Electrophilic Substitution at Saturated Carbon. XXVII. Carbanions as Intermediates in the Base-Catalyzed Methylene–Azomethine Rearrangement[1,2]

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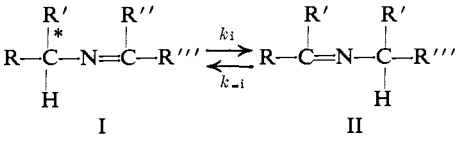
Abstract: The base-catalyzed methylene–azomethine rearrangement has been studied in the di-*p*-chlorophenylmethylene-α-phenylethylamine (V) and N-(α-methylbenzylidene)-*p,p'*-dichlorobenzhydrylamine (VI) systems in dioxane–ethylene glycol-O-*d* (potassium ethylene glycoxide) and in *t*-butyl alcohol-O-*d* (potassium *t*-butoxide). At equilibrium in *t*-butyl alcohol, V/VI was about unity at 75°. In the rearrangement of V to VI in ethylene glycol-O-d_2 at low conversion, recovered V showed no loss in optical activity and no deuterium incorporation. In the rearrangement of VI to V at low conversion in both media, recovered VI showed high deuterium incorporation. The latter fact excludes the concerted (one-stage) mechanism for prototropy advanced over 2 decades ago for the methylene–azomethine rearrangement in similar systems. The data are consistent with a mechanism that involves formation of an azaallylic anion which is protonated much faster at the benzhydryl than at the benzyl position. Such a mechanism brings into conformity the base-catalyzed methylene–azomethine and the allylic rearrangement of olefins.

The vast literature on the mechanism of the base-catalyzed methylene–azomethine rearrangement[4] embraces the study of a large variety of systems, only a few of which will be discussed here. Ingold and Wilson[4j,l] in studies of the rates of isomerization and racemization of the two optically active imines Ia and Ib observed that the rate constants for isomerization k_i and racemization (k_α) were equal in ethanol–sodium ethoxide.

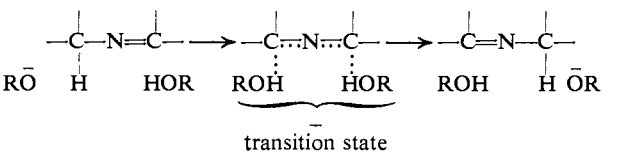


I II

	R	R′	R″	R‴
a	C_6H_5	CH_3	C_6H_5	*p*-ClC_6H_4
b	C_6H_5	CH_3	C_6H_5	C_6H_5
c	*p*-$C_6H_5C_6H_4$	C_6H_5	C_6H_5	H

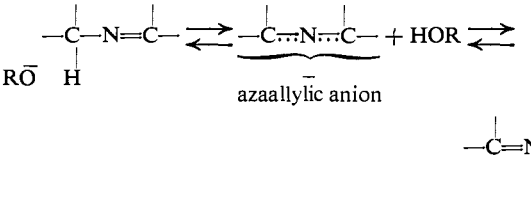
Two mechanisms were envisioned, one of which was one stage and involved no intermediates, the other of which was two stage and involved an azaallylic anion as intermediate. If the two-stage mechanism applied, then the anionic intermediate had to protonate much

One-stage or concerted mechanism



transition state

Two-stage or anionic mechanism



azaallylic anion

faster at the *benzhydryl* than at the benzyl position if $k_e = k_\alpha$. In an attempt to differentiate these two mechanisms, the isomerization of Ic in dioxane–ethanol–sodium ethoxide was examined.[4m] This compound met the requirements of the experiment with one unfortunate exception: it lacked the methyl group present in its predecessors. Again, the rates of isomerization and racemization were found to be equal. Should the two-stage mechanism operate, protonation would have had to occur essentially exclusively at the *benzyl position* in this system. These results were interpreted as being in conflict with the two-stage mechanism, and the one-stage mechanism was accepted.

Later, DeSalas and Wilson[4p] questioned this conclusion as a result of their study of the isomerization of III to IV and the reverse reaction in deuterated ethanol–sodium ethoxide. These authors observed that the rate of isotopic exchange of IV exceeded the rate for isomerization, and that the rate of isomerization of III exceeded the rate of isotopic exchange of the system as a whole. These results are inconsistent with the concerted mechanism.

Ossorio and Hughes[4o] repeated the isomerization of Ic in dioxane–deuterated ethanol–sodium ethoxide and found that for low conversions the racemization and isotopic exchange rates of the system as a whole

(1) This research was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research Grant No. AF-AFOSR-124-65.

(2) Some of the results and the main conclusions of this paper were reported in preliminary form: D. J. Cram and R. D. Guthrie, *J. Am. Chem. Soc.*, **87**, 397 (1965).

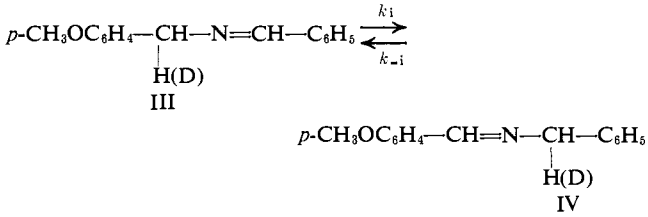
(3) National Science Foundation Postdoctoral Fellow.

