Hydrazines as Ambident Nucleophiles: the Site of Benzylation of *N*-Benzyl-*N*-phenylhydrazines

Peter A. S. Smith* and Gordon L. DeWall[1]

Contribution from the Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109. *Received October 27, 1976*

Abstract: Reinvestigation of the methylation of phenylhydrazine has firmly established that most reaction takes place at the N position, with a small amount at N′. Benzylation of *N*-benzyl-*N*-phenylhydrazine was also reinvestigated; at temperatures below 60 °C, the alkylation site is largely at the N position and kinetically controlled. At higher temperatures, thermodynamic control increases, and at 110 °C, the product is entirely *N*,*N*′-dibenzyl-*N*-phenylhydrazine. At 40 °C, better leaving groups give a higher proportion of N-benzylation. Lower polarity of the solvent favors N′-benzylation. The site and rate of benzylation and the susceptibility to thermodynamic vs. kinetic control are sensitive to substituents on the *N*-phenyl group. *N*,*N*-Dibenzyl-*N*-phenylhydrazinium salts rearrange on warming to nonquaternary salts by benzyl migration, which is greatly promoted by polar solvents, and occurs by a dealkylation–realkylation process. The corresponding hydroxides also rearrange readily; kinetic data are consistent with an amine *N*-imide intermediate. *N*-Benzyl-*N*-methyl-*N*-phenylhydrazinium hydroxide rearranges more slowly, and *N*,*N*-dimethyl-*N*-phenylhydrazinium hydroxide not at all.

The factors that influence the site of alkylation of ambident anions have been studied actively,[2,3] because of the implications for the structure of inorganic as well as organic anions and their importance in synthesis. Although much progress has been made, enigmatic aspects remain. Although there are several distinct structural types of ambident anions, each of which may have its own characteristic pattern of sensitivity to the various factors, most investigators have, for simplicity, treated the generalizations derived from a study of one type as valid for all types. The most commonly investigated type may be termed 1,3-delocalized anions (**1**), exemplified by enolate and phenolate anions. Gompper[3d] has proposed a classification of these according to whether the central atom, Y, bears an unshared pair of electrons. Distinct from these are the vicinally ambident species **2**, such as cyanide, sulfenate, and oximate ions, in which an unshared pair is present on each of two adjacent atoms (the last may also formally be placed in the 1,3-ambident category, but no unequivocal case of alkylation of an oxime at carbon has been reported). Vicinal ambident anions may be subdivided according to the multiplicity of the bond between the nucleophilic sites and the presence or absence of additional unshared pairs of electrons.

$$\underset{\mathbf{1}}{X{=}Y{-}Z{:}^- \leftrightarrow {}^-{:}X{-}Y{=}Z} \qquad \underset{\mathbf{2}}{{:}X{-}Z{:}}$$

Another source of difficulty is inherent in the nature of anions: there must be a counterion, whose degree of association with the anion may be strongly influenced by the circumstances of solvent, temperature, and concentration. A change of counterion, even from one alkali metal to another, may have a substantial effect on the distribution of site of attack on the anion.[2d]

Elucidation of the complexities might be aided by extending the ambident concept to uncharged nucleophiles. Two variables, the effect of the counterion and the distribution of the substrate among simple ions, ion pairs, and larger aggregates, would be eliminated, and one may be able to obtain less ambiguous information about the influences of medium, temperature, and electronic character of the reactants. 1,3-Delocalized ambident uncharged nucleophiles are represented by carboxamides, amidines, and enamines; vicinally uncharged nucleophiles are encountered with hydrazines and hydroxylamines. More complex examples are encountered in the nucleic acids, the behavior of which toward alkylating agents is important in chemotherapy of cancer.[4]

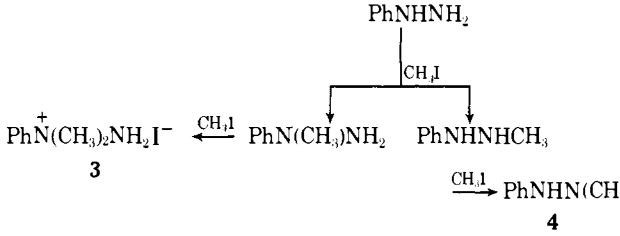
The present work is concerned with unsymmetrical hydrazines as representative vicinal ambident uncharged nucleophiles. There is much ad hoc information in the literature on alkylation of unsymmetrical hydrazines, but no systematic study appears to have been made. The recorded results may be summarized by the generalization that alkylation occurs exclusively or preferentially on the most highly substituted nitrogen atom, unless the size of the substituents is quite large.[5] *N*,*N*-Dimethylhydrazine, for example, reacts with methyl iodide to give solely the quaternary salt, *N*,*N*,*N*-trimethylhydrazinium iodide.[6] Surprisingly, phenylhydrazine is also reported to undergo methylation at the substituted nitrogen, giving eventually *N*,*N*-dimethyl-*N*-phenylhydrazinium iodide.[7] Because this fact implies a similar electronic effect by groups whose effects in other reactions are very different, the present work is addressed to the problem of alkylation of arylhydrazines. A concurrent purpose is to determine if the site selectivity in such reactions is sufficiently sensitive to conditions and structural variation for use as a probe to investigate general phenomena pertaining to ambident nucleophiles.

Results and Discussion

The methylation of phenylhydrazine was first reinvestigated. The phenyldimethylhydrazinium iodide obtained was found to be identical with the product formed[7b] in 77% yield by reaction of *N*-methyl-*N*-phenylhydrazine with methyl iodide, and the infrared spectrum (3100, 3200 cm^{-1}) was characteristic of N-H rather than $^+$N-H. Reductive cleavage gave dimethylaniline, thereby establishing the structure as *N*,*N*-dimethyl-*N*-phenylhydrazinium iodide (**3**).

$$PhNHNH_2 \xrightarrow{\text{xs } CH_3I} \underset{\mathbf{3}}{PhN^+(CH_3)_2NH_2I^-} \xleftarrow{CH_3I} PhN(CH_3)NH_2 \qquad (1)$$

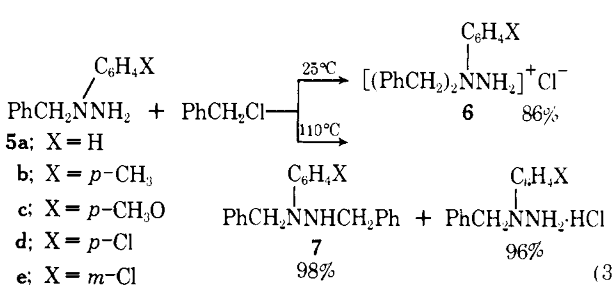
In a search for minor products, phenylhydrazine was treated with only 1 molar equiv of methyl iodide in benzene solution. Addition of ether precipitated the crude quaternary salt, which was then separated from other salts by dissolving in sodium hydroxide solution and extracting the liberated bases with ether (the quaternary hydroxide remained in the water layer and was subsequently converted to its chloride for isolation). The mother liquors and extracts, which contained phenylhydrazine and its nonquaternary methylation products, were treated with hydrogen chloride in ethanol/ether to precipitate phenylhydrazine hydrochloride, and the unprecipitated bases were separated by chromatography on silica gel. The quaternary salt **3** was obtained in 30.4% yield (15.2% based on phenylhydrazine), along with recovered phenylhydrazine (50.7%), *N*′,*N*′-dimethylphenylhydrazine (**4**) (15%; 7.5% based on phenylhydrazine), *N*-methyl-*N*-phenylhydrazine (1.5%), and intractable, colored, oxidation products (eq 2). No evidence for the presence of a quaternary salt derived from **4** in the material unaccounted for was observed, although we cannot rule out the possibility of a trace. The results are consistent with the report[7b] that benzylation of *N*-methyl-*N*-phenylhydrazine and methylation of *N*-benzyl-*N*-phenylhydrazine give the same quaternary salt, which must therefore have the structure $R_3N^+{-}NH_2$, and that treatment of *N*,*N*′-dimethyl-*N*-phenylhydrazine with methyl iodide gives only one quaternary salt, *N*,*N*,*N*′-trimethyl-*N*-phenylhydrazinium iodide, and a small amount of *N*,*N*′,*N*′-trimethyl-*N*-phenylhydrazine, the result of N′-alkylation.[6] Although the earlier reports are thus qualitatively confirmed, methylation of phenylhydrazine was not well-suited for further study, owing to experimental difficulties, the sensitivity of some of the compounds to oxidation, and susceptibility to N–N cleavage.



(2)

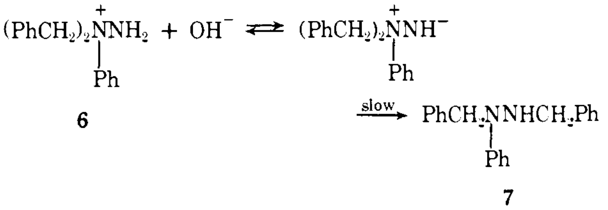
Benzylation of *N*-benzyl-*N*-phenylhydrazines (**5**) was chosen for the principal study because alkylation occurs to a significant extent on both nitrogens,[8] only one benzyl group is introduced short of forcing conditions, and the product mixture would, therefore, be a simply binary one, and the use of benzyl groups allows easy variation of electronic effects in the alkylating agent as well as in the nucleophile. In addition, the products are all easily separable and identifiable as solids and electronic effects are further susceptible to more profound variation by substitution on the *N*-phenyl group.

