bubbler. The flask was then placed in an oil bath and gradually heated to solvent reflux. The temperature of the oil bath was maintained at 100°. Reaction was allowed to continue until gas evolution ceased. The mixture was then allowed to cool to room temperature, internal standard was added, and analysis was performed.

Analysis.—The products of these reactions were analyzed by gas chromatography. Compounds were identified by comparison of their retention times to those of authentic materials. In some cases further authentication was made by collecting samples *via* glpc and comparing the infrared spectra and melting points.

Analyses were carried out on a gas chromatography instrument constructed at Case Western Reserve equipped with a 5 ft × 0.25 in. copper column packed with GE-SF-96 (20%) on Chromosorb P operated at 210° with a He inlet pressure of 32 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard, *p*-chlorobiphenyl, adjusting for molar thermal conductivity difference.

Synthetic Application.—*p*-Iodotoluene was prepared in 40% yield by a modification of the procedure described above. Iodine (150 g, 1.18 equiv) and amyl nitrite (140 g, 1.2 mol) were added to 1 l. of benzene in a 2-l., three-necked flask equipped with a mechanical stirrer and reflux condensor. *p*-Toluidine (107 g, 1.0 mol), dissolved in ~200 ml of benzene, was added dropwise over a 2-hr period. The reaction is sufficiently exothermic to bring the solution to reflux temperature without external heating; caution must be exercised in the rate of addition. The rate of nitrogen evolution is dependent on the amine and is accelerated in the presence of iodine and may become excessively vigorous. After allowing the reaction to reflux for an additional 2 hr, the mixture was washed with 700-ml portions of 5% sodium bisulfite solution, water, 5% potassium hydroxide solution, and water. Solvent was removed on a rotary evaporator and the remainder was steam distilled. The organic layer was extracted with petroleum ether (30–60°) and distilled under a vacuum to yield white plates, mp 34–35° (lit.[18] mp 35°), in 40% yield of >99% purity (glpc).

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[18] A. Edinger and P. Goldberg, *Ann.*, **157**, 347 (1871).

The Syntheses of Substituted Imidazo[1,2-*a*]pyridines *via* "Ylidelike" Intermediates

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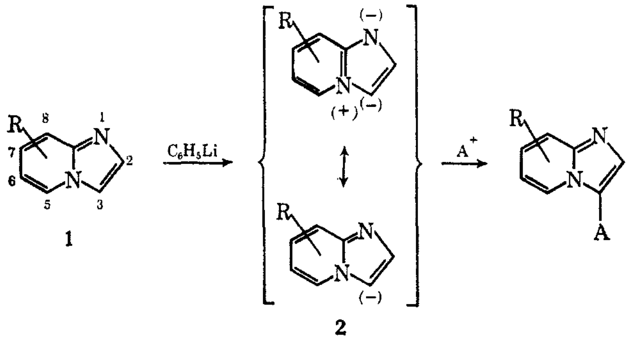
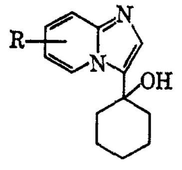
We have recently described the base-catalyzed protium–deuterium exchanges that occur in various "polyazaindenes."[1,2] The application of these observations to the syntheses of substituted imidazo[1,2-*a*]pyridines is outlined by the reaction sequence[3,4]



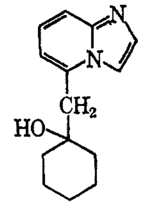
We now wish to report the syntheses of a number of substituted imidazo[1,2-*a*]pyridines by this method. The substances prepared by addition of cyclohexanone to compound **2** are represented by the general structure given for compounds **4–8**. The addition of dimethylformamide and phenyl isocyanate to compound **2** (R = H) affords the imidazo[1,2-*a*]pyridine-3-carboxaldehyde and -3-carboxanilide, respectively. The structure proofs of the various compounds rest upon their nmr (see Table I) and mass (see Experimental Section) spectra and the usual elemental analyses.



4, R = H
5, R = 6-CH_3
6, R = 7-CH_3
7, R = 8-CH_3
8, R = 2-CH_3

The considerable deshielding effect that the substituent in the three position has upon H_5 is of some interest and also contributes considerably to the structure elucidation of these compounds.

