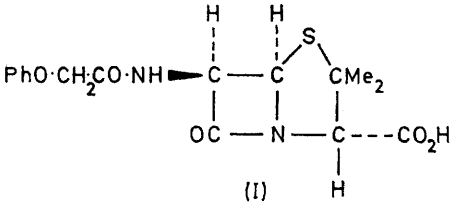
Studies on Lactams. Part XIV.[1] The Synthesis of a Structural Isomer of Penicillin

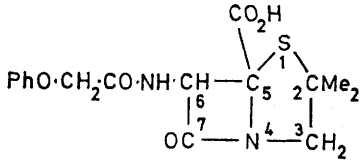
By **Ajay K. Bose, G. Spiegelman,** and **M. S. Manhas,** Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030, U.S.A.

5-Carboxy-2,2-dimethyl-6-phenoxyacetamidopenam, a structural isomer of penicillin V, was synthesized *via* an α-azido-β-lactam from t-butyl 5,5-dimethyl-2-thiazoline-2-carboxylate and azidoacetyl chloride. The 2-thiazoline was obtained from the readily synthesized t-butyl 5,5-dimethyl-3-thiazoline-2-carboxylate by isomerization under the influence of potassium t-butoxide. The α-azido-β-lactam t-butyl ester was catalytically reduced with hydrogen and acylated. The amido-ester was converted into the free acid on treatment with trifluoroacetic acid. Mainly from n.m.r. studies, the amido- and carboxy-groups were deduced to be *cis* to each other, and the penicillin sulphoxide type of conformation was suggested for the thiazolidine ring.

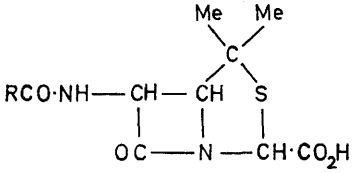
RECENTLY we described a convenient synthesis[2] of α-amido-β-lactams *via* α-azido-β-lactams and extended this method to the preparation[3] of 6-*epi*-penicillin V and various analogues of penicillin (I). We report here the synthesis[4] and the stereochemical features of 5-carboxy-2,2-dimethyl-6-phenoxyacetamidopenam (II), a structural isomer of penicillin (I).



(I)

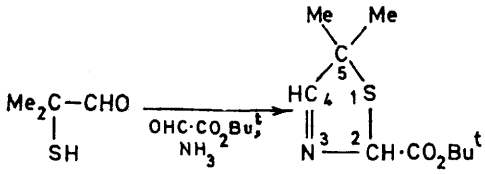


(II)

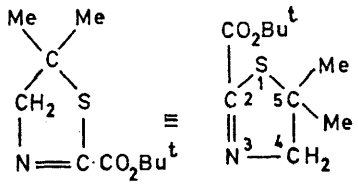


(III)

In an attempt to synthesize an isomer (III) of penicillin in which the position of the sulphur atom with respect to the β-lactam ring had been altered, the 3-thiazoline (IV)[1,5] was prepared from α-mercaptoisobutyraldehyde, ammonia, and t-butyl glyoxylate.[1,6] Condensation with azidoacetyl chloride and triethylamine gave a very low yield of a β-lactam from samples of the 3-thiazoline (IV) that had been chromatographed on basic alumina. The n.m.r. spectrum of this β-lactam, together with the effect of basic alumina on its formation, suggested that compound (IV) had partially isomerized to the 2-thiazoline (V) before conversion into the β-lactam. Indeed the 3-thiazoline (IV) could be isomerized in nearly quantitative yield in the presence of potassium t-butoxide. The n.m.r. spectra of compounds (IV) and (V) clearly differentiate these isomers: the methylene protons of (V) give rise to a two-proton singlet at τ 5·48 whereas an AB pattern (J 2·3 Hz; long-range coupling) is produced by the protons at C-2 and C-4 in (IV).[1]



(IV)



(V)

Treatment of the 2-thiazoline (V) with azidoacetyl chloride and triethylamine in methylene chloride led to a single crystalline product (VI) (86%), identified by its i.r. and n.m.r. spectra. The high yield of (VI) must be attributed to an effect of the 2-carboxylate substituent in the 2-thiazoline (V) on the β-lactam-forming reaction. This is not readily explained, but the same effect was observed in an earlier study on the synthesis of penicillins. Erickson[7] reported that benzyl 2-thiazoline-

[1] Part XIII, A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Chem. Soc.* (*C*), 1971, 188.

