Synthesis of 1-Hydroxy-2-pyridinethiones, 1-Hydroxy-2-pyridones and Halopyridine 1-Oxides: Reactions of Lithiopyridine 1-Oxides

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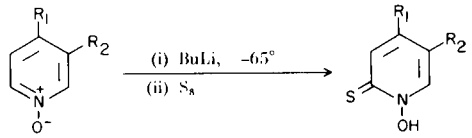
Sir:

Treatment of pyridine 1-oxides with *n*-butyllithium at −65° gives lithiopyridine 1-oxides which were shown to react with carbonyl compounds (1). Addition of sulfur in excess to the lithiopyridine 1-oxide solutions now provides a convenient route to the pharmacologically interesting 1-hydroxy-2-pyridinethiones, and interesting novel products are obtained by the addition of bromine.

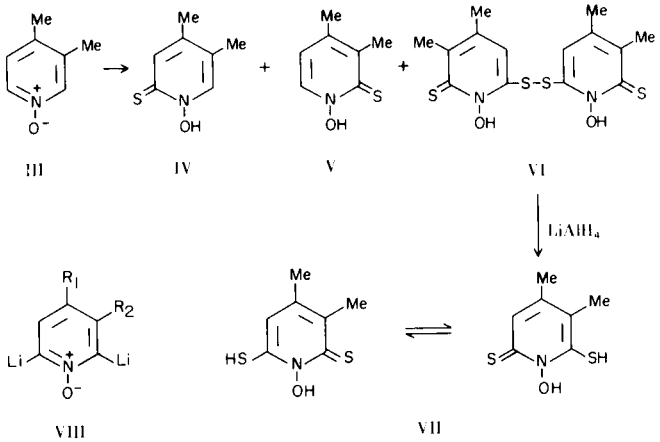
Pyridine 1-oxide (Ia) itself gave the parent 1-hydroxy-2-pyridinethione (IIa), m.p. 68°, [reported (2) m.p. 68-70°] in low (8%) yield, while 4-picoline 1-oxide (Ib) gave the 4-methyl derivative (IIb), m.p. 59°, in 39% yield (3). 4-Chloro-3-methylpyridine 1-oxide (Ic) gave the 6-thione (11.5%), m.p. 99-101°, a rather unstable compound which decomposes violently, together with at least one high molecular weight product. All of the 1-hydroxy-2-pyridinethiones (cyclic thiohydroxamic acids) gave zinc salts. 3,4-Lutidine 1-oxide (III) gave an interesting result:



I II

(a) $R_1 = R_2 = H$
(b) $R_1 = Me$, $R_2 = H$
(c) $R_1 = Cl$, $R_2 = Me$

both possible 1-hydroxy-2-pyridinethiones (IV) (24%), m.p. 121-122°, and (V) (12.5%), m.p. 128-129°, were obtained together with a dimeric product (VI) (37.4%), m.p. 186-187° (the orientation of the methyl groups is uncertain and two isomeric symmetrical structures are possible which could not be distinguished apart by mass or nmr spectroscopy or by its reactions. The unsymmetrical structure is eliminated since the nmr spectrum (in deuteriopyridine) exhibits only three peaks, one at τ 2.9, due to the two pyridine protons, and two at τ 7.46 and 7.97 due to the two types of methyl groups). Reduction of VI with lithium aluminum hydride gave the 1-hydroxythiol thione (VII), m.p. 120-122°, in quantitative yield. Compound VII yields a 2,4-dinitrophenylsulfenyl derivative, m.p. 175-177°, and a zinc salt, m.p. >300°. The formation of VI



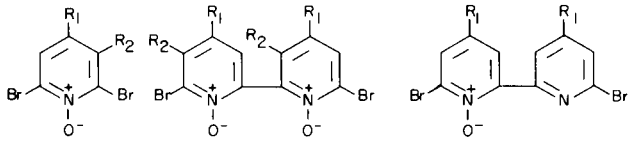
III IV V VI

VIII VII

suggests the possible intermediacy of the dilithio derivative (VIII; $R_1 = R_2 = Me$). No attempt has been made to optimize the yields in these or the other reactions described.

