pounds have been reported with varying results.[2,20] In the iodination of N-acTY and N-acMIT, significant salt effects are not observed at pH 7.11 and are small at pH 7.90 and 9.45. These results and the variance of the previous reports suggest that the salt effects are secondary. The fact that the effects on N-acTY and N-acMIT are of a similar magnitude further suggests that the equilibria displaced by the salts may well be on the buffer constituents rather than the reactants themselves. According to Debye–Hückel theory for dilute soutions, the slope of a plot of log k against $\mu^{1/2}$ depends in part on the product of the ionic charge of the reactants. This seems quite unlikely for more concentrated solutions.

Acknowledgment.—We gratefully acknowledge the help of Dr. Mones Berman in deriving eq. 12, in establishing our computer procedures, and for helpful criticism.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

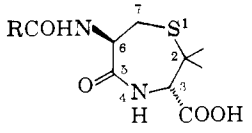
The Synthesis and Oxidative Rearrangement of Some 1,4-Thiazepines Related to the Penicillins[1-3]

BY NELSON J. LEONARD AND G. EDWIN WILSON, JR.[4]

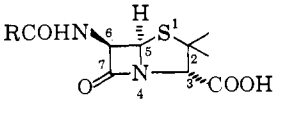
RECEIVED AUGUST 3, 1964

We have studied the synthesis, stereochemistry, and oxidative rearrangement of some 1,4-thiazepines related to the penicillins. 3D-Carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) was formed by the reaction of α-phenylacetamidoacrylic acid and D-penicillamine methyl ester hydrochloride in acetonitrile in the presence of dicyclohexylcarbodiimide and triethylamine, but none of the 3D-6L-diastereomer was isolated. Proof of the induced configuration 6D was provided by desulfurization of XIII with Raney nickel to give methyl N-(N'-phenylacetyl-D-alanyl)-D-valinate. The stereoisomer synthesized (XIII) is the thermodynamically more stable form. The oxidation of XIII by means of chlorine produced 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) and two isomeric 3-isothiazolones, methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) and methyl α-isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII). The oxidative formation of 3-isothiazolones was shown to have some generality. Photoreduction of XVI in ethyl mercaptan solution at 55° regenerated 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) while photoadducts of XVI were formed at 20° with ethanol, 2-propanol, and ethyl mercaptan (XVII–XX).

While an advanced stage has been reached in the elucidation of the intermediates involved in the pathway of penicillin biosynthesis,[5,6] including the isolation of the tripeptide γ-(α-aminoadipyl)cyst(e)inylvaline from the mycelium of *Penicillium chrysogenum*, the place in the sequence where oxidative condensation between the β-position of the cyst(e)ine moiety and the peptide nitrogen atom occurs has not been determined. We considered that the earlier suggestions of the transannular formation of the C–N bond across a substituted 1,4-thiazepine derivative (I → II)[7-9] had not as yet received a definitive test, and we were intrigued with the possibility of effecting a transannular synthesis of the bicyclic system present in penicillin. The requirement that the configurations at C-6 and C-3 of II be fixed before creation of the bicyclic ring system is implicit in the findings of Arnstein and his co-workers,[5,10] so that, at least in the biosynthetic conversion to penicillin, 3D-carboxy-2,2-dimethyl-5-oxo-6L-phenylacetamidoperhydro-1,4-thiazepine (I, R = $C_6H_5CH_2$) would be the desired stereomer to test, with the added provisions that it could serve as a competitive precursor and that the cells would be permeable to the compound.



I



II

The 1,4-thiazepines related to the penicillins have received relatively little attention, and the stereochemistry of these compounds has not been investigated. Previous syntheses leading to 3-carboxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (III)[11-13] and its closely related derivatives[9,14] have utilized open-chain starting materials and have generally employed a ring-closure step involving either addition of a thiol to an acrylate derivative or the formation of the amide C–N bond. Thus, 3-carbomethoxy-7-chloro-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (IV) and 3-carbomethoxy-2,2-dimethyl-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (VIII) were reported as products from condensations of

(1) This work was supported in part by a research grant (USPHS-RG 5829, currently GM-05829-06) from the National Institutes of Health, U. S. Public Health Service.

(2) N. J. Leonard and G. E. Wilson, Jr., *Tetrahedron Letters*, **No. 23**, 1465 (1964).

(3) N. J. Leonard and G. E. Wilson, Jr., *ibid.*, **No. 23**, 1471 (1964).

(4) National Science Foundation Fellow, 1961–1964.

(5) For lead references, see (a) H. R. V. Arnstein, M. Artman, D. Morris, and E. J. Toms, *Biochem. J.*, **76**, 353 (1960); (b) H. R. V. Arnstein and D. Morris, *ibid.*, **76**, 357 (1960); (d) H. R. V. Arnstein, D. Morris, and E. J. Toms, *Biochim. Biophys. Acta*, **35**, 561 (1959); (e) H. R. V. Arnstein and D. Morris, *Biochem. J.*, **71**, 8P (1959); (f) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(6) For reviews, see (a) H. R. V. Arnstein and P. T. Grant, *Bact. Rev.*, **20**, **133** (1956); (b) K. Ganapathi, *Experientia*, **13**, 172 (1957).

(7) D. J. D. Hockenhull, K. Ramachandran, and T. K. Walker, *Arch. Biochem.*, **23**, 160 (1949).

(8) J. C. Sheehan and A. J. Birch in discussion reported in "Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1958, p. 259.

(9) H. R. V. Arnstein and M. E. Clubb, *Biochem. J.*, **68**, 528 (1958).

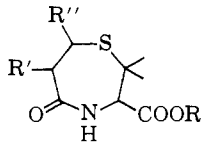
(10) H. R. V. Arnstein and J. C. Crawhall, *ibid.*, **65**, 18P (1957); **67**, 180 (1957).

(11) T. Wieland, G. Ohnacker, and W. Ziegler, *Chem. Ber.*, **90**, 194 (1957).

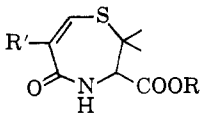
(12) I. L. Knunyants, O. V. Kil'disheva, and M. G. Lin'kova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 71 (1955); *Chem. Abstr.*, **50**, 1593 (1956).

(13) I. L. Knunyants and M. G. Lin'kova, *ibid.*, 62 (1955); *Chem. Abstr.*, **50**, 1592 (1956).

(14) I. L. Knunyants, O. V. Kil'disheva, M. P., Krasuskaya, M. G. Lin'kova, V. V. Shokina, Z. V. Benevolenskaya, and L. P. Rasteikene, *ibid.*, 1777 (1959); *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1702 (1959); *Chem. Abstr.*, **54**, 8843 (1960).



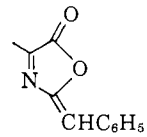
III, R = R′ = R″ = H
IV, R = CH_3, R′ = H, R″ = Cl
V, R = R″ = H, R′ = $C_6H_5CH_2CONH$
VI, R = CH_3, R′ = $C_6H_5CH_2CONH$, R″ = H
VII, R = CH_3, R′ = $C_6H_5CH_2CONH$, R″ = OCH_3



VIII, R = CH_3, R′ = H
IX, R = CH_3, R′ = o-$C_6H_4(CO)_2N$
X, R = CH_3, R′ = $C_6H_5CH_2SO_2NH$

penicillamine methyl ester with β-chloroacrylyl chloride.[12] Arnstein and Clubb[9] obtained 3-carboxy-2,2-dimethyl-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (V) by a ring-closure process utilizing α-phenylacetamidoacrylic ester. The product gave a negative nitroprusside test and could be hydrolyzed to the known β,β-dimethyllanthionine, thus establishing the gross structure. 3-Carbomethoxy-2,2-dimethyl-7-methoxy-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (VII) was considered to be the product obtained upon condensation of 2-benzyl-4-methoxymethylene-5(4)-oxazolone with D-penicillamine methyl ester.[15] Structures IX and X, 3-carbomethoxy-2,2-dimethyl-5-oxo-6-phthalimido-2,3,4,5-tetrahydro-1,4-thiazepine[16] and 6-benzylsulfonamido-3-carbomethoxy-2,2-dimethyl-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine,[17] were assigned the products resulting from attempted cyclization of the corresponding thiazolidine-2-acetic acids to penicillanic acid derivatives.

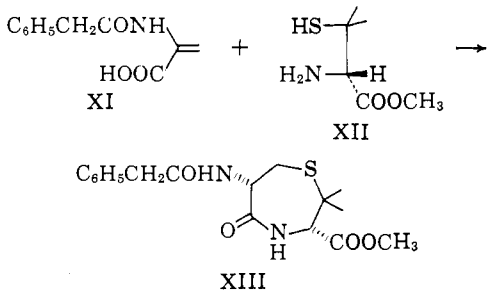
The synthesis of 3-carboxy-2,2-dimethyl-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (V) by Arnstein and Clubb[9] for testing as a possible intermediate in the biosynthesis of penicillin and that of the methyl ester VI reported by Knunyants and his co-workers[14] apparently did not employ optically active starting materials, and no attempt was made to assign relative configurations to the asymmetric centers at C-3 and C-6. In our laboratory, α-phenylacetamidoacrylic acid (XI) and D-penicillamine methyl ester (XII) hydrochloride, with dicyclohexylcarbodiimide as the dehydrating agent and an excess of triethylamine as the base, were found to undergo reaction in acetonitrile[18] to yield (72%) 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII), m.p. 172–174°. Efforts to isolate the second diastereomer from the mother liquors of XIII have not met with success. Under dehydration conditions,[19,20] upon formation of active esters[21] or with other amide-forming reagents,[19,20,22] α-phenylacetamidoacrylic acid is known to be converted to 2-benzylidene-4-methylpseudooxazol-5-one (XIV). Although XIV could not be isolated from



XIV

the reaction mixture in pure form, probably because of the ease with which it polymerizes,[20] it is considered to be a major constituent of the heavy orange oil which accompanied the product. Variations of the condensation reaction were attempted in an effort to obtain the second diastereomer in reasonable yield. When the reaction was run under high-dilution conditions[23] in acetonitrile with Woodward reagent K[24] as the condensing agent, isomer XIII was again isolated, but in reduced yield (50%), together with a large amount of the heavy orange oil. At normal concentrations, *ca.* 0.1 *M*, the yield of crystalline product XIII was further reduced to 20%.