[2] A. K. Bose and B. Anjaneyulu, *Chem. and Ind.*, 1966, 903; A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

[3] A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, 1968, **90**, 4506.

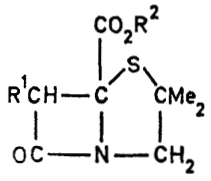
[4] Preliminary report, A. K. Bose, G. Spiegelman, and M. S. Manhas, *Chem. Comm.*, 1968, 321.

[5] M. Thiel, F. Asinger, and K. Schmeidel, *Annalen*, 1958, **611**, 121.

[6] N. Kornblum and H. W. Frazier, *J. Amer. Chem. Soc.*, 1966, **88**, 865.

[7] J. A. Erickson, Ph.D. Thesis, Massachusetts Institute of Technology, 1953.

2-carboxylate reacted with phthalimidoacetyl chloride and triethylamine to give an 85% yield of benzyl 6-phthalimidopenam-5-carboxylate. Although the benzyl ester was reduced to the free acid, there was no mention of any attempt to remove the phthaloyl group. It is unlikely that this group can be removed without scission of the β-lactam ring.

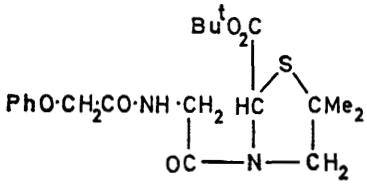


(VI) $R^1 = N_3$, $R^2 = Bu^t$
(VII) $R^1 = N_3$, $R^2 = H$
(VIII) $R^1 = NH_2$, $R^2 = Bu^t$
(IX) $R^1 = PhO{\cdot}CH_2CO{\cdot}NH$, $R^2 = Bu^t$
(XI) $R^1 = NH_2$, $R^2 = H$
(XII) $R^1 = PhO{\cdot}CH_2CO{\cdot}NH$, $R^2 = H$
(XIII) $R^1 = PhO{\cdot}CH_2CO{\cdot}NH$, $R^2 = Me$

Brief treatment of the azido-t-butyl ester (VI) with trifluoroacetic acid at room temperature led to a 70% yield of crystalline 6-azido-2,2-dimethylpenam-5-carboxylic acid (VII), $\lambda_{max.}$ 4·72 (N_3), 5·59 (β-lactam), and 5·79 μm (CO_2H), respectively. The n.m.r. spectrum was consistent with this assignment.

The azido-acid (VII) decomposed rapidly in hot benzene and slowly on exposure to light. Although this decomposition was not studied in detail, t.l.c. showed several spots suggesting that a complex mixture was formed. An attempt to convert the azido-acid (VII) into an amino-acid by reduction with hydrogen over an excess of platinum oxide failed.

Treatment of the azido-t-butyl ester (VI) with hydrogen and excess of platinum oxide resulted in complete reduction of the azide. The i.r. spectrum of the crude product exhibited a band at 6·0 μm in addition to bands corresponding to the expected amino-ester. Crystallization from hexane afforded 48% yield of a material (VIII) which could not be purified by repeated recrystallization. Treatment of this with phenoxyacetyl chloride in the presence of triethylamine, followed by column chromatography, gave two crystalline products. One, obtained in 32% yield, was the expected t-butyl 6-phenoxyacetamido-2,2-dimethylpenam-5-carboxylate (IX). The second (14%) was shown to have structure (X) on the basis of spectral data. A multiplet centred at τ 5·81 (2H) in the n.m.r. spectrum appears to be the AB portion of an ABX pattern with J_{AB} 13·5 and $J_{AX} = J_{BX} = 5$ Hz. This signal is assigned to the methylene protons of the glycyl fragment, coupled to each other and to the amide NH proton. A decoupling experiment supports this interpretation; irradiation at the frequency of the amide NH proton (a broad band centred at τ 2·5) caused the τ 5·81 signal to collapse to a broad singlet. The signal of the other methylene group appears as a singlet, which is unaffected when the frequency of the amide NH proton is irradiated. Cleavage of the C(5)–C(6) bond under the mild conditions used is unusual; * β-lactams are generally stable to catalytic hydrogenation. Moreover, one might expect that cleavage of the bond between the ring nitrogen atom and C-5 would be competitive with, or more favourable than, cleavage of the C(5)–C(6) bond. The low yield of isolated products suggests that other cleavages may have also occurred.