(4) (a) R. P. Ossorio and F. G. Herrera, *Anales Real Soc. Espan. Fis. Quim.* (Madrid), **50B**, 875 (1954); (b) R. P. Ossorio, F. G. Herrera, and A. Hildalgo, *ibid.*, **52B**, 123 (1956); (c) R. P. Ossorio, J. M. Gamboa, and R. M. Utrilla, *ibid.*, **53B**, 17 (1956); (d) R. P. Ossorio and A. Alemany, *ibid.*, **54B**, 471 (1958); (e) R. P. Ossorio, F. G. Herrera, R. M. Utrilla, A. Hidalgo, and J. M. Gamboa, *ibid.*, **54B**, 481 (1958); (f) R. M. Utrilla, *ibid.*, **54B**, 487 (1958); (g) F. G. Herrera and A. Hidalgo, *ibid.*, **55B**, 617 (1959); (h) F. G. Herrera, *ibid.*, **56B**, 909 (1960); (i) R. P. Ossorio and V. S. Del Olmo, *ibid.*, **56B**, 915 (1960); (j) C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 1493 (1933); (k) C. W. Shoppee, *ibid.*, 1225 (1931); (l) C. K. Ingold and C. L. Wilson, *ibid.*, 93 (1934); (m) S. K. Hsii, C. K. Ingold, and C. L. Wilson, *ibid.*, 1778 (1935); (n) F. G. Baddar and Z. Iskander, *ibid.*, 203 (1954); (o) R. P. Ossorio and E. D. Hughes, *ibid.*, 426 (1952); (p) E. DeSalas and C. L. Wilson, *ibid.*, 319 (1938).

Table I. Base-Catalyzed Isomerization, Racemization, and Exchange of Di-*p*-chlorophenylmethylene-α-phenylethylamine (V) and N-(α-Methylbenzylidene)-*p,p'*-dichlorobenzhydrylamine (VI)

Run no.	Substrate Compd	Substrate Concn, *M*	Solvent	Base Nature	Base *M*	Temp, C°	Time, sec × 10^{-4}	% yield	% isotope, exchange[k]
1[a]	V	0.18	50% diox–50% EG-OD[b]	EGOK	0.22[b]	100	3.55	5 ± 3[c]	0[d]
2	V	0.19	50% diox–50% EG-OD[b]	EGOK	0.22[b]	100	8.73	9 ± 5[c]	0[d]
3	VI	0.17	50% diox–50% EG-OD[b]	EGOK	0.22[b]	100	4.64	5[e]	95[f]
4	V	0.29	*t*-BuOH	*t*-BuOK	0.43	75	29.5	49[g]	...
5	VI	0.29	*t*-BuOH	*t*-BuOK	0.43	75	26.0	52[g]	...
6	V	0.26	*t*-BuOD	*t*-BuOK	0.078	75	4.02	8[g]	0[d]
7[h]	V	0.20	*t*-BuOD	*t*-BuOK	0.078	75	8.48	17[g]	0[d]
8	VI	0.28	*t*-BuOD	*t*-BuOK	0.078	75	0.360	3[i]	38[j]

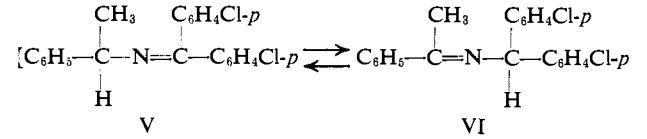
[a] Recovered starting material was hydrolyzed to α-phenylethylamine, which was 2.8 ± 2% racemized. [b] Preparted by mixing one part by volume of dioxane with one partb y volume of 0.44 *N* potassium glycoxide-O-*d* in ethylene glycol-O-*d*. [c] Determined by nmr with anisole as internal standard. [d] Determined by nmr intensity measurements on recovered α-phenylethylamine. [e] Based on actual yield of *p,p'*-dichlorobenzhydrylamine obtained upon hydrolysis of reaction product. [f] Determined by nmr intensity measurements of benzhydryl position of recovered VI. [g] Procedure C of Experimental Section with *p*-methoxyacetophenone as internal standard in vpc analysis. [h] The *p,p'*-dichlorobenzhydrylamine recovered by hydrolysis of the reaction mixture was found by nmr analysis to have only 0.50 proton at the benzhydryl position. [i] Procedure C of Experimental Section with *p,p'*-dimethoxybenzophenone as an internal standard in vpc analysis. [j] Based on combustion and falling-drop deuterium analysis of *p,p'*-dichlorobenzhydrylamine obtained by hydrolysis of reaction mixture. [k] Of starting material.



were equal to one another. Thus, for Ic → IIc, $k_i = k_\alpha = k_e$ (rate constant for isotopic exchange of the system as a whole). On the basis of this and the other equalities of rates, Ingold[5] states, "it proves the one-stage bimolecular mechanism B–SE2′,"[6] and considered the case closed.

In the last 10 years, Ossorio and co-workers[4a–i] have studied the racemization and isomerization of many alkyl-substituted N-benzylidenebenzylamine compounds. In no case, however, have these authors questioned the concerted mechanism.

The discovery of an intramolecular component in the base-catalyzed rearrangement of 3-phenyl-1-butene to *cis*- and *trans*-3-phenyl-2-butene,[7a] coupled with the fact that rearrangement competes with simple isotopic exchange,[7b] led us to reexamine the evidence for a one-stage mechanism in the similar methylene–azomethine rearrangement. Systems V and VI were chosen for study because of their great structural similarity to Ia and IIa on the one hand and to Ib and IIb on the other. It was anticipated that the equilibrium constant between V and VI would be close to unity as was observed with the three systems of Ingold. If for V → VI,



(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 572.

(6) This mechanism is actually termolecular and not bimolecular, since 1 mole of substrate, 1 mole of alcohol, and 1 mole of base are covalently involved in the rate- and product-determining transition state.

(7) (a) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **84**, 4358 (1962); (b) *ibid.*, **86**, 5466 (1964); (c) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 185.

