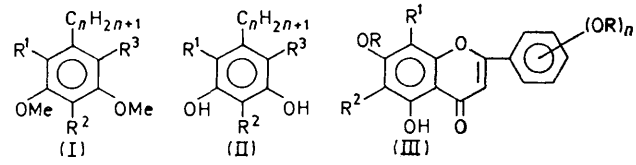
C-Demethylation and Methyl Group Migration during O-Demethylation with Pyridine Hydrochloride

By J. H. P. TYMAN

(*School of Chemistry, Brunel University, Kingston Lane, Uxbridge, Middlesex*)

Summary *C*-Demethylation and isomer formation as well as *O*-demethylation can take place in the reaction of pyridine hydrochloride with certain phenolic ethers.

PYRIDINE hydrochloride,[1] one of several acidic-type demethylating agents, is normally regarded as a mild reagent,[2] and was being used in the present work since an 'alkaline' method[3] was ineffective. In the demethylation of (I; R^1 = R^3 = H, R^2 = Me, n = 15) by refluxing with an excess of pyridine hydrochloride according to the procedure described for similar compounds,[4] the main product (II; R^1 = R^3 = H, R^2 = Me, n = 15) (64%) was accompanied by the isomer (II; R^1 = Me, R^2 = R^3 = H, n = 15) (5%) and a *C*-demethylated substance (II; R^1 = R^2 = R^3 = H, n = 15) (31%). In a similar way (I; R^1 = Me, R^2 = R^3 = H, n = 15) gave the expected product (II; R^1 = Me, R^2 = R^3 = H, n = 15) (34%), the isomer (II; R^2 = Me, R^1 = R^3 = H, n = 15) (22%) and the same *C*-demethylated substance as before. The figures given indicate approximate proportions of phenolic products although yields of the expected materials were 74% (4-methyl compound) and 51% (6-methyl compound) with very much less of the two accompanying materials in each case when less drastic pyridine hydrochloride demethylation was used. All substances were identified by their R_F values (t.l.c.), retention times (g.l.c.), mass and n.m.r. spectra alongside pure reference compounds. The reaction products were



separated by preparative t.l.c. and contained a small proportion of the original dimethyl ether, indicating that the formation of the preceeding substances was not due to excessively severe reaction conditions. Attempts to simulate the results by the demethylation of 2-methylresorcinol dimethyl ether were not significantly useful probably because the refluxing temperature was 70 °C

lower. The present results may be associated with the larger excess of reagent required. (I; $R^1 = R^2 = R^3 = H$, $n = 15$) gave simply the dihydric phenol (II; $R^1 = R^2 = R^3 = H$, $n = 15$) like the C_{19} and C_{21} compounds (I; $R^1 = R^2 = R^3 = H$, $n = 19$ and $n = 21$) which gave yields of 75% and 73%[4] respectively and it seems possible that *C*-demethyation and isomer formation involve an intermolecular rather than an intramolecular process. In the demethylation of (I; $R^1 = R^3 = Me$, $R^2 = H$, $n = 17$) under unstated conditions, but thought to be those of ref. 4, a 97% yield[5] of the phenol (II; $R^1 = R^3 = Me$, $R^2 = H$, $n = 17$) was described and the product compared with nor-β-leprosol, the demethylated material (by means of hydriodic acid).[6] The small differences in m.p. were ascribed to the presence of different homologues but could be equally due to small proportions of *C*-demethylated or isomeric compounds. The structural assignments are not being questioned in this case. No instances of *C*-demethylation or isomer formation have previously been observed with pyridine hydrochloride demethylations which have been reviewed[7] and only one case of *C*-de-ethylation, without isomer formation, accompanying the expected product.[8]

C-Demethylation and formation of isomers has been observed in the treatment of 2-alkoxy- and 3,4-dialkoxyphenyl substituted flavones (III) with aluminium chloride and with hydriodic acid.[9–11] Formation of phenolic isomers also arises with the latter reagent in cases where no C–Me compounds are present.[12] It is therefore worth noting that in the original synthesis[13] of (II; $R^1 = R^3 = Me$, $R^2 = H$, $n = 17$) where hydriodic acid was used in the final stage the wide difference of m.p. compared with those described[5,6] could be due to varying C–Me composition. The assignment of structures to the other synthetic products described may be open to doubt unless substantiated, as is possible nowadays, by spectroscopic means.

(*Received*, 1*st June* 1972; *Com.* 937.)

[1] V. Prey, *Chem. Ber.*, 1941, **74**, 1219; 1942, **75**, 350; 445.
[2] T. J. Curphey, E. J. Hofmann, and C. McDonald, *Chem. and Ind.*, 1967, 1138.
[3] I. M. Lockhart and N. E. Webb, *Chem. and Ind.*, 1970, 1230.
[4] E. Wenkert, E.-M. Loeser, S. N. Mahapatra, F. Schenka, and E. M. Wilson, *J. Org. Chem.*, 1964, **29**, 435.
[5] J. D. Bu'Lock and A. T. Hudson, *J. Chem. Soc.*, 1969, 61.
[6] J. A. Crowder, F. H. Stodola, and R. J. Anderson, *J. Biol. Chem.*, 1936, **114**, 431.
[7] R. Royer and P. Demersemann, *Bull. Soc. chim. France*, 1968, 2633.
[8] R. Royer and E. Bisagni, *Bull. Soc. chim. France*, 1960, 395.
[9] S. K. Mukerjee and T. S. Seshadri, *Chem. and Ind.*, 1955, 271.
[10] W. B. Whalley, *J. Chem. Soc.*, 1953, 3366.
[11] W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis, and R. Winter, *Chem. and Ind.*, 1953, 277.
[12] D. M. Donnelly, E. M. Philbin, and T. S. Wheeler, *Chem. and Ind.*, 1953, 163.
[13] M. Asano and S. Iguti, *J. Pharm. Soc. Japan*, 1951, **71**, 1218; *Chem. Abs.*, **46**, 60958.