H, 8.6. Found: C, 79.1; H, 8.7.

***trans*-α-Methyl-γ-phenylallyl alcohol (6-OH)**, bp 95–98 °C (1.4–1.6 mm), and ***trans*-α-phenyl-γ-methylallyl alcohol (10-OH)**, bp 81 °C (1.1 mm), were prepared as reported earlier.[26] The characterization of the alkylation products 7–9 and 11 (by NMR, high-resolution mass spectra, and elemental analysis) will be reported elsewhere.[7]

Alkylation of 5-Methyl-2-cyclohexenol (4-OH). In a typical experiment, 1.12 g (10 mmol) of 99% *cis*-4-OH was treated with 6.7 mL of 1.49 M ethereal CH_3Li. The resulting lithium alkoxide was added to a suspension of 1.90 g (10 mmol) of CuI and 20 mL of dry THF which in turn was prepared in a nitrogen-flushed, 250-mL flask equipped with a stirrer and septum. This solution was stirred for 0.5 h, and the resulting homogeneous yellow solution was chilled to −78 °C, after which 6.7 mL of 1.49 M ethereal CH_3Li was added over a period of about 5 min. Then 4.35 g (10 mmol) of (methylphenylamino)tributylphosphonium iodide (**1b**) in 40 mL of dry DMF was added and the cooling bath removed. The brown homogeneous solution was stirred for 3 h at room temperature, after which the reaction was quenched by adding the reaction mixture to a mixture of 30 mL of saturated aqueous NH_4Cl and 50 mL of ether containing 1.08 g of 1,5-cyclooctadiene (internal standard). After being stirred vigorously, the mixture was filtered, and the organic layer was separated, washed with 10 mL of 0.2 M HCl and 10 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The dried solution was concentrated by fractional distillation (Vigreux column), and isomer ratios and yields (~70%) were determined by capillary GC (230-ft column, UCON-LB-550-X, 80 °C). The results of these experiments are presented in Table II.

For alkylation of deuterated 4-OH, the products were isolated by preparative GC (10 ft × $^3/_8$ in. column, 20% UCON-LB-550-X on Chromasorb W, 80 °C). Proton-decoupled spectra gave signals at δ 1.28 (3-D-**5**) and 4.67 (1-D-**5**). Results are presented in Table I.

Alkylation of Methylphenylallyl Alcohols 6-OH and 10-OH. These alkylations were carried out on a 10-mmol scale by the procedure described above for alkylation of 4-OH. After concentration of the organic extract of the products, product compositions were determined by capillary GC (94-ft column, UCON LB-550-X, 75 °C). Identification of 7–9 and 11 was made by comparison of retention times with those for authentic samples.[7] In one experiment, the product mixture derived from 6-OH was isolated in 77% yield. Results of these experiments are shown by eq 2 and 3.

In a control experiment α-D-10-OH, prepared by LAD reduction of the corresponding ketone, was alkylated, and the products and unreacted alcohol were isolated as described above, except that the dilute HCl wash was omitted and the unreacted alcohol was isolated by vacuum distillation. Deuterium magnetic resonance showed the recovered alcohol to contain ~20% of the conjugated isomer (γ-D-6-OH).

Alkylation of *cis*-5-Methyl-2-cyclohexenyl Acetate (*cis*-4-OAc) and Mesotoate (*cis*-4-OTMB) with $LiCu(CH_3)(N(CH_3)Ph)$. To 1.90 g (10 mmol) of purified CuI in 20 mL of dry THF was added 10 mmol of lithium methylphenylamide (prepared at 0 °C by adding 8.3 mL of 1.20 M CH_3Li to 1.07 g of *N*-methylaniline), and the resulting solution was stirred 0.5 h at room temperature. The homogeneous clear yellow solution was chilled to −78 °C and changed to a cloudy black mixture. Addition of 8.3 mL of 1.20 M CH_3Li was followed immediately by addition of 1.54 g (10 mmol) of *cis*-4-OAc to the purple inhomogeneous solution. The stirred reaction mixture was warmed to room temperature and became clear yellow and then changed to cloudy green and finally to black. The mixture was quenched and worked up as described above for alkylation of 4-OH. Capillary GC showed the organic extract contained about 5% *trans*-**5**, 95% *cis*-**4**-OH, *tert*-butyl alcohol, and a trace of unreacted *cis*-**4**-OAc.

Alkylation of *cis*-**4**-OTNB by the above procedure gave a 54% yield (GC yield, 1,5-cyclooctadiene internal standard) of *trans*-**5**, and the remaining unreacted **4**-OTNB was ~99.8% cis isomer. No 4-OH (which results from carbonyl attack) was detected.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE 77-09139).

