Optically Active Amines. IX. (1)
The *N*-Formyl-1-(2-, 3-, and 4-pyridyl)ethylamines and the Primary Amines *via* the Leuckart Reaction

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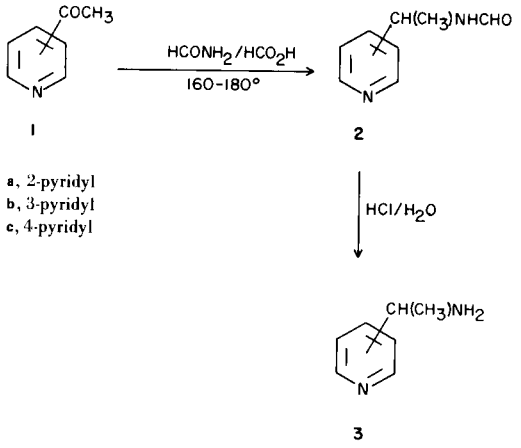
Although the Leuckart reaction has been used for the preparation of a wide variety of primary, secondary, and tertiary amines by the reductive amination of the respective aliphatic and carbocyclic aromatic aldehydes and ketones (2, 3), it has been used only in a few instances with aldehydes and ketones containing a heterocyclic aromatic group. These heterocyclic compounds include furfural (3), 2-thienyl alkyl ketones (3), 2- and 3-pyridylacetone (4-6), and some related 2-picolyl and 3-pyridyl ketones (4,5).

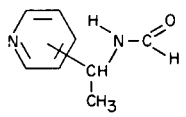
The Leuckart reaction has now been used for the preparation of 1-(2-, 3-, and 4-pyridyl)ethylamine (**3**) from the respective acetylpyridine (**1**). The 3-pyridyl isomer



(**3b**) was the first of these amines to be prepared earlier, this by way of the zinc-acetic acid reduction of the corresponding oxime (7). Although a quantitative conversion was reported for this reaction (7), subsequent efforts to achieve such a high yield using the reaction with this oxime (8) and with 2-acetylpyridine oxime (8) were unsuccessful (36 and 22% yields, respectively). Larger yields of the amines have been obtained by reduction of the 2-, 3-, and 4-acetylpyridine oximes with hydrogen at a moderate pressure (4 atm) on Raney nickel (65, 53, and 66%, respectively) (8). At a much higher pressure (200 atm) and this same catalyst the yield of the 1-(3-pyridyl)-ethylamine is higher (74%)(9).

The reductive amination of the acetylpyridines (**1**) with formamide-formic acid leads to the *N*-formyl derivatives of the amines (**2**) which are quite soluble in water and are hygroscopic. After dilution of the reaction mixture with water and adjustment of the alkalinity of the solution to at least *p*H 11, the amide can be removed from the solution by extraction with both chloroform and ether. The latter solvent is better since it tends to remove a smaller amount of tar. The organic solvent is then removed, and distillation of the residue affords the *N*-formyl derivative (**2**) (Table I). The latter is hydrolyzed to the primary amine (**3**) (Table I) or the crude amide can be hydrolyzed for a higher overall yield of the primary amine.

The NMR spectra of these compounds in deuteriochloroform are of some interest. In all of the spectra the pyridyl proton signals have chemical shifts and coupling patterns as expected (11). In the spectra of the primary amines, the methyl proton signals appear as a doublet centered at 1.31-1.38 ppm due to the coupling (J = 7.0 Hz) of these protons with the α proton. The resonance of the latter is seen as a quartet centered at 4.05-4.11 ppm. The amino protons give rise to a singlet at 1.72-1.82 ppm. In the spectra of the *N*-formyl derivatives, there is a doublet centered at 1.46-1.50 ppm (J = 7.0 Hz). There is also an additional small peak at 1.53-1.58 ppm, 4.0-4.5 Hz higher in frequency than the high frequency peak of the doublet. It is concluded that this additional peak is part of another doublet. The second peak of this doublet is 7.0 Hz lower in frequency and is obscured by the high frequency peak of the more intense doublet. These two doublets then arise from the resonance of the methyl protons. Two doublets are seen as the result of the restricted rotation about the carbonyl carbon to nitrogen bond giving rise to two NMR detectable rotational conformers, **4** and **5**, termed *cis* and *trans*, respectively (12). This same type of conformational isomerism has been detected in the NMR spectra of *N*-methyl, *N*-ethyl, *N*-isopropyl, and *N*-*t*-butylformamide (12). These compounds, neat or in benzene, were found to be 82-92% *trans*.



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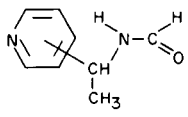

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The amount of the *trans* conformer is decreased when the steric size of the alkyl group becomes larger. For the *N*-acetyl and other *N*-alkylcarbonyl derivatives of these alkyl amines, only the *trans* conformer was detected (12).