N-Benzyl-*N*-phenylhydrazine (**5a**) has previously been alkylated with neat benzyl iodide or chloride;[9] the only product reported was the *N*,*N*-dibenzyl-*N*-phenylhydrazinium salt (**6**), which was also the product of treating phenylhydrazine with benzyl bromide.[10] These experiments were carried out from an essentially qualitative, preparative viewpoint, however. We were nevertheless surprised to find that our initial experiment, in which *N*-benzyl-*N*-phenylhydrazine was treated with neat benzyl chloride at 110 °C for 6 h, gave an entirely different result: *N*,*N*′-dibenzyl-*N*-phenylhydrazine (**7**) and the hydrochloride of the starting material were the only products (eq 3). Sharp separation was brought about simply by diluting the reaction mixture with ether and filtering. Identification and purity were confirmed by thin-layer chromatography and acid–base titration; no quaternary salt could be detected. In contrast, repetition of the experiment at ambient temperature for 4 days gave principally the quaternary salt **6** (86%) together with the products of eq 3 (14%). The identity of the quaternary salt was confirmed by reduction to *N*,*N*-dibenzylaniline with Raney nickel.



(3)

In attempting to separate the quaternary from the nonquaternary products by treatment with strong base, as had been done in the case of methylation of phenylhydrazine, we at first obtained erratic results. The cause was found to be base-catalyzed migration of benzyl groups from the cationic nitrogen to the adjacent one. *N*-Phenyl-*N*,*N*-dibenzylhydrazinium chloride (**6**) (or iodide), when passed in aqueous alcoholic solution through an Amberlite IRA-400 anion exchange column charged with hydroxide ion and then heated at 50 °C for 5 min, was essentially completely rearranged to *N*-phenyl-*N*,*N*′-dibenzylhydrazine (**7**), which was isolated in pure state as its hydrochloride in 76% yield. At 40 °C, the kinetics could be followed by acid–base titration; the results closely fit a graphic first-order plot, with a half-life of 5.5 h. This result is consistent with a rapid equilibrium between the quaternary hydroxide and the amine *N*-imide, in which the latter predominates and the rearrangement of which is rate determining (eq 4).[11]



$$\underset{\mathbf{6}}{(PhCH_2)_2\underset{Ph}{\overset{+}{N}}NH_2} + OH^- \rightleftharpoons (PhCH_2)_2\underset{Ph}{\overset{+}{N}}NH^- \xrightarrow{slow} \underset{\mathbf{7}}{PhCH_2\underset{Ph}{N}NHCH_2Ph} \quad (4)$$

Formation of amine *N*-imide would be expected to be much short of complete, for a reasonable estimate[11] of the acidity of quaternary hydrazinium ions is about pK_a 12–15. This value is based on measured[12] values of 3–5 for an amine *N*-acylimide and the general acid-strengthening effect of simple acyl groups of about 9–10 p*K* units (e.g., comparing the acidity of water with acetic acid, or ammonia with acetamide). In conformity with this inference, we found that the apparent rate constant for rearrangement of **6** hydroxide was markedly increased by either added hydroxide ion or added hydrazinium chloride (with due correction for salt effects) and was decreased by dilution. Either of the added species would, of course, shift the equilibrium further toward the amine *N*-imide. This situation closely parallels that for the Stevens rearrangement of α-acyl quaternary ammonium hydroxides, $R_3N^+CH_2COR$, which also shows first-order kinetics while being somewhat accelerated by higher concentrations of hydroxide ion.[13]

It was necessary to learn something of the sensitivity of the rearrangement to temperature and structure, in order to avoid interference with the study of site of alkylation. At 40 °C, *N*,*N*-dibenzyl-*p*-methoxyphenylhydrazinium hydroxide (**6c**) rearranged at a rate 30% slower than that of the unsubstituted compound (**6a**). At 45 °C, the rates for both **6a** and **6c** were doubled, a fact corresponding to an activation energy higher than 25 kcal/mol. At 35 °C, rearrangement was very slow, and at 30 °C, no rearrangement could be detected in the space of several hours. *N*-Methyl-*N*-benzylphenylhydrazinium hydroxide (**8**) was still slower and required a temperature of 55 °C to match the rate of **6a** at 45 °C. We were unable to effect rearrangement of **3** hydroxide under any conditions. In view of these observations, summarized in Table I, we carried out our assays of alkylation mixtures keeping the temperature below 30 °C during treatment with base; the results were henceforth uniformly reproducible.

A study of the composition of the products of benzylation of **5a** as a function of temperature was undertaken over the range 0–70 °C; owing to the slowness of reaction with benzyl chloride, benzyl iodide was used for the experiments at 0 °C; at 30 °C, both reagents gave the same product ratios,[14] although the iodide reacted nearly four times as fast. The results,

Table I. Apparent Rates of Rearrangement of Quaternary Hydrazinium Hydroxides (**6**) in Water

Hydroxide	Concn, 10^3 M	Temp, °C	$10^3 \times k_{\text{app}}$,[a] s^{-1}
6a	32	45	3.7
6a	32	40	1.8
6a	52	40	2.2
6a plus NaOH[b]	32	40	3.5
6a plus **6a** Cl^-[c]	39	40	3.3
6c	34	45	2.7
6c	34	40	1.3
8[d]	35	55	1.8

[a] Estimated accuracy ca. 10%. [b] 52×10^{-3} M. [c] 58×10^{-3} M. [d] $Ph(CH_3)(PhCH_2)N^+NH_2OH^-$.

summarized in Table II, show that the fraction of benzylation that occurs at the tertiary nitrogen falls sharply with increasing temperatures.

If the product composition should be kinetically controlled, the fraction of N-benzylation, n_N, would be equal to $k_N/(k_N + k_{N'})$. Substitution by the Arrhenius equation gives

$$n_N = 1 - n_{N'} = [1 + (A_{N'}/A_N)\, e^{(E_N - E_{N'})/RT}]^{-1}$$

where A_N and $A_{N'}$ are the Arrhenius preexponential factors, and E_N and $E_{N'}$ are the respective energies of activation. The measurements at the lowest temperatures, 0–30 °C and 30–40 °C, can be used to estimate the hypothetical values $A_{N'}/A_N = 129$, and $E_N - E_{N'} = 3.7$ kcal. By the use of these quantities, values for n_N at other temperatures can be calculated. The results, given in the last column of Table II, show that these expectations of kinetic control are departed from noticeably at 50 °C and markedly at 70 °C. It appears, therefore, that the composition of the product is in fact decreasingly subject to kinetic control as the temperature rises and equilibration comes into play (cf. Figure 1).

The foregoing observations imply that the quaternary salts **6** are capable of rearrangement to *N,N'*-dibenzyl-*N*-phenylhydrazine (**7**). Indeed, a sample of **6** chloride when heated at 100 °C (below its mp 153 °C) for 4 h gradually liquefied and eventually resolidified; the odor of benzyl chloride could be detected, and the residue consisted solely of the hydrochlorides of **7** (31%) and the debenzylation product, *N*-benzyl-*N*-phenylhydrazine (55%). A similar experiment carried out in refluxing ethanol gave **7** in 9% yield and the debenzylation product in 78% yield. The quaternary salt **6** was stable in ethanol at 40 °C, but in dimethylacetamide solution at 40 °C, debenzylation took place to the extent of 83% in 24 h.

The foregoing behavior is analogous to the redistribution reaction of alkylamines, which is catalyzed by quaternary salts and has been shown to involve alkylation–dealkylation equilibria, and to thermal dealkylation of quaternary ammonium salts.[15] Dealkylation of **6** is presumably brought about initially by S_N2 attack by halide ion on a benzyl group; subsequently, *N*-benzyl-*N*-phenylhydrazine may also serve as the attacking nucleophile, in reaction either with unchanged quaternary salt or with benzyl halide. Although its tertiary nitrogen is evidently the more nucleophilic site, reaction there would be unproductive, merely regenerating **5**; the much slower reaction at the less nucleophilic primary nitrogen, being essentially irreversible, would result in the gradual accumulation of **7**, to the extent that benzyl halide was not lost or intercepted by other nucleophilic species. The conversion of **6** to **7** represents a type of rearrangement that we believe has not been reported before. It may account for some of the apparently conflicting reports in the literature regarding alkylation of hydrazines.

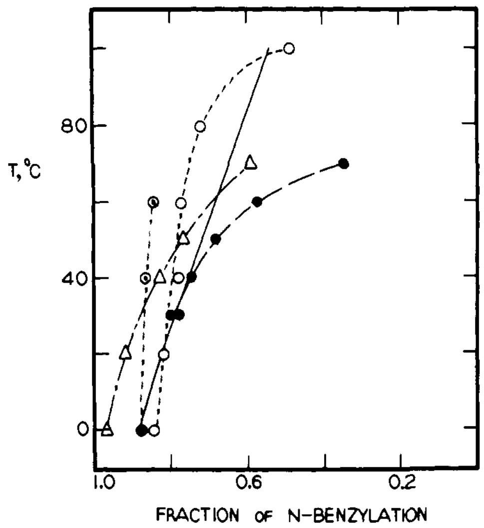


Figure 1. Benzylation of *N*-benzyl-*N*-arylhydrazines. The solid line is calculated for **5a** with benzyl chloride in ethanol, kinetic control (see Table II); ● is **5a** with benzyl chloride and iodide in ethanol, observed; ⊙ is **5a** with benzyl *p*-toluenesulfonate in toluene; ○ is **5a** with benzyl *p*-toluenesulfonate in ethanol; △ is **5b** with benzyl chloride and iodide in ethanol.

