193. *The Influences of Alkyl Groups in Carbonyl Compounds.*

By E. E. Ayling.

Recorded data of the relative influences of alkyl groups in series of alkyl derivatives show that, when the alkyl group is itself participating in the reaction, the normal sequence of relative inductive polar effects of the groups is generally observed. When the group is merely exerting a modifying influence, there is no similar uniformity. Abnormalities are frequent and these lead mainly to simple relative displacements in the polar sequence of the groups.

A survey of known examples, especially of carbonyl compounds, leads to the conclusion that a field effect is operative, in addition to the chain-transmitted effect, when a single alkyl chain is attached to a susceptible system. Confirmation of this view is found in an examination of the behaviour of aliphatic aldehydes in the Hantzsch pyridine condensation. The additional effect is considered to be due to the reversed field effect of the methyl group, which would be at a maximum with the propyl group and is not regarded as leading necessarily to co-ordination of hydrogen.

The behaviour of aralkyl aldehydes in the condensation shows that phenyl is comparable with methyl when substituted in the alkyl chain. Conjugation of an ethylenic link with the carbonyl group is found to be more effective in the aliphatic than in the aromatic series in decreasing the activity of the aldehyde carbonyl group in the condensation.

VARIOUS series of alkyl compounds have been studied from time to time in order to ascertain the relative effects of the alkyl groups in influencing a reaction. The theoretical sequence of the inductive polar effects of the alkyl groups, *viz.*,

$$\mathrm{Me} < \mathrm{Et} < \mathrm{Pr} < \mathrm{Bu}, \text{ etc.};\ n\text{-} < iso\text{-}, \text{ etc.}$$

is not universally followed and, from a survey of a number of recorded instances, it appears that several conclusions may be drawn. The possible agreement of an observed sequence with the theoretical one seems to depend, first, on whether the alkyl group is itself participating directly in the reaction or is merely exerting its influence in the reacting molecule. In the former case, the theoretical sequence of the alkyl groups is generally observed, as in the following typical examples: the elimination of various hydrocarbon radicals in the paraffinic degradation of quaternary phosphonium hydroxides (Fenton and Ingold, J. 1929, 2347), the diminution of the ratio k_{OH}/k_H in the hydrolysis of alkyl glyceric esters (Groocock, Ingold, and Jackson, J., 1930, 1057), and the competitive elimination of alkyl groups from unsymmetrical mercury dialkyls by means of alcoholic hydrogen chloride (Kharasch and Marker, *J. Amer. Chem. Soc.*, 1926, **48**, 3130; Kharasch and Flenner, *ibid.*, 1932, **54**, 674). The order observed for the relative activity of alkyl iodides in the formation of *C*-alkyl in preference to *O*-alkyl derivatives with dimethyl- and phenyl-dihydroresorcinols (Desai, J., 1932, 1080) is apparently the reverse of what would, at first sight, be expected. A similar reversal occurs, however, in the order found in the interaction of alkyl chlorides with iodides (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 477; compare Bennett, *Ann. Reports*, 1929, **26**, 138), now recognised as an example of nucleophilic substitution (Hughes and Ingold, J., 1935, 249). The hydrolysis of alkyl halides by means of alkali hydroxides, alkoxides, and aryl oxides in anhydrous alcohol has been examined by a number of workers, and the whole problem of such nucleophilic substitutions has been comprehensively discussed by Hughes and Ingold (*ibid.*; where also a full bibliography is given). With *n*-alkyl halides such reactions usually give the normal sequence for the *n*-alkyl groups.

With the second main type of reaction, that in which the alkyl group exerts its influence in the reacting compound, no similar uniformity prevails, even in apparently analogous cases. Departures from the normal sequence are frequent, but, in general, the anomalies lead to simple relative displacements in the sequence of groups, and in these cases the anomaly apparently begins with the propyl derivative. For instance, in the nitration of alkyl ethers of guaiacol (Allan and Robinson, J., 1926, 376), the sequence for the alkyl groups, as shown by the relative directive powers of the alkoxy-groups, is Me $<$ Bu^a $<$ Pr^a $<$ Et $<$ Pr$^\beta$, whereas with the corresponding quinol ethers the expected normal sequence is found (Robinson and Smith, *ibid.*, p. 392; Clarke, Robinson, and Smith, J., 1927, 2647). These results were attributed (Allan, Oxford, Robinson, and Smith, J., 1926, 406) to an increase, as the chain lengthens, in the proportion of the polar effect which is distributed over the molecule, the effect of the terminal methyl group of the *n*-propyl group being assumed to be largely distributed and only to a small extent transmitted through the chain.

Two cases, which at first sight appear to be analogous but yet yield different sequences of alkyl groups, arise from the nitration of phenylalkylsulphones and of alkyl benzoates. With the sulphones (Baldwin and Robinson, J., 1932, 1445), the order of diminishing percentage of *m*-nitro-derivative follows the normal sequence, Me $>$ Et $>$ Pr^a $>$ Bu $>$ Pr$^\beta$, whereas, with the alkyl benzoates (Zaki, J., 1928, 983), the corresponding order was found to be Me $>$ Pr^a $>$ Et $>$ *iso*-Bu $>$ Am $>$ Bu $>$ Pr$^\beta$ $>$ Hex. In this series, the propyl group is again displaced relatively to the ethyl group. The alternation between the odd and the even members of the *n*-alkyl series was considered by Zaki to be due to neutralisation of affinities through space between the carbonyl oxygen and the odd-numbered carbon atoms of the chain. From the observed results, the effect is apparently at a maximum with the third carbon atom of the propyl group.

