substitution in the mesitylene group, the pure chloro compound is most readily made by employing a calculated quantity of sulfuryl chloride. The pure bromo compound can be made by operating with free bromine in chloroform at low temperatures. These halogen compounds are interesting because they are as reactive as the halogen derivatives of triaryl methanes. The constants of the chloro and bromo compounds as well as those of the corresponding ethers are shown in the following table.

	Calcd.		Found			M. p.,
	C	H	C	H	Form	°C.
$C_{24}H_{21}O_2{\cdot}Cl$	76.5	5.6	76.4	5.9	Yellow plates	134
$C_{24}H_{21}O_2{\cdot}Br$	68.4	5.0	68.1	5.4	Yellow plates	152
$C_{24}H_{21}O_2{\cdot}OC_2H_5$	80.8	6.8	80.8	7.1	Prisms	121
$C_{24}H_{21}O_2{\cdot}OCH_3$	80.6	6.5	80.6	6.8	Prisms	68

Coupling. The Tetraketone, XVI.—The enolic form of the α-diketone develops a brown color in alcoholic solutions of ferric chloride but the color soon fades. When the reaction was carried out with larger quantities the product was a sparingly soluble compound which crystallized from ether–petroleum ether in deep yellow prisms and which melted at 194°. The structure of this product was established by a synthesis from the bromo compound of the diketone. For this purpose a solution of 3 g. of the bromo compound in 50 cc. of dry benzene was shaken for twelve hours with 20 g. of mercury. The result was the same compound that had been obtained from the enol. The yield was 80–85%.

Anal. Calcd. for $C_{48}H_{42}O_4$: C, 84.4; H, 6.2; mol. wt., 682. Found: C, 84.1; H, 6.6; mol. wt., 685.

Catalytic Reduction of β-Phenylbenzal Acetomesitylene.—Preliminary experiments showed that the unsaturated ketone is reduced more rapidly by palladium on calcium carbonate than by platinum and hydrogen. Accordingly solutions of 4 g. of the ketone in ethyl acetate and in ether were shaken with hydrogen in the presence of 2 g. of the palladium catalyst until the calculated volume of hydrogen had been absorbed. The rate was the same in both solvents, the time required being an hour and three quarters. The suspensions were filtered, the filtrate was diluted with five times its volume of petroleum ether and saturated with oxygen. As the principal product was the saturated ketone, it was impossible to isolate pure peroxide but a crude estimate based on oxidation of acidified potassium iodide and on conversion to the enol of the diketone indicated that the mixture contained 10–12% of peroxide.

Reduction with Zinc and Acetic Acid.—A solution of 3 g. of the unsaturated ketone in 20 cc. of glacial acetic acid, 20 cc. of ether and 0.5 cc. of water was cooled in a freezing mixture and treated in the course of three minutes with 2.5 g. of zinc dust. The mixture was shaken in the freezing mixture for another three minutes, then poured in a mixture of 10 cc. of ether and 40 cc. of petroleum ether and washed rapidly with ice water until free from zinc and from most of the acetic acid. From the resulting ether–petroleum ether solution oxygen precipitated 3 g. of peroxide —a yield of 90%.

Summary

The paper presents evidence that the system $C{=}C(OH)C_6H_2(CH_3)_3$ is unusually persistent in solution. By utilizing this peculiarity it was possible to prove that the catalytic reduction of α-diketones proceeds by 1,4-addition to the oxygen atoms, that the reduction of α,β-unsaturated ketones with palladium on calcium carbonate and hydrogen proceeds at least in part by 1,4-addition to the conjugated system and that the reduction of α,β-unsaturated ketones by zinc and acid proceeds whol y by 1,4-addition.

CAMBRIDGE, MASS. RECEIVED MARCH 22, 1937

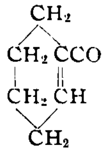
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Application of the Principle of Vinylogy to Unsaturated Ketones

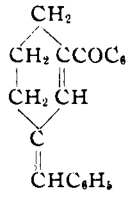
BY R. E. CHRIST[1] AND REYNOLD C. FUSON

A methyl group, separated from a carbonyl group by one vinylene unit, exhibits properties that are similar to those which it possesses when it is attached directly to the carbonyl group.[2] The present paper is an extension of this principle to ketones in which the vinylene group forms a part of a six-membered ring.

