107. *Aldol Condensation Products.*

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A study has been made of the water-soluble products obtainable from aldol by suitable condensation. An account is given of the preparation and reactions of these compounds and of their methyl and acetyl derivatives, for which structural formulæ have been deduced. It is suggested that the condensation occurring is of a simple aldol type, resulting in the formation of hydroxylated aldehydes which react as cyclic lactol forms.

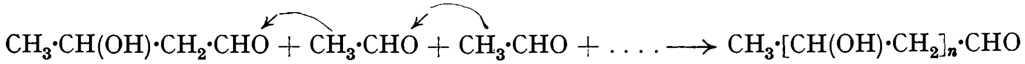
Whilst a considerable amount of work has been carried out recently on the condensation of unsaturated aldehydes, in particular of crotonaldehyde, very little appears to have been accomplished in the parallel cases of the saturated hydroxylated compounds derived from aldol. The condensation of acetaldehyde to aldol in the presence of dilute alkali is well known, and a further condensation under similar conditions can easily be effected, one such process having been described by Raper (J., 1907, **91**, 1831), who also gives an account of a preliminary investigation of the condensation products.

In the experiments now to be described, the starting material was obtained by the condensation of crude aldol in concentrated aqueous solution by the addition of small quantities of lime, the reaction being allowed to proceed until compounds ranging roughly from C_8 to C_{12} resulted. The product was a slightly viscid, yellow syrup, readily soluble in water or alcohol, insoluble in other organic solvents.

The aldol condensation product exerted a weakly reducing action, so the possibility of effecting a mild oxidation prior to a possible fractionation was investigated. This included oxidation by silver oxide, wherein silver deposits were formed but no silver salts could be isolated, and treatment with bromine water and aqueous potassium permanganate, there being in each case a rapid absorption of the reagent but no evidence for carboxylic compounds resulting. It was concluded that $-CHO \longrightarrow -CO{\cdot}OH$ was not the primary reaction involved, but that the compounds were vulnerable to oxidative attack possibly at a double bond. In permanganate oxidation there was always an evolution of carbon dioxide, and the reaction appeared to be analogous to that given by the methyl derivatives shortly to be described, where the reaction of a carbonyl group is eliminated. This absence of true aldehydic function was borne out by the difficulty experienced in effecting condensation with the usual carbonyl reagents, *e.g.*, phenylhydrazines, from which no satisfactory products could be isolated.

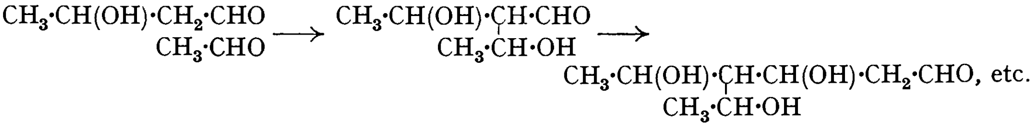
By treatment of the crude aldol product at room temperature with dry methyl alcohol containing a trace of hydrogen chloride, methyl derivatives were readily formed, the viscid syrupy product resembling the original material in appearance and viscosity, but differing greatly in solubility, being almost insoluble in water, readily soluble in alcohol and other organic solvents. The compounds so obtained were non-reducing and stable to alkali, but were rapidly demethylated on treatment with dilute mineral acid. Methoxyl estimations on various samples indicated that methylation proceeded to some fixed point, roughly constant figures being obtainable, which corresponded to that required for half acetal formation on the assumed degree of polymerisation.

From the fact that the starting material was obtained from crude aldol containing unchanged acetaldehyde, under conditions essentially similar to those applied for the preparation of aldol itself, it seemed plausible to assume that the final products may be regarded as acetaldehyde condensation products, the condensation being of an aldol type to give a mixture of closely related polymers restricted to some definite range. In order that such a process may be repeated indefinitely condensation must proceed regularly as indicated,



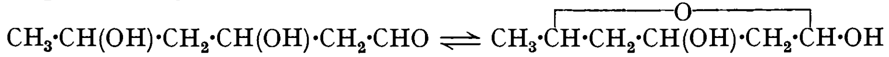
$$CH_3\cdot CH(OH)\cdot CH_2\cdot CHO + CH_3\cdot CHO + CH_3\cdot CHO + \ldots\ldots \longrightarrow CH_3\cdot[CH(OH)\cdot CH_2]_n\cdot CHO$$

although the possibility of aldolisation of the active α-methylene group in the aldol is not excluded and would give rise to branched chain compounds, *e.g.*,



$$\begin{matrix}CH_3\cdot CH(OH)\cdot CH_2\cdot CHO\\ CH_3\cdot CHO\end{matrix} \longrightarrow \begin{matrix}CH_3\cdot CH(OH)\cdot CH\cdot CHO\\ CH_3\cdot CH\cdot OH\end{matrix} \longrightarrow \begin{matrix}CH_3\cdot CH(OH)\cdot CH\cdot CH(OH)\cdot CH_2\cdot CHO\\ CH_3\cdot CH\cdot OH\end{matrix}\text{, etc.}$$