In analogy, the preferred conformation of the *N*-formyl-1-(2-, 3-, and 4-pyridyl)ethylamines is assumed to be *trans* (**5**). The integrated intensity of the signals assigned to the methyl protons gives the amount of the *trans* conformer to be about 85% in deuteriochloroform at about 35°. In these same spectra, the resonance of the α proton is a doublet of quartets centered at 5.12-5.27 ppm. This signal is seen as a quintet due to the equal coupling of this proton with the methyl and amido hydrogens, both coupling constants being 7.0 Hz. The peaks are broad due to weak coupling of this proton with the formyl group hydrogen (12). The quintet is changed to a quartet on exchange of the amido hydrogen with deuterium. The amido proton resonance is somewhat obscured by the formyl proton signal and is seen only as a broad hump centered at about 8.1 ppm with poorly defined peaks due to the quadrupole relaxation of the *N*-14 nucleus. Thus in neither the α proton nor the amido proton signals can the presence of two conformers be detected. The formyl proton resonance is usually seen as a broad singlet near 8.2 ppm. The broadening is due to the weak coupling of this proton to the α and methyl protons (12, 13). In the 2-pyridyl compound (**2a**), however, the formyl proton resonance occurs as an unsymmetrical signal with two resolved peaks at 8.25 and 8.27 ppm. The lower field and less intense peak is presumably associated with the formyl proton resonance of the *cis* conformer (**4**). The small separation of these peaks precluded an estimation of the concentration of each conformer by integration of the respective signals.

It is to be noted that the NMR spectra of *N*-benzoyl, *N*-acetyl, and *N*-formyl-α-phenylethylamine in deuteriochloroform and other solvents have been examined earlier (14). While in the published spectra for the *N*-benzoyl and *N*-acetyl compounds, chemical shift and coupling pattern assignments are in agreement with those made for the *N*-formyl-1-(2-, 3-, and 4-pyridyl) analogs, no mention was made of signals in the spectrum of *N*-formyl-α-phenylethylamine which suggest the presence of a highly restricted rotation about the carbonyl carbon to nitrogen bond.

EXPERIMENTAL

Melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Elemental analyses were done by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were measured with a Varian Model A-60 spectrometer (15) operating at 60 MHz on approximately 30-40% solutions in deuteriochloro-

TABLE I

1-(2-, 3-, and 4-Pyridyl)ethylamines and Their *N*-Formyl Derivatives

No.	B.p., °C (mm.)	n_D^{25} (M.p., °C)	Yield, % Leuckart (b)	Yield, % From Amide	Analyses, Found (a) C	H	N	Ref. (c)
2a	129-131 (3) (d)	1.5187	69		64.14	6.81	18.90 (e)	(10)
2b	170-172 (4) (d)	1.5389	61		63.13	7.41	17.67 (f)	(g)
2c	175-180 (1.5) (d)	(54-55) (h)	55		63.91	6.52	18.49	(g)
3a	60-64 (3) (i)	1.5240	71	81				(8, 10)
3b	71-75 (2) (i)	1.5301	53	72				(7, 8)
3c	110-112 (21) (i) (j)	1.5336	67	55				(8)

(a) Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65; mol. wt. 150.2. (b) For **3a-c**, these refer to the yields of the primary amines after hydrolyses of the crude amides and are based on the ketones. (c) Previously reported. (d) Obtained as a yellow to orange oil. (e) Mol. wt. found 146, osmetric in chloroform. (f) Hygroscopic, contaminated with about 2% water prior to analysis. (g) Not previously reported. (h) Recrystallized from ether as fine, white prisms. (i) Colorless oil which turns yellow on standing. (j) *N*-5-Bromosalicylidene crystallized from ethanol-water as fine, yellow needles, m.p. 89-90°. ***Anal.*** Calcd. for $C_{14}H_{13}BrN_2O$: C, 55.10; H, 4.29. Found: C, 54.61; H, 4.40.

form at about 35°. Chemical shifts are reported in ppm from TMS=0. Coupling constants were estimated to ± 0.5 Hz.

N-Formyl-1-(2-, 3-, and 4-pyridyl)ethylamine (**2**).

To 63.0 g. of formamide (1.40 moles) at 160-180° was added, over a 0.5 hour period with stirring, 12.1 g. of the respective acetylpyridine (**1**) (0.100 mole) in 15 ml. of 98% formic acid. When addition was complete an additional 15 ml. of 98% formic acid was added, and the mixture was heated at 160-180° for an additional 1.5 hours. The mixture was cooled and poured into 100 ml. of water, and the solution made alkaline to at least *pH* 11 with concentrated sodium hydroxide. This solution was thoroughly extracted with ether. The ethereal solution was dried (sodium sulfate), and the ether evaporated to give 12-13 g. of residue. Distillation of this residue gave a small forerun of formamide and then 8.2-10.4 g. of the respective *N*-formyl-1-(2-, 3-, and 4-pyridyl)-ethylamine (55-69%) with physical properties as shown in Table I.

In the case of **2c**, the *N*-formyl compound partially crystallized on cooling and was recrystallized from ether.

1-(2-, 3-, and 4-Pyridyl)ethylamine (**3**).

To 3.89 g. of the respective *N*-formyl-1-(2-, 3-, and 4-pyridyl)-ethylamine (**2**) (0.0259 mole) was added 18 ml. of 8.5 *N* hydrochloric acid and the mixture boiled for 5 hours. In the case of **2c** the solution was boiled for only 1.5 hours. The cooled solution was made alkaline to at least *p*H 11 with concentrated sodium hydroxide and was thoroughly extracted with ether. The ethereal solution was dried (sodium sulfate). Evaporation of the ether left 3-5 g. of residue. Distillation of this residue gave 1.74-2.55 g. of the respective 1-(2-, 3-, and 4-pyridyl)ethylamine (55-81%) with physical properties shown in Table I.

The hydrolyses of the crude *N*-formyl-1-(2-, 3-, and 4-pyridyl) ethylamines were done with the procedure outlined above and gave the primary amines (53-71% based on the ketones) with physical properties essentially the same as those shown in Table I.

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