[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Condensation of Aromatic Aldehydes with 2-Ethylpyridine and with 4-Ethylpyridine[1]

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A series of aromatic aldehydes has been condensed with 2-ethylpyridine and with 4-ethylpyridine in the presence of refluxing acetic anhydride as the condensing agent. The aldehydes were selected to represent a broad spectrum of carbonyl reactivity from *p*-nitrobenzaldehyde with a high carbonyl reactivity, through benzaldehyde, to *p*-dimethylaminobenzaldehyde with a very low order of inherent carbonyl reactivity. While 2-ethylpyridine gave good yields of condensation products with aldehydes of high carbonyl reactivity and with benzaldehyde, only traces of product or no reaction resulted with aldehydes of low reactivity such as *p*-methoxy- and *p*-dimethylaminobenzaldehyde. 4-Ethylpyridine gave very satisfactory yields with all of the aldehydes used, although the yields still paralleled the reactivity of the carbonyl groups of the aromatic aldehydes: $p\text{-NO}_2 > m\text{-NO}_2 > \text{H} > p\text{-CH}_3\text{O} > p\text{-(CH}_3)_2\text{N}$.

It has long been known that 2-methylpyridine[2] and 4-methylpyridine[3] are reactive for condensation with aromatic aldehydes. Kaufmann and Vallette[4] have shown that the quaternary salts of the 2-methylpyridines and quinolines react more readily and under milder conditions in condensation reactions than do the parent tertiary amines.

Analogous condensations between 2-ethylpyridine or 4-ethylpyridine, or their methiodides, and aromatic aldehydes have not been reported.

Earlier work from these laboratories reported the ready condensation of 2-methylpyridine methiodide[5] and 4-methylpyridine methiodide[6] with a series of aromatic aldehydes. Under similar reaction conditions no condensation occurred between 2-ethylpyridine methiodide[7] and certain aromatic aldehydes. The methiodide was used in this earlier work[7] because of the known[4-6] greater reactivity of quaternary salts over their parent tertiary amines. *p*-Dimethylaminobenzaldehyde is, and would be expected to be, an aldehyde of very low carbonyl reactivity.[8] Nevertheless, in addition to benzaldehyde this was chosen as the principal carbonyl reactant in the attempted reaction with 2-ethylpyridine methiodide[7] because of the outstandingly superior yields obtained from it with 2-methyl[5] and 4-methylpyridine methiodide.[6] Failure in these attempts to condense 2-ethylpyridine methiodide with aromatic aldehydes was attributed principally to steric hindrance to the reaction associated with the extra methyl group now located on the reactive methylene position.

Steric factors, if responsible for the lack of condensation with 2-ethylpyridine methiodide, could interfere with either the initial attack of the reactive methylene component on the carbonyl carbon and/or with the resonance possibilities in the final products. Steric hindrance to the initial attack could be lessened by using 2-ethylpyridine in place of its methiodide, thus eliminating the *o*-methyl present on the ring nitrogen of the methiodide. Also by using 2-ethylpyridine in place of its quaternary salt, resonance in the product would be expected to be a much less decisive factor in the course of the reaction, and thus steric interference with such resonance would be minimized.

Although use of 2-ethylpyridine in place of its methiodide should make the possibility for condensation more favorable by cutting down on steric hindrance to the reaction, certain other fundamental differences in reactivity inherently accompany this change. 2-Ethylpyridine should be less reactive than its salt as a reactive methylene compound and thus should require different and more drastic condensation conditions. In addition this tertiary amine should have an essentially different type of reactivity. The methylpyridine methiodides represent a type of reactive methylene for which best yields[5,6] were obtained with *p*-dimethylaminobenzaldehyde, an aldehyde of low carbonyl reactivity,[8] presumably because of favorable resonance possible in the product. Since the tertiary amines lack the same resonance possibilities in the products they are not only less reactive but belong to that type of reagent which should give best yields with aldehydes of high carbonyl reactivity.[8]

Having considered all these factors influencing reactivity and having predicted the pattern of results to be expected, 2-ethylpyridine and 4-ethylpyridine were condensed with a series of aromatic aldehydes of varied carbonyl reactivity. The reactants were refluxed in acetic anhydride solution in a modification of the procedure used by Shaw and Wagstaff[9] in some similar condensations with 2-methylpyridine. These authors[9] found their procedure to be superior to that of the earlier workers[2,3] who heated the reactants for long intervals at high temperatures in the presence of zinc chloride. A standard set of conditions was used in the present work to allow a comparison of the relative reactivities of both the aldehydes and of the two ethylpyridines.

2-Ethylpyridine condensed readily to give a high yield of product with *p*-nitrobenzaldehyde. Lesser but still very good yields were obtained with *m*-nitrobenzaldehyde and benzaldehyde. Anisaldehyde and *p*-dimethylaminobenzaldehyde gave lit-

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[1] This paper is Part IV of the series: Correlation of structure and reactivity of aromatic aldehydes.

[2] (a) E. Jacobsen and C. L. Reimer, *Ber.*, **16**, 2602 (1883); (b) H. Baurath, *ibid.*, **20**, 2719 (1887); **21**, 818 (1888); (c) K. Feist, *ibid.*, **34**, 464 (1901); (d) K. Feist, *Arch. Pharm.*, **240**, 244 (1902); (e) A. Ladenburg, *Ber.*, **36**, 118 (1903); (f) A. Ladenburg and E. Kroener, *ibid.*, **36**, 119 (1903), and many others.

[3] (a) C. Friedländer, *ibid.*, **38**, 159 (1905); (b) K. Friedländer, *ibid.*, **38**, 2838 (1905); (c) R. Baumert, *ibid.*, **39**, 2971 (1906); (d) M. Löwensohn, *ibid.*, **40**, 4860 (1907), and many others.

