

57. Synthesis of 1,2,3,4-Tetrahydro-4-oxothieno[3,2-*d*]pyrimidine and Perhydropyrimidine Derivates from Alkyl Dicyanoacetates

by Richard Neidlein* and Zhijhua Sui

Pharmazeutisch-Chemisches Institut der Universität Heidelberg, im Neuenheimer Feld 364, D-6900 Heidelberg

Dedicated to *Michael Hanack*, Tübingen, on the occasion of his 60th birthday

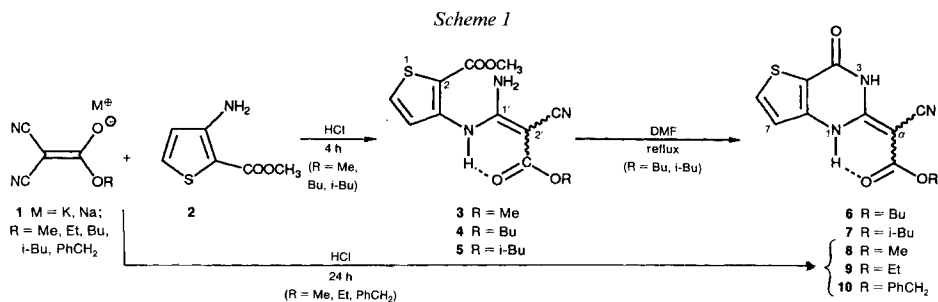
(11.II.91)

Nucleophilic addition of methyl 3-aminothiophene-2-carboxylate (**2**) as well as of β -alanine ethyl ester (**11**) to one CN group of the salts **1** of alkyl dicyanoacetates, followed by cyclization, yielded 1,2,3,4-tetrahydro-4-oxothieno[3,2-*d*]pyrimidine derivatives **6–10** (*Scheme 1*) and perhydropyrimidine derivatives **17–19** (*Scheme 2*), respectively.

We have recently embarked upon the syntheses of heterocyclic compounds such as imidazolidine [1], 1,3-oxazine [2], quinazoline derivatives [3], and some related compounds [4–7] from alkyl dicyanoacetates [8–16] which proved to be good synthons for synthesis of heterocyclic compounds. The CN groups in dicyanoacetates can easily be attacked by nucleophilic reagents such as halogenides, alcohols, and amines. It was thus of interest for us to investigate the possibilities of synthesis of six-membered and fused heterocyclic compounds from alkyl dicyanoacetates with corresponding nucleophilic reagents.

We now wish to report the synthesis of 1,2,3,4-tetrahydro-4-oxothieno[2,3-*d*]pyrimidine and perhydropyrimidine derivatives with ketene-aminal structure from alkyl dicyanoacetates.

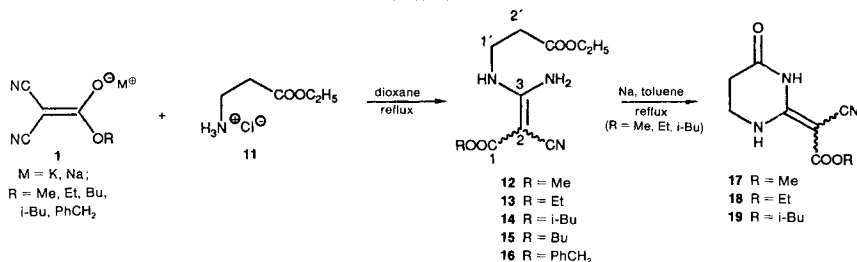
Treatment of the potassium salt **1** of alkyl dicyanoacetates with methyl 3-aminothiophene-2-carboxylate (**2**) in diluted HCl solution under reflux for 4 h afforded the methyl 3-{[2-(alkoxycarbonyl)-1-amino-2-cyanoethenyl]amino}thiophene-2-carboxylates **3–5**. Carboxylates **4** and **5** could be cyclized in high yields without catalyst in refluxing DMF to fused heterocyclic compounds, the alkyl 2-cyano-2-(1,2,3,4-tetrahydro-4-oxothieno[3,2-*d*]pyrimidin-2-ylidene)acetates **6** and **7** (*Scheme 1*). In the case of the salts **1** of



methyl, ethyl, or benzyl dicyanoacetate, the heterocycles **8–10** were directly obtained without any complications, after 24 h HCl treatment in the presence of **2**. All products **3–10** are stable and could be easily isolated and purified by recrystallization. Thus, this nucleophilic addition followed by cyclization provides a convenient method for the synthesis of thienopyrimidines with ketene aminal structure. The COOR group in **3–10** might be *cis*-configured with respect to the NH or N(1) moiety, in analogy to similar quinazoline derivatives for which we had determined the structure by X-ray diffraction [3].

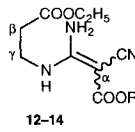
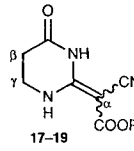
In view of the results of the reactions of **1** with α -amino acids, which led to imidazolidine derivatives [1], we attempted the synthesis of perhydropyrimidine derivatives from **1** and β -amino acids. Reactions of β -alanine ethyl ester hydrochloride (**11**) with the salts **1** in refluxing dioxane for 24 h led only to the ring-opened alkyl 3-amino-2-cyano-3-[(2-(ethoxycarbonyl)ethyl]amino}acrylates **12–16** (Scheme 2) which could not be cyclized under conditions similar to that used for the cyclization of **4** and **5** (see above). But if these acrylates, e.g. **12–14**, were treated in refluxing toluene in the presence of Na, the desired alkyl 2-cyano-2-(perhydro-4-oxypyrimidin-2-ylidene)acetates **17–19** were obtained in high yields (Scheme 2).

