The base afforded a yellow picrate from EtOH; mp 178°, mmp 177–178° with the authentic bufotenine dipicrate, remaining undepressed. The N_b-oxide was crystallized from Me_2CO–EtOH as rods, mp 217° (lit.[11] mp 217°).

Bufotenidine.—MeOH washings of the alumina column on evaporation left a brown basic gum (2.3 g), R_f 0.18 (as the major area of intensity with both Dragendorff and Ehrlich reagents) plus three other spots, R_f 0.0, 0.08, and 0.22. The major component was separated by preparative tlc over silica gel G using MeOH as the developer; R_f 0.16; uv, λ_{max} 218–220 and 284–288 mμ; red picrate from aqueous EtOH; mp 198–200°, mmp 198–200° (lit.[7] mp 198°) with authentic bufotenidine picrate, remaining undepressed.

A portion of the basic gum was directly converted to the picrate. The picrate was crystallized from aqueous EtOH as red needles, mp 198°. *Anal.* Calcd for $C_{13}H_{18}N_2O \cdot C_6H_3N_3O_7$: N, 15.67. Found: N, 15.82.

The base hydriodide crystallized from EtOH as light gray needles, mp 209–210°, mmp 209–210° with bufotenine methiodide, remaining undepressed. *Anal.* Calcd for $C_{13}H_{18}N_2O \cdot HI$: N, 8.09. Found: N, 7.93.

Fraction C. Water-Soluble Bases.—The pink reineckate complex, mp 168–170° dec, was dissolved in Me_2CO and passed through a column of De-acidite FF (pH 8).[12] The EtOH eluates on evaporation yielded a crystalline alkaloid (0.44 g), R_f 0.06 (plus two other minor components, R_f 0.16 and 0.31).

Dehydrobufotenine.—The crystalline compound, obtained above, had a double melting point, 202 and 217°, R_f 0.06 (paper) and 0.04 (tlc). The compound was identified as dehydrobufotenine,[6,7] mp 198 and 218°, on the basis of its physical and chemical properties and those of its salts; uv, λ_{max} 218–220 mμ (log ε 4.55) and 285 (3.98); violet color with α-nitroso-β-naphthol reagent;[5] and negative Jepson and Stevens test[10] for N_b-unsubstituted tryptamines. *Anal.* Calcd for $C_{12}H_{14}N_2O \cdot H_2O$: C, 65.45; H, 7.27; N, 12.72. Found: C, 64.98; H, 6.99; N, 12.81.

The HCl salt crystallized from EtOH as needles, mp 237–238° (lit.[7] mp 237–238°), and the HI salt crystallized from aqueous EtOH as light gray rods, mp 243–245° (lit.[7] mp 243–245°).

The picrate crystallized from aqueous EtOH as yellow needles, mp 182–184° (lit.[7] mp 183–184°). *Anal.* Calcd for $C_{12}H_{14}N_2O \cdot C_6H_3N_3O_7$: N, 16.27. Found: N, 15.98.

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The Reaction of Benzylpenicillenic Acid with Thiol-Containing Compounds. The Formation of a Possible Penicillin Antigenic Determinant[1]

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It has been shown that the penicilloyl determinant in penicillin allergy can be formed by the reaction of the penicillin degradation product, benzylpenicillenic acid, with free amino groups in proteins. This study was conducted to determine whether benzylpenicillenic acid could react similarly with another functional group in proteins, the SH group. The reactivity of benzylpenicillenic acid at pH 7.5 was measured spectrophotometrically and was found to be ten times greater with compounds having free sulfhydryl groups than those having free amino groups. Experiments using compounds with missing or blocked SH groups indicated the sulfhydryl group was the reactive species and suggested the possible formation of a product different from those reported previously. Tlc of the products of the reaction of benzylpenicillenic acid and ethanethiol at pH 7.5 disclosed the presence of four components. Characterization of these components by nmr and mass spectrometry revealed that they are stereoisomers of the thiol ester of benzylpenicilloic acid, α-ethylthiobenzylpenicilloate. These results indicate that benzylpenicillenic acid can react with free SH groups of protein to form thioesters in much the same way it reacts with free amino groups to form amides.

