doubtedly contributed also to this value. Table II gives values of k in mole^{-1} sec.$^{-1}$ corresponding to the various micrometer readings. The k's are given to four significant figures although a, the original concentration of reactants, is not known this well. This procedure was followed since it demonstrates the precision of the data which may be obtained from the method. The absolute value of k, however, is known no more accurately than from other methods.

TABLE II

Run VI a = 0.0912	T = 55.00°	Run VII a = 0.0979	T = 49.90°
Time, sec.	$k \times 10^4$	Time, sec.	$k \times 10^4$
2519	4.334	4262	2.658
2869	4.335	4777	2.656
3229	4.335	6253	2.672
3607	4.324	9148	2.667
3967	4.345	9605	2.672
5592	4.337	11935	2.643
6045	4.323	12850	2.663
7389	4.443	13951	2.653
9972	4.340		
10562	4.330		
12443	4.307		
23093	4.208		
27684	4.113		

Table III compares the values for the second order velocity constant of the reaction between acetic anhydride and ethyl alcohol in carbon tetrachloride obtained in three different studies. The method by which both Soper and Williams and Moelwyn-Hughes and Hinshelwood followed the reaction was essentially the same as that in which analytical results were obtained in the present work.

TABLE III

	a	T, °C.	$k \times 10^4$
S. and W.[a]		50	1.88
M-H. and H.	0.101	49.9	2.60
	.100	55.0[b]	4.25
This work	.0979	49.90	2.66
	.0912	55.00	4.34

[a] Concentrations were not given in these authors' paper. Presumably they are above 0.2 M since all other experiments recorded in the paper for which concentrations are given range from about 0.250 to over 1 M. This accounts for the lower value of k observed by S. & W. [b] M.-H. & H. did not perform an experiment at this temperature. The value given was obtained by interpolation of their values obtained for experiments at 49.9, 60.2 and 70.6°.

The only detailed data which Moelwyn-Hughes and Hinshelwood present show k's whose average deviation is 1.57%. Examination of Table II in this work discloses that the average deviation for the first ten readings of Run VI is 0.12%. This clearly demonstrates the increased relative precision which may be expected from the present method. The agreement between the average values of k may be fortuitous in some degree since Moelwyn-Hughes and Hinshelwood observed k's differing by as much as 1% for the same reaction in different fractions of solvents.

The decreasing velocity of the reaction observed by Soper and Williams but not by Moelwyn-Hughes and Hinshelwood seems definitely to be confirmed. Whereas Soper and Williams observed a slowing-down of about 3% change in k between the time the reaction at 50° had progressed 30 and 50%, a decrease of about 4.5% was observed for the same period at 55° in this work. No slowing down was observed in the data of Run VII since the reaction was followed up to only about 30% completion.

BALTIMORE 18, MD. RECEIVED APRIL 2, 1951

[CONTRIBUTION FROM THE HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Condensation of Formaldehyde with Compounds Containing Activated Hydrogens

BY J. T. HAYS, G. F. HAGER,* H. M. ENGELMANN AND H. M. SPURLIN

This paper describes a method of reducing side reactions in the preparation of monomethylol derivatives by the reaction of formaldehyde with compounds containing activated hydrogens. The reaction is carried out in a fractionating column operated to maintain a large excess of activated compound over formaldehyde and to remove the initial product from the reaction zone by rectification. Yields higher than previously reported for liquid phase condensations are obtained.

