Synthesis of Some Stable 7-Halo-1,4-thiazepines. Potential Substituted Penam Precursors

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The synthesis of some new 3-carbomethoxy-5-oxoperhydro-1,4-thiazepines is described. Halogenation studies led to the preparation of three potential substituted penam ring precursors: 6,7-dibromo-3-carbomethoxy-5-oxoperhydro-1,4-thiazepine, 3-carbomethoxy-6,7-dichloro-5-oxoperhydro-1,4-thiazepine, and 3-carbomethoxy-7-chloro-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine. Preliminary studies on the reactivity of these α-halothioethers showed that methanolysis to the corresponding methoxy-thiazepines may be carried out in nearly quantitative yields in the case of the first two derivatives; the third compound, on the other hand, led to an open-chain dehydrohalogenated product where C-7 is converted to the corresponding dimethyl acetal.

La synthèse de quelques nouvelles méthoxycarbonyl-3 oxo-5 perhydrothiazépines-1,4 est rapportée. Des études sur l'halogénation de ces composés ont conduit à la préparation de trois précurseurs possibles du noyau penam substitué: la dibromo-6,7 méthoxycarbonyl-3 oxo-5 perhydrothiazépine-1,4, la dichloro-6,7 méthoxycarbonyl-3 oxo-5 perhydrothiazépine-1,4, et la chloro-7 diméthyl-6,6 méthoxycarbonyl-3 oxo-5 perhydrothiazépine-1,4. Des études préliminaires sur la réactivité de ces α-halogénothioethers ont montré que, dans le cas des deux premiers dérivés, la méthanolyse pour donner les méthoxy thiazépines correspondantes peut être effectuée avec des rendements quasi-quantitatifs; le troisième composé, d'autre part, a conduit à un produit de déshydrohalogénation où le C-7 est transformé en diméthyl acétal correspondant.

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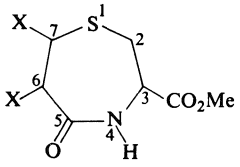
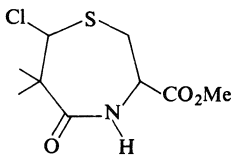
Introduction

During the last few years several reports of total syntheses of penam[3] derivatives have appeared in the literature (1–5). In all cases the β-lactam ring was formed on either a 1,3-thiazolidine or 1,3-thiazoline ring bearing the appropriate substitution.

However, to our knowledge, there is no known synthesis of a penam ring or of a penicillanic acid[3] starting from a seven-membered cyclic precursor. Although there are reports of attempts to achieve such a goal by Knunyants and coworkers (6) and also by Leonard and Wilson (7), this synthetic approach has never been thoroughly investigated due mainly to the unavailability of stable key intermediates such as 7-halo-1,4-thiazepines. It was therefore in an attempt to overcome this limiting factor that a program was initiated first to synthesize some stable 7-halo-1,4-thiazepines and subsequently to systematically investigate the possible modes of forming the elusive 4,7-bond. The model compounds chosen were 3-carbomethoxy-6,7-dihalo-5-oxoperhydro-1,4-thiazepine (**1**) and 3-carbomethoxy-7-chloro-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**2**) which upon cyclization could yield substituted derivatives of the penam ring system.



1
X = Br or Cl



2

It could easily be gleaned from the literature that 3-carbomethoxy-7-chloro-5-oxoperhydro-1,4-thiazepines were highly unstable due to their susceptibility to dehydrohalogenate (6, 7). It was hoped, in the case of **1**, that a *trans* dihalo derivative would resist dehydrohalogenation on

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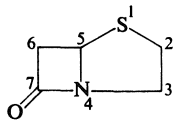
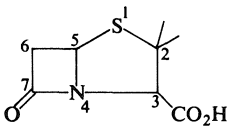
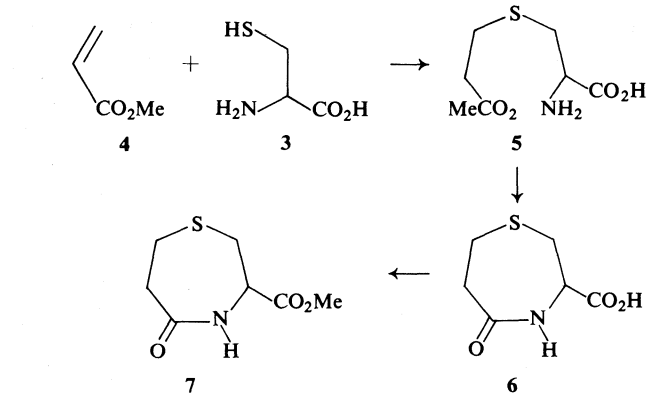
[3]The terms "penam" and "penicillanic acid" correspond to the following ring systems and carry no stereochemical implications, as first suggested by Sheehan *et al.* (21).



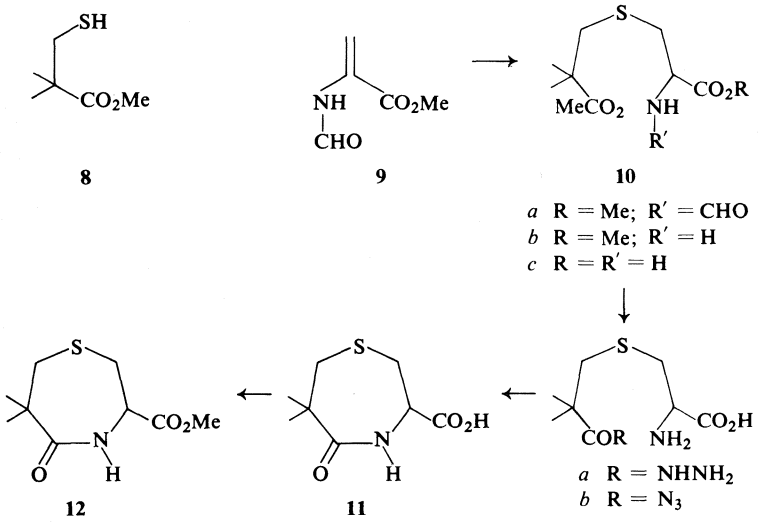
Penam



Penicillanic acid



SCHEME 1



SCHEME 2

stereoelectronic grounds and in the case of **2** that the monochloro derivative would resist elimination to a certain extent due to the lack of β-hydrogens.[4]