Scheme 2



The C=C bond in **3–10** and **12–19** is highly polarized by the pushpull effects of the CN and COOR groups (electron withdrawing) as well as the NH and NH₂ or NHCO groups (electron donating). One of the characteristics of such pushpull systems [17–20] is the very low ¹³C-NMR chemical shift of the carbon C-atom on the side of the electron-withdrawing groups of the C=C bond, since the electron densities on this C-atom are higher than normal. This was indeed observed in our investigations: The ¹³C-NMR chemical shifts of C(α) of **3–10** are *ca.* 57 ppm and those of **12–19** 53–56 ppm (normal C=C, 120 ppm). As

Table. Comparison of ¹³C-NMR Chemical Shifts of Some C-Atoms of Ring-Opened and Cyclization Products

									
		12–14				17–19			
	R	$\delta(\text{C}(\alpha))$	$\Delta\delta$	$\delta(\text{C}(\beta))$	$\Delta\delta$	$\delta(\text{C}(\alpha))$	$\Delta\delta$		
12	Me	53.6	2.7	33.2	-2.6	36.8	-0.3		
17		56.3		29.6		37.1			
13	Et	53.8	2.4	33.2	-2.6	36.8	-0.3		
18		56.2		29.6		37.1			
14	i-Bu	53.7	2.6	33.2	-2.6	36.7	-0.5		
19		56.3		29.6		37.2			

shown in the *Table*, the chemical shifts of C(α) of the ring-opened products **12–14** are at higher field than those of the perhydropyrimidines **17–19**. It appears that the electron-donating ability of the N-atom is decreased after amidization ($\text{NH}_2 \rightarrow \text{NHCO}$). This is in agreement with usual theoretical considerations.

Generous support of this work by *BASF AG, Verband der Chemischen Industrie – Fonds der Chemie and Deutsche Forschungsgemeinschaft* is gratefully acknowledged. We are indebted to Dr. W. Kramer, Mrs. G. Schormann, and Mr. G. Beutel for carrying out NMR spectra and elementary analyses and to Mr. H. Rudy and Mr. P. Weyrich for IR and mass spectra. Z. Sui thanks the *Konrad-Adenauer-Stiftung* for financial support; we also thank *Bayer AG and Hoechst AG* for generous gifts of chemicals.

Experimental Part

General. M.p.: Reichert hot-stage microscope; uncorrected. UV spectra (λ_{max} (log ϵ) in nm): Carl-Zeiss-DMR-10 spectrophotometer. IR spectra (in cm^{-1}): Perkin-Elmer-325 spectrophotometer. NMR spectra: Bruker-WM-250 spectrometer (^1H , 250.13 MHz; ^{13}C , 62.89 MHz); δ in ppm rel. to TMS ($= 0$ ppm), J in Hz; primary, secondary, tertiary, and quaternary C-atoms were differentiated either by off-resonance decoupling or J -modulated spin-echo experiments (signal phase: '+', = C or CH_2 ; '–', CH or CH_3). Mass spectra (m/z (%)): Varian-MAT-311-A instrument. Microanalyses: Heraeus automatic analyzer.

Methyl 3-{[1-Amino-2-cyano-2-(methoxycarbonyl)ethenyl]amino}thiophene-2-carboxylate (3). Typical Procedure. The K^+ salt of methyl dicyanoacetate (1.62 g, 10 mmol) was added to a suspension of methyl 3-aminothiophene-2-carboxylate (**2**; 1.57 g, 10 mmol) in conc. HCl (0.9 ml) and H_2O (20 ml). The mixture was refluxed for 4 h. After cooling, the precipitate was collected by filtration, washed with acetone, and then recrystallized from acetone: **3** (1.17 g, 42%). White crystals. M.p. 265° (dec.). UV/VIS (MeCN): 206 (4.116), 297 (4.335), 315 (4.277). IR (KBr): 3370m (NH); 3300w (NH); 3230m (NH); 3115w, 2965w (CH); 2110s (CN); 1685s (C=O); 1635s, 1600s (C=C). ^1H -NMR ((D_6) DMSO): 3.65 (s, $\text{CH}_3\text{OOC}-\text{C}(2')\text{COOCH}_3$); 3.83 (s, $\text{CH}_3\text{OOC}-\text{C}(2)$); 7.32 (d, $^3J(4,5) = 5.5$, H-C(4)); 7.74 (br. s, NH); 7.97 (d, $^3J(4,5) = 5.5$, H-C(5)); 9.0–11.5 (br., NH_2). ^{13}C -NMR ((D_6) DMSO): 50.8 (q, $\text{CH}_3\text{OOC}-\text{C}(2')$); 52.1 (q, $\text{CH}_3\text{OOC}-\text{C}(2)$); 57.0 (s, (2')); 115.5 (s, CN); 118.3 (s, C(2)); 123.2 (d, C(5)); 132.9 (d, C(4)); 141.1 (s, C(3)); 160.5 (s, CO-C(2)); 162.3 (C(1')); 168.4 (s, CO-C(2')). MS (80 eV, 156°): 283 (4, $[M + 2]^+$), 282 (12, $[M + 1]^+$), 281 (100, M^+), 265 (5, $[M - \text{CH}_3]^+$), 249 (21, $[264 - \text{CH}_3]^+$), 217 (95, $[M - 2\text{CH}_3\text{OH}]^+$). Anal. calc. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_4\text{S}$ (281.31): C 46.97, H 3.94, N 14.94, S 11.40; found: C 47.12, H 3.96, N 14.84, S 11.34.

