Fraction 1 was filtered, the filtrate (sparingly soluble in water) dissolved in 25 ml. of ether and the ether solution extracted several times with water. The ether solution then was dried over potassium hydroxide pellets. Distillation of the ether left 1.84 g. (12.2%) of a mobile oil which probably was 1,2,2,5,5-pentamethylpiperazine as it formed a viscous benzoyl derivative, which was readily soluble in dilute acid.

The solid part of fraction 1, which had the m.p. of VII, was combined with the alcohol distillate and column washings of the pyrolysis, and this combined solution benzoylated to give 1.90 g. (5.6%) of 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine, m.p. and mixed m.p. 276–279°.

Fraction 3 was triturated with 90–100° petroleum ether and filtered to give 0.3 g. (2%) of the crude dimeric amide (XXIX), m.p. 95–100°; seven recrystallizations of this material from 90–100° petroleum ether gave small, almost white crystals of constant m.p. 119–120°.

Anal. Calcd. for $C_{18}H_{36}N_4O$: C, 66.62; H, 11.18; N, 17.27. Found: C, 66.66; H, 10.70; N, 17.14.

Attempted Reductive Cyclization of XXVI.—The general method of Leonard and co-workers[10] was used as follows: A solution of 22.8 g. (0.1 mole) of XXVI, $n^{25}D$ 1.5604, and 100 ml. of purified dioxane was charged to a steel bomb with 15 g. of copper–chromium–barium oxide catalyst, and hydrogen was admitted to a pressure of 3100 p.s.i. The reaction was carried out with shaking at 250° for seven hours, during which time the pressure dropped 800 p.s.i. (calcd. for desired reaction: 541 p.s.i.).

The filtered reaction mixture was fractionated through a 20-cm. McMahon packed column at 738 mm. to give (1) 3.64 g. (25.5%) of crude 2,2,5,5-tetramethylpiperazine, b.p. 176–183°; (2) 6.74 g. of crystalline 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine, b.p. 240–252°; and (3) 2.8 g. of residue.

The non-crystalline portion of fraction 1 was combined with fractions 2 and 3 and exhaustively benzoylated. No volatile tertiary amine was obtained when the benzoylation mixture was subjected to steam distillation, showing that no reductive cyclization of XXVI had occurred.

Attempted Dieckmann Condensation of 1,4-Dicarbethoxymethyl-2,2,5,5-tetramethylpiperazine (XXVII).—A solution of 16 g. (0.05 mole) of XXVII in 50 ml. of dry benzene was added dropwise to a stirred slurry of 4.5 g. (0.18 mole) of sodium hydride in 100 ml. of dry benzene over a period of 90 minutes, first at room temperature and later at reflux. During this time it was attempted unsuccessfully to start a reaction by the addition of small amounts of absolute alcohol. After an additional 5 hours at reflux the batch was cooled to 10° and treated with 10.7 ml. (11.2 g., 0.18 mole) of glacial acetic acid. Later, 100 ml. of water was added, layers were separated, and the water layer was extracted once with 100 ml. of benzene. From the dried benzene solutions a single fraction of 12 g. (75%) of unchanged XXVII was obtained by distillation, b.p. 123–127° (0.3 mm.), m.p. 61–61.5°.

Attempted Acyloin Condensation of 1,4-Di-(3-carbethoxypropyl)-2,2,5,5-tetramethylpiperazine (XXVIII).—A general procedure[25] for the acyloin condensation was used in this experiment. The apparatus consisted of a 3-l. 3-necked round-bottomed flask, equipped with a side-arm separatory funnel, thermometer, reflux condenser and a Hershberg stirrer driven by a high-speed air motor. A slow stream of nitrogen was passed through the apparatus throughout the following operations. One liter of sodium-dried xylene was placed in the reaction flask and about 100 ml. distilled to remove traces of water from the system; then 30.9 g. (0.67 mole) of a 50% emulsion (from National Distillers Chemical Corp., Cincinnati, Ohio) of sodium in xylene was added at a temperature just below reflux.

