Aziridinyl Ketones XVII.
The Hydrogenation of 2-Phenyl-3-Aroylaziridines to Aziridinylcarbinols (1a)

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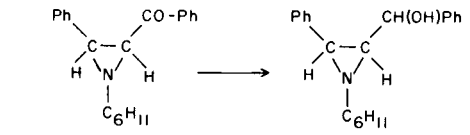
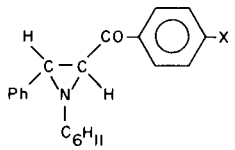
The sodium borohydride reduction of both *cis* and *trans*-1-cyclohexyl-2-phenyl-3-aroylaziridines provides in each case the corresponding carbinol as a mixture of the two possible diastereoisomeric racemates, whereas reduction of these ketones with lithium aluminum hydride or with lithium diisopropylamide provides only the racemate resulting from attack on the carbonyl group from the least hindered side. Catalytic hydrogenation of a *cis* aziridinyl ketone cleaved the aziridine ring and provided an amino carbinol.

Previous investigations of the chemistry of the *cis* and *trans* isomers of aziridinyl ketones have shown that the aziridine ring is quite sensitive to cleavage by acidic reagents (2). Basic reagents, under mild conditions, do not appear to cause destruction of the aziridine ring. For example, phenyllithium, as well as various Grignard reagents, readily adds to the carbonyl group without affecting the aziridine ring (3,4). In addition, the epimerization of *trans* to *cis* isomers with sodium methoxide in methanol has been demonstrated (1,5). Recently we have reported in a preliminary communication (6) that *cis*-2-phenyl-3-aroylaziridines undergo an unusual rearrangement in the presence of lithium diisopropylamide or lithium *N*-methylanilide to substituted indenones. The *trans* isomers are reduced to the corresponding *trans* carbinols by the former reagent, but do not react with the latter reagent. Since, from each *cis* or *trans* aziridinyl ketone, the corresponding carbinol could theoretically be obtained as two diastereoisomeric racemates, we have studied the reduction of some aziridinyl ketones by various reducing agents and have examined the p.m.r. spectra of the crude products.

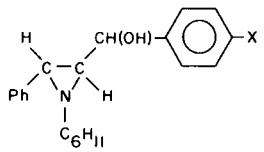


1 (7)
cis aziridinyl ketone

2
cis aziridinyl carbinols
2, m.p. 100°
2', m.p. 134°



3
trans aziridinyl ketones
3a(7), X = H
3b(8), X = Ph



4
trans aziridinyl carbinols
4a, X = H, m.p. 150°
4a', X = H, m.p. 106-108°
4b, X = Ph

Cram's rule of steric control of asymmetric induction predicts which stereoisomer will predominate in the product, *i.e.* the starting ketone will react preferentially in the conformation in which the carbonyl group is least hindered and this group will be attacked by the reagent from the less hindered side (9). However, as House points out (10), the stereochemical outcome of these reactions is often difficult to predict. Steric hindrance to approach of the reagent to the carbonyl function and the stability of the final product are two opposing factors which influence the steric course of the reduction. Cram's rule does not apply to catalytic reduction. Recently Karabatsos has described an empirical model on the basis of which semi-quantitative predictions of product stereospecificity resulting from chemical additions to carbonyl groups directly bonded to asymmetric carbon atoms are feasible (11).

Since metal hydrides may function as strong bases, it is possible that the aziridinyl ketones might be epimerized prior to reduction, via the enolate anion. However, racemizations are rarely observed in lithium aluminum hydride reductions and are less expected to occur with the much less basic borohydride anion (10).

The results of the reductions of some aziridinyl ketones are shown in Table I.

