Derivatives of 6-Aminopenicillanic Acid. V. Synthesis of 6-Aminopenicillanyl Alcohol and Certain Derivatives[1]

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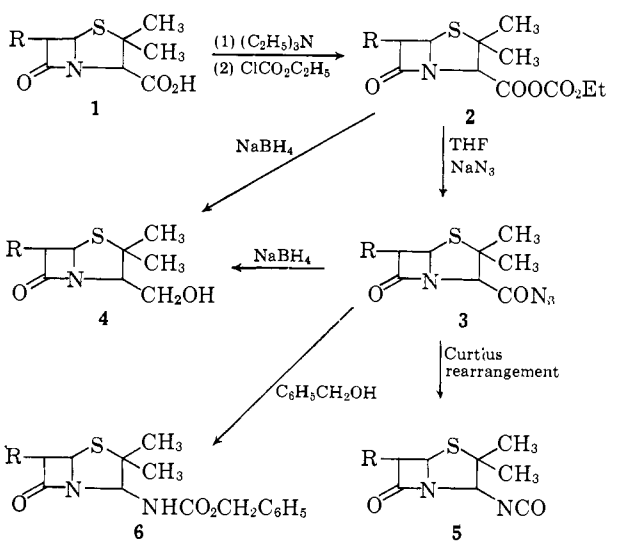
Received November 29, 1963

Acyl azides of various N-substituted 6-aminopenicillanic acids have been prepared by treatment of mixed carboxylic–carbonic anhydrides with sodium azide. By a seldom used, yet excellent, method of selective reduction, the acyl azides were converted to the N-substituted 6-aminopenicillanyl alcohols[2] with sodium borohydride. Direct reduction of a mixed anhydride with sodium borohydride in anhydrous tetrahydrofuran produced the corresponding alcohol, but the azide reduction is preferred. The parent 6-aminopenicillanyl alcohol was obtained by acid hydrolysis of 6-triphenylmethylaminopenicillanyl alcohol. Several functional derivatives of the N-substituted 6-aminopenicillanyl alcohols have been described.

The purpose of this report is to describe the facile conversion of N-substituted 6-aminopenicillanic acids (**1**) into the corresponding penicillanyl alcohols (**4**) *via* reduction of the acyl azides (**3**) with sodium borohydride as portrayed in Chart I.

Chart I



R = acylamino, carbobenzoxyamino, phthalimido, and triphenylmethylamino

The possibility of selectively reducing the acyl azides (**3**) to the corresponding alcohols (**4**) by means of borohydride without attacking the carbonyl function of the β-lactam ring of the penicillin nucleus was suggested by the novel chloramphenicol synthesis of Ehrhart, *et al.*[3] When the reduction was carried out on 6-phenylacetamidopenicillanic acid azide, prepared *in situ* from the mixed anhydride by an adaptation of the elegant Weinstock modification of the Curtius reaction,[4] analytically pure 6-phenylacetamidopenicillanyl alcohol (**4**, R = $C_6H_5CH_2CONH$–) was isolated in 78% yield based on the triethylammonium salt of benzylpenicillin. It was found expedient to conduct the reductions without isolation of the labile acid azides, although it was demonstrated that the isolation could be accomplished. For example, successive treatment of 6-phthalimidopenicillanic acid (**1**, R = phthalimido) with triethylamine, ethyl chloroformate, and sodium azide afforded crystalline 6-phthalimidopenicillanic acid azide in 81% yield. After storage of the azide for 2 days at 25° *in vacuo*, however, it was found that the Curtius rearrangement had proceeded with the formation of a quantitative yield of the corresponding isocyanate (**5**). Reaction of the acid azide (**3**) with benzyl alcohol produced the pure benzyl carbamate (**6**, R = phthalimido) in 91% yield, thus confirming the structural assignment.

Aside from the results of Ehrhart and co-workers,[3] who expected their reduction product would be an amine, no other reduction of an aliphatic acyl azide to the corresponding primary alcohol has been reported. It is noteworthy that Boyer and Ellzey, Jr.,[5] isolated a 29% yield of benzamide as the only identified product obtained from the reduction of benzoyl azide with sodium borohydride in aqueous dioxane. Benzenesulfonyl azide and methanesulfonyl azide were likewise reduced to the corresponding amides under similar conditions.

Alternatively, the alcohol function can be obtained by direct reduction of the mixed anhydride. For instance, treatment of the mixed anhydride, prepared *in situ* from the triethylammonium salt of benzylpenicillin and ethyl chloroformate in dry tetrahydrofuran, with sodium borohydride gave a 94% yield of 6-phenylacetamidopenicillanyl alcohol whose purity was only slightly inferior to that produced by reduction of the acid azide. Apparently the reduction of mixed anhydrides to the corresponding alcohols by sodium borohydride has not been described previously. Although unsymmetrical anhydrides of certain acylamino acids have been reduced to amino alcohols by means of lithium borohydride,[6] this more powerful reducing agent would probably not be sufficiently selective for use in the present application, as it has been reported to cleave amide bonds.[7] The striking effects

(1) For paper IV in this series see S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *J. Am. Chem. Soc.*, **85**, 643 (1963).

