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

by **Richard Neidlein*** and **Zhihua 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)

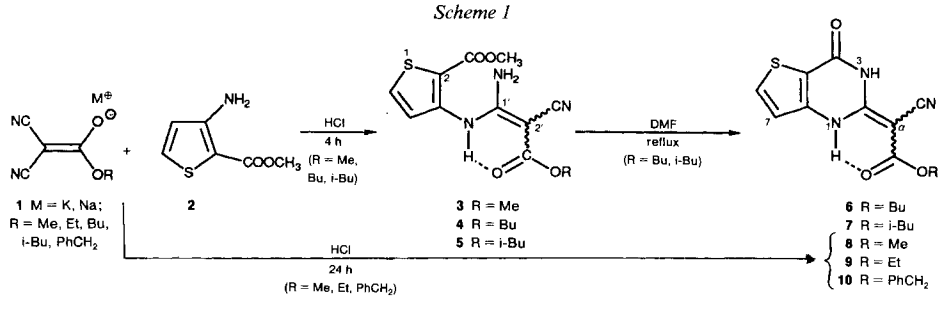
Nucleophilic addition of methyl 3-aminothiophene-2-carboxylate (**2**) as well as of β-alanine ethyl ester (**11**) to one CN group of the salts **1** of alkyl dicyanoacetates, followed by cyclization, yielded 1,2,3,4-tetrahydro-4-oxothieno[3,2-*d*]pyridimine derivatives **6**–**10** (*Scheme 1*) and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

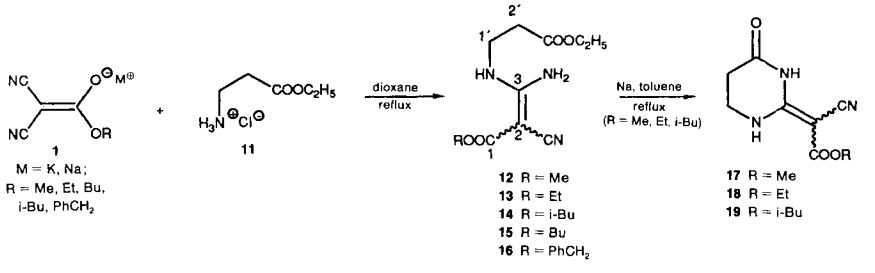
Scheme 1



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*-configurated 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].

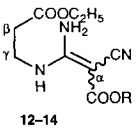
In view of the results of the reactions of **1** with α-amino acids, which led to imidazolidine derivatives [1], we attempted the synthesis of perhydropyrimidine derivatives from **1** and β-amino acids. Reactions of β-alanine ethyl ester hydrochloride (**11**) with the salts **1** in refluxing dioxane 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-oxopyrimidin-2-ylidene)acetates **17**–**19** were obtained in high yields (*Scheme 2*).

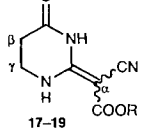
Scheme 2



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 NH_2 or NHCO groups (electron donating). One of the characteristics of such pushpull systems [17–20] is the very low ^{13}C-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 ^{13}C-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 ^{13}C-NMR Chemical Shifts of Some C-Atoms of Ring-Opened and Cyclization Products*





