[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Addition of Amines to 4-Vinylpyridine

BY ARTHUR P. PHILLIPS

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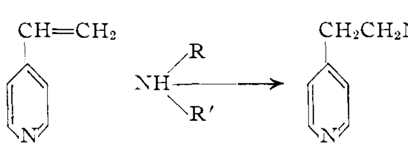
Fifteen 4-(substituted aminoethyl)-pyridines have been made by the addition of secondary and primary amines to 4-vinylpyridine. This addition reaction has been found to be greatly influenced by: 1, steric factors in the adding amine; 2, acid catalysis; and 3, polarity of the solvent.

A variety of 4-(substituted aminoethyl)-pyridines (I) were required as intermediates for another project. These compounds were made readily by the addition of fifteen secondary and primary amines to 4-vinylpyridine.



I

The addition of a few amines to 2-vinylpyridine[1] has been reported[2-4] and a few similar additions of amines to 4-vinylpyridine were carried out by Matuszko and Taurins.[5]

Standard reaction conditions were used for the reactions in order that semi-quantitative comparisons of the yields could be made and related to the structures of the amines. These conditions were to heat a mixture of 0.2 mole of 4-vinylpyridine and 0.3 mole of the amine for 20 hr. at 100°. Other than the standard conditions were used in some instances from necessity. Thus dimethylamine, which is a gas at ordinary temperature, was used as a 25% solution in water and the reaction mixture was left at room temperature. The diethylamine (b.p. 56°) reaction mixture refluxed on the steam-bath at less than the usual 100°. Two or more duplicate runs were made for each amine, and yields from these runs were reproducible within ± 3%. All yields are based on the amount (0.2 mole) of 4-vinylpyridine[6] used. In many cases, particularly when the yield of product was low, the unused reactant amine and/or 4-vinylpyridine was recovered from the reaction mixture. Although the latter results have not been included in Tables I and II, the combined recovery of product and of one or both of the reactants usually could be made nearly quantitative. The results obtained under the standard conditions for all of the amines, as well as the physical and analytical data for the products, are shown in Table I.

While the addition of amines to 4-vinylpyridine is (formally) a reversible process, the regular increase in yields with time, shown for several amines in Table II, indicates that the equilibrium point has not usually (if ever) been reached with the reaction times used in this study. It thus seems likely that the different yields obtained with the various amines (Table I) have resulted from differences in *rates of reaction* rather than from differences in positions of equilibria.

Variation in Yield with Amine Structure (Table I).—Significant and reproducible differences were observed in the yields obtained by the addition of different amines to 4-vinylpyridine under comparable reaction conditions. These differences are well illustrated by comparing the yields obtained with pyrrolidine and piperidine (expts. 1 and 2, Table I), morpholine and N-methylpiperazine (expts. 3 and 4, Table I), dimethylamine and diethylamine (expts. 5 and 6) and methylbenzylamine and ethylbenzylamine (expts. 7 and 8). The several pairs of amines listed do not differ significantly in basicity, and thus it is felt that steric hindrance in the adding amine is probably the most important factor responsible for these differences in yields.

As shown in Table I, the primary amines (expts. 11–15) gave very poor yields of adducts with 4-vinylpyridine and appear to be much less reactive than the related secondary amines in this reaction. Since these primary amines differ little in basicity from the closely related secondary amines and should not exceed them in steric hindrance, the reason for this lesser reactivity remains obscure for the present.

Effect of Reaction Conditions on Yields (Table II).—Dimethylamine gave excellent yields in the addition reaction under mild conditions. This result suggested that perhaps the aqueous medium used in this case had favored the reaction in some way. On this basis it seemed desirable to examine the effect of some changes in reaction conditions upon yields in this reaction. Pyrrolidine, as one of the best addends and a liquid of convenient boiling point, was selected for this purpose. Useful findings, made with pyrrolidine, were later applied to increase yields with the less reactive amines. This work is summarized in Table II.

The first four experiments of Table II show the effect on yield of a lower reaction temperature (expt. 2) and of shorter heating times (expts. 3 and 4). The effect of altering the pyrrolidine/4-vinylpyridine ratio is shown by expts. 4, 5 and 6. The conditions of expt. 4 were selected as the standard for a comparison of the effect of several solvents and catalysts on the yield in this reaction.

