TABLE VI

THE EFFECT OF ALKALI ON THE K_A BANDS OF SOME PHENOLS WHICH EXHIBIT HYBRID SPECTRA[a]

Compound	Solvent or pH	1st K_A band λ_{max} (mμ)	1st K_A band ϵ_{max}	2nd K_A band[b] λ_{max} (mμ)	2nd K_A band[b] ϵ_{max}
2-Methoxy-4-nitrophenol[c]	0.1 *N* HCl	*310*	*5500*	345	7100
	0.1 *N* NaOH	*320*	*1450*	433	17400
3-Methoxy-4-nitrophenol	Ethanol	*ca. 285*	*4840*	328	6900
	0.1 *N* alcoholic NaOH	263	4100	393.5	21300
2-Nitro-5-methoxyphenol	Cyclohexane	340	9000	307	8500
	0.25 *N* NaOH	317	6350	403	7570
3-Methoxy-4-hydroxybenzaldehyde[d]	Ethanol	277[e]	10800[e]	310	10900
	Alkaline ethanol	294[e]	2800[e]	353	30200
3-Methoxy-4-hydroxyacetophenone[e]	Ethanol	276[e]	10100[e]	303	8500
	Alkaline ethanol	*ca. 295*[e]	*3300*[e]	348	24000
2-Amino-4-nitrophenol[f]	pH 5	256	9800	315	5100
	pH 11	275	6900	446	13400

[a] Values italicized represent inflections. [b] Corresponding to chromophore containing the hydroxy group. [c] Ref. 24. [d] Ref. 25. [e] Estimated from graph. [f] Ref. 11.

phenol-type absorption, and appear only when this strong absorption is displaced by the action of alkali. The ability of phenols to ionize in alkaline solution can thus be put to advantage in the identification of bands in hybrid spectra. Table VI gives a number of examples of band identification by this method.

Incomplete conjugation caused by steric hindrance can also lead to the appearance of hybrid spectra, as is shown by the data of Wepster[18] (*cf.* also ref. 23 and 27) on a series of *ortho*-substituted 4-nitro-N,N-dimethylanilines (Table V). The spectrum of 4-nitro-N,N-dimethylaniline itself exhibits only one K_A band; that of the *o-t*-butyl-substituted compound also exhibits only one K_A band (corresponding to nitrobenzene-type absorption, because the N,N-dimethylamino group is no longer conjugated). However, the spectrum of 4-nitro-2,6-dimethyl-N,N-dimethylaniline, which compound is only partially sterically hindered, exhibits two K_A bands, which are ascribed separately to 4-nitro-N,N-dimethylaniline- and nitrobenzene-type absorption.

(27) (a) R. T. Arnold and P. N. Craig, *J. Am. Chem. Soc.*, **72**, 2728 (1950); (b) W. R. Remington, *ibid.*, **67**, 1838 (1945).

Experimental

Spectra were determined in duplicate on a Unicam SP 500 spectrophotometer. The wave-length accuracy is estimated to be ±0.5 mμ at 270 mμ, and ±1 mμ at 350 mμ. The precision of ϵ_{max} values is ±5% or better. Values were generally reproducible to ±2%.

The compounds used in this work were mostly commercial materials. Others were prepared by standard methods. All compounds were purified until their melting points or refractive indices showed them to be pure.

Acknowledgment.—The author thanks Professor W. F. Forbes of the University of Waterloo, Ontario, and Mr. F. R. Heather and Dr. E. G. Vaal of Thornton Research Centre, for their valuable help and advice.

Isomerization and Decomposition Products of Methicillin[1]

D. A. JOHNSON AND C. A. PANETTA

Chemical Development Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse 1, New York

Received December 23, 1963

In weakly acidic media, methicillin (**1**) isomerizes to 2,6-dimethoxyphenylpenicillenic acid (**2**) which then decomposes spontaneously to 2,6-dimethoxyphenylpenicilloic acid (**3**), 2,6-dimethoxyphenylpenilloic acid (**4**), 2,6-dimethoxyhippuric acid (**5**), N-formyl-D-penicillamine (**6**), and 3,10-bis(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0^{4,8}]tetradecane-7,14-dicarboxylic acid (**7**, see Scheme I). No penillic acid, penilloaldehyde, or penicillamine was detected as a product of this decomposition.

