MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. VIII. THE WOLFF REARRANGEMENT OF OPTICALLY ACTIVE DIAZOKETONES

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In 1912 Wolff (1) described a rearrangement which diazoketones undergo when they are treated with silver oxide in ammoniacal solution.

$$\begin{array}{c} & & & & \\ \parallel \\ R - C - C H N_2 & - \begin{array}{c} A g_2 O \\ \hline N H_2 \end{array} \rightarrow \begin{array}{c} R - C H_2 - C - N H_2 + N_2 \end{array}$$

In recent years this rearrangement has received considerable attention, and has been developed by Arndt and co-workers (2) as a general synthetic method for lengthening the carbon-carbon chain. It has also been shown that the transformation is catalyzed by finely divided metals such as silver, copper, and platinum.

Of the mechanisms that have been proposed for this rearrangement, the one formulated by Eistert (3) is of special interest. In the presence of the catalyst, the intermediate (II) follows the course of the reaction indicated by equations (b) and (c). In the absence of the catalyst, and in the presence of water and an acid such as formic acid, it adds water to give a keto alcohol as indicated in equation (d).

(a)
$$\begin{array}{c} \overset{O}{\overset{H}{\underset{i}{\overset{H}{\underset{i}{\overset{G}{\underset{i}{\underset{i}{\underset{i}{\atop}}}}}}}} H} & \overset{O}{\overset{H}{\underset{i}{\underset{i}{\atop}}} H} \\ R:C:\overset{O}{\underset{i}{\underset{i}{\underset{i}{\atop}}}} N::::N: \rightarrow R:C:\overset{O}{\underset{i}{\underset{i}{\atop}}} H \\ H \end{array}$$

(b)
$$\begin{array}{c} \overset{O}{\mathbb{R}} \overset{H}{\underset{\ldots}{\mathbb{C}}} \overset{\text{catalyst}}{\underset{\text{anionic migration}}{\text{migration}}} & \overset{H}{\underset{\ldots}{\mathbb{R}} \overset{H}{\underset{\ldots}{\mathbb{C}}} \overset{H}{\underset{\ldots}{\underset{\ldots}{\mathbb{C}}} \overset{H}{\underset{\ldots}{\mathbb{C}}} \overset{H}{\underset{\ldots}{\mathbb{C}}} \overset{H}{\underset{\ldots}$$

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$$\begin{array}{c} \begin{array}{c} H \\ (c) & R: \ddot{C}::C:: \ddot{O} & \underline{A:H} \\ (d) & R: \ddot{C}: \ddot{C}: \dot{O} & H \\ \vdots & H \end{array} & (A:H=NH_{3}; H_{2}O; RNH_{2}; ROH) \\ \begin{array}{c} H \\ \vdots \\ H \end{array} & (A:H=NH_{3}; H_{2}O; RNH_{2}; ROH) \\ \vdots \\ H \end{array} \\ \begin{array}{c} H \\ H \end{array} & (A:H=NH_{3}; H_{2}O; RNH_{2}; ROH) \\ \vdots \\ H \\ \end{array}$$

Evidence that a ketene (III) is formed as an intermediate in rearrangements of this type has been submitted by Staudinger and Hirzel (4). These investigators were able to isolate the ketene formed in the rearrangement of diazoacetoacetic ester. A similar result has been reported by Schroeter (5). Usually, however, the rearrangement is conducted in the presence of water, ammonia, alcohol, or an amine, and consequently an acid, an amide, an ester, or a substituted amide, as the case may be, is the first product of the reaction that can be isolated.

In studying the above proposed mechanism, it was of interest to us to note that this formulation closely parallels that now generally accepted for the Curtius rearrangement of the acid azides (6), where the first intermediate corresponding to the ketene is an isocyanate. The Curtius rearrangement, together with the related Hofmann and Lossen rearrangements of amides and hydroxamic acids respectively, has been extensively studied in recent years, and in the earlier papers of this series (7) describing experimental results on compounds in which the rearranging group is an optically active radical, it was shown that in every case the migrating group retained its asymmetry during the rearrangement process, and that the reaction was accompanied by no appreciable racemization.