Water favored the addition reaction considerably

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(1) The similar addition of a variety of amines to styrene, using metallic sodium as a catalyst, has been reported by (a) R. Wegler and G. Pieper, *Chem. Ber.*, **83**, 1 (1950); (b) H. Bestian, *et al.*, *Ann.*, **566**, 210 (1950); (c) J. D. Danforth, U. S. Patent #2,449,644 (Sept. 21, 1948); *C.A.*, **43**, 681[1] (1949).

(2) W. E. Doering and R. A. N. Weil, THIS JOURNAL, **69**, 2461 (1947)

(3) A. H. Sommers, M. Freifelder, H. B. Wright and A. W. Weston, *ibid.*, **75**, 57 (1953).

(4) (a) H. E. Reich and R. Levine, *ibid.*, **77**, 4913 (1955); (b) *ibid.*, **77**, 5434 (1955).

(5) A. J. Matuszko and A. Taurins, *Can. J. Chem.*, **32**, 538 (1954).

(6) Purchased from the Reilly Tar and Chemical Company. The Reilly product is specified as 95% minimum 4-vinylpyridine stabilized with 0.1% *t*-butylcatechol and was used without further purification.

TABLE I

REACTION OF 4-VINYLPYRIDINE WITH AMINES UNDER STANDARD CONDITIONS[a]

Reaction conditions				Products					Analyses, %			
									Carbon		Hydrogen	
Expt.	Amine	Time, hr.	Temp., °C.	Yield, %[b]	B.p. °C.	Mm.	Formula	M.p., °C.[c]	Calcd.	Found	Calcd.	Found
1	Pyrrolidine	20	100	90–95	151–152	16	$C_{11}H_{16}N_2$	216–217	53 0	52 8	7.3	7.3
2	Piperidine	20	100	60	157–158	15	$C_{12}H_{18}N_2$	225–226	54.7	54.7	7.7	7.9
3	Morpholine	20	100	45–50	131–132	1–2	$C_{11}H_{16}N_2O$	224–226	49.8	49.5	6.8	6.8
4	N-Methylpiperazine	24	100	60–65	167–168	12	$C_{12}H_{19}N_3$		70.2	70.1	9.3	9.4
5	Dimethylamine	20[d]	25	90	100–102	9	$C_9H_{14}N_2$	223–224	48.4	48.2	7.2	7.1
6	Diethylamine	24	65–75	0[b]	134–135	16	$C_{11}H_{18}N_2$	234–235	52.6	52.6	8.0	7.8
7	Methylbenzylamine	20	100	95	158–160	3–4	$C_{15}H_{18}N_2$		79.6	79.4	8.0	8.1
8	Ethylbenzylamine	20[e]	100	0[b]	180–181	7	$C_{16}H_{20}N_2$		80.0	80.4	8.4	8.1
9	*n*-Butylbenzylamine	96	100	55	167–168	2	$C_{18}H_{24}N_2$		80.6	81.1	9.0	9.3
10	N-Methylaniline	20	100	15	158–160	1–2	$C_{14}H_{16}N_2$		79.2	79.2	7.6	7.6
11	Methylamine	24[d,f]	25	0[b]	120	16	$C_8H_{12}N_2$	215–218	45.9	45.6	6.8	6.9
12	Ethylamine	24[g]	25	0[b]	127–128	16	$C_9H_{14}N_2$	154–155	48.4	48.8	7.2	7.7
13	*n*-Butylamine	24	100	<5	140[h]	11	$C_{11}H_{18}N_2$		74.1	74.0	10.2	10.3
14	Cyclohexylamine	24	100	<2	175–182[h]	15	$C_{13}H_{20}N_2$	213–215	56.3	56.1	8.0	7.9
15	Ethanolamine		25	50	188–193	15	$C_9H_{10}N_2O$	148–150[i]	45.2	45.3	6.7	6.6

[a] A mixture of 0.2 mole of 4-vinylpyridine and 0.3 mole of amine was heated for 20 hr. at 100°, with the few exceptions and variations shown in the table. [b] Yields, based on two or more runs, are reproducible within ±3%. Although 0% yields are shown for several amines, these products were obtained in satisfactory yields by various modifications of the reaction conditions as shown in Table II. The physical data and analyses are included here. [c] The melting points are for the dihydrochlorides of the products which were purified by crystallizations from mixtures of methyl or ethyl alcohol and ethyl acetate. Analyses are for the dihydrochlorides where these are listed, otherwise for the bases. [d] The amine was used as a 25% solution in water. [e] Only 0.1 mole of 4-vinylpyridine and 0.15 mole of amine were used in this case. [f] The ratio of amine to 4-vinylpyridine was 4/1. [g] The amine was used as a 33% solution in water. [h] Because of the low yields in this case the b.p. is not very reliable. [i] The ratio of amine to 4-vinylpyridine was 2/1; the reaction time was 6 months. The dihydrochloride melted at 148–150°, then resolidified and remelted at 238–240°.

