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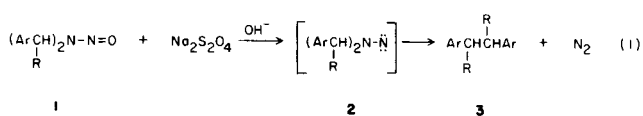
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The synthesis of *cis*- and *trans*-2,4-diphenylazetidines as well as that of their *N*-nitroso derivatives is described. The "abnormal" reduction of the *N*-nitrosamines gives a *cis-trans* mixture of the expected 1,2-diphenylcyclopropanes. However, no stereochemical correlations could be made owing to the base-induced isomerization of the starting *N*-nitrosamines during the course of the reaction.

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The so-called "abnormal" reduction of *N*-nitrosamines (Eq. 1), proceeding presumably *via* the corresponding *N*-nitrenes (2) is now a well-established reaction (4). As an extension of our previous investigations of the extrusion of

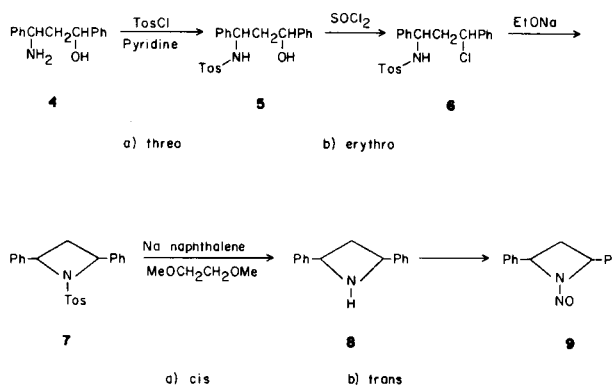


nitrogen from the sodium hydrosulfite reduction of α,ω -diphenyl substituted cyclic *N*-nitrosamines (5), the synthesis of *cis*- and *trans*-*N*-nitroso-2,4-diphenylazetidines (9a and 9b) was undertaken and is now being reported.

Synthesis and "Abnormal" Reduction.

The approach used by Vaughn and his group (6) was deemed most likely to lead the desired azetidines and Scheme 1 depicts the successful synthesis of 9a and 9b starting from the known *threo*- and *erythro*-3-amino-1,3-diphenylpropanols (4a and 4b) (7a,b). This route parallels very closely that recently reported by Freeman and his group (8) for the synthesis of *cis*- and *trans*-2,4-dimethylazetidines. An alternate synthesis of 4b involved the Friedel-Crafts acylation of benzene with β -(*N*-phthalimido)hydrocinnamoyl chloride. After reduction of the resulting protected aminoketone (9) with sodium borohydride, hydrazinolysis gave the imino alcohol 4b as the sole product. The sodium amalgam reduction of 3,5-diphenylisoxazolidine gave a mixture of the *threo*- and *erythro*-isomers (4a and 4b) from which the *threo*-isomer (4a) was separated (7a,10).

Of the many methods reported for the removal of the tosyl group, only those which seemed likely to leave the azetidine ring intact were investigated. Although sodium in *n*-amyl alcohol and in liquid ammonia gave 56% yield of 8a and 43% yield of 8b respectively, sodium



Scheme 1

naphthalene in dimethoxyethane (11) appears to be a more reliable method affording 8a and 8b in 65% and 20% (12) yields respectively. Since the free bases were found to be only about 94% pure and to be rather sensitive and unstable, they were converted to their hydrochloride salts. An excess of sodium naphthalene should be avoided and experimental manipulations should be performed as rapidly as possible in order to obtain best results. There was no evidence of *cis-trans* isomerization during this reaction. The stereochemical assignments, confirmed by their nmr spectra (see Experimental) were in complete accord with those made for *cis*- and *trans*-2,4-dimethylazetidines (8).

While nitrosation of *trans*-2,4-diphenylazetidine (8b) with sodium nitrite in aqueous acid gave an excellent yield of pure product 9b (85%), only complex mixtures were obtained on attempted nitrosation of 8a with sodium nitrite and acid, with 3-nitro-*N*-nitrosocarbazole in refluxing benzene (13) or with nitrosyl chloride in triethylamine (14). Eventually, nitrosation of the lithium salt of 8a in dimethoxyethane with nitrosyl chloride (15) gave the desired product 9a, albeit still contaminated with by-

products. Careful chromatographic purification was necessary to obtain a product which failed to crystallize completely but was homogeneous by tlc. Again, there was no evidence of isomer equilibration (16).

The reduction of **9a** and **9b** with sodium dithionite in the presence of sodium hydroxide gave 89-96% yields of a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes as the sole hydrocarbon products (Table 1) (17). However, the fact that **9a** and **9b** were isomerized as 70:30 equilibrium mixture under the conditions of the reaction renders any stereochemical correlation difficult on the basis of the present data (18).