(2) For convenience and simplicity the nomenclature adopted is based on the generally accepted trivial system of J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *ibid.*, **75**, 3293 (1953).

(3) G. Ehrhart, W. Siedel, and H. Nahm, *Chem. Ber.*, **90**, 2088 (1957).

(4) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(5) J. H. Boyer and J. Ellzey, Jr., *ibid.*, **23**, 127 (1958).

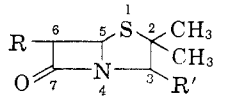
(6) K. Heyns and K. Stange, *Z. Naturforsch.*, **106**, 252 (1955); *Chem. Abstr.*, **50**, 7744 (1956).

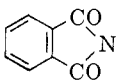
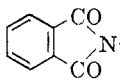
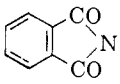
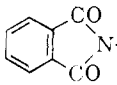
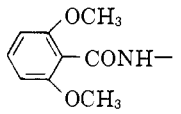
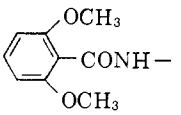
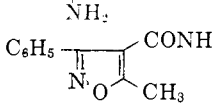
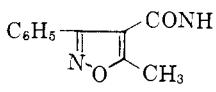
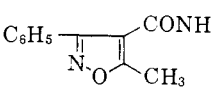
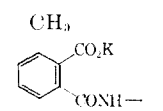
(7) J. C. Crawhall and D. F. Elliott, *Nature*, **175**, 299 (1955).

of different cations and solvents on the reducing power of the borohydride anion has been effectively summarized by Brown.[8]

An adaptation of the ingenious procedure used by Koe[9] for preparing the amide and methyl ester of 6-aminopenicillanic acid was advantageously employed to obtain the parent 6-aminopenicillanyl alcohol (**4**, R = NH_2). Treatment of a solution of 6-triphenylmethylaminopenicillanyl alcohol in anhydrous acetone with *p*-toluenesulfonic acid monohydrate led to the isolation of a 44% yield of analytically pure amino alcohol in the form of its *p*-toluenesulfonate salt.

TABLE I



No.	R	R'
I		—CON_3
II		—NCO
III		—$NHCOOCH_2C_6H_5$
XIV		—CH_2OH
IV	$C_6H_5CH_2CONH$—	—CH_2OH
XI	$C_6H_5CH_2CONH$—	—$CH_2OCONHC_6H_5$
XII	$C_6H_5CH_2CONH$—	—CH_2OCOCH_3
XIII	$C_6H_5CH_2CONH$—	—$CH_2OCOCH_2CH_2CO_2K$
V	$C_6H_5CH_2OCONH$—	—CH_2OH
VI	$(C_6H_5)_3CNH$—	—CH_2OH
XVI	$(C_6H_5)_3CNH$—	—CH_2OCOCH_3
VII		—CH_2OH
XVIII		—$CH_2OCONHC_6H_5$
VIII	$C_6H_5CHCONH$— NH_2	—CH_2OH
IX		—CH_2OH
XIX		—$CH_2OCOCH_2CH_2CO_2K$
XXI		—$CH_2OCONHC_6H_5$
X	$C_6H_5OCHCONH$— CH_3	—CH_2OH
XX	$C_6H_5OCHCONH$— CH_3	—$CH_2OCONHC_6H_5$
XV		—CH_2OH
XVII	p-$CH_3C_6H_4SO_3H \cdot H_2N$—	—CH_2OH

(8) H. C. Brown, *J. Chem. Educ.*, **38**, 173 (1963).
(9) B. K. Koe, *Nature*, **195**, 1200 (1963).

No difficulty was encountered in converting the N-substituted 6-aminopenicillanyl alcohols into various esters, including phenylcarbamates, alkali salts of acid succinates, and acetates. The representative alcohols and their derivatives are presented in Table I.

Microbiological Evaluation.—The compounds described were tested for antimicrobial activity by Dr. Joseph Lein and his associates in the Microbiology Department using techniques which have been published in detail.[10] Minimum inhibitory concentrations (MIC) of the compounds dissolved in N,N-dimethylacetamide (DMAC) were compared with that of 6-[D-(−)-α-aminophenylacetamido]penicillanic acid (ampicillin) for test organisms using a 2-fold serial dilution technique in heart infusion broth or broth diluted 1:1 with pooled human serum. The inocula were generally 10^4 dilutions of overnight cultures.

Against the penicillin-sensitive Smith strain of *Staphylococcus aureus* 6-phenylacetamido-, 6-[D-(−)-α-aminophenylacetamido]-, and 6-α-phenoxypropionamidopenicillanyl alcohols with MIC values of 3.1, 6.3, and 6.3 γ/ml., respectively, proved to be the most active members of the group. However, the most potent of the three is only about 0.01 as active as ampicillin (MIC = 0.031 γ ml.). Results of *in vivo* experiments were consistent with the poor activity. By the intramuscular route using the Smith strain of *Staphylococcus aureus*, the median curative dose in the mouse for 6-phenylacetamidopenicillanyl alcohol was found to be 31 mg./kg. compared to 0.4 mg./kg. for ampicillin.