The reaction of the lithiopyridine 1-oxides with oxygen gave the corresponding hydroxamic acids, but in lower yields than the sulfur derivatives. No product could be obtained from Ia itself, but Ib gave 1-hydroxy-4-methyl-2-pyridone (14%), m.p. 129-130° (4). 3,4-Lutidine 1-oxide (III) gave a mixture of 1-hydroxy-4,5-dimethyl-2-pyridone (14%), m.p. 195°, and 1-hydroxy-3,4-dimethyl-2-pyridone (10%), m.p. 169-170°.

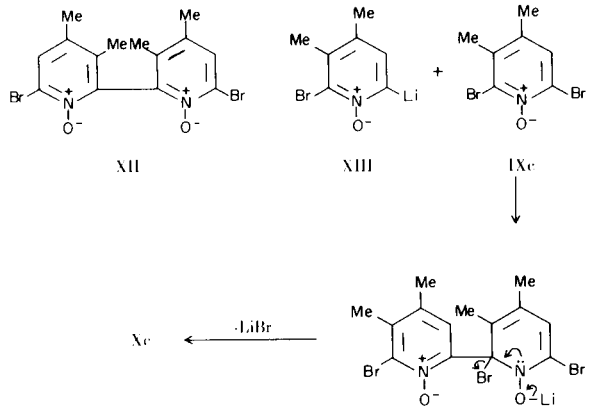
Addition of bromine to a cold (−65°) solution of the lithiopyridine 1-oxides in tetrahydrofuran gave a variety of dihalogenated products after short reaction periods whether or not the excess bromine was immediately removed by the addition of phenol. Three products were obtained from Ia and shown to be 2,6-dibromopyridine 1-oxide (IXa) (3%), m.p. 187-188° dec., [reported (5) m.p. 186.5-188.5°], 6,6′-dibromo-2,2′-dipyridyl 1,1′-di-



IX X XI

(a) $R_1 = R_2 = H$
(b) $R_1 = Me$, $R_2 = H$
(c) $R_1 = R_2 = Me$

oxide (Xa) (8.2%), m.p. 232-234° dec., and 6,6′-dibromo-2,2′-dipyridyl 1-oxide (XIa) (6.2%), m.p. 209-211° dec. Similarly, Ib gave IXb (5%), m.p. 154-155°, Xb (13%), m.p. 219-222° dec., and XIb (18%), m.p. 166-167°. On the other hand, III gave only 2,6-dibromo-3,4-dimethylpyridine 1-oxide (IXc) (13%), m.p. 144°, and Xc (4%), m.p. 200-202° dec. The structure of Xc was confirmed by its nmr spectrum. Had a symmetrical product, *e.g.* (XII), been the one formed one would have expected to see only one 2H peak due to the pyridine β-protons and two methyl peaks in the nmr. In actual practice, two 1H pyridine β-proton peaks were observed at τ 2.5 and 2.9 and four methyl singlet peaks were observed at τ 7.55, 7.7, 7.75 and 8, respectively, the ratio of the areas of the latter being 3:3:3:3. Xc undoubtedly arises from a nucleophilic addition of the monolithiated product (XIII) to IXc



and the observed orientation is consistent with the known effect of a 3-methyl group upon the addition of organolithium compounds to pyridines (6).

None of the bimolecular products were obtained in the reactions with chlorine gas. Pyridine 1-oxide gave a 4.5% yield of 2,6-dichloropyridine 1-oxide, m.p. 139-140° [reported (7) m.p. 139.5-140.5°], and III gave 2,6-dichloro-3,4-dimethylpyridine 1-oxide (8.8%), m.p. 165-166°.

In no case were any monobrominated or monochlorinated compounds obtained even when the amounts of halogen were decreased, and this implicates the intermediacy of the dianions VIII. No halogenated products were obtained in blank runs when the BuLi was omitted (8).

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