Tetrahydrobenzophenone (I) was prepared from benzoyl chloride and cyclohexene by use of the Friedel–Crafts synthesis. This compound was of particular interest, inasmuch as it offered the possibility of testing whether the activating influence of a carbonyl group outside the ring could be exerted on a methylene group which was a member of the ring. The ketone was found to react with benzaldehyde in an alcoholic solution, sodium ethoxide being used as a condensing agent. The product isolated was the expected ketone (II).



I



II

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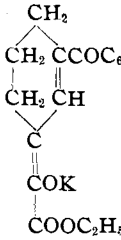
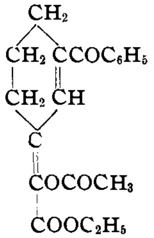
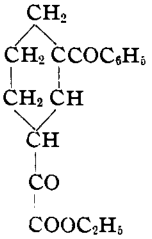
[1] Du Pont Post-doctorate Fellow.

[2] Fuson, Christ and Whitman, THIS JOURNAL, 58, 2450 (1936).

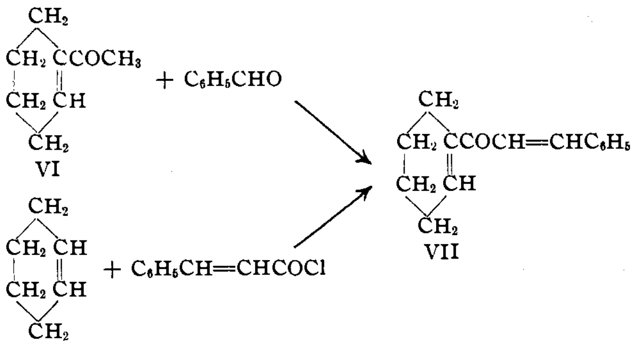
Tetrahydrobenzophenone was also condensed with ethyl oxalate in ether solution, potassium ethoxide being employed as a catalyst. The reaction led to the formation of the potassium salt (III). When treated with acetyl chloride, the salt was converted into the acetate (IV). The free keto ester (V) was produced by dissolving the potassium salt in water and acidifying with dilute hydrochloric acid.


III


IV

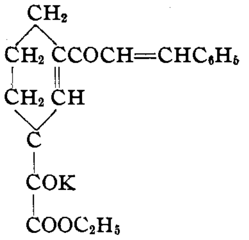

V

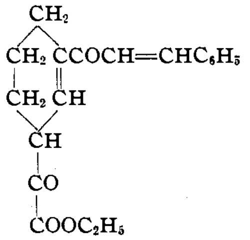
Tetrahydroacetophenone (VI) was chosen as a compound suitable for determining the relative reactivity of a methyl group adjacent to the carbonyl group and that of a methylene group separated from the carbonyl group by a linkage of the type —C=C—. The ketone was condensed with benzaldehyde in an alcoholic solution, sodium ethoxide being employed as a catalyst. The reaction product failed to give a positive iodoform test. This, along with its analysis, indicated that one molecule of aldehyde condensed with the methyl group in preference to the methylene group in the ring, giving the unsaturated ketone (VII). The identity of this compound was proved by its preparation from cinnamyl chloride and cyclohexene by means of the Friedel–Crafts method.


VI

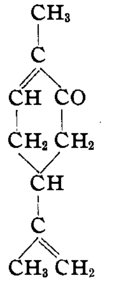
VII

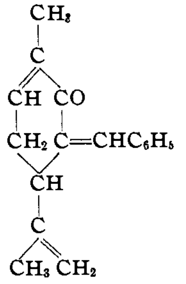
Benzaltetrahydroacetophenone (VII) in ether solution reacted with ethyl oxalate in the presence of potassium ethoxide to give the potassium salt (VIII). The free keto ester (IX) was produced by dissolving the salt in water and acidifying with dilute acid.

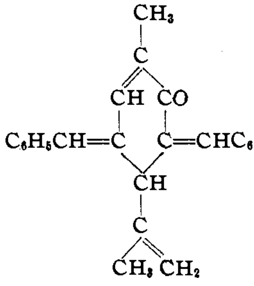

VIII


IX

Müller[3] reported that carvone (X) condensed readily with benzaldehyde in the presence of alkali to yield two different forms of benzylidenecarvone (XI). Wallach,[4] on the other hand, had reported the formation of an amorphous material.


