acetic acid in the presence of Se and speculate that Se is the reducing agent. While Se *is* formed in the reaction of the bromoimidazo-[1,2-*a*]pyridine **2a** with SeO_2 in refluxing acetic acid and thus could, in principle, cause the reduction, it is *not* formed in the reaction of parent **4** with SeO_2 in refluxing acetic acid. These observations also implicate acetic acid.

(19) Unpublished results, our laboratory; ref 5.

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(21) The found percentages of C, H, and N were multiplied by the same factor to obtain the compensated percentages. The factor is arbitrary since the structures of inorganic material and its combustion product are not known and therefore the percent inorganic material prior to combustion cannot be calculated. In any event, the found C, H, and N percentages are in the ratio of 14:11:5, as required.

An Example of the Amine Catalyzed Retro-Aldol Reaction. Dehydration and Cleavage of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol. A Case of Kinetic and Thermodynamic Competition

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Received March 3, 1976

The behavior of the two racemic pairs of 1-(3-chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol (1) on treatment with heat and acid is reported. Initially, in 85% phosphoric acid dehydration to the terminal olefin 2-(3-chlorophenyl)-3-phenyl-3-(2-pyridine)propene (**2**) occurs followed by isomerization to the conjugated, thermodynamically preferred material, 2-(3-chlorophenyl)-1-phenyl-1-(2-pyridine)propene (**3**). The dehydration pathway is in direct competition with fragmentation of **1** to 3-chloroacetophenone (**4**) and 2-benzylpyridine (**5**). Exclusive thermal rearrangement of **1** to **4** and **5** is the first example of an amine catalyzed retro-aldol reaction where the intermediate Schiff's base is contained within a heterocyclic ring. On the basis of greater thermal stability of isomer **1a** as compared to **1b**, structures are proposed for the two racemic pairs of compound **1**.

1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)-ethanol (**1**), on oral administration to the rat, possesses excellent hypocholesteremic activity and extremely low toxicity.[1] Unfortunately, in monkeys and man it is not hypocholesteremic.[1] Currently this dichotomy of activity is being investigated by examining the metabolic products obtained from dosages of radiolabeled **1** to both rats and monkeys and exploring its physical and chemical properties.[2,3] Knowledge gained by these studies hopefully will lead to the design and synthesis of compounds effective in man.

