tion of *o*-phenylenediamine. In a 100-ml. flask were placed 18.4 g. (0.123 mole) of *o*-*t*-butylaniline, 6.6 g. (0.123 eq.) of sodium carbonate, 35 g. of dry methanol and 35.0 g. (0.246 mole) of methyl iodide. After refluxing for 24 hours the vapor temperature was constant at 64°. An additional 10.0 g. (0.0704 mole) of methyl iodide was added and the reaction mixture refluxed for an additional 24 hours. There was no further reaction. The amine was isolated and rectified over phosphorus pentoxide in the Podbielniak Heligrid Column. There was obtained 15.7 g. (72%) of *o*-*t*-butyl-N,N-dimethylaniline: b.p. 91.0° at 10 mm., $n^{20}D$ 1.5040, m.p. (corrected to zero impurity) 2.8 ± 0.2° and purity 99.3 ± 0.4 mole %, both from cryoscopic data.[19]

Reaction of *o*-*t*-Butyl-N,N-dimethylaniline with Methyl Iodide.—Crude *o*-*t*-butyl-N,N-dimethylaniline and 45.6 g. of methyl iodide were heated under reflux for 12 days. After removal of the volatile constituents, the flask and its contents had increased in weight by 0.28 g. *versus* 6.21 g. calculated for formation of the quaternary salt.

Solutions of *o*-*t*-butyl-N,N-dimethylaniline and excess methyl iodide in acetonitrile were prepared, placed in sealed ampules, and maintained at 25°. From time to time an ampule was opened and analyzed for iodide ion. At 741 hours, an ampule required 0.12 ml. of 0.0988 *N* silver nitrate solution; at 1118 hr., 0.03 ml.; at 2006 hr., 0.09 ml. This compares to 10.43 ml. estimated for complete reaction. Within the precision of the measurements there is obviously no reaction.

Comparison of Coupling Reaction.—In each case, the coupling agent was prepared by adding 1.73 g. (0.01 mole) of sulfanilic acid (Baker C.P.) to 20 ml. of 2.5% sodium carbonate solution and dissolved by heating. The solution was cooled and 0.75 g. (0.011 mole) of sodium nitrite was added with stirring to effect complete solution. This solution was poured into a beaker containing 10 g. of crushed ice and 2 ml. of concentrated hydrochloric acid. The resulting suspension of diazotized sulfanilic acid was used without isolation.

In each case, 0.01 mole of tertiary amine (1.21 g. of N,N-dimethylaniline, 1.77 g. of *o*-*t*-butyl-N,N-dimethylaniline and 1.49 g. of 2,6,N,N-tetramethylaniline[22]) was dissolved in 0.6 g. of glacial acetic acid and the solution added with stirring to the suspension of diazotized sulfanilic acid.

A thick red paste was formed almost immediately from N,N-dimethylaniline. The addition of 7 ml. of 20% sodium hydroxide solution and subsequent boiling and slow cooling yielded about 2 g. of crystalline methyl orange. When *o*-*t*-butyl-N,N-dimethylaniline was treated in the same way, about half of the tertiary amine was recovered and no solid product was obtained. Nearly half of the 2,6,N,N-tetramethylaniline was recovered and only about 0.3 g. of orange solid was obtained.

Reaction of $\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-*o*-xylene-$\alpha,\alpha'$-diol[23] with Hydrogen Chloride.—In a 50-ml. separatory funnel were placed 20 ml. of concentrated hydrochloric acid and 2.0 g. (0.0103 mole) of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-*o*-xylene-$\alpha,\alpha'$-diol. A little ethyl ether was added to make the system homogeneous. The mixture was shaken at room temperature at frequent intervals over a period of 24 hours, diluted (1:1) with water and extracted with three portions of ethyl ether. The extract was washed with water and dried over calcium chloride. After removal of the ether by simple distillation, the remaining solid was sublimed at 28 mm. (bath at 70°). The white crystalline product (m.p. 71.5–72.0°) was obtained in a yield of 1.5 g. (83%) and was identified as the stable cyclic ether, $\alpha,\alpha,\alpha',\alpha'$-tetramethylphthalan.[16]

In a tared 50-ml. round-bottomed flask was placed 1.80 g. (0.0093 mole) of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-*o*-xylene-$\alpha,\alpha'$-diol. A slow stream of anhydrous hydrogen chloride was passed over the material at room temperature for 12 hours. The pink solid glycol was completely converted to liquid (one phase). The increase in weight was 0.15 g. which is consistent with the solubility of hydrogen chloride in the water produced if the ether was formed. The weight increase would have been approximately 0.5 g. if the monochloride was formed and 1.0 g. for the dichloride.

