[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, DIVISION OF BRISTOL-MYERS CO.]

Derivatives of 6-Aminopenicillanic Acid. II. Reactions with Isocyanates, Isothiocyanates, and Cyclic Anhydrides

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The base-catalyzed condensation of numerous isocyanates, isothiocyanates, and cyclic anhydrides with 6-aminopenicillanic acid (II) has been carried out. The *N*-substituted 6-aminopenicillanic acid derivatives thus obtained are described.

The availability of 6-aminopenicillanic acid (6-APA) (II) in quantity from fermentation procedures[1] has made possible the synthesis of many new and varied penicillins not amenable to production by direct biosynthetic methods.[2,3] In a previous communication[4] we have reported a series of new partially synthetic penicillins prepared from 6-aminopenicillanic acid and α-aryloxyalkanoic acids, one of which, potassium α-phenoxyethylpenicillin (Syncillin) has been shown to have considerable therapeutic value.[5]

It has now been determined, as shown in Fig. 1, that 6-aminopenicillanic acid (II) reacts readily in dimethylformamide or methylene chloride, and in the presence of an excess of triethylamine, with isocyanates and isothiocyanates (I) to give triethylammonium 6-(substituted ureido)- and 6-(substituted thioureido)penicillanates (III).[6]

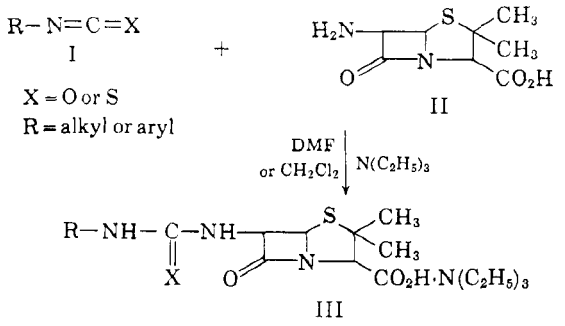


Fig. 1. Reactions of 6-aminopenicillanic acid with isocyanates and isothiocyanates

These compounds, which are described in Table I, were isolated as crystalline triethylammonium salts in yields varying from 28 to 91%. No attempts have been made to determine the conditions necessary for optimum yields.

The compounds described in Table II have been prepared by base-catalyzed condensations of 6-aminopenicillanic acid with a variety of cyclic anhydrides, as illustrated in Fig. 2, where phthalic anhydride is taken as an example.

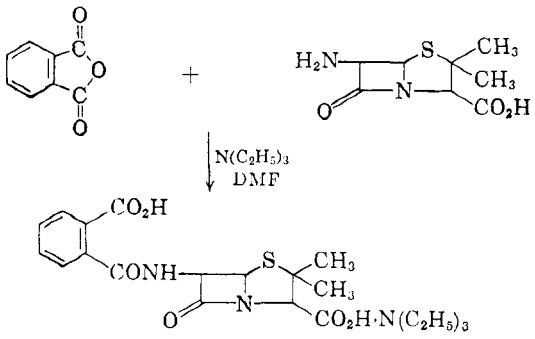


Fig. 2. Reactions of 6-aminopenicillanic acid with cyclic anhydrides

These compounds have also been isolated as crystalline triethylammonium salts. It is noteworthy that the compounds of Table II, although they possess two carboxyl groups, crystallized as monotriethylammonium salts even when the reaction was carried out in the presence of a large excess of the organic base. The part of the molecule carrying the triethylammonium cation was ascribed to the carboxyl group of the 6-aminopenicillanic acid moiety due to its strong acidic character.

An examination of the infrared spectra (potassium bromide) of the compounds of Tables I and II showed a strong absorption at 5.57–5.65 μ, indicating that the β-lactam ring of 6-aminopenicillanic acid had been preserved through these transformations. The presence of this four-membered lactam ring in these reaction products

(1) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(2) H. T. Clarke, J. R. Johnson, and R. Robinson, Editors, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 657.

(3) J. E. Philip *et al.*, *J. Biol. Chem.*, **189**, 479 (1951); O. K. Behrens and M. J. Kingkade, *J. Biol. Chem.*, **176**, 1047 (1948).