These compounds were prepared primarily as intermediates for further syntheses. The question as to whether or not the slight antimicrobial activity found can be ascribed, at least in part, to the presence of small quantities of active contaminants remains to be determined.

Experimental[11]

6-Phthalimidopenicillanic Acid Azide (I).—A solution of 34.6 g. (0.10 mole) of 6-phthalimidopenicillanic acid[12] and 14 ml. (0.10 mole) of triethylamine in 300 ml. of tetrahydrofuran (THF) was cooled to −10° and a solution of 10.8 g. (0.10 mole) of ethyl chloroformate in 50 ml. of THF was added. The resulting mixture was stirred at −10° for 1 hr., and then a solution of 6.5 g. (0.10 mole) of sodium azide in 50 ml. of water was added during a period of 30 min. The reaction mixture was diluted with an equal volume of water and the crystalline azide thus formed was collected by filtration, yielding 30 g. (81%). It was characterized by its infrared spectrum: azide, 2164 cm.$^{-1}$; phthalimide, 1825, 1725, and 1710 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; aromatic ring, 792 and 717 cm.$^{-1}$.

6-Phthalimido-2,2-dimethyl-3-penamyl Isocyanate (II).—When 6-phthalimidopenicillanic acid azide was dried under vacuum for 2 days at room temperature, it was converted quantitatively to the corresponding crystalline isocyanate,

(10) A. Gourevitch, G. A. Hunt, J. R. Lottinger, C. C. Carmack, and J. Lein, *Proc. Soc. Expl. Biol. Med.*, **107**, 455 (1961).
(11) We thank Mr. R. M. Downing and Mrs. C. Kaliaowski for the microanalyses. Infrared and n.m.r. spectra were run by Messers. D. Whitehead, A. Coon, and A. Vulcano. Infrared bands are reported in cm.$^{-1}$, and the spectra were obtained in potassium bromide disks unless otherwise specified. All structural assignments are supported by n.m.r. spectra. Melting points were determined either on a Kofler hot stage, a Fisher-Johns apparatus, or in open capillaries, and are all corrected. The assistance of R. B. Babel and G. Luke in preparing larger quantities of some of the compounds is gratefully acknowledged.
(12) J. C. Sheehan and Kenneth R. Henery-Logan, *J. Am. Chem. Soc.*, **84**, 2983 (1962).

m.p. 75° dec. Its infrared spectrum showed an intense isocyanate band at 2275 cm.$^{-1}$; phthalimide, 1806 and 1733 cm.$^{-1}$; β-lactam, 1797 cm.$^{-1}$; and aromatic ring, 795 and 716 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.79; N, 12.24. Found: C, 55.99, 55.64; H, 3.60, 3.63; N, 12.00, 12.29.

Benzyl N-(2,2-Dimethyl-6-phthalimido-3-penamyl)carbamate (III).—A solution containing 18.5 g. (0.050 mole) of 6-phthalimidopenicillanic acid azide and 10.8 g. (0.10 mole) of benzyl alcohol in 150 ml. of benzene was warmed to about 75° and stirred until evolution of nitrogen ceased. The reaction mixture was evaporated to dryness at reduced pressure and the crystalline residue was recrystallized from acetone–water and then from 2-propanol to a constant m.p. of 161–162°. The yield was 20.5 g. (91%). Its infrared spectrum had bands ascribed to NH, 3400 cm.$^{-1}$; β-lactam, phthalimide, and urethan carbonyls in two rather broad absorptions centering at 1785 and 1720 cm.$^{-1}$; and aromatic bands at 796 and 716 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{21}N_3O_5S$: C, 61.19; H, 4.65; N, 9.31. Found: C, 61.27; H, 4.86; N, 9.57.

6-Phenylacetamidopenicillanyl Alcohol (IV). A. Reduction of the Acid Azide.—A suspension of 43.5 g. (0.10 mole) of benzylpenicillin triethylammonium salt in 300 ml. of THF was cooled to −10° and a solution of 10.8 g. (0.10 mole) of ethyl chloroformate in 50 ml. of THF was added. The resulting mixture was stirred at −10° for 2 hr., when the solution became clear. Then a solution of 6.5 g. (0.10 mole) of sodium azide in 50 ml. of water was added during a period of 30 min. The reaction mixture was diluted with 100 ml. of ice–water, and 7.4 g. (0.20 mole) of sodium borohydride was added in small portions during the next 30 min. This stage of the reaction was carried out at 0–5°, and the pH was maintained in the range of 6 to 8 by occasional addition of glacial acetic acid. The solution was acidified to pH 6.0 with glacial acetic acid, diluted with 500 ml. of water, and extracted with three 250-ml. portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered, and the solvent was removed by vacuum distillation at 33°. The product was purified by solution in 300 ml. of dry ethyl acetate, filtration, and complete removal of the solvent under vacuum. The yield of amorphous solid was 25 g. (78%). The infrared spectrum showed NH and OH at 3280 cm.$^{-1}$; β-lactam, 1770 cm.$^{-1}$; amide, 1660 and 1530 cm.$^{-1}$; primary alcohol, 1042 cm.$^{-1}$; and aromatic, 730 and 700 cm.$^{-1}$.