(X)

The purified amino-t-butyl ester (VIII) was converted into the amino-acid (XI) by brief treatment with trifluoroacetic acid at room temperature. Neutralization of the acidic residue obtained on evaporation of the excess of trifluoroacetic acid gave a 35% yield of 6-amino-2,2-dimethylpenam-5-carboxylic acid (XI); 40% of the starting material was recovered. The identification of the amino-acid (XI) is based on its method of synthesis, its solubility properties, its spectral data, and its transformation into other products.

Acylation of the amino-acid (XI) with phenoxyacetyl chloride, *via* an established procedure for the preparation of penicillin V from 6-aminopenicillanic acid,[8] led to the acylamino-acid (XII), which was not isolated. Attempts to obtain the pure potassium salt of this acid (XII) were unsuccessful. However, the analytically pure methyl ester (XIII) was readily prepared by treatment with diazomethane.

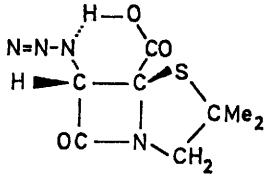
The stereochemistry of the compounds prepared in this investigation remains to be considered. In the synthesis of the azido-t-butyl ester (VI) it was found that only one of the two possible racemic isomers was formed. T.l.c. analysis and spectral data of the compounds derived from (VI) indicated that they also are single isomers. From the nature of the chemical transformations, and the absence of isomeric products, we concluded that all the bicyclic β-lactams derived from (VI) have the same stereochemistry. If the C-6 proton is *cis* to the carboxylic group, a relatively large and specific change in the chemical shift of the C-6 proton would be expected to occur when the nature of the carboxylic group is changed. The Table summarizes chemical shift data for the azido-t-butyl ester (VI) and its derivatives. Comparison of the chemical shifts of the C-2 methyl group, the C-3 protons, the t-butoxy-group, and the methylene protons of the phenoxyacetyl group in each compound shows that differences due to concentration, solvent, and effect of polar substituents on the overall magnetic environment are generally less than 0·1—0·2 p.p.m. The chemical

* Recently we have observed cleavage of the C(5)–C(6) bond in some other penam derivatives during hydrogenation. The findings will be reported at a future date.

[8] J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, 1962, **84**, 2983.

shift of the C-6 proton in the phenoxyacetamido-compounds exhibits a maximum difference of 0·23 p.p.m. between the methyl ester (XIII), the t-butyl ester (IX), and the potassium salt of (XI). This difference is not much larger than the general variation of the other proton signals. Consideration of the change in the carboxylic group from an ester in (IX) or (XIII) to an anion in the potassium salt of (XI) suggests that it is *trans* to the C-6 proton.

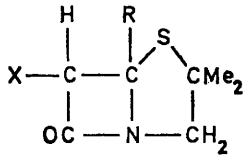
This stereochemical assignment is confirmed by data for the azido-compounds, where the change from t-butyl ester (VI) to carboxylic acid (VII) results in a 0·46 p.p.m. downfield shift of the C-6 proton signal. This difference is twice as large as that observed in the phenoxyacetamido-series and indicates that there is a unique effect in the azido-acid (VII). This effect can be seen in a molecular model, which reveals that when the azido-group is *cis* to the carboxy-group, a conformation of the latter exists in which the acidic proton can form a hydrogen bond with the azide nitrogen atom adjacent to C-6 with the formation of a six-membered ring [structure (A)]. The model displays no additional ring strain or unfavourable interactions as a result of the hydrogen bond. Precedent for the interaction of an acidic proton and an azide group is found in a recent study on the photodecarboxylation of α-azido-acids.[9]



(A)

The n.m.r. spectra also provide information concerning the conformation of thiazolidine ring in the compounds listed in the Table. Examination of the AB pattern observed for the C-3 protons reveals that, in each compound, the signal for the proton in the τ 7·0 region shows significant line broadening relative to the signal for the proton in the τ 6·0 region. This difference suggests the presence of long-range coupling. A decoupling experiment with compound (VI) produced line sharpening of the high and low field parts of the τ 7·02 signal when decoupling frequencies of +83 and +95 Hz, respectively, were applied. A change of ±4 Hz in the decoupling frequencies led to the loss of these effects.