Results and Discussion

Synthesis

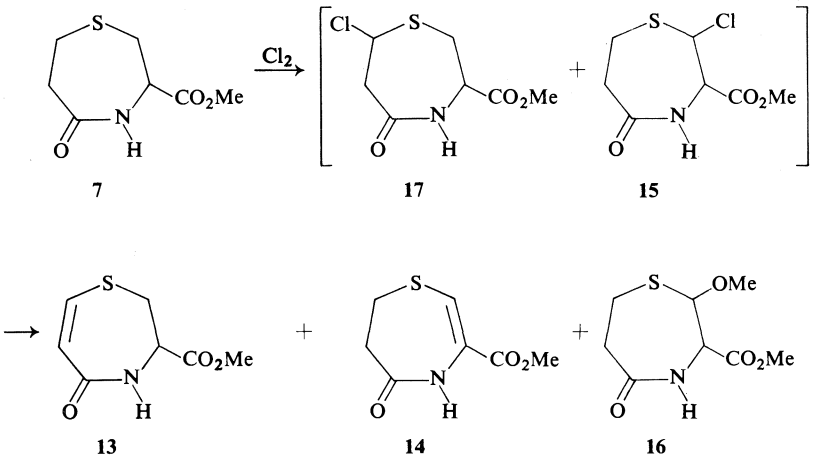
Synthesis of thiazepine **7** was readily achieved by combining known methods from the literature as outlined in Scheme 1.

In a first step, L-cysteine (**3**) was condensed with methyl acrylate (**4**) following a method reported by Foldi (8) for the case of ethyl acrylate. The resulting addition product **5**, obtained in a 90% yield, was then cyclized (9, 10) in a solution of methanol saturated with ammonia to yield 49% of 3-carboxy-5-oxoperhydro-1,4-thiazepine (**6**). Esterification of the acid **6**, effected by standard treatment with ethereal diazomethane, gave a nearly quantitative yield of the desired ester **7**. (See Experimental for comment on optical purity.)

In the case of the second parent compound **12**, a synthetic approach was devised which is shown in Scheme 2.

In the first instance, synthesis of the methyl mercaptopivalate moiety **8** was achieved by standard methods (11, 12) from hydroxypivalic acid (11). This mercapto ester **8** was then condensed with methyl α-formamidoacrylate (**9**) (13)

[4]Rearrangement in an E_1 process nevertheless remained possible.



SCHEME 3

under basic conditions (8) to yield 83% of the oily diester **10***a*. Removal of the formyl protecting group was effected in high yield in methanolic hydrogen chloride to give the corresponding amino diester **10***b*. An attempt to cyclize the latter by the methanol–ammonia method (*vide supra*) completely failed as ammonolysis of the amino ester moiety took place in quantitative yield; a prolonged reaction time gave no further change.

Due to the lower reactivity of the ester group on the pivalate moiety, cyclization was achieved using the acyl azide method (14). To that effect, amino diester **10***b* was partially saponified with a sodium carbonate solution to yield 95% of the expected acid-ester **10***c*. The latter compound upon treatment with hydrazine and subsequently with nitrous acid gave the required thiazepine **11** with a 22% yield. Esterification by the usual diazomethane procedure finally gave the parent 3-carbomethoxy-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**12**) in quantitative yield.

Halogenation

The reaction scheme expected to introduce halogen at C-6 and -7 proceeded via the 6,7-dehydro derivative **13** which, hopefully, could be halogenated on the double bond to yield the required *trans*-dihalo compound **1**.

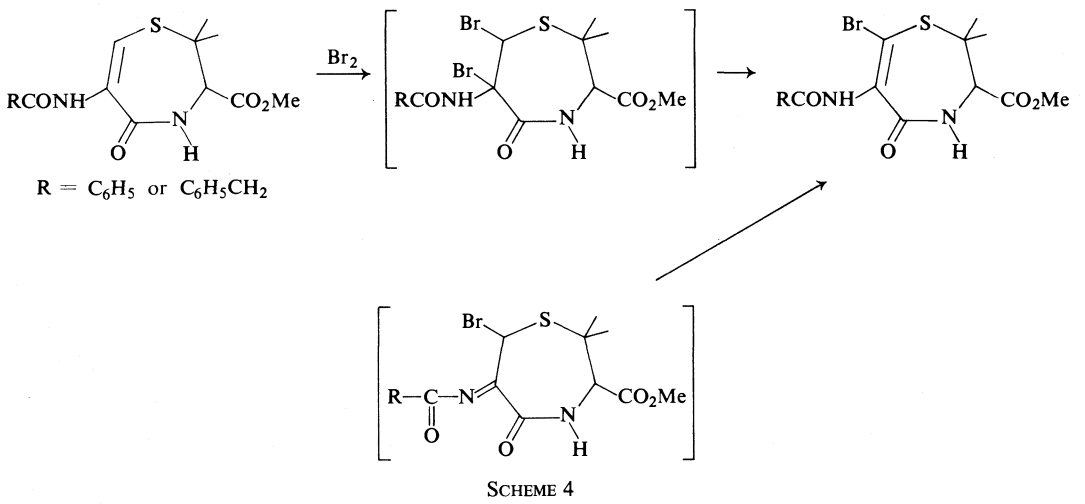
Preparation of 3-carbomethoxy-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**13**) was achieved easily using a known chlorination–dehydrochlorination procedure (7). Indeed it is well known that thioethers react with chlorinating agents to give α-chloro thioethers (15) which in turn may be dehydrohalogenated. In the case of 5-oxo-perhydro-1,4-thiazepines, the α-chloro thioether intermediates are quite unstable [5] probably due to the presence of a carbonyl group at the 5-position; under the reaction conditions stipulated by Leonard and Wilson (7) the intermediate α-chloro thioether formed is dehydrohalogenated *in situ* to yield directly the 2,3,4,5-tetrahydro-1,4-thiazepine.

