Norton P. Peet,* Shyam Sunder and Robert J. Barbuch

Merrell Dow Research Institute, Indianapolis Center, Building 219,
9550 Zionsville Road, Indianapolis, Indiana 46268

Anna P. Vinogradoff

Western Applied Science and Technology Laboratories, The Dow Chemical Company,
Loveridge Road, Pittsburg, California 94565

Received May 21, 1985

The Gewald syntheses were employed to prepare a series of 2-amino-3-carboethoxythiophenes, and the syntheses of two of these, namely, the 3,4-trimethylene (**1f**) and 3,4-tetramethylene (**1g**) derivatives, were examined in detail. In two preparations of **1f**, octahydro-6a-(4-morpholinyl)-2-thioxocyclopenta[*b*]pyrrole-3-carboxylic acid (**7**) was a co-product. The structure of **7** was ascertained from its 300 MHz ^{1}H nmr and ^{13}C nmr spectra, and by its conversion to 1,4,5,6-tetrahydro-2-mercaptocyclopenta[*b*]pyrrole-3-carboxylic acid ethyl ester (**8**). Isolation of **7** and other observations led to postulated mechanisms for three of the Gewald thiophene syntheses.

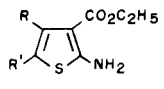
J. Heterocyclic Chem., **23**, 129 (1986).

Excellent synthetic methodology for a variety of substituted 2-aminothiophenes [1,2], 2-aminopyrroles [3] and 2-aminofurans [4] has been developed by Gewald and coworkers [5]. We recently required a series of 2-amino-3-carboalkoxythiophenes as starting materials for the synthesis of heterocycles with proposed biological activity. While the synthesis and biological activity of these planned heterocycles will be the subject of a later report, this paper will describe observations which we have made in employing the versatile methods of Gewald for the synthesis of 2-amino-3-carboalkoxythiophenes. It is interesting to note that several others have also recently used Gewald methodology to prepare 2-amino-3-carboxythiophene derivatives as starting materials for the sythesis of heterocyclic systems [6-15].

Notably, Gewald has described four synthetic methods for 2-amino-3-carboalkoxythiophenes. These methods involve (*i*) condensation of α-mercaptoketones or aldehydes with alkyl cyanoacetates [1,16]; (*ii*) treatment of aldehydes or ketones with alkyl cyanoacetates and elemental sulfur [2]; (*iii*) cyclization of acrylonitriles, obtained from condensing aldehydes or ketones with alkyl cyanoacetates, with elemental sulfur [2]; and (*iv*) the reaction of enamines, derived from ketones and morpholine or piperidine, with alkyl cyanoacetates and elemental sulfur [2].

We have prepared compounds **1a-g** for our study, using methods *ii*, *iii* and *iv*. In particular, we have studied the preparations of thiophenes **1f** and **1g**.

In Scheme 1 are shown the preparations of thiophene **1g**. Cyclohexanone (**2**) is a good substrate for all methods of preparation, as can be seen from the yields (recrystallized material) which are cited.

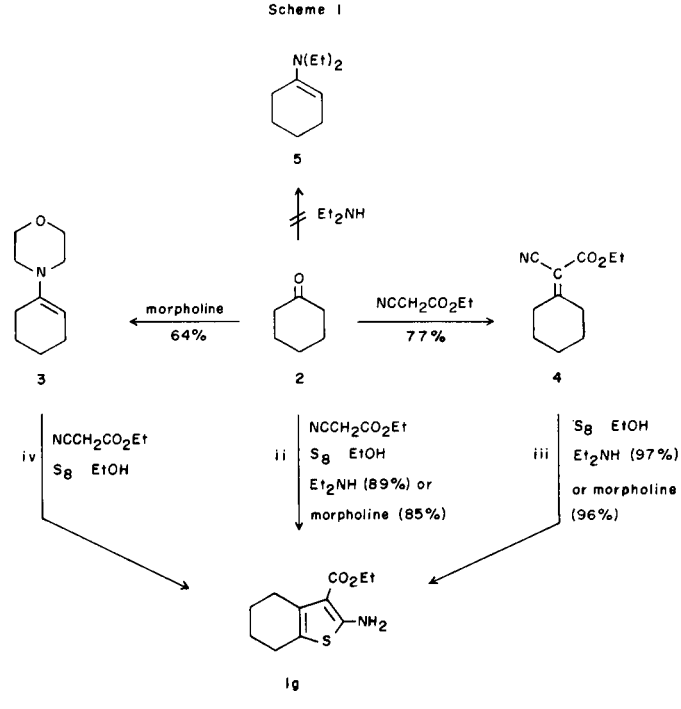


1a, R = H, R' = CH_3 **e**, R = CH_2CH_3, R' = CH_3
b, R = H, R' = $CH_2CH_2CH_3$ **f**, R, R' = $(CH_2)_3$
c, R = H, R' = C_6H_5 **g**, R, R' = $(CH_2)_4$
d, R = R' = CH_3

Cyclopentanone (**6**), it appears, is not an ideal substrate for any of the methods of thiophene preparation, as can be seen from the results shown in Scheme 2. The preparations which were most satisfactory for producing thiophene **1f** were methods *iii*, using either diethylamine or morpholine, and method *ii*, using diethylamine. The yields, however were low in all three cases.