Chemical shift data for substituted penam-5-carboxylates



Compound		Chemical shift [a]				
X	R	C(6)H	C(3)H_2 [b]	C(2)Me_2	Bu^t	O·CH_2
NHC(=O)·CH_2·OPh	CO_2Bu^t	4·63 [c]	7·11, 6·16	8·61, 8·52	8·61	5·60
NHC(=O)·CH_2·OPh	CO_2Me	4·55 [c]	7·03, 6·05	8·49		5·50
NHC(=O)·CH_2·OPh [d]	$CO_2^-K^+$	4·78	6·98, 6·03	8·57, 8·50		5·55
N_3	CO_2Bu^t	5·09	7·02, 6·08	8·52, 8·45	8·45	
N_3 [e]	CO_2H	4·63	7·03, 5·98	8·51, 8·45		
NH_2	CO_2Bu^t	5·61	7·20, 6·22	8·58, 8·52	8·52	
$^+NH_3$ [f]	CO_2D	4·83 [g]	6·79, 5·85	8·48, 8·41		

[a] τ ($CDCl_3$) unless otherwise specified. [b] AB pattern, *J* 12 Hz. [c] d, *J* 9 Hz. [d] Solvent D_2O. [e] Solvent $(CD_3)_2CO$. [f] Solvent 2N-DCl. [g] Estimated.

The observed frequencies agree with the values of +84 and +96 Hz calculated for long-range coupling to the C-2 methyl signal at τ 8·52 and prove that this coupling exists. A planar W-orientation is thought to be necessary for long-range coupling through four saturated bonds.[10] Two preferred conformations for the thiazolidine ring in penicillin derivatives have been established.[11] In penicillin G or V, the thiazolidine ring has an envelope conformation with C-3 out of the plane of the other four atoms and away from the C-6 amido-substituent [structure (B)]. In penicillin V sulphoxide the thiazolidine ring has an envelope conformation in which C-2 is out of plane of the other four atoms [*cf.* structure (C)].

The two possible conformations just described can be distinguished from each other by studies analogous to previous investigations of the anisotropic effect of a ring nitrogen atom lone electron pair on an adjacent methylene group.[12] In chair-shaped six-membered rings, if one of the methylene protons and the nitrogen lone pair are oriented *trans* and diaxial, then the chemical shift of that proton is 50—60 Hz to higher field than the shift of the other methylene proton. However, when a *trans*

[9] R. M. Moriarty and M. Rahman, *J. Amer. Chem. Soc.*, 1965, **87**, 2519.

[10] See, *e.g.*, N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field,' Holden-Day, San Francisco, 1964, p. 115.

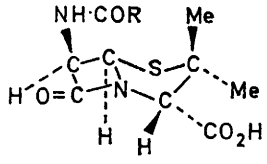
[11] (*a*) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408; (*b*) R. A. Archer and P. V. Demarco, *ibid.*, p. 1530; (*c*) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, p. 1528; (*d*) R. A. Archer, R. D. G. Cooper, P. V. Demarco, and L. R. F. Johnson, *Chem. Comm.*, 1970, 1291; (*e*) D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1969, **91**, 1529.

[12] J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 1967, **89**, 3761.

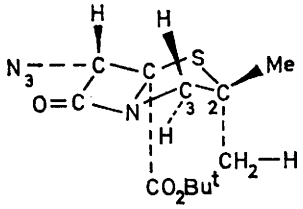
diaxial relationship does not exist, the difference in chemical shifts of the methylene protons is 25—30 Hz. The n.m.r. spectrum of compound (VI) shows a shift difference of 56 Hz. The signal at higher field (τ 7·02) can thus be assigned to the 3β-proton which is *trans* to the ring nitrogen lone pair. In view of the long-range coupling mentioned earlier, the methyl signal at τ 8·52 should be assigned to the 2α-methyl group.