If the initial step in the rearrangement of quaternary hydrazines is, in fact, thermolytic dealkylation by halide ion, it should be possible largely to arrest the reaction at this step by use of a solvent of low polarity, in which realkylation would be retarded. Indeed, we found that **6**, when heated in refluxing toluene, was mostly converted to **5a** (84%) and benzyl chloride (75%, isolated as benzyl α-naphthyl ether). Furthermore, the stability (both kinetic and thermodynamic) of salts of **6** toward thermolysis should be a function of the nucleophilicity of the anion. When samples of **6** as the *p*-toluenesulfonate, chloride, and iodide were separately heated in ethanol at 65 °C for 4 h,

Table II. Benzylation of *N*-Benzyl-*N*-phenylhydrazine with Benzyl Halides (0.40 M in ethanol; 25-h reaction time)

Temp, °C	Mol % **7**	Mol % **6**	Material balance[a]	Fraction of N-benzylation (n_N) Found	Calcd
0[b]	34.0	4.5	98.0	0.88	(0.88)
30[c]	62.9	15.5	89.9	0.80	(0.79)
30[d,e]	12.8	3.6	95.7	0.78	
40[d]	14.5	5.0	95.9	0.74	0.76
50[d]	23.4	10.9	95.2	0.68	0.72
60[d]	23.8	17.7	96.0	0.57	0.68
70[d]	11.3	21.6	93.3	0.35	0.65
110[d,f]				0.0	0.51

[a] Includes recovered **5a**. [b] With benzyl iodide, reaction time 17.5 h. [c] With benzyl iodide, reaction time 15.5 h. [d] With benzyl chloride. [e] Reaction time 46.5 h. [f] No solvent used.

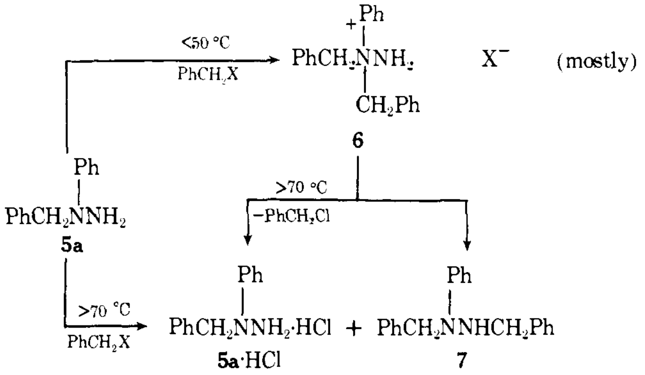
Table III. Benzylation of *N*-Benzyl-*N*-phenylhydrazine with Benzyl Tosylate (0.40 M; 25-h reaction time)

Temp, °C	Solvent[a]	Mol % **7**	Mol % **6**	Material balance[b]	Fraction of N-benzylation, n_N
0	E	46.7	6.4	95.0	0.88
0	T[c]	10.4	1.9	97.9	0.845
20	T[d]	23.1	5.1	95.9	0.82
40	E	41.7	6.4	95.6	0.87
40	T	32.4	9.2	97.2	0.78
60	E	30.7	5.7	94.1	0.84
60	T	55.0	16.4	97.5	0.77
80	T	54.5	21.3	95.0	0.72
100	T	36.2	38.5	96.5	0.485

[a] E = ethanol; T = toluene. [b] Includes recovered **5a**. [c] Reaction time 120 h. [d] Reaction time 72 h.

the yields of recovered quaternary salts were, respectively, 97.5, 81.8, and 62.5%, in accord with the foregoing expectation. When the experiment with the *p*-toluenesulfonate was repeated with the added presence of a molar equivalent of **5a**, recovery of **6** dropped to 93.2%; in addition, **7** and **5a** *p*-toluenesulfonate were each isolated in 4% yields (Scheme I). Since neither of the latter two compounds could be detected in the experiment without added **5a**, this result demonstrates that **5a** has a significant, albeit small, ability to act as a debenzylating agent by reaction at its N′ position. Debenzylation of **6** through reaction of **5a** at its N position may also have occurred, but that would have regenerated the reactants and would not have been detectable. Reaction of **5a** directly with **6**, or with benzyl tosylate formed from **6**, or both, would be consistent with the observations. Phenylhydrazine under the same conditions was more effective than any of the foregoing nucleophiles; recovery of **6** was only 36%.

Scheme I



The possibility that any conversion of **6** to **7** might occur through intramolecular shift of a benzyl group was investigated by heating **6** in the presence of a fourfold excess of *p*-chlorobenzyl chloride. The only nonquaternary hydrazine derivative that could be found was *N*-benzyl-*N′*-*p*-chlorobenzyl-*N*-phenylhydrazine; no **7** was detected. The possibility that there might be significant exchange of benzyl groups between **7** and *p*-chlorobenzyl chloride was eliminated by a control experiment; **7** was recovered in 91% yield after treating with a fourfold excess of *p*-chlorobenzyl chloride for 4 h at 100 °C.

The effect of a change in the leaving group was investigated by means of a study of product composition as a function of temperature, using **5a** and benzyl *p*-toluenesulfonate instead of benzyl chloride, in either ethanol or toluene solution. The results are summarized in Table III. The series in ethanol covers a more limited temperature range, owing to its lower boiling point and increasing interference by reaction of the benzylating agent with the solvent at higher temperature.

The ratio of N-benzylation to N′-benzylation is markedly higher for benzyl tosylate than for the chloride, as can be seen by comparing the fraction n_N at 40 °C in Tables II and III. This is consistent with the fact that tosylate is a better leaving group than chloride, and the transition state would, therefore, be expected to be looser and less subject to steric crowding. The fraction n_N is nearly linear with temperature from 0 to 80 °C and is consistent with kinetic control in that range; the sharp drop in n_N from 80 to 100 °C indicates incursion of thermodynamic control through rearrangement. It is significant that kinetic control extends to a higher temperature than with benzyl chloride, as is to be expected in view of the poorer nucleophilicity of tosylate anion (cf. Figure 1).

The data in Table III also show the existence of a significant effect of the solvent on the selectivity of the alkylating agent. Alkylation at the less substituted site is favored more in toluene than in ethanol at all temperatures. This qualitative observation is consistent with the concept of a tighter transition state in toluene, the less polar solvent, leading to accentuation of steric hindrance. Reaction in toluene is, of course, slower than in ethanol. Further interpretation will be deferred until a quantitative study of the solvent effect for its own sake can be undertaken.

Electronic effects were examined by determining the selectivity in benzylation of a group of *N*-benzyl-*N*-phenylhydrazines bearing meta or para substituents on the *N*-phenyl group. Benzyl chloride was used insofar as feasible, but at the lowest temperatures the rate of reaction was very slow, and benzyl iodide was of necessity used instead. It is recognized that this reduces the overall comparability of the results, but in view of the results from benzylation of **5a** with both the chloride and iodide, the effect may not be serious.

The *N*-*p*-tolyl analogue **5b** (Table IV) differed from **5a** in three respects: alkylation was qualitatively slightly faster; incursion of rearrangement to the more stable product became noticeable at a slightly higher temperature; and the selectivity ratio n_N was higher by about 0.09 at temperatures where kinetic control appeared to be dominant. These results accord with the expected electronic influence of a *p*-methyl group, which should increase the nucleophilicity of the substituted nitrogen atom and reduce its effectiveness as a leaving group in nucleophilic displacement on the benzyl group by halide ion in the quaternary salt (analogue of **6**).

Alkylation of the *N*-*p*-anisyl analogue **5c** did not yield comparable results, owing to side reactions and extensive decomposition. Reaction was noticeably faster than with the *N*-*p*-tolyl compound, but the products were not entirely analogous. After 25 h at 0 °C with benzyl iodide in ethanol, there were obtained the quaternary salt (analogue of **6**) in 56.8% yield, recovered starting material (7.5%), benzaldehyde *N*-benzyl-*N*-*p*-anisylhydrazone (6.5%), *N*,*N*-dibenzyl-*p*-anisidine (8.1%), *N*-benzyl-*p*-anisidine (1.3%), *p*-anisidine (1.9%), and intractable tar (17.9%).

The *N*-*p*-nitrophenyl analogue of **5** was very resistant to alkylation and had low solubility. Significant reaction was observed only at temperatures of 40 °C and above, using long reaction times. The only product was a small amount of

Table IV. Benzylation of *N*-Benzyl-*N*-(chlorophenyl)hydrazines with Benzyl Iodide in Ethanol

Temp, °C	Mol % benzylation At N	Mol % benzylation At N′	Material balance, %[a]	Fraction of N-benzylation, n_N
			A. *p*-Chloro Isomer	
0[b]	60.0	6.7	95.8	0.90
20[c]	42.2	14.2	97.0	0.75
40[c]	0.0	16.7	67	0.0
			B. *m*-Chloro Isomer	
0[b]	20.4	16.7	90.5	0.55
20[c]	0.0	9.8	84.6	0.0

[a] Includes recovered starting material. [b] Concentration of each reagent = 1 M; reaction time 49 h. [c] Concentration of each reagent = 0.40 M; reaction time 25 h.

benzaldehyde *N*-benzyl-*N*-*p*-nitrophenylhydrazone, which may have been formed by oxidation of *N*,*N*′-dibenzyl-*N*-*p*-nitrophenylhydrazine first formed. The benzylation of *p*-nitrophenylhydrazine is reported to proceed similarly.[16] This behavior is not unexpected in view of the effect of the *p*-nitro group in strongly reducing the nucleophilicity of the substituted nitrogen, and to a lesser but still large degree that of the unsubstituted nitrogen. The slow pace of the alkylation provides time for the incursion of such side reactions as oxidation.

The results of benzylation of the *p*-chloro and *m*-chloro analogues **5d** and **5e** are summarized in Table IV. The significant features are: the influence of debenzylation and rearrangement of the quaternary salt is marked even at 20 °C; the *p*-chloro isomer is approximately twice as reactive as the *m*-chloro isomer; and the fraction n_N is markedly lower for the *m*-chloro isomer.

The enhanced susceptibility to debenzylation is an expected consequence of electron withdrawal by the chloro substituents, which should facilitate nucleophilic attack at a benzyl group on a quaternized nitrogen. This circumstance was further confirmed by warming *N*,*N*-dibenzyl-*N*-*p*-chlorophenylhydrazinium iodide for a short time in ethanol at 40 °C; debenzylation was nearly complete (96%).

