Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.36; H, 5.13; N, 4.69.

The wave-length maxima for IIIa are λ 368, 358, 350, 342, 335, 329, 288, 277, 267, 256, and 232 mμ.

B. From 1-(2-benzyl)naphthyl 4-Pyridyl Ketone (VIa).—A mixture of 3.85 g. of VIa, 50 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was heated under reflux for 47 hr. and then worked up as was IIa in A. The product weighed 3.15 g. (87%), m.p. 218–221°.

12-(3-Pyridyl)benz[*a*]anthracene (IIIb). A. From 2-(2-Naphthylmethylphenyl 3-Pyridyl Ketone (IIb).—A mixture of 4.4 g. of IIb, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 18 hr. and then worked up as was IIIa in A. The product, 2.0 g. (48%), was recrystallized from ethanol giving pale yellow needles, m.p. 169–170°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.14; H, 4.93; N, 4.78.

The wave-length maxima for IIIb are λ 366, 360, 350, 343, 335, 289, 278, 269, 253, and 232 mμ.

B. From 1-(2-Benzyl)naphthyl 3-Pyridyl Ketone (VIb).—A mixture of 2.7 g. of VIb, 25 ml. of 48% hydrobromic acid, and 50 ml. of glacial acetic acid was sealed in a Carius tube and heated for 9 hr. at 180° and then worked up as was IIIa in A. The product, 1.7 g. (67%), on recrystallization from ethanol gave pale yellow needles, m.p. 169–170°. The same reaction conducted at reflux temperature for 48 hr. gave only 42% of IIIb.

12-(2-Pyridyl)benz[*a*]anthracene (IIIc). A. From 2-(2-Naphthylmethyl)phenyl 2-Pyridyl Ketone (IIc).—A mixture of 0.40 g. of IIc, 20 ml. of 48% hydrobromic acid, and 40 ml. of glacial acetic acid was heated under reflux for 13 hr. and worked up as was IIIa in A. The product, 0.17 g. (45%), was recrystallized from absolute ethanol giving white plate-like crystals, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.30; H, 4.93; N, 4.69.

The wave-length maxima for IIIc are λ 366, 368, 349, 342, 335, 288, 278, 268, 254, and 232 mμ.

B. From 1-(2-Benzyl)naphthyl 2-Pyridyl Ketimine (VII).—A mixture of 1.0 g. of VII, 15 ml. of 48% hydrobromic acid, and 30 ml. of glacial acetic acid was placed in a Carius tube and heated for 24 hr. at 180°. The product was chromatographed[24] giving 0.13 g. (14%) of IIIc.

12-(4-Pyridine N-oxide)benz[*a*]anthracene.—A solution of 1.0 g. of 12-(4-pyridyl)benz[*a*]anthracene in glacial acetic acid was oxidized with 30% hydrogen peroxide using the method of Boekelheide and Linn.[16] The product, 0.60 g. (57%), was recrystallized from ethanol giving white needles, m.p. 276.0–278.5° dec.

Anal. Calcd. for $C_{23}H_{15}NO$: C, 85.96; H, 4.70; N, 4.36. Found: C, 86.31; H, 4.77; N, 4.28.

The wave-length maxima for the N-oxide are λ 370, 360, 351, 343, 336, 288, 277, 268, 254, and 233 mμ.

3-Aza-10-Phenyldibenzo[*def*,*p*]chrysene (VIIIa).[28]—A solution of 0.50 g. of 12-(4-pyridyl)benz[*a*]anthracene in 75 ml. of benzene was heated under reflux, 1 g. of $AlCl_3$ was added, and the mixture was heated for 5 min. The mixture was cooled, decomposed with dilute hydrochloric acid, and neutralized. The aqueous layer was separated and extracted with benzene–acetone, and the organic solutions were combined, washed with water, and dried over calcium sulfate. The solution was concentrated to *ca.* 5 ml. and chromatographed on alumina using a mixture of benzene and petroleum ether (1:1) as the eluent. A colorless, blue fluorescent band was removed from which no pure material could be obtained. The remaining yellow band was removed using benzene as the eluant. Upon concentration and cooling there was obtained a yellow solid, m.p. 281–282°, yield 0.87 g. (14%).

The analytical sample was obtained by recrystallization from benzene as fine, yellow needles, m.p. 282–283°.

Anal. Calcd. for $C_{29}H_{17}N$: C, 91.79; H, 4.52; N, 3.69; mol. wt., 379. Found: C, 91.51; H, 4.42; N, 3.91. mol. wt. (Rast), 399 and 400.

The wave-length maxima for VIIIa are λ 331, 316, 300, 289, 265, 255, and 248 mμ.