In allergenic responses to simple compounds it is known that irreversible binding to protein is necessary for the simple chemical compound to sensitize and elicit an allergic reaction. Benzylpenicillenic acid, which forms spontaneously from benzylpenicillin,[2a] can react irreversibly with proteins[2b] and is believed to play a role in penicillin allergy.[3,4]

It has been demonstrated that penicilloyl compounds may be formed by reaction of either penicillenic acid[5,6] or by direct interaction of penicillin[7–9] with free amino groups of protein. The penicilloyl group is believed to be the major antigenic determinant in penicillin allergy.[10,11]

The present work is a study of the reactivity of benzylpenicillenic acid with another functional group found in proteins, the sulfhydryl group. Cysteine, N-acetylcysteine, serine, penicillamine, homocysteine, methionine, glutathione, ε-aminocaproic acid, 2-mercaptoethanol, and ethanethiol serve as model compounds for free amino groups and free as well as blocked SH groups of proteins. The reactivity of penicillin and penicillenic acid with these model compounds is compared, the implication being that penicillenic acid reacts with free SH groups of proteins to form thioesters in much the same way it reacts with free amino groups to form amides. The possibility that the product of this reaction, a penicilloyl thioester, may be a determinant of penicillin allergy is discussed.

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Results

The reaction of benzylpenicillenic acid at pH 7.50 was studied by noting the rate of change of the uv absorption spectrum at 322 mμ in 1.000-cm quartz cells in a Beckman DB spectrophotometer equipped with a thermostated cell compartment. The hydrolysis proceeds as a first-order reaction with a half-life interval of $T_{1/2}$ = 7.28 min at 37° (Table I). The main product of this reaction is benzylpenicilloic acid.[12] The presence of excess of certain compounds containing a nucleophilic species in the reaction mixture, providing additional pathways of reactivity, influences the rate of disappearance of benzylpenicillenic acid. Table I lists the model

TABLE I

THE REACTION OF BENZYLPENICILLENIC ACID WITH THIOL-CONTAINING COMPOUNDS[a]

Compd present in reaction mixture[b]	k_1 min^{-1} [c]	$T_{1/2}$, min[d]
...	0.0914	7.58
ε-Aminocaproic acid	0.0956	7.25
Serine	0.0930	7.46
Methionine	0.0861	8.05
N-Acetyl-L-cysteine	1.14	0.609
Cysteine	1.25	0.555
Homocysteine	0.911	0.762
Glutathione	1.20	0.577
Penicillamine	0.798	0.870
2-Mercaptoethanol	1.01	0.694

[a] Conditions: pH 7.50 0.1 *M* phosphate buffer, 37°, 3.0×10^{-5} *M* benzylpenicillenic acid. [b] 1×10^{-2} *M*. [c] $-$d(penicillenic acid)/t = k_1(penicillenic acid). Pseudo-first-order rate constant, an average of 3–5 runs all agreeing within 5%. [d] Half-life.

compounds. The concentration of compound used exceeded that of acid by a factor of 1000, enabling the use of pseudo-first-order rate kinetics. Results of the kinetic studies indicate the rate of reaction of benzylpenicillenic acid with compounds that have SH groups (N-acetylcysteine, cysteine, homocysteine, glutathione, penicillamine, and 2-mercaptoethanol) is ten times faster than that of compounds which lack the group or in which the group is blocked (ε-aminocaproic acid, serine, methionine). The presence of amino groups under the same conditions does not cause such rapid reactivity.

Ethanethiol was used as a model to examine reactions between benzylpenicillenic acid and free SH-containing compounds. The kinetics of the reaction under the conditions outlined (Table I) indicate k_1 = 0.560 min^{-1} and $T_{1/2}$ = 1.24 min. In a typical experiment a solution of ethanethiol in phosphate buffer pH 7.50 was added to benzylpenicillenic acid. The molar ratio of ethanethiol to penicillenic acid was 100:1. After less than 1 hr at room temperature all traces of the acid had disappeared. The reaction product was isolated and then methylated by treating it with CH_2N_2 (Et_2O). Tlc revealed the presence of four components. Figure 1 illustrates the column chromatographic separation of these components.

