Derivatives of 6-Aminopenicillanic Acid. VI. Synthesis of Some Derivatives of 6-Aminothiopenicillanic Acid[1]

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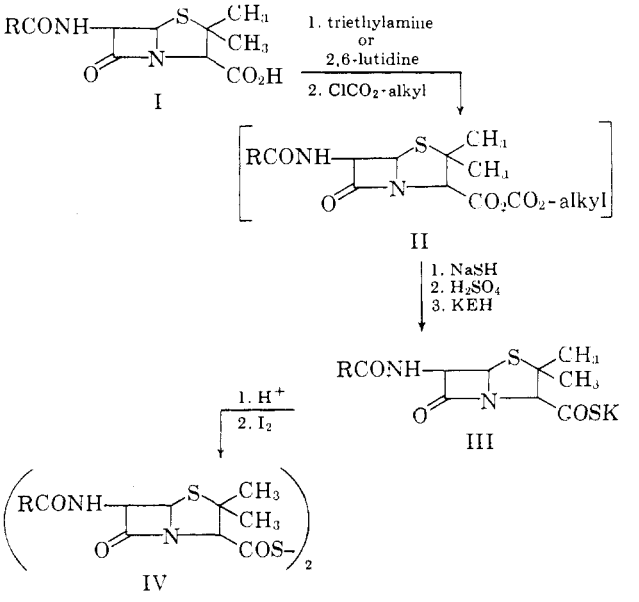
Mixed alkoxyformic anhydrides (II) of various penicillins (I) have been converted into the corresponding N-acylated 6-aminothiopenicillanic acids (III)[4] by treatment with NaSH. These penicillin thioacids have been oxidized to the corresponding amorphous bis(acyl) disulfides (IV) by means of iodine, and one representative disulfide has been described. In general, the penicillin thioacids and their corresponding disulfides are potent antimicrobial agents.

Several thiol esters of benzylpenicillin have been prepared in satisfactory yields by the interaction of thiols with benzylpenicillinic ethoxyformic anhydride.[5,6] Treatment of this mixed anhydride with H_2S in the presence of 1 equiv. of triethylamine, however, gave only intractable products instead of the expected thioacid.[7] When the amount of triethylamine used in the reaction was reduced to a few drops, the only product isolated was a 69% yield of the corresponding crystalline benzylpenicillinic thioanhydride.[7] In 1956, Johnson and Sheehan were successful in obtaining benzylpenicillin thioacid[8] by passing H_2S into a solution of benzylpenicillinic ethoxyformic anhydride in *the absence* of free organic base. Subsequently, the interesting antimicrobial properties of benzylpenicillin thioacid (Table I, **5**) prompted us to convert a variety of the penicillins[9] of therapeutic interest into the corresponding thioacids[10] in order to ascertain the effects of side-chain alterations on the microbiological activities of the penicillin thioacids.

In this communication is described an improved procedure of general application for preparing 6-acylaminothiopenicillanic acid derivatives as pictured in Scheme I.

Thus, a solution of the appropriate penicillin (I) in the form of the free acid in pure dry dimethylformamide (DMF) cooled below 0° was treated with exactly 1 equiv. of 2,6-lutidine or triethylamine. Then ethyl or isobutyl chloroformate was added and the reaction mixture was stirred at 0° or below for 10–20 min. The resulting mixed anhydride (II) was then treated with purified NaSH dissolved in DMF and added in one portion. After stirring for 10–45 min., the mixture was

SCHEME I



acidified to pH 2 with dilute H_2SO_4 with cooling and extracted with cold ether. The washed and dried ether extracts were treated with potassium 2-ethylhexanoate (KEH) to precipitate the salt of the thioacid (III) which was crystallized whenever possible. The amorphous alkali salts were purified by conversion into the corresponding N,N′-dibenzylethylenediamine (DBED) salts. The infrared and n.m.r. spectra are reported in detail for **7** and are representative for the whole group.