A solution of 62.0 g. (0.167 mole) of XXVIII in 550 ml. of dry xylene then was added to the vigorously stirred reaction mixture over a period of 90 minutes at 132–137°. After an additional half-hour stirring at this temperature the reaction mixture was cooled to room temperature and 5 ml. of methanol was added to destroy any excess sodium. Then 490 g. of 10% sulfuric acid (0.5 mole) was added gradually with stirring for another half-hour. Finally an excess of potassium carbonate was added and layers were separated; the aqueous layer was well extracted with ether and benzene and the combined organic solution was dried over anhydrous sodium sulfate, filtered and distilled. The only material obtained was 53 g. (85%) of the starting ester (XXVIII), b.p. 148–152° (0.18 mm.), m.p. 39–41°.

(25) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 1822 (1947).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Mold Metabolites. VII. The Constitution and Synthesis of a New Compound Related to Penicillin[1]

BY RUSSELL L. HODGSON,[2] I. R. C. BICK[3] AND DONALD J. CRAM[4]

RECEIVED JUNE 3, 1953

Treatment of residues obtained from the commercial production of penicillin with acetic anhydride and pyridine gave a new material, $C_9H_{14}N_2SO_2$. The provisional structure, 2-keto-4-acetyl-3,4,5,4′,3′,2′-(5′,5′-dimethylthiazolido)-piperazine (I), for the substance was derived from degradative experiments, and this structure was confirmed by synthesis of the substance and its degradation products. The probability that this compound is an artifact was demonstrated by its direct preparation from benzylpenilloic acid.

As an extension of earlier studies of compounds produced as by-products of commercial penicillin production,[5] the present investigation reports the isolation, determination of structure and synthesis of a new compound obtained from residues ordinarily discarded in the course of purifying the N-ethylpiperidine salt of penicillin G.[6]

Attempts to obtain crystalline compounds from these residues failed. Since the lack of solubility in organic solvents of the acids free from N-ethylpiperidine made them difficult to manipulate, the amorphous mixture of amine salts was acetylated with acetic anhydride and pyridine to give a mixture that was divided into its neutral, acidic and basic components. When submitted to chromatographic absorption on alumina, the neutral component was split into fractions from which were isolated a number of crystalline compounds, only one of which was obtained in sufficient quantity for further work.[7]

(1) Taken largely from the Ph.D. Dissertation of Russell L. Hodgson presented to the University of California at Los Angeles.

(2) Public Health Service Research Fellow of the National Institutes of Health, 1951–1953.

(3) Upjohn Postdoctoral Fellow at the University of California at Los Angeles.

(4) Requests for reprints should be addressed to this author.

(5) D. J. Cram and M. Tishler, THIS JOURNAL, **70**, 4238 (1948); D. J. Cram, *ibid.*, **70**, 4240 (1948).

(6) The authors are indebted to Merck and Co., Rahway, N. J., for a supply of this crude, amorphous mixture of N-ethylpiperidine salts of various acids, as well as for DL-penicillamine hydrochloride and sodium salt of penicillin G.

(7) The authors are indebted to Miss Yi-Hsien Sha who carried out preliminary isolation studies on the original mixture of salts.

Characterization and Degradation

This compound ($C_9H_{14}N_2SO_2$ or I) was characterized as a white, neutral, high melting solid with very slight optical activity. The following groups were found to be absent: ester (hydroxamic test), hydroxyl (xanthate test), carbonyl (Duke reagent), mercaptan and thioketone (iodine-azide test), and α-amino acid (ninhydrin test). The infrared spectrum in chloroform showed strong bands at 3.35, 6.0 (unsymmetrical) and 7.1 μ, and weak bands at 3.0, 7.6, 7.8, 8.1, 9.6, 9.8, 10.4 and 11.4 μ. In nujol mull, additional bands appeared at 12.5 and 14.7 μ. The terminal methyl number was found to be slightly greater than one (1.06), and one N-acetyl group was demonstrated to be present in the molecule.