The n.m.r. spectrum of this alcohol is shown in Fig. 1. The absorption peaks are assigned as follows: the strong singlet at 7.28 δ is due to the 5 protons on the benzene ring; the doublet of spacing 9 c.p.s. is centered at 6.59 δ and is attributed to the hydrogen on the amide nitrogen; the hydrogen to which it is coupled is in the 6-position of the penicillin nucleus and appears as a quartet centered at 5.50 δ; the hydrogen in position 5 appears as a doublet of spacing 4.2 c.p.s. due to interaction with the 6-proton and is centered at 5.27 δ; the strong peak at 3.60 δ is due to the absorption of benzylic protons and obscures a portion of the complex AB_2 pattern arising from absorption of the $>CHCH_2-$ protons at the 3-position; the hydroxyl proton appears at 3.24 δ and was observed to shift to a higher field upon dilution; and the remaining protons due to the two methyl groups appear at 1.40 and 1.30 δ.

Anal. Calcd. for $C_{16}H_{20}N_2O_3S$: C, 59.99; H, 6.29; N, 8.75. Found: C, 59.65; H, 6.03; N, 8.63.

B. Reduction of the Mixed Anhydride.—A flame-dried 500-ml. round-bottomed flask equipped with a stirrer, thermometer, and pressure-compensated dropping funnel was charged with a suspension of 10.9 g. (0.025 mole) of benzylpenicillin triethylammonium salt in 75 ml. of dry THF and placed in a nitrogen atmosphere. To the vigorously stirred suspension at −10° a solution of 2.7 g. (0.025 mole) of redistilled ethyl chloroformate in 15 ml. of dry THF was added during 10 min. After the resulting mixture had been stirred for 2 hr. at −8°, 1.9 g. (0.050 mole) of sodium borohydride was added in small portions over a 5-min. period. The reaction mixture was then stirred for 25 min. without the cooling bath. The mixture was diluted with 125 ml. of water and the product was extracted with two 100-ml. portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness at reduced pressure. The product, 7.5 g. (94%) of brittle foam, was shown by its infrared and n.m.r. spectra to be identical with the product obtained by procedure A.

Procedure A was employed in the preparation of the following penicillanyl alcohols.

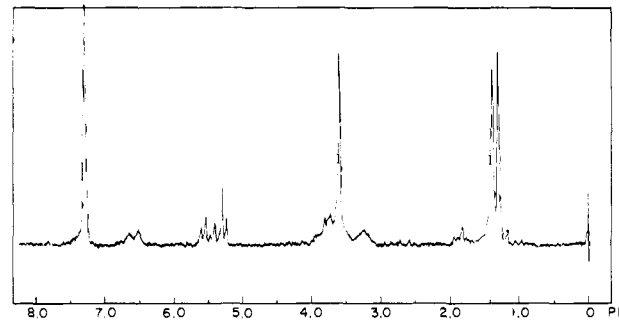


Fig. 1.—The 60 Mc./sec. n.m.r. spectrum of 6-phenylacetaminopenicillanyl alcohol measured on a 15% w./v. solution in deuteriochloroform.

6-Carbobenzoxyaminopenicillanyl Alcohol (V).—This substance was obtained in 87% yield as a glass which had characteristic infrared absorptions for NH and OH at 3400 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; and carbamate, 1725 and 1520 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 57.10; H, 5.80; N, 8.70, 8.60.

6-Triphenylmethylaminopenicillanyl Alcohol (VI).—A 36% yield of crystalline material, m.p. 155–170°, was obtained. It was recrystallized from a mixture of ether and Skellysolve B (petroleum ether, b.p. 60–68°) to a constant m.p. of 187–188°. Its infrared spectrum showed a sharp band for water of crystallization at 3460 cm.$^{-1}$; OH and NH, 3200 cm.$^{-1}$; β-lactam, 1760 cm.$^{-1}$; primary alcohol, 1050 cm.$^{-1}$; and complex aromatic bands at 1490, 775, 763, 748, and 706 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{28}N_2O_2S \cdot 0.5H_2O$: C, 71.49; H, 6.44; N, 6.31. Found: C, 71.75; H, 6.38; N, 6.15.

6-(2,6-Dimethoxybenzamido)penicillanyl Alcohol (VII).—The product was obtained in 80% yield as a viscous oil which crystallized from ethyl acetate; m.p. 146–148°. Its infrared spectrum indicated NH and OH at 3370 cm.$^{-1}$; β-lactam, 1785 cm.$^{-1}$; amide, 1660 and 1520 cm.$^{-1}$; primary alcohol, 1300 cm.$^{-1}$; and ether, 1250 and 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.65. Found: C, 55.20; H, 5.93; N, 7.75.

6-(D-α-Aminophenylacetamido)penicillanyl Alcohol (VIII).—Reduction of the azide of 6-(D-α-carbobenzoxyaminophenylacetamido)penicillanic acid gave the alcohol in 99% yield as a viscous oil which was characterized by infrared and n.m.r. spectra. Its infrared spectrum in methylene chloride had OH and NH at 3450 cm.$^{-1}$; β-lactam, 1775 cm.$^{-1}$; carbamate, 1725 cm.$^{-1}$; and amide, 1675 cm.$^{-1}$.

