Derivatives of 6-Aminopenicillanic Acid. VII.[1] Synthesis of Penicillin Aldehydes by a Novel Method

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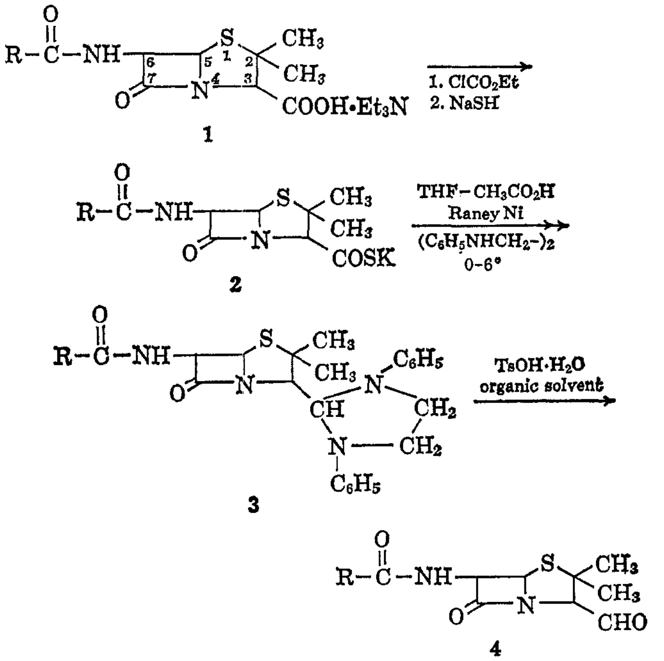
Examples of the hitherto unknown penicillin aldehydes (**4**) have been synthesized by a novel three-step process involving selective desulfurization of penicillin thioacid salts (**2**) under extremely mild conditions. The sequence provides an attractive method for preparing aldehydes from various acylamino acids, peptides, and sensitive carboxylic acids.

This communication describes the first reported synthesis of the hitherto unknown penicillin aldehydes.[2] They were readily obtained from commercially available penicillins by a convenient three-step process. First, a tertiary amine salt of a penicillin (1) (Scheme I) was converted through its ethoxyformic anhydride into the corresponding N-acylated 6-aminothiopenicillanic acid salt (2).[1] Second, the thio acid salt was introduced into an ice-cold, stirred suspension of commercial Raney nickel catalyst[3] in a homogeneous combination of tetrahydrofuran, acetic acid (catalyst), and N,N′-diphenylethylenediamine. This reagent served to trap the nascent aldehyde through formation of the imidazolidine derivative (3) and thus circumvent further reduction to the corresponding alcohol.[4] Third, regeneration of the desired 6-acylaminopenicillanal (4) was effected without appreciable cleavage of the sensitive β-lactam ring through the expedient of treating a solution of the crystalline imidazolidine (3) in a moist mixed solvent system (ether–acetone–dichloromethane of ratio about 3:1:1) with 2 equiv of *p*-toluenesulfonic acid monohydrate instead of employing the customary mineral acid for the hydrolysis.[4]

SCHEME I



Five representative 6-acylaminopenicillanals are presented in Table I. The low yield of compound **2** is ascribed to the relative inherent instability of benzylpenicillin and its derivatives. The importance of using the trapping reagent is illustrated by the low yield of 5% obtained for compound **5** when an attempt was made to shorten the procedure by omitting the N,N′-diphenylethylenediamine. In view of the experience of others,[5] it is probable that the chief product of the reduction was the corresponding alcohol.[6]

The penicillin aldehydes as a class reacted readily with sodium bisulfite to form typical crystalline water-soluble derivatives. This characteristic behavior has been exemplified by a description of the procedure used to prepare 6-phenoxyacetamidopenicillanal sodium bisulfite adduct.

The same process utilized to prepare the 6-acylaminopenicillanals was used advantageously to convert penicillin sulfoxides[7] *via* their thio acid salts into the corresponding aldehyde sulfoxides. The preparation of 6-phenoxyacetamidopenicillanal hydrate sulfoxide has been included as a typical example.