The study of the pinacol–pinacolin rearrangement has given data from which the relative influences of radicals have been obtained (for bibliography, see *Ann. Reports*, 1928, **25**, 134; 1930, **27**, 115; 1933, **30**, 181). For instance, Meerwein (*Annalen*, 1919, **419**, 121) and Tiffeneau and Lévy and their co-workers (compare *inter alia*, *Bull. Soc. chim.*, 1931, **49**, 1617) deduced relative values for the 'affinity capacities' of alkyl groups. The sequence obtained, Me $>$ Pr $>$ Bu $>$ Et, does not correspond with the capacity for electron release of the groups (compare Ingold, *Ann. Reports*, 1928, **25**, 134), but is regarded by Tiffeneau and Lévy (*loc. cit.*) as being in accord with the theory of alternating affinity. In general form, however, the sequence offers comparison with those observed by Allan and Robinson and by Zaki (*locc. cit.*).

Consideration of the relative influences of alkyl groups on the behaviour of a single group of compounds, such as the ketones and their derivatives, shows that concordant results are not obtained in different reactions. In the addition of sodium bisulphite to simple aliphatic ketones, the alkyl groups exert a normal influence, since the order of diminishing yields of bisulphite compounds (Stewart, J., 1905, **87**, 186) for the methyl alkyl ketones is Me $>$ Et $>$ Pr^a $>$ Pr$^\beta$ $>$ *tert.*-Bu. Similar sequences were also found for the same ketones in the formation of oximes (Stewart, *ibid.*, p. 410; Petrenko-Kritschenko and Kantscheff, *Ber.*, 1906, **39**, 1452) and phenylhydrazones (Petrenko-Kritschenko and Eltschaninoff, *J. Russ. Phys. Chem. Soc.*, 1903, **35**, 146; *Annalen*, 1905, **341**, 150). Observations on acetal formation with ketones (Carswell and Adkins, *J. Amer. Chem. Soc.*, 1928, **50**, 235) and on semicarbazone formation (Conant and Bartlett, *ibid.*, 1932, **54**, 2881) offer scarcely sufficient relevant data to enable conclusions to be drawn. With the former, however, the slight differences between the dimethyl, methyl ethyl, and methyl propyl ketones, in that order, and the big diminution with methyl *tert.*-butyl ketone seem to indicate that no abnormality is present.

Diverse results are obtained in two other cases, *viz.*, the stability of ketone cyanohydrins and the iodination of ketones. Lapworth and Manske (J., 1930, 1976) determined the dissociation constants for the cyanohydrins of a number of methyl alkyl and phenyl alkyl ketones, and considered that the effects observed on varying the size or structure of the alkyl groups admit of no simple interpretation. It was, however, concluded that the replacement of a hydrogen atom in the α-position in the alkyl group by methyl usually increases the stability of the corresponding cyanohydrin, whereas replacement of a β-hydrogen atom usually has slightly the opposite effect. This reversal of effect with the introduction of the γ-carbon atom corresponds with those observed with the guaiacol ethers and alkyl benzoates (see above).

The iodination of a series of methyl *n*-alkyl ketones (Dawson and Wheatley, J., 1910, **97**, 2048; Dawson and Ark, J., 1911, **99**, 1740) shows that the velocities vary irregularly with the nature of the alkyl group, and it was then considered that no satisfactory explanation could be offered. Since, however, in a ketone $-CH_2\cdot CO\cdot CH_2-$, the hydrogen atom may separate from either α-group, two enolising systems will be present simultaneously, and therefore it is not possible to correlate the velocities with any definite sequence of alkyl groups.

Such ambiguity is avoided in more recent observations (Evans, J., **1936**, 785) on the bromination of a series of phenyl alkyl ketones. The measured velocity is that of the acid-catalysed prototropic change, and this depends (Watson, Nathan, and Laurie, *J. Chem. Physics*, 1935, **3**, 170; Evans, Morgan, and Watson, J., 1935, 1170) upon (1) the rate of reaction between ketone and catalyst and (2) the proportion of the energised form which is transformed into the enol by ionisation of α-hydrogen. Introduction of α-alkyl groups into acetophenone will facilitate the former process but will decrease the tendency for the latter (cf. Evans, *loc. cit.*). Although, however, the facilitating influence of the alkyl substituents should increase gradually as the number of carbon atoms increases, if the groups exhibit their normal polar effects, the substitution acts directly on the seat of ionisation of the α-hydrogen, thus changing the enolising system. The governing factor in prototropic change is considered to be the reaction between ketone and catalyst (Nathan and Watson, J., 1933, 218, 890) and the energy of activation is associated with this stage (cf. Evans, Morgan, and Watson, *loc. cit.*) but the enolising system remains unchanged throughout the series in the prototropic systems, *e.g.*, nuclear-substituted acetophenones, with which a definite relationship has been observed between the energy of activation and the dipole moment of the substituent (Nathan and Watson, J., 1933, 890). The first substitution in acetophenone (to convert methyl into ethyl) might well cause a very large diminution in the ionising tendency of the α-hydrogen, subsequent increases in the length of the alkyl chain then causing further, but much smaller, diminution. The magnitude of the effect of the initial substitution of hydrogen by methyl in other systems is indicated by the facts that the introduction of a methyl group into benzene increases the rate of nitration about 14-fold (Ingold and Shaw, J., 1927, 2918) and, conversely, that the dissociation constant of formic acid is 10 times that of acetic acid ($K = 1\cdot77 \times 10^{-4}$ and $1\cdot75 \times 10^{-5}$ respectively; Harned and Owen, *J. Amer. Chem. Soc.*, 1930, **52**, 5079), the latter example furnishing a partial analogy to the present case. The sudden large increase in the energy of activation in passing from acetophenone to propiophenone, observed by Evans (*loc. cit.*), thus receives a simple explanation without recourse to his hypothesis of co-ordination between the β-hydrogen atom and the carbonyl oxygen in propiophenone.

