NOVEL INTRAMOLECULAR NITROGEN TO CARBON DOUBLE MIGRATION[1]

Shekhar Munavalli, Fu-Lian Hsu, and Edward J. Poziomek

U.S. Army Chemical Research, Development and Engineering Center
Research Directorate
Aberdeen Proving Ground, Maryland 21010-5423, USA

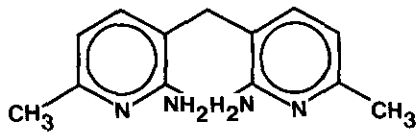
Abstract - Steric hindrance gives rise to an unusual nitrogen to carbon migration when 2-amino-6-methylpyridine is reacted with di-iodomethane at 140-150°C.

In continuation of our earlier work on the facile one-step synthesis of N,N'-methylene-2,2'-azapyridocyanines [2,3], we have further explored the scope of this reaction. We now wish to report an unusual non-acid/non-base catalyzed nitrogen to carbon double migration rearrangement. In the ordinary course of this reaction, the condensation of variously substituted 2-aminopyridines with di-iodomethane yields N,N'-methylene-2,2'azapyridocyanine derivatives. The structure of the parent compound has been further confirmed by single crystal X-ray analysis[4]. This is true even with 4-aminopyrimidine and 2-aminoquinoline[5,6]. The only exceptions we have so far encountered are the pyridines carrying electron-withdrawing substituents. It appears that the reaction is very sensitive to the eletronic environment present in the molecule. This report deals with the effect of steric hindrance. Thus, the presence of steric hindrance in 2-amino-6-methylpyridine has been observed to alter the normal course of the reaction and to result in di-3-(2-amino-6-methyl)-pyridylmethane. This non-acid/non-base catalyzed nitrogen to carbon intramolecular migration is reminiscent of the Sommelet-Hauser, the Stevens, and the nitraminopyridine/phenylnitramine rearrangements.

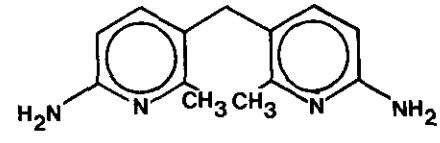
When a solution of 2-amino-6-methylpyridine (1.08 g, 0.01 mole) and methylene iodide (3.36 g, 0.0125 mole) in dry acetonitrile (30 ml) is heated in a pressure bottle for three days at 140-145°C, a golden yellow colored solid (0.31 g, m.p. >260°C) is obtained from the workup of the reaction mixture along with a considerable amount of tar-like polymeric material. Both the ^{1}H and ^{13}C-NMR spectra are consistent with structures 1A and 1B (a singlet, 2.3 ppm, 6H, two $-CH_3$ groups on the aromatic ring; a singlet, 3.75 ppm, 2H, methylene protons; a doublet, 6.75 ppm, 1H, β-H, J = 9 Hz; another doublet, 7.55 ppm, 1H, γ-H, J = 9 Hz; a singlet, 7.45 ppm, 4H, exchangeable Hs on the two $-NH_2$ groups. ^{13}C-NMR: $\underline{C}H_3$ = 17.1; $-\underline{C}H_2$ = 29.9; C = 110.8; C = 120.7; C = 145.5; C = 144.9; and C = 153.3, all ring carbons of the pyridine system). UV: max. 304 and 215 nm (EtOH). The compound on TLC gives only one spot. The MS ($CI-NH_3$) indicates the molecular weight to be 228 (expected 228). There are two major ms fragments at 107 and 121 corresponding to the ions

resulting from the expected benzylic cleavage.

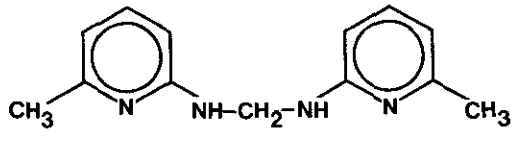
The formation of 1A/1B must have involved one of the two alternate pathways via the precursors 2A or 2B. If 2A is an immediate precursor in the formation of 1A or 1B , then it must undergo *simultaneous* double intramolecular nitrogen to carbon migrations. Obviously, this appears to be a highly unlikely possibility. On the other hand, if 2B is a potential precursor in the formation of 1A or 1B, then in a step-wise fashion it must first undergo migration, followed by re-alkylation of the amino group of 2-amino-6-picoline and a second intramolecular nitrogen to carbon rearrangement of the alkylated product to furnish 1A or 1B. Thus, the intermediate 2B could, via the first intramolecular rearrangement, give rise to 3 which in turn could react with 2-amino-6-methylpyridine present in the reaction mixture to give 4. A second intramolecular N to C migration could then result in 1A or 1B.



