A Mild Conversion of Halopyridines and Quinolines to the Corresponding Pyridone or Quinolone

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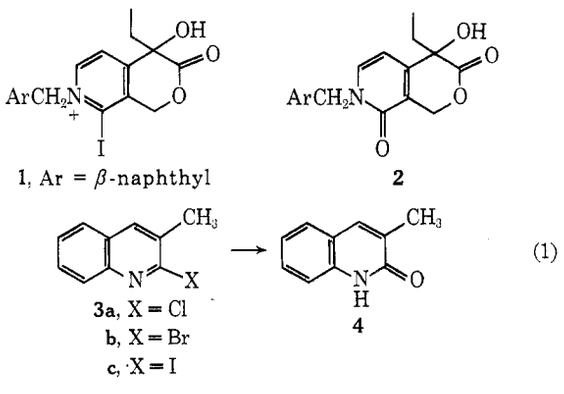
Received June 1, 1973

The conversion of halopyridinium salts to pyridones in good yields occurs by reaction with dimethyl sulfoxide at 100°. The reaction of 2-iodoquinolines to quinolones requires an acid catalyst but not quaternary salt formation. The 2-chloro- and 2-bromoquinolines can be converted by adding sodium iodide to form the iodo derivative. The reaction seems to be an oxidation-reduction rather than a simple hydrolysis.

A general method for the preparation of 2- or 4-oxo derivatives of nitrogen aromatic heterocycles involves the hydrolysis of the corresponding halogen derivative. The conversion can be accomplished in either acidic or basic medium; however, the reaction conditions are often extreme, limiting the kinds of substituents that can be present.[1] This conversion presented a particular problem in the preparation of analogs of camptothecin, which contains a pyridone ring.[2] The change in nmr spectrum of the iodopyridinium salt (**1**) which occurred when a dimethyl sulfoxide (DMSO) solution was allowed to stand led to the discovery of a novel method for causing this conversion. The nmr spectrum of a solution of **1** in DMSO after several days gave a doublet at 6.45 ppm which was characteristic of the 5 proton of a pyridone such as **2**. The formation of **2** was confirmed by isolation and characterization of the compound formed from the DMSO reaction.

To determine the generality of the reaction, 2-iodo-3-methylquinoline (**3c**) was treated with DMSO. No reaction was observed unless an acid was added. With 2-chloro- (**3a**) and 2-bromo-3-methylquinoline (**3b**) no reaction occurred unless sodium iodide was added to convert the halide to the 2-iodo derivative **3c**. These reactions were converted to a convenient synthetic procedure by mixing the haloquinoline, concentrated hydrochloric acid, and sodium iodide in DMSO to give high yields of the quinolone **4** (eq 1).



1, Ar = β-naphthyl

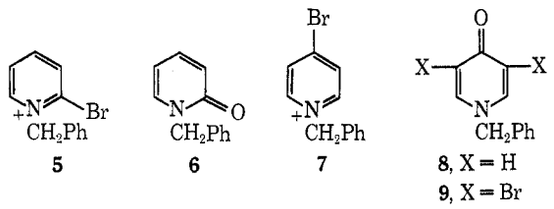
2

3a, X = Cl
b, X = Br
c, X = I

4

(1)

The corresponding condition which worked well with the quinoline series gave no reaction with 2-bromopyridine, although, the 2-iodopyridine could be obtained. The reaction of the quaternary salt, 1-benzyl-2-bromopyridinium bromide (**5**), with DMSO gave the 1-benzyl-2-pyridone (**6**) at 100° in <2 hr. The 1-benzyl-4-bromopyridinium bromide (**7**) was converted to the pyridone (**8**); however, **8** underwent bromination to give 1-benzyl-3,5-dibromo-4-pyridone (**9**) as

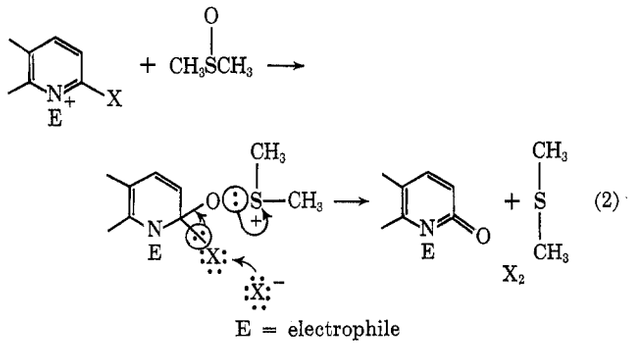


5 6 7 8, X = H 9, X = Br

the isolated product. Some unsubstituted pyridone **8** could be detected in the aqueous medium of the isolation.

During the course of this investigation the conversion of 4-chloroquinolines to 4-quinolones was reported to occur by treatment with DMSO.[3] The conversion occurred only with this heterocyclic ring system when a 3-alkoxycarbonyl substituent was present.

The results of Harris as well as those reported herein could be explained by hydrolysis of the halo heterocycle promoted by the highly polar solvent DMSO. The order of reactivity of the 2-haloquinolines (I > Br or Cl) and the *in situ* bromination of the 1-benzyl-4-pyridone (**8**) to form **9** are not readily explained by this mechanism, however. The reaction products and properties are consistent with a mechanism of nucleophilic addition of DMSO followed by an oxidation–reduction mechanism (eq 2) also implied by Harris.[3]



E = electrophile

(2)

It is evident that a ring system which can stabilize the product of nucleophilic addition is required. An electrophilic aromatic π system is required; so salts of the heterocyclic nitrogen or electron-withdrawing substituents must be present to cause a successful

(1) T. Kametani, *Tetrahedron*, **26**, 5753 (1970).

