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The Pyridylethylation of Active Hydrogen Compounds. III. The Reaction of 2-Vinylpyridine with Secondary Amines

BY HENRY E. REICH¹ AND ROBERT LEVINE

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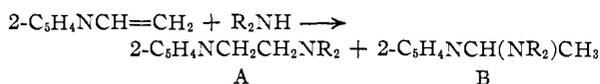
Several secondary amines have been condensed with 2-vinylpyridine under acidic conditions to give good yields of tertiary amines of the type $2\text{-C}_5\text{H}_4\text{NCH}_2\text{CH}_2\text{NR}_2$. Pyrrole and 2,5-dimethylpyrrole, which are too weakly basic to be pyridylethylated under acidic conditions, condense with 2-vinylpyridine in high yields with sodium metal as the catalyst. The structures of several of the products have been established by comparison with authentic samples prepared by the Mannich reaction and/or the carbamyl chloride route. Mechanisms for the pyridylethylation reactions are proposed.

In earlier work from this Laboratory the pyridylethylation of a number of ketones was reported.^{2,3}

The present report is concerned with the addition of a number of secondary amines to 2-vinylpyridine. Before our study was initiated, Doering and Weil⁴ reported the non-catalytic pyridylethylation of piperidine in 86% yield by refluxing 2-vinylpyridine with excess piperidine for six hours. These workers also found that when a solution of diethylamine and 2-vinylpyridine is heated at 165° for 15 hours a 12% yield of pyridylethylated product is obtained. After our study was in progress, Sommers, *et al.*,⁵ reported that although they were able to add piperidine, morpholine and 1-methylpiperazine to 2-vinylpyridine under non-catalytic conditions, similar reactions failed with diethylamine and dicyclohexylamine.

In the present study, nine secondary amines have been pyridylethylated using non-catalytic conditions or an acid (hydrochloric or acetic) as the condensing agent. These results are summarized in Table I.

Because the addition of an amine to the side chain of 2-vinylpyridine may, *a priori*, give rise to the isomeric compounds A and B, the structures of several of our products were established by preparing authentic samples.

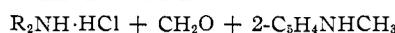


In the non-catalytic reaction between 2-vinylpyridine and diethylamine, Doering and Weil⁴ indicate that the compound obtained is 2-(β -diethylaminoethyl)-pyridine (I) (A, R = C₂H₅). As evidence for this structure these workers have used the facts that the melting points of their derivatives agree with those in the literature.⁶⁻⁹

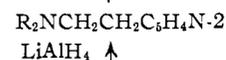
- (1) American Cyanamid Co. Research Fellow, 1952-1954.
- (2) R. Levine and M. H. Wilt, *THIS JOURNAL*, **74**, 342 (1952).
- (3) M. H. Wilt and R. Levine, *ibid.*, **75**, 1368 (1953).
- (4) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).
- (5) A. H. Sommers, M. Freifelder, H. B. Wright and A. W. Weston, *ibid.*, **75**, 57 (1952).
- (6) T. Héou-Féou, *Compt. rend.*, **192**, 1242 (1931).
- (7) T. Héou-Féou, *Bull. soc. chim. (France)*, [5] **2**, 105 (1935).
- (8) K. Löffler, *Ber.*, **37**, 161 (1904).
- (9) Although Héou-Féou^{6,7} claims to have made I by a Mannich reaction involving 2-picoline, pertinent analytical data do not appear in his papers. Also, Löffler claims to have prepared I by treating 2-(2-pyridyl)-ethanol with fuming hydrobromic acid and phosphorus in a sealed tube and treating the resulting bromide II with diethylamine. Based on his analytical data, there is little doubt that Löffler obtained either compound A or B (R = C₂H₅). However, it appeared to us

Although in our hands Héou-Féou's method^{6,7} for effecting the Mannich reaction gave only a tarry mixture, varying the experimental conditions gave a 23% yield of 2-(β -diethylaminoethyl)-pyridine (A, R = C₂H₅). The physical properties of both this compound and its dipicrate agree with those of the corresponding materials obtained by the direct pyridylethylation of diethylamine. The structure of the diethylamine-2-vinylpyridine adduct was established further by the carbamyl chloride route. The Mannich reaction (Table II) and/or the carbamyl chloride route (Table III) also were used to establish the structures of several of our other products.

