Preparation and New Reactions of Imidazo[1,2-a]pyridines

JOSEPH G. LOMBARDINO

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut

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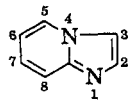
Details for the facile preparation of some imidazo[1,2-a]pyridines are presented. Acidity constants, proton nuclear magnetic resonance spectra, and ultraviolet spectra were determined for some members of this family of heterocyclic compounds. Application of the Mannich reaction to this system is reported and reactions of the Mannich products are discussed. In addition, the 2-methyl group in 2-methylimidazo[1,2-a]pyridine has been shown to participate in some reactions typical of other methyl-substituted heterocycles.

Compared to many other heterocyclic systems, relatively little is known about the chemical reactivity of imidazo[1,2-a]pyridine (I). A recent review by



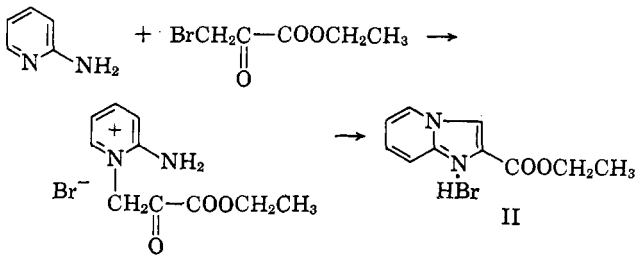
I

Mosby[1] and an older review by Kickhoffen[2] expertly summarize material published on this heterocyclic system while some publications dealing mainly with preparative methods have appeared since this area was reviewed.[3-14] Several new examples of I have now been prepared, their chemical reactivity in certain reactions has been investigated, and their n.m.r. spectra have been examined in detail.

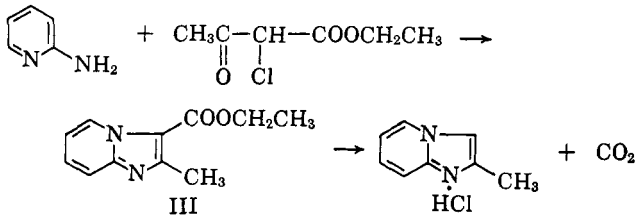
Preparation of Nuclei.—Mosby has suggested[1] a mild reaction procedure for the preparation of the parent compound I from 2-aminopyridine and chloroacetaldehyde in the presence of sodium bicarbonate. Such conditions are preferable to vigorous conditions used by Tschitschibabin[15] and have been applied by Roe[4] using bromoacetal. An improved, less time-consuming procedure for preparing I from chloroacetaldehyde is detailed in the Experimental section. Titration showed I to be as basic as 2-aminopyridine (pK_a = 6.7).[16]

Condensation of 2-aminopyridine and ethyl bromopyruvate proceeded smoothly in a two-step procedure to give ethyl imidazo[1,2-a]pyridine-2-carboxylate hydrobromide (II) in high yield.

An acidic imidazopyridine, 2-methylimidazo[1,2-a]-pyridine-3-carboxylic acid, was prepared from its corresponding ester III. Although preparation of III in several steps has previously been described,[17] it has now been found that 2-aminopyridine will cyclize selectively with ethyl 2-chloroacetoacetate to produce a good yield of ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (III) in one step. N.m.r. spectra of III (2-CH_3 group, τ 7.30) readily distinguished it from the



II

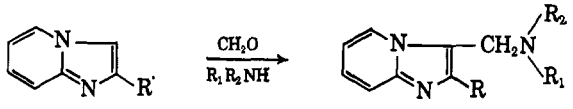


III

possible alternate product of this cyclization. Hydrolysis of III produced 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid which after decarboxylation to a liquid product was converted to a hydrochloride salt and shown to be identical with 2-methylimidazo[1,2-a]-pyridine hydrochloride.

Mannich Reactions.—In order to test whether I and related analogs might behave like indole under conditions of the Mannich reaction, I was combined with formaldehyde and a secondary amine. Under mild conditions, I reacted smoothly with a variety of secondary amines in aqueous acetic acid to produce a group of 3-dialkylaminomethylimidazo[1,2-a]pyridines (IV, Table I).

The 3-position of the side chain is assigned on the basis of the close similarity of ultraviolet and n.m.r. spectra of IV with those of the product VI obtained from the 2-methyl base V.



I, R=H
V, R=CH_3

IV, R=H
VI, R=CH_3

(1) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 460 ff.