Methicillin (sodium 2,6-dimethoxyphenylpenicillinate, **1**) is a semisynthetic penicillin which has gained clinical importance because of its resistance to destruction by the enzyme penicillinase.[2] Although highly effective when given by injection, it is ineffective when administered orally, probably because of its extreme lability toward acid. We wish to report on the course of the acid decomposition reactions.

The chemistry of the natural penicillins has been exhaustively investigated.[3] Under various acidic conditions, benzyl- and 2-pentenylpenicillins were reported to isomerize to their respective penillic acids or to decompose to D-penicillamine and the appropriate penilloaldehyde. In a more recent study of the decomposition of natural and semisynthetic penicillins in acidic solutions, Dennen and Davis indicated that the penillic and penicilloic acids were the main products formed.[4] An excellent and comprehensive study of spontaneous benzylpenicillin decomposition under mild conditions was recently reported by Hitomi, who identified ten products.[5]

(1) The trademark of Bristol Laboratories, a Division of Bristol-Myers Company, for methicillin is Staphcillin®.

(2) H. G. Steinman, *Proc. Soc. Exptl. Biol. Med.*, **106**, 227 (1961).

(3) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949.

(4) D. W. Dennen and W. W. Davis, *Antimicrobial Agents Chemotherapy*, 531 (1961).

(5) H. Hitomi, *Yakugaku Zasshi*, **79**, 1600 (1959); *Chem. Abstr.*, **54**, 10,996g (1960).

We have studied the decomposition of methicillin in weakly acidic aqueous or solvent solutions. The progress of the reaction was followed by thin-layer chromatography. Silica gel coated plates were spotted periodically, starting with zero time. Within a 48-hr. period, six zones were observed besides that of the starting material. Figure 1 shows their relative order on a typical plate.

Zone C was the first foreign zone to appear and could only be observed if the reaction mixture had not aged more than 2 days. This labile behavior corresponded with that of a yellow substance, produced in the degradation, which absorbed in the 333-mμ region (methicillin absorbs only at 283 mμ owing to the 2,6-dimethoxybenzoyl chromophore). The absorptivity at 333 mμ reached a peak and then decreased asymptotically with time. The yellow color and ultraviolet absorption were indicative of a penicillenic acid structure.[5,6] Using a known procedure for the preparation of penicillenic acids,[7] a yellow crystalline compound, which had strong absorption at 333 mμ, was obtained from methicillin. This compound gave a spot in the same position as that of zone C. It gave a deep blue transient color with ferric chloride reagent, which would indicate that a free thiol group was present. Additional chemical and physical tests, spectral evidence, elemental analysis, and the manner in which it was prepared indicated that the compound which produced zone C was 2,6-dimethoxyphenylpenicillenic acid (**2**).

The degradation of methicillin probably involves the penicillenic acid as a primary intermediate. This was indicated by the fact that when pure 2,6-dimethoxyphenylpenicillenic acid was subjected to decomposition conditions, similar to those used on methicillin, all of the same zones were observed on silica gel plates after about 2 days.

The penicilloic and penilloic acids (**3** and **4**, respectively) are normal penicillin degradation products, and their identification in the methicillin acid decomposition mixture was expected. The latter compound was most easily prepared and isolated by the treatment of methicillin with aqueous base, followed by decarboxylation. It gave a spot on a silica gel plate which corresponded with zone E. It was characterized by chemical and physical data and elemental analysis. The presence of a penilloic acid in a penicillin decomposition mixture usually presupposes the presence of the penicilloic acid as its precursor. The solid, which was decarboxylated to the penilloic acid **4**, showed the presence of a second zone on silica gel plates, which had the same R_f value as zone D. This solid gave a positive test with arsenomolybdic acid–mercuric chloride reagent which is reputed to be specific for penicilloic acids.[8] Owing to its labile nature, however, it could not be purified sufficiently for elemental analysis. 2,6-Dimethoxyphenylpenicilloic acid (**3**) was assigned to zone D.

A white solid was obtained, after aqueous acid degradation of methicillin, which was found to be homogeneous by thin-layer chromatography (zone F). It did not contain sulfur and its empirical formula $C_{11}H_{13}NO_5$, neutralization equivalent, and molecular weight determinations indicated that it was a fragment of the methicillin molecule. This compound contained no aldehyde or ketone group, but did contain an acidic group. Its ultraviolet and infrared spectra showed that it still contained the 2,6-dimethoxybenzamido group.