The series of ω-alkylacetophenones, beginning with propiophenone, should illustrate more clearly the influence of alkyl groups on the prototropic system. Although the lengthening of the *n*-alkyl chain causes a small continuous decrease in the energy of activation with simultaneous decrease in the probability factor, yet there is an apparent irregularity in the changes in both from compound to compound. This may be illustrated simply by the values for the velocity coefficients at any one temperature, which indicate an abnormal effect beginning with the propyl group. The diminution in value from the methyl ($k_{25^\circ} = 0\cdot104$) to the ethyl compound (0·072) is followed by a sharp rise to the propyl (0·085) and then a subsequent slight fall to the butyl compound (0·082). The series of groups, for $CH_2R\cdot CO\cdot Ph$, when arranged in order of magnitude, *viz.*, Me > Pr > Bu > Et, compares essentially with series previously cited in which there is a departure from the normal sequence (p. 1015).

The dissociation constants of the simple aliphatic acids should give a measure of the relative influences of the alkyl groups, but again there is no regular sequence, as shown by the following values for the constants :

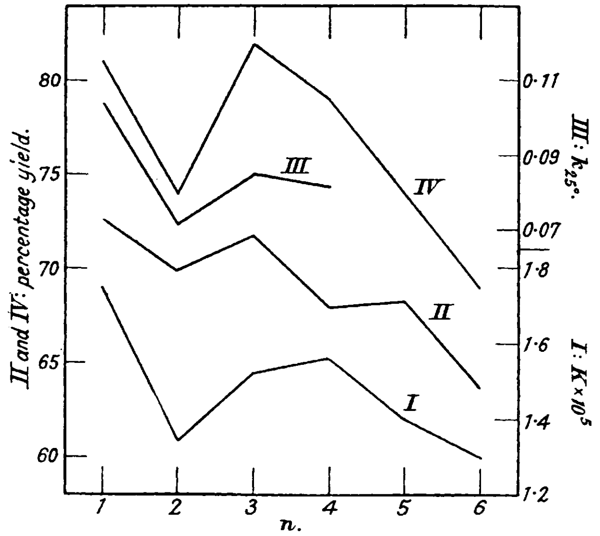
R in $R\cdot CO_2H$	Me	Et	Pr	Bu	Am	Hex
$K \times 10^5$	1·76 [1]	1·34 [2]	1·52 [2]	1·56 [3]	1·40 [3]	1·30 [3]

[1] Dippy and Williams, J., 1934, 1889. [2] Harned and co-workers, *J. Amer. Chem. Soc.*, 1933, **55**, 2379; 1934, **56**, 2039. [3] International Critical Tables, Vol. VI.

The general tendency in the series is for a decrease from acetic to *n*-heptoic acid but this is arrested by the marked increase with *n*-butyric acid, in which the propyl group is combined with the carboxyl group (the subsequent slight increase with the butyl compound is due to inaccuracy in the available values, since recent semi-precision measurements on *n*-valeric acid show that its constant is less than that of *n*-butyric acid; Dr. J. F. Dippy, private communication).

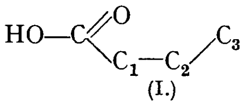
From the foregoing examples it is clear that, where there is a simple departure from the normal inductive sequence for the relative influences of alkyl groups the anomaly begins with the propyl group, and that the possibility is indicated for the operation of an additional influence which may be superimposed on the normal inductive effect. The postulates of Allan, Oxford, Robinson, and Smith and of Zaki (*locc. cit.*) were advanced to explain the observations of the respective authors and no indication was given of a wider application, although the former might be applicable to the cases of the pinacols, ethylene oxides, and ethylenic compounds studied by Tiffeneau and Lévy and their co-workers (*loc. cit.*) in which alkyl groups, influencing opposing electromeric systems, are compared in the same molecule. The second of the above hypotheses is based on the spatial relationship of a single alkyl chain to the atoms of the system to which it is attached, but it does not apply in every case, as is shown by the normal behaviour of the sulphones. A comparison of the latter with carboxylic esters, however, shows the type of system in which such an additional effect might be active. The presence of two co-ordinate links in sulphones gives an electronic structure which is not easily depolarised (cf. Ingold, Ingold, and Shaw, J., 1927, 816), whereas the carboxylic ester group is a mesomeric system (Ingold, *Chem. Reviews*, 1934, **15**, 244; Sidgwick, J., 1937, 697) and the resonant state of such a hybrid molecule should be influenced greatly by both chain-transmitted and field polar effects. The mesomeric carboxylic acid group and the keto-enol prototropic system, the ion of which has been regarded as mesomeric (Ingold, J., 1933, 1125), should also be influenced similarly. The comparison between the alkyl benzoates, the aliphatic carboxylic acids, and the ω-alkylacetophenones is best shown graphically, and in Fig. 1, *n*, the number of carbon atoms in the alkyl groups of $C_6H_5{\cdot}CO_2C_nH_{2n+1}$, $C_nH_{2n+1}{\cdot}CO_2H$, and $C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}C_nH_{2n+1}$, is plotted respectively against yield % in *m*-nitration (Curve II), dissociation constant (Curve I), and velocity coefficient of prototropic change at 25° (Curve III). The general agreement is too marked to be merely fortuitous, and leads to the

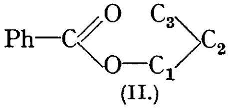
Fig. 1.