X


XI


XII

The principle of vinylogy suggests the possibility of the formation of dibenzylidenecarvone (XII). For this reason, the reaction of carvone with benzaldehyde was restudied. The ketone and aldehyde were condensed in alcoholic solution, in the presence of sodium ethoxide, to give benzylidenecarvone. No attempt was made to separate the two forms. Instead, the mixture was condensed with benzaldehyde again, and a product was obtained whose composition was that of the expected dibenzylidenecarvone (XII). However, it could not be crystallized from ordinary solvents.

This is analogous to the condensation of one molecule of menthenone (XIII) with two mole-

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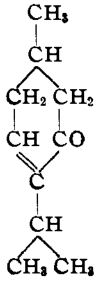
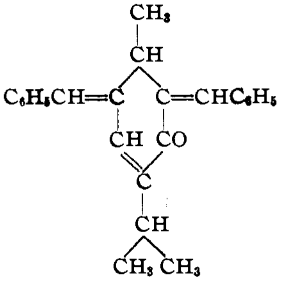
(3) Müller, *Ber.*, **54**, 1471 (1921).

(4) Wallach, *Ann.*, **305**, 274 (1899).

cules of benzaldehyde to produce dibenzylidenementhenone (XIV), as reported by Wallach.[5]


XIII


XIV

Experimental

Tetrahydrobenzophenone.—This substance was prepared by a modification of the method of Wieland and Beltog.[6]

One mole of benzoyl chloride, 86 g. of cyclohexene and 600 cc. of carbon disulfide were placed in a 2-liter, three-necked flask to which were attached a stirrer, reflux condenser and an inlet for aluminum chloride. The flask was cooled with an ice-bath and 133 g. of aluminum chloride was added cautiously while the solution was agitated vigorously. Afterward it was stirred for an additional six hours. The mixture was treated with iced hydrochloric acid, and the carbon disulfide layer was separated and dried with calcium chloride.

The solvent was removed, and 56 g. of potassium hydroxide, dissolved in 200 cc. of ethyl alcohol, was added. After three hours of refluxing, the alcohol was distilled. The residue was washed several times with water, and dissolved in ether. The solution was dried over calcium chloride and, after removal of the solvent, was distilled under reduced pressure. Two fractions were collected: (1) 74 g., b. p. 147° (8 mm.); n^{22}_D 1.5595; d^{22}_4 1.070: (2) 9 g., b. p. 174° (8 mm.).

Fraction (2) solidified upon cooling. Recrystallization from alcohol yielded colorless, well-developed needles melting at 110°. These were not studied further.

Fraction (1) was the desired tetrahydrobenzophenone, and represented a yield of 40% of the theoretical amount. It absorbed bromine readily, showing unsaturation.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.82; H, 7.58. Found: (semi-micro) C, 83.59; H, 7.75.

Condensation of Tetrahydrobenzophenone with Benzaldehyde.—To a solution of 6.2 g. of tetrahydrobenzophenone and 3.5 g. of benzaldehyde in 15 cc. of absolute alcohol maintained at 0° was added, with shaking, a solution of 1 g. of sodium in 10 cc. of absolute alcohol. The mixture soon assumed a gelatinous appearance, and gradually developed a reddish-brown color. It was allowed to stand for twelve hours in a stoppered flask. When it was diluted with water, a heavy yellow precipitate formed. Two crystallizations from alcohol gave faintly yellow crystals; m. p. 115°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: (semi-micro) C, 87.70; H, 6.67.

Condensation of Tetrahydrobenzophenone with Ethyl Oxalate.—A total of 7.8 g. of finely cut potassium was converted to potassium ethoxide by dissolving in 35 cc. of absolute alcohol. Two hundred cubic centimeters of dry ether was added, and the mixture was cooled to 0°.

To the ether solution was then added 18.6 g. of tetrahydrobenzophenone and 14.6 g. of ethyl oxalate dissolved in 50 cc. of ether. The mixture was allowed to stand for a period of twenty hours in an ice box; a heavy layer of orange crystals of the potassium salt (III) settled out.

The mixture was filtered rapidly, and the potassium salt was then washed several times with dry ether, and finally dried in a desiccator under reduced pressure. The weight of the final product was 29 g.; yield 89%.

The keto ester (V) was prepared by dissolving 19 g. of the potassium salt in 100 cc. of cold water and neutralizing with an excess of dilute hydrochloric acid solution. The ester was thrown out of solution as a yellow, semicrystalline mass. Two crystallizations from alcohol gave beautiful, faintly yellow needles. This compound begins to assume a deeper color at 85°, and finally melts at 92°. It dissolves in alkali, giving a light yellow solution.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.29; H, 6.34. Found: (semi-micro) C, 71.00; H, 6.32.

