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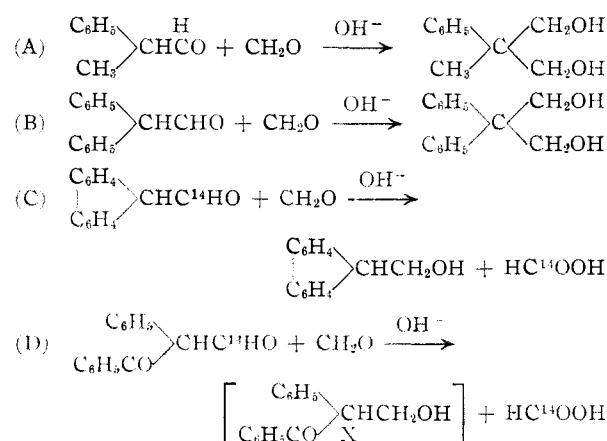
The Reaction of Formaldehyde with Aldehydes Containing One α -Hydrogen Atom¹

BY JOHN G. BURR, JR.

The reaction of formaldehyde in basic solution with diphenylacetaldehyde has been found to give β,β -diphenyltrimethylene glycol. The reaction of this same reagent with β -hydroxy- α -phenyl-(acrylo- β -C¹⁴)-phenone (formyldeoxybenzoin), has been found to give a derivative of α -hydroxymethyldeoxybenzoin with displacement of the formyl group as formic-C¹⁴ acid. There is also found 5-10% of the same derivative labeled with C¹⁴, presumably derived from direct reduction of the labeled diketone. These observations seem to be better correlated by the Cannizzaro reaction mechanism which involves intramolecular hydride ion transfer, than by the Cannizzaro reaction mechanism which demands an intermolecular hydride ion transfer.

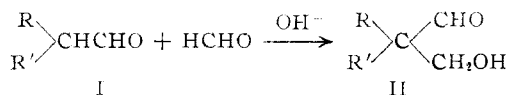
Introduction

As a result of the discovery that 9-(formyl-C¹⁴)-fluorene reacted with formaldehyde to give inactive 9-fluorene-methanol (with displacement of the formyl group as formic acid),² two similarly constituted aldehydes have been studied in an attempt to clarify this reaction. The results obtained with these two, diphenylacetaldehyde and formyldeoxybenzoin, are shown below, together with the previously reported reaction of methylphenylacetaldehyde.³ The aldehydes are arranged in the order of decreasing electron density at the α -carbon atom, as indicated by Conant and Wheland.⁴ It is evident



that these four similarly constituted aldehydes give two types of products. As shown below, it seems probable that this change in the nature of the product is related to the change in electron density at the α -carbon atom.

In the normal reaction of formaldehyde with aldehydes containing one alpha hydrogen atom, the first step probably involves the aldol addition of formaldehyde to the aldehyde to form an intermediate II.⁵



(1) This document is based upon work performed under Contract Number W-7405, eng. 26 for the Atomic Energy Commission at the Oak Ridge National Laboratory. It was presented in part before the Division of Organic Chemistry, Boston Meeting of the American Chemical Society, 1951.

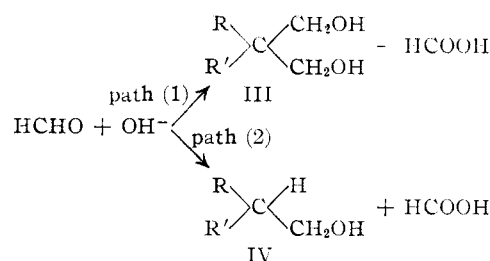
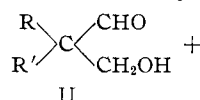
(2) J. G. Burr, *THIS JOURNAL*, **73**, 823 (1951).

(3) A. Franke, *Monatsh.*, **34**, 1904 (1913).

(4) J. B. Conant and G. W. Wheland, *THIS JOURNAL*, **54**, 1215 (1932).

(5) T. A. Geissman, R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1949, Chap. 3, p. 100.

This compound is then presumably reduced by excess formaldehyde to give the glycol III.



However, in reactions C and D above, the intermediate II, if it forms, loses the aldehyde group as formate to form a carbinol IV, as represented by path 2.