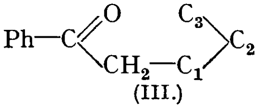


I. *Dissociation constants of aliphatic acids.*
II. m-*Nitration of alkyl benzoates.*
III. *Prototropy of alkylacetophenones.*
IV. *Hantzsch condensation with aliphatic aldehydes.*

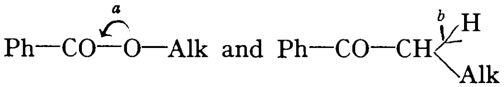
conclusion that a disturbing influence due to the operation of a 'field' or 'direct' effect, beginning with the introduction of the γ-carbon atom, is probable whenever the alkyl chain is attached to a 'susceptible' system. Although, on the basis of the values for *n* employed in the diagram, the C_3 atom in the acids (I) is the γ-atom from the carboxyl group, yet in the esters (II) and ketones (III) the C_3 atom is actually the δ-atom along the chain from the carbonyl group.


(I.)


(II.)


(III.)

The observed effects in the esters depend on the diminution of the *m*-orienting influence of the carboxylate group, and, in the ketones, on the ionisation of the α-hydrogen atom. The governing electron movements which are influenced are, therefore, *a* and *b* respectively in



and the C_3 atoms in (II) and (III) are the γ-atoms in the chain relatively to the atoms composing these key systems.

The normal influence of alkyl groups on the simple additive reactions of ketones indicates that such a field effect is apparently not operative in these compounds, although the carbonyl group must be regarded as a susceptible system. The heat of formation of the carbonyl group has been considered to be unusually high, thus indicating resonance between the two structures, $C=O$ and $\overset{+}{C}-\overset{-}{O}$ (Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606), and there is an increasing tendency for the adoption of the view that such resonance occurs (McKay, *Chem. and Ind.*, 1934, **53**, 870; Evans, Morgan, and Watson, J., 1935, 1170; Ives, this vol., p. 83). On the other hand, such an effect, if present, would be indistinguishable from ordinary inductive carbon–oxygen polarisation (cf. Ingold, *Chem. Reviews*, 1934, **15**, 243), and, furthermore, the smaller stability of the dipolar form renders unlikely the participation of the latter as an unperturbed structure, since such structures must not differ greatly in energy (cf. Hinshelwood, *Ann. Reports*, 1933, **30**, 44; Sidgwick, *ibid.*, 1934, **31**, 38; J., 1936, 535). In the hybrid structures of esters and amides there is neither a dipolar carbon–oxygen link nor a charged carbon atom, and a clear distinction has been made between carbonyl compounds, such as acids, esters, and amides, in which resonance is possible, and those, like ketones, in which it is not (Sidgwick, J., 1937, 697). It is thus desirable to consider the carbonyl group as a polarisable system only through the electromeric effect, especially in view of recent evidence from the force constants of bonds. The force constant for the $C=O$ link in formaldehyde ($13{\cdot}4 \times 10^5$ dynes/cm.) lies in the upper half of the double-bond range (7—15×10^5 dynes/cm.), *i.e.*, the half more remote from the single-bond range ($<7 \times 10^5$ dynes/cm.; cf. Sutherland, *Ann. Reports*, 1936, **33**, 64). Furthermore, Thompson and Linnett (J., 1937, 1392) consider that the force constants in various ethylenic and carbonyl compounds indicate that, although carbon dioxide and suboxide possess hybrid links, neither ethylene nor formaldehyde appears to be capable of existence in hybrid form.

The polarisable carbonyl group in ketones is undoubtedly influenced by chain-transmitted polar effects, and the absence of a field effect may possibly be due to a mutual interaction of the two alkyl groups, which are attached to the same carbon atom and influence the same polarisable system. Such an action would tend to modify their combined influence without necessarily disturbing the normal sequence of relative inductive effects.

Aliphatic aldehydes, with a single alkyl chain attached to the reactive group, should compare more closely with the type of system, acid and ester, which exhibits a field effect. No evidence has hitherto been available upon the relative behaviour of a series of aliphatic aldehydes. The observations of Ultée (*Rec. Trav. chim.*, 1909, **28**, 248) on cyanohydrin formation do not differentiate sufficiently between the aldehydes (cf. Lapworth and Manske, J., **1928**, 2540), and only two *n*-alkyl aldehydes have been examined quantitatively for semicarbazone formation (Michael, *J. Amer. Chem. Soc.*, 1919, **41**, 393; Conant and Bartlett, *loc. cit.*). A reaction which should give data for such a series is the Hantzsch pyridine condensation. It has been shown that the variations in the yields of the dihydropyridine derivatives from the simpler aromatic aldehydes can be correlated with the polar influences of the substituent groups. This is clearly illustrated by the opposing influences of the methyl and the nitro-group when introduced into benzaldehyde (Hinkel, Ayling, and Morgan, J., 1931, 1836). Although Hantzsch and his pupils employed the majority of the simpler aliphatic aldehydes in the synthesis, little information is available concerning the relative ease with which they undergo the condensation. The recorded yields of dihydropyridine derivatives usually range from 65 to 80% or are merely stated to be excellent and the conditions are not always comparable. Of the aldehydes used, only with acraldehyde was the reaction said to fail (Engelmann, *Annalen*, 1885, **231**, 67), but it has since been claimed that both this and crotonaldehyde give the condensation (Gryszkiewicz-Trochimowsky, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 1377; Gryszkiewicz-Trochimowsky and Pavlovskaja, *ibid.*, 1913, **45**, 935).