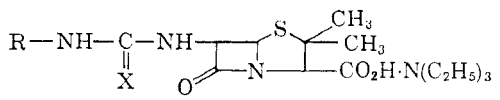
(4) Y. G. Perron, *et al.*, *J. Am. Chem. Soc.*, **82**, 3934 (1960).

(5)(a) M. H. Pindell, D. E. Tisch, and J. B. Hoekstra, *Antibiotics Annual 1959–1960*, Medical Encyclopedia, New York, p. 119; (b) E. M. Morigi, W. B. Wheatley, and H. Albright, *Antibiotics Annual 1959–1960*, Medical Encyclopedia, New York, p. 127; (c) G. A. Cronk, D. E. Naumann, H. Albright, and W. B. Wheatley, *Antibiotics Annual 1959–1960*, Medical Encyclopedia, New York, p. 133.

(6) According to presently accepted nomenclature these compounds are not penicillins and are therefore best considered as derivatives of 6-aminopenicillanic acid. [J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953)].

TABLE I

TRIETHYLAMMONIUM 6-(SUBSTITUTED UREIDO)- AND 6-(SUBSTITUTED THIOUREIDO)PENICILLANATES



R	X	Yield, %	Method	Dec.[b] Point	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
CH_3—	S	50	A	119–121	$C_{16}H_{30}N_4O_3S_2$	49.2	7.69	49.4	7.65
C_2H_5—	O	60	A	166–168	$C_{17}H_{32}N_4O_4S$	52.5	8.30	52.5	8.42
n-C_3H_7—	O	37	A	168–171	$C_{18}H_{34}N_4O_4S$	53.7	8.45	53.8	8.40
i-C_3H_7—	O	61	B	186–189	$C_{18}H_{34}N_4O_4S$	53.7	8.45	53.8	8.87
n-C_4H_9—	O	74	A	162–165	$C_{19}H_{36}N_4O_4S$	54.7	8.71	54.6	8.58
n-C_4H_9—	S	61	A	136–137	$C_{19}H_{36}N_4O_3S_2$	52.8	8.39	52.8	8.48
t-C_4H_9—	O	64	B	215–218	$C_{19}H_{36}N_4O_4S \cdot C_3H_8O$[c]	55.5	9.32	55.4	9.49
$(CH_3)_3C—CH_2C(CH_3)_2$—	O	82	B	179–181	$C_{23}H_{44}N_4O_4S$	58.5	9.32	58.8	9.47
$CH_2=CHCH_2$—	S	74	A	140–141	$C_{18}H_{32}N_4O_3S_2$	51.9	7.69	51.6	7.69
C_6H_{11}—[a]	O	72	B	192–195	$C_{21}H_{38}N_4O_4S$	57.0	8.60	56.8	8.88
C_6H_5—	O	28	A	180–182	$C_{21}H_{32}N_4O_4S$	57.8	7.34	57.7	7.25
2-CH_3—C_6H_4—	O	22	A	148–150	$C_{22}H_{34}N_4O_4S$	58.7	7.60	58.9	7.59
4-CH_3—C_6H_4—	O	67	B	158–160	$C_{22}H_{34}N_4O_4S$	58.6	7.58	58.9	7.74
2-Cl—C_6H_4—	O	65	A	173–175	$C_{21}H_{31}ClN_4O_4S$	53.6	6.58	53.4	6.85
4-Cl—C_6H_4—	O	53	A	154–157	$C_{21}H_{31}ClN_4O_4S$	53.6	6.58	53.6	6.94
2-CH_3O—C_6H_4—	O	91	A	173–175	$C_{22}H_{34}N_4O_5S$	56.7	7.29	56.4	7.21
4-CH_3O—C_6H_4—	O	42	B	152–154	$C_{22}H_{34}N_4O_5S$	56.7	7.29	56.5	7.54
C_6H_5—CH(CH$_3$)—	O	86	B	130–132	$C_{23}H_{36}N_4O_4S$	59.5	7.76	60.0	8.04

[a] Cyclohexyl. [b] All decomposition points are uncorrected. The decomposition point refers to the temperature at which complete decomposition, with evolution of gases, occurred. In many cases shrinking and darkening started many degrees below the complete decomposition point. [c] The compound crystallized from isopropyl alcohol as a monoisopropylate; a strong —OH band was evident in the infrared.

was further demonstrated by the quantitative hydroxylamine assay for penicillins.[7]

The 6-aminopenicillanic acid derivatives listed in Tables I and II show a low order of activity against microorganisms that are sensitive to penicillin G. However, some of these compounds are active against penicillin G-resistant bacteria. The antimicrobial action of these compounds will be reported in detail elsewhere.

