114. Synthesis of the Thiazolone Analogue of the Acetylcholinesterase Inhibitor, Huperzine A

by **Alan P. Kozikowski** and **Werner Tückmantel***

Trophix Pharmaceuticals, Inc., 40 Cragwood Road, South Plainfield, NJ 07080, USA

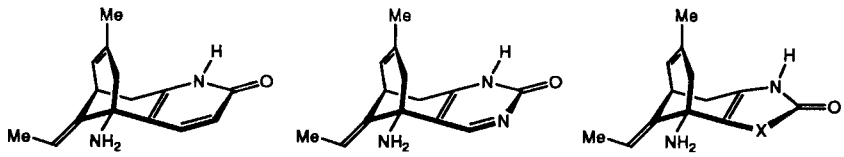
and **Ashima Saxena** and **Bhupendra P. Doctor**

Division of Biochemistry, Walter Reed Army Institute of Research, Washington, DC 20307, USA

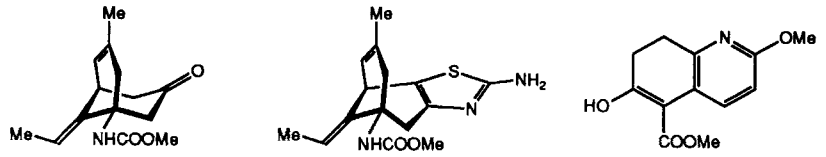
(23.III.94)

The preparation of an analogue **3a** of the acetylcholinesterase inhibitor, huperzine A (**1**), is described in which the pyridinone moiety of the natural product is replaced with a thiazolone moiety. The synthesis started from cyclohexane-1,4-dione monoethylene ketal (**7**) by first annulating the thiazole ring using the *Gewald* protocol (→**8**; *Scheme 1*) and then constructing the bicyclo[3.3.1]nonane substructure using our previously described *Michael* addition/aldol condensation methodology (*Scheme 3*). The central problem was the protection of the thiazolone carbonyl group; only the 2-unsubstituted thiazole survived the reaction conditions of the first half of the synthesis. Refunctionalization was later effected by lithiation and subsequent chlorination with hexachloroethane (**30**→**31**). Compound **3a** was ineffective in the acetylcholinesterase inhibition assay in concentrations up to 14 μM.

Introduction. – Huperzine A (**1**), an alkaloid isolated from the clubmoss *Huperzia serrata* (THUNB.) TREV. = *Lycopodium serratum* THUNB. which has long been used as a Chinese folk medicine [1], holds considerable promise in the treatment of *Alzheimer*'s disease due to its acetylcholinesterase (AChE) inhibition [2]. The scarcity of huperzine A from natural sources has induced us [3–5] and others [6] to develop total syntheses, and the desire to uncover structure-activity relationships in order to improve upon the natural product has spurred the preparation of numerous analogues [4] [5] [7]. Structural modifications investigated to date include those at the amino and pyridinone N-atoms, at the ethylidene group, and at the C_3 bridge as well as the replacement of the pyridinone by a benzene ring. Not surprisingly, the latter modification resulted in a poorly active compound as a consequence of the removal of several H-bonding interactions with amino-acid residues of its binding site. It occurred to us that the introduction of additional heteroatoms into the heterocyclic ring, rather than their removal, might by the same token result in compounds of improved cholinesterase inhibitory activity. We have pursued this concept along two lines and chosen the pyrimidinone **2** and the thiazolone **3a** as representative targets among π-deficient and π-excessive heterocycles, *i.e.*, systems in which either a single C-atom or a C=C bond is replaced by a heteroatom possessing a lone electron pair. Our preference for the thiazolone **3a** over the alternative targets, oxazolone **3b** and imidazolone **3c**, was determined by the following considerations: *1*) the naive assumption that, within this group of compounds, a thiazolone would constitute the closest approximation to the original pyridinone just as, among the simple heterocyclopentadienes, thiophene is the one that most closely resembles benzene; *2*) the expectation that the S-atom as the least electronegative among the heteroatom candidates



huperzine A (1) **2** **3a–c** X = S, O, NH

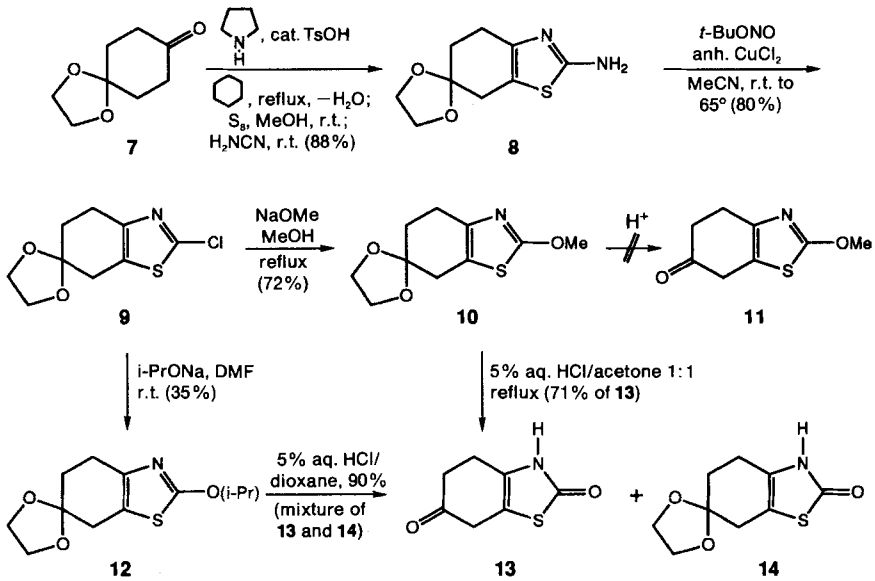


4 **5** **6**

should cause the smallest modification of the dipole moment (potentially detrimental to binding) and should not increase hydrophilicity (detrimental to the penetration of the blood-brain barrier); on the other hand, the higher polarizability of S as a third-row element in comparison with O and N might even further enhance binding through induced dipole-dipole interactions; *3*) the larger size of the S-atom compared to the O- or N-atom which, even though not fully equivalent to that of two C-atoms, should at least keep distortions around the lactam moiety, which is essential for binding, to the inevitable minimum; and *4*) the realization that our initial idea of increasing H-bonding capabilities, although potentially valid for compounds like **2**, might backfire for structures like **3b** or **3c** with the additional heteroatom in close proximity to the NH_2 group so that an intramolecular H-bond may be formed, thus actually reducing the degree of intermolecular H-bonding. The S-atom as a poor H-bond acceptor is the least conducive to this problem among the heteroatoms under consideration. While work on the pyrimidinone analogue **2** is still in progress [8], we report herein the synthesis and AChE inhibitory activity of the thiazolone analogue **3a**.

Synthesis. – The initial approach through which we had hoped to gain access to a variety of condensed heterocycles *via* a single advanced intermediate, the ketourethane **4**, was thwarted by the poor reactivity towards electrophiles of the ketone itself and the predominant or exclusive formation of the undesired regioisomer on reaction of its lithium enolate or pyrrolidine-derived enamine [8] [9]. Thus, application of the *Gewald* aminothiazole synthesis [10] to intermediate **4** resulted in the exclusive formation of the wrong skeletal isomer **5**, while only the endocyclic olefin reacted on attempted α-sulfenylation of the free ketone [9]. Whereas strategies such as protection of the more reactive of the α-methylene groups could conceivably be developed as a remedy, a more obvious approach would be to construct the thiazole ring at the onset and to develop the alicyclic portion of the molecule subsequently, in close analogy to the synthesis of huperzine A itself for which the β-ketoester **6** served as a key intermediate. We eventually obtained the target compound **3a** along these lines, but not without difficulties of another kind: the key problem turned out to be the appropriate masking of the carbonyl group of **3a** for which methoxy, convenient though it was for many pyridinone-based huperzine A analogues, proved to be an unsuitable choice in the present case.

