

REACTIONS OF PYRYLIUM AND PYRIDINIUM SALTS WITH AMINES

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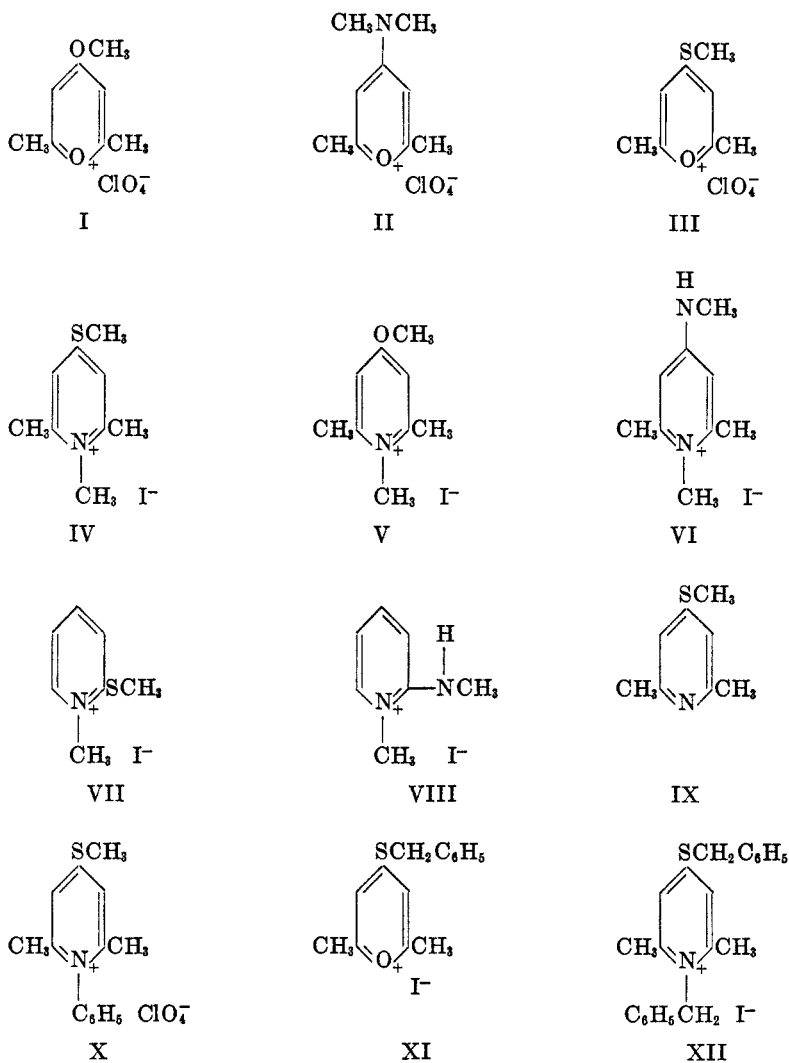
Certain substituents in the 4 position of pyrylium salts can be replaced by nucleophilic reagents. Anker and Cook (1) demonstrated that the methoxy group in 2,6-dimethyl-4-methoxypyrylium perchlorate (I) could be replaced by ethanol, benzylmercaptan, or by piperidine. In connection with the experiments described herein these observations of Anker and Cook were verified. It was further demonstrated that alkylmercapto groups in the 4 position of pyrylium salts could be replaced by secondary amines, but the reverse process was not easily accomplished. For example: 2,6-dimethyl-4-dimethylaminopyrylium perchlorate (II) was prepared from 2,6-dimethyl-4-methylmercaptopyrylium perchlorate (III) by treatment with dimethylamine, but II could be refluxed with methanol or with a solution of benzylmercaptan in methanol without any change. Other examples of replacement of alkylmercapto groups on the 4 position of pyrylium salts are recorded in the first section of the experimental part.

On the basis of these experiments and with consideration of the observations of Anker and Cook (1), the order of ease of replacement of groups in the 4 position of pyrylium salts is $\text{CH}_3\text{O}- > \text{CH}_3\text{S}- > \text{R}_2\text{N}-$. Experimental details in support of these statements will be apparent from a consideration of the experimental part, sections I and VI.