Characterization of the reaction product was accomplished in the following manner. The important nmr spectral shifts of β-methyl benzylpenicilloate and α,β-dimethyl benzylpenicilloate are illustrated in Table II. One of the components, the fastest moving (Figure 1), of

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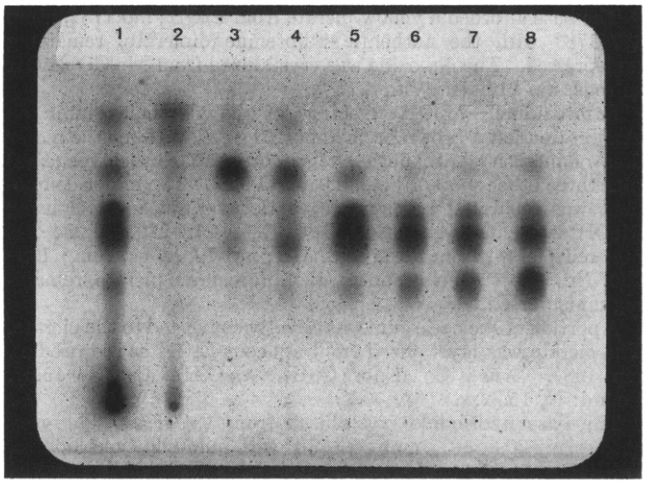
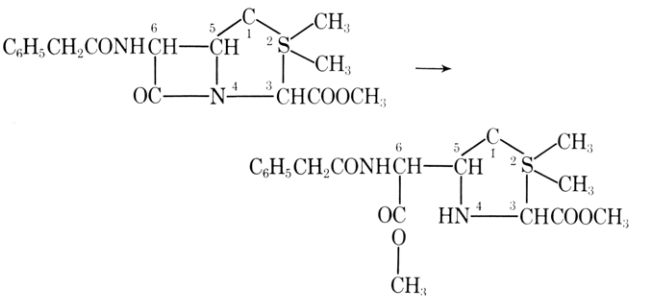


Figure 1.—Thin layer chromatogram (silica gel, ethyl acetate–benzene (30:70), iodine developer) of fractions collected in the column chromatographic separation of the products of the reaction of benzylpenicillenic acid with ethanethiol after treatment with diazomethane: 1 = initial reaction mixture, 2 = fractions 446–550, 3 = fractions 551–609, 4 = fractions 610–699, 5 = fractions 700–725, 6 = fractions 726–749, 7 = fractions 750–774, 8 = fractions 775–800.

TABLE II

PROTON CHEMICAL SHIFTS OF THE CONVERSION OF β-METHYL BENZYLPENICILLOATE TO α,β-DIMETHYL BENZYLPENICILLOATE



Compd	Shift, ppm (J, cps) H_6	H_5	H_3	*gem*-Me_2
β-Methyl benzylpenicilloate	5.62 or 5.57 (d) (4)	5.57 or 5.62 (d) (4)	4.41	1.46, 1.61
α,β-Dimethyl benzylpenicilloate	5.12 (d) (6)	4.55 (d) (6)	3.59	1.17, 1.47

the reaction product of benzylpenicillenic acid and ethanethiol was separated. Its nmr spectrum (Figure 2) shows an additional AB quartet centered at δ 2.83 ppm corresponding to the methylene group and a triplet centered at δ 1.17 ppm corresponding to the methyl group. Figure 3 illustrates the nmr spectrum of the four components present in lane 7 of Figure 1 and indicates that these are stereoisomers at C-5 and -6 of β-methyl α-ethylthiobenzylpenicilloate (Figure 4). Mass spectral analysis of the product consisting of four components appears in Table III and is identical with that of the single component. A molecular ion is present. The intensities of the more abundant fragments, together with their elemental composition as determined from a high-resolution mass spectrum, are listed in Table III and represent the first open β-lactam penicillin mass spectrum reported. Formation of these fragments can be rationalized as indicated at the top of Table III. The mass spectral data are consistent with nmr findings.

