[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Molecular Rearrangements Involving Optically Active Radicals. X. The Retention of Configuration in the Wolff Rearrangement

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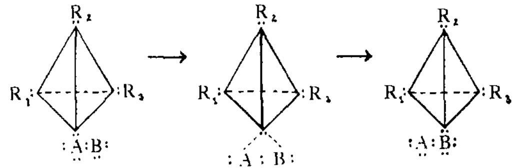
The modern formulation of molecular rearrangements originally proposed by Jones and by Stieglitz, and later developed by Whitmore[2] gives primary emphasis to changes occurring in a reactive intermediate designated $:\underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}$, where A and B are atoms such as carbon or nitrogen. The rearrangement process takes place with an internal oxidation and reduction in $:\underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}$ which leads to the transfer from A to B of a pair of electrons together with the atom or group held by it. For a consideration of this transfer when optically active groups are involved, it is convenient to follow the ideas expressed in Part I of this series[3] and to write

(I) 

This formulation is based on the assumption that the rearranging system at no time dissociates into neutral or charged free fragments, *i.e.*, the transformation is strictly intramolecular. Under these conditions the optically active group should not racemize during the process of rearrangement. Moreover, the formulation admits no mechanism for the inversion of configuration.[4] Previous parts of this series[3,5] have shown that the Curtius, Hofmann and Lossen degradations[3,5a,b,c] of optically active acid azides, amides, and hydroxamic acids, and the Wolff rearrangement of optically active diazoketones[5g,h] containing a quaternary asymmetric carbon atom proceed without appreciable racemization of the migrating group and are true intramolecular processes.[5a,d,g] It has also been shown that the rearrangement of optically active alkyl phenyl ethers which leads to *optically active products* cannot be explained on the basis of an intermolecular mechanism.[5f]

Until now the difficulty of relating rotation to configuration has prevented a rigid confirmation of the absence of the Walden inversion which is predicted by I. It is true that Bartlett and Knox[6] have shown that in hindered systems the Hofmann rearrangement may occur without inversion, and that a similar result has been obtained by Noyes[7] in the asymmetric degradation of the camphoric acids. But in the absence of a rigorous configurational relationship in the system $R_1R_2CHCOOH \rightarrow R_1R_2CHNH_2$, a general proof that this process is accompanied by retention of configuration cannot be constructed.

This important prediction of the formulation (I) may, however, be rigorously tested by means of the Wolff rearrangement of an optically active diazoketone, for the necessary configurational relationships are readily obtainable. We have achieved this by the cyclic process shown.

The acid chloride of (+)-2-methyl-2-phenylhexanoic acid, $[\alpha]^{20}D$ +24.0° (benzene), was converted by the action of diazomethane to (+)-1-diazo-3-methyl-3-phenylheptan-2-one, $[\alpha]^{20}D$ +65.0° (benzene). This compound was then allowed to rearrange in a solution of aqueous dioxane containing sodium thiosulfate and silver oxide. The (−)-3-methyl-3-phenylheptanoic acid, $\alpha^{20}D$ −6.35° (1-dm. tube without solvent), so formed was converted by diazomethane to its methyl ester, $[\alpha]^{20}D$ −14.9° (benzene). This ester was subjected to a Barbier–Wieland degradation. It gave (+)-2-methyl-2-phenylhexanoic acid. Thus, it was found to be configurationally identi-

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[2] For a discussion of the development of this formulation and its original applications see Whitmore, THIS JOURNAL, **54**, 3274 (1932).

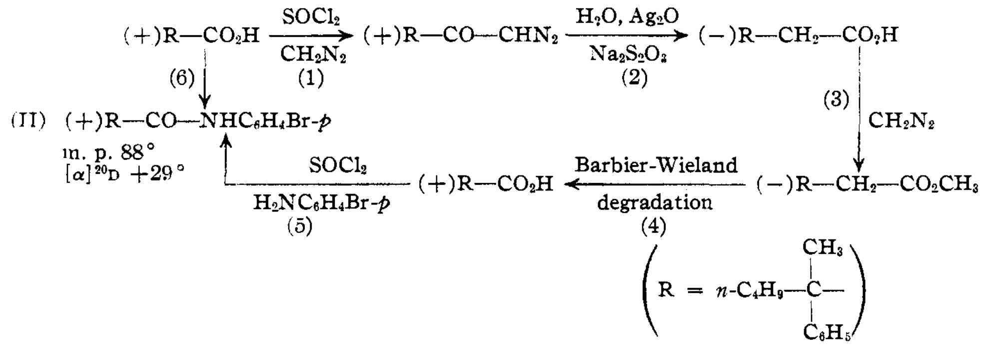
[3] Jones and Wallis, *ibid.*, **48**, 169 (1926).