Mannich Reaction



Carbamyl Chloride Route



We have found that several amines (diisopropylamine, di-*sec*-butylamine, dicyclohexylamine, pyrrole, 2,5-dimethylpyrrole and diphenylamine) could not be pyridylethylated under acidic conditions. It appears that the reaction failed with the first three amines because of steric reasons and that the second three amines failed to react because they are so feebly basic.

Therefore, it seemed reasonable that pyrrole, 2,5-dimethylpyrrole and diphenylamine might be pyridylethylated using sodium metal as the condensing agent—a method which had been used successfully earlier^{2,3} for the pyridylethylation of ketones. Under these conditions (Table I) although pyrrole gave an 89% yield and 2,5-dimethylpyrrole a 53% yield of pyridylethylated product, diphenylamine failed to react.

That pyrrole is pyridylethylated on its nitrogen atom is shown by the fact that a Zerewitinoff reaction with the product gave only 5% of methane in accord with the 4% obtained in a similar reaction with 2-(β -diethylaminoethyl)-pyridine. The evolution of these small amounts of methane probably is due to the fact that the Grignard reagent reacted

that II might not have been β -(2-pyridyl)-ethyl bromide but its rearranged isomer, α -(2-pyridyl)-ethyl bromide. It also is possible that under Löffler's conditions the intermediate bromide(s) might have been dehydrohalogenated by diethylamine to give a mixture of 2-vinylpyridine and diethylamine hydrobromide or 2-vinylpyridine hydrobromide and diethylamine. Then, each of these pairs of compounds theoretically could react to give the observed product. Using this reasoning, we treated 2-vinylpyridine with diethylamine hydrochloride and 2-vinylpyridine hydrochloride with diethylamine and obtained 20 and 22%, respectively, of the same product.

TABLE I: TERTIARY AMINES OF TYPE $C_3H_4N(CH_2CH_2NR_2)_2$

NR ₂	K _b	Reactants, moles Amine, 2-VP ^a	Catalyst (moles)	Yield, %	B.P., °C.	Mm.	Formula	Nitrogen, % Calcd.	Derivative	M.p., °C.	Formula	Nitrogen, % Found
N(CH ₃) ₂	7.4×10^{-4}	2	HCl ^b	84	101-103	17	C ₉ H ₁₄ N ₂	18.67	Dipicrate	177-178	C ₂₁ H ₃₀ N ₈ O ₁₄ ^m	17.41
N(C ₂ H ₅) ₂	1.2×10^{-3}	2	HOAc(2.0)	53	82-83	2	C ₁₁ H ₁₈ N ₂	15.73	Dipicrate	163.5-165	C ₂₃ H ₃₄ N ₈ O ₁₄	17.41
N(C ₃ H ₇ - <i>n</i>) ₂	1.0×10^{-3}	1	HOAc(1.0)	39	140-141	16	C ₁₁ H ₂₂ N ₂	13.60	Picrate	151-153	C ₁₉ H ₂₈ N ₅ O ₇	16.13
N(C ₄ H ₉ - <i>n</i>) ₂	2.0×10^{-3}	1	HOAc(1.0)	47	120-121	1.8	C ₁₃ H ₂₆ N ₂	11.97	Picrate	134-135	C ₂₁ H ₂₈ N ₅ O ₇	15.03
N(C ₄ H ₉ - <i>i</i>) ₂	6.5×10^{-4}	1	HOAc(0.2)	47	144-145	12	C ₁₁ H ₂₀ N ₂	11.97	Picrate	154-155	C ₂₁ H ₂₈ N ₅ O ₇	15.28
C ₆ H ₁₀ N ^c	1.2×10^{-3}	1	HOAc(1.0)	85	116-118	3.7	C ₁₁ H ₁₆ N ₂	14.58	Dipicrate	158.6-159.5 ^f	C ₁₇ H ₁₉ N ₅ O ₈	16.57
C ₄ H ₈ ON ^d	2.4×10^{-6}	1	None	50	105-106	0.5	C ₁₁ H ₁₆ N ₂ O	14.71	Picrate	145-146	C ₂₃ H ₃₂ N ₈ O ₁₄ ⁿ	17.43
C ₄ H ₈ N ^e	1.3×10^{-3}	1	HOAc(1.0)	83	96-97	2.2	C ₁₁ H ₁₆ N ₂	15.91	Picrate	157-158	C ₁₇ H ₁₉ N ₅ O ₇	17.43
C ₄ H ₈ N ^f	?	1	None	57	148-150	10	C ₁₁ H ₁₆ N ₂	16.28	Picrate	129.5-130.4	C ₁₇ H ₁₉ N ₅ O ₇	17.42
C ₆ H ₈ N ^g	?	2	Na(0.1)	53	124-125	1	C ₁₃ H ₁₆ N ₂	14.00	Picrate	163.5-165	C ₁₉ H ₁₉ N ₅ O ₇	16.09
N(CH ₂) ₂ C ₆ H ₆	2.5×10^{-10} ^h	1	HOAc(1.0)	77	141-143	1.1	C ₁₄ H ₁₆ N ₂	13.20	Picrate	167-168	C ₂₀ H ₁₉ N ₅ O ₇	15.87

