Derivatives of 6-Aminopenicillanic Acid. III. Reactions with N-Substituted Phthalamic Acids

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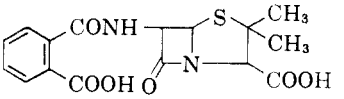
A number of new and previously described N-substituted phthalamic acids were used for the N-acylation of 6-aminopenicillanic acid (6-APA). The new 6-APA derivatives thus produced were isolated as sodium or potassium salts. The condensation of phthalamic acid with 6-APA failed to yield the expected product. It was found that both N-carbethoxyphthalamic acid and N-carbethoxyphthalimide afforded the same derivative, namely, 6-phthalimidopenicillanic acid. The antimicrobial activity and penicillinase resistance of the new penicillins described herein are discussed.

In a recent publication[1] we have reported the synthesis of a series of 6-aminopenicillanic acid (6-APA)[2] derivatives prepared from isocyanates, isothiocyanates and cyclic anhydrides. That report described compound I, prepared from phthalic anhydride and 6-APA, which has shown some appreciable activity against penicillin G-resistant bacteria. In an effort to increase this desirable type of anti-



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microbial activity, a variety of closely related compounds have been prepared. It was found that with certain N-substituted phthalamic acid derivatives of 6-APA this type of activity is somewhat increased. The object of this communication is to report the preparation, antimicrobial activity and penicillinase resistance of a series of compounds represented by general formula IV.

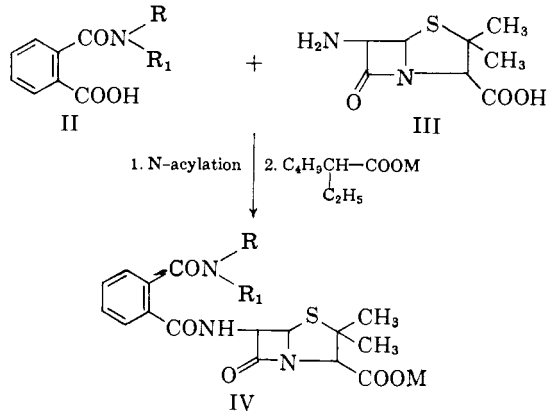
Chemistry.—In order to carry out this work a number of previously described phthalamic acids were used, but also numerous new ones

(1) Y. G. Perron, W. F. Minor, L. B. Crast and L. C. Cheney, *J. Org. Chem.*, **26**, 3365 (1961).

(2) The 6-APA used in this work was obtained from fermentation broth by a procedure recently disclosed by F. R. Batchelor, F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, *Nature*, **183**, 257 (1959).

were needed. These new N-substituted phthalamic acids[3] were prepared by treating phthalic anhydride with a variety of primary and secondary amines. Although the chemical literature contains a number of examples of this type of condensation using different solvents, we have found that acetone is the solvent of choice for this reaction. The new N-substituted phthalamic acids which we have prepared are described in Table I.

The new 6-APA derivatives listed in Table II were prepared by condensation of N-substituted phthalamic acids (II) with 6-APA (III) through the mixed carboxylic-carbonic anhydride method,[4] using either ethyl or isobutyl chloroformate. The 6-(N-substituted-N′-phthalamido)-penicillanic acids (IV)[5] thus obtained were isolated as sodium or potassium salts by cation interchange with sodium or potassium 2-ethylhexanoate.



The majority of the compounds derived from phthalamic acids and 6-APA were hygroscopic amorphous solids which were very difficult to isolate in a state of high purity. For this reason, although all the new phthalamic acids of Table I have been converted into 6-APA derivatives,[6] only those which could be obtained in analytically pure

(3) Many N-substituted phthalamic acids have shown some promise as plant growth regulators; see for example A. E. Smith and O. L. Hoffmann, Canadian Patent 519,684 (*C.A.*, **50**, 7484i (1956)).