2-Aza-10-phenyldibenzo[*def*,*p*]chrysene (VIIIb).—This product was obtained essentially as was compound VIIIa. One-half gram of 12-(3-pyridyl)benz[*a*]anthracene yielded 0.039 g. (6%) of fine, yellow needles, m.p. 258.0–259.5°.

Anal. Calcd. for $C_{29}H_{17}N$: C, 91.79; H, 4.52; N, 3.69. Found: C, 91.92; H, 4.78; N, 3.74.

The wave-length maxima for VIIIb are λ 331, 316, 300, 289, 258, 243, and 232 mμ.

(28) This is the best of 37 experiments.

The Chemistry of Pyridine. III. Substitution of 1-Alkoxy, 1-Acyloxy-, and 1-Sulfonyloxypyridinium Salts by Mercaptans

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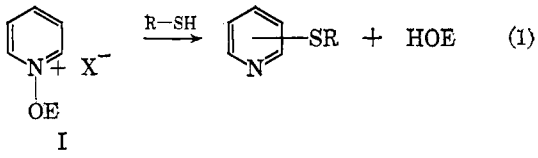
The substitution of pyridine N-oxide *via* N-alkoxy-, N-alkoxy-, N-acyloxy-, and N-sulfonyloxypyridinium salts with 1-butanethiol produced mixtures of 2-, 3-, and 4-butylmercaptopyridine. The yield of these sulfides and the distribution of the isomers depended on the reaction conditions and the nature of the departing substituent from the ring nitrogen of the pyridinium moiety. The mode of formation of the diverse products is discussed.

It had previously been shown[1,2] that N-alkoxypyridinium salts were substituted by mercaptans to form a mixture of alkylmercaptopyridines according to eq. 1.



I (1)

It was of interest to ascertain the course of this reaction when groups of different electronic disposition were attached to the ring nitrogen of I. This paper describes the reaction expressed by eq. 1 when E was ethyl, acetyl, benzoyl, and arenesulfonyl. It was found that a change of E from alkyl to acyl or sulfonyl resulted in different mixtures of alkylmercaptopyridines.

Before studying the substitution of the various pyridinium salts it was essential to establish if pyridine N-oxide itself would be substituted by mercaptide ion. When the N-oxide was treated with 1-butanethiol in the presence of sodium *n*-butylmercaptide, it was recovered partly, and no alkyl pyridyl sulfides could be detected.[3] Therefore it seemed essential to convert pyridine N-oxide first to a salt of type I before substitution by mercaptans could take place. The most available salts are the crystalline N-alkoxypyridinium salts (I, E is alkyl), which are readily formed when

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

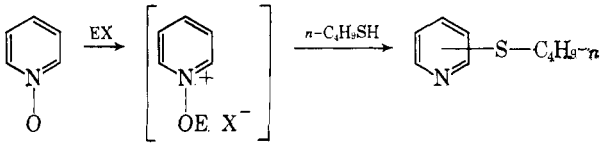
(2) L. Bauer and L. A. Gardella, *ibid.*, **28**, 1323 (1963).

(3) In conducting this experiment, cognizance was taken of the reduction of N-oxides with mercaptans described by D. I. Relyea, P. O. Tawney, and A. R. Williams [*ibid.*, **27**, 477 (1962)]. However, our experiment was performed in the presence of the sodium mercaptide.

pyridine N-oxide is treated with an alkyl halide, sulfate, or sulfonate. Attempts to isolate crystalline salts from pyridine N-oxide with acyl and sulfonyl halides met with little success, the products being labile hygroscopic solids or temperamental gums.[4] Hence, these salts were prepared *in situ* prior to reaction with mercaptan.

In our previous study,[1] it was shown that 1-ethoxypyridinium ethyl sulfate reacted with *n*-propylmercaptide ion to yield pyridine and a mixture of 3- and 4-propylmercaptopyridines. In a cognate experiment, the 1-ethoxypyridinium cation was attacked by *n*-butylmercaptide ion to furnish a mixture of 2-, 3-, and 4-butylmercaptopyridines in the ratio 4:15:6 (Table I). The three sulfides were separated

TABLE I



EX	Yield of sulfides, %	% of butylmercaptopyridine in sulfide mixture 2-	3-	4-	Method[a]
$(C_2H_5)_2SO_4$	15	16	60	24	F
p-$CH_3C_6H_4SO_3C_2H_5$	11	11	74	15	G
$(CH_3CO)_2O$	67	61	39		D
CH_3COCl	10	89	9	2	E
C_6H_5COCl	19	81	18	1	A
C_6H_5COCl	16	81	15	4	B
$C_6H_5SO_2Cl$	32	50	50		C

[a] See Experimental section.

