pared as above). The heterogeneous mixture did not show signs of reaction. After stirring this mixture for 5.0 min., ethanol (10 ml.) was added and the reaction mixture began to reflux vigorously and foamed considerably. When the foaming lessened, the reaction mixture was refluxed an additional 0.5 hr. on a steam bath, cooled and acidified with 10% hydrochloric acid and most of the solvent removed by distillation *in vacuo*. The residue was treated with water (300 ml.) and extracted with a 1:1 benzene–ether solution (four 100-ml. portions). The aqueous layer was then made basic with a 20% solution of sodium hydroxide, extracted with methylene chloride (five 200-ml. portions). After methylene chloride had been distilled, the residue was fractionated (the receiver placed in a 1:1 chloroform–carbon tetrachloride and Dry-ice bath) to yield pyridine (5.5 g.; 69.6% based on pyridine 1-oxide), b.p. 30–40° (16 mm.) and a mixture of 3- and 4-propylmercaptopyridines, (4.91 g.; 32.1% based on pyridine 1-oxide), b.p. 64–68° (1 mm.). Infrared spectra confirmed the presence of 3- and 4-isomers.

Anal. Calcd. for $C_8H_{11}NS$: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.56; H, 7.34; N, 8.86.

The fraction containing the mixture of 3- and 4-propylmercaptopyridines (4.91 g.) was placed on a column of alumina (100 g.; Alcoa activated alumina, grade F-20) in petroleum ether (10 ml.), b.p. 30–60°. The column was eluted with petroleum ether (b.p. 30–60°) with 500-ml. portions. The residue of each fraction was examined by its infrared spectrum, and carefully scrutinized for its components using the infrared spectra of pure 2-, 3- and 4-propylmercaptopyridines (recorded in Table I) as references. In particular, each fraction was examined for the presence of small quantities of isomeric impurities. For this purpose certain strong bands in the spectrum of each isomer were chosen. The first eluates from the column contained only the 3-isomer, characterized by strong sharp band at 1019 cm.$^{-1}$ which is apparently featured in many 3-substituted pyridines.[16] If the 2- and/or 4-isomers were present in these fractions, the presence of them would have been detected by absorption near 980 cm.$^{-1}$ since both isomers possess strong bands there. Furthermore, the 2- and 4-isomers show very strong bands near 1580 compared to a much weaker band at 1577 cm.$^{-1}$ for the 3-isomer. To distinguish if the 2- or the 4-isomer was the only contaminant, use of the overall patterns of the 2- and 4-isomers was made. The most distinguishing feature between these two isomers was the very strong band at 1452 for the 2-isomer, the strong band at 1465 cm.$^{-1}$ for the 4-isomer. Further elution then afforded the pure 4-isomer, free from 2- and 3-isomers shown by the absence of the 1452- and 1019-cm.$^{-1}$ bands, respectively.

In this particular experiment, 4500 ml. of petroleum ether eluted only 3-propylmercaptopyridine (4.50 g.; prior to distillation) which boiled between 123–124° at 16 mm., and weighed 4.1 g. (26.8% based on pyridine 1-oxide). Its refractive index ($n^{26}D$ 1.5550) and infrared spectrum were identical to the authentic sample made from 3-aminopyridine. Furthermore, its picrate (m.p. 113–115°) did not depress that made from the authentic sample.

Further elution of the column with anhydrous benzene (in 100-ml. portions, checking each fraction for its contents by means of infrared spectroscopy; a total of 200 ml.) yielded 4-propylmercaptopyridine (0.7 g.) which when distilled, b.p. 128–130° at 16 mm., weighed 0.55 g. (3.6% based on pyridine 1-oxide). Its infrared spectrum was identical to that of the sample made from 4-chloropyridine.

Reaction of 1-Ethoxypyridinium Ethyl Sulfate and Sodium *n*-Octylmercaptide.—Sodium hydride [4.8 g.; 0.2 mole (9.2 g. of a 53.2% suspension in mineral oil)] was added slowly in very small portions, with stirring, to 1-octanethiol (146 g.; 1.0 mole) contained in a 1-l. flask. Extreme care must be taken during the addition of sodium hydride to the 1-octanethiol, since the reaction is extremely exothermic and there is a tendency to char the sodium *n*-octylmercaptide. To the stirred suspension of sodium *n*-octylmercaptide in 1-octanethiol was added the gummy 1-ethoxypyridinium ethyl sulfate prepared from pyridine 1-oxide (9.5 g., 0.1 mole) as previously described. The rest of the procedure was the same as described. On work-up of the reaction mixture the fractions collected were pyridine, b.p. 30–40° (20 mm.), 1.0 g. (12.7%), and the 3- and 4-octylmercaptopyridines, b.p. 114–118° (2 mm.), 1.5 g. (6.7%). The presence of the mixture of the two isomeric sulfides was proven by the analysis of the infrared spectrum as evident from the strong bands at 1019 and 809 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.71; H, 9.32; N, 6.29.

This mixture afforded a picrate which crystallized from ethanol to a constant m.p. 83–85° which is below the melting points of the picrates of either the 3- and 4-isomers.

Anal. Calcd. for $C_{19}H_{24}N_4O_7S$: N, 12.38. Found: N, 12.09.