[4] It should be noted that this formulation is concerned primarily with the behavior of a group transferred with its electron pair from A to B. For experimental work on the course of rearrangement where A or B itself is an optically active group, *cf.* McKenzie, Roger and Wills, *J. Chem. Soc.*, 779 (1926); McKenzie, Roger and McKay, *ibid.*, 2597 (1932); Roger and McKay, *ibid.*, 332 (1933); Wallis and Bowman, *J. Org. Chem.*, **1**, 383 (1936); Bernstein and Whitmore, THIS JOURNAL, **61**, 1324 (1939). Here, in accordance with modern principles of aliphatic substitution [Olson and Long, *ibid.*, **56**, 1294 (1934); Bartlett and Pöckel, *ibid.*, **59**, 820 (1937); Hughes, *Trans. Faraday Soc.*, **34**, 202 (1938); Criegee and Plate, *Ber.*, **72**, 178 (1939)], inversion of configuration accompanied by varying amounts of racemization appears to be the rule.

[5] (a) Wallis, THIS JOURNAL, **51**, 2892 (1929); (b) Wallis and Nagel, *ibid.*, **53**, 2787 (1931); (c) Wallis and Dripps, *ibid.*, **55**, 1701 (1933); (d) Wallis and Moyer, *ibid.*, 2598 (1933); (e) Sprung and Wallis, *ibid.*, **56**, 1715 (1934); (f) Gilbert and Wallis, *J. Org. Chem.*, **5**, 184 (1940); (g) Lane and Wallis, *ibid.*, **6**, No. 3 (1941); (h) Lane, Willenz, Weissberger and Wallis, *ibid.*, **5**, 276 (1940).

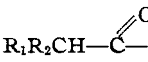
[6] Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939).

[7] Noyes, *Am. Chem. J.*, **16**, 500 (1894); Noyes and Potter, THIS JOURNAL, **37**, 189 (1915); **34**, 1067 (1912); Noyes and Nickell, *ibid.*, **36**, 118 (1914).



cal with the original diazoketone. The acid so obtained was identified as the crystalline (+)-2-methyl-2-phenylhexano-*p*-bromoanilide, m. p. 88°, $[\alpha]^{20}_{D}$ +29.0° (benzene), a derivative identical in every respect with that prepared similarly from the original (+)-2-methyl-2-phenylhexanoic acid from which the diazoketone was prepared.

Since only step (2) in the cycle (II) involved the breaking of a bond of the asymmetric center, it is clearly established that in this step the Wolff rearrangement proceeded without a Walden inversion. This is in accordance with the prediction of (I). We therefore submit that in any intramolecular rearrangement, a group migrating with its electron pair does not suffer a Walden inversion.

It should be noted that the only possible objection to be raised against this generalization is that the racemizations observed in Wolff rearrangements of (+)-benzylmethyldiazoacetone,[5h] indicate a real difference between the rearrangement mechanism for this process and for other processes assumed to be of type (I), *i.e.*, the Curtius rearrangement of (+)-benzylmethylacetazide where no racemization is observed.[3] We have presented experimental evidence against this objection elsewhere[5g] and have attributed the observed racemizations to enolization of the intermediate  $R_1R_2CH{-}\overset{O}{\overset{\|}{C}}{-}CH$ prior to rearrangement, the enolization being markedly catalyzed by the catalytic surfaces Ag^+, Ag(s) or Ag^+, Ag(s), Ag_2O(s) which are necessarily present if the rearrangement is to be conducted at temperatures below 180°.

It would be of great interest in this connection to conduct a quantitative investigation of the influences of such catalytic surfaces on the rate of enolization of the optically active ketone, $(C_6H_5CH_2)(CH_3)CHCOC_6H_5$, and to compare the results obtained with those of Conant and Carlson[8] on the homogeneous rate of enolization of this compound. Such an investigation is contemplated in the near future.

