26. The Synthesis of 3-Acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles

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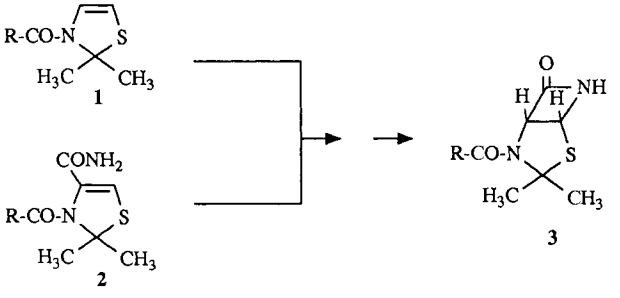
Acylation of 2,5-dihydro-2,2-dimethyl-1,3-thiazoles leads to 3-acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles as potential starting materials for the total synthesis of racemic cephalosporins.

1. Introduction. – In the first total synthesis of cephalosporin [1], we encountered initially considerable difficulties in the preparation of the crucial β-lactam intermediate **3** (R = *t*-BuO). In one of the various approaches to **3** investigated, we prepared 3-acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles **1** and 3-acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxamides **2** in order to try to convert **1** *via* cycloaddition or **2** *via* cyclization to **3** [2] [3] (*Scheme 1*).

Scheme 1



After completing our studies on 2-acyl-2,3-dihydro-1,3-thiazoles in 1965, we found out that a single 3-acyl-2,3-dihydro-2-methyl-1,3-thiazole had been prepared previously by *Sheehan et al.* [4]. Subsequently, the acylation of 2,5-dihydro-2-methyl-1,3-thiazole [5] as well as the formylation of methyl 2,5-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate to the corresponding 3-acyl-2,3-dihydro-1,3-thiazoles [6] were described.

2. 3-Acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles. – Reaction of 2,5-dihydro-2,2-dimethyl-1,3-thiazole **4**, which is readily available by condensation of mercaptoacetaldehyde dimer with NH_3 and acetone [7], with Ac_2O/Et_3N in boiling toluene afforded 3-acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole **1a** in 90% yield (*Scheme 2*). On using $AcCl/Et_3N$, 10% of the bicylic compound **5** was obtained, which could be prepared in

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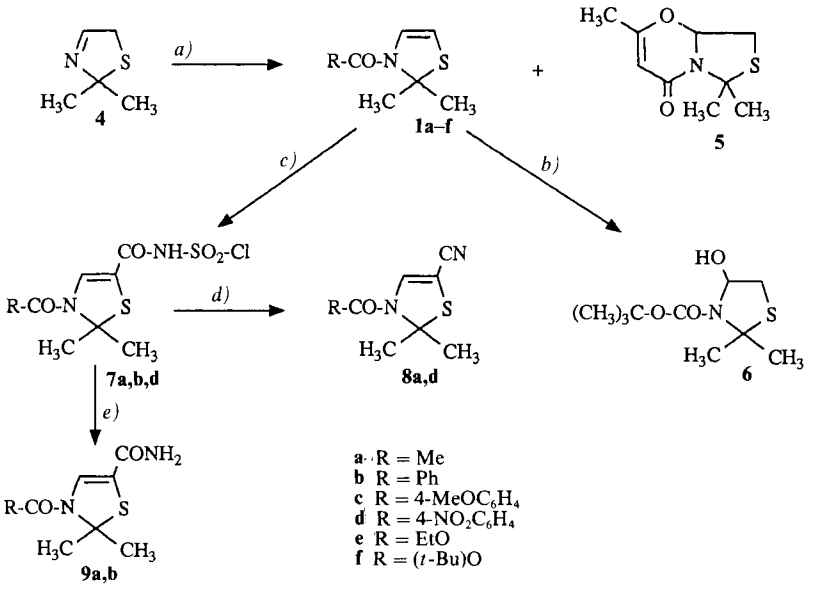
Scheme 2



a) Acylation (see text). *b)* $H_2O/CDCl_3$. *c)* $ClSO_2NCO$. *d)* Et_3N. *e)* H_2O/CH_2Cl_2.

80% yield by cycloaddition of diketene to **4**. Analogous condensations of diketene to acyclic and cyclic *Schiff* bases have been already reported [8] [9].

