Journal of Organometallic Chemistry, 139 (1977) 1—9

SILICON ANALOGS OF PHENOTHIAZINE *

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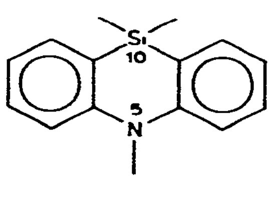
(Received March 30th, 1977)

Summary

Synthesis of tricyclic derivatives which contain both silicon and nitrogen in the central ring (phenazasilines) as well as a dimethylaminopropyl side chain bonded either to Si or to N are described Reaction of 4,4'-dibromo-2,2'-dilithio-*N*-(γ-dimethylaminopropyl)diphenylamine with Me_2SiCl_2 provides a ring brominated silicon analog of the tranquilizer promazine Reaction of 4,4'-dibromo-2,2'-dilithio-*N*-methyldiphenylamine with $MeSiHCl_2$ followed by SiH addition of the phenazasiline to allylamine provided the isomeric derivative Debromination of three phenazasilines with BuLi followed by hydrolysis demonstrated formation of both 2-bromophenazasilines as well as phenazasilines. Structural comparisons to phenothiazines are discussed

Introduction

Syntheses of tricyclic derivatives which contain both a silicon and a nitrogen heteroatom in the central ring, i.e., the phenazasilines, I, were first reported in the literature in the late 50's by Gilman and coworkers [1] The utility of these



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* Presented in part at the 10th Midwest Regional Meeting Amer. Chem. Soc. Carbondale, Ill. Oct. 1975.

** NSF-Undergraduate Research Participant, 1976.

compounds as high temperature additives for jet-engine lubricants spurred the early synthetic studies and these efforts have been reviewed [2]. The analogy between phenazasilines and the phenothiazine systems that form the basis of a series of clinically effective tranquilizers has not been pursued previously. Neuroleptics of the tricyclic class, such as the phenothiazine derivatives, contain a non-planar tricyclic nucleus bridged by a heteroatom, a three atom side chain bonded to the central ring of the tricycle and a nitrogen functional group which terminates the side chain. The more potent compounds usually contain electron-withdrawing substituents in the 2-position (relative to N). We wish to report here the synthesis of silicon analogs of phenothiazine derivatives which contain the structural features of the neuroleptics

The effects of replacing an $SiMe_2$ group for a S in the phenothiazine skeleton have been determined from a solid state crystal structural analysis of 2,8-dibromo-5-ethyl-5,10-dihydro-10,10-dimethylphenazasiline [3] and compared with the parameters reported for phenothiazine derivatives where the *exo*-cyclic N-group is Me [4], Et [5] and i-Pr [6] The C_{Ar}—Si—C_{Ar} and C_{Ar}—S—C_{Ar} bond angles are in the range 97 4° to 98 9° and the average C_{Ar}—Si bond distance is 1 855 Å compared to an average C_{Ar}—S distance of 1.765 Å in the three phenothiazane derivatives. The benzo group dihedral angle of 140.9° for the phenazasiline is midway between the range of 135.0 to 147.8° reported for the phenothiazines. No major structural differences were observed on replacement of S by $SiMe_2$.

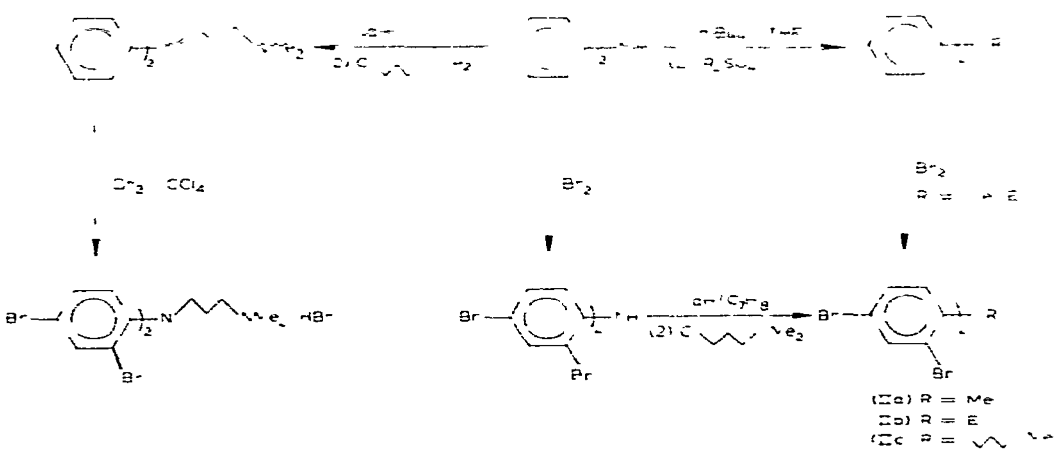
The carbon analog of 5,10-dihydro-10,10-dimethylphenazasiline, 9,9-dimethyl-10-dimethylaminopropylacridan, "dimethacrine", is a rapidly acting antidepressant in man, however, no structural information for this carbon analog is available at this time [7]. A related carbon analog, 9-dimethylaminopropyl-10-methylacridan, also exhibits psychotropic activity [8]