Table 1
Sodium Dithionite Reduction of **9a** and **9b** (a)

N-Nitroso Compound	Temperature (°C)	Total Yield	1,2-Diphenylcyclopropane (b)	
			<i>cis</i>	<i>trans</i>
9a (<i>cis</i>)	62°	96% (c)	15.6	84.4
9b (<i>trans</i>)	60°	89%	15.3	84.7

(a) In 1:1 ethanol-20% aqueous sodium hydroxide. (b) By vpc at 155°. (c) Two trace contaminants present by tlc.

An nmr study of the base-catalyzed isomerization (sodium methoxide in perdeuteriomethane) of *trans*-*N*-nitroso-2,4-diphenylazetidines (**9b**) showed that within 30 minutes at room temperature, the benzylic hydrogens had exchanged to an extent of 50% and that substantial amounts of the *cis*-isomer **9a** had formed; a similar isomerization of *trans*-*N*-nitroso-2,5-diphenylpyrrolidines to the *cis*-isomer had been previously reported (5). Apparently, the now well-established base-catalyzed isomerization of *N*-nitrosamines (5,16,19) is not a major factor in the case of 2,4-dimethylazetidines (8,19). Sodium dithionite reduction of *cis*- and *trans*-*N*-nitroso-2,4-dimethylazetidines in basic solution gave nearly identical ratios of *cis*- and *trans*-1,2-dimethylcyclopropanes as those obtained in the mercuric oxide oxidation of the corresponding *cis*- and *trans*-*N*-amino-2,4-dimethylazetidines, where isomerization of azetidines is presumably not a problem. Evidently, in the case of **9a** and **9b**, the presence of the phenyl groups caused the α -hydrogens to be much more susceptible to attack by base; the importance of subtle structural and conformational changes on this process is underscored by the fact that optically active α,α' -dimethyl *N*-nitrosodibenzylamine (20) was recovered unchanged after heating with sodium hydroxide in aqueous ethanol at 70° for 10 hours. Since the LAH reduction of **9b** resulted primarily (84% yield) in the extrusion of nitrogen and formation of the cyclopropanes (*trans*:*cis* ratio 59.8/40.2), no further attempts to obtain the *N*-aminoazetidines were made.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 Infracord, while the ultraviolet spectra were measured on a Cary Model 14 Spectrophotometer. The nmr spectra were determined on a Varian A-60 Spectrometer using TMS as an internal standard. Vapor phase chromatographic analyses were carried out isothermally on a Varian Aerograph Model 200 instrument using a 12 foot by 1/4 inch aluminum column packed with 10% SE 30 on 60/80 mesh Chromosorb W (AW-DMCS) and using a thermal conductivity detector. The diphenylcyclopropanes and diphenylpropenes were determined at about 150°, with the column then being heated to about 250° to detect higher boiling materials. Product ratios were determined by area measurement (height \times width at half height). Thin layer chromatography was carried out on 5 \times 20 cm coated plates obtained commercially. Analyses were performed by Mr. R. Boos and associates of the Merck Sharpe and Dohme Research Laboratories. The mass spectra were obtained by Mr. Jack Smith of the Merck, Sharpe and Dohme Research Laboratories using a CEC Model 21-110 spectrometer. The samples were introduced directly into the ion source at 70 eV.

threo-3-Benzal-amino-1,3-diphenylpropanol.

Application of the method of Stuhmer and Frey (7a) to 6.00 g. (26.4 mmoles) of the mixed isomers of 3-amino-1,3-diphenylpropanol (10) and 3.90 g. (36.7 mmoles) of benzaldehyde gave 3.14 g. (37% yield) of *threo*-3-benzal-amino-1,3-diphenylpropanol, m.p. 125.5-127°, lit. (7a) 125°. The nmr spectrum (deuteriochloroform) showed a singlet at δ 8.23 (benzal proton), a multiplet centered at δ 4.74 (benzylic protons) and a multiplet centered at δ 2.28 (methylene protons). The ir spectrum (chloroform) showed a strong absorption band at 1650 cm^{-1} (C=N) and a weak broad peak at 3450 cm^{-1} (OH).

The mother liquor from isolation of the *threo* isomer was concentrated to dryness *in vacuo* and the residue recrystallized from ethanol to yield *erythro*-3-benzal-amino-1,3-diphenylpropanol, m.p. 79-88°.

threo-3-Amino-1,3-diphenylpropanol (**4a**).

Hydrolysis of 46.46 g. (0.147 mole) of *threo*-benzal isomer by refluxing with 588 ml. (0.294 mole) of 0.5 *N* the hydrochloric acid with concomitant steam distillation of benzaldehyde gave 33.29 g. (quantitative yield) of **4a**, m.p. 125.5-126.5°, lit (7) 127°.

erythro-3-Amino-1,3-diphenylpropanol (**4b**). (a) From 3,5-Diphenylisoxazoline (7c).