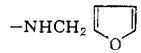
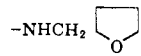
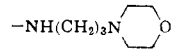
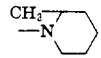
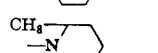
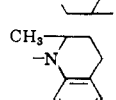
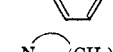
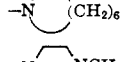
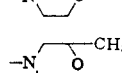
(4) Y. G. Perron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel and L. C. Cheney, *J. Am. Chem. Soc.*, **82**, 3934 (1960); this paper contains leading references to previous work using the mixed carboxylic-carbonic anhydride method.

(5) These compounds are named according to the nomenclature proposed for 6-APA; J. C. Sheehan, K. R. Henery-Logan and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953).

(6) The formation of the 6-APA derivatives was indicated by an examination of the infrared spectra of the reaction products, which showed the characteristic strong absorption band of the β-lactam carbonyl at 5.57–5.65 μ. The presence of this four-membered lactam ring was further demonstrated by the quantitative hydroxylamine assay for penicillins; J. H. Ford, *Anal. Chem.*, **19**, 1004 (1947).

TABLE I

N-SUBSTITUTED PHTHALAMIC ACIDS

—NRR1	M.p., °C.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
—NHC3H7-i	137–138	34	$C_{11}H_{13}NO_3$	63.8	64.2	6.32	6.12
—NHC4H9-i	129–131	44	$C_{12}H_{15}NO_3$	65.1	64.9	6.83	7.07
—NHC4H9-t	147–148	56	$C_{12}H_{15}NO_3$	65.1	65.6	6.83	7.02
—N(C3H7-i)2	184–186	42	$C_{14}H_{19}NO_3$	67.6	67.4	7.85	7.68
—N(CH2CH=CH2)2	76–77.5	46	$C_{14}H_{15}NO_3$	68.6	68.7	6.16	6.29
—NHC(CH3)2CH2C(CH3)3	115–117	15	$C_{16}H_{23}NO_3$	69.3	69.2	8.36	8.30
—NHCH2CH2C6H5	156–157	45	$C_{16}H_{15}NO_3$	71.4	71.5	5.61	5.76
—NHCH(CH3)CH2C6H5	195–196	96	$C_{17}H_{17}NO_3$	72.1	71.8	6.05	6.11
—NHCH(C6H5)2	225–226	82	$C_{21}H_{17}NO_3$	76.1	76.3	5.17	5.30
	130–131	72	$C_{13}H_{11}NO_4$	63.7	64.0	4.52	4.80
	128–129	66	$C_{13}H_{15}NO_4$	62.6	62.8	6.07	5.94
	162–163	90	$C_{16}H_{20}N_2O_4$	61.6	61.4	6.92	7.00
	132–134	79	$C_{12}H_{13}NO_3$	65.8	65.9	5.94	5.93
 [b]	133–135	78	$C_{13}H_{15}NO_3$	66.9	66.7	6.49	6.45
	139–140	77	$C_{13}H_{13}NO_3$	67.5	67.4	5.67	5.75
	151.5–153.5	45	$C_{14}H_{17}NO_3$	68.0	68.1	6.93	6.83
	117–120	18	$C_{16}H_{21}NO_3$	69.8	70.0	7.69	7.84
	164–165	70	$C_{18}H_{17}NO_3$	73.2	73.5	5.80	5.76
	149–150.5	75	$C_{14}H_{17}NO_3$	68.0	67.9	6.93	6.91
	274–276	94	$C_{13}H_{16}N_2O_3$	62.9	62.8	6.50	6.61
	114–116	83	$C_{12}H_{13}NO_4$	61.3	61.4	5.58	5.46
	147.5–149	48	$C_{14}H_{17}NO_4$	63.9	64.0	6.51	6.68

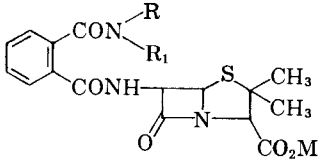
[a] All melting points are uncorrected. [b] Described by A. Piutti, *Ann.*, **227**, 197 (1885) only, as a "heavy oil."