both when used as a solvent (expt. 7 *vs.* expt. 4) and when added in small amount (expt. 10 *vs.* expt. 4). Absolute ethanol as a solvent was unfavorable to the reaction when compared either to water (expt. 8 *vs.* expt. 7) or to the use of no solvent (expt. 8 *vs.* expt. 4). Cyclohexane was most unfavorable as a solvent (expt. 9). Glacial acetic acid, chosen as a representative proton acid, when used either in catalytic (expt. 11) or molecular equivalent amounts (expt. 12), favored the addition reaction greatly.[7]

The effects of changing reaction conditions on the yields are also shown for several other amines in Table II and in the Experimental Part. The most noteworthy results are those for morpholine (see Experimental), diethylamine (expts. 13–15), ethylbenzylamine (expts. 16–19) and for the primary amines (see Experimental). These results show that with these less reactive amines, several of which gave no product under the standard conditions, yields can be increased greatly by use of: (1) acid catalysis, (2) water as the solvent, and (3) longer reaction times.

Mechanism.[8]—The generally accepted view of the addition of nucleophilic reagents to suitably polarized conjugated ethylenes is easily extended to include the addition of amines to 4-vinylpyridine. Thus initial attack by the unshared electrons of the amine on the electron-deficient terminal carbon of the polarized 4-vinylpyridine followed by the acquisition of a proton by the carbanion adjacent to the pyridine ring yields the protonated product. Formation of a transition state more polar than the reactants should be favored by a more polar medium, and this seems to be the case, for the reaction is accelerated in water (expt. 7) and inhibited in cyclohexane (expt. 9).

Small amounts of water (expt. 10) and more particularly small amounts of acetic acid (expt. 11) speed up the reaction quite out of proportion to any anticipated changes in polarity of the medium in these cases. It thus seems likely that the proton addition step may become more critical, particularly when the initial attack is made less favorable by factors such as steric congestion in the transition state. This second step formally resembles a triad prototropic shift, but available knowledge of such shifts suggests that a direct intramolecular transfer of the proton from nitrogen to carbon is unlikely and that collision with another proton-bearing particle is essential. In the absence of acids stronger than HNR_2, the only such proton source available would be the polar transition intermediate which is doubtless present in very low concentration. This view accounts for the increased efficiency of acetic acid as compared

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(7) Reich and Levine, references 4a and 4b, have used acid catalysis in addition reactions of amines to 2-vinylpyridine. Unfortunately, these authors have not indicated whether their reactions were run under any comparable set of conditions. Thus it is impossible to tell from their results whether the yields reported were ever really comparable for the several amines used or for the few instances in which a particular amine was run both with and without catalyst.

(8) Doering and Weil, ref. 2, pointed out in their paper in theoretical terms why it is reasonable to expect much greater polarization (and concomitant susceptibility to nucleophilic attack), with vinyl groups attached to the 2- or 4-positions of pyridine than with the vinyl group in the 3-position. They have said no more about the mechanism of the additions nor have they mentioned solvent effects or acid catalysis. Reich and Levine, ref. 4a, made a brief statement with regard to the probable mechanism of the addition of amines to 2-vinylpyridine under (1) uncatalyzed, (2) acid-catalyzed and (3) base-catalyzed conditions. While their statement, which deals only with the mode of initial attack, is essentially correct in so far as the uncatalyzed and base catalyzed reactions are concerned, it is not only inadequate but incorrect in relation to the acid-catalyzed process.