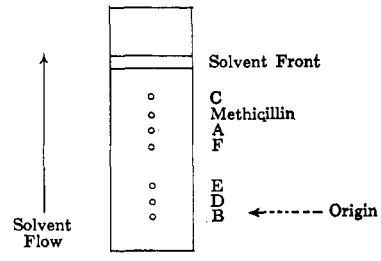


Figure 1.

The proof that zone F resulted from 2,6-dimethoxyhippuric acid (**5**), was attained by synthesis of this hippuric acid from known materials. 2,6-Dimethoxybenzoyl chloride was treated with benzyl glycinate to form benzyl 2,6-dimethoxyhippurate. Catalytic hydrogenolysis of the latter compound offered 2,6-dimethoxyhippuric acid (**5**) which was identical with compound F in every respect (melting point, R_f values, ultraviolet and infrared absorption properties, and solubilities).

The filtrates, resulting from the isolation of 2,6-dimethoxyhippuric acid from methicillin decomposition mixtures, were usually enriched in another compound which produced zone A on silica gel plates. This compound contained a free thiol group, and, even though it was never obtained completely pure, sulfur analyses indicated that this compound (A) was also only a part of the original penicillin. It was therefore assumed to be the remaining fragment after the 2,6-dimethoxyhippuric acid separates. The normal sulfur-containing fragment isolated from the degradation of benzyl or 2-pentenylpenicillin is D-penicillamine. However, compound A was not D-penicillamine; because it was not so soluble in water as the latter compound, it did not condense with carbonyl compounds (typical of D-penicillamine), nor did it give a zone in the same position as that of authentic D-penicillamine on a silica gel plate. Its neutralization equivalent, specific rotation, and solubilities agreed fairly well with N-formyl-D-penicillamine (**6**).

Authentic N-formyl-D-penicillamine was prepared by the formylation of D-penicillamine according to a known procedure.[9] Its melting point, behavior with ferric chloride and 2,4-dinitrophenylhydrazine reagents, and R_f value on a thin-layer plate were essentially identical. The final and conclusive proof that compound A was N-formyl-D-penicillamine (**6**) was supplied by infrared analysis. The spectrum of A was exactly the same as that of authentic N-formyl-D-penicillamine, except for a band at 1110 cm.$^{-1}$ in the former spectrum, which was due to the methoxyl group of the contaminating 2,6-dimethoxyhippuric acid (**5**).

N-Formyl-D-penicillamine, which has also been isolated as a degradation product of procaine benzylpenicillin,[5] and 2,6-dimethoxyhippuric acid were probably formed from 2,6-dimethoxyphenylpenicillenic acid (**2**), by hydration of the latter followed by a reverse aldol condensation.

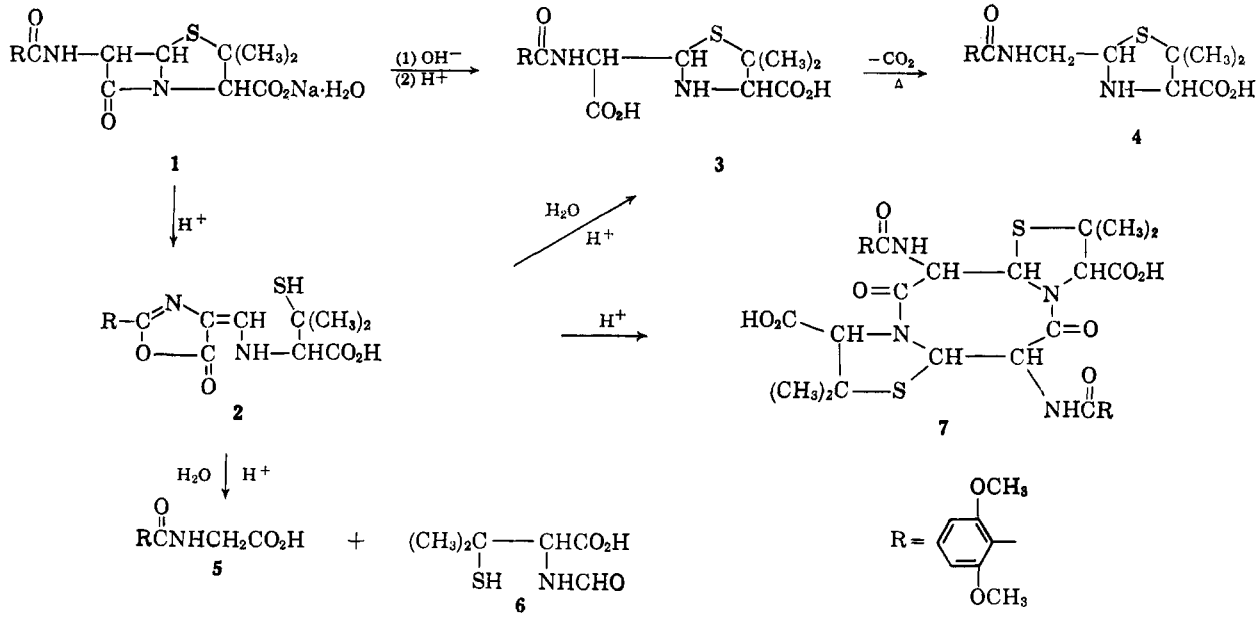
(6) N. Narasimhachari and G. Ramana Rao, *Hindustan Antibiot. Bull.*, **4**, 163 (1962); *Chem. Abstr.*, **57**, 16,758b (1962).