A solution of 19.2 g. (86.4 mmoles) of 3,5-diphenylisoxazoline (21,22) in 500 ml. of ether was added over 1.25 hours to a slurry of 5.10 g. (134 mmoles) of lithium aluminum hydride in 100 ml. of ether. The mixture was then heated at reflux for 6 hours, cooled in an ice bath, and then quenched by the successive addition of 5.1 ml. of water, 5.1 ml. of 15% sodium hydroxide, and 15.3 ml. of water. The inorganic salts were filtered and washed four times with 100 ml. of methylene chloride. Then the combined filtrate and washes were extracted once with 200 ml. of water containing 50 ml. of concentrated hydrochloric acid and twice with 100 ml. of water. After being washed with methylene chloride, the combined aqueous extracts were made strongly alkaline with 50% sodium hydroxide. The resulting precipitate was filtered, washed with water, and dried *in vacuo* to afford 17.74 g. (91% yield) of crude *erythro*-3-amino-1,3-diphenylpropanol (**4b**), m.p. 110-117°.

A sample of crude *erythro*-aminoalcohol (**4b**) was converted into its tartrate salt (recrystallized from water, m.p. 156.5-159°), reconverted into the free base, and recrystallized from heptane to give material melting at 121-122.5°, lit (7) 121-122°. The nmr spectrum showed absorptions at δ 1.97 (multiplet, methylene protons), δ 3.11 (broad singlet, active protons), δ 4.14 (triplet, benzylic protons at C-3), δ 4.88 (triplet, benzylic protons at C-1), and δ 7.28 (aromatic protons).

(b) From 1-(*N*-Phthalimido)-1,3-diphenylpropanone.

To a stirred solution of 20 g. of the 1-(*N*-phthalimido)-1,3-diphenylpropanone (9) in 350 ml. of warm methanol was added 2 g. of sodium borohydride in portions over a 30-minute period. The reaction mixture was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure and the residue hydrolyzed with 200 ml. of 1.2 *N* hydrochloric acid. The hydrolyzed mixture was then extracted with ether; the ethereal extract was washed with water until neutral to litmus, dried (sodium sulfate), and evaporated. A solution of 2.8 g. of hydrazine hydrate in 225 ml. of ethanol was then added to the residual oil and the mixture refluxed for 2 hours. After about 90 minutes, a solid began to precipitate. The solvent was removed from the cooled reaction mixture on a rotary evaporator. The residue was then digested with 60 ml. of 2 *N* hydrochloric acid on the steam bath for 15 minutes. The insoluble solids were removed from the cooled acidic extract by filtration. The filtrate was made alkaline by addition of 25% aqueous sodium hydroxide. The white crystalline solid that precipitated was collected and washed thoroughly with water; after drying in a vacuum desiccator oven phosphorus pentoxide for 24 hours, it weighed 5 g. (58%), m.p. 109-113°. Further purification of this solid (7) raised the melting point to 117-118°. However, the solid of m.p. 109-113° was found to be sufficiently pure for subsequent reactions.

erythro-3-Benzalmino-1,3-diphenylpropanol.

Two g. of *erythro* aminoalcohol (4b) (from the lithium aluminum hydride reduction, m.p. 112-117°) were subjected to the isomer separation procedure (7) without any precipitate being formed. The methanol was removed *in vacuo* and the residue recrystallized from ethanol to yield 1.55 g. (56% yield) of *erythro*-3-benzalmino-1,3-diphenylpropanol, m.p. 78-82°. Two recrystallizations from ethanol sharpened the melting point to 78.5-80.5°, lit (10) 82-83°. The ir spectrum exhibited weak absorption bands at 1640 cm^{-1} (C=N) and 3300 cm^{-1} (OH) and was different from the *threo*-isomer prepared above. The nmr spectrum was also quite different from that of the *threo*-isomer, showing absorption bands at δ 5.50 (singlet, benzal proton), a pair of doublets at δ 4.28 (benzylic proton) and a multiplet at δ 1.96 (methylene and hydroxyl protons). The nmr spectrum of the mother liquor from the first recrystallization was identical to that of the purified *erythro* benzal isomer and showed no evidence of *threo* benzal isomer.

3-Chloro-1,3-diphenylpropylamine.

A solution of 5.00 g. (22.0 mmoles) of 4b in 50 ml. of tetrahydrofuran was cooled in an ice bath and saturated with gaseous hydrogen chloride. Twenty-five milliliters of thionyl chloride was added, the mixture stirred at room temperature for 0.5 hours, and the volatiles removed *in vacuo*. The residue was dissolved in water and the solution cooled in an ice bath before being made alkaline with 50% sodium hydroxide. The resulting oil was extracted into ether and the ethereal extract washed with water and saturated sodium chloride solution. After drying over magnesium sulfate, the solution was evaporated *in vacuo* to give 7.03 g. of light brown oil. An aqueous silver nitrate test was positive only when heated.