The reaction of formaldehyde with compounds containing activated hydrogens, for example, ketones such as acetone and methyl ethyl ketone, is well known. Although the reaction may give the corresponding monomethylol derivative, complex mixtures have usually been obtained in actual practice.[1,2] A catalytic vapor-phase reaction of formaldehyde with acetone, methyl ethyl ketone and certain other ketones has been reported to give excellent yields of the corresponding unsaturated ketone, although large amounts of catalyst appear to be required for best results.[3] Landau and Irany[4] have recently studied the liquid-phase condensation of methyl ethyl ketone with formaldehyde; although they obtained high yields of crude condensation product (4-hydroxy-3-methyl-2-butanone), their over-all yields of methyl isopropenyl ketone were of the order of 50%, indicating that the crude condensation product was impure. It has been our experience that it is difficult to realize yields of greater than about 30% of monomethylol derivatives by the liquid-phase condensation of formaldehyde with acetone and with methyl ethyl ketone by methods previously

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(1) G. Morgan, N. J. L. Megson and K. W. Pepper, *Chemistry and Industry*, **57**, 885 (1938).

(2) T. White and R. N. Haward, *J. Chem. Soc.*, 25 (1943).

(3) J. H. Brant and R. L. Hasche, U. S. Patent 2,245,567, June 17, 1941.

(4) E. F. Landau and E. P. Irany, *J. Org. Chem.*, **12**, 422 (1947).

described in the literature. The general complicating reactions are: (1) reaction with more than one molecule of formaldehyde, (2) subsequent reactions of the compounds initially formed to give dehydration, cyclization and polymerization products, and (3) self-condensation of the activated compounds. As a result of these reactions, impure products are usually obtained and recoverable yields of the monomethylol derivatives are relatively low.

A method designated to minimize undesirable side reactions in the liquid-phase condensation of formaldehyde with acetone and methyl ethyl ketone and other compounds containing activated hydrogens has been developed in our laboratories[5] and has been shown to give higher yields than can readily be attained by methods previously described. This method utilizes a column which functions both as a reactor and as a fractionating column for separation of the products. In this apparatus, sketched in Fig. 1, formaldehyde and sodium hydroxide are added at the top of the column while the ketone is refluxing in the column operated below its flood point. Control of the rate of addition of formaldehyde and catalyst maintains a high ratio of ketone to formaldehyde in the reaction zone without requiring a large over-all excess; the rectifying action of the column causes the less volatile monomethylol derivative to be rapidly removed from the reaction zone; neutralization of the alkali catalyst in the boiling flask with a non-volatile acid avoids dehydration and polymerization reactions which occur on continued heating with alkali. These features to a large extent eliminate the undesirable reactions previously encountered in the liquid-phase condensation of formaldehyde with compounds containing activated hydrogens. This is demonstrated by the high yields of monomethylol derivatives obtained and by the negligible quantities of non-volatile by-products produced. Results with various compounds are shown in Table I.

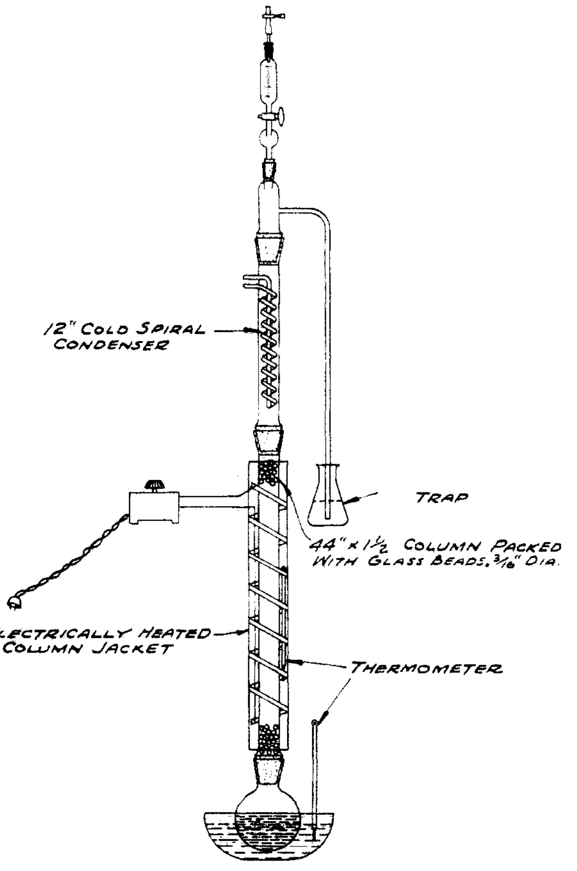

Fig. 1.—Apparatus for condensation of ketones with formaldehyde.