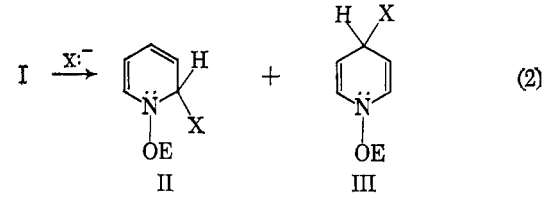
by chromatography on alumina and identified (as throughout this work) by comparing their infrared and n.m.r. spectra with those of authentic specimens. There was little variation in yield and isomer distribution of sulfides when the N-ethoxypyridinium moiety was accompanied by either the ethyl sulfate or *p*-toluenesulfonate anion (Table I). However, it was essential to conduct these experiments in the presence of sodium *n*-butylmercaptide, since no substitution was noted when this strong base was omitted. This point is relevant since, in the experiments with pyridinium salts carrying an electron-attracting group on the ring nitrogen, the reaction proceeded very well in 1-butanethiol alone.

The addition of 1-benzoyloxypyridinium chloride to a suspension of sodium *n*-butylmercaptide in excess mercaptan furnished a mixture of 2-, 3-, and 4-butylmercaptopyridines in a ratio of 20:4:1, in contrast to the predominance of the 3-isomer with the alkoxypyridinium salts. The total yield of mercaptopyridines and the isomer ratio, were not significantly different when the sodium mercaptide was omitted; in these experiments, 3-pyridyl benzoate was also produced. In similar fashion, the reaction of 1-benzenesulfonyloxypyridinium chloride with 1-butanethiol produced an equal mixture of 2- and 3-butylmercaptopyridines devoid of the multitude of products obtained when pyridine 1-oxide was heated with arenesulfonyl chloride.[5]

(4) V. J. Traynelis, A. I. Gallagher, and R. F. Martello [*J. Org. Chem.*, **26**, 4365 (1961)] managed to crystallize 1-acetoxy-2-picolinium picrate from the reaction of 2-picoline 1-oxide with picryl acetate.

The above experiments were conducted in a large excess of 1-butanethiol. In a different vein, the substitution of pyridine 1-oxide by 1-butanethiol was examined in a large excess of acetic anhydride. There was formed a good yield of 2- and 3-butylmercaptopyridine (61:39), again free from the 4-isomer. The products were accompanied by 2-, 3-, and 4-pyridinols (after hydrolysis), the 3-isomer being the major product.[6] In contrast to the excellent yield of sulfides from the reaction in excess acetic anhydride, the reaction of 1-acetoxypyridinium chloride with 1-butanethiol in the presence of sodium *n*-butylmercaptide afforded a poor yield of product.

No simple mechanism can be advanced to explain the observed α-, β-, and γ-substitution of salts of type I by mercaptans (*viz.*, mercaptide ion). There are described in the literature mechanisms to account for α- and γ- as distinct from β-substitution of I.[7] For α- and γ-substitution of I it was postulated that attack by a nucleophile present in the medium ($X:^-$) neutralizes the positive charge to form 1,2- and 1,4-dihydropyridines (II and III) as illustrated in eq. 2. Aromatization



(2)

of these intermediates, by the elimination of HOE, leads to the formation of 2- and 4-substituted pyridines. The general question now arises on the pathway of elimination of HOE. In intermediates II and III where the α- and γ-hydrogens are acidic enough, the first step may be removal of such hydrogens by base to form an anion which then loses OE^-. Such a sequence of events is shown in eq. 3 (for II only),[8] p. 2185.

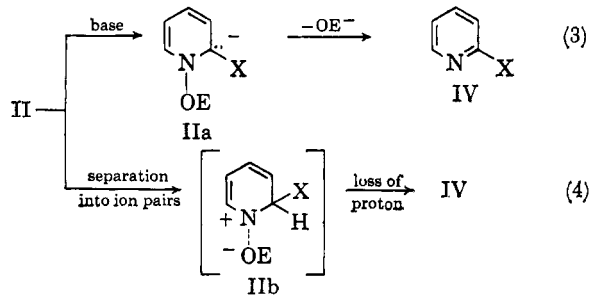
When abstraction of a proton from the α- or γ-position is not encouraged (*e.g.*, when X is SR), an alternate mechanism is suggested for the aromatization. This route calls for the separation of OE from II or III into ion pairs as the first step. For the 1,2-dihydropyridine, the loss of a proton from IIb creates the 2-substituted

(5) A recent paper by H. J. den Hertog, D. J. Buurman, and P. A. de Villiers [*Rec. trav. chim.*, **80**, 325 (1961)] summarized the products obtained from the reaction of pyridine N-oxide with *p*-toluenesulfonyl chloride at 160°. There was obtained pyridine, 2,3′-dipyridyl ether, 3-pyridyl *p*-toluenesulfonate, 1-(2′-pyridyl)-2-pyridone, as well as 1-(2′-pyridyl)-3 and -5-chloro-2-pyridones. The last three products can be explained if 2-chloropyridine is an intermediate in that reaction. It has been shown by F. Ramirez and P. W. von Ostwalden [*J. Am. Chem. Soc.*, **81**, 156 (1959)] that the reaction of 2-bromopyridine with pyridine N-oxide produced 1-(2′-pyridyl)-2-pyridone and its 3- and 5-bromo substitution products.

