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THE CONFIGURATIONAL RELATIONSHIP OF 1,2,2-TRIPHENYLETHYLAMINE AND 1,2,2-TRIPHENYLETHANOL

J. B. Christie

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CHAPTER I

INTRODUCTION

The reactions of compounds in the 1,2,2-triphenylethyl system have been grouped into two classes as a result of the radiochemical examination of the reaction products.[1-6] The first class included the acid-catalyzed elimination reactions of 1,2,2-triphenylethanol-1-C^{14}, 1-phenyl-C^{14}-2,2-diphenylethanol, and the acetates of these compounds. In these reactions a statistical distribution of the radioactivity was found in the products. In the second class of reactions, which included the hydrolyses and acetolyses of the p-toluenesulfonates of these same 1,2,2-triphenylethanols, the distribution of the radioactivity in the products was not statistical. Further, the extent of rearrangement of the labeled phenyl group was greater than the distribution of the chain label.

A statistical distribution of radioactivity in equation (1) required that $x = 0.500$ and in equation (2) that $y = 0.667$.

$$\begin{array}{ccccc} & \overset{A}{|} & & \overset{B}{|} & & \overset{B}{|} & \\ Ph_2CH- & \underset{*}{C}HPh & \longrightarrow & Ph_2CH\underset{*}{C}HPh & + & Ph-CH-\underset{*}{C}HPh_2 & \\ & 1 & & (1 - x) & & x & \end{array} \qquad (1)$$

$$\begin{array}{ccccc} & \overset{A}{|} & & \overset{B}{|} & & \overset{B}{|} & \\ Ph_2CH- & CHPh^{*} & \longrightarrow & Ph_2CH-CHPh^{*} & + & Ph-CH-CHPh_2^{*} & \\ & 1 & & (1 - y) & & y & \end{array} \qquad (2)$$

On the basis of the data collected during the studies, a

mechanism involving equilibrating classical carbonium ions was established for these reactions. It was shown that open ions were required and that bridged ions which proceeded directly from reactant to products were incompatible with the results.

The idea of bridged ions[7-9] as discrete intermediates in organic reactions was developed by Cram[10,11] to explain the stereochemical results of the acetolysis of p-toluenesulfonic esters of 3-phenyl-2-butanols. The concept of a bridged carbonium ion which controlled the configuration of the carbon atoms it spanned has been well established in Wagner-Meerwein rearrangements. The formation of bridged-ion pairs and the "internal return"[12-14] of these ion pairs was postulated in these rearrangements to account for the formation of isomerized, racemized reactant.

Despite the usefulness of the bridged-ion intermediates in explaining the results of Wagner-Meerwein rearrangements in systems in which assistance by the migrating group was important in bringing about ionization, such intermediates could not be responsible for the results of the reactions of compounds in the triphenylethyl system. This system presented a different situation, for the carbonium ions were highly stabilized by the adjacent phenyl group and did not require the participation of the neighboring phenyl group. If phenonium ions were postulated as the only intermediates in the reactions of the compounds of the 1,2,2-triphenylethyl system, it was necessary to guarantee certain unlikely conditions. First, the formation of cis- and trans-phenonium ions had to occur almost equally. Second, the rate of internal return by ion-pair collapse had to be greater than the rate of product formation.

In the first class of reactions of the 1,2,2-triphenylethyl system, once the open ions were formed, the rate of phenyl group migration was fast enough to allow equilibration of the ions before proton loss or nucleophilic attack occurred. The observed statistical distribution of radioactivity was the result of the equilibration of the ions. If symmetrical, bridged ions were the only intermediates an equal distribution of the phenyl label [(y) in equation (2)] would have resulted. Bridged ions could be postulated as the reaction intermediates only if the rate of internal return of the bridged-ion pairs was much faster than the rate of reaction of the bridged cations to yield product.

In the second group of reactions, the rate of nucleophilic attack upon, or proton loss from the open ions was fast compared with the rate of phenyl migration; thus complete equilibration of the ions was not possible and a statistical distribution of the radioactivity did not result. Through an analysis of these reactions of the second group, based on an open-ion mechanism, it was possible to estimate the rearrangement of the carbon-14 chain label from the rearrangement of the phenyl label. In view of the foregoing facts, as well as of the known steric requirements of the triphenylethyl system,[15,16] phenonium ions were unnecessary intermediates.

Any effect produced by internal return on the reactions of the 1,2,2-triphenylethyl system was eliminated in the study of the radiochemical consequences of the nitrous-acid deamination of 1,2,2-triphenylethylamine-1-C^{14} and 1-phenyl-C^{14}-2,2-diphenylethylamine, for in these reactions the elimination of nitrogen should result in the

irreversible formation of the carbonium ions.[17,18] It was seen from the results of the deaminations that a mechanism which involved equilibrating, classical carbonium ions was still the simplest representation possible for the reactions.

In the most recently published paper[6] on the 1,2,2-triphenylethyl system, the stereochemical consequences of the nitrous-acid deamination of optically pure 1,2,2-triphenylethylamine-1-C^{14} were studied and it was found that the deamination proceeded with some racemization. However, the products of the deamination were optically active. Since the mechanism for the deamination and similar reactions had been established as one involving open carbonium ions, not usually associated with stereospecificity, these results were of immediate interest.

The stereochemical and radiochemical results of the hydrolysis and acetolysis of optically active 1,2,2-triphenylethyl-1-C^{14} tosylate were also reported. It could be seen from an examination of the products that in all three reactions considerable racemization occurred. The products were, however, in all cases optically active. It was evident that the origin of this optical activity must be explained on the basis of net retention or inversion during the course of the reactions. The decision between these alternatives depended on the relationship of the configurations of the reactants and the products. It was found that (+)-1,2,2-triphenylethanol (carbinol exhibiting positive or clockwise rotation of plane polarized light), after conversion to the p-toluenesulfonate, yielded, by hydrolysis or acetolysis, (+)-1,2,2-triphenylethanol or (+)-1,2,2-triphenylethyl acetate. Since, in the preparation of the tosylate, the asymmetric center was undisturbed, it was concluded

that these solvolytic reactions proceeded with a net retention of configuration.

Whereas the solvolytic reactions provided a direct relationship of the configurations of the reactants and products, no such direct method was applicable to the deamination, in which the carbon-nitrogen bond of the asymmetric center was broken. The nitrous-acid deamination of (+)- or (-)-1,2,2-triphenylethylamine in water in the presence of hydrochloric acid and acetic acid produced from 88 to 92 per cent partially racemic 1,2,2-triphenylethanol whose specific rotation had the same sign as that of the amine reactant. In order to establish the course of the deamination reaction it was necessary to relate the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol.

At the inception of the present research, some evidence existed which indicated that amine and carbinol of like sign of rotation possessed the same configuration. Included in this evidence were the radiochemical results of the solvolytic and deamination reactions of phenyl- and chain-labeled compounds of the 1,2,2-triphenylethyl system, from which it was inferred that all three reactions proceeded through the same open carbonium-ion intermediates. Since the solvolyses took place with resulting retention of configuration, it seemed reasonable to speculate that the deamination proceeded also with retention of configuration. Additional evidence obtained by studying the differences in the solid-liquid phase relationships of mixtures of (+)-1,2,2-triphenylethyl acetate and (+)- or (-)-N-acetyl-1,2,2-triphenylethylamine[19-22] indicated that the compounds of like rotation were of like configuration. There was no evidence, however, of the formation of quasi-racemates or

eutectics to confirm this opinion. Finally, the optical rotatory dispersion curves produced by (+)-1,2,2-triphenylethyl acetate and (+)-N-acetyl-1,2,2-triphenylethylamine were similar. No Cotton effect[23] was observed, however, so that a positive conclusion was not reached. Thus the evidence which preceded the current study was presumptive, but hardly conclusive.

The purpose, therefore, for which the research reported in the present dissertation was undertaken was twofold: (1) to establish unambiguously the relationship of the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol, and (2) to establish the absolute configurations of these same compounds. The methods used to accomplish the objectives are briefly summarized in this introduction; the procedures and results comprise the body of the dissertation.

1) The first step in carrying out these objectives was the resolution of 1,2,2-triphenylethanol. Verification of the value of the specific rotation of completely resolved 1,2,2-triphenylethanol was necessary in order to measure the amount of stereospecificity which accompanies the reactions of the compounds in the triphenylethyl system. This resolution via classical methods had not been previously successful. It was known that fractional crystallization of optically active 1,2,2-triphenylethyl acetate from ethanol resulted in the enrichment of the mother liquors with the optically active acetate, whereas the racemic material crystallized preferentially. In this fashion, optically active acetate was obtained which produced optically active 1,2,2-triphenylethanol whose specific rotations were as high as $\pm 122^{\circ}$ in ethanol. It seemed likely to earlier researchers that this carbinol was optically

pure, since no further increase in rotation was produced when the precursor acetate or the carbinol were recrystallized. After several unsuccessful attempts, the present author resolved the acid-succinate ester using the optically active alkaloid, cinchonidine. The resolution was also carried out with (+)- and (-)-1,1-diphenyl-2-aminopropanol. The carbinols obtained from both resolutions possessed specific rotations of $\pm 122^{\circ}$ (ethanol).

2) The second step which concerned the author was finding a route by which the required relationship between the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol could be established. The discovery by White[24-27] and by Huisgen[28] that the decomposition of optically active N-nitroso-N-acylamines produced esters which possessed the same configuration as that of the amine reactant provided this route. A preliminary investigation was carried out to determine whether the reaction could be applied to the compounds in the triphenylethyl system. The amide, (+)-N-acetyl-1,2,2-triphenylethylamine-1-C^{14}, $\alpha]_D^{25^{\circ}} = +108^{\circ}$ (dioxane), was nitrosated in a solution of carbon tetrachloride which contained dinitrogen tetroxide. The N-nitroso amide was decomposed by heating the carbon tetrachloride solution and the resulting product was identified as 1,2,2-triphenylethyl acetate. The product, $\alpha]_D^{25^{\circ}} = +26^{\circ}$ (dioxane), after one crystallization, had the same sign of rotation as the rotation produced by the amine reactant. Since the decomposition had been shown to proceed with retention of configuration in systems such as optically active sec.-butylamine and optically pure α-phenylethylamine, this decomposition, subject to further study, provided the information which was needed to establish that

1,2,2-triphenylethylamine and 1,2,2-triphenylethanol which produced rotations having the same sign were of the same configuration. It was shown by examination of the carbon-14 content of the oxidation fragments of the 1,2,2-triphenylethyl-1,2-C^{14} acetate that 16 per cent rearrangement of the carbon-14 label had occurred. It seem conclusive in view of this preliminary study that the deamination of the amine proceeded through equilibrating carbonium ions and resulted in a product which had the same configurations as the amine which was deaminated.

3) A third study made by the author concerned the deamination of optically pure 1,2,2-triphenylethylamine in glacial acetic acid. The product of the deamination was optically active 1,2,2-triphenylethyl acetate, the same compound produced by the decomposition of optically pure N-nitroso-N-acetyl-1,2,2-triphenylethylamine. In addition, the extent of the optical activity of this product in both reactions was identical. It was hoped that the mechanism of the N-nitroso amide decomposition would be clarified through the results of the deamination.

4) The final inquiry made by the author established the absolute configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol through the relationship of these compounds to D-(-)-lactic acid and D-(+)-tartaric acid. The details of this relationship are discussed in Chapter V.

The optical rotations reported in the present work were measured on a Hilger standard polarimeter, model 412, manufactured by Hilger and Watts, Limited, London, England. The melting points were measured on a Kofler Hot Bench, distributed by William J. Hacker and Company, Incorporated, New York. The melting points are reported in degrees, centigrade.

CHAPTER II

THE RESOLUTION OF 1,2,2-TRIPHENYLETHANOL

Discussion

The conversion of racemic compounds to diastereoisomers, followed by the separation of the diastereoisomers, is a widely accepted method for resolving optically active acids and bases. In general, the racemic material is allowed to react with an optically active reagent and the diastereoisomers obtained therefrom are separated by utilizing the differences in their physical properties, usually by fractional crystallization. Racemic alcohols are also resolved through conversion to diastereoisomers, but it is necessary to prepare the acid-phthalate or acid-succinate esters of the alcohols, and then to allow the acid esters to react with optically active bases.

During the present research the resolution of 1,2,2-triphenylethanol was carried out using the succinate-acid ester. The (-)-enantiomer was obtained by the fractional crystallization of the cinchonidine salt of the acid ester followed by hydrolysis of the salt and reduction of the acid ester with lithium aluminum hydride.[29-31] The (-)-enantiomer was also obtained from the (+)-1,1-diphenyl-2-aminopropanol salt of the same ester; whereas the (+)-enantiomer was obtained by the fractional crystallization of the (-)-1,1-diphenyl-2-aminopropanol salt of this ester. The specific rotation of the enantiomers was equal and in opposite directions. It was also found, during the course of the resolution, that the acid-phthalate ester of

1,2,2-triphenylethanol could be resolved with quinidine; (-)-carbinol which was 70 per cent resolved was obtained from the salt of quinidine and the acid-phthalate ester.

An attempt to prepare the 3-nitrophthalate-acid esters of the carbinol was discontinued as it was not possible to separate the isomeric esters which were formed by the reaction of 1,2,2-triphenylethanol with 3-nitrophthalic anhydride.