For the various possibilities it is found that they have in common alternate hydroxylated carbon atoms, and in many cases there is a chain of six or more such carbon atoms terminated by an aldehyde group. From steric considerations, and by analogy with well-known cases of oxy-cyclo tautomerism in γ- and δ-hydroxy-aldehydes or -ketones, it seemed reasonable to suppose that these compounds should have a cyclic structure represented in the simplest case by



$$CH_3\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CHO \rightleftharpoons CH_3\cdot\overbrace{CH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CH}^{O}\cdot OH$$

Such a lactol ring structure seemed all the more probable in view of the modified aldehydic functions exhibited and the ready formation and stability of the methyl derivatives.

In order to obtain further insight into the constitution of these aldol products it was necessary first to isolate individuals from the supposed mixture of polymers. For this purpose a fractionation of the methyl derivatives seemed suitable, inasmuch as the molecule was thought to be stabilised by the presence of the lactol methyl group and it was hoped to use these compounds for the preparation of further derivatives. The crude methylated material was volatile at moderate temperatures and very low pressures, but a separation by fractional distillation was unsuccessful.

Pursuing a similar line of attack, it was thought that such compounds should be capable of further methylation to give methyl ether derivatives of the methyl-lactolides, to which the fractional distillation or other method for separation might then be applied. This also proved impracticable, since it was not possible to effect a further methylation of the crude methylated material or of the partly fractionated mixtures by the use of methyl iodide or methyl sulphate and alkali. On the other hand, by using either of these reagents with the original aldol product, it was possible to obtain methyl derivatives similar to those prepared by use of methyl alcohol, though usually of slightly lower methoxyl content.

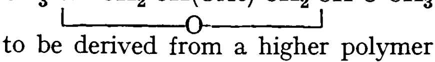
As an alternative to methylation, benzoylation of the methyl-lactolides was attempted but with no success.

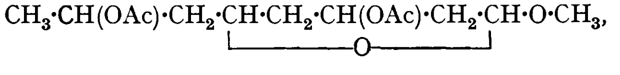
This incapacity for further methylation, pointing to the absence of hydroxyl groups, might be accounted for by a dehydration similar to the aldol–crotonaldehyde conversion, so tests for ethenoid reactivity were applied. Potassium permanganate in acetone was rapidly decolorised and there was a measurable absorption of hydrogen with a platinum catalyst, though in neither case could satisfactory quantitative relationships be established; with perbenzoic acid there was no reaction. The course of the reaction with bromine in chloroform or carbon tetrachloride solution suggested that substitution as well as addition had occurred. The evidence for unsaturation was inconclusive, an interpretation of the results being very considerably complicated by the fact that the fractionated products investigated were undoubtedly mixtures.

On the other hand there was definite evidence forthcoming for the presence of potential hydroxyl groups, in the possibility of acetylation, which gave rise to products separable by distillation into well-defined fractions. Preliminary experiments on the acetylation of the free aldol material under mild conditions had shown little promise, but derivatives of the methyl-lactolides were readily prepared by treatment with acetic anhydride at its boiling point. Moreover, it is perhaps significant that at lower temperatures reaction did not appear to proceed to any extent, even when the reactants were heated together for a considerable time, whereas under the conditions applied, reaction occurred rapidly and with considerable evolution of heat. The crude products so obtained were reddish-brown syrups, rather more mobile than the untreated material, and still retained the methyl-lactolide group intact.

This mixture of acetates was submitted to a fractional distillation at low pressures, a separation into sharply defined fractions being attainable after three distillations, the b. p. of the products being 15—20° lower than those of supposedly corresponding methyl-lactolides. They were readily distinguishable from the latter by the greater mobility of the lower fractions and their pleasant, ester-like smell, which showed an increased tendency to pungency in the more viscid, higher fractions. The two lowest fractions were taken for further investigation, as described in the experimental section, these being obtained in 10% and 20% yields, and from their physical constants were considered to be chemical individuals. Considerable difficulty was encountered in obtaining satisfactory analytical figures for these products in spite of their apparent purity, so notes on the nature of the difficulties and the special procedure adopted have been included.

