[CONTRIBUTION FROM THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE WELLCOME RESEARCH LABORATORIES]

THE CORRELATION OF STRUCTURE AND REACTIVITY OF AROMATIC ALDEHYDES. III.[1] THE CONDENSATION OF AROMATIC ALDEHYDES WITH HYDANTOIN[2]

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Although condensation reactions of aldehydes in general and of aromatic aldehydes in particular are well known and almost innumerable in diversity few attempts have been made to correlate structure with reactivity within this series of compounds. Considerable familiarity with the literature of this field and results observed during a continuing study of the chemistry of quinoline-2- and quinoline-4-aldehydes (1) have led to some insight into the factors influencing the relationship between structure and reactivity in condensation reactions of aromatic aldehydes. Most commonly these condensations have been base-catalyzed and the present discussion will be concerned with the base-catalyzed process. Correlations can similarly be made for the acid-catalyzed reactions but these will be treated elsewhere.

In Chart I is presented an outline of the sequence of steps believed to occur in the base-catalyzed condensation of an aromatic aldehyde with a reactive methylene compound using as an example hydantoin the specific subject of the present work.

The most important factors influencing reactivity in these condensation reactions and governing whether they take place at all and at what stage they stop are:

1. The susceptibility of the carbonyl carbon to nucleophilic attack, governed, in a series of *m*- and *p*-substituted aromatic aldehydes, mainly by resonance and electronic effects;
2. The reactivity of the particular active methylene compound used which is a function of the number and nature of the activating groups present;
3. The strength of the base catalyst, related in an inverse way to the reactivity of the active methylene employed;
4. The reaction conditions such as the medium used, duration, and temperature of the reaction;
5. The relative degree of resonance stabilization attained in the various possible products, such as E or G of Chart I, as compared with the reactants;
6. Steric factors which are minimized in comparisons involving a series of *m*- and *p*-substituted benzaldehydes.

In the current study the factors listed under 2, 3, 4, and 6 have been varied

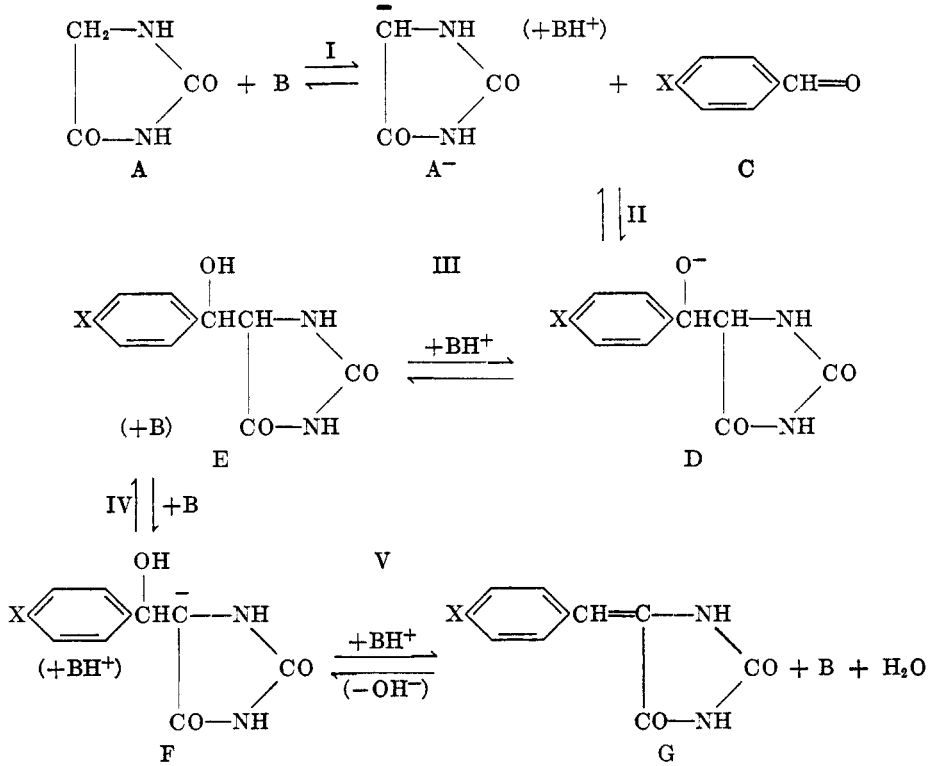
[1] Parts I and II of this series, previously unnumbered, are respectively: Phillips, *J. Org. Chem.*, **12**, 333 (1947) and **14**, 302 (1949).