Methyl 3-{[1-Amino-2-(butoxycarbonyl)-2-cyanoethenyl]amino}thiophene-2-carboxylate (4). As described for **3**, from the K^+ salt of butyl dicyanoacetate (2.4 g, 10 mmol) and **2** (1.57 g, 10 mmol) in conc. HCl (0.9 ml) and H_2O (30 ml): **4** (2.52 g, 78%). Light yellow powder. M.p. $172\text{--}173^\circ$ (acetone). UV/VIS (MeCN): 206 (4.166), 253 (4.371), 314 (4.298). IR (KBr): 3360m (NH); 3200w (NH); 3105m (NH); 2960w (CH); 2200s (CN); 1680s (C=O); 1590s (C=C). ^1H -NMR ((D_6) DMSO): 0.91 (t, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.36 (sext., $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.58 (quint., $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 3.83 (s, $\text{CH}_3\text{OOC}-\text{C}(2)$); 4.08 (t, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 7.32 (d, $^3J(4,5) = 5.5$, H-C(4)); 7.59 (br. s, NH); 7.97 (d, $^3J(4,5) = 5.5$, H-C(5)); 9.0–11.5 (br., NH_2). ^{13}C -NMR ((D_6) DMSO): 13.5 (q, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 18.6 (t, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 30.4 (t, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 52.1 (q, $\text{CH}_3\text{OOC}-\text{C}(2)$); 57.2 (s, C(2')); 63.0 (t, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 115.2 (s, CN); 118.3 (s, C(2)); 123.1 (d, (5)); 132.9 (d, C(4)); 141.1 (s, C(3)); 160.4 (s, CO-C(2)); 162.2 (s, C(1')); 168.0 (s, CO-C(2')). MS (80 eV, 164°): 25 (5, $[M + 2]^+$), 324 (16, $[M + 1]^+$), 323 (100, M^+), 267 (27, $[M - \text{C}_4\text{H}_8]^+$, McLafferty rearrangement), 250 (16, $[M - \text{C}_4\text{H}_9\text{O}]^+$), 249 (28, $[M - \text{C}_4\text{H}_9\text{OH}]^+$), 223 (22, $[249 - \text{CN}]^+$), 217 (78, $[249 - \text{CH}_3\text{OH}]^+$). Anal. calc. for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ (323.39): C 51.99, H 5.30, N 13.00, S 9.92; found: C 52.06, H 5.21, N 12.91, S 9.91.

Methyl 3-{[1-Amino-2-cyano-2-(isobutoxycarbonyl)ethenyl]amino}thiophene-2-carboxylate (5). As described for **3**, from the K^+ salt of isobutyl dicyanoacetate (1.02 g, 5 mmol) and **2** (0.785 g, 5 mmol) in conc. HCl (0.45 ml) and H_2O (30 ml): **5** (0.88 g, 54%). White crystals. M.p. $155\text{--}157^\circ$ (acetone). UV/VIS (MeCN): 210 (4.015), 255 (4.342), 315 (4.288). IR (KBr): 3360m (NH); 3180w (NH); 3100w (NH); 2980w (CH); 2880w, 2200s (CN); 1675s (C=O); 1630s, 1590s (C=C). ^1H -NMR ((D_6) DMSO): 0.92 (d, $(\text{CH}_3)_2\text{CHCH}_2$); 1.90 (sept., $(\text{CH}_3)_2\text{CHCH}_2$); 3.83 (s, $\text{CH}_3\text{OOC}-\text{C}(2)$); 3.87 (d, $(\text{CH}_3)_2\text{CHCH}_2$); 7.33 (d, $^3J(4,5) = 5.5$, H-C(4)); 7.89 (br. s, NH); 7.97 (d, $^3J(4,5) = 5.5$, H-C(5)); 9–11.5 (br. NH_2). ^{13}C -NMR ((D_6) DMSO): 18.8 (q, $(\text{CH}_3)_2\text{CHCH}_2$); 27.5 (–, $(\text{CH}_3)_2\text{CHCH}_2$); 52.1 (q, $\text{CH}_3\text{OOC}-\text{C}(2)$); 57.2 (+, C(2')); 69.0 (+, $(\text{CH}_3)_2\text{CHCH}_2$); 115.0 (+, CN); 118.2 (+, C(2)); 123.2 (–, C(5)); 132.9 (–, C(4)); 141.2 (+, C(3)); 160.5 (+, CO-C(2)); 162.3 (+, C(1')); 168.1 (+, CO-C(2')). MS (80 eV, 164°): 325 (6,

$[M + 2]^+$, 324 (17, $[M + 1]^+$), 323 (100, M^+). 267 (54, $[M - C_4H_8]^+$, *McLafferty* rearrangement), 250 (25, $[M - C_4H_9O]^+$), 249 (37, $[M - C_4H_9OH]^+$), 235 (18, $[267 - CH_3OH]^+$), 223 (49, $[249 - CN]^+$). Anal. calc. for $C_{14}H_{17}N_3O_4S$ (323.39): C 51.99, H 5.30, N 13.00, S 9.92; found: C 51.87, H 5.25, N 12.92, S 10.02.

Butyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothienof[3,2-d]pyrimidin-2-ylidene)acetate (6). A soln. of **4** (100 mg, 0.31 mmol) in abs. DMF (8 ml) was refluxed for 7 h. The solvent was evaporated and the residue recrystallized from acetone: white crystals (85 mg, 94%). M.p. 211–212°. UV/VIS (MeCN): 216 (4.124), 250 (4.177), 286 (4.408), 320 (3.974). IR (KBr): 3150w (NH); 3100w, 2960m (CH); 2220s (CN); 1700s (C=O); 1640s. 1H -NMR ($(D_6)DMSO$): 0.92 (t, $CH_3CH_2CH_2CH_2$); 1.38 (*sext.*, $CH_3CH_2CH_2CH_2$); 1.61 (*quint.*, $CH_3CH_2CH_2CH_2$); 4.15 (t, $CH_3CH_2CH_2CH_2$); 7.34 (d, $^3J(6,7) = 5$, H–C(7)); 8.22 (d, $^3J(6,7) = 5$, H–C(6)); 12.25 (br. s, NH); 12.74 (br. s, NH). ^{13}C -NMR ($(D_6)DMSO$): 13.5 (q, $CH_3CH_2CH_2CH_2$); 18.5 (t, $CH_3CH_2CH_2CH_2$); 30.3 (t, $CH_3CH_2CH_2CH_2$); 56.9 (s, C(α)); 63.9 (t, $CH_3CH_2CH_2CH_2$); 114.1 (s, CN); 116.6 (s, C(4a)); 119.3 (d, C(6)); 137.2 (d, C(7)); 145.8 (s, C(7a)); 154.6 (s, C(4)); 155.8 (s, C(2)); 168.3 (s, COOBu). MS (80 eV, 151°): 291 (33, M^+), 235 (36, $[M - C_4H_8]^+$), 218 (23, $[M - C_4H_9OH]^+$), 217 (100, $[M - C_4H_9OH]^+$), 191 (19, $[217 - CN]^+$). Anal. calc. for $C_{13}H_{13}N_3O_3S$ (291.35): C 53.59, H 4.50, N 14.43, S 11.01; found: C 53.74, H 4.47, N 14.38, S 10.83.

Isobutyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothienof[3,2-d]pyrimidin-2-ylidene)acetate (7). A soln. of **5** (100 mg, 0.31 mmol) in abs. DMF (3 ml) was refluxed for 8 h. The solvent was evaporated and the residue recrystallized from acetone/ CH_2Cl_2 2:1: white crystals (80 mg, 89%). M.p. 245–247°. UV/VIS (MeCN): 210 (4.129), 290 (4.486). IR (KBr): 3160w (NH); 3100w, 2960m (CH); 2220m (CN); 1705s (C=O); 1665s, 1635s. 1H -NMR ($(D_6)DMSO$): 0.92 (d, $(CH_3)_2CHCH_2$); 1.92 (*sept.*, $(CH_3)_2CHCH_2$); 3.92 (d, $(CH_3)_2CHCH_2$); 7.32 (d, $^3J(6,7) = 5$, H–C(7)); 8.20 (d, $^3J(6,7) = 5$, H–C(6)); 12.21 (br. s, NH); 12.70 (br. s, NH). ^{13}C -NMR ($(D_6)DMSO$): 18.7 (–, $(CH_3)_2CHCH_2$); 27.4 (–, $(CH_3)_2CHCH_2$); 56.9 (+, C(α)); 69.9 (+, $(CH_3)_2CHCH_2$); 114.2 (+, CN); 116.5 (+, C(4a)); 119.3 (–, C(6)); 137.2 (–, C(7)); 145.9 (+, C(7a)); 154.6 (+, C(4)); 155.9 (+, C(2)); 168.3 (+, COO(*i*-Bu)). MS (80 eV, 137°): 292 (4, $[M + 1]^+$), 291 (24, M^+), 235 (36, $[M - C_4H_8]^+$), 218 (23, $[M - C_4H_9OH]^+$), 217 (100, $[M - C_4H_9OH]^+$), 191 (8, $[217 - CN]^+$). Anal. calc. for $C_{13}H_{13}N_3O_3S$ (291.35): C 53.59, H 4.50, N 14.43, S 11.01; found: C 53.49, H 4.47, N 14.49.

Methyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothienof[3,2-d]pyrimidin-2-ylidene)acetate (8). *Typical Procedure*. The K^+ salt of methyl dicyanoacetate (1.62 g, 10 mmol) was added to a suspension of **2** (1.57 g, 10 mmol) in conc. HCl (0.9 ml) and H_2O (20 ml). The mixture was refluxed for 24 h. After cooling, the precipitate was collected by filtration, washed with acetone, and then recrystallized from acetate: **8** (0.89 g, 36%). White crystals. M.p. 275° (dec.). UV/VIS (MeCN): 217 (4.160), 252 (4.200), 286 (4.394), 344 (3.979). IR (KBr): 3160m (NH); 3100w, 2985w (CH); 2210s (CN); 1700s (C=O); 1685s (C=O); 1655s, 1625s, 1620s (C=C); 1525s, 1440s. 1H -NMR ($(D_6)DMSO$): 3.73 (s, COOCH₃); 7.34 (d, $^3J(6,7) = 5$, H–C(7)); 8.23 (d, $^3J(6,7) = 5$, H–C(6)); 12.20 (br. s, NH); 12.67 (br. s, NH). ^{13}C -NMR ($(D_6)DMSO$): 51.6 (q, COOCH₃); 56.8 (s, C(α)); 114.2 (s, CN); 116.5 (s, C(4a)); 119.2 (d, C(6)); 137.2 (d, C(7)); 145.7 (s, C(7a)); 154.4 (s, C(4)); 155.7 (s, C(2)); 168.6 (s, COOCH₃). MS (80 eV, 222°): 251 (4, $[M + 2]^+$), 250 (8, $[M + 1]^+$), 249 (100, M^+), 219 (6), 218 (24, $[M - CH_3O]^+$), 217 (100, $[M - CH_3OH]^+$). Anal. calc. for $C_{10}H_7N_3O_3S$ (249.27): C 48.49, H 2.83, N 16.86, S 12.87; found: C 48.30, H 2.86, N 16.76, S 12.65.

Ethyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothienof[3,2-d]pyrimidin-2-ylidene)acetate (9). As described for **8**, from the K^+ salt of ethyl dicyanoacetate (0.88 g, 5 mmol) and **2** (0.785 g, 5 mmol) in conc. HCl (0.45 ml) and H_2O (20 ml): **9** (0.38 g, 29%). White crystals. M.p. 268° (dec.). UV/VIS (MeCN): 218 (4.164), 252 (4.196), 287 (4.418), 343 (3.986). IR (KBr): 3150w (NH); 3100w, 2975w (CH); 2220m (CN); 1695s (C=O); 1660s (C=O); 1640s, 1635s. 1H -NMR ($(D_6)DMSO$): 1.25 (t, CH_3CH_2O); 4.20 (q, CH_3CH_2O); 7.33 (d, $^3J(6,7) = 5$, H–C(7)); 8.22 (d, $^3J(6,7) = 5$, H–C(6)); 12.27 (br. s, NH); 12.64 (br. s, NH). ^{13}C -NMR ($(D_6)DMSO$): 14.2 (q, CH_3CH_2O); 57.2 (s, C(α)); 60.3 (t, CH_3CH_2O); 114.1 (s, CN); 116.6 (s, C(4a)); 119.2 (d, C(6)); 137.2 (d, C(7)); 145.8 (s, C(7a)); 154.6 (s, C(4)); 155.8 (s, C(2)); 168.3 (s, COOC₂H₅). MS (80 eV, 174°): 264 (6, $[M + 1]^+$), 263 (56, M^+), 218 (19, $[M - CH_3CH_2O]^+$), 217 (100, $[M - CH_3CH_2OH]^+$), 191 (12, $[217 - CN]^+$). Anal. calc. for $C_{11}H_9N_3O_3S$ (263.29): C 50.18, H 3.45, N 15.96, S 12.18; found: C 50.41, H 3.47, N 15.98, S 12.01.

Benzyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothienof[3,2-d]pyrimidin-2-ylidene)acetate (10). As described for **8** from the Na^+ salt of benzyl dicyanoacetate (1.11 g, 5 mmol) and **2** (0.785 g, 5 mmol) in conc. HCl (0.45 ml) and H_2O (20 ml): **10** (1.08 g, 66%). White crystals. M.p. 287° (acetone). UV/VIS (MeCN): 202 (4.214), 252 (4.204), 285 (4.409), 315 (4.011). IR (KBr): 3160w, 3130w, 3100w, 2980w (CH); 2950w, 2210m (CN); 1700s (C=O); 1680s (C=O); 1625s. 1H -NMR ($(D_6)DMSO$): 5.24 (s, $PhCH_2$); 7.33–7.42 (m, Ph , H–C(7)); 8.23 (d, $^3J(6,7) = 5$, H–C(6)); 12.19 (br. s, NH); 12.62 (br. s, NH). ^{13}C -NMR ($(D_6)DMSO$): 56.9 (q, C(α)); 65.4 (t, $PhCH_2$); 114.3 (CN); 116.5 (s, C(4a)); 119.2 (d, C(6)); 127.7, 128.0, 128.4 (3d, CH of Ph); 136.1 (s, C of Ph); 137.2 (d, C(7)); 145.7 (s, C(7a)); 154.5 (C(4)); 155.8 (s, C(2)); 168.0 (s, COOC₂H₅). MS (80 eV, 230°): 26 (1, $[M + 1]^+$), 325 (8, M^+), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{16}H_{11}N_3O_3S$ (325.36): C 59.06, H 3.41, N 12.92, S 9.86; found: C 59.17, N 12.95, S 9.73.

Methyl 3-Amino-2-cyano-3-{[2-(ethoxycarbonyl)ethyl]amino}prop-2-enoate (12), *Typical Procedure*. A suspension of the K^+ salt of methyl dicyanoacetate (1.62 g, 10 mmol) and β -alanine ethyl ester hydrochloride (**11**; 1.54

g, 10 mmol) in abs. dioxane (40 ml) was refluxed under N_2 for 24 h and then filtered. The solvent of the filtrate was evaporated and the residue purified by column chromatography (silica gel, AcOEt): **12** (0.52, 22%). White crystals. M.p. 132–134° (AcOEt). UV/VIS (MeCN): 210 (4.000), 258 (4.344). IR (KBr): 3390, 3370m (NH₂); 3250m (NH); 2990w (CH); 2960w (CH); 2190s (CN); 1740s (C=O); 1680s (C=O); 1650s (C=C); 1620s (NH). ¹H-NMR ((D₆)DMSO): 1.20 (t, CH₃CH₂O); 2.58 (t, CH₂(2')); 3.46 (q, CH₂(1')); 3.57 (s, COOCH₃); 4.09 (q, CH₃CH₂O); 7.03 (br. s, NH₂); 8.10 (br. s, NH). ¹³C-NMR ((D₆)DMSO): 14.0 (–, CH₃CH₂O); 33.2 (+, CH₂(2')); 36.8 (+, CH₂(1')); 50.3 (–, COOCH₃); 53.6 (+, C(2)); 60.1 (+, CH₃CH₂O); 119.6 (+, CN); 162.2 (+, C(3)); 169.1 (+, C(1)); 171.0 (+, COOC₂H₅). MS (80 eV, 123°): 242 (12, [M + 1]⁺), 241 (100, M⁺), 212 (2, [M – C₂H₅]⁺), 210 (19, [M – CH₃O]⁺), 196 (21, [M – C₂H₅O]⁺), 168 (58, [196 – CO]⁺), 141 (11, [168 – HCN]⁺), 136 (24, [168 – CH₃OH]⁺). Anal. calc. for C₁₀H₁₅N₃O₄ (241.26): C 49.78, H 6.27, N 17.42; found: C 49.93, H 6.27, N 17.17.