In this paper it is our purpose to present for consideration the results of a similar study on the behavior of optically active diazoketones when they undergo the Wolff rearrangement, with a view of showing to what extent the formal parallelism between this rearrangement and the Curtius rearrangement may be accepted. *d*-Benzylmethyldiazoacetone, $(C_6H_5CH_2)(CH_3)CHCOCHN_2$, was chosen for these studies, since the work of Wallis and co-workers (6, 7) on the Curtius, Hofmann, and Lossen rearrangements was carried out on optically active compounds which contain the benzylmethylcarbinyl radical. This diazoketone, α_p^{20} + 134.3°; 1 dm. tube without solvent, was prepared by the action of diazomethane on *d*-benzylmethylacetyl chloride, α_p^{20} + 24.80°; 1 dm. tube without solvent. Similarly, an optically impure *levo* modification, α_p^{20} -14.03°, 5 cm. tube without solvent, was obtained from an incompletely resolved *levo*-benzylmethylacetic acid. Treatment of the completely resolved *dextro*-rotatory diazoketone with aqueous formic acid gave the corresponding keto alcohol with no appreciable racemization. Portions of the diazoketone were then subjected to the Wolff rearrangement under two sets of conditions. In the first series of experiments a small amount of silver ion was used as a catalyst. The diazoketone was dissolved in methyl alcohol which had been saturated previously at room temperature with ammonia gas. A small amount of silver nitrate was added, and then a rapid rearrangement occurred. On working up the product, an optically active β -methyl- β -benzylpropion-amide was obtained in a chemically pure state with an inversion of the sign of rotation. It was soon observed, however, that partial racemization had taken place during the rearrangement process. Thus, by crystallization methods, it was possible to obtain pure fractions of the amide ranging in activity from $[\alpha]_p^{20} - 2.63^{\circ}$ to $[\alpha]_p^{20} - 10.80^{\circ}$ (benzene).

In the second series of experiments the diazoketone was dissolved in a 30% aqueous dioxane solution containing some sodium thiosulfate. The latter was added to prevent precipitation of the silver salt of the organic acid which is subsequently formed. A small amount of silver oxide was then added as a catalyst, and a rapid rearrangement took place. The substituted propionic acid so obtained, however, showed no appreciable rotation. Its amide was also found to be completely inactive. In this instance the asymmetric group completely loses its asymmetry during rearrangement—a fact that stands out in sharp contrast to observations in studies on the Curtius, Hofmann, and Lossen rearrangements. In these rearrangements no appreciable racemization accompanies the reaction.

These results are also of interest in connection with certain experiments of Preobrashenski, Poljakowa, and Preobrashenski (8). In their work on the synthesis of d-homopilopic acid from d-pilopic acid:



these investigators reported that the Wolff rearrangement takes place with no racemization. It should be remembered, however, that the mole-

cule studied has two asymmetric carbon atoms, one of which (a) is not affected by the rearrangement process and thus may influence the stereochemical course of the reaction as a whole. Moreover, these workers reported rotations on materials only after they were prepared for analysis. Thus, it may be that in this case also, rearrangement is accompanied by partial or complete racemization of the asymmetric center (b), one of the two possible products being lost in the mother liquors during recrystallization.

In the interpretation of their results obtained in studies on the Curtius, Hofmann, and Lossen rearrangements, Wallis and his co-workers put forward the belief that optical stability is most easily explained on the basis of an electronic mechanism involving a shift of the group with its pair of electrons. This did not imply, however, that the migrating group is a carbanion. On the contrary, evidence was obtained (9) by them to show that at no time is the migrating group ever free from the sphere of influence of the rest of the molecule. Hence, if the Wolff rearrangement proceeded according to the mechanism suggested by Eistert as outlined above, which is strictly analogous to that of the Curtius rearrangement, then a similar retention of optical activity by the migrating group would have been expected. The behavior of *d*-benzylmethyldiazoacetone on rearrangement, however, shows that this is not the case. Partial or complete racemization of the migrating group occurs, depending upon the conditions of the experiment.

This striking difference in behavior suggests many possible interpretations. At first thought it might be argued that the racemization is due to the occurrence during reaction of a tautomerism involving the hydrogen atom on the asymmetric carbon atom in the diazoketone or in the intermediate products.



We are inclined, however, to reject this interpretation. The diazoketone is reasonably stable optically, even on distillation, and exhibits no such tautomerism in the solutions employed in the experiments; these solutions

or

are quite stable unless metallic catalysts are introduced. Furthermore, certain experiments on the optically active diazoketone, methylethylphenyldiazoacetone, $(CH_3)(C_2H_6)(C_6H_5)C-CO-CHN_2$, where such tautomerism can be ruled out, indicate here also that racemization accompanies the rearrangement. It may also be pointed out that the intermediates in the Curtius, Lossen, and Hofmann rearrangements of derivatives of *d*-benzylmethylacetic acid should have an equal opportunity for displaying this sort of tautomerism; yet this apparently never happens during the rearrangement process.