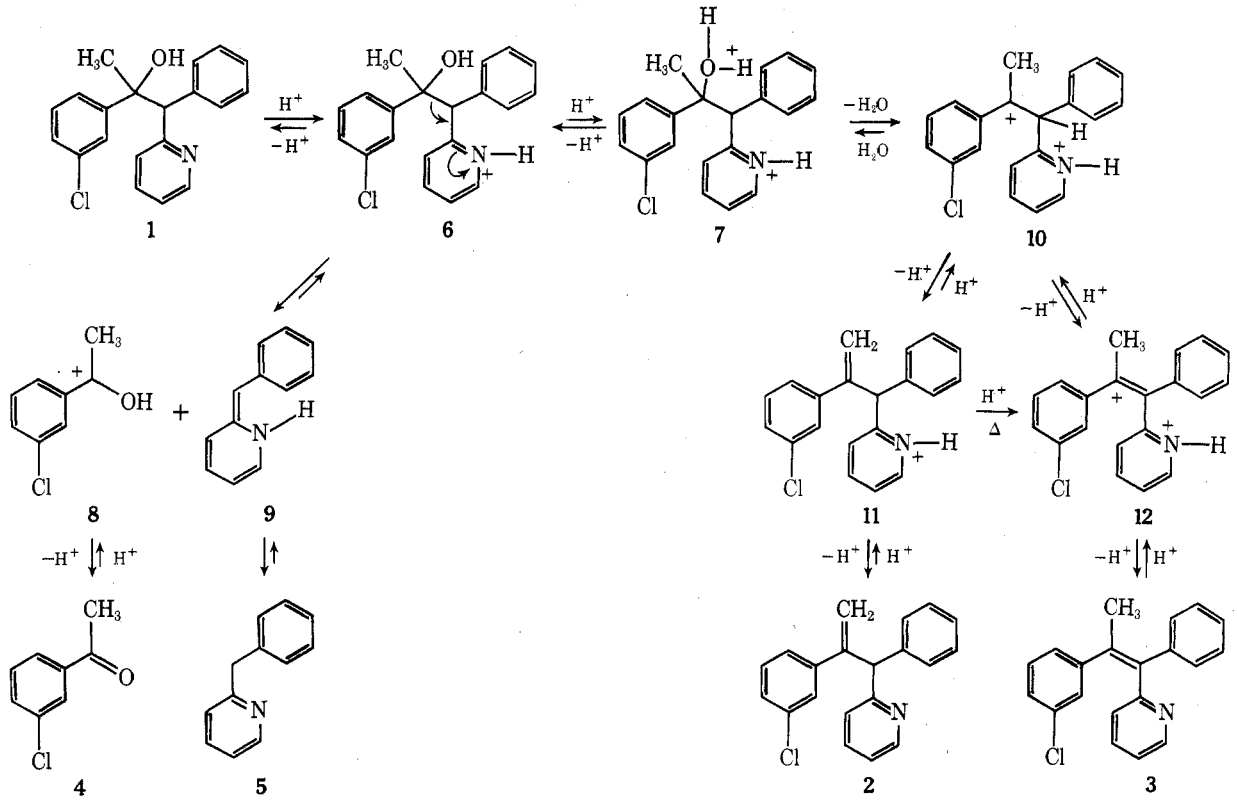
It should be noted that compound **1** contains two chiral centers and it is obtained from synthesis as a mixture of two racemic pairs.[1,2] These pairs, which can be separated by fractional crystallization, are distinguished by characteristic NMR and melting points. Only the higher melting racemate (**1a**) possesses significant ability to lower blood cholesterol levels in the rat. One of a number of likely candidates for a metabolite of **1** is the conjugated alkene, 2-(3-chlorophenyl)-1-phenyl-1-(2-pyridine)propene (**3**), derived from **1** by the loss of water. An earlier report[1] describes dehydration of a number of 2-(2-pyridyl)-1,2-diarylalkanols by treatment with 85% phosphoric acid at 100 °C for 3 h. Conjugated alkenes analogous to **3** were the only reported products.[1] The present study involves investigation of the behavior of alcohol **1** to treatment with phosphoric acid both as a pathway to the synthesis of possible metabolite **3** and to gain knowledge of its acid sensitivity with respect to decomposition.

Compound **1**, as a mixture of the two racemic pairs, was dissolved in 85% phosphoric acid and was stirred at 110 °C for 3 h. A white, crystalline solid was isolated from the reaction mixture in 33.4% yield after numerous purifications. It proved to be the terminal olefin **2** and not the expected conjugated alkene **3**. The reaction mixture also contained approximately equal amounts of 3-chloroacetophenone (**4**) and 2-benzylpyridine (**5**), small amounts of unreacted **1**, and a trace of a material which was later identified as the conjugated alkene **3** (Scheme I).

These results led to an investigation of the behavior of the higher and lower melting racemates of **1** separately but under identical conditions. When the higher melting racemate (**1a**) was treated under these conditions, **2** was again isolated but with a yield which had increased to 70%. Though all other side products were also present, combined they represented a much smaller percentage of the total product yield than that of the previous experiment (Table I). The lower melting racemate (**1b**), when treated in the same fashion, also produced the same five compounds. In this case, the high yield of decomposition products 3-chloroacetophenone and 2-benzylpyridine made separation of **2** or **3** from the reaction mixture difficult. These results coupled with earlier experimental findings[4] suggest that **1a** is more stable to conditions of heat and acid than its lower melting counterpart (**1b**). Yet these data do not explain the predominance of the dehydrated product **2** in preference to the expected conjugated alkene **3**.

When a mixture of both racemic pairs of **1** was submitted to identical reaction conditions for 5 h instead of the usual 3 h, the product distribution was essentially the same. But when the reaction time was extended to 24 h, a definite change took place. Conjugated alkene **3** was now present in substantial quantity along with **2** and decomposition products **4** and **5**. After treatment of **1** under these conditions for 72 h, only a trace of **2** remained, and **3**, now a major product, was isolated as a white, crystalline solid. These data strongly suggest that **2** is the initially formed kinetic product which is then isomerized to the thermodynamically more stable conjugated al-

Scheme I



kene **3** (Scheme I). This hypothesis was further substantiated when **2** was dissolved in 85% phosphoric acid and the mixture was immersed in a bath maintained at 110 °C. After 48 h of stirring under these conditions, conjugated alkene **3** was generated in greater than 85% yield. Only trace amounts of compounds **2**, **4**, and **5** were detected.