TABLE I

CONDENSATIONS WITH FORMALDEHYDE

Activated compound	Product	Yield (based on formaldehyde), %
$CH_3COC_2H_5$	$CH_3COCH(CH_3)CH_2OH$	91
CH_3COCH_3	$CH_3COCH_2CH_2OH$	84
$C_2H_5COC_2H_5$	$C_2H_5COCH(CH_3)CH_2OH$	75
CH_3NO_2	$CH_2(NO_2)CH_2OH$	64

These results indicate the general applicability of the method. Our work has involved detailed study of pertinent variables for the reactions with methyl ethyl ketone and with acetone and the yields given are those obtained for optimum conditions; those for diethyl ketone and for nitromethane are the results of isolated runs.

Methyl Ethyl Ketone Reaction.—In this reaction the ratio of ketone to formaldehyde in the reaction zone and the amount of sodium hydroxide catalyst (as measured by the *p*H of the formalin solution) were found to be the most important variables. When the column jacket temperature is suitably controlled to keep the column just below its flood point and when the over-all ratio of ketone to formaldehyde is large enough to assure vigorous reflux at the top of the column, the ratio of ketone to formaldehyde in the reaction zone is determined by the rate of addition of formaldehyde. As would be expected, slower addition of formaldehyde increases the yield of monomethylol derivative as shown in Fig. 2. A *p*H of 10.5 for the formalin solution appeared optimum under these conditions. However, in this condensation the *p*H did not appear to be critical from values of about 10.3 to 11.2 since yields of 75–85% were obtained for this range.

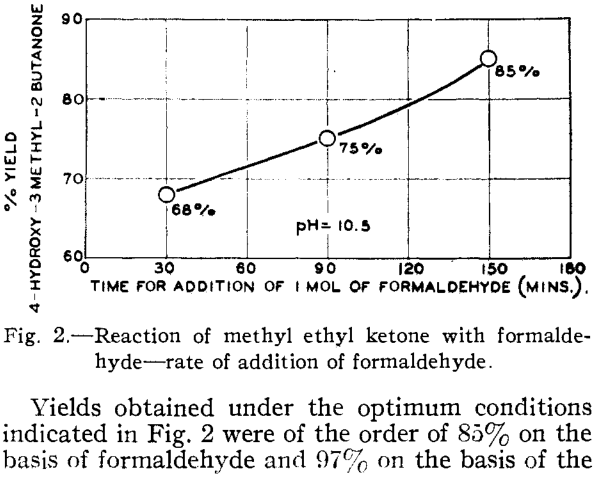

Fig. 2.—Reaction of methyl ethyl ketone with formaldehyde—rate of addition of formaldehyde.

Yields obtained under the optimum conditions indicated in Fig. 2 were of the order of 85% on the basis of formaldehyde and 97% on the basis of the

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[5] H. M. Spurlin, U. S. Patent 2,510,914, June 6, 1950.

methyl ethyl ketone used. Apparently polymerization of the formaldehyde in the alkaline solution was the most significant factor in the loss of formaldehyde. This was shown by placing the sodium hydroxide in the methyl ethyl ketone instead of the formalin; this procedure increased the yield to 91%. About 3% of unreacted formaldehyde was found in the crude reaction product. Thus a high degree of efficiency of use of formaldehyde has been achieved in the monosubstitution reaction.