When 1.0 g. of this mixture was placed on 20 g. of alumina (Alcoa, grade F-20), no sulfide was eluted with petroleum ether (b.p. 30–60°). However, each fraction (25-ml. portions; 675 ml. in all) eluted with 10% benzene in petroleum ether or benzene alone consisted only of mixture of the 3- and 4-isomers. The absence of the 2-isomers was established since all fractions did not show bands at 1456, 1043 and 984 cm.$^{-1}$ (see Table I).

Acknowledgment.—L. A. G. wishes to thank the University of Illinois for a Fellowship for the academic year 1960–1961 and a Teaching Fellowship for the academic year 1961–1962. We thank Dr. Charles L. Bell for his help with the interpretation of the infrared spectra, and Messrs. Thomas Dickerhofe and Richard Egan for their invaluable assistance in this work, particularly in the synthesis of 3-octylmercaptopyridine. The authors gratefu'ly acknowledge a grant (G 22191) from the National Science Foundation which helped to defray part of the cost of this work.

(16) It had been shown that 3-substituted pyridines absorb in the vicinity of 1020 cm.$^{-1}$ [A. R. Katritzky, A. R. Hands, and R. A. Jones, *J. Chem. Soc.*, 3165 (1958)]. For example, 3-chloropyridine absorbs at 1025, 3-aminopyridine at 1010, 3-nitropyridine at 1021, and 3-acetylpyridine at 1023 cm.$^{-1}$.

The Chemistry of Pyridine. II. The Reaction of 1-Alkoxypicolinium Salts with Mercaptide and Thiophenoxide Ions

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The reaction of 1-alkoxy-2- and 4-picolinium salts with thiophenoxide ion furnished 2- and 4-[(arylmercapto)-methyl]pyridines, respectively, but no nuclear substitution was observed. However, the similar reaction with mercaptide ion was considerably more complex. It was found that 1-alkoxy-4-picolinium salts with mercaptide ions yielded besides 4-[(alkylmercapto)methyl]pyridine also 2- and 3-alkylmercapto-4-picolines and 1,2-di(4-pyridyl)ethane. Explanations are rendered for the formation of these various products. Syntheses of a number of these thioethers as reference compounds are described.

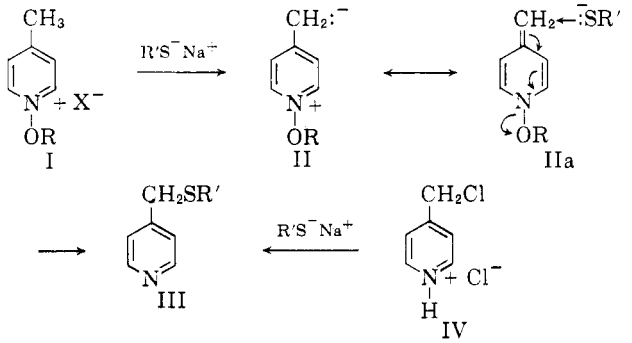
Nucleophilic attack by mercaptide ion on 1-alkoxypyridinium salts gave rise to a mixture of pyridine and 3- and 4-alkylmercaptopyridines.[2] However, thiophenoxide ion, under identical conditions, yielded only pyridine and no arylmercaptopyridines could be detected.[2] Pyridine produced in these reactions arises

(1) Abstracted from the Ph.D. thesis of Libero A. Gardella, University of Illinois at the Medical Center, Chicago 12, Ill., June, 1962; a part of this work was presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 4, 1961.

(2) L. Bauer and L. A. Gardella, part I, *J. Org. Chem.*, **28**, 1320 (1963).

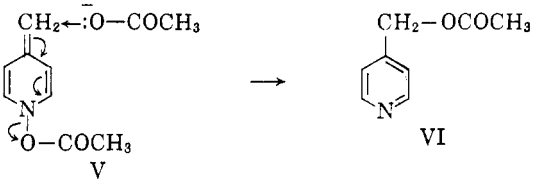
from nucleophilic attack by mercaptide or thiophenoxide ion on the N-alkoxy side chain, while the formation of the thioethers is the outcome of nuclear substitution. When the reaction of mercaptide and thiophenoxide ions was extended to 1-alkoxy-2- and -4-picolinium salts a variety of products were isolated. The reaction of thiophenoxide ions with 1-alkoxypicolinium salts is discussed first.

When 1-methoxy-4-picolinium methyl sulfate was added to an ethanol solution of sodium thiophenoxide, a vigorous reaction ensued. There was isolated a mixture of 4-picoline, its N-oxide and a crystalline unknown sulfur compound, m.p. 48–51°, $C_{12}H_{11}NS$. Three isomeric structures can be written for this unknown solid, *viz.*, 2- and 3-(phenylmercapto)-4-picoline and 4-[(phenylmercapto)methyl]pyridine, III (R′ = C_6H_5). Its nuclear magnetic resonance (n.m.r.) spectrum[3] clearly distinguished between the three isomeric thioethers. Its spectrum showed resonance characteristics of a pyridine possessing two pairs of equivalent protons (A_2B_2 type) as witnessed by the doublets centered at δ = 7.00 and 8.33 and also featured two other sharp bands, one due to the phenyl (δ = 7.12) and the other due to alkyl protons (δ = 3.85). Integration of the peaks due to the pyridine, phenyl and alkyl protons revealed them to be in ratio of 4:5:2. It then became apparent, that only structure III (R′ = C_6H_5) can be accommodated by this spectrum. Further confirmation of this structure was obtained when this thioether was synthesised from 4-(chloromethyl)pyridine hydrochloride, IV, and (two moles of) sodium thiophenoxide.



