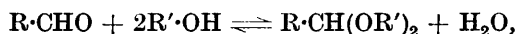


#### XIV.—*The Direct Acetalisation of Aldehydes.*

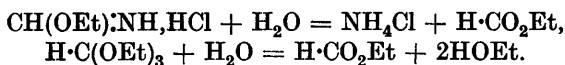
By ROBERT DOWNS HAWORTH and ARTHUR LAPWORTH.

THE researches of E. Fischer on the conversion of aldehydes into acetals by means of alcohol containing hydrogen chloride (*Ber.*, 1897, **30**, 3053; 1898, **31**, 345, 1989) suggested a close analogy between this process and the catalytic process for esterification of carboxylic acids. Delepine (*Compt. rend.*, 1900, **131**, 684, 745; 1901, **132**, 331, 969) showed that when aldehydes react with alcohols in presence of mineral acid an equilibrium is attained,



the speed of reaction increasing with the proportion of mineral acid acting as catalyst. As the equation indicates, the proportion of acetal formed is detrimentally affected by the presence of water, and there can be little doubt that this factor is of predominating importance in the case of ketones, the acetals of which class cannot be prepared by Fischer's method.

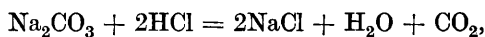
The methods used by Claisen for the conversion of aldehydes and ketones into acetals (*Ber.*, 1893, **26**, 2731; 1896, **29**, 1005, 2931; 1900, **33**, 3778; 1903, **36**, 3664; 1907, **40**, 3903; *Annalen*, 1894, **281**, 312; 1896, **291**, 43; 1897, **297**, 3) depend on the use of the hydrochlorides of formimido-esters or of orthoformic esters. Used as additions to an alcoholic system in which acetalisation is taking place, these agents may be considered to affect the final yield of acetal by eliminating water irreversibly from the system in accordance with the equations



The agents used by Claisen are theoretically almost ideal ones for this purpose, but their cost militates very seriously against their general use for the economical preparation of acetals in large quantities, and searches for cheap substitutes have not been fruitful. Direct acetalisation, by acidified alcohol, of aldehydes which yield readily volatile acetals, which can be removed from the system by distillation, appears to be relatively simple in certain cases; but in the majority of instances, including those dealt with in the practical part of the present paper, the properties of the acetals probably do not admit of separation by fractional distillation. In Fischer's method, the aldehyde is dissolved in absolute alcohol containing about 1 per cent. of hydrogen chloride, and, when acetalisation is judged to be complete, the whole is poured into water containing sodium hydroxide or potassium carbonate to neutralise the mineral acid which serves as catalyst, and which, if allowed to remain, would tend to cause rapid hydrolysis of the acetal; the acetal is subsequently isolated with ether, for example, by extraction.

The foregoing procedure has several disadvantages. The very considerable excess of strong alcohol is recovered, if at all, in a highly dilute condition, and the mass of liquid to be extracted is very large. Moreover, workers who have attempted to follow it, especially, but not only, with large quantities of material, have frequently found it difficult to obtain the yields mentioned by Fischer, and this is possibly to be ascribed to the hydrolysis of acetal by the water used for dilution while the neutralisation is

locally incomplete. It is evident that both these drawbacks would be eliminated by neutralising the catalyst with an agent which during the operation did not increase the ratio, water : alcohol, in the system. For this purpose, ammonia or organic bases suggest themselves; but the authors' experiments indicate that ammonium chloride itself is an effective catalyst; for this reason, and because of the complications likely to ensue, the systematic experiments in this direction have not been pursued, although in some cases these compounds might be adapted for the purpose. Carbonates, etc., of the alkali metals, being insoluble in strong alcohol, introduce the danger of imperfect neutralisation of catalyst with fatal results on the yields; their use would also tend to increase the proportion of water in the system during neutralisation,



