A Convenient Quaternization/Rearrangement Procedure for Conversion of Thiazoles to Medium- and Large-Sized *N,S*-Heterocycles[1]

Hans-Jürgen Federsel,* Gunilla Glasare,[2a] Christina Högström,[2b] Jan Wiestål,[2c] Barbara Zinko,[2d] and Christina Ödman[2e]

Chemical Process Development Laboratory, Astra Production Chemicals AB, S-151 85 Södertälje, Sweden

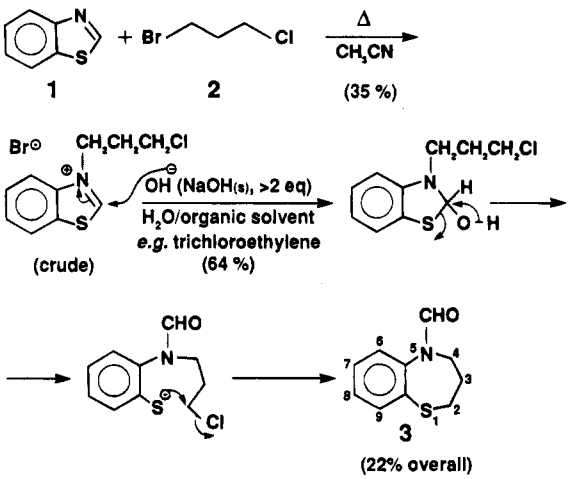
Received December 2, 1994®

A straightforward, two-step sequence capable of converting simple thiazoles into different sets of ring-expanded *N,S*-heterocycles of various sizes has been developed. The initial quaternizations of the heterocyclic moieties conducted with α,ω-dihaloalkanes (chain lengths from 2 to 8) in a 1:5 stoichiometry, afford the monoquaternary intermediates in isolated yields ranging from 16–71% (benzothiazole series, **9**) to 17–93% (thiazole series, **10**), respectively. In the subsequent OH^--induced rearrangement, an expeditious ring-opening/ring-closure event incorporates the previously attached alkyl side chain in the newly formed hetero ring. Here the yields of benzannelated products **11** lie in the interval from 39 to 82%, while the monocyclic counterparts **12** fall within 11 to 59%, which in an overall perspective makes this methodology preparatively significant for an array of new compounds up to (at least) 12-membered ring sizes.

In 1980, we briefly reported[3] a new type of OH^--induced ring expansion of *N*-(ω-haloalkyl) quaternized 5-membered heterocycles, notably thiazoles, as a part of a general study on the rearrangement of haloalkyl-substituted azolium systems under alkaline conditions.[4] Thus, we showed that quaternization of benzothiazole (**1**) with 1-bromo-3-chloropropane (**2**) followed by treatment with >2 equiv of NaOH in a H_2O/organic solvent two-phase system smoothly afforded the ring-enlarged benzothiazepine carboxaldehyde **3**, albeit in overall yields <25% (Scheme 1). The tentatively assigned reaction mechanism was subsequently [4d] corroborated by the results from our kinetic investigation of the ring transformation of 5-(chloroalkyl)thiazolium compounds.

Our efforts to synthesize even larger ring systems were not very successful; only a minute yield of the 8-membered thiazocine was obtained, severely limiting the range of ring sizes accessible with this methodology. The actual reason for this phenomenon was not identified at the time, but the quest for efficient synthetic procedures for these types of heterocycles retained its high priority due to the interest in their pharmacological properties. For example, compound **3** and its *des*-formyl derivative and their respective thiazocine analogues have been reported to possess antiulcer activity[5a] and a number of 1,4-benzothiazines display interesting anticancer properties.[5b] The literature syntheses of these types of 6- and 7-membered heterocycles[6a,b] are conducted by either condensing *o*-aminothiophenol with α,ω-dihalides[6c,d] (occasionally with chloroacetic acid[5b]) or by hydride reduction of oximes.[6e]

Scheme 1. Two-Step Conversion (Quaternization/Rearrangement) of Benzothiazole to Thiazepine Aldehyde 3



When using a more reactive α,ω-dihalide such as α,α′-dibromo-*o*-xylene as quaternizing agent, the fairly low yield envisaged in the alkylation step of the previous example was considerably improved and isolated yields around 80% were obtained throughout a series of analogous azoles (Scheme 2). The rearrangement gave more variable yields with the oxazole system offering the best result with a two-step yield of ~65%. Interestingly, this route gives access to the dibenzoxazocinecarboxaldehyde

® Abstract published in *Advance ACS Abstracts,* April 1, 1995.

(1) Presented in part as a poster at the "Gordon Research Conference on Heterocyclic Compounds" in New Hampton, NH, July 9–13, 1990, and orally at the "13th International Congress of Heterocyclic Chemistry" in Corvallis, OR, August 11–16, 1991.

(2) Undergraduate Research Participants from the Organic Chemistry Departments of the following Swedish institutions: (a) Royal Institute of Technology, Stockholm, 1988–89. (b) Stockholm University, Stockholm, 1990. (c) Stockholm University, Stockholm, 1991–1992. (d) Linköping University, Linköping, 1990. (e) Linköping University, Linköping, 1989.

(3) Federsel, H.-J.; Bergman, J. *Tetrahedron Lett.* **1980**, *21* (25), 2429–32.

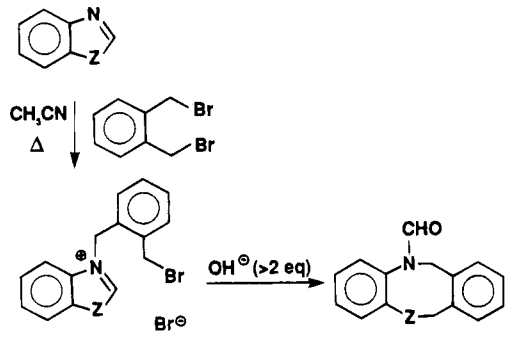
(4) (a) Federsel, H.-J.; Bergman, J.; Stenhede, U. *Heterocycles* **1979**, *12* (6), 751–56. (b) Federsel, H.-J.; Bergman, J. *Heterocycles* **1980**, *14* (1), 33–37. (c) Federsel, H.-J. Ph.D. Thesis, Royal Institute of Technology, Stockholm, 1980. (d) Federsel, H.-J.; Merényi, G. *J. Org. Chem.* **1981**, *46* (23), 4724–27.

(5) (a) Jap. Patent 202818, 1985 (to Kotobuki Seiyaku Co., Ltd.). (b) Gupta, R. R.; Dev, P. K.; Sharma, M. L.; Rajoria, C. M.; Gupta, A.; Nyati, M. *Anti-Cancer Drugs* **1993**, *4* (5), 589–592.

(6) (a) For a recent account on thiazines, see: Gupta, R. R; Kumar, M. In *Phenothiazines and 1,4-Benzothiazines - Chemical and Biomedical Aspects*; Gupta, R. R., Ed.; Elsevier: Amsterdam, 1988; pp 1–161. (b) For reviews on thiazepine chemistry, see: Wünsch, K.-H.; Ehlers, A. *Z. Chem.* **1970**, *10* (10), 361–370. Levai, A. *Khim. Geterotsikl. Soedin.* **1986**, (11), 1443–1452 (in Russian). (c) Mushkalo, L. K.; Fedorova, I. P. *Ukrain. Khim. Zhur.* **1954**, *20*, 305–307; *Chem. Abstr.* **1956**, *50*, 366e. (d) Florio, S.; Leng, J. L.; Stirling, C. J. M. *J. Heterocycl. Chem.* **1982**, *19* (2), 237–240. (e) Meshcheryakova, L. M.; Zagorevskii, V. A.; Orlova, E. K. *Khim. Geterotsikl. Soedin.* **1980**, (6), 853.

0022-3263/95/1960-2597$09.00/0

Scheme 2. Transformation of Various 1,3-Azoles to Dibenzazocines



4 a-c

Z	yield (%)		Z	yield (%)
O	80	a.	O	82
S	78	b.	S	41
Se	81	c.	Se	20

4a in a considerably simplified and higher yielding fashion than compared to the lengthy literature[7a] procedure (five steps; ~4% total yield). Both oxazocines and thiazocines have been pharmacologically evaluated for their effects on the central nervous system (CNS) and their antihistaminic activity.[7b]

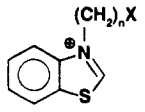
A careful scrutiny of the underlying crucial factors in this reaction sequence concomitantly with a product-targeted methods development has now resulted in a procedure, the details of which are presented in this paper, offering easy access to a variety of hitherto unknown heterocyclic compounds starting from simple thiazoles.

Results and Discussion

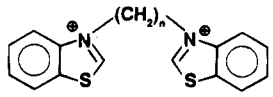
For reasons of clarity, our findings and interpretations are presented step-by-step, following the overall layout of the synthetic sequence.

Quaternization. The attachment of an alkyl group to a tertiary nitrogen is generally referred to as quaternization but, occasionally, also as the Menshutkin reaction after its originator.[8] This S_N2-like transformation generating a charged species, i.e., a quaternary ammonium salt from neutral reactants, has been carefully scrutinized since its discovery in 1890. In more recent years much effort has been devoted to studies on solvent effects, an area of considerable theoretical interest, focusing, i.e., on polarity and polarizability phenomena where this reaction type has assumed a central position.[9] One of the important findings thus reported is that quaternizations, contrary to reactions of ordinary S_N2-type, display a rate enhancement in polar solvents, which is attributed to an increased charge separation along the reaction path.[10]

Our earlier experiments[3,4c] with benzothiazole and α,ω-dihaloalkanes were all performed in a 1:1 stoichiometric mode using acetonitrile as the solvent of choice (with a few exceptions that were run in neat systems), because of its outstanding ability to generate crystalline materials. Other solvents like acetone, ethanol, dioxane, and dialkyl ethers, however, did not render any synthetically useful products or reduced the reaction rate to an impractically low level. This highly polarity-related and solvent-dependent observed behavior is in good accord with the literature reports. Lack of a suitable analytical methodology during the initial studies capable of determining the true chemical composition led to a situation where the isolated crude products were characterized only by their melting points and FAB (fast-atom bombardment)-type mass spectra, before directly using them *as is* in the subsequent step. Taking the bifunctional nature of the alkylating agents into account, there is an obvious possibility for the formation of not only the desired monoquaternaries **5** but also the bis products **6**.