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(4) A. M. Roe, *J. Chem. Soc.*, 2195 (1963).

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(7) L. Caglioti, G. Cainelli, and A. Selva, *Gazz chim. ital.*, **94**, 485 (1964).

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(9) R. Royer, E. Bisagni, and C. Hudry, *Bull. soc. chim. France*, 933 (1961).

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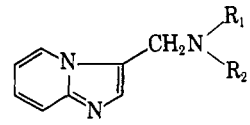
(15) A. E. Tschitschibabin, *Chem. Ber.*, **58**, 1704 (1925).

(16) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 145.

(17) R. Adams, and I. J. Pachter, *J. Am. Chem. Soc.*, **76**, 1845 (1954).

TABLE I

3-DIALKYLAMINOMETHYLIMIDAZO[1,2-*a*]PYRIDINES (IV)



R_1	R_2	Recrystn. solvent	Yield, %	M.p., °C.	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	*a*	78	82.5–83.5	$C_{10}H_{13}N_3$	68.54	7.48	23.92	68.50	7.73	23.99
$(CH_2)_5$		*b*	30	226–229 dec.	$C_{13}H_{17}N_3 \cdot 2HCl$	54.17	6.64	14.58	54.04	7.00	14.37
$HOCH_2CH_2$	$HOCH_2CH_2$	*c*	36	103–105	$C_{12}H_{17}N_3O_2$	61.25	7.28	17.86	60.96	7.08	17.42
$(CH_2)_2—N(CH_3)—(CH_2)_2$		*d*	54	242.5–244 dec.	$C_{13}H_{18}N_4 \cdot 3HCl$	45.96	6.23	16.49	45.69	6.31	16.34
$(CH_2)_2—O—(CH_2)_2$		*d*	37	229–231 dec.	$C_{12}H_{15}N_3O \cdot 2HCl$	49.67	5.87	14.48	49.46	5.88	14.45

[a] Ether. [b] Ethanol–ether. [c] Chloroform–hexane. [d] Methanol–ether.

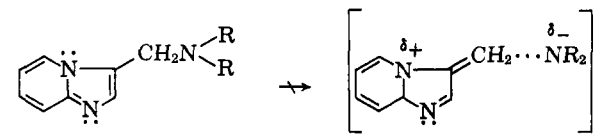
The base IV was converted to a side-chain methiodide (VII); no nuclear alkylation was observed.

Reactions of Substituted Imidazo[1,2-*a*]pyridines.—Unsuccessful attempts to deaminate reductively 3-dimethylaminomethylimidazo[1,2-*a*]pyridine hydrochloride (IV, R_1 and R_2 = CH_3) using palladium on carbon proceeded to consume 2 molar equiv. of hydrogen and then stop abruptly. Analysis of the product showed the 3-dimethylaminomethyl side chain to be retained; therefore, by analogy with other reported[18] reductions of imidazo[1,2-*a*]pyridines, it is assumed that the tetrahydro derivative is formed by reduction of the six-membered ring. As expected, characteristic imidazo[1,2-*a*]pyridine maxima in the ultraviolet were completely absent in this tetrahydro product.

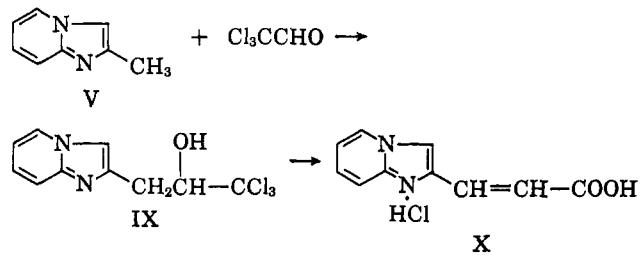
A reported technique for displacing dimethylamine from gramine[19] using cyanide ion failed when applied to IV (R_1 and R_2 = CH_3). Conditions were made increasingly severe but in no case was dimethylamine detected. Similarly, VI (R_1 and R_2 = CH_3) failed to react with cyanide ion under a variety of conditions. In most cases, unreacted starting material could be recovered but high temperatures were found to cause some slight decomposition. Prolonged reaction periods were without effect since starting material was recovered even after 57 hr. at reflux in ethanol–water.

Treatment of the methiodide salt VII with either cyanide ion or sodium diethyl acetaminomalonate did not displace trimethylamine. These failures to displace dimethylamine from either IV or VI, or trimethylamine from VII suggest that absence of both (a) a β-hydrogen and (b) readily delocalized π-electrons on the 1-nitrogen in an imidazo[1,2-*a*]pyridine system produce profound changes in reactivity when compared to gramine.

