Synthesis and Pharmacological Activities of Novel Bicyclic Thiazoline Derivatives as Hepatoprotective Agents. II. (7-Alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamide Derivatives

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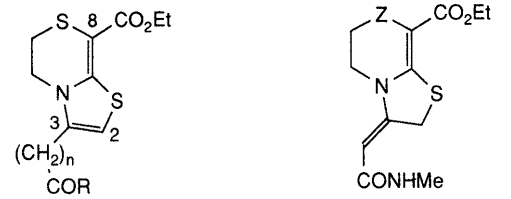
A series of exomethylenic bicyclic thiazoline derivatives (3a—i) was synthesized and evaluated for hepatoprotective activity against galactosamine-induced and monoclonal antibody-induced acute liver injuries in rats. The structure–activity relationships were investigated. Among the compounds synthesized, *N*-methyl-(7-isopropoxycarbonyl-6,6-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamide (3i) exhibited the most potent hepatoprotective activity. This compound suppressed galactosamine-induced hepatic injury at 100 mg/kg by oral administration and further prevented monoclonal antibody-induced hepatic injury at 30 mg/kg by intraperitoneal injection, as judged from the changes in serum transaminase activities.

Key words (7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamide; bicyclic thiazoline; hepatoprotective agent; galactosamine-induced hepatic injury; monoclonal antibody-induced hepatic injury; structure–activity relationship

In our previous paper,[1] we reported a new hepatoprotective agent, ethyl 3-methylcarbamoyl-5,6-dihydrothiazolo[2,3-*c*][1,4]-thiazine-8-carboxylate (**1a**, Fig. 1). This compound exhibits potent hepatoprotective activity against galactosamine-induced hepatic injury and monoclonal antibody-induced hepatic injury in rats. The structure–activity relationships (SAR) of **1a—d** suggested the importance of a conjugated system for hepatoprotective activity. Compounds **1a** and **1b**, in which a carbonyl group at the 3-position conjugates with the thiazole ring, exhibited hepatoprotective activity, whereas the non-conjugated methylene homologs **1c** and **1d** exhibited no activity. This result led us to investigate the activity of compound **2** having another conjugated system, an exomethylenic carbamoyl group, on the same ring.



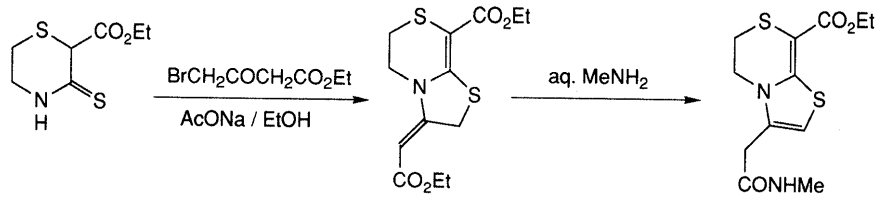
1a : R= NHMe, n=0
1b : R= OEt, n=0
1c : R= NHMe, n=1
1d : R= OEt, n=1

2 : Z=S
3a : Z= no atom

Fig. 1. Structure of **1**, **2** and **3a**

Our synthetic scheme for compound **2** is shown in Chart 1. The key intermediate (**5**) was prepared by reaction of the thiolactam **4**[1] with ethyl 4-bromoacetoacetate[2] in the presence of sodium acetate. The structure of **5** was determined by analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The signal of the olefinic proton (C<u>H</u>=) at the 2-position of ethyl 3-alkyl-5,6-dihydrothiazolo[2,3-*c*][1,4]thiazine-8-carboxylate derivatives was observed between δ 6.0 and 6.3.[1] On the other hand, the signal of C<u>H</u>= of **5** was observed at δ 5.50. However, the synthesis of **2** was unsuccessful because of isomerization to **1c** under the amidation conditions. We therefore planned to examine the hepatoprotective activities of exomethylenic compounds possessing a novel bicyclic thiazoline skeleton which would prevent the isomerization. This paper deals with the synthesis, hepatoprotective activities and SAR of (7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamide derivatives (**3**) as stable exomethylenic bicyclic thiazoline derivatives.

Molecular Design and Chemistry In order to prevent the isomerization of the exocyclic double bond to an endocyclic one, compound **3a** was designed, because it was suggested that the ring strain due to fusion of two five-membered rings would destabilize the structure of the



4 **5** **1c**

Chart 1

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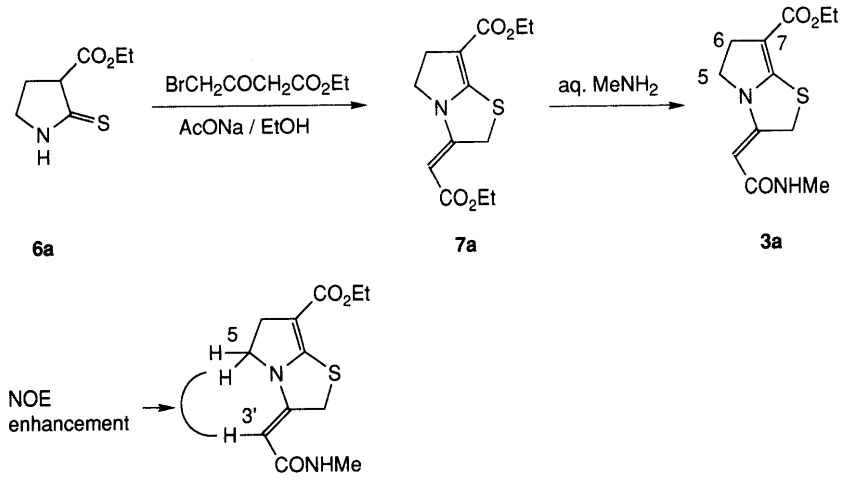
endocyclic isomer and consequently the desired compound **3a** might be preferentially formed.