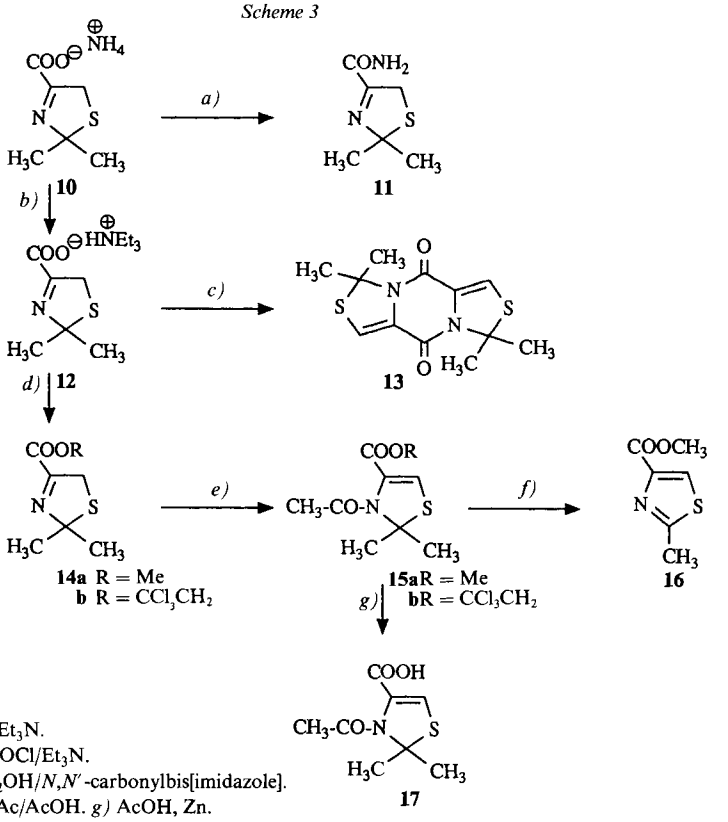
The reaction of 2,5-dihydro-2,2-dimethyl-1,3-thiazole **4** with benzoyl chloride, 4-methoxybenzoyl chloride as well as 4-nitrobenzoyl chloride and Et_3N in CH_2Cl_2 afforded the corresponding 3-aroyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles **1b–d** in 80–90% yield. Heating of **4** with diethyl dicarbonate/Pr_3N in boiling toluene furnished 90% of **1e**. As there was as yet no di(*tert*-butyl) dicarbonate commercially available, **4** was converted by NaH in 1,2-dimethoxyethane at 70° into the corresponding ambident anion, which was treated with (*tert*-butoxy)carbonyl azide to give in 13% yield the urethane **1f**. Reaction of the same ambident anion with ethyl chlorocarbonate gave the aforedescribed **1e** likewise in only 20% yield.

On standing in $CDCl_3$ in the presence of H_2O, **1f** was cleanly converted into the 4-hydroxy compound **6**, which was obviously formed by protonation at the 5-position followed by addition of H_2O to the 4-position. In view of this electrophilic attack at C(5) of **1f**, it was no surprise that reaction of the various 3-acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazoles **1** (including **1d**) with chlorosulfonyl isocyanate [10] resulted in exclusive electrophilic attack at the 5-position of these cyclic enamides to afford the corresponding 5-[*N*-(chlorosulfonyl)carboxamides] **7**, which could be converted by Et_3N to the corresponding nitriles **8** [3] or saponified to the corresponding carboxamides **9**.

Since cycloaddition of reactive isocyanates to **1** did not give the desired regioisomer (corresponding to **3**), no attempts were made to isolate any intermediate β-lactam on addition of chlorosulfonyl isocyanate to **1** and reductive removal of the chlorosulfonyl group at low temperature.

3. 3-Acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylates. – We thus turned our attention to the preparation of 3-acyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxamides as starting material for the β-lactam **3** (*Scheme 3*). Ammonium salt **10**, which can be prepared from 3-mercaptopyruvic acid, acetone, and NH_3 [11], was dehydrated by ethyl chlorocarbonate/Et_3N in 35% yield to the amide **11**. Treatment of **10** with Et_3N furnished the triethylammonium salt **12**, which was dehydrated by various agents such as Ac_2O/Et_3N or ethyl chlorocarbonate/Et_3N in low yield to the crystalline tricylic com-

Scheme 3



a) EtOCOCl/Et_3N. *b)* Et_3N.
c) Ac_2O/Et_3N or EtOCOCl/Et_3N.
d) Me_2SO_4 or CCl_3CH_2OH/*N,N'*-carbonylbis[imidazole].
e) Ac_2O/Et_3N. *f)* NaOAc/AcOH. *g)* AcOH, Zn.