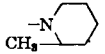
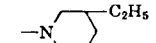
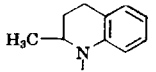
form were included in Table II.

The condensation of phthalamic acid (V) with 6-APA failed to give the desired derivative. The mixed carboxylic-carbonic anhydride method applied to this acid yielded mainly *o*-cyanobenzoic acid (VI) with a small amount of 6-(*o*-cyanobenzamido)-penicillanic acid (VII).

TABLE II

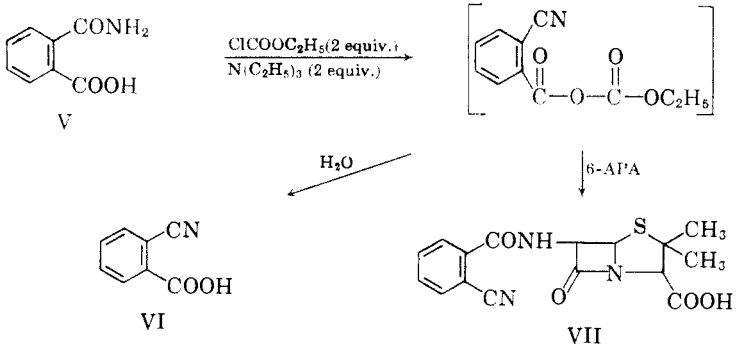
6-(N-SUBSTITUTED N′-PHTHALAMIDO)-PENICILLANIC ACIDS



Cpd.	—NRR$_1$	Metal Ion = M	Decomp. pt.,[a] °C.	Yield %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	—NHC$_2$H$_5$[b]	K	>100	67	$C_{18}H_{20}KN_3O_5S$	50.4	50.6	4.70	5.10
2	—NHC$_3$H$_7$-*n*	K	101–104	51	$C_{19}H_{22}KN_3O_5S \cdot H_2O$	49.4	48.9	5.24	5.28
3	—NHCH$_2$CH=CH$_2$[c]	K	160–164	46	$C_{19}H_{20}KN_3O_5S \cdot H_2O$	49.8	49.3	4.85	4.65
4	—NHC(CH$_3$)$_3$	K	136–137	52	$C_{20}H_{24}KN_3O_5S$	52.5	52.0	5.30	5.65
5	—NHCH(CH$_3$)C$_6$H$_5$[d]	Na	120–125	24	$C_{24}H_{24}NaN_3O_5S \cdot H_2O$	56.9	56.5	5.15	5.14
6	—NHC$_6$H$_{11}$[e]	K	130–135	55	$C_{22}H_{26}KN_3O_5S$	54.6	54.6	5.39	5.78
7	—N(C$_2$H$_5$)$_2$[f]	K	130–134	79	$C_{20}H_{24}KN_3O_5S$	52.5	52.6	5.25	5.50
8	—N(C$_3$H$_7$-*i*)$_2$	K	159–163	62	$C_{22}H_{28}KN_3O_5S$	54.4	54.6	5.81	6.14
9	—N(C$_4$H$_9$-*n*)$_2$[g]	K	115–120	47	$C_{24}H_{32}KN_3O_5S$	56.1	55.8	6.28	6.58
10	—N(C$_2$H$_5$)C$_6$H$_5$[f]	K	>100	60	$C_{24}H_{24}KN_3O_5S$	57.0	56.8	4.80	4.95
11		K	165–169	54	$C_{20}H_{22}KN_3O_6S \cdot H_2O$	49.4	49.0	4.95	4.95
12		Na	130–135	60	$C_{21}H_{24}NaN_3O_5S$	55.8	55.2	5.35	5.20
13		K	160–165	86	$C_{22}H_{26}KN_3O_5S$	54.6	55.0	5.38	5.60
14		K	145–148	60	$C_{24}H_{30}KN_3O_5S \cdot H_2O$	54.5	54.1	6.10	6.05
15		K	>150	82	$C_{26}H_{26}KN_3O_5S$	58.7	58.5	4.89	5.02

