[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

THE MECHANISM OF THE CONDENSATION OF PICOLINE METHIODIDES WITH AROMATIC ALDEHYDES: A NEW TYPE OF STERIC HINDRANCE

ARTHUR P. PHILLIPS

Received February 9, 1948

In a recent publication (1) the author presented a correlation between the color, yield, and resonance structure in the products of reaction of aromatic aldehydes with α-picoline methiodide. In discussing the variations of yields with the various aldehydes use was made of an interesting mechanism suggested by Mills (2). His mechanism was used at that time because: (a) Mills had *proved* beyond question that the reaction, under certain conditions, *could* go in the way he indicated; (b) the results could be explained satisfactorily in terms of it; (c) and the author then had no experimental evidence to indicate any lack in that older mechanism.

Now, however, a closer examination of the subject has led the author to the conclusion that the true mechanism of the reaction differs slightly but fundamentally from that postulated by Mills. Although Mills has proved that the steps he indicated would all work, the conditions in various steps, as isolated by him, were not those prevailing throughout the entire reaction under normal conditions. Furthermore, in at least one of his steps, it seems that several intermediate stages may have been ignored which, according to the more recent concepts of condensation reactions, should be considered. Thus we suggest that although the reaction *can* proceed as Mills indicated under his *artificial* conditions, under the *usual* conditions it follows a somewhat different and simpler course.

A brief outline of Mills' mechanism is shown in Fig. 1 [for a more extensive description see reference (1) or (2)].

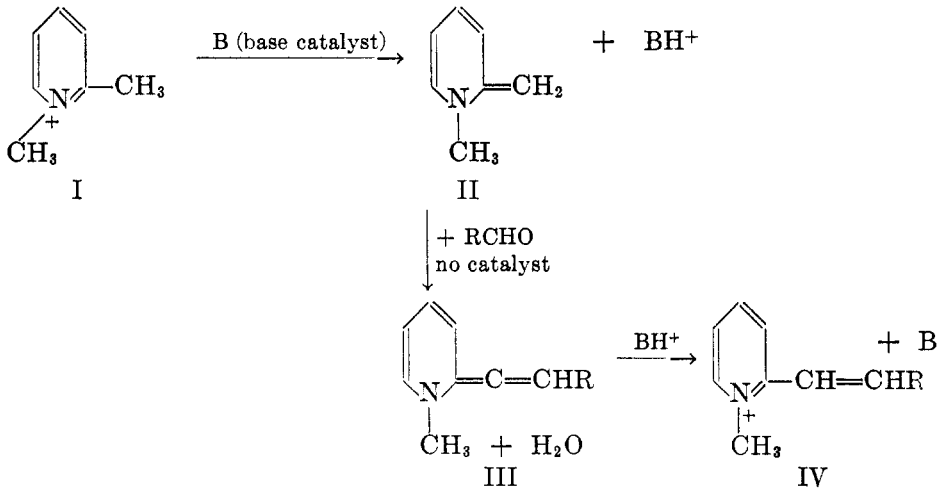


FIG. 1

It is suggested that even under Mills' conditions, where II + RCHO react to give III in the absence of a catalyst, it is necessary to insert several intermediate steps. The Fig. 2 sequence is offered as a reasonable one.