(7) B. B. Levine, *Arch. Biochem. Biophys.*, **93**, 50 (1961).

(8) S. C. Pan, *Anal. Chem.*, 26, 1438 (1954).

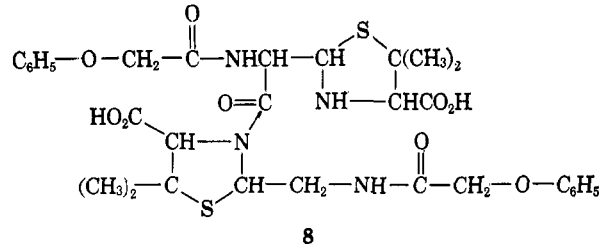
(9) Ref. 3, p. 467.

SCHEME I



Another crystalline reaction product separated during storage of a methyl isobutyl ketone solution of methicillin (pH 2.0) for several days. It did not move on a silica gel plate using the normal solvent system. This unknown, compound B, contained no free thiol group, and its infrared spectrum indicated a free carboxyl group. Its ultraviolet spectra contained only the 2,6-dimethoxybenzoyl peak. The fact that a molecular weight determination gave a value slightly larger than twice the neutralization equivalent intimated that compound B was a dimer of methicillin. Elemental analysis supported this fact. When the methyl ester of compound B was prepared, its molecular weight was found to be twice that of methicillin methyl ester, and this value, together with the elemental analysis, gave a molecular formula of $C_{36}H_{44}N_4O_{12}S_2$. Compound B was therefore assigned the structure of 3,10-bis-(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0.^{4,8}]tetradecane-7,14-dicarboxylic acid (**7**) which was consistent with the infrared and nuclear magnetic resonance spectra.

The open-chain counterpart of this structure in the phenoxymethylpenicillin series had already been described in the literature,[10] and is called a penilloinamide **8**. The possibility that compound B was the methicillin analog of **8** was abandoned when it was found that both the free acid and the methyl ester of B gave negative tests with iodine–sodium azide reagent. This reagent is specific for thiazolidines with unacylated nitrogen atoms.[11] The basic character expected in the methicillin analog of **8** was not apparent when either the free acid or the methyl ester of compound B was titrated under nonaqueous conditions with perchloric acid.



The formation of the tricyclic penicillenic acid dimer **7** from methicillin is unique in the chemistry of penicillins. It appears that no similar compound has been reported as the result of penicillin degradation.

Experimental[12]

The thin-layer chromatograms used in this work were prepared using Camag silica gel D5. Spotting was performed using 3 μl. of a 1% methanolic or aqueous solution. The solvent system[13] which gave best separations was 60% benzene–35% acetone–5% acetic acid, and the zones were spotted with a 0.5% aqueous potassium permanganate solution.