(2) R. E. Lyle, J. A. Bristol, M. J. Kane, and D. E. Portlock, *J. Org. Chem.*, **38**, 3268 (1973).

(3) N. D. Harris, *Synthesis*, 625 (1972).

reaction. Quinoline is more reactive than pyridine, for the dihydroquinolines are more stable than the dihydropyridines. A quaternary salt rather than a proton salt is required to form the intermediate in the later case. The failure of the 2-chloro- and 2-bromoquinolines to give a reaction probably reflects the higher oxidation potential of these substituents.

The formation of iodine and dimethyl sulfide in these reactions could readily be demonstrated; however, this is not conclusive since iodide ion is converted to iodine by DMSO in acidic medium.[4] The formation of 3,5-dibromo-4-pyridone (**9**) is clear proof for the presence of bromine as a reaction product from **7** with DMSO and strongly supports eq 2 as the reaction pathway. There are numerous examples of the oxidative replacement of halides from alkyl halides in which the removal of a proton initiates the oxidation–reduction reaction,[5] but these reactions of DMSO are the first examples of oxidation–reduction of a sulfoxonium salt initiated by loss of positive halogen.

On the basis of the probable mechanism it seems possible that oxidation of pyridinium salts to pyridones could be achieved with DMSO by addition–elimination. The pyridinium salts with 3 substituents which are electron withdrawing usually most readily add nucleophiles. Thus the reaction of 1-methyl-3-benzoylpyridinium iodide with DMSO was attempted but no oxidation occurred.

Experimental Section

Preparation of 3-Methyl-2-quinolone (4).—To 221 mg (0.0818 mmol) of 2-iodo-3-methylquinoline (**3a**) were added 3 ml of dry DMSO and 5 drops of concentrated hydrochloric acid. The mixture was heated at 100° for 24 hr, cooled, and diluted with water, and the mixture was filtered. The insoluble solid was 30 mg of 3-methyl-2-quinolone (**4**). The filtrate was extracted with ether and the ether extracts were washed with aqueous $NaHSO_3$, dried (K_2CO_3), and concentrated to give 70 mg of 3-methyl-2-quinolone (**4**) as a white solid, mp 237–240° (lit.[6] mp 237–239°). A mixture melting point showed no depression. The total yield was 91%.

The reactions of **3b** and **3c** were run as above; however, 0.3 g of sodium iodide was added. The reactions gave **4** in 92 and 82% yields, respectively.

Preparation of *N*-Benzyl-2-pyridone (6).—To 3.6 g (0.011 mol) of *N*-benzyl-2-bromopyridinium bromide (**5**) was added NaI and 20 ml of DMSO. The mixture was heated at 100° for 1.5 hr. During the reaction the mixture was monitored by uv absorption. After cooling, water, ether, and solid $NaHSO_3$ were added. The aqueous layer was extracted several times with ether, and the combined ether extracts were dried (K_2CO_3) and concentrated under reduced pressure to give 2.03 g (100%) of *N*-benzyl-2-pyridone (**6**) as a crude oil. Column chromatography on silica gel of the oil gave 1.32 g (65%) of *N*-benzyl-2-pyridone (**6**) as white crystals, mp 60–68°. Recrystallization of the solid from ether–hexane gave *N*-benzyl-2-pyridone (**6**) as white needles, mp 63–65° (lit.[7] mp 71.8–72.8°), picrate mp 130–131.5° (lit.[7] mp 129.5–130.5°).

Preparation of *N*-Benzyl-3,5-dibromo-4-pyridone (9).—To 2.0 g (0.006 mol) of 4-bromo-*N*-benzylpyridinium bromide (**7**) was added 10 ml of DMSO. This mixture was heated for 2.25 hr at 100° in an oil bath. The reaction was monitored by uv absorption. Water was added causing the loss of the yellow color of the solution, and a white solid precipitated from the solution.[8] The solid was collected by filtration to give 0.4 g (20%) of *N*-benzyl-3,5-dibromo-4-pyridone (**9**), mp 173–178°. Recrystallization of the solid from $HOAc \cdot H_2O$–ethanol (1:1) gave *N*-benzyl-3,5-dibromo-4-pyridone (**9**) as white needles, mp 196–199° (lit.[6] mp 184–186°). Another 0.24 g (12%) was obtained from the filtrate by extraction with ether to give a white solid, mp 188–193°; the total yield of *N*-benzyl-3,5-dibromo-4-pyridone (**9**) was 0.65 g (32%).

Acknowledgment.—The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by Grant CA-12149-02. This research was abstracted from the thesis of M. J. Kane submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. degree.

Registry No.—**3a**, 35820-73-6; **4**, 2721-59-7; **5**, 14532-01-5; **6**, 1753-62-4; **7**, 2589-30-2; **9**, 41366-77-2; DMSO, 67-68-5.

(4) G. Modena, G. Scorrano, D. Landini, and F. Montanari, *Tetrahedron Lett.*, **No. 28**, 3309 (1966).

(5) N. Kornblum, *J. Amer. Chem. Soc.*, **79**, 6562 (1957).

(6) G. Ornstein, *Chem. Ber.*, **40**, 1088 (1907).

(7) F. Krochnke and H. Schaefer, *Chem. Ber.*, **95**, 1104 (1962).

(8) The uv absorption spectrum of this layer indicated the presence of 1-benzyl-4-pyridone (**8**).