The behaviour of an aldehyde in the condensation has been regarded as governed by the influence of the attached group on the kationoid character of the carbonyl carbon atom (Hinkel, Ayling, and Morgan, *loc. cit.*). If the alkyl groups exert their normal inductive polar influence, it would be expected that the yield of dihydropyridine derivative would diminish as the series of aldehydes is ascended and that the following relations would be observed: Me > Et > Pr > higher alkyls; *n*- > *iso*-alkyl. If an additional field effect is superimposed, however, displacements in the normal sequence will occur and, from the examples already considered, any abnormality should begin with the propyl derivative, *i.e.*, *n*-butaldehyde.

The behaviour of the aldehydes in the Hantzsch condensation, under the standard conditions previously described (J., 1931, 1839), is summarised below, the data giving the mean yield % of dihydropyridine derivative from the aldehyde R·CHO:

R	Me	Et	Pr	*iso*Pr	Bu	*iso*Bu	Hex
Yield, %	81	74	82	66	79	75	69

It is at once evident that the normal sequence does not obtain, and the relative displacements in the *n*-alkyl series approximate closely to those observed with the alkyl benzoates, the ω-alkylacetophenones, and the aliphatic carboxylic acids. The comparison is illustrated by the inclusion of the graphical relationship for these aldehydes in Fig. 1, the yield of dihydropyridine derivative being plotted against the value of *n* in R. As in the previous cases, there is the marked fall in proceeding from the methyl to the ethyl compound, followed by a rise to the propyl, and a subsequent fall through the butyl to the hexyl compound.

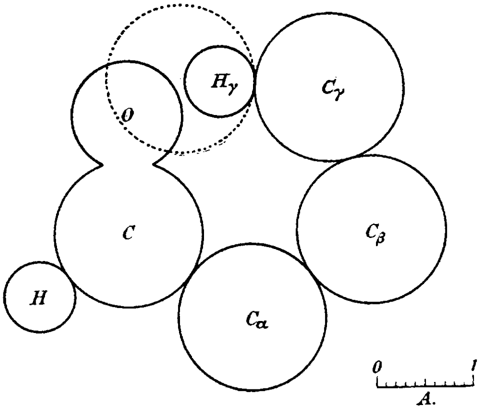
The positions of the *iso* groups are normal, each exerting a greater influence, shown by the smaller yield, than the corresponding *n*-alkyl group. The higher yield (by 9%) from the *iso*butyl than from the *iso*propyl derivative corresponds with the presence of γ-carbon atoms in the former and compares with the 8% higher yield from the propyl than from the ethyl derivative.

The agreement between the results obtained with the aliphatic aldehydes and the examples previously cited furnishes strong confirmation of the hypothesis that, when a single alkyl chain is attached to a 'susceptible' system, a field effect is operative in addition to the normal inductive (chain-transmitted) polar influence of the groups. The field effect in the aldehydes is regarded as due to an attraction by the methyl group of the unshared electrons of the carbonyl oxygen, thus increasing the internal polarisation of the carbonyl group. A similar influence of the methyl group on the unshared electrons of a tertiary nitrogen atom has been suggested for dimethyl-*o*-toluidine and α-picoline (Klaus and Baudisch, *Ber.*, 1918, **51**, 1041; Baudisch, *ibid.*, 1921, **54**, 416). This attraction for electrons is in the reverse sense to the electron-repulsive inductive effect of the methyl group, and such a reversed field effect has been attributed to the methyl group by Bennett and Mosses (J., 1930, 2366; cf. also Baddeley and Bennett, J., 1933, 263; Kenner and

Morton, J., 1934, 679; Evans, *loc. cit.*). It is not considered that this interaction between the methyl group and the unshared electrons of the carbonyl oxygen atom leads to the formation of a hydrogen bond, since there is no facilitating electron-attractive group combined with the carbon atom to absorb the negative charge which would result from the ionisation of a hydrogen atom. The presence of this type of group is essential for the co-ordination of a hydrogen atom attached to a saturated carbon atom, as, *e.g.*, in the complexes formed by chloroform with ethers, ketones, and quinoline (Macleod and Wilson, *Trans. Faraday Soc.*, 1935, **31**, 596; Earp and Glasstone, J., 1935, 1709, 1720; Moelwyn-Hughes and Sherman, J., 1936, 104; Huggins, *J. Org. Chem.*, 1936, **1**, 452) and in *o*-nitrotoluene (Sidgwick and Callow, J., 1924, **125**, 538; cf. Dippy, Evans, Gordon, Lewis, and Watson, J., 1937, 1424).

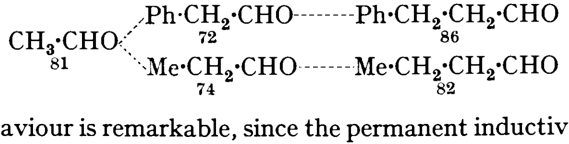
The first appearance of the field effect with the propyl group corresponds with the closest approach of the terminal methyl group in a coiled planar configuration. A limiting state for the relevant atoms in *n*-butaldehyde is represented in Fig. 2, based on the following covalent radii (in A.) and intervalency angles: C, single bond, 0·77; C, double bond, 0·67; O, double bond, 0·57 (Pauling and Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 1234); H, 0·37 (Sidgwick, "The Covalent Link in Chemistry," 1933, 83, 88; *Ann. Reports*, 1933, **30**, 113): $\mathrm{C}{<}^{\mathrm{C}}_{\mathrm{C}}$, 109·5°; $\mathrm{C}{\leqslant}^{\mathrm{O}}_{\mathrm{C}}$, 125° (cf. Sidgwick, "The Electronic Theory of Valency," 1929, 238). It is clear that the field effect is not likely to be a tangible one until the propyl group is reached in ascending the series. With the butyl derivative, such a simple planar configuration is not possible, since there would be an overlap between the terminal carbon atom (C_δ, dotted outline in Fig. 2) and the oxygen, and between the hydrogen atoms attached to C_δ and the carbonyl carbon atom. A field effect would be anticipated here, but not to such an extent as with the propyl compound, and the effect should diminish further with subsequent increase in the length of the alkyl chain, due to a gradual recession of the terminal methyl group from the oxygen.