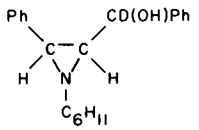
TABLE I

The Reduction of Aziridinyl Ketones to Aziridinyl Carbinols

Aziridinyl ketone	Reducing agent	Product composition, %
1	$LiAlH_4$	**2** 100; **2′** 0
1	$NaBH_4$	**2** 65; **2′** 35
1	H_2/Pd	**2** 28; **2′** 0; **6** 64
3a	$LiAlH_4$	**4a** 100; **4a′** 0
3a	$LiN(CHMe_2)_2$	**4a** 100; **4a′** 0
3a	$NaBH_4$	**4a** 85; **4a′** 15
3b	$LiAlH_4$	**4b** 100
3b	$LiN(CHMe_2)_2$	**4b** 100

Reduction of the *cis* aziridinyl ketone **1** with lithium aluminum hydride gave only one carbinol **2**, m.p. 100°. Sodium borohydride reduction of the same ketone gave a mixture of two diastereoisomeric racemates, **2** (65%) and **2′** m.p. 134° (35%). Reduction of the *trans* aziridinyl ketone **3a** presents the same feature: only one carbinol **4a**, m.p. 150° was obtained by reduction with lithium aluminum hydride, whereas two diastereoisomeric racemates, **4a** (85%) and **4a′** m.p. 106-108° (15%), resulted from sodium borohydride reduction. Lithium aluminum hydride reduction of the *trans* aziridinyl ketone **3b** gave only one carbinol, **4b**.

The p.m.r. spectra of the four possible stereoisomers of 1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine are shown in Figure 1. The data are reported in Table II together with the data for the deuterated *cis* aziridinyl carbinol **5**, prepared from the ketone **1** with lithium deuteride. The p.m.r. spectrum of each of these carbinols



5

is a first order AMX pattern with $J_{M,X}=0$. The low field doublet in the region δ 4.0-4.9 is assigned to the C-4 proton, coupled with the C-3 proton, as this signal is absent from the spectrum of the deuterated carbinol **5**. The doublet in the region δ 2.7-3.4 is due to the C-2 proton, coupled with the C-3 proton. The quartet at δ 1.9-2.5 corresponds to the C-3 proton, coupled with the C-2 and C-4 protons. The signals of the C-2, C-3, and C-4 protons of the *trans* isomers occur at lower fields than

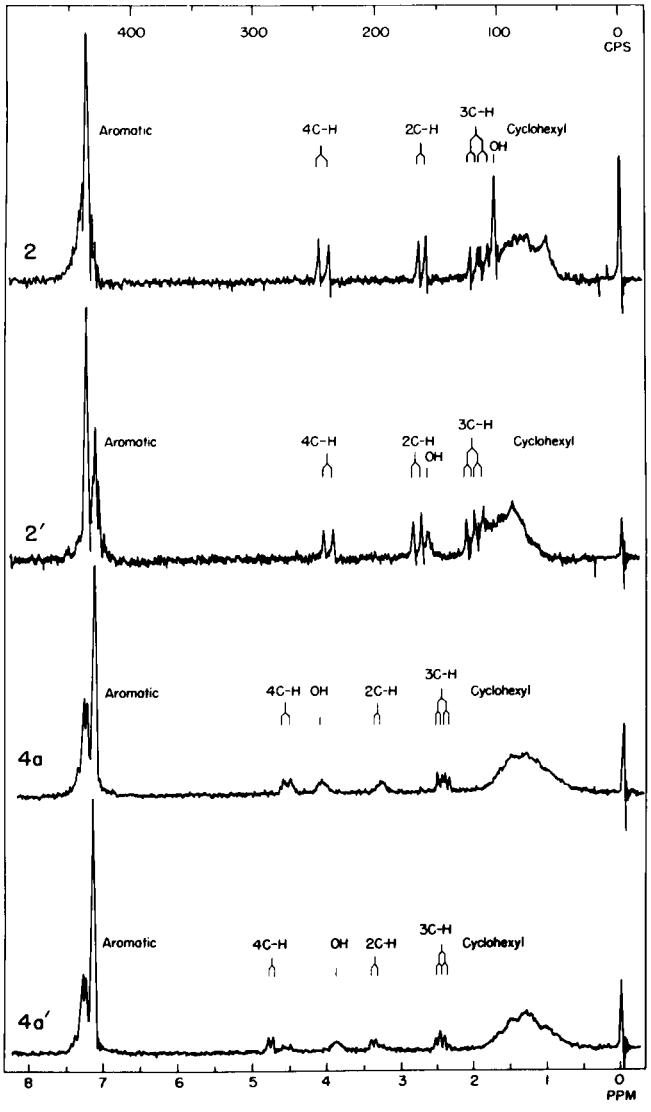
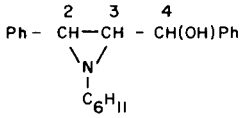


Figure 1. Pmr spectra of the stereoisomers of 1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine.