FOOTNOTES TO TABLE II

[a] All compounds in the table decomposed without melting, usually with previous darkening and sintering. [b] N-Ethylphthalamic acid was reported previously by B. Sakurai, *Bull. Chem. Soc. Japan*, **5**, 184 (1930). [c] N-Allylphthalamic acid has been reported by T. B. Johnson and D. B. Jones, *Amer. Chem. Jour.*, **45**, 355 (1911). [d] N-α-Methylbenzylphthalamic acid has been reported by F. G. Mann and J. Watson, *J. Chem. Soc.*, 510 (1947). [e] N-Cyclohexylphthalamic acid has been prepared by J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, Suppl. Issue, No. 1, 577 (1949). [f] N,N-Diethyl- and N-ethyl-N-phenylphthlamic acids have been reported by V. Horák and L. Novotný, *Chem. Listy*, **46**, 357 (1952). [g] N,N-Di-*n*-butylphthalamic acid was prepared by the method of O. Westphal and M. Eucken, *Ber.*, **76**, 1137 (1943).

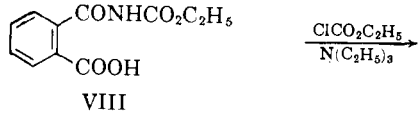


This result is not too surprising when the very recent report by Sauers and Cotter[7] is considered. These authors have shown that treatment of phthalamic acid with ethyl chloroformate and triethylamine gave rise, in excellent yield, to ethyl *o*-cyanobenzoate. The fact that they isolated the ethyl ester of *o*-cyanobenzoic acid, while we have obtained the free acid, can best be explained by a difference in experimental conditions. While their reactions were carried out in anhydrous media, our reaction conditions (see experimental section) were such that some water was introduced into the reaction mixture at a certain stage of the procedure. Furthermore, the total yields of compound VI and VII isolated from this reaction, being lower than 78%, did not exclude the possibility that some ethyl *o*-cyanobenzoate has been formed. However, no effort was made to isolate this ester from the reaction mixture.

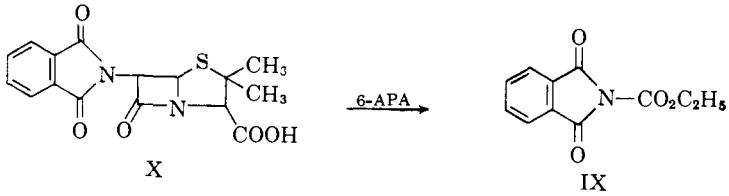
When N-carbethoxyphthalamic acid (VIII) was caused to react with 6-APA through the mixed carboxylic-carbonic anhydride procedure, 6-phthalimidopenicillanic acid (X) was obtained. This result

(7) C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).

is consistent with a recent report by Nefkens[8] who has shown that N-phthaloyl derivatives of amino acids are obtained, in high yields and under mild conditions, by treatment of these compounds with N-carbethoxyphthalimide (IX). The work of Nefkens, together with our isolation of 6-phthalimidopenicillanic acid from 6-APA and N-carbethoxyphthalamic acid, indicates that the reaction sequence VIII → IX—X is quite likely. When N-carbethoxyphthalimide



VIII



X IX

(IX) was condensed with 6-APA under the conditions prescribed by Nefkens for the N-phthaloylation of amino acids the product isolated was identical in every respect with the derivative obtained from N-carbethoxyphthalamic acid. The methyl ester of compound X, prepared by a totally synthetic route, has been described previously by Sheehan and Cruickshank.[9]

Microbiology.—Antimicrobial activity and penicillinase resistance were determined for these new penicillins. Minimum inhibitory concentrations were done using the standard two-fold serial dilution technique in heart infusion broth. The rate of destruction of various penicillins by staphylococcal penicillinase was measured by the Henry and Housewright manometric method.[10] The details of the microbiological techniques have been published previously.[11]

As can be seen from Table III, the new penicillins are less active than benzylpenicillin against the penicillin sensitive strain of *Staphylococcus aureus* (Smith) but are more active against the penicillin resist-

(8) G. H. L. Nefkens, *Nature*, **185**, 309 (1960); G. H. L. Nefkens, G. I. Tesser and R. J. F. Nivard, *Rec. Trav. Chem.*, **79**, 688 (1960).