The explanation of the difference in behavior of a migrating asymmetric group in the two types of rearrangement is more probably to be sought in some divergence of the detailed mechanisms in the two cases. For example, both Curtius and Wolff rearrangements may proceed by a process of internal oxidation and reduction such that at no time is the migrating group free, but that in the former the asymmetric carbon atom retains at all times its complete octet of electrons, while in the latter it is at some point left with only a sextet of electrons. It has been pointed out by Wallis (10), that such a sextet of electrons is, in general, incapable of preserving intact the asymmetry of a carbon atom in such an intramolecular process and leads to extensive or complete racemization, or sometimes by a special mechanism to Walden inversion. It is also possible that the rearrangement, when catalyzed by silver ions, may be an ionic process involving separation of the asymmetric group as a carbanion or carbonium ion respectively, depending on the conditions of experiment (dielectric constant of the medium, catalyst, etc.). The properties and optical stability of such ions have been investigated in recent years (11), and it has been found that carbonium ions are on the whole more liable to racemization than carbanions. Such reactions are markedly influenced by the solvent and by other ions present in the solution. If the energies of ionization in the two different ways are comparable, then one or both types of ionization may be expected, the relative extent of each depending on the activation energies of each process, which will depend on the particular nature of the reaction-medium. Thus it is possible that the rearrangement of *d*-benzylmethylacetyldiazomethane in methyl alcohol saturated with ammonia leads to a product not completely racemized because the process involves carbanions extensively as intermediates, while the rearrangement in aqueous dioxane leads to a completely racemized product, since the intermediates are largely carbonium ions. It is interesting to note in this connection that the silver ion in the first case is present as a complex cation $([Ag(NH_3)_2]^+)$, while in the second it is present as a complex anion ($[AgS_2O_3]^-$). We propose to investigate further whether this is of real significance.

In conclusion we should like to point out that the decision between the alternatives discussed in the preceding paragraph, could be definitely made, were data available on the Wolff rearrangement of the same character as those obtained by Wallis and Moyer (9) for the Hofmann rearrangement. For instance, the optically active diazoketone (V) should rearrange into the acid (VI) without loss of optical activity unless the



mechanism involves the definite separation of the optically active radical into a free fragment, in which case racemization due to free rotation around the axial C-C bond should result. A study of this type has not yet been made, but the diazoketone (V) is now being prepared in this laboratory and its behavior will be discussed in a later paper. The influence of dielectric constant of the medium is also being investigated, since this also will make itself evident if the reaction is ionic. The connection, however, between rate of reaction and dielectric constant is difficult to establish in this case, since the reaction rate is also very sensitive to the catalyst. It must be remembered that the rôle of the catalyst is as yet completely unknown, although it may be noted in passing that those catalysts satisfactory for the Wolff rearrangement are among those known to be effective in weakening the carbon-carbon and carbon-hydrogen bonds (i.e. the metallic hydrogenation-dehydrogenation catalysts) and may owe their efficacy to the promotion of reactions of the types discussed above at their surfaces.

EXPERIMENTAL

Preparation of d-benzylmethyldiazoacetone. This compound was prepared from d-benzylmethylacetic acid. The acid used in these experiments was prepared according to the method of Conrad (12), with a few modifications due to Jones and Wallis (6). It was resolved into its enantiomorphs by the method of Kipping and Hunter (13). In a 5 cm. tube without solvent, the acid displayed a rotation α_D^{∞} +11.35°. It was converted into its chloride by the method of Pickard and Yates (14). The chloride boiled at 89-90° (1.7 mm.). In a 5 cm. tube without solvent it gave a rotation α_D^{∞} +12.40°. From the acid chloride, the diazoketone was then prepared according to the method of Arndt and Eistert (2) for the general prepara-

tion of diazoketones from acid chlorides. The acid chloride (10 g.) was dissolved in 25 cc. of pure dry ether, and added drop by drop over a period of one-half hour, with mechanical stirring, to a solution of 8 g. of diazomethane in 400 cc. of dry ether, prepared according to the directions of Arndt and Amende (15). The solution was kept at 0° during the addition of the chloride and for one-half hour thereafter. Finally it was allowed to come to room temperature and was stirred for an additional two hours. After filtration of the solution to remove polymethylenes, the solvent was removed. The diazoketone was obtained as a clear, yellow oil, which was freed from the last traces of solvent by heating on the water-bath at 60° for one hour under a pressure of 15 mm.