Synthesis of **3a** was carried out as shown in Chart 2. Reaction of the thiolactam **6a**[3] with ethyl 4-bromoacetoacetate in the presence of sodium acetate gave **7a**. Compound **3a** was obtained as a single isomer in 90% yield by amidation of **7a**. The configuration of the carbamoyl group attached to exomethylenic carbon was determined as *E*-form because nuclear Overhauser effect (NOE) enhancement was observed between the signals of hydrogen atoms at the 5-position and at the 3′-position (indicated in Chart 2).

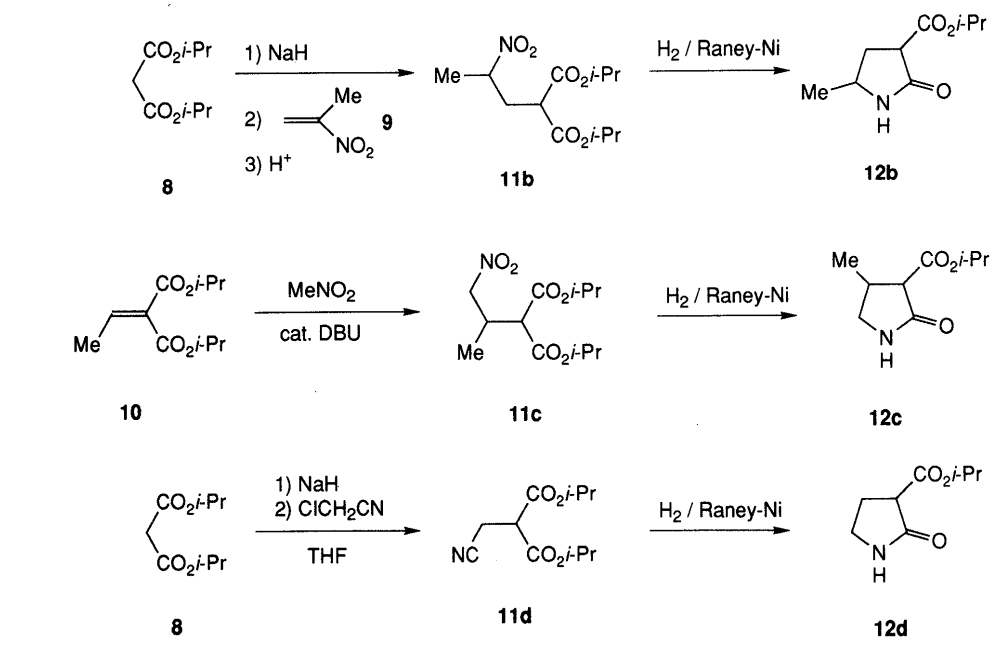
We examined the hepatoprotective activity of **3a**, and conducted further modification of **3a**, namely, transesterification at the 7-position, conversion of the carbamoyl group attached to exomethylenic carbon and methylation at the 5- or 6-position.

Synthesis The syntheses of key intermediates **6b—f** are shown in Chart 3. Addition of the sodium salt of diisopropyl malonate (**8**) to 2-nitropropene[4] (**9**) gave the nitro compound **11b**. Compound **11c** was prepared by the reaction of diisopropyl ethylidenemalonate[5] (**10**) with nitromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The nitro compounds (**11b** and **11c**)



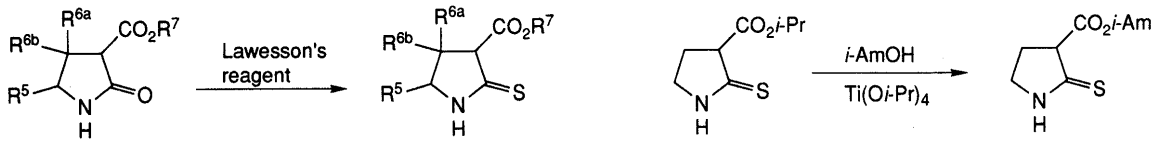
6a **7a** **3a** **3a**

Chart 2



8 **11b** **12b** **10** **11c** **12c** **8** **11d** **12d**

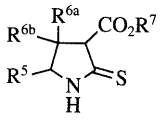
Method A Method B



12b-e **6b-e** **6d** **6f** (*i*-Am: -$(CH_2)_2CHMe_2$)

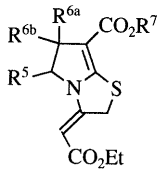
Chart 3

Table 1. Physicochemical Data for Alkoxy 2-Thioxopyrroridine-3-carboxylates (**6**)



Compound No.	R^5	R^{6a}	R^{6b}	R^7	Method (Yield (%))	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
6b	Me	H	H	iso-Pr	A (80)	123—125 (Et_2O–hexane)	$C_9H_{15}NO_2S$	53.70 (53.75)	7.51 (7.55)	6.96 (7.03)
6c	H	Me	H	iso-Pr	A (70)	60—62 ($CHCl_3$–hexane)	$C_9H_{15}NO_2S$	53.70 (53.68)	7.51 (7.42)	6.96 (6.95)
6d	H	H	H	iso-Pr	A (78)	67—68 ($CHCl_3$–hexane)	$C_8H_{13}NO_2S$	51.31 (51.17)	7.00 (6.79)	7.48 (7.20)
6e	H	Me	Me	iso-Pr	A (80)	101—102 ($CHCl_3$–hexane)	$C_{10}H_{17}NO_2S$	55.78 (55.65)	7.96 (8.05)	6.51 (6.38)
6f	H	H	H	iso-Am	B (19)	84—86 ($CHCl_3$–pet. ether)	$C_{10}H_{17}NO_2S$	55.78 (55.65)	7.96 (7.78)	6.51 (6.50)