5 (X = halogen)



6

Thus, a prime goal was to set up a suitable analytical control system, and considering the nature of the reaction matrix (unpolar reactants/highly polar products), liquid chromatography (HPLC) was our first choice. Fortunately, a reversed-phase procedure developed for the simultaneous monitoring of various thiazoles and for their quaternary analogues was available in the literature[11] and could, as it turned out, be adopted for our purpose without requiring any modifications whatsoever.

A series of products obtained from *equimolar* quaternizations were subjected to this analysis and the resulting chromatographic traces are displayed in Figure 1. What is evident is that the early, more polar region of each chromatogram holds two main peaks, the latter of which is systematically shifted toward longer retention times on increased alkyl chain length, while the former is affected only to a very minor extent. By combining this observation with the results from test runs using authentic samples of mono- and bispyridinium salts, which were found to elute in a reverse order, that is the bis compound appearing before its mono analogue, we conclude that the quaternized thiazoles also display this behavior. This is in good agreement with an expected prolongation of the retention times when successively attaching longer and more nonpolar substituents, an effect which is almost entirely outweighed by the double charges in the bis series retaining the highly polar character of these compounds.

The bis/mono ratio of the quaternary products as revealed by HPLC is in the range of 8–9:1 when using the relative abundancies from the charts expressed as simple area%. However, compensating for the markedly

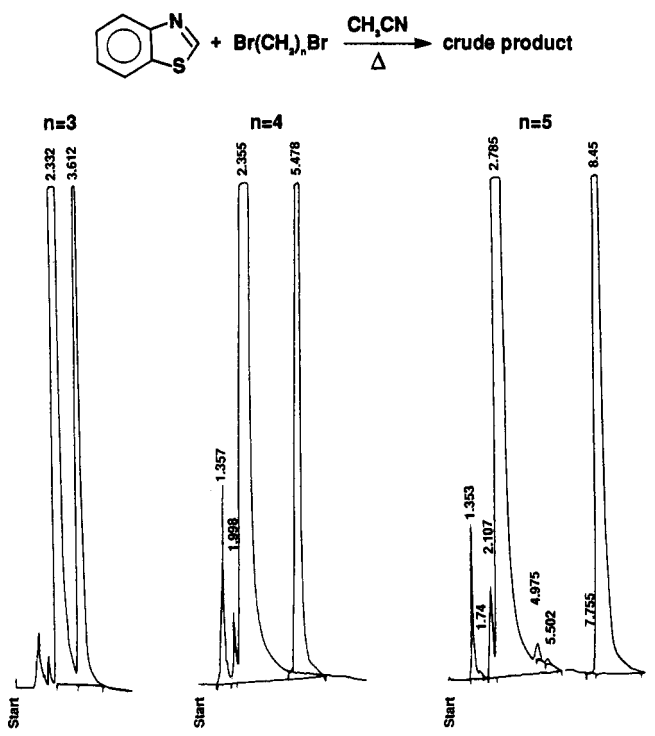
(7) (a) Yale, H. L.; Spitzmiller, E. R. *J. Heterocycl. Chem.* **1972**, *9* (4), 911–18. (b) Yale, H. L.; Sowinski, F. *J. Med. Chem.* **1964**, *7* (5), 609–614.

(8) For a review of the quaternization of heteroaromatic compounds, see: Zoltewicz, J. A.; Deady, L. W. In *Adv. Heterocycl. Chem.*; Katritzky, A. R., Boulton, A. J., Eds.; Associated Press: New York, 1978; Vol. 22, pp 71–121.

(9) (a) Abraham, M. H.; Grellier, P. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1735–1741. (b) Solà, M.; Lledós, A.; Duran, M.; Bertrán, J.; Abboud, J.-L. M. *J. Am. Chem. Soc.* **1991**, *113* (8), 2873–2879 and references cited therein.

(10) For a recent discussion of Menshutkin and ionic S_N2 reactions, see: Shaik, S.; Ioffe, A.; Reddy, A. C.; Pross, A. *J. Am. Chem. Soc.* **1994**, *116* (1), 262–273.

(11) Gustavii, K.; Ekstrand-Asker, K. *Acta Pharm. Suec.* **1986**, *23* (1), 21–30.



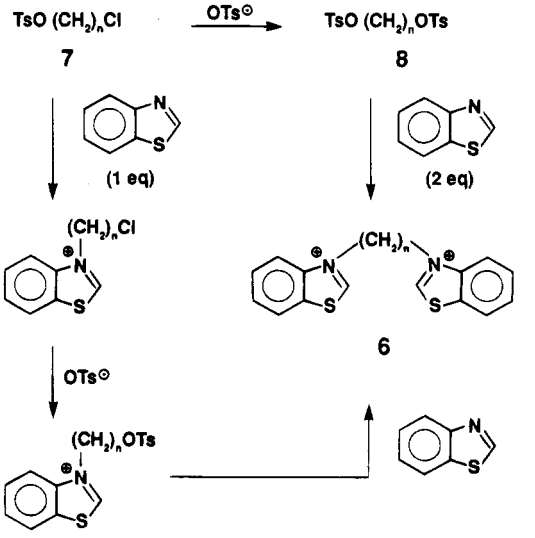
Column: RP-Select B, Lichrosorb 5μ, 4x125 mm
Wavelength: 226 nm
Flow: 0.8 ml/min
Mobile phase: MeOH/H_2O (35:65); pre-prepared aq phase composed of sodium hexanesulfonate (5mM) and tetramethylammonium hydrogensulfate (100mM), pH adj to 2.15

Figure 1. HPLC traces, showing only the frontal parts, of crude products from reacting benzothiazole with 1,3-dibromopropane (n = 3), 1,4-dibromobutane (n = 4), and 1,5-dibromopentane (n = 5), respectively. Unreacted benzothiazole appears at a retention time >17 min, while the dibromoalkanes are scarcely visible at the wavelength of detection (226 nm) due to their low UV absorbance (the diiodides, however, exhibiting an approximately 100-fold higher UV potency, would be easily monitored).

higher UV response for the bis salts due to the presence of *two* aromatic moieties (a factor close to 2 has been established experimentally), a more correct and relevant weight-based figure would be ca. 4–5:1. Thus, the low yields envisaged in the rearrangement step reflect the only 20% or so mono content in the crude material from 1:1-stoichiometric quaternizations, while the major component in each case, i.e. the bis analogues, are byproducts. The reasonable yield of the reaction in Scheme 1 can in all likelihood be traced back to the use of an unsymmetrical dihalide toward which the thiazole substrate is discriminative enough (Br^- vs Cl^- substitution–reactivity effect) to afford the monoquaternary as the main product. Unfortunately, this chemoselectivity was drastically reduced or even completely eliminated upon a further increase of the alkyl chain length beyond C_3.

Once this strongly contributing factor to the yield penalties envisaged in the ring expansion had thus been identified, it became evident that a modified quaternization procedure had to be devised offering a far better monoselectivity obtained. With reference to the results displayed in Scheme 1, it was argued that one possible way to effect this would be to increase the difference in the apparent leaving group activities between the two alkyl substituents, allowing both the quaternization to

Scheme 3. Tentative Reaction Pathways for the Quaternization of Benzothiazole with ω-Chlorotosylates under 1:1 Stoichiometry



proceed as expeditiously as possible at the first leaving group while maintaining the second at a potent enough level to guarantee a smooth nucleophilic displacement in the final step. For this purpose ω-chlorotosylates (**7**), easily accessible from an array of commercially available homologous chloro alcohols, seemed to be ideally suited to meet these requirements. The outcome was encouraging even if the observed mono/bis ratios of 1–2:1, irrespective of changes in type of solvent at equimolar conditions, were still unsatisfactorily low for a more general synthetic application. Our results can probably be attributed to a symmetrization process due to a liberated tosylate anion attacking either the quaternizing agent itself forming a ditosylate (**8**) *or* the chloroalkyl substituent in the monoquaternary. In any event, both cases led to the formation of bis byproduct **6** in the end (Scheme 3).

Obviously, other means had to be explored in order to try to further improve on the selectivity. A straightforward way by which this could be accomplished was to use an excess of alkylating agent and, quite arbitrarily, a ratio of 4–5:1 was choosen, conditions which incidentally were found to be well precedented in the literature for other heterocyclic systems.[12] This immediately gave a drastically increased purity up to a range of 75–80% w/w with regard to the target mono compounds when performing the reactions with symmetrical dihalides, i.e. dibromides or diiodides, in refluxing CH_3CN. The dihalide excess combined with the tendency of the thiazolium halide salts (in contrast to many of their tosylate counterparts) to crystallize during the fairly extended reaction times required (often 24–48 h) due to the sluggish reactivity of benzothiazole efficiently suppressed bis formation. To fine-tune this procedure further, a reduced factorial design study[13] was performed, which comprised an investigation of four different variables (factors): (i) nature of halogen in the quaternizing agent, (ii) chain length of the alkylating moiety, (iii) stoichiometry, and

(12) (a) Melloni, P.; Fusar-Bassini, D.; Dradi, E.; Confalonieri, C. *J. Heterocycl. Chem.* **1974**, *11* (5), 731–735. (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47* (24), 4077–4088.

(13) For a methodological description of this optimization technique, see for example: Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992.

Table 1. Reduced Factorial Design Plan for the Study of Benzothiazole Quaternization

factor	level +	level −
alkylating agent	diiodide	dibromide
dihaloalkane chain length	C_8	C_4
molar ratio of dihalide/ benzothiazole	5:1	2:1
[benzothiazole] in CH_3CN	0.5 M	2.0 M

(iv) concentration. Table 1 shows the exact experimental plan which required a total of eight runs conducted with identical reaction time (24 h) and work-up procedure. (Note that this experimental layout does not allow the identification of any interplay between the individual factors).

