[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL WORKS]

The Condensation of Aldehydes with Ketones and Some of the Products Derived from the Ketols

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The aldolization of ethanal has been studied quite thoroughly and applied to the industrial production of crotonaldehyde and *n*-butanol. The preparation of mixed ketols, on the other hand, by the interaction of aldehydes and ketones in presence of alkaline reagents has not been developed satisfactorily.

Because of the greater tendency of ethanal to react with itself than with acetone, acetaldol may turn out to be the main reaction product as was demonstrated by the writer.[1] Since acetone also condenses with itself,[2] diacetone alcohol may also be formed.

The presence of these by-products can be demonstrated readily by dehydrating the condensation products and fractionating the unsaturated ketones and aldehyde. In this manner, crotonaldehyde, which boils appreciably lower than ethylidene acetone and mesityl oxide, can be isolated and identified. The formation of diacetone alcohol can likewise be demonstrated in the condensation of other aldehydes with acetone. The above considerations, therefore, would lead to the conclusion that it would be impossible to prepare pure hydracetylacetone from the alkaline condensation of ethanal with acetone.

Grignard and Dubien[3] have developed a method for the preparation of heptanol-4-one-2 in a good yield (up to 80%) from *n*-butanal and acetone in presence of an inert solvent.

Eccott and Linstead[4] referring to the above process state that it results invariably in a mixture of ketol and unsaturated ketone.

We have demonstrated the formation of diacetone alcohol in appreciable amounts in the process used by Eccott and Linstead and isolated mesityl oxide in an amount corresponding to not less than 8% of the weight of *n*-butanal used.

Because of the sluggishness of the homologs[5] of acetone to ketolize, it was believed that the preparation of the pure mixed ketols in their reaction with aldehydes might be accomplished quite readily.

Powell[6] obtained a 45% yield of methyl-3-heptanol-4-one-2 from *n*-butanol and butanone.

Quite recently, Fisher and Chittenden[7] have condensed ethanal with

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(1) Kyriakides, THIS JOURNAL, **36**, 531 (1914).

(2) Koelichen, *Z. physik. Chem.*, **33**, 129 (1900); Hammarsten, *Ann.*, **421**, 293 (1920).

(3) V. Grignard and M. Dubien, *Ann. chim.*, (10) **2**, 286 (1924).

(4) E. N. Eccott and R. P. Linstead, *J. Chem. Soc.*, **133**, 911 (1930).

(5) Franke and Koehler, *Ann.*, **433**, 314 (1923); Colonge, *Bull. soc. chim.*, **49**, 444 (1931).

(6) Powell, THIS JOURNAL, **46**, 2514 (1924).

(7) Fisher and Chittenden, *Ind. Eng. Chem.*, **22**, 869 (1930).

butanone by the method developed by the writer[8] for the preparation of acetaldol. They obtained methyl-3-pentanol-4-one-2 in very poor yield. This is not surprising, since, in the condensation of an equimolecular mixture of the components, acetaldol must have been formed to a large extent.

Colonge[9] isolated methyl-3-pentanol-4-one-2 in 47.5% yield on ethanal by slowly dropping the aldehyde into approximately three moles of butanone containing an appreciable amount of alcoholic potassium hydroxide. We have established that ethanal condensed with even eight moles of butanone may give a considerable amount of acetaldol.

As we had demonstrated in the case of acetaldol,[10] we found that ketolization does not require the use of large amounts of alkali nor solvents, as indicated by others. The amount of alkali necessary to induce ketolization is extremely small and the reaction mixture can be distilled directly after neutralization of the alkali.

Excellent yields of the ketols are obtained by dropping the aldehyde slowly with vigorous agitation into an excess of butanone, containing an extremely small amount of free alkali, at a sufficiently slow rate that condensation with the ketone proceeds without accumulation of unreacted aldehyde. If these conditions are not observed, some aldol may be formed.