Table 2. Physicochemical Data for Ethyl (7-Alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetates (**7**)



Compound No.	R^5	R^{6a}	R^{6b}	R^7	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
7a	H	H	H	Et	75	148—149 ($CHCl_3$–EtOH)	$C_{13}H_{17}NO_4S \cdot 0.5H_2O$	53.41 (53.39)	6.21 (6.14)	4.79 (5.01)
7b	Me	H	H	iso-Pr	35	91—92 ($CHCl_3$–hexane)	$C_{15}H_{21}NO_4S$	57.86 (58.00)	6.80 (6.97)	4.50 (4.57)
7c	H	Me	H	iso-Pr	44	103—104 ($CHCl_3$–EtOH)	$C_{15}H_{21}NO_4S$	57.86 (57.92)	6.80 (6.61)	4.50 (4.36)
7d	H	H	H	iso-Pr	76	147—149 ($CHCl_3$–IPA[a])	$C_{14}H_{19}NO_4S$	56.54 (56.33)	6.44 (6.37)	4.71 (4.90)
7e	H	Me	Me	iso-Pr	64	132—133 EtOH	$C_{16}H_{23}NO_4S$	59.05 (59.15)	7.12 (7.07)	4.30 (4.23)
7f	H	H	H	iso-Am	52	133—135 (IPA–IPE[b])	$C_{16}H_{23}NO_4S$	59.05 (58.89)	7.12 (7.12)	4.30 (4.16)

a) IPA, isopropanol. *b*) IPE, diisopropyl ether.

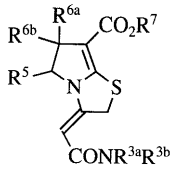
were catalytically reduced to the amines, which were simultaneously cyclized to afford the corresponding lactams (**12b** and **12c**). Compound **12d** was prepared by catalytic reduction[6] of **11d**, which was obtained by cyanomethylation of diisopropyl malonate, using Raney nickel under a pressure of 70—80 atmospheres of hydrogen. Isopropyl 4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (**12e**) was prepared in a manner analogous to that of Colonge and Pouchol.[7] Treatment of the lactams (**12b—e**) with Lawesson's reagent[8] afforded the corresponding thiolactams (**6b—e**) (method A). The isoamyl ester **6f** was synthesized from **6d** by transesterification using titanium (IV) tetraisopropoxide[9] as a catalyst (method B) (Table 1).

The synthetic routes to (7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamide derivatives (**3**) are shown in Chart 4. As described above, the condensation of the thiolactams with ethyl 4-bromoacetoacetate in the presence of sodium acetate afforded diesters (**7**), which were converted to amides (**3**) by using aqueous amine solutions (Tables 2 and 3). In the case of the synthesis of **3d**, the methoxycarbonyl derivative (**13**) was used as an intermediate instead of **7d**, because the reaction rate of **7d** with aqueous NH_4OH was very slow. As discussed for **3a**, amidation of **7b—f** and **13** gave solely the *E*-isomers (**3b—i**).

Also, compound **14**, which is an endocyclic isomer of **3b**, was obtained by treatment of **3b** with 1 N HCl (Chart 5).

Pharmacological Evaluation Compounds **3a—i** and **14** were tested for their hepatoprotective activities against galactosamine-induced hepatic injury and monoclonal

Table 3. Physicochemical Data for (7-Alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-3-ylidene)acetamides (**3**)



Compound No.	R^5	R^{6a}	R^{6b}	R^7	R^{3a}	R^{3b}	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
										C	H	N
3a	H	H	H	Et	Me	H	90	208—209 ($CHCl_3$–IPA)	$C_{12}H_{16}N_2O_3S$	53.71 (53.96)	6.01 6.17	10.44 10.30)
3b	H	H	H	iso-Pr	Me	H	55	197—198 ($CHCl_3$–IPA)	$C_{13}H_{18}N_2O_3S$	55.30 (55.20)	6.43 6.53	9.92 9.77)
3c	H	H	H	iso-Am	Me	H	76	188—189 ($CHCl_3$–IPA)	$C_{15}H_{22}N_2O_3S$	58.04 (58.15)	7.14 7.06	9.03 9.01)
3d	H	H	H	iso-Pr	H	H	53	228—230 ($CHCl_3$–MeOH)	$C_{12}H_{16}N_2O_3S$	53.71 (53.27)	6.01 5.98	10.44 10.28)
3e	H	H	H	iso-Pr	Me	Me	14	159—160 (IPA–IPE)	$C_{14}H_{20}N_2O_3S \cdot 0.5H_2O$	55.06 (54.80)	6.93 7.05	9.17 8.95)
3f	H	H	H	iso-Pr	Et	H	45	172—175 ($CHCl_3$–IPA)	$C_{14}H_{20}N_2O_3S$	56.73 (56.58)	6.80 6.53	9.45 9.43)
3g	Me	H	H	iso-Pr	Me	H	47	159—161 ($CHCl_3$–hexane)	$C_{14}H_{20}N_2O_3S$	56.73 (56.46)	6.80 7.16	9.45 9.16)
3h	H	Me	H	iso-Pr	Me	H	60	188—190 EtOH	$C_{14}H_{20}N_2O_3S$	56.73 (56.73)	6.80 6.60	9.45 9.33)
3i	H	Me	Me	iso-Pr	Me	H	87	Amorphous solid ($CHCl_3$–IPA)	$C_{15}H_{22}N_2O_3S$	58.04 (57.94)	7.14 7.28	9.03 8.96)