Discussion and results

Two basic methods have been developed for the generation of the phenazasiline framework. The earliest reported route involved the one-step reaction of a phenothiazine derivative with a silane, Ar_2SiH_2, at temperatures in excess of 200°C [1a,c]. Although this process has the advantage of insertion of an Ar_2Si unit into a preformed tricycle the yields are generally in the range, 1 to 7%. A second procedure requires the tedious preparation of 2,2′-dibromo-*N*-alkyldiphenylamines, precursors to the dilithio derivatives which form phenazasilines upon reaction with R_2SiCl_2 or R_2SiH_2 [1b,d]. A variation of the latter route was provided when it was shown that 2,2′,4,4′-tetrabromodiphenylamines (readily prepared from bromination of diphenylamine derivatives) react with BuLi preferentially in the *ortho* positions and thus provide access to 2,8-dibromophenazasilines [9].

A report that *N,N*-dimethylaniline is lithiated in the *ortho* position [10a,b] suggested a possible alternative and shorter route to phenazasilines if alkyldiphenylamines would undergo dilithiation in *ortho* positions. Gilman has reported the monolithiation of methyldiphenylamine with BuLi in refluxing ether (24 h) in low yields [10c] We examined the reaction of methyldiphenylamine with two to four moles BuLi in ether or THF at 0°C, room temperature or reflux followed by quenching with dimethyldichlorosilane and did not observe the formation of any product which could be identified as 5,10,10-trimethyl-9,10-dihydrophenazasiline (prepared by an alternate route) [11] Therefore, the scheme utilized for generation of the systems that are the subject of this study incorporated brominated diphenylamines. In the original report [9], diphenylamine was brominated and then alkylated, however, we found the reverse to be simpler Generation of the precursor amine tetrabromides is shown in Scheme 1. Bromination of *N*-(γ-dimethylaminopropyl)diphenylamine gave the CCl_4-insoluble hydrobromide salt of 2,2′,4,4′-tetrabromo-*N*-(γ-dimethylaminopropyl)-diphenylamine which was insoluble in base and difficult to purify The free amine was generated by coupling 2,2′,4,4′-tetrabromodiphenylamine with *N*,*N*-dimethylaminopropyl chloride in the presence of NaH on a small scale