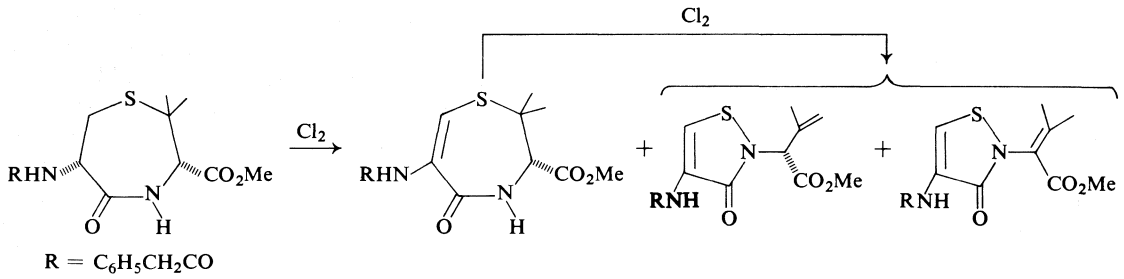
When the above conditions (7) were applied to perhydrothiazepine **7**, three products were obtained after chromatography on silica gel (see Scheme 3).

The desired product, 3-carbomethoxy-5-oxo-2,3,4,5,-tetrahydro-1,4-thiazepine (**13**), was formed in a 37% yield along with 19% of 3-carbomethoxy-5-oxo-4,5,6,7-tetrahydro-1,4-thiazepine (**14**) which results from the dehydrochlorination of the alternate intermediate **15**. Finally, a 1% yield of 3-carbomethoxy-2-methoxy-5-oxoperhydro-1,4-thiazepine (**16**) was obtained suggesting that intermediate **15** had, at least partially, resisted dehydrochlorination and reacted subsequently with the methanolic eluent on the chromatography column.

Concerning the introduction of two halogen atoms on the double bond of **13** in order hopefully to obtain a stable *trans*-6,7-dihalo compound, it

[5] Knunyants and co-workers (6) did report the successful preparation, by the above method, of some 7-halo-5-oxoperhydro-1,4-thiazepines; however, these were unstable and underwent dehydrohalogenation very readily. Repetition of the published procedure by Leonard and Wilson (7) did not yield the expected 7-halo-1,4-thiazepine.



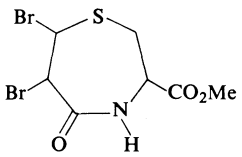


is important to note that Knunyants and coworkers (6) have carried out the bromination of a related thiazepine but without, however, succeeding to isolate the 6,7-dibromo derivative; instead there was always obtained an excellent yield of the corresponding dehydrobrominated product (see Scheme 4).

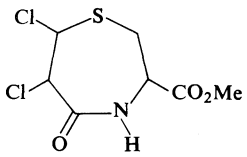
We feel, however, that this result does not militate against the presumed stability of *trans*-6,7-dihalo derivatives since dehydrohalogenation might well have gone through the corresponding acylimine (see Scheme 4) followed by tautomerization to the observed product (16).

Also of importance is the fact that Leonard and Wilson (7) in studying the chlorination at $-60°$ of a pure stereoisomer of the same thiazepine have observed, aside from the normal tetrahydrothiazepine expected, two other compounds resulting from further chlorination and rearrangement of the first reaction product (see Scheme 5).

In both cases cited above, no stable 7-halo perhydrothiazepine could be isolated. However, bromination of thiazepine **13** in dichloromethane yielded 78% of the desired 6,7-dibromo compound **18**, m.p. 133–134°. This compound could be kept for more than 1 month in dichloromethane solution but surprisingly decomposed after a few days when kept in the crystalline state.

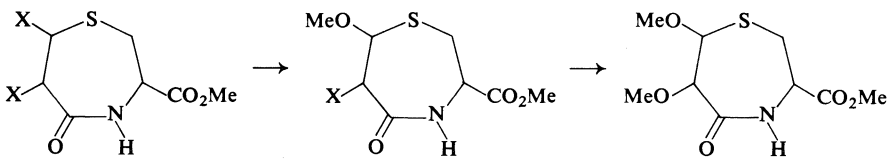


18



19

It is interesting to note that the 6,7-dibromo compound **18**, although slightly unstable can be obtained and kept while the 7-chloro derivative **17** could not even be isolated. This behavior could well be due to a *trans* configuration of the bromine atoms thus preventing the stereoelectronically preferred *trans*-coplanar arrangement of H and Br for a potential dehydrohalogenation.



18 X = Br
19 X = Cl

21 X = Br
22 X = Cl

20

Finally, heating the dibromo derivative **18** in the presence of powdered zinc in methanol yielded the original tetrahydrothiazepine **13** quantitatively showing that bromine had been introduced without modification to the basic skeleton of the molecule.

Having succeeded in preparing the 6,7-dibromothiazepine **18** it became interesting to seek conditions whereby chlorination of the tetrahydrothiazepine **13** would occur on the double bond rather than at the sulfur atom, as illustrated previously in Scheme 5. It was expected that a *trans*-6,7-dichloro derivative could show a greater degree of stability than the corresponding dibromo compound.

In the hope of increasing the polar character of the reactants and therefore altering the normal course of the reaction, the chlorination of tetrahydrothiazepine **13** was carried out in anhydrous nitromethane rather than dichloromethane. There was thus obtained a 60% yield of a solid, m.p. 158–160°, identified as 3-carbomethoxy-6,7-dichloro-5-oxoperhydro-1,4-thiazepine (**19**). As in the previous case treatment with zinc in methanol gave the original tetrahydrothiazepine **13**.