and, from this point of view, alkaline hydroxides would be preferable, as, owing to their solubility in alcohol, they would be likely to effect neutralisation rapidly in the cold, a condition which is obviously necessary if the proportion of water increases while catalyst is present. Solutions of sodium ethoxide, or a mixture of hydroxide and ethoxide, in alcohol of such strength that the proportion of water in the system is not increased by the process of neutralisation, have advantages over all other agents, and such solutions may now be readily prepared without the use of metallic sodium, as experiments made in the laboratory by Mr. T. K. Walker have demonstrated. Slight excess of alkali seems to be of little consequence in most cases, and although the literature contains records of the manufacture of acetals with the aid of powerfully alkaline solutions (*Annalen*, 1857, **102**, 363; 1868, **146**, 193; *Jahresber.*, 1876, 336), it is probably not quite generally realised that most saturated acetals, whilst excessively sensitive to acids, are stable towards the strongest alkalis. Acetals thus resemble the "ortho-esters" of carboxylic acids, and, like these, have the properties of ethers. The hydrolytic effect of alkalis is apparently restricted to compounds containing the  $>\text{C}=\text{O}$ ,  $>\text{C}=\text{N}-$ , and similar unsaturated groups. Whilst any serious effect of a very slight excess of alkali on the yield of acetal is seldom, if ever, to be feared, there is no doubt, with sensitive aliphatic compounds, a danger of some destruction of non-acetalised aldehyde during the recovery process. Experience with isovaleraldehyde, however, would indicate that, with reasonable care, loss due to this cause may be reduced to very small proportions.

## EXPERIMENTAL.

In order to economise space, it may be stated at this point that each of the acetals prepared during the investigation was examined as to its behaviour towards acids, alkalis, and hydrogen sulphite solutions. In every case, dilute mineral acids caused rapid hydrolysis, but no appreciable effect was observed with cold, concentrated alkalis, even after very prolonged contact. Cold solutions of sodium hydrogen sulphite, if smelling of sulphur dioxide, appeared to attack the acetals, although usually somewhat slowly, but if the odour of sulphur dioxide was removed by cautious addition of bicarbonate, the solutions no longer had any appreciable effect on the acetals of the saturated acetals, but still reacted slowly with the acetals of cinnamaldehyde and citronellal, converting them in the course of some days into pasty or even semi-solid masses. It seems not improbable that in these cases addition may take place at the  $\alpha\beta$ -unsaturated linking even in absence of the free aldehyde group; the speed of the change, however, is not so great as to render the use of such "neutralised bisulphite" impracticable for the purpose of removing free aldehyde from the crude acetal.

The ethyl alcohol used in all the experiments was dried by Winckler's method, with all precautions to ensure presence of dissolved calcium ethoxide in the alcohol before distillation. The "alcoholic hydrogen chloride" was made by passing into such alcohol 1 per cent. of dry hydrogen chloride, and the "alcoholic sodium ethoxide" by dissolving in it metallic sodium. In all instances, unless a statement to the contrary occurs, the acetals were isolated as follows: To the solution in which acetalisation had been carried out, there was added enough alcoholic sodium ethoxide to neutralise the mineral acid present, phenolphthalein being used as indicator. The alcohol was removed by distillation in a vacuum, the distilling flask being immersed during this process in a bath heated at about 30°. The residue left in the flask was then shaken with excess of a solution of sodium hydrogen sulphite to which enough sodium hydrogen carbonate had been added to remove all odour of sulphur dioxide ("neutralised bisulphite solution") and the undissolved oil extracted with ether. Finally, the ethereal extract was dried over solid potassium carbonate, evaporated, and the acetal purified by fractionation in a vacuum.

The percentage yields given represent in all cases the yield as compared with that theoretically possible. "Corrected" yields are calculated in the same way, but include the quantities of acetal volatilised in removing the excess of alcohol under the foregoing

condition, quantities which in a number of cases had to be determined by finding the loss experienced in working up known quantities in the same manner. The majority of the initial experiments were carried out in connexion with the conversion of benzaldehyde into its diethylacetal. This acetal is distinctly volatile in vapour of alcohol. It was found, for example, that under the conditions actually used for recovery of alcohol after acetalisation, about 1.4 grams of acetal out of a total of 11.4 grams were carried over with 100 c.c. of alcohol, and from a series of such observations a means of correcting the yields was secured. The acetal lost by proceeding in the foregoing manner could no doubt be retained by using an efficient column when operating on a large scale.