Under the reaction conditions, **1** mostly likely exists as its conjugate acid **6** and is in equilibrium with its diprotonated form **7**. The results suggest an initial competition between fragmentation of **6** to **4** and **5** via cation **8** and pyridyl tautomer **9** and dehydration of **7** to **2** (**11**) through common intermediate **10**. Once dehydration has taken place there is limited decomposition of **2** (**11**) or **3** (**12**) to **4** and **5** unless extended reaction times are employed. There also seems to be negligible direct conversion of **1** to **3** (**12**). Only after formation of kinetic product **2** (**11**) is there isomerization to the thermodynamically preferred alkene **3** (**12**). The kinetic dehydration preference can be rationalized in terms of a statistical factor and a less energetic transition state for methyl proton loss from cation **10**.

In order to verify preliminary information concerning the difference in thermal lability between **1a** and **1b**, solutions of both **1a** and **1b** were refluxed for 40 h in toluene (Table II). Under these conditions **1a** and **1b** were totally decomposed to 3-chloroacetophenone (**4**), 2-benzylpyridine (**5**), and trace amounts of secondary products. When these same reactions were carried out for 1 h, **1a** showed only 17% decomposition as compared to 36% for the low-melting racemic mixture **1b**. After a 4-h reflux, 82% of **1b** had decomposed, while only 56% of **1a** had undergone the same fate. In each of the 1- and 4-h experiments decomposition gave clearly only **4** and **5**.

This thermal rearrangement as depicted in Scheme II not only explains our results but also represents a specific example of the amine catalyzed retro-aldol reaction as well as an example of the more general retro-ene reaction[5] where the enophile and ene components are respectively the aromatic ketone (**4**) and a pyridyl tautomer (**9**). To our knowledge this is the first example where the intermediate Schiff's base or ene component is contained within a heterocyclic ring. It is generally accepted that the mechanism of this type of rearrangement involves fragmentation through a cyclic transition state such as **13**[6] with the possible involvement of **14** where

Table I. Reaction of Compound 1 in 85% H_3PO_4 at 110 °C

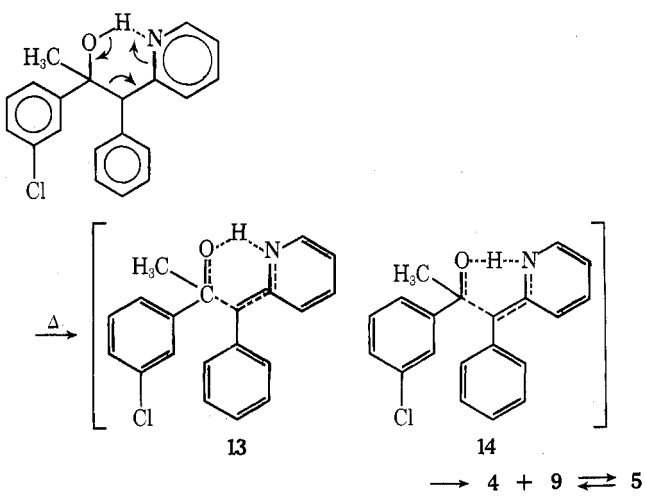
	Composition of 1, %			Composition of product mixture, %[b,c]				
No.	Higher melting racemate (**1a**)	Lower melting racemate (**1b**)	Duration of Reaction, h	**2**	**3**	2-Benzyl-pyridine	3-Chloro-acetophenone	**1**[a]
1	40	60	3	49	2	22	20	7
2	100	0	3	88	4	4	4	Trace
3	0	100	3	26	3	33	31	7
4	63	37	5	47	6	24	24	Trace
5	63	37	24	30	18	27	25	Trace
6	63	37	72	Trace	23	41	36	Trace

[a] Represents the sum of **1a** and **1b**. No interconversion between **1a** and **1b** was observed. [b] Values are ±3%. [c] Percentages are based upon molar ratios of products as determined by unique NMR measured protons for each product.