2,6-Dimethoxyphenylpenicillenic Acid (**2**).—The following procedure was adapted from that of Levine for the preparation of benzylpenicillenic acid.[7] Mercuric chloride, 16.3 g. (0.06 mole), was dissolved in 1 l. of water and this was added to a solution of 21.0 g. (0.05 mole) of methicillin in 1 l. of water. The turbid mixture was stirred at 37° for 3.0 hr. The yellow mercuric mercaptide, which separated, was collected and washed with 1 l. of cold water and 0.5 l. of ether. It was immediately suspended in 400 ml. of chloroform and 100 ml. of water, cooled to 8°, and treated with hydrogen sulfide gas for 15 min. The resulting black, thick slurry was filtered through a Sil-Flo-precoated funnel and the yellow organic layer was washed with water and dried over sodium sulfate. The chloroform solution was added to 2 l. of Skellysolve B (b.p. 60–70°). The yellow penicillenic acid which separated was stirred cold for about 10 min., filtered, washed with Skellysolve B, and dried in a vacuum desiccator over Drierite. It melted at 124.3-129.2° dec. and weighed 10.9 g. Attempts to purify further this solid were unsuccessful and usually led to degradation. It was stored in a nitrogen atmosphere. It gave a deep blue transient color with 5% aqueous ferric chlo-

(10) A. S. Khokhlov and E. V. Kachalina, *Antibiotiki*, **5**, No. 5, 41 (1960).

(11) Ref. 3, p. 927.

(12) All melting points are corrected. Microanalyses were performed by Mr. R. M. Downing, and the infrared, ultraviolet, nuclear magnetic resonance, and molecular weight measurements were made by Mr. D. F. Whitehead. The molecular weight determinations were run using a Mechrolab vapor pressure osmometer, Model 301.

(13) Dr. E. J. Richardson developed the solvent system for methicillin degradation products and prepared and ran all the plates used in this investigation.

ride reagent and essentially one spot (zone C) on a silica gel plate, λ_{max}^{MeOH} 333 mμ (ε 23,350). The infrared spectrum was consistent with the proposed structure.

Anal. Calcd. for $C_{17}H_{20}N_2O_6S \cdot 0.5H_2O$: C, 52.50; H, 5.42; N, 7.20; S, 8.23; H_2O, 2.31; mol. wt., 389.39. Found: C, 52.75; H, 5.12; N, 7.10; S, 7.82; Karl Fischer, 3.0; neut. equiv., 368; mol. wt. (in pyridine), 364.

2,6-Dimethoxyphenylpenilloic Acid (4).—Methicillin, 42 g. (0.1 mole), was dissolved in 100 ml. of water and treated with a cold solution of 4.0 g. (0.1 mole) of sodium hydroxide in 100 ml. of water. The yellow solution was stored at 5° for 16 hr. It was filtered through a Sil-Flo-precoated funnel and combined with 200 ml. of cold methyl isobutyl ketone. The pH was adjusted from 11.0 to 2.0 with 6 *N* hydrochloric acid while the temperature was maintained below 4°. An amorphous white solid separated which slowly crystallized. It was collected and dried. It weighed 24.9 g., melted at 131.3–132.2° dec., and gave a neutralization equivalent of 220, a blue color with arsenomolybdic acid–mercuric chloride reagent,[8] and zones E and D on a silica gel plate. These facts were used to calculate that the solid was approximately 85% penicilloic acid (**3**) and 15% penilloic acid (**4**). This solid, 10 g., was refluxed in 50 ml. of water and 40 ml. of 95% ethanol for 2.25 hr. (the ethanol was omitted in later runs). Gas evolution ceased after about 10 min. The solvent was removed by distillation at reduced pressure and was replaced with 50 ml. of methyl isobutyl ketone. A white solid, 3.1 g., separated from the cooled mixture, which was collected and recrystallized from hot water to yield white rods, m.p. 194.9–195.0° dec. It gave no color change with aqueous ferric chloride reagent or with arsenomolybdic acid–mercuric chloride reagent,[8] and gave a spot on a silica gel plate which was in the same position as zone E. It reacted instantaneously with iodine–sodium azide reagent[11] causing decolorization and gas evolution. The ultraviolet, infrared, and nuclear magnetic resonance spectra were consistent with the structure of 2,6-dimethoxyphenylpenilloic acid (**4**).

Anal. Calcd. for $C_{16}H_{22}N_2O_5S$: C, 54.23; H, 6.26; N, 7.91; S, 9.02; mol. wt., 354.35. Found: C, 53.90; H, 6.10; N, 7.98; S, 8.78; neut. equiv., 354; mol. wt. (in 95% ethanol), 354.