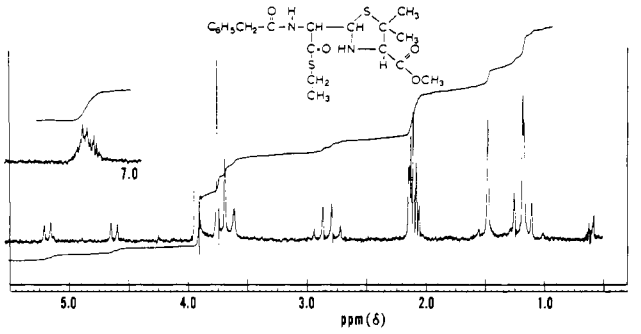


Figure 2.—Observed proton nmr spectrum at 100 Mc of Me_2CO-d_6–D_2O solution of a single isomer of β-methyl α-ethylthiobenzylpenicilloate.

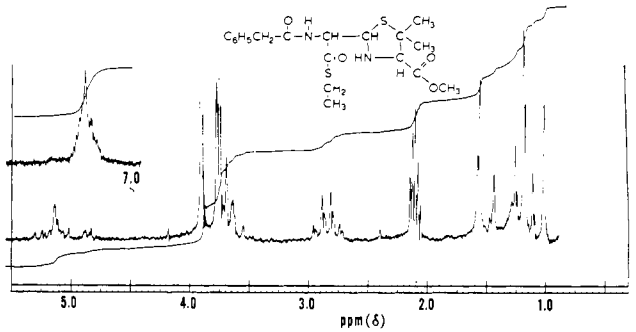
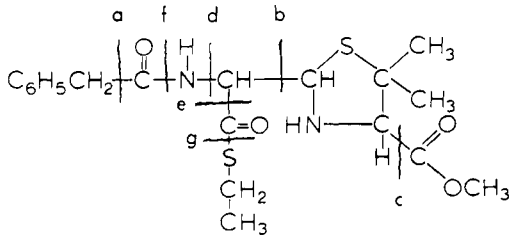


Figure 3.—Observed proton nmr spectrum at 100 Mc of Me_2CO-d_6–D_2O solution of an isomeric mixture of β-methyl α-ethylthiobenzylpenicilloate.

TABLE III

SIGNIFICANT FRAGMENTS IN THE MASS SPECTRUM OF β-METHYL-α-ETHYLTHIOBENZYLPENICILLOATE



m/e[a]	% rel abundance	Formula	Fission
91.05504	78	C_7H_7	a
114.03738	74	C_5H_8NS	b and c (−H)
174.05824	100	$C_7H_{12}O_2NS$	b
188.07569	56	$C_8H_{14}O_2NS$	d and e (+H)
203.08535	16	$C_8H_{15}O_2N_2S$	f and e (+H)
214.05387	41	$C_9H_{12}O_3NS$	d and g (−H)
321.12841	5	$C_{16}H_{21}O_3N_2S$	e
351.12114	4	$C_{17}H_{23}O_2N_2S_2$	c

[a] All measured masses were within 1.2 millimass units of calculated.

The stability of the thioester in the presence of amino groups was tested by addition of excess $EtNH_2$, maintaining a constant pH of 7.50. Under these conditions, the thioester is stable because at neutral pH there is usually only a small fraction of the amine present in the nucleophilic unprotonated form. When the same experiment was conducted without controlling pH (resulting pH was 12.0), α-ethylthiobenzylpenicilloate appeared to be converted to the corresponding amide, N-α-ethylbenzylpenicilloate.