The experimental findings show that the behaviour of aldol condensation products is unexpectedly complicated, so it is difficult to assign structural formulæ to the various derivatives obtained. A study of the methylated derivatives and their acetates renders their formulation as cyclic lactolides highly probable. From the behaviour of the more volatile acetate isolated (*acetate* I) and the analytical figures obtainable from it, it seems probable that it is derived from the lactol form of the simple linear condensation product of three molecules of acetaldehyde and that it may be represented by the structure $CH_3{\cdot}CH{\cdot}CH_2{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH{\cdot}O{\cdot}CH_3$. The second acetate isolated (*acetate* II) is thought to be derived from a higher polymer, resulting from the condensation of four molecules of acetaldehyde, and to have the structure

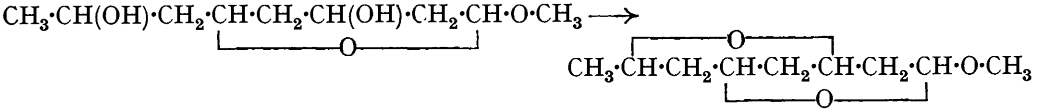




$$CH_3{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH{\cdot}CH_2{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH{\cdot}O{\cdot}CH_3,$$

which is in agreement with its chemical behaviour and the analyses obtainable from it.

In view of the impossibility of fractionating the methyl aldols completely, suggestions for their structure are more tentative, though by their close relationship to the acetates a corresponding formulation as methyl-lactolides of polyhydroxy-aldehydes is possible. To account for the apparent absence of hydroxyl groups and of definite unsaturation, it is thought that for the higher homologues dehydration with the formation of an anhydro-ring may have occurred, *e.g.*,



$$CH_3\cdot CH(OH)\cdot CH_2\cdot CH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CH\cdot O\cdot CH_3 \longrightarrow CH_3\cdot CH\cdot CH_2\cdot CH\cdot CH_2\cdot CH\cdot CH_2\cdot CH\cdot O\cdot CH_3$$

Acetylation would then be preceded by a fissure of the anhydro-ring, thus accounting for the vigorous conditions necessary and the course of the reaction with acetic anhydride.

EXPERIMENTAL.

Preparation of Aldol Condensation Products.—Aldol (100 g.), dissolved in an equal weight of water, was treated with lime (2 g.), added to the well-stirred mixture during 30 minutes. The reaction was carried out at room temperature, though there was an initial rise of 5° with a simultaneous development of yellow coloration and increase in viscosity. Stirring was continued for 3—4 hours; the titration figure for a small aliquot portion, treated with hydroxylamine hydrochloride for estimation of carbonyl group, had then decreased to one-third of its original value, this being taken as a rough index of the degree of condensation which had occurred. Lime was removed by precipitation as calcium carbonate, resinous material was extracted with chloroform, and the remaining aqueous solution was evaporated at 50°/20 mm., small quantities of side products, thought to be calcium salts, being precipitated by addition of acetone when the solution had been partly concentrated. The product was a slightly viscid, yellow syrup with an aldol-like smell, soluble in water and alcohol, very sparingly soluble in ether and other organic solvents. By heating in a stream of dry air for several hours at 45°/20 mm. there was a loss in weight of approximately 12%, the carbonyl figure being simultaneously reduced from 10·5% to 7·5%. This was accounted for by supposing that there was dehydration, together with removal of the most volatile products, including any unchanged aldol.

Oxidation Experiments on Aldol Condensation Products.—Qualitative tests showed that (i) ammoniacal silver nitrate was reduced very slowly at 50° and at a measurable rate at 100°, (ii) reduction of Fehling's solution occurred slowly at 100°, and (iii) bromine water and aqueous potassium permanganate were rapidly decolorised.

The following large-scale oxidations were attempted, and the reaction mixtures worked up chiefly with a view to isolating organic salts: (*a*) a 20% aqueous solution was treated with freshly precipitated silver oxide; (*b*) a concentrated aqueous solution was treated with bromine water, which led to the formation of strongly reducing material, acrid-smelling and lachrymatory, not sufficiently stable for isolation; (*c*) reaction with potassium permanganate, in aqueous or acetone solution, yielded no organic salts, though considerable quantities of potassium carbonate resulted from oxidative breakdown.

