-NO_2	CH_3	B	138-140	57
3i	8-OCH_3	H	A	218[b]	95	3s	8-CN	CH_3	B	117-119	50
3j	8-NO_2	H	A	160-162	54	3t	8-CH_3SO_2	CH_3	B	158-160	45
3k	8-CN	H	A	136-139	50	3u	10-Cl	CH_3	B	208[b]	46
3l	8-CH_3SO_2	H	A	193-194	55	3v	H	C_6H_5	B	215-217[b]	48
3m	7-/9-Cl	H	A	230[b]/71-73	25/36	3w	8-Cl	C_6H_5	B	85-87	63
3n	8-CH_3	CH_3	B	220[b]	48	3x	8-OCH_3	C_6H_5	B	177-180[b]	57
3o	8-Cl	CH_3	B	212[b]	75						

a) A:$NaOCH_3$ B: Et_3N b) mp of HCl salt

As can be noted from the table, the overall process can tolerate a wide variety of the substituents. However, the electron withdrawing substituents were found to decrease the yield to some extent, which could be attributable to the retarded formation of the cyclic aza-sulfonium intermediate 2 due to the decreased nucleophilicity of the amino groups. In fact, in the case of the nitro substituent (1r), two by products, (4) mp 121-123°C and (5) mp 126-128°C, were isolated which seemed to be resulted from the assumed initial intermediate (6).



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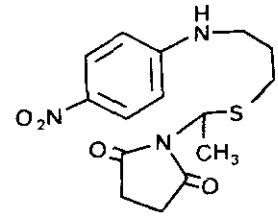

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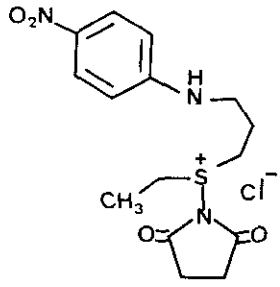

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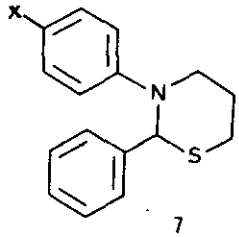
On the other hand, the reaction of N-(3-benzylthiopropyl)anilines (1v, w, x) proceeded in somewhat different fashion. That is, considering amounts of 1,3-thiazines (7)[8] were produced in addition to the benzothiazocines 3v, w, x. The formation of the 1,3-thiazines could be explained by the intramolecular Pummerer type reaction[9] of the assumed intermediate (8).



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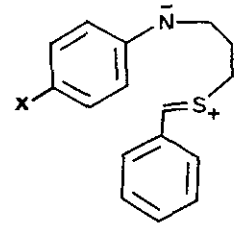
	x	mp °C	yield %
7v	H	63-65	32
7w	Cl	74-76	19
7x	OCH_3	oil	19



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A series of benzothiazocines were found to reduce gastric secretion in animal studies and some of them may have potential for clinical utility in the treatment of gastric ulcers.[1b, 10a] Details will be reported in near future.[10b]

REFERENCES AND NOTES

1. a) Studies on the Aza-sulfonium salts. III. Our proceeding reports on this account; K. Tomita, A. Terada, and R. Tachikawa, Heterocycles, 1976, 4, 729; K. Tomita, A. Terada, and R. Tachikawa, ibid., 1976, 4, 733. Recent review for Aza-sulfonium salts. See "The Chemistry of the Sulfonium Group", edited by C. T. M. Stirring, John wiley & Sons, p 578, 1981.
   b) Part of this work was presented at 103th Annual Meeting of the Pharmaceutical Society of Japan, April 4, 1983 (Tokyo), The 9th International Congress of Heterocyclic Chemistry, August 23, 1983 (Tokyo), and The Third French-Japanese Symposium on Medicinal and Fine Chemistry, September 6, 1983 (Shizuoka).
2. Related reactions; E. Vedej and J. P. Hagen, J. Amer. Chem. Soc., 1975, 97, 6878. P. G. Gassman and G. D. Gruetzmacher, J. Amer. Chem. Soc., 1974, 96, 5487.
3. (1b) was prepared as follows: Aniline was acylated with β-chloropropionyl chloride and then condensed with $NaSCH_3$ to give 3-methylthiopropionylanilide, mp 58-60°C. It was reduced with $LiAlH_4$ in THF to give (1b). 1b; bp 130°C/3mmHg; ^{1}H-NMR($CDCl_3$) δ 1.80(m, 2H, $-CH_2CH_2CH_2-$), 2.06(s, 3H, SCH_3), 2.55(t, 2H, CH_2S), 3.20(t, 2H, NCH_2), 6.55-7.35(m, 5H, C_6H_5).
4. 3b; ^{1}H-NMR($CDCl_3$) δ 1.90(m, 2H, $-CH_2CH_2CH_2-$), 2.56(t, 2H, SCH_2, J≈6Hz), 3.43(t, 2H, NCH_2, J=6Hz), 3.97(s, 2H, $ArCH_2S$), 6.6-7.3(m, 4H, C_6H_4).
5. The only literature available on the synthesis of (3b); by cyclization of 3-(2-aminobenzylmercapto)propionic acid followed by $LiAlH_4$ reduction in 5.5% overall yield: M. Uskokovic, G. Grethe, J. Iacobelli, and W. Wenner, J. Org. Chem., 1965, 30, 3111.
6. 2b; mp 80°C(dec.); ^{1}H-NMR($CDCl_3$) δ 2.90(m, 2H, $-CH_2CH_2CH_2-$), 3.30(s, 3H, SCH_3), 4.05(m, 2H, NCH_2), 4.50(t, 2H, SCH_2, J=7Hz), 7.00-7.50(m, 5H, C_6H_5).
7. Elemental analysis, mass molecular weight, NMR and IR spectral properties of all new compounds were consistent with the assigned structures.
8. 7v; ^{1}H-NMR($CDCl_3$) δ 1.3-3.6(m, 6H, $-CH_2CH_2CH_2-$), 6.0(s, 1H, ArCHS), 6.80-7.90 (m, 10H, aromatic); The structure of thiazine, 7v, was also determined by the fact that hydrolysis of 7v with conc HCl afforded benzaldehyde and its dithioacetal, $(C_6H_5NHCH_2CH_2CH_2S)_2CHC_6H_5$.
9. Similar reaction for the synthesis of 1,3-thiazin-6-ones was reported; I. Nagakura, H. Oka, and Y. Nitta, Heterocycles, 1975, 3, 453.
10. a) S. Miyamoto, H. Watanabe, M. Yoshimoto, S. Sato, K. Tomita, S. Kobayashi, C. Tamura, and S. Sato, The 10th Symposium of Structure-Activity-Relationships, December 7, 1983 (Kyoto). b) S. Kobayashi, M. Miyamoto, Y. Shimada, F. Asai, and F. Ito, The 57th General Meeting of Japanese Pharmacological Society, March 23-26, 1984 (Kyoto).

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