The 56 Hz difference in the chemical shifts of the C-3 protons in structure (VI) and the existence of long-range coupling between the C-3 proton at τ 7·02 and the C-2 methyl group at τ 8·52 are consistent with the assumption that the thiazolidine ring in (VI) has an envelope conformation with C-2 out of the plane of the other four atoms and away from the C-6 proton [structure (C)].

Since all the penam-5-carboxylates listed in the Table show similar long-range coupling for the high field C-3 proton and similar chemical shift differences between the C-3 protons, this assignment of the conformation of the thiazolidine ring should apply to all these compounds. In this conformation the 3β-proton and one of the protons of the 2α-methyl group are in the planar W-orientation necessary for long-range coupling.



(B)



(C)

The assignment of conformation made here for (VI) and related compounds is tentative. More definite evidence is being sought by a study of the n.m.r. and *X*-ray diffraction spectra of some penam analogues of (VI).

EXPERIMENTAL

M.p.s were determined with a Mel-Temp apparatus. I.r. spectra were recorded with a Perkin-Elmer Infracord. ^{1}H N.m.r. spectra of solutions containing tetramethylsilane as internal standard were taken with a Varian A-60A spectrometer. Decoupling experiments were performed with a Varian V-6058A decoupler.

Azidoacetyl chloride,[13] α-bromoisobutyraldehyde,[14] t-butyl glyoxylate,[1] and t-butyl 5,5-dimethyl-3-thiazoline-2-carboxylate [1] were prepared by known methods.

Isomerization of the 3-Thiazoline (IV) *to t-Butyl 5,5-Dimethyl-2-thiazoline-2-carboxylate* (V).—Dry t-butyl alcohol (15 ml) and potassium metal (0·1 g) were heated under reflux for 2 h under nitrogen. The solution was cooled to room temperature and the freshly distilled 3-thiazoline (IV) (10·4 g) was added. The solution immediately turned bright red. After 30 min the mixture was partitioned between ether (125 ml) and water (75 ml). The ether layer was washed with water (75 ml) and saturated salt solution (2 × 50 ml), dried, and concentrated to a red oil. Removal of t-butyl alcohol at 80° under reduced pressure gave the 2-*thiazoline* (9·8 g., 94%) as a light orange solid which was used as such for further reactions. Two sublimations at 30° and 0·03 mmHg afforded a sample, m.p. 80—82°, $\nu_{max.}$ (Nujol) 1767, 1730, 1609, and 1089 cm^{-1}, $\lambda_{max.}$ (cyclohexane) 278 nm (log ε 3·24), τ ($CDCl_3$) 8·48 (6H, s), 8·44 (9H, s), and 5·48 (2H, s) (Found: C, 55·95; H, 7·85; N, 6·6; S, 14·9. $C_{10}H_{17}NO_2S$ requires C, 55·8; H, 7·95; N, 6·5; S, 14·9%).

t-Butyl 6-Azido-2,2-dimethylpenam-5-carboxylate (VI).—To a solution containing the crude 2-thiazoline (V) (9·7 g) and triethylamine (7·0 ml) in methylene chloride (200 ml) was added at room temperature azidoacetyl chloride (6 g) in methylene chloride (125 ml) during 7 h under anhydrous conditions. The dark solution was stirred overnight, washed with water (4 × 200 ml), dried, filtered, and concentrated to obtain a dark solid. A solution of this in methylene chloride was filtered through a column (2·5 cm diam.) of Florisil (50 g). Evaporation of the first 200 ml of eluate gave an off-white solid that was recrystallized from hexane (60 ml) to obtain plates (11·7 g, 86%), m.p. 99—102° (decomp.), $\nu_{max.}$ (Nujol) 2687, 1783, and 1752 cm^{-1}, τ ($CDCl_3$) 8·52 (3H, s), (8·45 12H, s), 7·02br (1H, d, *J* 12·5 Hz), 6·08 (1H, d, *J* 12·5 Hz), and 5·09 (1H, s); irradiation at τ 8·52 caused the broad signal at τ 7·02 to become sharp (Found: C, 48·2; H, 5·8; N, 18·8; S, 10·6. $C_{12}H_{18}N_4O_3S$ requires C, 48·3; H, 6·1; N, 18·8; S, 10·75%).