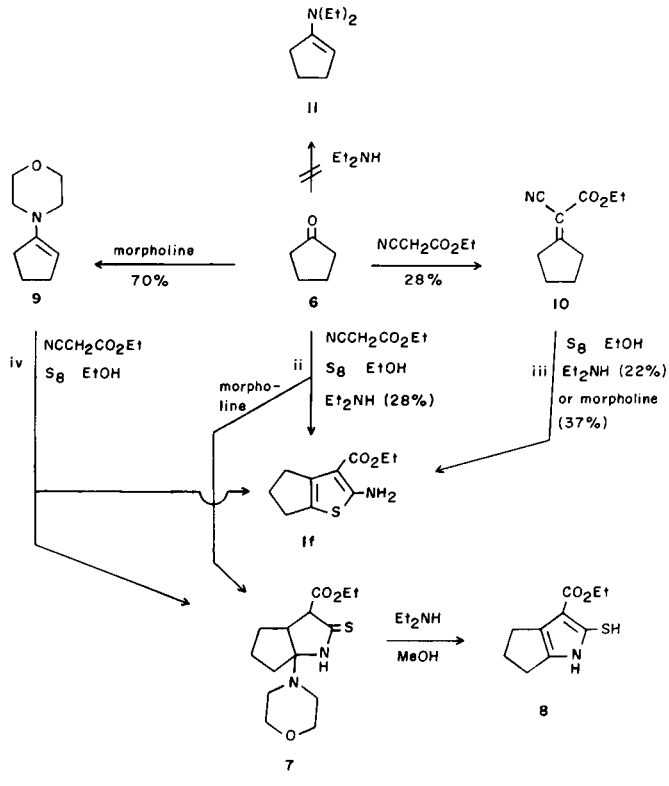
When morpholine was used as the amine base in method *ii*, the only isolated product was the interesting octahydro-6a-(4-morpholinyl)-2-thioxocyclopenta[*b*]pyrrole-3-carboxylic acid ethyl ester (**7**), whose structure was ascertained on the basis of detailed anlaysis of spectral data

Scheme I



(*vide infra*). Compound **7** was also produced from enamine **9** using method *ii*, along with thiophene **1f**. Compound **7** was converted to 1,4,5,6-tetrahydro-2-mercaptocyclopenta[*b*]pyrrole-3-carboxylic acid ethyl ester (**8**) by treatment with diethylamine in methanol at reflux. An apparent *syn* elimination [17] occurs from the *syn-periplanar* [18] conformation of **7**.

Scheme 2



In Table 1 is shown the proton-decoupled ^{13}C nmr data for compounds **7** and **8**. The assignments of all signals to carbon atoms in these structures are in complete agreement with expected resonances for carbon atoms residing in their particular environments. In structure **7**, from the field position of carbon 2 (198.3 ppm) it is clear that the thioamide functionality, and not a tautomerized form, is present. Likewise, in examining the field position of the corresponding carbon atom of **8** (126.0 ppm), it is clear that a thiocarbonyl functionality is not present. From a comparison of the other three carbon atoms of the pyrrolidine ring of **7** with the corresponding carbon atoms which make up the pyrrole ring of **8**, it is clear that tetrahedral centers are changing to trigonal centers in the conversion of **7** to **8**. Restricted rotation of the morpholinyl group of **7** in its sterically crowded environment is apparent, since the 2′ carbon signals fall at slightly different field positions (47.3 and 47.4 ppm).

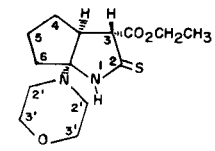
The 300 MHz ^1H nmr spectrum of **7** is shown in Figure 1. As with the ^{13}C nmr spectrum, the ^1H nmr spectral data is in good agreement with the assigned structure. Chemical shift values for all of the resonances, and their multiplicities and assignments, are listed in Table 2. The presence of a proton on C-3 and the NH signal at a downfield position (δ 9.19) further substantiates the *exo* thiocarbonyl double bond at C-2. It was possible to determine the stereochemistry around the C-3, C-3a bond. The protons at these two centers in this rigid system, which appear at δ 3.44 and δ 3.08, respectively, must be in a gauche rather than an eclipsed orientation, because of the magnitude of the coupling constant (J = 4.9 Hz) [19]. The assignments for the trimethylene bridge protons were made on the basis of decoupling experiments. It is interesting to note that the methylene protons of the ethyl ester are nonequivalent, presumably due to their proximity to a prochiral center.