Scheme 1

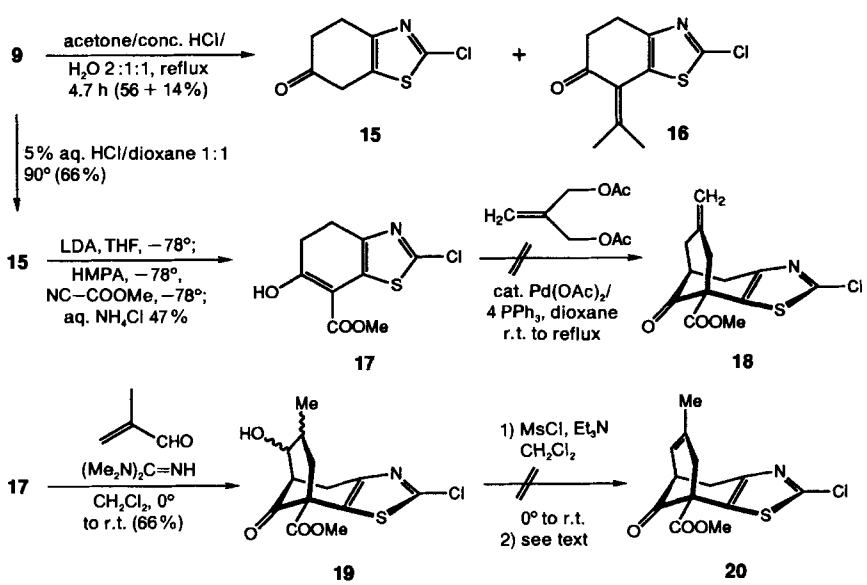


Formation of the required tetrahydrobenzothiazole skeleton was readily achieved starting from cyclohexane-1,4-dione monoethylene ketal (**7**, *Scheme 1*) by the procedure of *Gewald* and coworkers [10] which consists of enamine formation followed by reaction with elemental sulfur and subsequent addition of cyanamide. The outcome strongly depends on the choice of the amine in the enamine formation step: pyrrolidine gave the aminothiazole **8** in good yield, but contaminated with dark polymers, whereas with morpholine a much less colored product was obtained, but in only 48% yield. Fortunately, the material obtained using pyrrolidine was satisfactory for the following step in which the NH_2 group was replaced by a Cl-atom (→**9**) under the action of *tert*-butyl nitrite and anhydrous $CuCl_2$ in MeCN [11]. These conditions rather than the traditional *Sandmeyer* reaction were chosen because reported yields are usually superior, and because the stability of the ketal function in strong acid was doubtful. A rather sluggish nucleophilic substitution with NaOMe in boiling MeOH transformed chloride **9** into the methoxythiazole **10** which was subjected to various acidic conditions for ketal hydrolysis. Under the conditions applied in the synthesis of hyperzine A, *i.e.*, boiling in a mixture of 5% HCl/H_2O and acetone [4], only the product of concomitant hydrolysis of both the ketal and methyl-ether functions, tetrahydrobenzothiazoledione **13**, was formed; the same result was obtained with anhydrous HCl (from Me_3SiCl) in MeOH at room temperature. Only starting material was recovered on attempted transketalization with 0.045 equiv. of camphorsulfonic acid in boiling dry acetone, while decomposition took place with 1.1 equiv. of camphorsulfonic acid, even at room temperature. A monohydrolysis product was obtained in low and variable yield with an excess of acetyl chloride (the actual reagent is probably adventitious HCl) in benzene at room temperature [12], but this compound is the (ethylenedioxy)thiazolone **14** rather than the desired methoxy ketone **11**. In the expectation that a larger alkoxy group at the thiazole ring would reverse

the order of reactivity, chlorothiazole **9** was transformed into the isopropyl ether **12** (conditions not optimized) which on hydrolysis again furnished a mixture of **13** and **14**. Attempts at liberating the ketone function in the presence of an alkoxy group at C(2) were thereafter abandoned.

Since it was conceivable that the substitution of the Cl-atom by a MeO group could be executed at a later stage of the synthesis, we turned our attention to the hydrolysis of chloroketal **9** (*Scheme 2*). With boiling 5% aqueous HCl/acetone 1:1, the conversion was low. Increasing the HCl concentration forced the reaction to completion, but besides the desired ketone **15**, the product **16** of its aldol condensation with acetone was also obtained. A clean though still modest-yielding reaction took place in 5% aqueous HCl/dioxane at 90°; the highly crystalline product **15** was readily separated from small remainders of its very soluble precursor by recrystallization. When **15** was subjected to the same methoxycarbonylation procedure [4] as in the preparation of the huperzine-A intermediate **6** (KH, dimethyl carbonate as solvent, reflux), some starting material but no defined product was recovered. Under *Mander*'s conditions [13], on the other hand, a moderate yield of the desired β-keto ester **17** could be isolated. This intermediate failed to undergo the Pd-catalyzed double alkylation [5] with 2-methylidenepropane-1,3-diyl diacetate to give the tricycle **18** but instead furnished a small amount of a material which is probably the product of alkylation at the β-keto ester function only. Returning to the method originally developed for **6** [4], we reacted **17** with methacrolein (= 2-methylprop-2-enal) in the presence of catalytic amounts of 1,1,3,3-tetramethylguanidine and obtained, through a sequence of *Michael* and aldol reactions, the tricyclic aldol **19** which was readily mesylated. Heating the mesylate with NaOAc [4] in AcOH or DMF under reflux did not produce any of the elimination product **20**, while only insignificant traces of it were obtained on heating in 2,4,6-collidine (= 2,4,6-trimethylpyridine) at 170° [14] or with quinaldine in mesitylene at 160°. The failure of both annulation strategies is

