To our knowledge, III represents the only reported example of a furan capable of dimerizing in a Diels–Alder fashion and the first member of the 4,7-epoxybenzofuran ring system.[7] We have subsequently examined several other analogs [I, $R_1 = R_2 = CH_3$; $R_1 = R_2 = Ph$; $R_1 = R_2 = (CH_2)_4$] and 2-amino-3-carboxamido-4-methylfuran but encountered no evidence of dimerization in these compounds.

Experimental Section

Compound III was prepared according to the method of Gewald.[1] The nmr spectrum was obtained on a Joel JNM-C60HL instrument. The ^{14}N hetero spin decoupling was performed with a Schomandl MS100M frequency synthesizer. The ir spectrum was recorded on a Perkin-Elmer Model 257 grating spectrophotometer and the low resolution mass spectrum on an Hitachi Perkin-Elmer RMU-6E single-focusing mass spectrometer.

Registry No.—III, 35895-53-5.

(7) The 4,7-epoxyisobenzofuran system is well known: A. M. Patterson, L. T. Capell, and D. F. Walker, "Ring Index," 2nd ed, No. 2245, 1960, p 291.

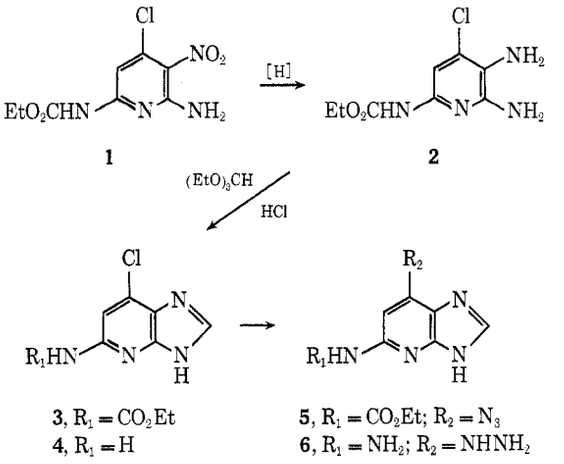
The Preparation of 5,7-Diamino-3*H*-imidazo[4,5-*b*]pyridine (2,6-Diamino-1-deazapurine)[1]

CARROLL TEMPLE, JR.,* BUFORD H. SMITH, JR., AND JOHN A. MONTGOMERY

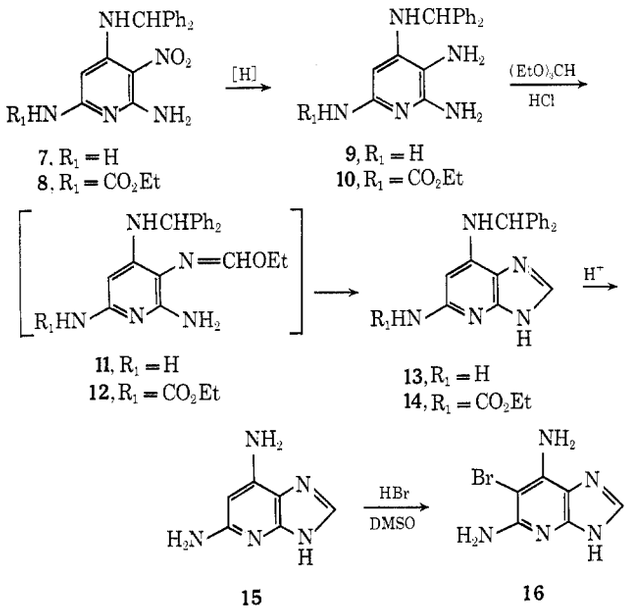
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received October 3, 1972

Recently the lack of reactivity of the chloro groups of both 5-amino-7-chloro- and 7-amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridine (2-amino-6-chloro- and 6-amino-2-chloro-1-deazapurine) was reported.[2,3] We considered two approaches for the preparation of 5,7-diamino-3*H*-imidazo[4,5-*b*]pyridine (**15**). The first method involved the preparation of ethyl 7-chloro-3*H*-imidazo[4,5-*b*]pyridine-5-carbamate (**3**) in which the ethoxycarbonyl moiety was expected to decrease the electron-donating ability of the 5-amino group and increase the reactivity of the 7-chloro group. Hydrogenation of **1**[4] with Raney nickel gave **2**, which was cyclized with the ethyl orthoformate–concentrated HCl reagent[5] to give **3**. However, treatment of **3** with sodium azide to give **5** either in hot 1:1 EtOH–H_2O or hot 1:1 $EtOCH_2CH_2OH$–H_2O was unsuccessful. The stability of the chloro group was demonstrated by treatment of **3** with NaOMe in refluxing PrOH to give the known 5-amino-7-chloro compound **4**.[2,3] In contrast, hydrazinolysis of **3** HCl with anhydrous hydrazine at reflux resulted in displacement of both the chloro and (ethoxycarbonyl)amino groups to give the 5,7-dihydrazino compound **6**.[6] Under milder conditions reaction of **4** with hydrazine was reported to give the corresponding 5-amino-7-hydrazino derivative.[3]