Conclusive proof that XIII represented the correct structure and stereochemistry was obtained by a combination of physical and chemical methods. Evidence for the gross features of the molecule was derived from the infrared and ultraviolet spectra. Infrared bands were found for amide N–H, 3380 cm.$^{-1}$; ester carbonyl, 1742 cm.$^{-1}$; and amide carbonyl, 1660 cm.$^{-1}$ ($CHCl_3$). A low-extinction region of absorption for the benzene nucleus was found in the ultraviolet spectrum. The material was ninhydrin and nitroprusside negative, but a sodium hydroxide fusion gave a nitroprusside-positive solution. Optical activity, $[\alpha]^{25}D$ −39.7° (0.6% in ethanol), was observed. The nuclear magnetic resonance spectrum showed complex multiplets centered at τ-values of 7.14 and 5.05 p.p.m. ($CDCl_3$) assignable, respectively, to the methylene protons adjacent to the sulfur atom[25] and to the tertiary hydrogen atom at C-6. The methylene multiplet collapsed to two singlets when irradiation was applied to saturate the C-6 proton. The appearance of two singlets in the perturbed spectrum is consistent with the chemical shift of 3.5 ± 0.5 c.p.s.[26] and an assumed coupling constant of 12–15 c.p.s.,[27] wherein the outer two peaks of the AB pattern were obscured by noise. Upon addition of deuterium oxide, the upfield amide resonance at τ 3.38 p.p.m.



XI + XII → XIII

(15) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p. 762.

(16) J. C. Sheehan and P. A. Cruickshank, *J. Am. Chem. Soc.*, **78**, 3680 (1956).

(17) J. C. Sheehan and P. A. Cruickshank, *ibid.*, **78**, 3683 (1956).

(18) The synthesis used here is essentially that used by Knunyants and his coworkers,[14] but the Russian workers used chloroform as the solvent and presumably racemic penicillamine methyl ester. The use of chloroform in this laboratory led to the isolation of a product containing a high-melting impurity, either dicyclohexylurea or an acylurea, which could not be removed from the desired product even after repeated crystallization.

(19) M. Brenner and K. Rüfenacht, *Helv. Chim. Acta*, **36**, 1832 (1953).

(20) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **72**, 833 (1950).

(21) M. Brenner and K. Rüfenacht, *Helv. Chim. Acta*, **37**, 203 (1954).

(22) M. Brenner and K. Rüfenacht, *ibid.*, **37**, 209 (1954).

(23) We are indebted to Dr. T. Sato for running the initial high dilution reaction.

(24) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

(25) G. V. D. Tiers, "Tables of τ-Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(26) The approximation of the chemical shift results from the fact that no calibration side band could be applied.

(27) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85.

disappeared and the doublet at τ 5.37 p.p.m. for the C-3 proton collapsed to a singlet. The n.m.r. spectrum also showed the presence of a phenyl ring, a benzylic methylene group, two magnetically nonequivalent methyl groups as singlets, and an ester methoxyl group, all at the expected positions.

Desulfurization of XIII with Raney nickel gave methyl N-(N'-phenylacetyl-D-alanyl)-D-valinate in 97% yield, the properties of which were identical in all respects with those of a sample synthesized from the amino acids by acid azide coupling and diazomethane esterification. The hydrogenolysis product was not identical with, and depressed the melting point of, a sample of methyl N-(N'-phenylacetyl-L-alanyl)-D-valinate obtained from the corresponding dipeptide.[28,29] In addition, the desulfurization product gave only alanine and valine upon acid hydrolysis as shown by paper and thin layer chromatographies. The mass spectrum confirmed the molecular weight and indicated some cleavages typical of the side chains, as well as unusual fragmentation patterns which will be discussed more fully in a sequel.

That only one (XIII) of the two possible 3D-diastereomers was isolated was significant, especially since a method to convert it to the desired isomer (I, methyl ester) would have to be found. Models show that in the probably stable chair (Fig. 1) and possibly stable boat (Fig. 2) conformations of XIII, the amide and ester side chains may occupy pseudo-equatorial positions. The isomer indicated would thus be the thermodynamically more stable isomeric form; reversing the stereochemistry at one of the two centers leads to the axial positioning of one of the groups with accompanying unfavorable transannular interactions and an increase of the ground-state energy of that isomer (*cf.* Fig. 4 for benzylpenicillin). It is, therefore, apparent that the formation of only one isomer is a reflection of thermodynamic control of the reaction, probably as a result of an equilibrium positioning of the side chain when C-6 is developing carbanionic character in the ring-closure step. Since Arnstein and Clubb's rejection of a transannular biosynthetic pathway was based on the nonutilization of stereochemically unidentified 1,4-thiazepine V, the observation that the 6D-3D (or 6L-3L) isomer is preponderant in a thermodynamically controlled synthesis carries significance in any experiments based upon mixtures of synthetic isomers.

In order that 3-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine or the acid be useful as a springboard for possible synthesis or biological conversion to penicillin G or the methyl ester, it is necessary to reverse the stereochemistry at C-6 in XIII. One method of incorporating unfavorable stereochemistry would involve the catalytic reduction of the dehydro derivative, since the less hindered approach to the hydrogen-on-catalyst surface should be the underside of the ring in Fig. 3.[30] Before pursuing the reduction route to the 6L-3D isomer of VI, however, it seemed desirable to investigate some properties of XIII, to establish firmly the relation between XIII and known

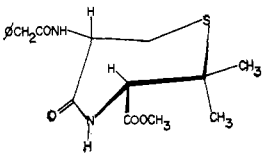


Figure 1.

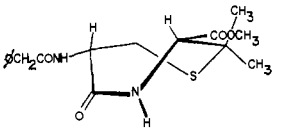
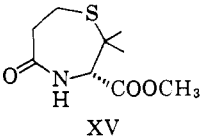


Figure 2.

1,4-thiazepine derivatives,[9,11-14] and to support all of the structural assignments.

Compound XIII was easily oxidized to the sulfone by potassium permanganate in aqueous acetic acid, whereas oxidation with finely ground sodium metaperiodate in aqueous ethanol[31] gave the sulfoxide. In order to test for biological activity, hydrolysis of the ester was necessary. Under mild conditions basic hydrolysis was totally unsuccessful, while those conditions severe enough to hydrolyze the ester also cleaved the side chain amide, giving phenylacetic acid as the sole acidic product. Attempts at acid hydrolysis were similarly unselective, but by the use of anhydrous lithium iodide in refluxing pyridine,[32,33] a salt of the acid corresponding to XIII could be isolated, actually the sodium salt according to the successive treatment employed. This hygroscopic solid precipitated from methanol as the hydrate upon addition of anhydrous ether. It gave negative ninhydrin and nitroprusside tests, indicating that the water, which was not readily removable by vacuum and heat, was water of hydration. Microbiological tests indicated that the sodium salt is essentially inactive when compared with penicillin G[34]; similarly, XIII is inactive. However, neither finding is unexpected, since, irrespective of whether activity may be found for the monocyclic system, the configuration at C-6 is foreign to the penicillins.

The 1,4-thiazepine derivative related to XIII but without a substituent at C-6, 3D-carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (XV), was ob-



XV

tained by the condensation and cyclization of acrylic acid with D-penicillamine methyl ester hydrochloride under high dilution conditions with Woodward reagent K. The crystalline ester obtained after work-up exhibited infrared absorption at 3400, 1730, and 1656 cm.$^{-1}$ (KBr disk) assignable to the amide N–H, the ester carbonyl, and the amide carbonyl stretching frequencies, respectively. The n.m.r. spectrum contained singlets for the methoxyl group, τ 6.21 p.p.m., as well as

(28) Merck Reports 1, 5, 9, 62 in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton, N. J., 1949, pp. 72, 260, 261.

(29) We wish to thank Dr. K. Folkers for providing a sample of the L-D-dipeptide for comparison.

(30) R. P. Linstead, W. von E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(31) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(32) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

(33) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *ibid.*, **44**, 540 (1961).

(34) We wish to thank Eli Lilly and Co., Indianapolis, Ind., for testing this material.

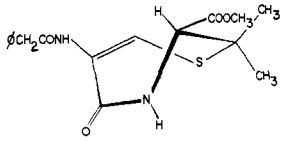


Figure 3.