2,6-Dimethoxyhippuric Acid (5). A. From Methicillin.—A solution of 21.0 g. (0.05 mole) of methicillin and 1 l. of water was stored at 37° for 8 days. It was filtered to separate a small amount of insoluble material and the pH of the filtrate was adjusted from 3.7 to 2.0. The filtrate was concentrated under reduced pressure to a volume of 200 ml. and this was cooled for 16 hr. in a refrigerator. Crystalline material separated which weighed 7.0 g. and contained several spots on a thin-layer chromatogram. After two recrystallizations from hot methanol, a nicely crystalline white solid was obtained which was homogeneous (zone F), melted at 222.0–223.0° dec., weighed about 1.0 g., gave no color change with 5% aqueous ferric chloride solution, and gave no precipitate with aqueous, alcoholic 2,4-dinitrophenylhydrazine reagent. It was soluble in 5% aqueous sodium bicarbonate and gave a negative test for sulfur after decomposition with sodium.[14] It gave a neutralization equivalent of 248 and molecular weight determinations (in 95% ethanol) of 237 and 242; λ_{max}^{MeOH} 282 mμ (ε 1530) and 240 (1220); the infrared spectrum was consistent with the assignment of the structure of 2,6-dimethoxyhippuric acid (**5**) to this solid.

B. From Benzyl Glycinate.—Glycine benzyl ester *p*-toluenesulfonate,[15] 33.7 g. (0.1 mole), was added to 300 ml. of methylene chloride, 200 ml. of water, and 14.0 ml. (10.1 g., 0.1 mole) of triethylamine, and the resulting mixture was stirred for 10 min. The organic layer was washed with water, dried over sodium sulfate, and treated with 15.4 ml. (11.2 g., 0.11 mole) of triethylamine.

In another flask, 2,6-dimethoxybenzoyl chloride was prepared. 2,6-Dimethoxybenzoic acid (18.2 g., 0.1 mole), 100 ml. of methylene chloride, 0.4 ml. of dimethylformamide, and 8.0 ml. (13.1 g., 0.11 mole) of thionyl chloride were combined and stirred at room temperature for 20 min. The excess thionyl chloride and solvent were removed *in vacuo* and replaced with 100 ml. of fresh methylene chloride. This solution was then added dropwise to the solution of benzyl glycinate held at 1–7°. The mixture was allowed to come to room temperature and was washed twice with 5% aqueous sodium bicarbonate solution, twice with 15% aqueous sulfuric acid, once with water, and dried. The methylene chloride solution was diluted with 2.5 l. of Skellysolve B (b.p. 60–70°) and white needles of (23.1 g.) benzyl 2,6-dimethoxyhippurate separated, and were collected and dried, m.p. 134.2–134.6°. The ultraviolet, infrared, and n.m.r. spectra were consistent with the proposed structure.

Benzyl 2,6-dimethoxyhippurate, 6.6 g. (0.02 mole), was dissolved in 130 ml. of methanol and 1.5 g. of 30% palladium on Celite and 4 drops of glacial acetic acid were added. The mixture was shaken under 51 p.s.i.g. of hydrogen. The theoretical amount of hydrogen was consumed within the first 5 min. The mixture was filtered hot through a Sil-Flo-precoated funnel. When cooled, white crystals (4.0 g.) separated from the filtrate, and were collected, and dried, m.p. 220.1–222.4° dec. This solid was identical with 2,6-dimethoxyhippuric acid (**5**) obtained from methicillin, with respect to thin-layer R_f values, ultraviolet and infrared absorption properties, and solubilities.

N-Formyl-D-penicillamine (6). A. From Methicillin.—The procedure for the preparation of 2,6-dimethoxyhippuric acid (**5**) from methicillin (*vide supra*) was followed, but the aqueous filtrate was concentrated further to separate 4.3 g. of a ferric chloride-positive solid, which melted at 143.0–151.4° dec. A 0.6-g. portion of this solid was recrystallized from 20 ml. of hot water using 0.3 g. of Darco KB. The white product, 0.4 g., m.p. 152.6–153.5° (with gas evolution), gave a very deep blue transient color with 5% aqueous ferric chloride reagent, but no precipitate with 2,4-dinitrophenylhydrazine reagent. Its silica gel chromatogram showed essentially two spots, the slowest one being that from 2,6-dimethoxyhippuric acid. Its neutralization equivalent was 190 (theory is 177), $[\alpha]^{25}D$ +50.0° (*c* 0.3, pyridine).

Anal. Found: S, 15.45.