6-Azido-2,2-dimethylpenam-5-carboxylic Acid (VII).—The azido-ester (1 g) in trifluoroacetic acid (5 ml) protected from moisture was swirled for 8 min at room temperature. Removal of trifluoroacetic acid under reduced pressure left a dark oil which was extracted with benzene (25 ml). Concentration of the benzene solution gave a semi-solid residue which on trituration with benzene (5 ml) gave *crystals* (0·44 g). The benzene filtrate contained mainly unchanged (VI), treatment of which with trifluoroacetic acid gave an additional 0·13 g of the acid (VII). Two recrystallizations from ether–hexane gave material, m.p. 116—117° (decomp.), $\nu_{max.}$ (Nujol) 3333—2500, 2122, 1791, and 1733 cm^{-1}, τ [$(CD_3)_2CO$] 8·51 (3H, s), 8·45 (3H, s), 7·03 (1H, d, *J* 12·5 Hz), 5·98 (1H, d, *J* 12·5 Hz), 4·63 (1H, s), and 0·75br (1H, s) (Found: C, 39·3; H, 4·15; N, 23·05. $C_8H_{10}N_4O_3S$ requires C, 39·65; H, 4·15; N, 23·15%).

t-Butyl 6-Amino-2,2-dimethylpenam-5-carboxylate (VIII).—A solution of the azido-ester (VI) (2·0 g) in ethyl acetate (100 ml) containing Adams catalyst (4·2 g) was shaken for 4 h under hydrogen (45 lb in^{-2}). Removal of the catalyst and solvent left a crude brown solid which was then refluxed with Norite in hexane solution. The hexane solution afforded the amine (0·87 g, 48%), m.p. 102—106°, $\nu_{max.}$ (Nujol) 3470, 3373, 1794, and 1733 cm^{-1}, τ ($CDCl_3$) 8·58 (3H, s), 8·52 (12H, s), 8·22 (2H, s), 7·20 (1H d, *J* 11·7 Hz), 6·22 (1H, d, *J* 11·7 Hz), and 5·61 (1H, s). This material was used without further purification.

Acylation of the Amino-ester (VIII).—A solution of phenoxyacetyl chloride (0·29 g) in methylene chloride (10 ml) was slowly added to a cold stirred solution of the crude reduction product obtained from 0·5 g of the azide (VI) in methylene chloride (125 ml) containing triethylamine (0·24 ml). The mixture was stirred for an additional 1 hr at room temperature and evaporated to a gum, which was extracted with ether (2 × 50 ml). Evaporation of the extracts left an orange residue that was chromatographed on a column of Florosil (15 g) with methylene chloride as eluant (25 ml

[13] T. Wieland and H. J. Hennig, *Chem. Ber.*, 1960, **93**, 1236.
[14] T. A. Favorskaya and D. A. Shkurgina, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 713 (*Chem. Abs.*, 1956, **50**, 2427i).

fractions). Fractions 2 and 3 afforded 0·27 and 0·04 g of a yellow gum. Elution was then continued with chloroform. Fractions 4—8 gave 0·23 g of a yellowish gum. Crystallization of fraction 2 from hexane–benzene mixture gave the *acyl derivative* (IX) (0·15 g), m.p. 130—132° (decomp.). The residue from fractions 3—8 when similarly crystallized provided compound (IX) (0·07 g) as the first crop. The mother liquor was concentrated and gave the *thiazolidine* (X) (0·1 g). The total yield of compound (IX) was 0·22 g (32%), needles, $\nu_{max.}$ (Nujol) 3363, 1801, 1730, 1699, and 1525 cm^{-1}, τ ($CDCl_3$) 8·61 (12H, s), 8·52 (3H, s), 7·11br (1H, d, J_{HH} 12 Hz), 6·16 (1H, d, J_{HH} 12 Hz), 5·60 (2H, s), 4·63 (1H, d, J_{HH} 9 Hz), and 2·6—3·4 (6H, m) (Found: C, 59·45; H, 6·15; N, 7·15. $C_{20}H_{26}N_2O_5S$ requires C, 59·1; H, 6·45; N, 6·9%).