The dehydration of the ketols to the unsaturated ketones was accomplished readily by the use of traces of halogen acid. This method[11] had given excellent results in the preparation of divinyl hydrocarbons from certain types of glycols and unsaturated alcohols.

The reduction of methyl-3-pentanol-4-one-2 to the corresponding glycol was made electrolytically[12] at a mercury cathode in a permanently bicarbonate solution. The glycol on dehydration with a trace of hydriodic acid gave a fairly good yield of the corresponding butadiene-1,3-hydrocarbon.

Experimental

1. **Simultaneous Formation of Acetaldol and Methyl-3-pentanol-4-one-2.**—Eleven hundred grams of neutral, freshly distilled butanone was charged into a 2-liter, 3-necked flask, carrying a thermometer dipping within the liquid. A solution of 100 g. of ethanal in 202 g. of butanone (made by distilling the aldehyde into the ketone immediately before use) was added to the flask, the mixture agitated vigorously and cooled at 7–9° during the reaction. Eight cc. of a 10% aqueous sodium hydroxide solution was added and the reaction continued at the indicated temperature for four hours. The reaction mixture was tested at intervals for free alkalinity.

One cc. more of the alkali was added and the reaction continued for one and three-fourths hours longer. Two grams of tartaric acid was then added, agitation continued for a while and the reaction mixture concentrated directly in partial vacuum through

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[8] Kyriakides, THIS JOURNAL, **36**, 532 (1914).

[9] Colonge, *Bull. soc. chim.*, **49**, 449 (1931).

[10] Kyriakides, THIS JOURNAL, **36**, 530 (1914).

[11] Kyriakides, *ibid.*, **36**, 987 (1914).

[12] U. S. Patent 1,094,315 (1914).

an efficient column (boiling point of butanone 45–50°). The last traces of butanone were driven off under the full vacuum of the water pump. The residue was dehydrated by heating with 2 cc. of 40% hydrobromic acid and distilling the reaction products through a short Vigreux column. The distillate was saturated with calcium chloride, the oil dried and carefully fractionated. Fractions were collected up to 105° (moist), 105–120°, and above 120°. The fractions were refractionated and 13 g. of crotonaldehyde boiling between 97–105° and 75 g. of crude methyl-3-pentene-3-one-2 boiling above 130° (up to 141°) were obtained.

In this experiment the molecular proportion of ethanal to butanone was 1:8.

2. **Methyl-3-pentanol-4-one-2,** $CH_3CHOHCH(CH_3)COCH_3$.—Eleven hundred grams of neutral, freshly distilled butanone was charged into the same reaction flask as in Experiment 1. The charge was treated with 7 cc. of 10% aqueous sodium hydroxide, agitated vigorously and cooled at 8–9° during the reaction. A solution of 103 g. of freshly distilled ethanal in 200 g. of neutral butanone was dropped in from a graduated dropping funnel at a fairly uniform rate over a period of five hours and the reaction continued for an extra hour. Alkalinity tests[13] showed the presence of free alkali throughout the reaction period. Two grams of tartaric acid was added, agitation continued for a short time, the unfiltered, colorless liquid concentrated through an efficient column, and finally freed from the last traces of butanone at 35 mm. The residue was distilled over directly: 242 g. of colorless ketone alcohol was obtained, which on refractionation boiled at 95–96° at about 35 mm. and weighed 231 g., which corresponds to an 85% yield on ethanal.

Butanone alone subjected to the action of the same proportion of alkali over the same length of time, did not give any significant amount of its ketol.

3. **Methyl-3-pentene-3-one-2,** $CH_3CH{=}C(CH_3)COCH_3$.—The 231 g. of the redistilled methylpentanolone obtained in the above experiment was treated with 1 cc. of 40% hydrobromic acid, distilled over a gauze through a medium sized Vigreux column and the dehydrated product was worked up as under Experiment 1. After drying, the total distillate was fractionated efficiently. The methylpentenone obtained, boiling at 138–141°, weighed 175 g. and amounted to 76.5% of the theoretical on the ethanal (experiment 2) and 90% on the methylpentanolone. The product on refractionation boiled completely at 139.5–141°. Colonge[9] gives the boiling point of methyl-3-pentene-3-one-2 as 136–138°. In the above fractionation even the few drops obtained below the boiling point of the unsaturated ketone failed to give the sharp smell which is characteristic of crotonaldehyde, indicating that the ketone alcohol was free from acetaldol.