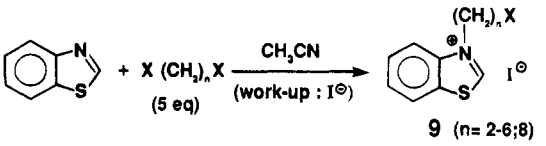
Two responses, the isolated yield and the mono/bis composition, were determined for each run and evaluated to identify the magnitude of their respective influence. The firm conclusions that can be drawn with regard to the observed effects are (a) 5:1 molar ratio at a 2 M concentration promotes a high yield and at the same time a higher bis content compared to 0.5 M runs, irrespective of which dihaloalkane is used, (b) at longer alkyl chain lengths the diiodides offer a marked yield increase, and (c) short chain dihaloalkanes give higher yields than longer ones while there is only a minor change in the mono/bis ratio.

A most important result of this limited study is the identification of a conflicting situation between the simultaneous achievement of high yield and low bis content. In effect, one of the two has to be given priority and because of our main objective to have this procedure developed into a practical preparative process, the former one was chosen. This approach, of course, demanded some kind of purification at the quaternary stage to facilitate isolation of the ring-expanded end product. Previous experience had shown that the material precipitating from quaternization reaction mixtures always contained some occluded benzothiazole base, which could not be eliminated solely by washing the filter cake. Instead, an extractive procedure was applied in which neutral contaminants were transferred into an organic phase at the stage of the aqueous thiazolium solution immediately preceding the rearrangement. By combining this method with a novel reprecipitation using NaI (2–4 equiv) as the salt-forming agent, the products **9** crystallized out in a fairly pure state (typically with a HPLC assay of 75–85% mono) from the aqueous phase as the I^- salts in quite respectable yields; see examples in Table 2.

When shifting from benzothiazole to thiazole in the quaternization step, however, this circumventory work-up procedure becomes unnecessary. Applying identical reaction conditions to those described previously, the mono selectivity is greatly enhanced to a level where the actual HPLC traces of the isolated crude materials (**10**) show hardly any bis impurities. Also the yields obtained are considerably better and frequently amount to a range of 80–90%; see Table 3. These marked improvements are, no doubt, a reflection of the increased pK_a value by some 1.3 units going from benzothiazole (pK_a 1.2) to thiazole (pK_a 2.5).[14] The significant increase in basicity increases reactivity toward *N*-alkylation compared to the sluggishness in the benzothiazole case, while at the same time suppressing bis byproduct formation.

(14) See ref 8, pp 98–100.

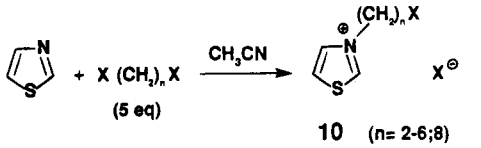
Table 2. Isolated Yields and Product Purities of a Homologous Series of *N*-(Haloalkyl)benzothiazolium Salts (9) as a Function of the Alkyl Group Chain Length



9 (n= 2-6;8)

n	X	relative purity (% w/w mono, HPLC)	yield (%)
2	Br	84	16
3	Br	70	57
4	Br	85	70
5	Br	75	54
6	Br	80	71
8	I	86	44

Table 3. Thiazole Quaternization with a Series of α,ω-Dihaloalkanes (Figures in Brackets Indicate Total Yield including Second Crop)



10 (n= 2-6;8)

n	X	yield, crude (%)
2	Br	17
3	I	81 (88)
4	I	90 (93)
5	I	72 (82)
6	I	91
8	I	81

In summary, the methodology developed for the quaternization step offers homologous series of products in yields varying from respectable to excellent with the exception of the haloethyl derivatives, which were isolated only in poor yields (ca. 20%). This phenomenon can be entirely ascribed to an elimination side reaction occurring with the 1,2-dihaloethanes, which in the case of the diiodides gives no isolable material (due to extensive I_2 formation). Preliminary attempts to recover unreacted dihaloalkane from the mother liquor, which is an issue of great economic significance once the synthesis is scaled up, at least when it comes to the quite expensive longer alkyl chain dihalides, have indicated that about $^3/_4$ of the excess (i.e. 3 of the 4 equiv) is accessible and can be recycled after distillation.

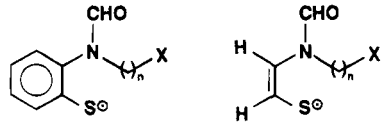
Rearrangement. Our initial methodology foresaw the use of an arbitrary amount of NaOH for the very ring opening of the thiazolium species as long as a final pH level >12 was obtained. In practice, this would mean an addition in the range of 10–15 equiv, to be compared with the theoretical consumption of only 2 equiv (see Scheme 1). A careful scrutiny of the whole reaction system, however, revealed that side products were formed under strongly alkaline conditions, which eventually led to the development of a titration-like procedure to allow a more fine-tuned pH adjustment. The reaction was thus monitored via a pH electrode and once reaching 11–12, which usually required 2.2–3 equiv of base depending on the actual pH in the aqueous thiazolium salt solution at the starting point, further addition was discontinued.

Whereas all short chain (n = 2–4) thiazole quaternay salts **10** displayed fair solubilities in H_2O at room temperature (ca. 3–10% w/v), a drastic decrease in this

respect was envisaged on going toward longer *N*-haloalkyl chain substituents, particularly in the benzothiazolium series **9**. To avoid having to conduct the rearrangement of these latter systems as well as the longer chain ($n \geq 5$) thiazole cases at very low concentrations (typically <0.1% w/v) with a concomitant reduction in capacity (expressed as product output per unit reaction volume), the use of methanol as cosolvent ($MeOH/H_2O \approx 2:1$) offered the possibility of operating at markedly higher levels ranging from ca. 0.7% (**9**, $n = 3$) to 0.2% (**9**, $n = 8$), without observing any increased tendency for *inter*molecular side reactions.

It appears essential to maintain the temperature during the ring expansion phase <~25–30 °C to depress byproduct formation and, thus, attempting to compensate for the poor solubilities by running at elevated temperatures (>~40–50 °C) only gives a complex reaction product requiring elaborate purification procedures. For practical purposes, the present methodology has been adopted to operate at ambient temperature, which yields a crude product that is easily upgraded to high purity (>97.5% GC assay) by a simple flash filtration. When integrating these improvements in the experimental scheme, the transformation of the previously described quaternized intermediates **9** and **10** to the respective ring-expanded products proceeds efficiently and expeditiously in yields ranging from rather impressive levels of at maximum ca. 80% for medium sizes (**11**, $n = 3$) down to a low 11% in the case of a 12-membered system (**12**, $n = 8$); see Table 4, parts a and b, for data from the two sets of rearrangements. (Note that compound **11**, $n = 3$, is identical to the previously mentioned **3**.)

Yieldwise, a side-by-side comparison of the two series reveals a somewhat randomized variation in the yield in the ring expansion step with the benzothiazolium case showing higher values starting from the 9-membered system ($n = 5$) and upward. The reason for the improved yield could be attributed to a difference in motional freedom between the transiently formed ring-opened species **13** and **14**, respectively, whereby the benzene ring

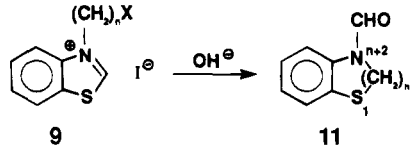


13 **14**

in the former case probably imparts a certain rigidity to the system promoting the desired *intra*molecular ring closure over various entropy-favored *inter*molecular side reactions, e.g. oligo- and polymerizations. Influences from enthalpy-affecting factors such as single bond torsional effects, bond angle deformation, and strain caused by through-space interactions of atoms or groups not directly bonded to each other are probably of major importance in controlling the ring-forming part of the whole rearrangement process.[15] Whether or not the ability to undergo resonance stabilization, an obviously discriminating property between the two sets of anionic intermediates, has any kind of impact on this transformation remains an open question.

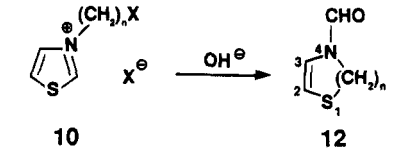
(15) For recent accounts on heterocyclizations, see: (a) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47* (44), 9131–9166. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49* (47), 10749–10784 and references cited therein.

Table 4. (a) Conversion of *N*-Haloalkyl-Substituted Benzothiazolium Salts 9 (top) and (b) Thiazolium Salts 10 (bottom) to Medium- and Large-Sized Heterocycles 11 and 12, Respectively[a]



9 **11**

		isolated yield (%)	
n	X	ring exp	from benzothiazole
2	Br	48	8
3	Br	82	47
4	Br	52	36
5	Br	71	38
6	Br	39	28
8	I	39	17



10 **12**

		isolated yield (%)	
n	X	ring exp	from thiazole
2	Br	59	10
3	I	47	41
4	I	52	48
5	I	50	41
6	I	37	34
8	I	11	9

[a] The right-hand columns show the isolated overall yields obtained via this two-step procedure.

An interesting feature displayed by the members of the two series of ring-expanded products (**11** and **12**), is the doubling of signals in their respective NMR spectra. The intensity of this phenomenon, i.e. the relative size of two connected peaks, varies from compound to compound in the range from 10–12:1 down to 1.7–1.8:1 but is, nevertheless, clearly visible throughout both product groups; see Figure 2 for a particularly instructive example.

Most logically, this phenomenon of atomic nonequivalence is yet another example of hindered rotation around the amide C–N bond due to its partial double-bond character.[16] As expected, the influence from steric interactions and diamagnetic anisotropy is largest in the very proximity of the amide functionality, while the more distant positions would experience gradually smaller effects. Thus, for the thiazine and thiazepine compounds **12** ($n = 2$ and 3), shift differences of 0.467 and 0.290 ppm, respectively, have been recorded for the olefinic α-proton resonances whereas the corresponding values for the β-hydrogens are 0.152 and 0.099 ppm, respectively. In comparison, the benzannelated analogues show a somewhat different picture with considerably smaller shift numbers for the α-position (0.1–0.15 ppm), the β-values remaining essentially constant. Also the apically positioned aromatic proton experiences this signal splitting

(16) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70* (5), 517–551 and references therein.