The effect of chlorine substitution on the nucleophilicity at the N position can be estimated if it is assumed that the effect parallels that on the corresponding anilines. The rate constants for the reaction of *p*- and *m*-chloroaniline with 2,4-dinitrofluorobenzene in ethanol at 30 °C are 10.2×10^{-2} and 2.28×10^{-4}, respectively,[17] and the values of pK_a are 4.1 and 3.5. These facts lead to the qualitative expectation that the *m*-chloro derivative of **5** would react more slowly and would give a lower fraction of N-alkylation than the para isomer, as was found. The very easy reversibility of alkylation precludes a quantitative comparison; the very limited data suggest that the *p*-chloro derivative **5d** does not differ greatly from the unsubstituted **5a** in both rate of alkylation and site selectivity (n_N), as might have been expected, considering that aniline reacts over eight times faster with 2,4-dinitrofluorobenzene than does *p*-chloroaniline[17] and is a considerably stronger base.

The effect of phenyl substitution on the relative nucleophilicities of the two nitrogen atoms in phenylhydrazine might be approximated by the relative nucleophilicities of aniline and ammonia. For reaction with benzyl chloride, the ratio 2.51 for $k_{\text{aniline}}/k_{\text{ammonia}}$ can be estimated by use of the Edwards equation[18] in the absence of direct experimental comparison. This is in qualitative accord with the observed predominance of benzylation at the phenyl-substituted nitrogen. However, use of the Edwards equation for reaction with methyl bromide leads to the ratio 0.66, which does not correspond to the observed result of methylation of phenylhydrazine. It is evident that substituent effects on the nucleophilicity of amine nitrogen cannot simply be carried over to the inherently more polarizable hydrazine system, where even such an electron-withdrawing group as *m*-chlorophenyl increases the nucleophilicity of the substituted nitrogen relative to the other (cf. Table IV). Alkylation of hydrazines nevertheless shows sufficient sensitivity to structural, thermal, and solvent effects to provide significant systems for investigation of ambident nucleophiles. However, when benzyl groups are involved, the complications that result considerably limit the extent and the usefulness of the data obtainable.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were obtained as Nujol mulls, unless otherwise indicated, with a Perkin-Elmer Infracord Model 137 or a Perkin-Elmer grating infrared spectrophotometer Model 237B. Vaporphase chromatography was performed with a Perkin-Elmer gas chromatograph Model 810 using a 6-ft stainless-steel column packed with 3% Versamid 900 on 80/100 mesh Chromosorb W(HMDS treated). Thin-layer chromatograms were obtained using Eastman chromagram sheet Type K301R. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Commercially available solvents and reagents were used, unless otherwise indicated, and were purified where necessary.

Methyl Iodide. Eastman White Label methyl iodide was dried with anhydrous calcium chloride and then distilled through a 400-mm column packed with copper turnings. The fraction boiling at 41–42 °C was collected and stored over copper in amber bottles.

Benzyl Chloride. Baker and Adamson Reagent Grade benzyl chloride was dried over anhydrous calcium chloride and then distilled in a dry apparatus, bp 177–177.5 °C (755 mm).

Benzyl iodide was prepared from benzyl chloride by reaction with potassium iodide in absolute ethanol: bp 81.5–82 °C (3 mm) [lit.[19a] 93 °C (10 mm)]; specific gravity 1.73 (lit.[19b] 1.73).

Benzyl *p*-toluenesulfonate was prepared from benzyl alcohol and *p*-toluenesulfonyl chloride in pyridine: mp 57–58 °C (lit.[19c] 57.8 °C). It was stored under dry petroleum ether at −10 °C and was recrystallized just before use.

Eastman White Label phenylhydrazine was fractionally distilled under reduced pressure through a 300-mm Vigreux column: bp 63–65 °C (1.5 mm).

***N*-Methyl-*N*-phenylhydrazine.** *N*-Methyl-*N*-phenylhydrazine was prepared according to the procedure of Hartman and Roll[20] in overall 59% yield: hydrochloride, mp 137–138 °C; IR 2700 and 2080 cm^{-1} ($R_2N-^{+}NH_3$);[21] titrimetric equiv 158.1 (calcd 158.64).

***N*-Benzyl-*N*-phenylhydrazine** was prepared by treating phenylhydrazine successively with sodamide and benzyl chloride:[22] yield 62%; bp 164–166 °C (1.5 mm); $n^{24.5}{}_D = 1.6177$; IR 3330 cm^{-1} (NH).

***N*-Benzyl-*N*-(*p*-nitrophenyl)hydrazine** was obtained in 58% overall yield from benzaldehyde *N*-phenyl-*N*-benzylhydrazone by nitration followed by cleavage with 2,4-dinitrophenylhydrazine and hydrochloric acid.[23] It had mp 123–124 °C (reported[23] 121 °C); IR 3310 cm^{-1} (NH), 705, and 740 cm^{-1} (RC_6H_5), and 830 cm^{-1} (*p*-RC_6H_4R').

(a) ***N*-Benzylanilines.**[24] In a 500-mL three-necked flask equipped with a thermometer, mechanical stirrer, and Dean-Stark trap were placed 1.0 mol of the appropriately substituted aniline, 108 g (1.0 mol) of benzyl alcohol, and 19 g of 85% potassium hydroxide pellets. The mixture was stirred and heated rapidly up to boiling and kept boiling vigorously enough to maintain a moderate rate of condensation in the water separator. When the water started to distill (pot temperature, 170–190 °C), one-third of a solution of 4 g of benzaldehyde in 32 mL of benzyl alcohol was added. The remaining two one-thirds were added in 10-min intervals. The benzyl alcohol which distilled over with the water was recycled to the pot. When no more water was collected (45 min to 1 h), the heat was removed. The temperature of the pot was 250–260 °C at this time. The reaction mixture was cooled to 50 °C and then poured into 500 mL of ice–water. The benzylated aniline which separated was isolated by filtration or extraction and purified by recrystallization or distillation. The *N*-benzyl-(R)anilines so prepared were R = *p*-methoxy,[25] *p*-methyl,[26] H,[27] *p*-chloro,[28] and *m*-chloro.[29]

(**b**) ***N*-Nitroso-*N*-benzylanilines.** In a 2-L three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel was placed 0.5 mol of the appropriately substituted *N*-benzylaniline. The amine was dissolved in 950 mL of acetic acid and 75 mL of concentrated hydrochloric acid and 150 g of ice was added. After cooling the mixture to 5 °C, a solution of 35 g (0.5 mol) of sodium nitrite in 125 mL of water was slowly added over a period of 30 min while the temperature was kept under 20 °C. The reaction mixture was stirred for 30 min more and then poured into 2 L of ice and water. The oil which separated was cooled and scratched until it crystallized. The crude nitrosamine was filtered, washed with water, and recrystallized. The *N*-benzyl-*N*-nitroso-(R)anilines obtained in 62–97% yields were R = *p*-methoxy,[30] *p*-methyl,[26] H,[31] *p*-chloro,[32] and *m*-chloro. The last had mp 44.5–45.5 °C.

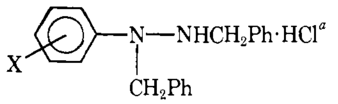
Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.48; H, 4.54; N, 11.50.

(c) **Benzaldehyde *N*-Benzyl-*N*-(substituted phenyl)hydrazones.** In a 3-L three-necked flask was placed a solution of 0.4 mol of the appropriately substituted *N*-nitroso-*N*-benzylaniline in 2 L of ethanol. To the vigorously stirred solution was added 104 g (1.6 mol) of zinc dust. The mixture was cooled to 10 °C and 240 mL of acetic acid was slowly added over a period of 25 min while the temperature was kept below 20 °C. The reaction mixture was filtered immediately and the solid was washed with acetic acid and ethanol. The filtrate was concentrated to 250 mL, and 500 mL of water was added. The mixture was made basic with 25% sodium hydroxide and extracted with ether. The ether was boiled off and the residual oil was dissolved in a hot solution of 400 mL of ethanol, 200 mL of water, and 110 mL of acetic acid; 40 mL of benzaldehyde was then added and the mixture was heated on a steam bath for 10 min. The mixture was slowly cooled to room temperature, and the benzaldehyde *N*-benzyl-*N*-arylhydrazone that crystallized was filtered off and washed with water and a little cold methanol. The benzaldehyde *N*-benzyl-*N*-(R)phenylhydrazones, obtained in 28–68% yields, were R = *p*-methoxy, *p*-methyl,[33] H,[34] *p*-chloro,[32] and *m*-chloro. The *p*-methoxy compound, mp 117.5–118.5 °C, and *m*-chloro compound, mp 115.5–116.5 °C, gave satisfactory analyses for C, H, and N.

(d) ***N*-Benzyl-*N*-(substituted phenyl)hydrazines.** In a 4-L flask were placed 0.3 mol of the appropriately substituted benzaldehyde *N*-benzyl-*N*-phenylhydrazone and 2.7 L of ethanol. The mixture was heated near boiling to dissolve the hydrazone, and 60 g of 2,4-dinitrophenylhydrazine and 37 mL of concentrated hydrochloric acid were then added. The mixture was heated on a steam bath for 1 h and left to cool. The 2,4-dinitrophenylhydrazone of benzaldehyde was filtered off and the filtrate was concentrated to a volume of 500 mL. To the stirred ethanolic solution were slowly added 1.5 L of ethyl ether and 2.0 L of petroleum ether to precipitate the *N*-benzyl-*N*-arylhydrazine hydrochloride, which was filtered, washed with ether, and dried. The free bases were liberated by treating the solids with aqueous sodium hydroxide and extracting with ether. The extracts were dried ($MgSO_4$), the ether was distilled off, and the residual oils were distilled in vacuo through a 300-mm Vigreux column. The *N*-benzyl-*N*-(R)phenylhydrazines and their hydrochlorides so obtained (15–79% yields) were R = *p*-methoxy,[35] *p*-methyl,[33,36] H,[34,37] *p*-chloro[29] (hydrochloride mp 172–173.5 °C), *m*-chloro[29] (hydrochloride mp 179–191 °C), and *p*-nitro[38] (hydrochloride mp 188–194 °C dec). Infrared spectra were in agreement with expectation, and equivalent weights of the hydrochlorides, from titration with sodium hydroxide, were correct.