Simultaneously with the above work, a route involving the cyclization of the 2,3,6-triamino-4-(diphenylmethyl)aminopyridines **9** and **10** was investigated. Hydrogenation of **7**[4] with Raney nickel at atmospheric pressure and room temperature gave **9**, isolated as a dihydrochloride. The cyclization of **9** with the ethyl orthoformate–concentrated HCl reagent at room temperature gave a mixture which was not purified but was shown to contain **13** as a major component (tlc). Hydrogenation of **8** with Raney nickel gave **10**, which was cyclized with ethyl orthoformate at room temperature to give **14**.[7] Presumably the cyclization of both **9** and **10** involves the ethoxymethyleneamino intermediates **11** and **12**, respectively.[8] Because of the greater nucleophilicity of the (diphenylmethyl)amino group of **11** and **12** compared with that of the 2-amino group, cyclization to the nitrogen of the (diphenylmethyl)amino group should be favored. How-



(1) This investigation was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. NIH-71-2021.

(2) D. G. Markees and G. W. Kidder, *J. Amer. Chem. Soc.*, **78**, 4130 (1956).

(3) J. E. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas*, **91**, 650 (1972).

(4) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).

(5) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 866 (1962).

(6) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960), report exchange aminations for purines and pyrimidines.

(7) C. Temple, Jr., B. H. Smith, and J. A. Montgomery, *J. Med. Chem.* in press.

(8) J. A. Montgomery and C. Temple, Jr., *J. Org. Chem.*, **25**, 395 (1960).

ever, the obtainment of **13** and **14** suggested that steric interaction between the (diphenylmethyl)amino and the ethoxymethylenamino groups blocked cyclization in this direction.[9] Cleavage of the urethane group of **14** with KOH–EtOH gave a pure sample of **13**.[7] Treatment of **13** with concentrated HCl at room temperature removed the diphenylmethyl group to give **15** 2HCl. The apparent pK_a value (determined potentiometrically) indicated that **15** (pK_a = 6.75) was more basic than 2,6-diaminopurine (pK_a = 5.09).[10] Also, removal of the diphenylmethyl group was effected with 30% HBr–HOAc to give a partial acetate salt of **15** 2HBr. The pmr spectrum in DMSO-d_6 showed that the two peaks for the ring CH protons of **15** decreased with time while the single-ring CH proton of a new compound increased. The latter resulted from oxidative bromination of **15**.[11] Confirmation was obtained by treatment of **15** 2HBr with DMSO to give the 6-bromo derivative **16** (M^+, 227, 229),[12] which also was obtained when the reaction was carried out in the presence of phenol. In addition, the pmr spectrum of **15** 2HBr in D_2O showed that the 6-CH proton underwent deuterium exchange.[13]

Experimental Section[14]

Ethyl 5,6-Diamino-4-chloro-2-pyridinecarbamate Hydrochloride (2).—A suspension of **1** (20.0 g)[4] in EtOH (1000 ml) was hydrogenated in the presence of Raney nickel (20 g, wet, washed with H_2O and EtOH) at atmospheric pressure and room temperature. The catalyst was removed by filtration (Celite), and the filtrate was evaporated to dryness *in vacuo*, yield 17.5 g (99%), mp 106–109°. A portion of this sample (2.5 g) was dissolved in Et_2O and acidified with ethanolic HCl to deposit the hydrochloride salt, yield 2.6 g (90% recovery), mp 196–197° dec.

Anal. Calcd for $C_8H_{11}ClN_4O_2 \cdot HCl$: C, 35.97; H, 4.53; Cl, 26.55; N, 20.98. Found: C, 36.36; H, 4.82; Cl, 26.10; N, 20.81.

Ethyl 7-Chloro-3*H*-imidazo[4,5-*b*]pyridine-5-carbamate (3).—Concentrated HCl (0.4 ml) was added to a solution of **2** HCl (1.00 g) in ethyl orthoformate (20 ml). After stirring at room temperature for 72 hr, the hydrochloride of **3** was collected by filtration and washed with Et_2O, yield 1.04 g (100%), mp >360°.