$k_i = k_\alpha$ for low conversions (as was observed for Ia → IIa and Ib → IIb),[5] a carbanion mechanism could apply only if protonation of the intermediate occurred essentially exclusively at the *benzhydryl* rather than at the α-methylbenzyl position. A test of the possibility could be made by examining the relative rates of isomerization of VI → V and of deuterium incorporation into VI. If deuterium incorporation was much faster than isomerization, then a carbanion intermediate would be required. This test of mechanism has been applied to V and VI in *t*-butyl alcohol–potassium *t*-butoxide, and in dioxane–ethylene glycol–potassium glycoxide.

Results

Unfortunately, direct analysis of mixtures V and VI by vapor phase chromatography (vpc) proved impossible because of decomposition of the compounds at the high temperatures required. In the two experiments (runs 1 and 2), in which optically active V was converted to VI in dioxane–ethylene glycol-O-*d*–potassium glycoxide-O-*d*, the per cent conversion was estimated by examining the nuclear magnetic resonance (nmr) spectrum of the whole sample in the presence of anisole added as an internal standard. The intensity of the methyl doublet of V that occurs at τ 8.53 and 8.63 was used for analysis (runs 1 and 2 of Table I). In run 1, the total products were hydrolyzed in aqueous acid, and the α-phenylethylamine was recovered by vpc techniques and found not to have racemized, nor to have undergone isotopic exchange. In run 2, in which V was 9 ± 5% isomerized, the starting material had not undergone any detectable exchange. In run 3, isomer VI was submitted to the same reaction conditions as were used in runs 1 and 2. Part of the total product was hydrolyzed, and the amount of *p,p'*-dichlorobenzhydrylamine produced used to calculate the extent of rearrangement of VI to V. The other part was used to determine by nmr the amount of exchange of unrearranged VI at the benzhydryl position (τ 4.33, singlet) with anisole added as standard. The results indicate that VI underwent 95% isotopic exchange with ethylene glycol-O-d_2 under

conditions that a maximum of only 5% isomerization had occurred.

In runs 4 and 5, V and VI were isomerized at 75° in *t*-butyl alcohol–potassium *t*-butoxide until equilibrium was reached. The products were submitted to acid hydrolysis, and the amounts of acetophenone relative to an internal standard were measured by vpc and found to be approximately equal in the two experiments. From these results, K_{eq}(V/VI) = 1.0. Runs 6, 7, and 8 were all conducted at 75° in *t*-butyl alcohol-O-*d*–potassium *t*-butoxide, and the products were analyzed by hydrolysis and vpc (internal standard). In run 6, V was about 8% isomerized, and the recovered V was found by nmr analysis to be free of deuterium. The same was true in run 7, which was carried to 17% conversion. Clearly, V isomerizes much faster than it undergoes isotopic exchange with *t*-butyl alcohol-O-*d*.

In run 8, VI was about 3% isomerized, the mixture was hydrolyzed, and the *p,p'*-dichlorobenzhydrylamine obtained from unrearranged VI was found to have undergone 38% deuterium incorporation (combustion and falling drop analysis confirmed by nmr measurement) at the benzhydryl position. Thus, VI undergoes isotopic exchange with *t*-butyl alcohol-O-*d* much faster than it isomerizes to V.

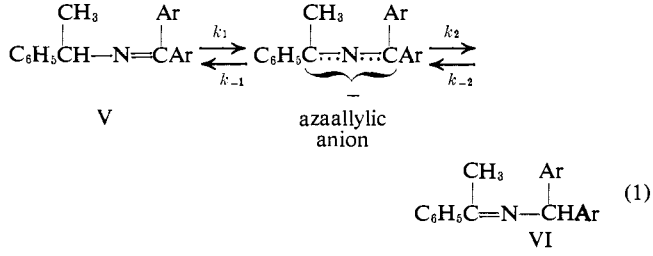
One-point, pseudo-first-order rate constants were calculated for V → equilibrium from runs 6 and 7, and amounted to 0.43 and 0.49 × 10^{-5} sec^{-1}, respectively. A similar calculation for VI → equilibrium (run 8) gave 1.4 × 10^{-5} sec^{-1}. Thus, V and VI go to the equilibrium mixture with rate constants that are close to one another as is required if the equilibrium constant for V ⇆ VI is equal to unity.

Although the probability was remote, it seemed possible that the imine isomerizations proceeded *via* an azacyclopropane type of intermediate. Accordingly, *cis*-1,2-diphenylethylenimine was submitted to the action of *t*-butyl alcohol-O-*d*, 0.44 *N* in potassium *t*-butoxide under conditions (50° and 8.19 × 10^3 sec) that N-benzylidenebenzylamine underwent 95% hydrogen–deuterium exchange of all three aliphatic protons (nmr analyses at τ 5.32 and 1.78 in carbon tetrachloride). The ethylenimine underwent less than 0.2% of isomerization to N-benzylidenebenzylamine (ultraviolet spectral analysis at λ 248 mμ, which is λ_{max} (log ε 4.306)).

Discussion

In a test of mechanism for the methylene–azomethine rearrangements, VI was found to undergo isotopic exchange much faster than isomerization in both dioxane–ethylene glycol-O-d_2–potassium ethylene glycoxide and in *t*-butyl alcohol-O-*d*–potassium *t*-butoxide. This result provides strong evidence that the conversion of VI to V proceeds through a carbanion intermediate in both media, and that the carbanion is protonated at the benzhydryl position much faster than at the benzyl position. The principle of microscopic reversibility requires that if VI proceeds to V *via* a carbanionic intermediate, the conversion of V to VI must proceed through that same intermediate. Thus, the concerted, termolecular scheme cannot apply to this system in these two media.