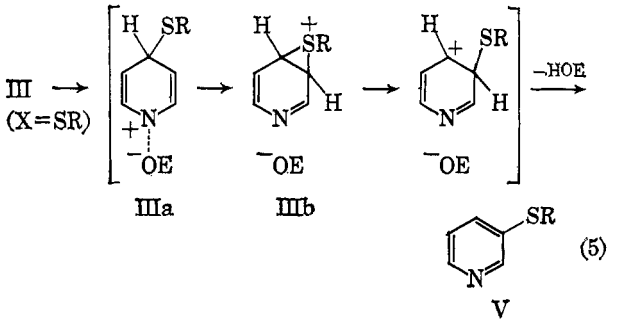
(6) The formation of 3-pyridinol in this reaction is surprising since the well-known substitution of pyridine N-oxide by acetic anhydride yielded only 2-pyridinol [see J. H. Markgraf, H. B. Brown, S. C. Mohr, and R. G. Peterson, *ibid.*, **85**, 958 (1963)]. We inspected the infrared spectrum of the pyridinol fraction from pyridine N-oxide and acetic anhydride and found no bands assignable to 3- or 4-pyridinol.

(7) The literature up to 1962 was summarized in ref. 1. More recently published substitution of pyridinium salts type I were reported by M. Hamana and his co-workers [*J. Pharm. Soc. Japan*, **82**, 519 (1962); *Chem. Pharm. Bull.* (Tokyo), **11**, 415, 1331 (1963)].

(8) Such a path has been suggested by H. Tani [*ibid.*, **7**, 930 (1959)] and W. E. Feely and E. M. Beaver [*J. Am. Chem. Soc.*, **81**, 4004 (1959)] for the reaction of 1-alkoxypyridinium salts (I, E is alkyl) with cyanide ion (X = CN) to form 2- and 4-pyridinecarbonitriles.



pyridines (eq. 4).[9] This mechanism is most apt to apply when the departing groups are acetate, benzoate, or sulfonate ions. This might explain the abundance of 2-butylmercaptopyridine in the products (Table I) in the substitution of 1-acetyloxy-, 1-benzoyloxy-, and 1-arenesulfonyloxypyridinium salts in contrast to the 1-alkoxyyridinium salts (Table I). However, the puzzling feature is the formation of the 3-butylmercaptopyridines. In the reaction in which an electron-attracting group is attached to nitrogen, 4-substitution is conspicuously small while 3-substitution is more pronounced. It is suggested that substitution at position 3 arises from the 1,4-dihydropyridine (III).



Separation of the latter into ion pairs (IIIa) creates a potential electrophilic center at the β-positions. Such polarization could induce migration of the nucleophilic thioether group *via* an episulfonium ion[10] (IIIb) to lead to V as indicated in eq. 5.[11]

The unexpected β-substitution of I by acyloxy ions in several of the reactions cannot be explained satisfactorily at present.[12] Further experiments are planned to investigate these reactions and their mechanisms in greater detail.

A number of investigators have searched for evidence for free-radical mechanism in the substitution of I, but thus far the reactions are better explained *via* ionic intermediates. In order to test if a free-radical mechanism was involved for the substitution of I by mercaptans, the following experiments were carried out. When 1-ethoxypyridinium ethyl sulfate was treated with 1-butanethiol and sodium *n*-butylmercaptide (as in F, Experimental section) in the presence of benzoyl peroxide, the same yield and isomer ratio of butylmercaptopyridines were obtained as when the peroxide was omitted. Also, the reaction of 1-ethoxypyridinium ethyl sulfate with 1-butanethiol in boiling carbon tetrachloride (24 hr.) in the presence of benzoyl peroxide did not furnish any 2-, 3-, or 4-butylmercaptopyridines. Again, the reaction of pyridine N-oxide with 1-butanethiol and benzoyl chloride (in the absence of sodium *n*-butylmercaptide) in carbon tetrachloride in the presence of benzoyl peroxide gave rise to the same mixture of thioethers as in A. These experiments tend to rule out a free-radical mechanism as the major pathway of these reactions.