EXPERIMENTAL

Isocyanates and isothiocyanates (I). Isopropyl, *tert*-butyl, 1,1,3,3-tetramethylbutyl, cyclohexyl, and 1-phenylethyl isocyanates were prepared by the base-catalyzed cleavage of the corresponding carbamates as reported by Bortnick and co-workers.[8] The remainder of the isocyanates and isothiocyanates were obtained from commercial sources.

Method A. Triethylammonium 6-(n-butylureido)penicillanate. The following example illustrates the general method. A stirred suspension of 21.6 g. (0.1 mole) of 6-aminopenicillanic acid (II) in 75 ml. of dimethylformamide was cooled to 0–5° and 50 ml. (0.36 mole) of triethylamine was added in one portion. With continued cooling and stirring there was added a solution of 9.9 g. (0.1 mole) of *n*-butyl isocyanate in 75 ml. of dimethylformamide; the temperature was kept below 5°. The mixture was stirred for 15 min. at 0–5° and then for 3 hr. at room temperature. The yellow solution was filtered through Super-Cel to remove a small amount of insoluble material and was then diluted nearly to the cloud-point with anhydrous ether. Scratching and cooling produced a heavy, crystalline precipitate, which was collected by filtration, washed with anhydrous ether, and dried *in vacuo* over phosphorous pentoxide. Yield: 30.8 g. (74%) of triethylammonium 6-(*n*-butylureido)penicillanate. The decomposition point and analysis are reported in Table I. In this case, as in the majority, the compound was analytically pure as isolated and no further purification was needed. In the few instances where purification was necessary the compounds were recrystallized from dimethylformamide-ether or isopropanol.

Method B. Triethylammonium 6-(isopropylureido)penicillanate. A suspension of 21.6 g. (0.10 mole) of 6-aminopenicillanic acid (II) in 200 ml. of methylene chloride and 30 ml. (0.22 mole) of triethylamine was stirred for 1 hr. at 25° and the solution was filtered to remove traces of insoluble material. To the stirred filtrate there was added dropwise a solution of 8.5 g. (0.10 mole) of isopropyl isocyanate in 30 ml. of methylene chloride. Shortly after completion of the addition a crystalline solid began to form. After 1 hr. at 25° the product was collected, washed in turn with methylene chloride and anhydrous ether, and dried as in Method A. The yield was 24.6 g. (61%). See Table I for the analysis and decomposition point.

Anhydrides. Diphenic anhydride was prepared as outlined by Roberts and Johnson.[9] All the other anhydrides were obtained from commercial sources.

Triethylammonium 6-(2-carboxybenzamido)penicillanate. The example given below is representative of the reaction between 6-aminopenicillanic acid and cyclic anhydrides. A mixture of 21.6 g. (0.1 mole) of 6-aminopenicillanic acid (II) in 60 ml. of dimethylformamide and 42 ml. (0.3 mole) of triethylamine was stirred for 1 hr. at 0–5°. A solution of 14.8 g. (0.1 mole) of phthalic anhydride in 60 ml. of dimethyl-

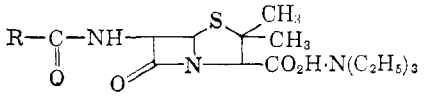
(7) J. H. Ford, *Anal. Chem.*, 19, 1004 (1947).