Experimental

Preparation of (+)-2-Methyl-2-phenylhexanoic Acid.—One hundred ten grams of this acid was prepared and resolved by the method of Conant and Carlson.[8] After three recrystallizations from dilute alcohol, the quinine salt of the acid had a specific rotation $[\alpha]^{20}_{D}$ −87.0° (c = 2.60, chloroform). Further recrystallization did not alter this value. The quinine salt on decomposition with dilute hydrochloric acid gave 27 g. of an acid of specific rotation $[\alpha]^{20}_{6563}$ +18.4°; $[\alpha]^{20}_{5893}$ +24.0°; $[\alpha]^{20}_{5463}$ +29.0° (c = 3.80, benzene); $[\alpha]^{20}_{5463}$ +14.3° (c= 3.80, alcohol) (Conant and Carlson report +13.7° under these conditions).

For identification, the acid was converted to the corresponding *p*-bromoanilide by the action of *p*-bromoaniline on the acid chloride. Three recrystallizations from dilute alcohol gave a product which melted at 88° and had the following specific rotations: $[\alpha]^{20}_{6563}$ +22.1°; $[\alpha]^{20}_{5893}$ +28.9°; $[\alpha]^{20}_{5463}$ +34.3° (c = 2.50, benzene).

Calcd. for $C_{19}H_{22}ONBr$: C, 63.33; H, 6.16; N, 3.89; Br, 22.18. Found: C, 63.3; H, 6.1; N, 3.7; Br, 22.4.

Preparation of (−)-3-Methyl-3-phenylheptanoic Acid.—By a method previously described,[5g] 10 g. of (+)-2-methyl-2-phenylhexanoic acid was converted to (+)-1-diazo-3-methyl-3-phenylheptan-2-one, $[\alpha]^{20}_{D}$ +65.0° (c = 14.1, benzene). This compound was then subjected to the Wolff rearrangement in a solution of aqueous dioxane containing silver oxide and sodium thiosulfate.[5g] The product, (−)-3-methyl-3-phenylheptanoic acid, boiled at 100° (0.01 mm.): α^{20}_{6563} −4.89°; α^{20}_{5893} −6.35°; α^{20}_{5463} −7.70° (1-dm. tube without solvent).

For identification, a portion of the acid was converted to the corresponding anilide by the action of aniline on its chloride. Two recrystallizations of the crude material from dilute alcohol gave the pure anilide: m. p. 76–77°; mixed m. p. with an authentic specimen[5g] of (−)-3-methyl-3-phenylheptanoanilide, 76–77°; $[\alpha]^{20}_{6563}$ −47.0°; $[\alpha]^{20}_{5893}$ −60.2°; $[\alpha]^{20}_{5463}$ −73.5° (c = 1.20, benzene).

Preparation of (−)-3-Methyl-3-phenylheptanoic Acid Methyl Ester.—To a solution of 2 g. of (−)-3-methyl-3-phenylheptanoic acid in 25 cc. of ether at 0° was added slowly and with shaking a solution of 1.0 g. of diazomethane in 50 cc. of ether. The mixture was allowed to stand for several hours at room temperature. It was then filtered, and the excess of diazomethane and ether was removed on

(8) Conant and Carlson, THIS JOURNAL, **54**, 4055 (1932).

the steam-bath under reduced pressure. The methyl ester boiled at 102–103° (2 mm.): $[\alpha]^{20}_{6563}$ −11.2°; $[\alpha]^{20}_{5893}$ −14.9°; $[\alpha]^{20}_{5463}$ −17.4° ($c = 4.00$, benzene).