Table II. Thermal Decomposition of 1 in Refluxing Toluene (bp 110.6 °C)

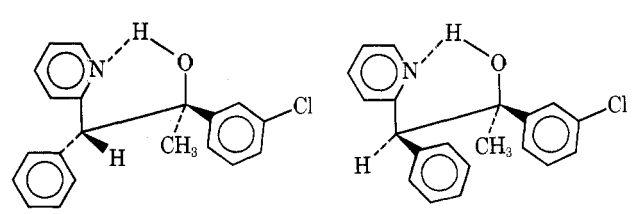
Isomer	Duration of reflux, h	% decomposition
1a	1	17
1b	1	36
1a	4	56
1b	4	82
1a	40	100
1b	40	100

Scheme II



a proton exists in a stable potential well during carbon–carbon bond cleavage.[7] This reaction, therefore, is most likely concerted but not necessarily so.[5] It must also be pointed out that even though in this rearrangement the aromaticity of the pyridine ring is disrupted, the energy cost should be minimal due to the extensive conjugation possessed by **9.**

A tentative assignment of stereochemistry to the high- and low-melting racemates of **1** can be made on the basis of their thermal stabilities and and postulated mechanism (Scheme II) for their thermal decomposition. This mechanism represents the most likely pathway for decomposition and necessitates a transition state depicted by structures **13** and **14** in which the hydroxyl proton is hydrogen bonded to the pyridyl nitrogen. Structures **15** and **16** show three-dimensional rela-



tionships encountered respectively as they approach the transition states necessary for decomposition. The two eclipsed phenyl rings of **16** render this transition state somewhat more unfavorable in comparison to the relatively uncrowded situation found in **15.**[8] On this basis, structure **15** is proposed as representing **1b,** the low-melting, thermally labile racemic pair, and **16,** its high melting, thermally more stable and physiologically active partner, **1a.**

Experimental Section

Melting points were determined with a Mel-Temp apparatus; they are uncorrected. NMR spectra were recorded by means of a Varian A-60A spectrometer with $CDCl_3$ as the solvent and Me_4Si as an internal standard. Elemental analyses were by Midwest Microlab, Ltd., Indianapolis, Ind.

Dehydration of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol (1). A General Procedure. Compound **1** (6.5 g, 0.02 mol) of isomer composition indicated in Table I was added to a flask containing 20 ml of 85% phosphoric acid (Mallinckrodt and analytical reagent grade) and a magnetic stirring bar. The reaction vessel, equipped with a water condenser, was immersed in an oil bath maintained at 110 °C and the reaction mixture was stirred for the period indicated in Table I. The mixture was then removed from the oil bath and allowed to come to room temperature before the yellow-orange homogeneous reaction solution was brought to pH 7.5–8.0 with 10% ammonium hydroxide (~500 ml). As the ammonium hydroxide was added, product separated from the water layer. The entire mixture was extracted with ether. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the ether was removed under reduced pressure. Analysis of the residue by NMR indicated the presence of the components shown in Table I. Accurate determination of the composition of these product mixtures by NMR was achieved due to distinct nonoverlapping signals from at least one characteristic proton of each constituent. In all reactions a nearly quantitative recovery of material was observed based on the analyzed composition of the product mixtures (6.1 g to 6.4 g). The identity of 3-chloroacetophenone (**4**) and 2-benzylpyridine (**5**) was established through their isolation by vacuum distillation of the product mixture from reaction 3 and comparison to authentic samples. In the case of reactions 1, 2, and 4 (Table I), recrystallizations of the crude product from *n*-hexane produced 2-(3-chlorophenyl)-3-phenyl-3-(2-pyridine)propane (**2**) (mp 90.5–92.0 °C): NMR δ 4.85 (broad s, 1 H), 5.64 (broad d, 2 H, vinyl H), 6.92–7.71 (broad m, 12 H, aromatic H), 8.48–8.68 (broad m, 1 H, pyridine H).

Anal. Calcd for $C_{20}H_{16}ClN$: C, 78.54; H, 5.28; N, 4.58. Found: C, 78.62; H, 5.26; N, 4.59.

For reaction number 6 the oil product mixture was dissolved in *n*-hexane–acetone (10:1) and 2-(3-chlorophenyl)-1-phenyl-1-(2-pyridine) propene (**3**) as a mixture of *Z* and *E* isomers (1.2 g, 20%) was obtained as a white, crystalline solid (mp 107–108 °C): NMR δ 2.11, 2.15 (two s, 3 H), 6.70–7.80 (broad m, 12 H, aromatic H), 8.30–8.75 (broad m, 1 H, pyridine H).