When pyridinium salts having a methoxyl group in the 4 position, or a methylmercapto group in the 2 or 4 position were treated with primary or secondary amines, the methoxyl or methylmercapto group was replaced by the amine reagent. For example, both 1,2,6-trimethyl-4-methylmercaptopyridinium iodide (IV) and 1,2,6-trimethyl-4-methoxypyridinium iodide (V) gave 1,2,6-trimethyl-4-methylaminopyridinium iodide (VI) when treated with aqueous methylamine. Under the same conditions 1-methyl-2-methylmercaptopyridinium iodide (VII) gave 1-methyl-2-methylaminopyridinium iodide (VIII). Other examples of replacements of this sort are described in sections II and III of the experimental part of this paper.

The replacement of groups in the 4 position on pyridinium salts seems to be limited to the use of amines as replacing groups. Compound V, for example, was recovered unchanged after refluxing with benzylmercaptan in ethanol for two hours.

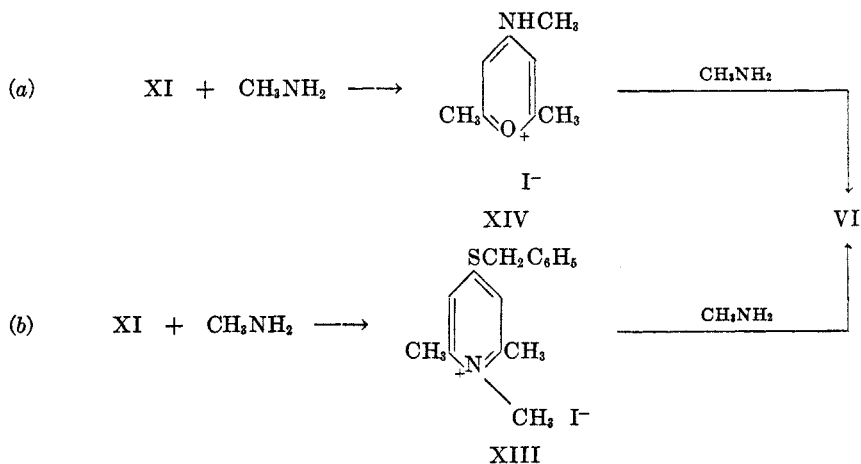
When pyrylium salts react with ammonia they are converted to pyridines, if primary amines are used pyridinium salts are produced. This reaction was first discovered by Baeyer (2) and subsequently extended by Dilthy (3) by Diels and Alder (4) and by Anker and Cook (1). The pyrylium salts containing substituted mercapto groups or substituted amino groups in the 4 position and reported herein: all reacted smoothly with ammonia or primary amines to give



pyridines or pyridinium salts as expected. Compound III, for example, reacted with ammonia to give IX. Compound III gave IV on treatment with methylamine, and 1-phenyl-2,6-dimethyl-4-methylmercaptopyridinium perchlorate (X) on treatment with aniline. 2,6-Dimethyl-4-benzylmercaptopyrylium iodide (XI) on treatment with benzylamine gave 1-benzyl-2,6-dimethyl-4-benzylmercaptopyridinium iodide (XII).

In connection with the reactions of pyrylium salts with primary amines the odor of mercaptan was usually noted. This observation suggested that in addition to the principle reaction, conversion of pyrylium salt to pyridinium salt, a second reaction occurred wherein the 4-alkylmercapto group was replaced by a primary amine group. A possible course for the reaction can be formulated on the

basis of the products obtained when XI was treated for a limited time with excess methylamine. In this case the two products 1,2,6-trimethyl-4-benzylmercaptopyridinium iodide (XIII) and VI were formed. The two possible reaction schemes for formation of VI are shown in the diagram.