Experimental[13]

Materials.—Pyridine N-oxide was obtained from Reilly Tar and Chemical Co.; 2- and 3-pyridinol, 2-pyridinethiol, and 4-chloropyridine from Aldrich Chemical Co.; 4-pyridinol from Winthrop Labs. The generous gifts of 1-butanethiol from Pennsalt Chemical Co. and Phillips Petroleum Co. are gratefully acknowledged. Petroleum ether used in this work refers to that fraction, b.p. 30–60°. Activated alumina used throughout this investigation was purchased from Alcoa (Grade F-20). Sodium hydride used in subsequent experiments was in the form of a 53% dispersion in mineral oil, available from Metal Hydrides, Inc.

Synthesis of Reference Compounds. 2-Butylmercaptopyridine.—A solution of 2-pyridinethiol (5.6 g., 0.05 mole) in 10% sodium hydroxide solution (50 ml.) was stirred with 1-bromobutane (7.0 g., 0.05 mole) first at 25° for 1.5 hr., then at 70° for 1 hr. After the usual work-up,[14] the **sulfide** (2.25 g., 27%) was distilled, b.p. 71° at 1 mm.

Anal. Calcd. for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.59; H, 7.72; N, 8.45.

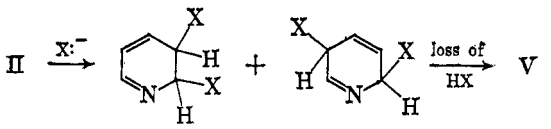
3-Butylmercaptopyridine.—A solution of 3-pyridinethiol hexachlorostannate[15] (6.66 g., 0.015 mole) in 10% sodium hydroxide solution (100 ml.) was stirred with 1-bromobutane (4.11 g., 0.03 mole) for 5 hr. at 25°. The mixture was extracted with ether. The ether layer was shaken with 10% hydrochloric acid. The **sulfide** was isolated from the acidic aqueous phase in the usual manner[14] and distilled *in vacuo*. Since the product was found to be impure, it was chromatographed on alumina (30 g.). It was eluted with petroleum ether–ether (9:1). Distillation furnished the pure sulfide (1.49 g., 30%), b.p. 141° at 31 mm.

Anal. Calcd. for $C_9H_{13}NS$ (as above). Found: C, 64.74; H, 7.73; N, 8.42.

(9) Such a mechanism may be responsible for the substitutions when pyridine N-oxide is treated with acid halides and anhydrides to form 2- and 4-substituted pyridines.[7] Few of these reactions have been examined in detail to discover their mechanism. A notable exception is the reaction of pyridine N-oxide with acetic anhydride to form 2-acetoxypyridine[8] which is postulated to proceed by means of the 1-acetoxypyridinium cation.

(10) Migration of a sulfide group to a potentially electrophilic center *via* episulfonium intermediates is a well-known phenomenon. For a recent summary, see K. D. Gundermann, *Angew. Chem.*, **75**, 1194 (1963).

(11) Another mechanism has been proposed to explain β-substitution; for a summary, see S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963). It has been suggested that, in intermediates II or III, the group OE is displaced by nucleophilic attack at one of the β-positions to form yet another dihydropyridine. This is illustrated for II. Aromatization to



form V is achieved when the elements HX are eliminated. In a basic medium, the most acidic proton in the new dihydropyridines are those at the β-position and this might account for the formation of the 3-substituted pyridine by such a path.

(12) Intermolecular rearrangement of II and III (X = OCOR) analogous to the one suggested in eq. 5 presents a possible mechanism. However, the role of mercaptan, if any, in this substitution is not understood at present.

(13) All melting 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 obtained using a Coleman nitrogen analyzer, Model 29.

(14) The procedure used to isolate the basic thioethers was as follows. If the reaction medium were basic, it was acidified with hydrochloric acid and extracted with ether or a mixture of ether–benzene (1:1) to remove neutral and acidic products. The aqueous phase was then made alkaline with 20% sodium hydroxide and the bases were extracted into methylene chloride. The methylene chloride solution was dried (sodium sulfate) and fractionally distilled.

(15) N. Steiger, *Chem. Abstr.*, **44**, 8380 (1950).

4-Butylmercaptopyridine.—This was prepared in 25% yield from 4-chloropyridine and 1-butanethiol as described for the synthesis of 2-propylmercaptopyridine.[1] The **sulfide** was distilled, placed on alumina, eluted by petroleum ether, and redistilled, b.p. 145–147° at 19 mm.

Anal. Calcd. for $C_9H_{13}NS$ (as above). Found: C, 64.43; H. 7.67; N, 8.60.

Reaction of Pyridine N-Oxide with 1-Butanethiol. A. In the Presence of Benzoyl Chloride.—Benzoyl chloride (14.1 g., 0.1 mole) was added dropwise, over a period of 40 min., to an ice-cold solution of pyridine N-oxide(9.5 g., 0.1 mole) in 1-butanethiol (100 ml.). During that time, a chalk-white suspension was formed. The mixture was then warmed on the steam bath for 0.5 hr., after which it was quenched by 15% hydrochloric acid (50 ml.). The two layers were separated and the organic phase was extracted once more with 15% hydrochloric acid (25 ml.). The combined acid layers were extracted once with an ether–benzene solution (1:1, 50 ml.) and worked up for pyridines as shown below. No attempt was made in this experiment to isolate neutral or acidic products.