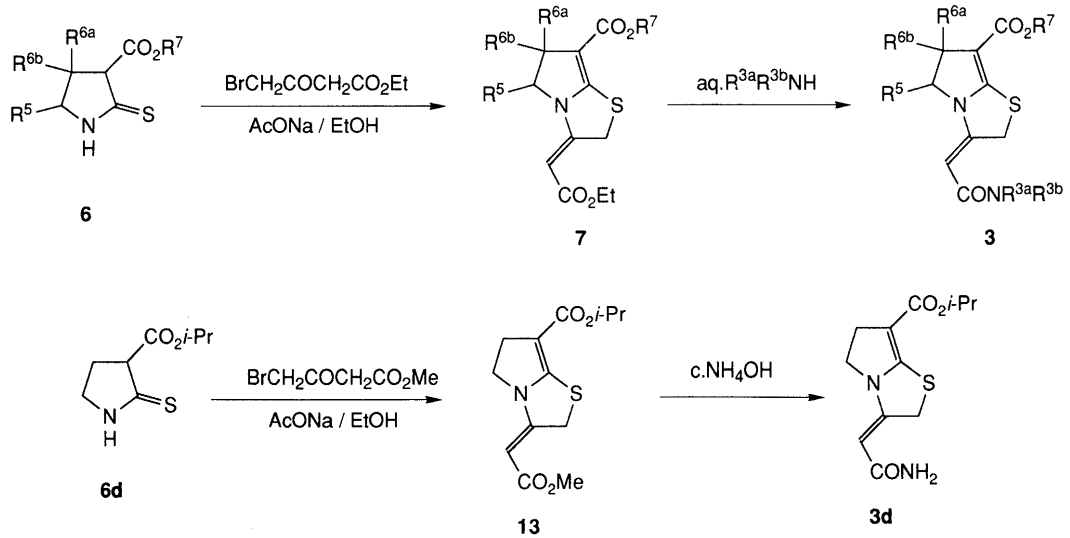


Chart 4

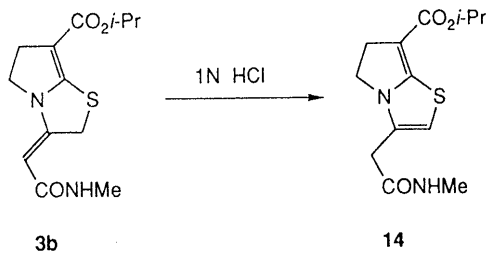


Chart 5

antibody-induced hepatic injury in rats according to the methods described in our previous paper.[1] The hepatoprotective activities were evaluated in terms of suppression (%) of the increase in serum transaminase (GPT) activity, and the results are summarized in Table 4.

Structure–Activity Relationships Compound **3a** showed potent hepatoprotective activities against both galactosamine and monoclonal antibody-induced hepatitis models. Replacement of an ethoxycarbonyl group of **3a** by an isopropoxycarbonyl group (**3b**) enhanced the hepatoprotective activity. Compound **14**, which is an endocyclic isomer of **3b**, exhibited weak activity against the monoclonal antibody-induced hepatitis model. It was suggested that the potent hepatoprotective activity of **3b** depended not only on the pyrrolo[2,1-*b*]thiazole ring system but also on the exomethylenic double bond moiety. The ac-

Table 4. Hepatoprotective Activities of Compounds **3** and Related Compounds against Monoclonal Antibody-Induced and Galactosamine-Induced Hepatitis in Rats

Compd. No.	Galactosamine-induced hepatitis[a] (% inhibition)		Monoclonal antibody-induced hepatitis[b] (% inhibition)
	100 mg/kg *p.o.*	300 mg/kg *p.o.*	30 mg/kg i.p.
3a	33	47[c]	64[d]
3b	40[c]	72[d]	90[d]
3c	9	29	55[d]
3d	n.d.	40	n.d.
3e	n.d.	n.d.	4
3f	n.d.	n.d.	51[d]
3g	−22	25	n.d.
3h	1	67	90[d]
3i	89[d]	96[d]	93[d]
14	45	54[c]	37
1a[1]	73[d]	68[d]	71[d]

n.d.: not determined. *a*) Suppression (%) of galactosamine-induced elevation of GPT in rats ($n=6$). *b*) Suppression (%) of monoclonal antibody-induced elevation of GPT in rats ($n=5$). *c*) $p<0.05$, *d*) $p<0.01$ *vs.* control.

tivity of **3b** against the monoclonal antibody-induced hepatitis model, in particular, was more potent than that of **1a** reported in our previous paper.[1] The conjugated system of **3b**, therefore, seemed to have higher potency than that of **1a**. On the basis of these pharmacological data, **3b** was selected as the lead compound for further modification.

The exchange of the isopropoxycarbonyl group of **3b** for an isoamyloxycarbonyl group (**3c**) caused a decrease in the activity. Replacement of the methylcarbamoyl group of **3b** by another carbamoyl group (**3d—f**) also reduced the activity. We further examined the effect of substituents at the 5 and 6 positions of **3b** upon the activity. Compound **3g**, which is a 5-methyl derivative of **3b**, showed weak activity. On the other hand, the hepatoprotective activity of compound **3h**, possessing a 6-methyl group, was comparable to that of **3b**. Thus, we examined the activity of the 6,6-dimethyl derivative (**3i**). This compound showed the most potent hepatoprotective activity in the two rat hepatitis models among our test compounds. Apparently the existence of hydrophobic or bulky substituents at the 6-position enhanced the hepatoprotective activity.

