Steric Inhibition of Resonance in the Two Diastereoisomeric 4-*t*-Butyl-N-methyl-N-phenylcyclohexylamines[1]

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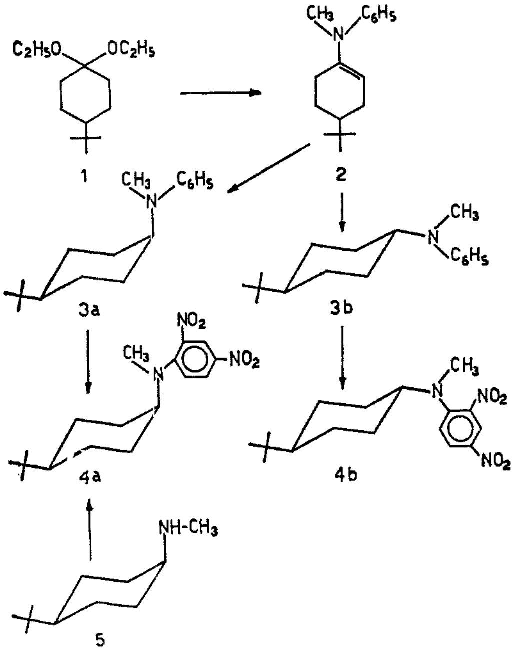
The title amines have been prepared, their configurations have been established by correlations with the known 4-*t*-butylcyclohexylamines, and their base strengths have been measured. The *cis*- (axial) amine (**3a**) is a stronger base than the *trans*- (equatorial) amine (**3b**), contrary to the order of basicity usually observed for conformational isomers and contrary to the order of basicity which is observed for the 4-*t*-butyl-N-cyclohexyl-N-methylcyclohexylamines (**6a** and **6b**) obtained by hydrogenation of **3a** and **3b**, respectively. The reversed order of basicity observed for **3a** and **3b** is attributed to steric inhibition of resonance in the *cis*- (axial) amine (**3a**) and this interpretation is supported by nmr and ultraviolet spectral evidence.

As an extension of the work concerning the preparation of optically active cycloalkenes by pyrolysis of optically active N-oxides,[2] we tried to prepare the N-oxides of *cis*- and *trans*-*t*-4-butyl-N-methyl-N-phenylcyclohexylamine. The instability of the latter compounds prevented their isolation in a pure state and their optical resolution; however, some peculiarities in the physical properties of the two amines, **3a** and **3b**, which were prepared in the course of this work, induced us to study them in some detail.

The two amines were prepared by condensation of the diethyl ketal of 4-*t*-butylcyclohexanone (1) with N-methylaniline, followed by catalytic reduction of enamine 2. The mixture thus obtained was found by glpc to contain the two diastereoisomers in a ratio of about 7 to 3. The more abundant *cis*-amine **3a**, mp 35–36°, was easily obtained pure by fractional crystallization of the hydrochlorides, while fractional distillation of the bases and column chromatography allowed the isolation of the *trans* isomer (see Scheme I), mp 50–51°.

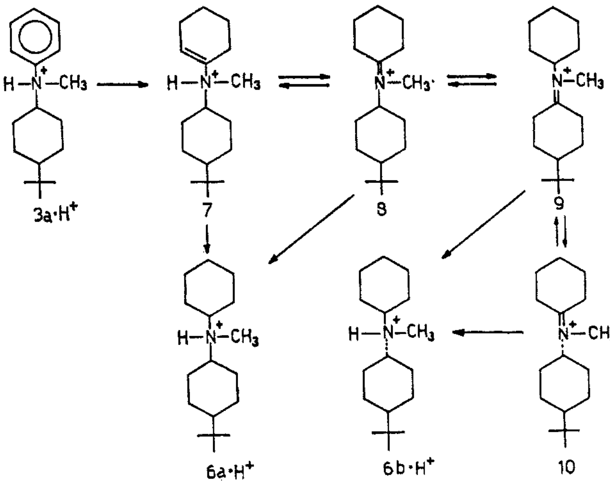
SCHEME I



The configurations of the two amines were determined as follows. Nitration of the lower melting amine gave a 2,4-dinitro derivative, which was found to have the *cis* configuration (**4a**), as it was identical with the compound obtained by reaction of 2,4-dinitrochlorobenzene with N-methyl-*cis*-4-*t*-butylcyclohexylamine (**5**). The latter compound was prepared from *cis*-4-*t*-butylcyclohexylamine, whose configuration is well established.[3]