The yield of compound (X) was 0·1 g (14%), needles, m.p. 127—128·5° (from benzene–hexane), $\nu_{max.}$ (Nujol) 3381, 1755, 1693, 1650, and 1525 cm^{-1}, τ ($CDCl_3$) 8·52 (12H, s), 8·44 (3H, s), 6·32 (2H, s), 5·81 (2H, m, AB of ABX, J_{AB} 13·5, $J_{AX} = J_{BX} = 5$ Hz), 5·46 (2H, s), 4·45 (1H, s), and 2·3—3·2 (6H, m); irradiation at τ 2·50 caused the multiplet at τ 5·81 to collapse to a broad singlet (Found: C, 58·9; H, 6·85. $C_{20}H_{28}N_2O_5S$ requires C, 58·8; H, 6·9%).

6-*Amino*-2,2-*dimethylpenam*-5-*carboxylic Acid* (XI). To trifluoroacetic acid (5 ml) in a flask protected by a drying tube was added the amino-ester (VIII) (0·86 g). The mixture was stirred for 6 min at room temperature. Most of the trifluoroacetic acid was removed at room temperature under reduced pressure. The residual oil was dissolved in cold methanol (10 ml) and stirred in an ice-bath. Aqueous potassium hydroxide was added dropwise until the solution was neutral. The precipitate was filtered off, washed with methanol, and dried to give the acid (XI) (0·24 g, 35%), m.p. 177—179° (decomp.). The filtrate was diluted with water and extracted with ether. The extract gave starting material (0·36 g, 42%). Repetition of the hydrolysis with trifluoroacetic acid with an 11 min reaction time gave a 39% yield of acid (XI), $\nu_{max.}$ (Nujol), 3083, 2603br, 2126—2070, 1784, 1650, and 1573 cm^{-1}, τ (2N-DCl) τ 8·48 (s), 8·41 (s), 6·79 (d, J_{HH} 13 Hz) and 5·85 (d, J_{HH} 13 Hz) (AB pattern), and 4·78—4·87 (strong).

Methyl 2,2-*Dimethyl*-6-*phenoxyacetamidopenam*-5-*carboxylate* (XIII).—The acid (XI) (0·21 g) was dissolved in stirred and ice-cooled aqueous 4% potassium hydrogen carbonate, and acetone (6 ml) was added. Phenoxyacetyl chloride (0·2 ml) in acetone (3 ml) was then added during 10 min. The solution was stirred for an additional 0·5 h at room temperature, then shaken with cold benzene (35 ml). The mixture was stored in a refrigerator for *ca.* 15 min, and the benzene layer was discarded. The aqueous phase was similarly washed with cold ether (2 × 10 ml). The cold aqueous solution was covered with cold ether (15 ml), cooled in an ice-bath, and swirled rapidly while cold aqueous 10% phosphoric acid was added dropwise till the solution showed pH 2—3. The aqueous phase was separated and rapidly extracted with cold ether (2 × 10 ml). The combined ether extracts were washed with cold water (15 ml), dried (Na_2SO_4) for several minutes in the cold, and filtered. A solution of diazomethane in ether was slowly added to the cold, stirred filtrate in an ice-bath until the yellow colour persisted. This solution was stirred for 0·5 h in an ice-bath and for 1 h at room temperature, and evaporated. The residual yellow oil slowly solidified; recrystallization from hexane–benzene gave the ester (XIII) (0·22 g, 61%) as needles, m.p. 138—140°, $\nu_{max.}$ (Nujol) 3224, 3083, 1808, 1758, 1685, and 1560 cm^{-1}, τ ($CDCl_3$) 8·49 (6H, s), 7·03 (1H, d, J_{HH} 12·2 Hz) and 6·05 (1H, d, J_{HH} 12·2 Hz) (AB pattern), 6·35 (3H, s), 5·50 (2H, s), 4·55 (1H, d, J_{HH} 9 Hz), and 2·4—3·3 (6H, m).

This research was supported in part by a grant from the U.S. Public Health Service.

[0/1747 *Received, October* 14*th*, 1970]