	R	δ(C(α))	Δδ	δ(C(β))	Δδ	δ(C(α))	Δδ
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 ($NH_2 \rightarrow NHCO$). 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* automatical 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): 3370*m* (NH); 3300*w* (NH); 3230*m* (NH); 3115*w*, 2965*w* (CH); 2110*s* (CN); 1685*s* (C=O); 1635*s*, 1600*s* (C=C). ^1H-NMR ((D$_6$)DMSO): 3.65 (*s*, CH_3OOC–C(2′)$COOCH_3$); 3.83 (*s*, CH_3OOC–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*, CH_3OOC–C(2′)); 52.1 (*q*, CH_3OOC–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*, *C*O–C(2)); 162.3 (C(1′)); 168.4 (*s*, *C*O–C(2′)). MS (80 eV, 156°): 283 (4, $[M + 2]^+$), 282 (12, $[M + 1]^+$), 281 (100, M^+), 265 (5, $[M - CH_3]^+$), 249 (21, $[264 - CH_3]^+$), 217 (95, $[M - 2CH_3OH]^+$). Anal. calc. for $C_{11}H_{11}N_3O_4S$ (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. 172–173° (acetone). UV/VIS (MeCN): 206 (4.166), 253 (4.371), 314 (4.298). IR (KBr): 3360*m* (NH); 3200*w* (NH); 3105*m* (NH); 2960*w* (CH); 2200*s* (CN); 1680*s* (C=O); 1590*s* (C=C). ^1H-NMR ((D$_6$)DMSO): 0.91 (*t*, $CH_3CH_2CH_2CH_2$); 1.36 (*sext.*, $CH_3CH_2CH_2CH_2$); 1.58 (*quint.*, $CH_3CH_2CH_2CH_2$); 3.83 (*s*, CH_3OOC–C(2)); 4.08 (*t*, $CH_3CH_2CH_2CH_2$); 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*, $CH_3CH_2CH_2CH_2$); 18.6 (*t*, $CH_3CH_2CH_2CH_2$); 30.4 (*t*, $CH_3CH_2CH_2CH_2$); 52.1 (*q*, CH_3OOC–C(2)); 57.2 (*s*, C(2′)); 63.0 (*t*, $CH_3CH_2CH_2CH_2$); 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*, *C*O–C(2)); 162.2 (*s*, C(1′)); 168.0 (*s*, *C*O–C(2′)). MS (80 eV, 164°): 25 (5, $[M + 2]^+$), 324 (16, $[M + 1]^+$), 323 (100, M^+), 267 (27, $[M - C_4H_8]^+$, *McLafferty* rearrangement), 250 (16, $[M - C_4H_9O]^+$), 249 (28, $[M - C_4H_9OH]^+$), 223 (22, $[249 - CN]^+$), 217 (78, $[249 - CH_3OH]^+$). 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 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. 155–157° (acetone). UV/VIS (MeCN): 210 (4.015), 255 (4.342), 315 (4.288). IR (KBr): 3360*m* (NH); 3180*w* (NH); 3100*w* (NH); 2980*w* (CH); 2880*w*, 2200*s* (CN); 1675*s* (C=O); 1630*s*, 1590*s* (C=C). ^1H-NMR ((D$_6$)DMSO): 0.92 (*d*, $(CH_3)_2CHCH_2$); 1.90 (*sept.*, $(CH_3)_2CHCH_2$); 3.83 (*s*, CH_3OOC–C(2)); 3.87 (*d*, $(CH_3)_2CHCH_2$); 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*, $(CH_3)_2CHCH_2$); 27.5 (–, $(CH_3)_2CHCH_2$); 52.1 (*q*, CH_3OOC–C(2)); 57.2 (+, C(2′)); 69.0 (+, $(CH_3)_2CHCH_2$); 115.0 (+, CN); 118.2 (+, C(2)); 123.2 (–, C(5)); 132.9 (–, C(4)); 141.2 (+, C(3)); 160.5 (+, *C*O–C(2)); 162.3 (+, C(1′)); 168.1 (+, *C*O–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-oxothieno[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): 3150*w* (NH); 3100*w*, 2960*m* (CH); 2220*s* (CN); 1700*s* (C=O); 1640*s*. ^{1}H-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*, $CH_3CH_2CH_2CH2$); 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, $[M-C_4H_9O]^+$), 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-oxothieno[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): 3160*w* (NH); 3100*w*, 2960*m* (CH); 2220*m* (CN); 1705*s* (C=O); 1665*s*, 1635*s*. ^{1}H-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, $[M-C_4H_9O]^+$), 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; found: C 53.49, H 4.47, N 14.49.