Anal. Calcd for $C_9H_9ClN_4O_2 \cdot HCl$: C, 39.00; H, 3.66; N, 20.22. Found: C, 39.46; H, 3.93; N, 20.16.

A portion of the above sample was suspended in H_2O and neutralized with aqueous NaOH. The solid was collected by filtration and recrystallized from a mixture of THF and petroleum ether (bp 85–105°), mp >350°.

Anal. Calcd for $C_9H_9ClN_4O_2$: C, 44.91; H, 3.77; Cl, 14.73; N, 23.28. Found: C, 45.20; H, 3.99; Cl, 14.46; N, 23.03.

5-Amino-7-chloro-3*H*-imidazo[4,5-*b*]pyridine (4).—A mixture of **3** HCl (1.0 g) and NaOMe (0.96 g) in EtOH (20 ml) protected with a drying tube was refluxed for 92 hr. Tlc of the reaction mixture indicated the presence of a considerable amount of **3**. The solvent was replaced with propanol, and the resulting mixture was refluxed for an additional 92 hr. Tlc of the reaction mixture showed the presence of only a trace amount of **3**. After the removal of the solvent, the resulting solid was heated in 1 *N* HCl (22 ml), the insoluble residue was removed by filtration, and the filtrate was adjusted to pH 5 (paper) with aqueous NaOH. The solution was chilled for 18 hr to deposit a partial hydrochloride of **4**, yield 0.28 g. The latter was treated with water (5 ml) containing $NaHCO_3$ (0.14 g) for 5 min. The insoluble residue was removed by filtration, and the filtrate was chilled to deposit **4**, which was dried *in vacuo* over P_2O_5 at 78°, yield 0.14 g (23%), mp 225–227°. The melting point of the hydrate was reported[2] as 229–231° after the loss of water >130°.

Anal. Calcd for $C_6H_5ClN_4$: C, 42.78; H, 2.99; N, 33.23. Found: C, 42.61; H, 3.03; N, 33.37.

5,7-Dihydrazino-3*H*-imidazo[4,5-*b*]pyridine (6).—A solution of **3**·HCl (5.0 g) in 95+% hydrazine (10 ml) was refluxed for 22 hr and evaporated to dryness *in vacuo*. The residue was suspended in H_2O, and the mixture was adjusted to pH 6 (paper) with glacial HOAc. The solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.92 g (28%), mp 269° dec.

Anal. Calcd for $C_6H_9N_7$: C, 40.22; H, 5.06; N, 54.72. Found: C, 40.37; H, 5.38; N, 54.65.

2,3,6-Triamino-4-[(diphenylmethyl)amino]pyridine Dihydrochloride (9).—A suspension of **7** (1.0 g)[4] in EtOH (125 ml) was hydrogenated in the presence of Raney nickel (2 g, wet, washed with H_2O and EtOH) at atmospheric pressure and room temperature. The resulting yellow suspension was heated to 70° under N_2 and filtered hot into a flask containing concentrated HCl (1.0 ml). The filtrate was evaporated to dryness *in vacuo;* the resulting solid was dissolved in warm EtOH, reprecipitated by the addition of Et_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.59 g (52%), mp ~215° dec. Tlc (1:1 $CHCl_3$–MeOH) showed two major spots, possibly a result of decomposition of the sample on the chromatogram.

Anal. Calcd for $C_{18}H_{19}N_5 \cdot 2HCl$: C, 57.14; H, 5.60; N, 18.51. Found: C, 56.98; H, 5.52; N, 18.25.

5,7-Diamino-3*H*-imidazo[4,5-*b*]pyridine (15). A.—A solution of **13** (4.93 g)[7] in 30% HBr in HOAc (50 ml) containing phenol (50 mg) was stirred at room temperature for 18 hr. The dihydrobromide partial acetate salt of **15** was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5 at 56°, yield 3.68 g (71%), mp >300°. The presence of HOAc in this sample was confirmed by the pmr spectrum.

Anal. Calcd for $C_6H_7N_5 \cdot 2HBr \cdot 0.35CH_3CO_2H$: C, 24.23; H, 3.15; Br, 48.13; N, 21.09. Found: C, 23.85; H, 2.87; Br, 48.01; N, 20.78.

B.—A suspension of **13** HCl (1.0 g)[7] in concentrated HCl (20 ml) was stirred at room temperature for 18 hr. The dihydrochloride salt of **15** was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5: yield 0.34 g (54%); mp >300°; pmr (DMSO-d_6) 5.88 (6 H), 8.55 (2 H), 10.22 (br, NH).

Anal. Calcd for $C_6H_7N_5 \cdot 2HCl$: C, 32.45; H, 4.09; Cl, 31.93; N, 31.54. Found: C, 32.61; H, 4.11; Cl, 32.05; N, 31.57.