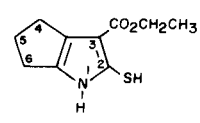
We feel that the formation of compound **7**, which results from both methods *ii* and *iv* but *not* from method *iii*, results from an intermediate which is common to *both* compounds **1f** and **7**. If this is true, compound **7** provides some genuine clues to the mechanisms by which thiophenes are formed by methods *ii*, *iii* and *iv*. In Schemes 3 and 4 are shown mechanisms which we propose for the formation of thiophenes **1f** and **1g**.

In Scheme 3 is shown our proposed mechanism initiating from the morpholinyl enamines of cyclopentanone (**9**) and cyclohexanone (**3**). This scheme relates to method *iv*, and also to method *ii*, but *only* when morpholine is the amine base which forms enamines from **6** and **2** *in situ*. Diethylamine did not undergo enamine formation with

Table 1

^{13}C NMR [a] Data for Compounds **7** and **8**

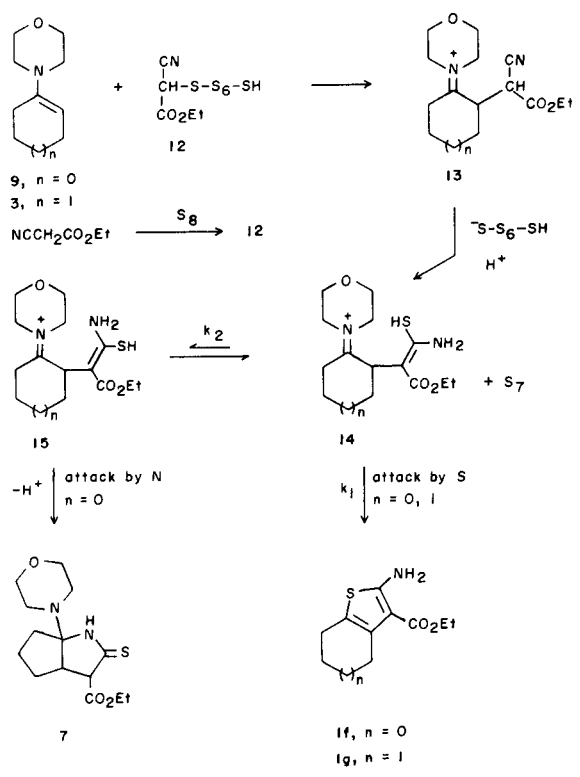




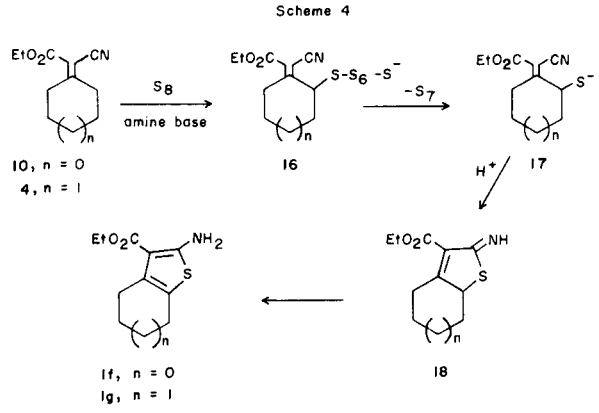
Compound **7**		Compound **8**	
Carbon	Chem Shift (ppm)	Carbon	Chem Shift (ppm)
2	198.3	2	126.0
3	97.2	3	114.0
3a	46.9	3a	129.8
4	33.3	4	26.1
5	23.5	5	25.0
6	37.4	6	27.7
6a	66.1	6a	139.6
2′	47.3, 47.4	C=O	163.6
3′	66.2	OCH_2	58.9
C=O	169.1	CH_3	14.0
OCH_2	60.7		
CH_3	13.9		

[a] Spectra were recorded in DMSO-d_6.

Scheme 3



Scheme 4



either cyclopentanone or cyclohexanone in our hands (see Experimental). We envision enamines **9** and **3** reacting with **12**, the species resulting from the sulfuration of ethyl cyanoacetate, to give the alkylated iminium intermediate **13**. There is good precedent for the formation of **12** from ethyl cyanoacetate and sulfur. The mechanism by which 3-thiazolines are formed from ketones, sulfur and ammonia is generally conceded to involve the initial formation of α-mercaptoketones, which result from α-S-S_6-SH ketones [20-22]. This reaction, which is formally a sulfur oxidation of carbon, readily occurs at ambient temperature.