Snyder and Eliel[20a] have shown that while gramine is a superior alkylating agent, 1-methylgramine is also capable of alkylating certain activated methylene groups. Cyanide ion, however, failed to displace dimethylamine from 1-methylgramine.[20a] Delocalization of the π-electrons of nitrogen probably aids in the activation of the side chain of 1-methylgramine by polarizing the side-chain C–N bond thus facilitating elimination of dimethylamine. Such a mechanism employing electronic contributions from either the 4-nitrogen or 1-nitrogen atom of a 3-dialkylaminomethylimidazo[1,2-*a*]pyridine is apparently not operative. A combined electronegative effect of *two* nitrogen atoms in the five-membered ring may discourage electron donation to the leaving dimethylamino function in the first step of a two-step mechanism.[20b]



To test whether the 2-methyl group in V would behave like methyl groups in certain other heterocycles (*e.g.*, 2- and 4-picolines, methylpyrazines, and methylpyrimidines[21]), V was treated with chloral to produce 2-(3,3,3-trichloro-2-hydroxy-1-propyl)imidazo[1,2-*a*]pyridine (IX) which on hydrolysis gave the acrylic acid X.



N.m.r. Spectra.—Values for chemical shifts are summarized in Tables II and III. Analogy to pyridine predicts the order of chemical shifts in the six-membered ring of I to be H-5 < H-7 < H-6 (*e.g.*, see Jackman[22] on pyridine where H-2 < H-4 < H-3). In fact, a downfield doublet was consistently found in every spectrum of I and analogs of I and was ascribable to the H-5, the proton adjacent to the hetero atom.[22] In every case, this doublet had J = 7 c.p.s. and was split by an upfield triplet which was assigned to the H-6. In almost every case, a second doublet (J = 9 c.p.s.) could be found just upfield from the H-5 and was assigned to the H-8. The latter doublet was split by a

(18) H. Kondo and Y. Mitsugi, *J. Pharm. Soc. Japan*, **57**, 397 (1937); *Chem. Abstr.*, **33**, 2139 (1939).

(19) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

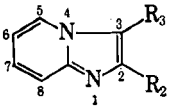
(20) (a) H. R. Snyder and E. L. Eliel, *ibid.*, **71**, 663 (1949); (b) A. F. Casy and J. L. Myers, *J. Chem. Soc.*, 4639 (1964).

(21) A. Einhorn, *Ann.*, **265**, 208 (1891); F. W. Tullock and S. M. McElvain, *J. Am. Chem. Soc.*, **61**, 961 (1939); R. C. Jones, E. Kornfield, and K. McLaughlin, *ibid.*, **72**, 3539 (1950).

(22) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, p. 64.

TABLE II

N.M.R. DATA FOR IMIDAZO[1,2-a]PYRIDINES[a,b]

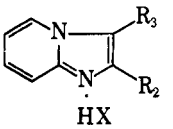


Compd.	Substituents	Solvent	R_2	R_3	H-2	H-3	H-5[c]	H-6[d]	H-7[d]	H-8[c]	Integration, protons
I	None	$CDCl_3$			*e*	*e*	1.85 (7)	3.28 (7)	2.88 (9)[f]		6[g]
III	$R_3 = COOCH_2CH_3$, $R_2 = CH_3$	$CDCl_3$	7.30				0.74 (7)	3.04 (7)	2.61 (9)	2.27 (9)	12
XI	$R_3 = COO^-Na^+$, $R_2 = CH_3$	D_2O	7.12				0.80 (7)	*e*	*e*	*e*	7[h]
IV	$R_3 = CH_2N(CH_3)_2$	$CDCl_3$		7.80 ($N-(CH_3)_2$) 6.31 (CH_2)	2.48		1.70 (7)	3.23 (7)	2.86 (9)	2.27 (9)	13
		D_2O		7.60 ($N-(CH_3)_2$) 6.14 (CH_2)	2.31		1.70 (7)	2.90 (7)	2.52 (9)	2.27 (9)	13
VII	$R_3 = CH_2{}^+N(CH_3)_3I^-$	D_2O		6.40 ($N-(CH_3)_3$) 4.56 (CH_2)	1.66		1.04 (7)	2.50 (7)	*g*	1.96 (9)	16[i]
VI	$R_3 = CH_2N(CH_3)_2$, $R_2 = CH_3$	$CDCl_3$	7.55	7.80 ($N-(CH_3)_2$) 6.33 (CH_2)			1.78 (7)	3.25 (7)	2.87 (9)	2.45 (9)	15