Bis(6-phenylmercaptoacetamidopenicillanyl) disulfide (**14**) was prepared from potassium 6-(phenylmercaptoacetamido)thiopenicillanate (**7**) and iodine in a mixture of ether and dilute HCl at pH 2.5. The disulfides were not obtained in crystalline form but were characterized by infrared and n.m.r. spectra and by microanalyses. The spectra of **14** are typical for the series of disulfides.

Microbiological Evaluation.—The compounds described here, and various analogs not obtained in analytically pure form, were evaluated by Dr. Joseph Lein and his associates in the Microbiology Department. Details of the techniques used have been published.[11] Minimum inhibitory concentrations (MIC) were determined by the standard 2-fold serial dilution tech-

(1) For paper V in this series see 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).

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(4) The simplified nomenclature is based on the convenient and generally accepted trivial system of J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3292 (1953).

(5) D. A. Johnson, *ibid.*, **75**, 3636 (1953).

(6) R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jansen, M. E. Trevett, and G. B. Webb, *J. Chem. Soc.*, 3733 (1953).

(7) R. M. Evans and A. B. A. Jansen, *ibid.*, 4037 (1954).

(8) D. A. Johnson and J. C. Sheehan, U. S. Patent 2,751,378 (1956); *Chem. Abstr.*, **51**, 4438 (1957).

(9) For an excellent review of penicillins and related structures see F. P. Doyle and J. H. C. Nayler, "Advances in Drug Research," Vol. 1, N. J. Harper and A. B. Simmonds, Ed., Academic Press Inc., New York, N. Y., 1964, pp. 1–69.

(10) For a review of thioacids and derivatives see E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, pp. 7–130.

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

nique in heart infusion broth in the absence of serum and in the presence of 50% pooled human serum. The inocula used to obtain the data in Table I were 10^4 dilutions of 18-hr. cultures. For comparison, the MIC values for the corresponding penicillins have been enclosed in parentheses and placed in the table. It is evident from the MIC data in Table I that the penicillin thioacids and the representative disulfide **14** derived from the thioacid **7** all possess high antimicrobial activity against the penicillin-sensitive Smith strain of *Staphylococcus aureus*. Some show significant activity against penicillin-resistant *S. aureus* strain 1633-2.[12]

Experimental Section[13]

Potassium 6-(Phenylmercaptoacetamido)thiopenicillanate (7).—The following procedure illustrates the general method used to prepare the penicillin thioacids listed in Table I with the exception of potassium 6-(phenylacetamido)thiopenicillanate (benzylpenicillin thioacid) (**5**).

A mixture of 12.1 g. (0.03 mole) of potassium 6-(phenylmercaptoacetamido)penicillanate[14,15] and 6.2 g. (0.040 mole) of triethylammonium chloride was stirred for 0.5 hr. at 25° in 420 ml. of CH_2Cl_2. The KCl was removed by filtration and the solvent was evaporated under reduced pressure at 30° to a gummy residue which was dissolved in 150 ml. of DMF. The solution was cooled to 0° and 3.3 g. (0.030 mole) of ethyl chloroformate was added and stirred for 10 min. A solution of 6.7 g. (0.06 mole) of purified NaSH (Fisher) in 75 ml. of DMF was added all at once and the stirring was continued for 0.5 hr. The DMF solution was poured into 1.1 l. of ice water and acidified with 6 *N* H_2SO_4 to pH 2. The mixture was extracted three times with 500 ml. of ether. The ether extracts were washed with water, dried (Na_2SO_4), and treated with 12 ml. (0.03 mole) of 50% potassium 2-ethylhexanoate (KEH) in ether. The crystals were collected, washed with acetone, and dried (P_2O_5) for 1 hr. at 1 mm. to obtain 7 g. of product. See Table I for analysis and properties. The infrared spectrum (KBr) showed absorptions (in $cm.^{-1}$) at 3325 (amide NH), 1780 with a shoulder at 1762 (β-lactam carbonyl), 1661 (amide carbonyl), 1540 (thiocarboxylate), and 741 and 690 (monosubstituted phenyl).