The extreme susceptibility of thio acids to hydrogenolysis by Raney nickel[8] enables one to remove selectively the thiol group under such mild conditions as to forestall appreciable attack on the vulnerable sulfide sulfur atom in the penicillin nucleus.[9] In general thio

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(1) Paper VI: W. J. Gottstein, R. B. Babel, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, C. A. Panetta, and L. C. Cheney, *J. Med. Chem.*, **8**, 794 (1965).

(2) The more precise name for penicillin aldehyde becomes 6-acylaminopenicillanal according to the generally accepted system of J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953).

(3) No. 28 Raney Active Nickel Catalyst in water, Raney Catalyst Division, W. R. Grace and Co., Chattanooga, Tenn.

(4) H. J. Bestmann and H. Schulz, *Chem. Ber.*, **92**, 530 (1959).

(5) O. Jeger, J. Norymberski, S. Szpilfogel, and V. Prelog, *Helv. Chim. Acta*, **29**, 684 (1946).

(6) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).

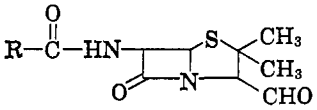
(7) J. M. Essery, Kathleen Dadabo, W. J. Gottstein, Ann Hallstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).

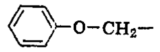
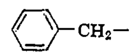
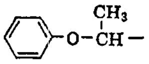
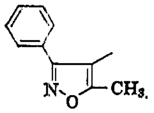
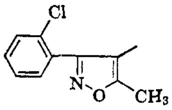
(8) It is noteworthy that only two cases have been found in the literature wherein a thio acid was used to prepare the corresponding aldehyde by hydrogenolysis with Raney nickel. (a) M. W. Cronyn and J. Jiu [*J. Am. Chem. Soc.*, **74**, 4726 (1952)] obtained a 30% yield of hippuraldehyde from thiohippuric acid by employing Raney nickel deactivated with acetone. (b) J. Bougault, E. Cattelain, and P. Chabrier [*Compt. Rend.*, **208**, 657 (1939); *Bull. Soc. Chim. France*, [5] **7**, 781 (1940)] reported the conversion of thioacetic acid into acetaldehyde by Raney nickel when ethanol was used as solvent. The known dehydrogenating effect of Raney nickel on ethanol, however, led M. L. Wolfrom and J. V. Karabinos [*J. Am. Chem. Soc.*, **68**, 1455 (1946)] to question the validity of this observation. (c) For a review of the synthesis of aldehydes by reductive desulfurization of thiol esters, see E. Mosettig, *Org. Reactions*, **8**, 229 (1954); H. Hauptmann and W. F. Walter, *Chem. Rev.*, **62**, 375 (1962); G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 389 (1962).

(9) Perhaps the most convincing chemical evidence for the β-lactam structure of penicillin was adduced by the preparation of dethiobenzylpenicillin from benzylpenicillin with Raney nickel under such mild conditions as to virtually preclude molecular rearrangement. (a) H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p 256; (b) H. Adkins, F. J. Brutschy, and M. McWhirter, *J. Am. Chem. Soc.*, **70**, 2610 (1948).

TABLE I

6-ACYLAMINOPENICILLANALS



Compd	R	Dec pt, °C[a]	Yield,[b] %	Formula	Carbon, %		Hydrogen, %	
					Calcd	Found	Calcd	Found
1		104–105 KM	47	$C_{16}H_{18}N_2O_4S \cdot 0.5H_2O$	56.25	56.09	5.36	5.50
2		100 OC	6	$C_{16}H_{18}N_2O_3S$	60.30	59.80	5.70	6.18
3		101 OC	41	$C_{17}H_{20}N_2O_4S$	58.60	58.90	5.80	6.13
4		100 OC	32	$C_{19}H_{19}N_3O_4S$	59.25	59.70	4.96	5.61
5		139–141 OC	38 (5)[c]	$C_{19}H_{18}ClN_3O_4S$	54.41	54.20	4.29	4.59

[a] Decomposition points determined on a Kofler hot stage microscope (KM) or in open capillaries (OC). [b] Over-all yield based on thio acid salt. With the exception of compound **1**, all the aldehydes were amorphous solids which showed a strong tendency to hydrate. Samples were dried *in vacuo* over P_2O_5 for 15 hr. [c] Yield obtained when the N,N′-diphenylethylenediamine was omitted.

acids are as readily prepared[8a,10] as the corresponding thiol esters.