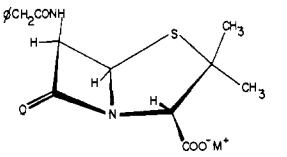
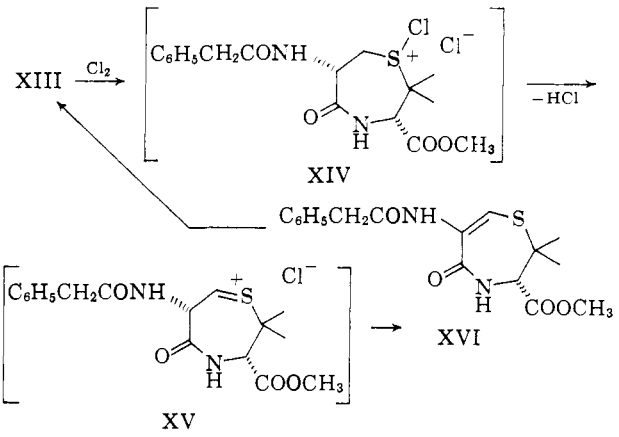


Figure 4.

for the *gem*-dimethyl group, τ 8.65 p.p.m. ($CDCl_3$). There were, in addition, a complex multiplet for the two sets of methylene protons centered at τ 7.13 p.p.m. and a complex doublet, τ 5.45 p.p.m., for the tertiary proton at C-3. This doublet collapsed to a singlet when the amide proton was exchanged with deuterium oxide. The data correlated well with those obtained for XIII, and the compound gave negative ninhydrin and nitroprusside tests. Upon basic hydrolysis, 3-carboxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine was obtained (77% yield), identical with a sample synthesized from optically active penicillamine by the method of Wieland, Ohnacker, and Ziegler.[11] The melting point of the ester XIII, 103.5–105.5°, differs greatly from that reported from Knunyants' laboratory,[12] 230–240°. In our hands, the acid was not readily esterified with diazomethane or with 2,2-dimethoxypropane.

We turned our attention next to the introduction of a 6,7-double bond in XIII. The procedure of Knunyants[14] to introduce unsaturation into VI (of unestablished stereochemistry), treatment of the cyclic sulfide with N-chlorosuccinimide, was reasonable in view of similar formation of unsaturated sulfides by the use of halogens on sulfides.[35] However, upon repetition of the published procedure using 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) we obtained a solid which did not have the properties previously described. The reaction mixture showed in thin layer chromatography the presence of three products. One of these, which was shown (see below) to be 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI), was subsequently isolated by chromatography on silica gel. Concurrently, it was discovered that chlorination of XIII in carbon tetrachloride–methylene chloride at −60° followed by dehydrochlorination at 60° afforded XVI in almost pure form. It could be freed from contaminants quite easily by a rapid silica gel chromatography.

That the material obtained was indeed XVI was easily established. Degradation into valine and alanine by Raney nickel desulfurization followed by acid hydrolysis attested to the nonrearranged nature of the amino acid components. The infrared absorption at 1745 cm.$^{-1}$ was consistent with the presence of a saturated ester grouping, and the elemental analysis indicted the presence of a new double bond or ring. The positions of the ultraviolet maxima, 235 (ϵ 9650) and 305 mμ (ϵ 5250) (EtOH), although not definitive in nature, were compatible with the expected shifts from the maxima of model compounds and tentatively assigned tetrahydro-1,4-thiazepines previously obtained.[16,17] The optical activity, $[\alpha]^{25}D$ 135° (3.5% in chloroform), showed that at least one stereomeric center had been retained. The n.m.r. spectrum confirmed the existence of the phenyl-



acetyl side chain, τ 2.72 and 6.37 p.p.m., ester methoxyl group, τ 6.21 p.p.m., and *gem*-dimethyl moiety, τ 8.48 and 8.72 p.p.m. ($CDCl_3$). The doublet, τ 5.82 p.p.m., J = 7 c.p.s., for H-3 collapsed to a singlet when the amide proton, which occurred as a broadened doublet at τ 2.86 p.p.m., was exchanged with deuterium oxide. Finally H-7 was found as a sharp singlet at τ 2.34 p.p.m. The position of this absorption corresponds well with that for the β-proton of *cis*-(3-*t*-butylthio)acrylamide,[3] τ 2.92 p.p.m., and *cis*-3-thiocyanoacrylamide, τ 2.79 p.p.m. (DMSO).[36] In the latter case, the assignment was substantiated by deuteration at the α-position.

Attempted catalytic hydrogenations of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) have thus far been unsuccessful, using palladium-on-carbon, platinum oxide, rhenium heptasulfide,[37] palladium chloride-on-carbon,[38] and P-1 nickel boride.[39] Diimide, formed *in situ* from potassium azodicarboxylate,[40] was ineffective as a reducing agent while the systems employing hydrazine, cupric ion, and an oxidizing agent such as air[41,42] or hydrogen peroxide[41,43] degraded the molecule. Temporarily thwarted, we turned to photochemical processes and found that photoreduction of XVI in ethyl mercaptan solution at 55° regenerated 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) in 68% yield, thereby adding chemical proof to the spectroscopic assignment of

(35) (a) W. E. Lawson and T. P. Dawson, *J. Am. Chem. Soc.*, **49**, 3119 (1927); (b) H. Böhme, *Chem. Ber.*, **69**, 1610 (1936); (c) H. Böhme, H. Fischer, and R. Frank, *Ann.*, **563**, 54 (1949); (d) H. Böhme and H.-J. Gran, *ibid.*, **577**, 68 (1952); (e) W. E. Truce, G. H. Birum, and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952); (f) F. G. Bordwell and B. M. Pitt, *ibid.*, **77**, 572 (1955); (g) G. F. Bennett, D. W. Goheen, and W. S. MacGregor, *J. Org. Chem.*, **28**, 2485 (1963).

(36) W. D. Crow and N. J. Leonard, *Tetrahedron Letters, No.* **23**, 1477 (1964).

(37) H. S. Broadbent, L. H. Slaugh, and N. L. Jarvis, *J. Am. Chem. Soc.*, **76**, 1519 (1954).

(38) R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, Jr., N. R. Easton, and K. Folkers, *ibid.*, **67**, 2092 (1945).

(39) C. A. Brown and H. C. Brown, *ibid.*, **85**, 1003 (1963).

(40) E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *ibid.*, **83**, 3725 (1961).

(41) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Letters*, 347 (1961).

(42) S. Hunig, H.-R. Müller, and W. Thier, *ibid.*, 353 (1961).

(43) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Am. Chem. Soc.*, **83**, 2957 (1961).

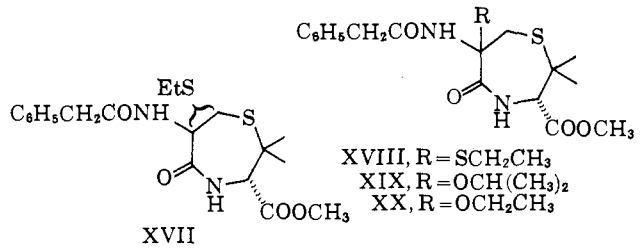
structure XVI. The reduced material proved spectrally identical with XIII; the optical rotation of the two compared within 0.4°. The melting point of the photoreduced material, 180–182°, was higher than that obtained initially for XIII, indicating that further purification of the "analytically pure" original had been effected. Attempts made to obtain any accompanying 3D-6L diastereomer by chromatography of the reaction mixture on silica gel were unsuccessful. This photoreduction must be regarded, therefore, as another example of stereospecificity in the generation of an optically active center at C-6.

In addition to the photoreduction product XIII, a 1:1 photoadduct of XVI with ethyl mercaptan, m.p. 206°, was isolated in 20% yield from the reaction at 55°. Changing the reaction conditions of the ethyl mercaptan photolysis changed the products and product ratios drastically. When the photolysis was done at 20° with only a partial solution of XVI, the character of the undissolved material gradually changed until a heavy suspension of fine filaments was present. After 9 hr. no XVI remained. The product mixture was easily separated into a chloroform-soluble fraction, which yielded a crystalline 1:1 photoadduct, m.p. 182°, 26%, and a chloroform-insoluble fraction, which gave the crystalline isomeric 1:1 photoadduct of m.p. 206°, 30%. Under these conditions, no material attributable to photoreduction was obtained.

When the 206° m.p. photoadduct was heated to 210° under a current of nitrogen, it was reconverted smoothly to XVI in high yield. In ethyl mercaptan solution the 182° m.p. isomer was stable at 55° for appreciably longer than the photolytic reaction time, no reduction product being found.

The analysis and osmometric molecular weight of the 206° m.p. isomer indicated that it was a monomeric 1:1 photoadduct of XVI and ethyl mercaptan, $C_{19}H_{26}N_2O_4S_2$, while the pyrolytic experiment demonstrated that no new carbon–carbon bond had been formed and that the new carbon–sulfur bond was at either C-6 or C-7. The n.m.r. spectrum obtained in dimethyl sulfoxide-d_6 was inconclusive regarding the position of sulfur attachment. Two methyl singlets and a methyl triplet, J = 6.5 c.p.s., occurred at τ 8.73, 8.82, and 8.94 p.p.m., respectively, with a total area for 9.2 protons. A broad multiplet at 7.52 p.p.m. with an area for 2.7 protons includes the peaks for the DMSO impurity and is assigned to the methylene of the ethyl group. The aromatic protons (area 5.0), the ring amide proton (doublet, J = 7 c.p.s., area 0.73), the proton at C-3 (doublet, J = 7 c.p.s., area 0.89), the ester methoxyl, and benzylic methylene groups (area 5.0) occurred at τ 2.75, 3.30, 5.47, 6.36, and 6.47 p.p.m., respectively. The broadened singlet at τ 6.82 p.p.m. (area 1.95) was assigned to the remaining ring protons. The accidental degeneracy of these two protons prevents one from obtaining any useful information about their relative position on the thiazepine ring. The 206° isomer was therefore assigned the ambiguous structure XVII.