Scheme *a* appeared to be the more probable one on the basis of the investigations of Anker and Cook (1). These investigators showed that 2,6-dimethyl-4-methoxy-pyrylium perchlorate gave rise to V (ClO_4^-) on treatment with one mole of methylamine, but that if two moles of methylamine were used VI (ClO_4^-) was formed. These investigators also stated that V (ClO_4^-) could not be converted to VI (ClO_4^-) by methylamine. This latter observation is not in accord with the results reported herein where numerous examples of replacement of groups on pyridinium salts are recorded. It is further apparent that the reactions of pyrylium salts with primary amines proceed by scheme *b*. That is, by a rapid reaction to form a pyridinium salt followed by a slow reaction of the pyridinium salt with any methylamine present.

EXPERIMENTAL

SECTION I. REPLACEMENT OF ALKYL-MERCAPTO GROUPS ON PYRYLIUM SALTS BY AMINES

2,6-Dimethyl-4-(1-piperidyl)pyrylium iodide. A solution of 5.6 g. (0.02 mole) of 2,6-dimethyl-4-methylmercaptopyrylium iodide and 1.70 g. (0.02 mole) of piperidine in 45 ml. of methanol was refluxed for 30 minutes. During this process there was olfactory evidence for the evolution of methyl mercaptan. The solvent was evaporated and the residue covered with 20 ml. of acetone. The salt which separated on standing, was washed with ether-acetone and crystallized from acetone. Yield, 3.8 g. (53%); m.p. 194–195° (dec.).

Anal. Calc'd for $\text{C}_{12}\text{H}_{18}\text{INO}$: C, 45.15; H, 5.68; N, 4.39.

Found: C, 45.23; H, 5.18; N, 4.69.

Anker and Cook (1) prepared this salt from a 2,6-dimethyl-4-methoxy-pyrylium salt and reported the melting point as 188–190°.

2,6-Dimethyl-4-(4-morpholinyl)pyrylium iodide. A solution of 8.4 g. of 2,6-dimethyl-4-methylmercaptopyrylium iodide and 2.7 g. of morpholine in 40 ml. of methanol was refluxed for 30 minutes. The solution was cooled and 70 ml. of ether added. The salt was sepa-

rated by filtration and washed with ether-methanol. Yield, 8.2 g. (86%); m.p. 209–212°. An analytical sample was recrystallized from acetone and melted at 214–215° (dec.).

Anal. Calc'd for $C_{11}H_{16}INO_2$: C, 41.14; H, 5.02; N, 4.36.

Found: C, 40.78; H, 4.83; N, 4.52.

2,6-Dimethyl-4-dimethylaminopyrylium perchlorate (II). A solution of 2.5 g. of 2,6-dimethyl-4-methylmercaptopyrylium perchlorate and 2 ml. 25% aqueous dimethylamine in 30 ml. of methanol was refluxed for 30 minutes. The methanol was evaporated and the residue was crystallized by cooling. The product was recrystallized from ethanol-ethyl acetate. Yield, 1.9 g. (75%); m.p. 184–185° (dec.).

Anal. Calc'd for $C_9H_{14}ClNO_5$: C, 42.95; H, 5.61; N, 5.57.

Found: C, 43.16; H, 5.75; N, 5.47.

SECTION II. REPLACEMENT OF ALKYLMERCAPTO GROUPS ON PYRIDINIUM SALTS BY AMINES

1,2,6-Trimethyl-4-methylaminopyridinium iodide (VI). A solution of 1.0 g. of 1,2,6-trimethyl-4-methylmercaptopyridinium iodide and 2 ml. of 25% aqueous methylamine in 10 ml. of ethanol was refluxed for one hour. The solution was cooled and the salt was precipitated with ether. Yield, 0.85 g. (90%); m.p. 274–275° (dec.).

Anal. Calc'd for $C_9H_{15}IN_2$: C, 38.86; H, 5.44.

Found: C, 39.41; H, 5.32.

1-Phenyl-2,6-dimethyl-4-methylaminopyridinium perchlorate. A solution of 0.70 g. of 1-phenyl-2,6-dimethyl-4-methylmercaptopyridinium perchlorate and 2 ml. of 25% aqueous methylamine in 10 ml. of ethanol was refluxed for one hour. The solvent was evaporated and the residue was crystallized from water. Yield, 0.60 g. (91%); m.p. 122°.