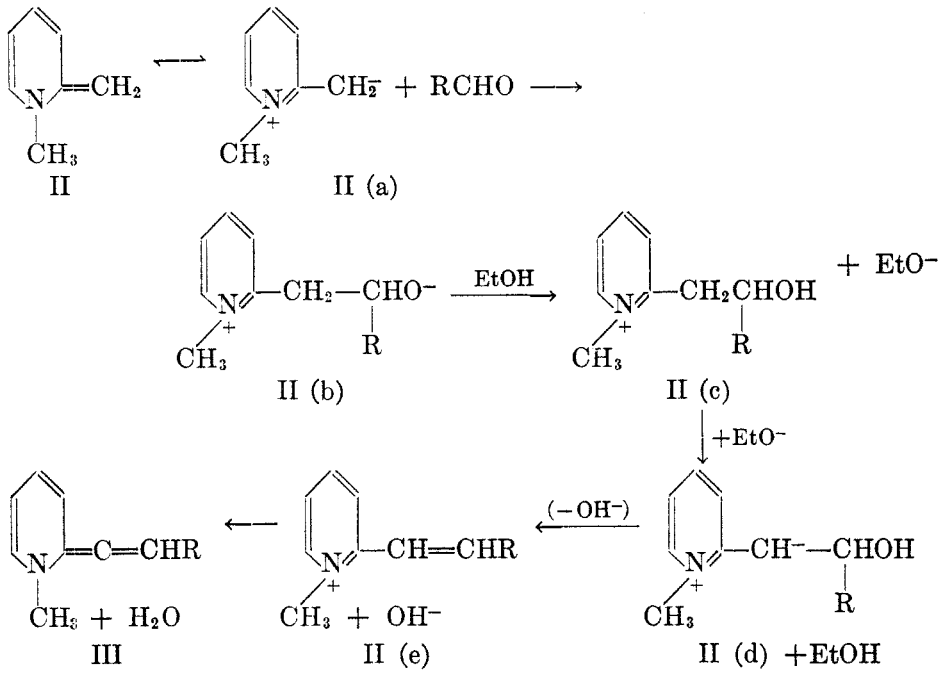


FIG. 2

Although it may not be possible to prove the nature of the mobile intermediates, some such lengthy and laborious process (Fig. 2) probably occurs under Mills' artificial conditions. Here in the absence of a basic catalyst, but in alcohol solution, it has been suggested that perhaps the alcohol may serve as a proton donor and a base catalyst in the transitory steps.

In the normal course of the condensation reaction, however, when piperidine catalyst remains in the reaction mixture, the simpler and more general sequence is suggested as shown in Fig. 3.

$$\text{II(b)} \xrightarrow{+BH^+} \text{II(c)} + B \xrightarrow{+B} \text{II(d)} + BH^+ \xrightarrow[(-OH^-)]{+BH^+} \text{IV} + B + H_2O$$

FIG. 3

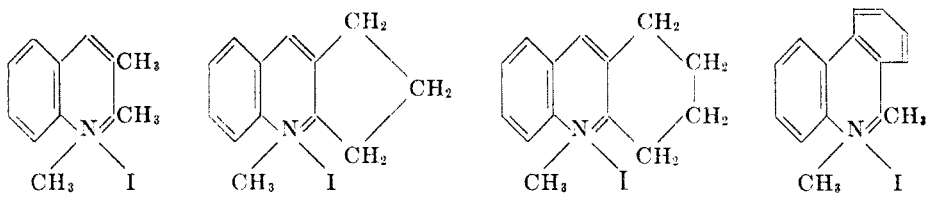
Here II (b), formed by the nucleophilic attack of the anionic fragment II (a) on the carbon of the aldehyde carbonyl, being a stronger base than piperidine B, abstracts H^+ from the cationic piperidinium ion BH^+ to produce II (c) and B. In the next step piperidine removes a proton from the α-methylene giving II (d) plus BH^+. The final and decisive step involves the loss of OH^- from II (d) giving the product IV, piperidine, and water.

This process is simply the application of the modern general theory of base catalyzed carbonyl condensations to the particular reaction under consideration.

An innovation has been made, however. Usually in discussions of aldol-like condensations a careful description of the probable mode of formation of the aldol is given, followed by a simple statement that the aldol readily loses water to form the unsaturated product. Although pains are taken to elucidate the mechanism of formation of the aldol, the matter is left hanging there with no follow-up mechanism of the dehydration process, and no indication as to how or why dehydration occurs. In Fig. 3 a reasonable sequence is shown all the way through production of the aldol intermediate and its dehydration to the final unsaturated product.

The experimental basis for the above and for certain further conclusions will now be outlined. If Mills' mechanism were correct it should follow that the methiodides of higher α-alkylpyridines or quinolines should be incapable of condensation under the usual conditions. Thus α-ethylpyridine methiodide and homologous compounds should not react. We have now made α-ethylpyridine methiodide and α-phenethylpyridine methiodide and neither of these, under the usual reaction conditions, gave even a trace of a condensation product with *p*-dimethylaminobenzaldehyde, and both aldehyde and alkylpyridine methiodide components were recovered unchanged from the reaction mixture in essentially quantitative amounts. *p*-Dimethylaminobenzaldehyde, which was used as the aldehyde component as it gave maximum yields with α- and γ-picoline methiodides, was recovered from the reaction mixture as its phenylhydrazone.

These results in themselves would seem to confirm Mills' ideas, but they do not stand alone. Petrow (3) working with somewhat analogous types of compounds in the quinoline and acridine series has reported some observations which seem highly significant in this connection. He has found that under the usual



V VI VII VIII

conditions (alcohol solution, piperidine catalyst), the compounds V, VI, VII, and VIII reacted with *p*-dimethylaminobenzaldehyde as follows: V and VI gave in the vicinity of 70% yields of the stilbazole-like products (analogous to the product obtained from α-picoline methiodide) while VII and VIII gave absolutely no condensation under those conditions, even when the severity of the reaction conditions was increased by the use of higher-boiling alcohols as solvent and longer reflux periods or by fusing the reactants and catalyst at elevated temperatures. [Using a different set of conditions suggested earlier by Shaw and Wagstaff (4) for condensation with the tertiary bases, and applied by him to the quaternary salts, Petrow obtained nearly quantitative yields of the corresponding stilbazole-like products from each of the four compounds, V, VI, VII, and VIII. His modification of the reaction involved heating the reactants for five

to ten minutes in refluxing acetic anhydride.] However, most important for our purpose are his results under the usual condensation conditions. (Results obtained under the other conditions indicate that by the proper application of force the reactions can be made to go.)