The above-mentioned carbon oxidation reaction conveniently provides a reduced sulfur species which can convert the nitrile to a thioamide functionality, to produce intermediates **14**. Structures **14** and **15** are postulated as equilibrium species, with equilibration resulting from tautomerization followed by rotation. At equilibrium, one would expect **14** to predominate, since the hydrogen bond between the amino group and the carboethoxy group should be stronger than the hydrogen bond between the sulfhydryl and carboethoxy groups [26]. However, the *initial* production of *only* **14** might be expected, since the sulfhydryl group results from the decay of an initially formed polysulfide, which has no hydrogen bonding capability.

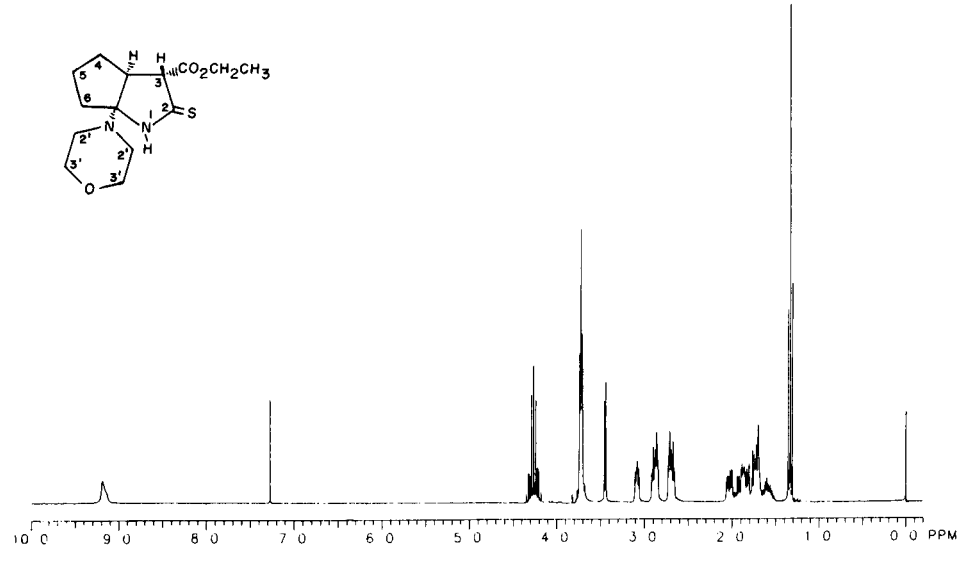
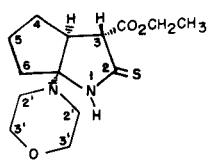


Figure 1. 300 MHz ^{1}H NMR Spectrum (Deuteriochloroform) of Octahydro-6a-(4-morpholinyl)-2-thioxocyclopenta[*b*]-pyrrole-3-carboxylic Acid Ethyl Ester (**7**).

Table 2

300 MHz ^{1}H NMR [a] Assignments for Compound **7**



Chemical Shift (δ)	Assignment	Multiplicity, J-values (Hz)
9.19	NH	br s
4.26	OCH_2	ddq, J_{gem} = 10.8, J_{vic} = 7.3
3.72	CH_2OCH_2	dd, J_{vic} = 4.4, 4.9
3.44	C3-H	d, $J_{3,3a}$ = 4.9
3.08	C3a-H	dd, $J_{3a,3}$ = 4.9, $J_{3a,4\alpha}$ = 6.9
2.87	CHNCH	ddd, J_{gem} = 11.7, J_{vic} = 4.4, 4.9
2.69	CHNCH	ddd, J_{gem} = 11.7, J_{vic} = 4.4, 4.9
2.03	C6-H	ddd, J_{gem} = 11.5, J_{vic} = 1.9, 5.8
1.96-1.85	C4α-H	m
1.90-1.80	C6-H	m
1.80-1.68	C4β-H, C5-H	m
1.68-1.50	C5-H	m
1.33	CH_3	t, J = 7.3

[a] Spectrum was recorded in DMSO-d_6.