The 182° isomer was amenable to spectroscopic assignment of structure. Analysis of osmometric molecular weight determination showed this to be a monomeric 1:1 photoadduct, while the n.m.r. spectrum defined the structure as XVIII. Peaks for methyl groups were found at τ 6.16, 8.46, 8.91, and 8.98 p.p.m., the last one being a triplet, J = 7 c.p.s. Phenylacetamide sidechain peaks occurred at τ 2.40 (NH), 2.65, and 6.40 p.p.m. The ring amide proton gave rise to a broad



doublet resonance, J = 8 c.p.s., at τ 3.50 p.p.m. coupled to the C-3 proton peak at τ 5.35 p.p.m.; and the ethyl methylene resonance was found as a broad multiplet, τ 7.85 p.p.m. The two protons at C-7 were found at τ 5.93 and 7.15 p.p.m. as doublets with a coupling constant of 17.0 c.p.s. The validity of the assignments of the two methylenes adjacent to the sulfur atoms in this way will become clearer upon consideration of the spectra of alcohol photoadducts. The chemical shift of 73 cycles between the peaks for the two chemically identical protons is uncommonly large and worthy of special mention.

Attempted photoreduction of XVI in isopropyl alcohol resulted in a photoadduct, $C_{20}H_{28}N_2O_5S$, assigned structure XIX on spectral grounds. The phenylacetamide protons are found as singlets at τ 2.02 (NH), 2.64, and 6.38 p.p.m. The methoxyl and ring *gem*-dimethyl singlets were found at τ 6.15, 8.43, and 8.92 p.p.m. The doublet, J = 6 c.p.s., at τ 9.05 p.p.m. attributed to the *gem*-dimethyl group of the isopropoxy side chain was split by the tertiary proton which occurred in the form of a broad, low multiplet 154 cycles downfield at τ 6.48 p.p.m., the position shown by double resonance. Amidst this low multiplet were four small peaks which were not coupled with resonances out of this region. They correspond to an AB pattern with J = 17 c.p.s. and δ = 43 cycles.

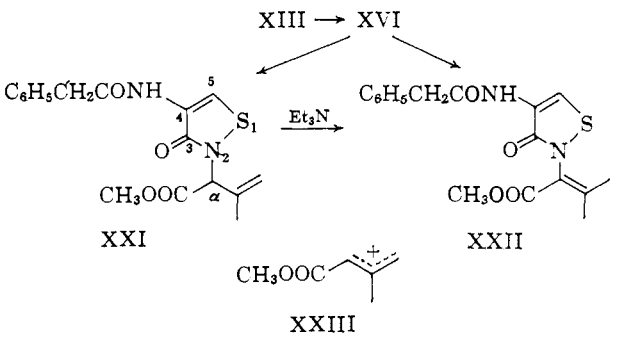
Ultraviolet irradiation of XVI in ethanol also afforded a 1:1 photoadduct, $C_{19}H_{26}N_2O_5S$ (XX). The positions of the ethyl group methyl and methylene resonances were verified by double resonance as was the coupling between the protons on C-3 and N-4. Upon irradiation of the methyl triplet, the complex pattern τ 6–7 collapses to four peaks, two of which are part of an AB pattern, assigned to the C-7 protons with J = 15 c.p.s., τ 6.79 p.p.m. The other two singlets, τ 6.78 and 6.87 p.p.m., are in actuality also an AB pattern attributed to the ethyl methylene protons adjacent to an optically active center, being, therefore, magnetically nonequivalent. The other portion of the C-7 AB pattern is partly hidden by the ester and benzylic resonances, but integration confirms its presence, its positon being 6.27 p.p.m.

Returning to the initial formation of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine, the steps in the conversion of XIII to XVI by chlorine oxidation seem unexceptional. Transformation of chlorosulfonium chloride XIV to sulfocarbonium intermediate XV (in covalent form an α-chlorosulfide) may be accomplished by loss of hydrogen chloride, and formation of the product XVI may result from a subsequent E1 elimination of the C-6 proton. The mechanism of the conversion XIV to XV

might be the equivalent of a bimolecular elimination in the aliphatic series, with chloride ion acting as a base.

Of interest to us was the possibility that a sulfocarbonium-type intermediate in either the biological or chemical system might provide a center at C-7 subject to nucleophilic attack by the opposed ring amide nitrogen atom. In the biological system, with the correct stereochemistry at C-6 and a carboxylate group at C-3, the conversion of this intermediate to benzylpenicillin satisfies all the requirements placed upon it by the isotopic labeling data of Arnstein and co-workers.[5,10] In the chemical system, the possibility of such a transformation prompted us to investigate this chlorination reaction more fully.

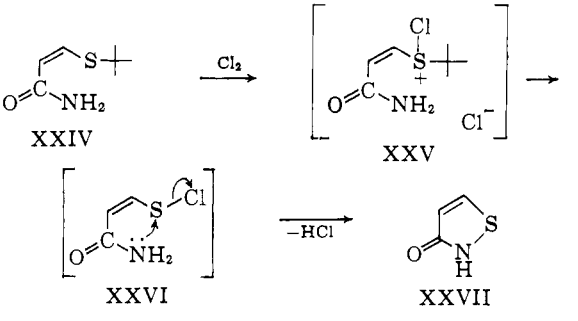
Thin layer chromatography of the reaction mixture obtained after chlorination of XIII at −60° and dehydrochlorination at 60° showed the presence of two compounds in addition to XVI and starting materials. The structures of these two compounds were shown to be the isomeric 3-isothiazolones XXI and XXII, the former optically active, the latter optically inactive. The interrelation between the two was shown by the isomerization of XXI to XXII by the action of triethylamine at room temperature in 30 min. The mass spectra of these compounds were virtually identical with the exception of a



prominent peak (52% of the base peak) at *m/e* 113 in the spectrum of XXI, which could be accounted for as the side-chain allylic cation XXIII derived by cleavage of the allylic C–N bond. In addition to the fragmentations observed in the mass spectrum, the infrared, ultraviolet, and n.m.r. spectral characteristics were consistent with assigned structure XXI, methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate,[44] $C_{17}H_{18}N_2O_5S$, m.p. 150–152°, $[\alpha]^{25}D$ −33.0° (0.2% in ethanol). The infrared band at 1739 cm.$^{-1}$ established that the ester group was unconjugated. The ultraviolet spectrum (ethanol) showed absorption at 222.5 mμ (sh, ε 10,200) with a maximum at 296.5 mμ (ε 10,800), consistent for a 3-isothiazolone[36] having the additional phenylacetamido group at C-4 (XXI). The n.m.r. spectrum disclosed a *single* methyl group with a proton signal at τ 8.22 p.p.m., which was broadened by the vinylic protons at 4.77 and 4.95. The resonance for the side-chain α-proton occurred at τ 4.40. The methyl ester, benzylic and aromatic protons were observed at 6.34, 6.27, and 2.67 p.p.m., respectively, and the very low-field signal, 1.40 p.p.m., was indicative of the 5-proton on the isothiazolone ring (see below).

The isomeric product, methyl α-isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII), m.p. 232–233°, was optically inactive. The infrared spectrum indicated that the ester group was conjugated (ν_{max}^{KBr} 1710 cm.$^{-1}$) while the n.m.r. spectrum indicated two methyl groups attached to a double bond (τ 7.82 and 8.19, in addition to the methyl ester at 6.24 p.p.m.). The N-attachment of the triply substituted double bond was shown by the presence of only one amide proton (1.02 p.p.m.) in XXII exchangeable with deuterium oxide. The ring system common to XXII and XXI was affirmed by the ultraviolet spectrum, λ_{max}^{EtOH} 295.5 mμ (ε 10,000), ~ 307 (ε 7900), and by the n.m.r. signal at τ 1.30 p.p.m. for the isothiazolone ring proton.

A probable intermediate in the reaction sequence XIII → XXI and XXII is the vinylsulfenyl chloride derived from XVI. In substantiation of this hypothesis, treatment of XVI with chlorine afforded XXI in greater than 90% yield as determined by n.m.r. and in 45% yield as isolated in crystalline form. In this case, the acidic character of the reaction mixture and the work-up procedure suppressed the isomerization to XXII. The easy conversion of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) and 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) to the isomeric 3-isothiazolone derivatives XXI and XXII represents an interesting new method for the formation of 3-isothiazolones involving cleavage of an S–C bond and generation of an S–N bond. Both to probe for the generality of the method and to provide a model compound for the n.m.r. and ultraviolet spectral assignments previously discussed, the synthesis of 3-isothiazolone (XXVII) was investigated. *cis*-(3-*t*-Butylthio)acrylamide (XXIV), m.p. 159–160.5°, formed by the base-catalyzed addition of *t*-butyl mercaptan to propiolamide, was converted by treatment with chlorine to 3-isothiazolone, m.p. 73–74°,[34] together with a large amount of seemingly polymeric material. The spectra of XXVII offered additional confirmation for the assigned structures XXI and XXII. In the n.m.r. spectrum ($CDCl_3$) the nuclear protons of 3-isothiazolone exhibited a typical AB pattern of two doublets, J = 5.0 c.p.s., centered at τ 1.56 (H-5) and 3.42 (H-4) p.p.m. The spectrum of 3-isothiazolone-4-*d*[36] allowed the assignment of the proton positions. The resonance of the N-proton occurred at τ −1.90 p.p.m. The ultraviolet maximum at 257 mμ (ε 6400), with a shoulder at 280 mμ (ε 1360), shifted to 279 mμ (ε 6740) in base.