SCHEME 1

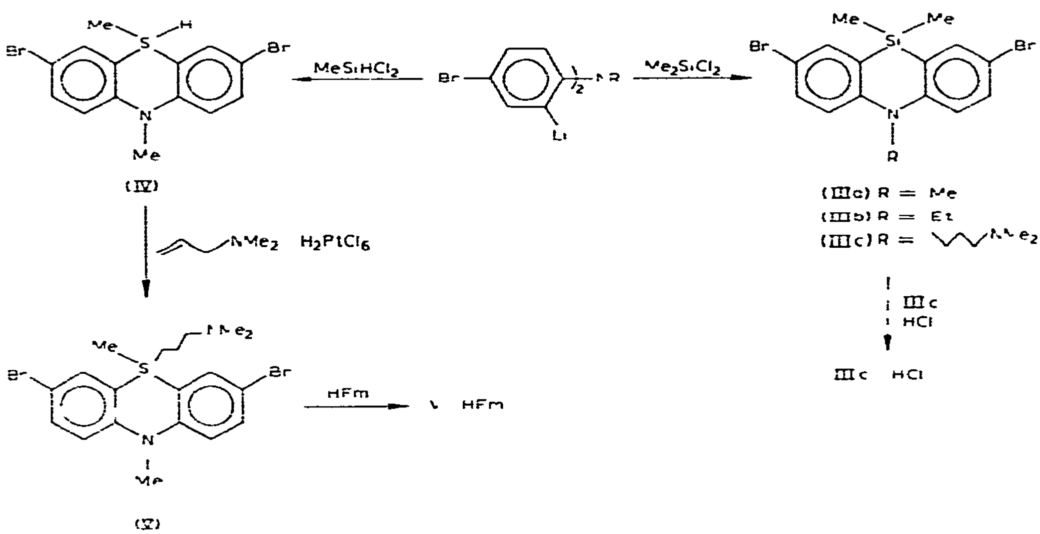


(10^{-3} mol) Attempts to increase the scale of this coupling reaction resulted in considerable reduction in yields of the desired amine

Reaction of the amine tetrabromides, II, with BuLi at 0°C followed by addition of the appropriate dichlorosilane gave the indicated 2,8-dibromophenazasilines, III and IV. Attachment of the propylamine side chain at the silicon hetero atom was accomplished through hydride addition of IV to allylamine in the presence of H_2PtCl_6 (Scheme 2). Reactions of amines, V and IIIc, with inorganic and organic acids frequently produced viscous oils which could not be induced to crystallize. After several attempts it was possible to obtain the crystalline fumarate salt of V and a crystalline hydrochloride salt of IIIc

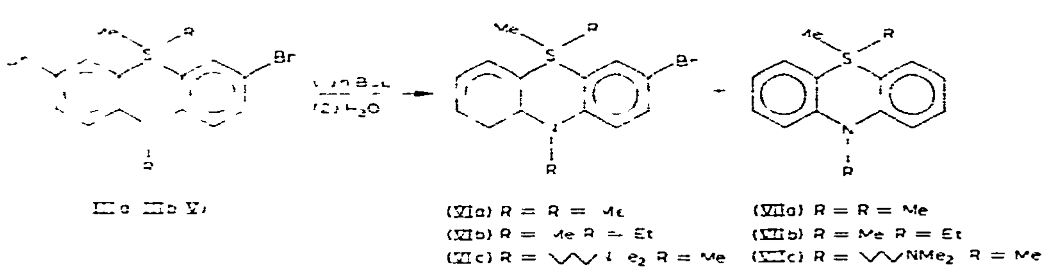
Debromination of the 2,8-dibromo-5-ethyl-1,10-diphenyl-5,10-dihydrophenazasiline has been reported from reaction with BuLi at 0°C followed by hydrolysis to give 5-ethyl-10,10-diphenyl-5,10-dihydrophenazasiline in 27% yields [9]. The attempted debromination reactions of the 2,8-dibromophenazasilines, IIIa, IIIb and V were not as straightforward as the literature case cited Even with excess BuLi and longer reaction times than those reported debromination was not complete. The NMR spectrum of the crude reaction product from IIIa after hydrolysis clearly showed the presence of two components. Although distilla-

SCHEME 2



tion of the crude reaction mixture which resulted from the debromination of IIIa with a 50% molar excess of BuLi afforded a solid with a 2°C melting point range this proved to be a mixture of VIa/VIIa in an approximate 3 · 1 ratio (Scheme 3) These could be separated by distillation of the solid followed by recrystallization, but VIIa could not be totally freed from VIa When the mole ratio of BuLi to IIIa was increased to 5 : 1 and the reaction time increased a 35% yield of purified VIIa was obtained. Although VIb and VIc were not isolated their presence in the reaction products was suggested from both NMR and mass spectral evidence and as in the previous case it was difficult to purify both VIIb and VIIc

SCHEME 3



The brominated phenazasilines have also been prepared by addition of bromine to 5,10-dihydrophenazasilines in CS_2 at −20°C. Extensive ring cleavage also occurs during the reaction and only the dibrominated products, 2,8-dibromo-5,10-dihydrophenazasilines were isolated [12]. Monobrominated phenazasilines such as VI have not been previously reported and such derivatives permit introduction of a substituent into the 4-position (relative to nitrogen). The more potent promazine derivatives are substituted in the 2-position (relative to nitrogen).