Attempts to degrade I through either basic or acidic hydrolysis gave either starting material or tars. However, the substance readily underwent reductive desulfurization with Raney nickel to give in 82% yield a compound, $C_9H_{16}N_2O_2$ (II), in which the original sulfur atom had been replaced with two hydrogens. The substance (II) gave a terminal methyl value of 1.34 and an N-CH_3 value of 0.95. The compound was neutral, gave no ninhydrin test, possessed no optical activity, and its infrared spectrum in chloroform showed the following absorption: strong bands at 3.3, 6.0 (broad peak), 7.0 and 7.5 μ and weak bands at 3.1, 7.7 and 9.6 μ.

Compound II when subjected to strong hydrolytic conditions in acid provided 85% of a mole of acetic acid, no carbon dioxide, and a 54% yield of a new substance, $C_7H_{16}N_2O_2$ (III).[8] Compound III gave an N-methyl value of 0.31 and a terminal methyl value of 0.47. The substance appeared to be a basic amino acid and readily formed a dihydrochloride.

These observations can be rationalized in terms of the structure N-(β-aminoethyl)-valine for compound III. The terminal methyl value is consistent with an unsubstituted isopropyl side-chain,[9] and a low N-methyl value is probable with the function, $-\overset{|}{\underset{|}{C}}-NH-CH_2-CH_2-NH_2$.[10] Furthermore, the melting point of the dihydrochloride of III corresponds to that reported[11] for a compound tentatively assigned the structure N-(β-aminoethyl)-valine dihydrochloride.

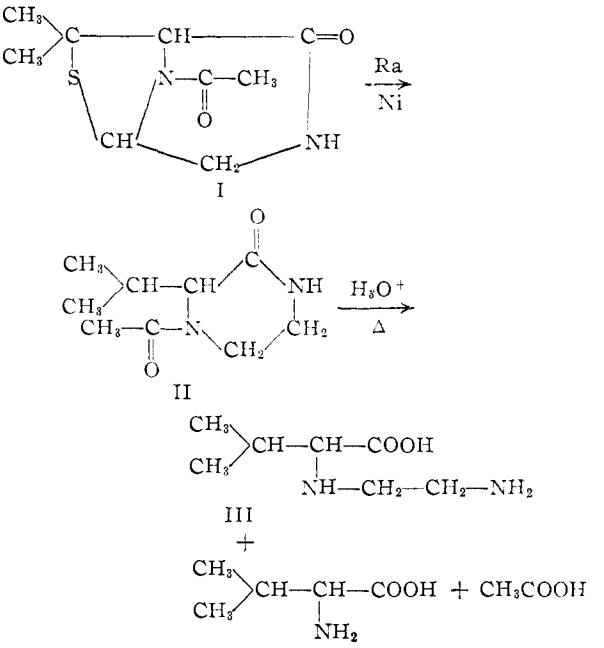
The assignment of provisional structures to II and I, respectively, as 3-isopropyl-2-piperazinone and 2-keto-4-acetyl-3,4,5,4',3',2'-(5',5'-dimethylthiazolido)-piperazine, is now possible. The diamido functions in structures I and II are consistent with the unsymmetrical bands occurring at 6.0 μ in the infrared spectra of the two compounds, and the band at 14.7 μ (nujol mull) found for compound I corresponds to the sulfide linkage of structure I.

(8) From one hydrolysis experiment under milder conditions a small yield of crystalline material was isolated which was demonstrated by paper chromatography to be valine.

(9) Valine itself gives a terminal methyl value of 0.22.

(10) The somewhat volatile compound, 1,2-diiodoethane, was probably incompletely produced in this determination.

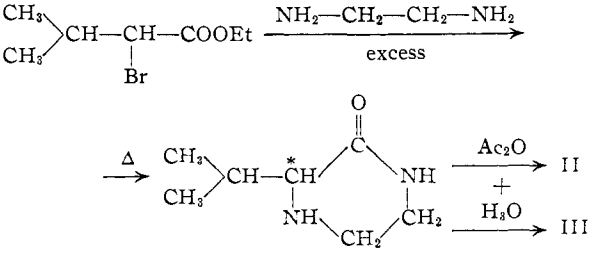
(11) R. L. Peck and K. Folkers, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, Chapter VII, p. 203.