Over 30 years ago, Brown introduced the concept of I-strain [27,28], which explained a great deal of experimental data dealing with trigonal centers in 5- and 6-membered rings [29]. Brown generalized that *exo* double bonds in a 6-membered ring were more reactive and less stable than *exo* double bonds in a 5-membered ring [29]. One of many sets of data which fit this generalization is the observation that cyclohexanone is significantly more reactive than cyclopentanone toward reagents which react with carbonyl groups [30,31]. Thus, we postulate that in intermediate **14**, internal nucleophilic attack at the iminium trigonal center by the sulfhydryl group should occur at a faster rate when n = 1 than when n = 0, due to the greater reactivity of the former. If k_1 for **14** (n = 1) is greater than k_2 for **14** (n = 1), then only thiophene **2** should result, which is the observed result. If k_2 is greater than k_1 for **14** (n = 0), then tautomerization of **14** (n = 0) would produce some **15** (n = 0) before all of **14** (n = 0) was convered to thiophene **1f**. The electrophilic iminium center of the intermediate **15** (n = 0) could then be internally trapped by the amino functionality to give pyrrolidinethione **7**.

Scheme 4 shows our postulated mechanism for method *ii*, when diethylamine is the base, and for method *iii*. Reactions of the carbanions of **10** and **4** with sulfur could produce sulfurated intermediates **16**, which could decay to mercaptide species **17**. Precedent for these transformations is again found in the mechanism postulated for the formation of 3-thiazolines from ketones, sulfur and ammonia [20-22]. Cyclization of intermediates **17** by mercaptide attack at the cyano group would lead to **18**, which could undergo prototropic rearrangement to produce thiophenes **1f** and **1g**.

In summary, we have isolated the unexpected pyrrolidinethione **7** from the Gewald syntheses of thiophene **1f**, and determined its structure by ^{13}C nmr and ^{1}H nmr spectroscopy. Elimination of morpholine from **7** gave mercaptopyrrole **8**, which confirmed our structural assignment for **7**. The isolation of **7** led to the assumption that **1f** and **7** are produced from a common intermediate. Based on this assumption and other observations, we have proposed mechanisms for three of the thiophene syntheses described by Gewald.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analysis for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

Materials.

2-Aminothiophene-3-carboxylic ethyl esters **1a-g** were prepared using the procedure described by Gewald [2], employing method *ii* as defined in the discussion section. Physical constants for **1a, 1c, 1d, 1f** and **1g** were in complete agreement with those reported by Gewald [2]. Compounds **1b** and **1e** have been prepared by Tinney, *et al.* [7] and Chakrabarti, *et al.* [8], respectively, but physical constants were not reported. Both of these compounds were purified by Kugelrohr distillation (*ca.* 150°) and **1e** solidified to a yellow solid, mp 40-41°. Yields of purified (distilled or recrystallized) material resulting from these preparations is as follows: **1a**, 58%; **1b**, 78%; **1c**, 57%; **1d**, 24%; and **1e**, 66%. All of the spectral data (ir, nmr and ms) for these compounds was in complete agreement with structure. For preparations of **1f** and **1g**, see Experimental.

Cyanocyclohexylideneacetic Acid Ethyl Ester (**4**).

A mixture of 113 g (1.00 mole) of ethyl cyanoacetate, 113 g (1.04 mmoles) of cyclohexanone (**2**), 12.0 g (0.200 mole) of acetic acid, 7.70 g (0.100 mole) of ammonium acetate and 100 ml of benzene was heated at reflux for 2.5 hours. The mixture was washed with brine (100 ml) and water (3 × 100 ml), and the aqueous washings were backwashed with benzene (2 × 50 ml). The combined benzene layers were dried (sodium sulfate) and concentrated, and the resulting oil was purified by Kugelrohr distillation at 150° [lit [32] bp 150-151° (9 mm)] to afford 148 g (77%) of **4**; ir (Nujol): 2190 (CN), 1730 (C=O), 1600 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 4.30 (q, J = 7 Hz, 2, OCH_2), 3.20-2.53 (m, 4, both vinylic CH_2 groups), 2.10-1.50 (m, 6, remaining CH_2 groups), 1.38 (t, J = 7 Hz, 3, OCH_2CH_3).

Cyanocyclopentylideneacetic Acid Ethyl Ester (**10**).

A mixture of 56.5 g (0.500 mole) of ethyl cyanoacetate, 47.9 g (0.570 mole) of cyclopentanone (**6**), 6.00 g (0.100 mole) of acetic acid, 3.85 g (50.0 mmoles) of ammonium acetate and 70 ml of benzene was heated at reflux, with Dean-Stark separation of water, for 3.5 hours. The mixture was cooled, washed with 10% sodium hydroxide solution (3 × 25 ml) and concentrated. The resulting ester was stirred with a solution of 65 g of sodium bisulfite in water (260 ml) for 2 days, and the clear solution was diluted with an equal volume of water and extracted with benzene (4 × 25 ml). The aqueous solution was then cooled in an icebath and diluted with a solution of 25 g of sodium hydroxide in 110 ml of water. The resulting mixture was extracted with toluene (3 × 100 ml). The toluene extracts

were concentrated, and the resulting solid was recrystallized (benzene-hexane) to afford 25.4 g (28%) of **10**, mp 54-55° (lit [33] mp 55-57°); ir (Nujol): 2190 (CN), 1720 (C=O), 1610 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 4.23 (q, J = 7 Hz, 2, OCH_2), 3.13-2.60 (m, 4, both vinylic CH_2 groups), 2.07-1.63 (m, 4, $C{=}CCH_2CH_2CH_2$), 1.33 (t, J = 7 Hz, 3, OCH_2CH_3); ms (70 eV, chemical ionization, methane): 180 (M^+ + 1), 208 (M^+ + 29), 220 (M^+ + 41).