Reductive cyclization of 2-nitrophenyl phenyl sulfide with $(EtO)_3P$ in refluxing cumene affords phenothiazine in 54% yield [13] This suggests a possible alternative route to phenazasilines from silanes such as $(o\text{-}NO_2C_6H_4)(C_6H_5)SiR_2$ Nitration of diphenyldimethylsilane with copper(II) nitrate in acetic anhydride according to the procedures developed for phenyltrimethylsilane [14] proceeds smoothly to afford 60% crude mononitrated product but separation of isomers has not yet been accomplished. Attempted cyclization of the crude diphenyldimethylsilane nitration product has not yet been successful and is under current investigation [11]

Experimental

General All reactions which involved alkyllithium or Grignard reagents and R_xSiCl_{4-x} reagents were carried out under an atmosphere of dry nitrogen in flame-dried glassware. IR spectra were determined as thin films or as Nujol mulls on a Perkin—Elmer 337 grating spectrophotometer Proton NMR spectra were recorded in CCl_4 or $CDCl_3$ on a Varian T-60 spectrophotometer (internal TMS as a reference unless otherwise specified) Mass spectral data were collected at 70 eV on an AEI MS-1201B mass spectrometer

All organosilicon halides were obtained commercially and were used without further purification Butyllithium, dialkylsulfates, diphenylamine and allylamine were used as supplied 2,8-Dibromo-5,10,10-trimethyl-5,10-dihydrophenazasiline and 2,8-dibromo-5-ethyl-10,10-dimethyl-5,10-dihydrophenazasiline were prepared as described from 2,2′,4,4′-tetrabromodiphenylalkylamine and dimethyldichlorosilane [9]

THF was dried by treatment with BuLi followed by distillation [15] Xylene was dried by refluxing over P_2O_5 for 18 h followed by distillation

Analyses were performed by Galbraith Laboratories, Inc , Knoxville, Tennessee

Synthesis of methyl- and ethyldiphenylamine To a solution of diphenylamine (17 g, 0.10 mol) in 300 ml anhydrous THF was added butyllithium (0.10 mol) dropwise with stirring After completion of the addition the reaction mixture was stirred an additional half-hour before adding dropwise a solution of dialkylsulfate (0.10 mol) in 20 ml THF. After heating at reflux for 18 h, 15 ml H_2O were added and the solvents stripped to give a red-brown oil Distillation afforded the product. Methyldiphenylamine, b p 118—130°C/0 35 mmHg, 84% (Lit. [16] 148—149°C/12 mmHg), ethyldiphenylamine, b p 115—120°C/0 2 mmHg, 68% (lit. [17] 152—153°C/12 mmHg).

Synthesis of N-(γ-dimethylaminopropyl)diphenylamine To a solution of diphenylamine (2.4 g, 0.014 mol) in 50 ml anhydrous xylene was added sodium hydride (1.7 g, 0.07 mol) and the slurry heated at reflux for 90 min. A solution of 3-dimethylaminopropyl chloride in 40 ml of xylene was slowly added at reflux and heating continued for 5 h after addition was completed. The cooled reaction mixture was poured into cold water, the organic layer separated and the aqueous layer extracted with ether and the organic layers combined. After drying over Na_2SO_4 the solvents were stripped and the resultant crude *N*-(γ-dimethylaminopropyl)diphenylamine distilled on a Kugelrohr apparatus, b.p.

140—170°C/0.1 mmHg, 3 2 g. ^{1}H NMR ($CDCl_3$) δ (ppm)· 7 2—6.6 (m, 9 8, aromatic), 3.9—3.5 (t, 2.0, NCH_2), 2.5—1.5 and 2 17 (overlapping m and s, 10.2, $CH_2CH_2NMe_2$). *m/e* 254. The crude amine was used without further purification for bromination reactions.

Bromination of alkylamines. Brominations were carried out in CCl_4/H_2O according to a previously published report [18] From methyldiphenylamine (15 g, 0.081 mol) and bromine (52 g, 0.32 mol) was obtained 32 g (80%) 2,2′,4,4′-tetrabromo-*N*-methyldiphenylamine, m.p. 139—141°C after recrystallization from CCl_4 (lit. [9] 142—144°C). ^{1}H NMR ($CDCl_3$) δ (ppm). 7 7—6.7 (m, 5,9, aromatics), 3 2 (s, 3.1, N—CH_3).