A solution of 9.00 g. (0.0192 mole) of this 6-(D-α-carbobenzoxyaminophenylacetamido)penicillanyl alcohol, 200 ml. of 2-propanol, 25 ml. of water, and 3 ml. of glacial acetic acid was hydrogenated in a Parr hydrogenation apparatus at an initial pressure of 3.5 kg./cm.^{2} for 3 hr. in the presence of 10 g. of 30% palladium on diatomaceous earth. The catalyst was removed by filtration and most of the solvent was distilled from the filtrate at reduced pressure. Water (75 ml.) was added to the residue and the mixture was extracted with 150 ml. of methylene chloride. The aqueous phase, which was found to be at pH 4.5, was adjusted to pH 7.5 with 20% sodium hydroxide and extracted with 50 ml. of methylene chloride. The methylene chloride extract was dried with sodium sulfate, filtered, and the solvent removed at reduced pressure to give 1.4 g. (16%) of product as a viscous oil which soon solidified. The infrared spectrum of this material in methylene chloride showed absorption attributed to water at 3600 cm.$^{-1}$; OH and NH, 3300 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; and amide, 1680 and 1520 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{21}N_3O_3S \cdot 0.5H_2O$: C, 55.79; H, 6.44; N, 12.20. Found: C, 55.65, 55.50; H, 6.37, 6.42; N, 12.68.

6-(5-Methyl-3-phenylisoxazole-4-carboxamido)penicillanyl Alcohol (IX).—The alcohol was obtained in 56% yield as a yellow solid which crystallized from ether; m.p. 121–122.5°. Its infrared spectrum showed absorptions at 3405 cm.$^{-1}$ for OH and NH; β-lactam, 1790 cm.$^{-1}$; amide, 1675 and 1515 cm.$^{-1}$; and aromatic, 1600 and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.80; H, 5.38; N, 10.80.

6-(DL-α-Phenoxypropionamido)penicillanyl Alcohol (X).—The product was obtained in 68% yield as a viscous, pale yellow oil which did not crystallize. Its infrared spectrum showed the

expected absorptions, with OH and NH at 3400 cm.$^{-1}$; β-lactam, 1785 cm.$^{-1}$; amide, 1685 cm.$^{-1}$; aromatic, 1600, 1590, 760, and 690 cm.$^{-1}$; and ether, 1230 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00. Found: C, 57.70; H, 6.29; N, 8.20.

6-Phenylacetamidopenicillanyl N-Phenylcarbamate (XI).—A solution containing 8.0 g. (0.025 mole) of 6-phenylacetamidopenicillamyl alcohol and 6.0 g. (0.050 mole) of phenyl isocyanate in 50 ml. of methylene chloride was stirred at room temperature for 30 min. and then heated at reflux for 5 min. It was cooled, filtered, and diluted to the cloud point with Skellysolve B. After 15 hr., 11 g. (100%) of the crude, crystalline product was collected by filtration. It was recrystallized from 250 ml. of 2-propanol to give 10.0 g. (90%) of purified product, m.p. 129–130°. The infrared spectrum of this material had characteristic absorptions for NH at 3270 cm.$^{-1}$; β-lactam, 1785 cm.$^{-1}$; carbamate, 1710 cm.$^{-1}$; amide, 1660 cm.$^{-1}$; and aromatic, 770 and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{25}N_3O_4S$: C, 62.85; H, 5.73; N, 9.58. Found: C, 62.50; H, 5.57; N, 9.68.

6-Phenylacetamidopenicillanyl Acetate (XII).—A solution of 1.531 g. (4.77 mmoles) of 6-phenylacetamidopenicillanyl alcohol in 20 ml. of acetic anhydride was heated on a steam bath for 30 min. The excess acetic anhydride was removed by vacuum co-distillation with benzene at 50°. The residue was vacuum-dried over phosphorus pentoxide to yield 1.734 g. (100%) of stiff gum. It was dissolved in 150 ml. of ether and extracted with two 100-ml. portions of 9% sodium bicarbonate solution, washed with water, dried over sodium sulfate, and filtered. The purified product was precipitated from the filtrate by dilution with pentane. The resulting gum, 640 mg. (37%), was dried to a fluff under vacuum. Its infrared spectrum in chloroform showed absorptions for NH at 3410 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; ester, 1740 cm.$^{-1}$; amide, 1675 cm.$^{-1}$; ester, 1215 cm.$^{-1}$; and aromatic, 785 and 670 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}N_2O_5S$: C, 59.93; H, 6.15; N, 7.77. Found: C, 59.40; H, 6.08; N, 7.90.