TABLE II

P.M.R. Spectral Data of Aziridinyl Carbinols (a)



Carbinol		Aromatic	4C-H	2C-H	3C-H	Cyclohexyl	$J_{2,3}$	$J_{3,4}$
	2	7.17-7.50 c	4.06 d	2.72 d	1.94 q	0.88-1.92 c	6.0 cps.	8.3 cps.
cis	**5**	7.15-7.54 c	----	2.68 d	1.89 d	0.83-2.00 c	6.3 cps.	----
	2'	7.09-7.42 c	3.99 d	2.80 d	2.00 q	1.10-2.08 c	6.5 cps.	7.5 cps.
trans	**4a**	7.24-7.45 c	4.58 d	3.35 d	2.47 q	0.65-2.00 c	4.0 cps	5.0 cps.
	4a'	7.27-7.41 c	4.88 d	3.42 d	2.54 t	0.83-1.92 c	3.5 cps.	4.0 cps.

(a) Spectra were determined in deuterochloroform solutions on a Varian A-60 spectrometer. Chemical shifts are given in parts per million (δ) relative to tetramethylsilane.

The positions of the hydroxyl proton signal are not reported since it is concentration dependent. In all spectra this signal was observed and was confirmed by deuterium exchange.

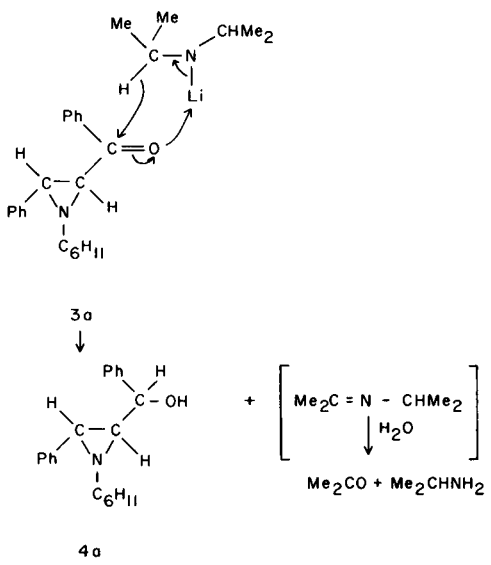
c = complex, d = doublet, q = quartet, t = triplet.

the corresponding signals of the *cis* isomers. From the data in Table II it can be seen that the two carbinols **2** and **2'** obtained from the *cis* ketone **1** have coupling constants, $J_{2,3}$, between the aziridine ring protons 2C-H and 3C-H of 6.0 and 6.5 cps., whereas the coupling constants $J_{2,3}$ of the carbinols **4a** and **4a'** obtained from the *trans* ketone **3a** are 4.0 and 3.5 cps. It is known that the coupling constant for the vicinal ring protons 2C-H and 3C-H of aziridines is greater for a *cis* isomer than for the corresponding *trans* isomer (1,12). This difference $J_{cis} > J_{trans}$ has also been found for protons on cyclopropane, oxirane, and thiirane rings (13). Thus, it is deduced that the aziridine ring of each carbinol has the same configuration as that of its ketone precursor and that there is no epimerization prior to reduction: the hydrides are not strong enough bases to effect the *trans* to *cis* epimerization of the aziridinyl ketones previously observed to occur in the presence of sodium methoxide (1,5).