(22) Supplied by Mr. M. Grayson (b. p. 80° (15 mm.), $n^{20}D$ 1.5138).

(23) Supplied by Mr. W. H. Bonner (m. p. 163–165°).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS, FORDHAM UNIVERSITY AND BROOKHAVEN NATIONAL LABORATORY]

Studies in the Mechanism of the Willgerodt Reaction. II. Direction of Migration of the Functional Group in Aliphatic Ketones[1]

BY EDWARD CERWONKA,[2] R. CHRISTIAN ANDERSON[3] AND ELLIS V. BROWN

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The direction of migration of the functional group during the transformation of normal aliphatic ketones into amides by the Willgerodt reaction has been studied with carbon-14. For unsymmetrical di-*n*-alkyl ketones the functional group shows a preferential tendency to migrate to the shorter end of the chain. This preferential tendency gradually increases as the number of carbon atoms is increased in the longer alkyl chain.

When a dialkyl rather than an aryl alkyl ketone undergoes the Willgerodt reaction the product is a corresponding alkyl carbonamide, as has been shown previously.[4,5] Thus, pinacolone $(CH_3)_3CCOCH_3$ gives *t*-butyl acetamide[4] $(CH_3)_3CH_2CONH_2$, while methyl isobutyl ketone $CH_3CH(CH_3)$-CH_2COCH_3 gives isocaproamide,[5] $CH_3CH(CH_3)$-$CH_2CH_2CONH_2$. In these cases the migration of the functional group is to the structurally simple end of the molecule. Since neither α,α-dimethylbutyramide, $CH_3CH_2C(CH_3)_2CONH_2$ is obtained from pinacolone nor α-methylvaleramide CH_3CH_2-$CH_2CH(CH_3)CONH_2$ from methyl isobutyl ketone, this migration is essentially unidirectional and therefore is similar to the behavior of aryl alkyl ketone. As predicted by the mechanisms proposed by Carmack and DeTar[6,7] and McMillan and King[8] no migration can occur past a quaternary carbon and thus the result with pinacolone is explicable. The case of the methyl isobutyl ketone has not been explored as far as a rationale for the mechanism is concerned. It is not possible with this example to separate factors influencing migration such as a structural feature (a secondary carbon in the chain) or probability (assuming, for example, equal chance of migration to either side of the original carbonyl group).

A straight chain aliphatic ketone, however,

(1) Work carried out under the auspices of the Atomic Energy Commission.

(2) A.E.C. Predoctoral Fellow, 1949–1951.

(3) Brookhaven National Laboratory.

(4) L. Cavalieri, D. B. Pattison and M. Carmack, THIS JOURNAL, **67**, 1783 (1945).

(5) J. A. King and F. H. McMillan, *ibid.*, **68**, 1269 (1946).

(6) M. Carmack and D. F. DeTar, *ibid.*, **68**, 2029 (1946).

(7) M. Carmack and M. A. Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, chap. II.

(8) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 632 (1946); F. H. McMillan and J. A. King, *ibid.*, **70**, 4143 (1948).

permits a choice in the direction of migration of the functional group to a terminal position. Normal butyramide would be the product expected from methyl ethyl ketone regardless of which terminal carbon was attained by the migrating group. The very fact that symmetrical normal alkyl ketones give products suggests the possibility that the function may "partially" migrate to each end in the case of unsymmetrical normal alkyl ketones, in the absence of overriding structural effects.