[a] Given as τ values. [b] Coupling constants (c.p.s.) in parentheses. [c] Doublets. [d] Triplets. [e] Complex, overlapping peaks. Values could not be assigned. [f] An unsymmetrical triplet (*e.g.*, for I, the H-7 triplet has τ 2.78, 2.88, 3.00) in every case. [g] H-2, -3, and -8 complex peaks integrate for three protons. [h] H-6, -7, and -8 peaks integrate for three protons. [i] H-6, -7, and -8 peaks integrate for three protons.

TABLE III

N.M.R. DATA FOR IMIDAZO[1,2-a]PYRIDINIUM HALIDES[a,b]



HX

Compd.	Substituents	Solvent	NH	R_2	R_3	H-2	H-3	H-5[c]	H-6[d]	H-7[d]	H-8	Integration, protons
V·HCl	$R_2 = CH_3$	$CDCl_3$	−5.16[e]	7.34			1.52	0.66 (7)	2.54 (7)	2.08 (9)	1.08 (9)	9
		D_2O	None	7.14			*f*	1.08 (7)	2.26 (7)	*f*	*f*	8[g]
II·HBr	$R_2 = COOCH_2CH_3$	$CDCl_3$	−3.12[e]				0.60	0.22 (7)	2.36 (7)	1.90 (9)	1.30 (9)	11
		D_2O	None				0.80	0.76 (7)	1.98 (7)	*f*	1.50 (9)	10
I·HBr	None	$CDCl_3$	−3.84[e]			1.20 (2)[c]	1.94 (2)[c]	0.6 (7)	2.42 (7)	*f*	1.60 (9)	7
		D_2O	None			1.44 (2)[c]	1.64 (2)[c]	0.86 (7)	*f*	*f*	*f*	6
IV·2HCl	$R_3 = CH_2{}^+NH(CH_3)_2Cl^-$	D_2O	None		4.44 (CH_2) 6.48 (2-CH_3)	1.06		0.5 (7)	*f*	*f*	*f*	13

[a] Given as τ values. [b] Coupling constants (c.p.s.) in parentheses. [c] Doublets. [d] Triplets. [e] Broad, flat peak. [f] Complex overlapping peaks; could not be assigned. [g] H-6, -7, and -8 integrate for four protons.

remaining triplet, assigned to the H-7, always found between the H-6 triplet and the H-8 doublet. In summary, then, chemical shifts in the six-membered ring portion of I or its derivatives occur in the order H-5 < H-8 < H-7 < H-6. Assignments for the H-2 and H-3 when occurring together in a molecule were often masked by a complex of peaks near τ 2.4 but values were obtained for certain compounds and are summarized in Tables II and III.[23]

Experimental[24]

Imidazo[1,2-a]pyridine (I).—Combination of 47 g. (0.5 mole) of 2-aminopyridine, 120 g. (0.6 mole) of a 40% solution of chloroacetaldehyde in water, 100 ml. of water, 400 ml. of ethanol, and 51 g. (0.6 mole) of sodium bicarbonate under a nitrogen atmosphere produced an evolution of carbon dioxide upon heating to reflux. After 2 hr. of refluxing the dark solution was cooled, concentrated under vacuum to 250 ml., added to 200 ml. of water, and extracted exhaustively with ether. The ether extracts were dried over sodium sulfate and evaporated, and the residual oil was distilled under vacuum. After a small forerun, 26.7 g. (45%) of a pale yellow liquid, b.p. 103° (1 mm.), was collected. An infrared spectrum exhibited a strong peak at 2.95 μ indicating a hydrate; many other members in this series were found to be hygroscopic and formed tenacious hydrates. The ultraviolet spectrum showed λ_{max}^{EtOH} 221 mμ (ϵ 28,400), 226 (23,600), 278 (3920), and 298 (3400).

N.m.r. spectra of this and the following compounds are summarized in Tables II and III.

A hydrobromide salt was prepared in ethanol solution and recrystallized from ethanol–ether: m.p. 187–189° (lit.[1] 186–187°); λ_{max}^{EtOH} 278 mμ (ϵ 5600), 226 (sh) (13,660), and 218 (20,880).