From reaction of ethyldiphenylamine (13.4 g, 0.070 mol) and bromine (44 g, 0.27 mol) was obtained 21 g (59%) of 2,2′,4,4′-tetrabromo-*N*-ethyldiphenylamine, m p. 128—131°C after recrystallization from CCl_4 (lit [3] 136 5—138 5°C) ^{1}H NMR ($CDCl_3$) δ (ppm): 7.7—6.7 (m, 6.2, aromatics) 3 8—3.6 (q, 1 7, CH_2); 1 4—1 0 (t, 3 1, CH_3)

Addition of bromine (8 0 g, 0 050 mol) to *N*-(γ-dimethylaminopropyl)diphenylamine (3.2 g, 0.013 mol) resulted in the formation of a CCl_4 insoluble precipitate which was recrystallized from CH_2Cl_2/EtOH to give 2,2′,4,4′-tetrabromo-*N*-(γ-dimethylaminopropyl)diphenylamine hydrobromide, m p 238—240°C (78%). The salt prepared by this route had identical spectral characteristics as and exhibited no mixed m p. depression with the salt prepared from the coupling reaction product The amine hydrobromide is insoluble in 4 *M* NaOH

Synthesis of 2,2′,4 4′-tetrabromo-N-(γ-dimethylaminopropyl)diphenylamine To a solution of 2,2′,4,4′-tetrabromodiphenylamine (2 11 g, 0 0043 mol) in 55 ml of dry xylenes was added 0 56 g of NaH and the mixture heated at reflux for 1 75 h at which time a solution of *N,N*-dimethylaminopropyl chloride (2.08 g, 0 017 mol) in 25 ml xylene was slowly added After an additional 5 h reflux the reaction mixture was poured into cold water and the organic layer separated. The aqueous layer was extracted with ether and combined with the xylene layer. The combined organic layers were dried over Na_2SO_4 prior to stripping the volatiles. Kugelrohr distillation gave crude 2,2′,4,4′-tetrabromo-*N*-(γ-dimethylaminopropyl)diphenylamine, b.p. 190—205°C/0.1 mmHg as 2.0 g (81% crude yield) of thick oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.7—6 7 (m, 6 1, aromatic), 3.7—3 3 (t, 1.8, NCH_2), 2 4—1.5 and 2.15 (overlapping m and s, 10.1, $CH_2CH_2NMe_2$). Attempts to double the scale of the reaction resulted in a decrease in yields to 47% and quadrupling the scale resulted in isolation of only 34% product

A 0.1 g sample of amine was dissolved in EtOH and 1/2 ml of 4 8% hydrobromic acid added The precipitated hydrobromide salt was recrystallized from EtOH, m p 238—240°C (dec.) (Found: C, 31 81; H, 3.12 $C_{17}H_{19}N_2Br_5$ calcd.: C, 31.33; H, 2.92%.) ^{1}H NMR ($CDCl_3$) δ (ppm): 7.6—6 7 (m, 6 0, aromatics); 3 7—3 4 (t), 3 4—2 9 (m), 2 6 (s), 2.5—1 8 (m, 13.0, $NCH_2CH_2CH_2NMe_2H$).

2,8-Dibromo-5,10-dimethyl-5,10-dihydrophenazasiline To a solution of 2,2′,4,4′-tetrabromo-*N*-methyldiphenylamine (20 g, 0 040 mol) in 150 ml. anhydrous ether, cooled to 0°C was added BuLi in hexane (2 3 *M*, 35 ml, 0 80 mol). The mixture was then stirred for 1 h and a solution of methyldichlorosilane in 50 ml ether (4.6 g, 0.040 mol) added dropwise. After completion of the addition the solution was allowed to warm to room temperature and stirred for 2 h The reaction mixture was hydrolyzed with saturated NH_4Cl solution and the organic layer decanted and dried over sodium sulfate After stripping the solvent the brown semisolid residue was distilled in a Kugelrohr apparatus to give crude 2,8-dibromo-5,10-dimethyl-5,10-dihydrophenazasiline, b p. 190—220°C/0 1 mmHg, 10 7 g Recrystallization from hexanes gave 5 3 g (27%) of pure silane, m p. 128—129°C (Found C, 44.02, H, 3 40. $C_{14}H_{13}BrNSi$ calcd C, 43 86, H, 3 39%) ^1H NMR ($CDCl_3$) δ (ppm). 7.6—6 7 (m, 6 1, aromatics), 5.0—4.7 (q, 0.9, SiH). 3 4 (s, 3.0, N—CH_3), 0 6 and 0 4 (d, 3.0, Si—CH_3)