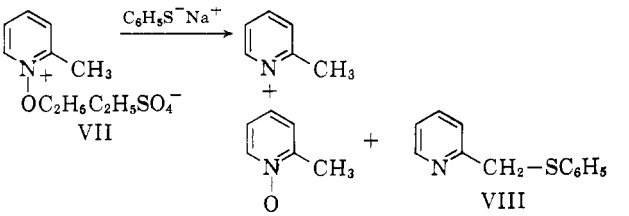
To explain the formation of III from I, the following mechanism is advanced. Abstraction of a proton by thiophenoxide ion from the active methylene group of I leads to the dipolar ion II, better represented by the neutral resonance hybrid, IIa. Further nucleophilic attack by thiophenoxide ion on the excyclic methylene group of IIa, with concerted departure of the alkoxide ion restores aromaticity to form III. This mechanism is in keeping with that proposed for the transformation of 4-picoline 1-oxide with acetic anhydride to 4-(acetoxymethyl)pyridine, VI. For that reaction, it has been postulated that the intermediate anhydro base, V, undergoes nucleophilic attack by acetate ion to form VI.[4]

The formation of 4-picoline and its N-oxide during the reaction of I with thiophenoxide ion stem from nucleophilic attack of thiophenoxide ion at the α-carbon of the N-alkoxy side chain.[2,5] In order to hinder reac-

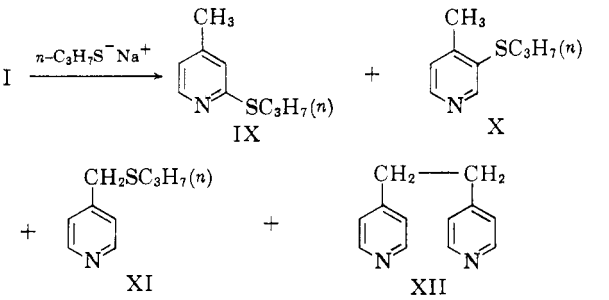


tion at that site, the bulk of the alkoxy substituent was increased. When R in I was changed from methyl to ethyl, the yield of III increased from 10 to 24%. It was found further that when I (R = ethyl) reacted with two moles of sodium thiophenoxide, the yield of III (R = C_6H_5) jumped from 24 to 65%. For these reactions, ethanol was found to be the best solvent.

The reaction of I (R = C_2H_5) was extended to *p*-*t*-butylthiophenoxide and *p*-chlorothiophenoxide to form the thioethers, III [R′ is *p*-(*t*-$C_4H_9C_6H_4$) and *p*-ClC_6H_4, respectively]. The reaction of 1-ethoxy-2-picolinium ethyl sulfate, VII, with sodium thiophenoxide was also explored. There was isolated 2-picoline (31%), its N-oxide (16%) and 2-[(phenylmercapto)methyl]pyridine, VIII (38%).



The reaction of I with mercaptide ions was considerably more complex and was studied extensively with two thiols, 1-propane- and 1-octanethiol. Treatment of I (R = C_2H_5) with sodium propylmercaptide in excess 1-propanethiol (containing a little ethanol) yielded the cleanest product. It consisted of 4-picoline, a mixture of (propylmercapto)pyridines (IX, X, and XI), and a high-boiling fraction which contained mostly 1,2-di(4-pyridyl)ethane, XII. The separation and identification of the thioethers is discussed first.

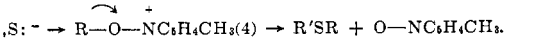


Column chromatography on alumina was attempted to separate the thioethers. Elution of successive fractions was followed by infrared spectroscopy and the spectra compared to reference compounds. For the purpose of identifying components of this mixture, 2-propylmercapto-4-picoline, IX, and 4-[(propylmer-

(3) Determined in carbon tetrachloride using tetramethylsilane as internal standard using the Varian A-60 spectrometer. We are indebted to Dr. L. F. Johnson of Varian Associates, Palo Alto, Calif., for this spectrum.

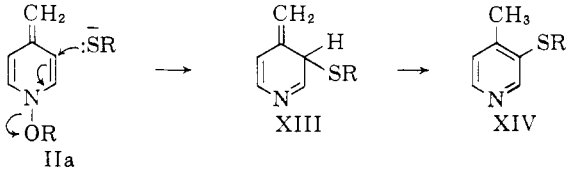
(4) For a study of mechanism of this reaction see (a) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **82**, 2744 (1960); (b) S. Oae, T. Kitao and Y. Kitaoka, *ibid.*, **84**, 3359 (1962).

(5) It had previously been reported by N. A. Coats and A. R. Katritzky [*J. Org. Chem.*, **24**, 1836 (1959)] that the reaction of 1-methoxypyridinium *p*-toluenesulfonate with sodium benzylmercaptide formed pyridine N-oxide, isolated as the picrate in 35% yield. This reaction can be regarded as a nucleophilic displacement reaction by mercaptide ion on the α-alkoxy group to form the N-oxide:

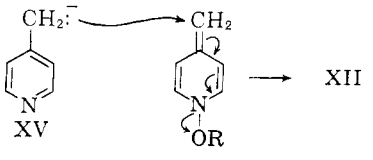


capto)methyl]pyridine, XI, were synthesized (see below). The first pure component was proved to be pure IX, identified by comparison with an authentic sample. The second compound corresponded to "a" (propylmercapto)methylpyridine. Raney nickel desulfurization of this sulfide yielded 4-picoline. But since the infrared spectrum and its picrate were different to those of authentic IX and XI, this thioether was assigned the remaining isomeric structure, X. The remaining fractions proved to be an inseparable mixture of X and XI, in varying proportions, as witnessed by the appearance in the infrared spectrum of the 1606- and 999-cm.$^{-1}$ bands, characteristic of XI. All attempts to effect complete separation of X and XI on acid or basic alumina of different activities as well as on silica gel, proved futile. The presence of XI in this mixture was proved when a *p*-toluenesulfonate could be crystallized from the original mixture.

