[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Condensation of Paraformaldehyde with Aromatic Ketones

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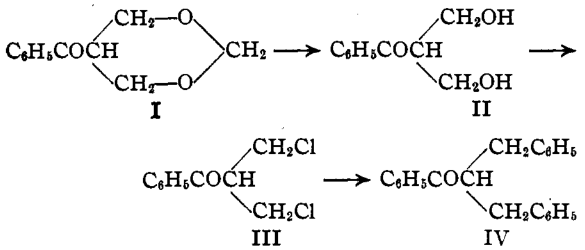
The condensation of simple aliphatic ketones has been studied thoroughly and can be caused to proceed in a controllable manner to give relatively simple products. With aromatic ketones, however, the reaction appears to take place only with difficulty. For example, the interaction of formaldehyde and acetophenone in the presence of various alkaline catalysts has been reported to give only complex products.[2] Using potassium carbonate as the catalyst Manta[3] converted propiophenone to a dimethylol derivative in which the carbonyl group had been reduced to a carbinol group. With isobutyrophenone Manta obtained a still more complex product. In Manta's experiments the reaction mixtures were heated.

We have found that simpler products are obtained if the reaction is carried out at room temperature and allowed to continue for a longer period. When acetophenone was treated with paraformaldehyde in methanol in the presence of potassium carbonate a high yield was obtained of a compound which proved to be the formal of the dimethylol derivative (I).

The structure of the formal was proved by the following transformations.

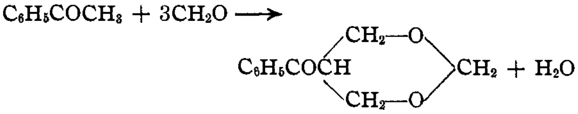


I II III IV

Treatment with concentrated hydrochloric acid converted it to the dichloro ketone (III) and formaldehyde. The latter was identified by formation of the β-naphthol derivative, di-β-naphtholmethane. The structure of the dichloro ketone was established by converting it into dibenzylacetophenone (IV) by the Friedel-Crafts method. An authentic specimen of this compound, made from acetophenone and benzyl chloride by the method of Nef,[4] proved to be identical.

The formal was hydrolyzed by treatment with concentrated sulfuric acid but the dimethylol derivative (II) could not be isolated.

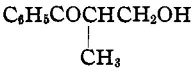
The foregoing facts indicate that the reaction between acetophenone and paraformaldehyde is represented by the equation



$$C_6H_5COCH_3 + 3CH_2O \longrightarrow C_6H_5COCH(CH_2O)_2CH_2 + H_2O$$

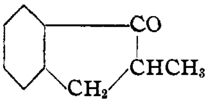
Although the ratio of aldehyde to ketone was varied considerably, the formal was always the chief product. This is remarkable because acetal formation generally does not take place in alkaline media. It is somewhat strange also that none of the early workers in the field have reported this reaction. However, the result is not entirely novel. In 1937, Gilbert, Morgan and Griffith[5] obtained a formal by treating methyl ethyl ketone with formaldehyde in the presence of sodium hydroxide.

Propiophenone reacted slowly with paraformaldehyde to give β-benzoylpropyl alcohol (V) which shows no tendency to undergo spontaneous dehydration. For example, it forms the corresponding urethan when treated with phenyl isocyanate.

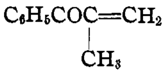


$C_6H_5COCH(CH_3)CH_2OH$

V



VI



$C_6H_5COC(CH_3){=}CH_2$

VII

Dehydration was effected, however, by the action of concentrated sulfuric acid. The product proved to be α-methylhydrindone (VI) and not the expected isopropenyl ketone (VII). Bromine brought about substitution giving α-bromo-α-methylhydrindone. The melting point of this derivative corresponds with that given by Salway and Kipping[6] for α-bromo-α-methylhydrindone. Confirmatory evidence for the structure of the α-methylhydrindone was obtained by oxidation which converted it to o-phthalic acid.

This ring closure involves the cyclodehydration

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[2] Van Marle and Tollens, *Ber.*, **36**, 1351 (1903); Tollens, *ibid.*, **37**, 1435 (1904); Schäfer and Tollens, *ibid.*, **39**, 2181 (1906).

[3] Manta, *J. prakt. Chem.*, **142**, 11 (1935).

[4] Nef, *Ann.*, **310**, 316 (1900).

[5] Gilbert, Morgan and Griffith, *J. Chem. Soc.*, 841 (1937).

[6] Salway and Kipping, *J. Chem. Soc.*, **95**, 166 (1909).

of a 2-aroyl-1-alkanol and is a novel method of synthesis of 2-alkyl-1-indanones.