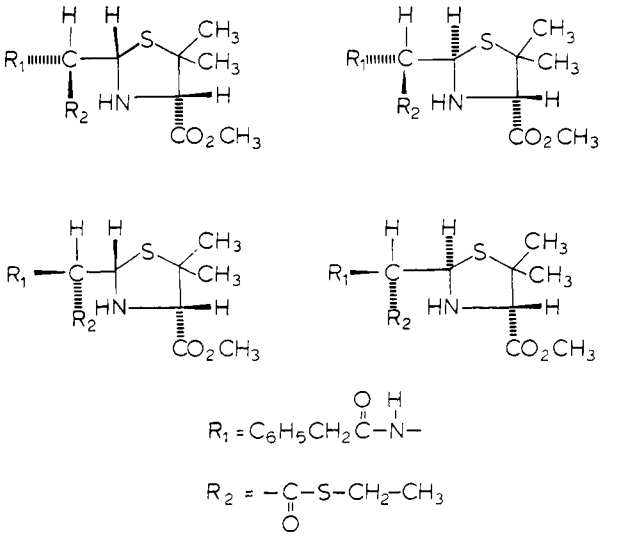


Figure 4.—Possible isomers of β-methyl α-ethylthiobenzylpenicilloate.

Discussion

In studying the mechanism of hypersensitivity to penicillins, it must be assumed that penicillin combines with protein to form an antigenic complex and that the various manifestations of hypersensitivity during further penicillin therapy are due to antibodies to this complex. It is known that simple molecules serve as haptens to initiate antibody formation when protein bound.[13,14] This can happen only when the molecule (penicillin in this case) is reactive and forms stable protein conjugates *in vitro*.[15] The chemical pathways leading to formation of this type of stable protein conjugate have been extensively studied.[9–11,16–18] The results are summarized below.

(A) Direct reaction of the β-lactam ring of penicillin with amino groups and with certain OH groups of the conjugate's carrier at neutral pH under physiological conditions occurs to form penicilloyl conjugates.

(B) Penicillenic acid, present as an impurity in penicillin solutions and/or developing *in vivo* after penicillin administration, forms penicilloyl conjugates.

(C) The penicilloyl conjugate has clearly emerged as the major determinant most frequently involved in penicillin allergy.

Arguments up to now have centered around the rate of reaction of the β-lactam of penicillins and the oxazolone of penicillenic acid with surface amino groups of proteins (primarily ε-amino groups of lysine residues) to form the major determinant, the penicilloyl amide linkage to a protein. Levine[10,19] has attributed anaphylactic reactions to determinants other than the penicilloyl determinant, *i.e.*, "minor" determinants which might have a much faster rate of conjugation. However, others[11,20,21] have found the penicilloyl

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(19) B. B. Levine, *Ann. Rev. Med.*, **17**, 23 (1966).

(20) A. L. De Weck, C. H. Schneider, and J. Gutersohn, *Intern. Arch. Allergy Appl. Immunol.*, **33**, 535 (1968).

(21) M. H. Grieco, *Arch. Internal Med.*, **119**, 141 (1967).

specificity is also involved in numerous cases of penicillin anaphylaxis. In addition to these hypotheses the theory was expressed recently that antigens responsible for allergic reactions to penicillins may not only be formed by conjugation of penicillin (or its derivatives) *in vivo* but may also be present as complete antigens in penicillin solutions.[22-24] Such antigens could be protein impurities carried along during the extraction procedure. De Weck, *et al.*,[20] have recently obtained evidence that minute amounts of protein impurities in commercial penicillin play a minor role in causing allergic reactions in sensitized patients and feel that low molecular weight compounds, either as eliciting small dimers or polymers or as reactive derivatives conjugating *in vivo*, are the main elements responsible for allergic reaction to penicillin.

According to the literature, the major determinant in penicillin allergy is the product of aminolysis of penicillin or penicillenic acid by ε-amino groups of lysine residues on proteins in the *in vivo* formation of the penicilloyl–protein conjugate. This reaction with the surface amino group can be visualized as having very little, if any, effect on the three-dimensional conformation of the protein. Results of the present study have shown a reactivity of penicillenic acid with another functional group found in proteins, the SH group. Ethanethiol was used as a model to establish the reaction product of penicillenic acid and compounds containing free SH; this product is a thioester heretofore unmentioned as a pathway to conjugation of penicillin to protein. Free SH groups of proteins are usually terminal or buried within the protein. It is believed that reaction of the oxazolone of penicillenic acid with the free SH group of a protein has much more potential to affect the three-dimensional conformation of the protein, thus forming a penicilloyl conjugate not only antigenic from an addition to the protein, but also by the potential distortion of the three-dimensional conformation of the protein.