*Methyl 2-Cyano-2-(1,2,3,4-tetrahydro-4-oxothieno[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): 3160*m* (NH); 3100*w*, 2985*w* (CH); 2210*s* (CN); 1700*s* (C=O); 1685*s* (C=O); 1655*s*, 1625*s*, 1620*s* (C=C); 1525*s*, 1440*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.73 (*s*, $COOCH_3$); 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*, $COOCH_3$); 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*, $COOCH_3$). 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-oxothieno[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): 3150*w* (NH); 3100*w*, 2975*w* (CH); 2220*m* (CN); 1695*s* (C=O); 1660*s* (C=O); 1640*s*, 1635*s*. ^{1}H-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*, $COOC_2H_5$). 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-oxothieno[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): 3160*w*, 3130*w*, 3100*w*, 2980*w* (CH); 2950*w*, 2210*m* (CN); 1700*s* (C=O); 1680*s* (C=O); 1625*s*. ^{1}H-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 (3*d*, 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*, $COOCH_2Ph$). 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 3.35, 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, 3370*m* (NH_2); 3250*m* (NH); 2990*w* (CH); 2960*w* (CH); 2190*s* (CN); 1740*s* (C=O); 1680*s* (C=O); 1650*s* (C=C); 1620*s* (NH). ^{1}H-NMR ((D$_6$)DMSO): 1.20 (*t*, CH_3CH_2O); 2.58 (*t*, $CH_2(2')$); 3.46 (*q*, $CH_2(1')$); 3.57 (*s*, $COOCH_3$); 4.09 (*q*, CH_3CH_2O); 7.03 (br. *s*, NH_2); 8.10 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 14.0 (–, CH_3CH_2O); 33.2 (+, $CH_2(2')$); 36.8 (+, $CH_2(1')$); 50.3 (–, $COOCH_3$); 53.6 (+, C(2)); 60.1 (+, CH_3CH_2O); 119.6 (+, CN); 162.2 (+, C(3)); 169.1 (+, C(1)); 171.0 (+, $COOC_2H_5$). MS (80 eV, 123°): 242 (12, $[M+1]^+$), 241 (100, M^+), 212 (2, $[M-C_2H_5]^+$), 210 (19, $[M-CH_3O]^+$), 196 (21, $[M-C_2H_5O]^+$), 168 (58, $[196-CO]^+$), 141 (11, $[168-HCN]^+$), 136 (24, $[168-CH_3OH]^+$). Anal. calc. for $C_{10}H_{15}N_3O_4$ (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, 3370*m* (NH_2); 3250*m* (NH); 2995*w* (CH); 2200*s* (CN); 1745*s* (C=O); 1685*s* (C=O); 1650*s* (C=C); 1615*s* (NH). ^{1}H-NMR ((D$_6$)DMSO): 1.17 (*t*, CH_3CH_2O); 1.20 (*t*, CH_3CH_2O); 2.58 (*t*, $CH_2(2')$); 3.45 (*q*, $CH_2(1')$); 4.04 (*q*, CH_3CH_2O); 4.08 (*q*, CH_3CH_2O); 7.53 (br. *s*, NH_2); 8.18 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 14.0 (–, CH_3CH_2O); 14.6 (–, CH_3CH_2O); 33.2 (+, C(2')); 36.8 (+, C(1')); 53.8 (+, C(2)); 58.5 (+, CH_3CH_2O); 60.1 (+, CH_3CH_2O); 119.6 (+, CN); 162.2 (+, C(3)); 168.8 (+, C(1)); 171.0 (+, C_2H_5OOC–C(2')). MS (80 eV, 120°): 256 (14, $[M+1]^+$), 225 (100, M^+), 210 (22, $[M-C_2H_5O]^+$), 182 (23, $[M-COOC_2H_5]^+$). Anal. calc. for $C_{11}H_{17}N_3O_4$ (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, 3360*m* (NH_2); 3250*m* (NH); 2980*w* (CH); 2960*w* (CH); 2950*w* (CH); 2220*s* (CN); 1710*s* (C=O); 1670*s* (C=O); 1645*s* (C=C); 1595*s* (NH). ^{1}H-NMR ((D$_6$)DMSO): 0.90 (*d*, $(CH_3)_2CHCH_2$); 1.19 (*t*, CH_3CH_2O); 1.84 (*sept.*, $(CH_3)_2CHCH_2$); 2.58 (*t*, $CH_2(2')$); 3.45 (*q*, $CH_2(1')$); 3.78 (*d*, $(CH_3)_2CHCH_2O$); 4.09 (*q*, CH_3CH_2O); 7.52 (br. *s*, NH_2); 8.15 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 14.0 (–, CH_3CH_2O); 18.8 (–, $(CH_3)_2CHCH_2$); 27.6 (–, $(CH_3)_2CHCH_2$); 33.2 (+, C(2')); 36.7 (+, C(1')); 53.7 (+, C(2)); 60.1 (+, CH_3CH_2O); 68.4 (+, $(CH_3)_2CHCH_2$); 119.4 (+, CN); 162.2 (C(3)); 168.8 (+, C(1)); 171.0 (+, C_2H_5OOC–C(2')). MS (80 eV, 141°): 284 (9, $[M+1]^+$), 283 (55, M^+), 238 (8, $[M-C_2H_5O]^+$), 227 (47, $[M-C_4H_8]^+$, *McLafferty* rearrangement), 210 (50, $[M-C_4H_9]^+$), 183 (55, $[210-HCN]^+$), 182 (17, $[M-COOC_2H_5]^+$). Anal. calc. for $C_{13}H_{21}N_3O_4$ (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, 3360*m* (NH_2); 3250*m* (NH); 2960*w* (CH); 2190*s* (CN); 1740*s* (C=O); 1680*s* (C=O); 1650*s* (C=C); 1615*s* (NH). ^{1}H-NMR ((D$_6$)DMSO): 0.91 (*t*, $CH_3CH_2CH_2CH_2$); 1.21 (*t*, CH_3CH_2O); 1.33 (*sext.