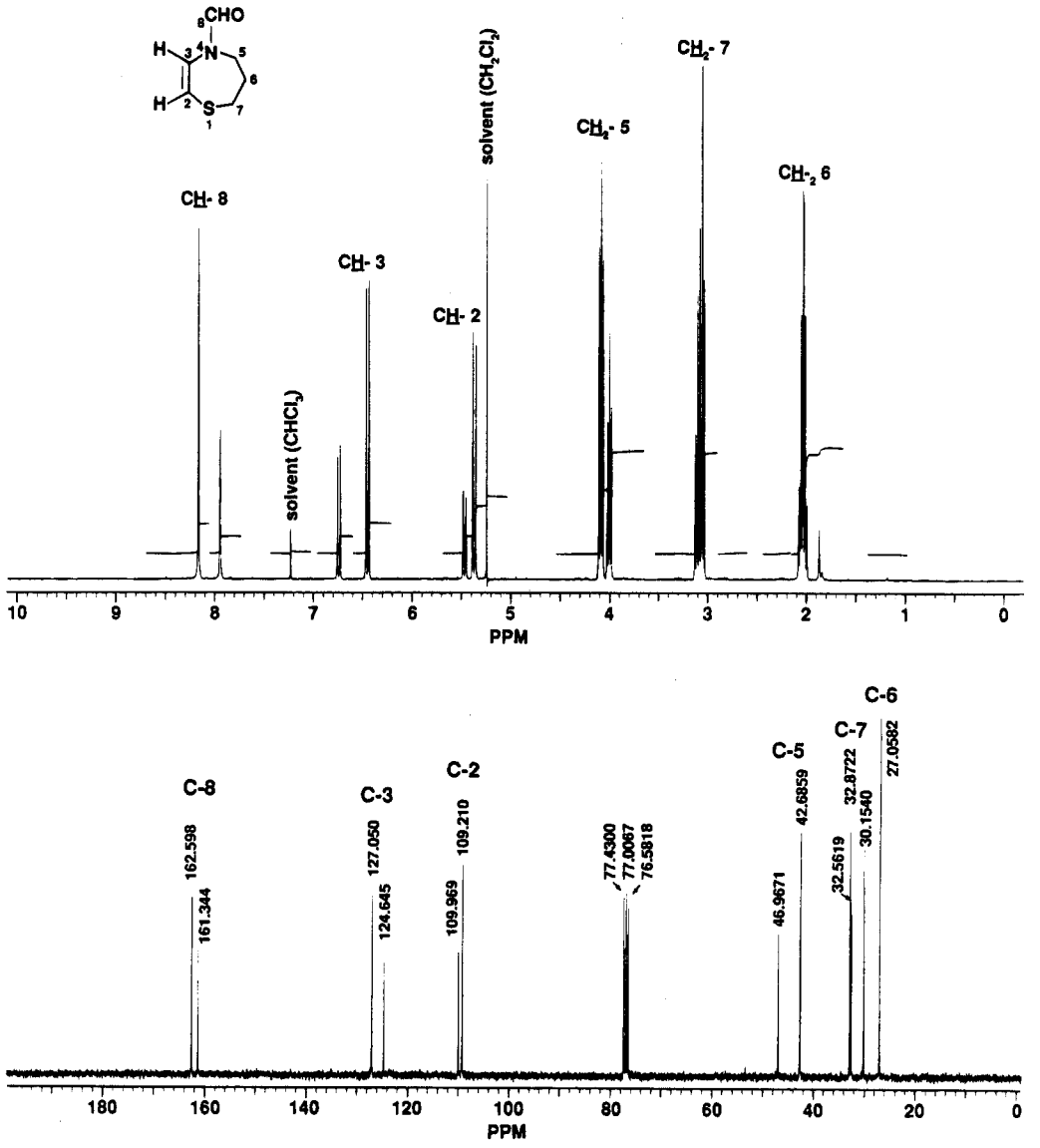
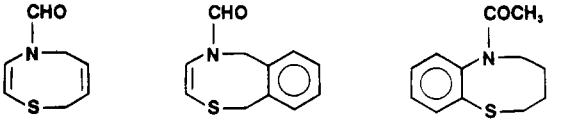


Figure 2. ^{1}H (top) and ^{13}C (bottom) NMR spectra (300 MHz and 75 MHz, respectively, $CDCl_3$, ambient temperature) of 1,4-thiazepine-carboxaldehyde **12** (n = 3) clearly showing the splitting of signals due to restricted amide bond rotation.

effect, albeit here the shift separation is rather small (~0.02 ppm).

Conclusions and Outlook

The present two-step procedure offers a simple and straightforward route to different classes of *N,S*-heterocycles, benzannelated and monocyclic, of medium and large sizes in overall yields ranging from respectable levels of in many cases 40–50% down to a few instances at only ~10%. These carboxaldehyde-functionalized compounds can be used either as building blocks for further transformations or be subsequently hydrolyzed (NaOH(aq) at elevated temperatures) to afford the parent heterocyclic systems, constituting valuable starting materials for various types of molecular manipulations, e.g. *N*-alkylations and aromatic substitutions. Work is in progress aiming at widening the scope of this methodology to comprise structurally more elaborate substrates, both with regard to the thiazole moiety (eventually also including oxazoles, imidazoles, and related systems) and the quaternizing agent. Preliminary results are indeed promising as is evidenced by the newly synthesized compounds **15**–**17**, however overall yields are still fairly low (10–20%).



15 **16** **17**

The possibility of achieving even larger ring systems (>12) in preparatively useful yields is indeed quite feasible, but would probably require further fine-tuning and optimization of the reaction conditions, both the quaternization (particularly pronounced for benzothiazole) and the rearrangement (especially for thiazole).

Experimental Section

Materials and Methods. With the exception of benzothiazole (Lancaster Synthesis), which was distilled (>99% GC) under vacuum prior to use, starting materials (i.e. thiazole and the various dihaloalkanes) were purchased from commercial

suppliers (Fluka, Janssen, E. Merck, Riedel-de Haën) in standard reagent grade qualities (>97–99% GC) and used without further purification or any other type of pretreatment. Solvents were of either chromatographic/analytical grade (CH_3CN, *tert*-butyl methyl ether) or of synthesis quality (CH_2Cl_2, MeOH). Flash filtration of the crude rearranged products was conducted on 40–63 μm silica gel 60 (E. Merck). All melting points and melting ranges were determined on a Büchi SMP 20 melting point apparatus in open capillary tubes and are uncorrected. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard 5890 instrument equipped with a fused silica capillary column (25 m × 0.31 mm; DB 5, film thickness 0.52 μm; J&W Scientific) and a flame ionization detector (FID), using a HP 3396 II integrator. High-performance liquid chromatography (HPLC) was run on a model M6000A from Varian Associates operating with a Shimadzu C-R3A integrator and a LiChrosorb RP-select B 5 μ column (4 × 125 mm) with a detection wavelength of 226 nm (details of the eluant system are given in connection with Figure 1). Mass spectra (MS) of the quaternized intermediates were taken on a Nermag R10-10 equipment configurationed for either desorptive chemical ionization (DCI) using methane (CH_4) as the ionizing agent or a fast-atom bombardment (FAB) setup with argon (Ar)-driven ionization via a MScan FAB gun and a sample application in a glycerol matrix, while those of the end products were obtained on a Hewlett-Packard 5970A mass-selective detector with a HP MS Chem Station working in the EI mode (ionizing voltage 70 eV). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini Spectrometer operating at 300 and 75 MHz, respectively of samples dissolved in DMSO-d_6 (quaternaries) or $CDCl_3$ (rearrangement products). Chemical shifts are reported in ppm on the δ scale downfield relative to tetramethylsilane (Me_4Si) and spectral splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; and br, broad. In cases where a doubling of signals is clearly distinguishable, the assignable shift numbers of the high intensity peak(s) are reported prior to the lower ones, separating the two groups of figures by a "/" sign. Combustion analyses were performed by Mikro Kemi AB, 752 28 Uppsala, Sweden.

General Procedure for Quaternizations. (a) Benzothiazole with Dibromoalkanes (Volumes Given Are Referred to a 25 mmol Scale). Benzothiazole (1 equiv) and the α,ω-dibromide (5 equiv) are added sequentially in one portion to CH_3CN (appropriate volume to afford [benzothiazole] = 2 M) at ambient temperature and the solution is refluxed ($t \approx 82$ °C) under stirring (magnetic bar) for ca. 24–75 h. The reaction mixture is cooled to <10 °C and enough H_2O (typically ~200 mL) is added to dissolve all of the solid precipitate. The water phase is washed with *tert*-butyl methyl ether (2 × ~50 mL) and the combined etheral phases reextracted with H_2O (25 mL). All water phases are combined and allowed to stand in the refrigerator (5–7 °C) overnight. The solid material (mainly bisquaternary) is filtered off and the aqueous filtrate is "doped" with NaI (4 equiv as a 6–7 M H_2O solution) and left in the refrigerator overnight. The crystalline product is isolated by filtration, washed with *tert*-butyl methyl ether (25 mL), and dried overnight (vacuum chamber or desiccator).

(b) Benzothiazole with Diiodoalkanes. The reaction and the workup are conducted as described above with the exception that the combined H_2O phases are allowed to crystallize to afford a first crop prior to treating the mother liquor with NaI (3 equiv as a ~7 M aqueous solution). After precipitation in the refrigerator overnight, the product (second crop) is isolated in the same fashion as indicated previously and combined with the first one. The reported yields obtained with methods a and b are corrected for the presence of bisquaternary and residual amounts of benzothiazole and H_2O.

(c) Thiazole with Dihaloalkanes. An analogous reaction procedure to the one outlined under a was adopted with a reflux time of 20 ± 4 h unless stated otherwise. After completion of the precipitation ($t \approx 5$ °C), the product is immediately filtered off, washed as indicated above (using a volume ~10 times the theoretical product weight), and subsequently dried. Yields are reported for the crude products and are uncorrected.