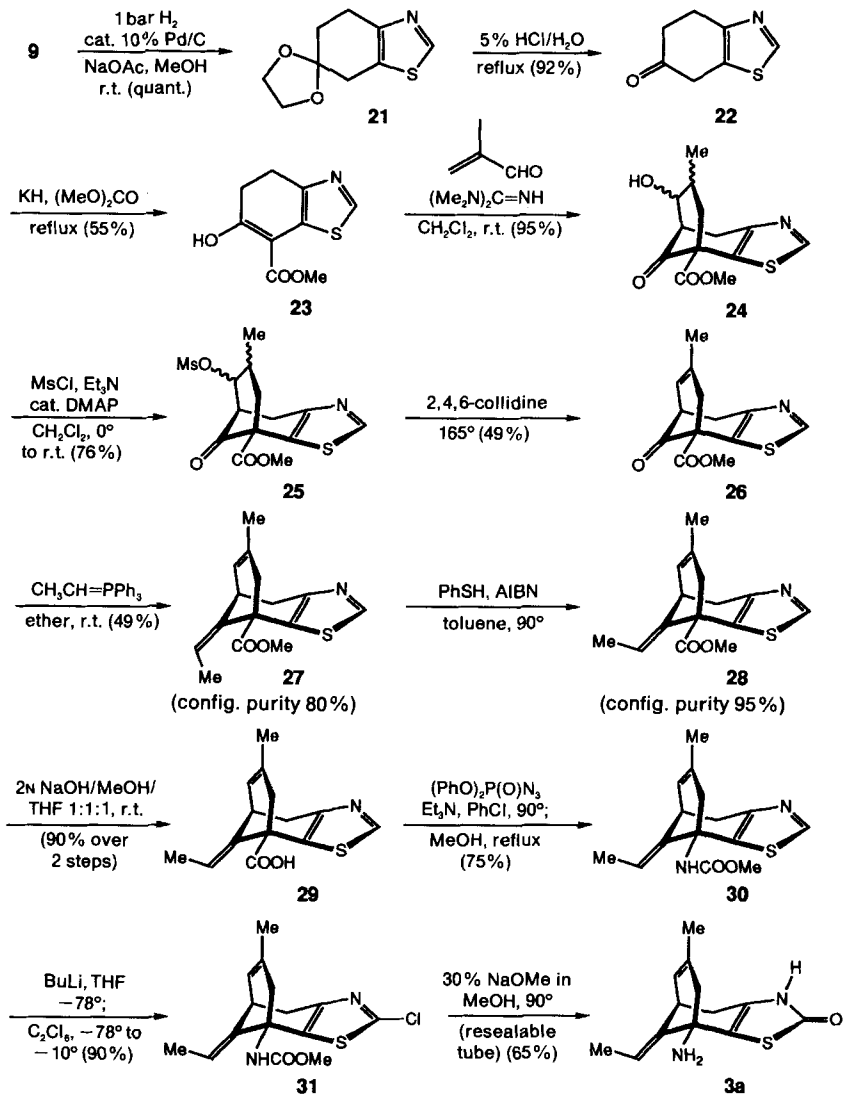
Scheme 2



probably a consequence of the reactivity of the chlorothiazole moiety towards Pd insertion and towards nucleophilic substitution under the drastic elimination conditions. Since the Cl-atom was anyway to be replaced later by a MeO group, the β-keto ester **17** and the aldol **19** were reacted with NaOMe in boiling MeOH in the hope of obtaining more robust intermediates but both, unfortunately, underwent decomposition.

As the last resort, we eventually considered removing the C(2) substituent. The resulting thiazoles were expected to be stable thermally and against nucleophiles, acids, and all but the strongest bases. In the last stages of the synthesis, the C(2) substituent would be restored *via* lithiation, a reaction well documented for the parent heterocycle [15]. Thus, hydrogenolysis of chloro ketal **9** over Pd/C furnished a quantitative yield of the dechlorinated ketal **21** which was hydrolyzed by boiling in 5% HCl/H_2O without organic cosolvent (*Scheme 3*). Methoxycarbonylation of the resulting ketone **22** by the *Mander* protocol gave an even poorer yield (38–43%) of the β-ketoester **23** than in the case of the chlorinated intermediate **15**; a somewhat better result was obtained with KH in boiling dimethyl carbonate. Neither reaction was clean, and significant amounts of starting material were recovered, unfortunately in too low purity for recycling. It appears that, under the last-mentioned conditions, very low solubility of the potassium enolate contributes to the unsatisfactory yield; at a point of the reaction when decomposition became serious as evidenced by the dark color of the mixture, TLC indicated the absence of starting material from the solution even though the conversion was found to be incomplete after workup. The following two steps, *Michael*-aldol reaction with methacrolein (→**24**) and mesylation (→**25**), proceeded uneventfully, and subsequent elimination of methanesulfonic acid was effected in 49% yield by heating in 2,4,6-collidine. The product **26** is highly crystalline, like the corresponding huperzine A intermediate, and thus readily purified. Introduction of the ethylidene side chain by a *Wittig* reaction with (ethylidene)triphenylphosphorane gave an unacceptable 19% yield in THF; in Et_2O, the (*Z*)-olefin **27** (configurational purity 80%) was obtained in 49% yield. As an alternative, the addition of an ethyl organometallic followed by dehydration was briefly attempted. Since the *Grignard* reagent was likely to attack the ester as well as the ketone function, an organotitanium reagent [16] from EtMgBr and $ClTi(i\text{-}PrO)_3$ was reacted with **26**; the only defined product, however, turned out to be the corresponding alcohol as the result of β-hydride transfer. Isomerization of the double bond of **27** (→**28**) was achieved as usual by the reversible addition of phenylthio radicals generated from thiophenol and 2,2′-azobis(isobutyronitrile) (AIBN = 2,2′-dimethyl-2,2′-azobis-[propanenitrile]) [17] which resulted in (*E*/*Z*) ratios of 5:1, 17:1, and 18:1 after the initial reaction and two iterations, respectively; the last value, therefore, represents the equilibrium composition. To obtain a configurationally homogeneous product, the subsequent saponification of the methyl ester was conducted under sufficiently mild conditions as to leave the sterically more hindered (*Z*)-ester **27** unreacted (→**29**). The reaction conditions given in *Scheme 3* reflect a significantly increased reactivity of both esters **27** and **28** in comparison with the corresponding huperzine A intermediates due to the smaller size (absence of attached H in the vicinity of the ring junction) of the thiazole compared to a pyridine ring. Transformation of the carboxyl group of **29** to a urethane function was then performed as usual by the azidophosphate modification [18] of the *Curtius* reaction (→**30**). At this point, the C(2) substituent had to be reintroduced. To this end, urethane **30** was deprotonated with 2.5 equiv. of BuLi in THF at −78°; the reaction

Scheme 3



was rapid as evidenced by the instantaneous appearance of a precipitate of the presumed dianion. Addition of hexachloroethane [19] delivered the chlorothiazole **31** in a gratifying 90% yield. Since the earlier-mentioned substitution of Cl by OMe during the preparation of **10** had proceeded only slowly and incompletely under the mild conditions employed, **31** was reacted with commercial 30% NaOMe in MeOH at 90° in a resealable tube to force the reaction to completion. To our delight, these drastic conditions not only effected the desired substitution, but additionally removed the *N*-methoxycarbonyl and *O*-methyl protective groups from the presumed methoxythiazole intermediate to procure the highly crystalline target thiazolone **3a** in 80% crude and 65% purified yield.

Biological Activity and Discussion. – The thiazolone analogue **3a** of huperzine A was tested for its ability to inhibit fetal bovine serum (FBS) acetylcholinesterase according to an established protocol [20]. To our initial surprise, no inhibition was observed using up to 14 μM concentrations of **3a**, while racemic huperzine A (**1**) typically exhibits a K_i of *ca.* 21 nM. In view of the reasoning presented in the *Introduction*, this result is at first glance unexpected. Closer examination of *Dreiding* models, however, reveals that the smaller size of the S-atom as compared to an ethylene unit in the pyridinone moiety of huperzine A does entail a small but significant displacement of the lactam O-atom as well as slight displacements of the lactam N-atom and its attached H-atom. The drastic dependence of the biological activity on the precise orientation of these atoms underlines once more their key importance for the binding of huperzine A and its analogues to AChE.