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid Ethyl Ester (**1g**).

Method *ii* (with Morpholine).

A mixture of 56.6 g (0.500 mole) of ethyl cyanoacetate, 49.1 g (0.500 mole) of cyclohexanone (**2**), 16.0 g (0.500 mole) of sulfur, 49.1 g (0.500 mole) of morpholine and 150 ml of ethanol was stirred at room temperature. An exotherm occurred and the reaction temperature reached 50°. After one hour, a thick precipitate was present. After standing overnight, the mixture was diluted with water and the solid was collected to give 115 g of crude product. Recrystallization (ethanol) afforded 95.2 g (85%) of **1g**, mp 114-115° (lit [2] mp 115°); ir (Nujol): 3490 and 3285 (NH_2), 1645 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 7.14 (br s, 2H, NH_2), 4.11 (q, J = 7 Hz, 2, OCH_2), 2.70-2.20 (m, 4H, C4-CH_2 and C5-CH_2), 1.80-1.40 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.19 (t, J = 7 Hz, 3, CH_3); ms (70 eV, electron impact) m/e 225 (molecular ion).

Method *ii* (with Diethylamine).

When diethylamine was substituted for morpholine in the above preparation, an 89% yield of **1g**, mp 112-113° (lit [2] mp 115°) was obtained.

Method *iii* (with Morpholine).

A mixture of 24.2 g (0.125 mole) of **4**, 4.00 g (0.125 mole) of sulfur, 15 ml of morpholine and 50 ml of ethanol was warmed on the steambath (< 50°) until solution resulted. After standing at room temperature for 40 minutes, a precipitate appeared. The mixture was diluted with water and the solid was collected to give 27.0 g (96%) of **1g**, mp 113-114° (lit [2] mp 115°), whose infrared spectrum was identical to that of **1g** prepared as in Method *ii*.

Method *iii* (with Diethylamine).

When diethylamine was substituted for morpholine in the above preparation, a 97% yield of **1g**, mp 113-114.5° (lit [2] mp 115°), was obtained.

Method *iv*.

A mixture of 53.1 g (0.317 mole) of the morpholine enamine of cyclohexanone [34], 35.9 g (0.317 mole) of ethyl cyanoacetate, 10.2 g (0.317 mole) of sulfur and 100 ml of ethanol was heated at 50-55° (steambath) for 2 hours. Solution initially resulted, but a crystalline solid was present after 2 hours. The mixture was allowed to stand for 15 hours and the solid was collected to give 53.7 g (75%) of **1g**, mp 113-114° (lit [2] mp 115°).

2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylic Acid Ethyl Ester (**1f**).

Method *ii* (with Diethylamine).

A mixture of 56.6 g (0.500 mole) of ethyl cyanoacetate, 42.1 g (0.500 mole) of cyclopentanone (**6**), 16.0 g (0.500 mole) of sulfur, 37.0 g (0.500 mole) of diethylamine and 100 ml of ethanol was heated on a steambath (40°) for 10 minutes, at which time an apparent exotherm occurred. The reaction mixture was then stirred at 35-40° for 3.5 hours and the resulting solution was diluted with water (125 ml). The resulting solid was collected and recrystallized from ethanol to yield 29.2 g (28%) of **1f**, mp 89° (lit [2] mp 91°); ir (Nujol): 3405 and 3290 (NH_2), 1645 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 7.06 (br s, 2H, NH_2), 4.06 (q, J = 7 Hz, 2H, OCH_2), 2.85-1.94 (m, 6H, $CH_2CH_2CH_2$), 1.20 (t, J = 7 Hz, 3H, CH_3); ms: (70 eV, electron impact) m/e 211 (molecular ion).

Method *ii* (with Morpholine).