Potassium 6-Phenylacetamidopenicillanyl Succinate (XIII).—A mixture of 16.0 g. (0.050 mole) of 6-phenylacetamidopenicillamyl alcohol, 6.0 ml. of triethylamine, 5.0 g. (0.050 mole) of succinic anhydride, and 200 ml. of methylene chloride was stirred for 1 hr. at room temperature and 1 hr. at reflux. The solvent was removed under reduced pressure and the residue was dissolved in 500 ml. of 2.5% aqueous sodium bicarbonate. It was extracted with 300 ml. of ether (discarded) and the aqueous solution was cooled in an ice bath. To this cooled solution was added 400 ml. of methyl isobutyl ketone (MIBK) and sufficient 40% phosphoric acid to lower the pH to 2. The MIBK extract was washed with water, dried briefly over sodium sulfate, filtered, and treated with 25 ml. of 50% potassium 2-ethylhexanoate (KEH) in 1-butanol. The oil which settled to the bottom was dissolved in 400 ml. of dry acetone, from which it crystallized to give 10.0 g. (43%) of product, m.p. 149–150° dec. The infrared spectrum of this compound agreed with the expected structure, with NH at 3300 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; ester, 1725 cm.$^{-1}$; amide, 1680 cm.$^{-1}$; carboxylate, 1580 cm.$^{-1}$; and aromatic, 700 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}N_2O_6SK$: C, 52.40; H, 5.06; N, 6.12. Found: C, 52.40; H, 5.07; N, 6.27.

6-Phthalimidopenicillanyl Alcohol (XIV).—The method described above was used to prepare 6-phthalimidopenicillanyl azide (I) on a 0.05 mole scale. A solution of the azide in 300 ml. of dioxane and 50 ml. of water was cooled to 5°. To the stirred solution was added 3.7 g. (0.10 mole) of sodium borohydride in portions so that the temperature was maintained at 5°. The pH of the solution was kept at 8.0–8.5 by suitable addition of glacial acetic acid. After the addition was completed, the mixture was stirred for 25 min. at 5°, then diluted with 250 ml. of water, and the pH adjusted to 6.5 by addition of more acetic acid. The weakly acidic solution was extracted 3 times with 200-ml. portions of methylene chloride, and the combined extracts were washed successively with 5% aqueous sodium bicarbonate solution and with cold water. After the extracts were dried (anhydrous magnesium sulfate) the solvent was evaporated to leave a clear gum, which was dissolved in a mixture of ethyl acetate and anhydrous ether and the solvents were removed at 30° (15 mm.). The residue was then a glass-like solid and on trituration with cold 2-propanol became crystalline; yield 8.6 g. (51%). A small portion was recrystallized for analysis from 2-propanol and gave white needles, m.p. 159–160.5°. Its infrared spectrum showed OH at 3500 cm.$^{-1}$; phthalimide, 1785 and 1720 cm.$^{-1}$; β-lactam, 1760 cm.$^{-1}$; primary alcohol, 1350, 1310, and 1045 cm.$^{-1}$; aromatic, 793 and 720 cm.$^{-1}$. Its n.m.r. spectrum showed all of the expected resonance lines, as well as the presence of 2-propanol.

Anal. Calcd. for $C_{16}H_{15}N_3O_4S \cdot 0.5C_3H_8O$: C, 58.01; H, 5.56; N, 7.73. Found: C, 57.85; H, 6.02; N, 7.72.

Potassium Salt of 6-(2-Carboxybenzamido)penicillanyl Alcohol (XV).—A solution of 10 g. (0.030 mole) of 6-phthalimidopenicillanyl alcohol in 200 ml. of THF and 200 ml. of water was maintained at pH 10–11 by the constant addition of 1 *N* sodium hydroxide. When 29 ml. of base (0.029 mole) had been added, the solution was extracted with three 200-ml. portions of methylene chloride and the aqueous phase was acidified to pH 3 with 40% phosphoric acid and again extracted with two 200-ml. portions of methylene chloride. The combined extracts of the acidified solution were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was dissolved in 100 ml. of ethyl acetate and treated successively with three 5.0-mmole portions of potassium 2-ethylhexanoate, the crystalline precipitate which formed with each treatment being filtered and dried. Infrared and n.m.r. spectra showed the third fraction (1.8 g.; 15%) to be the pure potassium salt of 6-(2-carboxybenzamido)-penicillanyl alcohol, having absorptions attributed to OH and NH at 3600 to 3000 cm.$^{-1}$; β-lactam, 1770 cm.$^{-1}$; amide, 1660 cm.$^{-1}$; carboxylate, 1400 cm.$^{-1}$; primary alcohol, 1310 and 1045 cm.$^{-1}$; and 1,2-disubstituted benzene at 750 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{17}N_3O_5SK$: C, 49.46; H, 4.41; N, 7.21. Found: C, 49.55; H, 5.02; N, 7.40, 7.25.

6-Triphenylmethylaminopenicillanyl Acetate (XVI).—A solution of 55 mg. of 6-triphenylmethylaminopenicillanyl alcohol in 1.0 ml. of acetic anhydride was heated on a steam bath for 1 hr. The solvent was removed under vacuum at 70° and the residual gum was evaporated repeatedly with benzene to remove traces of acetic acid and acetic anhydride. It was extracted into 15 ml. of hot Skellysolve B, cooled, and decanted from a trace of insoluble material. Complete removal of solvent under vacuum left 58 mg. (97%) of a fluffy, noncrystalline solid. Its infrared spectrum showed β-lactam at 1780 cm.$^{-1}$; ester, 1745 cm.$^{-1}$; aliphatic ester, 1230 cm.$^{-1}$; and aromatic bands at 1600, 1490, 770, 750, and 710 cm.$^{-1}$.