Acetone Reaction.—In the condensation of formaldehyde with acetone, the same variables are important as in the methyl ethyl ketone reaction. The rate of addition of formaldehyde under the reaction conditions is once more critical as shown in Fig. 3. From comparison with Fig. 2 it is apparent that acetone does not condense as rapidly as methyl ethyl ketone with formaldehyde. Nevertheless, in the longer reaction times, yields of the order of 85% on the basis of formaldehyde are also obtained in the acetone condensation. It was not possible to increase this yield by placing the sodium hydroxide catalyst in the acetone because acetone reacts with itself in the presence of alkali. On a larger scale, separate addition of the catalyst would be expected to have beneficial results.

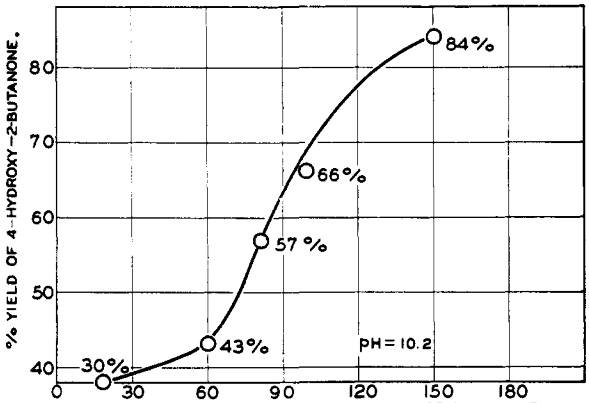

Fig. 3.—Rate of addition of formaldehyde.

The effect of *p*H, shown in Fig. 4, is very important. A value of 10.2 for the *p*H of the formalin solution appears optimum. The reaction is slower at lower *p*H. At a *p*H of 10.5, yellow resinous material is deposited in the column and more diacetone alcohol is also formed. It should be pointed out that even under the best conditions, 15% yields of diacetone alcohol are obtained in this reaction in contrast to the methyl ethyl ketone case where self-condensation products are negligible.

Precise control of the critical variables is essential to obtain the favorable results described in this condensation. However, these results show that excellent yields of 4-hydroxy-2-butanone can be obtained with proper control of conditions.

Effect of Rectification on the Condensation Reaction.—The condensation method described provides both for a high ratio of ketone to formaldehyde in the reaction zone and for continuous removal of the monomethylol derivative by rectification as it is formed. To determine whether the rectification feature contributes to the favorable results obtained, a special apparatus was constructed (Fig. 5). This apparatus provides a batch reactor (the liquid trap at the head of the column) which allows the continuous removal of the reaction products from the reaction zone. It thus approximates the distillation column used in our general method except that there is no provision for immediate removal of the initial reaction products by rectification. Experiments were carried out in this modified apparatus with formaldehyde being added at a rate to provide a 30:1 ratio of ketone to formaldehyde in the reactor; the reaction mixture was returned continuously to the column, the reaction products being returned to the boiling flask to be neutralized with citric acid and the ketone being distilled back to the reactor. Using this system, a maximum yield of monomethylol derivative (4-hydroxy-3-methyl-2-butanone) of 66% was obtained from methyl ethyl ketone and formaldehyde. The yield was raised

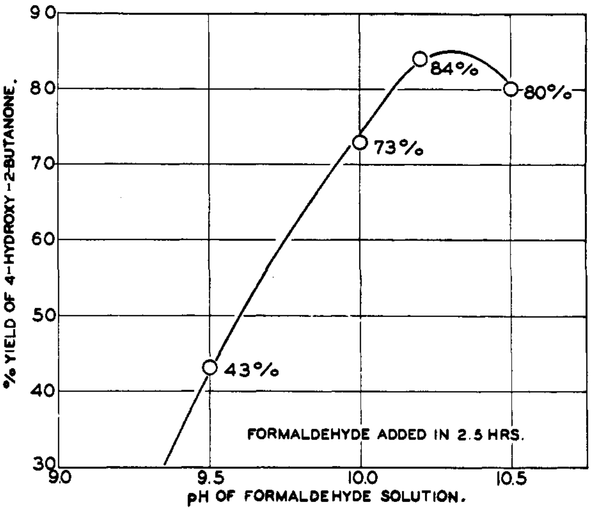

Fig. 4.—Effect of *p*H of formaldehyde solution.