A further point of interest is the observation that the protons of the 5-methyl group are the only protons of the various isomeric methylimidazo[1,2-*a*]pyridines that are sufficiently acidic to react with phenyllithium to yield, after treatment with cyclohexanone, compound **11**.



11

The structure proof of this compound rests upon its nmr spectrum (the absence of a methyl group) and the other identifying features reported in the Experimental Section. 3-Methylimidazo[1,2-*a*]pyridine could, potentially, afford a substance analogous to **11**. However, under the reaction conditions which give the products reported in this Note, *no reaction* occurs between phenyllithium and the 3-methyl compound, the latter being recovered from the reaction mixture. The reactivity of the 5-methyl group is reminiscent of that of the 2-methyl group in pyridines.[5]

Experimental Section[6]

(1-Hydroxycyclohexyl)imidazo[1,2-*a*]pyridines.—To a stirred solution of 2.6 mmol of the appropriate imidazo[1,2-*a*]pyridine

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[1] W. W. Paudler and L. S. Helmick, *Chem. Comm.*, 377 (1967).

[2] W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, **33**, 1087 (1968).

[3] During the course of this work, the reaction of pyridine N-oxides, under similar reaction conditions, with cyclohexanone was described and interpreted in terms of an ylide intermediate: R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

[4] A. W. Johnson ["Ylid Chemistry in Organic Chemistry, A series of monographs," Vol. 7, A. T. Blomquist, Ed., Academic Press Inc., New York, N. Y., 1966, suggests the use of the term "ylid" rather than "ylide."

[5] "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955: R. B. Woodward and E. C. Kornfeld, p 413; L. A. Walter, p 757, and elsewhere.

[6] Melting points are corrected. The nmr spectra were obtained with a Varian A-60 spectrometer and the mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

TABLE I

NMR SPECTRAL DATA OF
SOME SUBSTITUTED IMIDAZO[1,2-*a*]PYRIDINES[a]

Compd	Chemical shifts, τ: H_2	H_3	H_5	H_6	H_7	H_8	Substituents[d,e]
4[c]	2.69		1.22	3.23	2.88	2.53	
5[b]	2.92		1.56		3.12	2.72	7.76 (CH_3—)
6[c]	2.76		1.32	3.32		2.77	7.68 (CH_3—)
7[b]	3.10		1.42	3.36	3.18		7.52 (CH_3—)
8[b,g]			0.60	2.18[f]	2.63	2.18[f]	7 30 (CH_3—)
9[b]	1.67		0.40	2.89	2.45	2.19	0.05 (—CHO)
10[b]	1.64		0.42	(2.82)	(2.70)	(2.64)	−0.01 (>NH), 2.80 phenyl protons (multiplet)
11[c]	2.50	1.98		3.30	2.82	2.58	6.92 (—CH_2—)

[a] The spin–spin coupling constants of the heterocyclic ring protons are essentially the same as those reported for similar compounds (see ref 1 and 2 and references cited therein). Figures in parentheses indicate approximate chemical shifts only because of interference with other protons. [b] Dilute solutions in $CDCl_3$. [c] Dilute solutions in DMSO-d_6. [d] The chemical shifts of the hydroxyl protons (τ 4.92–6.82) are not listed for each compound. [e] A complex ten-proton multiplet due to the cyclohexyl protons occurs at approximately τ 8.25 ± 0.1 for compounds **4–8** and **11**. [f] Center of a complex two-proton multiplet due to H_6 and H_8. [g] In CF_3CO_2D.

TABLE II

ANALYTICAL DATA FOR
VARIOUS (1-HYDROXYCYCLOHEXYL)IMIDAZO[1,2-*a*]PYRIDINES

Compd	Mp, °C	Formula	Analyses, %: Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Mol wt (mass spectroscopy)	Yield, %
4	189–192	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	71.89	7.45	13.06	216	35
5	173–175	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.15	7.83	12.44	230	40
6	201–203	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	72.93	7 87	12.31	230	48
7	209–210	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.22	7.90	12.31	230	42
8	215–217	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.13	8.26	12.20	230	14
11	156–157	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.22	7.83	12.47	230	35