The n.m.r. spectrum of a D_2O solution had absorptions which were assigned as follows: a singlet at δ 7.32 due to the 5 aromatic protons, a doublet of spacing 4.5 c.p.s. at 5.66 due to the C-6 proton coupled to the C-5 proton, a corresponding doublet (J = 4.5 c.p.s.) at 5.51 due to the C-5 proton, a singlet at 4.60 from the C-3 proton, a singlet at 3.77 due to the methylene protons, and a singlet at 1.53 from the 6 protons of the *gem*-dimethyl groups.

It was not uncommon for the alkali salts of the thioacids to resist crystallization. In such cases a 0.5 molar equiv. of N,N'-dibenzylethylenediamine (DBED) diacetate was dissolved in water and added to an aqueous solution of the thiopenicillanate. The resulting mixture was adjusted to pH 6 by the addition of glacial acetic acid. The thioacid salt was collected and recrystallized as indicated in Table I. In Table I compounds **3**, **4**, and **14** were not obtained in crystalline form but were purified by trituration with the appropriate solvent.

Potassium 6-(Phenylmercaptoacetamido)penicillanate.—This biosynthetic penicillin[15] was prepared in 62% yield by the procedure (method A) outlined by Perron, *et al.*,[16] using phenylmercaptoacetyl chloride and 6-aminopenicillanic acid; m.p. 220–221° dec.

Anal. Calcd. for $C_{16}H_{15}KN_2O_4S_2$: C, 47.50; H, 4.24. Found: C, 47.31; H, 4.45.

Sodium 6-(*p*-Methoxyphenylmercaptoacetamido)penicillanate.[15]—A solution of *p*-methoxyphenylmercaptoacetyl chloride in 70 ml. of methylene chloride, prepared by treating 8.4 g. (0.05 mole) of *p*-methoxyphenylmercaptoacetic acid with an excess of redistilled $SOCl_2$ under reflux for 1 hr., was added dropwise to a solution of 10.8 g. (0.05 mole) of 6-aminopenicillanic acid and 14.1 ml. (0.1 mole) of triethylamine in 180 ml. of CH_2Cl_2 at 0°. The mixture was stirred at 10–15° for 0.5 hr. and shaken with 16 ml. of 6 *N* H_2SO_4 and 164 ml. of water at 5°. The methylene chloride layer was separated and the aqueous extract was washed twice with 150 ml. of ether. The organic extracts were combined, washed with water, and dried (Na_2SO_4). The filtrate was treated with 2.5 g. of decolorizing carbon (Darco KB), and the penicillin was precipitated by adding 20 ml. of 40% sodium 2-ethylhexanoate in 1-butanol. The light yellow crystals, m.p. 194–198° dec., were collected and weighed 9.2 g. (46%) after drying overnight over P_2O_5.

Anal. Calcd. for $C_{17}H_{19}N_2NaO_5S_2$: C, 48.79; H, 4.58. Found: C, 48.87; H, 4.84.

Potassium 6-(Phenylacetamido)thiopenicillanate (5).—An aqueous solution of 9.3 g. (0.025 mole) of potassium 6-(phenylacetamido)penicillanate (potassium penicillin G) was stirred with 30 ml. of methylene chloride while being adjusted to pH 2.0. The organic layer was dried (Na_2SO_4) and then diluted with 80 ml. of DMF and 3.4 ml. (3.2 g., 0.030 mole) of 2,6-lutidine. The resulting solution was cooled to −3° and 3.9 ml. (4.1 g., 0.030 mole) of isobutyl chloroformate was added with stirring. After 15 min., the cold mixture was added to a cold solution of 5.6 g. (0.1 mole) of NaSH in 50 ml. of DMF which was previously dried with Molecular Sieves (Linde 4A). The dark brown mixture was stirred and allowed to warm to room temperature (about 30 min.). It was then added to a cold mixture of 550 ml. of water and 300 ml. of methylene chloride. With stirring in an ice bath, the two-phase mixture was adjusted from pH 7.0 to 2.0 with 20% HCl. The methylene chloride layer was separated, dried, and treated with 19.3 ml. of a 27.5% solution of KEH in methyl isobutyl ketone (MIBK). The mixture was stirred in an ice bath for 45 min. and filtered to give 4.7 g. (48%) of colorless prisms. See Table I for analysis and properties.