pound **13**. Esterification of **12** with Me_2SO_4 afforded the corresponding ester **14a**, which could be acetylated to **15a**. Since **15a** gave on attempted transesterfication with NaOAc/AcOH *via* ring cleavage of **15a** and recyclization in nearly 90% yield the thiazole **16**, the trichloroethyl ester **14b** was prepared from **12** with CCl_3CH_2OH and *N,N'*-carbonylbis-[imidazole] in 63% yield. *N*-Acetylation of **14b** gave **15b** in 90% yield. First experiments showed that **15b** could be cleaved reductively [1] to the free acid **17**, which was then to be converted to the corresponding amide **2** (R = Me). But the optically active β-lactam **3** (R = *t*-BuO) had been prepared in the meantime by a different route starting from L-cysteine [1] so that the present racemic approach was abandoned.

Experimental Part

General. UV spectra: λ_{max} (ε) in nm. IR spectra: in cm^{-1}. ^{1}H-NMR spectra: δ in ppm rel. to TMS (= 0 ppm), J in Hz.

1. *2,5-Dihydro-2,2-dimethyl-1,3-thiazole* (**4**). A suspension of 1,4-dithiane-2,5-diol (m.p. 130–139°; 160 g, 1.05 mol) in acetone (5000 ml) was cooled with ice and a stream of dry NH_3 gas introduced with stirring. After 15 min, the ice-bath was removed whereupon the temp. rose to 25°. After 1.5 h of NH_3 treatment, the mixture had become nearly homogeneous. After filtration and washing of some insoluble material with acetone, the filtrate was concentrated to 400 ml, Et_2O (*ca.* 1.5 l) added as well as anh. $MgSO_4$. After filtration and concentration of the filtrate, the residue was distilled over a short *Vigreux* column at 42–43°/12 Torr: 194 g (80%) of colorless **4**. ^{1}H-NMR (60 MHz, CCl_4): 1.62 (*s*, 6 H); 3.99 (*d*, J = 2, 2 H); 7.19 (*t*, J = 2, 1 H).

2. *3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole* (**1a**). A mixture of **4** (5.67 ml, 0.05 mol), Ac_2O (9.45 ml, 0.1 mol), and Et_3N (15.3 ml, 0.11 mol) in abs. toluene (150 ml) was refluxed for 16 h with exclusion of humidity. A further quantity of Et_3N (3 ml), was added and heating continued for further 24 h. After pouring the crude mixture on ice containing 2N H_2SO_4 (50 ml) and stirring, the toluene layer was separated, washed with ice-cold 2N H_2SO_4 (50 ml), ice-water (2 × 30 ml) and sat. $NaHCO_3$ soln. (2 × 50 ml), dried ($MgSO_4$), and evaporated, and the residue dissolved in pentane (200 ml), filtered, and evaporated. The crude material (9.15 g) was chromatographed (300 g of neutral alumina (act. II), benzene). After 300 ml of forerun, the next 600 ml of yellowish eluate afforded 7.06 g (90%) of pure **1a**, m.p. 48–49°, which crystallized from pentane: big rods of anal. pure **1a**. M.p. 49–50°. UV (cyclohexane): 273 (8050). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.97 (*s*, 6 H); 2.13 (*s*, 3 H); 5.57 (*d*, J = 5, 1 H); 6.17 (*d*, J = 5, 1 H). Anal. calc. for $C_7H_{11}NOS$ (157.24): C 53.47, H 7.05, N 8.91, S 20.39; found: C 53.50, H 7.26, N 8.63, S 20.14.

3. *8,8a-Dihydro-2,6,6-trimethyl-(4H,6H)-thiazolo[4,3-b][1,3]oxazine* (**5**). A soln. of **4** (2.27 ml, 0.02 mol) and freshly distilled diketene (2.522 g, 0.03 mol) in abs. benzene (100 ml) was refluxed for 22 h under N_2. Then a further amount of diketene (2 ml) was added and heating continued for 16 h. After evaporation and codistillation with xylene (30 ml), the crude residue (4.59 g) was chromatographed (150 g of neutral alumina (act. II), benzene, then benzene/AcOEt 19:1): 3.16 g (79.5%) of crystalline **5**. Recrystallization from pentane gave an anal. sample. M.p. 48–50°. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.87 (*s*, 6 H); 1.95 (*d*, J = 1–2, 3 H); 3.3 (*d*, J = 5–6, 2 H); 5.19 (*q*, J = 1–2, 1 H); 5.56 (*t*, J = 5–6, 1 H). Anal. calc. for $C_9H_{13}NO_2$ (199.27): C 54.25, H 6.58, N 7.03, S 16.09; found: C 54.22, H 6.57, N 6.97, S 16.18.