The displacement of a formyl group from an aldehyde such as II probably is similar to the cleavage of formyl groups observed in the haloform reaction and the alkaline cleavage of certain acetylenic aldehydes⁶ and triphenylacetaldehyde.⁶

This sort of displacement has been explained⁷ by the addition of hydroxide ion to the aldehyde to give an ion such as V, which then loses formic acid and acquires a proton to give IV.

It is evident that this ionic intermediate, V, is the same as that required by the Geissman⁸ mechanism for the Cannizzaro reaction. This is shown in the sequence II \rightarrow V \rightarrow VI \rightarrow VII \rightarrow III. This mechanism thus serves as a useful correlation for all four of the reactions discussed in this paper. Subsequent reaction of the intermediate, V, once formed, can apparently depend upon the nature of the groups R and R'. If these groups sufficiently reduce the electron density of the alpha carbon atom then the ion, V, suffers cleavage of the formyl group rather than the normal crossed Cannizzaro reduction to III.

These four reactions cannot be easily correlated by the mechanism for the Cannizzaro reaction which has been proposed by Hammett⁹ and recently supported by Alexander.¹⁰ This mechanism would require, in this case, an intermolecular hydride ion transfer between the aldehyde intermediate (II)

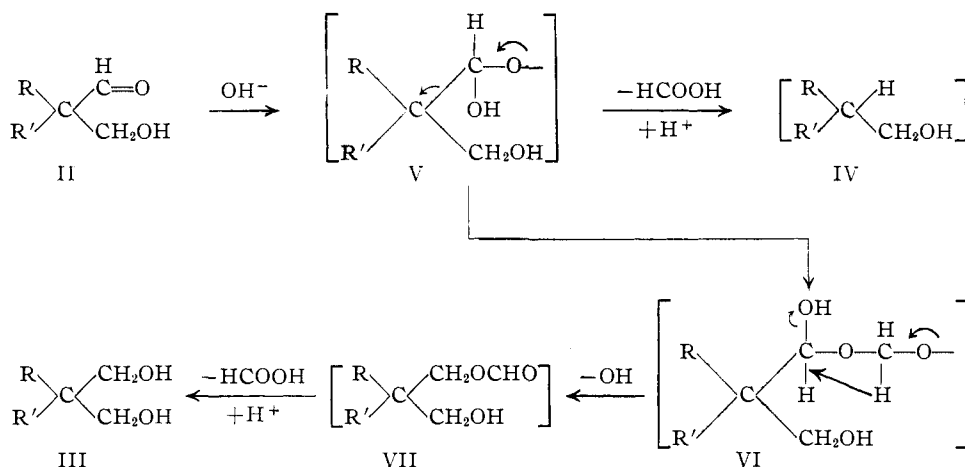
(6) T. A. Geissman, ref. 5, p. 99.

(7) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, New York, N. Y., 1950, p. 207.

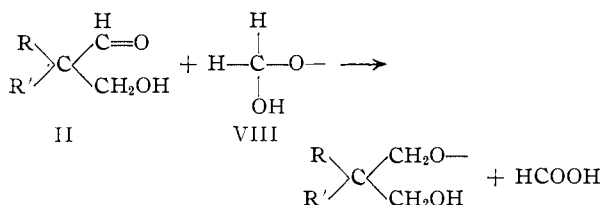
(8) T. A. Geissman, ref. 5, p. 96.

(9) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 350.

(10) E. R. Alexander, ref. 7, p. 168.

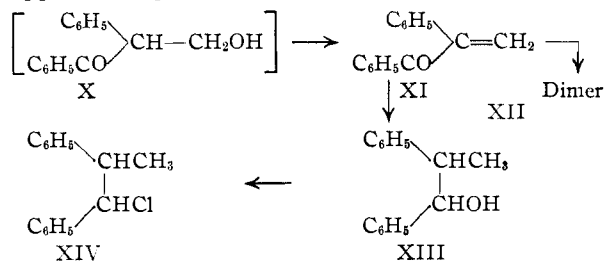


and the complex (VIII) formed by formaldehyde with hydroxide ion

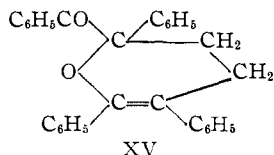


This does not explain the cleavage of the aldehydes involved in reactions C and D, which would then require a separate mechanism as shown above. The use of two altogether different mechanisms to explain the reactions of four aldehydes which are similar in most important respects does not seem desirable.

The reaction of formyldeoxybenzoin with basic formaldehyde solution (reaction D) offers several additional points of interest, since the product, X, apparently spontaneously dehydrated.