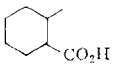
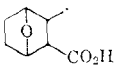
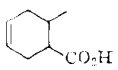
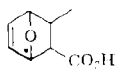
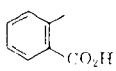
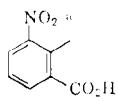
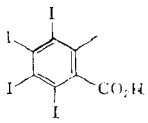
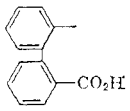
(8) N Bortnick, L. S. Luskin, M. D. Hurwitz, and A. W. Rytina, *J. Am. Chem. Soc.*, 78, 4358 (1956).

(9) R. C. Roberts and T. B. Johnson, *J. Am. Chem. Soc.* 47, 1399 (1925).

TABLE II

N-ACYLATION OF 6-AMINOPENICILLANIC ACID WITH CYCLIC ANHYDRIDES



R	Yield, %	Dec.[b] Point	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
	53	149–150	$C_{22}H_{37}N_3O_7S$	56.0	7.97	55.8	8.03
	90	150–153	$C_{22}H_{35}N_3O_7S$	54.3	7.27	54.5	7.10
	30	149–150	$C_{22}H_{35}N_3O_6S$	56.3	7.51	55.9	7.67
	70	200–202	$C_{16}H_{16}K_2N_2O_7S$[c]	42.0	3.52	41.8	4.02
	78	147–148	$C_{22}H_{31}N_3O_6S$	56.7	6.73	56.4	6.68
	20	76–79	$C_{22}H_{30}N_4O_8S$	51.3	5.93	51.8	6.20
	65	90–92	$C_{22}H_{27}I_4N_3O_6S$	31.4	3.95	31.3	4.56
	54	100–104	$C_{28}H_{35}N_3O_6S$	62.2	6.52	62.3	6.46

[a] Although another position isomer is possible, the structure of this derivative was assigned by analogy with the results obtained by Alexander and McElvain when they studied the reaction of 3-nitrophthalic anhydride with amines [J. W. Alexander and S. M. McElvain, *J. Am. Chem. Soc.*, **60**, 2285 (1938)]. [b] See footnote *c* of Table I. [c] The triethylammonium salt of this compound could not be purified; it was thus converted into its dipotassium salt by cation interchange with potassium 2-ethylhexanoate. As an example of this procedure see the preparation of disodium 6-(2-carboxybenzamido)penicillanate in the Experimental section.

formamide was then added dropwise at a rate which kept the temperature below 10°. The ice bath was removed and the mixture was stirred for 3.5 hr. at 25°. The yellow solution was filtered through Super-Cel and then diluted with 600 ml. of anhydrous ether. The precipitated oil slowly crystallized on prolonged cooling, scratching, and the addition of fresh ether. Yield: 36 g. (78%). An analysis sample was slurried with acetone. See Table II for decomposition point and analysis.

The majority of the products from 6-aminopenicillanic acid and cyclic anhydrides crystallized directly upon addition of ether to the reaction medium.

Disodium 6-(2-carboxybenzamido)penicillanate. The above procedure was repeated on the same scale, and after precipitation of the oily product the ether was decanted. The oil was dissolved in 100 ml. of water, layered with 100 ml. of ethyl acetate, chilled and neutralized to *p*H 2 with 40% sulfuric acid. After extraction the aqueous phase was extracted again with ethyl acetate and the combined extracts were washed twice with water and dried for 30 min. over anhydrous sodium sulfate. The dried ethyl acetate solution was treated with 73 ml. (0.22 mole) of a 50% solution of sodium 2-ethylhexanoate in *n*-butyl alcohol. After 1 hr. at 25° the product was collected by filtration, washed with acetone and dried *in vacuo* over phosphorus pentoxide. Yield: 24 g. (57%). An analysis sample was recrystallized by dissolving it in a mixture of *n*-butyl alcohol and water and removing the water azeotropically under reduced pressure; the sample had a decomposition point of 232–233°.

Anal. Calcd. for $C_{16}H_{14}Na_2N_2O_6S$: C, 46.0; H, 3.38. Found: C, 46.0; H, 3.76.

Acknowledgment. We wish to express our appreciation to D. L. Evans and D. F. Whitehead for infrared spectra, to R. M. Downing for the elemental analyses, and to P. Lau for the preparation of some of the isocyanates.

SYRACUSE 1, N. Y.