B. From D-Penicillamine.—N-Formyl-D-penicillamine was prepared from D-penicillamine *via* a known procedure.[9] The recrystallized product gave $[\alpha]^{25}D$ +63.97° (*c* 1, pyridine) and melted at 154.1–154.5° (with gas evolution). The melting point was not depressed after being admixed with similar material from methicillin. It was identical with N-formyl-D-penicillamine from methicillin in its behavior with ferric chloride and 2,4-dinitrophenylhydrazine reagents, in R_f value on silica gel plates, and in infrared spectrum (except for the 1110-cm.$^{-1}$ band in the material prepared from methicillin, which was due to the contamination of 2,6-dimethoxyhippuric acid, **5**).

3,10-Bis(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0^{4,8}]tetradecane-7,14-dicarboxylic Acid (7).—Methicillin (105 g., 0.25 mole) was taken up in 700 ml. of methyl isobutyl ketone at pH 2.0. The solution was dried and stored at room temperature for 7 days. A yellow solid separated, which was collected and dried. It weighed about 42 g. It was dissolved in 500 ml. of methanol and reprecipitated as a cream-colored semicrystalline solid by addition of two volumes of water. When dry, it melted at 176.7–178.3° dec. This procedure was repeated three more times, the last time using Darco KB. A white semicrystalline solid was obtained, m.p. 188.8–189.6° dec.; λ_{max}^{MeOH} 337 and 283 mμ; no color change with 5% aqueous ferric chloride solution. The 337-mμ peak became less intense with each successive crystallization. When the filtrate from this solid was concentrated *in vacuo*, a small amount (about 1.2 g.) of a white crystalline solid was obtained, m.p. 191.0–192.1° dec.; λ_{max}^{MeOH} 284 (ε 6700); ν_{max}^{KBr} 3400 (NH), 2900–3100 (CH), 1740 (C=O), 1660 (C=O), 1515 (NH), 1250 (Ph–O), and 1115 cm.$^{-1}$ (CH_3O). It gave no color change with the ferric chloride reagent and did not decolorize iodine–sodium azide reagent.[11] This solid gave one slightly elongated spot at the origin (zone B) on a silica gel plate. It also gave but one zone when run in a 95% methanol and 5% acetic acid solvent system in which its R_f value was much larger. No inflection of the titration curve was observed when this solid was titrated with perchloric acid in glacial acetic acid.

Anal. Calcd. for $C_{34}H_{40}N_4O_{12}S_2 \cdot 2H_2O$: C, 51.26; H, 5.56; N, 7.03; mol. wt., 796.7; H_2O, 4.5. Found: C, 51.25; H, 5.52; N, 6.57; neut. equiv., 383; mol. wt. (in 95% ethanol), 868; H_2O (Karl Fischer), 5.9.

Methyl Ester of 7.—N-Methyl-N-nitrosourea[16] (4.5 g. 0.044 mole) was slurried in 60 ml. of ether and cooled to 10° while 9.0

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 57–58.

(15) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(16) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 461.

ml. of 50% aqueous potassium hydroxide solution was added. The yellow ether layer was slowly decanted into a solution of 5.6 g. (0.007 mole) of the tricyclotetradecane dicarboxylic acid **7** in 50 ml. of methanol. After 15 min., the cooling bath was removed and 1.7 ml. of glacial acetic acid was added to the yellow solution. After another 15 min., the solution was concentrated under reduced pressure to a thick orange-yellow oil, 5.5 g. This was taken up in carbon tetrachloride, and a semicrystalline solid separated when the solution was diluted with Skellysolve B. This solid was then recrystallized once from 200 ml. of chloroform and 800 ml. of Skellysolve B, and once from 70 ml. of chloroform and 100 ml. of ether. When the filtrate from the second recrystallization was diluted with Skellysolve B, a small amount (0.5 g.) of a white crystalline solid was obtained, m.p. 136.7–138.6° dec.; λ_{max}^{MeOH} 283 mμ (ε 8650); ν_{max}^{KBr} 3400 (NH), 2900–3100 (CH), 1745 (C=O), 1665 (C=O), 1525 (NH) 1255 (Ph-O), and 1115 cm.$^{-1}$ (CH_3O). No color change with 5% aqueous ferric chloride reagent was produced and iodine–sodium azide reagent was not decolored. N.m.r. data shows δ 1.5 (CH_2) 12H; 3.8 (OCH_3) 18H, (N-CH) 6H; 6.6 (NH) 2H, (=CH-) 4H; 7.3 (=CH-) 3H (theory requires 2H). No inflection of the titration curve was observed when this solid was titrated with perchloric acid in glacial acetic acid.