Compound VI did react normally to give a considerable yield (though substantially less than the simple α-methyl derivatives gave) of the stilbazole-like product, and there seems to be no reason obvious to this author for considering the mechanism here to be any different from that prevalent with the methyl compounds, since the reaction conditions were similar. The fact that *one* higher homolog has been found which does react normally under the usual conditions, combined with the fact that the mechanism now being presented offers a simpler and more reasonable course of the reaction according to recent views, would seem to indicate that for the normal reaction, Mills' mechanism probably should now be modified in favor of the present one.

Other things remain to be clarified, notably the failure of reaction with compounds VII, VIII and with α-ethyl- and α-phenethyl-pyridine methiodides. In seeking an explanation for the unexpected non-reactivity of these compounds it seemed pertinent to review the principal factors known to influence reactivities of organic molecules: (a) electronic; (b) resonance; and (c) steric factors. It is fully appreciated that here, as in many other types of reactions, probably no one factor is solely responsible for variations in reactivity. If we assume a single mechanism as proposed here, under the normal reaction conditions, and if we then arrange representatives of varying structure of one reactant and compare their reactivities toward a common second reactant it rapidly becomes apparent what is probably the greatest source of variation in this series. Thus with *p*-dimethylaminobenzaldehyde and two to four hours refluxing in alcohol solution with piperidine catalyst the following methiodides gave the corresponding yields of condensation products: α-methylpyridine methiodide, 98%; compound VI, about 70%; compound VII, 0%; α-ethylpyridine methiodide, 0%. Now in going from α-methylpyridine methiodide to α-ethylpyridine methiodide there should be only slight electronic differences, in a direction, it is true, tending to decrease reactivity, for the electron releasing extra methyl would make the hydrogens on the α-methylene less susceptible to dissociation as protons, but differing so little between α-ethylpyridine methiodide, VI, and VII as to be incapable of explaining reaction in the case of VI. Similarly, it is believed that although resonance factors in the pyridine molecule may be varied minutely by the alterations listed in side chain structure, such changes would be too small to be responsible for such tremendous variations in reactivity, and furthermore again would not account for the positive results with compound VI. In this instance we suggest that the third factor, the steric one, is predominant in controlling the reactivity and it is possible to adduce numerous analogies in support of our belief.

In the case under discussion we have compared the reactivity of a reactive methylene compound with a single carbonyl component (*p*-dimethylaminobenzaldehyde) while changing systematically the structural environment about the

methylene. We suggest the variation in environment is principally steric and for the first analogy suggest a comparison between the reactivities of a series of aromatic carbonyl compounds, varied structurally so as to be analogous to the series of reactive methylenes, with a common second reactant. In view of the N-methyl group present in the series of α-alkylpyridine methiodides the carbonyl series would best be represented by 2-methylbenzaldehyde (as analogous to α-methylpyridine methiodide), by 2-methylacetophenone (as analogous to α-ethylpyridine methiodide), by 7-methyl-1-hydrindone (as analogous to VI), and by 8-methyl-1-tetralone (as analogous to VII). The excellent paper by Kadesch (5) presents extremely interesting results which fall into line with our analogy (for the last three carbonyl components) though it must be remembered that Kadesch compared the reactivities of the carbonyl compounds with the relatively small reactants, methylmagnesium iodide and hydroxylamine. Thus his results are only qualitatively in agreement with ours, for in our case the constant reactant, the aldehyde, was of considerable steric size in its own right. For a closer analogy we should consider some reaction of the above listed series of carbonyl components with a common second reactant, such as a reactive methylene, approximating in steric size the aromatic aldehyde of the converse series. In obtaining data from the literature it has been found that results are available which meet our requirements of showing up a wider divergence of reactivities in the carbonyl series, even in the absence of the methyl group, ortho, on the benzene ring, to the carbonyl substituent.

A satisfactory though not ideally constituted common reactant for comparing the reactivities of the series of carbonyl derivatives is cyanoacetic acid. Shemyakin and Trakhtenberg (6) reported their results of condensation of cyanoacetic acid with a series of aliphatic, alicyclic, and aromatic ketones. They mixed the ketone with two to three moles of the acid in the presence of piperidine and heated for two hours at 100–115°. With those ketones which reacted, the yields were between 70–90% and the products were the unsaturated nitriles resulting presumably by decarboxylation of the intermediate unsaturated cyanoacetic acids. Pertinent to our case, α-hydrindone gave condensation with yields in the range stated, while acetophenone gave no condensation. Although benzaldehyde was not included in their study, it is well known that it gives excellent yields of condensation products with the reactive methylene involved, under a variety of similar, mild conditions (7, 8).