Chlorination studies on the second model compound **12** also proved fruitful in yielding 67% of the desired 7-chlorothiazepine **2**. The position of the chlorine atom follows from the n.m.r. spectrum which shows a singlet at δ 4.90 for the C-7 methine proton; in the case of a 2-chloro derivative one would expect a doublet, unless of course the dihedral angle happened to be nearly 90° (17). However, the assigned structure **2** is strongly supported by results of the reactivity studies (see below).

Reactivity

Considering that the reported attempts (6, 7) to form a 4—7 bond starting from either a 7-halo-5-oxoperhydrothiazepine or the corresponding sulfonium ion, led only to the 6,7-dehydrohalogenated product it was necessary to seek mild conditions where elimination could be suppressed in favor of substitution by nitrogen in the 4 position.

Thus, treatment during 12 h of the 6,7-dibromothiazepine **18** in pyridine and methanol afforded an almost quantitative yield of the corresponding dimethoxy compound **20** and none of the desired penam derivative. On the other hand, the same 6,7-dimethoxy compound was obtained in 1 h when silver oxide or silver carbonate (18) was used instead of pyridine; yields were also quantitative in this case.

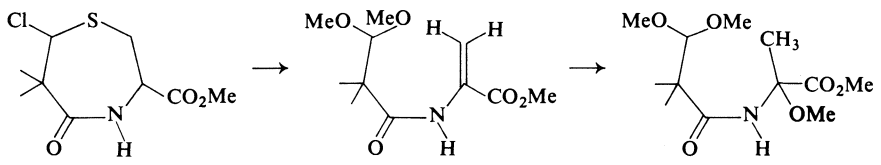
The action of pyridine and methanol on the 6,7-dichlorothiazepine **19** was also investigated. In this case the reaction is much slower: after 24 h of contact one can isolate a 77% yield of the monosubstitution product **22**. Examination of the fragmentation pattern in the mass spectrum corroborates the assignment made on the basis of n.m.r. data; indeed, a fragment at *m/e* 177 corresponds to the loss of methyl thioformate indicating that methanolysis takes place at C-7. This order of reactivity is also that which is expected *a priori*. Interestingly, it was later found that treatment of dibromo thiazepine **18** with silver carbonate in methanol for 20 min gave 23% of the 6-bromo-7-methoxy derivative **21**.

On the other hand, treatment of the 7-chloro-6,6-dimethyl model **2** with pyridine and methanol as above, yielded only unchanged starting material and no trace of substitution product; identical results were also observed in the case of silver oxide or silver carbonate in methanol at room temperature. However, in refluxing methanol in the presence of silver oxide or silver carbonate, a 95% yield of a new product was obtained after 1 h. The structure, which is easily derived by physical methods, corresponds to the open chain enamide **23**. A comparison of the n.m.r., i.r., and u.v. spectra of the enamide **23** to those of an authentic sample of methyl α-acetamidoacrylate was useful in confirming the assigned structure. Also in substantiation of structure **23**, the enamide was treated with a

TABLE 1. The i.r. and mass spectral data of the thiazepines

Compound	Infrared spectrum (cm^{-1}) NH	C=O ester	C=O lactam	Mass spectrum *m/e* 55*	M^+
2	3380	1750	1665	–	251
7	3380	1750	1670	+	189
12	3450	1735	1630	–	217
13	3390	1745	1650	–	187
14	3370	1710	1670	+	187
16	3420	1750	1675	+	217
18	3380	1750	1675	–	345
19	3470	1750	1680	–	257
20	3410	1750	1670	–	249
21	3380	1745	1670	–	297
22	3375	1745	1675	–	253

*An intense peak at *m/e* 55 is *characteristic of all* the 6,7-unsubstituted thiazepines reported herein, and most probably corresponds to $[CH_2{=}CH{-}C{=}O]^{\oplus}$. This fragment originates from C−5, −6, and −7 of the ring and its presence or absence is used advantageously to determine the substitution pattern in the chlorination reactions.



2 **23** **24**

methanol saturated with hydrogen chloride solution to give amide **24** resulting from the addition of methanol to the enamide moiety (20).

Although the desired cyclization failed to take place under both sets of conditions used, the two 7-haloperhydrothiazepine models available will now allow a systematic study of the feasibility of this particular reaction to be undertaken.

It may be of interest to add that very recently Edwards *et al.* (19) described the cyclization, under solvolytic conditions, dioxane – water – silver ion, of 5-chloro-azacyclooctan-2-one to 1-azabicyclo[3.3.0]octan-2-one.

Experimental

The i.r. spectra were determined on a Beckmann, model IR-8, spectrometer using chloroform as solvent (unless otherwise indicated). The n.m.r. spectra were determined either on a Varian A-60 or on a Jeol JNM-4H-100 spectrometer. Deuterochloroform was used as solvent unless otherwise indicated; the following abbreviations are employed: singlet (s), doublet (d), triplet (t), and multiplet (m). The u.v. spectra were measured on a Bausch and Lomb Spectronic 505 spectrometer, and the mass spectra on a Hitachi-Perkin-Elmer RMu-6D instrument. Microanalyses were by Midwest Microlab Inc., Indianapolis, Ind. Melting points are uncorrected.

S-(2-Carbomethoxyethyl)cysteine (5)

This compound was prepared following a method reported by Foldi (8) for the synthesis of *S*-(2-carboethoxyethyl)cysteine. Triethylamine (115 ml) and methyl acrylate (**4**) (51.0 g, 600 mmol) were added with stirring at 25° to a solution of *l*-cysteine hydrochloride hydrate (**3**) (87.5 g, 500 mmol) in ethanol (400 ml). The exothermic reaction which ensued was completed in a few minutes as indicated by a negative nitroprusside test. The resulting precipitate was filtered *in vacuo*, washed with boiling ethanol (2 × 100 ml), and then with ether (100 ml) to yield 90% (93 g) of a white solid melting at 208–209°; i.r. (Nujol): 3200–2000, 1730, 1610, and 1580 cm^{-1}; n.m.r. (CF_3COOH): δ 2.85 (m, 4H); 3.35 (m, 2H); 3.82 (s, 3H); 4.55 (m, 1H); 7.55 (broad m, 3H).