The conversions described above may follow a common pathway illustrated by XXIV → XXVII. The formation of the chlorosulfonium chloride XXV in the initial step can be succeeded by fragmentation to a

(44) This compound could be obtained in crystalline form conveniently from the reaction mixture resulting from treatment of XIII with N-chlorosuccinimide.

vinylsulfenyl chloride (XXVI),[45] which undergoes internal nucleophilic attack by the amide nitrogen to form the isothiazolone.

Of added interest to the oxidative formation of 4-isothiazolones here described is the preliminary observation that compounds XXI and XXII produce a zone of inhibition when placed in contact with an agar plate seeded with *B. subtilis*.

Experimental[46]

3D-Carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII).—To a solution of 10.0 g. (0.050 mole) of D-penicillamine methyl ester hydrochloride, 10.0 g. (0.049 mole) of α-phenylacetamidoacrylic acid, and 7.5 ml. (0.055 mole) of triethylamine in 300 ml. of acetonitrile at 25° was added with stirring 11.5 g. (0.056 mole) of N,N'-dicyclohexylcarbodiimide. The immediate precipitation of dicyclohexylurea was accompanied by a rise in temperature. Stirring at ambient temperature was continued for 8 hr. The mixture was filtered; the dicyclohexylurea was washed with acetonitrile; and the residue after removal of the solvent from the filtrate was taken up in chloroform, washed twice with 5% hydrochloric acid and once with saturated salt solution, dried over sodium sulfate, and evaporated to dryness under vacuum. The solid residue was dissolved in a minimum amount of absolute ethanol and allowed to crystallize finally at −20°. The product was collected by filtration as fine hair-like needles and was washed with a small amount of cold ethanol to remove the trace of yellow impurity. The yield after drying was 12.6 g. (72%) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII), m.p. 171–174°. Further recrystallization from ethanol afforded an analytically pure sample, m.p. 172–174° (reported[14] 167°); $[\alpha]^{25}D$ −39.7° (0.6% in ethanol), −36.5° (0.4% in chloroform); λ_{max}^{EtOH} 252 (ε 215), 258 (ε 218), 264 (ε 167), and 268 mμ (ε 102); $\nu_{max}^{CHCl_3}$ 3380 (N—H), 1742 (ester C=O), and 1660 cm.$^{-1}$ (amide C=O); n.m.r. signals ($CDCl_3$) occurred at τ 2.66, 3.38 d (J = 8 c.p.s.), 5.05, 5.37 d (J = 8 c.p.s.), 6.20, 6.40, 7.14 m, 8.64, and 8.72 p.p.m.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 7.99; mol. wt., 350.42. Found: C, 58.03; H, 6.43; N, 7.98; mol. wt., 350 (mass spectrum, molecular ion), 357 (osmometric in benzene).

3D-Carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine 1,1-Dioxide.—To 5 ml. of 5% potassium permanganate in 80% acetic acid–water was added 270 mg. (0.77 mmole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII). As soon as dissolution of the solid was complete the color was dispelled by dropwise addition of 30% hydrogen peroxide. The product (258 mg.) was crystallized from water; m.p. 160.5–162°; ν_{max}^{KBr} 3400 (amide N—H), 1743 (ester C=O), 1685 (amide C=O), 1662 (amide C=O), and 1108 cm.$^{-1}$ (S=O).

Anal. Calcd. for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.80; N, 7.32. Found: C, 53.10; H, 5.94; N, 7.48.

Methyl N-(N'-Phenylacetyl-D-alanyl)-D-valinate.—A solution of 1.5 g. (4.28 mmoles) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) with 15 ml. of W-2 Raney nickel[47] in 50 ml. of absolute ethanol was heated under reflux for 8 hr. Filtration through Filter-cel and evaporation of the solvent under vacuum left 1.32 g. (97%) of an oily residue which solidified when triturated with hexane. This material was crystallized from 4 ml. of ethyl acetate and 14 ml. of hexane to give 1.12 g. (88%) of methyl N-(N'-phenylacetyl-D-alanyl)-D-valinate as colorless needles, m.p. 114–115°. Further recrystallization afforded an analytical sample, m.p. 117.5–118°, $[\alpha]^{25}D$ 77.8° (2% in EtOH); $\nu_{max}^{CHCl_3}$ 3420 (amide N—H), 1738 (ester C=O), 1682 and 1650 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 2.63, 2.76 d, 3.52 m, 5.4 m, 6.25, 6.41, 7.9 m, 8.68 d (J = 7.0 c.p.s.), 9.13 d (J = 6.5 c.p.s.). The infrared and n.m.r. spectra and optical rotation of this material were identical with those of an authentic sample prepared from the amino acids. A mixture with the known material showed no depression in melting point.

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.72; H, 7.55; N, 8.75. Found: C, 63.43; H, 7.43; N, 8.56.

Methyl N-(N'-Phenylacetyl-D-alanyl)-D-valinate.—N-(N'-Phenylacetyl-D-alanyl)-D-valine, m.p. 201–203°, was prepared from D-valine and phenylacetyl-D-alanylhydrazide by azide coupling.[48] The dipeptide was esterified by dry ethereal diazomethane in ether–chloroform solution. Evaporation of the solvent from the reaction mixture and crystallization of the residue several times from ether–hexane afforded analytically pure material, m.p. 112–113°, $[\alpha]^{25}D$ 77.6° (2% in EtOH). Recrystallization of this material from ethyl acetate–hexane raised the melting point to 114.5–116°.

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.72; H, 7.55; N, 8.75. Found: C, 63.43; H, 7.68; N, 8.88.

Methyl N-(N'-Phenylacetyl-L-alanyl)-D-valinate.—N-(N'-Phenylacetyl-L-alanyl)-D-valine[28] was esterified in ether–chloroform solution with dry ethereal diazomethane. The solvent was evaporated, and the residual material was crystallized from chloroform–hexane as fine, colorless prisms, m.p. 141–142°, $[\alpha]^{25}D$ −43.1° (3% in EtOH); $\nu_{max}^{CHCl_3}$ 3420 and 3310 (N—H), 1738 (ester C=O), and 1682 and 1655 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 2.65, 2.8 m, 3.4 m, 5.4 m, 6.28, 6.40, 7.79 m, 8.65 d (J = 7 c.p.s.), 9.10 d (J = 6 c.p.s.), 9.12 d (J = 6 c.p.s.).

Anal. Found: C, 63.77; H, 7.69; N, 9.05.

Sodium 2,2-Dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine-3D-carboxylate.—A solution of 350 mg. (0.001 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) in 8 ml. of anhydrous pyridine was heated under reflux with 1.65 g. of anhydrous lithium iodide for 2 hr. under a nitrogen atmosphere. Methylene chloride (25 ml.) was added, and the clear yellow solution was extracted with 5% aqueous sodium bicarbonate solution until the extracts were neutral. The acidified aqueous extract was extracted with methylene chloride, and the organic layer was dried over sodium sulfate. The methylene chloride solution was filtered through a sintered glass funnel and extracted with 5% sodium bicarbonate solution to pH 7 (*ca.* 2 ml.), then with water. The combined aqueous extracts were filtered through a sintered glass funnel and lyophilized. The fluffy residue was partially dissolved in acetone and filtered. A solid, sodium 2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine-3D-carboxylate, precipitated upon addition of ethyl acetate. Two crystallizations of this material from anhydrous methanol–anhydrous ether afforded an analytical sample, m.p. 213° dec.; ν_{max}^{KBr} 3380 (amide N—H), 1650 (amide C=O), and 1620 cm.$^{-1}$ (carboxylate C=O).

Anal. Calcd. for $C_{16}H_{19}N_2O_4SNa \cdot H_2O$: C, 51.06; H, 5.62; N, 7.44. Found: C, 50.86; H, 5.82; N, 7.39.

This material does not lose its water of crystallization when heated at 100° under 1 mm. for 14 hr. A ninhydrin spot test was negative. Biological testing[34] indicated that this compound was less than 1% as active as penicillin G.

3D-Carboethoxy-2,2-dimethyl-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine, m.p. 123.5–125°, was prepared in 58% yield from D-penicillamine ethyl ester hydrochloride in a manner identical wth that used for the methyl ester; $\nu_{max}^{CHCl_3}$ 3375 (amide N—H), 1734 (ester C=O), and 1660 cm.$^{-1}$ (amide C=O); $[\alpha]^{25}D$ −42.2° (0.2% in ethanol); n.m.r. τ-values ($CDCl_3$): 2.72, 2.93 d, 3.55 m, 5.11 m, 5.46 d (J = 7.5 c.p.s.), 5.75 q (J = 7.3 c.p.s.), 6.44, 7.17 m, 8.63, 8.70 t (J = 7.3 c.p.s.), and 8.72 p.p.m.

(45) For lead references to the fragmentation of chlorosulfonium chlorides see (a) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951), and (b) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 2478 (1961).