Another common reactant, which in its steric size more closely resembles the common reactant aldehyde of the other series, is aniline. As is well known, benzaldehyde reacts rapidly and extensively with aniline under mild conditions (just mixing at room temperature) to produce the azomethine, benzalaniline, in yields of about 85% within fifteen minutes (9). Although the anil of acetophenone can be made, the conditions for its formation are much more strenuous and yields are much lower. Thus when a mixture of acetophenone with nearly two moles of aniline and a catalytic amount of aniline-zinc chloride double salt was heated in an oil-bath at 160–180° for one-half to one hour, yields of the anil in favorable cases were about 55% (10). Under the conditions for rapid forma-

tion of benzalaniline, no acetophenone anil is formed. No information has been discovered in the literature concerning the formation of anils from α-hydrindone or α-tetralone, though it would be reasonable to suppose they could be formed in yields and with degrees of ease intermediate between the anils of benzaldehyde and acetophenone.

Further confirmatory evidence has been obtained in another analogous case by comparing the reactivities of 2,4-dinitrotoluene and 2,4-dinitroethylbenzene toward condensation with *p*-dimethylaminobenzaldehyde in the presence of piperidine catalyst. With these derivatives, activation of the side-chain methylene appears to be closely similar in kind and degree to that present in the alkylpyridine methiodides. Results reported in the literature indicate that the same correlation between yields, color, and the resonance possibilities of the products may exist in this type of compound as in α-picoline methiodide. Thus Dippy, Hogarth, Watson, and Williams (11) heated equimolar amounts of *p*-dimethylaminobenzaldehyde and 2,4-dinitrotoluene with piperidine as catalyst for three to four hours at 100°, and obtained a 98% yield of the intensely colored stilbene (almost black). Using benzaldehyde under slightly different conditions, employing piperidine catalyst and longer reaction time, Bishop and Brady (12) obtained only 60% of the bright yellow stilbene. We have found that 2,4-dinitroethylbenzene does not condense with *p*-dimethylaminobenzaldehyde under conditions giving nearly quantitative yields with the methyl homolog. We were able to recover nearly completely the unreacted starting compounds, the aldehyde as its phenylhydrazone.

In the dinitroalkylbenzenes *no* classical valence bond intermediates, of the type written and isolated by Mills in the heterocyclic methyl methiodides, can be written. Since such discrete classical valence bond intermediates cannot be written for these compounds we cannot here explain the reactivity or lack of reactivity in terms of the attainability or incapability of attaining structures analogous to II or III. That these two analogous types of reaction are so closely alike in kind, degree, reaction conditions, catalyst, and effect of alkyl group size on reactivity, suggests the two react by the same mechanism. This would strongly support our mechanism and our steric explanation of the lack of reaction in the case of the higher alkyl derivatives.

In accumulating substantiating evidence for the predominantly steric nature of the non-reactivity of the alkyl (higher than methyl) pyridine methiodides and dinitrobenzenes with aromatic aldehydes, another line of approach is obvious. Since in going from a methyl side chain (100% yield) to the ethyl side chain (0% yield) we have already reached the limits of variation of the reactive methylene component, it is conceivable that by decreasing the steric size of the carbonyl component we might obtain condensation in cases where aromatic aldehydes give none. Formaldehyde is probably the most reactive carbonyl compound in general and is unquestionably the smallest.

Making the reasonable assumption that the *mechanism* of carbonyl reaction would not be altered in going over from aromatic aldehydes to formaldehyde it would be expected that in this shift the principal differences in the direction of

increased reactivity could properly be attributed to the decrease in steric resistance.

Considerable pertinent evidence is available in the literature. Although no instance has been found of the reaction of formaldehyde with 2,4-dinitroethylbenzene, 2,4-dinitrotoluene reacts with formaldehyde and piperidine to give as the principal product, and in good yield, the 1,3-dipiperidino-2-(2′,4′-dinitrophenyl)propane (13), presumably obtained as in Fig. 4.