Potentiometric titration of this hydrobromide salt in water solution using standard sodium hydroxide indicated a pK_a (pH at half-neutralization) of 6.72 and a neutralization equivalent of 199 (calcd. 199).

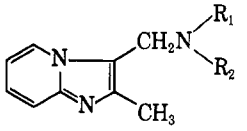
2-Methylimidazo[1,2-a]pyridine Hydrochloride.—A clear, yellow solution was obtained from 141 g. (1.5 mole) of 2-aminopyridine, 141 g. (1.5 moles) of chloro-2-propanone, and 900 ml. of ethanol after 24 hr. of refluxing. Evaporation to a small

(23) After submission of this manuscript, a publication by W. Paudler and H. Blewitt [*Tetrahedron*, **21**, 353 (1965)] appeared which reported n.m.r. spectra for some substituted imidazo[1,2-a]pyridines. Assignments are in general agreement with those reported herein. A different assignment for H-7 has also been reported: P. J. Black, M. L. Hefferenan, L. M. Jackman, O. N. Porter, and G. R. Underwood, *Australian J. Chem.*, **17**, 1128 (1964).

(24) Melting points were determined on a Thomas–Hoover melting point apparatus in open capillaries and are corrected. A Varian A-60 spectrometer, using tetramethylsilane as an external standard, was used to measure n.m.r spectra. Infrared spectra were measured in potassium bromide pellets.

TABLE IV

3-DIALKYLAMINOMETHYL-2-METHYLIMIDAZO[1,2-*a*]PYRIDINE HYDROCHLORIDES (VI)



R_1	R_2	Recrystn. solvent	Yield, %	M.p., °C.	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	*a*	91	280.5–282.5 dec.	$C_{11}H_{15}N_3 \cdot 2HCl$	50.39	6.54	16.03	50.53	6.35	15.99
$(CH_2)_5$		*a*	27	343.5 dec.	$C_{14}H_{19}N_3 \cdot 2HCl \cdot 0.5H_2O$	54.22	7.13	13.47	54.60	7.20	13.20
CH_3 | $(CH_2)_2—N—(CH_2)_2$		*b*	85	296–298 dec.	$C_{14}H_{20}N_4 \cdot 3HCl$	47.53	6.55	15.84	47.34	6.64	15.48
$(CH_2)_2—O—(CH_2)_2$		*c*	68	212–214 dec.	$C_{13}H_{17}N_3O \cdot 2HCl \cdot 0.5H_2O$	49.84	6.44	13.41	49.95	6.55	13.49

[a] Ethanol–ether. [b] Methanol. [c] Methanol–ether.

volume and addition of ether produced a soft solid. Recrystallization from ethanol yielded 59 g. (23%) of 2-methylimidazo[1,2-*a*]pyridine hydrochloride in two crops: m.p. 197–199.0°; λ_{max}^{EtOH} 222 mμ (ε 18,600), 232 (9480), and 281 (6540).

Anal. Calcd. for $C_8H_9ClN_2$: C, 56.98; H, 5.38; N, 16.62. Found: C, 57.15; H, 5.34; N, 16.44.

Titration in water with standard sodium hydroxide indicated a pK_a of 7.0 and a neutralization equivalent of 170 (calcd. 169).

Ethyl Imidazo[1,2-*a*]pyridine-2-carboxylate Hydrobromide (II).—Reaction of 2-aminopyridine (8.4 g., 0.09 mole) and ethyl bromopyruvate (17.6 g., 0.10 mole) in 75 ml. of dimethoxyethane produced 20.4 g. (84%) of a salt, m.p. 134–136°, most likely 2-amino-1-carbethoxycarbonylmethylpyridinium bromide. An infrared spectrum exhibited absorptions at 3.15 (NH), 5.69 (C=O), and 5.99 μ (C=O).

Refluxing 19 g. (0.066 mole) of the above salt in 500 ml. of ethanol for 2 hr. followed by concentration to 90 ml. and addition of ether produced a white solid. Filtration and drying yielded 15.8 g. (88%) of white needles, m.p. 174.5–175.5° (lit.[25] 155–157°). Recrystallization from ethanol–ether produced an analytically pure sample, m.p. 174.5–175.5°.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09; N, 10.34. Found: C, 44.15; H, 4.22; N, 10.31.