***N*,*N'*-Dibenzyl-*N*-(substituted phenyl)hydrazine Hydrochlorides.** A neat mixture of 5.0 mmol of the *N*-benzyl-*N*-arylhydrazine and 5.0 mmol of benzyl chloride was heated at 110 °C for 4 h. The mixture was cooled and 30 mL of ether was added. The solid hydrochloride of the starting hydrazine was removed by filtration. The filtrate was treated with hydrogen chloride and the precipitate was filtered off, dissolved in 10 mL of 65% ethanol, and treated with 0.5 mL of benzaldehyde on a steam bath for 5 min to remove unreacted *N*-benzyl-*N*-arylhydrazine as the hydrazone. After cooling and filtering from the hydrazone, the filtrate was concentrated on a rotary evaporator. The residue was treated with aqueous sodium hydroxide and extracted with ether. The extract was dried ($MgSO_4$) and treated with hydrogen chloride. The precipitated colorless hydrochlorides were filtered off and recrystallized from ethanol/ether mixture. The results are collected in Table V. All of the salts showed infrared absorption[21] at 2450–2670 cm^{-1} characteristic of $>NNH_2{}^{+}-$.

Table V. *N*,*N'*-Dibenzyl-*N*-(R)phenylhydrazine Hydrochlorides. Preparation of



R	Yield, %	Mp,[b] °C
p-CH_3[c,d]		135–137 dec
p-CH_3[e]	77	170–172 dec
H[f]	92	185–187 dec (lit.[i] 186)
p-Cl[g]	62	173–175 dec
m-Cl[h]	25	172–174 dec

[a] Equivalent weights obtained by titration with standardized sodium hydroxide were correct in each case. [b] All the melting points vary with the rate of heating. These values were obtained by putting the sample in the melting point apparatus approximately 10–15 °C below its melting points. [c] This compound was prepared by warming *N*,*N*-dibenzyl-*N*-(*p*-methoxyphenyl)hydrazinium hydroxide to cause rearrangement, followed by neutralization with HCl. [d] Anal. Calcd for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found: C, 70.99; H, 6.64; N, 7.81. [e] Anal. Calcd for $C_{21}H_{23}ClN_2$: C, 74.42; H, 6.84; N, 8.27. Found: C, 74.45; H, 6.75; N, 8.22. [f] Reaction time of 6 h instead of 4. [g] Anal. Calcd for $C_{20}H_{20}Cl_2N_2$: C, 66.85; H, 5.61; N, 7.80. Found: C, 66.91; H, 5.69; N, 7.72. [h] Anal. Calcd for $C_{20}H_{20}Cl_2N_2$: C, 66.85; H, 5.61; N, 7.80. Found: C, 66.64; H, 5.47; N, 7.89. [i] H. Franzen and F. Kraft, *J. Prakt. Chem.*, 84, 122 (1911).

***N*,*N'*,*N'*-Tribenzyl-*N*-phenylhydrazine.** A neat mixture of 2.88 g (10 mmol) of *N*,*N'*-dibenzyl-*N*-phenylhydrazine and 2.18 g (10 mmol) of benzyl iodide was heated at 100 °C for 4 h. After cooling, 30 mL of ether was added and the *N*,*N'*-dibenzyl-*N*-phenylhydrazine hydriodide was filtered off. The filtrate was treated with hydrogen chloride to precipitate the unreacted starting hydrazine. After removal of the hydrochloride salt, the filtrate was evaporated. The yellowish residual solid was washed with petroleum ether (bp 40–60 °C) and recrystallized twice from ethanol to yield 0.42 g (11%) of a white solid, mp 143–143.5 °C. There was no N–H absorption in the infrared spectrum.

Anal. Calcd for $C_{27}H_{26}N_2$: C, 85.67; H, 6.92. Found: C, 85.34; H, 6.91.

***N*,*N*-Dimethyl-*N*-phenylhydrazinium Iodide[7b] (3).** A mixture of 2.44 g (20 mmol) of *N*-methyl-*N*-phenylhydrazine, 10 mL of dry benzene, and 2.84 g (20 mmol) of methyl iodide was allowed to stand at room temperature for 24 h. The tan crystalline precipitate weighed 3.73 g (77%) after washing with ether, mp 101–103 °C; IR same as recrystallized. Two recrystallizations from an ethanol/ether mixture gave a 70% recovery of white solid: mp 118–119 °C dec (lit.[7b,39,40] 122, 125, 126 °C dec); IR 3200, 3100 cm^{-1} (NH), 690, 770 cm^{-1} (C_6H_5).

Anal. Calcd for $C_8H_{13}IN_2$: I, 48.05. Found: I, 47.83.

Reduction of 3. To a solution of 1.0 g of **3** in 50 mL of water were added 20 g of zinc and 50 mL of concentrated hydrochloric acid. The mixture was refluxed for 20 h, then made strongly alkaline, and extracted with ethyl ether. After drying (Na_2SO_4), the extract was treated with hydrogen chloride gas. The oil that separated was isolated by decantation and then was treated with aqueous base and extracted with ether. Evaporation of the dried (Na_2SO_4) extract left a liquid, the infrared spectrum of which was identical with that of *N*,*N*-dimethylaniline. The hydrochloride and picrate salts prepared from it did not depress the melting point of authentic samples.

Table VI. Quaternary Hydrazinium Salts **6**: $RC_6H_4(C_6H_5CH_2)_2N^+\text{-}NH_2X^-$

			Infrared absorptions, cm^{-1}		
R	X	Mp, °C	$-NH_2$	C_6H_5-	RC_6H_4R'
p-CH_3O[a]	Cl	136-137 dec	3280, 3100	755, 710	900
p-CH_3O	I	118-119 dec	3290, 3080	750, 700	860
p-CH_3[b]	Cl	154-155	3300, 3110	750, 700	900
p-CH_3	I	120-121 dec	3290, 3120	750, 700	900
H	Cl	151.5-152 (lit.[7b] 153-154)	3260, 3100	760, 700	
H	I	130-131 dec (lit.[9] 133-134)	3220, 3100	760, 700	
H	p-$ToSO_3$	183-184	3300, 3120	770, 715	
p-Cl[c]	Cl	137.5-138	3290, 3100	740, 710	900
p-Cl	I	107-108 dec	3240, 3120	740, 705	900
m-Cl[d]	Cl	114-115	3290, 3100	745, 705	875, 790, 695
m-Cl	I	99-100 dec	3280, 3100	750, 710	875, 780, 695

[a] Anal. Calcd for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found: 71.22; H, 6.46; N, 7.79. [b] Anal. Calcd for $C_{21}H_{23}ClN_2$: C, 74.42; H, 6.84; N, 8.27. Found: C, 74.54; H, 6.88; N, 8.32. [c] Anal. Calcd for $C_{20}H_{20}Cl_2N_2$: C, 66.85; H, 5.61; N, 7.80. Found: C, 66.91; H, 5.64; N, 7.84. [d] Anal. Calcd for $C_{20}H_{20}Cl_2N_2$: C, 66.85; H, 5.61; N, 7.80. Found: C, 66.81; H, 5.70; N, 7.71.

***N,N*-Dimethyl-*N*-phenylhydrazinium Chloride.** The corresponding iodide (**3**) was passed through a column of Amberlite IRA 400 ion-exchange resin charged with chloride. The product was isolated from its concentrated solution in ethanol by precipitation with ether: mp 186-187 °C dec (lit.[7b] 187-188 °C dec); IR 3060, 3170 (NH) and 690, 770 cm^{-1} (C_6H_5R).

***N′*-Methyl-*N*-phenylhydrazine.** *N′*-Formylphenylhydrazine,[41] mp 143-144 °C, was reduced with lithium aluminum hydride in refluxing tetrahydrofuran, and the crude product was treated with dry hydrogen chloride to obtain *N′*-methyl-*N*-phenylhydrazine hydrochloride: mp 160-162 °C (lit.[41] 160-161 °C), neutral equiv 158.1 (calcd 158.6); IR 3220, 3050 and 270, 250 cm^{-1} ($RNHNH_2R^+$).

***N′,N′*-Dimethyl-*N*-phenylhydrazine** (**4**) was prepared from *N′*-methyl-*N*-phenylhydrazine by formylation and reduction with lithium aluminum hydride according to the method of Kratzl and Berger[42] in 45% yield. The hydrochloride had mp 193-195 °C dec, neutral equiv 172.9 (calcd 172.67), and IR 3200, 3040 and 2610, 2470 cm^{-1} ($RNHNHR_2^+$).

Reaction of Phenylhydrazine with Methyl Iodide in Benzene. A solution of phenylhydrazine (10.81 g, 0.10 mol) and methyl iodide (14.19 g, 0.10 mol) in 20 mL of dry benzene was kept below 35 °C by external cooling until the initial reaction was over, after which the mixture was left at room temperature for 21 h. Addition of 250 mL of ether precipitated 19.61 g of solid, which was dissolved in 10 mL of water and treated with 50 mL of 25% sodium hydroxide, and the solution was extracted with four 100-mL portions of ether. The aqueous layer was neutralized with hydrochloric acid and passed through a column of 50 g of Amberlite IRA 400 resin, chloride form. The effluent was concentrated on a rotary evaporator to a solid mass, 50 mL of warm ethanol was added, and the inorganic salts were removed by filtration. The ion-exchange and precipitation process was repeated, and the resulting solution was concentrated on a rotary evaporator to ca. 5 mL. Addition of ether precipitated 2.62 g (15.2 mmol) of *N,N*-dimethyl-*N*-phenylhydrazinium chloride, identified by its IR spectrum, which was identical with that of the known compound, and by its mp 185-187 °C dec (lit.[7b] 187-188 °C, dec), not depressed when mixed with an authentic sample.