*Conversion of Benzaldehyde into its Diethylacetal.*

*Process A.*—A series of experiments was carried out on the acetalisation of benzaldehyde with 1 per cent. alcoholic hydrogen chloride (p. 79) at about 18°, the acetal formed being estimated as above described. It was found that after two days no further increase in the yield could be detected. The following results were obtained by varying the ratio of alcohol to benzaldehyde :

	A.	B.	C.	D.	E.
Ratio of alcohol : benzaldehyde by weight .....	4.04	8.06	10.2	16.3	31.5
Percentage of acetal actually isolated	52.3	55.5	56.5	56.5	54.5
Correction for loss by volatilisation	3.1	6.6	8.5	13.1	25.8
Total percentage yield.....	55.5	62.1	65.0	69.6	80.3

It may be noted that the yield actually obtained by operating in the above way was decidedly larger than that obtained by Fischer when using the same proportions of alcohol and benzaldehyde.

Study of the table given indicates clearly that whilst the total quantity of acetal formed may be greatly increased by raising the proportion of alcohol, there is in practice a proportion which it would not be economical to exceed, having regard to cost of recovery of material used. Under laboratory conditions, this proportion is perhaps about 5 to 8, according to the efficiency of the column used in removing excess of alcohol.

Attempts were made to ascertain whether the ideal dehydrating agents used by Claisen, namely, ethyl orthoformate and ethyl imidoformate, could be replaced by ethyl orthoborate, or by silicon tetrachloride, but the yield was not improved by addition of the former of these, and was depressed by the latter.

*Process B. An Adaptation of Young's Method of Dehydration of Alcohol to the Preparation of Acetals.*—One part by weight of benz-

aldehyde was dissolved in 10 parts by weight of alcoholic hydrogen chloride and 17 parts by weight of benzene, and the whole heated to boiling in an apparatus of glass constructed so that the vapours containing the ternary mixtures of alcohol, benzene, and water were condensed and returned automatically to a flask containing excess of calcium carbide; this flask was heated in an oil-bath at 110—120° and the partly dried vapours from it were liquefied in a second condenser and returned to the original vessel, in which acetalisation was taking place. After thirty hours, the heating of the first vessel was discontinued, the whole of the liquid from the flask of carbide allowed to volatilise into it, and then the liquid was cooled and worked up as in the previous experiments. The weight of acetal actually isolated was 66 per cent. of the quantity theoretically possible, and this compares very favourably with the figure (36 per cent.) obtained by Fischer's original method. If correction be made for the amount of acetal volatilised in the recovery of alcohol, the total yield works out to 74 per cent.

#### *Use of Ammonium Chloride as Catalyst.*

Claisen (*Ber.*, 1907, **40**, 3906) used this salt as catalyst in effecting acetalisation of aldehydes and ketones by means of ethyl orthoformate, but the application of this agent in place of hydrogen chloride in direct acetalisation by alcohol does not seem to have been tried.

The present authors have found that benzaldehyde, when left with anhydrous alcohol containing 0.6 per cent. of its weight of ammonium chloride for two days and worked up by the sodium ethoxide method, gives a yield of acetal only about 5 per cent. less than when hydrogen chloride is used as catalyst. When applied by method *B*, the results are even better than with hydrogen chloride, and in an experiment closely corresponding with the one above described in detail a yield of acetal amounting to 74 per cent. was realised, or 82.4 per cent. when corrected for loss due to volatility in alcohol vapour.

#### *Anisaldehyde.*

The diethylacetal of the aldehyde closely resembles that of benzaldehyde, but is less volatile in alcohol vapour. The authors obtained it in yield rather less than 40 per cent. by the application of cold alcoholic hydrogen chloride for four days, or by boiling with alcohol containing ammonium chloride (0.6 per cent.), the product being worked up in both instances by the sodium ethoxide

method. Fischer's method has been applied to the preparation of the dimethylacetal only.

### *Piperonal.*

Piperonal is decidedly more difficult to convert into acetal than is either benzaldehyde or anisaldehyde. Fischer obtained a yield of dimethylacetal amounting to only 25 per cent. Using hydrogen chloride as catalyst in the cold or ammonium chloride at the boiling point of alcohol, the present authors were able to isolate 22 per cent. and 25 per cent. respectively of diethylacetal. It is probable, therefore, that these quantities correspond fairly closely with quantities present at equilibrium when the initial ratio of piperonal to alcohol is about 1 : 10.