Reaction of the Potassium Salt (III) with Acetyl Chloride.—Ten grams of the salt was mixed with 5 g. of acetyl chloride dissolved in 75 cc. of ether and allowed to stand for a period of twenty hours at room temperature.

Water was added, and the insoluble ether layer was separated and washed several times. The solvent was then evaporated, leaving a yellow crystalline mass of the acetyl derivative (IV). Two crystallizations from alcohol gave 4.5 g. of almost colorless needles; m. p. 92°.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.47; H, 6.14. Found: (semi-micro) C, 69.53; H, 6.36.

Preparation of Tetrahydroacetophenone.—This compound was made by a modification of the directions of Darzens.[7]

A mixture of 158 g. of acetyl chloride, 172 g. of cyclohexene and 1 liter of carbon disulfide was placed in a 3-liter, three-necked flask to which was attached a stirrer, reflux condenser and an inlet for aluminum chloride. The flask was cooled to 0°, and 266 g. of aluminum chloride was added, with stirring. Afterward, the mixture was stirred for two hours at room temperature. It was then treated with iced hydrochloric acid. The carbon disulfide layer was separated and dried with calcium chloride.

The solvent was removed, and the residue was distilled twice at reduced pressure from an excess of sodium carbonate to eliminate hydrogen chloride. The fraction, having a boiling point of 195–200°, was collected as the tetrahydroacetophenone. The yield was 155 g., or 62% of the theoretical amount.

The semicarbazone, a known compound,[7] melted at 220–221°.

Condensation of Tetrahydroacetophenone with Benzaldehyde.—A solution of 24.8 g. of tetrahydroacetophenone and 21.2 g. of benzaldehyde in 100 cc. of 95% alcohol was cooled to 0°. Two grams of sodium dissolved in 40 cc. of absolute alcohol was added slowly, with shaking. The solution assumed a reddish color and took on a gelatinous appearance. The mixture was allowed to stand in a stop-

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[5] Wallach, *Ann.*, **305**, 273 (1899).

[6] Wieland and Beltog, *Ber.*, **55**, 2246 (1922).

[7] Darzens, *Compt. rend.*, **150**, 707 (1910).

pered flask for four days. Steam was then led through to remove the alcohol, and the residual material was dissolved in ether. The solution was dried over calcium chloride and distilled under reduced pressure. A total of 1.7 g. of unchanged reactants was recovered.

In addition, there was obtained 16.6 g. of a light yellow oil having a boiling point of 160–165° (4 mm.). When allowed to stand in a refrigerator for a short time, it solidified. Crystallization from alcohol gave almost colorless crystals; m. p. 68°. This substance was benzaltetrahydroacetophenone; it absorbed bromine readily, showing unsaturation. It failed to give an iodoform reaction.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85; H, 7.60. Found: (semi-micro) C, 84.62; H, 7.79.

Benzaltetrahydroacetophenone.—This compound was prepared for comparison from cinnamyl chloride and cyclohexene by means of the Friedel–Crafts method.

One hundred twenty grams of cinnamyl chloride and 59.5 g. of cyclohexene were dissolved in 100 cc. of carbon disulfide. The solution was added dropwise to a mixture of 106.5 g. of aluminum chloride and 400 cc. of carbon disulfide maintained at a temperature of 0°. Stirring was continued for an additional two hours at room temperature. The mixture was hydrolyzed with iced hydrochloric acid. The carbon disulfide layer was separated and dried with calcium chloride.

The solvent was removed, and the remainder was distilled at reduced pressure from an excess of sodium carbonate to remove hydrogen chloride. Two fractions were collected: (1) Four grams, b. p. 80–130° (4 mm.). This fraction was not studied further. (2) Fifty grams, b. p. 160–165° (4 mm.). This fraction solidified upon cooling. Crystallization from alcohol gave almost colorless crystals; m. p. 68°. A mixed melting point with the benzaltetrahydroacetophenone described previously showed no depression.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85; H, 7.60. Found: (semi-micro) C, 84.69; H, 7.77.