Barbier–Wieland[9] Degradation of (−)-3-Methyl-3-phenylheptanoic Acid Methyl Ester.—The methyl ester (1.8 g.) dissolved in 15 cc. of dry benzene was added slowly with shaking in the cold to a Grignard reagent prepared from 20 g. of bromobenzene and 3.2 g. of finely cut magnesium ribbon in 50 cc. of anhydrous ether. The mixture was refluxed for two hours on the steam-bath. Twenty-five cubic centimeters of dry benzene was then added, and the solvent was distilled as completely as possible over a period of two hours. The residue was heated for an additional two hours on the steam-bath. It was then cooled, diluted with benzene, and poured over a mixture of crushed ice and ammonium chloride. The benzene solution of the product was filtered and evaporated. The residue was then refluxed for two hours with 30 cc. of 0.5 *N* alcoholic sodium hydroxide to saponify any unchanged ester. Most of the alcohol was removed under reduced pressure, and the residue was dissolved in benzene, washed several times with water, filtered, and evaporated. The residue was then distilled with steam for six hours to remove diphenyl. Finally, the product was taken up in benzene and the filtered solution evaporated under reduced pressure. The crude (−)-1,1,3-triphenyl-3-methylheptan-1-ol (2.6 g.) so obtained had a specific rotation $[\alpha]^{20}_{\text{D}}$ −16.3° ($c = 3.00$, benzene).

The carbinol was then refluxed for thirty minutes with 10 cc. of acetic anhydride. After the excess of the reagent had been removed under reduced pressure, the residue was treated with hot water to destroy traces of the anhydride. The product was taken up in benzene, washed with water, and the solution filtered and evaporated under reduced pressure. The crude (−)-1,1,3-triphenyl-3-methylheptene-1 so obtained had a specific rotation $[\alpha]^{20}_{\text{D}}$ −20.2° ($c = 2.50$, benzene).

Without further purification, the olefin was dissolved in 20 cc. of purified glacial acetic acid (distilled over potassium permanganate). To this solution at 15° was added with mechanical stirring a solution of 2.5 g. of chromium trioxide in 2 cc. of water and 5 cc. of purified glacial acetic acid. The addition was regulated so as to consume one-half hour, and stirring was continued at 15° for an additional fifteen minutes. The solution was then chilled to −10°, and the excess of chromium trioxide was decomposed at such a rate that the temperature remained below 10°. When this had been accomplished, the solvent was removed under reduced pressure. The residue was diluted with 100 cc. of 2 *N* hydrochloric acid and extracted with ether. The ether solution was washed first with 2 *N* hydrochloric acid and then with water. The organic acid was then extracted from it with 5% potassium hydroxide solution. The alkaline extract was washed with ether and acidified with hydrochloric acid. The process of extraction with ether, washing, and final extraction with 5% potassium hydroxide solution was repeated. The alkaline extract was acidified with hydrochloric acid, and the organic acid was taken up in benzene. The benzene solution was washed with water, filtered, and evaporated under reduced pressure. One-half gram of an acid was obtained which had a specific rotation $[\alpha]^{20}_{\text{D}}$ +20.0° ($c = 2.50$, benzene).

Identification of the Acid Obtained in the Barbier–Wieland Degradation.—By the action of *p*-bromoaniline upon its chloride, the acid obtained as described in the preceding paragraph was converted to the corresponding *p*-bromoanilide. The crude material had a specific rotation $[\alpha]^{20}_{\text{D}}$ +23.0° ($c = 2.75$, benzene). Two recrystallizations from dilute alcohol gave pure (+)-3-methyl-3-phenylheptano-*p*-bromoanilide: m. p. 87–88°; mixed m. p. with the analytical sample described in the first paragraph, 87–88°; $[\alpha]^{20}_{6563}$ +22.0°; $[\alpha]^{20}_{5983}$ +29.0°; $[\alpha]^{20}_{5463}$ +34.0° ($c = 1.00$, benzene).

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Summary

(−)-3-Methyl-3-phenylheptanoic acid has been prepared by a Wolff rearrangement of (+)-1-diazo-3-methyl-3-phenylheptan-2-one. A Barbier–Wieland degradation of the methyl ester of this acid gives (+)-2-methyl-2-phenylhexanoic acid, which is configurationally identical with (+)-1-diazo-3-methyl-3-phenylheptan-2-one. The Wolff rearrangement, therefore, proceeds without configurational inversion of the migrating group.

A discussion of these results is given in terms of the modern electronic concept of molecular rearrangements. It is concluded that in any intramolecular rearrangement, a group migrating with its electron pair does not suffer a Walden inversion.

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[9] Barbier and Locquin, *Compt. rend.*, **156**, 1443 (1913); Wieland. Schlichting and Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926); *cf.* also Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).