The formation of these three sulfides by the reaction of I (R = ethyl) with propylmercaptide ion can be explained in the following manner: Nucleophilic attack of the mercaptide ion on the active methylene group of I follows the path suggested for that for thiophenoxide ion (see above). Since the 4-position of the pyridine ring is blocked, nuclear substitution may occur at the 2- and 3-position. Attack at the 3-position may follow the mechanism, which has been suggested to explain the formation of 3-acetoxy-4-picoline during the reaction of 4-picoline 1-oxide with acetic anhydride.[4] This involves nuclear attack by the acetate ion on V with the departure of the N-acetoxy moiety to form 3-acetoxy-4-picoline. To apply this mechanism to our reaction it would involve nucleophilic attack of mercaptide ion on IIa (the counterpart on the anhydrobase, V) with the concomitant loss at alkoxide ion to form XIII or its stable tautomer XIV.



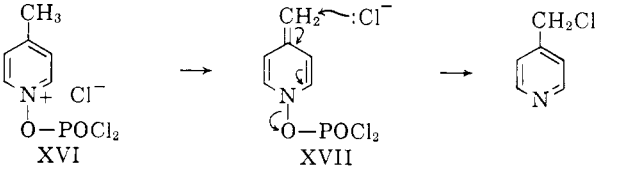
The unexpected formation of 1,2-di(4-pyridyl)ethane, XII, during this reaction remains to be explained. It may be produced in the following manner: Attack of the mercaptide ion on the α-carbon of the N-alkoxy side chain can give rise to 4-picoline (equation 2 in ref. 2). In the medium of the reaction, mercaptide ion can act as a strong base and abstract a proton from 4-picoline to form its anion, XV. Acting as a competing nucleophile, XV may also attack IIa in a manner similar to the mercaptide ion to form XII.



The reaction of I (R = C_2H_5) with octylmercaptide ion in excess thiol containing some ethanol (10:1; v./v.) afforded 4-picoline, a "middle" fraction which consisted of a mixture of three sulfides, the *n*-octyl analogs IX, X, and XI, and some 1,2-di(4-pyridyl)ethane, XII. The mixture of sulfides was partially resolved by column chromatography. For an effective separation, it became necessary to use a large ratio of alumina to thioether (100:1) and collect the eluate in small volumes. It was found that petroleum ether (b.p. 30–60°) first eluted pure 2-octylmercapto-4-picoline and then pure 3-octylmercapto-4-picoline. However, subsequent eluates of the latter were contaminated by 4-[(octylmercapto)methyl]pyridine. Again, the presence of these three isomers were spotted by using the characteristic infrared bands.

Synthesis of Reference Compounds.—For the purpose of identifying the products of the reaction described above, a number of alkyl- and arylmercapto substituted 2- and 4-picolines were synthesized by alternate routes. These sulfides are listed in Table II. The reaction of 2- and 4-(chloromethyl)pyridine hydrochloride with two moles of thiol and sodium ethoxide (to form the anion) in ethanol furnished the corresponding sulfides. The reaction for the 4-isomers is represented by the conversion of IV to III. A series of 2-alkylmercapto-4-picolines was prepared from 2-chloro-4-picoline by reaction with mercaptide ion as described before.[2] 2-Chloro-4-picoline was made unequivocally from 2-amino-4-picoline by the low temperature diazotization in the presence of fuming hydrochloric acid.[6] Reaction of 2-chloro-4-picoline with thiophenol afforded 2-phenylmercapto-4-picoline, made for comparison with 4-[(phenylmercapto)methyl] pyridine obtained from the reaction of I with thiophenoxide ion.

Another method for the preparation of 2-chloro-4-picoline seemed feasible to us based on some related reactions reported in the literature. It has been shown that the reaction of 2-picoline 1-oxide and 2,6-lutidine 1-oxide with phosphorus oxychloride affords predominantly 4-chloro-2-picoline and 2,6-dimethyl-4-chloropyridine, respectively.[7] However, these reaction products were accompanied by a small amount of the halogenated sidechain products, *viz.*, 2-(chloromethyl)pyridine and 2-(chloromethyl)-6-methylpyridine. By an analogous reaction, it seemed possible to us to treat 4-picoline 1-oxide with phosphorus oxychloride and obtain 2-chloro-4-picoline. When this reaction was carried out as described for the 2-picoline 1-oxide, a (chloromethyl)pyridine was obtained. Reaction of it with thiophenol (hydrogen chloride to be absorbed by the pyridine moiety) furnished a 55% yield of 4-[(phenylmercapto)methyl]pyridine identical in all respects to that made from 4-(chloromethyl)pyridine. From this observation, we conclude that the reaction of 4-picoline 1-oxide with phosphorus oxychloride yields predominantly 4-chloromethylpyridine. The first intermediate of this reaction may be XVI which loses the elements of hydrogen chloride to give XVII. Nucleophilic attack by chloride ion on XVII with the simultaneous loss of the phosphorus moiety leads to 4-chloromethylpyridine. This reaction may proceed



(6) O. Seide, *Ber.*, **57**, 791 (1924).