An acute toxicity study of **3i** was also carried out in mice (1—3 g/kg *p.o.*). No acute toxicological signs were observed even at 3 g/kg with this compound. In conclusion, this novel compound, **3i**, which exhibited potent hepatoprotective activity and low toxicity, was selected for further development as a new hepatoprotective agent.

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX-90Q spectrometer using dimethyl sulfoxide-d_6 (DMSO-d_6) or $CDCl_3$ as a solvent and Me_4Si as an internal standard. Signal multiplicities are represented by s (singlet), br (broad), d (doublet), t (triplet), q (quartet), dd (double doublets), sep (septet) and m (multiplet). Chemical shifts are expressed in δ (ppm) values and coupling constants are expressed in hertz (Hz). Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrometer using KBr disks. Elemental analyses were performed on a Perkin–Elmer Model 240C elemental analyzer. Organic extracts were dried over Na_2SO_4. Silica gel (Merck, Kiesel gel 60, 0.05—0.2 mm) was used for column chromatography.

Ethyl (8-Ethoxycarbonyl-2,3,5,6-tetrahydrothiazolo[2,3-*c*][1,4]-thiazin-3-ylidene)acetate (5) Ethyl 4-bromoacetoacetate[2] (2.6 g, 12 mmol) was added to a suspension of **4** (2.0 g, 10 mmol) and sodium acetate (anhydrous) (1.4 g, 17 mmol) in EtOH (30 ml) at room temperature. The mixture was stirred at the same temperature for 5 h and then refluxed for 20 min. The resulting precipitate was collected and washed with water. The solid was dissolved in $CHCl_3$ and the solution was washed with water and dried. After removal of the solvent, the resulting solid was recrystallized from EtOH to give 0.97 g (32%) of **5** as colorless crystals, mp 160—161 °C. IR: 1698, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, $J=7$ Hz), 1.33 (3H, t, $J=7$ Hz), 2.9—3.2 (2H, m) 3.7—4.2 (2H, m), 4.16 (2H, q, $J=7$ Hz), 4.26 (2H, q, $J=7$ Hz), 4.43 (2H, d, $J=2$ Hz), 5.16 (1H, t, $J=2$ Hz). *Anal.* Calcd for $C_{13}H_{17}NO_4S_2$: C, 49.51; H, 5.43; N, 4.44. Found: C, 49.43; H, 5.41; N, 4.33.

Attempt to Synthesize Compound 2. Formation of *N*-Methyl-(8-ethoxycarbonyl-5,6-dihydrothiazolo[2,3-*c*][1,4]thiazin-3-yl)acetamide (1c) A suspension of **5** (1.7 g, 5.4 mmol) in 40% aqueous $MeNH_2$ (50 ml) was stirred at room temperature for 24 h. Water (50 ml) was added to the mixture. The precipitate was collected, washed with water, and recrystallized from MeOH to give 0.67 g (41%) of **1c** as colorless crystals, mp 198—200 °C. IR: 1652, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, $J=7$ Hz), 2.85 (3H, d, $J=4$ Hz), 2.9—3.2 (2H, m), 3.47 (2H, s), 4.1—4.3 (2H, m), 4.30 (2H, q, $J=7$ Hz), 5.95 (1H, br s), 6.23 (1H, s). *Anal.* Calcd for $C_{12}H_{16}N_2O_3S_2$: C, 47.98; H, 5.37; N, 9.33. Found: C, 47.66; H, 5.52; N, 9.27.

Diisopropyl 3-Nitrobutane-1,1-dicarboxylate (11b) Diisopropyl malonate (90.8 g, 0.483 mol) was added dropwise to a suspension of sodium hydride (60% oil dispersion, 19.5 g, 0.488 mol) in tetrahydrofuran (THF) (300 ml) at 0 °C, and the mixture was stirred at room temperature for 30 min. It was cooled to 0 °C, then 2-nitropropene[4] (40.0 g, 0.460 mol) was added, and the resulting mixture was stirred at room temperature for 20 h. After addition of acetic acid (35 ml), the whole was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, and the solution was washed with water and dried. After removal of the solvent, the crude product was purified by distillation (bp_3 130—150 °C) to give **11b** (62.0 g, 49%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (12H, d, $J=7$ Hz), 1.60 (3H, d, $J=6$ Hz), 2.1—2.7 (2H, m), 3.48 (1H, dd, $J=6$, 8 Hz), 4.5—4.9 (1H, m), 5.10 (1H, sep, $J=7$ Hz), 5.12 (1H, sep, $J=7$ Hz).

Diisopropyl 2-Methyl-3-nitropropane-1,1-dicarboxylate (11c) DBU (7.0 ml, 0.047 mol) was added to a stirred mixture of diisopropyl ethylidenemalonate[5] (189 g, 0.883 mol) and nitromethane (70.0 g, 1.15 mol) was added at room temperature. The temperature of the reaction mixture rose to 60 °C. The mixture was stirred for 2 h, while maintaining the reaction temperature at 40—50 °C. Further DBU (3.0 ml, 0.02 mol) was added, and the mixture was stirred at 40—50 °C for 2 h. After cooling, the reaction mixture was dissolved in toluene. The toluene solution was washed with 1 N HCl and subsequently four times with water, then dried and concentrated *in vacuo* to give **11c** (226 g, 93%) as a pale yellow oil, which was used for the subsequent reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d, $J=6$ Hz), 1.26 (12H, d, $J=6$ Hz), 2.9—3.3 (1H, m), 3.41 (1H, d, $J=7$ Hz), 4.50 (1H, dd, $J=14$, 8 Hz), 4.71 (1H, dd, $J=14$, 6 Hz), 5.15 (2H, sep, $J=6$ Hz).