4. *3-Benzoyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole* (**1b**). To a soln. of **4** (9.6 ml, 0.084 mol) and abs. Et_3N 28.4 ml) in abs. CH_2Cl_2 (200 ml), freshly distilled PhCOCl (19.5 ml, 0.168 mol) in CH_2Cl_2 (50 ml) was added at −10° during 70 min. After standing at 0° for 54 h at 0°, the dark mixture was poured on ice-cold sat. $NaHCO_3$ soln. and extracted with CH_2Cl_2. After drying ($MgSO_4$) and evaporation of the extracts, the dark residue (27.0 g) was repeatedly treated with hexane/CH_2Cl_2 to give 24.9 g of extract, which was chromatographed (700 g of neutral alumina (act. III), benzene): 15.073 g (81.8%) of crude crystalline **1b** (m.p. 48–49°). Recrystallization from hexane gave an anal. sample. M.p. 49–49.5°. UV (cyclohexane): 263 (5800), 300 (4550). ^{1}H-NMR (60 MHz, $CDCl_3$): 2,1 (*s*, 6 H); 5.43 (*d*, J = 5, 1 H); 6.09 (*d*, J = 5, 1 H); 7.47 (*m*, 5 H). Anal. calc. for $C_{12}H_{13}NOS$ (219.21): C 65.72, H 5.98, N 6.39; found: C 65.82, H 6.17, N 6.35.

5. *2,3-Dihydro-3-(4-methoxybenzoyl)-2,2-dimethyl-1,3-thiazole* (**1c**) was prepared analogously to **1b** and recrystallized from pentane. M.p. 69.5–70°. UV (cyclohexane): 245 (13000), 284 (6900). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.05 (*s*, 6 H); 3.84 (*s*, 3 H); 5.50 (*d*, J = 5, 1 H); 6.15 (*d*, J = 5, 1 H); 6.9 (*m*, 2 H); 7.52 (*m*, 2 H). Anal. calc. for $C_{13}H_{15}NO_2S$ (249.3): C 62.67, H 6.06, N 5.62; found: C 62.70, H 6.17, N 5.68.

6. *2,3-Dihydro-2,2-dimethyl-3-(4-nitrobenzoyl)-1,3-thiazole* (**1d**) was prepared analogously to **1b** and recrystallized from hexane. M.p. 112–112.5°. UV (cyclohexane): 260 (14200), 360 (1700). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.1 (*s*, 6 H); 5.62 (*d*, J = 5, 1 H); 5.96 (*d*, J = 1 H); 7.69 (*m*, 2 H); 8.30 (*m*, 2 H). Anal. calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C 54.53, H 4.58, S 12.13; found: C 54.54, H 4.82, S 10.72.

7. *Ethyl 2,3-Dihydro-2,2-dimethyl-1,3-thiazole-3-carboxylate* (**1e**). A soln. of **4** (2.26 ml, 0.02 mol), diethyl dicarbonate (4.86 g, 0.03 mol) and Pr_3N (5.68 ml, 0.03 mol) in abs. toluene (100 ml) was refluxed under N_2 for 96 h. Then, a further amount of diethyl dicarbonate (0.02 mol) was added and heating continued for 48 h. After cooling and workup as described for **1b**, the dark residue (3.92 g, 100%) of homogeneous **1e** was redistilled at 54°/0.05–0.1 Torr to give anal. pure **1e**. UV (EtOH): 260 (7200). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.29 (*t*, J = 7, 3 H); 1.9 (*s*, 6 H); 4.22 (*q*, J = 7, 2 H); 5.27 (*d*, J = 5, 1 H); 6.41 (*d*, J = 5, 1 H). Anal. calc. for $C_8H_{13}NO_2S$ (187.27): C 51.31, H 7.00, N 7.48; found: C 50.86, H 6.99, N 7.67.