3-Carboxy-5-oxoperhydro-1,4-thiazepine (6)

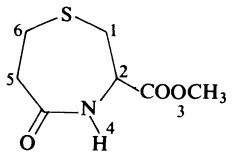
A solution of thioether **5** (41.4 g, 200 mmol) in methanol saturated with ammonia (1.2 l) was stirred at room temperature for 7 days. The solvent was then evaporated to dryness, and the residue dissolved in water (400 ml). The solid which precipitated upon acidification to p*H* 2 with concentrated hydrochloric acid was filtered *in vacuo* and washed with cold water (50 ml). Recrystallization from acetone yielded 49% (17.1 g) of the thiazepine **6**, m.p. 218–219°. The i.r. (Nujol): 3320, 3100–2300, 1715 and 1610 cm^{-1}; n.m.r. (CF_3COOH): δ 2.8–3.4(m, 6H); 4.85 (m, 1H); 8.40 (d, 1H).

Anal. Calcd. for $C_6H_9NO_3S$: C, 41.13; H, 5.18; N, 7.99. Found: C, 41.41; H, 5.27; N, 7.73.

3-Carbomethoxy-5-oxoperhydro-1,4-thiazepine (7)

A solution of perhydrothiazepine **6** (17.5 g, 100 mmol) in methanol (200 ml) was cooled in an ice bath; an ice-cold solution of diazomethane in ether was then slowly added, until the precipitate formed was completely dissolved and evolution of nitrogen ceased. Evaporation of the solvent *in vacuo* and recrystallization of the residue

TABLE 2. The n.m.r. spectral data of the thiazepines



Compound	Position						
	1	2	3	4	5	6	Other
2	2.8–3.6(m)	4.70(m)	3.92(s)	6.80(m)	—	4.90(s)	1.53(6H, s)
7	2.90(m)	4.50(m)	3.82(s)	6.65(m)	2.90(m)	2.90(m)	
12	2.2–3.2(m)	4.50(m)	3.74(s)	6.40(m)	—	2.2–3.2(m)	1.20(3H, s) 1.25(3H, s)
13	3.40(m)	4.55(m)	3.82(s)	7.12(m)	6.02 (d, J = 12 Hz)	6.65 (d, J = 12 Hz)	
14	7.78(s)	—	3.85(s)	7.10(m)	3.10(m)	3.10(m)	
16	4.80 (d, J = 7 Hz)	4.32 (q, J = 7 Hz, J' = 8)	3.85(s)	6.70 (d, J = 8 Hz)	2.1–3.1	2.1–3.1	3.45(3H, s)
18	3.2(m)	5.0(m)	3.92(s)	6.85(m)	5.0 (d, J = 6 Hz)	5.30 (d, J = 6 Hz)	
19	3.20(m)	4.9(m)	3.88(s)	6.82(m)	4.9 (d, J = 6 Hz)	5.20 (d, J = 6 Hz)	
20	2.7–3.3(m)	4.42(m)	3.82(s)	6.80(m)	3.72 (d, J = 3 Hz)	4.88 (d, J = 3 Hz)	3.48(3H, s) 3.50(3H, s)
21	3.0(m)	4.82(q)	3.85(s)	6.70(m)	4.83 (d, J = 6.0 Hz)	4.50 (d, J = 6.0 Hz)	3.50(3H, s)
22	3.00(m)	4.90(m)	3.88(s)	6.80(m)	4.85 (d, J = 6.5 Hz)	4.55 (d, J = 6.5 Hz)	3.52(3H, s)

from ether gave 92% (17.3 g) of thiazepine **7**, m.p. 91–92°. The i.r.: 3380, 1750 and 1670 cm^{-1}; n.m.r.: δ 2.90 (m, 6H); 3.82 (s, 3H); 4.50 (m, 1H); 6.65 (m, 1H).

Anal. Calcd. for $C_7H_{11}NO_3S$: C, 44.42; H, 5.86; N, 7.40. Found: C, 44.54; H, 5.98; N, 7.67.

The optical purity of this compound and its derivatives has not been determined; however, following observations made in a related series where the methanol–ammonia method was used, it is probable that the compounds are at least partly racemized.

*Methyl α-Formamidoacrylate (**9**)*

Compound **9** was prepared according to the method described by Frankel and Reichmann (13); m.p. 50–52° (lit. 53° (13)). The yield for the addition of formamide on pyruvic acid was only 10%, although Frankel and Reichmann report a 20% yield for this reaction.

Bromopivalic Acid

Bromopivalic acid was prepared, as reported by Greene and Hagemeyer (11), from hydroxy pivalic acid and 48% hydrobromic acid. The yield obtained was 70%, m.p. 44° (lit. 75% yield, m.p. 46–48° (11)).

Mercaptopivalic Acid

Thiourea (47 g, 620 mmol) was added to a solution of bromopivalic acid (110 g, 608 mmol) in absolute ethanol (250 ml), and the resulting mixture heated to reflux for 12 h. Sodium hydroxide (72 g) in water (300 ml) was then added and the mixture heated to reflux under nitrogen for a further 3 h. Hydrated sodium sulfide (50 g) was then added to the reaction mixture and the solvent evaporated under vacuum until crystals began to appear. The mixture was cooled in ice, covered with ether (300 ml) and neutralized to p*H* 3 with 20% sulfuric acid. The organic layer was diluted with ether and the resulting solution washed with water saturated with sodium chloride and dried over anhydrous sodium sulfate. The ether was evaporated *in vacuo* and the remaining oil distilled under reduced pressure, to give 73% (60 g) of mercaptopivalic acid; b.p. 120°/15 mm. The i.r.: 3000, 2580, and 1700 cm^{-1}; n.m.r. (DMSO-d_6): δ 1.18 (s, 6H); 2.14 (s, 2H).