The amines **3a** and **3b** were transformed into **6a** and **6b** by catalytic reduction of their hydrochlorides. While **3b** yielded only **6b**, the *cis*-amine **3a** gave a mixture containing about 70% **6a** and 20% **6b**. This partial isomerization during the reduction of the less stable isomer could perhaps be explained by a partial equilibration of an enamine intermediate (**7**) of the reduction, as shown in **7–10**. The driving force for such a transformation could be the relief of strain in passing from **8** to **9** or **10** (see Scheme II).

SCHEME II



In the following discussion it will be assumed that the two amines, **3a** and **3b**, exist essentially in the chair conformations indicated in the formulas, with equatorial *t*-butyl groups. While there can be no doubt that this assumption is correct for the *trans*-amine, it probably holds also for the *cis* isomer, as the conformational energy of the methylanilino group should not differ too much from that of a dimethylamino or isopropyl group and should be considerably lower than that of a *t*-butyl group.[4] Alternative twist-boat conformations

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[1] Dedicated to Professor Remo de Fazi, on the occasion of his 75th birthday.

[2] G. Berti and G. Bellucci, *Tetrahedron Letters*, 3853 (1964).

[3] D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Am. Chem. Soc.*, **81**, 3330 (1959).

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 458.

cannot, however, be ruled out completely if one considers the results of Booth[5] in his nmr study of N-(*cis*-4-*t*-butylcyclohexyl)phthalimide.

The base strengths of the four amines, **3a**, **3b**, **6a**, and **6b**, were measured potentiometrically in 80% Methyl Cellosolve–water (see Table I). While the pK_a' of the *trans*-amine **3b** was found, as expected, to equal that of N-methyl-N-phenylcyclohexylamine, that of the *cis*-amine **3a** was larger by about 0.45 pK units. This is in apparent contrast to the fact that usually axial amino groups exhibit lower base strengths than equatorial ones, as was shown, for instance, by Sicher, Jonáš, and Tichý[6] for several substituted cyclohexylamines. This apparent discrepancy can, however, be well explained by considering our amines as substituted anilines, rather than as substituted cyclohexylamines. Steric inhibition of resonance has a well-known base-strengthening effect on anilines;[7] it is therefore likely that a conformationally rigid cyclohexyl group attached to the aniline nitrogen through an axial bond should exert a stronger effect of steric inhibition of resonance than the same group when attached through an equatorial bond. Such a base-strengthening effect could well outweigh the base-weakening effect due to the steric strain (or to steric inhibition of solvation) in the conjugated acid, which is responsible for the usual lower basicity of axial amines.

TABLE I

pK_a' OF AMINES IN 80% METHYL CELLOSOLVE

Amine	pK_a'
N-Methyl-N-phenylcyclohexylamine	4.34
trans-4-*t*-Butyl-N-methyl-N-phenylcyclohexylamine (**3b**)	4.35
cis-4-*t*-Butyl-N-methyl-N-phenylcyclohexylamine (**3a**)	4.79
N-Methyldicyclohexylamine	9.25
trans-4-*t*-Butyl-N-methyldicyclohexylamine (**6b**)	9.19
cis-4-*t*-Butyl-N-methyldicyclohexylamine (**6a**)	8.74

A further confirmation of the fact that steric inhibition of resonance is responsible for the higher basicity of **3a** was given by the observation that in passing to the saturated amines **6a** and **6b** the order is reversed, the *trans* isomer being more basic by about 0.5 pK unit than the *cis* isomer, as would be expected for a less hindered equatorial amino group. There has been in recent treatments of base strengths of aliphatic amines a tendency to emphasize inductive and solvation effects over steric strain effects. In particular Hall[8] and Condon[9] found for tertiary amines good correlations between values of pK_a calculated on the basis of Taft σ constants of substituents, and experimental ones, even in the case of amines with bulky substituents. The present data for **6a** and **6b**, as well as those of Sicher[6] and of Bird and Cookson,[10] prove that, at least in alicyclic systems and in mixtures of organic solvents with water, steric effects can play an important role in determining more subtle differences in base strengths.