8. tert-*Butyl 2,3-Dihydro-2,2-dimethyl-1,3-thiazole-3-carboxylate* (**1f**). To a soln. of **4** (4.52 ml, 0.04 mol) in abs. 1,2-dimethoxyethane (70 ml), 50% NaH in oil (2.88 g, 0.06 mol) was added and the mixture refluxed for 40 min, whereupon 1200 ml of H_2 were evolved. After cooling to 22°, a soln. of (*t*-BuO)CON_3 (8.2 ml, 0.06 mol) in abs. 1,2-dimethoxyethane (30 ml) was added under N_2 within 30 min. After heating to 50° for 3 h, the mixture was cooled to +6° and excess dry ice slowly added to neutralize the mixture followed by 100 ml of ice-water. After extraction with benzene (4 × 70 ml), drying ($MgSO_4$), and evaporation, the residual oil (13.0 g) was chromatographed (360 g *Florisil* (60–100 mesh, benzene)). The first 800 ml of benzene eluted 0.903 g of (*t*-BuO)CON_3. The next fractions consisted of 1.08 g (13%) of **1f**, which was distilled at 80°/0.001 Torr to give an anal. sample. UV (EtOH): 263 (24300). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.50 (*s*, 9 H); 1.88 (*s*, 6 H); 5.38 (*d*, *J* = 5, 1 H); 6.36 (*d*, *J* = 5, 1 H). Anal. calc. for $C_{10}H_{17}NO_2S$ (215.32): C 55.78, H 7.96; found: C 55.92, H 7.90.

9. tert-*Butyl 4-Hydroxy-2,2-dimethyl-1,3-thiazolidine-3-carboxylate* (**6**). On standing of an ^{1}H-NMR sample of **1f** in $CDCl_3$, **1f** was hydrated to **6**, which had been obtained by *Gosteli* [12] previously *via* a different route. After recrystallization from pentane, the m.p. was 66°. ^{1}H-NMR (60 MHz, CCl_4): 1.48 (*s*, 9 H); 1.68 (*s*, 3 H); 1.75 (*s*, 3 H); 2.78 (*q*, *J* = 12, 2.5, 1 H); 3.12 (*q*, *J* = 12, 4.5, 1 H); 5.65 (*m*, 1 H). MS: 233 (M^+), 215 ([$M - H_2O$]$^+$), 159 ([$M - H_2O$ – isobutylene]$^+$), 115, 100. Anal. calc. for $C_{10}H_{19}NO_3S$ (233.34): C 51.48, H 8.21, N 6.00; found: C 51.45, H 8.06, N 6.01.

10. *3-Acetyl-*N*-(chlorosulfonyl)-2,3-dihydro-2,2-dimethyl-1,3-thiazole-5-carboxamide* (**7a**). A soln. of **1a** (3.143 g, 0.02 mol) in Et_2O (100 ml) was cooled to −18° and a soln. of *N*-chlorosulfonyl isocyanate (1.92 ml, 0.022 mol) in abs. Et_2O (20 ml) added slowly within 40 min with vigorous stirring, whereupon **7a** precipitated. After 3 h at −15°, the mixture was quickly filtered and the precipitate washed with abs. Et_2O under N_2 to give 5.44 g (91%) of **7a**. M.p. 115–120°. ^{1}H-NMR (60 MHz, CD_3COCD_3): 1.97 (*s*, 6 H); 2.29 (*s*, 3 H); 7.86 (*s*, 1 H). Anal. calc. for $C_8H_{11}ClN_2O_4S_2$ (298.77): C 32.16, H 3.71; found: C 32.96, H 4.06.

11. *3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-5-carbonitrile* (**8a**). To a suspension of **7a** (0.668 g, 0.0025 mol) in abs. MeCN (15 ml), a soln. of abs. Et_3N (3 ml) MeCN (5 ml) was added within 10 min. On stirring for 50 min at −10°, then 45 min at 24°, all the precipitate formed during the reaction passed into soln. After evaporation and extraction of the residue with benzene (20 ml), evaporation gave brown oil (0.6 g), which was chromatographed (84 g *Florisil* (60–100 mesh), CH_2Cl_2). On elution with CH_2Cl_2/AcOEt 8:2→6:4, 0.275 g (67%) of **8a**, m.p. 98–100°, were obtained, which gave on sublimation at 78°/0.005 Torr an anal. sample. M.p. 103.5–104°. UV (cyclohexane): 214 (10000), 323 (9500). IR (CH_2Cl_2): 2220, 1700, 1605. ^{1}H-NMR (60 MHz, CCl_4): 1.98 (*s*, 6 H); 2.16 (*s*, 3 H); 6.96 (*s*). Anal. calc. for $C_8H_{10}N_2OS$ (182.25): C 52.72, H 5.53, N 15.37; found: C 52.61, H 5.54, N 15.47.