Condensation of Benzaltetrahydroacetophenone with Ethyl Oxalate.—To a solution of 4.9 g. of potassium in 22 cc. of absolute alcohol was added 150 cc. of dry ether, and the mixture was cooled in an ice-bath. To the solution was added a solution of 13.2 g. of the ketone and 9.1 g. of ethyl oxalate in 50 cc. of ether. The mixture was allowed to stand for a period of twenty-four hours in an ice box; a heavy layer of brilliant red crystals of the potassium salt (VIII) settled out.

The mixture was filtered, washed several times with dry ether, and then dried under reduced pressure. The weight of the final product was 19.2 g.; yield, 88% of the theoretical amount.

The keto ester (IX) was prepared almost quantitatively by dissolving the salt in cold water and neutralizing with dilute hydrochloric acid. The ester was thrown out of solution as a yellow, viscous mass. Two crystallizations from alcohol gave yellow crystals; m. p. 131–132°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.03; H, 6.46. Found: (semi-micro) C, 72.91; H, 6.58.

Condensation of Benzaldehyde with Carvone.—A solution of 75 g. of the ketone and 53 g. of the aldehyde in 200 cc. of absolute alcohol was cooled to 0°, and 10 g. of sodium dissolved in 75 cc. of absolute alcohol was added gradually, with shaking. The solution soon acquired a reddish-brown color and a gelatinous appearance. It was allowed to stand for an additional forty-eight hours at room temperature. The alcohol was removed by steam distillation, and the viscous residue was dissolved in ether. The solution was washed with dilute acid, dried over calcium chloride and then distilled under reduced pressure. There was recovered 15.3 g. of unchanged reactants. In addition, two other fractions were obtained:

(1) Forty grams, b. p. 153° (3 mm.), a faintly yellow color; $n^{24.5}D$ 1.6040. The analysis corresponded to benzylidenecarvone, which was found by Müller[3] to exist in two different forms. No attempt was made here to separate them, however, as the fraction was to be further treated with benzaldehyde to see if a dibenzylidenecarvone could be prepared.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.66; H, 7.62. Found: (semi-micro) C, 85.65; H, 7.64.

(2) Twenty-two grams of higher-boiling, yellow, viscous liquid whose range of boiling point varied from 180 to 225° at 3 mm. pressure. Most of the material distilled in the vicinity of 210° (3 mm.). When cooled, it formed a glassy solid which could be crushed to an amorphous powder. The properties were very similar to those of dibenzylidenecarvone described in the next paragraph.

Condensation of Benzylidenecarvone with Benzaldehyde.—To a solution of 20 g. of ketone, 9 g. of benzaldehyde and 50 cc. of absolute alcohol, cooled to 0°, was added slowly, with shaking, 2 g. of sodium dissolved in 25 cc. of alcohol. The solution changed to a brownish-red gelatinous mass after a short time. It was allowed to stand an additional forty-eight hours at room temperature, and was finally warmed for an hour on a steam-bath. The alcohol was then removed by steam distillation, and the residual viscous material was washed with dilute acid, extracted with ether, dried over calcium chloride and distilled under reduced pressure. Two fractions were obtained: (1) Two and five-tenths grams, having a b. p. of 153° (3 mm.). This was unchanged benzylidenecarvone.

(2) Fifteen and five-tenths grams, having a b. p. of 210° (3 mm.). This was a very viscous yellow liquid which, when cooled, formed a glassy solid that could be crushed to an amorphous powder, but which could not be crystallized from ordinary solvents. This was undoubtedly the amorphous material prepared by Wallach, but not analyzed or investigated further. The composition corresponds to dibenzylidenecarvone which would be the product formed by the condensation of two molecules of benzaldehyde with one of carvone.

Anal. Calcd. for $C_{24}H_{22}O$: C, 88.30; H, 6.80. Found: (semi-micro) C, 88.15; H, 6.94.

Summary

Tetrahydrobenzophenone (I) has been prepared from benzoyl chloride and cyclohexene by use of the Friedel–Crafts synthesis. The ketone was found to react with benzaldehyde and ethyl oxalate, due to the reactivity of hydrogen atoms on the γ-carbon atom.

Tetrahydroacetophenone (VI) has been pre-

pared in an analogous manner. It, likewise, was condensed with benzaldehyde, producing benzaltetrahydroacetophenone (VII), which, in turn, was condensed with ethyl oxalate to form the keto ester (IX).

Carvone (X) was condensed with two molecules of benzaldehyde to yield an amorphous product whose composition was that of dibenzylidenecarvone (XII).