Anal. Calc'd for $C_{14}H_{17}ClN_2O_4$: C, 53.76; H, 5.48.

Found: C, 53.52; H, 5.14.

1-Phenyl-2,6-dimethyl-4-dimethylaminopyridinium perchlorate. A solution of 0.70 g. of 1-phenyl-2,6-dimethyl-4-methylmercaptopyridinium perchlorate and 3 ml. of 25% aqueous dimethylamine in 10 ml. of ethanol was refluxed for one hour. The solvent was evaporated and the residue was crystallized from water. There was obtained 0.60 g. (85%) of salt melting at 171–172° (dec.).

Anal. Calc'd for $C_{15}H_{19}ClN_2O_4$: C, 55.13; H, 5.86.

Found: C, 55.64; H, 5.68.

1-Phenyl-2,6-dimethyl-4-(4-morpholinyl)pyridinium perchlorate. A solution of 0.70 g. of 1-phenyl-2,6-dimethyl-4-methylmercaptopyridinium perchlorate and 2 ml. of morpholine in 10 ml. of ethanol was refluxed for one hour. The solvent was evaporated and the residue was crystallized by cooling. Recrystallization from water gave 0.75 g. (95%) of product m.p. 200–201°.

Anal. Calc'd for $C_{17}H_{21}ClN_2O_5$: C, 55.36; H, 5.74.

Found: C, 56.11; H, 5.74.

1-Methyl-2-methylaminopyridinium iodide (VIII). Two g. of 1-methyl-2-methylmercaptopyridinium iodide was refluxed for one hour with 4 ml. of 25% aqueous methylamine in 15 ml. of ethyl alcohol. The solvent was evaporated and the residue was crystallized by cooling in an acetone-Dry Ice bath and scratching with an applicator stick. The salt recrystallized from ethyl alcohol-ethyl acetate, melted at 160° and weighed 1.2 g. (64%).

Anal. Calc'd for $C_7H_{11}IN_2$: C, 33.61; H, 4.43; N, 11.20.

Found: C, 33.98; H, 4.44; N, 10.49.

SECTION III. REPLACEMENT OF METHOXY GROUPS ON PYRIDINIUM SALTS BY AMINES

1,2,6-Trimethyl-4-methylaminopyridinium iodide (VI). A solution of 1.4 g. of 1,2,6-trimethyl-4-methoxypyridinium iodide and 3 ml. of 25% aqueous methylamine in 15 ml. of ethanol was refluxed for one hour. The solution was cooled, an equal volume of ether was added, and the salt was separated by filtration. The product, 1.4 g. (100%), m.p. 274–275°, was identical with the material described above.

1,2,6-Trimethyl-4-dimethylaminopyridinium iodide. A solution of 1.0 g. of 1,2,6-trimethyl-4-methoxypyridinium iodide and 2 ml. of 25% aqueous dimethylamine in 15 ml. of ethanol was refluxed for one hour. The solution was cooled, and an equal volume of ether was added. The product was separated and recrystallized from ethanol. Yield, 1.0 g. (95%); m.p. 308–309°.

Anal. Calc'd for $C_{10}H_{17}IN_2$: C, 41.10; H, 5.87.

Found: C, 41.63; H, 5.54.

The corresponding *perchlorate* was prepared by treating a warm aqueous solution of the iodide with perchloric acid. It was recrystallized from water and melted at 270–271°.

Anal. Calc'd for $C_{10}H_{17}ClN_2O_4$: C, 45.37; H, 6.47.

Found: C, 45.34; H, 6.72.

SECTION IV. REACTIONS OF PYRYLIUM SALTS WITH PRIMARY AMINES

1-Benzyl-2,6-dimethyl-4-benzylmercaptopyridinium iodide (XII). A solution of 3.59 g. (0.01 mole) of 2,6-dimethyl-4-benzylmercaptopyrylium iodide and 1.07 g. (0.01 mole) of benzylamine in 15 ml. of ethanol was refluxed for 30 minutes, cooled, and filtered. Thus there was obtained 3.58 g. (80%) of the salt melting at 188–189° (dec.). The salt was recrystallized from ethanol.