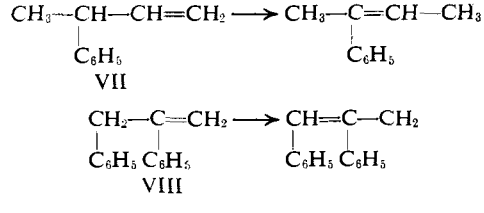
In contrast to the one-stage concerted mechanism, the two-stage carbanion mechanism provides an internally consistent explanation of the results. Although only one-point, pseudo-first-order rate constants can be calculated from the data of Table I, it is convenient to discuss the mechanism in terms of the relative values of rate constants. These are defined in eq 1, which depicts the two-stage, anionic mechanism, and k_i, k_α, and k_e which are defined as the initial rate constants for



isomerization of V to VI, for racemization of V, and for deuterium incorporation into the system taken as a whole, respectively. The rate constants, k_{-i} and k_e', refer to the rates at which VI goes to V, and VI undergoes isotopic exchange, respectively.

In the isomerization of V to VI in dioxane–ethylene glycol-O-d_2, after a few per cent conversion (run 1), the α-phenylethylamine isolated from the hydrolysis was within experimental error of possessing the same rotation as that amine used to prepare V. Furthermore, it contained no deuterium. This result is consistent with $k_i = k_\alpha$. For the conversion of VI to V in the same medium, VI underwent isotopic exchange much faster than V was produced. If V isomerized to VI with no intramolecular component, then $k_i = k_\alpha = k_e$. Likewise, if $k_{-2}[k_2/(k_2 + k_{-1})]$ is enough greater than k_1, then $k_i = k_\alpha = k_e$ even if V rearranges to VI with an intramolecular component. If it is assumed that the azaallylic anion collapse ratio (k_{-1}/k_2) shows no isotope effect, then this ratio can be estimated from the relative rates of isomerization and deuterium incorporation of VI (k_e'/k_{-i}). In *t*-butyl alcohol this ratio was about 20, whereas in dioxane–ethylene glycol it was greater than 10. Apparently proton or deuteron capture occurs at the benzhydryl position at least an order of magnitude faster than at the α-phenylethyl position in spite of the fact that V and VI are of about the same energy.

Intervention of an anionic intermediate in the methylene–azomethine rearrangement brings the reaction into conformity with the base-catalyzed allylic rearrangement of olefins.[7b,8] It is interesting that the rearrangements of V, VII, and VIII in *t*-butyl alcohol-O-*d*–potassium *t*-butoxide all proceeded with intramolecularity that ranged only from 36 to 55%. The fact that VI undergoes isotopic exchange with the medium much faster than V → VI precluded measurements of the intramolecular component of the latter reaction.



Compounds V and VI of the present investigation differ in structure from Ia and IIa and Ib and IIb by the

(8) (a) D. H. Hunter and D. J. Cram, *J. Am. Chem. Soc.*, **86**, 5478 (1964); (b) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 175.

presence or absence of chlorine atoms in the *para* position of the benzene rings of the benzhydryl part of the molecule. The dioxane–ethylene glycol–glycoxide medium of the present investigation also resembles the dioxane–ethanol–ethoxide medium used for the isomerizations of Ia and IIa.[4j,l,m] The results of the isomerization of V → VI are consistent with $k_i = k_\alpha$, as was observed for Ia → IIa and Ib → IIb. The similarities of structure, medium, and behavior in the isomerizations of V, Ia, and Ib lead us to conclude that the isomerizations studied by Ingold, *et al.*,[4j,l,m] proceeded by a two-stage, anionic mechanism. Such a mechanism also explains the results of DeSalas and Wilson[4p] in the isomerization of III → IV and the reverse reaction. Thus, $k_e'/k_{-i} > 1$ for IV is possible if the collapse ratio of the anionic intermediate favors IV over III. Furthermore, $k_i > k_e$ for III → IV if the reaction proceeds with an intramolecular component. The results are analogous to those observed in the present investigation. Finally, it seems highly probable that the methylene–azomethine rearrangement in general proceeds through anionic intermediates. Differences in behavior with substituent and medium effects largely reflect changes in the relative values of k_1, k_2, k_{-1}, and k_{-2}, and changes in the size of the intramolecular component of the reaction. In any case, the concerted, one-stage mechanism[5] is without a firm foundation.

Experimental Section

(−)-α-Phenylethylamine. From 125 g of racemic α-phenylethylamine and 156 g of *d*-tartaric acid in 2.2 l. of methanol, the tartrate salt[9] was obtained (95.5 g), which was recrystallized. This salt was converted to the free amine to give 18.8 g (30% of theory) of material, α^{25}_{546} −43.68° (*l* 1 dm, neat). This material was combined with that from other resolutions and crops, and the entire sample distilled through a 24-in. spinning-band column to give material used in further experiments, bp 86.5–87.5° (25 mm), α^{25}_{546} −44.6° (*l* 1 dm, neat), $\alpha^{25}D$ −37.6° (*l* 1 dm, neat), $n^{25}D$ 1.5247, lit.[9] $\alpha^{22}D$ −38.3° (*l* 1 dm, neat).