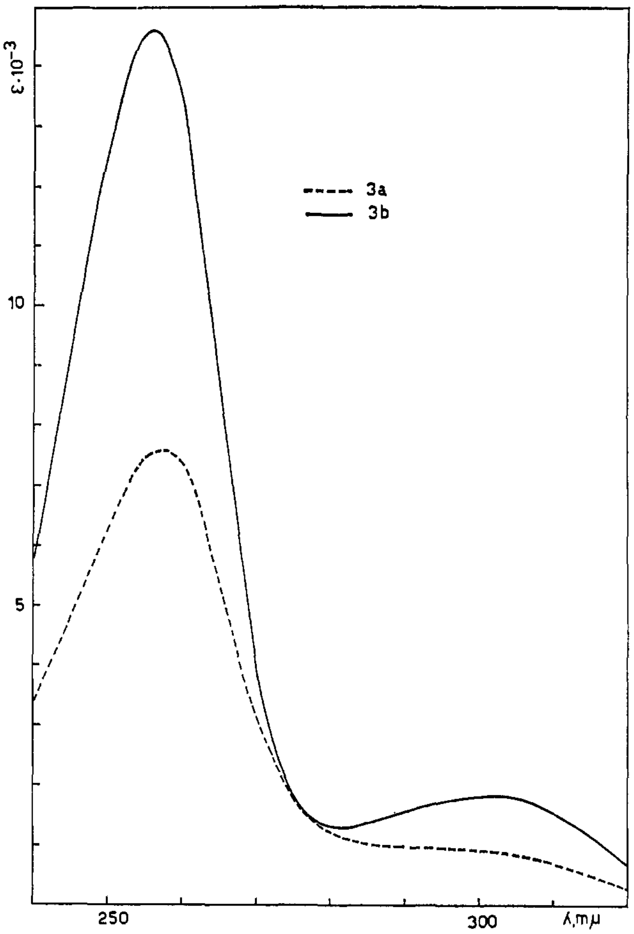

Figure 1.—Ultraviolet absorption spectra of **3a** and **3b** in ethanol solution.

The considerable difference in the degree of steric inhibition of resonance for the amines **3a** and **3b** is confirmed by their ultraviolet spectra (Figure 1): the *trans*-amine has a much larger extinction coefficient than the *cis* isomer. A somewhat similar case was reported by Hawthorne and Cram,[11] who found slight differences in the ultraviolet spectra of diastereoisomeric 2,4-dinitroanilines carrying asymmetric groups on the nitrogen atom and in the *ortho* position. Ours appears, however, to be the first case reported of different base strengths owing to differences in steric inhibition of resonance, in compounds differing only in the configuration of groups attached to nitrogen.

The nmr spectra of the amines **3a** and **3b** also show some interesting features. In the spectra taken in deuteriochloroform (Figure 2) the ring proton α to nitrogen (H_α) gives an unresolved broad signal for both amines, being the X part of an A_2B_2X system, which is presumably further broadened by slight coupling with the N^{14} nucleus and by the quadrupolar relaxation of the same nucleus. This signal is found at τ 6.75 (half-band width *ca.* 10 cps) for the *cis*-amine and at 6.60 (half-band width *ca.* 16 cps) for the *trans*-amine. The half-band widths are in accordance with what would be expected on the basis of the configurational and conformational assignments, as the larger values of the axial–axial coupling constants should produce a broader signal when H_α is axial,[12] as in the *trans*-

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(5) H. Booth and G. C. Gidley, *Tetrahedron Letters*, 1449 (1964).

(6) M. Tichý, J. Jonáš, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959); J. Sicher, J. Jonáš, and M. Tichý, *Tetrahedron Letters*, 825 (1963).

(7) B. M. Wepster in "Progress in Stereochemistry," Vol. 2, W. Klyne and P. B. D. de La Mare, Ed., Butterworth and Co. (Publishers) Ltd., London, 1958, p 126.

(8) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(9) F. E. Condon, *ibid.*, **87**, 4485 (1965).

(10) C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 2343 (1960).

(11) F. Hawthorne and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5859 (1952).

(12) H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brügel, *Ann.*, **683**, 64 (1965).