Anal. Calc'd for $C_{21}H_{22}INS$: C, 56.38; H, 4.96; N, 3.13.

Found: C, 56.49; H, 4.84; N, 3.25.

The corresponding *perchlorate* was prepared by treating a hot aqueous solution of the iodide with perchloric acid. It was recrystallized from ethanol and melted at 204–205° (dec.).

Anal. Calc'd for $C_{21}H_{22}ClNO_4S$: C, 60.06; H, 5.28.

Found: C, 60.62; H, 5.24.

1-Benzyl-2,6-dimethyl-4-(1-piperidyl)pyridinium iodide. A solution of 2.6 g. of 2,6-dimethyl-4-(1-piperidyl)pyrylium iodide and 1 ml. of benzylamine in 10 ml. of alcohol was refluxed for 30 minutes, cooled, and filtered. There was obtained 2.9 g. (90%) of salt melting at 203–204° (dec.). An analytical sample was recrystallized from methanol.

Anal. Calc'd for $C_{19}H_{25}IN_2$: C, 55.88; H, 6.17; N, 6.86.

Found: C, 56.17; H, 5.93; N, 7.00.

1-Benzyl-2,6-dimethyl-4-(4-morpholinyl)pyridinium iodide. A solution of 3.2 g. of 2,6-dimethyl-4-(4-morpholinyl)pyrylium iodide and 1.1 g. of benzylamine in 10 ml. of methanol was refluxed for one-half hour. To the cooled mixture 20 ml. of ether was added and the salt was isolated by filtration. Yield, 3.9 g. (97%); m.p. 222–223° (dec.). An analytical sample was recrystallized from ethanol; m.p. 223–224° (dec.).

Anal. Calc'd for $C_{18}H_{23}IN_2O$: C, 52.69; H, 5.65; N, 6.83.

Found: C, 53.52; H, 5.35; N, 7.00.

1,2,6-Trimethyl-4-methoxypyridinium iodide (V). To a solution of 9.1 g. of 2,6-dimethyl-4-methoxypyrylium iodide in 50 ml. methanol in an ice-bath, 4.4 ml. of 25% aqueous methylamine dissolved in 30 ml. of methanol was added slowly. The solution then was refluxed for 30 minutes, the solvent was evaporated, and the residue was covered with acetone. After standing overnight 4 g. (42%) of salt separated. On recrystallization from ethanol this salt melted at 204–205° in agreement with the melting point as reported by Anker and Cook (1).

1,2,6-Trimethyl-4-methylmercaptopyridinium iodide (IV). To a solution of 2.8 g. of 2,6-dimethyl-4-methylmercaptopyrylium iodide in 15 ml. of methanol, a solution of 1.25 g. of 25% aqueous methylamine in 15 ml. of methanol was added. The solution then was refluxed for 30 minutes. The solvent was removed and the residue was crystallized on cooling and scratching in an acetone-Dry Ice bath. Recrystallization from ethanol gave 2.4 g. (81%) of salt melting at 241–242° (dec.). Michaelis and Holken (7) reported the melting point at 236°.

Anal. Calc'd for $C_9H_{14}INS$: C, 36.62; H, 4.78.

Found: C, 37.40; H, 4.90.

The corresponding *perchlorate* was prepared by treating a hot aqueous solution of the iodide with perchloric acid. It was recrystallized from water and melted at 216–217°.

Anal. Calc'd for $C_9H_{11}ClNO_4S$: N, 5.23. Found: N, 5.37.

1-Phenyl-2,6-dimethyl-4-methylmercaptopyridinium perchlorate. A solution of 4.3 g. of 2,6-dimethyl-4-methylmercaptopyrylium perchlorate and 1.52 ml. of aniline in 40 ml. of methanol was refluxed on a steam-bath for 30 minutes. The solvent was evaporated and the residue was crystallized on cooling in acetone-Dry Ice with scratching. Recrystallization from ethanol yielded 3.3 g. (60%) of product melting at 153°.