FIG. 2.



In the other series of carbonyl compounds which have been considered, although the field effect probably influences the whole mesomeric system, yet similar conditions prevail. *n*-Butyric acid corresponds with the nearest planar approach of the terminal methyl to the symmetrical mesomeric carboxyl group without overlap. In the unsymmetrical esters and alkylacetophenones, the propyl derivatives correspond with the nearest planar approach of the methyl group to the atoms composing the respective key systems (cf. p. 1018).

In addition to the aliphatic aldehydes, the behaviour of two aralkyl aldehydes, phenylacetaldehyde and β-phenylpropaldehyde, has been examined in the Hantzsch condensation, in order to compare the relative influences of phenyl and methyl groups in an alkyl chain. The results obtained agree with the observation of Lapworth and Manske (*loc. cit.*) that the replacement of a methyl by a phenyl group in an alkyl chain has scarcely any influence on the stability of a ketone cyanohydrin. The yields (%) in the condensation are:



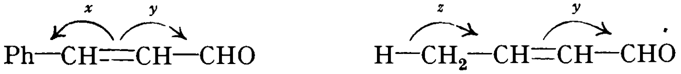
$$\begin{array}{lllll} & \nearrow & \underset{72}{\mathrm{Ph{\cdot}CH_2{\cdot}CHO}} & \cdots\cdots & \underset{86}{\mathrm{Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CHO}} \\ \underset{81}{\mathrm{CH_3{\cdot}CHO}} & & & & \\ & \searrow & \underset{74}{\mathrm{Me{\cdot}CH_2{\cdot}CHO}} & \cdots\cdots & \underset{82}{\mathrm{Me{\cdot}CH_2{\cdot}CH_2{\cdot}CHO}} \end{array}$$

The similarity in behaviour is remarkable, since the permanent inductive effect of the phenyl ($-I$) is opposite to that of the methyl group ($+I$), and in the phenyl aliphatic acids the substitution of phenyl for methyl increases the dissociation constant (Dippy and Lewis, J., 1937, 1010). The lower yield from phenylacetaldehyde than from acetaldehyde appears to furnish another example of the subordination of the polar influence of phenyl to that of methylene (*idem, ibid.*). The yield with β-phenylpropaldehyde is noteworthy as being the highest from any alkyl or aralkyl aldehyde examined, and must be attributed to the direct action through space of the intrinsic attraction of the phenyl group for electrons (compare *idem*).

The influence of an ethylenic link conjugated with the carbonyl group has been observed with crotonaldehyde and cinnamaldehyde. A comparison of the yields from these aldehydes with those from the corresponding saturated aldehydes confirms the view that conjugation tends to stabilise the carbonyl form of an aldehyde or ketone (Lapworth and Manske, J., 1928, 2535).

$\mathrm{Me{\cdot}CH:CH{\cdot}CHO}$	37	$\mathrm{Ph{\cdot}CH:CH{\cdot}CHO}$	74
$\mathrm{Me{\cdot}CH_2{\cdot}CH_2{\cdot}CHO}$	82	$\mathrm{Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CHO}$	86

The lowering of the activity of the aldehyde, represented by the diminution in yield, is much more marked with crotonic than with cinnamic aldehyde. This may be attributed to either of two factors : (1) the conjugation of the ethylenic link in cinnamaldehyde with the benzene nucleus (*x*), which would act oppositely to the conjugation of the ethylenic link with the carbonyl group (*y*), or (2) the operation in crotonaldehyde of the additional mechanism for electron-release by methyl groups (*z*) (Baker and Nathan, J., 1935, 1845) which would augment the conjugation (*y*). On the data available it is not possible to decide whether only one or both of these occur, but the difference is so large that it may well arise through the influence of both factors.



$$\mathrm{Ph{-}CH{=}CH{-}CHO} \qquad \mathrm{H{-}CH_2{-}CH{=}CH{-}CHO}$$

A general comparison of the results obtained with alkyl and with aromatic aldehydes in the Hantzsch condensation shows one important feature. The range of yields from the former (66—86%), except crotonaldehyde, is very much smaller than the range from the latter (0—88%) (J., 1931, 1837; 1932, 1113; 1935, 816). An essential difference between the two series is that the aromatic aldehydes have the benzene nucleus attached to the carbonyl group. The presence of this mesomeric system will facilitate the polar influences of substituents, the benzene nucleus being a much more efficient transmitter than a saturated chain. The influences may even be augmented, since substitution appears usually to cause an increase in the resonance energy of benzene (Pauling and Sherman, *loc. cit.*).