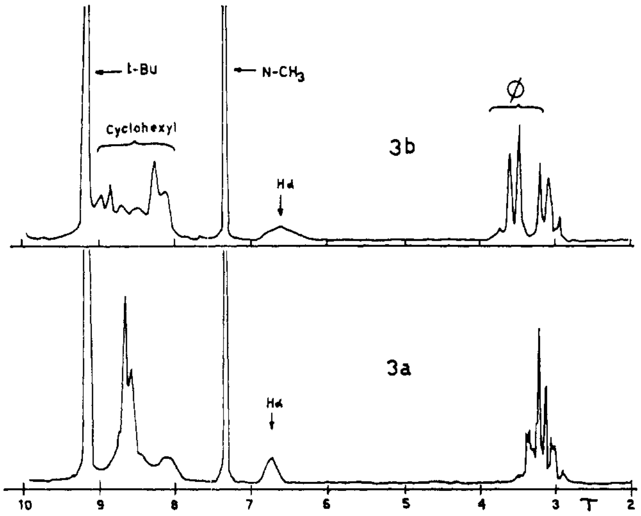

Figure 2.—Nmr spectra of **3a** and **3b** in deuteriochloroform.

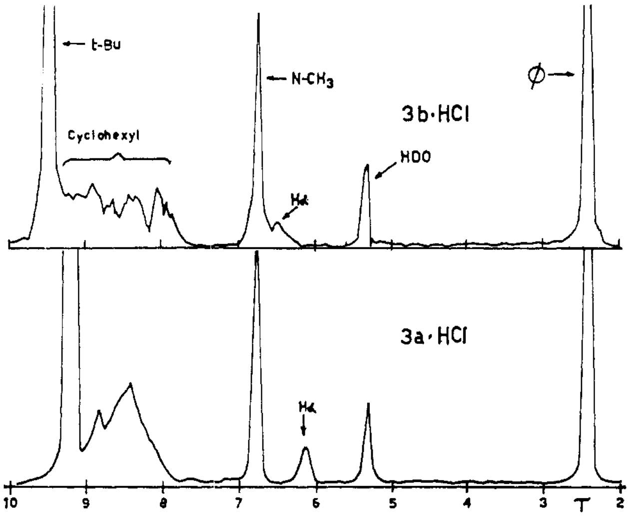

Figure 3.—Nmr spectra of the hydrochlorides of **3a** and **3b** in deuterium oxide.

amine. On the other hand the higher τ value for the H_α in the *cis*-amine is in contrast with the usual rule that equatorial protons absorb at lower frequencies than axial ones.[13] This inversion can be ascribed to the presence of the phenyl group: the higher degree of resonance stabilization in the *trans*-amine implies a higher tendency toward coplanarity of the phenyl group with the carbon atoms attached to nitrogen and consequently some rigidity around the N-phenyl bond. Inspection of models shows that in this case the axial H_α may well lie within the deshielding region around the phenyl group in the conformation of lowest energy of the molecule. The smaller sp_2 character of the N-phenyl bond in the *cis*-amine, on the other hand, allows for a more free rotation around this bond and may well bring the equatorial H_α in the phenyl shielding region. An alternative or complementary explanation could be found in the lower electron density on nitrogen in the *trans*-amine, which could cause a stronger inductive deshielding effect on the H_α; for instance, H_α is found at τ 7.22 in *sec*-butylamine, and at 6.59 in N-*sec*-butylaniline.[14] It is, however, not clear why such effects should not be operative also on the N-methyl protons, the signals for which are instead found at exactly the same field in both isomers.

In the nmr spectra of the hydrochlorides of **3a** and **3b** in deuterium oxide (Figure 3) the H_α signals are found in the right order: τ 6.13 for the equatorial proton of the *cis* isomer and about 6.6 for the axial proton of the *trans* isomer (in the latter case the vicinity of the H_α and N-methyl signals prevents an exact measurement of τ). Evidently, the passage to the cation eliminates the perturbing effects of the aromatic ring and restores a normal situation.

It is also interesting to observe the shapes of the phenyl proton pattern. While in the *trans*-amine it shows the usual spread for aniline derivatives,[15] in the *cis*-amine this pattern becomes narrower, and it coalesces into a single line in the hydrochlorides. This can evidently be brought into relation with the amount of delocalization of the nitrogen free pair and gives a further proof of the higher degree of steric inhibition of resonance in the *cis*-amine. The fact that aromatic protons give a single peak in anilinium salts had been observed before.[16]

Also the shapes of the signals for the alicyclic protons are quite different in **3a** and **3b**: they show a narrower band in the *cis* isomer, as found for other cyclohexylamines and decalins[12] carrying axial substituents. Actually, the ring-proton resonance pattern of **3a** is very similar to that reported by Feltkamp[12] for *cis*-N,N-dimethyl-4-*t*-butylcyclohexylamine, a point that is in accordance with the hypothesis, put forward in the beginning, of chair conformation **3a**.