(9) J. C. Sheehan and P. A. Cruickshank, *J. Am. Chem. Soc.*, **78**, 3680 (1956).

(10) R. J. Henry and R. D. Housewright, *J. Biol. Chem.*, **167**, 559 (1947).

(11) A. Gourevitch, G. A. Hunt, J. R. Luttinger, C. C. Carmack and J. Lein, *Proc. Soc. Exptl. Biol. and Med.*, **107**, 455 (1961).

TABLE III

MICROBIOLOGICAL PROPERTIES OF PENICILLINS

Cpd.	Minimum Inhibitory Concentrations, mcg./ml. against Smith Strain	1633-2 Strain	Rate of Destruction by Staphylococcal Penicillinase (Arbitrary Units)
1	1.6	3.1	3.7
2	1.3	3.1	0.7
3	0.8	1.6	2.2
4	3.1	3.1	0.6
5	1.6	3.1	1.2
6	2.2	3.1	0.9
7	0.8	0.8	2.9
8	3.1	6.3	0.9
9	1.6	1.6	2.2
10	0.8	1.6	8.7
11	3.1	6.3	6.5
12	1.6	1.6	—
13	1.6	6.3	2.0
14	1.6	3.1	1.9
15	1.6	3.1	0.8
Benzylpenicillin-standard	0.01	50	100

tant organism (strain 1633–2). Whereas the minimum inhibitory concentration of benzylpenicillin against strain 1633–2 is several thousand times higher than that against the sensitive strain, this ratio is only 2:4 for the new penicillins.

That this activity of the new penicillins against the resistant organisms is due to the decreased susceptibility of the penicillins to the penicillinase is indicated by the last column of this table. The rate of destruction of these penicillins by penicillinase ranges from 1/10 to 1/160 of the rate of destruction of benzylpenicillin.

Experimental[12]

N-Substituted Phthalamic Acids (II).—The procedure described below for the preparation of N-*t*-butylphthalamic acid is typical of the method used for the preparation of the compounds listed in Table I. No attempt was made to determine the conditions necessary for optimum yields. All of the amines necessary for the preparation of these compounds were obtained from commercial sources. In many cases the reaction products crystallized out of the reaction mixture and were collected by filtration. In cases where this did not occur, crystallization could be induced sometimes by scratching the wall of the reaction flask. If this also failed, the product was isolated by removal of the solvent at reduced pressure.

To a stirred suspension of 74 g. (0.5 mole) of phthalic anhydride in 200 ml. of

(12) All melting and decomposition points are uncorrected.

acetone was added dropwise, at room temperature, a solution of 36.5 g. (0.5 mole) of *t*-butylamine in 200 ml. of acetone. When the addition had been completed, the resulting warm solution was stirred at room temperature during 2 hr. The white crystalline material was collected by filtration and recrystallized from methyl isobutyl ketone. This procedure yielded 61.4 g. (56%) of pure crystalline N-*t*-butylphthalamic acid melting at 147–148°. See Table I for analysis.

Potassium 6-(N-*t*-Butyl-N'-phthalamido)-penicillanate (IV).—The following procedure illustrates the general method employed for the preparation of the compounds listed in Table II. No attempt was made to determine the conditions necessary for optimum yields.