A picrate salt was prepared from II after first treating II with 1 *M* sodium ethoxide, filtering the sodium bromide, and adding excess saturated picric acid in ethanol. Cooling to 0° produced a yellow solid which after filtration and drying melted at 162.5–163.5° (lit.[25] 162–163°); λ_{max}^{EtOH} 221 mμ (sh) (ε 44,700), 225 (46,500), 261 (sh) (2420), 272 (2900), 281 (3080), 300 (4100), 311 (3920), and 325 (sh) (2200).

Ethyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (III).—In a round-bottomed flask under a nitrogen atmosphere was placed 18.8 g. (0.20 mole) of 2-aminopyridine, 16.5 g. (0.10 mole) of ethyl 2-chloroacetoacetate, and 200 ml. of dimethoxyethane. After refluxing for 3 hr., the reaction was concentrated to dryness and the residual orange oil was partitioned between ether–water. After drying, the ether extracts were evaporated and the residual oil was allowed to crystallize. Recrystallization from ether–hexane gave 13.5 g. (66%) of needles: m.p. 69.5–70.5°; λ_{max}^{EtOH} 240 mμ (ε 63,000), 246 (77,000), 294 (21,700), and 308 (sh) (19,000).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.76. Found: C, 64.69; H, 5.79; N, 13.64.

Sodium 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate(XI).—Hydrolysis of 5.1 g. (0.025 mole) of ester III with exactly 1 equiv. of 1 *N* sodium hydroxide for 3 hr. on a steam bath followed by evaporation to dryness and thorough trituration with ether yielded a white solid, 4.59 (83%), which did not melt below 333°. An infrared spectrum exhibited carboxylate absorptions (6.3 and 7.05 μ): λ_{max}^{EtOH} 237 mμ (ε 43,600), 243 (50,000), and 292 (11,300).

Decarboxylation of 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylic Acid.—A sample of sodium 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate was dissolved in ethanol, an equivalent amount of 12 *N* hydrochloric acid was added, sodium chloride was filtered after cooling, and the filtrate was evaporated to dryness. The resulting solid carboxylic acid had a variable decomposition point depending on the rate of heating: 154–156° dec., 164–166° dec., and 170–171° dec. (lit.[17] 195–197° dec. depending on the rate of heating).

All of the above solid was slowly heated in a flask to 240° until no further gas evolution was seen. On cooling, the black residue was triturated with ether and the ether was evaporated to dryness. To the liquid residue was added excess ethanolic hydrochloric acid and the resulting solution was evaporated to dryness. Three more treatments with ethanol, evaporating to dryness each time, gave a pale yellow solid, **2-methylimidazo[1,2-*a*]pyridine hydrochloride**, m.p. 185–190°. An infrared spectrum was identical to one of authentic V HCl prepared above. A mixture melting point with authentic V HCl (m.p. 194–195°) melted at 190–195°.

3-Dialkylaminomethylimidazo[1,2-*a*]pyridines (IV).—Reactions of various secondary amines with imidazo[1,2-*a*]pyridine (I) under conditions of the Mannich reaction were all essentially identical. One example using dimethylamine will suffice for all.

In a round-bottomed flask cooled to 0° was placed 7.0 g. (0.117 mole) of glacial acetic acid, 3.8 g. (0.047 mole) of 37% aqueous formalin solution, 4.3 g. (0.048 mole) of 50% dimethylamine in water, and 5.3 g. (0.05 mole) of imidazo[1,2-*a*]pyridine. After being placed under a nitrogen atmosphere, the reaction was warmed to 50° for 2 hr. and then allowed to stir overnight at room temperature. Basification with 10% sodium hydroxide was followed by extraction with a total of 300 ml. of ether. Combination of the ether washes followed by drying and evaporation yielded 6.99 g. (78%) of a white solid, m.p. 77.5–80.5°.

In cases where products did not crystallize readily, hydrochloric acid salts were prepared in methanol solution using excess methanolic hydrochloric acid. Evaporation to a small volume and addition of ether precipitated the salt. Table I summarizes physical data for various examples of this reaction.

Potentiometric titration of IV (R_1 and R_2 = methyl) in water using standard hydrochloric acid indicated a neutralization equivalent of 177 (calcd. 175), pK_a (pH at half-neutralization) = 7.65. Titration in perchloric–acetic acid solvent showed a neutralization equivalent of 88 (calcd. for the diacid base 175/2 = 87.5). An ultraviolet spectrum of IV (R_1 and R_2 = CH_3) showed λ_{max}^{EtOH} 224 mμ (ε 31,810), 228 (31,000), 281 (4100), and 302 (3140).