^a 2-VP = 2-vinylpyridine. ^b The amine was used as its hydrochloride. ^c C₆H₁₀N is the 1-piperidino radical. ^d C₄H₈ON = the 1-morpholino radical. ^e C₄H₈N = the 1-pyrrolidino radical. ^f C₄H₈N = the 1-pyrryl radical. ^g C₆H₈N = the 2,5-dimethyl-1-pyrryl radical. ^h N. F. Hall and M. R. Sprinkle, THIS JOURNAL, 54, 3469 (1932). ⁱ H. Scudder, "The Electrical Conductivity and Ionization Constants of Organic Compounds," D. Van Nostrand Co., Inc., New York, N. Y., 1914, p. 261. ^j A. R. Ingram and W. F. Luder, THIS JOURNAL, 64, 3043 (1942). ^k L. C. Craig and R. M. Hixon, *ibid.*, 53, 4370 (1931). ^l Reported m.p. 159-160°. ^m *Anal.* Calcd. C, 41.45; H, 3.29. Found: C, 41.56; H, 3.48. ⁿ *Anal.* Calcd. C, 42.46; H, 3.39. Found: C, 42.66; H, 3.39.

TABLE II

TERTIARY AMINES FROM THE MANNICH REACTION BETWEEN 2-PICOLINE, FORMALDEHYDE AND SECONDARY AMINES

Secondary amine	l-Amines, 2-C ₅ H ₄ NCH ₂ CH ₂ NR ₂ yield, % ^a
Dimethylamine	6
Diethylamine	23 ^b
Di- <i>n</i> -propylamine	16
Di- <i>n</i> -butylamine	13
Diisobutylamine	19
Morpholine	4 ^c
Piperidine	11

^a Constants of these amines and their picrates agree with those listed in Table I. ^b Analysis appears in Experimental section. ^c There also was obtained 70% yield of N,N-dimorpholinomethane, b.p. 116-122° at 10 mm. (M. Zief and J. P. Mason, *J. Org. Chem.*, 8, 1 (1943)).

TABLE III

TERTIARY AMINES FROM THE LITHIUM ALUMINUM HYDRIDE REDUCTION OF AMIDES PREPARED BY THE ACYLATION OF 2-PICOLYLITHIUM WITH CARBAMYL CHLORIDES

Carbamyl chloride	Amides, 2-C ₅ H ₄ -NCH ₂ CONR ₂ ^a yield, %	Amines, 2-C ₅ H ₄ -NCH ₂ CH ₂ NR ₂ yield, % ^b
(CH ₃) ₂ NCOCI	8.0 ^b	43.0
(C ₂ H ₅) ₂ NCOCI	46.0 ^b	56.0
(<i>n</i> -C ₄ H ₉) ₂ NCOCI	68.3 ^c	45.0
C ₆ H ₅ N(CH ₃)COCI	43.0 ^d	40.0

^a 2-C₅H₄N = 2-pyridyl radical. ^b Behaved erratically on analysis. ^c *Anal.* Calcd. for C₁₃H₂₄N₂O: N, 11.29. Found: N, 11.43. ^d *Anal.* Calcd. for C₁₄H₁₄N₂O: N, 12.39. Found: N, 11.88. ^e Constants of these amines and their picrates agree with those listed in Table I.

to a small extent with the slightly acidic hydrogen atoms of the methylene group which is attached to the pyridine ring of these tertiary amines.