Experimental Section

4-*t*-Butylcyclohexanone was prepared by oxidation of 4-*t*-butylcyclohexanol (mixed isomers) with chromic acid, according to Winstein and Holness.[17] A better yield was obtained by the following modification. The mixed 4-*t*-butylcyclohexanols (30 g) in 300 ml of acetone (distilled over $KMnO_4$) were cooled at 0° and treated dropwise under stirring with 48 ml of an 8 *N* solution of chromic acid (Jones reagent), prepared by dissolving 26.7 g of chromium trioxide in 23 ml of concentrated sulfuric acid and diluting with water to 100 ml;[18] the temperature was kept below 10°. After 15 min the solution was poured into 1500 ml of water and extracted with five 100-ml portions of petroleum ether (bp 30–50°); the extract was evaporated to 50 ml and stored in a refrigerator. The pure ketone (23 g), mp 48–50° (lit.[16] mp 47.5–48.5°), crystallized, and another 3 g was obtained on concentration of the mother liquor.

***cis*- and *trans*-4-*t*-Butyl-N-methyl-N-phenylcyclohexylamines (3a and 3b).**—A mixture of 40.5 g (0.26 mole) of 4-*t*-butylcyclohexanone and 38.9 g (0.26 mole) of ethyl orthoformate was treated with 5 drops of concentrated sulfuric acid. An exothermic reaction commenced; after the mixture had cooled to room temperature, the acid was neutralized with a solution of sodium ethoxide in ethanol and the product was fractionally distilled *in vacuo*. After elimination of the ethyl formate, 50 g of the diethyl ketal **1**, bp 88–93° (1.5 mm), $n^{30}D$ 1.4430, was collected. The infrared spectrum showed a small contamination with 4-*t*-butylcyclohexanone, but the product was used in the next step without further purification. The ketal (50 g, 0.22 mole) and N-methylaniline (35 g, 0.33 mole) were heated in a flask, provided with a 50-cm Vigreux column. The tempera-

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(13) L. M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press Ltd., Oxford, England, 1959, p 116.

(14) N. S. Bhacca, D. P. Hollis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectra No. 88 and 568.

(15) Reference 14, Spectrum No. 568.

(16) T. Isobe and G. Hazato, *J. Chem. Phys.*, **30**, 1371 (1959); G. Fraenkel, *ibid.*, **39**, 1614 (1963); M. Ohnishi and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **12**, 938 (1964).

(17) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(18) C. Djerassi, R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

ture was brought rapidly to 140°, then slowly raised to 240°; the mixture was left at this temperature until the distillation of ethanol ceased; and 20 ml of ethanol was obtained (theoretical value, 25 ml). The residue was distilled *in vacuo*. After a forerun of N-methylaniline and *t*-butylcyclohexanone, 44 g of the enamine **2**, bp 137–140° (1.5 mm), n^{28}_{D} 1.5405, was collected. The enamine (32.2 g) was dissolved in 200 ml of pure cyclohexane and hydrogenated over 1 g of 5% platinum on charcoal at room temperature and atmospheric pressure. The uptake of hydrogen ceased after 2 hr, when 2550 ml had been absorbed (theoretical value 2950 ml). The solution was filtered and evaporated and the residue was distilled *in vacuo*. After a small forerun of *t*-butylcyclohexanone and N-methylaniline, the following fractions were collected: I (11.5 g), bp 138–140° (1.4 mm), n^{28}_{D} 1.5275; II (9.8 g), bp 140–143° (1.4 mm), n^{28}_{D} 1.5309; III (6 g), bp 143–146° (1.4 mm), n^{28}_{D} 1.5328. Fractions I and II were combined and treated with a slight excess of hydrogen chloride in dry ether; 17.3 g of solid precipitate formed, which was crystallized from acetone to give 10.7 g of the hydrochloride of the *cis*-amine **3a**, mp 166–168°.

Anal. Calcd for $C_{17}H_{27}N \cdot HCl$: C, 72.45; H, 10.02. Found: C, 72.79; H, 10.09.