Diastereoisomers of Potassium 6-(α-Phenoxypropionamido)penicillanate.—Both epimers of phenethicillin were prepared as described by Perron, *et al.*,[16] with the exception that dehydroabietylamine was used advantageously as the resolving agent for obtaining (+)-α-phenoxypropionic acid.[17]

Potassium 6-[(−)-α-Phenoxy-*n*-butyramido]penicillanate.—Potassium 6-(DL-α-phenoxy-*n*-butyramido)penicillanate as reported by Perron, *et al.*,[15] was prepared by the addition of 48.3 g. (0.245 mole) of DL-α-phenoxy-*n*-butyryl chloride in 100 ml. of acetone to a solution of 52.8 g. (0.245 mole) of 6-aminopenicillanic acid and 61.7 g. (0.734 mole) of $NaHCO_3$ in 370 ml. of water and 270 ml. of acetone at 5°. The mixture was stirred for 10 min. and extracted twice with MIBK. To the aqueous phase was added 500 ml. of MIBK and the mixture was acidified to pH 2 with 42% phosphoric acid. The organic layer was separated and the aqueous phase was extracted again with MIBK. To the combined extracts was added 96 ml. (0.24 mole) of a solution of KEH in 1-butanol. The clear solution was evaporated under reduced pressure (water pump) on a rotary evaporator at 40° until the salt crystallized. The crystals were collected by filtration, washed with MIBK and acetone to obtain 26.6 g. (26.1%), m.p. 210–212° dec., $[\alpha]^{24}D$ +204° (*c* 0.994, water), lit.[18] $[\alpha]^{25}D$ +202° (*c* 1.58, water). Further recrystallization failed to change the rotation.

Potassium 6-[(+)-α-Phenoxy-*n*-butyramido]penicillanate.—The MIBK filtrate obtained from the previous experiment was extracted twice with 500 ml. of water. To the aqueous extracts was added a solution of 30 g. (0.085 mole) of DBED diacetate in 250 ml. of water. The salt was collected, washed with water, and air dried. After recrystallization with 800 ml. of methanol and 500 ml. of water, 25 g. of white crystals were obtained, m.p. 107–112° dec. The salt was suspended at pH 2 in 300 ml. of dilute phosphoric acid and 300 ml. of MIBK. The mixture was shaken vigorously until all of the solid had dissolved. The MIBK solution was separated and washed with water, a solution

(12) More complete microbiological aspects will be presented in a forthcoming paper by J. A. Bach, T. Pursiano, A. Gourevitch, and J. Lein.

(13) All decomposition points are uncorrected and were determined as indicated in Table I. The infrared spectra were recorded on a Beckman IR 9 spectrometer. The n.m.r. spectra were obtained in deuterium oxide or deuteriochloroform solution with tetramethylsilane as a reference using a Varian A-60 spectrometer. Optical rotations were determined on a Rudolph polarimeter.

(14) Described below.

(15) O. K. Behrens, R. G. Jones, Q. F. Soper, and J. W. Corse, U. S. Patent 2,623,876 (1952); *Chem. Abstr.*, **47**, 2944 (1953).

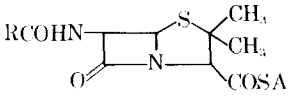
(16) Y. G. Perron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **82**, 3934 (1960).