S-Ethyl and S-benzyl esters of several 6-acylaminothiopenicillanic acids failed to afford appreciable yields of the corresponding 6-acylaminopenicillanals when used in place of the corresponding thio acid salts in the described process. The use of commercial Raney nickel[3] gave satisfactory results, whereas no penicillin aldehyde was isolated when acetone–deactivated Raney nickel[11] was investigated.

In the past, reduction of an amino acid ester by means of sodium amalgam has apparently been the most common method for preparing amino aldehydes.[12] The process developed for the synthesis of 6-acylaminopenicillanals appears to be eminently well suited for transforming numerous acylamino acids, various peptides, and certain other carboxylic acids of sensitive constitution into the corresponding aldehydes.

Experimental Section[13]

The following procedures illustrate the general method used to prepare the penicillin imidazolidines (**3**) and aldehydes (**4**).

3-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,2-dimethyl-6-phenoxyacetamidopenam.—A 52-g portion of Raney Active Nickel No. 28 was washed by decantation three times with 100 ml of absolute alcohol and four times with 100-ml portions of tetrahydrofuran (THF). The catalyst was transferred to a three-neck flask and vigorously stirred with 160 ml of THF containing 3.2 ml of glacial acetic acid, 5.0 g (0.024 mole) of N,N′-diphenylethylenediamine, and 10 ml of water. The temperature was lowered to 0° and 6.55 g (0.016 mole) of potassium 6-(phenoxyacetamido)thiopenicillanate[1] dissolved in a mixture of 60 ml of THF and 6.3 ml of water was added all at once. The mixture was stirred for 15 min at 0–6° and the catalyst was removed by filtration over diatomaceous earth (Supercel). The cake was washed with 250 ml of THF and the filtrate was evaporated to dryness under reduced pressure at 35°. The residue was dried under reduced pressure at 35° by azeotropic distillation with ethyl acetate. The anhydrous solid was dissolved in 500 ml of ether and heated under reflux for 0.5 hr. The white crystals which separated were collected and recrystallized from 100 ml of boiling ethyl acetate to yield 2.7 g of product which melted at 174–175°. *Anal.* Calcd for $C_{30}H_{32}N_4O_3S$: C, 68.15; H, 6.11; S, 6.05. Found: C, 68.00; H, 5.98; S, 6.04. A second crop was recovered from the ethyl acetate filtrate after evaporation of the solvent and trituration with ether. The crystals weighed 1.4 g and melted at 167–170° (50% total yield).

The infrared spectrum (KBr) showed absorptions (cm^{-1}) at 3415, amide NH; 2960, 2920, and 2860, CH_3 and CH_2; 1774, β-lactam carbonyl; 1712, amide carbonyl; 1600, aromatic C=C; 753 and 700, monosubstituted phenyl.

The nmr spectrum gave absorptions which were assigned as follows: a complex pattern between δ 7.5 and 6.5 which included the 15 aromatic protons and the amide proton; a complex pattern between δ 5.7 and 5.3 which when run at a sweep width of 100 cps was resolved to give the following absorptions, a quartet centered at δ 5.54 due to the C_6 proton which is coupled to the C_5 proton (J = 4.1 cps) and to the amide proton (J = *ca.* 9 cps), a doublet of spacing 6.6 cps centered at δ 5.4 due to the imidazolidine methyne proton which is coupled to the C_3 proton, and a doublet of spacing 4.1 cps centered at δ 5.35 due to the C_5 proton; a singlet at δ 4.47 from the protons of the methylene group adjacent to the oxygen; a doublet of spacing 6.6 cps centered at δ 4.04 due to the C_3 proton; a poorly resolved pattern between δ 3.9 and 3.1 which included the four methylene protons of the imidazolidine ring and an apparent singlet which included the six protons of the *gem*-dimethyl groups.