Ethyl 3-Amino-2-cyano-3-{[2-(ethoxycarbonyl)ethyl]amino}prop-2-enoate (13). As described for **12**, from the K⁺ salt of ethyl dicyanoacetate (1.76 g, 10 mmol) and **11** (1.54 g, 10 mmol) in abs. dioxane (50 ml): **13** (0.55 g, 22%). White crystals. M.p. 124–126° (AcOEt). UV/VIS (MeCN): 210 (4.102), 258 (4.359). IR (KBr): 3390, 3370m (NH₂); 3250m (NH); 2995w (CH); 2200s (CN); 1745s (C=O); 1685s (C=O); 1650s (C=C); 1615s (NH). ¹H-NMR ((D₆)DMSO): 1.17 (t, CH₃CH₂O); 1.20 (t, CH₃CH₂O); 2.58 (t, CH₂(2')); 3.45 (q, CH₂(1')); 4.04 (q, CH₃CH₂O); 4.08 (q, CH₃CH₂O); 7.53 (br. s, NH₂); 8.18 (br. s, NH). ¹³C-NMR ((D₆)DMSO): 14.0 (–, CH₃CH₂O); 14.6 (–, CH₃CH₂O); 33.2 (+, C(2')); 36.8 (+, C(1')); 53.8 (+, C(2)); 58.5 (+, CH₃CH₂O); 60.1 (+, CH₃CH₂O); 119.6 (+, CN); 162.2 (+, C(3)); 168.8 (+, C(1)); 171.0 (+, C₂H₅OOC–C(2')). MS (80 eV, 120°): 256 (14, [M + 1]⁺), 225 (100, M⁺), 210 (22, [M – C₂H₅O]⁺), 182 (23, [M – COOC₂H₅]⁺). Anal. calc. for C₁₁H₁₇N₃O₄ (255.29): C 51.75, H 6.71, N 16.46; found: C 52.01, H 6.73, N 16.29.

Isobutyl 3-Amino-2-cyano-3-{[2-(ethoxycarbonyl)ethyl]amino}prop-2-enoate (14). As described for **12**, from the K⁺ salt of isobutyl dicyanoacetate (4.08 g, 20 mmol) and **11** (3.07 g, 20 mmol) in abs. dioxane (100 ml): **14** (1.56 g, 28%). White crystals. M.p. 111–112° (AcOEt). UV/VIS (MeCN): 210 (3.971), 258 (4.380). IR (KBr): 3420, 3360m (NH₂); 3250m (NH); 2980w (CH); 2960w (CH); 2950w (CH); 2220s (CN); 1710s (C=O); 1670s (C=O); 1645s (C=C); 1595s (NH). ¹H-NMR ((D₆)DMSO): 0.90 (d, (CH₃)₂CHCH₂); 1.19 (t, CH₃CH₂O); 1.84 (sept., (CH₃)₂CHCH₂); 2.58 (t, CH₂(2')); 3.45 (q, CH₂(1')); 3.78 (d, (CH₃)₂CHCH₂); 4.09 (q, CH₃CH₂O); 7.52 (br. s, NH₂); 8.15 (br. s, NH). ¹³C-NMR ((D₆)DMSO): 14.0 (–, CH₃CH₂O); 18.8 (–, (CH₃)₂CHCH₂); 27.6 (–, (CH₃)₂CHCH₂); 33.2 (+, C(2')); 36.7 (+, C(1')); 53.7 (+, C(2)); 60.1 (+, CH₃CH₂O); 68.4 (+, (CH₃)₂CHCH₂); 119.4 (+, CN); 162.2 (C(3)); 168.8 (+, C(1)); 171.0 (+, C₂H₅OOC–C(2')). MS (80 eV, 141°): 284 (9, [M + 1]⁺), 283 (55, M⁺), 238 (8, [M – C₂H₅O]⁺), 227 (47, [M – C₄H₉]⁺, McLafferty rearrangement), 210 (50, [M – C₄H₉]⁺), 183 (55, [210 – HCN]⁺), 182 (17, [M – COOC₂H₅]⁺). Anal. calc. for C₁₃H₂₁N₃O₄ (283.34): C 55.11, H 7.47, N 14.83; found: C 55.30, H 7.48, N 14.77.