Experimental

The Action of Formaldehyde on Acetophenone.—A mixture of 45 g. of paraformaldehyde, 180 g. of acetophenone, 2 g. of potassium carbonate and 300 cc. of methyl alcohol was shaken for seven days at room temperature and poured into a liter of water. The mixture was acidified with hydrochloric acid and extracted with four 100-cc. portions of benzene. The combined benzene extracts were washed three times with water. The solvent was evaporated and the residue distilled under diminished pressure. Sixty-four grams of acetophenone was recovered. Eighty-five grams of the formal of 2-benzoyltrimethylene glycol was obtained; b. p. 124–126° (3 mm.). The residue remaining in the flask was a heavy viscous resin. The formal reduced Benedict's solution and gave a silver mirror with Tollens' reagent.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.71; H, 6.29. Found: C, 68.91; H, 6.5.

The Action of Hydrochloric Acid on the Formal.—Five grams of the formal was shaken with 50 cc. of concentrated hydrochloric acid at room temperature for twenty-four hours. The mixture was then allowed to stand until the oil had solidified completely. The solid was collected on a filter, the filtrate was diluted to 150 cc. and to it were added 7.5 g. of β-naphthol and 30 cc. of ethyl alcohol. The mixture was boiled for five minutes and allowed to cool. The crystals which formed weighed 6 g. After recrystallization from dilute ethyl alcohol the compound melted at 190–191°, with darkening at 180°. It was evidently di-β-naphtholmethane.

The yield of the solid chloro compound—1,3-dichloro-2-benzoylpropane—was 5 g.; m. p. 56–57°.

Anal. Calcd. for $C_{10}H_{10}OCl_2$: C, 55.3; H, 4.6; Cl, 32.67. Found: C, 55.73; H, 4.55; Cl, 32.97.

Condensation of 1,3-Dichloro-2-benzoylpropane with Benzene.—To a solution of 10 g. of the dichloride in 200 cc. of dry benzene was added all at once 8 g. of anhydrous aluminum chloride. The mixture was shaken overnight and decomposed with ice. The oily product obtained by benzene extraction solidified after several hours and was recrystallized from 80% ethyl alcohol; m. p. 78°. A mixed melting point determination showed the compound to be α,α-dibenzylacetophenone.

The Action of Sulfuric Acid on the Formal of 2-Benzoyltrimethylene Glycol.—Ten grams of the formal was poured into 50 cc. of concentrated sulfuric acid, with stirring. The mixture became warm and the odor of formaldehyde was discernible. After standing for ten minutes, it was poured into 500 cc. of water. By extracting this mixture with ether there was obtained a pungent lachrymatory oil. Distillation gave a small amount of yellow liquid; b. p. 101–105° (3 mm.). The residue set to a resin which was insoluble in alcohol and acetone. The distillate also resinified when allowed to stand.

The Reaction of Propiophenone with Formaldehyde.—A mixture of 40 g. of propiophenone, 9 g. of paraformaldehyde, 4 g. of potassium carbonate and 200 cc. of methyl alcohol was shaken at room temperature for four days. It was then poured into a liter of water. The resulting mixture was acidified with hydrochloric acid and extracted with three 60-cc. portions of benzene. The combined benzene extracts were washed three times with water and the solvent evaporated. By distillation of the residue there was obtained 32 g. of propiophenone and 8 g. of an oil boiling at 143–145° (5 mm.). The residue was negligible.

The 32 g. of recovered propiophenone was shaken for seven days with a mixture of 7.5 g. of paraformaldehyde, 2 g. of potassium carbonate and 100 cc. of methyl alcohol. From this run 16 g. of the oil was obtained. It was 2-benzoylpropyl alcohol.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.12; H, 7.37. Found: C, 73.31; H, 7.58.

The phenylurethan (from 80% methyl alcohol) melted at 86–87°.

Anal. Calcd. for $C_{17}H_{17}O_3N$: N, 4.94. Found: N, 5.2.

α-Methylhydrindone.—Ten grams of the keto alcohol was poured into 50 cc. of cold sulfuric acid, with stirring. The stirring was continued for two hours and the mixture was poured into 500 cc. of water. Extraction with ether gave 6 g. of α-methylhydrindone; b. p. 88–90° (3 mm.).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.15; H, 6.9. Found: C, 82.22; H, 7.2.

Oxidation with dilute nitric acid gave a high yield of *o*-phthalic acid.

α-Bromo-α-methylhydrindone.—To a solution of 1 cc. of the α-methylhydrindone in 10 cc. of carbon tetrachloride was added from a pipet a solution of bromine in carbon tetrachloride. The addition was continued until a slight color persisted. Approximately 11 cc. of a solution containing 0.05 g. of bromine per cubic centimeter was added. The reaction was accompanied by copious evolution of hydrogen bromide. The solvent was evaporated and the residual oil solidified after being allowed to stand for several days. The bromohydrindone crystallized from dilute alcohol in large, colorless plates; m. p. 72–73°.

Summary

The condensation of paraformaldehyde with acetophenone has been carried out in methanol with potassium carbonate as the catalyst. An excellent yield is obtained of the formal (I) of the dimethylol derivative.

Similar treatment of propiophenone gives the monomethylol derivative (V). When dehydrated this compound is transformed into α-methylhydrindone (VI).

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