The majority of the alkyldihydropyridine derivatives prepared by Hantzsch and his pupils are normally oxidised by dinitrogen trioxide to the corresponding pyridine derivative. Two recorded exceptions are 4-*iso*propyl- and 4-benzyl-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylic esters, both of which yield 2 : 6-dimethylpyridine-3 : 5-dicarboxylic ester, the substituent group in the 4-position being eliminated (Engelmann, *Annalen*, 1885, **231**, 47; Jeanrenaud, *Ber.*, 1888, **21**, 1783). A similar elimination has been found to occur with each of these compounds when N-nitric acid is used as the oxidant. An exception in the aromatic series is the dihydropyridine derivative from *p*-dimethylaminobenzaldehyde, which gives *p*-nitrosodimethylaniline nitrate with dinitrogen trioxide (Hinkel and Cremer, J., 1920, **117**, 137). In this instance, it was found that with sulphur normal oxidation results, and the use of sulphur is equally efficacious with the above two alkyldihydro-derivatives, oxidation proceeding smoothly to give the 4-iso*propyl*- and *4-benzyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylic esters*. The 4-n-*butyldihydropyridine* derivative, formed from *n*-valeraldehyde, is oxidised normally with N-nitric acid. The 4-β-*phenylethyldihydropyridine* derivative, from β-phenylpropaldehyde, only acts slowly with the latter reagent and tends to deposit a crystalline *nitrate* of the pyridine base; normal oxidation proceeds easily with sulphur.

EXPERIMENTAL.

Materials.—The aldehydes, except acetaldehyde, and ethyl acetoacetate were purchased as pure materials. Acetaldehyde was prepared from paraldehyde. For purification, they were subjected to repeated fractional distillation under either atmospheric or reduced pressure, with the usual rejection of initial and final fractions, and were distilled immediately before use. The following b. p.'s provide additional data or distinguish between alternatives quoted in Beilstein: *n*-butaldehyde, b. p. 75·5°/777·5 mm.; *n*-valeraldehyde, b. p. 103°/767 mm.; *iso*valeraldehyde, b. p. 93°/764 mm.; cinnamaldehyde, b. p. 134°/19 mm.; β-phenylpropaldehyde, b. p. 101·5°/10·5 mm.; phenylacetaldehyde, b. p. 82°/10 mm., 93°/20 mm.

Hantzsch's Condensation with the Aldehydes.—The standard procedure previously described (Hinkel, Ayling, and Morgan, J., **1931**, 1839) was employed, except for minor details in the isolation of some of the products (described later) necessitated by the solubility in methyl alcohol of the dihydropyridine derivatives from some of the higher aldehydes. With each aldehyde the condensation was carried out in duplicate, the mean of the yields being the value quoted in the theoretical portion. The use of M/10 instead of M/20 proportions gave no appreciable difference with propaldehyde, and the former were used with acetaldehyde, a confirmatory condensation being made with acetaldehyde-ammonia using the customary M/20 quantities. The condensations with *n*-valeraldehyde and β-phenylpropaldehyde have not previously been described.

Ethyl 2 : 6-*dimethyl*-4-n-*butyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from methyl alcohol in a mass of prismatic needles, m. p. 97° (Found: C, 65·9; H, 8·5; N, 4·6. $C_{17}H_{27}O_4N$ requires C, 66·0; H, 8·7; N, 4·5%). Yields: 12·0 and 12·3 g., 77·7 and 79·6%. The corresponding 4-β-*phenylethyl* compound crystallised from methyl alcohol in clusters of almost colourless prismatic needles, m. p. 112° (Found: C, 70·2; H, 7·4; N, 4·1. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6; N, 3·9%). Yields: 15·2 and 15·4 g., 85·2 and 86·3%.

The results with the remaining aldehydes are summarised below. When there was an appreciable difference between the m. p. found for the dihydropyridine derivative and that recorded in the literature the derivative was analysed, the results being given in the following section.

Dihydropyridime derivatives.

Aldehyde.	Yields (g.).	Yields (%).	M. p.	M. p. (lit.).
Acetic	21·6,* 21·8*	80·9, 81·65	130°	131° [1]
Propionic	10·5, 20·6*	74·7, 73·3	110	110 [3]
n-Butyric	12·1, 12·15	82·0, 82·4	125·5	118 [4]
*iso*Butyric	9·9, 9·7	67·1, 65·8	97	97 [3]
*iso*Valeric	11·7, 11·5	75·7, 74·4	97	100 [3]
n-Heptoic	11·5, 11·7	68·2, 69·4	56	54 [4]
Phenylacetic	12·3, 12·3	—, 71·7	119	115 [5]
Cinnamic	13·1, 13·3	73·8, 74·9	148	148—149 [2]
Crotonic	5·4, 5·5	36·9, 37·5	145	144·5—145·5 [6]

* M/10-proportions.

References: [1] Hantzsch, *Annalen*, 1882, **215**, 1. [2] Epstein, *ibid.*, 1885, **231**, 3. [3] Engelmann, *ibid.*, p. 37. [4] Jaeckle, *ibid.*, 1888, **246**, 32. [5] Jeanrenaud, *Ber.*, 1888, **21**, 1783. [6] Gryszkiewicz-Trochimowsky, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 1377.

Additional condensations, fresh materials being used throughout, were carried out with several of the aldehydes, and the concordant results obtained confirm the reproducible nature of the experiments: aldehyde-ammonia, 10·9 g., 81·65%; *n*-heptaldehyde, 11·5 and 11·7 g., 68·2 and 69·4%; phenylacetaldehyde, 12·3 and 12·5 g., 71·7 and 72·9%; β-phenylpropaldehyde, 15·4 g., 86·3%.