Treatment of 3-Chloro-1,3-diphenylpropylamine with *p*-Toluenesulfonyl Chloride.

To a cold (0°) solution of the 3-chloro-1,3-diphenylpropylamine prepared above (assumed 5.40 g., 22.0 mmoles) in 75 ml. of dry pyridine was added 4.61 g. (24.2 mmoles) of *p*-toluenesulfonyl chloride in small portions over 15 minutes. After stirring for 2 hours, the reaction mixture, which had slowly warmed to room temperature, was poured into 1 l. of water and the precipitated gum extracted into ether. The ethereal extract was washed successively with water, dilute hydrochloric acid, water, and saturated sodium chloride solution. After drying over magnesium sulfate, the solvent was removed *in vacuo*. The brown syrupy residue (8.64 g., 98% yield) was essentially one spot on tlc (alumina, chloroform) and gave a negative aqueous silver nitrate test but a positive hot methanolic silver nitrate test. The ir and nmr spectra of a similar run made on a smaller scale were best interpreted as a mixture of *erythro*- and *threo*-1-chloro-

1,3-diphenyl-3-*p*-toluenesulfonamidopropane (6b and 6a).

Cyclization of the Chlorotosylamide Prepared from Chloropropylamine.

The chlorotosylamide prepared above (1.20 g., 3.00 mmoles), sodium ethoxide (5.73 ml. of 0.524 *N*, 3.00 mmoles), and 120 ml. of ethanol were heated at reflux for 1.5 hours. The reaction mixture was filtered while hot to remove sodium chloride, and the filtrate concentrated *in vacuo* to about 30 ml. The white solid was filtered, washed with ethanol, and dried to afford 0.45 g. (41% yield) of *trans*-2,4-diphenyl-1-*p*-toluenesulfonylazetidine (7b), identical to that prepared below by m.p. and mixture m.p. Nmr examination of the mother liquor indicated a *cis/trans* ratio of 2:1.

threo-1,3-Diphenyl-3-*p*-toluenesulfonamidopropanol (5a).

To a cold (0°) slurry of 1.00 g. (4.41 mmoles) of 4a in 5 ml. of dry pyridine was added 0.925 g. (4.85 mmoles) of *p*-toluenesulfonyl chloride in small portions over 10 minutes. The solution was allowed to stir for 2.5 hours while the temperature slowly became ambient and then poured into 50 ml. of water. The resulting oil was extracted into methylene chloride and the extract washed with dilute hydrochloric acid, water, and saturated sodium chloride solution. After drying (magnesium sulfate), the solvent was removed *in vacuo* to give an oil (1.27 g.). Crystallization from carbon tetrachloride yielded 0.73 g. (43% yield) of 5a, m.p. 123-125°. The nmr spectrum (deuteriochloroform) showed absorption at δ 2.00 (broadened triplet, methylene protons), δ 2.27 (singlet, tosyl methyl protons), δ 3.05 (broad singlet, hydroxyl proton), δ 4.91 to 4.38 (multiplet, benzylic protons), δ 6.39 (doublet, tosylamide proton), δ 7.21 to 6.94 (multiplet, aromatic protons), and δ 7.54 (doublet, downfield half of tosyl quartet). The ir spectrum exhibited bands due to NH and OH (3250 and 3500 cm^{-1}) and sulfonamide (1150 and 1310 cm^{-1}).

An analytical sample, prepared by repeated recrystallization from carbon tetrachloride (or chloroform-hexane), was single spot on tlc (alumina, chloroform) and melted at 126.5-128°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S}$: C, 69.24; H, 6.08; N, 3.67; S, 8.40. Found: C, 69.12; H, 6.02; N, 3.80; S, 8.45.

erythro-1,3-Diphenyl-3-*p*-toluenesulfonamidopropanol (5b).

To a slurry of 2.27 g. (10.0 mmoles) of 4b in 10 ml. of dry pyridine, cooled to 0°, was added portionwise 2.10 g. (11.0 mmoles) of *p*-toluenesulfonyl chloride over 10 minutes. The slurry was allowed to stir 2 hours while slowly warming to room temperature and then poured into 100 ml. of water. The solid was filtered, washed, and dried *in vacuo* to afford 3.94 g. of crude 5b, m.p. 124-127°, as a pyridine solvate. A solution of crude product in methylene chloride was washed with dilute hydrochloric acid, water, and saturated sodium chloride solution, and then dried over magnesium sulfate. Removal of the solvent *in vacuo* gave an oil which was crystallized from carbon tetrachloride to give 2.48 g. (65% yield) of *erythro*-1,3-diphenyl-3-*p*-toluenesulfonamidopropanol, m.p. 106-109°.