Furthermore, the observed difference in terminal methyl values of compounds I and II is analogous to the difference found for the two model compounds, penicillamine (value of 0.20)[12] and N-(β-aminoethyl)-valine (0.47). The decrease in the N-methyl value in passing from compound II to III might be rationalized in terms of structures II and III as a consequence of the amido resonance of system II making the production of volatile iodide[10] more complete. These observations coupled with the analytical data and analogies from penicillin chemistry are consistent with the tentative structures for compounds I and II, the former containing two centers of asymmetry, and the latter, one. The virtually racemic character of compounds I and II will be considered in the discussion section.

Synthesis

Compounds II and III were prepared by a method[13] the steps of which are formulated. Comparison of the synthetic materials with their counter-

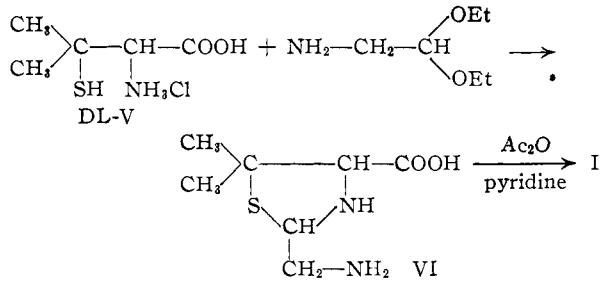


parts from the degradative experiments demonstrated their respective identities. Compound I was synthesized from racemic penicillamine (V)[6] by the method outlined in the formulations, the first step of which has been previously reported.[14] Comparison of the synthetic material (racemic)

(12) E. P. Abraham, *et al.*, *ibid.*, Chapter II, p. 16.

(13) S. R. Aspinall [THIS JOURNAL, **62**, 1202 (1940)] developed this method for the preparation of monoketopiperazines.

(14) E. V. Brown, reference 11, Chapter XVII, p. 485.

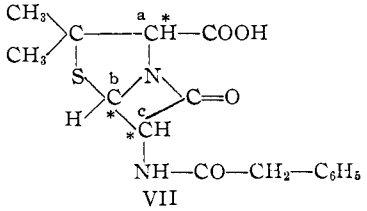


DL-V

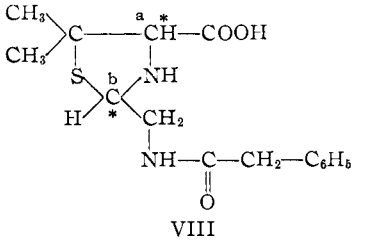
VI

with that obtained from the penicillin residues proved the identity of the two samples. Thus all three structures assigned on the basis of degradative experiments were confirmed by synthesis.[15]

In an attempt to explain the virtually racemic character of the original compound (I) obtained from the penicillin residues (I contains two asymmetric centers) as well as to obtain information regarding its genesis, compound I, penicillin G (VII) and optically active benzylpenilloic acid (VIII)[16] were each submitted to the acetylation procedure originally applied to the penicillin residues. Although compound I was recovered in about 50% yield, no sign of I was found in the mixture obtained



VII

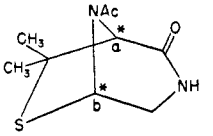


VIII

from penicillin G. However, from optically active VIII was obtained a partially racemized but highly optically active modification of 2-keto-4 - acetyl - 3,4,5,4',3',2' - (5',5' - dimethylthiazolido)-piperazine (IA).[17] Since the infrared spectrum of this active material was identical with that of the virtually racemic material obtained from the penicillin residues, the former compound appears to be an enantiomer and the latter essentially a racemate, both belonging to the same diastereomeric family.

Discussion

Although structure I contains two asymmetric centers and can theoretically exist in four stereomeric forms, two are clearly eliminated on geometric grounds. In penicillin itself, all of the asymmetric centers (*e.g.*, a and b in VII) are known relative to D-glyceraldehyde[18] and the spatial arrangement of the thiazolidine ring has been determined by X-ray crystallography.[19] Since IA was prepared from penicillin (VII) *via* VIII, the following projection formula must apply to Compound IA, as well as to that small fraction



IA

of compound I which was optically active.[17,20] Since the acetylating conditions used on the original penicillin residues and on VIII were identical, and since the product (I) in the former case was virtually racemic and in the latter the product (IA) was highly optically active, it is concluded that the precursor of I in the penicillin residues must have been very highly racemized. In all probability, this precursor was highly racemized benzylpenilloic acid (VIII).