Diisopropyl 2-Cyanoethane-1,1-dicarboxylate (11d) Diisopropyl malonate (56.4 g, 0.300 mol) was added dropwise to a suspension of sodium hydride (60% oil dispersion, 12.0 g, 0.300 mol) in THF (200 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. It was cooled to 0 °C, chloroacetonitrile (23.0 g, 0.305 mol) was added to it, and the resulting mixture was stirred for 5 h at room temperature. After addition of acetic acid (10 ml), the whole was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, and the solution was washed with water and dried. After removal of the solvent, the crude product was purified by distillation (bp_4 125—140 °C) to give **11d** (41.8 g, 81%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (12H, d, $J=7$ Hz), 2.90 (2H, d, $J=7$ Hz), 3.64 (2H, d, $J=7$ Hz), 5.12 (2H, sep, $J=7$ Hz).

Isopropyl 5-Methyl-2-oxopyrrolidine-3-carboxylate (12b) A solution of **11b** (62.0 g, 0.225 mol) in isopropanol (IPA) (300 ml) was added to a mixture of Raney nickel (20 ml) and IPA (50 ml). The resulting mixture was stirred under a hydrogen atmosphere at 50—60 °C for 8 h, then cooled to room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography using a mixture of $CHCl_3$ and AcOEt (2 : 1). The eluate

was evaporated and the resulting solid was recrystallized from $CHCl_3$–*n*-hexane to give **12b** (15.3 g, 37%) as colorless crystals, mp 80—82 °C. IR: 1730, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (observed as a mixture of two diastereomers (1 : 1)) δ: 1.24 (6H, d, J=6 Hz), 1.32 (6H, J=6 Hz), 1.33 (6H, J=6 Hz), 1.7—2.2 (2H, m), 2.3—2.8 (2H, m), 3.43 (1H, t, J=9 Hz), 3.44 (1H, dd, J=9, 4 Hz), 3.5—4.1 (2H, m), 5.12 (1H, sep, J=6 Hz), 5.14 (1H, sep, J=6 Hz), 7.40 (2H, br s). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.49; H, 8.26; N, 7.62.

Isopropyl 4-Methyl-2-oxopyrrolidine-3-carboxylate (12c) The title compound was prepared from **11c** (57.3 g, 0.208 mol) by the same procedure as described above. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residual pale yellow oil (37.7 g, 98%) was used for the subsequent reaction without further purification. ^{1}H-NMR ($CDCl_3$) (the ratio of two diastereomers could not be determined) δ: 1.1—1.4 (9H, m), 2.8—3.1 (3H, m), 3.3—3.8 (1H, m), 5.12 (1H, sep, J=6 Hz), 6.90 (1H, br s).

Isopropyl 2-Oxopyrrolidine-3-carboxylate (12d) A solution of **11d** (40.0 g, 0.176 mol) in IPA (50 ml) was added to a mixture of Raney nickel (6.0 g) and IPA (200 ml). The resulting mixture was stirred under a pressure of 70—80 atmospheres of hydrogen at 70—80 °C for 5 h, then cooled to room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography with a mixture of $CHCl_3$ and EtOH (97 : 3) as the eluant. The eluate was evaporated and the resulting solid was recrystallized from diisopropylether (IPE)–*n*-hexane to give **12d** (17.0 g, 56%) as colorless crystals, mp 73—76 °C. IR: 1728, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=6 Hz), 1.29 (3H, d, J=6 Hz), 2.2—2.6 (2H, m), 3.2—3.6 (3H, m), 5.08 (1H, sep, J=6 Hz), 6.48 (1H, br s). *Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.05; H, 7.61; N, 8.38.

Isopropyl 4,4-Dimethyl-2-oxopyrrolidine-3-carboxylate (12e) The title compound was prepared in the same manner as reported by Colonge and Pouchol[7] using diisopropyl malonate instead of diethyl malonate, mp 113—116 °C (recrystallized from IPA–hexane). IR: 1742, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.26 (3H, d, J=6 Hz), 1.27 (3H, s), 1.28 (3H, d, J=6 Hz), 2.95 (1H, s), 3.05 (1H, dd, J=9, 1 Hz), 3.31 (1H, d, J=9 Hz), 5.08 (1H, sep, J=6 Hz), 7.02 (1H, br s). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.37; H, 8.75; N, 7.08.

Isopropyl 2-Thioxopyrrolidine-3-carboxylates (6b—e, Method A) A suspension of **12b** (14.8 g, 80.0 mmol) and Lawesson's reagent[6] (17.5 g, 43.3 mmol) in benzene (200 ml) was stirred at 60—70 °C for 2 h. After cooling, insoluble material was filtered off. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel with benzene and subsequently with a mixture of $CHCl_3$ and AcOEt (5 : 1). The $CHCl_3$–AcOEt eluate was concentrated, and the resulting solid was recrystallized from Et_2O–hexane to give **6b** (12.9 g, 80%) as pale yellow crystals, mp 123—125 °C. IR: 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (observed as a mixture of two diastereomers (1 : 1)) δ: 1.28 (6H, d, J=6 Hz), 1.30 (6H, d, J=6 Hz), 1.38 (6H, d, J=6 Hz), 1.9—2.2 (2H, m), 2.5—2.7 (2H, m), 3.76 (1H, t, J=9 Hz), 3.83 (1H, dd, J=9, 4 Hz), 4.0—4.3 (2H, m), 5.07 (1H, sep, J=6 Hz), 5.11 (1H, sep, J=6 Hz), 8.45 (1H, br s), 8.52 (1H, br s).