[2] The experimental part of this paper represents the work done by Mr. James G. Murphy and submitted to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science.

a minimum amount and where possible have been regulated in such a way as to favor a realization of differences depending chiefly on points 1 and 5.

It was anticipated that substituents on the ring of the aromatic aldehyde would markedly influence the yields obtained as well as the nature of the product, in condensation reactions, by affecting the positive character of the carbonyl carbon and thus modifying its susceptibility to nucleophilic attack. Subsequent work substantiated the prediction that factors favoring the susceptibility of the

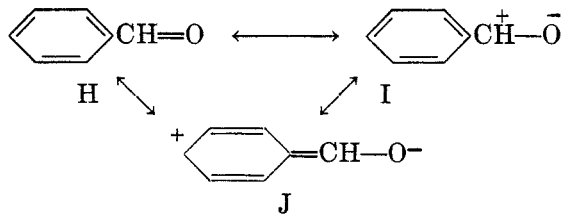
CHART I*



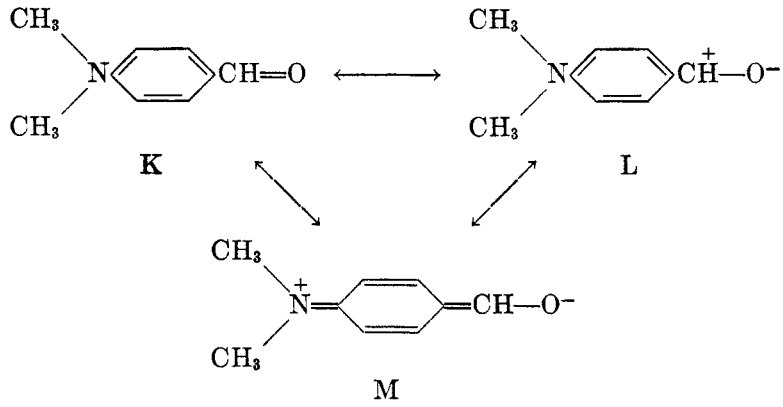
* B = base catalyst such as piperidine, diethylamine, or triethylamine.
X = in this study H, NO_2, CH_3O, $(CH_3)_2N$.

carbonyl carbon to nucleophilic attack should also favor the stabilization of the aldol product (such as E of Chart I).

It was predicted that strong electron-releasing groups would lead to diminished reactivity and strong electron-attracting groups would produce increased reactivity. In benzaldehyde the reactivity for condensation with nucleophilic reactants can be ascribed principally to the contribution of form (I) to the resonance state. The contribution of forms such as (J) would diminish the effective positive nature of the carbonyl carbon so that considering the resonance factor alone benzaldehyde would have a lesser reactivity than an aliphatic aldehyde.

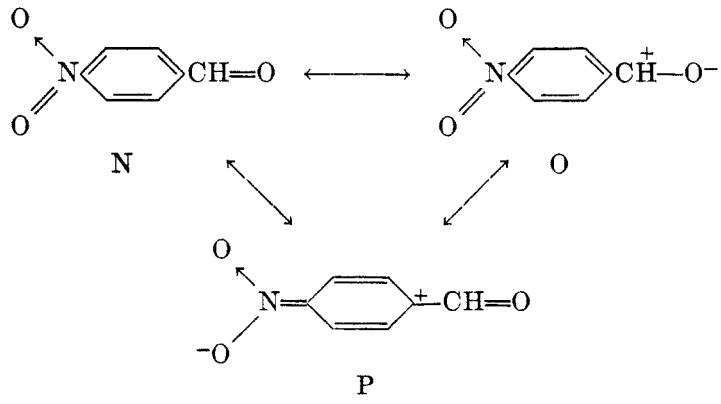


When a strong electron-releasing group is present as in *p*-dimethylaminobenzaldehyde the powerful contribution of form M would be of far greater im-



portance to the structure of the molecule than J is to benzaldehyde, thus rendering the aldehyde carbonyl much less susceptible to nucleophilic attack than that of benzaldehyde. Similar, though probably weaker, effects would be anticipated in *p*-methoxybenzaldehyde and in other aromatic aldehydes bearing electron-releasing substituents.