Concentration of the filtrate from the first crop gave an additional 0.07 g of **15**·2HCl. The total yield was 0.41 g (65%).

5,7-Diamino-6-bromo-3*H*-imidazo[4,5-*b*]pyridine Hydrobromide (16).—A suspension of **15** 2HBr·0.35HOAc (200 mg) in DMSO (5 ml) was stirred at room temperature for 18 hr. The resulting solution was evaporated to dryness *in vacuo*. The residue was washed with $CHCl_3$, recrystallized from a mixture of ethanol–heptane, and dried *in vacuo* over P_2O_5 at 78°: yield 75 mg (39%); mp 260° dec; M^+ 227, 229. The presence of DMSO in this sample was confirmed by the pmr spectrum: pmr (DMSO-d_6) 7.65 (br, NH), 8.37 (2 H).

Anal. Calcd for $C_6H_5BrN_5 \cdot HBr \cdot 0.1Me_2SO$: C, 23.50; H, 2.41; Br, 50.44; N, 22.10. Found: C, 23.98; H, 2.55; Br, 50.34; N, 22.15.

Concentration of the recrystallization filtrate gave an additional 50 mg of **16**, mp 260° dec. The total yield was 65.5%.

Similar results were obtained when this reaction was carried out in the presence of phenol (50 mg).

Registry No.—**1**, 6506-86-1; **2**, 37437-06-2; **2** HCl, 37436-93-4; **3**, 37436-94-5; **3** HCl, 37436-95-6; **4**, 37436-96-7; **4** HCl, 37437-07-3; **6**, 37436-97-8; **7**, 6506-85-0; **9** 2HCl, 37436-98-9; **13**, 37436-99-0; **13**

(9) Unpublished results supported this conclusion. Nitrosation of **10** occurred between the 3-amino and 4-(diphenylmethyl)amino groups to give a *v*-triazolo[4,5-*c*]pyridine, presumably formed *via* a 3-diazopyridine intermediate.

(10) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

(11) W. D. Ranky and D. C. Nelson, "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, I, Chapter 17, p 175, discuss oxidative brominations using mixtures of HBr and DMSO.

(12) J. A. Montgomery and N. F. Wood, *J. Org. Chem.*, **29**, 734 (1964), reported bromination of 5,7-diamino-3-methylpyrido[3,4-*b*]pyrazine in the pyridine ring.

(13) Complete experimental details for all new compounds will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-613. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(14) Melting points were determined on a Mel-Temp apparatus, and thin layer chromatograms (silica gel H) were developed with mixtures of $CHCl_3$ and MeOH. Pmr spectra were determined with Varian A-60A and XL-100-15 spectrometers with TMS as an internal reference.

HCl, 37437-09-5; **14**, 37437-00-6; **15**, 37437-01-7; **15** 2HBr, 37437-02-8; **15** 2HCl, 37437-03-9; **16**, 37437-04-0; **16** HBr, 37439-95-5.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations.

An Empirical Correlation of Proton Magnetic Resonance Chemical Shifts for α Hydrogen to Lone-Pair Electrons

CHARLES C. PRICE

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received September 31, 1972

We[1] earlier proposed an empirical rule to explain the upfield pmr shift of α H in neopentyl ethers and neopentylamines on the basis of (1) a restricted conformation at the C–X bond and (2) an empirical postulate that the α H was shifted downfield by 1.7 ppm when skew to an unshared electron pair on O or N, but was unshifted when trans. We now wish to report how remarkably well this latter simple postulate correlates the pmr chemical shifts for H α to unshared electron pairs in the first-, second-, and third-period elements in examples where conformation is not a complication, the methyl compounds.

The experimental values are listed in Table I, together with values calculated on the basis of the simple

TABLE I

PMR CHEMICAL SHIFTS FOR METHYL GROUPS ON SELECTED FIRST-, SECOND-, AND THIRD-PERIOD ELEMENTS, δ

IV	V	VI	VII
Me_3CCH_3	Me_2NCH_3	$MeOCH_3$	FCH_3
0.94	2.12 (2.07)[a]	3.24 (3.21)[b]	4.25 (4.34)[c]
Me_3SiCH_3	Me_2PCH_3	$MeSCH_3$	$ClCH_3$
0.00	0.94 (1.0)[a]	2.08 (2.0)[b]	3.05 (3.0)[c]
Me_3GeCH_3	Me_2AsCH_3	$MeSeCH_3$	$BrCH_3$
0.13[d]	0.88[e] (0.96)[a]	1.95[f] (1.80)[b]	2.68 (2.63)[c]