The racemic 1,2,2-triphenylethanol used in this research was prepared using the method described by Bonner and Collins.[1]

The Preparation of the Acid Esters of 1,2,2-Triphenylethanol

The preparation of the 3-nitrophthalate-acid ester of 1,2,2-triphenylethanol. The 3-nitrophthalate-acid ester was prepared using a modification of the procedure described by Elhafez and Cram.[32] A solution of 50 ml. of pyridine containing 19 g. (0.07 mole) of 1,2,2-triphenylethanol and 13.5 g. (0.07 mole) of 3-nitrophthalic anhydride was heated on the steam bath for one hour. The solution was poured into a mixture of ice and 6 N sulfuric acid and the white solid which precipitated was filtered from the solution and washed with water. The attempts to purify the ester were unsuccessful, and since it was reasonable to assume that the product obtained was a mixture of the α- and β-isomers of the ester, this line of endeavor was discontinued. The melting point of the crude product was 220-240°.

The preparation of the phthalate-acid ester of 1,2,2-triphenylethanol. A solution containing 20 g. (0.073 mole) of 1,2,2-triphenylethanol and 10.9 g. (0.074 mole) of phthalic anhydride in 50 ml. of pyridine was warmed on the steam bath for two hours. The solution was

cooled and poured into 200 ml. of 6 N sulfuric acid. The solid was collected, washed with water, and purified by dissolving it in ten per cent sodium bicarbonate solution and extracting the alkaline solution with ether to remove the nonacidic material. The acid ester was recovered by acidifying the alkaline solution with hydrochloric acid. After recrystallization from ethanol and water, 17 g. (63 per cent) of material were recovered, m.p. 184-185°.

The preparation of the succinate-acid ester of 1,2,2-triphenylethanol. A solution containing 100 g. (0.37 mole) of 1,2,2-triphenylethanol and 35 g. (0.37 mole) of succinic anhydride in 250 ml. of pyridine was heated on the steam bath for four hours and allowed to stand at room temperature overnight. The solution was then poured into a mixture of cracked ice, 380 ml. of sulfuric acid, and one liter of water. The viscous oil which initially formed later crystallized in the aqueous solution. It was filtered from the solution, washed with water and methanol, dried and then washed with hot hexane to remove the unreacted carbinol. The dried, unrecrystallized ester amounted to 110 g. (79 per cent), m.p. 166-168°. This crude ester was used for the resolutions. A small fraction, recrystallized slowly from ethanol, had a melting point of 170-171°. After recrystallization from acetic acid (70 ml.) and water (20 ml.), the melting point was 176-177°. The melting point reported for this ester is 177.5-178°.[1]

The Resolution of the Acid Esters of 1,2,2-Triphenylethanol

The resolution of the phthalate-acid ester of 1,2,2-triphenylethanol with quinidine. Two grams (0.005 mole) of the phthalate-acid

ester of 1,2,2-triphenylethanol and 1.75 g. (0.005 mole) of quinidine were dissolved in 25 ml. of ethanol. The solution was set aside for several weeks. At the end of this time no crystallization had occurred. The remaining ethanol was evaporated and 20 ml. of benzene were added to the oily residue. The mixture was heated to dissolve the oil and hexane was added dropwise until the solution became cloudy. The solution was heated again and then it was left standing overnight. The crystals which formed were filtered from the solution and were twice recrystallized from 1:1 benzene-hexane. The melting point was indistinct, about 150°, $\alpha]_{D}^{25^{\circ}} = +191^{\circ}$ (ethanol).

The salt was dissolved in benzene and 20 ml. of water were added. The mixture was stirred vigorously while concentrated hydrochloric acid was added dropwise until the solution was acid to pHydrion paper (pH 6). The benzene layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The benzene was evaporated to a volume of 10 ml. and then hexane was added dropwise. The ester which precipitated was filtered from the solution and dried, $\alpha]_{D}^{25^{\circ}} = +55^{\circ}$ (ethanol). The ester was dissolved in ether and reduced with lithium aluminum hydride. The ether solution was washed with water and two per cent sodium hydroxide solution and then it was dried with anhydrous magnesium sulfate. The carbinol, 0.1 g., was recovered as an oil when the ether was evaporated. After the carbinol was recrystallized from hexane, the specific rotation was $+86^{\circ}$ in ethanol. It was apparent that resolution was taking place but no further attempt to purify the salt was made as other methods were proving more successful.

The resolution of the succinate-acid ester of 1,2,2-triphenylethanol with cinchonidine. A solution of 110 g. (0.29 mole) of the succinate ester of 1,2,2-triphenylethanol and 87 g. (0.29 mole) of cinchonidine in three liters of benzene was prepared. After two days the crystals which had separated were filtered from the solution. This material was identified as cinchonidine. After it was recrystallized from benzene, the specific rotation was -48° in pyridine, and this value did not change with additional recrystallization. The melting point was $198\text{-}200^{\circ}$ and did not change when this material was mixed with cinchonidine, $\alpha]_{D}^{25^{\circ}} = -49^{\circ}$ (pyridine). After the removal of 40 g. of cinchonidine, the volume of the solution was reduced to approximately 500 ml., and 30 g. of the salt of the succinate-acid ester were obtained. Recrystallization from a 1:1 benzene-hexane mixture, followed by recrystallization from benzene, left 14 g. (14 per cent) of the salt, $\alpha]_{D}^{25^{\circ}} = -52^{\circ}$ (pyridine), $\alpha]_{D}^{25^{\circ}} = -83^{\circ}$ (ethanol), m.p. $168\text{-}169^{\circ}$. The specific rotation did not change with further recrystallization.

In another experiment, 94 g. (0.25 mole) of the ester were dissolved in two liters of benzene. A solution of 41 g. (0.14 mole, ten per cent excess of one half an equivalent amount) of cinchonidine in 600 ml. of benzene and 70 ml. of ethanol (to dissolve the cinchonidine) was added to the first solution. No crystallization took place; benzene was evaporated until the volume was reduced to about 500 ml. The solution was seeded with crystals of the salt obtained previously and after two days, 40 g. of material were obtained. Two recrystallizations from a 1:1 benzene-hexane solution left 11 g. (12 per cent) of salt, m.p. 168-169 , $\alpha]_{D}^{25^{\circ}} = -48$ (pyridine), $\alpha]_{D}^{25^{\circ}} = -83^{\circ}$ (ethanol),

unchanged by additional recrystallizations. The resolved succinate-acid ester of (-)-1,2,2-triphenylethanol was obtained by the acid hydrolysis of the cinchonidine salt. A solution of 13.5 g. of the salt in 200 ml. of benzene was treated with 1.85 ml. of 37 per cent hydrochloric acid in 200 ml. of water. The two-phase solution was stirred for one hour and an additional six drops of concentrated hydrochloric acid were added. After the benzene was evaporated the white solid which remained was filtered, and was washed with water. The solid was dried, and recrystallized from a 1:1 benzene-hexane solution and 3 g. of material, m.p. 165-166°, were obtained. A mixture-melting point of this material and the cinchonidine salt of the ester (m.p. 167-168°) exhibited a depression of fifteen degrees. The specific rotation of the ester was -84° in benzene and -33° in ethanol, and did not change when the ester was recrystallized.

The resolved ester, 4.5 g. (0.012 mole), was added to 300 ml. of ether to form a slurry, which was added slowly to 0.9 g. (0.023 mole) of lithium aluminum hydride in 50 ml. of ether. After the initial reaction had subsided the solution was heated gently for one hour. The reaction mixture was decomposed by the cautious addition of water until the supernatant solution was clear. The supernatant liquid was decanted from the precipitated lithium and aluminum hydroxides and washed with water. Evaporation of the ether left a clear oil which was crystallized from hexane. Three grams of material, m.p. 80-81°, $\alpha]_D^{25^\circ} = -123^\circ$ (ethanol), were obtained (91 per cent).

<u>The resolution of the succinate-acid ester of 1,2,2-triphenylethanol with enantiomeric 1,1-diphenyl-2-aminopropanol.</u> A solution

containing 53 g. (0.142 mole) of the succinate-acid ester and 32.1 g. (0.142 mole) of (-)-1,1-diphenyl-2-aminopropanol (prepared and resolved by Dr. B. M. Benjamin) in 200 ml. of ethanol, was set aside for several days. Approximately 20 g. of material, $\alpha]_D^{25^\circ} = +14^\circ$ (ethanol), crystallized and were filtered from the solution. After five recrystallizations from ethanol, 3.4 g. of salt, $\alpha]_D^{25^\circ} = +25^\circ$ (ethanol), were obtained. The rotation of this material did not change with two additional recrystallizations.

The salt was hydrolyzed as described in the section on the cinchonidine salt. Reduction of the ester, $\alpha]_D^{25^\circ} = +34^\circ$ (ethanol), produced 1.6 g. of carbinol, $\alpha]_D^{25^\circ} = +120^\circ$ (ethanol). An additional 6 g. of salt were obtained from the mother liquors of the ethanol recrystallizations.

The mother liquors of this resolution were combined and, after hydrolysis, the succinate-acid ester was recovered. A portion of this ester, 6.6 g. (0.018 mole), and 4.0 g. (0.018 mole) of (+)-1,1-diphenyl-2-aminopropanol were dissolved in 25 ml. of ethanol. The salt obtained from this solution was recrystallized from ethanol until the specific rotation reached a constant value of $+29^\circ$ in ethanol. The desired (-)-ester (+)-aminoalcohol salt was not obtained. This salt was later prepared using 0.19 g. (0.005 mole) of pure (-)-1,2,2-triphenylethyl acid succinate recovered from the resolution with cinchonidine and 0.115 g. (0.005 mole) of (+)-1,1-diphenyl-2-aminopropanol. The salt was recrystallized from ethanol, $\alpha]_D^{25^\circ} = -25^\circ$ (ethanol), and crystals of this salt were used to seed the mother liquors from which the diastereomeric salt had been removed. In this manner, the salt of the

(-)-ester was obtained.

The new compounds from these resolutions were analyzed by Huffman Microanalytical Laboratories, Wheatridge, Colorado, and the results of these analyses were listed in Table 1.

TABLE 1

ANALYSES OF THE COMPOUNDS PREPARED DURING THE RESOLUTION OF 1,2,2-TRIPHENYLETHANOL

Compound	Carbon		Hydrogen	
	Calc'd	Found	Calc'd	Found
(-)-1,2,2-Triphenylethanol acid succinate, cinchonidine salt...	76.20	76.29,76.56	6.63	6.66,6.51
(-)-1,2,2-Triphenylethanol acid succinate.....	77.00	76.94,76.61	5.91	5.84,5.69
(-)-1,2,2-Triphenylethanol.....	87.56	87.30	6.61	6.65
(+)-1,2,2-Triphenylethanol acid succinate, (-)-1,1-diphenyl-2-aminopropanol salt.....	77.83	77.98,77.75	6.53	6.55,6.42
(+)-1,2,2-Triphenylethanol acid succinate.....	77.00	76.63,76.72	5.91	5.79,5.84
(+)-1,2,2-Triphenylethanol.....	87.56	87.51,87.47	6.61	6.58,6.64
(-)-1,2,2-Triphenylethanol acid succinate, (+)-1,1-diphenyl-2-aminopropanol salt.....	77.83	77.99,77.96	6.53	6.47,6.53

CHAPTER III

THE DEAMINATION OF 1,2,2-TRIPHENYLETHYLAMINE

Discussion

The deamination of (-)-1,2,2-triphenylethylamine-1-C^{14} was carried out by adding anhydrous potassium nitrite to a solution of the amine in glacial acetic acid. Partially racemic 1,2,2-triphenylethyl-1,2-C^{14} acetate was the only product found, in contrast to the variety of products identified by previous investigators,[5,6] when the deamination was carried out in aqueous solution in the presence of hydrochloric acid and acetic acid. An aliquot of the reaction product from the deamination in acetic acid was removed and the remaining material was resolved to yield a racemic fraction and an optically pure fraction. The optically pure fraction presumably possessed the same configuration as the amine reactant. The three fractions were oxidized and cleaved to benzophenone and benzoic acid. The extent of rearrangement of the carbon-14 label in each of the fractions was determined by assaying the 2,4-dinitrophenylhydrazone of the benzophenone for carbon-14 content (see Table 2 in this chapter). A comparison of the carbon-14 contents of the various fractions indicated that the value obtained for the original sample was too low to be compatible with the values obtained for the racemic and resolved fractions. This particular sample, which represented the over-all results of the deamination, had not been purified, for it was feared that purification would affect the optical

activity of the sample. The presence of a small quantity of unreacted amine was suspected as the most likely explanation for the anomalous result. Examination of a deamination product from racemic amine showed that approximately two per cent unreacted amine was, in fact, present, thus confirming this suspicion. The deamination was then repeated using (+)-1,2,2-triphenylethylamine-1-C^{14}, care being taken to insure complete removal of amine from the product. The results (Tables 2 and 3) of both sets of experiments were in excellent agreement.