The free base **3a** separated as an oil, which crystallized only after several months, to give prisms, mp 35–36°. Glpc gave a single peak, with a retention time of 55 min (2-m Apiezon L column, 220°, He 50 ml/min).

The combined ether and acetone mother liquors were evaporated, the residue was made alkaline with sodium hydroxide, and the free base was combined with fraction III and redistilled *in vacuo* to give the following fractions: Ia (2.6 g), bp 122–124° (0.5 mm); IIa (4.8 g), bp 124–128° (0.5 mm); IIIa (2.8 g), bp 128° (0.5 mm). Glpc showed that Ia was composed of about equal amounts of **3a** and **3b** (retention time 89 min, same conditions as above), fraction IIIa of 95% **3b** and 5% **3a**. The latter fraction crystallized after several weeks in the refrigerator, and was recrystallized from pentane to give pure **3b**, mp 50–51°.

Anal. Calcd for $C_{17}H_{27}N$: C, 83.20; H, 11.09. Found: C, 83.28; H, 10.77.

The hydrochloride of **3b**, mp 155–158°, was prepared with hydrogen chloride in ether.

The combined fractions Ia and IIa were chromatographed through a 26 × 2 cm column of acidic alumina (activity I); petroleum ether (bp 30–50°) was used as the eluent; and 20-ml fractions were collected. The first six fractions, when treated with hydrogen chloride in ether, yielded 2.1 g of **3a**·HCl. Fractions 12–50 gave 3.5 g **3b**, containing about 10% **3a**.

Attempts at the Preparation of the N-Oxides of 3a and 3b.—When 1 g of the amine **3a** was treated with an equimolar amount of *p*-nitroperoxybenzoic acid in 30 ml of chloroform and left at 0° for 48 hr, the peroxy acid was used up completely. The solution was washed with saturated sodium carbonate solution and evaporated *in vacuo*. The residual oil, which consisted mostly of the N-oxide, could not be induced to crystallize; it slowly decomposed, even at 0°, with formation of *t*-butylcyclohexene. Also attempts to prepare solid salts with several optically active acids failed. The use of peroxyacetic acid and of hydrogen peroxide gave no better results. Negative results were also obtained with the amine **3b**.

***trans*-4-*t*-Butyl-N-(2,4-dinitrophenyl)-N-methylcyclohexylamine (4b).**—A solution of 1 g of the amine **3b** in 3 ml of acetic anhydride was cooled at −10°, treated slowly with 0.5 ml of nitric acid (*d* 1.52), then diluted with ethanol. The precipitate was dissolved in chloroform and washed with 2 *N* sodium carbonate, the solvent was evaporated, and the residue was crystallized from ethanol to yield 0.5 g of **4b**, mp 146–148°.

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51. Found: C, 61.11; H, 7.65.

***cis*-4-*t*-Butyl-N-(2,4-dinitrophenyl)-N-methylcyclohexylamine (4a).** A.—A solution of 1.3 g of **3a** in 3.5 ml of acetic anhydride was treated dropwise, under stirring, with 0.65 ml of nitric acid (*d* 1.52) at 5–10°, then poured into water, and extracted with chloroform. The organic layer was washed with 2 *N* sodium carbonate and evaporated and the residue was crystallized twice from ethanol to give 0.4 g of **4a**, mp 111–113°.

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51. Found: C, 61.05; H, 7.66.

B.—A mixture of 1.3 g of *cis*-4-*t*-butylcyclohexylamine HCl,[19] 0.5 g of sodium formate, and 1.4 g of formic acid was heated for 2 hr at 130–140°, diluted with ether, and filtered; the ether solution was washed with 2 *N* hydrochloric acid, 2 *N* sodium carbonate, and water and dried over magnesium sulfate. Evaporation and crystallization from petroleum ether (bp 30–50°) gave 0.6 g of *cis*-4-*t*-butyl-N-formylcyclohexylamine, mp 100.5–101.5°.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55. Found: C, 71.81; H, 11.59.