To a stirred and cooled (−15°) solution of 22.1 g. (0.1 mole) of N-*t*-butylphthalamic acid and 14 ml. (0.1 mole) of triethylamine in 200 ml. of dry tetrahydrofuran was added, dropwise, 10.8 g. (0.1 mole) of ethyl chloroformate at such a rate as to maintain the internal temperature below −5°. When the addition had been completed the reaction mixture was stirred during 5–10 min. at below −5° and then, with vigorous stirring, a cold solution of 21.6 g. (0.1 mole) of 6-APA, 15 ml. of triethylamine and 100 ml. of water was added rapidly. The temperature rose to +5° and a copious evolution of carbon dioxide occurred. When the temperature began to fall again the cooling bath was removed and the reaction mixture was kept stirred during 2 hr. After dilution with 200 ml. of water the reaction mixture was extracted twice with 500 ml. portions of methyl isobutyl ketone (MIBK). The aqueous phase was layered with 300 ml. of MIBK, cooled in an ice bath, and slowly acidified to pH 2 with 40% sulfuric acid. The MIBK extract was washed twice with 100 ml. portions of cold water and dried briefly over anhydrous sodium sulfate. After filtration, the filtrate was treated with 40 ml. of a 50% solution of potassium 2-ethylhexanoate in 1-butanol. The resulting solid was collected by filtration, washed several times with small portions of dry acetone and dried over P_2O_5 at reduced pressure; yield, 24 g. (52%), dec. point 136–137°. In cases where the salt did not precipitate directly, the solution was concentrated *in vacuo* and upon dilution with dry ether the product was obtained as an amorphous solid.

Reaction of Phthalamic Acid (V) with 6-APA.—The procedure employed was essentially the one described above for the preparation of potassium 6-(N-*t*-butyl-N'-phthalamido)-penicillanate (IV).

The reaction was carried out with 16.5 g. (0.1 mole) of phthalamic acid, 28 ml. (0.2 mole) of triethylamine, 21.6 g. (0.2 mole) of ethyl chloroformate and 21.6 g. (0.1 mole) of 6-APA dissolved in 100 ml. of water containing 15 ml. of triethylamine. The final MIBK extract, after washing with water and drying, was treated with 40 ml. of a 50% solution of potassium 2-ethylhexanoate in 1-butanol. The crystalline solid which was formed was collected by filtration; the filtrate was saved for further work-up. The solid was dissolved in water, the solution acidified to pH 2 and the material thus obtained was recrystallized from 95% ethanol. There was obtained 8.5 g. (58%) of crystalline solid which possessed all the infrared characteristics of *o*-cyanobenzoic acid (VI); m.p. 182–183° (lit.[13] 184°).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.4; H, 3.45. Found: C, 65.8; H, 3.80.

The MIBK filtrate from the above solid was concentrated to one third its original volume. An amorphous solid (7.7 g., 20%) was isolated upon dilution of this concd. solution with dry ether. All attempts to obtain this product in an

(13) J. Scheiber, *Ber.*, **45**, 2398 (1912).

analytically pure form failed. However, the infrared spectrum of this material had all of the absorption bands expected for potassium 6-(*o*-cyanobenzamido)-penicillanate (VII). Furthermore this compound elicited some antimicrobial properties typical of 6-APA derivatives.

N-Carbethoxyphthalimide (IX).[14]—To a suspension of 95 g. (0.5 mole) of potassium phthalimide in 500 ml. of dry refluxing benzene, 64 g. (0.52 mole) of ethyl chloroformate was added dropwise. The mixture was then kept at reflux temperature during 2 hr.; after standing for 18 hr. at room temperature the potassium chloride was filtered off, washed with 100 ml. of benzene and the combined filtrates were concentrated to half volume under reduced pressure. Upon dilution with 400 ml. of boiling petroleum ether (b.p. 60–71°) and cooling, 93 g. (85%) of N-carbethoxyphthalimide deposited; m.p. 88–90° (lit.[14] 87–89°).

N-Carbethoxyphthalamic Acid (VIII).[14]—N-Carbethoxyphthalimide (93 g.) was shaken during 15 min. with 500 ml. of a 10% aqueous sodium hydroxide solution. The mixture was filtered from insoluble material and the filtrate was carefully acidified, in the cold, with 6 *N* hydrochloric acid to pH 2. The product was extracted into chloroform (3 × 300-ml. portions) and after the organic phase was washed once with 100 ml. of water it was evaporated to dryness at reduced pressure. The solid residue was recrystallized from ethyl acetate, yielding 40 g. (35%) of crystalline material melting at 119–120°. The reported melting point for this compound is 60–70°, the wide temperature range indicating that the product obtained by Heller and Jacobsohn[14] was amorphous. In our hands a crystalline compound was obtained which had an infrared spectrum consistent with structure VIII.