Methylated Aldol Products.—Trial experiments showed that methylation was possible with methyl alcohol containing 1% of hydrogen chloride, and that the methoxyl content of the product was increased from 12% to 16% by the use of carefully dried material and reagent. Similar products (OMe, 11%) were obtained by refluxing the aldol product with twice its weight of methyl iodide and an equivalent weight of silver oxide for several hours, or by treatment with excess of methyl sulphate and equivalent amounts of aqueous sodium hydroxide in methyl-alcoholic solution, though in the latter case it was difficult to avoid resinification. Further methylation of any of these products by similar treatment with methyl iodide or with methyl sulphate and alkali in the presence of alcohol, acetone or dioxan was not effected.

The following procedure was found to be the most satisfactory for large-scale preparations, in giving products with the highest and most consistent methoxyl content. Aldol material, previously heated for 8—10 hours at 45°/20 mm. with a current of dry air passing through, was dissolved in thirteen times its weight of dry methyl alcohol containing 0·7% of hydrogen chloride, and was kept for 12 hours at room temperature. After neutralisation with lead carbonate and filtration, the solution was evaporated at 45°/20 mm. and finally dried by heating for 1 hour at 50°/20 mm. The yield was 92% of the weight of dried starting material (approx. 100 g.) and the average methoxyl figure was 14%. The methyl-alcohol distillate obtained in this preparation invariably contained appreciable amounts of volatile material, possibly aldol dimethylacetal, which was neglected. It was frequently found that in spite of every attempt to adhere to a standard procedure, the products resulting were darker and more viscid and contained only 9% of methoxyl. These were thought to have been formed by initial polymerisation of the aldol material in the presence of the traces of acid necessary for the methylation, and were not used for further investigation.

The methylated product was a pale yellow syrup of medium viscosity, soluble in organic solvents and very sparingly soluble in water. It was non-reducing towards silver nitrate and Fehling's solution, and only absorbed bromine from chloroform solution very slowly. Potassium permanganate in acetone solution was rapidly decolorised.

A fractional distillation of 80 g. was effected, the final distillation being carried out in a Widmer flask immersed in a carefully controlled bath, small fractions being collected over a narrow temperature range. Figures for typical lower fractions are given :

Fract.	Press., mm.	Bath temp.	B. p.	Yield, g.	$n_D^{20\cdot5°}$	OMe, %.
1	0·07	77—80°	50—51°	5·31	1·4464	19·2
3	0·06	90—110	50	0·92	1·4519	17·4
6	0·12	106	82	1·06	1·4622	12·1
7	0·12	109	84	3·04	1·4616	11·5

Investigation of Methyl Aldol Products.—Qualitative tests on unfractionated material suggested the presence of unsaturated linkages, and the following methods were adopted in order to establish the existence of ethenoid links and, if possible, to assess them.

(*a*) Bromine absorption in chloroform proceeded slowly, requiring several hours to go to completion, the reagent being added in small quantities with time for complete absorption between successive additions. The reaction mixture developed acidity, which was less marked on repetition in carbon tetrachloride solution, where the rate of absorption was also decreased and amounted to less than half of that expected on the assumed molecular weight.

(*b*) Hydrogenation with a platinum oxide catalyst was found to be most effective in glacial acetic acid solution, ethyl- and methyl-alcoholic solutions also being tried, and was complete in 50 minutes. For the lower fractions the absorption measured corresponded to approximately half that expected for one double bond. For the higher fractions absorption was proportionally greater, but was not found to increase by prolonged heat treatment prior to the hydrogenation.

(*c*) Treatment of fractionated methyl aldol with dilute aqueous or dry acetone solution of potassium permanganate showed an oxygen absorption roughly corresponding to the hydrogenation figures. Reaction was rapid at first and then slowed down considerably, not reaching an end-point for several hours.

Acetylated Methyl Aldol Products.—Preliminary experiments indicated the necessity for vigorous conditions for acetylation, modified procedures in which similar reaction mixtures were heated for 1—3 hours at 50—100° being unsatisfactory, since, although it seemed probable that some reaction had occurred, yet the products retained many of the characteristic properties of untreated methyl aldol material, and could not be satisfactorily separated, as was the case with those to be described.

A mixture of unfractionated methyl aldol material (50 g.) with acetic anhydride (100 g.) and anhydrous sodium acetate (15 g.) was heated cautiously to 130°; reaction then set in, causing vigorous ebullition. The reaction was allowed to proceed to completion, heating was recontinued for 10 minutes, and most of the excess of acetic anhydride was then rapidly distilled off. The hot mixture was poured slowly into a large volume of well-stirred ice-cold water (4 l.), whereby a red viscid syrup separated, which was extracted with chloroform after 1 hour. The extract was washed free from acid and, on removal of the solvent, gave a reddish-brown, semi-viscid syrup, the yield corresponding to 116% by weight of the starting material.