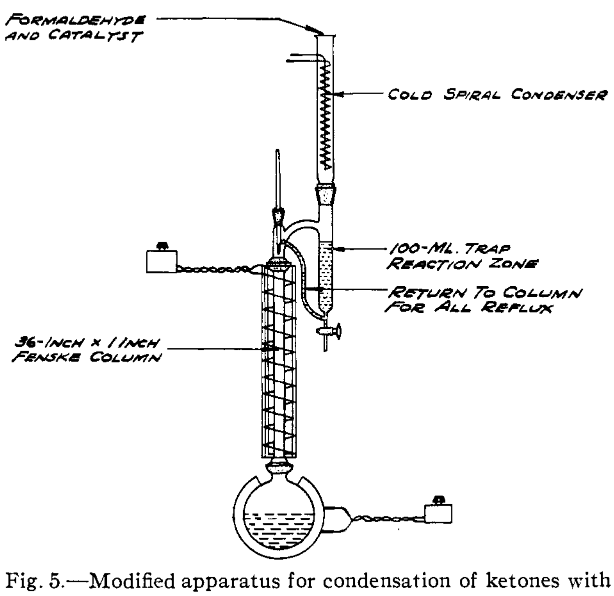

Fig. 5.—Modified apparatus for condensation of ketones with formaldehyde.

to 84% by simply removing the liquid trap between the column and reflux condenser and operating as previously described. This demonstrates conclusively the beneficial effects of removing the initial reaction product from the reaction zone as rapidly as possible, as is accomplished in the distillation column.

Column and Packing Requirements.—The optimum conditions for our condensation method are so intimately related to column dimensions and type of packing that we felt it necessary to attempt to determine requirements which would enable the favorable results described to be reproduced. We have concluded in the case of the methyl ethyl ketone–formaldehyde condensation that the ketone to formaldehyde ratio in the reaction zone should be about 30:1. When this ratio is maintained, the condensation can be carried out satisfactorily in a column having a length about six times its diameter and packed with glass helices or similar packing having a large surface area. Specifications will vary for each reaction but these limits for one case indicate the general nature of the requirements to get maximum efficiency with the method.

Conclusions.—The method described appears to be a general method of obtaining monomethylol derivatives in the condensation of formaldehyde with compounds containing activated hydrogens (Table I). The specific nature of the substitution reaction has been further confirmed in the case of the methyl ethyl ketone and acetone reactions by dehydration of the hydroxybutanones obtained to methyl isopropenyl ketone and methyl vinyl ketone in nearly quantitative yields.[6] It is felt that the principles of this method are generally applicable to the control of other reactions which are difficult to stop at the monosubstitution stage.

Experimental

Materials.—Methyl ethyl ketone was used directly as obtained from the R. W. Greef Co., New York.

Acetone was used as obtained from Commercial Solvents, New York.

Formaldehyde was J. T. Baker 36–37% reagent grade.

10% sodium hydroxide catalyst solution was prepared by dissolving 50 g. of 96% sodium hydroxide pellets (Merck and Co., Inc.) in 450 g. of distilled water.

10% citric acid solution was prepared by dissolving 50 g. of citric acid monohydrate (J. T. Baker and Co.) in 450 g. of distilled water.