A mixture of 56.6 g (0.500 mole) of ethyl cyanoacetate, 42.1 g (0.500 mole) of cyclopentanone (**6**), 16.5 g (0.500 mole) of sulfur, 50 ml of morpholine and 150 ml of ethanol was heated (50°) on a steambath for 3 hours and then stirred for 3 days. The mixture was filtered and the filtrate was treated with water. The solid which resulted was collected, and combined with the solid obtained in similar fashion from another experiment, to yield 20.3 g. Recrystallization (ethanol) afforded 12.6 g (4%) of octahydro-6a-(4-morpholinyl)-2-thioxocyclopenta[*b*]pyrrole-3-carboxylic acid ethyl ester (**7**), mp 161-162°; ir (Nujol): 3135 (NH), 1725 (C=O) cm^{-1}; for ^1H nmr and ^{13}C nmr spectral data, see Figure 1 (and Table 2) and Table 1, respectively; ms: (70 eV, chemical ionization, methane) 299 (M^+ + 1), 327 (M^+ + 29), 339 (M^+ + 41).

Anal. Calcd. for $C_{14}H_{22}N_2O_3S$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.55; H, 7.51; N, 9.13.

Method *iii* (with Diethylamine).

A mixture of 10.0 g (55.8 mmoles) of **10**, 1.79 g (55.8 mmoles) of sulfur, 15 ml of diethylamine and 50 ml of ethanol was heated on the steambath (< 50°) for a few minutes, and the resulting solution was allowed to stir at room temperature for 15 hours. The solution was concentrated and the residue was partitioned between water and methylene chloride. The methylene chloride layer was concentrated and the resulting solid was recrystallized (ethanol) to give 2.65 g (22%) of **1f**, mp 87-88° (lit [2] mp 91°), whose infrared spectrum (Nujol) was identical to that of **1f** prepared by Method *ii*.

Method *iii* (with Morpholine).

When morpholine was substituted for diethylamine in the above preparation, a 13.1-g quantity of oil resulted from concentration of the methylene chloride layer. From tlc it was determined that neither **7** or **8** were components of this oil. This oil was applied to a 1200-ml (dry volume) column of flash chromatography silica gel (Baker, 7024-R, average particle size 40 μm) and eluted with 1:3::ethyl acetate:hexane to remove, after concentration of the appropriate fractions and recrystallization (ethanol), 4.40 g (37%) of **1f**, mp 87-88° (lit [2] mp 91°), whose infrared spectrum (Nujol) was identical to that of **1f** prepared by Method *ii*.

Method *iv*.

A mixture of 54.0 g (0.352 mole) of the morpholine enamine of cyclopentanone (34), 39.8 g (0.352 mole) of ethyl cyanoacetate, 11.3 g (0.352 mole) of sulfur and 100 ml of ethanol was heated at 60° (steambath) for 3-4 hours. The resulting solution was allowed to stand at room temperature for 15 hours and concentrated. The resulting viscous oil, after standing for *ca.* 2 weeks, deposited a crystalline solid. The mixture was triturated with ether and a small volume of ethanol and the solid collected to give 7.08 g (7%) of **7**, whose infrared spectrum was identical with that of **7** prepared using Method *ii*. The filtrate was subjected to Kugelrohr distillation (160°) to yield a solid, which afforded, after recrystallization (ethanol), 2.6 g (3.5%) of **1f**, mp 84° (lit [2] mp 91°), whose infrared spectrum (Nujol) was identical to that of **1f** prepared by Method *ii*.

1,4,5,6-Tetrahydro-2-mercaptocyclopenta[*b*]pyrrole-3-carboxylic Acid Ethyl Ester (**8**).

A solution of 1.00 g (3.35 mmoles) of **7** and 1 ml of diethylamine in 100 ml of methanol was heated at reflux for 3 hours. After stirring at room temperature for 15 hours, the solution was concentrated to a small volume, cooled, and the resulting crystals were collected and washed with ether to afford 0.250 g (35%) of **8**, mp 159-160°; ir (Nujol): 3350, 3315 and 3225 (NH), 1695 and 1685 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 10.27 (br s, 1H, NH), 4.30 (q, J = 7 Hz, 2, OCH_2), 3.03-2.00 (m, 6H, $CH_2CH_2CH_2$), 1.33 (t, J = 7 Hz, 3, CH_3); for ^{13}C nmr spectrum, see Table 1; ms: (70 eV, electron impact) m/e 211 (molecular ion); ms: (70 eV, chemical ionization) 212 (M^+ + 1), 240 (M^+ + 29), 252 (M^+ + 41).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.51; H, 5.87; N, 6.35.

REFERENCES AND NOTES

[1] K. Gewald, *Chem. Ber.*, **98**, 3571 (1965).

[2] K. Gewald, E. Schinke and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).

[3] K. Gewald, *Z. Chem.*, **1**, 349 (1961); *Chem. Abstr.*, **58**, 496h (1963).

[4] K. Gewald, *Chem. Ber.*, **99**, 1002 (1966).