In an attempt to discover the direction of migration of the functional group in aliphatic ketones several unsymmetrical normal alkyl ketones were synthesized, in which a terminal position was labeled with carbon-14. Willgerodt reactions were carried out on these ketones and the amide products isolated. By means of a Hofmann reaction on each amide followed by assay of the degradation products, amine and carbon dioxide, the following data were obtained.

$$C^{14}H_3CH_2COCH_3 \xrightarrow[H_2O]{(NH_4)_2SS_x} CH_3CH_2CH_2C^{14}ONH_2\ (40\%) + C^{14}H_3CH_2CH_2CONH_2\ (60\%)$$

$$CH_3CH_2CH_2COC^{14}H_3 \xrightarrow[H_2O]{(NH_4)_2SS_x} C^{14}H_3CH_2CH_2CH_2CONH_2\ (32\%) + CH_3CH_2CH_2CH_2C^{14}ONH_2\ (68\%)$$

$$C_5H_{11}COC^{14}H_3 \xrightarrow[H_2O]{(NH_4)_2SS_x} C^{14}H_3(CH_2)_5CONH_2\ (14\%) + C_6H_{13}C^{14}ONH_2\ (86\%)$$

It was found that satisfactory syntheses of labeled methyl ketones could be effected by adding the proper nitrile to methylmagnesium iodide, with the Grignard in 10% excess, according to the method of Hauser and Humphlett.[9] The ketimine hydrochloride hydrolyzes at room temperature and the ketone is fractionated from the ether layer. The observation has been made in the literature that dialkyl ketimine salts have not been isolated.[10-12]

TABLE I

RADIO ASSAY DATA

Compound	Specific activity[a]
$C^{14}H_3CH_2COCH_3$	340 (4 × 85)
$C^{14}H_3CH_2CH_2CONH_2 + CH_3CH_2CH_2C^{14}ONH_2$	348 (4 × 87)
$CO_2 + C^{14}O_2$	140
$C^{14}H_3CH_2CH_2NH_2 + CH_3CH_2CH_2NH_2$	201 (3 × 67)
$CH_3CH_2CH_2COC^{14}H_3$	330 (5 × 66)
$CH_3CH_2CH_2CH_2C^{14}ONH_2 + C^{14}H_3CH_2CH_2CH_2CONH_2$	325 (5 × 65)
$C^{14}O_2 + CO_2$	220
$CH_3CH_2CH_2CH_2NH_2 + C^{14}H_3CH_2CH_2CH_2NH_2$	108 (4 × 27)
$C_5H_{11}COC^{14}H_3$	280 (7 × 40)
$C_6H_{13}C^{14}ONH_2 + C^{14}H_3(CH_2)_5CONH_2$	294 (7 × 42)
$C^{14}O_2 + CO_2$	245
$C_6H_{13}NH_2 + C^{14}H_3(CH_2)_5NH_2$	42 (6 × 7)

[a] See end of "Experimental" section for definition of these values.

(9) C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **13**, 359 (1950).

(10) G. Mignonac, *Compt. rend.*, **169**, 237 (1919); **170**, 936 (1920).

(11) P. L. Pickard and C. W. Young, THIS JOURNAL, **73**, 42 (1951).

(12) J. B. Culbertson, *ibid.*, **73**, 4818 (1951).

In the case of methyl ethyl ketone a better synthesis consists in the alkylation of acetoacetic ester, followed by ketonic hydrolysis to give 2-butanone-4-C-14.

The relative abundances of the isotopic isomers in the equations above were deduced from the combustion and degradation data of Table I. In the case of a symmetrical dialkyl ketone one would expect the abundance to be 50–50, barring an isotope effect. For unsymmetrical di-*n*-alkyl ketones the functional group shows a preferential tendency to migrate to the shorter end of the chain. This preferential tendency gradually increases as the length of the longer alkyl chain is increased.

Experimental

Preparation of 2-Butanone-4-C-14 ($C^{14}H_3CH_2COCH_3$).—Ethyl α-acetopropionate-β-C-14 ($C^{14}H_3(CH_3CO)COOC_2H_5$) was first prepared, following a method given in "Organic Syntheses"[13] for the preparation of ethyl *n*-butylacetoacetate. Using 1.6 g. of sodium (0.070 mole), 9.37 g. of ethyl acetoacetate (0.072 mole) and 9.12 g. of methyl iodide-C-14 in 100 ml. of absolute ethanol, there was obtained 6.6 g. of an ester mixture (alkylated and non-alkylated), boiling over the range 67–75° at 12 mm.

The mixture was subjected to a ketonic decarboxylation following a method given in "Organic Syntheses"[14] for the preparation of methyl *n*-amyl ketone. Acetone, the product of decarboxylation of ethyl acetoacetate, is removed during the separation and fractionation of the methyl ethyl ketone. The yield of 2-butanone-4-C-14 boiling at 78–80° was 2.0 g., representing an over-all yield of 40% based on methyl iodide-C-14.

