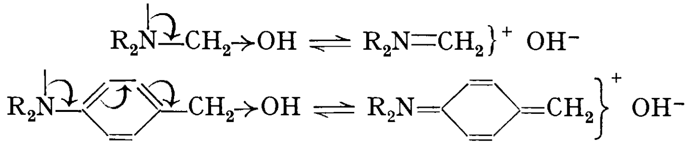
242. *A Contribution to the Chemistry of the Knoevenagel and Similar Reactions.*

By L. H. SMITH and K. N. WELCH.

OF the various theories put forward to explain the function of secondary bases as catalysts in Knoevenagel's reaction, the one which has received most support from recent experiments (cf. Mannich and Ganz, *Ber.*, 1922, **55**, 3486; Dilthey, *Ber.*, 1929, **62**, 1609; Rodionow and Postovskaja, *J. Amer. Chem. Soc.*, 1929, **51**, 841) is that the secondary base and the aldehyde form an intermediate compound of the type $NR_2{\cdot}CHR'{\cdot}OH$ (I), in which the hydroxyl group is " activated " by the tertiary nitrogen atom. Substances of type (I) are of extreme instability, however, and so the isolation of a compound of the type $NR_2{\cdot}CHR'{\cdot}CHR''_2$ (II) by the reaction of compounds containing the "active" methylene group with the reaction product of a secondary amine and an aldehyde is no proof that combination takes place by elimination of water between (I) and the substance containing the active methylene group; but the process may consist in the regeneration of the aldehyde and amine from (I), reaction of the aldehyde and the compound containing the active methylene group to form a compound of the type $OH{\cdot}CHR'{\cdot}CHR''_2$ (III), and reaction of this with the amine. Thus it has been found that $C(CH_2{\cdot}OH)_2(CO_2Et)_2$ and $CEt(CH_2{\cdot}OH)(CO_2Et)_2$ readily react with piperidine to give unstable products of the amino-ester-type.

It seemed possible that further light might be thrown on this reaction by employing substances of the type *p*-$NR_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH$, since the activating effect of the tertiary nitrogen atom on the hydroxyl group should be transmitted from the *p*-position through the ring. It would seem that this activation is to be accounted for on modern theories of electronic structure [cf., *inter alia*, Robinson, " Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions "] by the " anionoid " or " electron-donating " character of the $R_2\overset{|}{N}$— group which will tend to allow the hydroxyl group to separate as an ion, thus :



$$R_2N{-}CH_2{\rightarrow}OH \rightleftharpoons R_2N{=}CH_2\}^+\ OH^-$$

This would account for the catalytic action of the hydrogen ion (see p. 1138) by its removing the hydroxyl ions as water and thus forcing the equilibrium towards the right. It would also account for the inhibiting effect of excess of acid, under which conditions the $R_2\overset{|}{N}$— group will exist as $R_2\overset{H^+}{\overset{|}{N}}$— and thus lose its " electron donating " character.

As dimethylaminobenzyl alcohol itself is now readily available (see Smith and Welch, this vol., p. 730), it has formed the starting point of the investigation. This alcohol has been condensed with a number of substances containing the hydrogen atom activated by attachment to (1) the carbon atom of a methylene group between two acyl groups, (2) the benzene nucleus in the *o*- or *p*-position to a hydroxyl group, (3) a nitrogen atom as in primary or secondary amines, (4) a benzene nucleus in the *p*-position to a tertiary nitrogen atom. In many cases the reaction takes place smoothly without a catalyst, but in some cases the addition of triethylamine was found advantageous, probably not because of any direct catalytic action but because of its removal of any acid catalyst which (except in the case of condensation with amines) brings about undesirable side reactions (see below). The reaction bears a close analogy to the reaction of the hypothetical intermediate compound (I) ; *e.g.*, *p*-dimethylaminobenzyl alcohol condenses with dibenzoylmethane to give *αα-dibenzoyl-β-p-dimethylaminophenylethane* [reaction type (I)] and also to give ααγγ-tetrabenzoylpropane with elimination of dimethylaniline, which then condenses with another molecule of dimethylaminobenzyl alcohol to give tetramethyldiaminodiphenylmethane [reaction type (II)]. With phenols, reaction type (I) predominates; *e.g.*, phenol itself gives 4-dimethylamino-4′-hydroxydiphenylmethane, identical with that produced by condensation of dimethylaniline and 3 : 5-dibromo-4-hydroxybenzyl bromide and reduction of the resulting compound (Strecker, *Annalen*, 1904, **334**, 339). Resorcinol similarly gives *4-dimethylamino-2′ : 4′-dihydroxydiphenylmethane*, and α- and β-naphthols give respectively the 4- and the *1-dimethylaminobenzylnaphthol*, the constitution of the last two compounds being established by the fact that the former readily gives a nitroso-derivative which forms a red co-ordination complex with cobalt, whereas the latter gives with difficulty a nitroso-compound which does not form such a co-ordination compound.