The formyl derivative (0.45 g) in 5 ml of ether was added to 0.220 g of lithium aluminum hydride in 15 ml of ether and the mixture was refluxed 6 hr; an excess of 20% sodium hydroxide was then added; the ether layer was dried over magnesium sulfate and treated with a slight excess of hydrogen chloride in ether; the hydrochloride of *cis*-4-*t*-butyl-N-methylcyclohexylamine (0.3 g), mp 228–229° (from acetone), was thus obtained. A solution of 50 mg of this hydrochloride in 3 ml of 95% ethanol was neutralized with ethanolic sodium hydroxide, treated with 50 mg of 2,4-dinitrochlorobenzene, and refluxed for 90 min. On cooling, 30 mg of **4a**, mp 112–114°, separated. It had the same infrared spectrum and did not cause depression in melting point with the compound prepared according to A, while its spectrum was distinctly different from that of the *trans* compound **4b**.

***trans*-4-*t*-Butyl-N-methyldicyclohexylamine Hydrochloride (6b).**—A solution of 1 g of **3b** hydrochloride in 10 ml of ethanol was hydrogenated over 0.1 g of Adams platinum at 50° and atmospheric pressure until the uptake of gas ceased. Filtration, vacuum evaporation of the solvent, and two crystallizations from acetone gave 0.7 g of **6b**, mp 235–237.5°.

Anal. Calcd for $C_{17}H_{33}N \cdot HCl$: C, 70.90; H, 11.91. Found: C, 71.10; H, 11.78.

The free base obtained from the hydrochloride gave a single peak on glpc.

***cis*-4-*t*-Butyl-N-methyldicyclohexylamine Hydrochloride (6a).**—When the hydrochloride of **3a** (2.3 g) was hydrogenated as described above, a mixture of hydrochlorides was formed. Glpc of the free bases showed that it consisted of about 70% of the *cis*-amine **6a**, 20% of the *trans*-amine **6b**, and 10% of two products with much lower retention times, possibly formed by hydrogenolysis of C–N bonds. The separation of pure **6a** by fractional crystallization of the hydrochlorides failed. A better method was found in the fractional precipitation of a solution of the free bases in ether with hydrogen chloride in ether. The first fractions contained most of the *trans*-amine, while the following ones contained almost pure **6a**·HCl, which was obtained pure (0.4 g) after crystallization from acetone (single glpc peak), mp 171–172.5°.

Anal. Calcd for $C_{17}H_{33}N \cdot HCl$: C, 70.90; H, 11.91. Found: C, 70.61; H, 11.72.

N-Methyl-N-phenylcyclohexylamine was prepared by methylation of N-phenylcyclohexylamine with dimethyl sulfate for 5 hr on a steam bath, and gave a hydrochloride, mp 127–129° (from acetone).[20]

Anal. Calcd for $C_{13}H_{19}N \cdot HCl$: Cl, 15.8. Found: Cl, 15.5.

N-Methyldicyclohexylamine hydrochloride, mp 195–196° (lit.[21] mp 193–194°), was obtained from dicyclohexylamine, by methylation with formaldehyde. It was also prepared by reduction of N-methyl-N-phenylcyclohexylamine hydrochloride, according to the method described above for the preparation of compound **6a**.

Physical Measurements.—Melting points were determined on a Kofler apparatus. Ultraviolet spectra were measured with a Beckman DU spectrophotometer. Glpc analyses were carried out with a Perkin-Elmer 116E gas chromatograph with a flame ionization detector.

Dissociation constants were determined at 25° by potentiometric titration of *ca.* 4 × 10^{-3} *M* solutions of the hydrochlorides in 80% (v/v) Methyl Cellosolve–water with tetramethylammonium hydroxide, according to an extension[22] of the method of Simon, *et al.*,[23] on a larger scale. All determinations were run

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[19] M. Tichý, J. Jonáš, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959).

[20] The melting point of 196° given by M. Busch and F. Gebelein [*J. Prakt. Chem.*, [2] **115**, 123 (1927)] is obviously due to an error.

[21] F. F. Blicke and F. B. Zienty, *J. Am. Chem. Soc.*, **61**, 94 (1939).

[22] M. Svoboda, J. Jonáš, and J. Sicher, *Collection Czech. Chem. Commun.*, **23**, 1551 (1958).

[23] W. Simon, E. Kováts, L. H. Chopard-dit-Jean, and E. Heilbronner, *Helv. Chim. Acta*, **37**, 1872 (1954).

at least in duplicate, with a Beckman Model G and a Metrohm Model E 300 pH meter, using glass-calomel electrodes. The instruments were checked with buffers at pH 4.00 and 9.00 and with pure benzoic acid before and after each series of runs; the values given in Table I should be correct within ±0.05 pK units.