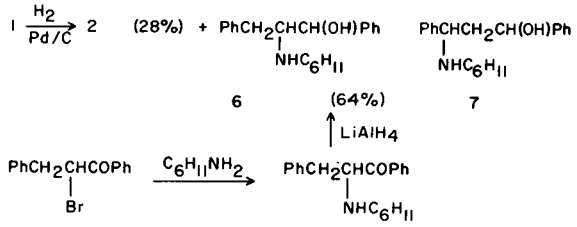
With lithium aluminum hydride as the reducing agent only one diastereoisomeric racemate was obtained in each case (Table I) and it is logical to assume that it corresponds to attack on the ketone from the less hindered side. When sodium borohydride was used, both **1** and **3a** gave mixtures of the two possible diastereoisomeric racemates in which the proportions of the carbinols **2'** and **4a'** formed by attack on the ketones from the more hindered side were respectively 35% and 15% (Table I). These results are consistent with the fact that the borohydride anion is less bulky than the aluminum hydride anion.

Since the conformations of the aziridinyl ketones are known (14), the configurations of the diastereoisomers of the aziridinyl carbinols can be assigned. In solution, the *cis* aziridinyl ketones exist in both the non-conjugated *gauche* and the conjugated *cisoid* conformations. Reduction of both of these rotamers from the least hindered side (*i.e.* opposite to the $N\text{-}C_6H_{11}$ group) produces the *erythro* diastereoisomer **2**, m.p. 100°. Attack on the carbonyl group from the more hindered side provides the *threo* diastereoisomer **2'**, m.p. 134° (Fig. 2). The *trans* aziridinyl ketones have a conjugated *cisoid* conformation (14) and attack on the carbonyl group from the least hindered side leads to the *erythro* diastereoisomer **4a**, m.p. 150°. Attack from the more hindered side produces the *threo* diastereoisomer **4a'** m.p. 106-108° (Fig. 3).

The carbinol **4a**, corresponding to attack on the ketone from the less hindered side, was also obtained by reduction of **3a** with lithium diisopropylamide. Similarly, the reduction of **3b** by this reagent gave only the carbinol **4b**, identical with the product obtained by lithium aluminum hydride reduction. This reaction probably occurs via a cyclic transition state similar to that proposed for the Meerwein-Ponndorf reduction.



Catalytic reduction of the *cis* aziridinyl ketone **1** with palladium on charcoal gave a 28% yield of the aziridinyl carbinol **2**: no **2'** was detected. A second product, obtained in a larger amount (64%) from the same reaction mixture, reacted with only one equivalent of hydrogen chloride and thus did not contain an aziridine ring. The aziridine ring might cleave in two possible ways to produce **6** and/or **7**. Since the oxirane ring of α-epoxyketones usually cleaves, on catalytic reduction, to give, 1,2-diols (15) (products analogous to **6**), an unambiguous synthesis of **6** was undertaken by treating α-bromo-α-benzylacetophenone with cyclohexylamine and then reducing the α-aminoketone with lithium aluminum hydride. The structure of **6** was thus established to be 2-cyclohexylamino-1,3-diphenyl-1-hydroxypropane.



EXPERIMENTAL

Infrared spectra were determined on a Perkin-Elmer model 237 grating spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois.

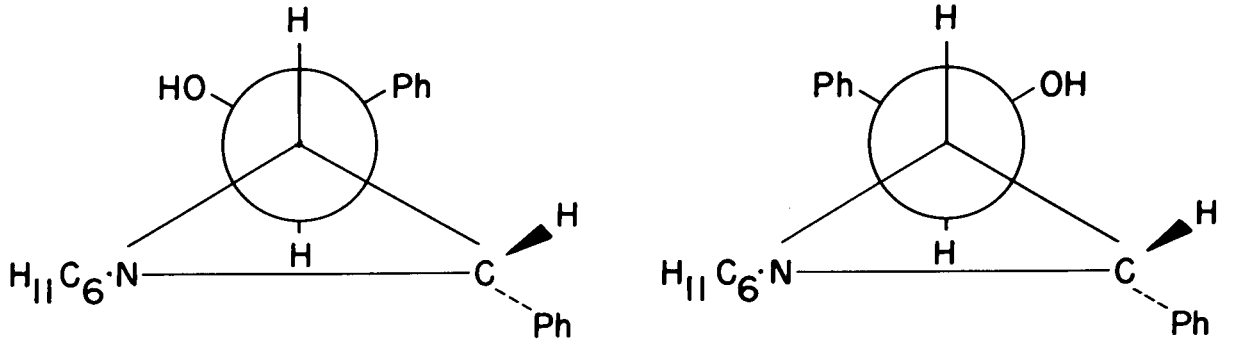
Reduction of **1** with Lithium Aluminum Hydride.