Compounds **6c—e** were obtained by a procedure similar to that described for **6b**; the yields, melting points and elemental analysis data are given in Table 1. The IR and ^{1}H-NMR data are as follows.

6c: IR: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (observed as a single isomer) δ: 1.19 (3H, d, J=7 Hz), 1.29 (3H, d, J=6 Hz), 1.32 (3H, d, J=6 Hz), 2.95 (1H, dddq, J=7 Hz), 3.23 (1H, dd, J=11, 7 Hz), 3.37 (1H, d, J=7 Hz), 3.86 (1H, dd, J=11, 7 Hz), 5.11 (1H, sep, J=6 Hz), 8.50 (1H, br s).

6d: IR: 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=6 Hz), 1.30 (3H, d, J=6 Hz), 2.3—2.7 (2H, m), 3.6—4.0 (3H, m), 5.10 (1H, sep, J=6 Hz), 8.50 (1H, br s).

6e: IR: 1726 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.23 (3H, s), 1.27 (3H, d, J=6 Hz), 1.30 (3H, d, J=6 Hz), 3.27 (1H, dd, J=11, 1 Hz), 3.39 (1H, s), 3.68 (1H, d, J=11 Hz), 5.09 (1H, sep, J=6 Hz), 8.39 (1H, br s).

3-Methylbutyl 2-Thioxopyrrolidine-3-carboxylate (6f, Method B) A solution of **6d** (15.0 g, 80.2 mmol) and titanium(IV) tetraisopropoxide (30 ml, 0.10 mol) in 3-methyl-1-butanol (150 ml) was refluxed for 3 d, then cooled. Water was added to it, and the resulting mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was washed with brine and dried. After removal of the solvent, the residue was chromatographed on silica gel eluting with a mixture of CH_2Cl_2 and AcOEt (9 : 1). The eluate was evaporated and the resulting solid was recrystallized from $CHCl_3$–petroleum ether to give **6f** (3.2 g, 19%) as colorless crystals, mp 84—86 °C. IR: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (6H, d, J=6 Hz), 1.4—1.9 (3H, m), 2.4—2.7 (2H, m), 3.6—4.1 (3H, m), 4.28 (2H, t, J=6 Hz), 8.40 (1H, br s).

Ethyl (7-Ethoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetates (7a—f) Ethyl 4-bromoacetoacetate[2] (31.5 g, 0.151 mol) was added to a suspension of **6a**[3] (20.0 g, 0.116 mol) and sodium acetate (anhydrous) (12.5 g, 0.152 mol) in EtOH (200 ml) at room temperature. The mixture was stirred at the same temperature for 3 h and water (200 ml) was added. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$–EtOH to give **7a** (25.1 g, 75%) as colorless crystals, mp 148—149 °C. IR: 1694, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.29 (3H, t, J=7 Hz), 3.18 (2H, br t), 3.68 (2H, br t), 4.14 (2H, q, J=7 Hz), 4.19 (2H, q, J=7 Hz), 4.81 (3H, br s).

Compounds **7b—f** were obtained by a procedure similar to that described for **7a**; the yields, melting points and elemental analysis data are given in Table 2. The IR and ^{1}H-NMR data are as follows.

7b: IR: 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=6 Hz), 1.27 (3H, t, J=7 Hz), 1.37 (3H, t, J=7 Hz), 2.72 (1H, dd, J=16, 3 Hz), 3.46 (1H, dd, J=16, 10 Hz), 4.14 (2H, q, J=7 Hz), 4.2—4.4 (1H, m), 4.79 (2H, d, J=2 Hz), 4.98 (1H, t, J=2 Hz), 5.12 (1H, sep, J=6 Hz).

7c: IR: 1690, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (12H, m), 3.1—3.9 (3H, m), 4.19 (2H, q, J=7 Hz), 4.76 (2H, d, J=2 Hz), 4.84 (1H, t, J=2 Hz), 5.07 (1H, sep, J=7 Hz).

7d: IR: 1694, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, d, J=6 Hz), 1.27 (3H, t, J=7 Hz), 3.17 (2H, br t), 3.67 (2H, br t), 4.14 (2H, q, J=7 Hz), 4.81 (3H, br s), 5.06 (1H, sep, J=6 Hz).

7e: IR: 1692, 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.28 (6H, d, J=6 Hz), 1.40 (6H, s), 3.38 (2H, s), 4.14 (2H, q, J=7 Hz), 4.76 (2H, d, J=2 Hz), 4.86 (1H, t, J=2 Hz), 5.07 (1H, sep, J=6 Hz).

7f: IR: 1690, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=7 Hz), 1.29 (3H, t, J=7 Hz), 1.5—1.9 (3H, m), 3.19 (2H, br t), 3.68 (2H, br t), 4.15 (2H, q, J=7 Hz), 4.15 (2H, t, J=7 Hz), 4.83 (3H, br s).

Methyl (7-Isopropoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetate (13) Methyl 4-bromoacetoacetate[10] (13.6 g, 70 mmol) was added to a suspension of **6d** (10.0 g, 53 mmol) and sodium acetate (anhydrous) (6.0 g, 73 mmol) in EtOH (70 ml) at room temperature. The mixture was stirred at the same temperature for 4 h, then water (70 ml) was added. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$–EtOH to give **13** (9.0 g, 60%) as colorless crystals, mp 165—166 °C. IR: 1694, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=6 Hz), 3.24 (2H, br t), 3.73 (2H, br t), 3.74 (3H, s), 4.90 (3H, br s), 5.12 (1H, sep, J=6 Hz). *Anal.* Calcd for $C_{13}H_{17}NO_4S$: C, 55.10; H, 6.05; N, 4.94. Found: C, 55.20; H, 6.14; N, 4.81.