URBANA, ILLINOIS RECEIVED MARCH 15, 1937

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

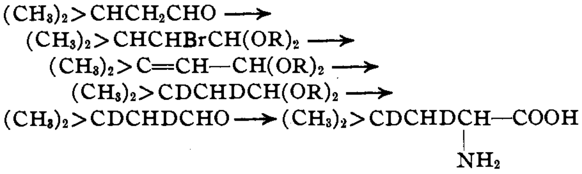
Dideuteriovaline and Dideuterioleucine

BY C. R. KINNEY AND ROGER ADAMS[1]

Analogs of two of the essential amino acids, valine and leucine, have been prepared in which two hydrogen atoms have been substituted by deuterium atoms. These new products are being tested in growth experiments to determine whether they may replace valine and leucine.

It is desirable, if not essential, for the deuterium to be introduced into such positions that during the reactions involved in the synthesis or in the animal body before metabolism actually starts, it will not be replaced by hydrogen. Thus, the deuterium atoms must not be substituted on the amino or carboxyl groups. Moreover, deuterium on a carbon atom from which rearrangement of the deuterium to oxygen or other similar atoms might take place, must be avoided.

The preparation of α-aminoisovaleric-β,γ-d_2 acid (dideuteriovaline) and of α-aminoisohexanoic-β,γ-d_2 acid (dideuterioleucine) from isobutyraldehyde and isovaleraldehyde, respectively, was carried out as illustrated by the following series of reactions for dideuterioleucine



$$\begin{array}{l}(CH_3)_2{>}CHCH_2CHO \longrightarrow \\ \quad (CH_3)_2{>}CHCHBrCH(OR)_2 \longrightarrow \\ \qquad (CH_3)_2{>}C{=}CH{-}CH(OR)_2 \longrightarrow \\ \qquad\quad (CH_3)_2{>}CDCHDCH(OR)_2 \longrightarrow \\ (CH_3)_2{>}CDCHDCHO \longrightarrow (CH_3)_2{>}CDCHD\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH\end{array}$$

It is obvious that in the intermediates isopentanal-β,γ-d_2 and isobutanal-β,γ-d_2, a deuterium on the carbon atom α to the aldehyde group exists; secondary in the former, tertiary in the latter. Both aldehydes theoretically are capable of enolization and thus it is possible that one of the deuterium atoms might be replaced at the intermediate aldehyde stage. A greater tendency to enolization would be expected in the molecule with the tertiary deuterium.

Analyses of the amino acids for deuterium indicated that the dideuteriovaline from the isobutanal-β,γ-d_2 contained about 25% less deuterium and the dideuterioleucine from the isopentanal-β,γ-d_2 6.5% less deuterium than the calculated amount. It is probable that an error of the magnitude of the latter might be introduced in the preparation of the isopentanal-β,γ-d_2 so that any appreciable loss of deuterium through enolization and hydrolysis is not indicated. On the other hand, the error of 25% in the dideuteriovaline probably is due in part to the purity of the isobutanal-β,γ-d_2, but principally to the replacement of deuterium by hydrogen during the transformation of the isobutanal-β,γ-d_2-diethylacetal through the aldehyde to the amino acid. In connection with these operations, it is significant that the deuterium in the intermediates, in spite of rather vigorous conditions in the presence of water and acids, is removed only where enolization may occur and then merely to a minor degree.

The authors desire to express their thanks to Dr. David Rittenberg of the Department of Biochemistry of Columbia University Medical School for his kindness in carrying out the deuterium analyses on the amino acids.

Experimental

α-Bromoisobutyraldehyde Diethylacetal.—Isobutyraldehyde was brominated according to the method[2] used for the preparation of α-bromoisovaleraldehyde diethylacetal. The crude product was fractionated carefully and the product, b. p. 78–82° (28 mm.), used for the subsequent reaction; yield 88%. Completely purified material boils at 80° (28 mm.).

Isobutanal Diethylacetal.—This was prepared according to directions[2] for making isovaleraldehyde diethylacetal except that it was found advantageous after treatment with molten potassium hydroxide to drop water slowly into the hot mixture until sufficient had been added to dissolve

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(1) For the last paper in this field see Leffler and Adams, THIS JOURNAL, **58**, 1555 (1936).

(2) Fischer, Ertel and Loewenberg, *Ber.*, **64B**, 30 (1931); Dworak and Prodinger, *Monatsh.*, **53**, 590 (1929).