Experimental

Isolation of 2-Keto-4-acetyl-3,4,5,4',3',2'-(5',5'-dimethylthiazolido)-piperazine (I) from Pencillin-N-ethylpiperidine Salt Residues.—A mixture of 1 kg. of residues, 2 l. of pyridine and 2 l. of acetic anhyride was heated on a steam-bath for six hours, and the product was cooled, poured on ice and made basic with saturated sodium carbonate solution. The product was extracted with chloroform, the chloroform was washed with water, with dilute sulfuric acid (three times), with water, and the solution was dried. The chloroform solution was diluted with two volumes of benzene, and the resulting mixture was adsorbed on a column of basic alumina. The column was first washed with a 2–1 benzene–chloroform solution, and the desired product (I) was eluted with a 2–1 chloroform–benzene solution. Evaporation of this eluate gave crystalline material which after recrystallizing from acetone (twice) amounted to 8 g., m.p. 214–215°, $[\alpha]^{26}D$ −3.6° (*c* 2 in $CHCl_3$).

Anal. Calcd. for $C_9H_{14}N_2SO_2$: C, 50.44; H, 6.59; N, 13.07; S, 14.96; CH_3O, 14.48; CH_3CO, 20.09; CH_3N, 7.02; mol. wt., 214. Found: C, 50.51; H, 6.59; N, 13.55, 13.72; S, 14.95; CH_3O, 5.0; CH_3CO, 21.5; CH_3N, 0.6; mol. wt. (Rast), 235, 201.

The above substance was found to be sparingly soluble in cold water, and its solubility was not enhanced by the addition of either acid or base. Duplicate terminal methyl determinations gave values of 1.07 and 1.04.

Desulfurization of 2-Keto-4-acetyl-3,4,5,4',3',2'-(5',5'-dimethylthiazolido)-piperazine (I).—A mixture of 2.27 g. of I, 150 ml. of water and 20 g. of Raney nickel[21] was heated to reflux temperature (four minutes) and held at that temperature for four minutes. The mixture was immediately cooled, and the nickel was collected and thoroughly washed with water. The combined filtrates were extracted with ten 250-ml. portions of chloroform, and the chloroform extracts were combined, dried and the solvent was evaporated under re-

(15) One other example of a substance that contains the noval ring system of I has been reported [A. H. Cook and I. M. Heilbron, ref. 11, Chapter XXV, p. 971, and R. Mozingo and K. Folkers, *ibid.*, Chapter XVIII, pp. 554, 627].

(16) This compound was prepared from penicillin G [R. Mozingo and K. Folkers, ref. 11, Chapter XVIII, p. 563].

(17) The material (IA) prepared from benzylpenilloic acid was 22 times as active as I obtained from the penicillin residues, although the sign of rotation was the same.

(18) H. M. Crooks, Jr., ref. 11, Chapter XVI, p. 455; E. Kaczka and K. Folkers, *ibid.*, Chapter IX, p. 248; F. Barrow and G. W. Ferguson, *J. Chem. Soc.*, 410 (1935); M. L. Wolfrom, R. U. Lemieux and S. M. Olin, THIS JOURNAL, **71**, 2870 (1949).

(19) D. Crowfoot, C. W. Bunn, B. W. Rogers-Low and A. Turner-Jones, ref. 11, Chapter XI, pp. 349–350.

(20) It has been demonstrated [R. Mozingo and K. Folkers, ref. 11, Chapter XVIII, p. 541] that the asymmetric carbon atom b of compound VIII epimerizes much more readily than asymmetric carbon atom a.

(21) Prepared from Raney alloy by treatment with 6.3 *N* NaOH. After the alloy was added to the basic solution, the mixture was heated one hour on a steam-bath and then thoroughly washed with H_2O.

duced pressure. The resulting yellow oil deposited 1.42 g. of product (an additional 0.18 g. was obtained by evaporation of the aqueous solution). The crude product was recrystallized three times from benzene to give 1.09 g. (56% yield) of 4-acetyl-3-isopropyl-2-piperazinone (II) as diamond-shaped plates, m.p. 98.4–99.8°.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21; N-CH_3, 8.16. Found: C, 58.51; H, 8.70; N, 15.21; N-CH_3, 7.76.