Anal. Calcd for $C_{20}H_{16}ClN$: C, 78.54; H, 5.28; Cl, 11.59; N, 4.58. Found: C, 78.39; H, 5.13; Cl, 11.42; N, 4.56.

Isomerization of 2-(3-Chlorophenyl)-3-phenyl-3-(2-pyridine)propene (2) to 2-(3-Chlorophenyl)-1-phenyl-1-(2-pyridine)propene (3). A 50-ml round-bottom flask, containing a magnetic stirring bar and equipped with a water condenser, was charged with 1.25 g (0.0041 mol) of 2-(3-chlorophenyl)-3-phenyl-3-(2-pyridine) propene (**2**) and 10 ml of 85% phosphoric acid. The reaction mixture was immersed in an oil bath maintained at 110 °C and was stirred at this temperature for 48 h. The reaction mixture was then worked up as in the previous experiments, affording 1.04 g (85%) of white, crystalline solid **3.** This material was free from the usual by-products, **4** and **5.**

Thermal Rearrangement of 1. A General Procedure. A racemic mixture of compound **1** (either **1a** or **1b**) (100 mg, 0.31 mmol) and 10 ml of toluene (spectra grade, bp 110.6 °C) were placed in a 25-ml round-bottom flask. The flask was equipped with a reflux condenser which was topped with a N_2 inlet adapter for maintaining the reaction under a N_2 atmosphere. After the system was flushed with N_2, the solution was brought to reflux and held at reflux for the time indicated in Table II. The reaction mixture was cooled to room temperature and the toluene was carefully removed by rotary evaporation. In each case the residue represented a quantitative recovery of material which was a mixture of **1a** or **1b,** 2-benzylpyridine, and 3-chloroacetophenone, with the exception of the 40-h experiment from which no starting material was isolated. The composition of residues and the percentages of decomposition were determined by NMR spectroscopy.

Acknowledgments. This work was supported by Grant GM 19815 from the National Institutes of Health, Bethesda, Md.

Registry No.—**1a,** 59980-71-1; **1b,** 59980-72-2; **2,** 59922-62-2; *E*-**3,** 59922-63-3; *Z*-**3,** 59922-64-4.

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(4) Purification of **1** and separation of the higher and lower melting racemic pairs has been attempted by a number of methods. Sublimation of **1** totally decomposed the lower melting enantiomeric pair to 2-benzylpyridine and 3-chloroacetophenone while the higher melting pair showed only slight decomposition. Preparative thin layer chromatography on silica gel plate of a mixture of both pairs using a mixture of *n*-hexane, chloroform, and acetic acid (50:40:10) as solvent again caused extensive decomposition of the lower melting racemic mixture while leaving the higher melting racemate relatively intact.
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Reaction of *N*-(Triorganosilylmethyl)dialkylamines with Benzyne

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Received May 25, 1976

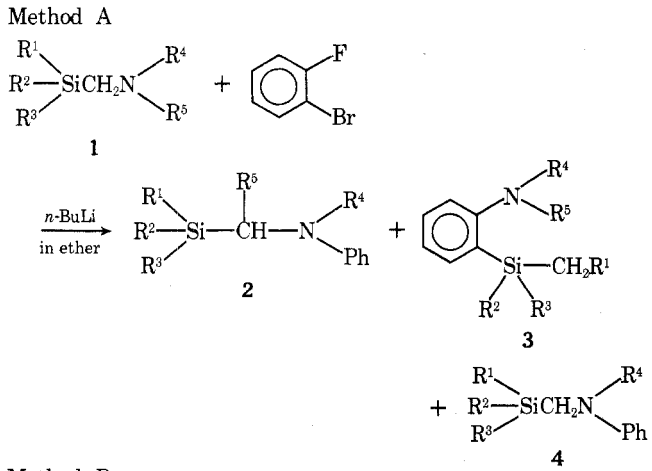
N-(Triorganosilylmethyl)dialkylamines (**1**) having at least one phenyl substituent on the silicon reacted with benzyne to give *N*-alkyl-*N*-(1-triorganosilylalkyl)anilines (**2**, Stevens rearrangement products) and *o*-diorganobenzylsilyl-*N*,*N*-dialkylanilines (**3**, anionic rearrangement products of the silyl group). The presence of two stable intermediates, betaine (**8**) giving **3** and ylide (**9**) giving **2**, was proved by carbonation or methylation.