An analytical sample prepared by several recrystallizations from carbon tetrachloride melted at 109-111°. The nmr spectrum (deuteriochloroform) showed absorption at δ 2.00 (multiplet, methylene protons), δ 2.28 (singlet, tosyl methyl protons), δ 2.90 (broadened singlet, hydroxyl proton), δ 4.48 (merged quintet, benzylic protons), δ 6.33 (multiplet, aromatic protons) and δ 7.47 (doublet, downfield half of tosyl quartet). The ir spectrum (chloroform) exhibited absorption at 3300 and 3600 cm^{-1} (NH and OH) and 1310 and 1150 cm^{-1} (sulfonamide).

Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S}$: C, 69.24; H, 6.08; N, 3.67; S, 8.40. Found: C, 69.10; H, 6.02; N, 3.83; S, 8.54.

Evaporation of the mother liquor from the recrystallization of a crude sample of 5b yielded 4 g. of a solid which was chromatographed on 100 g. of Woelm neutral alumina (activity grade I) using 200 ml. of benzene as the solvent. The yellow oil (1 g.) obtained after evaporation of the solvent was triturated with and recrystallized from hexane twice to give 0.42 g. of a compound, m.p. 82-84°, identical to an authentic sample of *cis*-2-benzyl-3-phenyl-1-*p*-toluenesulfonylaziridine, m.p. 81-83°, prepared in 70% yield from *cis*-2-benzyl-3-phenylaziridine (23) and tosyl chloride in pyridine. Evidently *cis*-2-benzyl-3-phenylaziridine was formed as a by-product of the LAH reduction of 3,5-diphenylisoxazolidine as reported

by Kotera and his group (7c,23).

Anal. Calcd. for $C_{22}H_{21}NO_2S$: C, 72.76; H, 5.82; N, 3.85; S, 8.82. Found: C, 72.95; H, 5.55; N, 4.05; S, 8.54.

threo-1-Chloro-1,3-diphenyl-3-*p*-toluenesulfonamidopropane (6a).

To 7.64 g. (20 mmoles) of *threo*-tosylamidopropanol (5a) was added 12 ml. of thionyl chloride. After the initial vigorous reaction had subsided, the mixture was refluxed gently on the steam bath for 30 minutes. The cooled, darkly colored solution was poured over cracked ice. After thawing, the water was decanted from the precipitated gum. The gum was then taken up in ether, and the ethereal solution dried over anhydrous magnesium sulfate. After removal of solids by filtration, pentane was added to the filtrate until incipient turbidity. Crystallization occurred in the cold, yielding 4.6 g. (58%). An additional crystallization from ether/pentane gave an analytical sample, m.p. 110-111°.

Anal. Calcd. for $C_{22}H_{22}NCISO_2$: C, 66.10; H, 5.52; N, 3.51; S, 8.00; Cl, 8.87. Found: C, 66.13; H, 5.76; N, 3.42; S, 8.07; Cl, 8.63.

erythro-1-Chloro-1,3-diphenyl-3-*p*-toluenesulfonamidopropane (6b).

A solution of 7.64 g. (20.0 mmoles) of *erythro*-tosylamidopropanol (5b) in 40 ml. of thionyl chloride was heated at reflux for 0.5 hour. The excess thionyl chloride was removed *in vacuo*, and the white gummy residue was washed three times with carbon tetrachloride; crystallization could not be induced. The ir spectrum (carbon tetrachloride) indicated the presence of NH (3270 cm^{-1}) and sulfonamide (1320 and 1150 cm^{-1}).

cis-2,4-Diphenyl-1-*p*-toluenesulfonylazetidene (7a).

Crude *threo*-tosylaminopropyl chloride (6a) (assumed 20.0 mmoles) was treated in the same manner as described for 7b to afford 5.13 g. (71% yield) of 7a, m.p. 139-141°, single spot on tlc (alumina, chloroform). The ir spectrum (chloroform) indicated the absence of NH or OH and the presence of a sulfonamide (1340 and 1150 cm^{-1}). An analytical sample was obtained by recrystallization from ethanol, m.p. 139-141°.

Anal. Calcd. for $C_{22}H_{21}NO_2S$: C, 72.68; H, 5.82; N, 3.86; S, 8.82. Found: C, 72.89; H, 5.93; N, 3.95; S, 8.88.

Besides the aromatic hydrogens (complex multiplet centered at δ 7.44) and the benzylic hydrogens (triplet centered at δ 5.00, $J = 8.5$ Hz), the non-equivalent hydrogens of the methylene group of 7a displayed two overlapping sextets, one centered at δ 3.03 (H-*trans* to phenyl groups, $J_{AM} = 8.5$ Hz and $J_{MX} = 12.3$ Hz) and the other at δ 1.88 (H-*cis* to phenyl groups, $J_{AX} = 8.5$ Hz and $J_{MX} = 12.3$ Hz); the methyl substituent of the tosyl group partially obscures the *cis*-hydrogen signal which appears at δ 2.37.

trans-2,4-Diphenyl-1-*p*-toluenesulfonylazetidene (7b).