Trimethylimidazo[1,2-*a*]pyridylmeth-3-ylammonium Iodide (VII).—After stirring a solution of 2.0 g. (0.0116 mole) of 3-dimethylaminomethylimidazo[1,2-*a*]pyridine and 1.65 g. (0.0116 mole) of methyl iodide in 20 ml. of ethanol for 20 min., a heavy white precipitate appeared. Continued stirring for a total of 3 hr. at room temperature followed by addition of 20 ml. of ether, cooling, and filtration gave 3.0 g. (81%) of a monomethiodide salt, m.p. 200° dec. Recrystallization from ethanol did not affect the melting point; λ_{max}^{EtOH} 224 mμ (ε 45,800), 228 (sh), 280 (5210), 272 (sh), and 304 (sh).

Anal. Calcd. for $C_{11}H_{16}IN_3 \cdot H_2O$: C, 39.40; H, 5.37; N, 12.50. Found: C, 39.20; H, 5.31; N, 12.74.

3-Dialkylaminomethyl-2-methylimidazo[1,2-*a*]pyridines (VI).—Using conditions identical with those described above for the 2-desmethyl analog IV, a series of Mannich products (VI) were prepared using 2-methylimidazo[1,2-*a*]pyridine (V). The base V was liberated from its hydrochloride salt in ethanol solution by using sodium ethoxide (equimolar), filtration of sodium chloride at 0°, and evaporation of all solvent to a residual liquid (very

(25) See reference 1, p. 471, last entry on the Table. Mode of preparation was not specified.

hygroscopic) which was used immediately. Table IV summarizes physical data of various examples of VI. Hydrochloric acid salts were prepared as described above.

For 3-dimethylamino-2-methylimidazo[1,2-*a*]pyridine monohydrate (free base, m.p. 60–63°) the ultraviolet spectrum showed λ_{max}^{EtOH} 228 mμ (ε 27,700), 234 (27,700), 284 (3961), and 306 (3500); potentiometric titration with aqueous hydrochloric acid indicated a pK_a (pH at half-neutralization) of 7.35 and a neutralization equivalent of 204 (calcd. 207).

2-(3,3,3-Trichloro-2-hydroxy-1-propyl)imidazo[1,2-*a*]pyridine Hydrochloride (IX).—The free base V was prepared as described above for the preparation of VI. To 4.4 g. (0.033 mole) of V was added 25 ml. of chloral and the dark red solution was heated on a steam bath for 24 hr. Cooling caused solidification of the reaction, due mainly to the presence of a trimer of chloral. Reheating the reaction produced a suspension which was filtered while hot and the solids were washed with a little ether. A tan solid, m.p. 249.5–252.5° dec., 4.79 g. (51%), resulted. Recrystallization from ethanol–ether gave a white solid, m.p. 240.5–241.5° dec.

Anal. Calcd. for $C_{10}H_9Cl_3N_2O \cdot HCl$: C, 38.00; H, 3.19; N, 8.87. Found: C, 37.85; H, 3.31; N, 8.52.

β-(Imidazo[1,2-*a*]pyrid-2-yl)acrylic Acid Hydrochloride (X).—To 1.6 g. (0.005 mole) of IX in 3 ml. of ethanol at reflux, was slowly added a solution of 1.0 g. (0.025 mole) of sodium hydroxide in 2 ml. of water. After vigorous reaction subsided, the mixture was refluxed for 20 min. Cooling, filtration, and evaporation yielded a red-yellow residue which was redissolved in 25 ml. of ethanol and acidified with excess ethanolic hydrochloric acid. Cooling, filtration, and evaporation of the filtrate produced a light pink solid, 0.56 g. (51%), m.p. 245.5–247.5° dec. An analytical sample was crystallized from ethanol–ether: m.p. 252.5–254.5° dec.; λ_{max}^{EtOH} 248 mμ (ε 17,200), 256 (20,800), 300 (6700), and 324 (8050).

Anal. Calcd. for $C_{10}H_8N_2O_2 \cdot HCl$: C, 53.46; H, 4.04; N, 12.47. Found: C, 53.80; H, 4.35; N, 12.85.