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The Reaction of Grignard Reagents with N,N-Dialkyl-N-(phenylthiomethyl)amines

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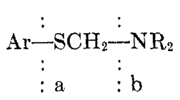
Treatment of $ArSCH_2NR_2$ with R'MgX generally produces $R'CH_2NR_2$ in good yields. The following amines were thus prepared: N-*n*-amyl-, N-isobutyl-, N-(*p*-dimethylamino)benzyl-, and N-(2,4,6-trimethyl)benzylpiperidine, as well as N-4-butenyl-, N-isobutyl-, and N-benzylmorpholine. The attempted preparation of N-neoamylpiperidine under similar conditions failed, N-methylpiperidine being formed.

The preparation of tertiary amines by treating N-alkoxymethyl-N,N-dialkylamines with Grignard reagents has been well established.[3,4] There is also one report of the preparation of N-benzyl-N,N-dimethylamine from N,N-dimethyl-N-(nonylthiomethyl)amine.[5]

The analogous reaction with arylthiomethylamines has not been described. We were led to investigate this reaction as part of our studies of the cleavage patterns of arylthiomethylamines. *A priori*, two modes of cleavage are feasible, as shown. From

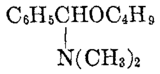


$$\underset{:\,a}{Ar\overset{:}{—}}SCH_2\underset{:\,b}{\overset{:}{—}}NR_2$$

analogy to the alkoxymethylamines one would expect bond a to break and with a Grignard reagent R'MgX to yield the tertiary amine $R'CH_2NR_2$. However, on the basis of a recent report concerning the mechanism of the acid-catalyzed rearrangement of N-arylthiomethyl-N-arylamines to *p*-arylthiomethylanilines,[6] in which a cleavage to a resonance-stabilized sulfonium-carbonium ion is postulated, it was conceivable that bond b might break and yield with a Grignard reagent the corresponding sulfide $ArSCH_2R'$.

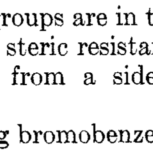
In all instances, with the exception of *t*-butylmagnesium chloride, the Grignard reagents, prepared in the usual fashion from the corresponding halides,[7] yielded the expected tertiary amines in excellent yields. In Table I are listed the amines obtained from N-phenylthiomethylpiperidine, including boiling or melting points and the melting points of the picrates of these amines. In Table II are listed data concerning the amines obtained from N-phenylthiomethylmorpholine.

In general, the reactions carried out by adding an ether solution of the phenylthiomethylamine to the preformed Grignard reagent were very vigorous and rapid. In fact they had to be moderated by adding the thiomethylamine slowly. The *t*-butylmagnesium chloride and the 2,4,6-trimethylphenylmagnesium bromide were exceptions. The former had to be refluxed for a long time and the expected neoamylpiperidine did not form to any significant extent, if at all. Instead a reduction to N-methylpiperidine took place with a simultaneous liberation of isobutylene. This is undoubtedly due to steric hindrance to which Grignard reactions are sensitive. It is analogous to the reduction of α-methyl-α-piperidineacetonitrile to N-ethylpiperidine[8] and of α-dimethylaminobenzyl butyl ether



$$C_6H_5\underset{\displaystyle N(CH_3)_2}{\underset{|}{C}}HOC_4H_9$$

to N,N-dimethylbenzylamine[9] by *t*-butylmagnesium bromide. The following six-membered cyclic transition state is most likely involved.



It is remarkable that, though reacting sluggishly, the mesitylene derivative forms the corresponding amine in a yield of 81% of the theory, when the reaction is carried out at the temperature of refluxing tetrahydrofuran. Since the methyl groups are in the plane of the benzene ring, there is little steric resistance to the attack of the Grignard reagent from a side perpendicular to the plane of the ring.

When employing bromobenzene, it was found that it is not necessary to preform the Grignard reagent, but rather the reaction, once started, proceeds very vigorously with equally good yields when all of the reactants are introduced together, *i.e.*, when C_6H_5Br and $C_6H_5SCH_2NR_2$ in ether are added to a suspension of magnesium turnings in ether. This appeared surprising for sulfide compounds have been reported as inhibiting the formation of the Grignard reagent.[10] When

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