Preparation of 2-Pentanone-1-C-14 ($C_3H_7COC^{14}H_3$).—This procedure was modified from the method of Hauser and Humphlett.[9] A 250-ml. round-bottom three-necked flask was fitted with a mechanical stirrer, a cold-finger reflux condenser with attached drying tube, and a dropping funnel with a compensating side-arm. The cooling agent for the condenser was Dry Ice–trichloroethylene. To 1.7 g. (0.071 mole) of dry magnesium turnings in 120 ml. of anhydrous ether there was added with stirring methyl iodide-C-14 (9.33 g., 0.066 mole) dissolved in an equal volume of dry ether. The Grignard reaction was carried out in the hood, the condenser coolant being constantly replenished. Titration of the Grignard reagent by a standard procedure[15] showed it to contain 0.064 mole.

Freshly distilled butyronitrile (40 g., 0.058 mole), boiling at 116–118° was dissolved in an equal volume of dry ether. With constant stirring of the Grignard, the nitrile was added from the dropping funnel.

After stirring for three hours the mixture was hydrolyzed by running in 100 ml. of an aqueous solution of ammonium chloride (20% by weight), while the solution was kept at −15° by means of a Dry Ice–trichloroethylene cooling bath. Stirring was continued during this addition and during a subsequent addition of hydrochloric acid (20 ml. of 1:1 solution). The cooling bath was removed and the mixture stirred at room temperature for an hour. At the end of this time the ether layer was separated and fractionally distilled, thereby separating the ketone from unreacted nitrile. There was obtained 1.9 g. of 2-pentanone-1-C-14 boiling at 100–102° (33% of the theoretical amount based on methyl iodide-C-14).

Preparation of 2-Heptanone-1-C-14 ($C_5H_{11}COC^{14}H_3$).—This synthesis was the same as that of 2-pentanone-1-C-14 except that 5.2 g. (0.054 mole) of capronitrile was added to the Grignard reagent instead of butyronitrile. The yield of 2-heptanone-1-C-14 was 2.2 g. (36%).

Willgerodt Reactions.—The Willgerodt reactions were carried out using the technique of Cavalieri, Pattison and Carmack[3] for aliphatic ketones.

In an eight-inch Pyrex ignition tube there were sealed 20 g. of sulfur, 1.0 g. of ketone, 2.0 ml. of dioxane and 4.0 ml. of

(13) C. S. Marvel and F. D. Hager, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc, New York, N. Y., 1941, pp. 248–249.

(14) J. R. Johnson and F. D. Hager, ref. 13, pp. 351–353.

(15) H. Gilman, E. A. Zoellner and J. B. Dickey, THIS JOURNAL, **51**, 1276 (1929).

ammonium polysulfide. The tube was heated electrically five hours at 165–170°, cooled and opened. The contents were washed into a beaker with concentrated ammonia and evaporated to dryness. The residue was leached with 20 ml. of boiling water and again evaporated to dryness. This residue was again leached with 5 ml. of boiling water and a third evaporation to dryness was made. After this final evaporation the beaker was allowed to stand on the steam-bath and the amide gradually sublimed on the walls of the container. Crystals were removed batchwise and collected. The product obtained in this manner had a satisfactory melting point.

By this technique there was obtained 120 mg. of *n*-butyramide, m.p. 116° (yield 10%), and 300 mg. of *n*-valeramide, m.p. 108° (yield 25%). This is the first reported production of *n*-butyramide from methyl ethyl ketone by the Willgerodt reaction and the product showed no melting point depression when mixed with an authentic sample of *n*-butyramide. The 25% yield of *n*-valeramide compares well with a yield of 31% previously reported.[3]

The reaction mixture from methyl amyl ketone was evaporated to dryness, then leached with 20 ml. of boiling water. After evaporation to half the volume, then cooling, the *n*-heptanamide crystallized. When recrystallized from hot water, it melted at 95–96°. The yield was 30% as compared with a previously reported 38%.[3]

Analytical Procedure.—The method of wet combustion of organic samples containing C-14 followed the technique of Steele and Sfortunato.[16]

When a relatively volatile liquid, *e.g.*, methyl ethyl ketone was assayed, the arm of the combustion tube containing the sample was chilled with liquid nitrogen during the evacuation process.