***N*-Methyl-(7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetamides (3a—c, g—i)** A suspension of **7a** (2.0 g, 7.1 mmol) in 40% aqueous $MeNH_2$ (50 ml) was stirred at room temperature for 48 h, then water (100 ml) was added. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$–IPA to give **3a** (1.7 g, 90%) as yellow crystals, mp 208—209 °C. IR: 1654 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 2.84 (3H, d, J=5 Hz), 3.18 (2H, br t), 3.64 (2H, br t), 4.20 (2H, q, J=7 Hz), 4.73 (1H, br s), 4.90 (2H, br s), 5.25 (1H, br s).

Compounds **3b—c** and **3g—i** were obtained by a procedure similar to that described for **3a**; the yields, melting points and elemental analysis data are given in Table 3. The IR and ^{1}H-NMR data are as follows.

3b: IR: 1662, 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, d, J=6 Hz), 2.87 (3H, d, J=5 Hz), 3.20 (2H, br t), 3.66 (2H, br t), 4.76 (1H, br s), 4.96 (2H, br s), 5.10 (1H, sep, J=6 Hz), 5.25 (1H, br s).

3c: IR: 1692, 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=7 Hz), 1.5—1.9 (3H, m), 2.86 (3H, d, J=5 Hz), 3.18 (2H, br t), 3.64 (2H, br t), 4.18 (2H, t, J=7 Hz), 4.73 (1H, br s), 4.90 (2H, br s), 5.20 (1H, br s).

3g: IR: 1668, 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, d, J=6 Hz), 1.30 (3H, d, J=6 Hz), 2.68 (1H, dd, J=15, 4 Hz), 2.83 (3H, d, J=5 Hz), 3.40 (1H, dd, J=15, 9 Hz), 4.0—4.4 (1H, m), 4.88 (3H, br s), 5.04 (1H, sep, J=6 Hz), 5.40 (1H, br s).

3h: IR: 1690, 1656 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=6 Hz), 1.31 (3H, d, J=6 Hz), 2.84 (3H, d, J=5 Hz), 3.1—3.8 (3H, m), 4.72 (1H, br s), 4.86 (2H, br s), 5.06 (1H, sep, J=6 Hz), 5.20 (1H, br s).

3i: IR: 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=6 Hz), 1.40 (6H, s), 2.83 (3H, d, J=5 Hz), 3.32 (2H, s), 4.81 (3H, br s, J=7 Hz), 5.06 (1H, sep, J=6 Hz), 5.65 (1H, br s).

(7-Isopropoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetamide (3d) A suspension of **13** (5.0 g, 18 mmol) in 28% aqueous NH_4OH (100 ml) was stirred at room temperature for 4 d, then water (100 ml) was added. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$–MeOH to give **3d** (2.5 g, 52%) as colorless crystals, mp 228—230 °C. IR: 1684, 1652 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (6H, d, J=6 Hz), 3.09 (2H, br t), 3.64 (2H, br t), 4.78 (2H, br s), 4.94 (1H, sep, J=6 Hz), 5.00 (1H, br s), 6.40 (2H, br s).

***N*,*N*-Dimethyl-(7-isopropoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetamide (3e)** A suspension of **7d** (3.0 g, 10 mmol) in 50% aqueous Me_2NH (50 ml) was stirred at room temperature for 14 d, then water (50 ml) was added. The precipitate was collected, washed with water, and recrystallized from IPA–IPE to give **3e** (0.42 g, 14%) as colorless crystals, mp 159—160 °C. IR: 1686, 1634 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=6 Hz), 3.06 (6H, s), 3.21 (2H, br t), 3.72 (2H, br t), 4.95 (2H, br s), 5.11 (1H, sep, J=6 Hz), 5.13 (1H, br s).

***N*-Ethyl-(7-isopropoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazol-2-ylidene)acetamide (3f)** A suspension of **7d** (4.0 g, 13 mmol) in 35% aqueous $EtNH_2$ (70 ml) was stirred for 10 d at room temperature, then water (50 ml) was added. The precipitate was collected, washed with water, and recrystallized from $CHCl_3$–IPA to give **3f** (1.8 g, 45%) as colorless crystals, mp 172—175 °C. IR: 1690, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7 Hz), 1.30 (6H, d, J=6 Hz), 3.1—3.8 (6H, m), 4.76 (1H, br s), 4.95 (2H, br s), 5.12 (1H, sep, J=6 Hz), 5.24 (1H, br s).

***N*-Methyl-(7-isopropoxycarbonyl-5,6-dihydropyrrolo[2,1-*b*]thiazol-3-yl)acetamide (14)** Compound **3b** (2.1 g, 7.4 mmol) was added to 1 N HCl (50 ml) at room temperature. The mixture was stirred at the same temperature for 1 h, then 1 N NaOH (60 ml) was added and the whole was extracted with $CHCl_3$. The organic layer was washed with water and dried. The solvent was removed and the product was recrystallized from Et_2O–IPE to give **14** (1.6 g, 76%) as colorless crystals, mp 109—112 °C. IR: 1682, 1636 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, d, J=6 Hz), 2.84 (2H, d, J=5 Hz), 3.18 (2H, br t), 3.30 (2H, s), 4.98 (2H, br t), 5.06 (1H, sep, J=6 Hz), 5.70 (1H, br s), 5.84 (1H, br s). *Anal.* Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92. Found: C, 55.11; H, 6.47; N, 9.90.

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