General Procedure for Rearrangement of Thiazolium and Benzothiazolium Compounds. Species belonging to the former group are either dissolved in pure H_2O ($n = 2–4$) at concentrations in the range 0.1–0.4 M (longer chain lengths require more dilute solutions), while compounds with $n \geq 5$ need the admixture of MeOH as a cosolvent typically in a 1:1–2 ratio affording end concentration <0.1 M. Members of the latter class, however, do all demand a two-component MeOH/H_2O system in a 2:1 ratio to afford complete dissolution at concentrations ranging from 0.01 M ($n = 2$) down to 0.004 M ($n = 8$). The addition of 1 M NaOH(aq) is conducted at ambient temperature over a period of 10 ± 5 min with continuous monitoring of the pH up to an end level of 11.2 ± 0.3. While starting the work-up procedure more or less instantaneously for the medium-sized products ($n = 2–5$) by either extracting with CH_2Cl_2 (thiazole series) or by evaporating off the MeOH prior to extraction (benzothiazole series), a prolonged reaction time (up to 1 h) is allowed for the larger systems ($n > 5$). The organic extracts (typically 2 × 25–50 mL from a 5 mmol run) are concentrated and filtered through a silica column (loaded with packing material 30 ± 5 times the crude product weight) using CH_2Cl_2 as eluant (50–100 mL on a 5 mmol scale). Evaporation to dryness affords the final product, which, if required, can be recrystallized from a mixture of CH_2Cl_2 and cyclohexane (~1:20). Yield figures are corrected for the actual content of desired product according to GC analysis.

***N*-(2′-Bromoethyl)benzothiazolium Iodide (9, $n = 2$).** Allowing benzothiazole (3.38 g, 25.0 mmol) and 1,2-dibromoethane (23.5 g, 125.0 mmol) to react for 48 h afforded 1.78 g (16% yield corrected for assay) of crude product **9** ($n = 2$) as dark, brownish-green crystals: ^1H NMR (DMSO-d_6) δ 4.09–4.13 (t, 2 H, CH_2-2′), 5.33–5.37 (t, 2 H, CH_2-1′), 7.84–7.97 (m, 2 H, aromatic CH-5 and 6), 8.47–8.50 (d, 1 H, CH-7), 8.55–8.57 (d, 1 H, CH-4), 10.70 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 30.4 (C-2′), 52.9 (C-1′), 117.3, 125.5, 128.6, 129.7 (aromatic C-4, 5, 6, and 7), 131.4 (C-7[a]), 139.9 (C-4[a]), 166.0 (C-2); MS (FAB, positive ion mode) m/z 242/244 (M^+).

***N*-(3′-Bromo-1′-propyl)benzothiazolium Iodide (9, $n = 3$).** Benzothiazole (7.71 g, 57.0 mmol) and 1,3-dibromopropane (57.54 g, 285 mmol) were allowed to react for 75 h to afford 18.07 g (57% yield corrected for assay) of crude product **9** ($n = 3$) as yellow crystals: ^1H NMR (DMSO-d_6) δ 2.49–2.55 (m, 2 H, CH_2-2′), 3.65–3.69 (t, 2 H, CH_2-3′), 4.95–4.99 (t, 2 H, CH_2-1′), 7.84–7.97 (m, 2 H, aromatic CH-5 and 6), 8.42–8.45 (d, 1 H, CH-7), 8.53–8.56 (d, 1 H, CH-4), 10.65 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 30.5 (C-2′), 31.3 (C-3′), 51.2 (C-1′), 117.0, 125.4, 128.4, 129.6 (aromatic C-4, 5, 6, and 7), 131.7 (C-7[a]), 140.3 (C-4[a]), 165.2 (C-2); MS (FAB, positive ion mode) m/z 256/258 (M^+).

***N*-(4′-Bromo-1′-butyl)benzothiazolium Iodide (9, $n = 4$).** Benzothiazole (3.38 g, 25.0 mmol) and 1,4-dibromobutane (26.99 g, 125.0 mmol) were allowed to react for 24 h to afford 8.28 g (70% yield corrected for assay and including 0.18 g isolated from the mother liquor) of crude product **9** ($n = 4$) as yellow crystals: ^1H NMR (DMSO-d_6) δ 1.86–1.95 and 2.00–2.12 (2 m, 4 H, CH_2-2′ and 3′), 3.57–3.61 (t, 2 H, CH_2-4′), 4.90–4.94 (t, 2 H, CH_2-1′), 7.82–7.88 and 7.91–7.96 (2 t, 2 H, aromatic CH-5 and 6), 8.45–8.47 (d, 1 H, CH-7), 8.55–8.58 (d, 1 H, CH-4), 10.67 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 27.4 and 28.9 (C-2′ and C-3′), 34.2 (C-4′), 51.5 (C-1′), 117.2, 125.4, 128.4, 129.6 (aromatic C-4, 5, 6, and 7), 131.6 (C-7[a]), 140.2 (C-4[a]), 164.5 (C-2); MS (FAB, positive ion mode) m/z 270/272 (M^+).

***N*-(5′-Bromo-1′-pentyl)benzothiazolium Iodide (9, $n = 5$).** Allowing benzothiazole (3.38 g, 25.0 mmol) and 1,5-dibromopentane (28.74 g, 125.0 mmol) to react for 48 h afforded 8.30 g (54% yield corrected for assay) of crude product **9** ($n = 5$) as yellow crystals: ^1H NMR (DMSO-d_6) δ 1.43–1.49 (m, 2 H, CH_2-3′), 1.78–1.88 and 1.95–2.02 (2 m, 4 H, CH_2-2′ and 4′), 3.51–3.55 (t, 2 H, CH_2-5′), 4.84–4.89 (t, 2 H, CH_2-1′), 7.83–7.96 (m, 2 H, aromatic CH-5 and 6), 8.43–8.46 (d, 1 H, CH-7), 8.52–8.55 (d, 1 H, CH-4), 10.63 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 24.3, 27.6, 31.5 (C-2′, 3′, and 4′), 34.9 (C-5′), 52.2

(C-1′), 117.3, 125.3, 128.5, 129.6 (aromatic C-4, 5, 6, and 7), 131.6 (C-7[a]), 140.2 (C-4[a]), 164.4 (C-2); MS (FAB, positive ion mode) m/z 284/286 (M^+).

***N*-(6′-Bromo-1′-hexyl)benzothiazolium Iodide (9, n = 6).** After benzothiazole (2.52 g, 18.6 mmol) and 1,6-dibromohexane (22.69 g, 93.0 mmol) were refluxed together for 39 h, the crude reaction mixture was taken up in H_2O (45 mL) which on treatment according to the methods description was allowed to stand in the refrigerator overnight. Since no precipitate had been formed, NaI (11.2 g, 75 mmol, dissolved in 10 mL H_2O) was added, causing the formation of an oil which crystallized on standing overnight (refrigerator) to afford 7.05 g (71% yield corrected for assay) of the yellow-brownish crude product **9** (n = 6): ^{1}H NMR (DMSO-d_6) δ 1.32–1.42 (m, 4 H, CH_2-3′ and 4′), 1.67–1.83 and 1.94–2.09 (2 m, 4 H, CH_2-2′ and 5′), 3.25–3.30 (t, 2 H, CH_2-6′), 4.83–4.88 (t, 2 H, CH_2-1′), 7.85–7.98 (m, 2 H, aromatic CH-5 and 6), 8.44–8.47 (d, 1 H, CH-7), 8.54–8.56 (d, 1 H, CH-4), 10.63 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 8.8, 24.6, 28.4, 29.2 (C-2′, 3′, 4′, and 5′), 32.6 (C-6′), 52.4 (C-1′), 117.2, 125.3, 128.4, 129.6 (aromatic C-4, 5, 6, and 7), 131.6 (C-7[a]), 140.2 (C-4[a]), 164.4 (C-2); MS (FAB, positive ion mode) m/z 298/300 (M^+).

***N*-(8′-Iodo-1′-octyl)benzothiazolium Iodide (9, n = 8).** Benzothiazole (3.38 g, 25.0 mmol) and 1,8-diiodooctane (45.74 g, 125.0 mmol) were allowed to react for 24 h to afford 6.55 g (44% yield, corrected for assay and comprised of a first and second crop) of crude product **9** (n = 8) as orange-colored crystals: ^{1}H NMR (DMSO-d_6) δ 1.27–1.30 (br s, 8 H, CH_2-3′, 4′, 5′, and 6′), 1.66–1.73 and 1.91–1.93 (2 m, 4 H, CH_2-2′ and 7′), 3.22–3.26 (t, 2 H, CH_2-8′), 4.82–4.86 (t, 2 H, CH_2-1′), 7.83–7.96 (m, 2 H, aromatic CH-5 and 6), 8.42–8.45 (d, 1 H, CH-7), 8.52–8.54 (d, 1 H, CH-4), 10.61 (s, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 9.2 (C-8′), 25.6, 27.6, 28.2, 28.5, 29.7, 32 (C-2′, 3′, 4′, 5′, 6′, and 7′), 52.5 (C-1′), 117.2, 125.3, 128.4, 129.6 (aromatic C-4, 5, 6, and 7), 131.6 (C-7[a]), 140.2 (C-4[a]), 164.3 (C-2); MS (FAB, positive ion mode) m/z 374 (M^+).

***N*-(2′-Bromoethyl)thiazolium Bromide (10, n = 2).** Thiazole (4.26 g, 50.0 mmol) and 1,2-dibromoethane (46.97 g, 250.0 mmol) were heated at reflux for 6 h to afford 2.35 g (17%) of crude product **10** (n = 2) as slightly yellowish crystals: ^{1}H NMR (DMSO-d_6) δ 4.05–4.09 (t, 2 H, CH_2-2′), 5.02–5.06 (t, 2 H, CH_2-1′), 8.41–8.43 (t, 1 H, CH-5), 8.68–8.70 (d, 1 H, CH-4), 10.35–10.36 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 31.3 (C-2′), 55.1 (C-1′), 127.1 (C-5), 136.9 (C-4), 160.5 (C-2); MS (DCI) m/z 193 (M^++1).

