Tetrahedron Letters,Vol.27,No.49,pp 5997-6000,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

AN ADVENTITIOUS SYNTHESIS OF A 5-METHYLIMIDAZO[4,5-c]PYRIDINE DERIVATIVE*

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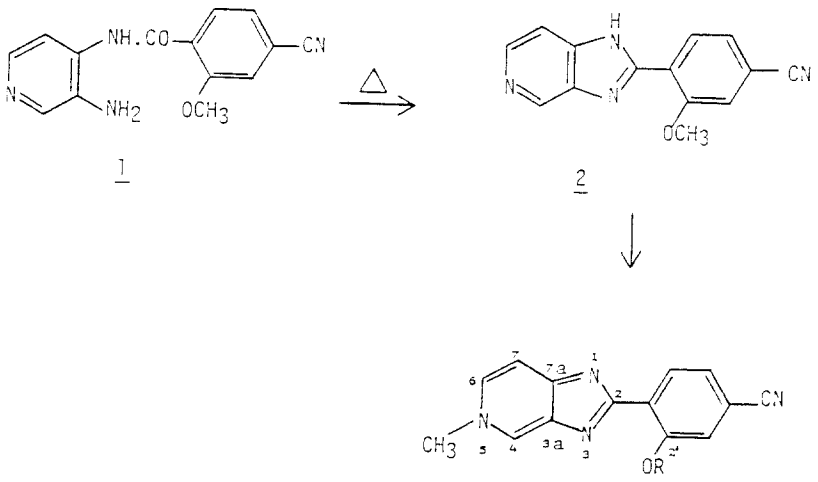
Abstract: At 210° in the melt 2-(4-Cyano-2-methoxyphenyl)-1H-imidazo[4,5-c]pyridine(2) undergoes isomerization to give 2-(4-cyano-2-hydroxyphenyl)-5-methylimidazo[4,5-c]pyridine (3a).

2-Aryl-1H-imidazo[4,5-c]pyridines[1] and related heterocycles[2] are of much current interest as cardiotonic agents. During investigations to obtain such agents with an improved pharmacological profile we attempted to convert[3] the amide 1[4] to the 1H-imidazo[4,5-c]pyridine derivative 2[2]. We observed that when the hydrochloride salt of 1 was heated at 205° in the melt for 5 minutes a new heterocycle, which was clearly not the desired product, was produced in almost quantitative yield. Thermolysis of the free base of 1 at 205° in the melt also yielded the same new heterocycle m.p. 187-9°, in ca. 70% yield but thermolysis in ethylene glycol solution at 195° in the presence of small quantities of concentrated hydrochloric acid gave the desired 2 mono hydrochloride, m.p. 289-294°in ca. 30% yield. When 2 was heated at 205° for 5 minutes it was converted cleanly into the same product as above. This new product was easy to detect since it was slightly more polar on t.l.c. than 2 and displayed a bright yellow fluorescence under u.v. light in contrast to 2 which showed blue fluorescence.



1 → 2 → 3

3 a R = H
b R = CH_3

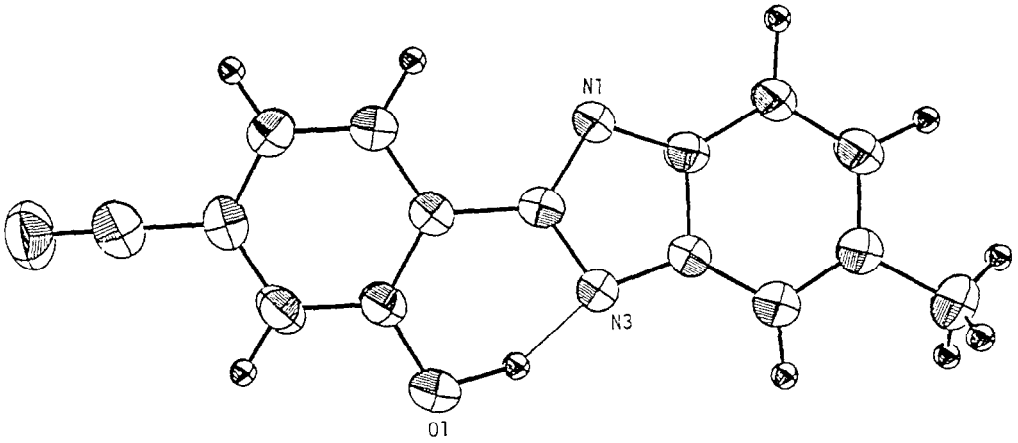
Microanalytical data and mass spectrometry on the new pyrolysis product indicated it was an isomer of 2 $C_{14}H_{10}N_4O$, M^+(250). Detailed analysis of the ^1H and ^{13}C n.m.r. spectra and comparison with those of 2 suggested structure 3a for the pyrolysis product. ^1H nmr (dmso-d6) 4.30 (s, 3H, N-CH3), 7.34 (d x d, 1H, J = 8.1, 1.6 Hz, H5'), 7.43 (d, 1H, J = 1.6 Hz, H3'), 7.92 (d, 1H, J = 6.8 Hz, H7), 8.26 (d, 1H, J 6.8 Hz, H6), 8.41 (d. 1H, J 8.1 Hz, H6'), 9.17 (s, 1H, H4). ^{13}C nmr ppm 46.3 (NCH_3), 112.4 (C7 JC7-H7, 171Hz), 113.1 (C4'), 118.5 and 120.2 (C1', CN), 120.9 (C3'), (JC3'-H3', 168 Hz), 122.2 (C5', JC5'-H5', 168 Hz), 129.2 (C6', JC6'-H6', 165 Hz), 134 (C4; C6, JC4-H4, 127 Hz, JC6-H6, 187Hz), 141.4 (C7a), 151.1 (C3a), 158.3 (C2'), 165.6 (C2).