TABLE 2

RESULTS OF THE DEAMINATION OF (-)-1,2,2-TRIPHENYL-ETHYLAMINE-1-C^{14} IN ACETIC ACID AT 23°

$\alpha]^{25}_{D}$ of the Products, $Ph_2C^{*}H\overset{O}{\overset{\|}{C}}-O-CH_3$ $C^{*}HPh$, (Dioxane)		Per Cent C^{14} Rearrangement
-24.2°	.....	23.8
-60.5°	.....	24.9
0°	.....	27.1

Per cent inversion
for the reaction 30.0

The extent of carbon-14 rearrangement exhibited by the products from the deamination of the enantiomeric amines was not identical, although the degree of inversion in both reactions was the same. The differences in the extent of carbon-14 rearrangement was probably the result of the method of the deamination. The rate of addition of solid potassium nitrite to the acetic acid solution of the amines could not be controlled sufficiently in the two experiments, thus permitting the pH

of the solutions to vary in an irregular fashion. Since the rate of reaction of the carbonium-ion intermediates with acetate ion to form product is undoubtedly dependent upon the pH of the solutions, the extent of rearrangement of the carbon-14 in the products should be expected to vary with changing pH of the solution.

TABLE 3

RESULTS OF THE DEAMINATION OF (+)-1,2,2-TRIPHENYL-ETHYLAMINE-1-C^{14} IN ACETIC ACID AT 23°

$\alpha]_D^{25}$	Per Cent C^{14} Rearrangement
48.5° (Ethanol)[a]	22.8
61.5° (Dioxane)	20.2
0° (Dioxane)	24.5

Per cent inversion
for the reaction 30.1

[a]Determined for the carbinol which was obtained by reduction and purification of an aliquot of the original reaction mixture.

The study of the deamination of optically pure 1,2,2-triphenylethylamine-1-C^{14} in acetic acid was undertaken in order that more information on the deamination reaction in the triphenylethyl system could be gathered. The equilibrating, classical carbonium-ion mechanism was supported by the data. Further, it was hoped that the data obtained would be valuable in an interpretation of the mechanism of the decomposition of optically pure N-nitroso-N-acetyl-1,2,2-triphenylethylamine in acetic acid. The product which exhibited a rotation of the same sign as the starting amine was formed with less migration of the carbon-14 label than the product which produced rotation of the opposite sign,

thus eliminating bridged ions as the sole method of configurational control. The solvolysis reactions proceeded with retention of configuration, and the deamination in acetic acid, like the deamination in aqueous solution, apparently proceeded through the same intermediates as the solvolyses. The deamination in acetic acid was further support then that the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol which produced rotation of the same sign had the same configuration.

Experimental

The preparation of 1,2,2-triphenylethylamine-1-C^{14}. The preparation of the amine has been described in detail by Bonner and Collins.[1,5] Their procedure was followed exactly in the preparation of the amine used in the present research. The crude amine was resolved by the method of Collins, Bonner and Lester.[6]

The amine that was obtained by neutralization of the (+)-10-camphorsulfonic acid salt, $\alpha]_D^{25^\circ} = +10^\circ$ (ethanol), was recrystallized from hexane in Dry Ice, $\alpha]_D^{25^\circ} = -73^\circ$ (ethanol). The value of the rotation did not change on further recrystallization. The enantiomer obtained by neutralization of the (+)-tartaric acid salt, $\alpha]_D^{25^\circ} = +54^\circ$ (pyridine), was recrystallized from hexane in Dry Ice, $\alpha]_D^{25^\circ} = +74^\circ$ (ethanol).

The deamination of (-)-1,2,2-triphenylethylamine-1-C^{14} (l-II) in acetic acid. A solution of 150 ml. of glacial acetic acid and 3.0 g. (0.011 mole) of l-II radiochemical assay 7.07 ± 0.01 mc. C^{14}/mole, was placed in a water bath at 23-24°. The addition of 15.7 g. (0.19 mole) of

potassium nitrite required twenty minutes. The reaction mixture was stirred vigorously during the addition and for an additional hour. The mixture was poured into 600 ml. of water and the aqueous solution was extracted with ether. The ether extractions were washed with water and ten per cent sodium bicarbonate solution. The extracts were dried with anhydrous magnesium sulfate and filtered through a Norit pad. The volume of the ether solution was adjusted to 200 ml. in a volumetric flask and two 10 ml. aliquots were removed. The first aliquot was evaporated to dryness and 0.1484 g., $\alpha]_D^{25^\circ} = -24^\circ$ (dioxane), was obtained. It was calculated from the value of the rotation produced by resolved (-)-1,2,2-triphenylethyl acetate, $\alpha]_D^{25^\circ} = -60^\circ$ (dioxane), that 30 per cent inversion had occurred during the deamination.

The second aliquot was reduced with lithium aluminum hydride and the carbinol obtained from the reduction, $\alpha]_D^{25^\circ} = -41^\circ$ (ethanol), 0.118 g., was oxidized in 2 ml. of acetic acid with 0.12 g. of chromic anhydride and 1 ml. of water. After one hour the benzhydryl phenyl ketone was filtered from the oxidation mixture and was oxidized and cleaved to benzophenone and benzoic acid as described by Bonner and Collins.[5]

The remaining ether solution from the deamination was evaporated to dryness. The residue, 3.02 g., was dissolved in ethanol and a small quantity of crystals, 1.4 g., was collected. These crystals were recrystallized five times to obtain 0.4 g. of completely racemic 1,2,2-triphenylethyl-1,2-C^{14} acetate.

The ethanolic mother liquor from the initial crystallization was fractionally crystallized. Five very small portions of crystals, of

gradually increasing optical rotation, were removed. A sixth portion of crystals, $\alpha]_D^{25^\circ} = -60^\circ$ (dioxane), was obtained. Both the racemic fraction and the optically pure fraction were reduced to the carbinols, oxidized to benzhydryl phenyl ketone, and then to benzophenone and benzoic acid. The results of the assays of the 2,4-dinitrophenylhydrazones of the benzophenone fractions were listed in Table 2.

The ethanolic mother liquors from the fractional crystallizations were combined and evaporated to a heavy, yellow oil. This oil was reduced with lithium aluminum hydride and when the ether was evaporated from the reduction solution, 0.746 g. of oil was recovered. It was dissolved in 50 ml. of hexane and passed through a 10 in. column of 1 in. diameter, filled with Fisher Adsorption Alumina, 80-200 mesh. Nothing was removed from the column when it was eluted with an additional 250 ml. of hexane. It appeared that no 1,2,2-triphenylethylene was formed during the deamination in glacial acetic acid. The column was eluted with ethanol and 0.71 g. of carbinol, $\alpha]_D^{25^\circ} = -110^\circ$ (ethanol), was recovered.

<u>The deamination of racemic 1,2,2-triphenylethylamine-1-C^{14} (II) in acetic acid</u>. A solution of 1.65 g. (0.006 mole) of II in 83 ml. of glacial acetic acid was placed in a water bath maintained at 23-24°. A total of 8.65 g. (0.10 mole) of potassium nitrite was added to the stirred solution over a period of twelve minutes. The mixture was stirred for an additional thirty minutes and then it was poured into 300 ml. of water. The aqueous solution was extracted with ether. The ether extracts were washed with sodium bicarbonate solution until the acetic acid was neutralized; they were washed with water, dried and

filtered through a pad of Norit and Celite. The solution was treated with lithium aluminum hydride to deacetylate the 1,2,2-triphenylethyl-1,2-C^{14} acetate. After the reduction, the ether solution was washed with five 10 ml. portions of 0.5 N hydrochloric acid. The acid washings were neutralized with ten per cent sodium hydroxide and the solution was extracted with ether. The ether extracts were dried, and the ether was evaporated in an air stream. An oil, 0.03 g., was recovered which represented approximately two per cent of the starting amine. The oil was acetylated with 10 ml. of pyridine and 10 ml. of acetic anhydride. A solid derivative, m.p. 210-212°, was obtained from the acetylation mixture. No depression in the melting point was observed when this derivative was mixed with an authentic sample of racemic N-acetyl-1,2,2-triphenylethylamine.

The deamination of (+)-1,2,2-triphenylethylamine-1-C^{14} (d-II) in acetic acid. The deamination was performed as described in the previous experiment. The reaction mixture was composed of 2.0 g. (0.0073 mole) of (d-II), radiochemical assay 7.07 ± 0.03 mc. C^{14}/mole, in 100 ml. of glacial acetic acid and 10.5 g. (0.12 mole) of potassium nitrite. After the crude product was recovered it was reduced and extracted with dilute hydrochloric acid to remove unreacted amine. The purified product was acetylated after an aliquot was removed. It was calculated from the specific rotation of the carbinol in this aliquot, $\alpha]_D^{25°} = +48.5°$ (ethanol), that 30.1 per cent inversion had occurred.

The acetylated material was fractionally crystallized as described above and racemic and resolved fractions were obtained. The results of the radiochemical assays were reported in Table 3. Infrared

spectra of the products were obtained in order to ascertain their purity. The infrared analysis of mixtures of 1,2,2-triphenylethyl acetate and N-acetyl-1,2,2-triphenylethylamine is described in a later section.

CHAPTER IV

THE DECOMPOSITION OF N-NITROSO-N-ACETYL-1,2,2-TRIPHENYLETHYLAMINE

Historical Notes

The first published report on the preparation of an N-nitroso amide came from O. Fischer[33] when he described a product with the composition and properties of N-nitrosoacetanilide which was formed in almost quantitative yield when acetanilide was treated with nitrous acid. Fischer described the compound as having a yellow color. He said that it exploded on strong heating and regenerated acetanilide when it was reduced with zinc dust in ethanol. Later, Fischer reported[34] the preparation of three similar compounds using substituted anilides. In addition, he noted that none of these compounds was reduced to a phenylhydrazine.

A new method for the preparation of N-nitroso amides was reported by Pechmann.[35] He found that when a basic solution of diazotoluene reacted with benzoyl chloride a substance was produced with the same properties as one of the compounds previously prepared by Fischer. Wohl[36] confirmed the work of Pechmann by showing that diazobenzenes did react with benzoyl chloride in the presence of cold, excess base. Further work by Pechmann and Frobenius[37] resulted in the preparation of additional compounds. They showed that reaction of an alkaline solution of diazobenzene with acetic anhydride resulted in the same compound prepared by Fischer by the action of nitrous acid on acetanilide.

The use of N-nitrosoacetanilide as an arylating agent was first demonstrated by Bamberger[38] when he prepared biphenyl by decomposing N-nitrosoacetanilide in benzene.

Other reactions of N-nitroso amides were investigated by Chancel[39] and by Pechmann[40] and both noted the formation of esters when the compounds decomposed in alcohols. When Pechmann subjected N-nitroso-N-benzoylbenzylamine to decomposition in ethanol he reported the evolution of ethyl nitrite. In the residues left after distillation of the ethanol, he was able to identify a variety of products including benzoylbenzylamine, benzoic acid, benzylamine, benzyl benzoate, and benzyl ethyl ether.

For some time the main interest in the N-nitroso amides was in connection with their arylations and derivatives.[41-44] Paal and Apitzsch,[41] in search for new derivatives, found that when N-nitroso-N-acetylbenzylamine suffered decomposition in ethanol, benzyl ethyl ether was produced; whereas when the decomposition was carried out in propanol, benzyl n-propyl ether was formed.

The interest in the mechanism of the decomposition and reactions of N-nitroso amides became apparent with the work of Bamberger[45] on diazotization and arylations. Bamberger pointed out in 1920, that as early as 1894[46] he had suspected that a "tautomerism" occurred between the N-nitroso amide and a diazo ester.

$$PhN(NO)COCH_3 \rightleftharpoons PhNNO(COCH_3)$$

Grieve and Hey,[47,48] and later, Butterworth and Hey,[49] began the numerous studies of the kinetics of the decompositions with their study

of the nitrogen elimination from N-nitrosoacetanilide and substituted N-nitroso-N-acylarylamines. The reactions were found to be first order with respect to the N-nitroso amide, and the rates were independent of the nuclear substituents on the aryl amine group and of the solvents used.

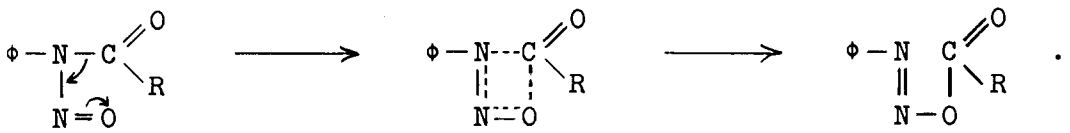
The arylation reactions of N-nitrosoacetanilide were used by Waters[50] to study the possible free radical mechanism of the decomposition. He demonstrated that when the N-nitrosoacetanilide was decomposed in dry solvents in the presence of metals that the metals were attacked. He also reported the liberation of CO_2 when the compound was decomposed in acetic anhydride, and concluded that the CO_2 was due to the reaction of the transient form of neutral acetate radicals:

$$\cdot OCOCH_3 \longrightarrow CO_2 + \cdot CH_3 \quad .$$

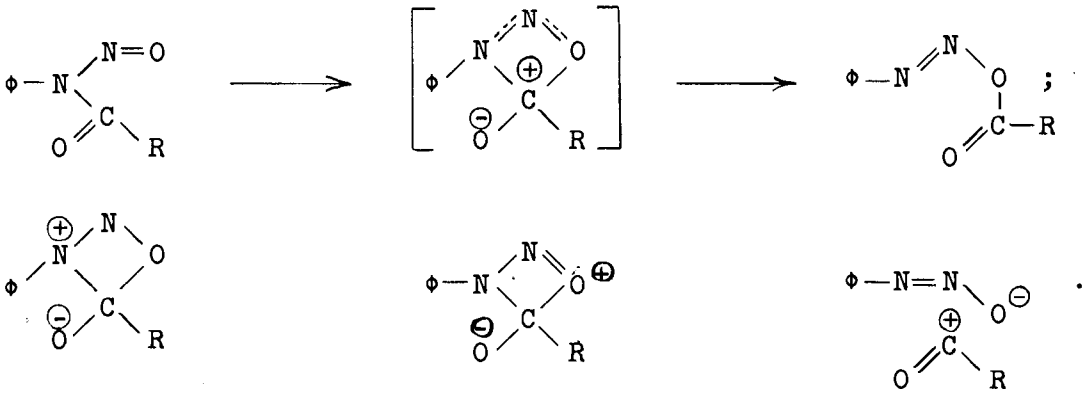
Support for the formation of free radicals in the decomposition of N-nitrosoacetanilide in aromatic solvents was provided much later by the work of DeTar and Scheifele,[51] who, however, did not detect the presence of CO_2 during the reaction. A mechanism involving free radicals was postulated[49,52] for the reaction soon after Waters' work was published. The reaction of N-nitrosoacetanilide with pyridine was studied and it was found that mixtures of $\underline{\alpha}$-, $\underline{\beta}$- and $\underline{\gamma}$-phenylpyridines in yields of 60 per cent were produced.