***N*-(3′-Iodo-1′-propyl)thiazolium Iodide (10, n = 3).** Reaction of thiazole (2.02 g, 23.75 mmol) and 1,3-diiodopropane (35.14 g, 118.75 mmol) afforded 8.00 g (88%, comprised of a first crop of 7.38 g and a second one of 0.62 g) of crude product **10** (n = 3) as faintly yellow crystals: ^{1}H NMR (DMSO-d_6) δ 2.38–2.47 (p, 2 H, CH_2-2′), 3.19–3.23 (t, 2 H, CH_2-3′), 4.57–4.62 (t, 2 H, CH_2-1′), 8.35–8.37 (dd, 1 H, CH-5), 8.59–8.60 (dd, 1 H, CH-4), 10.21 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 1.7 (C-3′), 32.9 (C-2′), 55.1 (C-1′), 127.0 (C-5), 137.0 (C-4), 159.7 (C-2); MS (DCI) m/z 254 (M^+).

***N*-(4′-Iodo-1′-butyl)thiazolium Iodide (10, n = 4).** Thiazole (2.55 g, 30.0 mmol) and 1,4-diiodobutane (46.49 g, 150.0 mmol) were allowed to react to afford 11.0 g (93%, including a first crop of 10.65 g and a second one of 0.35 g) of crude product **10** (n = 4) as beige-white crystals: ^{1}H NMR (DMSO-d_6) δ 1.68–1.78 and 1.90–1.98 (2 m, 4 H, CH_2-2′ and 3′), 3.26–3.30 (t, 2 H, CH_2-4′), 4.57–4.62 (t, 2 H, CH_2-1′), 8.36–8.38 (dd, 1 H, CH-5), 8.58–8.60 (dd, 1 H, CH-4), 10.21 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 7.2 (C-4′), 29.4 (C-3′), 30.7 (C-2′), 53.4 (C-1′), 127.1 (C-5), 137.0 (C-4), 159.3 (C-2); MS (DCI) m/z 268 (M^+).

***N*-(5′-Iodo-1′-pentyl)thiazolium Iodide (10, n = 5).** The reaction between thiazole (1.70 g, 20.0 mmol) and 1,5-diiodopentane (32.39 g, 100.0 mmol) afforded 6.71 g (82%, composed of 5.87 g from the first crop and 0.84 g from the second) of crude product **10** (n = 5) as dark brownish-yellow crystals: ^{1}H NMR (DMSO-d_6) δ 1.25–1.36 (p, 2 H, CH_2-3′), 1.73–1.82 and 1.85–1.94 (2 p, 4 H, CH_2-2′ and 4′), 3.24–3.29 (t, 2 H, CH_2-5′), 4.53–4.58 (t, 2 H, CH_2-1′), 8.36–8.37 (dd, 1 H, CH-5), 8.59–8.61 (dd, 1 H, CH-4), 10.21 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 8.6 (C-5′), 26.3 (C-4′), 28.4 (C-3′), 32.0 (C-2′), 54.2 (C-1′), 127.0 (C-5), 137.0 (C-4), 159.2 (C-2); MS (DCI) m/z 282 (M^+).

***N*-(6′-Iodo-1′-hexyl)thiazolium Iodide (10, n = 6).** Allowing thiazole (1.00 g, 11.75 mmol) and 1,6-diiodohexane (19.86 g, 58.75 mmol) to react afforded 4.53 g (91%) of crude product **10** (n = 6) as slightly yellowish crystals: ^{1}H NMR (DMSO-d_6) δ 1.19–1.29 and 1.31–1.41 (2 p, 4 H, CH_2-3′ and 4′), 1.69–1.78 and 1.82–1.92 (2 p, 4 H, CH_2-2′ and 5′), 3.23–3.27 (t, 2 H, CH_2-6′), 4.52–4.56 (t, 2 H, CH_2-1′), 8.35–8.37 (dd, 1 H, CH-5), 8.60–8.61 (dd, 1 H, CH-4), 10.21 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 8.9 (C-6′), 24.3 (C-5′), 29.1 and 29.3 (C-4′ and 3′), 32.5 (C-2′), 54.4 (C-1′), 126.9 (C-5), 137.0 (C-4), 159.1 (C-2); MS (DCI) m/z 296 (M^+).

***N*-(8′-Iodo-1′-octyl)thiazolium Iodide (10, n = 8).** Thiazole (1.19 g, 14.0 mmol) and 1,8-diiodooctane (25.62g, 70.0 mmol) were allowed to react to afford 5.14 g (81%) of crude product **10** (n = 8) as intensely yellow crystals: ^{1}H NMR (DMSO-d_6) δ 1.26 (br s, 8 H, CH_2-3′, 4′, 5′, and 6′), 1.67–1.76 and 1.81–1.91 (2 p, 4 H, CH_2-2′ and 7′), 3.23–3.27 (t, 2 H, CH_2-8′), 4.52–4.56 (t, 2 H, CH_2-1′), 8.35–8.37 (dd, 1 H, CH-5), 8.59–8.61 (dd, 1 H, CH-4), 10.20 (d, 1 H, CH-2); ^{13}C NMR (DMSO-d_6) δ 9.2 (C-8′), 25.3 (C-7′), 27.6, 28.1, 29.5, 29.7 (C-3′, 4′, 5′, and 6′), 32.7 (C-2′), 54.5 (C-1′), 126.9 (C-5), 137.0 (C-4), 159.1 (C-2); MS (FAB, positive ion mode) m/z 324 (M^+), 239 (M^+ − thiazole).

2,3-Dihydro-4*H*-1,4-benzothiazine-4-carboxaldehyde (11, n = 2). Treatment of **9** (n = 2) (0.93 g, 2.08 mmol corrected for assay) dissolved in a mixture of MeOH (150 mL) and H_2O (75 mL) with aqueous NaOH (5.0 mL, ~2.4 equiv), afforded 0.18 g (48%) of product **11** (n = 2) after purification as slightly brownish crystals: mp 68.8 °C (lit.[4c] mp 68.0–68.5 °C); ^{1}H NMR ($CDCl_3$) δ 3.11–3.15 (p, 2 H, CH_2-2), 4.04–4.08 (p, 2 H, CH_2-3), 7.04–7.15 (m, 3 H, aromatic CH-6, 7, and 8), 7.19–7.23 (m, 1 H, aromatic CH-5), 8.61 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 27.3 (C-2), 38.4 (C-3), 120.6 (C-8), 125.3 and 125.8 (C-6 and 7), 126.4 (C-8[a]), 127.5 (C-5), 135.0 (C-5[a]), 161.1 (CHO); MS (EI) m/z (relative intensity) 180 (M^+ + 1, 10), 179 (M^+, 84), 150 (M^+ − CHO, 31), 136 (M^+ − NCHO, 100). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81; O, 8.93; S, 17.89. Found: C, 60.2; H, 5.1; N, 7.6; O, 9.0; S, 18.1.

3,4-Dihydro-1,5-benzothiazepine-5(2*H*)-carboxaldehyde (11, n = 3). To a solution of **9** (n = 3) (2.00 g, 3.56 mmol corrected for assay) in MeOH (200 mL) and H_2O (100 mL) was added NaOH(aq) (10.5 mL, ~2.9 equiv) to afford 0.57 g (82%) of product **11** (n = 3) after purification as weakly brownish crystals: mp 90.1 °C (lit.[3] mp 82.5–84.5 °C); ^{1}H NMR ($CDCl_3$) δ 2.09–2.17 (m, 2 H, CH_2-3), 2.79–2.82 (q, 2 H, CH_2-2), 3.71 (br s, 2 H, CH_2-4), 7.04–7.07 (dd, 1 H, aromatic CH-9), 7.14–7.26 (m, 2 H, aromatic CH-7 and 8), 7.48–7.51 (dd, 1 H, aromatic CH-6), 8.20 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 29.6 (C-3), 31.7 (C-2), 44.5 (C-4), 127.0, 127.8, 128.3 (C-7, 8, and 9), 132.7 (C-6), 134.3 (C-9[a]), 143.5 (C-6[a]), 162.1 (CHO); MS (EI) m/z (relative intensity) 193 (M^+, 55), 160 (M^+ − SH, 45), 136 (M^+ − CH_2NCHO, 100). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; O, 8.28; S, 16.59. Found: C, 62.1; H, 5.7; N, 7.2; O, 8.1; S, 16.9.

2,3,4,5-Tetrahydro-6*H*-1,6-benzothiazocine-6-carboxaldehyde (11, n = 4). A solution of **9** (n = 4) (2.00 g, 4.21 mmol corrected for assay) in MeOH (350 mL) and H_2O (160 mL) was treated with aqueous NaOH (10.5 mL, ~2.5 equiv) to afford 0.46 g (52%) of product **11** (n = 4) after purification as yellow-brown crystals. A recrystallization changed the color to white: melting range 85.0–85.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.67–1.74 and 1.86–1.93 (2 m, 4 H, CH_2-3 and 4), 2.83–2.89 (p, 2 H, CH_2-2), 3.83–3.86/3.70–3.74 (2 t, 2 H, doubling of CH_2-5 in a ~8:1 ratio due to hindered amide rotation), 7.19–7.25 (m, 1 H, aromatic CH-10), 7.29–7.41 (m, 2 H, aromatic CH-8 and 9), 7.63–7.69 (m, 1 H, aromatic CH-7), 8.11/8.36 (2 s, 1 H, 2 CHO in 7:1); ^{13}C NMR ($CDCl_3$) δ 25.0/26.1 (doubling of C-3), 29.0/29.1 (doubling of C-4), 36.1/36.8 (doubling of C-2), 46.8/52.5 (doubling of C-5), 129.2/128.5, 129.3, 129.5/130.0 (partial doubling of aromatic C-8, 9, and 10), 134.8/135.7 (doubling of C-7), 136.3 (C-10[a]), 142.5 (C-7[a]), 163.7/162.5 (doubling of CHO); MS (EI) m/z (relative intensity) 207 (M^+, 49), 174 (M^+ − SH, 26), 136 (M^+ − CH_2CH_2NCHO, 100). Anal. Calcd for $C_{11}H_{13}$-

NOS: C, 63.74; H, 6.32; N, 6.76; O, 7.72; S, 15.47. Found: C, 63.8; H, 6.4; N, 6.8; O, 7.4; S, 15.6.