With primary and secondary amines similarly, reaction type (I) predominates; *e.g.*, *p*-toluidine readily reacts to give *p*-dimethylaminobenzyl-*p*-tolylamine, identical with the compound prepared by the action of anhydroformaldehyde-*p*-toluidine on a mixture of dimethylaniline and *p*-toluidine hydrochloride (Cohn and Fischer, *Ber.*, 1900, **33**, 2590), and diphenylamine reacts similarly. In the case of *o*-nitroaniline, however, the reaction proceeds exclusively as reaction type (II) to give methylenebis-*o*-nitroaniline.

It is noteworthy that *p*-dimethylaminobenzyl alcohol and strong bases such as piperidine and diethylamine undergo no ready reaction, and also no facile reaction was found to take place with ammonia, benzyl mercaptan, or hydrogen sulphide.

The reaction with dimethylaniline is particularly interesting in view of its bearing on the mechanism of the formation of " tetramethyl-base " (IV) and similar reactions in which *p*-dimethylaminobenzyl alcohol would seem to be the obvious intermediate compound; thus the reaction would proceed in two stages :

$$NMe_2{\cdot}C_6H_5 + CH_2O \longrightarrow NMe_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH \longrightarrow NMe_2Ph + CH_2(C_6H_4{\cdot}NMe_2)_2 \quad \text{(IV.)}$$

Von Braun and Kruber (*Ber.*, 1912, **45**, 2077) suggested that the reactions of $NMe_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}NH{\cdot}C_6H_4Me$ (V) with a number of compounds, especially phenols and amines, in acid solution were probably not accounted for by its hydrolysis with formation of dimethylaminobenzyl alcohol, since they found that substances of somewhat similar constitution to dimethylaminobenzyl alcohol and also " dimethylaminobenzyl alcohol " (see below) itself did not readily condense with amines under the conditions which were employed for the condensation of (V) with the phenols and amines. (For a similar reason, those authors considered that the formation of tetramethyl-base could not be accounted for by the intermediate formation of *p*-dimethylaminobenzyl alcohol.) Moreover, they explained the readier reaction of substances of the type $NHMe{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH$, where the nitrogen is not tertiary, as being due to the intermediate formation of a quinonoid type of compound. In order to test this theory for the case of the condensation of dimethylaminobenzyl alcohol with dimethylaniline, a study has been made of the comparative rates of this reaction and that of dimethylaniline with formaldehyde. Although no accurate measurements were obtained, it was found that the former reaction takes place very readily indeed in the presence of a trace of hydrogen chloride (contrary to the suggestion of von Braun and Kruber) and is very much faster than the latter, thus lending support to the idea that dimethylaminobenzyl alcohol is an intermediate stage in the formation of tetramethyl-base. It must also be pointed out that the compound described by von Braun and Kruber as dimethylaminobenzyl alcohol was not this substance, as shown by Clemo and Smith (J., 1928, 2423 ; see also Smith and Welch, *loc. cit.*).

It is further noteworthy that although a trace of acid strongly catalyses this reaction, and also that with *p*-toluidine, both alkali and excess of acid greatly decelerate the reaction ; for instance, in the preparation of *p*-dimethylaminobenzyl alcohol, a large excess of acid is used to inhibit this side reaction.

EXPERIMENTAL.