Experimental Part

General. Column chromatography (CC): *Selecto* No. *176644* silica gel, particle size 0.063–0.200 mm. Thin layer chromatography (TLC): *EM Science* No. *5715* silica gel *60* F_{254} glass plates, layer thickness 0.25 mm; visualization by UV or $KMnO_4$. M.p.: *Thomas-Hoover* capillary melting-point apparatus, uncorrected; all temp. in °C. IR: *Mattson Galaxy 2020;* absorptions in cm^{-1}. NMR: *Bruker AC-300;* in $CDCl_3$ unless stated otherwise; chemical shifts δ in ppm downfield from $SiMe_4$, coupling constants J in Hz; $SiMe_4$ (^1H, $\delta = 0$) or $CDCl_3$ (^{13}C, $\delta = 77.09$) as internal ref. MS (EI mode): *Hewlett-Packard 5971A* and *VG 70-SE;* peaks listed as *m/z* (% rel. intensity). CHN Analyses: *Oneida Research Services, Inc.*, Whitesboro, NY.

2-Amino-6-(ethylenedioxy)-4,5,6,7-tetrahydrobenzothiazole (**8**). A soln. of cyclohexane-1,4-dione monoethylene ketal (7, 7.80 g, 50 mmol), pyrrolidine (4.35 ml, 52 mmol), and $TsOH \cdot H_2O$ (48 mg, 0.25 mmol) in cyclohexane (20 ml) was refluxed under Ar for 50 min (*Dean-Stark* trap filled with cyclohexane). After cooling, the soln. was decanted from tar and evaporated. Dry MeOH (15 ml) and sulfur powder (1.60 g, 6.25 mmol of S_8) were added, and the mixture was stirred for 15 min at r.t. With H_2O cooling, cyanamide (2.10 g, 50 mmol) in MeOH (10 ml) was added within 20 min. The mixture was stirred in the H_2O bath for 3 h and without temp. control for 14 h, evaporated, and crystallized (CH_2Cl_2/hexane 1:1 (100 ml); seeding helpful) to obtain a dark green solid (8.09 g). The mother liquor, after CC (CH_2Cl_2/MeOH 15:1) and crystallization (CH_2Cl_2/hexane), afforded another 1.21 g of **8** (total: 9.30 g, 88%). The anal. sample was obtained from a run using morpholine in place of pyrrolidine which gave a less colored product, albeit in only 48% yield, by crystallization from $CHCl_3$/hexane. M.p. 142–143°. IR (KBr): 3379, 3308, 3127, 1647, 1543, 1128, 1030. ^1H-NMR: 5.23 (br., 2 H); 4.02 (*s*, 4 H); 2.80 (*s*, 2 H); 2.74 (*tt*, $J = 1.5, 6.5, 2$ H); 1.95 (*t*, $J = 6.5$, 2 H). ^{13}C-NMR: 166.22, 144.46, 114.87, 108.38, 64.65, 33.70, 31.66, 24.66. MS: 212 (43, M^+), 167, 139, 126 (100). Anal. calc. for $C_9H_{12}N_2O_2S$ (212.27): C 50.93, H 5.70, N 13.20; found: C 50.82, H 5.70, N 13.21.

2-Chloro-6-(ethylenedioxy)-4,5,6,7-tetrahydrobenzothiazole (**9**). To a stirred suspension of powdered anh. $CuCl_2$ (9.0 g, 67 mmol) in dry MeCN (110 ml) which was kept at r.t. by means of a H_2O bath was added *tert*-butyl nitrite (10.0 ml, 84 mmol) all at once, then after 10 min **8** (11.9 g, 56 mmol) in portions over 1.5 h. The mixture was stirred under a drying tube ($CaCl_2$) at r.t. for 1.5 h and at 65° for 2.5 h, then silica gel (50 g) was added, and the mixture was evaporated. CC (75 g of silica gel, AcOEt/hexane 1:3) and bulb-to-bulb distillation at 140° (oven)/0.1 Torr gave **9** (10.4 g, 80%). Yellow oil. IR (film): 1433, 1146, 1061, 1026. ^1H-NMR: 4.04 (*s*, 4 H); 2.96–2.89 (*m*, 4 H); 2.00 (*t*, $J = 7$, 2 H). ^{13}C-NMR: 149.04, 148.26, 128.18, 107.63, 64.71, 33.78, 31.53, 24.83. MS: 233, 231 (28, 67, M^+); 218, 216; 196; 161, 159; 160, 158; 86 (100). Anal. calc. for $C_9H_{10}ClNO_2S$ (231.70): C 46.66, H 4.35, N 6.05; found: C 46.45, H 4.33, N 5.92.

6-(Ethylenedioxy)-2-methoxy-4,5,6,7-tetrahydrobenzothiazole (**10**). NaOMe was prepared from Na (0.53 g, 23 mmol) and dry MeOH (17 ml), **9** (3.21 g, 13.8 mmol) added, and the mixture refluxed under Ar for 21.5 h. After evaporation, the residue was distributed between H_2O (50 ml) and CH_2Cl_2 (3 × 25 ml). The org. phases were dried (K_2CO_3) and evaporated. CC (AcOEt/hexane 1:6, then 1:2) yielded, after a small forerun (mainly **9**), **10** (2.27 g, 72%) as an oil which gradually solidified. An anal. sample was obtained by bulb-to-bulb distillation (oven 120°/0.05 Torr). M.p. 61–62°. IR (film): 1532, 1231, 1061, 1036. ^1H-NMR: 4.03 (*s*, 4 H); 4.01 (*s*, 3 H); 2.82 (*s*, 2 H); 2.79 (*tt*, $J = 1.5, 6.5, 2$ H); 1.98 (*t*, $J = 6.5$, 2 H). ^{13}C-NMR: 173.33, 142.80, 117.41, 108.13, 64.76, 58.07, 33.83, 31.86, 25.11. MS: 227 (57, M^+), 212, 141 (100). Anal. calc. for $C_{10}H_{13}NO_3S$ (227.28): C 52.85, H 5.77, N 6.16; found: C 52.80, H 5.74, N 6.11.

6-(Ethylenedioxy)-4,5,6,7-tetrahydro-2-isopropoxybenzothiazole (**12**). NaH (68 mg, 1.7 mmol) was washed with THF and suspended in DMF (0.3 ml). After cautious addition of i-PrOH (145 µl, 1.9 mmol), the mixture was stirred at r.t. for 5 min, and a soln. of **9** (39 mg, 169 µmol) in DMF (0.3 ml) was added. The mixture was stirred at r.t. for 140 min, then 20% aq. NH_4Cl soln. (0.2 ml) was added, and the volatiles were evaporated. The residue was directly filtered over silica gel (AcOEt/hexane 1:2): 15 mg (35%) of **12**. Oil. IR (film): 1516, 1371, 1233, 1103, 1038. ^{1}H-NMR: 5.10 (*sept.*, J = 6, 1 H); 4.02 (*s*, 4 H); 2.83–2.74 (*m*, 4 H); 1.97 (*t*, J = 6.5, 2 H); 1.37 (*d*, J = 6, 6 H). ^{13}C-NMR: 172.33, 142.76, 116.63, 108.21, 74.97, 64.76, 33.81, 31.89, 25.16, 21.93. MS: 255 (28, M^+), 213 (100), 212, 169, 86.