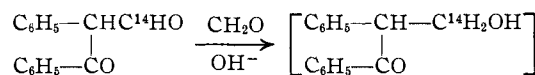
The dehydration product, XI, was identified by reduction to the carbinol, XIII, which gave a known chloride, XIV. It was found that the product XI (an oil) upon standing was slowly but completely converted to a dimer melting at 108–110°. The dimer gave no carbonyl group reactions, nor any of the hydroxyl group, and did not absorb hydrogen. The structure XV is suggested for this dimer by analogy with the known¹¹ dimers of other α,β -unsaturated ketones.



(11) K. Alder, H. Offermanns and E. Ruden, *Ber.*, **74B**, 905 (1941).

It would be expected to have both a highly hindered double bond, and also a highly hindered carbonyl group. Further investigation of this substance is in progress.

In addition, the reaction of the labeled formyldeoxybenzoin gave intermediates, XI, XIII and XIV which, despite careful purification, retained 3–10% of the molar C^{14} activity of the starting material. It seems probable from this evidence that, concurrent with the above-mentioned displacement reaction, there must be a small amount of direct reduction of the aldehyde.



The formation of this same product by two different reaction paths could not have been observed, except by the use of isotopic carbon. The possibilities suggested by the discovery of this direct reduction of the formyl ketone are being explored by the study of the reaction of formaldehyde with other labeled formylketones.

Acknowledgment.—The author wishes to express his sincere thanks to Dr. O. K. Neville for his assistance in formulating and expressing many of the ideas contained in this article.

Experimental¹²

β,β -Diphenyltrimethylene Glycol.—Diphenylacetaldehyde (9 g.), prepared by the rearrangement of either hydrobenzoin or α,α -diphenylethylene glycol, was dissolved in 50 ml. of 10% sodium hydroxide and treated with 10 ml. of 37% formalin solution overnight. The oil, which separated and was removed with ether, weighed 9 g. The product, distilled at 1 mm. pressure, partly crystallized. Recrystallization from benzene-pentane gave 2.1 g. of colorless microplates which melted at 102–103°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_2$: C, 78.8; H, 7.07; OH, 14.9. Found: C, 78.6; H, 6.61; OH, 14.0.

The compound formed a dibenzoate melting at 107–108° (depressed by admixture with diol).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_4$: C, 79.8; H, 5.59. Found: C, 79.3; H, 5.52.

Reaction of β -Hydroxy- α -phenylacrylophenone (Formyldeoxybenzoin) with Formaldehyde.—Desoxybenzoin (103 g.) was converted to formyldeoxybenzoin with a solution

(12) All melting points were taken on a Fisher-Johns block and are uncorrected. C^{14} assays were accomplished by a wet combustion of compounds, and ion chamber counting of the carbon dioxide on a vibrating reed electrometer. Microassays for carbon and hydrogen were by H. W. Galbraith, Knoxville, Tennessee.

of 33 g. of commercial sodium methoxide and 62 ml. of ethyl formate in 200 ml. of alcohol. The unreacted ketone weighed 30.5 g. The moist enol (91 g.) suspended in 200 ml. of 37% formalin was treated with a solution of 23 g. of potassium hydroxide in a mixture of 150 ml. of alcohol and 30 ml. of water. After the solution was stirred overnight and poured into water, the insoluble oil (75 g.) was extracted with ether and distilled at less than 1 mm. pressure. The distillate, collected in five very similar fractions, weighed 60.7 g. The analytical data obtained for the purest fraction, n_D^{25} 1.6028, d_4^{25} 1.101, b.p. 133–133.8°, is shown in Table I.

TABLE I
ANALYTICAL DATA FOR COMPOUND XI

Determination	Method	Found	Calcd. for $C_{16}H_{16}O$ (XI)
Molecular weight	B.p. elevation in benzene	213	208
Carbonyl, %	Hydroxylamine hydrochloride ¹⁴	13.0	13.4
Mol. refr.		65.0 ^a	63.8
Hydrogenation ^b	Adams PtO ₂ in alcohol	2.0 mols	2 mols

^a This is an exaltation of 1.2 units, which is not surprising for a carbonyl-group conjugated with phenyl group and a double bond. ^b Normal pressure.

A 10-g. portion of the compound X was hydrogenated. The product distilled at 130° at 1 mm. pressure, n_D^{25} 1.556, and was converted to the chloride, XIV, m.p. 139–140°, by the procedure of Kayser.¹³

Anal. Calcd. for $C_{16}H_{16}Cl$: Cl, 15.1. Found: Cl, 15.3.