[4] A. Kaufmann and L. G. Vallette, *ibid.*, **45**, 1736 (1912).

[5] A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).

[6] A. P. Phillips, *ibid.*, **14**, 302 (1949).

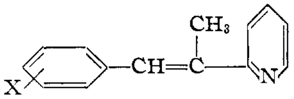
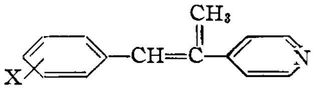
[7] A. P. Phillips, *ibid.*, **13**, 622 (1948).

[8] A. P. Phillips and J. G. Murphy, *ibid.*, **16**, 954 (1951).

[9] B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933).

TABLE I

CONDENSATIONS OF 2-ETHYLPYRIDINE AND 4-ETHYLPYRIDINE WITH AROMATIC ALDEHYDES[a]

X	Yield, %[b]	M.p. or b.p. (mm.) °C.	Crystn. solvent[c]	Recovered reactants, %[d]		Formula	Carbon, %		Hydrogen, %	
				Aldehyde	Ethylpyridine		Calcd.	Found	Calcd.	Found
		A. 2-Ethylpyridine								
4-NO_2	90	95–96	M			$C_{14}H_{12}N_2O_2$	70.0	69.7	5.0	5.0
3-NO_2	70	195–196	M.Ea			$C_{14}H_{12}N_2O_2 \cdot HCl$	60.7	61.0	4.7	4.7
H	70	144–145 (1)		20	20	$C_{14}H_{13}N$	86.1	86.1	6.7	6.5
4-CH_3O	<5	195–200 (10)		95	95	$C_{15}H_{15}NO$[e]	80.0	79.8	6.7	6.5
4-$(CH_3)_2N$	0			98	95	$C_{16}H_{18}N_2$	80.7		7.6	
		B. 4-Ethylpyridine								
4-NO_2	90	110–111	B.H.			$C_{14}H_{12}N_2O_2$	70.0	70.1	5.0	5.0
3-NO_2	80	114–115	A			$C_{14}H_{12}N_2O_2$	70.0	70.1	5.0	5.0
H	80	72–73	H	10	10	$C_{14}H_{13}N$	86.1	86.0	6.7	6.7
4-CH_3O	65	83–84	H	30	20	$C_{15}H_{15}NO$	80.0	80.0	6.7	6.5
4-$(CH_3)_2N$	60	164–165	M	30	30	$C_{16}H_{18}N_2$	80.7	80.4	7.6	7.6

[a] The standard reaction conditions are those described in the Experimental part. [b] Yields given are of purified product and are accurate within ±3%. [c] A = ethanol; B = benzene; Ea = ethyl acetate; H = hexane; M = methanol. [d] The unreacted aldehydes and ethylpyridine were distilled or crystallized and identified by melting point or boiling point. The recovered aldehydes were further converted into their known phenylhydrazones which were identified by melting point. [e] Gave a picrate, crystallized from methanol, m.p. 140–141°. *Anal.* Calcd. for $C_{21}H_{18}N_4O_8$: C, 55.5; H, 4.0. Found: C, 55.5; H, 4.0.

tle or no condensation under the same reaction conditions. Results are summarized in Table IA.

4-Ethylpyridine gave good yields with all of the aldehydes used. As predicted highest yields resulted from *p*-nitrobenzaldehyde (90%) and lowest from *p*-dimethylaminobenzaldehyde (60%). In this series the less reactive aldehydes, anisaldehyde and *p*-dimethylaminobenzaldehyde, again gave the poorest yields, but these were still very substantial, being 65 and 60%, respectively. The results for 4-ethylpyridine are shown in Table IB.

With aromatic aldehydes of low carbonyl reactivity 4-ethylpyridine gave very significantly greater yields than did 2-ethylpyridine. This difference in reactivity was not as apparent with the aldehydes of higher inherent carbonyl reactivity.

This greater reactivity of 4-ethylpyridine compared with 2-ethylpyridine is just the reverse of the order of activities reported for the 2-methyl and 4-methyl compounds of the pyridine[10] and quinoline[11] series. The earlier work on this point has not given consideration to the many factors which may influence the reactivity of both the carbonyl component and the reactive methylene.

Experimental

A typical procedure is described below. All of the condensations were run under these standard conditions and in duplicate.

A mixture of 0.1 mole of 2(or 4)-ethylpyridine, 0.1 mole of the aromatic aldehyde and 0.12 mole of acetic anhydride was refluxed for five hours in a metal-bath at 190 ± 2°. At the end of the reflux period the mixture was distilled quickly to remove the low-boiling fractions. In cases where significant condensation had occurred the first fraction to come over boiled at 118–120° (acetic acid) but when no condensation had taken place the first fraction came over at 138–140° (acetic anhydride). After all acetic acid and/or anhydride and most of any unreacted ethylpyridine had been removed, the residue was poured into 100 cc. of cold water. This mixture was made strongly basic (to *p*H 11) with dilute alkali. When the products were solids they crystallized; they were filtered off and purified by recrystallization. When the products were liquids they were taken up in ether, dried over anhydrous potassium carbonate, and were then purified by distillation *in vacuo*. In these latter cases, as well as when the products were solids, unreacted liquid aldehydes were recovered and separated by distillation *in vacuo*.

The pertinent experimental details for all the reactions and products are included in Table IA and B.

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(10) F. W. Bergstrom, *Chem. Revs.*, **35**, 77 (1944), page 118.

(11) F. W. Bergstrom, *ibid.*, **35**, 77 (1944), page 182.