12. *3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-5-carboxamide* (**9a**). A suspension of crude **7a** (8.00 g, 0.0267 mol) in 150 ml of H_2O/CH_2Cl_2 1:1 was stirred vigorously for 2 h at 24°. After exhaustive continuous extraction of the aq. phase with CH_2Cl_2 for 48 h, 4.896 g (91.7%) of crystalline **9a** (m.p. 155–157°) were obtained, which gave on recrystallization from benzene an anal. sample. M.p. 156.5–157.5°. UV (EtOH): 329 (9200). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.01 (*s*, 6 H); 2.23 (*s*, 3 H); 7.14 (*s*, 1 H). Anal. calc. for $C_8H_{10}N_2OS$ (182.25): C 52.72, H 5.57, N 15.37; found: C 52.61, H 5.54, N 15.47.

13. *2,3-Dihydro-2,2-dimethyl-3-(4-nitrobenzoyl)-1,3-thiazole-5-carbonitrile* (**8d**). Chlorosulfonyl isocyanate was added at −15° in Et_2O to **1d**, as described for the preparation of **7a**. Subsequent treatment of **7d** with Et_3N in abs. MeCN as described for the preparation of **8a**, gave pure **8d**. M.p. 151–151.5° after recrystallization from hexane. UV (EtOH): 255 (10300), 317 (7500). IR (CH_2Cl_2): 2215, 1680, 1600. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.12 (*s*, 6 H); 6.64 (*s*, 1 H); 7.71 (*d*, *J* = 9, 2 H); 8.35 (*d*, *J* = 9, 2 H). Anal. calc. for $C_{13}H_{11}N_3O_3S$ (289.31): C 53.91, H 3.83, N 14.52; found: C 54.08, H 4.11, N 14.84.

14. *3-Benzoyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-5-carboxamide* (**9b**). Following the procedure for the preparation of **7a** and its conversion to **9a**, addition of chlorosulfonyl isocyanate to **1b** and subsequent hydrolysis with H_2O/CH_2Cl_2 gave **9b**. M.p. 161–162° (benzene). ^{1}H-NMR (60 MHz, $CDCl_3$): 2.1 (*s*, 6 H); 7.12 (*s*, 1 H); 7.48 (*m*, 5 H). Anal. calc. for $C_{13}H_{14}N_2O_2S$ (262.33): C 59.52, H 5.38, N 10.68; found: C 59.59, H 5.35, N 10.60.

15. *Ammonium 2,5-Dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate* (**10**). Mercapto-pyruvic acid was condensed with NH_3 and acetone at −15° in MeOH according to [11] to give crude **10** (m.p. 150–155° (dec.)) in 74% yield, which was obtained pure on recrystallization from MeOH. M.p. 163–165° (dec.). ^{1}H-NMR (60 MHz, D_2O): 1.67 (*s*, 6 H); 4.29 (*s*, 2 H).

16. *2,5-Dihydro-2,2-dimethyl-1,3-thiazole-4-carboxamide* (**11**). A suspension of **10** (3.524 g, 0.03 mol) and Et_3N (4.2 ml, 0.03 mol) in CH_2Cl_2 (175 ml) was treated at 0° with stirring within 10 min with a soln. of ethyl

chloroformate (4.2 ml, 0.044 mol) in CH_2Cl_2 (35 ml). After 66 h at 24° and workup with ice-cold $NaHCO_3$ soln. and CH_2Cl_2, 2.442 g of crude product were obtained, which were crystallized from benzene/cylohexane to give in three crops 1.12 g (35%) of crude yellowish **11** (m.p. 138–141°). A further recrystallization from benzene/cyclohexane furnished an anal. sample. M.p. 141.5–142°. IR (CH_2Cl_2): 3509, 1684, 1563, 851. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.7 (*s*, 6 H); 4.3 (*s*, 2 H). Anal. calc. for $C_6H_{10}N_2OS$ (158.22): C 45.55, H 6.37, N 17.71; found: C 45.73, H 6.45, N 17.62.