The hydrochloric acid solution containing the pyridines was boiled under reflux for 2 hr. (This was necessary to hydrolyze pyridyl benzoates present. It was also found that the butylmercaptopyridines were stable to such a hydrolysis.). On cooling, the acid fraction was extracted once more with ether–benzene (1:1, 75 ml.) and then made alkaline with 20% sodium hydroxide and extracted with methylene chloride (five 50-ml. portions). Distillation of the extract afforded the mixture of butylmercaptopyridines (3.50 g., b.p. 140–146° at 25 mm.).

The butylmercaptopyridines were separated by column chromatography on alumina (70 g.). 2-Butylmercaptopyridine (2.57 g.) was eluted by petroleum ether (700 ml.) and by petroleum ether–benzene (9:1, 200 ml.); 3-butylmercaptopyridine (0.57 g.), by petroleum ether–benzene (1:1, 100 ml.) and benzene (400 ml.); and 4-butylmercaptopyridine (0.04 g.), by benzene–ether (9:1, 100 ml.) and ether (100 ml.). The combined yield of pure sulfides was 3.18 g. This represents a 19% yield based on 0.1 mole of pyridine N-oxide or 36% if the recovered pyridine N-oxide (see below) is taken into account.

The basic solution from above was neutralized with hydrochloric acid and evaporated *in vacuo*. The dry residue was extracted with 2-propanol (100 ml.) and that solvent was removed *in vacuo*. The residue (5.15 g.) was boiled down with benzene to remove the last traces of 2-propanol before placing it onto activated alumina (50 g.). Elution with methylene chloride (1200 ml.) and methylene chloride–ethanol (3:1, 50 ml.) afforded pyridine N-oxide (4.43 g., 47%). Further elution with methylene chloride–ethanol (3:1, 300 ml.) gave 3-pyridinol (0.24 g., 3% based on 0.1 mole), m.p. and m.m.p. 127°.

The pyridine N-oxide and pyridinol fractions were examined carefully for the presence of 2- and 4-pyridinol (infrared spectroscopy), but neither could be detected.

Several experiments with some modification to A are briefly mentioned here. When the reaction of pyridine N-oxide (0.1 mole) with 1-butanethiol (0.3 mole) was carried out in benzene (100 ml.) instead of excess mercaptan, there was isolated the same mixture of 2- and 3-butylmercaptopyridines (3.4 g.), b.p. 140–160° at 35 mm. Further distillation furnished a thick oil (2.71 g.), b.p. 129–140° at 0.5 mm., which set to a semisolid on cooling. Its infrared spectrum was identical with 3-pyridyl benzoate which was prepared from 3-pyridinol and benzoyl chloride.[16] The **ester** was characterized by a picrate, m.p. 155–156° (from ethanol), undepressed on admixture of the known[17] picrate. Hydrolysis of the ester isolated in this reaction gave 3-pyridinol, m.p. and m.m.p. 127°.

In a similar experiment as above but using carbon tetrachloride (100 ml.), benzoyl peroxide (1 g., 0.004 mole) was added in portions to the boiling solution (over a period of 8 hr.). This experiment yielded the same mixture of sulfides (2.2 g.) and 3-pyridyl benzoate (2.3 g.).

B. Reaction of 1-Benzoyloxypyridinium Chloride with Sodium *n*-Butylmercaptide.—Benzoyl chloride (14.1 g., 0.1 mole) was added dropwise to freshly distilled pyridine N-oxide (9.5 g., 0.1 mole). The mixture became warm and turned into a paste which finally set into a dry, mobile powder. This powder was used immediately in the next step without further treatment.

Sodium hydride (9.1 g. of a 53% suspension in mineral oil, 0.2 mole) was added in three portions to 1-butanethiol (125 ml.) at 0° with stirring. Sodium *n*-butylmercaptide separated as a fine suspension in excess mercaptan. To this stirred mixture was added 1-benzoyloxypyridinium chloride and the mixture was heated at 100° for 2 hr.

The reaction was then quenched with ice-cold 10% hydrochloric acid and the basic fraction was isolated as usual.[14] Distillation of the bases afforded a mixture of butylmercaptopyridines (3.13 g.), b.p. 142–145 (24 mm.), which were separated on alumina as described above. The yield and isomer ratios are contained in Table I.

In these experiments, no 3-pyridyl benzoate was isolated after the sulfides had distilled. Hence, no attempts were made to examine the aqueous phase (after the sulfides were extracted) for pyridinols or to isolate unchanged pyridine N-oxide.