(7) T. Kato, *J. Pharm. Soc. Japan*, **75**, 1239 (1955); *Chem. Abstr.*, **50**, 8665 (1956).

along lines similar to the reaction of 2,6-lutidine 1-oxide with *p*-toluenesulfonylchloride to give 2-(chloromethyl)-6-methylpyridine in 43% yield.[8]

The infrared spectra of the two isomers, 2-(phenylmercapto)-4-picoline and 4-[(phenylmercapto)methyl] pyridine as well as the three isomeric propylmercaptomethylpyridines, IX, X, XI, are listed in Table I.

Experimental[9]

Starting Materials.—2- and 4-picoline 1-oxide were obtained from Reilly Coal Tar and Chemical Corp., Indianapolis, Ind.; 2- and 4-(chloromethyl)pyridine hydrochlorides from Aldrich Chemical Co., Milwaukee, Wis. We gratefully acknowledge the generous and kind gifts of: 1-propane and 1-octanethiols from Pennsalt Chemical Corp., Philadelphia, Pa. and Phillips Petroleum Co., Bartlesville, Okla.; *p*-chlorothiophenol from Evans Chemetics, Inc., New York, N. Y.

TABLE I

INFRARED ABSORPTION BANDS (CM.$^{-1}$) OF SOME OF THE THIOETHERS

4-[(Phenylmercapto)-methyl]-pyridine	2-Phenylmercapto-4-picoline	4-[(Propylmercapto)-methyl]-pyridine	2-Propylmercapto-4-picoline	3-Propylmercapto-4-picoline
3275 w-b	3350 w-b	3305 m-b	3353 w-b	3253 w-b
3070 s	3050 sh		3058 sh	
2975 s-b	3000 vs	2959 vs	2959 vs	2959 vs
			2935 sh	2935 sh
	2875 sh	2885 sh	2870 s	2861 s
2486 w-b	2492 w-b	2492 w-b	2467 vw-b	2467 w-b
1941 w-b		2000 vw	1926 vw	
			1614 sh	
1603 vs	1596 vs-b	1606 vs	1595 vs	
1586 s				1580 s
1565 s		1567 m	1549 s	
	1536 s		1539 sh	
		1509 sh		
1496 sh		1495 w		
1483 s	1478 sh			1478 s
	1465 vs	1465 s	1465 s-b	1463 s
1442 s	1444 vs	1442 sh	1442 sh	1442 sh
1420 s		1422 s		
	1396 sh			1401 s
	1381 vs	1381 m	1374 s	1381 s
				1365 sh
		1335 w	1335 vw	
	1304 w	1297 m	1289 sh	1289 m
	1284 s		1284 s	
1248 s-b	1243 s-b	1243 s-b	1253 sh	
			1238 s	1238 s
		1223 sh		
		1207 sh		
		1194 sh		1172 w
		1141 vw-b		
	1121 vs		1120 vs	
1088 s	1087 vs	1091 w	1096 s	1106 s
1069 s	1067 m	1067 m		1060 w
		1050 vw	1050 vw	
1024 s	1024 s		1045 vw	1043 s
			1041 vw	
999 sh	999 m	999 s		
995 s	989 s		985 s	
887 s		892 m-b	897 w	897 vw
	872 s		872 s	
831 m		837 sh		827 s
819 m	823 s		820 s	
		804 s		

Synthesis of Reference Compounds: (A) 2-and 4-[Aryl (or Alkyl)mercaptomethyl]pyridines from 2- and 4-(Chloromethyl)-pyridine Hydrochlorides.—A general procedure has been developed for the synthesis of these thioethers. To a solution of sodium ethoxide (0.2 g.-atom of sodium dissolved in 100 ml. in ethanol) was added the thiol (0.2 mole) followed by the requisite (chloromethyl)pyridine hydrochloride (0.1 mole). The mixture was heated on a steam bath for 2 hr., cooled, and solvents removed at 30 mm. (If one expects a highly volatile thioether, the solution may be acidified prior to the last step.) The residue was acidified with 10% hydrochloric acid (100 ml.) and extracted with a mixture of ether–benzene (1:1; five 30-ml. portions to remove neutral and acidic products). Methylene chloride may be used for this extract, but we have found that several of the hydrochlorides were appreciably soluble in that solvent. The aqueous phase was made alkaline with 20% sodium hydroxide and extracted with methylene chloride (eight 30-ml. portions). Distillation of this extract afforded the thioethers. Their physical constants, analyses, and derivatives are listed in Table II under method A.