Anal. Calc'd for $C_{14}H_{16}ClNO_4S$: C, 50.98; H, 4.89.

Found: C, 51.20; H, 4.99.

Reaction of 2,6-dimethyl-4-benzylmercaptopyrylium iodide with excess methylamine. To a solution of 3.3 g. of 2,6-dimethyl-4-benzylmercaptopyrylium iodide in 30 ml. of methanol, 4 ml. of 25% aqueous methylamine was added and the solution was refluxed for 15 minutes. This reaction mixture was concentrated to 10 ml., treated with 30 ml. of ether, and cooled to induce crystallization. The crude product (2.3 g., m.p. 170–180°), was crystallized from a mixture of ethyl acetate-ethanol (3:1). The first crop of crystals weighed 0.82 g. and melted at 272–275° (dec.). Recrystallization from ethanol gave a product, m.p. 274–275°, identical with 1,2,6-trimethyl-4-methylaminopyridinium iodide (VI).

After separation of VI ether was added to the mother liquors and the mixture was cooled in an acetone-Dry-Ice bath. This treatment gave 1.2 g. of salt; m.p. 170–175°. Recrystallization from ethanol and then from water gave a product, m.p. 186–187°, which was 1,2,6-trimethyl-4-benzylmercaptopyridinium iodide (XIII).

Anal. Calc'd for $C_{15}H_{18}INS$: C, 48.52; H, 4.89; N, 3.77.

Found: C, 48.63; H, 4.65; N, 4.02.

SECTION V. REACTIONS OF PYRYLIUM SALTS WITH AMMONIA

4-Methylmercapto-2,6-lutidine. To 10.0 g. of 2,6-dimethyl-4-methylmercaptopyrylium iodide in 10 ml. of water, 30 ml. of 15% ammonium hydroxide containing 8 g. of ammonium carbonate was added. The mixture was heated on a steam-bath for 10 minutes, cooled, and extracted with ether. The ether was removed and the base was distilled *in vacuo*. Yield, 4.60 g. (85%); b.p. 88–89° (2 mm.). A sample was recrystallized from Skellysolve A in an ice-salt bath and it melted at 51°.

Anal. Calc'd for $C_8H_{11}NS$: C, 62.70; H, 7.24; N, 9.14.

Found: C, 62.37; H, 7.26; N, 9.26.

The *picrate*, recrystallized from ethanol, melted at 171°.

Anal. Calc'd for $C_{14}H_{14}N_4O_7S$: C, 43.98; H, 3.69; N, 14.66.

Found: C, 44.16; H, 3.44; N, 14.65.

Marekwald and coworkers (5) reported a melting point of 51° for the base and 171° for the *picrate*.

4-Benzylmercapto-2,6-lutidine. To 10 g. of 2,6-dimethyl-4-benzylmercaptopyrylium iodide in 10 ml. of water, 30 ml. of 15% ammonium hydroxide solution containing 8 g. of ammonium carbonate was added. The mixture was heated on the steam-bath for 15 minutes. The base was isolated as above. Yield, 4.78 g. (75%); b.p. 166–172° (5 mm.). On cooling the oil crystallized. Recrystallization from Skellysolve A gave a product melting at 56°.

Anal. Calc'd for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11.

Found: C, 73.31; H, 6.67; N, 6.25.

The *picrate*, recrystallized from ethanol, melted at 171°.

Anal. Calc'd for $C_{20}H_{18}N_4O_7S$: C, 52.40; H, 3.96; N, 12.22.

Found: C, 52.46; H, 3.79; N, 12.53.

Anker and Cook (1) reported the base as an oil and the *picrate* as melting at 171°.