Three mechanisms may be visualized for the pyridylethylation of amines depending on whether the reaction is (1) uncatalyzed, (2) base-catalyzed or (3) acid-catalyzed. The uncatalyzed and acid-catalyzed reactions appear to be initiated by the attack of the amine to be pyridylethylated or its ammonium ion,¹⁰ respectively, on the electron-deficient terminal carbon atom of the vinyl group. The sodium-catalyzed (basic) reactions probably involve the addition of the anion of the secondary amine (formed from the amine and sodium metal)

(10) Since the dialkylamines which can be pyridylethylated under acidic conditions are stronger bases (Table I) than 2-vinylpyridine ($K_b = 8.3 \times 10^{-10}$, this value was kindly determined by Mr. T. R. Harkins of this department) and since there is never enough acid present in the medium to convert both the dialkylamine and the 2-vinylpyridine to their ammonium salts, it is not unreasonable to assume that the secondary amine gets a larger share of the available acid than the 2-vinylpyridine.

to 2-vinylpyridine in much the same way that sodio-malonic ester reacts with 2-vinylpyridine.⁴

Experimental

In this section six typical experiments are described in detail.¹¹

The Non-catalytic Pyridylethylation of Morpholine.—A mixture of morpholine (43.5 g., 0.5 mole) and 2-vinylpyridine (52.5 g., 0.5 mole) was refluxed for eight hours and distilled to give 48.0 g. (50%) of N-[2-(2-pyridyl)-ethyl]-morpholine, b.p. 105–106° at 0.5 mm. *Anal.* Calcd. for C₁₁H₁₆O₂N₂: N, 14.58. Found: N, 14.71. The compound gave a monopicate, m.p. 145–146° (from 95% ethanol). *Anal.* Calcd. for C₁₇H₁₉O₂N₂: N, 16.62. Found: N, 16.57. A dipicrate, m.p. 184.5–185.8° (from 95% ethanol), was obtained by refluxing the monopicate with an acetone solution of picric acid. *Anal.* Calcd. for C₂₃H₂₇O₁₅N₃: C, 42.46; H, 3.39. Found: C, 42.66; H, 3.39.

In addition to the pyridylethylated morpholine, there were obtained 19.0 g. of recovered morpholine, b.p. 53–57° at 9 mm., and 28.0 g. of a tarry, non-distillable residue.

The Acid-catalyzed Pyridylethylation of N-Methylaniline.—A solution of N-methylaniline (64.3 g., 0.6 mole), 2-vinylpyridine (63.0 g., 0.6 mole) and glacial acetic acid (36.0 g., 0.6 mole) in 250 ml. of absolute methanol was refluxed for eight hours and allowed to stand at room temperature for nine hours. The methanol was removed by distillation, the residue was poured onto ice and the mixture was made strongly basic with 10% sodium hydroxide solution. The basic solution was extracted with several portions of ether, the combined extracts were dried over sodium sulfate, the solvent was removed and the residue was distilled in vacuum to give 11.0 g. of 2-vinylpyridine, b.p. 57° at 12 mm.; 13.1 g. of N-methylaniline, b.p. 43–47° at 1.2 mm.; and 97.8 g. (77%) of 2-[(2-N-methylanilino)-ethyl]-pyridine, b.p. 141–142.5° at 1.1 mm. *Anal.* Calcd. for C₁₄H₁₆N₂: N, 13.20. Found: N, 13.35. The compound gave a monopicate, m.p. 167–167.9° (from 95% ethanol). *Anal.* Calcd. for C₂₀H₁₉O₇N₃: N, 15.87. Found: N, 16.00.

The Sodium-catalyzed Pyridylethylation of Pyrrole.—To a rapidly stirred solution of pyrrole (67.0 g., 1.0 mole) and 2-vinylpyridine (52.5 g., 0.5 mole), 1.15 g. (0.05 mole) of small pieces of sodium metal was added. Since no apparent reaction took place on the addition of the sodium, the mixture was heated cautiously to refluxing and then refluxed for two hours. To the cooled mixture 5 ml. of absolute ethanol was added and the contents of the flask were poured onto a mixture of ice and water. The combined ether extracts of the basic solution were dried over sodium sulfate and the solvent was removed by distillation. The residue was distilled in vacuum to give 76.5 g. (89%) of N-[2-(2-pyridyl)-ethyl]-pyrrole, b.p. 148–150° at 10 mm. *Anal.* Calcd. for C₁₁H₁₂N₂: N, 16.28. Found: N, 16.42. The amine gave a monopicate, m.p. 129.5–130.4° (from 95% ethanol). *Anal.* Calcd. for C₁₇H₁₅O₇N₃: N, 17.45. Found: N, 17.42.