Butyl 3-Amino-2-cyano-3-{[2-(ethoxycarbonyl)ethyl]amino}prop-2-enoate (15). As described for **12**, from the K⁺ salt of butyl dicyanoacetate (4.08 g, 20 mmol) and **11** (3.07 g, 20 mmol) in abs. dioxane (100 ml): **15** (1.61 g, 28%). White crystals. M.p. 98–100° (AcOEt). UV/VIS (MeCN): 210 (4.011), 258 (4.379). IR (KBr): 3400, 3360m (NH₂); 3250m (NH); 2960w (CH); 2190s (CN); 1740s (C=O); 1680s (C=O); 1650s (C=C); 1615s (NH). ¹H-NMR ((D₆)DMSO): 0.91 (t, CH₃CH₂CH₂CH₂); 1.21 (t, CH₃CH₂O); 1.33 (sext., CH₃CH₂CH₂CH₂); 1.53 (quint., CH₃CH₂CH₂CH₂); 2.56 (t, CH₂(2')); 3.45 (q, CH₂(1')); 4.08 (q, CH₃CH₂O); 7.51 (br. s, NH₂); 8.19 (br. s, NH). ¹³C-NMR ((D₆)DMSO): 13.7 (–, CH₃CH₂CH₂); 14.0 (–, CH₃CH₂O); 18.6 (+, CH₃CH₂CH₂CH₂); 30.6 (+, CH₃CH₂CH₂CH₂); 33.2 (+, C(2')); 36.7 (+, C(1')); 53.8 (+, C(2)); 60.1 (+, CH₃CH₂O); 62.2 (+, CH₃CH₂CH₂CH₂); 119.5 (+, CN); 162.2 (+, C(3)); 168.8 (+, C(1)); 171.0 (+, C₂H₅OOC–C(2')). MS (80 eV, 131°): 284 (15, [M + 1]⁺), 283 (100, M⁺), 238 (11, [M – C₂H₅O]⁺), 227 (51, [M – C₄H₉]⁺, McLafferty rearrangement), 210 (54, [M – C₄H₉]⁺), 183 (63, [210 – HCN]⁺), 182 (15, [M – COOC₂H₅]⁺). Anal. calc. for C₁₃H₂₁N₃O₄ (283.34): C 55.11, H 7.47, N 14.83; found: C 55.28, H 7.43, N 14.83.

Benzyl 3-Amino-2-cyano-3-{[2-(ethoxycarbonyl)ethyl]amino}prop-2-enoate (16). As described for **12**, from the Na⁺ salt of benzyl dicyanoacetate (2.22 g, 10 mmol) and **11** (1.54 g, 10 mmol) in abs. dioxane (50 ml): **16** (0.65 g, 21%). White crystals. M.p. 116–118° (AcOEt). UV/VIS (MeCN): 258 (4.426). IR (KBr): 3395, 3360m (NH₂); 3250m (NH); 3000w; 2975w (CH); 2220s (CN); 1740s (C=O); 1680s (C=O); 1660m (C=C); 1645s; 1610s (NH). ¹H-NMR ((D₆)DMSO): 1.20 (t, CH₃CH₂O); 2.58 (t, CH₂(2')); 3.47 (q, CH₂(1')); 4.09 (q, CH₃CH₂O); 5.08 (s, PhCH₂); 7.24–7.42 (m, Ph); 7.58 (br. s, NH₂); 8.18 (br. s, NH). ¹³C-NMR ((D₆)DMSO): 14.0 (–, CH₃CH₂O); 33.2 (+, C(2')); 36.8 (+, C(1')); 53.8 (+, C(2)); 60.1 (+, CH₃CH₂O); 68.9 (+, PhCH₂); 119.4 (+, CN); 127.3, 127.6, 128.4 (–, CH of Ph); 137.3 (+, C of Ph); 162.1 (+, C(3)); 168.4 (+, C(1)); 171.0 (+, C₂H₅OOC–C(2')). MS (80 eV, 153°): 317 (17, M⁺), 272 (1, [M – C₂H₅O]⁺), 244 (1, [272 – CO]⁺), 210 (4, [M – BzO]⁺), 200 (2, [244 – CO₂]⁺), 183 (10, [210 – HCN]⁺), 91 (100, C₇H₇⁺). Anal. calc. for C₁₆H₁₉N₃O₄ (317.36): C 60.55, H 6.03, N 13.24; found: C 60.80, H 6.01, N 13.07.

Methyl 2-Cyano-2-(perhydro-4-oxopyrimidin-2-ylidene)acetate (17). Typical Procedure. Na (10 mg) was added to a soln. of **12** (60 mg, 0.25 mmol) in abs. toluene (25 ml). The suspension was refluxed for 7 h and stirred at r.t. for further 12 h. The soln. was acidified with dil. H₂SO₄ soln. and then extracted with AcOEt. The combined org. layer was dried (MgSO₄) and evaporated and the residue purified by prep. TLC (silica gel, AcOEt): **17** (34 mg, 71 %). White crystals. M.p. 196–198° (AcOEt). UV/VIS (MeCN): 208 (4.071), 282 (4.383). IR (KBr): 3280_w (NH); 2800_w (CH); 2220_m (CN); 1730_s (C=O); 1665_s (C=O); 1635_s (C=C). ¹H-NMR ((D₆)DMSO): 2.51 (*t*, CH₂(5)); 3.55 (*t*, CH₂(6)); 4.87 (*s*, CH₃O); 8.83 (*br. s*, NH); 11.08 (*br. s*, NH). ¹³C-NMR ((D₆)DMSO): 29.6 (+, C(5)); 37.1 (+, C(6)); 51.2 (–, CH₃O); 56.2 (+, C(α)); 117.1 (+, CN); 159.2 (+, C(2)); 166.9 (+, COO); 168.1 (+, C(4)). MS (80 eV, 130°): 196 (8, [*M* – 1]⁺), 195 (86, *M*⁺), 167 (2, [*M* – CO]⁺), 164 (26, [181 – CH₃O]⁺), 155 (4), 141 (11, [167 – CN]⁺), 136 (6, [164 – CO]⁺). Anal. calc. for C₈H₉N₃O₃ (195.19): C 49.23, H 4.65, N 21.53; found: C 49.28, H 4.64, N 21.53.