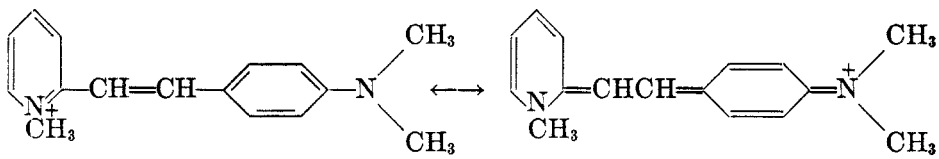
In aldehydes possessing electron-attracting groups, such as *p*-nitrobenzaldehyde, beside the contribution of form O, form P also acts to increase the positive character of the carbonyl carbon and thus to facilitate attack by a nucleophilic fragment. The diminished reactivity brought about by the contribution of a form analogous to form J of benzaldehyde would not be expected to play as



important a role in *p*-nitrobenzaldehyde since such a structure would be opposed by form P. The net result of this indirect activation, in the absence of any direct interaction between the nitro and carbonyl, is a slightly greater reactivity for *p*-nitrobenzaldehyde than for benzaldehyde. A similar activation would be anticipated for *m*-nitrobenzaldehyde and for other aldehydes bearing strong electron-attracting groups.

The above viewpoint agrees well with the previously reported behavior of aromatic aldehydes in reactions of this type. Thus while *p*-dimethylaminobenzaldehyde does not undergo the Perkin reaction (or gives extremely poor yields), benzaldehyde and *p*-nitrobenzaldehyde react well. While *p*-dimethylaminobenzaldehyde does not react with hydantoin (or at least no product has yet been reported) *p*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, and benzaldehyde do react.

The situation is more complex when strong resonance is possible in the final product. It was found that in the condensation of 2- or 4-picoline methiodides with aromatic aldehydes[1] that aldehydes of both types give good yields of the stilbazole methiodides. High yields from carbonyl-activated aldehydes are readily explained as outlined above. High yields from the carbonyl de-activated aldehydes, like *p*-dimethylaminobenzaldehyde, result under these circumstances from the strong favorable resonance which arises in the products, for example (Q↔R), which seems to more than make up for the unfavorable initial condensation step.



Q R

In addition to affecting the susceptibility of the carbonyl carbon to nucleophilic attack, a substituent on the ring of the aromatic aldehyde should also affect the stability of an aldol product, once formed, relative to either the starting reactants or the unsaturated product. This aldol stabilizing action should be greatest for the strong electron-attracting groups such as *p*-nitro- where both the mesomeric and the inductive effects would act in the same direction as these effects produced by the newly formed hydroxymethylene group, and would be least for strong electron-releasing groups such as *p*-dimethylamino- where the more important mesomeric effect would actually act in opposition to aldol stability as well as to the original nucleophilic attack.

Thus in the case of *p*-nitrobenzaldehyde (X = NO_2 in Chart I) just as the individual resonance interactions of the carbonyl and the nitro with the benzene ring were in conflict or opposition (forms such as J and P) so any resonance interactions of the unsaturated side chain shown in the product (G in Chart I) with the benzene ring would be in direct opposition to the nitrobenzene resonance. Formation of the saturated hydroxymethylene side chain found in the aldol product (E in Chart I), however, not only eliminates the conflicting resonance effects associated with the unsaturated carbonyl but substitutes a weak

electron release effect, both by hyperconjugation and by induction, to interact, though weakly, at least favorably with the nitro group.

With *p*-dimethylaminobenzaldehyde (X = $(CH_3)_2N$ in Chart I) because of the strong favorable resonance interaction between the two substituents on the benzene ring indicated in (M), nucleophilic attack on the carbonyl carbon will be rendered less favorable. If any reaction does occur the unsaturated type of product (G of Chart I) should be favored over the intermediate aldol (E in Chart I) since in this case any resonance interaction between the unsaturated side chain and the ring should be extended and amplified by the *p*-dimethylamino group in the same favorable fashion, though in varying degree, as in the aldehyde itself.

The two effects, carbonyl activation and aldol stabilization, are thus seen to be related and to depend upon the same structural features.