6-Phenoxyacetamidopenicillanal (1, Table I).—To a solution of 10.5 g (0.19 mole) of 3-(1′,3′-diphenyl-2′-imidazolidinyl)-2,2-dimethyl-6-phenoxyacetamidopenam dissolved in 100 ml of dry acetone, 100 ml of methylene chloride, and 300 ml of anhydrous ether was added a solution of 7.1 g (0.37 mole) of *p*-toluenesulfonic acid monohydrate dissolved in 50 ml of methylene chloride, 50 ml of dry acetone, 150 ml of ether, and 1.5 ml of water. A heavy precipitate formed immediately and the slurry was stirred for 0.5 hr at 25°. The mixture was diluted with 1.1 l. of ether and filtered over diatomaceous earth (Supercel). The filtrate was extracted twice with 100-ml portions of water, dried over anhydrous sodium sulfate, and evaporated under reduced

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(10) J. C. Sheehan and D. A. Johnson, *J. Am. Chem. Soc.*, **74**, 4726 (1952).

(11) A. V. McIntosh, A. M. Searcy, E. M. Meinzer, and R. H. Levin, *ibid.*, **71**, 3317 (1949), and references cited therein.

(12) A. Lawson, *J. Chem. Soc.*, 1443 (1957), and references cited therein.

(13) All melting and decomposition points are uncorrected. The infrared spectra were recorded on a Beckman IR 9 spectrometer. The nmr spectra were run on a Varian A-60 spectrometer at a sweep width of 500 cps using deuteriochloroform solutions with the exception of the spectrum of 6-phenoxyacetamidopenicillanal hydrate sulfoxide for which it was necessary to add dimethyl sulfoxide-d_6 to effect complete solution. Tetramethylsilane was the internal standard and the chemical shifts are expressed as δ, parts per million, from tetramethylsilane.

pressure at 35° to yield a light yellow residue which was dissolved in 100 ml of dry ether. After cooling in an ice bath, the mixture was filtered and 2.1 g of white needles was obtained, mp 106–108°. The filtrate was stored in an open vessel for 24 hr at 20° after addition of 1.5 ml of water and a second crop was obtained which weighed 3.9 g, mp 104–105° (95% total yield). The infrared spectrum (KBr) showed absorptions (cm^{-1}) near 3370 (br), which includes amide NH; 1780, β-lactam carbonyl; 1730, aldehyde carbonyl; 1690, amide carbonyl; 1588 and 1598, aromatic C=C; 690 and 730 monosubstituted phenyl.

The nmr spectrum had absorption peaks which were assigned as follows: a doublet of spacing 2.3 cps centered at δ 9.56 due to the aldehyde proton which is coupled to the C_3 proton; a complex pattern between δ 6.7 and 7.5 ascribed to the five aromatic protons and the amide proton; a quartet centered at δ 5.79 due to the C_6 proton which is coupled to the amide proton (J = 9 cps) and to the C_5 proton (J = 4.3 cps); a doublet of spacing 4.3 cps centered at δ 5.51 due to the C_5 proton; a singlet at δ 4.52 from the protons of the methylene group; a doublet (J = 2.3 cps) centered at δ 4.23 due to the C_3 proton; and singlets at δ 1.59 and 1.55 due to the *gem*-dimethyl protons.

6-Phenoxyacetamidopenicillanal Sodium Bisulfite Adduct.—To a saturated solution of 104 mg (0.001 mole) of sodium bisulfite in water was added a solution of 350 mg (0.001 mole) of 6-phenoxyacetamidopenicillanal in 5 ml of THF. The mixture was shaken in a warm water bath at 50° for 1 min, cooled to room temperature, and 50 ml of ethyl acetate was added. An oil separated which was removed by decantation and triturated twice with 50-ml portions of ethyl acetate. The solid crystallized and was collected, washed with ethyl acetate, and dried *in vacuo* over P_2O_5. The white crystals weighed 440 mg (96% yield), mp 125° dec. *Anal.* Calcd for $C_{16}H_{19}N_2NaO_7S_2 \cdot H_2O$: C, 42.20; H, 4.64. Found: C, 42.00; H, 4.40.

The infrared spectrum (KBr) showed absorption (cm^{-1}) at 3400, OH, NH; 1775, β-lactam carbonyl; 1685, amide carbonyl; 1600 and 1500, phenyl; 1200, bisulfite.