3,4,5,7-Tetrahydrobenzothiazole-2,6-dione (**13**). A soln. of **10** (66 mg, 0.29 mmol) in acetone/5% aq. HCl soln. (0.7 ml each) was refluxed for 3 h. Crystallization for 2 h at 4° yielded yellowish **13** (35 mg, 71%). M.p. 212–215°. IR (KBr): 3146, 3063, 1723, 1657, 1649, 791, 611. ^{1}H-NMR ((D$_6$)DMSO): 11.16 (br., 1 H); 3.21 (*t*, J = 1.5, 2 H); 2.72–2.57 (*m*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 205.27, 172.00, 127.49, 105.35, 37.52, 37.22, 22.05. MS: 169 (100, M^+), 141, 127, 113, 99, 86, 58. Anal. calc. for $C_7H_7NO_2S$ (169.20): C 49.69, H 4.17, N 8.28; found: C 49.90, H 4.08, N 8.28.

6-(Ethylenedioxy)-4,5,6,7-tetrahydrobenzothiazol-2(3H)-one (**14**). A soln. of **10** (538 mg, 2.37 mmol) and AcCl (0.50 ml, 7.1 mmol) in benzene (2.4 ml) was kept at r.t. for 102 h. Evaporation and CC (AcOEt/hexane 1:2, then 1:0) yielded 484 mg (90%) of **10**, followed by 49 mg (10%) of **14**. Colorless solid. Even the low conversion given here was not consistently reproducible. ^{1}H-NMR ((D$_6$)DMSO): 5.15 (br. *s*, 1 H); 3.92 (*s*, 4 H); 2.51 (*s*, 2 H, overlapping with solvent signal); 2.39 (*m*, 2 H); 1.83 (*t*, J = 6.5). ^{13}C-NMR ((D$_6$)DMSO): 171.94, 127.07, 106.88, 106.21, 63.98, 33.42, 30.41, 21.40.

2-Chloro-4,7-dihydrobenzothiazol-6(5H)-one (**15**). A soln. of **9** (9.6 g, 41.4 mmol) in 5% aq. HCl soln./dioxane (83 ml each) was stirred at 90° under Ar for 18 h. After cooling and evaporation of most of the solvent, the pH was adjusted to 7–8 with sat. $NaHCO_3$ soln. and the precipitate taken up in CH_2Cl_2. The org. phase was evaporated with silica gel (50 g) and the residue filtered over silica gel (75 g, AcOEt/hexane 1:3). Evaporation to a small volume yielded yellowish crystals (5.14 g, 66%) in two fractions. An anal. sample of **15** was recrystallized from boiling hexane. Off-white needles. M.p. 104–105°. IR (KBr): 1699, 1441, 1406, 1061, 970. ^{1}H-NMR: 3.57 (*t*, J = 1.5, 2 H); 3.16 (*tt*, J = 1.5, 7, 2 H); 2.77 (*t*, J = 7, 2 H). ^{13}C-NMR: 204.87, 150.49, 148.32, 127.21, 38.63, 37.41, 25.47. MS: 189, 187 (15, 42, M^+); 158, 156; 147, 145 (37, 100); 124; 110; 97; 84. Anal. calc. for C_7H_6ClNOS (187.64): C 44.81, H 3.22, N 7.46; found: C 44.80, H 3.18, N 7.39.

Methyl 2-Chloro-4,5-dihydro-6-hydroxybenzothiazole-7-carboxylate (**17**). Lithium diisopropylamide (LDA) was prepared by adding dropwise 1.6M BuLi in hexane (19 ml, 30 mmol) to (i-Pr)$_2$NH (4.6 ml, 33 mmol) in THF (40 ml) at −78° and stirring at 0° for 30 min. After recooling to −78°, a soln. of **15** (5.14 g, 27.4 mmol) in THF (40 ml) was added dropwise in 10 min. The mixture was stirred for 45 min, hexamethylphosphoric triamide (HMPA; 4.8 ml, 27.6 mmol) and methyl cyanoformate (2.7 ml, 34 mmol) were added dropwise with a 10-min interval, and the mixture was kept at −78° for another 30 min. Then sat. aq. NH_4Cl soln. (20 ml) was added, the mixture thawed, THF removed by partial evaporation, and the mixture extracted with CH_2Cl_2 (2 × 50 ml). The org. phase was adsorbed on silica gel (30 g) and subjected to CC (AcOEt/toluene 1:12, 1:8, 1:6, then 1:4): **17** (3.19 g, 47%). Light-yellow solid. The anal. sample was recrystallized from boiling hexane. R_f (AcOEt/toluene 1:9) *ca.* 0.42. M.p. 122°. IR (KBr): 1653, 1595, 1437, 1217, 1055, 835. ^{1}H-NMR: 12.65 (br., 1 H); 3.91 (*s*, 3 H); 3.00 (*t*, J = 8.5, 2 H); 2.80 (*t*, J = 8.5, 2 H). ^{13}C-NMR: 175.21, 168.87, 147.93, 142.11, 125.70, 95.78, 52.21, 29.40, 23.41. MS: 247, 245 (11, 37, M^+); 215, 213 (37, 100); 187, 185; 159, 157; 96. Anal. calc. for $C_9H_8ClNO_3S$ (245.68): C 44.00, H 3.28, N 5.70; found: C 44.09, H 3.09, N 5.64.

6-(Ethylenedioxy)-4,5,6,7-tetrahydrobenzothiazole (**21**). A soln./suspension of **9** (6.46 g, 27.9 mmol) and anh. NaOAc (2.29 g, 27.9 mmol) in MeOH (130 ml) was hydrogenated over 10% Pd/C (0.69 g) under a pressure of 4.5 bar for 10 h. The mixture was concentrated and the residue filtered over silica gel (70 g) of which the 4th part had been saturated with NH_3 gas (AcOEt/hexane 1:1): **21** (5.65 g, 102%). Colorless oil. The anal. sample was obtained by bulb-to-bulb distillation (oven 125–130°/0.06 Torr). IR (film): 1414, 1127, 1061, 1038, 947, 853. ^{1}H-NMR: 8.61 (*s*, 1 H); 4.05 (*s*, 4 H); 3.07–3.00 (*m*, 4 H); 2.04 (*t*, J = 7, 2 H). ^{13}C-NMR: 150.80, 150.13, 126.10, 108.39, 64.79, 33.97, 31.74, 24.72. MS: 197 (100, M^+), 182, 125, 111, 97, 86 (93).

4,7-Dihydrobenzothiazol-6(5H)-one (**22**). A soln. of **21** (5.65 g, 28.6 mmol) in 5% aq. HCl soln. (65 ml) was refluxed under Ar for 7 h. After cooling, ice and sat. $NaHCO_3$ soln. (400 ml) were added, and the product was extracted into CH_2Cl_2 (5 × 50 ml). Drying ($MgSO_4$) and filtration over a short plug of silica gel (Et_2O) furnished **22** (4.04 g, 92%). Light-yellow waxy solid. The anal. sample was purified by bulb-to-bulb distillation (oven 100°/0.08 Torr). IR (film): 1723, 1715, 1416, 1279, 1177, 882. ^{1}H-NMR: 8.70 (*s*, 1 H); 3.67 (*s*, 2 H); 3.26 (*tt*, J = 1.5, 7, 2 H); 2.79 (*t*, J = 7, 2 H). ^{13}C-NMR: 206.35, 151.90, 150.18, 125.30, 38.69, 37.61, 25.25. MS: 153 (100, M^+), 125, 124, 111 (100), 97, 84. Anal. calc. for C_7H_7NOS (153.20): C 54.88, H 4.61, N 9.14; found: C 55.33, H 4.77, N 9.06.