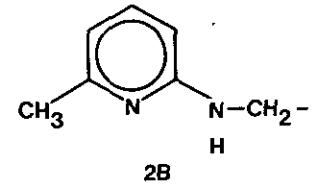
1A



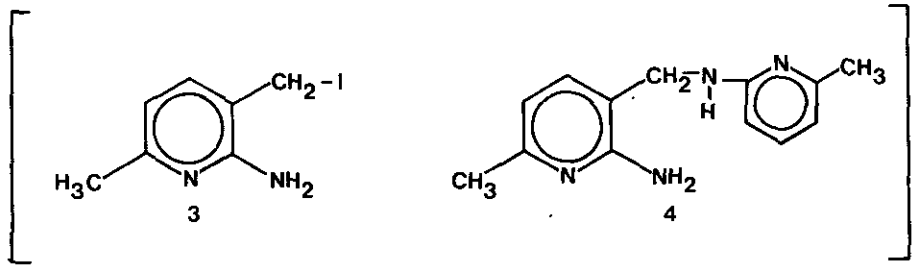
1B



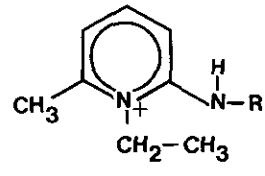
2A



2B



3 4



5,R = CH_2CH_3

6,R = H

The choice between 1A and 1B is primarily based on the accepted belief that intramolecular rearrangements generally favor the ortho-product and in part on the analogy of the product formation in the Stevens rearrangement[7-11] and the nitraminopyridine rearrangement [12-18]. The Stevens rearrangement is known to furnish ortho substituted tertiary amines. However, the Stevens rearrangement requires strong bases such as alkali metal amides and potassium t-butoxide as catalysts. Unlike the Stevens rearrangement, the migration we have observed does not require strong bases as catalysts. Neither does it require the presence of benzylic or allylic hydrogens as does the Stevens rearrangement. In this context, it must be stated that the above does not appear to be a rigid requirement[10,19]. Thus, the decomposition of the betaine formed by the addition of N,N-dimethylaniline to 2,3,4,5-tetrafluorobenzyne in petroleum ether containing N,N-dimethylaniline yielded N-methyl-2-methyl-3,4,5,6-tetrafluorophenylaniline[19].

The classical nitraminopyridine rearrangement requires strong acids, and the product distribution under these conditions depends on the type and concentration of the acid. The mechanism of 2-nitraminopyridine has been reported to be similar to that involved in the rearrangement of phenylnitramine[15]. The intramolecular rearrangement of phenylnitramine gave 95% of the ortho-substituted derivative[20]. Thermally induced rearrangement of N-methyl-N-p-nitrophenylnitramine in dichloromethane gave the ortho-compound as the major product[18]. The product formation ratio in the photochemical rearrangement of 2-nitraminopyridine favors the ortho over para by a margin of 6.3 to 1[21]. Although the mechanism of 2-nitraminopyridine is not well understood, it is accepted that the mechanism of the rearrangement usually is intramolecular. These considerations further support our contention that the rearrangement we have observed yields the ortho-substituted product. If our contention that 2B is an intermediate is true, then one ought to be able to isolate the stipulated intermediate 2B. The remaining two intermediates, namely 3 and 4, are probably unstable under the present experimental conditions. This is supported by the fact that quaternanry salts 2- and 4-amino-pyridines are highly reactive[23]. Indeed when the reaction mixture is refluxed in acetonitrile for three days, a light yellow colored solid is obtained. The ^{1}H-NMR of this product is consistent with structure 2B (a singlet, 2.35 ppm, 3H, $-CH_3$; multiplet, 4.45 ppm, 2H, $-N-CH_2-$; a multiplet, 6.85 ppm, 2H, 2 Hs; another multiplet, 7.85 ppm, 1H, γ-H).

This unusual non-base catalyzed double intramolecular nitrogen to carbon migration is a direct consequence of the steric hindrance. Similar observation regarding the role of steric hindrance in the methylation of 2,2-dimethylaminopyridine has been recently reported[23]. When the substituents are present on the C_3, C_4, and C_5 carbon atoms of the pyridine ring, the ring nitrogen is easily accessible to alkylation leading to the azapyridocyanine derivatives. However, when there

are substituents on both C_2 and C_6, the ring nitrogen is under considerable steric hindrance. Consequently, the exocyclic amino group gets alkylated to give 2B, which then undergoes the rearrangement.