Notes on the Condensations with Certain Aldehydes.—n-*Butaldehyde.* No difficulty was experienced in isolating the product (clusters of colourless needles from methyl alcohol), immediate crystallisation occurring on cooling the reaction mixture (cf. Jaeckle, *loc. cit.*, who, however, used gaseous ammonia and no definite volume of alcohol)(Found: C, 64·6; H, 8·4. Calc.: C, 65·1; H, 8·5%). iso*Butaldehyde.* Crystallisation occurred on allowing the reaction mixture to stand after cooling (cf. Engelmann, *loc. cit.*); 75% aqueous methyl alcohol was used for washing the product. iso*Valeraldehyde.* The product did not crystallise readily (compare Engelmann) and it was found best to allow all the alcohol to evaporate, whereupon the product solidified, and then to treat it with 75% aqueous methyl alcohol; in the later stages, light petroleum (b. p. 40—60°) was used for washing the separated solid (Found: C, 66·0; H, 8·5. Calc.: C, 66·0; H, 8·7%). n-*Heptaldehyde.* The product did not crystallise readily and, owing to its solubility in the alcohols and to its tendency to liquefy with aqueous alcohols, the alcohol was allowed to evaporate completely from the reaction mixture, and the resulting solid was washed with light petroleum (b. p. 40—60°)(Found: C, 68·0; H, 9·2. Calc.: C, 67·7; H, 9·2%). *Phenylacetaldehyde.* Aqueous methyl alcohol was used for washing in the later stages (Found : C, 70·4; H, 7·3. Calc. : C, 70·0; H, 7·3%). *Cinnamaldehyde.* Epstein (*loc. cit.*) comments on the heat evolved when the reactants are mixed for this condensation; under the conditions employed here, there is some evolution of heat on mixing with all aldehydes, and this one is not abnormal, several others comparing with it. *Crotonaldehyde.* After the separation of as much solid as possible from the sticky reaction mixture, the latter was dissolved in ether and washed with 4N-sodium hydroxide, 4N-hydrochloric acid, and then water; the product from the dried extract yielded a further small quantity of solid with aqueous methyl alcohol (Found : C, 65·2; H, 7·9; N, 4·7. Calc. : C, 65·5; H, 7·9; N, 4·8%).

Oxidation of Dihydropyridine Derivatives with Nitric Acid.—The *iso*propyldihydropyridine derivative (1 g.) was heated under reflux with N-nitric acid (50 c.c.) until complete solution occurred (2 hours). The cooled, filtered solution was made alkaline with solid sodium carbonate, and the resulting precipitate separated. Crystallisation from aqueous methyl alcohol yielded ethyl 2 : 6-dimethylpyridine-3 : 5-dicarboxylate in fine, hair-like needles, m. p. 73° (Found : C, 62·3; H, 6·7; N, 5·6. Calc. : C, 62·1; H, 6·7; N, 5·6%).

The *n*-butyldihydropyridine derivative (3 g. at a time), treated as described above, yielded an oil which was extracted with ether. Fractionation of the dried (sodium sulphate) extract yielded *ethyl* 2 : 6-*dimethyl*-4-n-*butylpyridine*-3 : 5-*dicarboxylate* as a colourless oil, b. p. 198 199°/16 mm. (Found : C, 66·7; H, 7·9; N, 4·9. $C_{17}H_{25}O_4N$ requires C, 66·5; H, 8·1; N, 4·6%).

The benzyldihydropyridine derivative (2 g.) yielded ethyl 2 : 6-dimethylpyridine-3 : 5-dicarboxylate, m. p. and mixed m. p. 73°. An odour of benzaldehyde was perceptible after the oxidation.

The β-phenylethyldihydropyridine derivative (2 g.) only oxidised very slowly, a little remaining even after 40 hours' heating. The filtered acid solution deposited the *nitrate* of ethyl 4-β-phenylethyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate as iridescent needles, m. p. 128° (Found : N, 6·4. $C_{21}H_{25}O_4N,HNO_3$ requires N, 6·7%). Basification of the above acid solution, without separation of the nitrate, and extraction yielded the pyridine base, m. p. and mixed m. p. 34° (see below).

Oxidation of Dihydropyridine Derivatives with Sulphur.—The *iso*propyldihydropyridine derivative (12 g.) and sublimed sulphur (1·3 g.) were heated at 200° until the molten mixture became clear and free from gas bubbles (1·25 hours), no sulphur then remaining. The thick liquid obtained on cooling was extracted with 4N-hydrochloric acid, the extract filtered, and solid sodium carbonate added. The liberated oil was extracted with ether, and fractionation of the dried (sodium sulphate) extract yielded *ethyl* 2 : 6-*dimethyl*-4-iso*propylpyridine*-3 : 5-*dicarboxylate* as an almost colourless oil, b. p. 183°/11 mm. (Found : C, 65·4; H, 7·6. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·8%).

The benzyldihydropyridine derivative (10·75 g.) and sulphur (1 g.) were heated at 200° for 45 minutes. On the addition of 4N-hydrochloric acid, fine, silky needles of the hydrochloride separated, but these dissolved on addition of water. Treatment of the solution, as above, yielded *ethyl* 4-*benzyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* as a colourless oil, b. p. 225°/12 mm., which solidified on long standing and gave m. p. 46° (Found: C, 70·7; H, 6·6; N, 4·1. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7; N, 4·1%). On adding a small volume of 4N-hydrochloric acid to the liquid base, it began to dissolve and then almost immediately the *hydrochloride* separated as fine, colourless, silky needles, m. p. 89° (Found : HCl, 9·3. $C_{20}H_{23}O_4N,HCl$ requires HCl, 9·7%), soluble in excess of acid but salted out by sodium chloride.

The β-phenylethyldihydropyridine derivative (8·95 g.) and sulphur (0·8 g.) were heated at 170° for 1·25 hours. The above procedure being followed, a solid (probably the hydrochloride of the pyridine base) separated during the addition of the sodium carbonate, but it was decomposed as the addition was continued. Extraction and fractionation of the liberated oil yielded *ethyl* 4-β-*phenylethyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* as a colourless oil, b. p. 246—247°/18 mm., which solidified on long standing and then had m. p. 34° (Found : C, 70·5; H, 6·9; N, 3·7. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0; N, 3·9%).

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