The technique involved in the Hofmann degradation of the aliphatic amides was the same as that described in a previous paper for phenylacetamide,[17] except that the molar proportions of amide, bromine and barium hydroxide, were changed from 1:2:3 to 1:1.1:3, to give a better yield of aliphatic amine. Propylamine was obtained in 60% yield and was combusted as the hydrochloride (m.p. 156°). Butylamine was obtained in about the same yield and was also oxidized as the hydrochloride (m.p. 193°). Hexylamine hydrochloride (70% yield) melted at 215°. The yields of carbon dioxide in the degradations of the aliphatic amides varied from 70–75%.

The definition of specific activity (Table I) is again[17] the number of counts per minute above background per square centimeter of an "infinitely thick" layer of barium carbonate. In a combustion, the number of counts is multiplied by the number of carbon atoms in the compound to correct for dilution by non-tagged carbon atoms, as was explained previously.

Acknowledgment.—Our thanks are expressed to Dr. R. W. Dodson for making available the facilities of the Chemistry Department at the Brookhaven National Laboratory.

(16) R. Steel and T. Sfortunato, "Techniques in the Use of C-14," Brookhaven National Laboratory Publication BNL-T-6, 1949.

(17) E. V. Brown, E. Cerwonka and R. C. Anderson, THIS JOURNAL **73**, 3735 (1951).

UPTON, L. I., N. Y.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS OF FORDHAM UNIVERSITY AND BROOKHAVEN NATIONAL LABORATORY]

Studies in the Mechanism of the Willgerodt Reaction. III. Nature of the Labile Intermediate[1]

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The nature of the labile intermediate participating in the Willgerodt reaction with phenyl *n*-butyl ketone has been investigated using deuterium as a tracer. δ-Phenylvaleramide, the reaction product from this ketone, was found to have retained only 5% of the deuterium which had originally replaced hydrogen on the beta carbon of the alkyl side chain. This evidence is interpreted as indicating that an unsaturated intermediate has been formed during the course of the Willgerodt reaction.

In the first paper[4] of this series experimental evidence was presented to show that no rearrangement of the carbon skeleton of acetophenone takes place in the Willgerodt reaction, either in the formation of phenylacetamide or of the ammonium phenylacetate by-product.

Once it had been established that the structure of the carbon skeleton of the starting compound remained unchanged during the course of the Willgerodt reaction, interest was focused on the possible manner by which the oxygen function could migrate to its terminal position on the alkyl chain. If the migration were stepwise, as was the feeling of most investigators, compounds intermediate between the starting ketone and final amide might exist as such and could be isolated. Due possibly to their extreme reactivity under the reaction conditions, these compounds have not yet been obtained.

Failing in the isolation of intermediates, the approach of several workers in this field has been to introduce possible intermediates into the reaction, instead of the usual starting compound, and to study the results. From the behavior of such "manufactured" intermediates deductions as to the mechanism of migration of the functional group have been made by Carmack and DeTar[5] and McMillan and King.[6]

Carmack and DeTar noted that unsaturated hydrocarbons, acetylenic or olefinic, give products of the same nature as ketones. Consequently, these authors believe that there must be one fundamental mechanism involving the preliminary formation of a labile intermediate which has an unsaturated C–C bond in the side chain.[5b] That this unsaturated carbon bond is largely acetylenic in character is suggested further by the relatively good yields of product obtained from straight chain ketones as compared with those obtained from the isomeric branched-chain compounds. Obviously, there can be no triply bonded intermediate in the case of the branched-chain ketone without loss of a carbon atom or chain at the point of branching.

(1) Research carried out under the auspices of the U. S. Atomic Energy Commission.

(2) A.E.C. Predoctoral Fellow, 1949–1951.

(3) Brookhaven National Laboratory.

(4) E. V. Brown, E. Cerwonka and R. C. Anderson, THIS JOURNAL, **73**, 3735 (1951).

(5) (a) M. Carmack and D. F. DeTar, *ibid.*, **68**, 2029 (1946); (b) M. Carmack and M. A. Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, chap. 2.

(6) (a) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 632 (1946); (b) F. H. McMillan and J. A. King, *ibid.*, **70**, 1143 (1948).