17. *3,3,8,8-Tetramethyl-3*H,*5*H,*8*H,*10*H-*bisthiazolo[3,4*-a:*3′,4′*-d*]pyrazine-5,10-dione* (**13**). To a soln. of **10** (8.81 g, 0.05 mol) in MeOH (200 ml), Et_3N (10 ml) was added and stirred for 15 min. After evaporation and codistillation with AcOEt (50 ml), the residue was dissolved in AcOEt (75 ml) and refluxed for 30 min with 4-nitrobenzoyl chloride (8.58 g, 0.05 mol), whereupon the mixture turned dark and a precipitate formed. After stirring for 14 h at 24°, the $Et_3N \cdot HCl$ was filtered and washed with AcOEt. After adding benzene (150 ml), the filtrate was washed with sat. aq. $NaHCO_3$ soln. and subsequently with sat. aq. NaCl soln. After drying ($MgSO_4$), the org. phase gave, on evaporation, 8.873 g of crude product, which was extracted with benzene to give, on concentration, 0.176 g of **13**. The mother liquor was chromatographed (600 g of neutral alumina (act. II), benzene): 0.48 g of **13**. Combined yield of **13**, 0.656 g (4.6%). Recrystallization from MeOH afforded an anal. sample. M.p. 288–289° (in a sealed capillary). UV (EtOH): 270 (4300), 372 (21900). IR ($CHCl_3$): 1653, 1590, 1370, 1287, 1065, 866. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.07 (*s*, 12 H); 6.73 (*s*, 2 H). MS: 282 (M^+), 267, 249, 239, 225, 221, 199, 140, 126, 98, 94, 84, 78, 69, 56, 41. Anal. calc. for $C_{12}H_{14}N_2O_2S_2$ (282.38): C 51.04, H 5.00, N 9.92; found: C 50.85, H 4.85, N 9.93.

18. *Methyl 2,5-Dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate* (**14a**). To a soln. of **10** (26.43 g, 0.15 mol) in MeOH (800 ml), Et(i-Pr)$_2$N (27 g, 0.21 mol) was added and stirred for 15 min. After evaporation and codistillation with abs. toluene (60 ml), the residue was dissolved in dry AcOEt (600 ml) and Me_2SO_4 (14.1 ml, 0.15 mol) added. After stirring for 21 h, the mixture was shaken with ice-cold sat. aq. $NaHCO_3$ soln. (150 ml) and the org. phase diluted with C_6H_6 (600 ml). After separating the layers and washing the org. phase twice with sat. aq. NaCl soln., the combined org. phase was dried ($MgSO_4$) and evaporated, whereupon the reddish brown crude **14a** crystallized spontaneously. On extraction with pentane, pure crystalline **14a**, m.p. 70.5–71.5°, was obtained in several crops. Total yield: 16.02 g (61.6%). IR (CH_2Cl_2): 1724, 1324, 1227, 1078, 847. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.73 (*s*, 6 H); 3.92 (*s*, 3 H); 4.30 (*s*, 2 H). Anal. calc. for $C_7H_{11}NO_2S$ (173.24): C 48.53, H 6.40, N 8.09; found: C 48.23, H 6.44, N 8.20.

19. *2,2,2-Trichloroethyl 2,5-Dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate* (**14b**). A suspension of **10** (7.048 g, 0.04 mol) and Et_3N (6.95 ml, 0.05 mol) in MeOH (200 ml) was stirred for 30 min until practically everything had passed into soln. After evaporation and codistillation with abs. toluene (150 ml), the thus obtained triethylammonium salt **12** was treated with abs. THF (150 ml) and *N,N′*-carbonyl bis[imidazole] (7 g, 0.043 mol), whereupon everything passed rapidly into soln. and the mixture turned dark brown. This brown soln. was added within 20 min to a soln. of imidazole (1.4 g), CCl_3CH_2OH (7 ml, 0.0725 mol), and 50% NaH in oil (0.162 g) in abs. THF (60 ml), which had been stirred until all evolution of H_2 had ceased. After 1.5 h, the clear mixture was evaporated and the residue taken up in Et_2O (100 ml) and H_2O (100 ml). After workup as described under **14a**, the residue was first extracted with CH_2Cl_2/hexane and the combined extract (7.428 g) then with pentane to give 6.47 g (55%) of anal. pure **14b**. M.p. 83.5–84.5°. IR (CH_2Cl_2): 1764, 1736, 1650, 1362, 1307, 1212, 1196, 1142, 1093, 1052, 845, 816. ^{1}H-NMR (60 MHz, CCl_4): 1.72 (*s*, 6 H); 4.25 (*s*, 2 H); 4.85 (*s*, 2 H). Anal. calc. for $C_8H_{10}Cl_3NO_2S$ (290.60): C 33.07, H 3.47, Cl 36.60, S 11.03; found: C 33.39, H 3.29, Cl 37.12, S 11.19.