### *Cinnamaldehyde.*

This was selected as an example of an unsaturated fatty-aromatic aldehyde. Its dimethylacetal has been obtained both by Fischer and by Claisen. Applying much the same conditions for preparing this acetal as were used by Fischer in making the corresponding dimethylacetal (*Ber.*, 1898, **31**, 1990), but working up the product by the sodium ethoxide method and removing unchanged aldehyde by rapid treatment with "neutralised bisulphite solution," a 35 per cent. yield of acetal was obtained; this figure, corrected for loss due to volatility in alcohol, corresponds with a total of 40 per cent. of the theoretical quantity. There is considerable formation of brown tar, no matter how the product is worked up. By reducing the proportion of hydrogen chloride to 0.7 per cent. and prolonging the action for four days, the yield was increased by 3—4 per cent. Using ammonium chloride (0.6 per cent.) as catalyst, the total quantity of acetal formed after five days in the cold was 42 per cent., but in this instance there was no formation of tar, and nearly the whole of the non-acetalised aldehyde was recovered as oxime.

It does not appear to be advantageous in the case of cinnamaldehyde to apply the modified Young dehydration process (p. 80), as, owing to the heating necessary, much tar is formed even when ammonium chloride is used, and there is loss both of aldehyde and acetal.

### *Citronellal and Citral.*

The dimethylacetal of citronellal has been prepared by Harries (*Ber.*, 1900, **33**, 857), who used Fischer's method and obtained it in 56 per cent. yield. The present authors isolated the diethylacetal

(b. p. 122—125°/12 mm.) in 60 per cent. yield by leaving citronellal with five times its volume of alcoholic hydrogen chloride at the ordinary temperature for eight days, then working the product by the hydrogen sulphite method and using a column in recovering excess of alcohol. A yield of about 50 per cent. was obtained when the aldehyde was boiled with ten times its volume of alcohol containing ammonium chloride (0·6 per cent.) as catalyst.

There is but little formation of tarry products when citronellal is acetalised in either of the above ways, and the bulk of the aldehyde which has escaped acetalisation can be recovered. In these respects, the aldehyde differs greatly from citral, which yields not more than 15 per cent. of product having the properties of an acetal (b. p. 140—142°/15 mm.) and is mainly converted into tarry products.

#### *iso Valeraldehyde.*

The diethylacetal of *isovaleraldehyde* has previously been made by Alsberg (*Jahresber.*, 1864, 485), who describes it as an oil having a pleasant, fruity odour and boiling at 158·2°. In the experiments made by the present authors, the acetal isolated boiled at 152—153°.

Although appreciably volatile with alcohol vapour, especially during recovery from alcoholic solution with the aid of a vacuum, the acetal may be separated from alcohol with little loss by distilling at the ordinary pressure and using a column.

Using Fischer's method for acetalisation, but working up the product after nine days in the cold by the sodium ethoxide method, the acetal was isolated in yield amounting to 32 per cent. of that theoretically possible, whilst nearly the whole of the remainder of the aldehyde was recovered as sodium hydrogen sulphite compound. Using ammonium chloride (6·6 per cent.) as catalyst and boiling for twelve hours, the same yield of acetal as before was obtained, and a slight improvement was effected by applying the modified Young dehydration process (p. 80). Most of the aldehyde which escaped acetalisation was found as bisulphite compound in the wash-liquors.

#### *m-Nitrobenzaldehyde.*

Fischer has previously prepared the dimethylacetals of *o*- and *p*-nitrobenzaldehydes by his process, the yields being 70 and 77 per cent. respectively. The present authors, by leaving *m*-nitrobenzaldehyde for six days with five times its weight of alcoholic hydrogen chloride and working up the product by the sodium ethoxide process, obtained a yield of diethylacetal corresponding



with 78 per cent. of the theoretical amount. The acetal had the properties assigned it by Claisen (*Ber.*, 1898, **31**, 1016).