The diazoketone so prepared showed no trace of chloride either in the Beilstein test or on treatment with silver nitrate in ethyl alcohol. It was readily soluble in alcohol, ether, acetone, and benzene, insoluble in water. It was not obtained in crystalline form. When kept in a glass-stoppered bottle, the inner surface of which was free from etching, in a refrigerator, it was stable for an indefinite period. In a 5 cm. tube without solvent it gave a rotation $\alpha_2^{n0} + 67.2^{\circ}$.

The filtrates from the fractional crystallizations of the quinine salt of benzylmethylacetic acid were worked up and a mixed *levo* acid was obtained. This was converted to the corresponding mixed *levo* diazoketone by the method just described for the preparation of the pure *dextro* modification. Its rotation in a 5 cm. tube without solvent was $\alpha_{\rm D}^{20} -27.90^{\circ}$. At 0.08 mm. pressure on a bath at 95-100°, the diazoketone distilled over with slight decomposition. An analysis of the product for nitrogen gave:

Cale'd for C₁₁H₁₂N₂O: N, 14.89. Found: N, 14.17.

Hydrolysis of the mixed 1-diazoketone to 4-phenyl-3-methylbutan-2-on-1-ol. Three grams of the mixed l-diazoketone was treated with 30 cc. of 50% formic acid solution at room temperature. Nitrogen was violently evolved, and the solution became intensely orange-yellow. After one hour the reaction had stopped, and the solution was filtered, diluted with water, and extracted with ether. The ether extract was treated with concentrated sodium bicarbonate solution until neutral. It was then washed with water, dried over anhydrous sodium sulfate, filtered, and the ether removed on a water-bath. The residual brownish liquid was distilled at 56-62° at 0.002 mm. pressure. Yield 2 g. or 70.4% of the theory. In a 5 cm. tube without solvent the keto alcohol showed a rotation $\alpha_{\rm D}^{\infty}$ -14.03°. For identification a sample of the freshly distilled keto alcohol was treated with *p*-nitrobenzoyl chloride and a small amount of pyridine. The *p*-nitrobenzoate was crystallized from a mixture of alcohol and petroleum ether. Melting point of pure product, 73°.

Anal. Calc'd for C₁₈H₁₇NO₅: C, 66.05; H, 5.20.

Found: C, 65.94; H, 5.12.

Rearrangement of the d-diazoketone in methanol saturated with ammonia. Thirtyfive cubic centimeters of methanol was saturated with dry ammonia gas at 20°. Three grams of d-benzylmethyldiazoacetone was then added, whereupon the solution deepened in color to orange-red but remained clear. To the solution was added slowly and with shaking, 10 cc. of a saturated solution of silver nitrate in 80% (aqueous) methanol. Evolution of nitrogen commenced at once. After two hours no further evolution of nitrogen could be observed. The solution was then freed from solvent under reduced pressure on the water-bath at 30°, and the oily residue was extracted with ether until only a small amount of silver nitrate and silver powder remained. The ether solution was decolorized with animal charcoal, filtered, and dried over anhydrous sodium sulfate. On removal of the ether from the dried solution, a straw-colored oil was left, which was taken up in benzene and examined for optical activity. A solution of the substance in 10 cc. of benzene showed a rotation of $\alpha_{\mathbf{p}}^{\infty} + 0.5^{\circ}$ (2 dm. tube). On addition of an equal amount of light petroleum ether, crystals of β -benzyl- β -methyl-propionamide separated. Some 2.5 g. of crude crystals was obtained. The mother liquor still exhibited a positive rotation. On evaporation of the solvent, a yellow oil remained which refused to crystallize. This was again subjected to a treatment with ammonia and silver in methanol as described above. This time, when the solvent was finally removed, a crystallize product was obtained, which was united with the first fraction. Three recrystallizations from a 50% solution of light petroleum ether in benzene gave one gram of leafy white crystals of melting point 80-81°. It had $[\alpha]_{\mathbf{p}}^{\infty} - 9.30^{\circ}$ in benzene (0.156 g. of the substance in 5.00 cc. of solution gave $\alpha_{\mathbf{p}}^{\infty} - 0.58^{\circ}$ in a 2 dm. tube).

Anal. Calc'd for C₁₁H₁₅NO: C, 74.54; H, 8.5.

Found: C, 74.34; H, 8.3.

The mother liquors from the recrystallizations were worked up and 0.5 g. of additional amide obtained. Melting point: 78-89°; $[\alpha]_{\rm D}^{\infty} -2.63^{\circ}$ (0.114 g. of amide in 5.00 cc. of benzene gave $\alpha_{\rm D}^{\infty} -0.12^{\circ}$).

Anal. Calc'd for C₁₁H₁₅NO: C, 74.54; H, 8.53.

Found: C, 74.43; H, 8.54.