2,8-Dibromo-5,10-dimethyl-10-(γ-dimethylaminopropyl)-5,10-dihydrophenazasiline (V) 2,8-Dibromo-5,10-dimethyl-5,10-dihydrophenazasiline (3 9 g, 0 01 mol) and 2 ml *N,N*-dimethylallylamine were heated at reflux in the presence of chloroplatinic acid for 5 h Methylene chloride was added and the solution filtered to remove 0 8 g of insoluble solid The filtrate was boiled with EtOH and upon cooling, 3.15 g of crude product was obtained. Recrystallization from EtOH provided pure 2,8-dibromo-5,10-dimethyl-10-(γ-dimethylamino-propyl)-5,10-dihydrophenazasiline, m.p. 126—127 5°C. (Found C, 48 41, H, 5 14. $C_{19}H_{24}Br_2SiN_2$ calcd. C, 48 72, H, 5.13%.) ^1H NMR ($CDCl_3$) δ (ppm). 7.6—6.7 (m, 5 8, aromatics), 3.4 (s, 3,1, NMe), 2 3—2 0 (m, 8 0, CH_2NMe_2), 1.5—1.0 (m, 1 6, CH_2), 0 9—0 8 (m, 5.5, CH_2SiCH_3).

Fumarate salt of V To a recrystallized sample of 2,8-dibromo-5,10-dimethyl-10-(γ-dimethylaminopropyl)-5,10-dihydrophenazasiline (0 99 g, 2 1 × 10^{-3} mol) in 5 ml warm EtOH was added a warm solution of fumaric acid (0 21 g, 2.1 × 10^{-3} mol) in 5 ml EtOH After stripping solvents a thick oil was obtained The oil was dissolved in a minimum quantity of hot EtOAc Upon cooling an oil separates and slow evaporation of the mother liquor afforded 0 28 g of the fumarate salt of V, m p. 164—165 5°C (Found: C, 46 99, H, 4.71 $C_{23}H_{30}SiN_2O_4$-Br_2 calcd · C, 47 09, H, 5.12%.)

Debromination studies (a) 2,8-Dibromo-4-ethyl-10,10-dimethyl-5,10-dihydro-phenazasiline (3.8 g, 0.087 mol) was added to anhydrous ether and BuLi/hexanes (0 017 mol. 3.0 *M*) added dropwise with stirring. After addition was complete the mixture was stirred an additional 20 min followed by hydrolysis with 25 ml of water. After separation of the water layer the ether layer was stripped to give a yellow oil which contained a mixture of products Dissolution of the oil in hot hexanes followed by cooling gave 1 g of solid material. After two recrystallizations from EtOH, 0.25 g (11%) of 5-ethyl-10,10-dimethyl-5,10-dihydro-phenazasiline was obtained of m p. 66—67°C (lit. [19] 69.5—70°C). ^1H NMR ($CDCl_3$) δ (ppm): 7.4—6 6 (m, 7 9, aromatics), 4.3—3 9 (q, 1 8, CH_2); 1.6—1 3 (t, 3 3, CH_3), 0 4 (s, 6.0, $SiMe_2$) *m/e* 253

(b) To 2,8-dibromo-5,10,10-trimethyl-5,10-dihydrophenazasiline (1 3 g, 0.0033 mol) in 25 ml ether cooled to 2°C was added BuLi (0 091 mol, 2 29 *M*) over a period of 1/2 h. The mixture was allowed to warm slowly to room temperature and then stirred for 1 h before addition of 25 ml water. After separation of the organic layer and evaporation of the ether the residue was distilled on a Kugelrohr apparatus to give 0 8 g oil, b p. 135—160°C/0 1 mmHg A cooled solution of the oil in absolute ethanol afforded a solid of m p. 67—69°C which proved to be a mixture of two compounds. The solid was redistilled to give a 0.16 g fraction, b p. 135—150°C/0.2 mmHg, which was recrystallized from 95%

EtOH to give impure 5,10,10-trimethyl-5,10-dihydrophenazasiline, m p 98.5—99.5°C. (Found: C, 73.33; H, 5.07; $C_{15}H_{17}SiN$ calcd.: C, 75 3; H, 7.11%.) *m/e* 239. ^1H NMR ($CDCl_3$) δ (ppm): 7.7—6.4 (m, 7.6, aromatics), 3.5 (s, 3.1, N—Me), 0.4 (s, 6.3, $SiMe_2$).