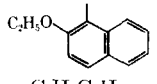
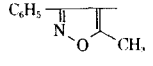
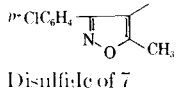
(17) W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, **30**, 2072 (1965).

(18) Eli Lilly and Co., British Patent 924,037 (1963); *Chem. Abstr.*, **59**, 8757 (1963).

TABLE 1

DERIVATIVES OF 6-AMINOTHIOPENICILLANIC ACID



Compd.	R	A	Pen.[a]	Solvent[b]	Dec. pt., °C.[c]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	MIC, γ/ml., *vs. S. aureus*[d,e] —— Sensitive - - - : (−) Serum	(+) Serum	—— Resistant — ·-·: (−) Serum	(+) Serum
1	$C_6H_5OC(CH_3)H$ (−) isomer	K	*f*	AqB	212–213 (FJ)	63	$C_{17}H_{19}KN_2O_4S_2$	48.77	49.15	4.57	4.72	0.029 (0.031)	0.062 (0.062)	1.2 (>100)	4.6 (>100)
2	$C_6H_5OC(CH_3)H$ (+) isomer	K	*f, g*	AqB	195–196 (FJ)	32	$C_{17}H_{19}KN_2O_4S_2$	48.77	49.25	4.57	4.62	0.13 (0.031)	0.25 (0.13)	6.3 (75)	6.3 (>75)
3	$C_6H_5OC(C_2H_5)H$ (−) isomer	K	*h, i*	AmE	140 (OC)	57	$C_{18}H_{21}KN_2O_4S_2$	49.97	49.95	4.89	5.05	0.093 (0.062)	1.9 (0.13)	0.8 (>100)	4.0 (>100)
4	$C_6H_5OC(C_2H_5)H$ (+) isomer	K	*h, i*	AmE	135 (OC)	66	$C_{18}H_{21}KN_2O_4S_2$	49.97	50.10	4.89	4.96	0.093 (0.062)	0.36 (0.062)	3.1 (25)	6.3 (25)
5	$C_6H_5CH_2$	K	*j*	MC	179–180 (OC)	31	$C_{16}H_{17}KN_2O_4S_2{\cdot}0.5H_2O$	48.34	48.24	4.56	4.51	0.012 (0.012)	0.031 (0.024)	37 (>100)	37 (>100)
6	$C_6H_5OCH_2$	K	*j*	AqB	196–207 (KS)	44	$C_{16}H_{17}KN_2O_4S_2$	47.50	47.59	4.24	4.18	0.016 (0.04)	0.13 (0.16)	75 (6.25)	75 (25)
7	$C_6H_5SCH_2$	K	*h, k*	AqB	220–223 (KS)	55	$C_{16}H_{17}KN_2O_3S_3$	45.68	45.88	4.07	4.02	0.012 (...)	0.062 (...)	100 (1.6)	100 (25)
8	*p*-$CH_3OC_6H_4SCH_2$	K	*h, k*	AqB	212–214 (KS)	16	$C_{17}H_{19}KN_2O_4S_3{\cdot}0.5H_2O$	44.42	44.48	4.39	4.28	0.016 (0.05)	0.20 (0.2)	40 (25)	25 (25)
9		K	*l*	Ac	88–95 (OC)	13	$C_{21}H_{21}KN_2O_4S_2{\cdot}2H_2O$	49.98	50.40	4.99	4.72	0.19 (0.2)	3.1 (1.6)	0.4 (0.40)	4.1 (6.3)
10	*o*-$C_6H_5C_6H_4$	D[g]	*m*	Ac-M	114–117 (OC)	20	$C_{58}H_{60}N_6O_6S_4$	65.38	65.58	5.68	5.66	0.12 (0.4)	1.6 (1.6)	0.8 (0.8)	4.5 (1.6)
11	2,6-$(CH_3O)_2C_6H_3$	D[h]	*o*	M	125 (OC)	25	$C_{50}H_{50}N_6O_{10}S_4$	57.11	56.95	5.85	5.65	1.0 (1.25)	6.3 (1.25)	3.1 (2.5)	4.5 (2.5)
12		D[i]	*p*	W	85–90 (FJ)	45	$C_{51}H_{58}N_8O_8S_4{\cdot}3H_2O$	57.42	57.50	5.71	5.75	0.13 (0.062)	3.1 (0.8)	0.4 (0.4)	6.3 (1.6)
13		D[k]	*q*	M	131–133 (OC)	26	$C_{54}H_{56}Cl_2N_8O_8S_4{\cdot}H_2O$	55.80	55.60	5.03	5.21	0.25 (0.2)	9.4 (3.1)	0.6 (0.4)	6.3 (3.1)
14	Disulfide of 7			Am	88–90 (FJ)	75	$C_{32}H_{34}N_4O_6S_6$	50.37	50.20	4.49	4.55	0.062	1.0	63	>50