20. *Methyl 3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate* (**15a**). A mixture of **14a** (10.4 g, 0.06 mol), Ac_2O (17 ml, 0.18 mol), and Et_3N (12.5 ml, 0.09 mol) in abs. toluene (175 ml) was refluxed for 14 h. After evaporation, the residue was codistilled with xylene (2 × 50 ml), then with toluene (50 ml). The crude residue (26 g) was distilled at 80–90°/0.01 Torr to give 11.47 g (89%) of pure **15a**. After chromatography (silica gel, benzene/AcOEt) and distillation, an anal. sample was obtained, which crystallized partly. M.p. 31–34°. UV (EtOH): 222 (6100), 275 (4200), 321 (7850). IR (CH_2Cl_2): 1715, 1667, 1563, 1361, 1220, 1020, 847. ^{1}H-NMR (60 MHz, CCl_4): 1.86 (*s*, 6 H); 1.88 (*s*, 3 H); 6.82 (*s*, 1 H). Anal. calc. for $C_9H_{13}NO_3S$: C 50.22, H 6.09, N 6.51; found: C 49.98, H 6.14, N 6.65.

21. *2,2,2-Trichloroethyl 3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylate* (**15b**). A soln. of **14b** (2.906 g, 0.01 mol), Et_3N (1.52 ml, 0.015 mol), and Ac_2O (2.83 ml, 0.03 mol) in abs. toluene (50 ml) was refluxed for 18 h under exclusion of moisture. After evaporation and codistillation of the residue with xylene (2 × 50 ml), the dark residue (3.248 g) was extracted with CH_2Cl_2/hexane, the combined hexane extract evaporated, and the residue chromatographed (145 g of silica gel). After a forerun with benzene, elution with benzene/AcOEt 9:1 and 8:2 gave 2.598 g (78.1%) of pure **15b**. Crystallization from pentane yielded an anal. pure sample. M.p. 54.5–55°. UV

(EtOH): 228 (6350), 275 (3600), 328 (8200). ^{1}H-NMR (60 MHz, CCl_4): 1.88 (*s*, 6 H); 1.94 (*s*, 3 H); 4.80 (*s*, 2 H); 7.08 (*s*, 1 H). Anal. calc. for $C_{10}H_{12}Cl_3NO_3S$ (332.63): C 36.11, H 3.64, N 4.21; found: C 36.15, H 3.54, N 4.23.

22. *Methyl 2-Methyl-1,3-thiazole-4-carboxylate* (**16**). A soln. of **15a** (0.127 g, 0.58 mmol) and anh. NaOAc (0.053 g), in AcOH (20 ml) was refluxed for 19 h, whereupon the starting material had disappeared (TLC (C_6H_6/AcOEt 3:1)). After evaporation and treatment of the brownish residue with 200 mg of citric acid, ice-water, and CH_2Cl_2, the combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to give 0.092 g (100%) of **16**, which crystallized spontaneously in colorless needles (m.p. 56–57°). An anal. sample was obtained on sublimation at 90°/0.01 Torr. M.p. 57–58° ([13]: 58°). UV (EtOH): 228 (6690). ^{1}H-NMR ($CDCl_3$): 2.76 (*s*, 3 H); 3.95 (*s*, 3 H); 8.05 (*s*, 1 H). Anal. calc. for $C_6H_7NO_2S$ (157.19): C 45.85, H 4.49, N 8.91; found: C 46.12, H 4.64, N 9.16.

23. *3-Acetyl-2,3-dihydro-2,2-dimethyl-1,3-thiazole-4-carboxylic Acid* (**17**). A soln. of **15b** (0.242 g, 0.72 mmol) in 90% AcOH (5 ml) was stirred at 24° and Zn-powder (1.942 g) added in small portions within 5 h. The mixture was filtered, and the insoluble salts were carefully washed with AcOH (15 ml) and subsequently with toluene (75 ml). After evaporation of the filtrate, the residue was dissolved in CH_2Cl_2 and treated for 45 min with a stream of H_2S, whereupon a milky precipitate of ZnS formed. Filtration over a layer of Na_2SO_4 and washing with CH_2Cl_2 gave 66 mg (45%) of crude **17**. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.9 (*s*, 6 H); 2.1 (*s*, 3 H); 8.9 (*s*, 1 H).

On treatment of an aliquot of **17** with a soln. of diazomethane in Et_2O, the methyl ester **15a** was obtained having an identical IR spectrum and chromatographic behavior as authentic **15a**.

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