Independent studies on the rates of nitrogen elimination and azo-coupling were carried out by Huisgen and Horeld,[53] Huisgen and coworkers,[54-58] and by Hey, Stuart-Webb and Williams,[59] and for many N-nitroso-N-acylarylamines both reactions were found to be first order

with respect to the N-nitroso amide and to proceed at the same rate in benzene. This was the best evidence yet reported that the reactions had a common intermediate. In both studies, the authors agreed that the intermediate was the diazo ester formed by the rearrangement of the N-nitroso amide, and that the speed of this rearrangement was rate-determining. Huisgen and coworkers, and Hey and coworkers, stated that their experimental data supported the view that the diazo ester intermediate was formed in a slow, intramolecular step:



In addition to the kinetic evidence, Huisgen[60] showed a resonance stabilization was possible in the formation of the intermediate by an intramolecular path:



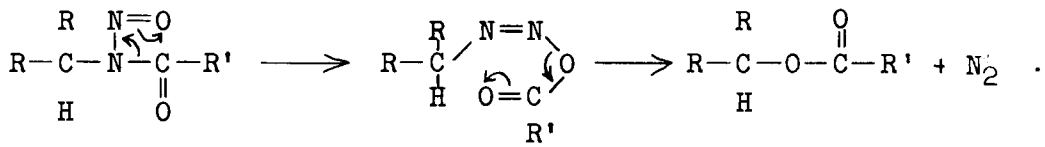
The products and rates for the acid-catalyzed decompositions of N-nitroso-N-acetylamines were studied by Heyns and Bedenburg[61] by measuring the conductivity of the solutions. They included the calculated activation energies for several of the amines used. Another

interesting study was made by Bollinger, Hayes and Siegel[62] on the base-catalyzed decomposition of N-nitroso-N-cyclohexylurethan.

Attention to the variety of products obtainable by the decomposition of N-nitroso amides was increasing. Newman[63] prepared hexahydrobenzaldehyde by treating 3-nitroso-1-oxa-3-azaspiro(4,5)decan-2-one with base. He later[64] showed that 3-nitroso-2-oxazolidones decomposed to form aldehydes, ketones, acetylines and vinyl ethers. N-nitrosolactams were shown[65,66] to eliminate nitrogen to form many products including lactones. The preparation of esters in comparatively good yields was shown[61] by the decomposition of N-nitroso-N-acetyl-n-butylamine to n-butylacetate and small amounts of sec.-butylacetate.

A thorough investigation of the geometric isomerism of the N-nitroso-N-acylarylamines was made by Huisgen and his coworkers.[56-58] They showed that in the intramolecular azo-coupling of diazo esters to give indazoles that the trans-diazo configuration was sterically favorable.[67]

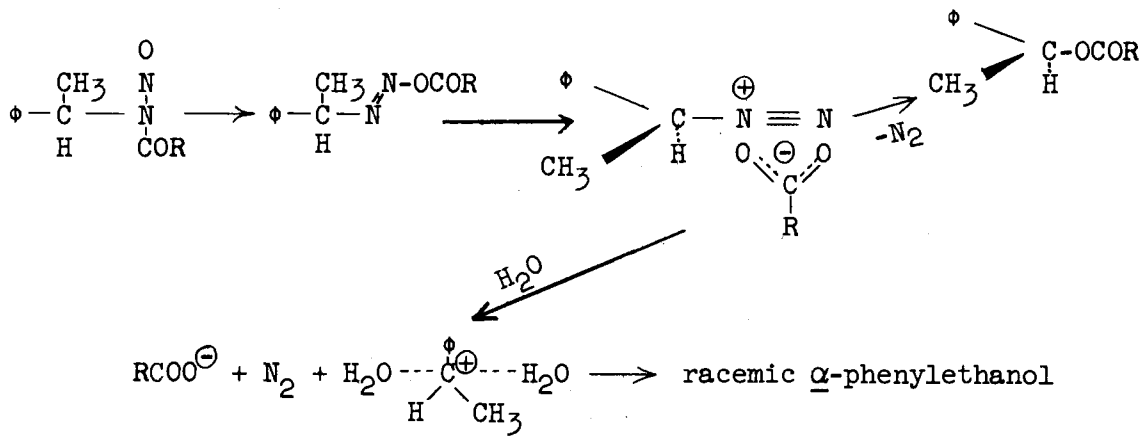
Only recently, however, was a new aspect of this reaction investigated. In a communication by White,[24] it was announced that preliminary work had shown that the decomposition of N-nitroso amides could be used as a method to deaminate aliphatic amines to give esters, predominately, with olefins and acids as elimination products. In addition, White indicated that elimination of nitrogen and formation of the ester proceeded with retention of optical configuration as shown with optically active sec.-butylamine. This retention of configuration, White concluded, was the result of an intramolecular reaction, a new type of S_Ni cyclic rearrangement:



Later, in a series of three papers,[25-27] White elucidated the preparation and mechanism of the decomposition of N-alkyl-N-nitrosoamides. He described five methods of preparation, and listed the products from the decomposition of several N-nitrosoacetamides, benzamides and 3,5-dinitrobenzamides in a variety of solvents. White used his data to arrive at a mechanism, the first stage of which involved the formation of the diazo ester. The second stage, in which nitrogen was eliminated, was visualized as an $S_N\underline{i}$ reaction, and the studies on optically active <u>sec</u>.-butylamine showed that, depending on the reaction conditions, the products of this second stage were formed by intramolecular retention, intramolecular inversion or intermolecular inversion. The work presented on the decomposition of optically active N-nitroso-N-acetyl-<u>α</u>-phenylethylamine indicated that this rearrangement proceeded with a higher degree of retention of configuration which was relatively independent of the solvent.

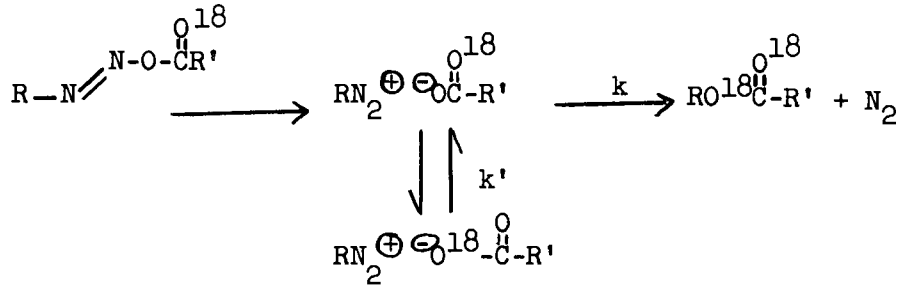
Huisgen and Rüchardt[28] published a significant paper on the steric course of the alkyl-diazo ester decomposition in which they showed that N-nitroso-N-acyl-<u>α</u>-phenylethylamine rearranged to the acyl-diazo ester, and decomposed with the elimination of nitrogen to produce optically active esters. They showed that the extent of retention of configuration was dependent upon the polarity of the solvent in which the decomposition was performed, and that it decreased with the increased polarity of the solvent. Numerous experiments were reported

in which foreign carboxylic acids were added. The esters formed by exchange with these added acids were produced with less retention of configuration than the esters which formed without exchange with the foreign acids. The authors described the reaction on the basis of an ion pair formed by the decomposition of the diazo ester in the transition state. Several factors which could have accounted for the lack of complete stereospecificity of the reaction in nonpolar solvents were discussed.



The latest significant publication on the decomposition was a communication by White[68] in which he described the results obtained for the decomposition of N-nitroso-N-cyclohexyl- and N-nitroso-N-α-phenylethylnapthamide-O^{18}. In each case, it was found that over half of the total amount of the oxygen-18 remained in the carbonyl group. When the optically pure derivative of α-phenylethylamine underwent decomposition, the product was separated into a resolved fraction and a racemic fraction. Both fractions contained the same amount of oxygen-18, therefore, both enantiomers were formed with an equal distribution of oxygen-18. White proposed a mechanism, reminiscent of Huisgen's ion

pairs, involving partial mixing of the oxygen atoms prior to the step in which the final configurations were determined.



where k > k'

Kinetics

The kinetics of the decompositions of many N-nitroso amides have been carefully studied by a variety of methods including the measurement of the nitrogen eliminated, the rate of azo-coupling, and the conductivity of the solutions. In all cases, the reactions were found to be first order with respect to the N-nitroso compound. Despite this apparently well-established fact, it was felt that a determination of the order and rate for the decomposition of N-nitroso-N-acetyl-1,2,2-triphenylethylamine was important and necessary if the reaction were to be used to determine the relationship of the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol.

The rate of the decomposition of (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (1-X) in p-cymene and in acetic acid was determined by observing the change in the magnitude of the optical rotation of the solutions with time.

The preparation of the sample. A weighed 50 ml. volumetric flask containing 0.5 g. of 1-X was placed in the constant temperature

bath which was set at the desired temperature. The sample was diluted to volume with solvent which had been previously warmed to the temperature in the bath. Approximately 20 ml. of the sample were placed in the jacketed polarimeter tube through which circulated water from the constant-temperature bath. The unused sample was placed in the bath for the remainder of the determination. The magnitude of the optical rotations exhibited by the solutions was recorded at varying time intervals until no further change in rotation was detected. The sample in the polarimeter tube was combined with the sample in the bath and the solvent was evaporated. The residue was dissolved in ethanol and the products were separated into a fraction of pure (+)-1,2,2-triphenylethyl-1,2-C^{14} acetate, $[\alpha]_D^{25^\circ} = +60^\circ$ (dioxane), and a partially racemic fraction by fractional crystallization. The optically pure material concentrated in the mother liquors and was crystallized from the solution after several partially racemic fractions were removed. It was not possible to obtain a completely racemic fraction because of the small amount of material. The two fractions were oxidized to benzophenone (and benzoic acid) and the carbon-14 content of the 2,4-dinitrophenylhydrazones of the benzophenone were determined. The extent of rearrangement of the chain label was calculated from the assays for the product of retained configuration, of inverted configuration, and for the racemic product. The results are listed in Table 4.

The purification of the p-cymene. The p-cymene used for the kinetic experiment at 34.0° was obtained from Eastman Organic Chemicals, Distillation Products Industries, Division of the Eastman Kodak Company. It was washed with cold, concentrated sulfuric acid until little color

TABLE 4

PRELIMINARY RESULTS OF THE DECOMPOSITION OF (-)-N-NITROSO-N-ACETYL-1,2,2-TRIPHENYLETHYLAMINE-1-C^{14} (1-X)

Exp.	Solvent	Temp. °C	k, Hrs^{-1}	Per Cent C^{14} Rearrangement in Retained Product	Per Cent C^{14} Rearrangement in Inverted Product	Per Cent C^{14} Rearrangement in Racemic Product
1	p-Cymene	34.7	$0.067 \pm (1.5 \times 10^{-4})$	20.6	a	a
2	Acetic acid	34.7	$0.323 \pm (9.0 \times 10^{-4})$	27.4	36.4[b]	31.9[b]
3	Acetic acid	40.5	$0.830 \pm (1.0 \times 10^{-2})$	26.0	44.6[b]	35.3[b]
4	Acetic acid	47.7	$1.760 \pm (1.3 \times 10^{-2})$	25.9	54.5[b]	40.2[b]

[a]The partially racemic fractions in this experiment were lost in an accident during the fractional crystallization.

[b]These values were found to be incorrect owing to the presence of amide reactant in the samples which were assayed. See Table 5 for the correct results.

change was apparent. The p-cymene was then washed with distilled water, dried with anhydrous magnesium sulfate and potassium carbonate, and distilled. The fraction boiling at 174-175° was collected and passed through an 18 in. column of alumina. The magnitude of the optical rotation produced by this purified material was -0.01° (neat) compared to a value of +0.11° (neat) obtained before the purification.

The purification of the acetic acid.[69] The acetic acid used in the kinetic experiments was Analytical Reagent supplied by Mallinckrodt Chemical Works. It was boiled with five per cent potassium permanganate for several hours and then it was distilled over triacetyl borate. The fraction which boiled at 117-118° was collected.