Di-*p*-chlorophenyldichloromethane. The procedure was patterned after that employed for diphenyldichloromethane.[10] A mixture of 24.7 g of *p,p'*-dichlorobenzophenone (Matheson Coleman and Bell material, recrystallized from chloroform–ethanol, mp 144–145°) and 21.3 g of phosphorus pentachloride was heated at 140–150° for 2.2 hr. The mixture was poured over crushed ice, and the solids were collected and dried, wt 32.8 g. The pentane-soluble fraction was recrystallized from pentane to give 25.0 g (83%) of first crop, mp 48.5–50.5°, which when recrystallized from pentane gave 20.7 g (69%), mp 50–52°. Two additional recrystallizations gave material used in subsequent experiments, mp 51–53.5°. *Anal.* Calcd for $C_{13}H_8Cl_4$: C, 51.02; H, 2.64. Found: C, 51.25; H, 2.61.

Di-*p*-chlorophenylmethylene-α-phenylethylamine (V). A mixture of di-*p*-chlorophenyldichloromethane (19.4 g) and (−)-α-phenylethylamine (23.8 g) was heated at 125° for 4 hr. The reaction mixture was cooled, and the semicrystalline mass was dissolved in 250 ml of pentane and extracted with two 100-ml portions of cold 3% aqueous acetic acid. The pentane extract was dried and evaporated to give a viscous oil, 22.1 g (99%). Vapor phase chromatography of a sample of this material on a 3-ft, 0.25-in. column packed with 20% SE-30 silicone gum on 60–80 mesh firebrick at 263° showed a major peak that accounted for 86% of the totaled peak areas, and no peak that corresponded to the product of double-bond migration, N-(α-methylbenzylidene)-*p,p'*-dichlorobenzhydrylamine. This material was distilled through a short, heated column. A first fraction (3.4 g) was collected at 155° (2 μ), and the product (12.1 g) was collected at 145–159° (0.6 to 1.0 μ). This material was redistilled and a center cut (7.0 g) was collected at 125–135° (0.1–0.2 μ). This material was 97% pure by vpc and gave 1.5% acetophenone when hydrolyzed (see subsequent procedure). A second preparation gave 0.8% acetophenone upon hydrolysis, and this latter material was used for runs 4, 6, and 7 of Table I. *Anal.* Calcd for $C_{21}H_{17}Cl_2N$: C, 71.19; H, 4.84. Found: C, 71.40; H, 5.03.

The infrared spectrum of this material gave a strong band at 6.15 μ (C=N stretch) in carbon tetrachloride. The ultraviolet spectrum in ethanol gave λ_{max} 255 mμ (log ε 4.30) and λ_{min} 232 mμ (log ε 4.13). The nmr spectrum taken as a 20–50% solution in carbon tetrachloride exhibited a complex multiplet at τ 2.3 to 3.2 (aromatic hydrogens, 13.0), a quartet centered at τ 5.57 (benzyl hydrogen, 0.87), a doublet centered at τ 8.58 (methyl hydrogens, 2.5, J_{AB} = 6.5 cps).

***p,p'*-Dichlorobenzhydrylamine by Reduction of *p,p'*-Dichlorobenzophenone Oxime with Zinc and Acetic Acid.** To a cooled mixture of recrystallized *p,p'*-dichlorobenzophenone in 500 ml of ethanol and 127 g of potassium hydroxide in 105 ml of water, was added slowly 45.0 g of hydroxylamine hydrochloride. The mixture was stirred for 28 hr at 25°, diluted with 1 l. of water and excess solid carbon dioxide. The product was collected and dried, wt 52.5 g (99%), mp 131–134°, and recrystallized from 50% ethanol–water and dried to give 51.2 g of material, mp 135–137°, lit.[11] 135–137°.

Acetic anhydride (82 ml) was heated with 41 ml of water at 110° for 15 min. The mixture was cooled to 75° and 20.4 g of the above oxime was added. Zinc dust (26 g) was added in small portions with stirring over a period of 1 hr, and the reaction mixture was stirred at 75° for 4 hr and allowed to stand at 25° for 8 hr. The resulting mixture was diluted with 80 ml of water and filtered, and the filtrate was washed with acetic acid–water. The filtrate was evaporated at 50°, and the residue was mixed with 10% aqueous sodium hydroxide and ether. The ether layer was washed with saturated aqueous sodium chloride, dried, and evaporated. The residue was triturated with pentane, and the insoluble part was treated first with 50 ml of 10% sodium hydroxide and pentane. The combined pentane layers were dried and evaporated, and the residue (15 g) was chromatographed on 100 g of activated alumina (activity grade 1) made up in 1:1 ether–pentane. The product was eluted in the first 600 ml of eluate (ether–pentane), wt 12.6 g, which was recrystallized twice from pentane, wt 9.7 g, mp 58.5–60.5°.

In a second preparation of *p,p'*-dichlorobenzhydrylamine, lithium aluminum hydride (5.5 g) was covered with 50 ml of tetrahydrofuran (freshly distilled from the reagent), and *p,p'*-dichlorobenzophenone oxime (18.0 g) in 50 ml of tetrahydrofuran was added with stirring. The reaction mixture was held at 65° for 10 hr and then held at reflux for 6 hr. To the cooled mixture, was added dropwise 7 ml of saturated aqueous sodium sulfate. After addition of 250 ml of ether, the mixture was filtered through Celite, the pad was washed, and the solvent was evaporated to give a white solid (15.5 g), which after two recrystallizations from pentane gave 7.3 g (43%) of the amine, mp 57–61°. An analytical sample was prepared by filtering a pentane solution of the amine through activated grade 1 alumina, mp 60–61.5°. *Anal.* Calcd for $C_{13}H_{11}Cl_2N$: C, 61.96; H, 4.40. Found: C, 62.22; H, 4.46.