(46) All melting points are uncorrected. N.m.r. spectra were obtained with a Varian Associates Model A-60 spectrometer equipped with a variable temperature probe. The chemical shifts were measured using tetramethylsilane as an internal standard for spectra run in deuteriochloroform and as an external standard for spectra run in deuterium oxide. Double resonance experiments were performed with a Varian Associates Model V-4300B spectrometer equipped with a superstabilizer. The mass spectra were obtained using an Atlas CH4 mass spectrometer equipped with a TO4 inlet system. Infrared spectra were obtained using a Perkin–Elmer automatic recording infrared spectrophotometer Model 21 or Model 521. Ultraviolet spectra were obtained using a Cary Model 15 spectrophotometer. Optical rotations were measured on a Bendix Ericson ETL-NPL automatic polarimeter, type 143 A, in a 1-cm. cell using a sodium lamp. Molecular weight determinations were carried out with a Mechrolab vapor pressure osmometer, Model 301 A.

The authors wish to thank Mr. J. Nemeth and his associates for microanalyses and molecular weight (osmometric) determinations, Mr. D. H. Johnson and his associates for the n.m.r. and infrared spectra, Mr. O. W. Norton for the double resonance spectra and Dr. T. H. Kinstle and his associates for the mass spectra.

(47) Commercial Raney nickel obtained from Raney Catalyst Co., Inc., Chattanooga, Tenn., was used.

(48) The procedure used was idential with that reported for the L-D material.[28]

Anal. Calcd. for $C_{18}H_{24}N_2O_4S$: C, 59.31; H, 6.64; N, 7.69; mol. wt., 364.45. Found: C, 59.28; H, 6.69; N, 7.57; mol. wt., 364 (mass spectrum, molecular ion).

3D-Carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (XV).—A solution of 1.44 g. (0.02 mole) of acrylic acid, neutralized by 2.8 ml. (0.02 mole) of triethylamine, in 250 ml. of anhydrous acetonitrile was added to 5.06 g. (0.02 mole) of N-ethyl-5-phenylisoxazolium-3′-sulfonate (Woodward reagent K),[24] and the mixture was stirred until all the solid had dissolved. A second solution was prepared from 3.97 g. (0.02 mole) of D-penicillamine methyl ester hydrochloride and 2.8 ml. of triethylamine in 250 ml. of acetonitrile. Both solutions were filtered through sintered glass funnels, then added simultaneously to 1.5 l. of dry acetonitrile containing 5 ml. of Triton B butoxide (40% in butanol) with high-speed stirring under a current of nitrogen over a period of 8 hr. Stirring was continued for an additional 11 hr., after which the solvent was removed *in vacuo*, and the residue was partitioned between 100 ml. of water and 500 ml. of chloroform. The aqueous layer was washed with an additional 500 ml. of chloroform, and the combined chloroform extracts were evaporated to *ca.* 20 ml. *in vacuo*, washed with 10% sodium carbonate solution, dried over sodium sulfate, and chromatographed on 125 g. of Florisil. The fraction eluted with ether–methanol (95:5) was collected and evaporated to dryness. Crystallization of the residue from hexane gave colorless needles of 3D-carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (XV), m.p 103.5–105.5° (reported for DL[12] 230–240° dec.), $[\alpha]^{25}D$ −90.3° (1% in EtOH); ν_{max}^{KBr} 3400 (amide N–H), 1730 (ester C=O), and 1656 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 5.45 m, 6.21, 7.13 m, and 8.65. Two recrystallizations from hexane afforded colorless needles of analytically pure material, m.p. 107–108°.

Anal. Calcd. for $C_9H_{15}NO_3S$: C, 49.74; H, 6.96; N, 6.45; mol. wt., 217.28. Found: C, 49.90; H, 6.90; N, 6.35; mol. wt., 217 (mass spectrum, molecular ion).

3D-Carboxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine.—Hydrolysis of 100 mg. (0.47 mmole) of 3D-carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (XV) at 50° for 2 hr. with 0.05 *N* sodium hydroxide solution followed by acidification of the solution precipitated 71 mg. (76%) of powdery 3D-carboxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine which was recrystallized from water as fine white prisms, m.p. 274° dec. (reported for DL 260° dec.,[11] 276–277°,[12] 266–270°[13]). This material was identical spectrally and by mixture melting point with a sample prepared by the method of Wieland, Ohnacker, and Zeigler[11]; ν_{max}^{KBr} 3200 (amide N—H), 1705 (carboxylic acid C=O), and 1596 cm.$^{-1}$ (amide C=O).

3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI).—One equivalent of a 0.42 *M* solution of chlorine in carbon tetrachloride (54 ml.) was allowed to drip slowly, with stirring, into a solution of 8.0 g. (0.022 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) dissolved in 100 ml. of methylene chloride and maintained at Dry Ice temperature. The solution eventually became a thin gel. Stirring at Dry Ice temperature was continued for 2 hr. After warming slowly to room temperature, the slightly yellow solution was heated with stirring at 60° under a reflux condenser and nitrogen current. Hydrogen chloride was evolved rapidly, and heating was continued until gas evolution had stopped (*ca.* 8 hr.).

The solution was evaporated to dryness on the rotary evaporator. The residual gum was dissolved in 30 ml. of ethyl acetate. Two crops of impure 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) were obtained by first cooling the ethyl acetate solution overnight at 0°, and refrigeration again of the combined filtrate and ethyl acetate washings of the first crop, at −15° after sufficient hexane had been added to turn the solution to near cloudiness at room temperature. A total of 4.1 g. (53%) was thus obtained. Repeated crystallization from ethanol gave an analytically pure sample, m.p. 142.8–143° (reported[14] 185°); ν_{max}^{KBr} 1745 (ester C=O) and 1660 cm.$^{-1}$ (amide C=O); λ_{max}^{EtOH} 235 (ϵ 9650), 305 mμ (ϵ 5250); $[\alpha]^{25}D$ 135° (3.5% in chloroform); n.m.r. τ-values ($CDCl_3$): 2.34, 2.72, 2.86 d (J = 7 c.p.s.), 5.82 d (J = 7 c.p.s.), 6.21, 6.37, 8.48, and 8.72 p.p.m.

Anal. Calcd. for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; mol. wt., 348.41. Found: C, 58.66; H, 5.89; N, 7.88; mol. wt., 348 (mass spectrum, molecular ion).

Alternatively the crude XVI was purified by chromatography on 400 g. of silica gel (Grace Chemical Co., #923) in a column 5.5 × 26.5 cm. The crude material was added in chloroform solution. The first ultraviolet-absorbing fraction was eluted with ether–ethyl acetate (90:10). The eluent was then changed to ethyl acetate to elute XVI, m.p. 142–143° after one crystallization from ethanol.

3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine 1,1-Dioxide.—To a solution of 600 mg. (1.7 mmoles) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine in 10 ml. of ether was added 7.6 ml. of 0.455 *N* ethereal monoperphthalic acid, and the mixture was refluxed with stirring for 28 hr. The solid precipitate was removed by filtration. A suspension of the solid precipitate in 5% sodium bicarbonate solution was extracted with ethyl acetate. Evaporation of the ethyl acetate solution left 333 mg. (53%) of crude product which crystallized as colorless needles from 25 ml. of ethyl acetate and 30 ml. of hexane, m.p. 213–215° dec. Recrystallization from the same solvent mixture afforded analytical material, m.p. 215.5–217.5°; ν_{max}^{KBr} 3400 (amide N—H), 1738 (ester C=O), 1614 (C=C), 1685, 1662 (amide C=O), 1300 (sulfone S=O), and 1106 cm.$^{-1}$ (sulfone S=O); λ_{max}^{EtOH} 261 mμ (ϵ 13,160).

Anal. Calcd. for $C_{17}H_{20}N_2O_6S$: C, 53.66; H, 5.30; N, 7.36. Found: C, 53.88; H, 5.34; N, 7.36.

3D-Carbomethoxy-2,2-dimethyl-6-isopropoxy-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (XIX).—A solution of 540 mg. (0.15 mmole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) in 400 ml. of 2-propanol was irradiated with a 450-watt Hanovia ultraviolet lamp, Model 679A, through a Pyrex filter at 20°. After 4 hr. the concentration of starting material, assayed by its ultraviolet absorption, was less than 10% of its initial value. The solvent was removed, and the glassy residue was extracted with 75 ml. of ether. Evaporation *in vacuo* of the obtained filtrate, when 200 ml. of hexane was added to the solution and the resulting suspension was filtered, left a residue which was crystallized from hexane, finally at −20°, to give 162 mg. (25%) of 3D-carbomethoxy-2,2-dimethyl-6-isopropoxy-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (XIX) as a white powder, m.p. 132–146°. Recrystallization from hexane left 110 mg. of material, m.p. 136–148°; chromatography of this material on silica gel with ether eluent gave 106 mg. of needles (from hexane), m.p. 149.5–150.5°. Recrystallization from hexane gave an analytical sample, m.p. 148.5–150°; ν_{max}^{KBr} 1745 (ester C=O) and 1660 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 2.02, 2.64, 3.31 d (J = 9 c.p.s.), 5.33 d (J = 9 c.p.s.), 6.15, 6.18 d (J = 17 c.p.s.), 6.38, 6.48 m, 6.89 d (J = 17 c.p.s.), 8.43, 8.92, and 9.05 p.p.m. d (J = 6 c.p.s.).

Anal. Calcd. for $C_{20}H_{28}N_2O_5S$: C, 58.80; H, 6.91; N, 6.86. Found: C, 58.75; H, 6.75; N, 6.70.