4-(4-Morpholinyl)-2,6-lutidine. A solution of 3.4 g. of 2,6-dimethyl-4-(4-morpholinyl)-pyrylium iodide and 10 ml. of 15% ammonium hydroxide solution containing 8 g. of ammonium carbonate was heated on a steam-bath for one-half hour. The cooled solution was

extracted thoroughly with chloroform. The chloroform was evaporated and the residue was crystallized from Skellysolve B. Yield, 1.9 g. (94%); m.p. 124°.

Anal. Calc'd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.38; N, 14.57.

Found: C, 69.11; H, 8.03; N, 14.75.

The *picrate*, recrystallized from ethanol, melted at 180°.

Anal. Calc'd for $C_{17}H_{19}N_3O_8$: C, 48.45; H, 4.55; N, 16.62.

Found: C, 48.35; H, 4.19; N, 16.47.

SECTION VI. ATTEMPTED REPLACEMENT REACTIONS ON SOME PYRIDINIUM AND PYRYLIUM SALTS

A solution of 1.4 g. of 1,2,6-trimethyl-4-methoxypyridinium iodide (V) and 2 ml. of benzyl mercaptan in 15 ml. of ethanol was refluxed for 2 hours. From the reaction mixture 1.35 g. of unchanged V was recovered.

A solution of 1.25 g. of 2,6-dimethyl-4-dimethylaminopyrylium perchlorate (II) and 1 ml. of benzyl mercaptan in 30 ml. of methanol was refluxed for one hour. The solution was cooled and the salt was precipitated with ether. The product, 1.15 g.; m.p. 184–185°, was identical with starting material.

SECTION VII. PREPARATION OF STARTING MATERIALS

2,6-Dimethyl-4-methoxypyrylium iodide. This salt was prepared by the procedure of Anker and Cook (1). To 31 g. of 2,6-dimethyl-4-pyrone 43 g. of methyl sulfate and 4 ml. of methanol was added and the mixture heated on a steam-bath for 15 minutes. The mixture was allowed to cool and 150 g. of sodium iodide in 150 ml. of water was added slowly. After standing for two hours the mixture was filtered and the residue was washed with acetone. There was thus obtained 40 g. (60%) of the salt melting at 110°.

2,6-Dimethyl-4-benzylmercaptopyrylium iodide and perchlorate. The preparation of the iodide was described by King, Ozog, and Moffat (6). The perchlorate was prepared by treatment of an aqueous solution of the iodide with 70% sodium perchlorate. The product separated on cooling and was crystallized from methanol. Yield, 87%; m.p. 145–146° (dec.).

2,6-Dimethyl-4-methylmercaptopyrylium iodide and perchlorate. The iodide was prepared as described in (6). The perchlorate was prepared from the iodide by treatment with perchloric acid in aqueous solution. The product separated on cooling and was crystallized from methanol. Yield, 95%; m.p. 178°.

1-Methyl-2-methylmercaptopyridinium iodide. This compound was prepared according to the direction of Michaelis and Holken (7); m.p. 155–156°.

SUMMARY

Methoxy, or alkylmercapto groups on the 4 position of pyrylium salts are easily replaced by secondary amines. The order of ease of replacement is CH_3O- > CH_3S- > R_2N- .

Alkylmercapto groups in the 2, or 4 positions, and methoxy groups in the 4 position of pyridinium salts are easily replaced by secondary amines.

Some new 4-substituted lutidines and 4-substituted 2,6-dimethylpyridinium salts are reported.

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REFERENCES

- (1) ANKER AND COOK, *J. Chem. Soc.*, 117 (1946).
- (2) BAEBER, *Ber.*, **43**, 2338 (1910).
- (3) DILTHEY, *J. prakt. Chem.*, **101**, 177 (1921).
- (4) DIELS AND ALDER, *Ber.*, **60**, 716 (1927).
- (5) MARCKWALD, KLEMM, AND TRABERT, *Ber.*, **33**, 1562 (1900).
- (6) KING, OZOG, AND MOFFAT, *J. Am. Chem. Soc.*, **73**, 300 (1951).
- (7) MICHAELIS AND HOLKEN, *Ann.*, **331**, 249 (1904).