The determination of the rotations. The polarimeter tube used in the kinetic experiments was 2.0 dm. in length. The tube was equipped with glass end covers which were connected to the tube with Neoprene washers. The tube was manufactured with a central opening for filling and an air-cooled condenser was placed in this opening after the tube was filled. A thermometer was suspended through the condenser so that the bulb was immersed in the liquid in the tube. The tube was fitted with a metallic jacket and was connected to the constant-temperature bath. After the tube was filled, the solution was mixed by carefully tipping the tube back and forth. The tube was placed in the polarimeter and the condenser and thermometer was set in position. The temperature of the liquid in the tube was controlled to within $\pm$ 0.1°. The magnitude of the optical rotations produced by the solution was recorded at varying time intervals until no further change in optical rotation was detected. The length of time of the observations varied from as long as

six days for the experiment in p-cymene at 34.5° to six hours for the experiment in acetic acid at 47.7°. The number of observations taken varied from 40 in the experiment in p-cymene at 34.5°, to 20 in the experiment in acetic acid at 47.7°.

The calculations. The decomposition of l-X was shown to be first order with respect to the concentration of l-X by plotting the values of log $(\alpha_o - \alpha_\infty)$, a number proportional to the concentration of l-X at time t, against time. The rate constants were calculated from the following equation:[70]

$$k = \frac{2.303}{t} \log \frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty}$$

where:

α_o = initial observed rotation,

α_∞ = final observed rotation,

$\alpha_o - \alpha_\infty$ = initial concentration of l-X,

$\alpha_t - \alpha_\infty$ = concentration of l-X at time t,

t = time of observed value.

The calculations necessary for the determination of the reaction rate constants were carried out on the ORACLE.[71] Dr. M. H. Lietzke was the author of the code which was used and he adapted it to the conditions of this problem. In each of the cases studied, the ORACLE was provided with the experimental data which were the observed rotations and the time at which the rotations were measured. A value for the initial observed rotation was obtained by a graphical extrapolation of the first several observations. A series of trial values for α_∞, the final observed rotation, were obtained from the initial graphs

of log (α_t - α_∞) against time, and were supplied to the ORACLE. For each trial value of α_∞ the ORACLE calculated a reaction rate constant and the standard error of fit which resulted from the use of that particular value of α_∞. The values for the standard error of fit were plotted against the trial values for α_∞. In all the cases, the curves obtained from these graphs passed through a minimum value. The α_∞ value at the minimum was used as the best estimation of the final rotation. The reaction rate which had been calculated for that value was used as the reaction rate of the reaction under the conditions of the study.

The results. The reaction rate constants and the carbon-14 data obtained by assaying the oxidation fragments of the reaction products are listed in Table 4.

It can be seen that l-X decomposed in acetic acid approximately five times faster than it decomposed in p-cymene at the same temperature. From the percentages of carbon-14 rearrangement, it appeared that the product which was formed with retention of configuration had undergone a constant amount of rearrangement of the chain label. The product of inverted configuration apparently exhibited an increase in the amount of rearrangement of the chain label with increase in temperature.

These preliminary studies were investigated more closely so that the stereochemical and radiochemical results of the decomposition could be used to clarify the mechanism of the decomposition of N-nitroso-N-acetyl-1,2,2-triphenylethylamine.

The Decomposition of Enantiomeric N-Nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14}

The thermal decomposition of (+)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (d-X) in the absence of a solvent. It was seen from the preliminary study of the decomposition of the N-nitroso derivative of (+)-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} [(2) Introduction] that the main product of the reaction was 1,2,2-triphenylethyl acetate which exhibited a rotation of the same sign as that shown by the reactant. In addition, rearrangement of the carbon-14 chain label had occurred. If the triphenylethyl system were considered analogous to the systems studied by Huisgen and White, the amine and the carbinol whose specific rotations were of similar sign must be of identical configuration. An investigation of the reaction was made to clarify the mechanism sufficiently to use the reaction as positive proof of the relationship of the configurations.

A dry, 250 ml. flask containing 3.0 g. (0.087 mole) of d-X was placed in an oil bath and was heated slowly until the temperature of the bath reached 94-95° when the solid decomposed explosively. The solid residue, 2.6 g., remaining in the flask was dissolved in ether and a small amount of unreacted (-)-N-acetyl-1,2,2-triphenylethylamine was filtered from the solution. The product was reduced with lithium aluminum hydride; the 1,2,2-triphenylethanol-1,2-C^{14} was dissolved in hexane and passed through a 12 in. column of chromatographic alumina. Elution of the column with hexane did not remove any material from the column. Elution of the column with ethanol removed the carbinol. An aliquot of the carbinol was removed and the specific rotation of the

sample was determined. The remaining carbinol was extracted with ten per cent solution of (+)-10-camphorsulfonic acid to remove any amine which might have been formed by reduction of the amide reactant. The carbinol was reacetylated with acetic anhydride in pyridine and the acetate was resolved by fractional crystallization from ethanol. A racemic fraction, a resolved fraction, and the partially racemic original fraction used to obtain the percentage of inversion of the reaction, were oxidized and degraded to benzophenone and benzoic acid; the 2,4-dinitrophenylhydrazones were assayed. The results are listed in Table 5.

The decomposition of (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (1-X) in benzene. A 250 ml. volumetric flask containing 2.5 g. (0.0072 mole) of (1-X) was filled with benzene. After three weeks the benzene was removed by evaporation and the residue was dissolved in ether. A small amount of unreacted amide was filtered from the solution. The product was reduced with lithium aluminum hydride and the carbinol was examined chromatographically on an alumina column. Since there was no olefinic material found, it was concluded that no elimination had occurred during the decomposition in the absence of solvent or in benzene. Any 1,2,2-triphenylethylene formed by an elimination reaction would have been removed from the alumina when it was washed with hexane.[6] An aliquot of the carbinol was removed and the percentage of inversion resulting from the reaction was determined from the specific rotation. The remaining carbinol was acetylated and resolved by fractional crystallization. The results of the carbon-14 rearrangement obtained from the assay of the 2,4-dinitrophenylhydrazones are listed in Table 5.

TABLE 5

RESULTS OF THE DECOMPOSITIONS OF ENANTIOMERIC N-NITROSO-N-ACETYL-1,2,2-TRIPHENYLETHYLAMINE-1-C^{14}

Exp.	Solvent	Temp. °C.	Per Cent Inversion	Per Cent C^{14} Rearrangement in Retained Product	Per Cent C^{14} Rearrangement in Inverted Product	Per Cent C^{14} Rearrangement in Racemic Product
1	None	94-5°	24.4	15.7	29.1	22.4
2	Benzene	23°	23	15.4	22.4	18.9
3	p-Cymene	34.7°	25,24			
4	Acetic acid	34.7°	29,30			
5	Acetic acid	40.5°	30,29.5,29	28.1	38.8	33.2
6	Acetic acid	47.7°	29,28.5	25.7	40.1	32.9
7	Acetic acid	59.0°	30.5	28.9	39.4	34.1

The decomposition of (+)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (d-X) in acetic acid at 59.0°. It was seen from the data obtained from the kinetic studies that the carbon-14 rearrangement in the product which possessed the same configuration as that of the reactant apparently remained constant while the extent of rearrangement in the product of inverted configuration increased as the temperature of the decomposition was increased. In order to verify this observation, the decomposition of 1.075 g. (0.003 mole) of d-X in 100 ml. of acetic acid was carried out at 59.0°. When racemic 1,2,2-triphenylethyl-1,2-C^{14} acetate (IX) was recovered, an inspection of the infrared spectrum which it produced showed that there was no amide [(-)-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (l-V)] present. A fraction was eventually obtained from the mother liquors which was believed to be pure (-)-1,2,2-triphenylethyl-1,2-C^{14} acetate (l-IX) but an examination of the infrared spectrum produced by this material showed that amide l-V was present. The presence of labeled reactant in the fractions which were oxidized and assayed would lead to serious discrepancies in the values for the carbon-14 rearrangement. The amide was removed by reducing the products of this experiment with lithium aluminum hydride and washing the ether extracts from the reduction with 0.03 N hydrochloric acid in order to remove any amine formed by the simultaneous reduction of the amide. The carbinol obtained by evaporating the ether from the purified solution was dissolved in 1:1 hexane-benzene mixture, and it was examined chromatographically. No olefinic material was found. The carbinol was acetylated and resolved in the usual fashion. The infrared spectra produced by the purified products were obtained before their

oxidation or assay to insure the complete removal of amide. The results reported in Table 5 showed that no increase in the carbon-14 rearrangement in the product of inverted configuration had occurred at this higher temperature. The trend which was observed in the results of the kinetic experiments (Table 4) was apparently caused by amide in the samples which were assayed.

The effect of 0.05 N hydrochloric acid on (-)-1,2,2-triphenylethanol (l-III). A sample of optically pure l-III, $\alpha]_D^{25^\circ} = -122^\circ$ (ethanol), was dissolved in ether and stirred vigorously with 10 ml. of 0.05 N hydrochloric acid for one hour. At the end of this time the ether layer was removed and the carbinol was recovered. The specific rotation of the carbinol, $\alpha]_D^{25^\circ} = -122^\circ$ (ethanol), showed that no racemization had occurred. In the purification procedure used for the products of the decompositions, the carbinols obtained by the reduction of the products were washed with dilute hydrochloric acid. It was, therefore, necessary to show that the carbinol retained its optical purity during this procedure.

The infrared spectrometric analysis of mixtures of 1,2,2-triphenylethyl acetate (XIII) and N-acetyl-1,2,2-triphenylethylamine (XIV). The preparation of enantiomeric N-nitroso-N-acetyl-1,2,2-triphenylethylamine from enantiomeric N-acetyl-1,2,2-triphenylethylamine resulted usually in a 70 to 90 per cent yield of the desired N-nitroso amide. This material decomposed when it was recrystallized so that only partial purification was possible. During the preparation of the N-nitroso amide, the precipitated product was washed with hexane and the more insoluble amide was left behind. However, unreacted amide which

dissolved in the hexane carried through the decompositions, as was seen when the products of the experiment in acetic acid at 59.0° (Table 5) were examined, and caused the radiochemical assays of the products to be inconsistent.

An inspection of the infrared spectra produced by pure XIII and XIV indicated that small amounts of the amide XIV could be detected in the presence of XIII. Samples of the acetate XIII containing 1.0, 2.0 and 5.0 per cent of the amide XIV were prepared by carefully grinding weighed samples of the compounds. Potassium bromide pellets of the mixtures were prepared and duplicate spectra were obtained for each mixture. A careful comparison of these spectra with the spectra of the pure compounds showed that the presence of 2.0 per cent of the amide could be detected by infrared spectroscopy. It was also noted that the melting points of all of these mixtures were identical with the melting point of the pure acetate, XIII, (m.p. 156-157°).

The decomposition of (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} (1-X) in acetic acid at 40.5° and at 47.7°. The decompositions of 1-X at 40.5° and 47.7° were repeated in order to check the results obtained from the kinetic experiments (Table 4). The products were purified as described in the experiment at 59.0°. The results were different from those previously obtained and are included in Table 5. The purity of the samples used in determining the carbon-14 rearrangement was established by examination of the infrared spectra produced by these samples.

The percentage of inversion produced in the decomposition of enantiomeric N-nitroso-N-acetyl-1,2,2-triphenylethylamine in acetic acid and in p-cymene. Reproducible values for the amount of inversion of configuration occurring during the decompositions were obtained and are included in Table 5. These values were determined by decomposing small, duplicate samples of the N-nitroso amide in the constant-temperature bath in the desired solvent and at the required temperature. When the decompositions were complete, the products were reduced with lithium aluminum hydride and extracted with dilute hydrochloric acid to purify them. Occasionally, after the reduction of the products and extraction with acid, a small amount of amide was detected when the carbinol was dissolved in hexane. The amide was considerably less soluble and was filtered from the solution. All the amide was removed by repeating this procedure for the samples showed no trace of amide when the infrared spectra which they produced were examined. The specific rotations of the dried carbinols were used in these experiments to determine the percentage of inversion during the course of the decompositions.

The Decomposition of Enantiomeric N-Nitroso-N-(acetyl-2-C^{14})-1,2,2-triphenylethylamine (d-XI and l-XI) in Acetic Acid at 40.5°

It was seen by comparing the reaction rate constants for the decomposition of the N-nitroso amide l-X in p-cymene at 34.7° and in acetic acid at 34.7° that the reaction proceeded approximately five times faster in acetic acid. The decomposition of d-XI and l-XI was carried out in order to determine the role of the acetic acid in the

reaction. Unlabeled 1,2,2-triphenylethylamine was resolved and separated into its enantiomers. The resolved amine was acetylated with labeled acetic anhydride and nitrosated with nitrosyl chloride. The N-nitroso amides thus prepared were decomposed in acetic acid and the extent of exchange with the solvent was measured by the change in the amount of carbon-14 in the products.

A solution of 2.12 g. (0.006 mole) of d-XI in 200 ml. of acetic acid was decomposed in the constant-temperature bath. The product resulting from the decomposition was fractionally crystallized and a racemic and a resolved fraction were obtained. The purity of these fractions was determined by examining the infrared spectra they produced after repeated recrystallization. The fractions were assayed and the amount of carbon-14 associated with the various fractions are listed in Table 6.