The original basic ether extract (400 mL) was concentrated on a rotary evaporator, dried ($MgSO_4$), and treated with hydrogen chloride, which precipitated 7.96 g of solid. This material was warmed with 20 mL of ethanol, and 200 mL of ether was then added. Filtration gave 7.33 g (50.7 mmol) of phenylhydrazine hydrochloride, identified by its mp 237-238 °C (lit.[43] 240 °C), IR spectrum (identical with that of the known hydrochloride), and its neutral equiv, 144.2 (calcd 144.6).

The mother liquor from this procedure was combined with the first filtrate from the original reaction mixture. The solvents were removed on a rotary evaporator and the residual oil was chromatographed on silica gel with petroleum ether and benzene and the effluent fractions were treated with hydrogen chloride. There was thus obtained 1.304 g (7.55 mmol) of *N′,N′*-dimethyl-*N*-phenylhydrazine hydrochloride, mp 192-194 °C dec, and 0.232 g (1.46 mmol) of *N*-methyl-*N*-phenylhydrazine hydrochloride, mp 137-138 °C dec. The compounds had IR spectra and TLC R_f factors identical with those of the respective authentic compounds, and mixture melting points showed no depression. Colored substances developed at various stages during the separation procedures. Although they were removed by chromatography, they caused unavoidable losses.

***N,N*-Dibenzyl-*N*-phenylhydrazinium Salts (6).** The appropriate *N*-benzyl-*N*-(substituted phenyl)hydrazine was mixed with benzyl iodide in ethanol solution at 0 °C, and the salt that separated was recrystallized from ethanol. The chloride salts were prepared from the iodides by passing the latter through a column of Amberlite IRA 400 ion-exchange resin charged with chloride. The properties of the quaternary hydrazinium salts (**6**) so prepared are recorded in Table VI.

Reduction of *N,N*-Dibenzyl-*N*-phenylhydrazinium (6) Iodide. A mixture of 1.40 g (3.36 mmol) of **6** iodide, 40 mL of *tert*-butyl alcohol, and 10 g of Raney nickel W-2 was refluxed for 3 h. The nickel was removed by filtration and the *tert*-butyl alcohol was boiled off. The residual oil crystallized upon cooling to give 0.75 g (83%) of a white solid; after recrystallization from petroleum ether (bp 40-60 °C), its mp was 65-66 °C (lit.[44] for *N,N*-dibenzylaniline, 67 °C), and showed no N-H in the IR spectrum. The picrate had mp 130-132 °C (lit.[44] for *N,N*-dibenzylaniline picrate, 131-132 °C).

Quaternary Hydrazinium Hydroxides and the General Procedure for the Kinetic Study of Their Rearrangements. The hydroxides were prepared from the halides by means of an ion-exchange resin. For each milliequivalent of quaternary hydrazinium halide, 4 g of Amberlite IRA resin, chloride form, was used. The resin was preswelled in 25 mL of 4% sodium hydroxide for 5 min before filling the column. After the resin had settled, 125 mL of 4% sodium hydroxide was slowly passed through it (2-3 drops/s), and it was washed free of excess base with 200-250 mL of distilled water (2-3 drops/s).

A solution of approximately 1 mmol of appropriate hydrazinium halide in 10-15 mL of distilled water was slowly run through the column (1-2 drops/s). Collection of the effluent was begun when it tested basic to pH paper. Distilled water was added to the column when the liquid level of the solution fell to the top of the resin. The 20-23 mL of effluent collected was transferred to a 25-mL volumetric flask and diluted to the mark. The usual yield of the quaternary hydrazinium hydroxide was 85-90%. In experiments carried out in the presence of excess hydroxide or hydrazinium cation, the desired quantity of sodium hydroxide solution or quaternary hydrazinium halide was added before the solution was made up to 25 mL. The hydroxide solution was then placed in a constant-temperature bath (±0.1 °C). Aliquots of 2 mL were removed periodically and titrated with 0.100 N hydrochloric acid, using phenolphthalein as indicator because it was not sensitive to the weakly basic rearrangement product. The results are summarized in Table I.

Rearrangement of 6 Hydroxide. (A) In Water. A mixture of 0.650 g (2.0 mmol) of **6** chloride and 25 mL of 5% sodium hydroxide was heated at ca. 50 °C for a few minutes. The insoluble rearrangement product was extracted with ether, dried ($MgSO_4$), and treated with hydrogen chloride, which precipitated 0.385 g of a salt, identical with a known sample of **7** hydrochloride according to IR spectrum, mp

185-187 °C dec (lit.[45] 186 °C), mmp 184-186 °C dec, and TLC. Reduction with Raney nickel W-2 in *tert*-butyl alcohol gave a mixture of *N*-benzylaniline and benzylamine (identified by VPC and TLC).

(B) In 65% Ethanol. A solution of 0.395 g (0.95 mol) of **6** iodide in 50 mL of 65% aqueous ethanol was passed through a column of 3 g of Amberlite IRA 400, charged with hydroxide, and the effluent warmed at 50-60 °C for 5 min and then acidified with hydrochloric acid. The solution was concentrated on a rotary evaporator to yield 0.234 g (76%) of *N*,*N*′-dibenzyl-*N*-phenylhydrazine hydrochloride. The recrystallized material (from ethanol) had mp 185-186 °C dec (lit.[45] 186 °C), and IR spectrum identical with an authentic sample.

Rearrangement of 6c Ethoxide in Ethanol. A solution of 1.7 mmol of sodium ethoxide in 3 mL of absolute ethanol was added to a solution of 0.532 g (1.5 mmol) of **6c** chloride in 15 mL of absolute ethanol. The mixture was cooled in ice, 3 mL of ether was added, and the precipitated sodium chloride was filtered off. The filtrate was warmed at 50-60 °C for 5 min and treated with hydrogen chloride. The solution was concentrated on a rotary evaporator to a volume of approximately 5 mL and 35 mL of ether was added to precipitate 0.384 g (72%) of salt, identified as **7c** hydrochloride. The recrystallized material (from ethanol) had mp 135-137 °C dec, IR 2450-2700 cm^{-1} ($R_2N-NH_2R^+$), neutral equiv 354.9 (calcd 354.88).

Anal. Calcd for $C_{21}H_{23}H_2ClO$: C, 71.07; H, 6.53; N, 7.89. Found: C, 70.99; H, 6.64; N, 7.81.

A sample of the free base was allowed to oxidize slowly in air to a pale yellow solid. Recrystallization from an ethanol/petroleum ether mixture gave benzaldehyde *N*-benzyl-*N*-(*p*-methoxyphenyl)hydrazone: IR identical with that of an authentic sample; mp 116-117 °C; mmp 116-118 °C.

Rearrangement of 6c Hydroxide. A mixture of 2.0 g (5.6 mmol) of **6c** chloride and 50 mL of 5% sodium hydroxide was heated at 50-60 °C for about 5 min. The product was extracted with ether, dried ($MgSO_4$), and treated with hydrogen chloride to yield 1.5 g (75%) of salt. Recrystallization from ethanol/ether gave pure **7c** hydrochloride, mp 134-136 °C dec, IR spectrum identical with that of authentic material.

***N*-Benzyl-*N*-methyl-*N*-phenylhydrazinium iodide** was prepared from *N*-methyl-*N*-phenylhydrazine and benzyl iodide in ethanol at 0 °C. After 40 h, the product was precipitated by addition of ether, washed with ether, and recrystallized from a methanol/ether mixture: mp 120 °C dec (lit.[7b] 122 °C); IR 3080, 3190 cm^{-1} ($R_3N^+-NH_2$).

Anal. Calcd for $C_{14}H_{17}IN_2$: I, 37.30. Found, I, 37.29.

Benzaldehyde *N*-methyl-*N*-phenylhydrazone was prepared from *N*-methyl-*N*-phenylhydrazine and benzaldehyde and had mp 102-103 °C (lit.[46] 102-102.5 °C).

***N*′-Benzyl-*N*-methyl-*N*-phenylhydrazine Hydrochloride.** A solution of 0.84 g (4.0 mmol) of benzaldehyde *N*-methyl-*N*-phenylhydrazone in 4 mL of 1:1 ether/tetrahydrofuran was added to a stirred mixture of 0.20 g (5.0 mmol) of lithium aluminum hydride in 8 mL of 1:1 ether/tetrahydrofuran and the mixture was refluxed for 3 h. The excess hydride was destroyed with wet tetrahydrofuran, water was added, and the mixture was extracted with ether. The ether solution was dried ($MgSO_4$) and treated with hydrogen chloride. Removal of the solvent left a yellow oil. The free base was liberated with aqueous sodium hydroxide, extracted with ether, dried, and treated with hydrogen chloride. Addition of petroleum ether to the cloud point and chilling at −10 °C for 24 h gave a white crystalline solid, which was filtered off and washed with ether, yield 0.42 g (84%). Recrystallization from ethanol/petroleum ether yielded an analytical sample: mp 123-124 °C, IR 2450-2700 cm^{-1} ($R_2N-NH_2R^+$); neutral equiv 248.60 (calcd 248.76). TLC showed only one spot.

Anal. Calcd for $C_{14}H_{17}ClN_2$: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.79; H, 6.91; N, 11.14.