*Reduction of m-Nitrobenzaldehydediethylacetal.*

The reduction of nitro-acetals in the aromatic series does not seem to have been previously accomplished. The authors effected the reduction of *m*-nitrobenzaldehydediethylacetal as follows: Sodium sulphide crystals (50 grams) were dissolved in water (50 c.c.) and partly converted into the hydrosulphide by addition of concentrated hydrochloric acid (25 grams); the resulting solution, which had an alkaline reaction, was added to alcohol (90 c.c.) containing 15 grams of the acetal, when heat was evolved and the mixture became red. Reduction was completed by boiling for six hours, the alcohol was then removed by distillation through a column, and the residue, which still showed a distinct alkaline reaction, was cooled and extracted with ether. Evaporation of the washed and dried ethereal extract yielded a yellow oil, which was freed from volatile impurities by heating for some time in a vacuum at 100°. There is little doubt that the above oil was impure *m*-aminobenzaldehydediethylacetal. It contained no free aldehyde, as it was unaffected by cold "neutralised bisulphite" solution, free hydroxylamine, or phenylhydrazine. It was nearly insoluble in water, but dissolved in dilute mineral acid, being at once converted into a salt of *m*-aminobenzaldehyde, which was precipitated in a powder on subsequent addition of alkali. Heated with hydriodic acid, the oil gave off a volatile liquid, evidently ethyl iodide, and with a mixture of benzoic and sulphuric acids evolved the odour of ethyl benzoate. The behaviour of the oil towards phenylcarbimide is somewhat striking; considerable evolution of heat occurs on mixing, and a yellow precipitate separates; this, when purified, melts at 168°, and appears to consist exclusively of the phenylcarbamide derived from the aminoaldehyde (Found: C = 70.3; H = 5.1; N = 11.9.  $\text{CHO} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{C}_6\text{H}_5$  requires C = 70.0; H = 5.0; N = 11.7 per cent.), as it gives no test for acetal, but reacts at once with phenylhydrazine, giving a phenylhydrazone which forms yellow crystals melting at 196° (Found: C = 72.9; H = 5.7; N = 17.1.  $\text{C}_{20}\text{H}_{18}\text{ON}_4$  requires C = 72.7; H = 5.5; N = 17.0 per cent.). In similar manner, when the aminoacetal is shaken with benzoyl chloride suspended in aqueous sodium hydroxide solution, even when the conditions are maintained alkaline throughout, the odour of ethyl benzoate becomes perceptible and the crystalline product obtained (m. p. 115–116°) is the benzoyl derivative of *m*-aminobenzaldehyde

(Found : C = 74.4; H = 4.9; N = 6.3.  $\text{CHO} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CO} \cdot \text{C}_6\text{H}_5$  requires C = 74.7; H = 5.0; N = 6.2 per cent.), as indicated by response to tests for free aldehyde (phenylhydrazone, m. p. 212°. Found : C = 75.8; H = 5.5; N = 13.5.  $\text{C}_{20}\text{H}_{17}\text{ON}_3$  requires C = 76.2; H = 5.4; N = 13.3 per cent.) and by the negative results obtained on applying tests for the acetal complex.

The aminoacetal in ethyl acetate solution yields a crystalline precipitate with picric acid, but this is a picrate of the free aldehyde.

Thus, whilst the aminoacetal does not respond to any test distinctive of free aldehyde, it reacts with agents which attack the free amino-group, but in all the cases examined only the derivatives of the aldehyde and not of the acetal have been isolated and it has not yet been determined whether this result may be modified by rigid exclusion of moisture.

### *Summary.*

The complete stability of acetals towards alkalis and their great sensitiveness to acids render it possible to foresee the conditions necessary to avoid reversal of the acetalisation of aldehydes by alcoholic hydrogen chloride, and one process is described which satisfies these conditions and permits of the ready isolation of numerous acetals and recovery of excess of strong alcohol.

Ammonium chloride may be used as catalyst in place of the hydrogen chloride in Fischer's process for acetalisation. By adapting Young's process for the dehydration of alcohol by distillation with benzene, and using ammonium chloride as catalyst, larger yields of acetal than by Fischer's original method may be obtained.

Cold aqueous solutions of sodium hydrogen sulphite, which have been freed from all odour of sulphur dioxide by means of sodium hydrogen carbonate, have no action on the acetals of the saturated aldehydes which have been examined, but very slowly alter the acetals of cinnamaldehyde and of citronellal.

*m*-Nitrobenzaldehydediethylacetal may be reduced to *m*-aminobenzaldehydediethylacetal by means of an alkaline solution of sodium hydrosulphide.

It is desired to acknowledge a grant made to one of us (R. D. H.) by the Department of Scientific and Industrial Research, with the aid of which some of the work described was carried out.