Methyl Ethyl Ketone–Formaldehyde Condensation. (General Procedure.)—The apparatus is shown in Fig. 1. In the boiling flask were placed 72 g. (1.0 mole) of methyl ethyl ketone and 5 ml. of 10% citric acid solution. The ketone was brought to strong reflux by adjusting the column jacket temperature to 120° and the oil-bath to 140°. Fifty ml. of distilled water was placed in the gas trap and 43 g. of formaldehyde solution (0.5 mole) was added dropwise from the dropping funnel at the top over a period of one hour. The *p*H of the formaldehyde solution had previously been adjusted to 10.5 by the addition of approximately 1.0 ml. of 10% sodium hydroxide solution. When all the formaldehyde had been added, the column was maintained at reflux conditions for an additional ten minutes. Heating was stopped, the 50 ml. of water in the trap was used to rinse the column, and the whole allowed to drain for one-half hour.

The reaction mixture was then distilled from an ordinary Claisen flask under reduced pressure with the receiver and two subsequent traps being immersed in a Dry Ice bath. From the receiver and traps was recovered 123.0 g. of colorless liquid which contained 0.92% or 1.14 g. of formaldehyde as determined by polarographic analysis. Forty-two grams (83%) of 4-hydroxy-3-methyl-2-butanone, b.p. 92–95° at 20 mm., n^{20}D 1.4326, was also collected.

Experiments varying the *p*H of the formaldehyde solution and the rate of addition of formaldehyde were run in the same manner.

Condensation with the Catalyst in the Ketone.—The apparatus for this experiment was the same as in Fig. 1 except that it was equipped with two dropping funnels. Seventy-two grams (1.0 mole) of methyl ethyl ketone and 5.0 ml. of 10% citric acid solution were placed in the boiling flask. The ketone was brought to strong reflux by adjusting the column jacket temperature to 120° and the oil-bath temperature to 150°. After equilibrium conditions were established in the column, there was added simultaneously from the dropping funnels: (1) 85 g. of formaldehyde solution (1.0 mole of formaldehyde) at *p*H 3.8 and (2) 72 g. (1.0 mole) of methyl ethyl ketone containing 2.0 ml. of 10% sodium hydroxide solution. The addition required four hours.

The heating was discontinued and the column rinsed with 100 ml. of distilled water. The reaction mixture and washings were distilled *in vacuo* through an 18-in. Fenske column packed with $^3/_{32}$-in. glass helices. After a forerun of methyl ethyl ketone and water, there was collected 93.0 g. (91%) of 4-hydroxy-3-methyl-2-butanone, b.p. 90–93° at 20 mm., and n^{20}D 1.4320.

Acetone–Formaldehyde Condensation.—The apparatus used was that shown in Fig. 1. In the boiling flask were placed 174 g. (3.0 moles) of acetone and 5 ml. of 10% citric acid solution. After the acetone was brought to strong reflux by adjusting the column jacket temperature to 80° and the oil-bath to 130°, there was added dropwise 79 ml. of formaldehyde solution (1.0 mole of formaldehyde) during a period of 2.5 hours. The *p*H of the formaldehyde solution had previously been adjusted to 10.2 by use of 10% sodium hydroxide solution. No water was placed in the gas trap in this experiment, nor was the column rinsed other than by a ten-minute reflux after addition of the formaldehyde.

While still acid, the excess acetone and water were removed by distillation *in vacuo* through an 8-in. × 1-in. column packed with glass helices. Subsequent fractionation of the residual liquid through an 18-in. × 1-in. column packed with $^3/_{32}$-in. glass helices gave the following fractions: (1) diacetone-alcohol (13.3 g.), b.p. 62–68° at 12 mm., n^{20}D 1.4235; (2) 4-hydroxy-2-butanone (74.1 g.), b.p. 73–76° at 12 mm., n^{20}D 1.4290.[7] This corresponds to an 84% yield based on the formaldehyde originally added. Experiments varying the *p*H of the formaldehyde solution and the rate of addition of the formaldehyde were run in the same manner.