A solution of **1** (5.0 g., 0.016 mole) in benzene (20 ml.) was added to a suspension of lithium aluminum hydride (1.0 g., 0.026 mole) in ether (80 ml.) and the mixture was refluxed for three hours and then cooled. Excess of hydride was decomposed with water (1 ml.). A quantity of 15% aqueous sodium hydroxide (1 ml.) and water (2.5 ml.) were added and the mixture was filtered. Removal of solvent from the dried (magnesium sulfate) filtrate provided crude *cis*-1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine (**2**) (4.1 g., 77%) as a white solid, m.p. 94-98°. The pmr spectrum of the crude product showed the presence of only one diastereoisomer. Two recrystallizations from ethanol provided pure **2**, m.p. 100°; infrared absorption ν (carbon tetrachloride), 3620 and 3460-3440 cm^{-1} (OH).

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.13; H, 8.08; N, 4.74.

Reduction of **1** with Lithium Aluminum Deuteride.

When **1** (0.50 g.) was reduced with lithium aluminum deuteride (0.10 g.) by the procedure described above, *cis*-1-cyclohexyl-2-phenyl-3-(α-deuterio-α-hydroxybenzyl)aziridine (**5**) was obtained as white crystals (from hexane), m.p. 100°.



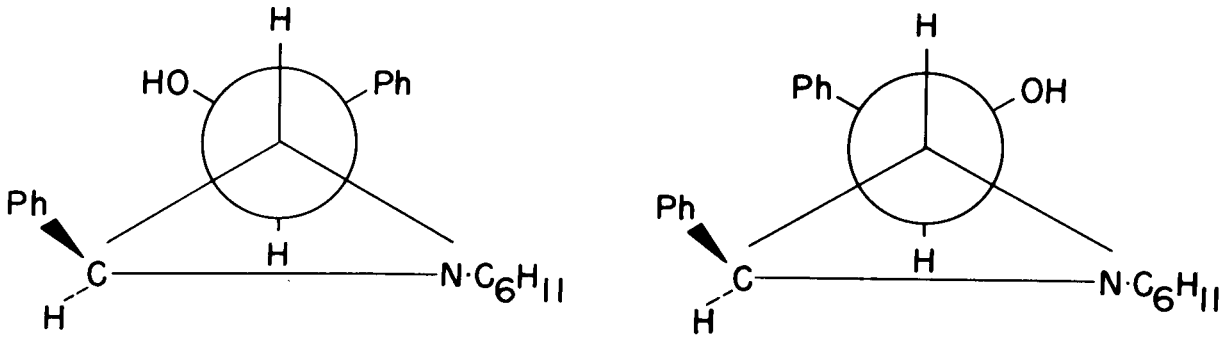
Erythro (one enantiomer)

2, m.p. 100°

Threo (one enantiomer)

2', m.p. 134°.

Fig. 2 - The diastereoisomers of cis-1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine.



Erythro (one enantiomer)

4a, m.p. 150°

Threo (one enantiomer)

4a', m.p. 106-108°.

Fig. 3 - The diastereoisomers of trans-1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine.

Reduction of **3a** with Lithium Aluminum Hydride.

trans-1-Cyclohexyl-2-phenyl-3-benzoylaziridine (2.0 g., 0.0065 mole), when reduced with lithium aluminum hydride (0.38 g., 0.01 mole) by the above procedure gave crude *trans*-1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine (**4a**) (1.1 g., 55%); m.p. 139-141°. The pmr spectrum showed the presence of only one diastereoisomer. Two recrystallizations from petroleum ether (b.p. 60-70°) provided pure **4a** as white needles, m.p. 150°; infrared absorption ν (carbon tetrachloride), 3600 and 3450 cm^{-1} (OH).