Methyl 4,5-Dihydro-6-hydroxybenzothiazole-7-carboxylate (**23**). A suspension of KH (3.36 g, 90.5 mmol) in dry dimethyl carbonate (140 ml) was heated to reflux under Ar. A soln. of **22** (5.16 g, 33.7 mmol) in dry dimethyl carbonate (60 ml) was added dropwise within 10 min. The red suspension was refluxed for 4.7 h, cooled, and cautiously hydrolyzed with MeOH (10 ml), followed by 20% NH_4Cl soln. (40 ml). After partial evaporation, the residue was partitioned between H_2O (200 ml) and CH_2Cl_2 (100 + 3 × 30 ml). The org. phases were concentrated, filtered over a short plug of silica gel (AcOEt), and purified by CC (AcOEt/hexane 1:2, then 1:1): **23** (3.93 g, 55%) as a yellow solid, followed by very impure **22** (1.35 g). An anal. sample of **23** was obtained by recrystallization from boiling hexane. M.p. 70.5–71.5°. IR (film): 1651, 1589, 1445, 1240, 1221. ^{1}H-NMR: 12.75 (*s*, 1 H); 8.50 (*s*, 1 H); 3.93 (*s*, 3 H); 3.11 (*t*, *J* = 8.5, 2 H); 2.82 (*t*, *J* = 8.5, 2 H). ^{13}C-NMR: 175.45, 169.45, 149.26, 145.19, 123.80, 96.14, 52.05, 29.74, 23.38. Anal. calc. for $C_9H_9NO_3S$ (211.24): C 51.17, H 4.29, N 6.63; found: C 51.15, H 4.22, N 6.65.

*Methyl 5,6,7,8-Tetrahydro-6-hydroxy-7-methyl-10-oxo-5,9-methanocycloocta[*d*]thiazole-9(4*H*)-carboxylate* (**24**). Into a soln. of **23** (1.07 g, 5.06 mmol) and 1,1,3,3-tetramethylguanidine (125 µl, 1.0 mmol) in CH_2Cl_2 (15 ml) which was cooled in an acetone/CO_2 bath was vacuum-transferred methacrolein (95% purity; 1.4 ml, 16 mmol). The mixture was kept at r.t. for 24 h, then evaporated, and the residue was filtered over silica gel (AcOEt/hexane 1:1 for forerun, then AcOEt): **24** (1.36 g, 95%). Light-yellow foam. IR (film): 1742, 1267. ^{1}H-NMR (complex; 3 major diastereoisomers): 8.79, 8.78, 8.77 (each *s*, H–C(2)); 3.86, 3.85, 3.81 (each *s*, MeO); 1.05, 1.03, 0.90 (each *d*, *J* = 7, Me–C(7)). MS: 281 (46, M^+), 249, 224, 194, 164, 136, 86, 84, 49 (100). HR-MS: 281.0708 (M^+, $C_{13}H_{15}NO_4S$, calc. 281.0722).

*Methyl 5,6,7,8-Tetrahydro-7-methyl-6-[(methylsulfonyl)oxy]-10-oxo-5,9-methanocycloocta[*d*]thiazole-9(4*H*)-carboxylate* (**25**). To a soln. of **24** (1.32 g, 4.69 mmol), 4-(dimethylamino)pyridine (DMAP; 28 mg, 0.23 mmol), and Et_3N (0.92 ml, 6.6 mmol) in CH_2Cl_2 (20 ml) was added dropwise with ice cooling within 20 min $MeSO_2Cl$ (0.47 ml, 6.1 mmol) in CH_2Cl_2 (3 ml). Stirring was continued for 20 min at 0° and for 3 h at r.t. After evaporation, CC (AcOEt/hexane 1:2, then AcOEt) yielded **24** (1.29 g, 76%). Light-yellow foam. IR (film): 1746, 1732, 1358, 1262, 1175, 957, 943, 914. ^{1}H-NMR (complex, 2 major and at least 1 minor diastereoisomer): 8.81, 8.79 (each *s*, H–C(2)); 4.89 (minor), 4.75 (major), 4.62 (major; each *dd*, *J* = 5 and 11, 4.5 and 8, and 5 and 11, resp., H–C(6)); 3.87, 3.86, 3.83 (each *s*, MeO); 3.11, 3.09, 3.08 (each *s*, MeS); 1.09, 0.94 (each *d*, *J* = 7, Me–C(7)). MS: 359 (47, M^+), 300, 280, 263, 236, 235, 220, 176 (100), 136. HR-MS: 359.0508 (M^+, $C_{14}H_{17}NO_6S_2$, calc. 359.0497).

*Methyl 5,8-Dihydro-7-methyl-10-oxo-5,9-methanocycloocta[*d*]thiazole-9(4*H*)-carboxylate* (**26**). A soln. of **25** (3.87 g, 10.8 mmol) in dry 2,4,6-collidine (60 ml) was stirred under N_2 at 165° for 16 h. After cooling, the volatiles were pumped off, and the residue was taken up in a small volume of CH_2Cl_2 and chromatographed (silica gel, AcOEt/hexane 2:3, then 7:3). Residual collidine was removed by drying *i.v.* at 60°. The resulting amber glass (1.81 g) was seeded and the resulting semisolid triturated in a mortar with AcOEt/hexane 1:9, filtered with suction, washed with the same solvent, and dried *i.v.*: **26** (1.38 g, 49%). Amber solid. The colorless anal. sample was obtained by bulb-to-bulb distillation (oven 160°/0.1 Torr) and recrystallization from boiling AcOEt/hexane 1:15. M.p. 92–94°. IR (film): 1746, 1730, 1433, 1416, 1273, 1250. ^{1}H-NMR: 8.77 (*s*, 1 H); 5.44 (narrow *m*, 1 H); 3.82 (*s*, 3 H); 3.46, 2.59 ('*q*', *AB*, *J* = 17.5, *A* part br., 2 H); 3.34, 3.26 ('*q*', *AB*, *J* = 16.5, *A* and *B* part *d*, *J* = 5 and 1.5, resp., 2 H); 3.17 (narrow *m*, 1 H); 1.65 (*s*, 3 H). ^{13}C-NMR: 204.96, 169.90, 153.28, 149.32, 133.70, 130.75, 123.36, 57.85, 52.94, 45.86, 44.74, 34.16, 22.94. MS: 263 (34, M^+), 231, 220, 203, 176 (100). Anal. calc. for $C_{13}H_{13}NO_3S$ (263.31): C 59.30, H 4.98, N 5.32; found: C 59.21, H 5.03, N 5.29.

*Methyl (*Z*)-10-Ethylidene-5,8-dihydro-7-methyl-5,9-methanocycloocta[*d*]thiazole-9(4*H*)-carboxylate* (**27**). To a stirred suspension of $EtPPh_3Br$ (8.05 g, 21.7 mmol) in dry Et_2O (80 ml) was added dropwise under Ar at 0° 1.6M BuLi in hexane (13.0 ml, 20.8 mmol). After 40 min at r.t., **26** (1.43 g, 5.43 mmol) in Et_2O (30 ml) was added dropwise at r.t. within 15 min. Stirring was continued for 20 min, then H_2O (5 ml) and 20% NH_4Cl soln. (25 ml) were added with ice cooling. The aq. phase was extracted with Et_2O (3 × 50 ml). Drying ($MgSO_4$) of the extract, evaporation, and CC (AcOEt/hexane 1:3, then 1:1) yielded **27** (728 mg, 49%; (*E*/*Z*) 1:4). Oil. IR (film): 2913, 1730, 1433, 1414, 1252, 845, 756. ^{1}H-NMR ((*Z*)-isomer only): 8.66 (*s*, 1 H); 5.55 (*q*, *J* = 7, 1 H); 5.40 (narrow *m*, 1 H); 3.77 (*s*, 3 H); *ca.* 3.15–3.0 (*m*, 3 H); 2.88 (*d*, *J* = 14.5, 1 H); 2.25 (*d*, *J* = 17, 1 H); 1.57 (*s*, 3 H); 1.51 (*d*, *J* = 7, 3 H). ^{13}C-NMR ((*Z*)-isomer only): 175.31, 151.13, 150.71, 135.26, 132.49, 125.36, 116.99, 52.50, 48.95, 44.38, 43.51, 33.76, 22.75, 12.36 (1 C not detected). MS: 275 (9, M^+), 260, 216 (100). HR-MS: 275.0985 (M^+, $C_{15}H_{17}NO_2S$, calc. 275.0980).

