Simple Method for Demethylation of Quaternised Nitrogen Heterocyclic Compounds

By D. AUMANN and L. W. DEADY*

(*Department of Organic Chemistry, La Trobe University, Bundoora, Victoria* 3083, *Australia*)

Summary Some *N*-methyl-pyridinium, -quinolinium, and -isoquinolinium iodides have been successfully demethylated by heating in dimethylformamide solution under reflux.

THERE are many methods for the quaternisation of nitrogen heterocycles.[1] However, such reactions are irreversible under normal reaction conditions and there are no general methods for the dequaternisation of these compounds. We report here that demethylation of *N*-methylpyridinium iodide and related compounds can be achieved by heating in dimethylformamide solution under reflux.

The development of this reaction stemmed from the observation that 2-iodo-1-methylquinolinium iodide, when heated under reflux for 3 h in DMF, gave an almost quantitative yield of 2-quinolone. The displacement of the iodo-group under these conditions can be attributed to a rapid reaction with moisture in the commercial DMF sample, but the accompanying demethylation was unexpected. We have therefore treated several quaternised heterocycles under identical conditions to test the generality of the reaction.

The reactions (1·5 g methiodide in 15 ml DMF) were monitored directly by n.m.r., reaction being indicated by disappearance of the *N*-methyl peak and upfield shift of the aromatic proton signals in the dequaternised species relative to those in the starting materials. The results in the Table show that all compounds studied demethylated successfully, with varying ease. Reactions were estimated by n.m.r. to be at least 90% complete (with the exception of pyridine) in the times given.

TABLE

Times required for demethylation[a]

Methiodide	Reflux time (t/h)	Methiodide	Reflux time (t/h)
Quinoline	16	Pyridine	96
4-Methylquinoline	24	2-Methylpyridine	94
2-Methylquinoline	6	2,6-Dimethylpyridine	45
Isoquinoline	80	Nicotinonitrile	15

[a] Reaction was at least 90% complete in this time, except for pyridine (*ca.* 70%).

Formation of the demethylated heterocycle was confirmed by isolation of the picrate, after adding water to the reaction mixture. No attempt was made, in general, to check on the yield of isolable heterocycle but the n.m.r. spectra indicated that reactions were clean and that the yields would be high. In one reaction of nicotinonitrile methiodide, the aqueous reaction mixture was extracted with chloroform. This extract, after being dried and concentrated, gave an 86% yield of nicotinonitrile picrate.

The effect of structure on the rate of demethylation is of interest. The quinolinium compounds reacted relatively rapidly and we attribute this to instability caused by non-bonded interaction between 8-H and the *N*-methyl group. Surprisingly, however, with respect to such steric effects, demethylation of 1,2,6-trimethylpyridinium iodide, though significantly faster than 1-methylpyridinium iodide, reacted more slowly than 1,2-dimethylquinolinium iodide.

Apart from steric acceleration, this demethylation reaction ought to be favoured by electron-withdrawing substituents in the heterocycle. It appears, from the reactivity of the nicotinonitrile compound, that a significant substituent electronic effect does indeed occur.

(*Received, 8th November* 1972; *Com.* 1876.)

---

[1] G. F. Duffin, *Adv. Heterocyclic Chem.*, 1964, **3**, 2.