3,4,5,6-Tetrahydro-1,7-benzothiazonine-7(2*H*)-carboxaldehyde (11, *n* = 5). A solution of **9** (*n* = 5) (2.00 g, 3.28 mmol corrected for assay) in MeOH (350 mL) and H_2O (150 mL) was treated with aqueous NaOH (9.8 mL, ~3.0 equiv) to afford product **11** (*n* = 5) in two fractions, 0.26 g from recrystallization and 0.28 g as a precipitate from the mother liquor (total yield 71%, corrected for low assay (~91% GC) of first crop), as white crystals: melting range 56.9–58.8 °C (second crop); ^{1}H NMR ($CDCl_3$) δ 1.51 and 1.71 (2 br s, 6 H, CH_2-3, 4, and 5), 2.77–2.81 (t, 2 H, CH_2-2), 3.83 (br s, 2 H, CH_2-6), 7.25–7.35 and 7.41–7.47 (2 m, 3 H, aromatic CH-9, 10, and 11), 7.71–7.75 (dd, 1 H, aromatic CH-8), 8.16/8.36 (2 s, 1 H, doubling of CHO in ~13:1); ^{13}C NMR ($CDCl_3$) δ (values for doublet signals are not reported) 22.3, 23.5, and 25.5 (C-3, 4, and 5), 36.1 (C-2), 45.7 (C-6), 128.1, 128.7, and 130.1 (aromatic C-9, 10, and 11), 134.5 (C-11^a), 137.6 (C-8), 144.8 (C-8^a), 164.2 (CHO); MS (EI) *m*/*z* (relative intensity) 221 (M^+, 82), 174 (M^+ − CH_2SH, 63), 136 (M^+ − $CH_2CH_2CH_2NCHO$, 100). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; O, 7.23; S, 14.49. Found: C, 65.1; H, 6.8; N, 6.2; O, 7.3; S, 14.8.

2,3,4,5,6,7-Hexahydro-8*H*-1,8-benzothiazecine-8-carboxaldehyde (11, *n* = 6). To a solution of **9** (*n* = 6) (2.00 g, 3.75 mmol corrected for assay) in MeOH (500 mL) and H_2O (250 mL) was added NaOH(aq) (10.6 mL, ~3.2 equiv) to afford 0.35 g (39%) of product **11** (*n* = 6) after purification as white crystals: melting range 101.1–103.2 °C; ^{1}H NMR ($CDCl_3$) δ 0.92, 1.45, and 1.83 (3 br s, 8 H, CH_2-3, 4, 5, and 6), 2.45 and 3.08 (2 br s, 2 H, $CH_{\alpha+\beta}$-2), 3.45 and 4.63 (2 br s, 2 H, $CH_{\alpha+\beta}$-7), 7.27–7.32 and 7.40–7.46 (2 m, 3 H, aromatic CH-10, 11, and 12), 7.75–7.77 (m, 1 H, aromatic CH-9), 8.20/8.31 (2 s, 1 H, doubling of CHO in ~9:1); ^{13}C NMR ($CDCl_3$) δ (no doubling signals reported besides CHO) 21.2, 21.5, 23.9, and 25.5 (C-3, 4, 5, and 6), 37.6 (C-2), 43.3 (C-7), 125.1, 127.6, and 129.7 (aromatic C-10, 11, and 12), 130.9 (C-12^a), 138.1 (C-9), 143.9 (C-9^a), 164.2/162.3 (CHO); MS (EI) *m*/*z* (relative intensity) 235 (M^+, 83), 174 (M^+ − CH_2CH_2SH, 35), 136 (M^+ − $(CH_2)_4NCHO$, 100). Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95; O, 6.80; S, 13.62. Found: C, 65.7; H, 7.2; N, 5.7.

2,3,4,5,6,7,8,9-Octahydro-10*H*-1,10-benzothiaazacyclododecine-10-carboxaldehyde (11, *n* = 8). A solution of **9** (*n* = 8) (1.44 g, 2.43 mmol corrected for assay) in MeOH (400 mL) and H_2O (200 mL) was treated with aqueous NaOH (6.1 mL, ~2.8 equiv) and left to stand in the refrigerator for 1 h. To the opaque solution formed was added another portion of MeOH (400 mL), and the resulting mixture was stored overnight in the refrigerator. Concentration, flash fitration, and precipitation of the crude, oily residue from *n*-hexane afforded 0.25 g (39%) of product **11** (*n* = 8) as white crystals: melting range 78.2–80.4 °C; ^{1}H NMR ($CDCl_3$) δ 1.0–1.9 (br s, 12 H, CH_2-3, 4, 5, 6, 7, and 8), 2.8–3.2 (br s, 2 H, CH_2-2), 3.4 and 4.5 (2 br s, 2 H, $CH_{\alpha+\beta}$-9), 7.16–7.31 (m, 3 H, aromatic CH-12, 13, and 14), 7.57–7.62 (m, 1 H, aromatic CH-11), 8.11/8.29 (2 s, 1 H, doubling of CHO in ~4.2:1); ^{13}C NMR ($CDCl_3$) δ (no doubling signals reported besides CHO) 22.4, 22.8, 23.2, 24.3, 25.6, and 26.2 (C-3, 4, 5, 6, 7, and 8), 36.9 (C-2), 44.6 (C-9), 126.0, 127.3, and 127.5 (aromatic C-12, 13, and 14), 132.6 (C-11), 134.1 (C-14^a), 140.7 (C-11^a), 164.0/161.8 (CHO); MS (EI) *m*/*z* (relative intensity) 263 (M^+, 85), 202 (M^+ − CH_2CH_2SH, 31), 188 (M^+ − $(CH_2)_3SH$, 59), 136 (M^+ − $(CH_2)_6NCHO$, 100). Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32; O, 6.07; S, 12.17. Found: C, 68.6; H, 8.1; N, 5.1; O, 6.1; S, 12.2.

2,3-Dihydro-4*H*-1,4-thiazine-4-carboxaldehyde (12, *n* = 2). A solution of **10** (*n* = 2) (1.36 g, 4.98 mmol) in H_2O (15 mL) was treated with NaOH(aq) (10.3 mL, ~2.1 equiv) to afford 0.38 g (59%) of product **12** (*n* = 2) after purification as a slightly yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~2.2:1) 2.96–2.99/3.06–3.09 (2 t, 2 H, CH_2-6), 3.99–4.02/3.88–3.91 (2 p, 2 H, CH_2-5), 5.39–5.42/5.54–5.57 (2 d, 1 H, olefinic CH-2), 6.66–6.68/7.12–7.15 (2 d, 1 H, olefinic CH-3), 8.22/7.93 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 24.3/25.4 (C-6), 39.4/44.6 (C-5), 101.2/104.0 (olefinic C-2), 121.3/118.2 (olefinic C-3), 161.4/160.2 (CHO); MS (EI) *m*/*z* (relative intensity) 129 (M^+, 86), 86 (M^+ − NCHO, 53), 68 (M^+ − 61, 52), 28 (M^+ − 101, 100). Anal. Calcd for C_5H_7NOS: C, 46.49; H, 5.46; N, 10.84; O, 12.38; S, 24.82. Found: C, 46.2; H, 5.5; N, 10.8; O, 12.3; S, 25.2.

6,7-Dihydro-1,4-thiazepine-4(5*H*)-carboxaldehyde (12, *n* = 3). Treatment of **10** (*n* = 3) (1.91 g, 5.01 mmol) dissolved in H_2O (25 mL) with aqueous NaOH (11 mL, ~2.2 equiv) afforded 0.34 g (47%) of product **12** (*n* = 3) as a slightly yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~1.8:1) 1.99–2.08 (p, 2 H, CH_2-6), 3.04–3.13 (p, 2 H, CH_2-7), 4.07–4.11/3.98–4.02 (2 t, 2 H, CH_2-5), 5.36–5.38/5.46–5.48 (2 d, 1 H, olefinic CH-2), 6.44–6.47/6.73–6.76 (2 d, 1 H, olefinic CH-3), 8.17/7.95 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 27.1/30.2 (C-6), 32.9/32.6 (C-7), 42.7/47.0 (C-5), 109.2/110.0 (olefinic C-2), 127.1/124.6 (olefinic C-3), 162.6/161.3 (CHO); MS (EI) *m*/*z* (relative intensity) 143 (M^+, 79), 86 (M^+ − CH_2NCHO, 100), 59 (M^+ − 84, 53). Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; O, 11.17; S, 22.39. Found: C, 50.3; H, 6.5; N, 9.6; O, 11.2; S, 22.3.

5,6,7,8-Tetrahydro-4*H*-1,4-thiazocine-4-carboxaldehyde (12, *n* = 4). A solution of **10** (*n* = 4) (1.98 g, 5.01 mmol) in H_2O (50 mL) was treated with NaOH(aq) (11.6 mL, ~2.3 equiv) to afford 0.41 g (52%) of product **12** (*n* = 4) after purification as a silghtly yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~2.4:1) 1.75–1.84 and 1.85–1.94 (2 m, 4 H, CH_2-6 and 7), 2.79–2.86 (2 t, 2 H, CH_2-8), 4.30–4.34/4.20–4.24 (2 t, 2 H, CH_2-5), 5.34–5.37/5.43–5.46 (2 d, 1 H, olefinic CH-2), 6.73–6.75/7.18–7.21 (2 d, 1 H, olefinic CH-3), 8.27/7.98 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 24.1 and 27.8/23.8 and 30.0 (C-6 and 7), 34.3/32.9 (C-8), 40.4/45.1 (C-5), 101.6/102.8 (olefinic C-2), 134.2/130.3 (olefinic C-3), 163.5/162.7 (CHO); MS (EI) *m*/*z* (relative intensity) 157 (M^+, 100), 86 (M^+ − CH_2NCHO, 47), 70 (M^+ − 87, 52), 59 (M^+ − 98, 32). Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91; O, 10.18; S, 20.39. Found: C, 53.4; H, 7.2; N, 8.9; O, 10.5; S, 20.2.