This indicates that the product was partially racemic. This was confirmed by the change of specific rotation of a portion on recrystallization from water. The crystals, separated and dried, had a specific rotation $[\alpha]_{\rm p}^{20} -7.21^{\circ}$, while the amide left in the mother liquor had a rotation $[\alpha]_{\rm p}^{20} -10.80^{\circ}$.

Rearrangement of the d-diazoketone in 25% (aqueous) dioxane. Three grams of d-benzylmethyldiazoacetone was dissolved in 25 cc. of dioxane. To this solution was added, with shaking, 80 cc. of a suspension of freshly precipitated silver oxide in 100 cc. of 5% sodium thiosulfate solution. Reaction commenced at once, as evidenced by a rapid evolution of nitrogen, the solution rapidly turning red. The mixture was shaken for ten minutes and then heated to 50° on the water-bath for two or three minutes. Reaction was then complete. The excess silver oxide was filtered out, and the solution extracted several times with small portions of ether. These extracts were discarded. The clear aqueous solution was acidified carefully with dilute hydrochloric acid, saturated with sodium chloride, and extracted four times with ether. The ether extracts were united and extracted several times with a solution of 2 N sodium hydroxide. This effected a separation of the organic acid from sulfur precipitated by the action of hydrochloric acid on sodium thiosulfate.

The united sodium hydroxide extracts were acidified with hydrochloric acid, saturated with sodium chloride, and extracted with ether as before. The ether solution of the organic acid was decolorized with animal charcoal, filtered, and dried over anhydrous sodium sulfate. On final removal of the ether, 2 g. of a straw-colored oil was obtained which was completely *optically inactive*.

The β -benzyl- β -methylpropionic acid itself was not obtained in crystalline form. For analysis it was converted to the acid chloride by treatment with thionyl chloride. The chloride was then added drop by drop with stirring to 100 cc. of concentrated ammonium hydroxide at 0°. The mixture was allowed to stand overnight, and the precipitated amide was recrystallized from 50% benzene-petroleum ether solution. Three recrystallizations sufficed to give a pure product of sharp melting point 83°.

Anal. Calc'd for C₁₁H₁₅NO: C, 74.54; H, 8.53.

Found: C, 74.55; H, 8.47.

Rearrangement of d-methylethylphenyldiazoacetone. This diazoketone was prepared by a method similar to that outlined above for d-benzylmethyldiazoacetone. Five grams of an incompletely resolved methylethylphenylacetic acid, $[\alpha]_{p}^{\infty} + 6.90^{\circ}$, prepared by the method of Wallis and Bowman (10), was converted to the acid chloride by reaction with thionyl chloride. The chloride so prepared was dissolved in 200 cc. of dry ether and treated with an excess of diazomethane. After the reaction was completed the excess of diazomethane and the solvent were removed at 30° under diminished pressure. Five grams of a yellow viscous oil was obtained. Qualitative tests showed it to be free from halides.

Two grams of the material was dissolved in 15 cc. of pure dioxane, and to the solution was added slowly 40 cc. of a mixture of 2 g. of freshly precipitated silver oxide in 100 cc. of 5% aqueous solution of sodium thiosulfate. A reaction began immediately as evidenced by the evolution of nitrogen, and the color of the reaction-mixture changed rapidly to deep red. After two hours the reaction was complete. The solid silver-silver oxide mixture was then removed by filtration, and the filtrate was extracted several times with ether. Both ether extract and aqueous solution were optically inactive. From the aqueous solution was obtained on acidification 0.5 g. of an optically inactive acid.

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SUMMARY

Benzylmethyldiazoacetone has been prepared in a pure *dextro* and a mixed *levo* modification.

Evidence is submitted to show that: (a) On treatment with acids in the absence of a catalyst, this compound gives an optically active keto alcohol without appreciable racemization.

(b) On treatment with ammonia in the presence of a catalyst, the compound undergoes a Wolff rearrangement to give a partially racemized β -methyl- β -benzylpropionamide.

(c) On treatment with water in the presence of a catalyst, the compound undergoes a Wolff rearrangement to give an optically inactive β -methyl- β -benzylpropionic acid.

Methylethylphenyldiazoacetone has been prepared in a mixed *dextro* modification. When this compound undergoes the Wolff rearrangement in the presence of water and a catalyst, an optically inactive acid likewise results.

A discussion of these results is given with special reference to the relation of the detailed mechanism of the Wolff rearrangement to that of the Curtius, Hofmann, and Lossen rearrangements, in which the benzylmethylcarbinyl radical retains its asymmetry without appreciable racemization during the rearrangement process.

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