Catalytic Reduction of 3-Dimethylaminomethylimidazo[1,2-*a*]-pyridine.—After saturating a suspension of 0.75 g. of 10% palladium on charcoal in 10 ml. of ethanol with hydrogen at atmospheric pressure, a solution of 0.7 g. (0.005 mole) of 3-dimethylaminomethylimidazo[1,2-*a*]pyridine in 30 ml. of ethanol and 0.88 ml. of 6 *N* hydrochloric acid was added. Stirring at room temperature overnight allowed absorption of 268 cc. (100%, 2 equiv.) of hydrogen. No further hydrogen was absorbed. Filtration and concentration followed by addition of ether produced 0.59 g. (60%) of a white solid in two crops, probably **dimethylaminomethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine dihydrochloride**, m.p. 233–240°. Recrystallization from ethanol–ether gave m.p. 251.5–253.5°.

Anal. Calcd. for $C_{10}H_{17}N_3 \cdot 2HCl$: C, 47.62; H, 7.59; N, 16.66. Found: C, 47.40; H, 7.35; N, 16.84.

An ultraviolet spectrum in ethanol exhibited no maxima but absorption decreased steadily from 220 to approximately 350 mμ.

Attempts to Displace Dimethylamine from IV or VI. A.—Combining 4.0 g. (0.023 mole) of 3-dimethylaminomethylimidazo[1,2-*a*]pyridine (IV, R_1 and R_2 = methyl), 6.09 (0.122 mole) of sodium cyanide, 50 ml. of ethanol, and 14 ml. of water produced a pale yellow suspension which was refluxed for 3 days. Cooling produced a solid shown to be sodium cyanide. Evaporation of the filtrate to dryness produced a residue which was triturated with acetone. Evaporation of the acetone yielded 3.3 g. (83% recovery) of starting material, m.p. 74.5–79.5°, m.m.p. 76–80°. The infrared spectrum was identical with that of IV (R_1 and R_2 = methyl).

B.—In dimethyl sulfoxide solvent with excess sodium cyanide at 175° for 7.5 hr., IV (R_1 and R_2 = methyl) was essentially unaffected (paper chromatogram evidence).

C.—Attempted reaction of VI (R_1 and R_2 = methyl) with sodium cyanide in ethanol–water produced no dimethylamine during 57 hr. of reflux. Evaporation to dryness and acetone trituration followed by evaporation of the acetone yielded 68% of recovered starting material, m.p. 62.5–65.5°; mixture melting point with authentic VI (R_1 and R_2 = CH_3, m.p. 60–63°) was 61.5–64.5°.

Attempts to Displace Trimethylamine from VII. A.—Treatment of 0.64 g. (0.002 mole) of VII with 0.5 g. of sodium cyanide, 10 ml. of ethanol, and 10 ml. of water produced no significant gas evolution after attaining reflux temperature. The pale yellow solution was refluxed for 70 hr. with no change in appearance. After evaporation, paper chromatographic evidence showed significant amounts of starting material together with a few trace impurities.

B.—An attempt to displace trimethylamine from VII using sodium diethyl acetamidomalonate in refluxing toluene produced no significant gas evolution during 24 hr. of refluxing. Paper chromatographic analysis showed unchanged VII as a major spot.

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4,6-Dinitrobenzofuroxan. I. Covalent Hydration[1]

WILLIAM P. NORRIS AND JAMES OSMUNDSEN

Chemistry Division, Research Department, U. S. Naval Ordnance Test Station, China Lake, California

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4,6-Dinitrobenzofuroxan (I) reacts with bases, including water, to give classical Meisenheimer addition compounds (IIIa) characteristic of polynitroaromatics. The behavior of I is unusual because of the formation of an addition compound with the very weak base water. The acid resulting from the adduction of water is sufficiently strong to liberate carbon dioxide from bicarbonate. The structure of IIIa is established from analytical data, ultraviolet, infrared, and n.m.r. spectroscopic data and deuterium and O^{18} exchange experiments.

Since 4,6-dinitrobenzofuroxan (I) was first prepared its acidic character in aqueous solution has intrigued investigators.[2–6] It has no obviously acidic functional group, except that it is a strong π acid, forming complexes with many aromatic hydrocarbons,[7] yet it readily displaces carbon dioxide from bicarbonates to give stable salts. Treatment of the salts with mineral acids regenerates I. π acids of comparable or greater strength, such as 1,3,5-trinitrobenzene, 5,6-dinitrobenzofuroxan, and benzotrifuroxan, do not displace carbon dioxide from bicarbonate solutions under the same conditions.

4,6-Dinitrobenzofuroxan titrates as a strong monobasic acid in 50% ethanol showing a pH of 7.0 at the

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