Diethyl Ketone Condensation.—This reaction was carried out in the same way as the other condensations. Two hundred and fifteen grams (2.5 moles) of diethyl ketone and 5 ml. of 10% citric acid were placed in the boiling flask. Fifty grams (0.62 mole) of formaldehyde solution adjusted to a *p*H of 10.5 with 10% sodium hydroxide solution was added dropwise. After all the formaldehyde had been added, the crude reaction mixture was adjusted to a *p*H of 7 with 10% citric acid solution, and most of the excess diethyl ketone was distilled off at atmospheric pressure. Fractional distillation at 30 mm. yielded 52.5 g. (75% based on formaldehyde) of 5-hydroxy-4-methyl-3-pentanone, b.p. 109–111° at 30 mm.

Nitromethane Reaction.—The apparatus was essentially the same as in the condensations already described except that the delivery tube which was originally immersed in water in the trap was connected to a manostat set at 120 mm. At this pressure the temperature within the column was 52° during the period of condensation.

In the boiling flask were placed 183 g. (3.0 moles) of nitromethane (Commercial Solvents technical grade purified by shaking with 10% K_2CO_3, drying over $CaCl_2$, and distilling; b.p. 100–101°) and 5 ml. of 10% citric acid solution. The nitromethane was brought to a strong reflux by adjusting the column jacket temperature to 100° and the oil-bath to 135°. Then one mole of formaldehyde (in 36% solu-

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(6) We have worked out acid dehydration methods for preparation of these unsaturated ketones; their preparation will be the subject of a future communication.

(7) The refractive index is reported by White and Haward[2] as n^{15}D 1.435. We feel that our value of 1.4290 is more nearly correct since White and Haward's sample was probably contaminated with 4-hydroxy-3-methylene-2-butanone.

tion), pH adjusted to 10.0 with 10% sodium hydroxide, was added slowly during 2.5 hours. Distillation of the colorless product yielded a forerun of nitromethane and water and 58.6 g. (64% based on formaldehyde), of β-nitroethanol, b.p. 95–99° at 7–8 mm.

Condensation of Methyl Ethyl Ketone with Formaldehyde in Modified Apparatus.—The apparatus used is shown in Fig. 5. In the boiling flask was placed 504 g. (7.0 moles) of methyl ethyl ketone and 2 g. of citric acid. During a period of seven hours, 320 g. (4.0 moles) of Merck 37.5% formaldehyde (adjusted to pH 10.5 with sodium hydroxide) was added dropwise, while the column was operated at the point of incipient flooding. Distillation of the products through a short Claisen-type still-head gave 270 g. (66.1%) of 4-hydroxy-3-methyl-2-butanone, b.p. 90–92° at 20 mm.

The previous experiment was duplicated exactly except that the trap between the condenser and the column was removed. Distillation of the products gave 341.4 g. (83.6%) of 4-hydroxy-3-methyl-2-butanone, b.p. 90–92° at 20 mm.

Wilmington, Delaware Received May 1, 1951

[Contribution from the Research Laboratories of Merck & Co., Inc.]

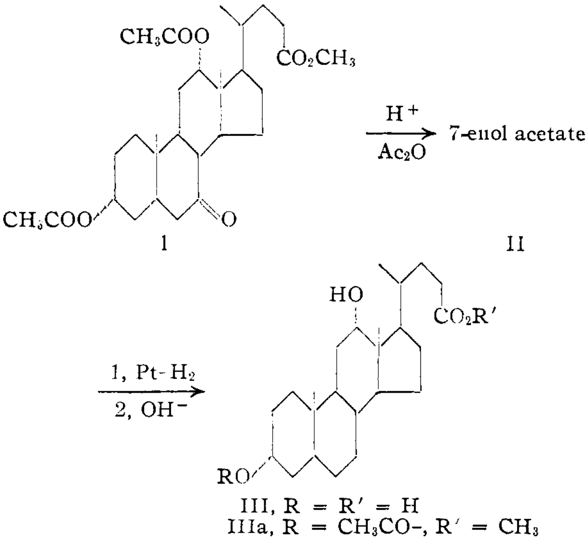
A New Route to Desoxycholic Acid

By Ralph Hirschmann, Malcolm Brown and N. L. Wendler

Catalytic hydrogenation of the enol acetates of 7-keto bile acids has provided a new route to the corresponding 7-desoxy acids.