Ethyl 2-Cyano-2-(perhydro-4-oxopyrimidin-2-ylidene)acetate (18). As described for **17**, from **13** (200 mg, 0.78 mmol) and Na (20 mg) in toluene (50 ml): **18** (112 mg, 69 %). White crystals. M.p. 146–148° (EtOH). UV/VIS (MeCN): 208 (4.250), 282 (4.403). IR (KBr): 3310_w (NH); 2950_w (CH); 2220_m (CN); 1730_s (C=O); 1670_s (C=O); 1640_s (C=C). ¹H-NMR ((D₆)DMSO): 1.20 (*t*, CH₃CH₂O); 2.66 (*t*, CH₂(5)); 3.54 (*t*, CH₂(6)); 4.13 (*s*, CH₃CH₂O); 8.76 (*br. s*, NH); 11.13 (*br. s*, NH). ¹³C-NMR ((D₆)DMSO): 14.3 (–, CH₃CH₂); 29.6 (+, C(5)); 37.1 (+, C(6)); 56.2 (+, C(α)); 59.8 (+, CH₃CH₂O); 117.1 (+, CN); 159.3 (+, C(2)); 167.0 (+, COO); 167.9 (+, C(4)). MS (80 eV, 90°): 209 (71, *M*⁺), 181 (17, [*M* – C₂H₄]⁺, *McLafferty* rearrangement), 164 (17, [*M* – C₂H₅O]⁺), 137 (41, [164 – HCN]⁺). Anal. calc. for C₉H₁₁N₃O₃ (209.22): C 51.67, H 5.30, N 20.09; found: C 51.87, H 5.32, N 20.07.

Isobutyl 2-Cyano-2-(perhydro-4-oxopyrimidin-2-ylidene)acetate (19). As described for **17** from **14** (200 mg, 0.71 mmol) and Na (20 mg) in toluene (50 ml): **19** (136 mg, 81 %). White crystals. M.p. 178–180° (AcOEt). UV/VIS (MeCN): 208 (4.237), 282 (4.418). IR (KBr): 3300_w (NH); 2900_w (CH); 2210_m (CN); 1730_s (C=O); 1670_s (C=O); 1645_s (C=C). ¹H-NMR ((D₆)DMSO): 0.90 (*d*, (CH₃)₂CHCH₂); 1.89 (*sept.*, (CH₃)₂CHCH₂); 2.68 (*t*, CH₃(5)); 3.55 (*t*, CH₂(6)); 4.87 (*d*, (CH₃)₂CHCH₂); 8.76 (*br. s*, NH); 11.08 (*br. s*, NH). ¹³C-NMR ((D₆)DMSO): 18.7 (–, (CH₃)₂CHCH₂); 27.5 (–, (CH₃)₂CHCH₂); 29.6 (+, C(5)); 37.2 (+, C(6)); 56.3 (+, C(α)); 69.4 (+, (CH₃)₂CHCH₂); 117.0 (+, CN); 159.3 (+, C(2)); 167.0 (+, COO); 167.9 (+, C(4)). MS (80 eV, 90°): 237 (24, *M*⁺), 195 (2), 182 (17, [*M* – C₄H₉]⁺), 181 (100, [*M* – C₄H₈]⁺, *McLafferty* rearrangement). Anal. calc. for C₁₁H₁₅N₃O₃ (237.27): C 55.68, H 6.37, N 17.72; found: C 55.49, H 6.27, N 17.48.

REFERENCES

- [1] R. Neidlein, Z. Sui, *Chem. Ber.* **1990**, *123*, 2203.
- [2] R. Neidlein, Z. Sui, *Synthesis* **1990**, 959.
- [3] R. Neidlein, Z. Sui, *Rev. Roum. Chim.* **1991**, in press.
- [4] R. Neidlein, Z. Sui, submitted to *Synthesis*.
- [5] R. Neidlein, D. Kikelj, *Chem. Ber.* **1988**, *121*, 1817.
- [6] R. Neidlein, D. Kikelj, *Synthesis* **1988**, 981.
- [7] R. Neidlein, D. Kikelj, W. Kramer, M. Spraul, *Chem. Ber.* **1988**, *121*, 1703.
- [8] R. Neidlein, D. Kikelj, W. Kramer, Z. Sui, R. Boese, D. Bläser, D. Kocjan, *Chem. Ber.* **1989**, *122*, 1341.
- [9] B. C. Hesse, *J. Am. Chem. Soc.* **1896**, *18*, 723.
- [10] F. Arndt, H. Scholz, E. Frobel, *Liebigs Ann. Chem.* **1936**, 521, 95.
- [11] J. A. Elvidge, P. N. Judson, A. Percival, R. Shah, *J. Chem. Soc., Perkin Trans. I* **1983**, 1741.
- [12] A. Dornow, H. Grabhoffer, *Chem. Ber.* **1958**, *91*, 1824.
- [13] W. J. Middleton, E. L. Little, D. Coffman, V. A. Engelhardt, *J. Am. Chem. Soc.* **1958**, *80*, 2795.
- [14] R. Schenk, H. Finken, *Liebigs Ann. Chem.* **1928**, 462, 158.
- [15] D. Martin, S. Rackow, *Chem. Ber.* **1965**, *98*, 3662.
- [16] E. Grigat, R. Putter, E. Mühlbauer, *Chem. Ber.* **1965**, *98*, 3777.
- [17] J. Sandström, J. Wennerbeck, *Acta Chem. Scand., Sect. B* **1978**, *32*, 421.
- [18] J. Wennerbeck, J. Sandström, *Org. Magn. Reson.* **1972**, *4*, 783.
- [19] H. Kessler, *Chem. Ber.* **1970**, *103*, 973.