N-(α-Methylbenzylidene)-*p,p'*-dichlorobenzhydrylamine (VI). A solution of 0.096 g of *p,p'*-dichlorobenzhydrylamine in 0.5 ml of ethanol was added to 0.5 ml of saturated aqueous zinc chloride followed by 1 ml of ethanol. Water was added (*ca.* 5 ml) until precipitation was complete. The precipitate was collected, dried, and used as a catalyst in the subsequent reaction.[12]

A mixture of 9.46 g of *p,p'*-dichlorobenzhydrylamine and 4.96 g of acetophenone dissolved in 35 ml of *p*-xylene was treated with 0.080 g of the above catalyst. The solvent was distilled until a bath temperature of 225° was reached. Fresh xylene (25 ml) was added and similarly evaporated, and the process repeated, the entire operation taking 3 hr. The residue was film dried under vacuum and dissolved in pentane, and the solution was cooled to give 8.0 g of crystalline product. Recrystallization of this material from about 200 ml of pentane gave 6.5 g of the imine (49%), mp 79–100°. An additional recrystallization gave mp 100–102°. *Anal.* Calcd for $C_{21}H_{17}Cl_2N$: C, 71.19; H, 4.84. Found: C, 71.24; H, 4.61.

The infrared spectrum of this material (VI) in chloroform gave a strong band at 6.12 μ (C=N stretch). The ultraviolet spectrum in ethanol gave λ_{max} 232 mμ (log ε 4.45). The nmr spectrum exhibited a complex multiplet from τ 2.08 to 3.05 (aromatic hydrogens,

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13.0), a singlet at τ 4.33 (benzhydryl hydrogen, 0.9), and a singlet at τ 7.82 (methyl hydrogens, 2.92).

Isomerization Reactions. The imine was weighed into a glass tube fitted with a rubber stopper through which two small-diameter glass tubes passed, one leading through a stopcock to a standard taper joint and the other flanged to accept a rubber septum. The tube was alternately evacuated and flushed with nitrogen (passed over hot copper turnings and through Ascarite and silica gel). The solvent and base solutions were stored in closed vessels under purified nitrogen, and samples were removed with a calibrated syringe. The base solution was standardized by titration with aqueous hydrochloric acid (1% accuracy) to a methyl red–bromocresol green end point. The concentrations of reagents were calculated on the assumption of additive volumes with no correction for a volume increase due to imine. The punctured septum was covered with another septum of slightly larger diameter. The contents of the tube were degassed; the tube was sealed under vacuum and placed in a constant-temperature bath. After the desired time, the tube was cooled and opened. The contents was washed into a mixture of 50 ml of benzene and 25 ml of water containing enough 1% aqueous acetic acid to neutralize the base present. The benzene layer was washed with 10 ml of water and 1 ml of 5% sodium bicarbonate solution, and dried by suction filtration through a pad of powdered, anhydrous sodium sulfate. The benzene was removed on a rotatory evaporator under vacuum until its odor was not detectable (pure nitrogen was blown over the surface of the film). With this procedure, better than 99% of the beginning weight of imine was accounted for. If an nmr or vpc standard was required, it was introduced at this point. The mixture was then either dissolved in a suitable nmr or vpc solvent and subjected to hydrolysis as described below.

Attempts to Analyze Directly Mixtures of N-(α-Methylbenzylidene)-p,p'-dichlorobenzhydrylamine (VI) and Di-p-chlorophenylmethylene-α-phenylethylamine (V). Attempts to carry out direct vpc on the products of isomerization were unsuccessful owing to decomposition of the imine with the longer retention time (VI). At an oven temperature of 240° on a 3-ft column of 20% SE-30 (silicone gum) on 60–80 mesh firebrick with injector and collector temperature about the same as the column temperature and a helium flow rate of 100 ml/min, the ratio of peak areas (V/VI) was about 1.5 of the true value. Attempts to purify the imines by preparative vpc under the same conditions led to extensive decomposition of imine VI. Therefore, analyses were performed on the hydrolysis products of the two imines.

Procedures for Hydrolysis of Mixtures of N-(α-Methylbenzylidene)-p,p'-dichlorobenzhydrylamine (VI) and Di-p-chlorophenylmethylene-α-phenylethylamine (V). Procedure A. The mixture to be hydrolyzed (200–600 mg) was treated with 10 ml of 20% aqueous sulfuric acid, and the mixture was refluxed for 45 min. **Procedure B.** The mixture to be hydrolyzed (200–600 mg) was refluxed with 10 ml of 15% aqueous hydrochloric acid for 1.25 hr. **Procedure C.** The mixture to be hydrolyzed (200–600 mg) was refluxed with 7 ml of 15% hydrochloric acid and 7 ml of methanol for 45 min.

The procedures used for isolation of products varied with the purpose of the experiment. For separation of neutral materials, the solution obtained after allowing the hydrolysis mixture to cool to 25° was extracted continuously on a liquid–liquid extractor for 24 hr with either ether or pentane. Pentane was always used in conjunction with procedure C. When isolation of all hydrolysis products or of basic hydrolysis products was desired, either the initial hydrolysis mixture or the extracted (24 hr) hydrolysis mixture was treated with 6 ml of 30% aqueous sodium hydroxide (or 1.8–2.0 g of solid sodium hydroxide). The resulting basic solution was extracted continuously with ether or pentane for 24 hr. The extracts were dried over anhydrous sodium sulfate since magnesium sulfate preferentially removed α-phenylethylamine.

When α-phenylethylamine needed to be isolated, the neutral materials were first extracted (see above), and then the basic materials after the solution was made basic (see above). Samples prepared in this way contained less than 1% acetophenone. The amine was then isolated in a pure state by preparative vpc on a 4-ft, $^3/_8$-in column packed with 20% SE-30 (silicone gum) on 80–100 mesh Chromosorb W. The column temperature was 98° with the preheater at 215°. The product was collected with a simple U-tube immersed in Dry Ice–acetone. About 90% of theory of the amine was recovered in control experiments.