*Methyl Mercaptopivalate (**8**)*

A solution of mercaptopivalic acid (60 g, 448 mmol) in anhydrous methanol was saturated with anhydrous hydrogen chloride and then stirred at room temperature for 6 h. The solvent was evaporated to dryness and the residue taken up in ether, and washed twice with a 5% sodium bicarbonate solution. After drying over anhydrous sodium sulfate the ether was evaporated under vacuum and the remaining oil distilled under reduced pressure, yielding 62% (40 g) of methyl mercaptopivalate (**8**), b.p. 40°/0.05 mm. The i.r.: 2580 and 1730 cm^{-1}; n.m.r.: δ 1.26 (s, 6H); 1.45 (t, 1H); 2.69 (d, 2H); 3.69 (s, 3H).

Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.65; H, 8.15. Found: C, 49.05; H, 8.43.

*Methyl N-Formyl S-(2-Carbomethoxy-2-methyl propyl)-cysteinate (**10a**)*

Methyl α-formamidoacrylate (**9**) (1.04 g, 8.07 mmol) was added to a solution of methyl mercaptopivalate (**8**) (1.19 g, 8.07 mmol) in methanol (25 ml). Three drops of triethylamine were then added and the mixture stirred at room temperature for 4 h. The solvent was evaporated to dryness and the residue chromatographed on silica gel using ether as eluent. The diester **10*a*** was obtained as an oil (1.85 g, 83%) which was used for the next step without further purification. The i.r. (CH_2Cl_2): 3430, 1735 and 1690 cm^{-1}; n.m.r.: δ 1.25 (s, 6H); 2.78 (s, 2H); 3.03 (d, 2H); 3.71 (s, 3H); 3.79 (s, 3H); 4.90 (m, 1H); 6.85 (m, 1H); 8.27 (s, 1H).

*Methyl S-(2-Carbomethoxy-2-methyl propyl)cysteinate (**10b**)*

Diester **10*a*** (100 mg, 3.61 mmol) was dissolved in methanol (10 ml) and the resulting solution saturated with dry hydrogen chloride and stirred at room temperature for 1 h. The solvent was then evaporated to dryness and the remaining oil taken up in ether. The organic layer was washed with a 5% sodium carbonate solution. After drying over anhydrous sodium sulfate, the ether was evaporated and compound **10*b*** (0.087 g, 95%) was obtained as a yellow oil which was used without further purification. The i.r. (CH_2Cl_2): 3400, 1730, 1380 and 1360 cm^{-1}; n.m.r.: δ 1.26 (s, 6H); 2.82 (s, 2H); 3.0 (m, 2H); 3.71 (s, 3H); 3.75 (m, 1H); 3.78 (s, 3H).

*S-(2-Carbomethoxy-2-methyl propyl)cysteine Hydrochloride (**10c**)*

Amino-diester **10*b*** (4.0 g, 16.1 mmol) was added to a 10% sodium carbonate solution (150 ml) and the resulting mixture stirred at room temperature for 1 h, after which it was acidified to p*H* 0 by careful addition of 6 *N* hydrochloric acid. The aqueous solution was then concentrated to 75 ml by evaporation under vacuum. The precipitate formed was filtered and recrystallized from 6 *N* HCl, to yield 95% (4.2 g) of the amino-diacid monoester hydrochloride **10*c***, m.p. 245° (dec.), which was used without further purification. The i.r. (Nujol): 3000, 2800, 1720 and 1700 cm^{-1}; n.m.r. (D_2O): δ 1.65 (s, 6H); 3.30 (s, 2H); 3.58 (d, 2H); 4.13 (s, 3H); 4.70 (t, 1H); 5.22 (HDO).

*3-Carboxy-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**11**)*

A mixture of acid-ester hydrochloride **10*c*** (3.0 g, 11.1 mmol) and redistilled hydrazine hydrate (20 ml) was heated to reflux for 2 h. The excess hydrazine hydrate was evaporated to dryness; the residue was taken up in *n*-butanol (5 ml) and the solvent once again evaporated *in vacuo*. The residue was dissolved in methanol and the remaining crystals of hydrazine hydrochloride filtered. The methanolic filtrate was evaporated to dryness to yield 56% (1.45 g) of the required hydrazide as a gum.

The crude hydrazide (1.45 g, 6.18 mmol) was dissolved in 2 *N* hydrochloric acid (62 ml) at 0° and sodium nitrite (0.428 g, 6.18 mmol) added. The mixture was stirred at 0° for 15 min, and then poured into ice-cold water (3.6 l). The solution was neutralized by the addition of sodium bicarbonate (7.8 g) and kept at 4° for 40 h in the refrigerator. The mixture was then acidified to p*H* 4 with 2 *N* hydrochloric acid (about 50 ml) and the water evaporated under vacuum to a final volume of 175 ml. Crystals which appeared during the evaporation were filtered under vacuum. Recrystallization from ethanol–ether yielded 40% (495 mg) of 3-carboxy-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**11**) m.p. 218–220°. The i.r. (Nujol);

3340, 1720 and 1555 cm^{-1}; n.m.r. (DMSO-d_6): δ 1.15 (s, 3H); 1.20 (s, 3H); 2.3–3.2 (m, 4H); 4.55 (m, 1H); 6.53 (d, 1H).

Anal. Calcd. for $C_8H_{13}NO_3S$: C, 47.27; H, 6.44. Found: C, 47.12; H, 6.87.