*Methyl (*E*)-10-Ethylidene-5,8-dihydro-7-methyl-5,9-methanocycloocta[*d*]thiazole-9(4*H*)-carboxylate* (**28**). A soln. of **27** (727 mg, 2.64 mmol; (*E*/*Z*) 1:4), thiophenol (0.54 ml, 5.3 mmol), and AIBN (435 mg, 2.65 mmol) in toluene (10 ml) was stirred under N_2 at 90° for 11 h. Amounts of PhSH and AIBN equal to the initial ones were added twice, and the reaction was continued for 9 and 13 h, resp. ^{1}H-NMR control: (*E*/*Z*) 5:1, 17:1, and 18:1 after 11, 20, and 33 h. Direct CC (hexane, then AcOEt/hexane 1:3) gave crude oily **28** (779 mg) still exhibiting weak ^{1}H-NMR signals for PhS groups. IR (film): 2932, 1732, 1433, 1414, 1248. ^{1}H-NMR ((*E*)-isomer only): 8.66 (*s*,

1 H); 5.40 (br. *d*, *J* = 5, 1 H); 5.15 (*q*, *J* = 7, 1 H); 3.81 (*s*, 3 H); 3.66 (narrow *m*, 1 H); 3.10, 2.18 ('*q*', *AB*, *J* = 17, *A* part br., 2 H); 3.02, 2.93 ('*q*', *AB*, *J* = 16, *A* part *dd*, *J* = 1, 5, *B* part *d*, *J* = 2, 2 H); 1.71 (*d*, *J* = 7, 3 H); 1.56 (*s*, 3 H). ^{13}C-NMR ((*E*)-isomer only): 173.91, 151.58, 150.60, 136.49, 132.62, 123.75, 115.57, 64.74, 52.52, 44.32, 33.51, 32.59, 29.40, 23.44, 22.77. MS: 275 (5, M^+), 260, 216 (100). HR-MS: 275.0962 (M^+, $C_{15}H_{17}NO_2S$, calc. 275.0980).

(E)-10-Ethylidene-5,8-dihydro-7-methyl-5,9-methanocycloocta[d]thiazole-9(4H)-carboxylic Acid (**29**). A soln. of **28** (611 mg, 2.22 mmol) in THF and MeOH (4.5 ml each) was stirred for 8 h at r.t. with 1M aq. NaOH (4.45 ml). After addition of H_2O and brine (150/20 ml), neutral materials were removed by washing with Et_2O (2 × 75 ml). The aq. phase was acidified with 0.5M H_3PO_4 (18 ml) and extracted with CH_2Cl_2 (3 × 50 ml). Drying ($MgSO_4$), evaporation, and drying *i.v.* gave **29** (486 mg, 90% over 2 steps) as a yellowish foam which was satisfactory for use in the next step. IR (film): 2928, 1713, 1412, 1250, 737. ^{1}H-NMR: 8.82 (*s*, 1 H); *ca.* 8.65 (very br., 1 H); 5.45 (*q*, *J* = 6.5, 1 H); 5.40 (narrow *m*, 1 H); 3.68 (narrow *m*, 1 H); 3.13, 2.22 ('*q*', *AB*, *J* = 17, *A* part br., 2 H); 3.04, 2.96 ('*q*', *AB*, *J* = 16, *A* and *B* part *d*, *J* = 5 and 2, resp., 2 H); 1.74 (*d*, *J* = 6.5, 3 H); 1.58 (*s*, 3 H). ^{13}C-NMR: 176.73, 152.42, 150.19, 135.88, 133.20, 132.75, 123.78, 116.02, 52.55, 44.41, 33.27, 32.42, 22.84, 12.93. MS: 261 (32, M^+), 246, 216 (100). HR-MS: 261.0841 (M^+, $C_{14}H_{15}NO_2S$, calc. 261.0824).

Methyl (E)-10-Ethylidene-5,8-dihydro-7-methyl-5,9-methanocycloocta[d]thiazole-9(4H)-carbamate (**30**). A soln. of **29** (476 mg, 1.82 mmol), Et_3N (254 µl, 1.82 mmol), and diphenyl azidophosphate (392 µl, 1.82 mmol) in PhCl (5.5 ml) was heated under N_2 to 90° for 5 h. After addition of dry MeOH (11 ml), the mixture was refluxed under N_2 for 8 h. The volatiles were evaporated, and CC (AcOEt/hexane 2:3, then 1:1) of the residue gave **30** (399 mg, 75%) as an off-white foam. IR (film): 3306, 2928, 1723, 1537, 1248, 1055, 731. ^{1}H-NMR: 8.61 (*s*, 1 H); 5.43 (narrow *m*, 1 H); 5.39 (*q*, *J* = 7, 1 H); 5.31 (br. *s*, 1 H); 3.73 (narrow *m*, 1 H); 3.65 (br. *s*, 3 H); 3.00, 2.88 ('*q*', *AB*, *J* = 16, both parts *d*, *J* = 4.5 and 2, resp., 2 H); 2.63, 2.45 ('*q*', *AB*, *J* = 16, *A* part very br., *B* part br., 2 H); 1.73 (*d*, *J* = 7, 3 H); 1.55 (*s*, 3 H). ^{13}C-NMR: 154.9 (br.), 150.90, 150.77, 136.32, 135.99, 132.14, 124.84, 112.84, 57.71, 52.13, 47.8 (br.), 34.06, 33.12, 22.62, 12.67. MS: 290 (19, M^+), 275, 243, 215, 200 (100), 192. HR-MS: 290.1089 (M^+, $C_{15}H_{18}N_2O_2S$, calc. 290.1078).