Relatively few aldol-type condensation products are recorded as compared with the tremendous number of unsaturated types. Certain examples are known, however. Thus the condensation of benzaldehyde with succinic anhydride under mild Perkin reaction conditions (2) leads to γ-phenylparaconic acid produced by the lactonization of the hydroxy-acid intermediate. Recent work (1a) showed that quinoline-2- and quinoline-4-aldehydes give aldol products with hydantoin. Other investigations (1b, 1d, 3, 4) have indicated that the quinoline aldehydes have an exceptional tendency to form stable aldol-like substances.

In testing the hypothesis that substituents on the aromatic aldehyde should affect both the nature of the product obtained as well as the yields in condensation reactions it was realized that certain reactants might favor the desired result more than others. Thus a highly activated reactive methylene compound might too easily be carried beyond the aldol stage to give the unsaturated product. Since previous work (1a) had shown that hydantoin gave stable aldols when it reacted with 2- or 4-quinoline aldehyde while the other reactive methylene compounds used yielded only unsaturated products, hydantoin seemed well suited for the problem at hand. And in view of the well-known similarities in chemical behavior between 4- (or 2-) substituted pyridines (or quinolines) and 4- (or 2-) substituted nitrophenyl derivatives, as well as the relationships between structure and reactivity discussed above, it seemed that *p*-nitrobenzaldehyde would probably produce a stable aldol with hydantoin while *p*-dimethylaminobenzaldehyde either would not react at all or would give the unsaturated type of product.

In this work the first aim was to try to obtain the aldol intermediates indicated and then to study the effect of aldehyde structure on the nature and yields of the products obtained. To facilitate the obtaining of aldols mild reaction conditions were selected. To permit semiquantitative comparisons of results at least one of the unconsumed reactants as well as the product was recovered.

EXPERIMENTAL[3]

Reagents. Hydantoin was prepared by the reaction of glycine and cyanic acid (5) followed by cyclization with constant boiling hydrochloric acid. Recrystallized from water it melted at 221–222°.

[3] All melting points are uncorrected.

Benzaldehyde (b.p. 68–69° at 15 mm.) and *p*-methoxybenzaldehyde (b.p. 143–144° at 31 mm.) were purified by vacuum-distillation. *p*-Nitrobenzaldehyde (m.p. 106.5°), *m*-nitrobenzaldehyde (m.p. 57–58°), and *p*-dimethylaminobenzaldehyde (m.p. 73–74°) were purified by recrystallization from aqueous alcohol, followed by drying.

Initial exploratory experiments were performed using benzaldehyde. The general procedure given below is that used with each of the aldehydes in turn to furnish the data included in Table II. It represents the conditions selected for convenience and as favorable for producing aldol-like products as determined by a series of runs in which benzaldehyde was the only carbonyl component and in which the catalyst, catalyst concentration, and reaction time were varied giving the results shown in Table I.

Preparation of the 5-(α-hydroxybenzyl)hydantoins. Hydantoin and the aromatic aldehyde, 0.01 mole of each, were refluxed for two hours in 17 cc. of aqueous alcohol (alcohol-water, 7:10 by volume) containing 0.0007 mole of piperidine as the catalyst. At the end of this time the reaction mixture was cooled and the reaction quenched by the addition of 0.0007 mole

TABLE I

EFFECT OF VARIATION OF CONDITIONS IN THE CONDENSATION OF BENZALDEHYDE AND HYDANTOIN[a]

EXP'T NO.	CATALYST	CATALYST CONC. (mole)	REFLUX TIME; hours	YIELD OF CRUDE PRODUCT, %[b]	BENZALDEHYDE RECOVERED, %	RATIO OF 5-BENZYLIDENEHYDANTOIN TO CRUDE PRODUCT
1	Piperidine	0.0007	2	22	77	0.00
2	Triethylamine	.0007	2	22	74	.00
3	Piperidine acetate	.0007	2	0	84	—
4	Piperidine	.0007	24	28	66	.20
5	Triethylamine	.0007	24	19	66	.17
6	Triethylamine	.01	2	32	66	.28
7	Triethylamine	.01	96	56	22	.90

[a] Benzaldehyde and hydantoin, 0.01 mole of each, were refluxed in aqueous alcohol of the strength specified in the experimental part.