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.41; H, 8.12; N, 4.70.

Reduction of **3b** with Lithium Aluminum Hydride.

trans-1-Cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)aziridine (2.20 g., 0.0058 mole) was reduced with lithium aluminum hydride (0.33 g., 0.0058 mole) by the procedure previously described. Crude *trans*-1-cyclohexyl-2-phenyl-3-(α-hydroxy-*p*-phenylbenzyl)-aziridine (2.18 g., 98.5%) was obtained, m.p. 180-185°. The pmr spectrum of this crude product showed the presence of only one diastereoisomer. Two recrystallizations from light petroleum (b.p. 60-80°) provided the pure carbinol **4b** as white crystals, m.p. 191-193°; infrared absorption ν (carbon tetrachloride), 3630 and 3450 cm^{-1} (OH).

Anal. Calcd. for $C_{27}H_{29}NO$: C, 84.55; H, 7.62; N, 3.65. Found: C, 84.85; H, 7.53; N, 3.68.

Reduction of **3a** with Lithium Diisopropylamide.

Diisopropylamine (2.8 ml., 0.020 mole) was added dropwise to a stirred solution of butyllithium (0.016 mole) in hexane (7 ml.) and ether (20 ml.). The solution was stirred for 10 minutes and then *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine (2.0 g., 0.0066 mole) was added portionwise. The mixture was refluxed for three hours, cooled, and poured into icewater (30 g.). The ether layer was separated and the aqueous phase was extracted with ether (2 x 5 ml.). The combined ether extracts were dried (magnesium sulfate) and the ether was evaporated to provide a sticky solid (2.22 g.) which was dissolved in boiling petroleum ether (b.p. 60-70°). On cooling, the carbinol **4a** was obtained as white needles (1.21 g., 60%), m.p. 139-141°. The pmr spectrum of this product showed the presence of only one diastereoisomer. Two crystallizations from petroleum ether (b.p. 60-70°) provided pure **4a**, m.p. 150°, identical (mixed m.p., infrared and pmr spectra) with the product of the lithium aluminum hydride reduction of **3a**.

Reduction of **3b** with Lithium Diisopropylamide.

Treatment of *trans*-1-cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)-aziridine (2.2 g., 0.0058 mole) with lithium diisopropylamide [prepared from butyllithium (0.016 mole) and diisopropylamine (2.8 ml., 0.20 mole)] by the procedure described above provided crude *trans*-1-cyclohexyl-2-phenyl-3-(α-hydroxy-*p*-phenylbenzyl) aziridine (**4b**) (1.60 g., 72%), m.p. 180-185°. The pmr spectrum showed the presence of only one diastereoisomer. Two recrystallizations from petroleum ether (b.p. 60-80°) provided pure **4b** as white crystals, m.p. 193-194°, identical (mixed m.p., infrared and pmr spectra) with the carbinol obtained from the lithium aluminum hydride reduction of **3b**.

Reduction of **1** with Sodium Borohydride.

To a stirred solution of **1** (1.00 g., 0.0032 mole) in methanol (66 ml.) was added a solution of sodium borohydride (0.14 g., 0.0037 mole) in water (3.3 ml.). The solution was stirred at 27° for three hours and the solvents removed by distillation *in vacuo*. To the residue was added water (15 ml.) and the mixture was extracted with ether (2 x 30 ml.). The combined ether extracts were dried (magnesium sulfate) and the solvent was evaporated to provide crude *cis*-1-cyclohexyl-2-phenyl-3-(α-hydroxybenzyl)aziridine (0.97 g., 96%), m.p. 91-100°. The pmr spectrum of this crude product showed it to be a mixture of two diastereoisomeric carbinols **2** (65%) and **2'** (35%). The two isomers were separated by fractional crystallization from hexane. The less soluble isomer **2'** was obtained as white plates, m.p. 134°; infrared absorption ν (carbon tetrachloride), 3590 and 3400 cm^{-1} (OH).

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.26; H, 8.13; N, 4.52.