Recent work[25] in our laboratories has shown that no such reactivity of compounds containing only free SH groups with the β-lactam of penicillin exists. We feel that reaction of penicillenic acid with thiol-containing compounds to form a thioester represents a unique pathway, that this pathway when applied to free SH groups of proteins has the potential to affect the three-dimensional conformation of the protein, and that these coupled effects may prove to be antigenically important in penicillin allergy. It is, therefore, suggested that penicillenic acid reacts with free SH groups of proteins to form thioesters, essentially stable under physiological conditions, in much the same way it reacts with free amino groups to form amides and that the product of this reaction, a penicilloyl thioester, may be a determinant of penicillin allergy.

Experimental Section

Benzylpenicillenic Acid.—The method used for the preparation of benzylpenicillenic acid was that of Levine.[12] A solution of 18.0 g (48.4 mmoles) of potassium benzylpenicillin in 300 ml of H_2O was mixed with a solution containing 16.32 g (60 mmoles) of $HgCl_2$ (Baker reagent) in 300 ml of H_2O. The mixture was allowed to stand for 3 hr at room temperature. The resulting precipitated mercuric mercaptide of benzylpenicillenic acid was collected and washed (cold H_2O, Et_2O). The mercaptide was suspended in a mixture of 1 l. of C_6H_6 and 400 ml of H_2O and was decomposed with H_2S at 10°. The C_6H_6 layer was separated, washed three times with cold H_2O, dried ($CaSO_4$), and lyophilized. Benzylpenicillenic acid was obtained as an amorphous white powder (3.36 g, 20.8%), mp 79–83° dec, $\lambda_{max}^{abs\ EtOH}$ 322 mμ (ε 23,333); lit.[26] for synthetic crystalline DL-benzylpenicillenic acid, λ_{max} 322 mμ (ε 26,600). The nitroprusside test was positive. *Anal.* ($C_{16}H_{18}N_2O_4S$): C, H, N, O, S.

Phosphate Buffer Solution.—KH_2PO_4 and Na_2HPO_4 (Mallinckrodt reagents) were used in the proper proportions for a 0.1 *M* pH 7.50 aqueous solution.

Model Compounds.—Cysteine, N-acetyl-L-cysteine, serine, penicillamine, homocysteine, methionine, glutathione, ε-aminocaproic acid, 2-mercaptoethanol, and EtSH were available commercially.

Reaction of Benzylpenicillenic Acid with EtSH.—A solution of 26.88 g of ethanethiol (Eastman Organic Chemicals) in 568 ml of 0.1 *M* phosphate buffer at pH 7.50 was added to 2.0 g of benzylpenicillenic acid dissolved in 6 ml of absolute EtOH. The resulting mixture was kept at room temperature and stirred while small incremental additions of 1 *N* NaOH maintained the pH at 7.50. Spectrophotomeric examination of the reaction mixture after 1 hr revealed the absence of the 322-mμ maximum absorption peak characteristic of the reactant. The reaction mixture was placed under vacuum to remove the excess ethanethiol, the aqueous mixture was subsequently lyophilized, and the residue was extracted with anhydrous MeOH. The insoluble residue was discarded, and the MeOH was evaporated under vacuum, resulting in a residue weighing 2.45 g (94.5%). This residue was taken into H_2O and layered with EtOAc; pH of the mixture was lowered to 2.5 with 1 *N* HCl. The aqueous solution was extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated under vacuum (residue 2.08 g).