*3-Carbomethoxy-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**12**)*

A solution of thiazepine **11** (1.0 g, 4.93 mmol) in methanol (10 ml) was treated with a solution of diazomethane in ether until the evolution of nitrogen ceased and the reaction mixture took on a faint yellow color. The solvent was evaporated to dryness and the residue recrystallized from ether, to yield 80% (0.85 g) of 3-carbomethoxy-6,6-dimethyl-5-oxo-perhydro-1,4-thiazepine (**12**), m.p. 89–89.5°. The i.r. (Nujol): 3450, 1735 and 1630 cm^{-1}; n.m.r.: δ 1.20 (s, 3H); 1.25 (s, 3H); 2.2–3.2 (m, 4H); 3.74 (s, 3H); 4.50 (m, 1H); 6.40 (m, 1H).

Anal. Calcd. for $C_9H_{15}NO_3S$: C, 49.85; H, 6.97. Found: C, 49.92; H, 7.04.

Reaction of 3-Carbomethoxy-5-oxoperhydro-1,4-thiazepine (7) with Chlorine

A solution of the thiazepine **7** (18.9 g, 100 mmol) in anhydrous dichloromethane (500 ml) was cooled in a mixture of Dry Ice and acetone and slowly treated (dropwise) with 1 equiv of chlorine in carbon tetrachloride (182 ml, 0.55 *M*). The resulting mixture was stirred for 2 h at −65° and, after removal of the cooling bath, allowed to warm up to room temperature, at which point evolution of hydrogen chloride could be observed. After a 2 h reflux, the solution was concentrated *in vacuo*, the oily residue dissolved in a minimum amount of chloroform and chromatographed on silica gel.

Three products were obtained by eluting successively with ether (first product) and methanol–ether (1:20) (second and third products):

(*i*) 3-Carbomethoxy-5-oxo-4,5,6,7-tetrahydro-1,4-thiazepine (**14**) (3.5 g, 19%), m.p. 88–89° (ether); u.v.: 298 mμ (ε 1700).

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.84; N, 7.48. Found: C, 44.71; H, 5.03; N, 7.48.

(*ii*) 3-Carbomethoxy-2-methoxy-5-oxoperhydro-1,4-thiazepine (**16**) (0.60 g, ~1%), m.p. 148–149°.

Anal. Calcd. for $C_8H_{13}NO_4S$: C, 43.82; H, 5.98; N, 6.39. Found: C, 44.15; H, 6.05; N, 6.42.

(*iii*) 3-Carbomethoxy-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**13**) (6.9 g, 37%), m.p. 131–132° (methanol–ether); u.v.: 227 (ε 4900) and 279 mμ (ε 7700).

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.84; N, 7.48. Found: C, 45.14; H, 5.02; N, 7.48.

*6,7-Dibromo-3-carbomethoxy-5-oxoperhydro-1,4-thiazepine (**18**)*

A solution of thiazepine **13** (0.935 g, 5 mmol) in anhydrous dichloromethane (100 ml) was treated (dropwise) with a solution of bromine in carbon tetrachloride (5.5 ml, 0.92 *M*). The solvent was then evaporated *in vacuo*, and the residue chromatographed on a silica gel column, eluting with dichloromethane. Recrystallization from chloroform–ether yielded 78% of dibromothiazepine **18**, m.p. 133–134°. The i.r. (CH_2Cl_2): 3380, 1750 and 1675 cm^{-1}; n.m.r.: δ 3.25 (m, 2H); 3.92 (s, 3H); 5.05 (d + m, 2H); 5.30 (d, 1H); 6.85 (m, 1H).

Anal. Calcd. for $C_7H_9Br_2NO_3S$: C, 24.22; H, 2.62. Found: C, 24.27; H, 2.52.

*Reaction of 3-Carbomethoxy-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**13**) with Chlorine*

A stirred solution of thiazepine **13** (1.87 g, 10 mmol) in nitromethane was slowly treated (dropwise) with chlorine in carbon tetrachloride (11 mmol; 20 ml, 0.54 *M*). Evaporation of the solvent *in vacuo* and chromatography of the residue on silica gel, eluting with dichloromethane, gave a first product in a 60% yield: 3-carbomethoxy-6,7-dichloro-5-oxoperhydro-1,4-thiazepine (**19**) (1.54 g), m.p. 158–160° (chloroform–ether).

Anal. Calcd. for $C_7H_9Cl_2NO_3S$: C, 32.57; H, 3.51. Found: C, 32.48; H, 3.63.

Further elution with dichloromethane gave 3% (340 mg) of an unseparable mixture of two products: probably a dichloro thiazepine (isomer of **19**) and the corresponding unsaturated chlorothiazepine u.v. (C_2H_5OH): 290 mμ.

*Reaction of the Dichlorothiazepine **19** with Zinc*

A mixture of the dichlorothiazepine **19** (10 mg) and zinc powder (50 mg) in methanol (10 ml) is heated to reflux for 30 min. After filtration and evaporation of the solvent, t.l.c. on silica gel using ether or methanol–ether 1:20 as eluent showed a complete transformation into 3-carbomethoxy-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**13**).

*Reaction of the Dibromothiazepine **18** with Zinc*

The above procedure applied to the dibromothiazepine **18** gave quantitatively the same results.

*3-Carbomethoxy-7-chloro-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**2**)*

A solution of thiazepine **12** (1.926 g, 8.88 mmol) in methylene chloride (150 ml) was cooled to −65° in a Dry Ice – acetone bath, and treated dropwise with a solution of chlorine in carbon tetrachloride (8.8 mmol; 27 ml, 0.34 *M*). The mixture was stirred at −65° for 1 h and then heated to reflux for 20 h. The solvent was evaporated under vacuum and the residue recrystallized from carbon tetrachloride, to yield 67% (1.40 g) of chloro derivative **2**, m.p. 148.5°. The i.r. (CCl_4): 3380, 1750 and 1665 cm^{-1}; n.m.r.: δ 1.53 (s, 6H); 2.8–3.6 (m, 2H); 3.92 (s, 3H); 4.7 (m, 1H); 4.90 (s, 1H); 6.80 (m, 1H).

Anal. Calcd. for $C_9H_{14}ClNO_3S$: C, 42.94; H, 5.61. Found: C, 43.20; H, 5.69.