Fractionation of the acetates was carried out similarly to that of the methyl aldol products, though in this case the more volatile products were distilled at 20 mm. because of their relatively greater volatility. In the first distillation there was evidence of a separation, which appeared to be complete after the third fractionation, as indicated by b. p., refractive index, and analysis. From a consideration of the data, some of which are recorded below, the estimated yields of the two compounds isolated approximated to 10% and 20%.

Fract.	Press., mm.	Bath temp.	B. p.	Yield, g.	$n_D^{20\cdot5°}$.
1	22	131°	107°	2·69	1·4260
2	21	131	107	2·35	1·4279
5	19	139	109	0·77	—
7	20	139	108°	3·23	1·4466
8	0·14	106	83	5·32	1·4463
9	0·17	108	83·5	5·91	1·4457

These acetyl derivatives were colourless syrups, the lower fractions mobile with fragrant smell, higher fractions (not shown in the table) more viscid and not sweet-smelling. They were all insoluble in water and readily soluble in organic solvents, non-reducing towards Fehling's solution or ammoniacal silver nitrate, and did not undergo hydrogenation. There was no reaction with bromine in chloroform or with potassium permanganate in acetone, except after long standing; reaction then slowly developed and thereafter proceeded at a measurable rate.

From three such complete fractionations it was possible to obtain, in equivalent yields, fractions thought to contain chemically pure individuals as shown by constancy of b. p. and refractive index. These were the acetylated methyl-lactolides I and II referred to in the discussion.

Acetate I, obtained from fraction (2) above by redistillation, was a very hygroscopic, pleasant-smelling, colourless, mobile liquid, b. p. 107°/21 mm., $n_D^{20\cdot5°}$ 1·4270 [Found: C, 56·7; H, 8·2; OMe (max.), 16·3; Ac, 31·6 by alkaline estimation, 28·5 by acid hydrolysis; *M*, in benzene, 186. $C_9H_{16}O_4$ requires C, 57·5; H, 8·5; OMe, 16·5; Ac, 22·9%; *M*, 188].

Acetate II, obtained from fraction (8) above by redistillation, was a hygroscopic, slightly viscid liquid, less fragrant-smelling than acetate I, b. p. 83°/0·15 mm., $n_D^{20\cdot5°}$ 1·4460 [Found: C, 57·5; H, 8·1; OMe (max.), 11·6; Ac, 35·8 by alkaline estimation; *M*, in benzene, 270. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·0; OMe, 11·3; Ac, 31·3%; *M*, 274].

Comments on analytical figures. (a) C and H figures were very consistent for samples of different batches and are in much better agreement with those required for higher homologues in each case, *i.e.*, acetate I as $C_{13}H_{22}O_6$ and acetate II as $C_{17}H_{28}O_8$. In spite of rigorous fractionation acetate I always gave a slight acid reaction, thought to be due to acetic acid, which might explain the low carbon figure. Acetate II gave no such acid reaction and for its high carbon value some other explanation is necessary, the analytical figures for various samples being equally consistent.

(b) Zeisel estimations were carried out with the utmost care by semi-micro-methods. It was necessary in all cases to start the reaction in the cold and to warm very gradually to avoid resinification as far as possible. In order to reach an end-point, it was necessary to continue the reaction for 3 hours, the formation of methyl iodide being very slow after the first hour. Typical figures for acetate II are: 9·6, 10·9, and 11·6% for 1, 2, and 3 hours respectively.

(c) Deacetylation proceeded very readily, but it was difficult to achieve a quantitative estimation owing to the possibility of further reaction with alkali or, in the case of acid hydrolysis, to avoid complications by simultaneous demethylation. For macro-acetyl determinations N/10-sodium hydroxide or -barium hydroxide was used, the reaction being allowed to proceed for 1 hour at 50°, in aqueous acetone solution and in an atmosphere of nitrogen. Consistent figures were obtainable in spite of the appearance of a yellow indicator-like side product, which somewhat obscured the end-point of the titration.

Comparative micro-acetyl estimations using acid or alkaline hydrolysis gave lower values in the former case.

(d) Molecular-weight determinations on the acetates were made by cryoscopic methods in benzene, glacial acetic acid, and camphor as solvents. In acetic acid precaution was taken to exclude atmospheric moisture, yet the values obtained were lower than those in benzene, *e.g.*, acetate I 174 and 186 respectively, and decreased with concentration, *e.g.*, 177 for 0·1847 g. and 169 for 0·2971 g. in 25 g. of solvent. In benzene solution results were more consistent, yet lower values were obtained after several hours than immediately after solution; *e.g.*, for acetate II, 220 $\longrightarrow$ 270.

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