3D-Carbomethoxy-2,2-dimethyl-6-ethoxy-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (XX) was prepared by the same procedure as given above for XIX, but in ethanol solution; m.p. 165–166° (from hexane), ν_{max}^{KBr} 1732 (ester C=O) and 1662 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 2.15, 2.61, 3.36 d (J = 9 c.p.s.), 5.27 d (J = 9 c.p.s.), 6.13, 6.27 d (J = 15 c.p.s.), 6.79 d (J = 15 c.p.s.), 6.8 m, 8.42, 8.90 t (J = 7 c.p.s.), 8.92 p.p.m.

Anal. Calcd. for $C_{19}H_{26}N_2O_5S$: C, 57.82; H, 6.63; N, 7.09. Found: C, 58.03; H, 6.59; N, 7.11.

Photolysis of 3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) in Ethyl Mercaptan at 20°.—A partial solution of 0.92 g. (0.002 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI), which n.m.r. analysis had shown to be 79% pure, in *ca.* 12 ml. of ethyl mercaptan was irradiated in a sealed Carius tube by a Sperti sun lamp, Model P-109, the Carius tube being kept at a temperature of 20° by a cooling bath. Irradiation was continued for 29 hr., and the tube was turned periodically so that the fine hair-like needles which grew on the lighted side would not impede the reaction. The tube was opened; the contents were washed into a beaker with chloroform; and the solvent was removed on a steam-bath. The residue, 0.494 g. (42%), m.p. 205–207°, from partial solution of the solid reaction product in 20 ml. of chloroform was a material (XVII) isomeric with 3D-carbomethoxy-2,2-dimethyl-6-ethylthio-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine. Recrystallization from ethanol raised the melting point to 206–206.5°; ν_{max}^{KBr} 1740 (ester C=O), 1674 (amide C=O), and 1656 cm.$^{-1}$ (amide C=O); n.m.r. τ-values (DMSO-d_6) at 50°: 1.20, 2.75, 3.30 d (J = 7.5 c.p.s.), 5.47 d (J = 7.5 c.p.s.), 6.36, 6.47, 6.82, 7.52 m, 8.73, 8.82, 8.94 t (J = 6.5 c.p.s.).

Anal. Calcd. for $C_{19}H_{26}N_2O_4S_2$: C, 55.58; H, 6.38; N, 6.82;

mol. wt., 410.55. Found: C, 55.54; H, 6.44; N, 6.58; mol. wt., 433 (osmometric in acetone)

The chloroform-soluble fraction obtained from the partial solution of the reaction mixture was applied to a column of 70 g. of silica gel. Elution with ether separated this mixture into two fractions, the second of which was 0.128 g. of the 206° m.p. isomer. The total yield of this isomer was thus raised to 67%. The first fraction, 0.119 g. (10%) of a soft solid, was crystallized from ethanol to give 0.048 g. (4%) of needles of 3D-carbomethoxy-2,2-dimethyl-6-ethylthio-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (XVIII), m.p. 180–181.5°. An analytical sample had m.p. 182.5–182.7°; ν_{max}^{KBr} 1736 (ester C=O), 1675 (amide C=O), and 1654 cm.$^{-1}$ (amide C=O); n.m.r. τ-values ($CDCl_3$): 2.40, 2.65, 3.50 d (J = 8 c.p.s.) 5.35 d (J = 8 c.p.s.), 5.93 d (J = 17.0 c.p.s.), 6.16, 6.40, 7.15 d (J = 17.0 c.p.s.), 7.85, 8.46, 8.91, 8.98 t p.p.m. (J = 7 c.p.s.).

Anal. Found: C, 55.40; H, 6.32; N, 6.79.

Photoreduction of 3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI).—A solution of 0.97 g. (0.002 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI, 82% pure) in 12 ml. of ethyl mercaptan in a sealed Carius tube was irradiated for 35 hr. at a distance of 2.5 in. from the arc of a Sperti sun lamp, Model P-109. The temperature was about 55°. During the irradiation fine needles were deposited in the tube. The tube was opened, and the material was washed out with chloroform. Evaporation of the solvent on the steam bath left a solid which was partially dissolved in 15 ml. of chloroform and filtered. The filtrate was applied to a column of 130 g. of silica gel which was then eluted with ether to yield two fractions. The first solid fraction, 0.083 g., was identical and was combined with the chloroform-insoluble fraction from the reaction mixture, 0.178 g. This material, now 0.26 g., was recrystallized from ethanol to give 0.183 g. (20%) of the isomer (XVII) of 3D-carbomethoxy-2,2-dimethyl-6-ethylthio-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine of m.p. 206–206.5°. The second fraction, 720 mg., m.p. 172–173° after crystallization from ethanol, was 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII). After allowing for the 18% of XIII present in the starting material, the yield is equivalent to a 68% photoreduction.

This reaction was repeated using 0.440 g. (0.0012 mole) of pure 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine, m.p. 142–143°, the irradiation proceeding for 70 hr. From this reaction there was obtained 0.12 g. (37%) of the ethyl mercaptan adduct and 0.20 g. (45%) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine. The n.m.r. spectrum of the latter was identical with that of an authentic sample and the optical rotation, $[\alpha]^{25}D$ −39.3° (0.5% in EtOH), was compatible with the value of −39.7° obtained previously. The melting point of this material, 180–182°, was somewhat higher than the original, suggesting that the further reaction had discriminated against a trace of impurity consistently present in XIII obtained from penicillamine methyl ester hydrochloride.

Pyrolysis of the Ethyl Mercatpan Adduct of 3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine, M.p. 205.5–206.5°.—The ethyl mercaptan adduct, m.p. 205.5–206.5°, of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVII), 80 mg., was maintained at a temperature of 210° under a current of nitrogen for 1 hr. The remaining brown melt, cooled and dissolved in deuteriochloroform, showed the n.m.r. spectrum of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI), indicating that the total amount of impurities was no more than 5%. Chromatographic purification of this material on 2 g. of silica gel with an ether eluent afforded, after crystallization from ethanol, 20 mg. (30%) of slightly tan crystals of XVI, m.p. 140–143°.

Photoreduction of the Ethyl Mercaptan Adduct of 3D-Carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVII), M.p. 205.5-206.5°, in Ethyl Mercaptan.—A suspension of 48 mg. of the ethyl mercaptan adduct of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVII), m.p. 205.5–206.5°, in 3 ml. of ethyl mercaptan was irradiated by a Speri sun lamp, Model P-109, at a distance of 2 in. from the arc for 48 hr. The solvent was removed, and the product, dissolved in deuteriochloroform, was analyzed by n.m.r. The n.m.r. spectrum showed the crude material to be mainly 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII), and removal of the deuteriochloroform and crystallization of the mass from ethanol gave 29 mg. (71%) of fine white crystals of XIII, m.p. 178–180°.

Methyl α-D-Isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) from XIII.—A solution of 3.5 g. (0.01 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) and 1.7 g. (0.01 mole) of N-chlorosuccinimide in 75 ml. of methylene chloride was irradiated at reflux by a Sperti sun lamp, Model P-109, until evolution of hydrogen chloride had ceased.[49] The mixture was cooled, and the volume was reduced to 25 ml. The solution was washed with 50 ml. of water, dried over magnesium sulfate, and evaporated to dryness under vacuum. The oily residue was taken up in 9 ml. of absolute ethanol, seeded, and allowed to crystallize at −20°.[50] The short needles were collected by filtration, 0.410 g. (12%), and recrystallized from 7.5 ml. of absolute ethanol to give 0.14 g. of methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI), m.p. 150–152°; ν_{max}^{KBr} 3365, 1739, 1680, 1625, 1580, 1520, and 1490 cm.$^{-1}$; λ_{max}^{EtOH} 296.5 mμ (ε 10,800) with a shoulder at 222.5 mμ (ε 10,200); $[\alpha]^{25}D$ −40.6° (9% in chloroform), −33.0° (0.2% in ethanol); n.m.r. τ-values: 1.40, 2.67, 4.40, 4.77, 4.95, 6.27, 6.34, and 8.22 p.p.m.

Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; mol. wt., 346.40. Found: C, 59.03; H, 5.38; N, 8.11; mol. wt., 346 (mass spectrum, molecular ion).

Methyl α-D-Isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) from XVI.—To a solution of 348 mg. (1 mmole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) in 5 ml. of chloroform at room temperature was added 2.2 ml. (1 mmole) of a 0.46 M solution of chlorine in methylene chloride. After being swirled for 15 min., the reaction gave a negative starch–iodide test. The solution was warmed on the steam bath until evolution of hydrogen chloride had ceased. An n.m.r. spectrum of this solution showed that 50% of the starting material remained. The chlorination–dehydrochlorination was repeated, whereupon the n.m.r. spectrum showed that greater than 90% of the starting material had undergone reaction and that the only product formed in greater than trace amounts was methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI). The solid residue remaining after removal of the solvent under vacuum was crystallized from 7 ml. of absolute ethanol at −20° to give 156 mg. (45%) of colorless crystals of XXI, m.p. 149.5–151°.

Methyl α-D-Isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) by N-Chlorosuccinimide Oxidation of XVI.—To a solution of 348 mg. (1 mmole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) in 3 ml. of chloroform was added 134 mg. (1 mmole) of N-chlorosuccinimide and a trace of dibenzoyl peroxide. The mixture was swirled until a slight temperature increase was noted, then it was left to stand for 2 hr. Analysis of the crude reaction mixture by n.m.r. showed that the main product was methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) with smaller amounts of minor side products and unreacted starting material. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness under vacuum. The semicrystalline solid remaining was dissolved in 5 ml. of absolute ethanol and allowed to crystallize at −20°, giving 168 mg. (49%) of fine, slightly tan needles of XXI, m.p. 146.5–151°.