*3-Carbomethoxy-6-chloro-7-methoxy-5-oxoperhydro-1,4-thiazepine (**22**)*

A solution of 3-carbomethoxy-6,7-dichloro-5-oxoperhydro-1,4-thiazepine (**19**) (100 mg, 0.4 mmol) and pyridine (63 mg, 0.8 mmol) in methanol (10 ml) was stirred at room temperature for 24 h. The t.l.c. (silica gel, ether) showed the presence of two products, the dimethoxy thiazepine **20** at R_f 0.1 and the chloro-methoxy thiazepine **22** at R_f 0.5. Evaporation of the solvent and chromatography on silica gel (10 g) eluting with dichloromethane yielded 77% (75 mg) of 3-carbomethoxy-6-chloro-7-methoxy-5-oxoperhydro-1,4-thiazepine (**22**), m.p. 151–152° (chloroform–ether). The i.r.: 3375, 1745 and 1675 cm^{-1}; n.m.r.: δ 3.00 (m, 2H); 3.52 (s, 3H); 3.88 (s, 3H); 4.55 (d, 1H); 4.85 (d, 1H); 4.90 (m, 1H); 6.80 (m, 1H).

Anal. Calcd. for $C_8H_{12}NO_4SCl$: C, 37.87; H, 4.77, N, 5.52. Found: C, 37.74; H, 4.69; N, 5.46.

*3-Carbomethoxy-6,7-dimethoxy-5-oxoperhydro-1,4-thiazepine (**20**)*

Method A

A mixture of 3-carbomethoxy-6,7-dibromo-5-oxoperhydro-1,4-thiazepine (**18**) (160 mg, 0.43 mmol) and pyridine (68 mg, 0.86 mmol) in methanol (20 ml) was stirred at room temperature for 12 h. After evaporation of the solvent under vacuum, the reaction product was dissolved in a small amount of dichloromethane and chromatographed on silica gel (20 g) using ether–dichloromethane (1:20) as eluent to yield 98% (113 mg) of 3-carbomethoxy-6,7-dimethoxy-5-oxoperhydro-1,4-thiazepine (**20**), m.p. 154–155°. The i.r.: 3410, 1750 and 1670 cm^{-1}; n.m.r.: δ 2.7–3.3 (m, 2H); 3.48 (s, 3H); 3.50 (s, 3H); 3.72 (d, 1H); 3.82 (s, 3H); 4.42 (m, 1H); 4.88 (d, 1H); 6.80 (m, 1H).

Anal. Calcd. for $C_9H_{15}NO_5S$: C, 43.36; H, 6.06. Found: C, 43.49; H, 6.14.

Method B

A mixture of the dibromo thiazepine **18** (36 mg, 0.10 mmol) and silver carbonate (100 mg, 0.40 mmol) in methanol (10 ml) was stirred at room temperature for 2 h. Filtration of the solution on Celite and evaporation of the solvent under vacuum gave, after recrystallization from chloroform–ether, a nearly quantitative yield of the dimethoxy thiazepine **20**, identical in all respects to the product obtained in method A.

The same result is obtained if silver oxide is used instead of silver carbonate.

*6-Bromo-3-carbomethoxy-7-methoxy-5-oxoperhydro-1,4-thiazepine (**21**)*

A mixture of 6,7-dibromo-3-carbomethoxy-5-oxoperhydro-1,4-thiazepine (**18**) (500 mg, 1.35 mmol) and silver carbonate (1.35 g, 5.4 mmol) in methanol (50 ml) was stirred at room temperature for 20 min. The t.l.c. then showed disappearance of the starting material and the presence of two reaction products. The mixture was filtered on Celite, the solvent evaporated under vacuum and the residue chromatographed on a silica gel column (50 g) using ether as eluent. Evaporation of the first fractions yielded 23% (100 mg) of 6-bromo-3-carbomethoxy-7-methoxy-5-oxoperhydro-1,4-thiazepine (**21**) melting, after recrystallization from chloroform–ether, at 108–110°; *m/e* 296.9651; calcd. 296.9671.

The second spot observed on t.l.c. corresponds to the 6,7-dimethoxy compound **20**.

*Reaction of Thiazepine **2** with Silver Oxide and Methanol*

A mixture of 3-carboxy-7-chloro-6,6-dimethyl-5-oxoperhydro-1,4-thiazepine (**2**) (100 mg, 0.40 mmol) and silver oxide (250 mg, 1.1 mmol) in methanol (15 ml) was heated to reflux for 1 h. The mixture was then filtered on Celite, the solvent evaporated *in vacuo* and the residue chromatographed on a silica gel column (10 g) using dichloromethane as eluent. The enamide **23** (90 mg) was obtained as an oil with a 92% yield. The i.r. (CH_2Cl_2): 3330, 1720 and 1675 cm^{-1}; n.m.r.: δ 1.24 (s, 6H); 3.60 (s, 6H); 3.89 (s, 3H); 4.23 (s, 1H); 5.90 (d, 1H); 6.66 (s, 1H); 9.33 (m, 1H); *m/e*: 245.

*Reaction of Enamide **23** with Methanolic Hydrogen Chloride*

The enamide **23** (90 mg, 0.368 mmol) was dissolved in anhydrous methanol (10 ml) saturated with hydrogen chloride, and the resulting solution stirred at 25° for 3 h. The hydrogen chloride was then neutralized by careful addition of solid sodium bicarbonate, the solvent evaporated to dryness and the residue taken up in ether. The inorganic salts were filtered and the reaction products separated by preparative t.l.c. using ether as eluent, to yield 50% (50 mg) of the oily amide **24**. The i.r. (CH_2Cl_2): 3380, 1745, and 1680 cm^{-1}; n.m.r.: δ 1.16 (s, 6H); 1.70 (s, 3H); 3.24 (s, 3H); 3.55 (s, 6H); 3.83 (s, 3H); 3.18 (s, 1H); 7.60 (m, 1H).

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