Attempted Rearrangement of *N*-Benzyl-*N*-methyl-*N*-phenylhydrazinium Hydroxide. A solution of 0.106 g (0.4 mmol) of *N*,*N*-dimethyl-*N*-phenylhydrazinium iodide in 6 mL of distilled water was passed through an ion-exchange column containing 1.6 g of Amberlite IRA 400 resin, charged with hydroxide. The basic effluent was heated at 80 °C for 3 h and then acidified with hydrochloric acid. The water was removed on a rotary evaporator to give a white solid, which was dissolved in 1 mL of hot ethanol and reprecipitated with a large excess of ether. The yield of recovered **3** chloride, mp 186-187 °C dec (lit.[7b] 187-188 °C dec), was 0.059 g (0.34 mol, 86%). The IR spectrum showed the absence of substituted hydrazine hydrochloride salts.

Benzylation Reactions. (A) Using Benzyl Chloride or Iodide. Generally, solutions of 10.00 mmol of the *N*-benzyl-*N*-arylhydrazine in 12.5 mL of absolute ethanol and 10.00 mmol of the benzyl halide in 12.5 mL of absolute ethanol were brought to the desired temperature ±0.1 °C in a constant temperature bath for 45 min, mixed, and allowed to react for a fixed time. In the case of *N*-benzyl-*N*-chlorophenylhydrazines at 0 °C, 10.00 mmol of the hydrazine and 10.00 mmol of benzyl iodide in 10 mL of absolute ethanol were used.

(B) Using Benzyl *p*-Toluenesulfonate. For reactions in ethanol, 10.00 mmol of benzyl *p*-toluenesulfonate was added directly to a solution of 10.00 mmol of *N*-benzyl-*N*-phenylhydrazine in 25 mL of absolute ethanol, which had been brought to the desired temperature, and allowed to react for 25 h.

For reactions in toluene, solutions of 10.00 mmol of *N*-benzyl-*N*-phenylhydrazine in 12.5 mL of dry toluene and 10.00 mmol of benzyl *p*-toluenesulfonate in 12.5 mL of dry toluene were brought to the desired temperature, mixed, and allowed to react for fixed times.

All reactions were quenched by adding to a mixture of 25-50 mL of ether and 100-150 mL of petroleum ether (bp 90-100 °C). The precipitated solid, if any, was filtered off, washed with ether, and dried (fraction A). The combined filtrates were concentrated on a rotary evaporator under reduced pressure at 40-50 °C to a volume of ca. 35-40 mL, petroleum ether (bp 90-100 °C) was added, and the process was repeated. The solid thus precipitated was filtered off, washed with ether, and dried (fraction B). The ether wash and filtrate were treated with hydrogen chloride to precipitate the remaining hydrazines in solution. The hydrochloride salts were filtered off, washed with ether, and dried (fraction C). The filtrate was concentrated on a rotary evaporator and the residual oil (fraction D) was examined by thin-layer chromatography. If any of the benzaldehyde *N*-benzyl-*N*-arylhydrazone, which arises from the oxidation of **7**, or the *N*,*N*-dibenzylaniline, which arises from the nitrogen-nitrogen bond cleavage of **6**, were detected, these were isolated by column chromatography.

For the benzylation of **5a** with benzyl *p*-toluenesulfonate in toluene, the work-up procedure was slightly modified. The reaction mixture was added to a mixture of 25 mL of ethyl ether and 100 mL of petroleum ether and cooled in ice. The precipitate was filtered off, washed with ether, and dried. The filtrate was treated with hydrogen chloride. The hydrochloride salts were filtered off, washed with ether, and dried. The filtrate was concentrated on a rotary evaporator, treated with aqueous sodium hydroxide on a steam bath for a few minutes, and extracted with ether. The ether solution was dried with magnesium sulfate, concentrated, and chromatographed on silica gel with petroleum ether and benzene.

Assay of Products. The components of the several fractions were determined qualitatively by a combination of infrared spectroscopy and thin-layer chromatography. Owing to the distinctly different absorptions of N-H in the infrared for $R_3N^+-NH_2$ (3050-3200 cm^{-1}), $R_2N-{}^+NH_3$ (2650-2670 cm^{-1}), and $R_2N-NH_2R^+$ (2450-2700 cm^{-1}), the presence of any or all of the compounds was easily ascertained. Thin-layer chromatographic analysis was useful for verifying the presence of R_2N-NH_2 and R_2N-NHR. The use of silica gel as the absorbant was particularly helpful, since the R_f values were then inversely related to the basic strength of the hydrazines. Melting points were seldom relied upon for identification, since the products were usually mixtures and many of the melting points are actually decomposition points which vary markedly with the rate of heating.

The quantitative composition of the products was determined by a combination of titrimetric and gravimetric analysis. Standard sodium hydroxide with phenolphthalein as an indicator was used to titrate the acidic hydrazine salts, and silver halide precipitation with silver nitrate solution was used to determine the total halide. The data from these methods when combined with the identity of the components in the several fractions, which were essentially binary mixtures, allowed the compositions to be calculated; see Tables II-IV.

Reaction of Benzyl Chloride with 5a at 110 °C. A neat mixture of 9.91 g (50.0 mmol) of *N*-benzyl-*N*-phenylhydrazine and 6.35 g (50.0 mmol) of benzyl chloride was heated at 110 °C for 6 h, after which 100 mL of ether was added; 5.53 g of hydrochloride salts was filtered off. The filtrate was treated with hydrogen chloride to yield another fraction, 7.61 g of hydrochloride salts. The foregoing method of analysis indicated these fractions to consist of 24.0 mmol of **5a** (as the hydrochloride) and 23.1 mmol of **7** (as the hydrochloride) (material balance 94.2%). No *N*,*N*-dibenzyl-*N*-phenylhydrazinium chloride was detected.

Reaction of Benzyl Chloride with 5a at Room Temperature. A neat mixture of 1.9826 g (10.00 mmol) of **5a** and 1.2653 g (10.00 mmol) of benzyl chloride was allowed to react at room temperature for 4 days. Addition of 25 mL of ether precipitated 1.233 g of solid, which was filtered off. The filtrate was treated with hydrogen chloride to yield 1.423 g of hydrochloride salts. Analysis showed the reaction product to consist of 3.39 mmol of *N*,*N*-dibenzyl-*N*-phenylhydrazinium chloride, 5.90 mmol of **5a** (as the hydrochloride), and 0.52 mmol of **7** (as the hydrochloride). The fraction of N-benzylation was 0.867 and 0.133 for N′-benzylation (material balance was 98.1%).

Reaction of 5c with Benzyl Iodide in Ethanol at 0 °C. A solution of 3.425 g (15 mmol) of **5c** and 3.2707 g (15 mmol) of benzyl iodide in 37.5 mL of absolute ethanol was allowed to stand for 25 h. Addition of 300 mL of petroleum ether to the dark red mixture precipitated 3.800 g (8.52 mmol) of *N*,*N*-dibenzyl-*N*-(*p*-methoxyphenyl)hydrazinium iodide (**6c**): mp 118–119 °C dec; IR 3290, 3080 cm^{-1} (R_3N^+–NH_2). Anal. Calcd for $C_{21}H_{23}IN_2O$: I, 28.43. Found I, 28.45. The filtrate was treated with hydrogen chloride, but only a blackish oil was obtained. The solvents were removed on a rotary evaporator and the residue was treated with aqueous sodium hydroxide and then extracted with ether. After drying ($MgSO_4$), the ether was boiled off and the residue was chromatographed on silica gel and eluted with benzene and ether. The following substances were eluted: benzaldehyde *N*-benzyl-*N*-(*p*-methoxyphenyl)hydrazone (0.97 mmol, mp 115–116 °C, mmp 115–116 °C); *N*,*N*-dibenzyl-*p*-anisidine (1.22 mmol, mp 80–81 °C, mmp 80–81 °C); *N*-benzyl-*p*-anisidine (0.20 mmol); *N*-benzyl-*N*-*p*-anisylhydrazine (1.13 mmol); and *p*-anisidine (0.29 mmol). These compounds were identified by comparison of the infrared spectra of their hydrochlorides with those of the known compounds and by their TLC R_f values. The remaining 17.9% of material was lost as tars and intractable oils.

Thermolysis of 6. (A) **At 100 °C without Solvent.** *N*,*N*-Dibenzyl-*N*-phenylhydrazinium chloride (**6**, 0.325 g, 1.0 mmol) was heated at 100 °C for 4 h in a 2-mL stoppered flask. After 2.5 h, the solid had liquefied and by 4 h there was both solid and liquid present. Ethyl ether and petroleum ether were added and the white solid (0.77 g, 0.32 mmol) that precipitated was identified as *N*-benzyl-*N*-phenylhydrazine hydrochloride by its mp, 170–172 °C, and the identity of its IR spectrum to that of the known compound. The filtrate was treated with hydrogen chloride to yield 0.153 g (0.54 mmol) of hydrochloride salts. Analysis by infrared TLC and titration showed the composition to be 0.23 mmol of *N*-benzyl-*N*-phenylhydrazine hydrochloride and 0.31 mmol of **7** hydrochloride. None of the starting material was detected.

(**B**) **In Refluxing Ethanol.** A solution of 0.650 g (2.0 mmol) of **6** chloride in 5.0 mL of ethanol was refluxed for 5.5 h. The mixture was poured into 75 mL of petroleum ether (bp 90–100 °C) and concentrated on a rotary evaporator. This process was repeated, and the solid (0.195 g, 0.75 mmol) was then filtered from residual liquid. Analysis by infrared, TLC, gravimetric determination of chloride, and alkalimetric titration showed the solid to consist of 0.22 mmol of starting material and 0.53 mmol of *N*-benzyl-*N*-phenylhydrazine hydrochloride. Treating the filtrate with hydrogen chloride precipitated 0.213 g (0.82 mmol) of hydrochloride salt, which was found to consist of 0.64 mmol of *N*-benzyl-*N*-phenylhydrazine hydrochloride and 0.18 mmol of **7** hydrochloride. Analysis of the filtrate from this by TLC showed the remaining material to be benzaldehyde *N*-benzyl-*N*-phenylhydrazone, produced by the air oxidation of **7**.