The liquid product, XI, after standing for a week and a half, deposited crystals, m.p. 107–108°, from alcohol solution and in a few weeks was almost completely solid.

Anal. Calcd. for $C_{30}H_{24}O_2$: mol. wt., 416; C, 86.3; H, 5.82. Found: mol. wt., 420; C, 85.7; H, 6.04.

This dimer did not react with hydroxylamine in the procedure of Siggia¹⁴ nor did it absorb hydrogen at normal pressure in the presence of platinum. It did not react with phthalic anhydride in the presence of pyridine¹⁵ (showing the absence of hydroxyl function). The ultraviolet spectra had a single maximum at 241 m μ (log E_M 4.22), which is characteristic of a conjugated carbonyl function. The infrared spectrum (paste in Nujol) showed absorption peaks characteristic of carbonyl function, but none where the hydroxyl bands might be expected.

(13) B. Kayser, *Ann.*, **6**, 171 (1936).

(14) S. Siggia, "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 17.

(15) *Ibid.*, p. 17.

Preparation of β -Hydroxy- α -phenyl-(acrylo- β -C¹⁴)-phenone and Its Reaction with Formaldehyde.—To a solution of 15.70 g. of desoxybenzoin (80 mmoles) (Eastman Kodak material which had been digested with dilute sodium hydroxide and crystallized from methanol) in 50 ml. of ether was added 2.0 ml. of ethyl formate-C¹⁴ (25 mmoles containing about 10 μ c. of C¹⁴/mmole) and 4.86 ml. of inactive ethyl formate (making a total of 85.6 mmoles of ethyl formate). This solution was stirred in an atmosphere of nitrogen with 4.86 g. of sodium methoxide (90 mmoles) for 60 hours at room temperature, and was then hydrolyzed with water. The ether layer was extracted several times with dilute sodium hydroxide. The residual ether layer contained no activity and was therefore discarded. The aqueous extracts were washed with ether, chilled and then acidified cautiously. The air-dried yellow granular precipitate weighed 9.53 g. (53%) and melted at 80–82°. *Assay*: 3.02 μ c. of C¹⁴/mmole.

A small portion of this was converted to the benzoate, m.p. 106–107°, which was crystallized from dilute ethanol. *Assay*: 3.00 μ c. of C¹⁴/mmole.

If this preparation was carried out in alcohol solution, as in the inactive run above, with equimolar amounts of reactants, the yield of labeled desoxybenzoin was only 31% and it was only 92% pure.

The bulk of this crude enol (8.05 g., 35.9 mmoles) was stirred overnight (20 hours) with 16.5 ml. of formalin solution and 40 ml. of 90% ethanol containing 4.5 g. of potassium hydroxide (80 mmoles). The solution was homogeneous at the start but became turbid. It was poured into water. Ether extraction of this mixture gave 8.65 g. of an oil which was distilled at high vacuum to give 3.67 g. of a colorless oil, n_D^{25} 1.5890; and a second fraction which was 2.28 g. of a thick viscous yellow oil, n_D^{25} 1.5910. The first fraction upon hydrogenation at normal pressure using 100 mg. of platinum oxide took one mole of hydrogen in two hours. The product was recovered and fractionated at high vacuum. The first fraction (b.p. 100–112°, n_D^{25} 1.5582) was 1.17 g. of a colorless oil and the second fraction was 2.11 g. of a colorless oil, b.p. 112–125°, n_D^{25} 1.5662, which upon assay showed the presence of 0.091 μ c. of C¹⁴/mmole (calculated as XIII), or 3% of the molar activity of the formylfluorene. In another run, this fraction (containing 5% of the aldehyde activity) was converted to the chloride, XIV, m.p. 135–137° (mixture m.p. with authentic sample, 135–139°) which contained 10% of the aldehyde activity.

In one of these runs, where 20.4 μ c. of formyl-desoxybenzoin (10.85 mmoles) was used, the aqueous fraction from the product work-up was diluted with 1.00 g. of non-radioactive sodium formate, the solution concentrated, slightly acidified and treated with S-benzylthiuronium chloride. The precipitated salt, m.p. 146–147°, contained 0.456 μ c. of C¹⁴/mmole, or 57% of the theoretical 0.797 μ c./mmole.

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