*αα-Dibenzoyl-*β*-p-dimethylaminophenylethane.*—Dibenzoylmethane (7·5 g.) and *p*-dimethylaminobenzyl alcohol (5 g.) were heated in an oil-bath at 155—170° in the presence of 0·5 c.c. of triethylamine for one hour; the product was extracted from tarry matter by stirring with 5 c.c. of benzene and standing in the ice-box for two days. The crystals (5 g.) were collected, shaken with 5*N*-hydrochloric acid, and again filtered off. The filtrate was made alkaline with 50% potassium hydroxide, and the yellow crystals were filtered off, and recrystallised twice from benzene–light petroleum, giving *αα-dibenzoyl-*β*-p-dimethylaminophenylethane* (2 g.), pale yellow needles, m. p. 132—133° (Found : C, 80·8; H, 6·6; N, 3·9. $C_{24}H_{23}O_2N$ requires C, 80·7; H, 6·4; N, 3·9%). The residual solid, insoluble in hydrochloric acid, was washed with water, dried, and recrystallised from the same mixed solvent, giving ααγγ-tetrabenzoylpropane (2 g.), m. p. 173—175°, not depressed by admixture with an authentic specimen. In the absence of triethylamine the reaction proceeded even more readily, but almost entirely as reaction type (II).

4-Dimethylamino-4′-hydroxydiphenylmethane.—Phenol (3 g.) and *p*-dimethylaminobenzyl alcohol (5 g.) were condensed together and the product worked up under the same conditions as above; the white crystals of 4-dimethylamino-4′-hydroxydiphenylmethane (yield 0·8 g.) were recrystallised from light petroleum, m. p. 107—108° (Strecker gives m. p. 108—109°) (Found : N, 6·0. Calc. for $C_{15}H_{17}ON$: N, 6·2%).

4-Dimethylamino-2′ : 4′-dihydroxydiphenylmethane.—*p*-Dimethylaminobenzyl alcohol (5 g.), resorcinol (4·5 g.), and 0·5 c.c. of triethylamine were heated in an oil-bath at 125—140° for one hour. The product was dissolved in ethyl acetate, treated with animal charcoal, and filtered. On cooling in ice, pale pink crystals of *4-dimethylamino-2′ : 4′-dihydroxydiphenylmethane* (2·5 g.) were obtained, which are best purified by recrystallisation from aqueous methyl alcohol. The substance forms long, pale pink needles, m. p. 172·5° (slight decomp.) (Found : N, 5·9. $C_{15}H_{17}O_2N$ requires N, 5·8%).

1-*Dimethylaminobenzyl*-2-*naphthol.*—*p*-Dimethylaminobenzyl alcohol (5 g.) and β-naphthol (4·75 g.) without a catalyst reacted as before at 140° in one hour. The solid product was recrystallised from benzene, forming pale yellow crystals, m. p. 143° (slight decomp.) (yield 4·5 g.) (Found: C, 82·2; H, 7·2; N, 5·1. $C_{19}H_{19}ON$ requires C, 82·3; H, 6·9; N, 5·1%). Nitrous acid gave a brown coloration with this substance, but a nitroso-compound could not be isolated, and the crude product did not give a co-ordination compound with cobalt salts.

4-*Dimethylaminobenzyl*-1-*naphthol.*—In precisely analogous manner, this *compound* was obtained from α-naphthol; it crystallised from benzene (charcoal) as pale pink crystals (yield 2·5 g.). After a second recrystallisation from aqueous methyl alcohol, it formed pale pink silky needles, m. p. 148—149° (slight decomp.) (Found: N, 5·1%). It gave with alcoholic ferric chloride a fine carmine coloration; and on treatment in the usual way with nitrous acid, it yielded a nitroso-derivative as a voluminous brown precipitate, which on solution in dilute acetic acid, addition of a cobalt salt, and boiling, gave a fine red coloration which was precipitated by the addition of sodium acetate as a red-brown precipitate, almost indistinguishable from that formed by nitroso-α-naphthol, except that it was soluble in, and stable towards, dilute mineral acids. The condensation of *m*-2-xylenol with dimethylaminobenzyl alcohol led only to a glassy solid which could not be recrystallised; quinol did not react. Moreover, the reactions with phenols did not proceed in the desired direction in the presence of a trace of acid, probably owing to auto-condensation of the *p*-dimethylaminobenzyl alcohol; neither did the reaction proceed smoothly in pyridine solution.