4. **Methyl-3-pentenediol-2,4,** $CH_3CHOHCH(CH_3)CHOHCH_3$.—A rectangular jar 25.5 × 15.7 cm. and 26 cm. high was immersed in an ice and water bath. The bottom of the jar was covered with a layer of mercury (400 sq. cm.) which was used as the cathode. A porous cup carrying a sheet of nickel as anode was used for the anolyte: 406 g. of methyl-3-pentanol-4-one-2 was dissolved in 2 liters of a 10% potassium bicarbonate solution and poured into the cathode compartment. In order to preserve the bicarbonate alkalinity of the catholyte the liquid was agitated and a good stream of carbon dioxide bubbled through. The anode liquid consisted of a strong solution of potassium carbonate, which was continuously replenished as migration took place and cooled with a stream of cold water running through a glass coil.

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(13) This test is carried out by rubbing a glass rod against the walls of the reaction flask and then on a piece of phenolphthalein paper. Because of the minute quantity of the alkali present and its insolubility in the reaction mixture, this test is delicate and in case it is negative must be repeated. Should the test be definitely negative at any stage of the reaction, the addition of aldehyde must be discontinued and alkalinity immediately established by the addition of 1 to 2 cc. at a time of 10% alkali.

Reduction was carried out at a cathode temperature of about 20° for twenty-two hours at 11 amperes and 23 volts. The catholyte was tested at intervals by spotting on phenolphthalein paper to make sure that the solution was in the bicarbonate state. The cathode liquid was concentrated *in vacuo*, filtered, further concentrated, filtered and the cake washed with a little cold water. The oil which separated out was drawn off and the aqueous layer extracted with alcohol. The combined oil and alcohol was concentrated, filtered from the carbonate, the latter washed with alcohol, and fractionated *in vacuo;* 273 g. of the glycol boiling at 124–126° at 36 mm. was collected, which corresponds to 66% of the theoretical yield.[14]

5. **Methyl-3-pentadiene-1,3,** $CH_3CH{=}C(CH_3)CH{=}CH_2$.—This product has been described by Fisher and Chittenden.[7] A 125-cc. flask connected with a short Vigreux column was charged with 30 g. of methyl-3-pentanediol-2,4 and treated with 2 cc. of concentrated hydriodic acid.[11] The mixture was heated and the reaction products distilled at about 90° through a short column. At the same time, 200 g. of fresh glycol was dropped in at a rate corresponding to that distilling over. The distillate after drying was fractionated slowly through an efficient column, and fractions collected up to 85°, 85–110° and 110–145°. On refractionation 103 g. of the diene (64% of the theoretical) was obtained, boiling at 75–80°. This product needs further purification as it contains some aldehydic impurities.

6. **Methyl-3-heptanol-4-one-2,** $CH_3CH_2CH_2CHOHCH(CH_3)COCH_3$.—A mixture of 700 g. of butanone and 15 cc. of 10% sodium hydroxide was agitated vigorously at 20°; 100 g. of freshly distilled *n*-butanal was dropped in over a period of six hours and the reaction continued for one hour longer at 20°; 3.5 g. of tartaric acid was added and filtered after half an hour. After the distillation of unreacted butanone under partial vacuum (recovery almost quantitative), the reaction product was distilled at 30 mm.; 155.5 g. of main product was collected boiling from 105–120° (mostly 112–116°). Assuming this to be free from aldol the yield of ketol is approximately 78% of the theoretical from *n*-butanal.