TABLE 6

RESULTS OF THE DECOMPOSITION OF ENANTIOMERIC N-NITROSO-N-(ACETYL-2-C^{14})-1,2,2-TRIPHENYLETHYLAMINE (d-XI AND l-XI) IN ACETIC ACID AT 40.5°

Enantiomer	Per Cent[a] Inversion	Per Cent C^{14} Retained Product	Per Cent C^{14} Inverted Product	Per Cent C^{14} Racemic Product
(+)	30	41.7	11.0	26.4
(-)	30	42.2	12.3	27.3

[a]Determined at this temperature by previous experiment (Table 5).

The experiment was repeated using the (-)-enantiomer, l-XI, and the results of this experiment, which duplicated those obtained from the decomposition of d-XI, are also listed in Table 6.

It was significant that the product exhibiting the same sign of rotation as the amide reactant was associated with a higher percentage of the labeled acetoxyl group. This indicated that in the triphenylethyl system, as in other studies by Huisgen and by White, the decomposition proceeded with predominant retention of configuration. In addition, the product exhibiting the same sign of rotation as that of the reactant must have had the same configuration as the reactant. Regardless of the mechanism of the decomposition, it was inconceivable that had the reaction proceeded with predominant inversion, the labeled acetoxyl group could have been available in sufficient quantity for the backside attack of the asymmetric center so that the major product formed could have contained the largest amount of the labeled acetoxyl group.

The Decomposition of Racemic N-Nitroso-N-(acetyl 2-C^{14})-1,2,2-triphenylethylamine (XI)

The decomposition in acetic acid at 34.5° and at 60.2°. Racemic N-(acetyl-2-C^{14})-1,2,2-triphenylethylamine (XI) was nitrosated and a 1.0 g. (0.003 mole) sample was dissolved in 100 ml. of acetic acid. The solution was placed in the constant-temperature bath which was set at 34.5°. The sample was removed after thirty hours. The bath was then set at 60.2° and another 1.0 g. sample, dissolved in 100 ml. of acetic acid, was placed in the bath. This sample was removed after twenty hours. The solvent was removed from both samples by evaporating it in

an air stream. The products, in both cases, were dissolved in ethanol, treated with Norit, filtered, and set aside to crystallize. The products were recrystallized three times, and then their infrared spectra were examined. The presence of a small amount of amide was detected in the samples. The material was recrystallized five additional times, and an examination of the spectra then showed that it was pure. The products from both decompositions were assayed and the results are listed in Table 7.

TABLE 7

RESULTS OF THE DECOMPOSITION OF RACEMIC N-NITROSO-N-(ACETYL-2-C^{14})-1,2,2-TRIPHENYL-ETHYLAMINE (XI) IN ACETIC ACID

Temperature	Mc. C^{14}/Mole in the Product	Per Cent C^{14} in the Product
34.5°	2.65 ± 0.005	32.5
40.5°	2.61 ± 0.01	31.8
50.5° with 5 equivalents of sodium acetate	2.55 ± 0.02	31.0
60.2°	2.36 ± 0.00	28.7

The decomposition in acetic acid at 40.5°. A 1.0 g. (0.003 mole) sample of the N-nitroso amide prepared for the previous experiment was dissolved in 100 ml. of acetic acid and was placed in the constant-temperature bath at 40.5°. The sample was removed after thirty hours and was purified as described in the experiments at 34.5° and at 60.2°.

The results are included in Table 7.

The decomposition in acetic acid at 40.5° in the presence of added sodium acetate. A 2.0 g. (0.006 mole) sample of the N-nitroso amide prepared for the previous experiments was dissolved in 200 ml. of acetic acid which contained 2.4 g. (0.03 mole) of sodium acetate. The solution was placed in the constant-temperature bath at the same time as the sample which did not contain sodium acetate. Both samples were removed after thirty hours. After the acetic acid was evaporated, this sample was washed several times with water to remove the sodium acetate. It was then purified in the manner previously described. The results of the assay of the purified product are included in Table 7.

The Preparation of the Reactants

Enantiomeric N-acetyl-1,2,2-triphenylethylamine-1-C^{14}. Eight grams (0.029 mole) of pure (-)-1,2,2-triphenylethylamine-1-C^{14}, $\alpha]_D^{25^\circ} = -73^\circ$ (ethanol), were dissolved in 100 ml. of pyridine, and 100 ml. of acetic anhydride were added. The mixture was heated on the steam bath for four hours and then was poured into 200 g. of cracked ice. The cold, aqueous mixture was filtered and the white solid which had precipitated was washed repeatedly with cold water. This product amounted to 9.0 g. (97 per cent) after one recrystallization from ethanol, m.p. 230-231°, $\alpha]_D^{25^\circ} = -106^\circ$ (dioxane) or -73° (chloroform), radiochemical assay 7.07 ± 0.01 mc. C^{14}/mole.

Enantiomeric (+)-amide was prepared in the same manner. Seven grams (0.026 mole) of pure (-)-amine, $\alpha]_D^{25^\circ} = +73^\circ$ (ethanol), yielded 7.0 g. (86 per cent) of amide, m.p. 230-231°, $\alpha]_D^{25^\circ} = +109^\circ$ (dioxane)

or +74° (chloroform), radiochemical assay 7.07 ± 0.03 mc. C^{14}/mole.

Enantiomeric N-(acetyl-2-C^{14})-1,2,2-triphenylethylamine. A mixture of 5.7 g. (0.07 mole) of freshly fused sodium acetate-2-C^{14} and 5.5 g. (0.07 mole) of acetyl chloride was stirred vigorously for two hours in a flask connected to a water-cooled reflux condenser. At the end of this time, 3.7 g. (0.014 mole) of (-)-1,2,2-triphenylethylamine, $\alpha]_D^{25°}$ = -72° (ethanol), dissolved in 15 ml. of pyridine, were added to the mixture. After twenty-four hours, the reaction slurry was poured into 200 g. of cracked ice and the precipitated amide was removed by filtration. The crude product, 4.7 g., was dissolved in ethanol, filtered through a Norit pad, and recrystallized, $\alpha]_D^{25°}$ = -105° (dioxane), radiochemical assay 8.03 ± 0.04 mc. C^{14}/mole.

The enantiomeric amide was similarly prepared from a mixture of 5.7 g. (0.07 mole) of fused and ground sodium acetate-2-C^{14} and 5.5 g. (0.07 mole) of acetyl chloride to which was added a solution containing 2.4 g. (0.009 mole) of (+)-amine, $\alpha]_D^{25°}$ = +73° (ethanol), in 15 ml. of pyridine. The yield of the product was 2.9 g. (92 per cent), $\alpha]_D^{25°}$ = +107° (dioxane), +74° (chloroform), radiochemical assay 7.94 ± 0.02 mc. C^{14}/mole.

Enantiomeric N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} and enantiomeric N-nitroso-N-(acetyl-2-C^{14})-1,2,2-triphenylethylamine. All of the N-nitroso amides used during the course of this research were prepared by an adaptation of the method of France, Heilbron and Hey.[72]

A solution containing 3.07 g. (0.01 mole) of (-)-N-acetyl-1,2,2-triphenylethylamine-1-C^{14}, $\alpha]_D^{25°}$ = -105° (dioxane), radiochemical

assay 7.07 ± 0.01 mc. C^{14}/mole, in 30 ml. of dry pyridine (dried over calcium sulfate) was cooled to 10-15°. To this solution were added 25 ml. of dry pyridine through which nitrosyl chloride (obtained from the Matheson Company, Carlstadt, N. J.) had been bubbled for ten minutes. The addition was done dropwise and with vigorous stirring. A second portion of dry pyridine (20 ml.) similarly saturated with nitrosyl chloride was also added dropwise and with stirring. The pyridine through which the nitrosyl chloride was bubbled was cooled in an ice-salt bath. After the addition of both portions of pyridine-nitrosyl chloride, the reaction mixture was stirred for fifteen minutes in an ice bath and then for fifteen minutes at room temperature. The reaction slurry was slowly poured over 500 g. of ice, with stirring; the bright yellow-colored solid was filtered and washed with cold water. The solid was air-dried for several hours to remove most of the water, then it was washed with six 50 ml. portions of hexane. The washings were dried with anhydrous magnesium sulfate, filtered, and placed in an ice bath. The hexane was evaporated from the solution in an air stream, and the material recovered amounted to 2.9 g. (85 per cent), m.p. with decomposition 110-114°, $\alpha]_D^{25^\circ} = -324^\circ$ (benzene). During the course of the preparation, considerable care was taken to exclude moisture from the solutions and apparatus. After bubbling the nitrosyl chloride through the dry pyridine solutions for approximately ten minutes, the pyridine became saturated as evidenced by the dense, white fumes which began to escape from the solutions.

Elemental analysis of this material was provided by Galbraith Analytical Laboratory, Knoxville, Tennessee. For $C_{22}H_{20}N_2O_3$, the calculated percentages were: C, 76.72; H, 5.85; N, 8.14; the

percentages found were: C, 79.80, 79.62; H, 6.07, 6.25; N, 6.41, 6.46. The product was assayed in order to determine the approximate purity. The molecular weight values obtained from the assays are listed in Table 8.

TABLE 8

MOLECULAR WEIGHT OF (+)-N-NITROSO-N-ACETYL-1,2,2-TRIPHENYLETHYLAMINE-1-C^{14}

Date of Assay	M. W. Found
11-7-58	348.2
11-7-58	340.8
11-14-58	344.5
11-14-58	341.3
11-14-58	344.0

Molecular weight calculated, 344.4

Average molecular weight found, 343.8 $\pm$ 1.3

The elemental analysis indicated that the N-nitroso amide was not pure, and changes in the optical rotations indicated that any attempt to purify the material by recrystallization resulted in further decomposition. Since the molecular weight of the contaminating amide was 316.4, the molecular weight determinations could not be relied upon for an accurate estimation of the purity of the sample.

The enantiomeric (-)-N-nitroso amide was prepared from 3.0 g. (0.01 mole) of (+)-N-acetyl-1,2,2-triphenylethylamine-1-C^{14}, $\alpha]_D^{25^\circ}$ = +109°(dioxane), radiochemical assay 7.07 $\pm$ 0.03 mc. C^{14}/mole. It was nitrosated as described above, and the hexane washings contained 3.15 g.

(96 per cent) of the yellow derivative, m.p. 112-118° with decomposition, $\alpha]_{D}^{25^{\circ}} = -320^{\circ}$ (benzene).

The nitrosation was repeated many times. The yields of the crude product varied from 70 to 98 per cent and seemed to depend upon the amount of water present and the length of time the reaction mixtures were stirred after the pyridine-nitrosyl chloride solutions were added. Usually the nitrosyl chloride was partially dried by bubbling it through three inches of 85 per cent phosphoric acid before it was added to the pyridine. After thirty minutes' stirring, the reaction mixture was poured into cracked ice; further stirring resulted in the decomposition of the product.

It should be noted that the N-nitroso amide produced by the nitrosation of optically pure (-)-N-acetyl-1,2,2-triphenylethylamine exhibited a specific rotation which had a positive sign, (+). Amide of (+) specific rotation produced N-nitroso amide of (-) specific rotation. The difference in the signs of rotation was the basis for the use of optical rotations to determine the kinetics of the decompositions.

Conclusions

From the data in Tables 2 through 7, it can be seen that certain startling similarities exist between the decomposition of N-nitroso-N-acetyl-1,2,2-triphenylethylamine and the deamination of 1,2,2-triphenylethylamine in acetic acid: (1) the stereochemical results of both reactions are identical; (2) the inverted product resulting from each reaction exhibits more carbon-14 rearrangement than does the product of retained configuration.

Since the open carbonium-ion nature of the deamination of 1,2,2-triphenylethylamine in aqueous media has been clearly demonstrated,[6] and since the present work confirms this mechanism for the deamination in acetic acid, it seems possible that the mechanisms in acetic acid of both the decomposition and the deamination reactions are the same. If this mechanism is applied to the decomposition of (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine, the reaction paths can be illustrated as shown in Chart 1. This representation of the mechanism implies that the products (A and B) associated with retention of the labeled acetoxyl group were formed by the collapse of the initially formed ion pairs. The small amount of material of inverted configuration which was associated with the labeled acetoxyl group is explained by the presence of a small amount of N-nitroso-N-acetyl-1,2,2-triphenylethylamine reactant in a less-preferred conformation. While it is certainly probable that the preferred rotational isomer for 1,2,2-triphenylethyl derivatives is the one in which the phenyl groups are spaced at a maximum possible distance, or in which they are <u>trans</u>, the existence of small amounts of less-favorable rotational isomers, in which the phenyl groups are <u>cis</u> is certainly to be expected.[15] An attempt was made to prove that rearrangement accompanied retention of the labeled acetoxyl group. A material balance was established, using this mechanism, and assuming that products A and B were formed in equal amounts. However, it was equally possible to maintain a material balance assuming that B was not formed; that is, that no chain-labeled rearrangement occurred simultaneously with formation of product which retained its labeled acetoxyl group.