The more soluble isomer **2** was obtained as white crystals, m.p. 100°, and was identical (mixed m.p., infrared and pmr spectra) with the product of the lithium aluminum hydride reduction of **1**.

Reduction of **3a** with Sodium Borohydride.

To a stirred solution of **3a** (6.10 g., 0.020 mole) in methanol (400 ml.) was added a solution of sodium borohydride (0.945 g., 0.025 mole) in water (20 ml.). The solution was stirred at room temperature for three hours. The solvents were distilled *in vacuo* and water (100 ml.) was added to the residue. The resulting white solid was removed by filtration, washed with water, and dried (phosphorus pentoxide), *in vacuo*. The crude carbinol (5.58 g., 91%) was shown by pmr spectroscopy to consist of two diastereoisomers, **4a** (85%) and **4a'** (15%). The two isomers were separated by fractional crystallization from hexane. The less soluble isomer **4a** was obtained as white needles, m.p. 150° and was identical (mixed m.p., infrared and pmr spectra) with the product of the lithium aluminum hydride reduction of **3a**. The more soluble isomer **4a'** was obtained as white crystals, m.p. 106-108°.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.22; H, 8.19; N, 4.55.

The Catalytic Reduction of **1**.

A solution of **1** (5.0 g.) in benzene (75 ml.) and glacial acetic acid (1 ml.) was hydrogenated in the presence of 10% palladium on charcoal catalyst (1 g.) at 40 lbs/in^2 for 5 hours at room temperature. After removal of the catalyst by filtration, solvents were distilled from the filtrate *in vacuo* to leave a yellow oil which solidified on trituration with petroleum ether (b.p. 60-70°). Extraction of this yellow solid with boiling hexane left a solid which, after two recrystallizations from ethanol, was obtained as white crystals (1.4 g., 28%), m.p. 100°. This solid was identical (mixed m.p., infrared and pmr spectra) with an authentic sample of the *cis* aziridinyl carbinol **2**. The hexane extract, on cooling, provided white crystals (3.2 g., 64%) of 2-cyclohexylamino-1,3-diphenyl-1-hydroxypropane (**6**) m.p. 89-90° (from hexane).

Anal. Calcd. for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.44; H, 9.06; N, 4.41.

Treatment of **6** in a benzene-ether solution with dry hydrogen chloride gave the hydrochloride of **6**, m.p. 175-178°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: C, 72.91; H, 8.16; Cl, 10.25. N, 4.05. Found: C, 72.94; H, 8.36; Cl, 10.04; N, 4.00.

Synthesis of 2-Cyclohexylamino-1,3-diphenyl-1-hydroxypropane (**6**).

A solution of α-bromo-α-benzylacetophenone (16) (2.0 g., 0.0069 mole) and cyclohexylamine (4.8 ml., 0.04 mole) in benzene (10 ml.) was refluxed for 24 hours. Cyclohexylamine hydrobromide was filtered from the cooled solution and the filtrate was washed repeatedly with water and dried (magnesium sulfate). Evaporation of the benzene left the α-cyclohexylamino-α-benzylacetophenone as a yellow oil which could not be crystallized. The crude α-aminoketone was dissolved in ether and refluxed with lithium aluminum hydride (0.76 g., 0.02 mole) for 24 hours. The reaction mixture was hydrolyzed by the successive addition of water (0.76 ml.), 15% aqueous sodium hydroxide (0.76 ml.), and water (2.3 ml.). The mixture was filtered and the solvent was evaporated from the dried (magnesium sulfate) filtrate to leave an oil, which was dissolved in boiling hexane. On cooling crude 2-cyclohexylamino-1,3-diphenyl-1-hydroxypropane was obtained as a white solid (0.85 g., 40%), m.p. 86-89°. Two recrystallizations from hexane provided the pure compound, the m.p., 89-90°, being undepressed on admixture with the product obtained from the catalytic hydrogenation of **1**.

Acknowledgment.

This work was supported in part by Grant No, CA02931 from the National Cancer Institute of the United States Public Health Service.

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Received November 20, 1967 Lincoln, Nebraska 68508