The total crude *erythro*-tosylamidopropyl chloride (6b) (assumed 20.0 mmoles) in 800 ml. of absolute ethanol was treated with 42 ml. (22.0 mmoles) of 0.52 *N* sodium ethoxide and the solution heated at reflux for 2 hours. After filtration (hot) to remove sodium chloride, the filtrate was concentrated *in vacuo* to about 75 ml. The precipitate was removed by filtration, washed with ethanol, and dried to give 4.86 g. (68% yield) of 7b, m.p. 175-177°. The ir spectrum (chloroform) showed absorption at 1330 and 1150 cm^{-1} (sulfonamide) with no absorption in the 3200-3500 cm^{-1} region (OH or NH). An analytical sample recrystallized from ethanol melted at 175-177.5°.

Anal. Calcd. for $C_{22}H_{21}NO_2S$: C, 72.68; H, 5.82; N, 3.86; S, 8.82. Found: C, 72.66; H, 6.05; N, 3.68; S, 8.88.

In addition to the methyl hydrogens at δ 2.32 (3H) and aromatic hydrogens at δ 7.50 (10H) and 6.98 (4H), the *trans*-isomer displayed two triplets, one centered at δ 5.43 (2H, $J = 7$ Hz, benzylic hydrogens) and the other centered at δ 2.68 (2H, $J = 7$ Hz, CH_2).

cis-2,4-Diphenylazetidene (8a).

To a refluxing solution of 15.6 g. (43 mmoles) of *cis*-2,4-diphenyl-*p*-tosylazetidene in 300 ml. of *n*-amyl alcohol was added 18.4 g. sodium (0.8 gram-atom) in 1 g. portions. The portions of sodium were added after the preceding portion had completely reacted with the solvent. After the addition, heating was discontinued, and the turbid mixture was allowed to

cool to room temperature overnight. Water (150 ml.) was added to the reaction flask and the entire contents transferred to a separatory funnel. After thorough mixing, the phases were separated. The organic layer was washed with several portions of water until the wash was neutral to litmus. The aqueous layer and water washes were combined and extracted with ether. The ethereal phase was washed with water and then added to the original organic layer. The combined organic phase was then extracted, successively, with two portions of cold 2 *N* sulfuric acid (90 ml.). The combined acid extract was made strongly basic by addition of solid potassium hydroxide, while cooling in an ice-bath. Water was added to dissolve precipitated salt. The aqueous phase was re-extracted with ether; the ethereal layer was washed (water), dried (sodium sulfate), and evaporated, leaving a pale yellow oil (5.1 g., 56%). Distillation of the oil *in vacuo* yielded a fraction (1 g., 11%) with b.p. 117-120°/0.3 mm, $n_D^{25} = 1.5895$.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.13; H, 7.17; N, 6.70. Found: C, 86.38; H, 7.25; N, 6.91.

cis-2,4-Diphenylazetidene (8a) Hydrochloride.

In a manner identical to that used for the *trans*-tosylazetidene (7b), 1.93 g. (5.32 mmoles) of *cis*-2,4-diphenyl-1-*p*-toluenesulfonylazetidene (7a) was treated with 45 ml. of sodium naphthalene solution (13.5 mmoles) to give 0.80 g. (72% yield) of *cis*-2,4-diphenylazetidene as a colorless oil. The nmr spectrum (carbon tetrachloride) exhibited absorption at δ 2.25 to 1.75 (multiplet, methylene protons), δ 4.68 (broad triplet, $J = 8$ Hz, benzylic protons), and δ 7.58 to 7.05 (complex multiplet, aromatic protons). Cooling caused the benzylic triplet to sharpen. Vpc analysis (247°) showed one major component (90%, retention time 3 minutes) and one minor component (10%, retention time 4 minutes).

Conversion to the hydrochloride salt with ethereal hydrogen chloride afforded 0.88 g. (94% conversion) of material melting at 140.5-144°. The nmr spectrum (deuterium oxide, trimethylsilylpropanesulfonic acid sodium salt) showed absorptions at δ 4.00 to 3.00 (complex multiplet, methylene protons), δ 4.83 (singlet, exchangeable protons), δ 5.74 (triplet, $J = 9$ Hz, benzylic protons), and δ 7.65 (singlet, aromatic protons).

trans-2,4-Diphenylazetidene (8b).