At the time this work was initiated, the only method available for the synthetic preparation of desoxycholic acid consisted in the oxidation of cholic acid or its ester to 3(α),12(α)-dihydroxy-7-ketocholanic acid followed by a Wolff–Kishner reduction of this intermediate.[1] We wish to report a new method for effecting the conversion of cholic to desoxycholic acid.

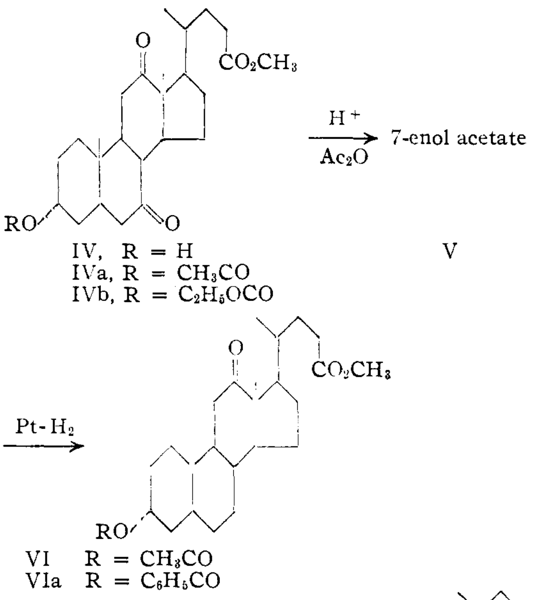
Treatment of methyl 3(α),12(α)-diacetoxy-7-ketocholanate (I) under conditions of enol acetylation either with acetic anhydride[2] or isopropenyl acetate[3] in the presence of p-toluenesulfonic acid was found to produce methyl 3(α),7,12(α)-triacetoxycholenate (II). Subsequent hydrogenation of this individual with platinum in acetic acid followed by saponification afforded desoxycholic acid (III) in 30–35% yield from I.



I II

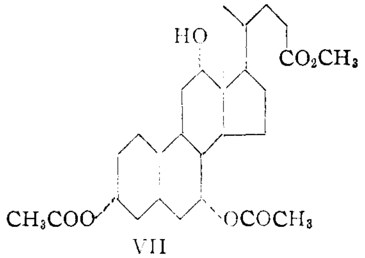
III, R = R′ = H
IIIa, R = CH$_3$CO–, R′ = CH$_3$

Under similar conditions methyl 3(α)-acetoxy-7,12-diketocholanate (IVa) yielded the 7-*mono*-enol acetate V. This compound was in turn hydrogenated to give methyl 3(α)-acetoxy-12-ketocholanate (VI) and its 12-dihydro derivative IIIa as the predominant products together with small amounts of cholic acid ester diacetate (VII).[4]



IV, R = H
IVa, R = CH$_3$CO
IVb, R = C$_2$H$_5$OCO

VI R = CH$_3$CO
VIa R = C$_6$H$_5$CO



VII

It is noteworthy that the 12-carbonyl group of IV did not participate to any measurable extent in the enol acetylation reaction. This fact was further substantiated by the failure of VIa to react under conditions of enol acetylation.

Experimental

Methyl 3(α),7-Diacetoxy-12-keto-cholenate (Va).—A mixture of acetic acid and acetic anhydride was distilled[2] for

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[1] Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N.Y., 1949, p. 128.

[2] Bedoukian, This Journal, **67**, 1430 (1945).

[3] Hagemeyer and Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

[4] It has been observed recently by Inhoffen, Stoeck, Kölling and Stoeck (*Ann.*, **568**, 52 (1950)) that cholestenone can be converted along similar lines to cholestane.