In order to examine the scope of the nitrogen to carbon migration, a solution of equimolar amounts of 2-amino-6-picoline and ethyl iodide in acetonitrile was heated under pressure at 145-150° for two days. The usual processing of the reaction mixture gave a solid containing a mixture of 2-ethylamino-6-methyl-N-ethylpyridinium iodide [5, 48%. ^{1}H-NMR: s, 2.63 ppm, CH_3; s, 8.06 ppm, NH; dq, 3.38 ppm, N-CH_2, J= 7.3, 5.5 Hz; t, 1.39 ppm, N-CH_2-CH_3, J = 7.3 Hz; q, 4.55 ppm, N-CH_2, J = 7.3 Hz; t, 1.51 ppm, N-CH_2-CH_3, J = 7.3 Hz; m, 6.64 ppm, γH, and m, 7.57-7.76 ppm, 2βH. ^{13}C-NMR: NH-CH_2-CH_3, 12.68; N-CH_2-CH_3, 13.79; -CH_3, 20.8; NH-CH_2, 37.73; N-CH_2, 45.13; C(2) 154.74; C(3) 106.72; C(4) 141.0; C(5) 114.24 and C(6) 146.59], 2-amino-6-methyl-N-ethylpyridinium iodide [6, 5%. ^{1}H-NMR: t, 1.48 ppm, -CH_2-CH_3, J= 7.3 Hz; s, 2.60 ppm, CH_3; q, 4.50 ppm, -CH_2-CH_3, J = 7.3 Hz; m, 6.64 ppm, γH; and m, 7.57-7.76 ppm, 2βH, all PyHs] and 2-amino-6-picoline (47%). The above results lead us to the conclusion that the observed nitrogen to carbon migration is not of a general nature. Nitrogen to carbon migration of N-benzylpyridnium salts catalyzed by Cu-bronze at 240-270°C has been reported to give benzyl-substituted pyridines[24].

REFERENCES

1. This was presented at the 190th American Chemical Society National Meeting, Chicago, September 8-13, 1985; Abstract Number ORGN-297.

2. S. Munavalli and E. J. Poziomek, 188th A.C.S. National Meeting, Philadelphia, August 26-31, 1984; Abstract Number ORGN-261. (Synthesis, in press).

3. S. Munavalli and E. J. Poziomek (Patent application filed).

4. S. Munavalli, C. Day and E. J. Poziomek (Submitted Acta. Cryst. C).

5. S. Munavalli, F. L. Hsu and E. J. Poziomek, 189th A.C.S. National Meeting, Miami, April 28-May 3, 1985; Abstract Number ORGN-128; Heterocycles, 1986, 24, 1983.

6. S. Munavalli, F. L. Hsu and E. J. Poziomek, Chem and Ind., 1985, 797.

7. T. S. Stevens, J. Chem. Soc., 1930, 2107.

8. R. A. W. Johnstone and T. S. Stevens, J. Chem. Soc., Chem. Comm., 1955, 4487.

9. (a) W. D. Ollis, M. Ray and I. O. Sutherland, J. Chem. Soc., Chem. Comm., 1975, 543. (b) U. H. Dolling, G. L. Closs, A. H. Cohen and W. D. Ollis, ibid., 1975, 545.

10. W. E. Truce and D. L. Heuring, ibid., 1969, 1499.

11. U. Schollkopf, G. Ostermann and J. Schossig, Tetrahedron Lett., 1969, 2619.

12. F. Korte, Chem Ber., 1952, 85, 1012.

13. L. N. Pino and W. S. Zehrung, J. Amer. Chem. Soc., 1955, 77, 3154.

14. A. Thomas, P. Tomasik and G. Herman-Matusiak, Bull. Acad. Pol. Sci., Ser. Sci. Chem., 1975, 23, 311.

15. E. E. Pasternack and P. Tomasik, ibid., 1978, 26, 417.

16. L. W. Deady and O. L. Korytsky, Austr. J. Chem., 1983, 36, 1159, 2035.

17. L. W. Deady, M. R. Grimmett and C. H. Potts, Tetrahedron 1979, 35, 2895.

18. T. J. Barnes and W. J. Hickinbottom, J. Chem. Soc., 1961, 2616.

19. H. Heaney and T. J. Ward, J. Chem. Soc., Chem. Comm., 1969, 810.

20. E. D. Hughes and G. T. Jones, J. Chem. Soc., 1950, 2678.

21. J. Sepiol and P. Tomasik, Acta. Chim, Hung., 1983, 113, 159.

22. G. B. Barlin and A. C. Young, J. Chem. Soc., Perkins Trans. I, 1972, 1269.

23. G. Barberi, R. Benassi, R. Grandi, V. M. Pagnoni and F. Faddei, Org. Magn. Reson., 1979, 12, 159.

24. K. Tsuda, Y. Sato and S. Saeki, Chem. Pharm. Bull. (Japan), 1953, 1, 307.

Received, 11th August, 1986