p-*Dimethylaminobenzyl*-p-*tolylamine.*—*p*-Dimethylaminobenzyl alcohol (5 g.) and *p*-toluidine (3·5 g.) were heated in the presence of 0·5 c.c. of triethylamine at 190—200° C. for one hour. The product was recrystallised from methylated spirits, forming pale yellow crystals (yield 4 g.), m. p. 101°, which could not be raised to 105° (Cohn and Fischer, *Ber.*, 1900, **33**, 2590) by repeated crystallisation. However, the crystalline form and solubility relations were in agreement with those described by those authors for *p*-dimethylaminobenzyl-*p*-tolylamine (Found: N, 11·64. Calc. for $C_{16}H_{20}N_2$: N, 11·66%). This reaction also proceeded readily by the use of an acid catalyst; the alcohol (1·5 g.) and *p*-toluidine (0·75 g.) with one drop of concentrated hydrochloric acid gave a yield of 1·5 g. in 12 hours at 37°.

Diphenyl-p-*dimethylaminobenzylamine.*—Diphenylamine (3·5 g.) and *p*-dimethylaminobenzyl alcohol (3 g.) reacted in the presence of 0·3 g. of triethylamine at 200—205° for 2 hours. After standing for 11 days, a solid product separated, which was filtered off and recrystallised first from alcohol and then from ligroin. The *amine* forms colourless needles, m. p. 80—81° (Found: N, 9·45. $C_{21}H_{22}N_2$ requires N, 9·3%); it is very soluble in light petroleum, and its solution in sulphuric acid gives with a trace of nitric acid the blue-violet colour which appears to be characteristic of diphenylamine and its *N*-substitution derivatives; moreover, it gives no colour with lead peroxide and acetic acid. That the above formulation is probably correct is also shown by its non-identity with the only other probable product of the reaction *p*-(*p*'-dimethylaminobenzyl)diphenylamine (Höchster Farbw., D.R.P. 107718), which is an oil and gives a blue colour with lead dioxide and acetic acid such as is given by derivatives of *pp*'-diaminodiphenylmethane.

Methylenebis-o-*nitroaniline.*—*p*-Dimethylaminobenzyl alcohol (2 g.) and *o*-nitroaniline (2 g.) reacted readily in the absence of a catalyst at 130° in 1 hour, and the solid product (1·5 g.) on recrystallisation from alcohol had m. p. 195°, unchanged by admixture with an authentic specimen.

4 : 4'-*Tetramethyldiaminodiphenylmethane* ("*Tetramethyl-base*").—(1) Dimethylaniline (1 g.) and dimethylaminobenzyl alcohol (1 g.) with one drop of hydrochloric acid solidified completely to a theoretical yield of the base after 3 days at room temperature, or after 1 minute's boiling. (2) An almost theoretical yield was obtained by heating the same quantities of reagents for ½ hour at 180° in the presence of a few drops of triethylamine.

In order to test von Braun and Kruber's suggestion that dimethylaminobenzyl alcohol could not be the intermediate in the preparation of tetramethyl-base, the following comparative experiments were performed. (*a*) 2 G. of dimethylaniline, 0·6 g. of 40% formaldehyde, and 3 drops of concentrated hydrochloric acid were mixed, and alcohol added to give a homogeneous solution; (*b*) 1 g. of dimethylaniline, 1 g. of *p*-dimethylaminobenzyl alcohol, and 3 drops of concentrated hydrochloric acid were mixed, and alcohol added to make the volume of the mixture equal to that of (*a*). Both mixtures were placed in a thermostat at 37°, and the rate of formation of the base was determined by the appearance of a blue colour when a small portion of the mixture was treated in acetic acid solution with lead dioxide, and also by the appearance of crystals in the liquid on seeding. After one hour, (*b*) developed a deep blue colour with lead dioxide, whereas (*a*) gave no trace of blue. After two hours, both mixtures were cooled, and then (*a*) on seeding deposited no crystals of base, whereas (*b*) went completely solid without seeding. At the end of 4 hours, (*a*) was still liquid at 37°, while (*b*) had almost entirely solidified.

UNIVERSITY OF MELBOURNE.

[*Received, April* 19*th*, 1934.]