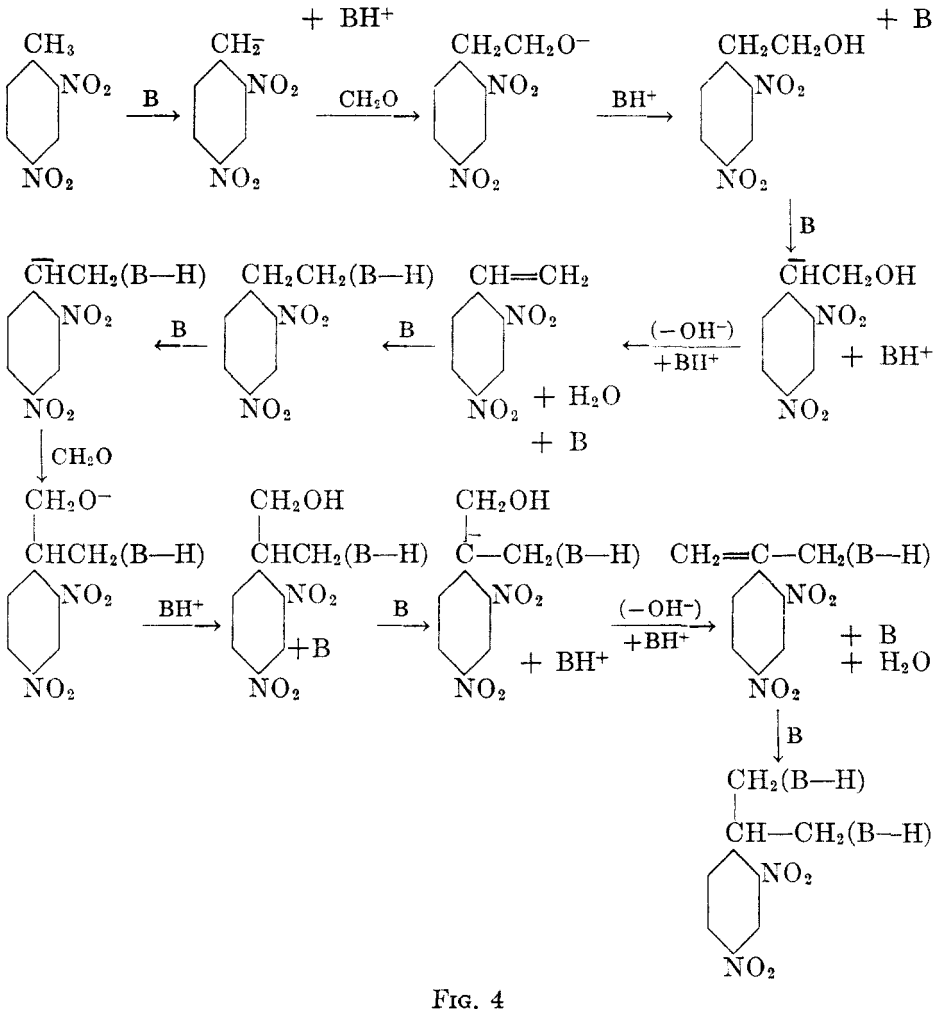
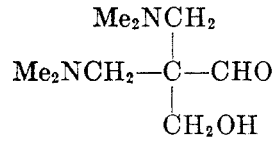


FIG. 4

From the sequence of reactions depicted in Fig. 4 it can be seen that although the starting reactive methylene is originally a methyl group, after the reaction has proceeded half way the reactive methylene would then be part of a substituted ethyl group, but reaction continues with the introduction of a second aldehyde residue. Presumably because of the lesser steric requirements of the formaldehyde, the first formed ethyl derivative reacts with a second molecule.

Small though the steric requirements of formaldehyde are, after the introduction of two aldehyde groups the composite result of the various effects, electronic and probably mainly steric, is to prevent the introduction of a third aldehyde residue. By the above scheme, reaction with a third molecule of formaldehyde could proceed only to the hydroxymethyl stage anyway.

The illustration used above is an example of the Mannich reaction, for which the mechanism is not known with certainty. Bodendorf and Koralewski (14) have obtained evidence indicating that with dimethylamine and formaldehyde and various reactive methylenes, dimethylaminomethanol is not an intermediate step, and they have also shown that with antipyrine the hydroxymethylantipyrine does not constitute an intermediate, although the methylols of acetone and cyclohexanone do react. We now suggest that in the Mannich reaction it may be impossible to put forward a single mechanism to explain all cases. In line with our present discussion we believe that wherever possible the Mannich reaction mechanism will conform to the above scheme, mediated by a hydroxymethyl reactive methylene compound, which under the reaction conditions, and in the presence of a hydrogen on the carbon β to the hydroxyl and α to the activating group, will dehydrate to the vinyl derivative which then adds the amine to form the Mannich base product. It is well known that a vinyl group α to an unsaturated activating group (CN, COOR, etc.) reacts rapidly and nearly quantitatively with amines. In support of this belief is the work of Mannich and coworkers (15) who with acetaldehyde, for example, have shown that the only product isolated is the following:



Formation of this product agrees with our postulation that the third hydrogen on an activated methyl may react with formaldehyde to form the methylol, but should be incapable of going on to the aminomethyl stage. The fact that such compounds as antipyrine and phenols give good yields of Mannich bases suggest that for these types of reactive "methylenes" an entirely different mechanism must exist.

Our proposed mechanism (for reaction between aromatic aldehydes and picoline methiodides) as contrasted with Mills' mechanism, involves no difference in the type of reaction but only in the degree of reactivity between the α-picoline methiodides and the tertiary bases. On this basis certain analogies with teriary base reactions should be acceptable as substantiating evidence, both for our mechanism and for the steric nature of lack of reactivity of the higher alkyl derivatives.