[a] Ref. to starting penicillin (Pen.). [b] Solvent for recrystallization: AqB, aqueous 1-butanol; AmE, amorphous compound triturated with ether; MC, CH_2Cl_2; Ac, acetone; Ac-M, acetone-methanol; M, crystals triturated with methanol; W, crystals washed with water; Am, amorphous product from ether. [c] Decomposition point determined on a Fisher-Johns apparatus (FJ), in open capillaries (OC), or on a Kofler hot stage microscope (KS). [d] Average of two determinations. [e] For comparison, the MIC values for the corresponding penicillins are placed in parentheses. [f] Ref. 16. [g] Ref. 17. [h] Ref. 14. [i] Ref. 18. [j] Commercially available. [k] Ref. 15. [l] E. G. Brain, F. P. Doyle, M. D. Mehta, D. Miller, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, 491 (1963). [m] A. Courevitch, C. T. Holdrege, G. A. Hunt, W. F. Minor, C. C. Flanigan, L. C. Cheney, and J. Lein, *Antibiot. Chemotherapy*, **12**, 318 (1962). [n] D = neutral salt of *N,N'*-dibenzylethylenediamine. [o] F. P. Doyle, J. H. C. Nayler, and G. N. Rolinson, U. S. Patent 2,951,839 (1960); *Chem. Abstr.*, **55**, 4535 (1961). [p] F. P. Doyle and J. H. C. Nayler, U. S. Patent 2,996,501 (1961); *Chem. Abstr.*, **56**, 5971 (1962). [q] F. P. Doyle, J. C. Hanson, A. A. W. Lang, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, 5838 (1963).

of KEH (20 ml., 0.05 mole) in 1-butanol was added, and the MIBK was evaporated at reduced pressure (water pump) at 40° on the rotary evaporator to give 5.5 g. (38%) of white crystals after drying *in vacuo* (P_2O_5); $[\alpha]^{24}D$ +229° (*c* 1.02, water). A direct comparison of the n.m.r. spectrum of this specimen with the n.m.r. spectrum of pure potassium 6-[(+)-α-phenoxypropionamido]penicillanate[16] indicated essential optical purity.

Anal. Calcd. for $C_{18}H_{21}KN_2O_5S \cdot H_2O$: C, 49.75; H, 5.33. Found: C, 49.40; H, 5.18.