Anal. Calcd. for $C_{35}H_{36}N_2O_3S$: C, 71.57; H, 6.21. Found: C, 71.50; H, 6.47.

6-Aminopenicillanyl Alcohol, *p*-Toluenesulfonate Salt (XVII).—A solution of 0.750 g. (1.68 mmoles) of 6-triphenylmethylaminopenicillamyl alcohol in 10 ml. of dry acetone was stirred with 0.320 g. (1.68 mmoles) of *p*-toluenesulfonic acid monohydrate for 30 min. at 25°. The solvent was evaporated under a stream of nitrogen and the gummy residue was triturated with 100 ml. of dry ether, which washed out triphenylcarbinol obtained from the ether solution in 81% purified yield and identified by melting point and infrared spectrum) and left the product as a filtrable solid. The crude yield of noncrystalline material was 0.63 g. (quantitative). It was reprecipitated 5 times from dry acetone by the addition of dry ether to give 0.28 g. (44%) of amorphous solid, m.p. *ca.* 100°. Its infrared spectrum was as expected, with combined OH and NH absorptions at 3430–3380 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; and bands characteristic of *p*-toluenesulfonic acid at 1205, 1125, 1037, 1010, 816, and 685 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}N_2O_5S_2$: C, 48.11; H, 5.92. Found: C, 48.40; H, 5.83.

6-(2,6-Dimethoxybenzamido)penicillanyl N-Phenylcarbamate (XVIII).—A solution of 3.7 g. (0.010 mole) of 6-(2,6-dimethoxybenzamido)penicillanyl alcohol and 1.19 g. (0.010 mole) of phenyl isocyanate in 25 ml. of methylene chloride was stored at room temperature for 20 hr. An additional 50 ml. of methylene chloride was added. Dilution with 150 ml. of Skellysolve B caused an oil to separate. The solvent was partially distilled at reduced pressure until about 25 ml. of solvent plus a semisolid gum remained. The solvent was decanted and the gum triturated with Skellysolve B to give as the product an amorphous solid which, after collecting by filtration and drying *in vacuo* over phosphorus pentoxide, amounted to 3.4 g. (70%). The infrared spectrum had typical bands for NH at 3300 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; urethan, 1740 cm.$^{-1}$; amide, 1670 cm.$^{-1}$; and aromatic, 705 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{27}N_3O_6S$: C, 59.36; H, 5.61; N, 8.65. Found: C, 59.50; H, 6.02; N, 8.07.

Sodium 6-(5-Methyl-3-phenylisoxazole-4-carboxamido)penicillanyl Succinate (XIX).—A solution of 4.0 g. (0.010 mole) of 6-(5-methyl-3-phenylisoxazole-4-carboxamido)penicillanyl al-

cohol, 1.0 g. (0.010 mole) of succinic anhydride, and 15 drops of triethylamine in 50 ml. of methylene chloride was refluxed for 30 min. and then evaporated *in vacuo*. The residue was dissolved in 75 ml. of MIBK and extracted twice with 30-ml. portions of 5% sodium bicarbonate solution. The combined extracts were washed with ether (30 ml.), acidified to pH 2 with 20% sulfuric acid, and extracted twice with 35-ml. portions of ether. The combined ethereal extracts were washed twice with 10-ml. portions of water, dried over sodium sulfate, filtered, and treated with 3.5 ml. (0.01 mole) of a 50% solution of sodium 2-ethylhexanoate in 1-butanol. The product crystallized on standing at 8° for 17 hr. It was collected and dried *in vacuo* over phosphorus pentoxide; weight, 1.5 g. (28%); m.p. 195.5–197.5° dec. The infrared spectrum indicated the presence of NH at 3350 cm.$^{-1}$; β-lactam, 1780 cm.$^{-1}$; ester, 1730 cm.$^{-1}$; amide, 1670 cm.$^{-1}$; carboxylate, 1590 cm.$^{-1}$; primary ester, 1160 cm.$^{-1}$; and aromatic, 1570 and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{24}N_3O_7SNa \cdot 0.5H_2O$: C, 53.27; H, 4.86; N, 8.10. Found: C, 53.50; H, 4.72; N, 8.16.

6-(DL-α-Phenoxypropionamido)penicillanyl N-Phenylcarbamate (XX).—A solution of 3.0 g. (8.5 mmoles) of 6-(DL-α-phenoxypropionamido)penicillanyl alcohol in 25 ml. of dry benzene was treated with 1.1 ml. (0.01 mole) of phenyl isocyanate. After 7 days at room temperature the solution was concentrated and the residual amber gum was dissolved in ether, from which it crystallized on scratching. The product was recrystallized from benzene and Skellysolve B to yield 1.05 g. (26%) of white solid, m.p. 164.5–167.5°. The infrared spectrum was consistent with the expected structure, having NH at 3345 cm.$^{-1}$; β-lactam, 1787 cm.$^{-1}$; carbamate, 1739 cm.$^{-1}$; amide, 1680 cm.$^{-1}$; phenyl ether, 1225 cm.$^{-1}$; and aromatic bands at 1600, 760, and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{27}N_3O_5S$: C, 61.38; H, 5.80; N, 8.95. Found: C, 61.00; H, 5.63; N, 8.90.