Silicon has a high affinity for ylide carbanions and exerts a stabilizing effect on these carbanions.[1,2] Phosphorus, arsenic, and sulfur ylides having a silicon substituent directly attached to the carbanion have been synthesized as distillable oils.[3] The stabilizing effect of silicon upon a nitrogen ylide is not well investigated. In an earlier paper[4] we reported that the reaction of *N*-(trimethylsilylmethyl)dimethylamine (**1d**) with benzyne gave predominantly *N*-methyl-*N*-(1-trimethylsilylethyl)-aniline (**2d**) which was produced by the Stevens rearrangement of a silyl ylide intermediate (**9d**). However, the Stevens rearrangement competed with a new anionic rearrangement of the silyl group in the benzyne reaction of *N*-(triorganosilylmethyl)dialkylamines (**1a–c** and **1e–i**) having at least one phenyl substituent on the silicon atom. Aminomethyltriorganosilanes (**1a–j**) were synthesized by reaction of triorganosilyllithium with dialkylaminomethyl phenyl sulfides (method C in Table II) or by reaction of triorganochloromethylsilanes with dialkylamines (method D).

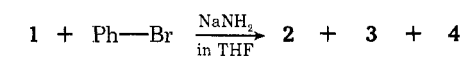
When to a mixture of *N*-(diorganophenylsilylmethyl)-dimethylamines (**1a–c**) and *o*-fluorobromobenzene in ether was added *n*-butyllithium at −25 to −40 °C, then the mixture was heated at reflux (method A in Scheme I and Table I), two

Scheme I

Method A

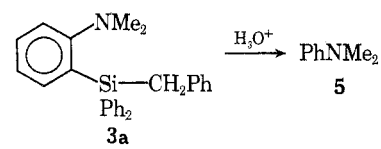


Method B



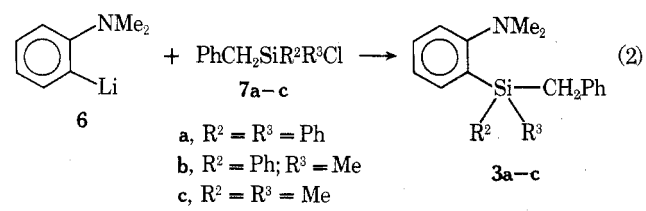
isomeric bases were obtained. Analytical data of these isomers revealed that they were grouped into two types of *N*-methylaniline derivatives (**2** and **3**). One group was assigned to the Stevens [1,2] rearrangement product, *N*-methyl-*N*-(1-diorganophenylsilylethyl)anilines (**2a–c**) (see Table III).

NMR spectra of the other group indicated the presence of benzyl and dimethylamino groups (Table IV). Acid hydrolysis of **3a** gave *N*,*N*-dimethylaniline (**5**, eq 1). Thus the structures



(1)

of **3a–c** were presumed to be *o*-diorganobenzylsilyl-*N*,*N*-dimethylaniline, and they were confirmed by spectroscopic comparisons with authentic samples prepared by the reaction of *o*-lithio-*N*,*N*-dimethylaniline (**6**) (prepared by reaction of *o*-bromo-*N*,*N*-dimethylaniline with *n*-butyllithium) with the corresponding diorganobenzylchlorosilane (**7a–c**) (eq 2).



(2)

When **1a–c** were allowed to react with benzyne generated by the reaction of bromobenzene with sodium amide in boiling THF (method B in Scheme I and Table I), the same reaction products were obtained in lower yields than those of method A. The benzyne reaction of *N*-(diorganophenylsilylmethyl)-dialkylamines (**1e–i**) having β hydrogens in *N*-alkyl substituents also gave predominantly the silyl rearrangement products (**3e–i**). Yields of the Stevens rearrangement product (**2h**) and the Hofmann elimination product (**4g**) were quite low.

The formation of **3** could be explicable as a result of the anionic rearrangement of a silyl group to a carbanion in a betaine intermediate (**8**) accompanied by the shift of a phenyl group from the silicon to the neighboring carbon (eq 3 in Scheme II). The related rearrangements have been observed