Compound II gave terminal methyl values of 1.41 and 1.28. The substance proved to be soluble in acetone, benzene and water (to give a solution neutral to litmus) and gave no color with ninhydrin.

Acid Hydrolysis of 4-Acetyl-3-isopropyl-2-piperazinone (II). A. Isolation of Valine.—A solution of 0.50 g. of II in 25 ml. of 20% sulfuric acid was held at reflux in an atmosphere of nitrogen for 24 hours. The volatile product was then steam distilled, and the distillate when titrated with barium hydroxide solution indicated that 85% of a mole of acetic acid was liberated. The non-volatile hydrolysate was diluted to 250 ml. with water and was passed through an Amberlite IR-4B ion-exchange column to remove the sulfuric acid. The eluate was concentrated to a small volume, and the last traces of water were removed by lyophilization. The resulting brown glass (0.20 g.) was dissolved in water, and a brown oil was precipitated by adding acetone. This oil slowly deposited white crystals which were washed with ethanol and recrystallized from water–ethanol to give a trace of white crystalline product, m.p. 260–265° (with sublimation and decomp.). This material gave a strong ninhydrin test, and was identified as valine through the use of a descending paper chromatogram (Whatman filter paper No. 1). With a phenol–water developer, the crystals gave an R_f value of 0.73 as compared with 0.75 for valine; with a butanol–water developer the crystals gave an R_f value of 0.16 as compared to 0.17 obtained for valine.

B. Isolation of N-(β-Aminoethyl)-valine (III).—A solution of 0.475 g. of II in 10 ml. of 50% sulfuric acid was held at reflux for 24 hours, cooled and diluted to 100 ml. The resulting solution was passed through a column of Amberlite IR-4B ion-exchange resin and the column was then washed with 300 ml. of water. The combined eluates were concentrated to a white solid which was crystallized from water–ethanol to give colorless needles of III, wt. 0.222 g. (54% yield), m.p. 191–192° dec.

Anal. Calcd. for $C_7H_{16}N_2O_2$: C, 52.47; H, 10.07; N, 17.49; N-CH_3, 9.4. Found: C, 52.21; H, 10.15; N, 18.38; N-CH_3, 2.9.

Compound III was optically inactive, gave a strong ninhydrin test and gave the following R_f values on a descending paper chromatogram (Whatman paper, No. 1): phenol–water, 0.65; butanol–water, 0.072. The compound gave terminal methyl values of 0.62 and 0.32.

The dihydrochloride of III was prepared by dissolving 0.022 g. of material in three drops of water and adding 0.5 ml. of concentrated hydrochloric acid. Evaporation of the mixture gave a white solid which was crystallized from methanol–ether to give 0.027 g. (83% yield) of micro-crystals, m.p. 214–215° dec.

Anal. Calcd. for $C_7H_{16}N_2O_2 \cdot 2HCl$: C, 36.06; H, 7.78. Found: C, 36.32; H, 7.64.

Synthesis of 3-Isopropyl-2-piperazinone.—A solution of α-bromoisovaleric acid (34 g.) in 218 ml. of ethanol and 2 ml. of sulfuric acid was held at reflux for 20 hours. Solid potassium carbonate was then added until the solution was basic to litmus. Ether was then added, the mixture was filtered and the solvent was evaporated under reduced pressure to give a yellow oil which was submitted to fractional distillation at 30 mm. The ester was collected at 93°, wt. 28 g. (72% yield).

Anal. Calcd. for $C_7H_{13}O_2Br$: C, 40.21; H, 6.27. Found: C, 40.34; H, 6.56.