[5] The Gewald syntheses and other synthetic routes to thiophenes are reviewed by E. Campaigne in "Comprehensive Heterocyclic Chemistry", Volume 4, C. W. Bird and G. W. H. Cheeseman, eds, Pergamon Press, New York, NY, 1984, pp 863-934.

[6] J. K. Chakrabarti, T. A. Hicks, T. M. Hotten and D. E. Tupper, *J. Chem. Soc., Perkin Trans. I*, 937 (1978).

[7] D. L. Temple, J. P. Yevich, R. R. Covington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey and M. J. Bartek, *J. Med. Chem.*, **22**, 505 (1979).

[8] F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, D. T. Connor, R. J. Sorenson and D. J. Herzig, *J. Med. Chem.*, **24**, 878 (1981).

[9] J. K. Chakrabarti, T. M. Hotten, S. E. Morgan, I. A. Pullar, D. M. Rackham, F. C. Risius, S. Wedley, M. O. Chaney and N. D. Jones, *J. Med. Chem.*, **25**, 1133 (1982).

[10] R. Bohm, R. Pech and E. Schneider, *Pharmazie*, **38**, 135 (1983).

[11] R. Bohm and R. Pech, *Pharmazie*, **38**, 136 (1983).

[12] G. Haubold, R. Pech, G. Bernath, J. Lazar, K. Csukonyi and R. Hirschelmann, *Pharmazie*, **38**, 269 (1983).

[13] M. Schellhase, R. Bohm and R. Pech, *Pharmazie*, **39**, 19 (1984).

[14] F. Eiden and G. Felbermeir, *Arch. Pharm.*, **317**, 675 (1984).

[15] C. J. Shishoo, M. B. Devani, U. S. Pathak, S. Ananthan, V. S. Bhadi, G. V. Ullas, K. S. Jain, I. S. Rathod, D. S. Talati and N. H. Doshi, *J. Heterocyclic Chem.*, **21**, 375 (1984).

[16] Other methods related to this method include the condensations of α-haloketones with malononitrile and related acidic nitriles, followed by treatment of the resulting α,β-unsaturated nitriles with sodium hydrogen sulfide to give thiophenes [1].

[17] B. Capon, M. J. Perkins and C. W. Rees, "Organic Reaction Mechanisms", John Wiley and Sons, New York, NY, 1968, pp 114-118.

[18] J. March, "Advanced Organic Chemistry", Second Edition, McGraw-Hill Book Company, New York, NY, 1977, p 897.

[19] R. M. Silverstein, G. C. Bassler and T. C. Merrill, "Spectrophotometric Identification of Organic Compounds", Fourth Ed, John Wiley and Sons, Inc, New York, NY, 1981, p 210.

[20] W. A. Pryor, "Mechanisms of Sulfur Reactions", McGraw-Hill Book Company, Inc., New York, NY, 1962, pp 153-155.

[21] F. Asinger and H. Offermanns, *Angew. Chem., Int. Ed. Engl.*, **6**, 907 (1967).

[22] A good method for preparing α-mercaptoketones involves the formation and subsequent hydrolysis of 3-thiazolines [23]. Treatment of an α-mercaptoketone with the corresponding ketone and ammonia results in thiazoline formation [24,25]. Both of these observations support the notion that α-mercaptoketones are intermediates in the formation of 3-thiazolines from ketones, sulfur and ammonia.

[23] F. Asinger, W. Schafer and G. Herkelmann, *Ann. Chem.*, **672**, 179 (1964).

[24] F. Asinger, M. Thiel and G. Esser, *Ann. Chem.*, **610**, 33 (1957).

[25] F. Asinger, M. Thiel and E. Pallas, *Ann. Chem.*, **602**, 37 (1957).

[26] J. March, "Advanced Organic Chemistry", Second Ed, McGraw-Hill Book Company, Inc., New York, NY, 1977, p 77.

[27] H. C. Brown, R. S. Fletcher and R. B. Johannesen, *J. Am. Chem. Soc.*,, **73**, 212 (1951).

[28] H. C. Brown and M. Borkowski, *J. Am. Chem. Soc.*, **74**, 1894 (1952).

[29] H. C. Brown, J. H Brewster and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

[30] F. P. Price and L. P. Hammett, *J. Am. Chem. Soc.*, **63**, 2387 (1941).

[31] V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

[32] A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

[33] M. Jackman, A. J. Bergman and S. Archer, *J. Am. Chem. Soc.*, **70**, 497 (1948).

[34] This enamine was prepared by heating stoichiometric amounts of the ketone and morpholine in benzene at reflux, with azeotropic removal of water. No water was removed and no enamine resulted when diethylamine was used in this same procedure, even when a catalytic amount of *p*-toluenesulfonic acid was added.