Anal. Calcd. for $C_{36}H_{44}N_4O_{12}S_2$: C, 54.82; H, 5.62; N, 7.10; mol. wt., 788.9. Found: C, 55.30; H, 5.78; N, 7.28; mol. wt. (in 95% ethanol), 798.

Synthesis of Thioethers. Amide Solvent-Promoted Nucleophilic Displacement of Halide by Thiolate Ion

J. ROBERT CAMPBELL

The Organic Chemicals Division, Research Department, Monsanto Chemical Company, St. Louis, Missouri

Received December 26, 1963

A new general procedure for synthesizing aryl thioethers *via* nucleophilic displacement of aryl halide by thiolate ion is reported. The reaction is shown to be dependent upon amide solvents exclusively with more than simple catalysis involved. Many different thioethers, both old and new, have been prepared in very good yield by this method.

Methods for the preparation of aryl thioethers have generally suffered from limited applicability in that activated reactants, severe reaction conditions, complicated procedures, or a combination of these requirements were involved.[1-5] Parker[6] has stated that unsymmetrical aryl sulfides can be prepared in high yields providing the halogen substrate is activated by at least one powerful electron-withdrawing substituent.

A recent method[7] developed in these laboratories involving reaction of disulfides with copper in the presence of halides has provided a means of synthesizing many different thioethers in a convenient way. An even more convenient and general sulfide preparation is described in the present paper. The method involves simply heating an alkali metal thiolate (either aliphatic or aromatic) and a halide together in an amide solvent. Results are summarized in Tables I and II.

$$\underset{(R)}{ArSK} + Ar'X \xrightarrow[\text{solvent}]{\text{amide}} \underset{(R)}{ArSAr'} + KX$$

An indication of the generality of the method is evident from the variety of sulfides reported. Not only is the method valuable for the preparation of polyaryl sulfides, but it also provides a convenient way to alkyl aryl sulfides from alkane thiols and aryl halides.

Examination of the data in Table I covering experiments on the preparation of bis(phenylmercapto)benzenes in certain solvents illustrates this method's amide solvent dependency. First attempts at aryl thioether synthesis involved Ullmann-like conditions found in aryl ether preparations where aryl halide and potassium aryl thiolate were heated in excess thiol at temperatures above 200° in the presence of copper salts. No reaction occurred, presumably because of the extreme insolubility of the potassium thiolate even under drastic conditions. Various high boiling solvents then were employed to attempt solution of the salt, but without avail until dimethylformamide was employed. The effectiveness of this solvent in solubilizing all reactants and in promoting formation of aryl thioethers from aryl thiolates and activated aryl halides has been described previously,[5,8] but was thought to be limited to activated halides. As shown in Table I, dimethylformamide serves in unactivated cases also, giving poorer yields of product.

Higher amide solvents, *i.e.*, N,N-dimethylacetamide, N,N-dimethylbutyramide, N,N-dibutylacetamide, and N-methyl-2-pyrrolidone, proved even more effective presumably because of their higher boiling points, thus higher reaction temperatures. For reasons of availability and ease of removal, dimethylacetamide was considered to be the solvent of choice and then was used most frequently. The utility of these amides apparently stems from two properties: (1) their ability to solubilize potassium aryl thiolates, and (2) their evident participation in the reaction. The first property has already been mentioned, but the second requires elaboration.

Prior to discussion of solvent participation it should be pointed out that the reaction appears to be a bimolecular nucleophilic substitution. Examination of data in Table I shows that it differs from an Ullmann-type reaction since no copper catalyst is really necessary. Preliminary kinetic and spectral data indicate the reaction is second order and that no other mechanisms are operating. Detailed kinetics and a suggested

(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., Inc., New York, N. Y., 1960, p. 28.

(2) E. Müller, *et al.*, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. IX, Georg Thieme Verlag, Stuttgart, 1955, pp. 97-118.

(3) J. F. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.*, **79**, 5967 (1957).

(4) R. Adams, W. Reifschneider, and M. D. Nair, *Croat. Chem. Acta*, **29**, 277 (1957); R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

(5) J. H. Uhlenbrock, *Rec. trav. chim.*, **80**, 1057 (1961).

(6) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, Inc., New York, N. Y., 1961, p. 107.

(7) J. R. Campbell, *J. Org. Chem.*, **27**, 2207 (1962).

(8) J. R. Campbell and R. E. Hatton, *ibid.*, **26**, 2480 (1961).