Preparation of 4-[(Phenylmercapto)methyl]pyridine *via* the Product of Reaction of 4-Picoline 1-Oxide with Phosphorus Oxychloride.—A chloroform solution of 4-picoline 1-oxide (10.9 g.; 0.1 mole in 50 ml.) was added dropwise, with stirring, to a chloroform solution of phosphorus oxychloride (19.2 g.; 0.125 mole (in 50 ml.), and the mixture was refluxed for 5.5 hr. The mixture was poured onto ice and made alkaline with sodium hydroxide at 5°. The inorganic salts were removed by filtration. The filtrate was extracted with chloroform (eight 50-ml. portions). and the organic extract distilled. The yield of the "chloropico, line" was 4.5 g. (35%), b.p. 39–40° (1.5 mm.). This "chloropicoline" (2.60 g.; 0.02 mole) and thiophenol (2.20 g.; 0.02 mole) were heated at 150–160° for 4 hr. On cooling crystals formed. The product was made basic with 10% aqueous sodium hydroxide and extracted, worked up as in A to yield 4-[(phenylmercapto)-methyl]pyridine 2.25 g. (55% yield based on the chloro compound) identical to the thioether described in method A.

(B) 2-Alkylmercapto-4-picolines.—These were prepared essentially by the method of Profft.[10] A typical experiment is described for the synthesis of 2-octylmercapto-4-picoline: Potassium hydroxide (1.4 g.; 0.025 mole) was dissolved in a solution of N,N-dimethylformamide (40 ml.) and 1-octanethiol (3.65 g., 0.025 mole). To this was added 2-chloro-4-picoline[6] (3.18 g.) and the reaction mixture heated on a steam bath for 3.0 hr., cooled, acidified with concentrated hydrochloric acid, and worked up as in method A. The products are listed in Table II.

2-Phenylmercapto-4-picoline.—The method follows that of Brooker, *et. al.*[11] Triethylamine (2.02 g.; 0.02 mole) was added in small portions, with shaking, to a mixture of 2-chloro-4-methylpyridine (1.27 g.; 0.01 mole) and thiophenol (2.20 g.; 0.02 mole). When the addition was completed, the reaction mixture was refluxed on a steam bath for 5.0 hr. The reaction mixture was cooled, made alkaline, and worked up as in A and the product recorded in Table II.

(C) Reaction of 1-Ethoxy-2- and 4-Picolinium Salts with Thiophenoxide Ions.—A typical experiment is described. 1-Ethoxy-4-picolinium ethyl sulfate[12] was prepared by heating 4-picoline 1-oxide (10.9 g., 0.1 mole) with ethyl sulfate (15.4 g.; 0.1 mole) at 100° for 2 hr. The sirup which was washed with dry ether (two 25-ml. potions) was dissolved in ethanol (25 ml.) and used immediately in the next step.

To a stirred ice-cold solution of sodium thiophenoxide in ethanol [made by dissolving sodium (4.6 g.; 0.2 g.-atom) in 100 ml. ethanol and adding thiophenol (22.0 g.; 0.2 mole)] was added the ethanol solution of 1-ethoxy-4-picolinium ethyl sulfate prepared above. The addition was controlled to maintain the temperature between 10 and 30°. After the completion of the addition, the reaction was stirred at room temperature for 0.5

(8) E. Matsumura, T. Hirooka and K. Imagawa, *Nippon Kagaku Zasshi*, **82**, 616 (1961).

(9) All melting points and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Dr. Kurt Eder, Geneva, Switzerland. Some of the nitrogen analyses were performed using a Coleman Nitrogen Analyzer, Model 29.

(10) E. Proft and W. Rolle, *J. prakt. Chem.*, (4) **11**, 32 (1960). The method of Brooker[11] as described below for the preparation of 2-arylmercaptopyridines failed to yield thioethers when mercaptans were used.

(11) L. G. S. Brooker, *et. al.*, *J. Am. Chem. Soc.*, **73**, 5326 (1951).

(12) The salt was not crystallized but was characterized as the picrate, m.p. 96–97° (from ethanol). O. Červinka, *Collection Czech. Chem. Commun.*, **27**, 567 (1962), reports its m.p. 99°.