From run 8, p,p'-dichlorobenzhydrylamine was essentially the only amine produced on hydrolysis of the reaction mixture. The basic fraction from the extraction procedure was sublimed at 50° (0.07 mm) to give pure amine, mp 60–62°, undepressed by admixture with an authentic sample.

Determination of the Rotation of α-Phenylethylamine from Hydrolyses of Reaction Mixtures. Because of the high rotation of optically pure α-phenylethylamine and the small amount typically isolated from the hydrolysis of reaction mixtures, it was convenient to measure the rotations in dioxane solution. The following rotations were taken in dioxane solution on pure amine of rotation α^{25}_{546} −44.56° (l 1 dm, neat): wt of amine, 58.9 mg, volume of solution, 1.00 ml, $[\alpha]^{25}_{546}$ −46.0°; wt of amine, 44.3 mg, volume of solution, 1.00 ml, $[\alpha]^{25}_{546}$ −46.2°; wt of amine, 48.5 mg, volume of solution, 2.00 ml, $[\alpha]^{25}_{546}$ −45.3°. This amine was shown to be optically stable to the vpc chromatographic procedure by subjecting the above sample to that procedure. The product gave the following rotation in dioxane: wt of amine, 69.6 mg, volume of solution, 1.00 ml, $[\alpha]^{25}_{546}$ −46.6°.

Analysis of Products of Hydrolysis. The most volatile products of hydrolysis, α-phenylethylamine and acetophenone, were selected for analysis by vpc. From a variety of columns tried, the best results were obtained with a packing of 10% Carbowax 6000 on Teflon (Haloport F) or Fluoropak, or phenyl ether on Teflon. These packings eliminated the severe tailing of the amine on firebrick or chromosorb. The following results were obtained for analysis of synthetic mixtures of acetophenone and α-phenylethylamine on a 10-ft, 0.25-in. column packed with 5% phenyl ether on Teflon at a column temperature of 135° and a helium flow rate of 25 ml/min. The samples were made up by weight in tetrahydrofuran. The mole per cent values for α-phenylethylamine were: calcd 8.85, found 8.49, 8.52, and 8.43; calcd 19.9, found 20.6 and 20.4; calcd 28.7, found 29.0 and 28.8. The mole per cent values for acetophenone were: calcd 54.4, found 53.1, 53.4, 53.6, 54.0, and 54.5; calcd 36.9, found 34.9, 35.1, 35.6, and 34.4; calcd 27.2, found 25.0, 25.0, and 25.8; calcd 16.8, found 15.2, 15.4, 15.7, 15.5, and 15.9; calcd 8.60, found 7.68, 7.93, 7.25, and 7.76.

A second and more accurate procedure involved use of internal standards, anisole or p-methoxyacetophenone, the latter being the better. The following analytical data were obtained for synthetic mixtures of p-methoxyacetophenone and acetophenone with a 10-ft, 0.25-in. column packed with 5% phenyl ether (five rings) on Teflon at an oven temperature of 184° and a helium flow rate of 28 ml/min. Results are reported in mole per cent acetophenone: calcd 53.3, found 49.9, 49.9, and 50.5; calcd 53.0, found 49.7, 49.7, 48.6, 49.0, and 48.4; calcd 39.4, found 38.0, 38.1, and 38.1; calcd 27.3, found 25.4, 26.2, and 25.2; calcd 19.0, found 16.8, 17.0, and 16.5; calcd 10.0, found 9.40, 9.12, 8.97, and 9.16; calcd 10.4, found 9.11, 9.42, and 9.26. A correction factor, $\alpha = 1.12 \pm 0.03$, was applied to those unknowns with a mole per cent of acetophenone greater than 8, eq 2 being employed. With mixtures that contained large

$$\text{mole fraction of acetophenone} = \frac{(\alpha \text{ area under acetophenone peak})}{(\alpha \text{ area under acetophenone peak}) + \text{area under } p\text{-methoxyacetophenone peak}} \quad (2)$$

amounts of acetophenone, p,p'-dimethoxybenzophenone was used as an internal standard for p,p'-dichlorobenzophenone. Analyses were similar to those described above.

Controls on Hydrolysis and Analytical Procedures. Known mixtures of imines were hydrolyzed by procedure A; the products were neutralized and extracted with ether. The ether extract was dried and concentrated, and tetrahydrofuran was added to give a homogeneous solution. Analytical vpc was performed on a 10-ft, 0.25-in. column packed with Carbowax 6000 on Teflon at 147°, with a helium flow rate of 30 ml/min. Corrected values were obtained by comparing the results with those observed for known mixtures of α-phenylethylamine and acetophenone under the same analytical conditions and similar proportions. The results are reported in mole per cent acetophenone: calcd 19.3, found 20.7, 20.1, 18.7, and 19.6 (average corrected found value, 20.0); calcd, 41.1, found 45.2, 44.6, 45.0, and 45.1 average corrected found value, 44.7); calcd 86.1, found 90.2, 90.4, and 89.9 (averaged corrected found value, 87.8).