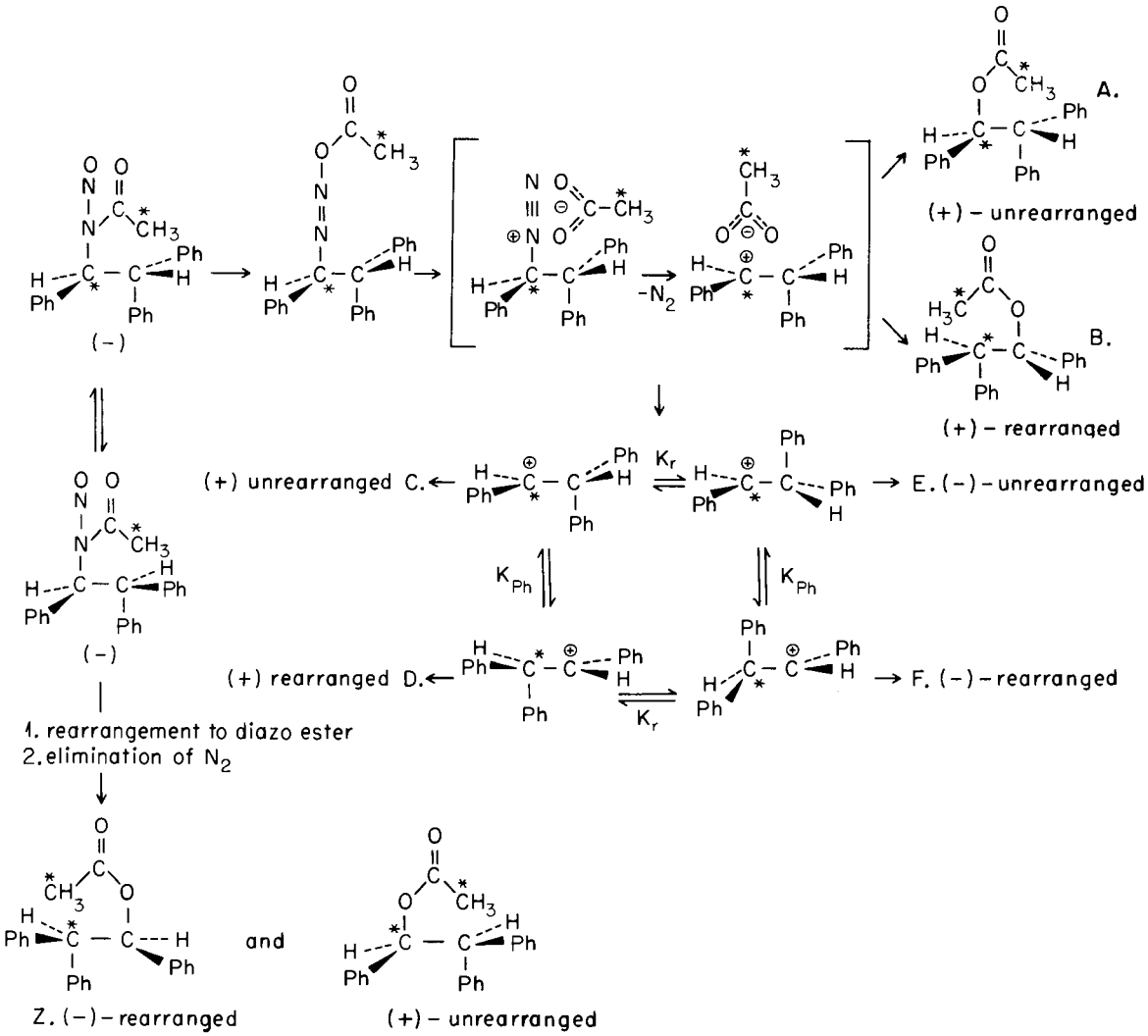


CHART 1. A POSSIBLE MECHANISM FOR THE DECOMPOSITION OF (-)-N-NITROSO-N-(ACETYL-2-C^{14})-1,2,2-TRIPHENYLETHYLAMINE-1-C^{14}.

Using the data in Tables 5 and 6 it can be shown that,

Average amount of retention	= 0.706.
Average amount of inversion	= 0.294.
Product of retained configuration which also retained the labeled acetoxyl group	= (0.419)(0.706) = 0.296.
Product of inverted configuration which retained the labeled acetoxyl group	= (0.116)(0.294) = 0.0342.
Product of retained configuration which lost the labeled acetoxyl group	= (0.706)-(0.296) = 0.41.
Product of inverted configuration which lost the labeled acetoxyl group	= (0.294)-(0.034) = 0.26.
Average amount of rearrangement of the chain label in the product of retained configuration	= 0.276.
Average amount of rearrangement of the chain label in the product of inverted configuration	= 0.394.
Total amount of product of retained configuration which underwent rearrangement of the chain label	= (0.706)(0.276) = 0.195.
Total amount of product of inverted configuration which underwent rearrangement of the chain label	= (0.294)(0.394) = 0.116.

Referring to the reaction chart, and assuming that A and B were formed in equal amounts, it was calculated that:

A + B + C + D = 0.706, product of retained configuration,

A + B = 0.296/2 = 0.148,

C + D = 0.41, product of retained configuration which had retained the labeled acetoxyl group,

B + D = 0.195, product of retained configuration which had undergone rearrangement of the chain label,

$D = 0.195 - 0.148 = 0.047,$

$C = 0.41 - 0.047 = 0.363,$

$E + F + Z = 0.294$, product of inverted configuration,

$Z = 0.034$, product of inverted configuration which had retained the labeled acetoxyl group,

$E + F = 0.260$, product of inverted configuration which had lost the labeled acetoxyl group,

$F + Z = 0.116$, product of inverted configuration which had undergone rearrangement of the chain label,

$F = 0.082,$

and $E = 0.178.$

The material balance for this case was:

$A = 0.148$

$B = 0.148$

$C = 0.363$

$D = 0.047$

$E = 0.178$

$F = 0.082$

$Z = \underline{0.034}$

1.000

A similar balance was arrived at if it were assumed that B was not formed, that is, that none of the product which possessed the same configuration as the reactant, retained the labeled acetoxyl group and underwent simultaneous chain-label rearrangement:

$$
\begin{aligned}
A &= 0.296 \\
B &= 0.000 \\
C &= 0.215 \\
D &= 0.195 \\
E &= 0.178 \\
F &= 0.082 \\
Z &= \underline{0.034} \\
& \quad 1.000.
\end{aligned}
$$

Since a material balance is possible in both of these cases, it was not possible to associate rearrangement of the chain label with retention of the labeled acetoxyl group. If such a connection were established, the intervention of a cyclic mechanism could be excluded, at least to the extent that this association was possible.

If the assumption were made that B was produced to the complete exclusion of A, the material balance was completely upset, and a negative value resulted for the amount of product D. If a cyclic mechanism were operating exclusively, the production of B with complete exclusion of A might be possible.

The amount of retention and the amount of carbon-14 rearrangement in the products of the decomposition of the N-nitroso amide in acetic acid were constant at the different temperatures at which the N-nitroso amide was decomposed. In addition, in the case of the racemic compound (Table 7), there was very little change in the amount of acetoxyl label which was retained at different temperatures, and no change when sodium acetate was added. Deaminations of amines with nitrous acid show no such independence of results from the reaction

conditions. Ott[73] has shown that radical change in the steric results accompanied the deamination of α-phenylethylamine when the solvent was changed from glacial acetic acid to acetic acid with increasing amounts of water to aqueous acetic acid with added sodium acetate. The results reported[6] on the amount of rearrangement of the carbon-14 in the products of the nitrous-acid deamination of 1,2,2-triphenylethylamine-1-C^{14} in aqueous media at 37° and at 25° showed that the extent of rearrangement changed at the higher temperature.

The small differences in the total amount of carbon-14 rearrangement in the products of the deamination of 1,2,2-triphenylethylamine-1-C^{14} and the decomposition of N-nitroso-N-acetyl-1,2,2-triphenylethylamine-1-C^{14} can be accounted for by the change in basicity of the solutions during the deamination as a result of adding potassium nitrite. The change in basicity might also be expected to change the stereochemical results of the reaction, however, it has been shown that the ratio of the rate of rotation about the carbon-carbon bond to the rate of phenyl migration, in the 1,2,2-triphenylethyl system, is approximately two to one.[74] It is therefore expected that the amount of retention of configuration would be much less affected by the presence of an increased amount of acetoxyl ion than would the amount of carbon-14 rearrangement.

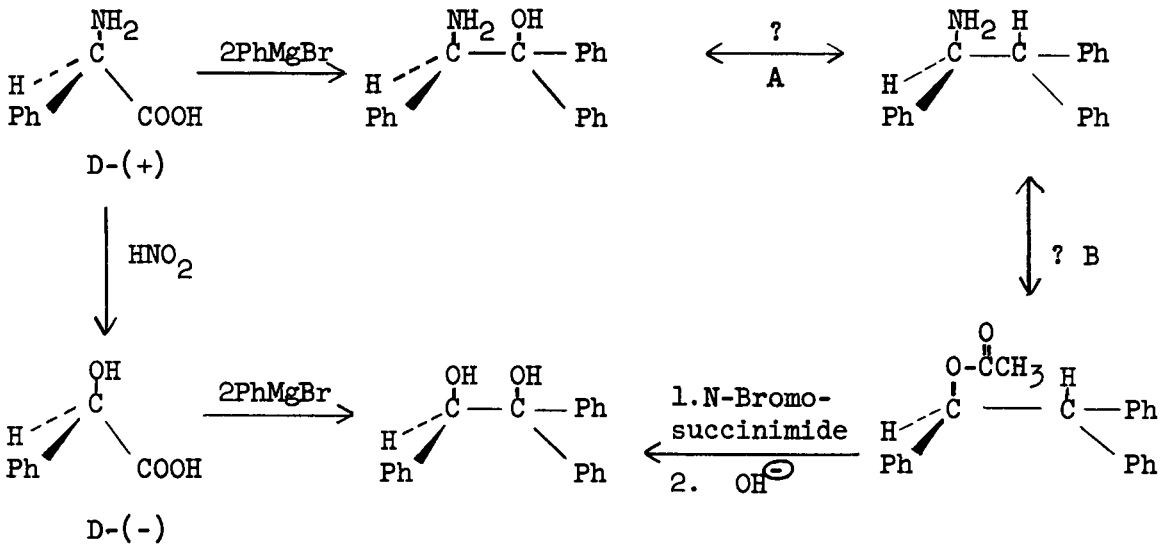
An important step in proving the similarity of the mechanism of the deamination of 1,2,2-triphenylethylamine and the decomposition of N-nitroso-N-acetyl-1,2,2-triphenylethylamine in acetic acid would be accomplished if it is possible to perform the deamination under conditions which can be duplicated in the decomposition of the N-nitroso

amide. It was felt that this problem was beyond the scope of the present work. An additional important experiment which was suggested by these results is the decomposition of a different amide in acetic acid. For example, the decomposition of optically active N-nitroso-N-benzoyl-1,2,2-triphenylethylamine in acetic acid should produce both 1,2,2-triphenylethyl acetate and 1,2,2-triphenylethyl benzoate. The separation of these products and the determination of the chain-label rearrangement will answer the question as to whether rearrangement of the chain label occurs simultaneously with retention of the benzoyl group. A double labeling experiment may be necessary before a decision can be reached between an ion-pair mechanism and a concerted, cyclic mechanism. The use of double labeling in the study of the deamination of 1,2,2-triphenylethylamine[6] in aqueous media enabled the investigators to rule out the intervention of bridged ions as the cause of the retention of configuration which accompanied the reaction.

CHAPTER V

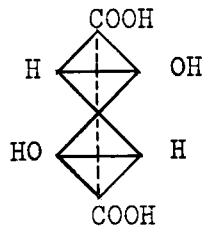
THE ABSOLUTE CONFIGURATIONS OF 1,2,2-TRIPHENYLETHYLAMINE AND 1,2,2-TRIPHENYLETHANOL

At the time the present research was begun, a scheme for the chemical relation of the configurations of 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol had been worked out.[75] This scheme involved relating the amine, the acetate of the carbinol, and 1,2,2-triphenylethylene glycol to (-)-mandelic acid, and can be illustrated by the following series of reactions:



Several attempts to complete the cycle had been made prior to the present work, and the (+)-carbinol had been successfully related to (-)-mandelic acid by converting (+)-1,2,2-triphenylethyl acetate to

1,2,2-triphenylethylene glycol.[75] Attempts to convert the amine to the amino alcohol (Reaction A) were not successful, however. In the course of the present work, an attempt was made to provide the missing link by converting the amino alcohol into the amine (Reaction A) but this was similarly unsuccessful. The investigation of the decomposition of optically active N-nitroso-N-acetyl-1,2,2-triphenylethylamine proved that 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol which exhibited the same sign of optical rotation had the same configurations. This relationship made it possible to complete a cycle of reactions and to relate both compounds to (-)-mandelic acid through optically active 1,2,2-triphenylethylene glycol (Chart 2). Once the configurations of the triphenylethyl derivatives had been related to (-)-mandelic acid, it became possible to designate the absolute configurations of these derivatives. The determination of the absolute configuration of optically active molecules through the use of anomolous X-ray scattering techniques was described first by Bijvoet, in 1949.[76-78] Very soon after, he established the absolute configuration of sodium rubidium tartrate[78,80] by using K $\underline{\alpha}$ X-rays to excite the rubidium atoms, and thus demonstrated that E. Fischer's convention of assigning the D configuration to dextro-rotatory tartaric acid[81] was fortunately correct. This significant work makes it possible to determine the absolute configuration of any compound which can be related to tartaric acid.