Methylation of the Reaction Product of Benzylpenicillenic Acid with EtSH.—The separated product (2.08 g) was methylated by treatment with CH_2N_2 in Et_2O. Tlc (silica gel, EtOAc–C_6H_6 (30:70) solvent system, I_2 developed) demonstrated four components.

Purification of β-Methyl α-Ethylthiobenzylpenicilloate Isomers.—The methylated product (2.17 g) was dissolved in a minimum of CH_2Cl_2 and placed on a column packed with 95 g of silica gel (Davison Chemical, grade 62) in C_6H_6. The column was eluted with 5% EtOAc in C_6H_6 at a rate of 1 ml/min. Ten-milliliter fractions were collected. Two of these fractions contained one isomer which was separated (17 mg) for nmr analysis. The isomeric mixture could not be separated further. Elemental analysis of the isomeric mixture in the form of a glass was ($C_{19}H_{26}N_2O_4S_2$) C, 55.60; H, 6.39; N, 6.83; S, 15.63. Found: C, 55.62; H, 6.53; N, 6.64; S, 15.50.

Reaction of α-Ethylthiobenzylpenicilloate Isomers with $EtNH_2$.—The procedure used to prepare the reaction mixture containing α-ethylthiobenzylpenicilloate was described earlier. To 300 ml (one-half) of this mixture was added $EtNH_2$ (27.05 g) (Eastman Organic Chemicals) in 262 ml of 0.1 *M* phosphate buffer with resulting pH adjusted to 7.50; the other half served as a control. After 2 hr at room temperature the reaction mixtures were placed under vacuum to remove excess EtSH and $EtNH_2$. Treatment hereafter was identical with that described above through the methylation procedure, and the product was found to be the thioester. This entire procedure was repeated adding $EtNH_2$ without pH control (resulting pH 12.0). The product was not the thioester, but appeared instead from nmr analysis to be the corresponding amide.

Kinetic Studies.—All kinetic measurements were made in aqueous buffer on a Beckman Model DB spectrophotometer equipped with a cell compartment thermostated at 37 ± 0.1° using 1.00-cm quartz cells. Phosphate buffer solutions in glass-stoppered flasks under nitrogen containing 1×10^{-2} *M* of the appropriate model compound and 1 mg/ml of Versene were prepared prior to each run. These solutions were thermostated

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(24) E. T. Knudsen, O. P. W. Robinson, E. A. P. Croydon, and E. C. Tees, *ibid.*, I, 1184 (1967).

(25) E. S. Wagner, W. W. Davis, M. Gorman, and R. M. Gale, presented in part at the VIIIth Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, N. Y., Oct 1968.

(26) A. H. Livermore, F. H. Carpenter, R. W. Holley, and V. du Vigneaud, *J. Biol. Chem.*, **175**, 721 (1948).

in the same constant-temperature bath which maintained the cell compartment temperature.

The initial reaction mixture of 3.0 ml of 0.1 *M* phosphate buffer at pH 7.50 containing the appropriate model compound was placed in a stoppered, quartz 1.00-cm Beckman cell. A solution of benzylpenicillenic acid in absolute EtOH (0.01 ml) was injected into the reaction cell, producing a concentration of reactant of 3.0×10^{-5} *M*. Optical density measurements were then recorded as a function of time. Spectrophotometric determination of the disappearance of benzylpenicillenic acid was followed at 322 mμ.

Since the concentration of model compound used was greater than the concentration of benzylpenicillenic acid by a factor of 1000, pseudo-first-order rate constants could be obtained. The infinity point was determined in all runs. One obtained, therefore, upon plotting the logarithm of the difference between the optical density at infinity and the optical density at the time in question against time, a straight line directly proportional to the pseudo-first-order rate constant for the reaction. Each run was repeated several times.

Nmr Studies.—Nmr spectra (Me_2CO-d_6–D_2O) were obtained on a Varian HA-100 internal lock nuclear magnetic resonance spectrometer and were used to characterize the methylated products of the reaction of benzylpenicillenic acid and EtSH. The spectrometer was in the frequency sweep mode, and signals were measured relative to TMS as internal standard. Sample concentrations were less than 5% w/v. Signals were read to ±0.03 ppm.

