C-Alkylation of 1,5-Naphthyridine Derivatives by Methyl Iodide

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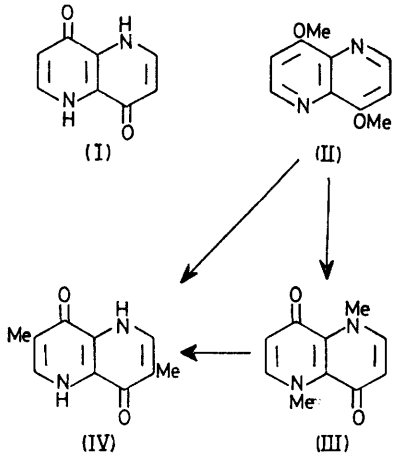
Summary Thermal reaction of 4,8-dimethoxy-1,5-naphthyridine with methyl iodide yields *C*-alkylated products regiospecifically; an electrophilic substitution mechanism is proposed.

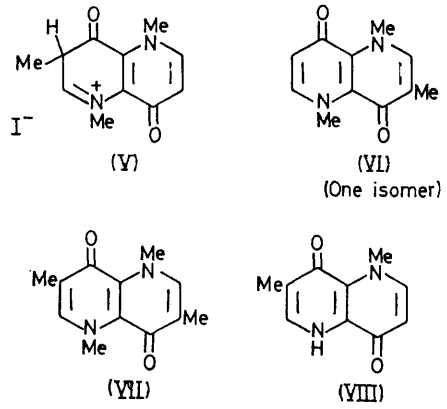
THE direct introduction of alkyl groups into heteroaromatic compounds is difficult to achieve under conditions normally used to alkylate simple aromatic substrates. For aza-aromatic compounds a number of alkylation procedures have been developed which either circumvent or take

advantage of the decreased electron density of ring carbon atoms, the recently reported nucleophilic substitution method of Taylor and Martin[1] being the most significant advance. Examples of electrophilic alkylation of aza-aromatic compounds are quite uncommon and are non-existent in the case of naphthyridines.[2] An example in the pyridine series is the thermal reaction of triphenylmethyl chloride with either 2-pyridone or *N*-methyl-2-pyridone to yield in both cases 5-triphenylmethyl-2-pyridone, the methyl group having been lost. We report here a similar reaction which we have observed in connection with our studies on tautomerism in 1,5-naphthyridine-4(1*H*),8(5*H*)-dione (I).



The Lander rearrangement[4] of 4,8-dimethoxy-1,5-naphthyridine† (II), m.p. 214—216 °C, in the solid state with MeI (1 mol. equiv., 2·5 h in sealed ampoule at 225 °C) produced the expected 1,5-dimethyl compound (III), 78%, m.p. 273—275·5 °C, purified either by recrystallization from benzene or gradient sublimation at 110 °C. In contrast, when the reaction time was prolonged to 12 h, a new compound was isolated which was insoluble in benzene and sublimable only above 230 °C. Purification of the sublimed material by dissolution in base and reprecipitation with acid followed by a final recrystallization from water yielded the centrosymmetric, ring-methylated naphthyridine (IV), 55%, m.p. >300 °C, identified by comparison of its spectral (n.m.r., i.r., and u.v.) and chemical properties with those of compounds (I) and (III).

The *N*-methylated derivative (III) was produced when (II) was heated in the absence of MeI or with MeI in diphenyl ether solution. Compound (IV) was not detected under these conditions. Heating (III) alone at 225 °C (10 h) yielded only recovered starting material but in the presence of MeI (III) yielded (IV), (53% isolated) along with small amounts of tri- and tetra-methylated species detected in the mass spectrum of the crude product.‡ Similarly, heating (III) with CD_3I (0·85 mol. equiv., 228 °C, 16 h) yielded crude material shown by its mass spectrum to contain di-, tri-, and tetra-methylated species. Purification of this substance as described above removed tri- and tetra-methylated compounds as shown by mass spectroscopy, yielding (IV) which was shown (n.m.r.) to contain one CD_3 group. Heating the precursor (I) with MeI (4·5 mol. equiv., 228 °C, 12 h) led to essentially quantitative recovery of unchanged (I).



We believe that the transformation (II) → (IV) takes place *via* (III) which undergoes electrophilic attack by MeI at C-3 and C-7 with formation of a naphthyridinium intermediate such as (V). That the *N*-methyl groups of (V) are cleaved in a separate step following proton loss is indicated by the detection of tri- and tetra-methylated species [presumably (VI) and (VII)] in the mass spectrum of crude (IV) and by the fact that (I) is inert under similar reaction conditions. The proposed mechanism implies that (VIII), which we have isolated in erratic yield and purity [contaminated with (III)] is produced through Lander rearrangement of (II) at temperatures < 225 °C. The structure of (VIII) was assigned on the basis of its n.m.r. and i.r. spectra.§

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† Satisfactory analytical and spectroscopic data were obtained for compounds (I)—(IV). In addition, the structures of (II) and (III) were proven by *X*-ray structure determination (R. Harlow and S. H. Simonsen, unpublished results).

‡ The reaction (II) → (IV) was not examined for tri- and tetra-methylated products.

§ The spectroscopic data referred to in this Communication were made available to the referees.

[1] E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, 1974, **96**, 3095, and references therein.
[2] See for example, C. F. H. Allen, *Chem. Rev.*, 1950, **47**, 275; M. J. Weiss and C. R. Hauser in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1961, **7**, ch. 2; W. W. Paudler and T. J. Kress *Adv. Heterocyclic Chem.*, 1970, **11**, 123; W. W. Paudler and T. J. Kress in 'Topics in Heterocyclic Chemistry,' ed. R. N. Castle, Wiley-Interscience, New York, 1969, ch. 4.
[3] R. Adams, J. Hine, and J. Campbell, *J. Amer. Chem. Soc.*, 1949, **71**, 387.
[4] P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, 1970, **90**, 1569, and references therein.