On the first of these points the work of Kaplan and Lindwall (16) and other earlier workers (17, 18) has shown that 2-methyl-pyridines and -quinolines react with aromatic aldehydes, either in the presence or absence of a basic catalyst such as piperidine to give aldol-like intermediates, which are stable enough to

be isolated, but which can be dehydrated readily when treated with various dehydrating reagents. We consider this further evidence for our mechanism, for here the aldol intermediates (analogous to IIc) are stable enough for isolation, as might be expected, whereas the greater activation of the α-methylenic hydrogen in the methiodides and the greater resonance stabilization in the dehydration products with the methiodides makes the aldol an unstable intermediate with the latter.

With regard to the second of these points, the steric one, although α-picoline is much less reactive for condensation that its methiodide, on heating at 130–140° for several hours with formaldehyde (the picoline itself probably serving as catalyst here) moderate yields of mono- and di-hydroxymethyl-α-picolines can be obtained, yields of the two depending somewhat on the proportion of formaldehyde used, the temperature, and duration of heating. Little if any trihydroxymethyl compound is produced, though moderate yields of the latter can be obtained by long heating of excess formaldehyde with the mono- or di-hydroxymethyl compounds (19, 20, 21, 22).

With α-ethylpyridine, and depending on temperature and length of heating, formaldehyde yields mainly either the mono- or di-hydroxymethyl compound (22, 23).

These facts indicate that with a smaller carbonyl component reaction with the higher alkylpyridine homologs is no longer excluded.

Under similar reaction conditions γ-methylpyridine appears to be more reactive and gives as the principal product with formaldehyde the trihydroxymethyl compound even when only one mole of formaldehyde is used. With 3-ethyl-4-methylpyridine only the dihydroxymethyl derivative is obtained, probably a consequence of the steric hindrance of the adjacent alkyl (24, 25).

In the reaction of α-picoline methiodide with formaldehyde no discrete products have been isolated, as apparently polymeric resinous products were formed. Using formaldehyde with piperidine under a variety of conditions it has been impossible to isolate a pure crystalline substance, although there was abundant evidence of rapid reaction.

Difficulties involved here are indicated by the fact that 2-β-hydroxyethylpyridine reacts violently with methyl iodide to give mixtures of the methiodides of 2-β-hydroxyethylpyridine and 2-vinylpyridine, neither of which was characterized as such, but only through conversion first to chlorides, which were then isolated as platinichlorides (19).

Further work is in progress exploring the role of steric, resonance, and electronic effects in the reactivities of active methylenes of the pyridine series. An attempt will be made to show whether the difference in reactivity of α- and γ-picolines, as shown by the results with formaldehyde, is associated principally with resonance or steric factors.

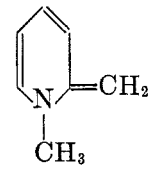
Although we have here postulated a new mechanism for the condensation of aromatic aldehydes with α-picoline methiodide, and with compounds of similar type, this does not in any way negate the correlations between structure and yields stated earlier (1). The facts basic to that correlation remain, and can be

explained equally well in terms of the new hypothesis. All that is necessary is to reword the explanation to fit the new mechanism.

We shall consider the entire sequence of steps

$$\text{I} \rightleftharpoons \text{II (a)} \rightleftharpoons \text{II (b)} \rightleftharpoons \text{II (c)} \rightleftharpoons \text{II (d)} \rightleftharpoons \text{IV}$$

comprising our mechanism as reversible. That the over-all reaction is reversible has been shown by the work of Koenigs, Köhler, and Blindow (26) who, on treating α-stilbazole methiodide with concentrated aqueous alkali, found that benzaldehyde was liberated (isolated and identified as its phenylhydrazone) along with α-pyridonemethide, (which was isolated and identified as its reaction product with carbon disulfide or phenylisothiocyanate).



We still consider that the driving force of the reaction will depend on the increase in resonance stabilization gained in IV over the various starting compounds or intermediates. Thus, considering that the initial steps do occur, formation of II (a) and II (b), as they obviously do with a wide variety of aromatic aldehydes (and there is undoubtedly considerable variation in the ease of reaction at this stage depending on the resonance and electronic structures of the various aldehydes), then regardless of the relative ease of formation of the first mobile intermediate and its successors, the determining factor as to the extent and rate of reaction will lie in the decisive final step in which important resonance within the complete molecule if first possible. The magnitude of the increase in resonance in the final product as compared with that in its precursors determines the extent of the reaction and stability of the product. In the earlier discussion this was expressed in terms of the relative base strengths of the allene intermediate, for attracting protons from BH^+. According to our new mechanism we would express it in terms of the ease of release of OH^- from the anionic intermediate II (d). This is simply a different form of base strength expressed for a different final intermediate.