Mass Spectrometry.—A CEC-110B high-resolution mass spectrometer was used to determine the molecular weight of the methylated products of the reaction of benzylpenicillenic acid and EtSH.

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Centrally Acting Emetics. III. Derivatives of β-Naphthylamine[1a,b]

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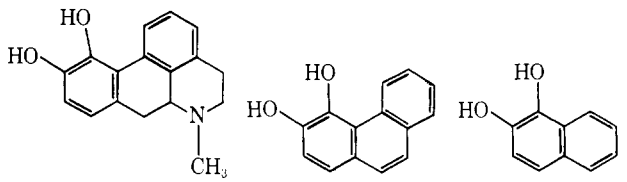
The synthesis of a series of β-naphthylamine derivatives closely corresponding to a portion of the apomorphine molecule was undertaken to investigate structure–activity relationships of this centrally active emetic. Employing independent synthetic routes, derivatives of 2-amino-5,6-naphthalenediol and of 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol have been prepared. Biological test data are presented.

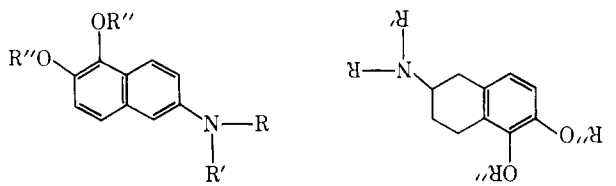
Relatively few systematic attempts have been made to elucidate the emetic pharmacophore of apomorphine (**1**), or of other emetic aporphine derivatives. Eddy, in an extensive series of papers,[2] presented data on a series of phenanthrenediols **2** and derivatives which can be viewed as fragments or analogs of fragments of the apomorphine molecule. Some of the compounds pos-



1 2 3

sessed emetic activity in cats, albeit of a lower order than apomorphine. Eddy did not report test data on naphthalenediols **3**, nor on any diols of types **2** and **3** which also possessed an amino function. Thrift[3] prepared 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (an isomer of compound **11** below) as an analog of adrenergic amines, but possible emetic effects were not mentioned. A search of the literature revealed no other reports of simple amino derivatives of **2** or **3**.

The present work was based on the assumption that the apomorphine molecule is more complex than is necessary for maximal emetic activity, and on the premise that significant pharmacophoric groups in apomorphine are the 1,2-diphenolic moiety and the amino function. The simplest fragment of the apomorphine molecule which could be visualized to possess emetic activity was a 2-aminonaphthalene-5,6-diol system. Accordingly, structures **4**–**12** were chosen for study.



4, R = R′ = H; R″ = CH_3
5, R = R′ = R″ = H
6, R = H; R′ = R″ = CH_3
7, R = R″ = H; R′ = CH_3
8, R = R′ = R″ = CH_3
9, R = R′ = CH_3; R″ = H

10, R = R′ = H; R″ = CH_3
11, R = H; R′ = R″ = CH_3
12, R = R′ = R″ = CH_3

Dreiding models indicated that distances between the phenolic groups and the nitrogen atom are almost the same in these naphthalene derivatives as in apomorphine. Since the ring system of apomorphine is rigid and almost planar, evaluation of the emetic activity of **4**–**9** is of

(1) (a) Part II: M. V. Koch, J. G. Cannon, and A. M. Burkman, *J. Med. Chem.*, **11**, 977 (1968). (b) This investigation was supported in part by Grant NB-04349, National Institute of Neurological Diseases and Blindness, and in part by National Institutes of Health predoctoral fellowship GM-19445 (W. K. S.). Abstracted in part from a thesis submitted by W. K. S. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1965. (c) To whom all correspondence should be addressed.

(2) This work was summarized and discussed by L. F. Small, N. B. Eddy, E. Mosettig, and C. K. Himmelsbach, *Public Health Rept. (U. S.), Suppl.*, **138**, 1 (1938).

(3) R. I. Thrift, *J. Chem. Soc., C*, 288 (1967).