(11) The 2-vinylpyridine was kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

There also were obtained 31.0 g. of pyrrole, b.p. 35–40° at 15 mm.; 4.8 g. of 2-vinylpyridine, b.p. 35–45° at 9–12 mm.; 4.0 g. of a tarry, non-distillable residue.

Mannich Reaction Using 2-Picoline, Formaldehyde and Diethylamine Hydrochloride.—A rapidly stirred mixture of diethylamine hydrochloride (22.7 g., 0.207 mole), formaldehyde (6.2 g., 0.207 mole) in the form of paraformaldehyde and 2-picoline (38.5 g., 0.414 mole) was refluxed for 15 minutes. The cooled mixture then was poured onto ice and made strongly basic with 10% sodium hydroxide. The basic solution was extracted with several portions of ether, the ether extracts were dried over sodium sulfate, the ether was removed at atmospheric pressure and the residue was fractionated in vacuum to give 8.5 g. (23%) of 2-(2-diethylaminoethyl)-pyridine, b.p. 78–80° at 1.4 mm.; 28.1 g. of 2-picoline, b.p. 35–40° at 30 mm.; 3.0 g. of non-distillable tarry residue. *Anal.* of the 2-(2-diethylaminoethyl)-pyridine: Calcd. for C₁₁H₁₈N₂: N, 15.73. Found: N, 15.59. This amine gave a dipicrate, m.p. 164–165°^{4,8} (from 95% ethanol). *Anal.* Calcd. for C₂₃H₂₄O₁₄N₃: N, 17.61. Found: N, 17.41. This dipicrate showed no depression in melting point when mixed with a sample prepared from the amine obtained by the direct pyridylethylation of diethylamine.

The Acylation of 2-Picolylithium with Di-n-butylcarbonyl Chloride.—Di-n-butylcarbonyl chloride¹² (28.7 g., 0.15 mole), dissolved in 50 ml. of anhydrous ether, was added over a one-half hour period to a rapidly stirred solution of 2-picolylithium (0.3 mole)^{13,14} at 5°. The cooling bath was removed and the reaction mixture stirred for an additional hour. Then, the mixture was poured onto ice and extracted with several portions of ether. The combined ether extracts were dried over sodium sulfate and the solvent was removed at atmospheric pressure. The residue was distilled in vacuum to give 7.3 g. of 2-picoline, b.p. 40–43° at 30–33 mm., and 25.4 g. (68%) of N,N-di-n-butyl-2-pyridylacetamide, b.p. 156–158° at 1.8 mm. *Anal.* Calcd. for C₁₅H₂₃O₂N₂: N, 11.29. Found: N, 11.43.

Reduction of N,N-Di-n-butyl-2-pyridylacetamide to 2-(2-Di-n-butylaminoethyl)-pyridine.—N,N-Di-n-butyl-2-pyridylacetamide (7.0 g., 0.028 mole) was reduced by an ether solution of lithium aluminum hydride (5.3 g. in 100 ml. of ether) using the method of Uffer and Schlittler.¹⁵ On processing the reaction mixture there were obtained 3.0 g. (45%) of the tertiary amine, 2-(2-di-n-butylaminoethyl)-pyridine, b.p. 138° at 3.4 mm., and 2.0 g. of recovered N,N-di-n-butyl-2-pyridylacetamide, b.p. 157–158° at 2 mm. The tertiary amine formed a picrate, m.p. 134–134.4° alone and when mixed with a sample of the picrate of the material made by the direct pyridylethylation of di-n-butylamine.

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(12) This and the other carbonyl chlorides used in this study were kindly supplied through the courtesy of Dr. Harry Gamrath, Monsanto Chemical Co., St. Louis, Mo.

(13) N. N. Goldberg, L. B. Barkley and R. Levine, *THIS JOURNAL*, **73**, 4301 (1951).

(14) N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

(15) A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).