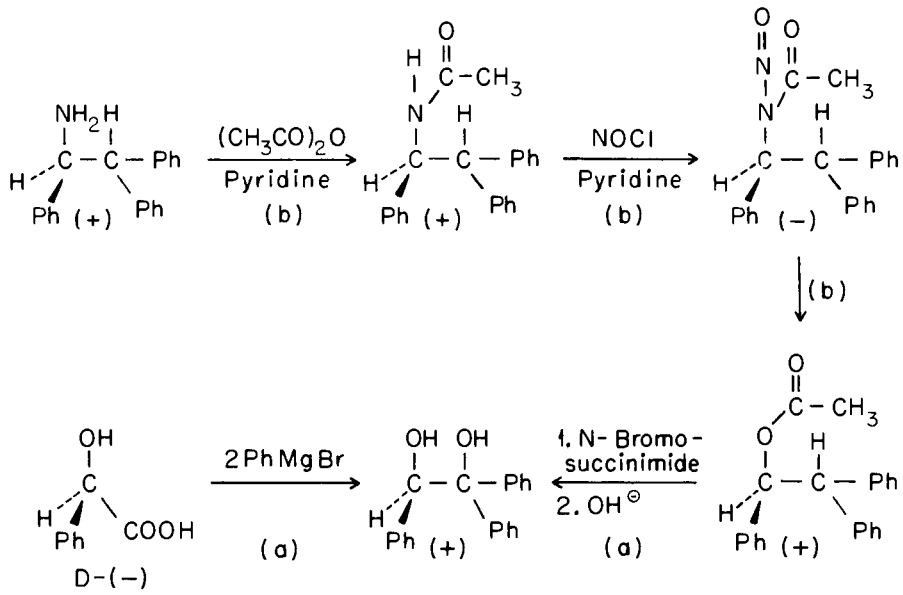


CHART 2. THE CHEMICAL RELATIONSHIP BETWEEN (+)-1,2,2-TRIPHENYLETHYL COMPOUNDS AND D-(-)-MANDELIC ACID

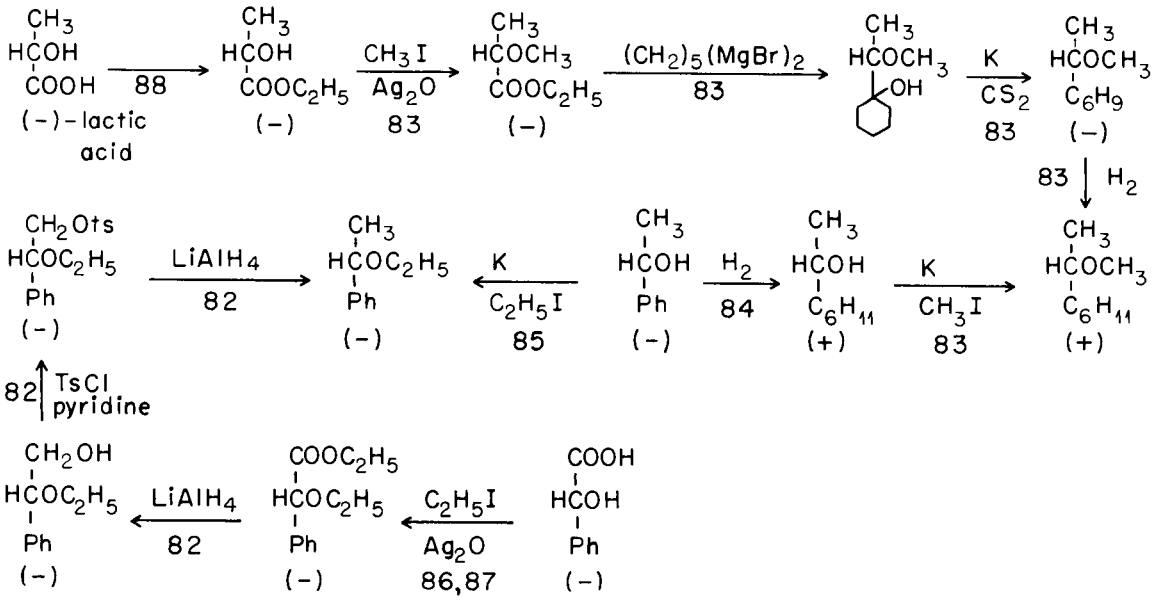


CHART 3. THE CHEMICAL RELATIONSHIP BETWEEN D-(-)-MANDELIC ACID AND D-(-)-LACTIC ACID

The configuration of (-)-mandelic acid has been related to the configuration of (-)-lactic acid by Mislow[82] who converted the acid into (-)-ethyl-α-methylbenzyl ether. Mislow correlated his research with that which was reported in the literature,[83-88] thus completing a series of reactions which established the relationship (Chart 3). The relationship between (-)-lactic acid and (+)-glyceraldehyde has been established by Freudenberg[89] and (+)-glyceraldehyde has been related to (+)-tartaric acid through the work of several investigators (Chart 4). It follows from these relationships that (+)-1,2,2-triphenylethyl acetate, (+)-1,2,2-triphenylethanol, (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine, (+)-N-acetyl-1,2,2-triphenylethylamine and (+)-1,2,2-triphenylethylamine are all members of the D series of optically active organic molecules. It is interesting that (+)-tartaric acid has been related to both (+)-glyceraldehyde and to (-)-glyceraldehyde. The first relationship was shown in Chart 4. The second relationship was established by Wohl and Momber[93,94] and is illustrated in Chart 5. The confusion arose because the configuration of the bottom carbon atom, in the tartaric acid diagram, was related to D-(+)-glyceraldehyde in the reactions of Chart 5, which reverses the conventions necessary for the interpretation of these molecules by plane projections.[95] In Chart 4, the configuration of the top carbon atom was related to D-(+)-glyceraldehyde.

A system for specifying the configuration of organic molecules has been proposed by Cahn, Ingold and Prelog.[96,97] The advent of absolute configurations has made it possible to express the configuration of asymmetric carbon atoms without relying on genetic connections

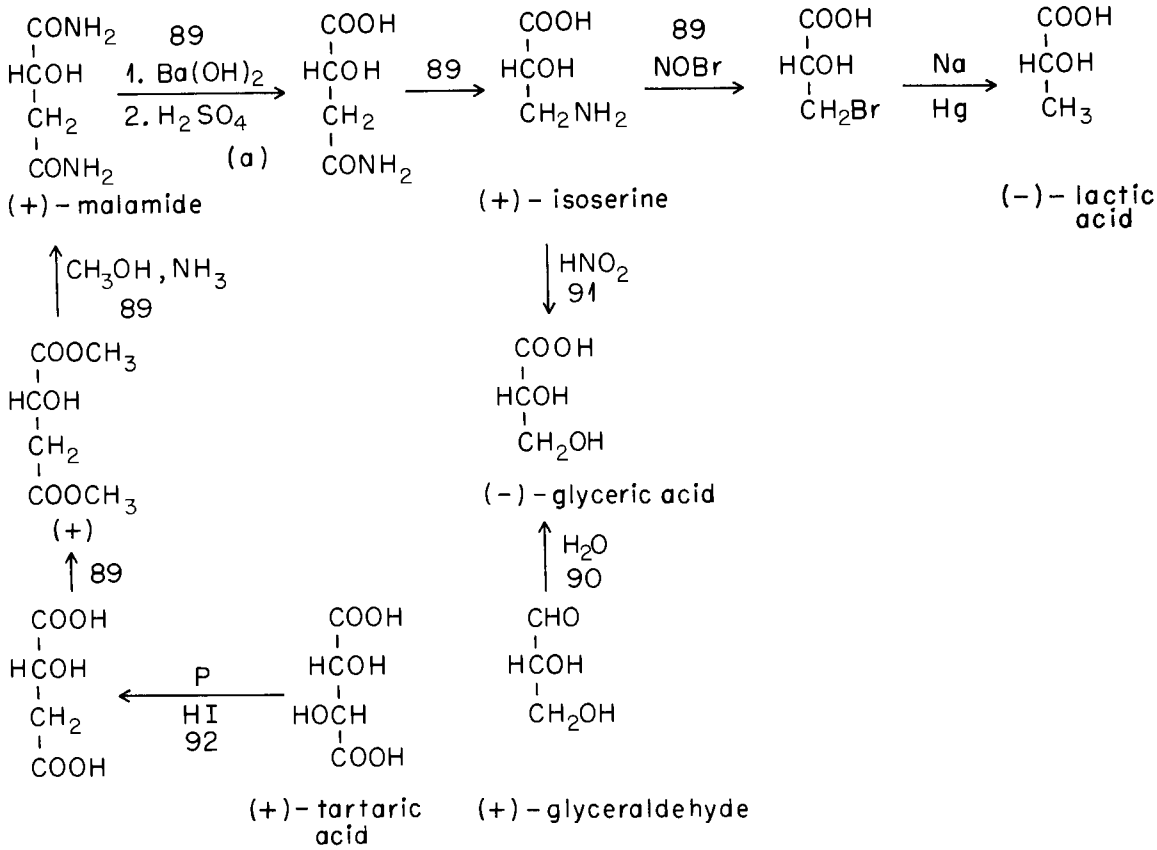


CHART 4. THE CHEMICAL RELATIONSHIP BETWEEN D-(-)-LACTIC ACID, D-(+)-GLYCERALDEHYDE AND D-(+)-TARTARIC ACID

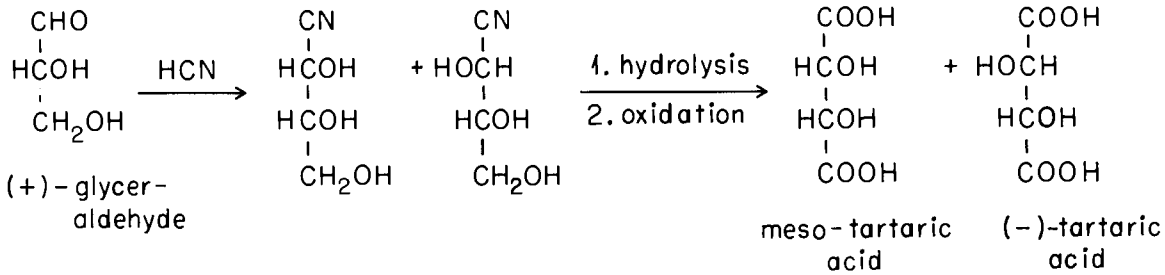


CHART 5. THE APPARENT CHEMICAL RELATIONSHIP BETWEEN (-)-TARTARIC ACID AND D-(+)-GLYCERALDEHYDE

and conventions. The authors of this system cite tartaric acid as an example of the confusion which results when genetic assumptions are introduced in the designation of configurations. Their system, which involves ordering the groups attached to the asymmetric center in order of decreasing or increasing atomic number, was applied to the derivatives in the 1,2,2-triphenylethyl system. The following compounds were designated S (sinister): (+)-1,2,2-triphenylethylamine, (+)-N-acetyl-1,2,2-triphenylethylamine, (-)-N-nitroso-N-acetyl-1,2,2-triphenylethylamine, (+)-1,2,2-triphenylethanol, and (+)-1,2,2-triphenylethyl acetate. The other member of the series was designated R (rectus), (+)-1,2,2-triphenylethylene glycol.

CHAPTER VI

SUMMARY AND CONCLUSIONS

The research described in these pages was directed toward the completion of two objectives. The first objective was to determine the relationship of the configurations of optically active 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol. The second objective was to establish the absolute configurations of the compounds of the 1,2,2-triphenylethyl system.

The first objective was successfully completed by chemically relating the configurations of the amine and the carbinol through the decomposition of optically pure N-nitroso-N-acetyl-1,2,2-triphenylethylamine in acetic acid. The decomposition of optically active N-nitroso amides has been previously shown to produce esters which possess the same configuration as the amide reactants. The product of the decomposition of optically pure N-nitroso-N-acetyl-1,2,2-triphenylethylamine was optically active 1,2,2-triphenylethyl acetate which exhibited the same sign of rotation as the amide reactant, indicating that N-acetyl-12,2-triphenylethylamine and 1,2,2-triphenylethyl acetate (and by direct consequence, 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol) which exhibited the same sign of rotation had the same configurations. In the decomposition of optically pure N-nitroso-N-(acetyl-2-C^{14})-1,2,2-triphenylethylamine, the product exhibiting the same sign of rotation as the amide reactant also possessed the greatest

amount of the labeled acetoxyl group. This was final and complete proof that 1,2,2-triphenylethylamine and 1,2,2-triphenylethanol of like sign of rotation were of like configuration.

The second objective of this research was successfully completed by establishing that the absolute configurations of (+)-1,2,2-triphenylethylamine and (+)-1,2,2-triphenylethanol are designated as D. This was determined by the relationship of these compounds to (+)-1,2,2-triphenylethylene glycol which had been related to D-(-)-mandelic acid. The generic relation between D-(-)-mandelic acid, D-(-)-lactic acid, D-(+)-glyceraldehyde and D-(+)-tartaric acid were shown. The absolute configurations of the compounds of the 1,2,2-triphenylethyl system were also expressed in the terminology of Cahn, Ingold and Prelog.

In addition to the successful achievement of the objectives originally established, studies of the kinetics and mechanism of the N-nitroso amide decomposition in acetic acid, and the deamination of the amine in acetic acid were made. These studies have pointed out important similarities in the two reactions, and they have indicated certain decisive experiments which should help to clarify the much-disputed mechanisms of these reactions.

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