6-(5-Methyl-3-phenylisoxazole-4-carboxamido)penicillanyl N-Phenylcarbamate (XXI).—A solution of 870 mg. (2.2 mmoles) of 6-(5-methyl-3-phenylisoxazole-4-carboxamido)penicillanyl alcohol and 330 mg. (3.0 mmoles) of phenyl isocyanate in 20 ml. of dimethylformamide was allowed to stand at 25° for 10 days. It was diluted with 80 ml. of water and cooled. The crystalline solid was collected, dissolved in 75 ml. of ethyl acetate, and concentrated to dryness *in vacuo*. The residue was redissolved in ethyl acetate, concentrated to a small volume, and filtered to remove a small amount of crystalline product which was identified as carbanilide by melting point and infrared spectrum. Dilution of the ethyl acetate solution with Skellysolve B gave a crystalline solid. It was dissolved in methylene chloride, filtered to remove a trace of insoluble material, concentrated to dryness *in vacuo*, and recrystallized in turn from ethyl acetate and benzene–Skellysolve B. After drying *in vacuo* over phosphorus pentoxide the product weighed 300 mg. (33%) and had m.p. 150.5–151°. An infrared spectrum showed absorptions for NH at 3280 cm.$^{-1}$, β-lactam, 1785 cm.$^{-1}$; carbamate, 1738 cm.$^{-1}$; amide, 1670 cm.$^{-1}$; and aromatic at 765 and 700 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{26}N_4O_5S$: C, 61.50; H, 5.16; N, 11.10. Found: C, 61.10; H, 4.98; N, 11.05.

Synthetic Schistosomicides. V. N-(Mono- and dialkylaminoalkyl)-1,4-naphthalenediamines and Related Naphthylamines[1]

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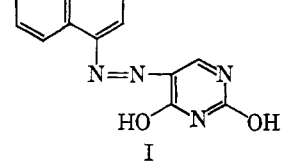
Received January 8, 1964

A group of N-(mono- and dialkylaminoalkyl)-1,4-naphthalenediamines (IV) (Tables I and II), which represent potential metabolites of various 1-(mono- and dialkylaminoalkylamino)-4-naphthylazo schistosomicides (III), has been prepared by hydrogenolysis of the appropriate N-mono- and N,N-dialkyl-N′-(4-phenylazo-1-naphthyl)-alkylenediamines. N²-(2-Diethylaminoethyl)-1,2-naphthalenediamine (V), 1,4-bis[2-(4-amino-1-naphthylamino)ethyl]piperazine (VIa), and N,N′′-[methyliminobis(trimethylene)]di-1,4-naphthalenediamine (VIb) were prepared in a similar manner. Alternatively, N-(2-diethylaminoethyl)-1,4-naphthalenediamine (IIb), N-(2-diethylaminoethyl)-N-methyl-1,4-naphthalenediamine (VII), and 4-(2-diethylaminoethylthio)-1-naphthylamine (X) were obtained from the corresponding nitronaphthalenes by catalytic hydrogenation. Condensation of IIb with diethyl (ethoxymethylene)malonate, ethyl 2-cyano-3-ethoxyacrylate, 4,7-dichloroquinoline, 6,9-dichloro-2-methoxyacridine, and 2-chlorotriethylamine afforded diethyl {{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}-amino}methylene}malonate (XI), ethyl 2-cyano-3-{{4-[(2-diethylaminoethyl)amino]-1-naphthyl}amino}acrylate (XII), 7-chloro-4-[4-(2-diethylaminoethylamino)-1-naphthylamino]quinoline (XIII), 6-chloro-9-[4-(2-diethylaminoethylamino)-1-naphthylamino]-2-methoxyacridine (XIV), and N,N′-bis(2-diethylaminoethyl)-1,4-naphthalenediamine (XV), respectively. Many of the N-(dialkylaminoalkyl)-1,4-naphthalenediamines are highly active against experimental *Schistosoma mansoni* infections in mice. Structure–activity relationships and biochemical studies are summarized.

In a previous communication[2] it was reported that 5-(4-amino-1-naphthylazo)uracil (ANU) (Ia) exhibits good activity against *Schistosoma mansoni* in experimental animals. Additional studies in these laboratories[3] revealed that the antischistosome activity of ANU was markedly enhanced when a diethylaminoethyl side chain was atttached to the aromatic amine (Ib). Potent antischistosome activity was also observed among a variety of related 1-(mono- and dialkylaminoalkylamino)-4-naphthylazo compounds (III).[1,3–5]



I

a, R=H
b, R=$(CH_2)_2N(C_2H_5)_2$

(1) Presented before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 5–10, 1964. Previous paper: E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **6**, 646 (1963).

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