[b] The crude product was mainly or entirely the aldol in most experiments.

of acetic acid. The volume was adjusted to 25 cc. with the aqueous alcohol, and a 2.5-cc. aliquot was used for an aldehyde determination as the 2,4-dinitrophenylhydrazone by the method of Houghton (6).

Ten cc. of water was added to the remaining 22.5 cc. and the mixture was concentrated by boiling to 10 cc. (this served to boil off alcohol and steam-distill unreacted aldehyde leaving an essentially aqueous solution). This concentrate was diluted with water to 24 cc. (this is sufficient to keep 0.01 mole of hydantoin in solution). Any aldol which crystallized on cooling to room temperature was filtered and dried to constant weight. This weight was used to calculate the yield of crude aldol product in Tables I and II. Purifications of the products obtained are described below. No products could be isolated from the reaction of *p*-dimethylaminobenzaldehyde or *p*-methoxybenzaldehyde (see Table II) with hydantoin.

In the studies summarized in Table I certain modifications of reaction conditions produced variable amounts of unsaturated condensation products.

Separation of 5-benzylidenehydantoin from the crude reaction product. To estimate the ratio of 5-benzylidenehydantoin to crude product, 0.20 g. of the latter was dissolved in 53 cc. of boiling water. On cooling any 5-benzylidenehydantoin which separated was filtered and dried to constant weight. All samples of 5-benzylidenehydantoin obtained in this way appeared to be essentially pure and melted within the range 221–223°. The melting point

reported (7) is 220°. To confirm the identity of this substance a combined sample, twice recrystallized from water, m.p. 221.5–222°, was analyzed.

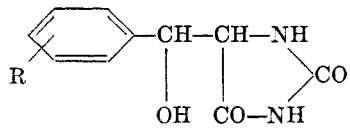
Anal. Calc'd for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3.

Found: C, 63.6; H, 4.3.

The reaction conditions described in the general procedure for the preparation of aldol-type products, as determined by the studies incorporated in Table I and which seemed to give a minimum (0%) of unsaturated product, were then applied to the condensation of hydantoin with benzaldehyde, *m*-nitro, *p*-nitro-, *p*-methoxy-, and *p*-dimethylamino-benzaldehyde. Although the over-all results are presented in Table II, a few additional details on the isolation of the products are given here.

TABLE II

ALDOL PRODUCTS FROM THE CONDENSATION OF AROMATIC ALDEHYDES WITH HYDANTOIN[a]



R	YIELD OF PRODUCT, %	ALDEHYDE RECOVERED, %	PRODUCT M.P., °C.	ANALYSES			
				Carbon		Hydrogen	
				Calc'd	Found	Calc'd	Found
p-NO_2	87	11	253–254	47.8	48.0	3.6	3.6
					48.0		3.6
m-NO_2	79	21	216–217	47.8	48.3	3.6	3.5
H	22	77	213–214[b]	58.2	58.2	4.9	5.0
			183–185[c]	58.2	58.2	4.9	4.7
p-CH_3O	0[d]	82					
p-$(CH_3)_2N$	0	106					

[a] The data in Table II were obtained using the standardized conditions worked out for comparing the yields of aldols obtained; see experimental part. [b] This m.p. and analysis are for the higher-melting aldol; see experimental part. [c] This m.p. and analysis are for the lower-melting aldol; see experimental part. [d] Although no aldol product could be isolated a slight yield, 2%, of the unsaturated 5-(*p*-methoxybenzylidene)hydantoin was obtained. After two recrystallizations from aqueous alcohol the melting point was 250–251° [Reported m.p. 247° (8)].

Anal. Calc'd for $C_{11}H_{10}N_2O_3$: C, 60.5; H, 4.6. Found: C, 60.8; H, 4.4.

5-(α-Hydroxybenzyl)hydantoin. This substance occurred in two different forms which are probably two racemic mixtures, and which were separated by taking advantage of the difference in their rates of crystallization from water. This preparation was repeated on a 0.1-mole scale to facilitate manipulation in the separation of the two forms. The 4.3 g. of crude product was dissolved in 50 cc. of boiling water. On rapid cooling to 25° the higher-melting aldol crystallized out and was removed. From the filtrate, on standing, the lower-melting aldol slowly crystallized. Further amounts of the lower-melting form were obtained by redissolving the higher-melting aldol in the spent mother liquor and repeating the above process until no more of the low-melting aldol was obtained. In this way, from 4.3 g. of crude product 1.8 g. of higher-melting aldol (m.p. 212–213°) and 1.6 g. of lower-melting aldol (m.p. 174–181°) resulted. Each form was then further purified by recrystallization from the minimum amount of water.