Isomerization of Methyl α-D-Isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) to Methyl α-Isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII).—A 50-mg. sample of methyl α-D-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate (XXI) was dissolved in 0.8 ml. of chloroform to which was added 0.01 ml. of triethylamine and 3 drops of water. The mixture was swirled, then allowed to stand at room temperature for 2 hr. The volatile fractions were removed; an n.m.r. spectrum in deuteriochloroform showed that complete isomerization to methyl α-isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII) had taken place. After removal of the deuteriochloroform, crystallization of the crude material from ethanol provided 30 mg. (60%) of colorless needles of the isomerized prod-

(49) Alternatively the reaction mixture could be allowed to stand for 24 hrs. without ultraviolet irradiation, but with 20 mg. of dibenzoyl peroxide added. These conditions have been reported to give a compound erroneously assigned structure XVI.[14]

(50) Spontaneous crystallization will take place after about 1 week at −20°.

uct, m.p. 232–233°. The m.p. and mixture m.p. were identical with that of a sample of XXII obtained as described below.

Methyl α-Isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII).—To a solution of 4.0 g. (0.01 mole) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (XIII) and 2.0 g. (0.015 mole) of N-chlorosuccinimide in 30 ml. of chloroform was added with swirling 20 mg. of dibenzoyl peroxide. After an induction period of about 10 min. a sharp rise in temperature was noted. After 3 hr. the yellow solution had returned to room temperature and no starting material was detectable by thin layer chromatography on silica gel. The chloroform solution was washed with 30 ml. of water to remove succinimide, dried over sodium sulfate, and applied, in a total volume of 46 ml. of chloroform solution, to a column made from 400 g. of Florisil, 5.5 × 30 cm. Elution was carried out with ether–ethyl acetate mixtures and the optical density at 295 mμ was recorded for each 70-ml. fraction. Fractions 1–14 contained no product. From fractions 15–35 were isolated 0.82 g. (21%) of crude methyl α-isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate (XXII) as colorless needles. Recrystallization of this material from ethanol, after washing a chloroform solution of this material with water to remove any succinimide, gave an analytically pure sample, m.p. 232.2–233.1°; ν_{max}^{KBr} 3270, 1710, 1680, 1619, 1572, 1525, and 1489 cm.$^{-1}$; λ_{max}^{EtOH} 295.5 mμ (ε 10,020) with a shoulder at 307 mμ (ε 7900); $[\alpha]^{25}D \leq 2°$; n.m.r. τ-values: 1.02, 1.30, 2.68, 6.24, 6.37, 7.82, and 8.19 p.p.m.

Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; mol. wt., 346.40. Found: C, 58.90; H, 5.31; N, 8.23; mol. wt., 346 (mass spectrum, molecular ion). Fractions 40–65 afforded 1.6 g. (40%) of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (XVI) as an impure oil which could be crystallized from ethyl acetate–hexane.

***cis*-(3-*t*-Butylthio)acrylamide (XXIV).**—To a solution of 4.0 g. (0.058 mole) of propiolamide and 5.2 g. (0.058 mole) of *t*-butyl mercaptan in 20 ml. of ethanol in a flask surmounted by a condenser was added 5 mg. of sodium methoxide. The system was closed from the atmosphere until the initially exothermic reaction had subsided, approximately 2 min. Removal of the solvent after cooling the reaction left a soft, orange solid. Crystallization of this mass from methylene chloride–hexane at Dry Ice temperature gave 5.8 g. of slightly yellowish plates of *cis*-(3-*t*-butylthio)acrylamide, m.p. 159–160.5°. Concentration of the mother liquors afforded an additional 1.2 g. of the *cis* isomer, raising the yield to 76%; $\nu_{max}^{CHCl_3}$ 3050, 3465, 3390, 3315, 3150, 1664 (amide C=O), 1590, and 1570 cm.$^{-1}$ (amide C=O); λ_{max}^{EtOH} 215 (ε 2060) and 282 mμ (ε 13,000); n.m.r. τ-values ($CDCl_3$): 2.93 d (J = 10.5 c.p.s.), 4.13 d, and 8.62 p.p.m.

Anal. Calcd. for $C_7H_{13}NOS$: C, 52.79; H, 8.23; N, 8.80. Found: C, 52.87; H, 8.23; N, 8.86.

The mother liquors from the second crystallization were evaporated to dryness. Hexane extraction of the remaining solid gave some material identified by n.m.r. as the *trans* isomer, doublets at τ 2.20 and 4.03 p.p.m. (J = 15.0 c.p.s.), and a singlet at τ 8.58 p.p.m. This material crystallized poorly from hexane, m.p. 76–76.5°, and it decomposed upon attempted sublimation.

3-Isothiazolone.—To a solution of 2.5 g. (15.7 mmoles) of *cis*-(3-*t*-butylthio)acrylamide (XXIV) in a mixture of 40 ml. of chloroform and 10 ml. of ethyl acetate at −60° was added dropwise and with stirring 31.5 ml. (15.7 mmoles) of chlorine, 0.5 *M* in carbon tetrachloride. After 1 hr. at this temperature, the mixture was warmed to reflux while a current of nitrogen was bubbled through it to remove the hydrogen chloride formed. After 2 hr. the elimination of hydrogen chloride had ceased. The solvent was replaced by 30 ml. of water, and 10 ml. of 2 *N* sodium hydroxide solution was added. The aqueous solution was extracted twice with ether, carefully neutralized, and extracted continuously with ether for 2 hr. The ether solution was dried over sodium sulfate and evaporated *in vacuo* to leave 0.38 g. (24%) of a yellow oil. The oil was partly dissolved in 20 ml. of water, filtered, and the aqueous solution was extracted continuously with ether for 2 hr. Removal of the ether solvent after drying left crystalline 3-isothiazolone. Recrystallization from hexane and two sublimations afforded an analytical sample, m.p. 73–74°; $\nu_{max}^{CCl_4}$ 3090, 3030, 2980, 2800, 2690, 2630, 2540, 1659, 1639, 1573, 1546, 1420, 1328, 1072, 988, 868, 832, 681, and 602 cm.$^{-1}$; λ_{max}^{EtOH} 257 mμ (ε 6400) with a shoulder at 280 mμ (ε 1350); in base a shift to 279 mμ (ε 6750) was observed for the maximum. 3-Isothiazolone showed n.m.r. signals at τ-values ($CDCl_3$) −1.90, 1.56 d (J = 5.0 c.p.s.), and 3.42 d p.p.m.

Anal. Calcd. for C_3H_3NOS: C, 35.62; H, 2.99; N, 13.85. Found: C, 35.55; H, 3.00; N, 13.78.

General Procedure for Degradation of the 1,4-Thiazepines and 3-Isothiazolones to Amino Acids.—A 10-mg. sample of material was heated under reflux with *ca.* 1 g. of Raney nickel W-2 in about 10 ml. of absolute ethanol for 2 hr. The Raney nickel was washed three times with absolute ethanol by decantation before use. A check was made before and after the reaction to make sure the catalyst was pyrophoric. To the residue remaining after gravity filtration of the reaction mixture and evaporation of the ethanol under vacuum on a rotary evaporator was added 1 ml. of 8 *N* sulfuric acid, and the solution was heated under reflux for 4 hr. Neutralization of the cooled reaction mixture to pH 6 with barium hydroxide, vacuum filtration, and lavation of the precipitate with hot water was followed by removal of the water under vacuum on a rotary evaporator to a volume of *ca.* 1 ml. This solution was then subjected to thin layer chromatography[51] on silica gel G with 1-butanol–acetic acid–water (60:15:25) and phenol–water (75:25), on cellulose MN 300 G (Merck) with phenol–water (75:25), and to paper chromatography with phenol–water (80:20) and 1-butanol–acetic acid–water (60:15:25). Valine and alanine were chromatographed together with the unknowns as standards. Double spotting was carried out to make sure that the R_f values of standard and unknowns did not change each other. Valine could be distinguished from α-aminobutyric acid by t.l.c. on silica gel with phenol–water (75:25).

Thin Layer Chromatography.—Thin layer chromatograms were run on silica gel G plates (Merck) equilibrated with atmospheric moisture and developed with ether eluent. They were then sprayed sequentially with three developing reagents in the order given: reagent 1, 0.4% disodium fluorescein in water; dark spots on a fluorescent yellow background were seen under a long wave length ultraviolet lamp. Reagent 2, 1% potassium permanganate in 5% sodium carbonate solution; yellow spots on a purple background were observed. Reagent 3, Dragendorff reagent; brown spots on a yellow background were observed. This reagent was prepared by dissolving 7.1 g. of bismuth subcarbonate in 20–25 ml. of 30% nitric acid and adding this solution slowly and with stirring to a hot solution of 28 g. of potassium iodide and 1 ml. of 6 *N* hydrochloric acid in *ca.* 5 ml. of water. The stock solution is prepared by cooling the above to about 15°, filtering, and diluting to 100 ml. The spray solution is made by adding in order 5 ml. of 6 *N* hydrochloric acid, 20 ml. of water, and 2 ml. of stock solution.[52]

(51) K. Randerath, "Thin Layer Chromatography," Academic Press, Inc., New York, N. Y., 1963, p. 93 ff.

(52) This procedure, obtained from Dr. Tozo Fuji, is a modification of the one found in R. J. Block, E. L. Durrum, and G. Zweig, "A Manual of Paper Chromatography and Paper Electrophoresis," Academic Press, Inc., New York, N. Y., 1958, p. 360 f.