The second fraction, 0.49 g, b.p. 160—170°C/0 2 mmHg, was recrystallized from EtOH to give 2-bromo-5,10,10-trimethyl-5,10-dihydrophenazasiline, m p. 70 5—72°C. (Found: C, 57 18; H, 5 23 $C_{15}H_{16}SiNBr$ calcd : C, 56 60, H, 5.03%) *m/e* 317 (based on ^{79}Br). ^1H NMR ($CDCl_3$) δ (ppm), 7 8—6 8 (m, 6 8, aromatics), 3.4 (s, 3.2, NMe); 0.45 (s, 6 0, $SiMe_2$)

In a second debromination attempt, the azasiline dibromide (2 5 g, 0 0063 mol) in 25 ml ether was mixed with BuLi (0.032 mol) at 0°C for 3 h After hydrolysis, 1.3 g solid, m p. 80—85°C was isolated from the ether layer. Recrystallization from 95% EtOH afforded 0.53 g 5,10,10-trimethyl-5,10-dihydrophenazasiline, m.p. 99—100 5°C. A purified sample, m.p 101—102.5°C, was obtained after distillation and recrystallization from i-PrOH (Found· C, 73 78; H, 7.13. $C_{15}H_{17}SiN$ calcd.: C, 75 3, H, 7 11%.) *m/e* 239

(c) To 2,8-dibromo-5,10-dimethyl-10-(γ-dimethylaminopropyl-5,10-dihydrophenazasiline (1 8 g, 0.0038 mol) in 25 ml ether cooled to 2°C was added BuLi (0.0096 mol, 2 29 *M*) and the solution stirred for 1 h before addition of water The crude product recovered from the ether layer was distilled on a Kugelrohr apparatus to give 0.3 g oil, b p. 150—160° C/0.1 mmHg which was recrystallized from aqueous ethanol to give 0.1 g solid. Further recrystallization from i-PrOH provided an analytical sample of 5,10-dimethyl-10-(γ-dimethylaminopropyl)-5,10-dihydrophenazasiline, m.p. 63 5—64°C. (Found. C, 72 55, H, 8.09. $C_{19}H_{26}N_2Si$ calcd.: C, 73 54; H, 8 38%.) *m/e* 310 ^1H NMR ($CDCl_3$) δ (ppm): 7 2—6 5 (m, 7.9, aromatics); 3 3 (s, 3 1, N—Me); 2 3—1.9 (s + t, 7 6 CH_2NMe_2); 1 4—0 4 (m + s, 7.3, $MeSiCH_2CH_2$).

Synthesis of 2,8-dibromo-5-(γ-dimethylaminopropyl)-10,10-dimethyl-5,10-dihydrophenazasiline. A solution of 2,2′,4,4′-tetrabromo-*N*-(γ-dimethylaminopropyl)diphenylamine (2.5 g, 0.0044 mol) in 50 ml ether was cooled with an ice/salt bath and a solution of n-BuLi (0.009 mol, 2.29 *M*) added After stirring the cooled mixture for 1/2 h, a solution of Me_2SiCl_2 (0 57 g, 0 0044 mol) in 25 ml ether was added dropwise. After the addition was complete the solution was warmed to room temperature and stirred an additional 2 h. After hydrolysis, the crude product that was obtained from the ether layer was distilled on a Kugelrohr apparatus to give 0 86 g oil, b p. 210—225°C/0 1 mmHg. The distilled portion was eluted with benzene over 70 g basic alumina to give 0 56 g of oil which could not be induced to crystallize.

A solid derivative was prepared by dissolving 0.28 g of benzene eluted fraction in $Et_2O/CHCl_3$ and adding gaseous HCl After stirring the solvents the solid residue was recrystallized twice from $CHCl_3$/xylene to give 0.09 g 2,8-dibromo-5-(γ-dimethylaminopropyl)-10,10-dimethyl-5,10-dihydrophenazasiline hydrochloride hydrate, m.p. 172—173°C. (Found· C, 43.90; H, 4.88. $C_{19}H_{24}N_2SiBr_2 \cdot HCl \cdot H_2O$ calcd : C, 43.60, H, 5.16%.)

Acknowledgement

We gratefully acknowledge the partial support of this work by the National Science Foundation through the Undergraduate Research Participation Program and the support of NIH research grant number R01NS10903 from National Institute of Neurological Diseases and Stroke.

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