Of particular diagnostic value were the differences in chemical shift between the N-CH_3 of 3a and the OCH_3 of 2 (4.06, C^{13} 56.7 p.p.m.), and the sharpness of many signals for (3a) in contrast to those of 2 where tautomerism leads to line broadening. In addition n.O.e. studies on 3a showed enhancements at H4 and H6 on irradiation of the methyl signal. No enhancement was observed at any of the phenyl protons. Since reports of well-characterized examples of 5-substituted imidazo[4,5-c]pyridines are rare[5-7] we wished to confirm our n.m.r. assignments by an independent synthesis

of 3. Thus reaction of 2 with methyl iodide in DMA at room temperature and subsequent treatment with 4N NaOH gave 3b as the sole product. Demethylation of 3b with BBr_3 in CH_2Cl_2 (reflux, 4h) gave a sample of 3a identical with that obtained from the pyrolysis experiments. X-ray crystallographic analysis[8] of the pyrolysis product confirmed the 5-methylimidazo[4,5-c]pyridine structure and indicated a planar arrangement of rings with a strong N3...H-O bond. (See diagram below)

Studies of the scope and mechanism of this thermal O → N methyl migration[9] indicate that the rearrangement occurs with a range of heterocyclic substrates (e.g. purines, 1H-imidazo[4,5-b]pyridines etc.) and with other alkyl groups (e.g. ethyl, allyl). Migrations are facilitated by electron-withdrawing groups in the phenyl ring, can occur from meta- or para-ether groups and are believed to occur by an intermolecular process (crossover experiments).

Details of these studies will be reported elsewhere.



ORTEP diagram of 3a. N3-HO bond distance 1.50 angstroms

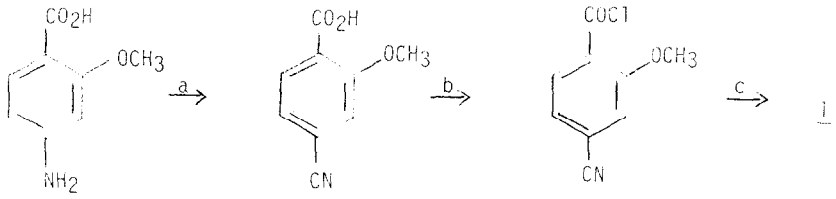
References and Notes

1. D. W. Robertson, E. E. Beedle, J. H. Krushinski, G. Don Pollock, H. Wilson, V. L. Wyss and J. S. Hayes, J. Med. Chem., 1985, 28, 717.

2. Dr. Karl Thomae GmbH, Arzneim-Forsch/Drug Res., 1981, 31(1), 129-278.

3. A similar conversion of this type, that is of 2-amino-3-(2,4-dimethoxy benzoyl)aminopyridine hydrochloride to 2-(2,4-dimethoxyphenyl) -1H-imidazo[4,5-b]pyridine hydrochloride has been reported under the same conditions; British Patent 1,445,824, Dr. Karl-Thomae G.m.b.H. (Chem. Abs. 82, 4251y)

4. Prepared by the following route:-



a. $NaNO_2$, 2N HCl, CuCN b. $SOCl_2$ c. 3,4-diaminopyridine
Structure I was inferred from the good agreement of the observed chemical shifts of the pyridyl ring protons [δ ($CDCl_3$) 7.75 (H5), 8.16(H6), 8.25 (H2) with those calculated from substituent constants. In addition an n.O.e. enhancement was observed for H2 on irradiation of the amino signal..

5. G.B. Barlin, J. Chem. Soc., (B), 1966, 285.

6. G.B. Barlin and M.D. Fenn, Aust. J. Chem., 1981, 34, 1341.

7. G. Cleve, H. Gibian, G.A. Hoyer, D. Rahtz, E. Schroder and G. Schulz, Liebigs Ann. Chem., 1971, 747, 158.

8. Performed as a service by the crystallographic staff of Molecular Structure Corporation, 3304 Longmire Drive, College Station, Texas 77840, U.S.A. The full list of parameters has been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Longfield Road, Cambridge, CB2 1EW.

9. O→N Methyl migrations are rare. For a recent example in a ranitidine precursor see J. Herzig, A. Antebi, A. Nudelman and H. E. Gottlieb, J. Org. Chem., 1986, 51, 730.

Acknowledgements

We are indebted to Miss Gita Shah for expert technical assistance and to Dr. W. R. King for valuable discussion.

(Received in UK 13 October 1986)