Potassium 6-(Phenoxyacetamido)thiopenicillanate Sulfoxide.—This thio acid was prepared by the general method recently described,[1] starting with 36 g (0.099 mole) of 6-phenoxyacetamidopenicillanic acid sulfoxide,[7] 9.9 g (0.099 mole) of triethylamine, 10.6 g (0.099 mole) of ethyl chloroformate, and 9.1 g (0.164 mole) of sodium hydrosulfide. Ethyl acetate was used in place of ether as the extracting solvent. Light yellow crystals of the potassium salt were obtained after treatment with potassium 2-ethylhexanoate. The salt was recrystallized from wet 1-butanol to obtain 20 g (48%) of crystals which decomposed at 195°. *Anal.* Calcd for $C_{16}H_{17}KN_2O_5S_2$: C, 45.69; H, 4.08. Found: C, 45.55; H, 4.14.

3-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,2-dimethyl-6-phenoxyacetamidopenam Sulfoxide.—This compound was prepared by the procedure described above, starting with 1.28 g (0.003 mole) of potassium 6-(phenoxyacetamido)thiopenicillanate sulfoxide. A crystalline solid was obtained in 35% yield, mp 171–172°. *Anal.* Calcd for $C_{30}H_{32}N_4O_4S$: C, 66.15; H, 5.92. Found: C, 66.20; H, 5.98. The infrared spectrum (KBr) showed absorptions (cm^{-1}) at 3400, amide NH; 1790, β-lactam carbonyl; 1690, amide carbonyl; 1595, aromatic C=C; 755 and 695, monosubstituted phenyl. The nmr spectrum had absorptions which were assigned as follows: a doublet of 11 cps spacing centered at δ 8.20 due to the amide proton which is coupled to the C_6 proton; a complex pattern between δ 7.5 and 6.5 which includes the 15 aromatic protons; a quartet centered at δ 5.82 assigned to the C_6 proton which is coupled to the amide proton (J = 11 cps) and to the C_5 proton (J = 4.8 cps); a doublet of spacing 7.6 cps centered at δ 5.48 due to the imidazolidine methyne proton which is coupled to the C_3 proton; a doublet of spacing 4.8 cps centered at 4.85 due to the C_5 proton; a singlet at δ 4.43 from the protons of the methylene group adjacent to the oxygen; a doublet of spacing 7.6 cps centered at δ 4.30 due to the C_3 proton; a complex pattern from δ 4.0 to 3.1 which includes the four methylene protons of the imidazolidine group and singlets at δ 1.67 and 1.27 from the six *gem*-dimethyl protons.

6-Phenoxyacetamidopenicillanal Hydrate Sulfoxide Monohydrate.—This compound was prepared by the procedure described above in 43% yield, mp 98–100°. *Anal.* Calcd for $C_{16}H_{20}N_2O_6S \cdot H_2O$: C, 49.74; H, 5.74; N, 7.25. Found: C, 49.50; H, 5.55; N, 7.24. The infrared spectrum (KBr) showed (cm^{-1}) absorptions at 3400, OH; 3390, amide NH; 1780, β-lactam carbonyl; 1667, amide carbonyl; 1600 and 1585, aromatic C=C; 695, monosubstituted phenyl. There was no evidence of aldehyde carbonyl. The nmr spectrum indicated the presence of the anhydrous aldehyde group as a contaminant at a level of *ca.* 20 mole % of the sample. The absorptions which can be assigned to the hydrated aldehyde structure are as follows: a doublet of spacing 10.6 cps centered at δ 8.33 due to the amide proton which is coupled to the C_6 proton; a complex pattern from δ 7.5 to 6.7 which includes the five aromatic protons; a quartet centered at δ 5.92 due to the C_6 proton which is coupled to the amide proton (J = 10.6 cps) and to the C_5 proton (J = 4.8 cps); a doublet of spacing 4.8 cps centered at δ 5.08 due to the C_5 proton; a doublet of spacing 7.3 cps centered at δ 4.95 arising from the hydrated aldehyde proton which is coupled to the C_3 proton; a singlet at δ 4.53 from the protons of the methylene group adjacent to the oxygen; a doublet of spacing 7.3 cps centered at δ 3.82 arising from the C_3 proton and singlets at δ 1.35 and 1.61 from the six *gem*-dimethyl protons.

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