TABLE II

EFFECT OF REACTION CONDITIONS ON THE YIELD IN THE ADDITION OF SEVERAL AMINES[a] TO 4-VINYLPYRIDINE

Expt.	Ratio (moles) amine to 4-vinylpyridine	Reaction conditions: Time hr.	Temp., °C.	Other	Product yield, %
			A. Pyrrolidine		
1	1.5/1	20	100		90–95
2	1.5/1	24	25		35–40
3	1.5/1	4	100		50–55
4	1.5/1	2	100		40–43
5	1/1	2	100		37–39
6	3/1	2	100		52–55
7	1.5/1	2	100	25% in water	90–95
8	1.5/1	2	85–90	25% in ethanol	20
9	1.5/1	2	80–85	25% in cyclohexane	<2
10	1.5/1	2	100	with 4 cc. water	60–65
11	1.5/1	2	100	with 1 cc. glacial acetic acid	90–95
12	1/1	2	100	with 1 molar equiv. of glacial acetic acid	85–90
			B. Diethylamine		
13	1.5/1	20	reflux 65–75		0
14	1.5/1	96	reflux 65–75		2–5
15	1.5/1	24	100	25% in water	50
			C. Ethylbenzylamine		
16	1.5/1	20	100		0
17	1.5/1	96	100		60–65
18	1.5/1	26	100	with 1 cc. glacial acetic acid	80–85
19	1.5/1	20	100	with 6 g. of product added at start	17 (net)

[a] Results with several other amines are described in the Experimental Part.

to water in favoring this reaction, as shown by experiments 10–11 and 16–18. The function of an acid catalyst[9] would seem to be, then, to supply, presumably as the ammonium ions $H_2\overset{+}{N}R_2$, a much richer source of protons for the completion of the second step of the addition.

Further work on the reactions of the vinylpyridines with a variety of reactants is under way.

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Experimental

The experimental results are presented in Tables I and II. Two illustrative reaction procedures are described here.

Addition of Pyrrolidine to 4-Vinylpyridine. A. Without Catalyst, 2 Hr. Reaction Time (Expt. 4, Table II).—A mixture of 21 g. (0.2 mole) of 4-vinylpyridine and 21 g. (0.3 mole) of pyrrolidine was heated for 2 hr. on a steam-bath (at 100°). The unreacted amine was removed by evaporation on the steam-bath *in vacuo*. Distillation of the residue *in vacuo* gave 12 g. (60%) of recovered 4-vinylpyridine, b.p. 70–90° at 16 mm., and 14 g. (40%) of 4-(pyrrolidinoethyl)-pyridine, b.p. 151° at 16 mm.

B. In the Presence of Acetic Acid Equivalent to the Pyrrolidine.—Addition of 12 g. (0.2 mole) of glacial acetic acid to a cooled mixture of 21 g. (0.2 mole) of 4-vinylpyridine and 14 g. (0.2 mole) of pyrrolidine gave an exothermal reaction. The reaction mixture was heated for 2 hr. on a steam-bath (at 100°). At the end of the heating period the reaction mixture was cooled rapidly, water and excess alkali (to *p*H > 11) were added and the product was extracted with ether. After short drying over anhydrous potassium carbonate the ether was removed and the product distilled *in vacuo*. The yield was 32 g. (90%) of product, b.p. 151–152° at 16 mm.

The results showing the effect of the variation of reaction conditions on the yields in the additions to 4-vinylpyridine, shown for several amines in Table II, are summarized for the remaining amines below.

Morpholine.—When the amine to 4-vinylpyridine ratio was 1.5/1 with heating at 100° for 4 hr., the yield of product was 18%. Under the same conditions in the presence of 4 cc. of water, the yield was 45% and in the presence of 1 cc. of glacial acetic acid, it was 95%.

Methylamine.—With an amine to 4-vinylpyridine ratio of 2/1 no yield of product was obtained after 24 hr. at 25°; after 96 hr. at 40°, the yield was 55%. This amine was used as a 25% solution in water.

Ethylamine.—Under conditions similar to those for methylamine this amine gave 0% of product after 24 hr. at 25° and 50% yield after 96 hr. at 40°. The amine was used as a 33% solution in water.

Cyclohexylamine.—With an amine to 4-vinylpyridine ratio of 1.5/1 this amine gave < 2% of product after 24 hr. at 100° or after 2 months at 25°. After 4 months at 25° about 5–10% of product was isolated.

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(9) A more obvious way for acid catalysis to operate would be through protonation of the nitrogen of 4-vinylpyridine. This should facilitate the addition of amines both by accentuating the polarization of the vinyl group and thus favoring the initial attack and by offering a more favorable condition for resonance in the transition state. In spite of these attractive possibilities, it seems unlikely that this type of catalysis is involved when small amounts of catalyst are used. For this to be possible the feebly basic 4-vinylpyridine would be competing for protons with an excess of the 10^7 times more basic amine (pyrrolidine) when the molar ratio of pyrrolidine to acetic acid is about 20/1.