5-(α-Hydroxy-m-nitrobenzyl)hydantoin. The bulk of this product crystallized when the reaction mixture was quenched. This was combined with that obtained after concentration of the reaction mixture and adjustment to final volume. The product was twice recrystallized from aqueous alcohol.

5-(α-Hydroxy-p-nitrobenzyl)hydantoin. Most of this substance separated during the reaction and was combined with the second crop obtained in the regular working-up procedure. It was recrystallized three times from aqueous alcohol.

DISCUSSION

The aldol-like intermediates postulated for the reaction between aromatic aldehydes and hydantoin were obtained readily in favorable cases. The success in isolating these aldols may be attributed in part to the use of milder conditions than those employed by earlier investigators (7–11).

The analogy drawn between quinoline-4-aldehyde and *p*-nitrobenzaldehyde which suggested that the latter, too, might form a stable aldol with hydantoin seems to have been sound. The predicted influence of substituents on the ring of the aromatic aldehyde (discussed in the introductory section) in modifying the resonance state of the molecule and thus affecting both the susceptibility of the carbonyl carbon to nucleophilic attack and also the stability of the aldol intermediate, once it is formed, appears to agree well with the subsequently determined experimental results. Thus, as compared with benzaldehyde, *p*-nitro- and *m*-nitro-benzaldehyde are more reactive in this condensation while *p*-methoxy- and *p*-dimethylamino-benzaldehyde are less reactive both as to the magnitude of yields obtained and also in the relative stability of the aldol form. The slight yield obtained with *p*-methoxybenzaldehyde proved to be unsaturated in nature in accord with the lack of aldol stabilization expected in this instance. A wide range of reactivity has been noted for the aldehydes used, and conditions which gave an 87% yield of aldol with *p*-nitrobenzaldehyde gave no product with *p*-dimethylaminobenzaldehyde (Table II), while the other aldehydes gave intermediate yields.

It is of interest to note that piperidine acetate is without catalytic activity for this condensation (experiment 3; Table I), although it has been reported as a catalyst for certain condensations involving active methylene compounds (12, 13) and in the condensation of cinnamaldehyde with crotonaldehyde to form phenylpolyenals (14). The lack of catalytic activity in the present condensation established the validity of adding acetic acid equivalent to the base catalyst used in order to quench the reaction.

Since a secondary amine such as piperidine can condense with an aromatic aldehyde and thereby possibly decrease the effective amount of catalyst available, comparisons of piperidine with the tertiary base, triethylamine, were made. Experiments 1 and 2, 4 and 5 of Table I show that there is no significant difference between piperidine and triethylamine as catalysts for this condensation.

It was found that increase of reaction time at constant catalyst concentration leads to an increased amount of unsaturated compound in the product at the expense of the aldol (in Table I compare experiments: 4 with 1; 5 with 2; and 7 with 6).

Increase of the concentration of the basic catalyst while holding the reaction time constant leads to an increased ratio of 5-benzylidenehydantoin to crude product as well as to a moderate gain in total yield (Table I; compare experiments 6 and 2).

Thus either prolonged exposure to the catalytic amount of base or a shorter contact with a more concentrated solution of the base caused, to a greater extent, the loss of the elements of water from the aldol product with the formation of the unsaturated 5-benzylidenehydantoin.

SUMMARY

Aldol-like products have been prepared by the condensation of hydantoin with aromatic aldehydes bearing appropriate substituents.

The study of the correlation between chemical structure and reactivity in aromatic aldehydes has been continued in the condensation with hydantoin. In agreement with theoretically predicted results the effect of substituents on the aromatic aldehyde upon the reactivity of the aldehyde parallels their effect upon aldol stability and follows the order:

$$p\text{-}NO_2 > m\text{-}NO_2 \gg H \gg p\text{-}CH_3O > p\text{-}(CH_3)_2N$$

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