The importance of the resonance as a determining factor in the final stage is emphasized by the fact that the yields were best with those aldehydes in which resonance would be most favorable in the products. But in the earlier stages of the reaction sequence, the original nucleophilic attack on the aldehyde carbonyl carbon, the aldehydes giving poorer yields (those substituted with electronegative substituents) would be expected to react most rapidly and completely.

EXPERIMENTAL

α-Ethylpyridine methiodide. α-Ethylpyridine was prepared by the catalytic hydrogenation of α-vinylpyridine using Adams' catalyst in methanolic hydrogen chloride. After two distillations 11 g. of the base, b.p. 146–150°, was treated with 11 cc. of methyl iodide and the mixture was refluxed for four hours. Precipitation of the product with ether gave 25 g.

(100%) of the methiodide, which after recrystallization from ethanol-ether had the m.p. 95–96°.

Anal. Calc'd for $C_8H_{12}IN$: I, 50.98. Found: I, 51.06.

The white crystalline material on standing, even in a closed, dark bottle, rapidly darkened in color and then could not be repurified to obtain any considerable amount of pure colorless substance. Even the pure material could be recrystallized only with some difficulty and usually with considerable losses, especially if manipulations were extended.

α-Phenethylpyridine methiodide. α-Phenethylpyridine was similarly prepared by the hydrogenation of α-stilbazole using Adams' catalyst in methanolic hydrogen chloride. These reductions were performed at 1–3 atm. overpressure of hydrogen at room temperature. The base stilbazoles do not reduce under these conditions in alcohol solution. In the presence of more than a molar equivalent of hydrogen chloride reduction proceeds slowly and is restricted to the side chain double bond or can be stopped at that stage. This is in contrast to the α-stilbazole methiodides which are reduced rapidly in alcohol solution, under the same conditions, to the corresponding phenethylpiperidines. α-Phenethylpyridine, 9 g., plus 6 cc. of methyl iodide in 20 cc. of methanol was refluxed for four hours. On cooling, a pale yellow crystalline product was obtained; yield 12.5 g., (80%). After recrystallization from ethanol the product melted at 190–191°.

Anal. Calc'd for $C_{14}H_{16}IN$: C, 51.68; H, 4.95; I, 39.06.
Found: C, 51.94; H, 4.95; I, 39.19.

Attempted condensation of α-ethylpyridine methiodide with p-dimethylaminobenzaldehyde. A mixture of 2.5 g. (0.01 *M*) of α-ethylpyridine methiodide, 2 g. (0.013 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine in 15 cc. of methanol was refluxed for four hours on the steam-bath. The reaction mixture was then evaporated to dryness and unreacted aldehyde was extracted with ether. The ether-insoluble residue, after crystallization from ethanol-ether, gave 2.4 g. (96% recovery) of unreacted α-ethylpyridine methiodide, white crystals, m.p. 89–90°. The ether extract, after evaporation to dryness, was treated with 2 g. of phenylhydrazine in 20 cc. of ethanol and was then heated for thirty minutes on the steam-bath. Cooling this reaction mixture gave 2.9 g. (91% recovery) of the phenylhydrazone of *p*-dimethylaminobenzaldehyde as tan crystals, m.p. 148–149°.

Attempted condensation of α-phenethylpyridine methiodide with p-dimethylaminobenzaldehyde. (a) A mixture of 1.6 g. (0.005 *M*) of α-phenethylpyridine methiodide, 1.5 g. (0.01 *M*) of *p*-dimethylaminobenzaldehyde and 3 drops of piperidine in 20 cc. of ethanol was refluxed for five hours. After evaporation to dryness the residue was extracted with ether to remove all unreacted aldehyde. The ether-insoluble fraction was crystallized from ethanol and gave 1.6 g. (100%) of recovered, unreacted methiodide, as light orange crystals, m.p. 189–191°.

Anal. Calc'd for $C_{14}H_{16}IN$: C, 51.68; H, 4.95.
Found: C, 51.96; H, 4.66.

The ether extract, after evaporation to dryness, was treated with 2 g. of phenylhydrazine in 20 cc. of ethanol. After heating in the usual way there was obtained 95% of the phenylhydrazone of *p*-dimethylaminobenzaldehyde, m.p. 148–149°.

(b) [Petrow's special conditions (3)]. A mixture of 1.6 g. of α-phenethylpyridine methiodide and 1.5 g. of *p*-dimethylaminobenzaldehyde was added to 50 cc. of boiling acetic anhydride. After refluxing for ten minutes, the chilled reaction mixture gave 1.2 g. (75%) of recovered, unreacted methiodide as yellow crystals, m.p. 190–191°. From the mother liquors only starting materials were obtained.

Attempted condensation of α-phenethylpyridine methiodide with benzaldehyde. A mixture of 1.6 g. (0.005 *M*) of α-phenethylpyridine methiodide, 1.5 g. (0.015 *M*) of benzaldehyde, and 6 drops of piperidine in 20 cc. of ethanol was refluxed two hours. Cooling the reaction mix-

ture gave 1.6 g. (100%) of unchanged starting methiodide as pale yellow crystals, m.p. 189–191°.