6,7,8,9-Tetrahydro-1,4-thiazonine-4(5*H*)-carboxaldehyde (12, *n* = 5). To a solution of **10** (*n* = 5) (2.07 g, 5.06 mmol) in MeOH (200 mL) and H_2O (100 mL) was added aqueous NaOH (11.3 mL, ~2.2 equiv) to afford 0.43 g (50%) of product **12** (*n* = 5) after purification as a brownish liquid: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~4:1) 1.58–1.80 and 1.83–1.91 (2 br m, 6 H, CH_2-6, 7, and 8), 2.63–2.70 (2 t, 2 H, CH_2-9), 4.31–4.37/4.53–4.56 (2 t, 2 H, CH_2-5), 5.54–5.58 (d, 1 H, olefinic CH-2), 6.60–6.64/7.26–7.30 (2 d, 1 H, olefinic CH-3), 8.31/8.12 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 23.8, 28.9, and 30.8/31.1 and 32.9 (C-6, 7, and 8), 35.6/37.0 (C-9), 42.6/45.2 (C-5), 104.8/102.6 (olefinic C-2), 135.5/132.6 (olefinic C-3), 164.2/163.6 (CHO); MS (EI) *m*/*z* (relative intensity) 171 (M^+, 16), 124 (M^+ − 47, 36), 86 (M^+ − $(CH_2)_3NCHO$, 63), 70 (M^+ − 101, 98), 59 (M^+ − 112, 85). Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18; O, 9.34; S, 18.72. Found: C, 55.7; H, 7.8; N, 7.8.

5,6,7,8,9,10-Hexahydro-4*H*-1,4-thiazecine-4-carboxaldehyde (12, *n* = 6). Treatment of **10** (*n* = 6) (0.85 g, 2.01 mmol) dissolved in MeOH (25 mL) and H_2O (25 mL) with aqueous NaOH until reaching pH ~ 10.9 afforded 0.14 g (37%) of product **12** (*n* = 6) after purification as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~9:1) 1.50–1.65 (2 br s, 8 H, CH_2-6, 7, 8, and 9), 2.51–2.54/2.57–2.61 (2 t, 2 H, CH_2-10), 3.63–3.67/3.99–4.04 (2 t, 2 H, CH_2-5), 5.83–5.85/5.66–5.68 (2 d, 1 H, olefinic CH-2), 6.41–6.43/6.69–6.71 (2 d, 1 H, olefinic CH-3), 8.21/8.01 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.4, 23.6, and 24.7 (C-6, 7, 8, and 9), 32.8/35.2 (C-10), 42.7/44.0 (C-5), 113.8/111.2 (olefinic C-2), 137.4/130.8 (olefinic C-3), 162.8/162.6 (CHO); MS (EI) *m*/*z* (relative intensity) 185 (M^+, 58), 138 (M^+ − 47, 60), 124 (M^+ − 61, 75), 86 (M^+ − $(CH_2)_4NCHO$, 53), 41 (M^+ − 144, 100). Anal. Calcd for $C_9H_{15}NOS$: C, 58.34; H, 8.16; N, 7.56; O, 8.63; S, 17.31. Found: C, 58.4; H, 8.4; N, 7.4; O, 8.8; S, 17.1.

1-Thia-4-azacyclododec-2-ene-4-carboxaldehyde (12, *n* = 8). A solution of **10** (*n* = 8) (0.40 g, 0.89 mmol) in MeOH (500 mL) and H_2O (250 mL) was treated with NaOH(aq) (4.1 mL, ~4.6 equiv) during 1 h to afford 21.0 mg (11%) of product **12** (*n* = 8) after purification as white crystals: melting range 68.1–70.5 °C; ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~6.7:1) 1.26–1.53 (2 br s, 12 H, CH_2-6, 7, 8, 9, 10, and 11), 2.58–2.61 (t, 2 H, CH_2-12), 3.49–3.56 (br s, 2 H, CH_2-5), 5.80–

5.83 (d, 1 H, olefinic CH-2), 6.17–6.19/6.00–6.01 (2 d, 1 H, olefinic CH-3), 8.18/8.08 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.6, 24.6, 24.8, 25.9, and 27.9 (C-6, 7, 8, 9, 10, and 11), 35.5 (C-12), 43.1 (C-5), 118.1 (olefinic C-2), 131.5 (olefinic C-3), 162.7 (CHO); MS (EI) m/z (relative intensity) 213 (M^+, 26), 138 ($M^+ - 75$, 45), 86 ($M^+ - (CH_2)_6NCHO$, 38), 55 ($M^+ - 158$, 46), 41 ($M^+ - 172$, 100). Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98; N, 6.56; O, 7.50; S, 15.03. Found: C, 62.1; H, 9.3; N, 6.2; O, 7.4; S, 14.7.

5,8-Dihydro-4*H*-1,4-thiazocine-4-carboxaldehyde (15). To a solution of *N*-(4′-bromo-*cis*-2′-buten-1′-yl)thiazolium iodide (1.00 g, 2.89 mmol; synthesized in 44% yield from thiazole and 1,4-dibromo-*cis*-2-butene according to the standard procedure described above) in MeOH (200 mL) and H_2O (100 mL) was added NaOH(aq) (5.8 mL, ~2.0 equiv) to afford 0.09 g (20%) of product **15** after purification as a slightly brownish oil: ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~1.9:1) 3.61–3.84 (br m, 2 H, CH_2-8), 4.24–4.29/3.88–3.93 (2 + 2 d, 1 H, olefinic CH-7), 5.25–5.40 (br m, 2 H, CH_2-5), 5.41–5.44/5.57–5.59 (2 d, 1 H, olefinic CH-2), 5.77–5.89 (br m, 1 H, olefinic CH-6), 6.66–6.68/7.15–7.18 (2 d, 1 H, olefinic CH-3), 8.27/7.94 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 40.2/41.3 (C-8), 43.6/49.2 (C-5), 101.2/104.0 (olefinic C-2), 118.7/118.2 and 121.0/118.9 (olefinic C-6 and 7), 133.7/133.6 (olefinic C-3), 161.5/160.4 (CHO); MS (EI) m/z (relative intensity) 155 (M^+, 36), 122 ($M^+ - 33$, 23), 94 ($M^+ - 61$, 30), 86 ($M^+ - 69$, 37), 59 ($M^+ - 94$, 54), 54 (M^+ – SCH=CHNCHO, 71), 45 ($M^+ - 110$, 82), 39 ($M^+ - 116$, 80), 28 ($M^+ - 127$, 100). Anal. Calcd for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02; O, 10.31; S, 20.66. Found: H, 5.8; N, 9.0.

1,6-Dihydro-5*H*-2,5-benzothiazocine-5-carboxaldehyde (16). A solution of *N*-[2′-(bromomethyl)benzyl]thiazolium bromide (1.50 g, 4.30 mmol; synthesized in 66% yield from thiazole and α,α′-dibromo-*o*-xylene) in MeOH (600 mL) and H_2O (300 mL) was treated with aqueous NaOH (10.5 mL, ~2.4 equiv) to afford 0.23 g (26%) of product **16** after purification as slightly off-white crystals: melting range 42.6–44.8 °C; ^{1}H NMR ($CDCl_3$) δ (ratio of doubling signals ~2.4:1) 4.06/4.07 (2 s, 2 H, CH_2-1), 5.01/5.10 (2 s, 2 H, CH_2-6), 5.99–6.02/6.02–6.06 (2 d, 1 H, olefinic CH-3), 6.60–6.63/7.03–7.06 (2 d, 1 H, olefinic CH-4), 7.12–7.34 (br m, 4 H, aromatic CH-7, 8, 9, and 10), 8.27/8.12 (2 s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 37.6/39.5 (C-1), 46.7/49.7 (C-6), 118.4/114.4 (olefinic C-3), 127.9/127.6, 128.1, 128.4/128.6 (partial doubling of aromatic C-8, 9, and 10), 129.9/129.3 (aromatic C-7), 130.11/130.07 (olefinic C-4), 135.0 (C-10^a), 135.2 (C-7^a), 163.5/164.1 (CHO); MS (EI) m/z (relative intensity) 205 (M^+, 31), 135 ($M^+ - 70$, 31), 104 (M^+ – SCH=CHNCHO, 100), 103 ($M^+ - 102$, 51), 78 ($M^+ - 127$, 61), 77 ($M^+ - 128$, 40). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; O, 7.80; S, 15.62. Found: C, 64.5; H, 5.7; N, 6.8; S, 15.3.

6-Acetyl-2,3,4,5-tetrahydro-6*H*-1,6-benzothiazocine (17). Treatment of *N*-(4′-iodo-1′-butyl)-2-methylbenzothiazolium iodide (1.52 g, 3.31 mmol; obtained in 64% yield from 2-methylbenzothiazole and 1,4-diiodobutane) dissolved in MeOH (500 mL) and H_2O (250 mL) with aqueous NaOH (8 mL, ~2.4 equiv) afforded 0.11 g (15%) of product **17** as white crystals: melting range 92.5–94.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.47–1.55, 1.75–1.79, 1.97–2.02 (3 m, 4 H, $CH_{\alpha+\beta}$-3 and 4), 1.81 (s, 3 H, CH_3), 2.70–2.79, 2.87–2.95 (2 q + 2 t, 2 H, $CH_{\alpha+\beta}$-2), 2.99–3.09, 4.80–4.89 (2 d + t + d, 2 H, $CH_{\alpha+\beta}$-5), 7.17–7.20 (2 d, 1 H, aromatic CH-10), 7.27–7.39 (br m, 2 H, aromatic CH-8 and 9), 7.60–7.63 (2 d, 1 H, aromatic CH-7); ^{13}C NMR ($CDCl_3$) δ 22.8 (CH_3), 24.5 (C-3), 29.4 (C-4), 35.4 (C-2), 48.8 (C-5), 128.6, 128.8, 129.3 (aromatic C-8, 9, and 10), 134.4 (aromatic C-7), 135.8 (C-10^a), 144.1 (C-7^a), 170.8 (amide C=O); MS (EI) m/z (relative intensity) 221 (M^+, 8), 136 ($M^+ - CH_2CH_2NCOCH_3$, 59), 109 ($M^+ - 112$, 22), 65 ($M^+ - 156$, 23), 43 ($M^+ - C_6H_4S(CH_2)_4N$, 100). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; O, 7.23; S, 14.49. Found: H, 7.0; N, 6.0.

Acknowledgment. The analytical support provided by the following colleagues at Astra throughout this work is highly appreciated: Kerstin Asker (HPLC), Britt-Marie Gawell (EI-MS), Hans Thorin (NMR), and Sten-Åke Wikström (FAB-MS).

JO942034T