To a stirred suspension of 2 g. (5.5 mmoles) *trans*-2,4-diphenyl-*p*-toluenesulfonylazetidene (7b) in 300 ml. of liquid ammonia was added metallic sodium slivers. The pieces of sodium were added one at a time until a dark greenish-blue color persisted. The color was then discharged by addition of powdered ammonium chloride. The ammonia was allowed to evaporate and the residue treated with 100 ml. of water. The contents of the reaction flask were transferred to a separatory funnel with ether. After thorough mixing, the phases were separated. The ethereal layer was washed with portions of water until the wash was neutral to litmus, and then extracted, successively, with two portions of cold 1 *N* sulfuric acid (15 ml.). The combined acid extract was made alkaline with solid potassium hydroxide and re-extracted with ether. The ethereal layer was washed (water), dried (sodium sulfate), and evaporated, leaving 0.5 g. (43%) of a yellow oil. The oil was dissolved in 15 ml. of a saturated ethanolic solution of picric acid. By addition of water (30 ml.), a crystalline product was obtained, 0.9 g. (39%), m.p. 181-183.5°. Recrystallization from hot 50% aqueous alcohol gave an analytical sample, m.p. 183-185°.

Anal. Calcd. for $C_{21}H_{19}N_2O_2$: C, 57.50; H, 4.10; N, 12.80. Found: C, 57.50; H, 4.21; N, 12.67.

trans-2,4-Diphenylazetidene (8b) Hydrochloride.

Sodium Naphthalene.

Sublimed naphthalene (1.920 g., 15.0 mmoles) was dissolved in 50 ml. of dry, peroxide-free dimethoxyethane in a dry, 100 ml. 3-neck flask equipped with glass stirrer, rubber septum, and nitrogen purging system. The system was flushed well with nitrogen, and 0.35 g. (15.0 mmoles) of sodium was added in small pieces. The solution became dark green within 15 minutes but was stirred overnight at room temperature to allow all the sodium to dissolve.

trans-Tosylazetidine (**7b**) (2.70 g., 7.44 mmoles) was dissolved in 170 ml. of dry, peroxide-free dimethoxyethane contained in a dry, 500 ml., 3-neck flask equipped with glass stirrer, rubber septum, condenser, and system for purging with nitrogen. After thorough flushing with nitrogen, the solution was heated to reflux. The sodium naphthalene solution was added as rapidly as possible from a 50 ml. syringe, fitted with an #18 gauge needle, until a pink color persisted (50 ml. required 15 mmoles). The reaction was immediately quenched by the addition of 2 ml. of water. Then the dimethoxyethane was removed *in vacuo* and the residue treated with 50 ml. of water. The product was extracted into benzene, and the organic solution washed with water. This was followed by extraction into dilute acid and washing with benzene. The aqueous acid extract was cooled, made alkaline with 50% sodium hydroxide, and the oil extracted with ether. After washing (water and saturated sodium chloride solution) and drying (magnesium sulfate), the solvent was removed *in vacuo* to yield 0.49 g. (32% yield) of a colorless oil which crystallized when chilled. The nmr spectrum (carbon tetrachloride) exhibited absorption at δ 2.25 (broad singlet, NH), δ 2.63 (triplet, J = 7.5 Hz, methylene protons), δ 4.88 (broad triplet, J = 7.5 Hz, benzylic protons) and δ 7.57 to 7.12 (complex multiplet, aromatic protons). Chilling the sample caused the benzylic proton signal to sharpen considerably. Vpc analysis (247°) showed one major component (94%, retention time 3-1/2 minutes) and one minor component (6%, retention time 4 minutes).

The crude base was dissolved in 50 ml. of ether, 0.4 ml. of 6.5 N ethereal hydrogen chloride added, and the precipitate isolated. This gave 0.55 g. (95% conversion) of *trans*-2,4-diphenylazetidine hydrochloride, m.p. 135-138°. Recrystallization from ethanol-ether (1:2) (68% recovery) afforded a product melting at 151-153°. The nmr spectrum (deuterium oxide, trimethylsilylpropanesulfonic acid sodium salt) showed absorption at δ 3.27 (triplet, J = 8 Hz, methylene protons), δ 4.68 (singlet, exchangeable protons), δ 5.65 (triplet, J = 8 Hz, benzylic protons) and δ 7.57 (singlet, aromatic protons).

In a similar run which gave a 23% yield of **8b**, the **7b** was recovered in the following manner. The benzene solution which remained after the dilute acid extraction, was dried (magnesium sulfate) and the solvent removed *in vacuo*. The residue was then slurried with pentane, filtered, and the precipitate washed several times with pentane to yield 1.93 g. (71% recovery) of crude **7b**, m.p. 160-168°. Recrystallization from ethanol gave 1.31 g. (48% recovery) of material melting at 175-176.5°, single spot on tlc (alumina, chloroform).

cis-N-Nitroso-2,4-diphenylazetidine (**9a**).