(C) **In Dimethylacetamide at 40 °C.** A solution of 0.283 g (0.87 mmol) of **6** chloride in 25 mL of dimethylacetamide was heated at 40 °C for 24 h. The solvent was removed under vacuum at 40 °C (10 min required); 25 mL of ether was then added and 0.050 g (0.15 mmol) of solid, identified as **6** chloride, was filtered off. Treating the filtrate with hydrogen chloride precipitated 0.140 g (0.60 mmol) of *N*-benzyl-*N*-phenylhydrazine hydrochloride, identified from its IR spectrum (identical with known sample), mp 170–171 °C, and its neutral equiv, 234.9 (calcd 234.73). The extent of debenzylation was thus 83%.

(**D**) **In Aniline at 100 °C.** A mixture of 0.0873 g (0.27 mmol) of **6** chloride and 0.222 g (2.39 mmol) of aniline was heated at 100 °C for 3 h. After cooling, ethyl ether was added and the solid was filtered off. The 0.0308 g (0.24 mmol) of solid was identified as aniline hydrochloride from its infrared spectrum, identical with that of an authentic sample, its mp 195–196 °C (lit.[47] 198 °C), and mmp 195–196 °C. The filtrate was concentrated to a yellow oil, which was treated with benzenesulfonyl chloride and 5% sodium hydroxide. The solid that precipitated was extracted with ether. Acidification of the aqueous alkaline layer precipitated 0.2015 g of benzenesulfonanilide, identified by its IR spectrum and its mp 110–111 °C (lit.[48] 110 °C). The ether solution was concentrated and petroleum ether was added to precipitate a cream solid: 0.0175 g; mp 115–116 °C, undepressed by mixture with *N*-benzylbenzenesulfonanilide; IR spectra superimposable.

***p*-Chlorobenzaldehyde *N*-Benzyl-*N*-phenylhydrazone.** Upon heating a solution of 0.99 g of *N*-benzyl-*N*-phenylhydrazine and 0.70 g of *p*-chlorobenzaldehyde in 10 mL of ethanol, the hydrazone precipitated. After recrystallization from ethanol, it weighed 1.2 g; mp 127.5–128.5 °C.

Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.88; H, 5.34; N, 8.73. Found: C, 75.12; H, 5.35; N, 8.69.

Thermolysis of 6 Chloride in *p*-Chlorobenzyl Chloride at 100 °C. A mixture of 0.325 g (1.0 mmol) of **6** chloride and 0.644 g (4.0 mmol) of *p*-chlorobenzyl chloride was heated at 100 °C for 4 h. After cooling, it was poured into 100 mL of 1:1 ether/petroleum ether; 0.080 g (0.32 mmol) of *N*-benzyl-*N*-phenylhydrazine hydrochloride was removed by filtration. Treating the filtrate with hydrogen chloride precipitated 0.160 g (0.52 mmol) of hydrochloride salts: IR 2650–2660, 2000–2020 (R_2N–$^+NH_2R$), 705, 750, 825 cm^{-1} (C_6H_5– and *p*-C_6H_4–). TLC of the bases freed from these hydrochlorides showed two compounds, one identified as *N*-benzyl-*N*-phenylhydrazine and the other with an R_f value just slightly larger than that of **7**. The free bases were chromatographed on silica gel using petroleum ether and benzene. The fraction containing the trisubstituted hydrazine was treated with hydrogen chloride; the white precipitate, mp 160–162 °C, had neutral equiv of 359.25 (calcd for *N*-benzyl-*N*′-(*p*-chlorobenzyl)-*N*-phenylhydrazine (**7d**) hydrochloride 359.30): IR 2400–2700 (R_2N–$^+NH_2R$), 845 (*p*-C_6H_4–), 810 (Ar–Cl) cm^{-1}.

The free base dissolved in 3 mL of ethanol was warmed with 0.3 g of mercuric oxide for a few minutes after adding 1 drop of hydrazine hydrate. The mixture was filtered hot, concentrated, and cooled to precipitate the white hydrazone. The TLC (one spot) and the IR spectrum were identical with those of *p*-chlorobenzaldehyde *N*-benzyl-*N*-phenylhydrazone. The solid melted at 119–123 °C, mmp 115–125 °C. Since recrystallization did not improve the melting point, the material, evidently a mixture of the two isomers, was refluxed for 15 min in acidic aqueous ethanol. The solid that crystallized on cooling had mp 127–128 °C, mmp 127–128.5 °C with authentic *p*-chlorobenzaldehyde *N*-benzyl-*N*-phenylhydrazone. No evidence of the presence of benzaldehyde *N*-benzyl-*N*-phenylhydrazone (mp 110 °C) was detected.

Thermolysis of *p*-Chlorobenzyl Chloride and 7 at 100 °C. A mixture of 0.288 g (1.0 mmol) of **7** and 0.644 g (4.0 mmol) of *p*-chlorobenzyl chloride was heated at 100 °C for 4 h. Addition of 1:1 ether/petroleum ether and passing in hydrogen chloride precipitated 0.295 g (91%) of **7** hydrochloride: mp 184–186 °C dec; mmp 185–187 °C dec; neutral equiv 324.7 (calcd 324.85). Their spectrum showed no absorption characteristic of 1,4-disubstituted benzene.

Thermolysis of 6 Chloride in Refluxing Toluene. A mixture of 0.325 g (1.0 mmol) of **6** chloride and 10 mL of dry toluene was refluxed for 6 h. A trace amount of unidentified solid was removed by filtration. The filtrate was treated with hydrogen chloride to yield 0.197 g (84%) of *N*-benzyl-*N*-phenylhydrazine hydrochloride: mp 170–172 °C; neutral equiv 234.8 (calcd 234.73); IR 2660, 2020 cm^{-1} (–$^+NH_3$). The filtrate was concentrated and then briefly exposed to vacuum to remove the final traces of hydrogen chloride. A warm solution of 0.144 g (1.0 mmol) of α-naphthol and 0.054 g (1.0 mmol) of sodium methoxide in 4 mL of dry methanol was added and refluxed for 6 h. Ethyl ether was added to precipitate the sodium chloride, which was filtered off. The solvents were removed and the residual oil was chromatographed on silica gel with a petroleum ether/benzene mixture to yield 0.175 g (75%) of benzyl α-naphthyl ether: mp and mmp 77–78 °C (lit.[49] 77–77.5 °C); IR superimposable on that of an authentic sample.

Stability of 6 Chloride in Ethanol at 65 °C. A solution of 0.325 g (1.0 mmol) of **6** chloride in 5 mL of ethanol was heated at 65 °C for 4 h. The starting material (0.24 g) was precipitated by adding 15 mL of ether and 50 mL of petroleum ether (bp 90–100 °C); partial concentration of the filtrate gave a further 0.026 g. The recovery of **6** chloride was 81.8%: IR superimposable on that of starting material; mp 151–152 °C (cf. Table VI). Titration with sodium hydroxide detected no *N*-benzyl-*N*-phenylhydrazine hydrochloride or other acidic component in the solid.

Stability of 6 Iodide in Ethanol at 65 °C. In an experiment similar to that with **6** chloride, the recovery of **6** iodide, mp 130-131 °C, was 62.5%; titration of the solid with sodium hydroxide showed it to be free of *N*-benzyl-*N*-phenylhydrazine hydriodide. Evaporation of the filtrate left a black semisolid which could not be identified.

Stability of 6 *p*-Toluenesulfonate. (A) In Ethanol at 65 °C. In a similar experiment using **6** *p*-toluenesulfonate, recovery was 97.5%. Titration with sodium hydroxide showed the absence of nonquaternary salts.

(B) With *N*-Benzyl-*N*-phenylhydrazine in Ethanol at 65 °C. A solution of 0.460 g (1.0 mmol) of **6** *p*-toluenesulfonate and 0.198 g (1.0 mmol) of *N*-benzyl-*N*-phenylhydrazine in 5 mL of ethanol was heated at 65 °C for 4 h. After cooling, 15 mL of ether and 50 mL of petroleum ether (bp 90-100 °C) were added. The white precipitate was filtered off and washed with ether, weight 0.443 g. Assay in the manner described showed it to consist of 0.932 mmol of starting material and 0.038 mmol of *N*-benzyl-*N*-phenylhydrazinium *p*-toluenesulfonate. The filtrate was treated with hydrogen chloride, the precipitated salts were collected and treated with aqueous sodium hydroxide, and the free bases were extracted with ether, dried ($MgSO_4$), and chromatographed on silica gel with benzene. The only significant eluted fraction was treated with hydrogen chloride, which gave 0.013 g (0.040 mmol) of **7** hydrochloride: mp 184-186 °C dec; IR 2450-2700 cm^{-1} ($R_2N{-}^{+}NH_2R$).

(C) With Phenylhydrazine in Ethanol at 65 °C. A solution of 0.460 g (1.0 mmol) of **6** *p*-toluenesulfonate and 0.108 g (1.0 mmol) of phenylhydrazine in 5 mL of ethanol was heated at 65 °C for 4 h. After cooling, 15 mL of ether and 50 mL of petroleum ether (bp 90-100 °C) were added. The white precipitate was filtered off, weight 0.329 g; partial concentration of the filtrate gave a further 0.037 g. Infrared and titrimetric assay of the combined solid showed it to contain 0.363 mmol (36.3% recovery) of **6** *p*-toluenesulfonate. The other component had the same TLC R_f factor as *N*-benzyl-*N*′-phenylhydrazine, with which the IR spectrum of the mixture was consistent.

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