Methyl (E)-2-Chloro-10-ethylidene-5,8-dihydro-7-methyl-5,9-methanocycloocta[d]thiazole-9(4H)-carbamate (**31**). To a soln. of **30** (155 mg, 534 µmol) in dry THF (3 ml) was added dropwise at −78° under Ar 1.5M BuLi in hexane (0.89 ml, 1.33 mmol). The resulting suspension of the dilithio derivative was stirred at −78° for 30 min, after which period C_2Cl_6 (0.38 g, 1.6 mmol) in THF (3 ml) was added dropwise within 10 min. The temp. was allowed to rise to −10° within 20 min, whereafter 20% NH_4Cl soln. (1 ml) was added. After partial evaporation, H_2O (10 ml) was added and the product extracted into CH_2Cl_2 (3 × 10 ml). Evaporation was followed by CC (AcOEt/hexane 1:4): **31** (156 mg, 90%). Colorless foam which slowly crystallized on standing. M.p. 174–179°. IR (film): 3308, 2932, 1713, 1532, 1429, 1263, 1242, 1078, 733. ^{1}H-NMR: 5.42 (br. *dd*, *J* = 1.5, 5, 1 H); 5.36 (*q*, *J* = 7, 1 H); 5.21 (br. *s*, 1 H); 3.66 (br. *s*, 1 + 3 H); 2.90, 2.75 ('*q*', *AB*, *J* = 16, both parts *d*, *J* = 5 and 2, resp., 2 H); 2.49 (br. *s*, 2 H); 1.72 (*d*, *J* = 7, 3 H); 1.58 (*s*, 3 H). ^{13}C-NMR: 154.9 (br.), 149.60, 148.87, 138.16, 135.32, 132.20, 124.81, 113.06, 57.48, 52.24, 47.7 (br.), 33.86, 33.06, 22.60, 12.62. MS: 326, 324 (7, 17, M^+); 311, 309; 289; 279, 277; 251, 249; 236, 234 (41, 100), 192. Anal. calc. for $C_{15}H_{17}ClN_2O_2S$ (324.83): C 55.47, H 5.28, N 8.62; found: C 55.68, H 5.20, N 8.34.

(E)-9-Amino-10-ethylidene-4,5,8,9-tetrahydro-7-methyl-5,9-methanocycloocta[d]thiazol-2(3H)-one (**3a**). A soln. of **31** (40.7 mg, 125 µmol) in 30% NaOMe/MeOH (1 ml) was heated under N_2 in a resealable tube to 90° for 25 h. After cooling, 20% NH_4Cl soln. was added to adjust the pH to *ca.* 6. The soln. was extracted with CH_2Cl_2 (5 × 10 ml), and the extracts were dried ($MgSO_4$) and evaporated. The resulting glass was taken up in a small volume of hot AcOEt; crystallization began at r.t. and was completed at −20°: slightly impure, amber **3a** (25.0 mg, 80%). One recrystallization from AcOEt yielded yellowish crystals (20.1 mg, 65%). M.p. 183–186° (dec.). IR (KBr): 3360, 3136, 3028, 2901, 1632, 1439, 1206, 864, 833, 637, 592. ^{1}H-NMR ($CDCl_3$ + few drops of CD_3OD): 5.47 (*q*, *J* = 7, 1 H); 5.41 (br. *d*, *J* = 5.5, 1 H); 3.62 (narrow *m*, 1 H); 2.85 (position variable, br. *s*, NH_2, NH); 2.55, 2.30 ('*q*', *AB*, *J* = 16, *A* part *dd*, *J* = 1.5, 5, *B* part *d*, *J* = 1.5, 2 H); 2.32, 2.05 ('*q*', *AB*, *J* = 17, *B* part br., 2 H); 1.70 (*d*, *J* = 7, 3 H); 1.64 (*s*, 3 H). ^{13}C-NMR (same solvent): 175.18, 141.21, 134.29, 127.87, 123.61, 119.26, 111.25, 54.25, 46.66, 32.95, 30.54, 22.52, 12.16. MS: 248 (100, M^+), 233, 219, 205, 193. Anal. calc. for $C_{13}H_{16}N_2OS$ (248.34): C 62.87, H 6.49, N 11.28; found: C 62.36, H 6.23, N 10.99.

REFERENCES

[1] J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi, *Can. J. Chem.* **1986,** *64,* 837; see also W. A. Ayer, L. M. Browne, H. Orszanska, Z. Valenta, J.-S. Liu, *ibid.* **1989,** *67,* 1538.

[2] A. P. Kozikowski, E. Thiels, X. C. Tang, I. Hanin, in 'Advances in Medicinal Chemistry', Eds. B. E. Maryanoff and C. A. Maryanoff, JAI Press, Greenwich, CT, 1992, Vol. 1, pp. 175–205, and ref. cit. therein.

[3] Y. Xia, A. P. Kozikowski, *J. Am. Chem. Soc.* **1989,** *111,* 4116; A. P. Kozikowski, E. R. Reddy, C. P. Miller, *J. Chem. Soc., Perkin Trans. 1* **1990,** 195; F. Yamada, A. P. Kozikowski, E. R. Reddy, Y.-P. Pang, J. H. Miller, M. McKinney, *J. Am. Chem. Soc.* **1991,** *113,* 4695.

[4] A. P. Kozikowski, Y. Xia, E. R. Reddy, W. Tückmantel, I. Hanin, X. C. Tang, *J. Org. Chem.* **1991,** *56,* 4636.

[5] A. P. Kozikowski, G. Campiani, P. Aagaard, M. McKinney, *J. Chem. Soc., Chem. Commun.* **1993,** 860; G. Campiani, L.-Q. Sun, A. P. Kozikowski, P. Aagaard, M. McKinney, *J. Org. Chem.* **1993,** *58,* 7660.

[6] L. Qian, R. Ji, *Tetrahedron Lett.* **1989,** *30,* 2089; W.-P. Chen, F.-Q. Yang, *Chinese J. Pharmaceuticals* **1991,** *22,* 256; *Chinese J. Med. Chem.* **1992,** *2,* 34.

[7] J.-S. Liu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, B.-F. Qi, Y.-L- Zhu, *Acta Chim. Sin.* **1986,** *44,* 1035; Y. Xia, E. R. Reddy, A. P. Kozikowski, *Tetrahedron Lett.* **1989,** *30,* 3291; A. P. Kozikowski, C. P. Miller, F. Yamada, Y.-P. Pang, J. H. Miller, M. McKinney, R. G. Ball, *J. Med. Chem.* **1991,** *34,* 3399.

[8] A. P. Kozikowski, G. Campiani, unpublished results.

[9] A. P. Kozikowski, G. Campiani, W. Tückmantel, *Heterocycles,* in press.

[10] K. Gewald, H. Spies, R. Mayer, *J. Prakt. Chem.* **1970,** *312,* 776.

[11] M. P. Doyle, B. Siegfried, J. F. Dellaria, Jr., *J. Org. Chem.* **1977,** *42,* 2426.

[12] S. Kwiatkowski, A. Wolinski, *Monatsh. Chem.* **1984,** *115,* 869.

[13] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1983,** *24,* 5428; K. E. Henegar, J. D. Winkler, *ibid.* **1987,** *28,* 1051.

[14] Z.-I. Horii, T. Imanishi, S.-W. Kim, I. Ninomiya, *Chem. Pharm. Bull.* **1968,** *16,* 1918.

[15] J. Metzger, B. Koether, *Bull. Soc. Chim. Fr.* **1953,** 708; J. Beraud, J. Metzger, *ibid.* **1962,** 2072.

[16] M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek, S. Mans, *Chem. Ber.* **1985,** *118,* 1421.

[17] D. S. Sgoutas, F. A. Kummerow, *Lipids* **1969,** *4,* 283; U. T. Bhalerao, H. Rapoport, *J. Am. Chem. Soc.* **1971,** *93,* 4835.

[18] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972,** *94,* 6203.

[19] J. Kattenberg, E. R. De Waard, H. O. Huisman, *Tetrahedron* **1973,** *29,* 4149; *ibid.* **1974,** *30,* 463.

[20] Y. Ashani, J. O. Peggins, III, B. P. Doctor, *Biochem. Biophys. Res. Commun.* **1992,** *184,* 719.