in 10 ml of anhydrous ether was added dropwise, under a deoxygenated and dried nitrogen atmosphere, 1.5 ml of a 2.14 *M* solution of phenyllithium in a 70 : 30 mixture of benzene–ether (purchased from Alfa Inorganics, Inc., Beverly, Mass.). The brown to dark pink reaction mixture was stirred for 10 min (extension of the stirring time did not affect the yield of the product) and treated with 3 mmol of cyclohexanone in 10 ml of anhydrous ether. The color of the mixture changed gradually to a yellow-orange. After 30 min, the reaction mixture was treated with water and the organic layer was separated and extracted with 5% aqueous HCl. The aqueous layer then exhaustively extracted with chloroform and washed with 5% HCl. The combined acid solution was washed with chloroform and basified with solid sodium carbonate to precipitate a solid product (for 8-methylimidazo[1,2-*a*]pyridine) or oil, that was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and chromatographed on alumina (activity III). Elution with chloroform gave the solid product that was purified by recrystallization from dilute ethanol or by sublimation. The analytical and physical data are given in Table II.

3-Formylimidazo[1,2-*a*]pyridine. A.—A solution of 660 mg (5.6 mmol) of imidazo[1,2-*a*]pyridine in 25 ml of anhydrous ether was treated with 3 ml of the phenyllithium solution according to the above procedure and with 400 mg of N,N-dimethylformamide in 10 ml of anhydrous ether. The brown reaction mixture was stirred until an orange mixture resulted (*ca.* 1 hr) and water was added. The aqueous layer was exhaustively extracted with ether, and the combined ether layers were dried over anhydrous sulfate and concentrated under reduced pressure to give a yellow oily solid. The $CHCl_3$-soluble portion of the product was chromatographed on alumina (activity III). Elution with chloroform afforded 200 mg (24%) of product (mp 117–119°). The product was crystallized from ligroin (bp 95–105°) and sublimed [70° (0.4 mm)] to yield colorless needles: mp 117–119°; pmr ($CDCl_3$), CHO at τ 0.05.

Anal. Calcd for $C_8H_6N_2O \cdot H_2O$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.60; H, 4.68; N, 16.72; mol wt (mass spectroscopy), 146.

The semicarbazone was found to have mp 265° dec.

Anal. Calcd for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 53.09; H, 4.45; N, 34.04.

B.—The reaction was also carried out by a reversed addition procedure (addition of the imidazo[1,2-*a*]pyridine solution into the phenyllithium solution) to obtain the aldehyde **9** in 17% yield. A reaction at ice bath temperature gave unreacted starting material.

C.—Procedure B was carried out at room temperature by using 0.01 mol of imidazo[1,2-*a*]pyridine, 8 ml of a *ca.* 1.6 *M* butyllithium solution in hexane (purchased from Foote Mineral Co., Exton, Pa.), and 0.8 g of N,N-dimethylformamide in 16 ml of anhydrous ether to give the aldehyde **9** in 30% yield.

3-Imidazo[1,2-*a*]pyridinecarboxyanilide (**10**).—Procedure B was adapted by using 1.18 g (0.01 mol) of imidazo[1,2-*a*]pyridine in 15 ml of anhydrous ether, 8 ml of the phenyllithium solution diluted with 10 ml of anhydrous ether, and a solution of 1.2 g of phenyl isocyanate in 15 ml of anhydrous ether. The green reaction mixture was stirred for 30 min, treated with 10 ml of absolute ethanol,[7] stirred for 30 min, and treated with water. The organic layer was extracted with 5% HCl. Basification of the acid solution with solid sodium carbonate gave a yellow precipitate that crystallized from ethanol to yield 250 mg (15%) of colorless needles: mp 225°; pmr (DMSO-d_6), NH at τ − 0.01.

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.62; H, 4.54; N, 17.73; mol wt (mass spectroscopy) 237.

Chloroform extraction of the aqueous layer separated from the reaction mixture, followed by acid–base extraction and chromatography on alumina eluting with chloroform, gave 0.87 g of the starting material.

Registry No.—**4**, 15833-18-8; **5**, 15833-19-9; **6**, 15833-20-2; **7**, 15833-23-5; **8**, 15833-24-6; **9**, 6188-43-8; **9** semicarbazone, 15833-21-3; **10**, 15833-22-4; **11**, 15856-41-4.

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(7) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953).