In another experiment made at 28° using 8 moles of butanone to 1 of butanal an 82% yield of crude ketol was obtained.

7. **Methyl-3-heptene-3-one-2,** $CH_3CH_2CH_2CH{=}C(CH_3)COCH_3$.—This product, which is obtained from methyl-3-heptanol-4-one-2, has been described by Powell[6] who obtained it using iodine as dehydrating agent. We carried out the dehydration under partial vacuum using a trace of hydrogen bromide and obtained the unsaturated ketone in a 92.5% yield from the ketol, which corresponds to a 72% yield from butanal. The product boiled under atmospheric pressure from 170–177°, over 90% coming over at 174–176°.

Summary

In condensing ethanal or *n*-butanal with butanone to form the mixed ketols, the ketone is used in considerable excess and the reaction is carried out with vigorous agitation by dropping the aldehyde slowly into the ketone, containing a very small amount of free aqueous alkali. The resulting ketol can be isolated by direct fractionation after neutralization of the alkali. In this manner, a high yield of the mixed ketol is obtained with minimum dehydration.

The unreacted ketone can be recovered almost quantitatively.

The ketols are readily dehydrated in excellent yields to the corre-

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[14] The yield of butanediol-1,3 in a similar electrolytic reduction was 87% of the theoretical from pure acetaldol; while in one experiment diacetone alcohol gave a 78% of methyl-2-pentanediol-2,4.

sponding unsaturated ketones with traces of a halogen acid, preferably hydrobromic.

The low molecular weight ketols are reduced readily to the corresponding glycols electrolytically at a mercury cathode in a permanently bicarbonate solution.

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Para-Aminophenyl Urethans as Local Anesthetics

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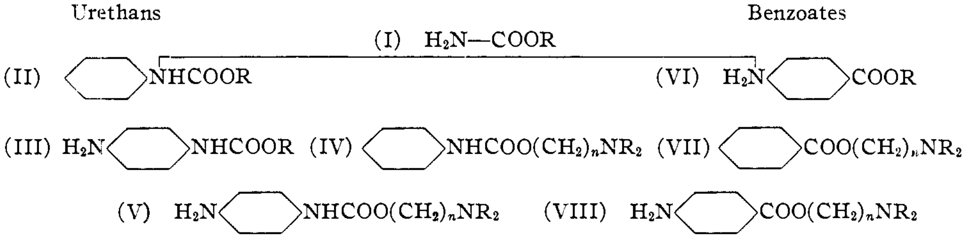
A comparison of the structures for compounds of the novocaine type (VIII) with those for *p*-aminophenyl urethans (III) shows that the transposition of the nitrogen atom results in an isomeric substance whose local anesthetic properties should be very interesting to study.

CHART I



The parallelism is quite interesting for (VIII) is an ester of *p*-aminophenylformic acid whereas (III) is an ester of *p*-aminophenylcarbamic acid. The simple phenyl urethans (II) which are isomeric with alkyl *p*-aminobenzoates (VI) and with benzoates of amino alcohols (VII) are known to possess local anesthetic action. Since urethans[1] (I) cause general anesthesia and phenyl urethans[2] (II and IV) are known to possess local anesthetizing power, the introduction of an amino group first into the benzene ring (III) and then into the side chain (V), thus making the urethan more like novocaine, should produce interesting variations of these molecules and at the same time complete a logical series of structural changes from urethan to novocaine as indicated in Chart I. An excellent review of the relationship between local anesthetic activity and structure in compounds of types IV, VI, VII and VIII has been prepared by Hirschfelder and Bieter.[3]

The purpose of the present communication is to describe the preparation

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[1] Dixon, "Manual of Pharmacology," Arnold, London, 1908, p. 68.

[2] Fromherz, *Arch. exp. Path. Pharm.*, **76**, 257 (1914); Rider, *J. Pharmacol.*, **39**, 457 (1930); THIS JOURNAL, **52**, 2115 (1930).

[3] Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).