Bis(6-phenylmercaptoacetamidopenicillanyl) Disulfide (14).—To 105 mg. (0.25 mmole) of potassium 6-(phenylmercaptoacetamido)thiopenicillanate dissolved in 10 ml. of water was added concentrated HCl to pH 2.5. The solution was layered with 10 ml. of ether and treated with 2 ml. of 0.1 *N* iodine in ether. The ether was washed with 2% aqueous $NaHCO_3$ solution and finally with water and dried ($MgSO_4$). The ether was evaporated and the residue was dried *in vacuo* (0.1 mm.) for 17 hr. to yield 70 mg. (75%) of amorphous solid. See Table I for analysis and properties. The major infrared absorptions (in $cm.^{-1}$) in KBr were a broad absorption near 3370 (includes the amide NH), 1798 (β-lactam carbonyl), 1731 and 1715 (penicillanic acid disulfide carbonyl), 1685 (amide carbonyl), and 740 and 690 (monosubstituted phenyl). The n.m.r. spectrum of a solution of the disulfide in $CDCl_3$ had absorption peaks which were assigned as follows: a doublet of spacing 9 c.p.s. at δ 7.59 due to the amide proton which is coupled to the C-6 proton, a singlet at 7.36 due to the 5 aromatic protons, a quartet centered at 5.84 ascribed to the C-6 proton which is coupled to the amide proton (J = 9 c.p.s.) and to the C-5 proton (J = 4.5 c.p.s.), the C-5 proton gave rise to a doublet of spacing 4.5 c.p.s. at 5.55, a singlet at 4.37 due to the C-3 proton, a singlet at 3.68 from the protons of the methylene group, and singlets at 1.60 and 1.51 due to the *gem*-dimethyl protons.

Acknowledgments.—We wish to express our thanks to David F. Whitehead and Albert Vulcano for the interpretation of the infrared and n.m.r. spectra and to R. M. Downing and C. Kalinowski for the elemental analyses. For the microbiological data we are indebted to Dr. Joseph Lein, Dr. Alexander Gourevitch, Dr. John A. Bach, and their associates.

Studies on 2-(α-Hydroxybenzyl)benzimidazole (HBB) Analogs. I. Synthesis of 8-(α-Hydroxybenzyl)purines, the Diaza Analogs of HBB[1a,b]

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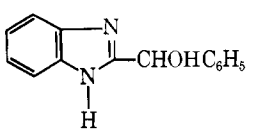
The antiviral activity displayed by a number of 2-(α-hydroxybenzyl)benzimidazoles (HBB) and several purines has initiated the synthesis of some 8-(α-hydroxybenzyl)purines. These compounds were prepared by the cyclization of 4-amino-5-(acetylmandelamino)pyrimidines which were in turn prepared by the reaction of 4,5-diaminopyrimidines with acetylmandelyl chloride. Preliminary testing results of these diaza analogs of HBB against Sarcoma 180 and KB cell culture are reported. 8-(α-Hydroxybenzyl)purine was found to be inactive against type 1 and 2 polio virus *in vitro*.

The interesting biological activity of 2-(α-hydroxybenzyl)benzimidazole (HBB, I), which suppresses poliomyelitis virus infection in mice, was first described in 1958.[2] Later, Tamm, *et al.*,[3] reported that HBB and its 6-chloro derivative showed selective inhibition against type 2 polio virus. Recently, O'Sullivan and Wallis[4] showed that 1-alkyl-substituted HBB compounds had powerful activity in tissue culture against types 1, 2, and 3 polio virus and possessed protection to ERK cells against the cytopathogenicity of entero viruses. Compounds of this type have been shown to inhibit the synthesis of virus-directed RNA polymerase,[5] of viral RNA,[6] and viral coat protein.[6a]



I

Much light has been cast on structure–activity relationships in this series of compounds.[3,4,7,8] Hydrogen bonding and metal chelation have also been investigated. From the information available at present, it appears that the α-hydroxybenzyl moiety in I is not only of fundamental importance but rather specific for the virus inhibitory action of HBB. 2-Hydroxymethyl and 2-(α-hydroxyethyl) derivatives of benzimidazole, for instance, were inactive.[3] The corresponding 2-benzoyl and 2-benzyl derivatives were less active with little selectivity of action.[3] The fact that 2-(*o*-hydroxybenzyl)benzimidazole (II) possesses similar antiviral activities but the isomeric *p*-hydroxy derivative failed to do so[9] indicated that the existence of intramolecular hydrogen bonding and/or steric requirements[10] plays an important role in this type of

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