*, $CH_3CH_2CH_2CH_2$); 1.53 (*quint.*, $CH_3CH_2CH_2CH_2$); 2.56 (*t*, $CH_2(2')$); 3.45 (*q*, $CH_2(1')$); 4.08 (*q*, CH_3CH_2O); 7.51 (br. *s*, NH_2); 8.19 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 13.7 (–, $CH_3CH_2CH_2$); 14.0 (–, CH_3CH_2O); 18.6 (+, $CH_3CH_2CH_2CH_2$); 30.6 (+, $CH_3CH_2CH_2CH_2$); 33.2 (+, C(2')); 36.7 (+, C(1')); 53.8 (+, C(2)); 60.1 (+, CH_3CH_2O); 62.2 (+, $CH_3CH_2CH_2CH_2$); 119.5 (+, CN); 162.2 (+, C(3)); 168.8 (+, C(1)); 171.0 (+, C_2H_5OOC–C(2')). MS (80 eV, 131°): 284 (15, $[M+1]^+$), 283 (100, M^+), 238 (11, $[M-C_2H_5O]^+$), 227 (51, $[M-C_4H_8]^+$, *McLafferty* rearrangement), 210 (54, $[M-C_4H_9]^+$), 183 (63, $[210-HCN]^+$), 182 (15, $[M-COOC_2H_5]^+$). Anal. calc. for $C_{13}H_{21}N_3O_4$ (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, 3360*m* (NH_2); 3250*m* (NH); 3000*w*; 2975*w* (CH); 2220*s* (CN); 1740*s* (C=O); 1680*s* (C=O); 1660*m* (C=C); 1645*s*; 1610*s* (NH). ^{1}H-NMR ((D$_6$)DMSO): 1.20 (*t*, CH_3CH_2O); 2.58 (*t*, $CH_2(2')$); 3.47 (*q*, $CH_2(1')$); 4.09 (*q*, CH_3CH_2O); 5.08 (*s*, $PhCH_2$); 7.24–7.42 (*m*, Ph); 7.58 (br. *s*, NH_2); 8.18 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 14.0 (–, CH_3CH_2O); 33.2 (+, C(2')); 36.8 (+, C(1')); 53.8 (+, C(2)); 60.1 (+, CH_3CH_2O); 68.9 (+, $PhCH_2$); 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 (+, C_2H_5OOC–C(2')). MS (80 eV, 153°): 317 (17, M^+), 272 (1, $[M-C_2H_5O]^+$), 244 (1, $[272-CO]^+$), 210 (4, $[M-BzO]^+$), 200 (2, $[244-CO_2]^+$), 183 (10, $[210-HCN]^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{16}H_{19}N_3O_4$ (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. H_2SO_4 soln. and then extracted with AcOEt. The combined org. layer was dried ($MgSO_4$) 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). ^{1}H-NMR ((D$_6$)DMSO): 2.51 (*t*, CH_2(5)); 3.55 (*t*, CH_2(6)); 4.87 (*s*, CH_3O); 8.83 (br. *s*, NH); 11.08 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 29.6 (+, C(5)); 37.1 (+, C(6)); 51.2 (–, CH_3O); 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, $[181-CH_3O]^+$), 155 (4), 141 (11, $[167-CN]^+$), 136 (6, $[164-CO]^+$). Anal. calc. for $C_8H_9N_3O_3$ (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). ^{1}H-NMR ((D$_6$)DMSO): 1.20 (*t*, CH_3CH_2O); 2.66 (*t*, CH_2(5)); 3.54 (*t*, CH_2(6)); 4.13 (*s*, CH_3CH_2O); 8.76 (br. *s*, NH); 11.13 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 14.3 (–, CH_3CH_2); 29.6 (+, C(5)); 37.1 (+, C(6)); 56.2 (+, C(α)); 59.8 (+, CH_3CH_2O); 117.1 (+, CN); 159.3 (+, C(2)); 167.0 (+, COO); 167.9 (+, C(4)). MS (80 eV, 90°): 209 (71, M^+), 181 (17, $[M-C_2H_4]^+$, *McLafferty* rearrangement), 164 (17, $[M-C_2H_5O]^+$), 137 (41, $[164-HCN]^+$). Anal. calc. for $C_9H_{11}N_3O_3$ (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). ^{1}H-NMR ((D$_6$)DMSO): 0.90 (*d*, $(CH_3)_2CHCH_2$); 1.89 (*sept.*, $(CH_3)_2CHCH_2$); 2.68 (*t*, CH_2(5)); 3.55 (*t*, CH_2(6)); 4.87 (*d*, $(CH_3)_2CHCH_2$); 8.76 (br. *s*, NH); 11.08 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 18.7 (–, $(CH_3)_2CHCH_2$); 27.5 (–, $(CH_3)_2CHCH_2$); 29.6 (+, C(5)); 37.2 (+, C(6)); 56.3 (+, C(α)); 69.4 (+, $(CH_3)_2CHCH_2$); 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, $[M-C_4H_9]^+$), 181 (100, $[M-C_4H_8]^+$, *McLafferty* rearrangement). Anal. calc. for $C_{11}H_{15}N_3O_3$ (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. 1* **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.