C. In the Presence of Benzenesulfonyl Chloride.—To an ice-cold solution of pyridine N-oxide in 1-butanethiol (9.5 g., 0.1 mole in 100 ml.) was added benzenesulfonyl chloride (17.7 g., 0.1 mole) as described in A. A fine white suspension resulted and the mixture was heated on the steam bath for 0.5 hr., during which time a colorless gum separated from the colorless solution. The reaction was quenched by 15% hydrochloric acid (50 ml.) and the reaction mixture was worked up for butylmercaptopyridines, pyridinols, and unchanged pyridine N-oxide as described under A. The sulfides were again separated by chromatography on alumina, and their yields and isomer distribution are listed in Table I.

All attempts to find pyridinols (in the hydrolyzed aqueous basic fraction) failed. This fraction contained only pyridine N-oxide (3.81 g., 40%, after chromatography on alumina).

In an attempt to carry out this reaction in the presence of sodium *n*-butylmercaptide, benzenesulfonyl chloride was added to a suspension of sodium *n*-butylmercaptide in a solution of pyridine N-oxide in excess 1-butanethiol. However, unlike C, only 0.24 g. of butylmercaptopyridines (1%) was obtained. In earlier experiments attempts to prepare solid N-arenesulfonyloxypyridinium salts by mixing pyridine N-oxide and benzene and *p*-toluenesulfonyl chloride neat, in a manner analogous to the preparation of N-benzoyloxypyridinium chloride (see B), were not successful.

D. In the Presence of Acetic Anhydride.—A solution of pyridine N-oxide (9.5 g., 0.1 mole) and 1-butanethiol (32 ml., 0.3 mole) in acetic anhydride (100 ml.) was boiled under reflux for 2 hr. The solution was concentrated *in vacuo* (at 17 mm.) and then boiled with 25 ml. of 15% hydrochloric acid for 0.5 hr. (to hydrolyze esters). The acid solution was extracted with 1:1 ether–benzene, and concentrated to half its volume several times to remove acetic acid since it interferes with work-up for pyridinols. It was then made alkaline with 20% sodium hydroxide. The basic fraction was extracted with methylene chloride (five 50-ml. portions). Distillation of this extract afforded a fraction (11.16 g.), b.p. 136–143° at 28 mm.

Part of this fraction (2.79 g.) was placed on alumina (60 g.) and the isomers were eluted as follows: 2-butylmercaptopyridine (1.69 g.) by petroleum ether (600 ml.) and petroleum ether–benzene (19:1, 100 ml.), and the 3-isomer (1.1 g.) by petroleum ether–benzene (1:1, 100 ml.) and benzene (300 ml.).

The basic aqueous solution was neutralized and evaporated to dryness. The residue was extracted by 2-propanol, that solvent was removed *in vacuo*, and the residue was extracted with hot benzene. On cooling, 3-pyridinol (0.44 g.) was obtained which was identified by its melting point and infrared spectrum.

E. As 1-Acetoxypyridinium Chloride, and in the Presence of Sodium *n*-Butylmercaptide.—The salt from pyridine N-oxide and acetyl chloride was difficult to isolate, and hence the following procedure was adopted. Acetyl chloride (7.8 g., 0.1 mole) was added dropwise to a solution of pyridine N-oxide (9.5 g., 0.1 mole) in 50 ml. of benzene. A white suspension was formed which was added to a suspension of sodium *n*-butylmercaptide in 1-butanethiol (prepared as in B). After the mixture was heated at 100° for 2 hr., it was worked up as in A. The **sulfides** were separated as usual and are listed in Table I.

F. As 1-Ethoxypyridinium Ethyl Sulfate.—Ethoxypyridinium ethyl sulfate was prepared and used as described previously.[1]

(16) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

(17) H. Bojarska-Dahlig and T. Urbanski, *Chem. Abstr.*, **48**, 1338 (1954).

The addition of 1-ethoxypyridinium ethyl sulfate to sodium *n*-butylmercaptide in 1-butanethiol and subsequent reaction at 100° for 0.5 hr. gave, after the usual work-up (see A), butylmercaptopyridines listed in Table I.

G. As 1-Ethoxypyridinium *p*-Toluenesulfonate.—Pyridine N-oxide (4.75 g., 0.05 mole) was heated with ethyl *p*-toluenesulfonate (10.0 g., 0.05 mole) at 100° for 1.5 hr. The sirup was washed with ether and the resultant salt was added to a suspension of sodium *n*-butylmercaptide in excess 1-butanethiol as in B. Work-up according to the general method (see A) gave the sulfides listed in Table I.