TABLE II

Substituents of pyridine ring	B.p., °C. (pressure), refractive index (m.p., solvent of cryst.)	Method	Yield, %	Mol. formula	Analyses, %	C	H	N	Derivative	Solvent of cryst.	M.p., °C.	Mol. formula	Analyses, %	C	H	N
2-(Phenylmercapto)methyl	123–127° (0.4 mm.)	A	81	$C_{12}H_{11}NS$	Calcd.	71.60	5.51	6.96	Hydrochloride	Ethanol–ether	137–138	$C_{12}H_{12}NSCl$	Calcd.	...	..	5.89
	$n^{27.5}D$ 1.6210	C	38		Found	71.76	5.54	7.12					Found	...	..	6.21
2-(Propylmercapto)methyl	90–93° (4 mm.)	A	97	$C_9H_{13}NS$	Calcd.	64.61	7.83	8.38	..	...	...	..	..	...	..	...
	$n^{30.5}D$ 1.5373				Found	65.06	7.76	8.12								
4-(Phenylmercapto)methyl	126–128° (1 mm.)	A	89	$C_{12}H_{11}NS$	Calcd.	71.60	5.51	6.96	Hydrochloride	Ethanol–ether	142–144	$C_{12}H_{12}NSCl$	Calcd.	60.62	5.09	5.89
	$n^{24}D$ 1.6194	C	65		Found	71.67	5.59	7.19					Found	60.74	5.26	6.01
	(48–51°) from pet. ether, b.p. 30–60°								Picrate	Ethanol	131–132	$C_{18}H_{14}N_4O_7S$	Calcd.	...	..	13.02
													Found	...	..	12.94
4-(*p*-Chlorophenylmercapto)methyl	136–141° (0.3 mm.)	C	50	$C_{12}H_{10}NSCl$	Calcd.	...	..	5.94	Hydrochloride	Ethanol	212–213	$C_{12}H_{11}NSCl_2$	Calcd.	52.95	4.07	5.15
					Found	...	..	6.27					Found	52.85	4.15	5.03
4-(*p*-*t*-Butylphenylmercapto)methyl	152–157° (0.06 mm.)	C	53	$C_{16}H_{19}NS$	Calcd.	74.66	7.47	5.44	Hydrochloride	Acetone–ethanol (trace)	215–217	$C_{16}H_{20}NSCl$	Calcd.	65.40	6.86	4.77
	(52–54°) from pet. ether, b.p. 30–60°				Found	74.72	7.42	5.21					Found	65.84	6.96	4.51
4-(Propylmercapto)methyl	100–105° (3 mm.)	A	96	$C_9H_{13}NS$	Calcd.	64.61	7.83	8.38	*p*-Toluenesulfonate	Acetone	115–117	$C_{16}H_2NO_3S_2$	Calcd.	...	..	4.13
					Found	64.38	7.81	8.09					Found	...	..	4.37
									Picrate	Ethanol	129–131	$C_{15}H_{16}N_4O_7S$	Calcd.	...	..	14.14
													Found	...	..	13.89
4-(Octylmercapto)methyl	142° (1.1 mm.)	A	93	$C_{14}H_{23}NS$	Calcd.	70.82	9.77	5.90	*p*-Toluenesulfonate	Acetone	116–117	$C_{21}H_{31}NO_3S_2$	Calcd.	...	..	3.42
					Found	70.64	9.75	6.06					Found	...	..	3.56
2-Phenylmercapto-4-methyl	125° (0.3 mm.)	B	100	$C_{12}H_{11}NS$	Calcd.	71.60	5.51	6.96	...	...	...	...	...	...	..	...
					Found	71.35	5.67	7.46								
2-Propylmercapto-4-methyl	67° (2 mm.)	B	42	$C_9H_{13}NS$	Calcd.	64.61	7.83	8.38	Picrate	Ethanol	137–139	$C_{15}H_{16}N_4O_7S$	Calcd.	...	..	14.14
					Found	64.40	7.98	8.34					Found	...	..	13.91
2-Octylmercapto-4-methyl	135–138 (0.5 mm.)	B	79	$C_{14}H_{23}NS$	Calcd.	70.82	9.77	5.90	...	...	...	...	...	...	..	...
	$n^{29}D$ 1.5120				Found	70.09	9.87	5.64								
3-Propylmercapto-4-methyl	139–140° (21 mm.)	D	...	$C_9H_{13}NS$	Calcd.	64.61	7.83	8.38	Picrate	Ethanol	140–143	$C_{15}H_{16}N_4O_7S$	Calcd.	...	..	14.14
	$n^{25}D$ 1.5510				Found	64.65	7.89	8.29					Found	...	..	14.60
3-Octylmercapto-4-methyl	125–127° (0.25 mm.)	D	...	$C_{14}H_{23}NS$	Calcd.	70.82	9.77	5.98	Picrate	Ethanol	120–122	$C_{20}H_{26}N_4O_7S$	Calcd.	...	..	12.01
	$n^{34}D$ 1.5188				Found	70.87	9.97	5.90					Found	...	..	11.70

hr. and then evaporated at 35° *in vacuo*. The residue was acidified and worked up as described in method A.

The only modification in the work-up was to wash the methylene chloride extract containing the **thioether** several times with water prior to distillation. This procedure was found to be of advantage as it removes most of 4-picoline 1-oxide due to its inherent solubility in water. This avoided contamination of the higher boiling thioethers with the N-oxide.

The reaction with thiophenoxide afforded 4-picoline, b.p. 40–50° at 13 mm. (3.2 g.; 34%) and 13 g. of 4-[(phenylmercapto)methyl]pyridine (listed in Table II). Other thioethers made in this fashion are listed in Table II under method C.

When 2-picoline 1-oxide was substituted in this reaction, the same procedure was followed. In its reaction with sodium thiophenoxide under the conditions described, there was obtained 2-picoline (3.0 g.; 31%) b.p. 40–50° at 13 mm., 2-picoline 1-oxide (1.7 g.; 16%) b.p. 85–100° at 0.5 mm., and the thioether listed in Table II.

(D) **Reaction of 1-Ethoxy 4-Picolinium Salts with Mercaptide Ions.** (a) **With Propylmercaptide Ion.**—Sodium propylmercaptide was prepared by the addition of sodium hydride (4.8 g.; 0.2 mole) to 1-propanethiol (76 g.; 1 mole). To the resulting suspension was added the ethanol solution of the 1-ethoxy salt prepared above under C (but dissolved in 10 ml. ethanol only) and the mixture heated under reflux for 0.5 hr. The solvents were then evaporated *in vacuo* and the residue worked up as described in method A. Distillation of the basic fraction gave 4-picoline, b.p. 40–50° at 20 mm. (4.0 g.; 43%), a mixture of thioethers (see below), b.p. 80–95° at 2.0 mm. (8.0 g.; 47.9%), and 1,2-di(4-pyridyl)ethane XII, b.p. 130–150° at 2 mm. (0.8 g.; 8.7%), whose identification is described below.