A solution of 20.9 g. of the above ethyl α-bromoisovalerate in 150 ml. of absolute ethanol was added slowly (four hours) to a stirred refluxing solution of 120 g. of pure ethylenediamine (distilled from sodium) in 600 ml. of absolute ethanol. After the solution had been stirred at reflux for an additional two hours, a solution of potassium ethylate (3.9 g. of potassium plus excess absolute ethanol) was added to the hot stirred solution (30 minutes). The mixture was then cooled, filtered and the filtrate was evaporated to a mixture of an oil and solid. The solid was collected and the oil was heated at 205–210° at 3 to 4 mm. An oil distilled at b.p. 143–145°, wt. 9.7 g. This material crystallized when cooled, and it was recrystallized three times from ethyl acetate–pentane (chucky wedges), m.p. 93.4–94.6°.

Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.12; H, 9.92. Found: C, 59.21, 59.68; H, 9.46, 9.53.

Acetylation of 3-Isopropyl-2-piperazinone.—Acetic anhydride (10 ml.) and 0.50 g. of 3-isopropyl-2-piperazinone were mixed and allowed to stand for two hours. The excess acetic anhydride was evaporated under reduced pressure, and the viscous yellow residue was crystallized and recrystallized from benzene (plates), wt. 0.38 g., m.p. 98.6–99.8°, m.m.p. with II obtained from I, 98.6–99.8°.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75. Found: C, 58.51; H, 8.54.

Hydrolysis of 3-Isopropyl-2-piperazinone to N-(β-Aminoethyl)-valine (III).—A mixture of 3-isopropyl-2-piperazinone (1.0 g.) and 40 ml. of 20% sulfuric acid was held at reflux for 48 hours and allowed to stand several days at room temperature. The product was isolated by the procedure used for the isolation of III from II as starting material. The substance amounted to 0.65 g., m.p. 191.2–192.4° dec., m.m.p. with II, 191.2–192.8°.

Anal. Calcd. for $C_7H_{16}N_2O_2$: C, 52.47; H, 10.07. Found: C, 52.47; H, 10.07.

The identity of the materials obtained by synthesis and degradation was further demonstrated by comparative R_f values obtained from descending paper-strip chromatograms (Whatman paper No. 1)

Compound	Butanol–water–acetic acid	77% aqueous ethanol–diethylamine
III	0.47	0.77
N-(β-Aminoethyl)-valine	.46	.77
Mixture of two	.48	Not done

Synthesis of (DL)-2-Keto-4-acetyl-3,4,5,4′,3′,2′-(5,5′-dimethylthiazolido)-piperazine (I) from 2-Aminomethyl-5,5-dimethylthiazolidone-4-carboxylic Acid.—The same acetylation procedure used on the original penicillin residues was applied to 2-aminomethyl-5,5-dimethylthiazolidine-4-carboxylic acid,[14] and the product was submitted to the same isolation procedure. From 0.050 g. of starting acid (m.p. 190–192° dec., was isolated 0.038 g. of product, m.p. 214–215.2°, m.m.p. with compound I 213.8–215.2°. Penicillin G when submitted to the same procedure gave no crystalline products.

Anal. Calcd. for $C_9H_{14}N_2SO_2$: C, 50.44; H, 6.59. Found: C, 50.14; H, 6.90.

Synthesis of Partially Racemized (−)-2-Keto-4-acetyl-3,4,5,4′,3′,2′-(5′,5′-dimethylthiazolido)-piperazine (IA) from (+)-Benzylpenilloic Acid.—The same acetylation procedure used on the original penicillin residues was applied to (+)-benzylpenilloic acid,[16] and the product was submitted to the same isolation procedure. From 0.50 g. of benzylpenilloic acid (m.p. 82–97°, $[\alpha]_D$ +66°) (*c* 1.8 in acetone) was obtained 0.17 g. of crystalline product, a portion of which was recrystallized once from acetone, m.p. 210–231°), $[\alpha]_D$ −80° (*c* 2 in $CHCl_3$). The remainder of the product (0.14 g.) after six recrystallizations from acetone gave 0.024 g. of material, m.p. 210–213°, traces of solid left up to 220°, m.m.p. with I, 210–215°, $[\alpha]_D$ −58° (*c* 1.2 in $CHCl_3$).

Anal. Calcd. for $C_9H_{14}N_2SO_2$: C, 50.44; H, 6.59. Found: C, 50.44; H, 6.37.

The infrared spectrum of this material in chloroform solution proved to be identical with the spectrum of compound I.

LOS ANGELES, CALIF.