[a] The calculated value in parentheses is $\delta_{IV} + 2\Delta/3$; for first-period elements, $\Delta = 1.7$ ppm; for second, $\Delta = 1.5$ ppm; for third, $\Delta = 1.25$ ppm. [b] The calculated value is $\delta_{IV} + 4\Delta/3$. [c] The calculated value is $\delta_{IV} + 2\Delta$. [d] H. Schmidbaur, *Chem. Ber.*, **97**, 1639 (1964). [e] C. R. Russ, Ph.D. Dissertation, Department of Chemistry, University of Pennsylvania, 1965. [f] G. Klose, *Ann. Phys.*, **8**, 220 (1961).

postulate made earlier.[1] The only adjustment made in calculating the parenthetical values was to alter the $\Delta = 1.7$ ppm per skew unshared pair for first-period elements to $\Delta = 1.5$ ppm per skew unshared pair for the second-period elements and to $\Delta = 1.25$ ppm for the third-period elements.

For methyl fluoride (or chloride or bromide), each H must be flanked by two skew unshared pairs so the downfield shift will be 2Δ. Therefore the calculated $\delta_{CH_3F} = \delta_{Me_4C} + 2\Delta = 4.34$. For dimethyl ether (or sulfide or selenide) one hydrogen will be flanked by two skew unshared pairs, the other two by one each. The average downfield shift will then be $4\Delta/3$. Similarly for trimethylamine (or phosphine or arsine), two H will be flanked by a single skew unshared pair, the third by none, so the average downfield shift will be $2\Delta/3$.

Inspection of Table I reveals that all the calculated shifts, based on our empirical rule, agree with experiment within less than 0.1 ppm (except for Me_2Se, where the difference is 0.15 ppm). Since all these literature data are not in the same solvent, this may be one factor in the small discrepancies between experimental and calculated values for δ.

Since the form of the relationships in Table I is a simple linear correlation, these data could, of course, be fit to other factors, *e.g.*, the number of methyl groups attached to the heteroatom. There have, of course, been extensive efforts to correlate the chemical shifts with electronegativity.[2] The marked upfield shifts in neopentyl ether and amines[1] and other steric factors influencing the chemical shifts[2b] indicates that electronegativity is at least not the only factor affecting chemical shifts.

The complication of preferred conformation for primary alkyl groups, RCH_2, on O or N was discussed earlier.[1] An examination of ethyl halides suggests yet another possible factor which may influence the NMR shift of α H in primary and secondary alkyl groups. The normal downfield shift on substituting an H by CH_3 is about 0.3 ppm (see Table II). In

TABLE II

PMR CHEMICAL SHIFTS FOR METHYL, ETHYL, AND ISOPROPYL COMPOUNDS, δ

X	CH_3X	RCH_2X	R_2CHX
CH_3	0.9	1.2	1.5
OH	3.4	3.55 (3.70)[a]	3.85 (4.0)
OCOR	3.65	4.10 (3.95)	5.0 (4.25)
F	4.25	4.35 (4.55)	(4.85)
Cl	3.05	3.4 (3.35)	4.0 (3.65)
Br	2.7	3.3 (3.0)	4.1 (3.3)

[a] The parenthetical values are those calculated assuming that the downfield shift for introducing R in place of H in CH_3X would be the same as for X = CH_3.

ethyl fluoride and alcohol, the actual downfield shift is somewhat less; for chlorine and especially bromine and OCOR it is appreciably more. In the secondary alkyl derivatives, the enhanced downfield shift compared to calculated (see Table II) is much more marked, again increasing with the size of the group X. Simple scale molecular models, using standard bond angles, bond radii, and van der Waals radii, show that the van der Waals radii of β-H and F or O interpenetrate less than 0.2 Å, whereas the interpenetration is 0.45 Å for Cl and 0.5 Å for Br. A significant repulsive effect at the latter degree of interpenetration could be relieved by bending the C–C–X angle slightly outward.[3] A consequence of this would be to bring the α H closer

(1) C. C. Price, *Tetrahedron Lett.*, 4527 (1971).

(2) (a) B. P. Dailey and J. N. Shoolery, *J. Amer. Chem. Soc.*, **77**, 3977 (1955); (b) H. Spresecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961); (c) J. C. Muller, *Bull. Soc. Chim. Fr.*, 2022 (1964).

(3) Values reported for the C–C–X bond angles in ethyl halides are 109.5, 110.5, 110.5, and 112° for F, Cl, Br, and I, respectively (see "Tables of Interatomic Distances," L. E. Sutton, Ed., The Chemical Society, London, 1958 and 1965).