Separation of the Thioethers IX, X, and XI.—The mixture (5.0 g.) was placed on alumina (100 g.; Alcoa, activated, Grade F-20) with petroleum ether (b.p. 30–60°). Elution with the first two fractions (two 200-ml. lots) yielded 0.71 g. whose infrared spectrum was identical to 2-propylmercapto-4-picoline. Distillation yielded 0.38 g. of the thioether, b.p. 133–136° (20 mm.), $n^{25}D$ 1.5500, whose picrate m.p. 137–139° was underpressed by the picrate of the sample prepared in B.

Continued elution with an additional 200 ml. of petroleum ether (b.p. 30–60°) affords a fraction which consisted of a mixture. Further elution with the same solvent furnished seven fractions (1400 ml. in all) which contained pure 3-propylmercapto-4-picoline (1.87 g. in all). Distillation gave an analytical sample (0.88 g.) whose physical constants are recorded in Table II. Its picrate (m.p. 140–143°) depressed the m.p. of that of 2-propylmercapto-4-picoline (m.p. 137–139°) to 113–127°. Desulfurization of this thioether (0.5 g.) was achieved with W-5 Raney nickel (three teaspoons, *ca.* 20 g.) in boiling acetone (150 ml.) for 20 hr. Work-up of the reaction mixture yielded 4-picoline (0.3 g.), b.p. 30–50° (20 mm.). The picrate, m.p. 161–163° (from ethanol), did not depress that of an authentic sample, m.p. 165–166°, and the infrared spectra of the two picrates were superimposable.

Further elution of the chromatograph with an additional fifteen fractions (3000 ml. of petroleum ether, b.p. 30–60°) yielded in each a mixture of 3-propylmercapto-4-picoline and 4-[(propylmercapto)methyl]pyridine in varying proportions. Rechromatography of this fraction (after it was redistilled) on fresh alumina again only effected partial separation as described above.

The highest boiling fraction obtained in this experiment was dissolved in acetone and treated with an excess of *p*-toluenesulfonic acid. The **salt** so formed crystallized from acetone or ethanol, m.p. 245–246°.

Anal. Calcd. for $C_{26}H_{28}N_2S_2O_6$: C, 59.06; H, 5.34; N, 5.30. Found: C, 59.12; H, 5.49; N, 5.56.

The *p*-toluenesulfonate made from sample of 1,2-di(4-pyridyl)ethane (purchased from Aldrich Chemical Co., Milwaukee, Wis.) was identical to the sample isolated above (melting point, mixture melting point, and infrared spectrum).

When the reaction described above is carried out in ethanol alone, there was isolated 4-picoline (67.7%), the mixture of sulfides (18%), and XII (15%). A similar reaction performed in N,N-dimethylformamide produced the mixture of sulfides in 30% and XII in 11% yield.

(b) **With Octylmercaptide Ion.**—The experiment was performed essentially as in a. 1-Ethoxy-4-picolinium ethyl sulfate (from 0.1 mole of 4-picoline 1-oxide) was dissolved in 25 ml. ethanol. Sodium octylmercaptide was prepared by dissolving sodium (4.6 g.) in ethanol (50 ml.) and 1-octanethiol (100 ml.). The 1-ethoxy salt was now added and the reaction heated at 100° for 0.5 hr. and then worked up as in A. Two fractions were isolated: 4-picoline (6.8 g.; 73%), b.p. 40–50° (14 mm.), and the **thioethers** and 1,2-(4-pyridyl)ethane, XII (4.2 g.), b.p. 130–150° (0.7 mm.). Separation of XII from the thioethers was accomplished as follows: When the mixture was treated with excess dry *p*-toluenesulfonic acid in acetone and a small amount of dry ether, the *p*-toluenesulfonate of XII (see above), m.p. 240–244°, crystallized. The solid was filtered off and the mother liquor[13] evaporated to dryness. The residue was treated with 20% sodium hydroxide, extracted with methylene chloride, and redistilled. The **thioethers** boiled at 138–141° (1.1 mm.).

Chromatography of the thioethers (5.0 g.) on Alcoa activated alumina (100 g., grade F-20) effected the following separations when 200-ml. portions were collected. The first fraction eluted by petroleum ether, b.p. 30–60°, contained pure 2-octylmercapto-4-picoline (0.5 g.). The next seven fractions (1400 ml. of the same eluent) yielded 1.2 g. of 3-octylmercapto-4-picoline whose constants are recorded in Table II. Further elution by petroleum ether simply gave mixtures of 3-octylmercapto-4-picoline and 4-[(octylmercapto)methyl]pyridine, as ascertained by the examinations of the infrared spectra of these fractions.

When this reaction was performed by the addition of the 1-ethoxy-4-picolinium salt (in N,N-dimethylformamide) to a suspension of sodium octylmercaptide in N,N-dimethylformamide and excess 1-octanethiol, the fraction containing the thioethers and XII (b.p. 133–160° at 0.8 mm.) was improved (7.5 g. from 0.1 mole of 4-picoline 1-oxide). Separation of the components as shown above indicated it to be a similar mixture.

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(13) In one experiment, another crop of crystals, m.p. 113–115°, was obtained on slow evaporation of this mother liquor. The m.p. was undepressed on admixture with a sample of 4-[(octylmercapto)methyl]pyridine *p*-toluenesulfonate made in A, (m.p. 116–117°). However, the yield of this salt was poor and no other fractions could be separated by fractional crystallization. Hence, chromatography was resorted to again as described previously.