cis-2,4-Diphenylazetidine (0.56 g., 2.68 mmoles) was dissolved in 25 ml. of dry dimethoxyethane contained in a dry, 50 ml., 3-neck round bottom flask fitted with stirrer, rubber septum, and nitrogen purging system. After cooling in an ice bath and thorough flushing with nitrogen, 1.78 ml. of methyl lithium in ether (5.1%, d = 0.71 g./ml., 2.95 mmoles) was added by syringe. The dark red solution was stirred 5 minutes, and then 3.75 ml. (0.787 mmoles/ml., 2.95 mmoles) of nitrosyl chloride in dry dimethoxyethane was added. The reaction was quenched after 5 minutes by adding 1 ml. of water. The dimethoxyethane was removed *in vacuo*, and the residue was taken up in benzene. After washing successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide, water, saturated sodium solution, and drying (magnesium sulfate), the solution was evaporated *in vacuo* to afford 0.52 g. (81% yield) of crude **9a**. Tlc analysis (alumina, benzene) indicated one major and 5 minor components. This material was chromatographed on 200 g. of Woelm neutral alumina (activity grade III, dry column technique) eluting with benzene (5 ml. fractions). Combining fraction 17 to 33 inclusive and removing the solvent *in vacuo* gave 0.34 g. of a brownish oil, essentially single spot on tlc (alumina, benzene). Rechromatography on 100 g. of Woelm neutral alumina as before yielded 0.28 g. (84% recovery) of **9a** as a yellow oil and white solid mixture. This material was single spot on tlc (alumina, benzene); uv (cyclohexane): 398 nm (ϵ = 89), 241 nm (ϵ = 6,120); ir (carbon tetrachloride): 690-695 cm^{-1} , 1210-1220 cm^{-1} (broad), 1420-1440 cm^{-1} .

In addition to aromatic peaks at δ 7.51 and 7.28, the nmr spectrum of

9a (deuteriochloroform) displayed two broad triplets at δ 6.24 and 5.62 for the benzylic hydrogens and complex multiplet at δ 3.52 and 2.24 for the methylene hydrogens.

trans-N-Nitroso-2,4-diphenylazetidine (**9b**).

A solution of 0.38 g. (1.53 mmoles) of *trans*-2,4-diphenylazetidine hydrochloride in 20 ml. of water and 0.1 ml. of acetic acid was cooled in an ice bath, and a solution of 0.13 g. (1.84 mmoles) of sodium nitrite in 5 ml. of water added dropwise over 1 hour. The resulting slurry was allowed to stir 0.5 hour at 0°, then 33 hours at room temperature. The product was filtered, washed with water, and dried *in vacuo* to give 0.31 g. (85% yield) of **9b**, m.p. 107-108.5°. The material was single spot on tlc (alumina, chloroform).

An analytical sample, purified by sublimation (90-100°/0.1 mm), melted at 105.5-197°; uv (cyclohexane): 398 nm (ϵ = 83), 245 nm (ϵ = 5,289); ir: 690-695 cm^{-1} , 1210-1220 cm^{-1} (broad), 1420-1440 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.52; H, 6.01; N, 11.56.

The aromatic hydrogens of **9b** appeared as two sharp peaks at δ 7.33 and 7.22 and the benzylic hydrogens showed two triplets (with fine structure) at δ 6.20 and 5.70 while the methylene hydrogens exhibited a triplet with fine structure at δ 2.77.

Sodium Dithionite Reduction of **9a** and **9b**.

An 80-120 mg. sample of the *N*-nitrosoazetidine and ~10 ml. of a 20% sodium hydroxide solution in aqueous ethanol (1:1) in a 25 ml., 3-necked flask equipped with magnetic stirrer, a solids addition tube containing two equivalents of sodium dithionite and a condenser connected to a gas buret. The flask was placed in an oil bath at ~60° and flushed with nitrogen for 0.5 hour. After the system was sealed, the sodium dithionite was added all at once. Nitrogen elimination commenced after about 10 minutes and continued for about 2 hours. The reaction mixture was allowed to stir for a total of 2.5 hours and then cooled to room temperature. An equal volume of saturated sodium chloride solution was added and the oil extracted into ether. After washing (water and saturated sodium chloride solution) and drying (magnesium sulfate), the solvent was removed *in vacuo* to give 90% (from **9a**) and 96% (from **9b**) of product. The analysis (alumina, benzene) of the product from **9b** showed only one spot while two traces contaminants were present in the product from **9a**.

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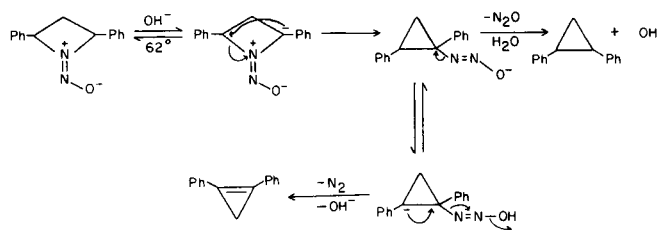
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(18) Either **9a** or **9b** equilibrated to a 70:30 mixture (nmr) of **9a** and **9b** after 2 hours with 20% sodium hydroxide in aqueous ethanol at 62°

under nitrogen. Since there was no evidence for any other products (one spot by tlc), it is unlikely that a mechanism such as that depicted below is operative.



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