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Steroids. CCXL.[1,2] The Reaction of Steroidal Alcohols with 2-Chloro-1,1,2-trifluorotriethylamine

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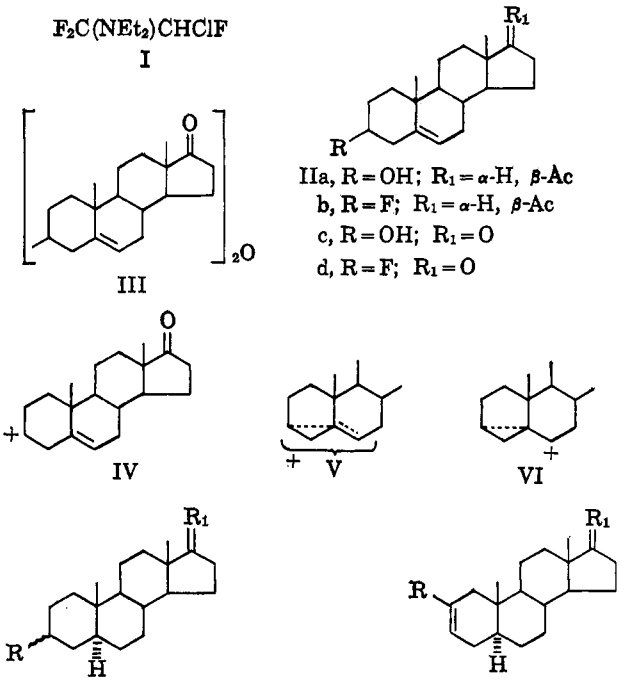
The reaction of 2-chloro-1,1,2-trifluorotriethylamine (I) with steroidal alcohols is described. Primary and secondary hydroxy steroids generally yield products resulting from replacement of hydroxyl by fluorine, ester formation, simple dehydration, dehydration accompanied by rearrangement, and ether formation. Tertiary alcohols undergo dehydration with or without concomitant rearrangement. The dependence of product formation on the nature of the steroidal alcohol, solvent, and reaction temperature is discussed. Nuclear magnetic resonance spectral data are analyzed for the various alcohols and reaction products.

The remarkable enhancement of biological activity in steroid hormones resulting from introduction of fluorine at various sites in the steroid molecule is well documented in the chemical literature.[3] During the past decade a number of synthetic routes to fluoro steroids have been developed in pursuit of further derivatives.[4] The recent observation of Yarovenko and Raksha that 2-chloro-1,1,2-trifluorotriethylamine (I) reacts readily under mild conditions with primary aliphatic alcohols to give replacement of hydroxyl by fluorine,[5] prompted us to investigate the utility of this reagent for the preparation of fluoro steroids.[2] Ayer, in a preliminary communication, has recently described a similar investigation of the reactions of the amine I with steroidal alcohols.[6]

When 3β-hydroxypregn-5-en-20-one (IIa) was treated with the fluorinating reagent I in dry tetrahydrofuran, there was obtained the 3β-fluoro derivative IIb.[3,7] Reaction proceeded with over-all retention of configuration. However, when a mixture of 3β-hydroxyandrost-5-en-17-one (IIc), 1.5 molar equiv. of the reagent I, and dry methylene chloride were refluxed briefly, two products could be isolated by chromatography on Florisil.[8] The less polar product consisted of the known 3β-fluoro derivative IId[6,7] (58%). The more polar product proved to be the ether III (4.8%), the structure of which was established by elementary analysis, n.m.r. spectroscopy, and mass spectrometry.[9] Ayer,[6] using different reaction conditions, obtained only



(1) Steroids CCXXXIX: L. H. Knox, E. Velarde, and A. D. Cross *J. Am. Chem. Soc.*, **85**, 2533 (1963). The present paper also constitutes Spectra and Stereochemistry, part X; part IX, A. D. Cross and P. Crabbé, *ibid.*, **86**, 1221 (1964).

(2) A preliminary account of this work was published by L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962).

(3) For leading references, see A. Bowers, P. G. Holton, E. Denot, M. C. Loza, and R. Urquiza, *J. Am. Chem. Soc.*, **84**, 1050 (1962).

(4) For a review of methods currently available for the introduction of fluorine into the steroid system, see J. W. Chamberlin, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p. 155.

(5) N. N. Yarovenko and M. A. Raksha, *Zh. Obskch. Khim.*, **29**, 2159 (1959); *cf. Chem. Abstr.*, **54**, 9724*h* (1960).

(6) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(7) (a) T. N. Jacobsen and E. V. Jensen, *Chem. Ind.* (London), 172, (1957); (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 4813 (1957).

(8) Florisil is a magnesium silicate marketed by the Floridin Co., Hancock, W. Va.

(9) Determinations carried out on a C.E.C. 21-1036 mass spectrometer equipped with a "direct inlet" system [see J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia*, **19**, 211 (1963)].