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.8; H, 4.68. Found: C, 55.9; H, 4.68.

6-Phthalimidopenicillanic Acid X. Procedure A. From N-Carbethoxyphthalamic Acid.—This compound was prepared by essentially the same procedure as the one described above for the preparation of potassium 6-(N-*t*-butyl-N′-phthalamido)-penicillanate (IV). From 23.7 g. (0.1 mole) of N-carbethoxyphthalamic acid, 10.8 g. (0.1 mole) of ethyl chloroformate, 14 ml. (0.1 mole) of triethylamine and 21.6 g. (0.1 mole) of a 6-APA solution in water containing 14 ml. of triethylamine, 14 g. (30%) of potassium 6-phthalimidopenicillanate was obtained. This potassium salt was dissolved in a water–acetone mixture (3:1) and the stirred solution was acidified slowly with 6 *N* hydrochloric acid. The white crystalline solid thus obtained was collected by filtration and recrystallized from acetone. This procedure afforded 10 g. (29%) of pure 6-phthalimidopenicillanic acid melting at 178–180° dec.

Anal. Calcd. for $C_{16}H_{14}N_2O_5S$: C, 55.5; H, 4.05; N, 8.09. Found: C, 55.6; H, 4.10; N, 8.03.

Procedure B. From N-Carbethoxyphthalimide.—To a stirred solution containing 21.6 g. (0.1 mole) of 6-APA, 16.8 g. (0.2 mole) of sodium bicarbonate, 200 ml. of water and 100 ml. of acetone was added, in one portion, 21.9 g. (0.1 mole) of N-carbethoxyphthalimide. After stirring during 1 hr. an almost clear solution was obtained. After the removal of a small amount of insoluble material by filtration, the cooled and stirred filtrate was slowly acidified with 40% aqueous phosphoric acid. The crystalline solid thus formed was filtered off, washed with cold water and recrystallized from acetone; yield 21 g. (61%), m.p. 178–180°.

Anal. Found: C, 55.4; H, 4.15; N, 8.10.

(14) G. Heller and P. Jacobsohn, *Ber.*, **54**, 1107 (1921).

The infrared spectrum of this material was superimposable upon the spectrum obtained from the product of procedure A described above.

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N(α-D-Penicilloyl) Amines as Univalent Hapten Inhibitors of Antibody-Dependent Allergic Reactions to Penicillin[1]

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A series of N-(α-D-penicilloyl) amines (α-diastereoisomers) was prepared by reaction of penicillins (benzylpenicillin, dimethoxyphenylpenicillin, and allylmercaptomethylpenicillin) with various amines. Methods for the preparation of diastereoisomeric mixtures of these penicilloyl amines, and a spectrophotometric method for their quantitative assay are given. Quantitative comparative data were obtained showing the diastereoisomeric mixtures of the penicilloyl amines to be capable of specifically inhibiting the *in vivo* and *in vitro* reactions of rabbit anti-penicillin antibodies with a conjugated penicillin antigen (benzylpenicilloyl-human *gamma*-globulin). These data suggest that these penicilloyl amine haptens may be useful as therapeutic agents to prevent and treat antibody-dependent allergic reactions to penicillin in man.

In previous studies on the mechanism of antigenicity of benzylpenicillin, the diastereoisomeric mixture of ε-N-(α-D-benzylpenicilloyl)-lysine groups (IIi) (which are finally formed by the reaction of benzylpenicillin with lysine ε-amino groups of tissue proteins) were identified as the major antigenic determinants responsible for allergy to benzylpenicillin.[3-5] The diastereoisomeric mixture of ε-N-(α-

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