Better results were obtained when acetophenone was compared to p-methoxyacetophenone as an internal standard. The following data were obtained by subjecting synthetic mixtures of p-methoxyacetophenone and imine VI to hydrolysis procedure C. Analysis was performed on the phenyl ether column previously described, and the results were corrected through use of eq 1. The results are reported in mole per cent acetophenone: calcd, 44.4, found 42.3, 42.7, and 42.1 (average corrected found value, 45.1); calcd 25.9, found 23.8, 23.6, 23.4, 22.6, and 22.8 (average corrected value,

25.0); calcd 17.0, found 16.4, 15.6, 15.7, and 15.5 (average corrected found value, 17.4); calcd 6.56, found 5.47, 5.96, 6.12, 5.83, 6.10, 5.72, and 5.85 (average corrected found value, 6.54).

Attempt to Isomerize *cis*-2,3-Diphenylethylenimine. A solution of 63.3 mg of *cis*-2,3-diphenylethylenimine[13] in 1.113 ml of 0.443 *N* potassium *t*-butoxide in *t*-butyl alcohol-O-*d* was held at 50% for 137 min under the conditions used for the other isomerizations. The product was isolated as before and sublimed at 60° (0.07 mm) to give 49.4 mg of starting material (85%), mp 82–83°, undepressed by admixture with an authentic sample.[13]

Analysis of Products by Nmr Procedures. The combined starting material and reaction product, isolated quantitatively in the manner described, were treated with a weighed amount of standard: anisole (runs 1, 2, and 3), *p*-methoxyacetophenone (runs 4, 5, 6, and 7) or di-*p*-methoxybenzophenone (run 8), and dissolved in CCl_4 (runs 1, 2 and 3) or $CDCl_3$ (runs 6, 7, and 8), enough solvent being used to effect complete solution. The nmr spectrum was then taken on a Varian A-60. In runs 1 and 2, the doublet of the methyl group of V was integrated and compared to the standard to obtain a crude estimate of the per cent isomerization. The per cent product could not be measured directly because of extensive exchange of both methyl and benzhydryl hydrogens. The per cent exchange of the α-phenylethyl hydrogen was determined by comparison of methyl and α-phenylethyl peak areas for V.

Solvents and Solutions. The following deuterated solvents were used: *t*-butyl alcohol-O-*d*,[7b] 96–98% of one atom of deuterium per molecule; ethylene glycol-O-d_2,[14] at least 99.5% deuterated as indicated in the name. All alcohols were dried and purified by distillation from molecular sieves onto molecular sieves. Potassium alkoxide solutions were prepared as described elsewhere.[8a] Dioxane was purified by the method of Hess and Frahm.[15]

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Electrophilic Substitution at Saturated Carbon. XXVIII. The Stereochemical Capabilities of Vinyl Anions[1]

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Abstract: The base-catalyzed isomerization and hydrogen isotope vinyl exchange of *cis*- and *trans*-stilbene, *cis*- and *trans*-α,α′-dideuteriostilbene, and *cis*- and *trans*-*p*-nitrostilbene with solvent were studied. Solutions of potassium *t*-butoxide in *t*-butyl alcohol, in *t*-butyl alcohol–tetrahydrofuran, and in *t*-butyl alcohol–dimethyl sulfoxide, of potassium hydroxide in dimethyl sulfoxide, of dimsylpotassium in dimethyl sulfoxide, and of potassium methoxide in methanol and in methanol–dimethyl sulfoxide appropriately deuterated or nondeuterated were employed as media. All isotopic exchanges of both of the *cis* isomers to give *cis* isomers occurred through vinyl intermediates. Those *cis* to *trans* isomerizations carried out in *t*-butyl alcohol, *t*-butyl alcohol–tetrahydrofuran, and in dimethyl sulfoxide probably occurred mainly through vinyl anion intermediates. Those isomerizations observed in methanol or dimethyl sulfoxide–methanol mixtures clearly went by an addition–elimination mechanism. The ratio of rate constants (estimated) of isotopic exchange of *cis*-stilbene to that of isomerization (k_e^c/k_i^c) changed in a systematic manner from 5×10^3 to 0.8 as a *t*-butyl alcohol medium was enriched in dimethyl sulfoxide. In dimethyl sulfoxide–dimsylpotassium, the isomerization of *cis*- to *trans*-stilbene occurred with about 32% retention of the isotopic label, even though an anionic intermediate is involved. In *t*-butyl alcohol–potassium *t*-butoxide, the k_e^c/k_i^c for *cis*-*p*-nitrostilbene was about unity. In solvents that contained methanol, the isomerization of this system occurred by an addition–elimination mechanism. In both systems, the *cis* isomers underwent isotopic exchange faster than the *trans* isomers by one to two powers of ten. The *p*-nitrostilbene system was many orders of magnitude more reactive than the stilbene system in both isomerization and exchange reactions. Media rich in dimethyl sulfoxide gave rates of reaction many powers of ten faster than the hydroxylic solvents.

Information about the configurational stability of vinyl anions has come from three main sources. Various vinyl organometallic compounds have been prepared and converted to other compounds.[2] The geometric stability was found to vary with changes in substrate and solvent. Vinyl anions are isoelectronic with N-substituted imines, and the behavior of such imines has been used as a model for the capabilities of vinyl anions. For example, the geometric stabilities of N-substituted imines vary with the capacity of substituents to exert both inductive and mesomeric effects.[3]

The geometric stability of vinyl anions generated by proton abstraction can be inferred from the base-catalyzed rearrangement of 1-halo-2,2-diphenylethylenes.[4] Exchange of vinyl protons was concurrent with rearrangement, both reactions being faster than isomerization. Exchange, isomerization, and elimination reactions of 1,2-dihaloethylenes have also been studied,[5] and the relative rates of these processes pointed to stereochemical stability for the vinyl anion. Preliminary results on the vinyl anion derived from *cis*-stilbene in *t*-butyl alcohol indicated a tendency toward geometric stability.[6]

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