Condensation of 2,4-dinitrotoluene with p-dimethylaminobenzaldehyde. A mixture of 3.6 g. (0.02 *M*) of 2,4-dinitrotoluene, 3.0 g. (0.02 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine was heated for four hours on the steam-bath. A solid cake was formed during the reaction. After cooling, this was filtered off, washed with hexane, and gave 6.3 g. (100%) of the stilbene product, m.p. 180–181°.

Attempted condensation of 2,4-dinitroethylbenzene with p-dimethylaminobenzaldehyde. A mixture of 2 g. (0.01 *M*) of 2,4-dinitroethylbenzene (27), 1.5 g. (0.01 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine was heated for five hours on the steam-bath. The reaction mixture was taken up in ether and thoroughly extracted with 4 *N* hydrochloric acid to remove all basic material. Evaporation of the dried ether layer gave 2 g. (100%) of recovered dinitroethylbenzene, as a dark liquid. The aqueous acid solution was basified strongly with 40% potassium hydroxide and extracted with ether. The ether extract was evaporated and the residue on treatment with phenylhydrazine in ethanol gave 92% of the calculated amount of *p*-dimethylaminobenzaldehyde phenylhydrazone, m.p. 148–149°.

SUMMARY

2-Ethyl and 2-phenethyl-pyridine methiodides have been prepared and do not condense with *p*-dimethylaminobenzaldehyde in alcohol solution in the presence of piperidine catalyst. 2,4-Dinitroethylbenzene, likewise, does not condense with the same aldehyde under similar conditions. The methyl homologs under identical conditions gave quantitative yields of condensation products. These data and considerable information available in the literature have been analyzed and interpreted to present a new mechanism for the reaction of aromatic aldehydes with compounds of the type of α-picoline methiodide. The failure of reaction with the higher alkyl homologs has been interpreted as due principally to steric factors, and considerable substantiating information has been brought forth on this point.

TUCKAHOE 7, NEW YORK

REFERENCES

(1) PHILLIPS, *J. Org. Chem.*, **12,** 333 (1947).
(2) MILLS AND RAPER, *J. Chem. Soc.*, **127,** 2466 (1925).
(3) PETROW, *J. Chem. Soc.*, 18 (1945).
(4) SHAW AND WAGSTAFF, *J. Chem. Soc.*, 77 (1933).
(5) KADESCH, *J. Am. Chem. Soc.*, **66,** 1207 (1944).
(6) SHEMYAKIN AND TRAKHTENBERG, *Chem. Abstr.* **34,** 3676[8] (1940).
(7) RODINOW AND FEDOROWA, *Arch. Pharm.*, **271,** 292 (1933).
(8) KNOEVENAGEL, *Chem. Zentr.*, **1905** II, 179, 1702.
(9) BIGELOW AND EATOUGH, GILMAN AND ROBINSON, in GILMAN AND BLATT, *Org. Synth.*, Coll. Vol. I, 2nd. Ed., p. 80.
(10) REDDELIEN, *Ber.*, **43,** 2476 (1910).
(11) DIPPY, HOGARTH, WATSON, AND WILLIAMS, *J. Soc. Chem. Ind.*, **56, 396** (1937).
(12) BISHOP AND BRADY, *J. Chem. Soc.*, **121,** 2364 (1922).
(13) KERMACK AND MUIR, *J. Chem. Soc.*, 300 (1933).
(14) BODENDORF AND KORALEWSKI, *Arch. Pharm.*, **271,** 101 (1933).
(15) MANNICH, LESSER, AND SILTEN, *Ber.*, **65,** 378 (1932).
(16) KAPLAN AND LINDWALL, *J. Am. Chem. Soc.*, **65,** 927 (1943).

(17) ROTH, *Ber.*, **33**, 3476 (1900).
(18) LÖFFLER AND GRUNERT, *Ber.*, **40**, 1342 (1907).
(19) LADENBURG, *Ann.*, **301**, 124 (1898).
(20) LIPP AND RICHARD, *Ber.*, **37**, 737 (1904).
(21) LIPP AND ZIRNGIBL, *Ber.*, **39**, 1045 (1906).
(22) KOENIGS AND HAPPE, *Ber.*, **35**, 1343 (1902).
(23) LÖFFLER AND GROSSE, *Ber.*, **40**, 1325 (1907).
(24) KOENIGS AND HAPPE, *Ber.*, **36**, 2905 (1903).
(25) KOENIGS, *Ber.*, **35**, 1349 (1902).
(26) KOENIGS, KÖHLER, AND BLINDOW, *Ber.*, **58**, 933 (1925).
(27) WEISWEILLER, *Monatsh.*, **21**, 39 (1900).