Registry No. 1a, 34257-63-1; **1b**, 67660-23-5; *trans*-4-OH, 22031-97-6; *cis*-4-OH, 22049-46-3; *cis*-α-D-4-OH, 73964-44-0; *cis*-γ-D-4-OH, 73964-43-9; *cis*-4-OTMB, 76807-00-6; *cis*-4-OAc, 61221-47-4; *cis*-**5**, 17516-95-9; *trans*-**5**, 56021-63-7; 3-D-**5**, 76807-01-7; 1-D-**5**, 76807-02-8; **6**-OH, 36004-04-3; γ-D-**6**-OH, 76807-03-9; **7**, 15325-61-8; **8**, 42461-65-4; **9**, 76807-04-0; **10**-OH, 52755-39-2; α-D-**10**-OH, 76807-05-1; **11**, 15325-56-1; $LiCu(CH_3)(N(CH_3)_2)Ph$, 76793-71-0; *N*-phenyltriphenylphosphinimine, 2325-27-1; methyl iodide, 74-88-4; phenyl azide, 622-37-7; tributylphosphine, 998-40-3; mesitoyl chloride, 938-18-1.

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Stereoselectivity in the Formation of Heterocyclic Amine Oxides

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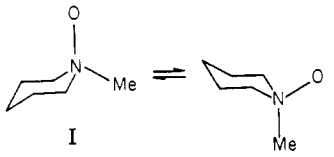
The stereoselectivity of the oxidation of *N*-alkylpiperidines was studied with the aid of the conformationally biassing 4-*tert*-butyl substituent. The stereoselectivity was always >95% and showed little sensitivity to the nature of the *N*-alkyl substituent. The axial approach was found to be the predominating stereochemical oxidation path. A brief study of the effects of solvent, temperature, and oxidant on the stereoselectivity was made. The 1,4-dimethylpiperazine system was investigated, and its oxidation at room temperature resulted in 100% of *trans*-1,4-dimethylpiperazine 1,4-dioxide. A method to modulate the stereoselectivity in the formation of saturated heterocyclic amine oxides was developed by inverting the sequence of introduction of the nitrogen substituents. With *cis*-8-methyl-8-azabicyclo[4.3.0]nonane oxidation is preferred from that side of the molecule which is sterically more hindered.

We have demonstrated that amine oxides are excellent reagents in organometallic chemistry.[1] Specifically, they oxidize CO → CO_2 in monomeric and cluster organometallic carbonyl compounds. This reaction facilitates surgical removal of a single CO group. Depending on the nature of the complex, either disengagement of organic ligands or activation of the complex takes place. Indeed, these reactions were usefully exploited by others in organometallic chemistry.[2]

(1) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336; **1975**, 829.

0022-3263/81/1946-2148$01.25/0

In conjunction with the above idea, we are actively exploring the stereochemistry and conformational analysis of amine oxides. Previously[3] we have investigated the course of oxidation of 1-methylpiperidine and found that with H_2O_2 (25 °C) the axial approach predominates to the extent of 95%. Such analysis was made possible by conformationally biassing the ring with the 4-*tert*-butyl group. It was also possible to evaluate the equilibrium constant for I ⇄ II by using NMR techniques. This study was



I II

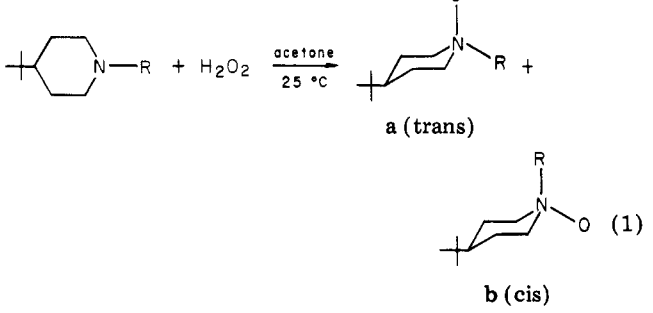
conducted in several solvents, and invariably I was found to be more stable than II. The group conformational free energy value of the oxygen atom, a value not hitherto known, was also evaluated.

It is evident, primarily from the work of Kawazoe[4] that alkyl substitution at the 2- and 6-positions of the piperidine ring accelerates equatorial relative to axial oxidation of the N atom. Thus, stereoselectivity was lost in the oxidation of 2-ethyl-1-methylpiperidine (a 1:1 mixture of the two isomers was obtained) as opposed to 95% stereoselectivity obtained in the oxidation of 1-methylpiperidine.

In the present work we have investigated the following points: (a) the effect of N-substitution on the stereoselectivity of oxidation of piperidine; (b) the stereochemistry of oxidation of 1,4-dimethylpiperazine and *cis*-8-methyl-8-azabicyclo[4.3.0]nonane; (c) the development of a new synthetic approach by which the stereoselectivity could be modulated.

Results and Discussion

(I) Oxidation of *N*-Alkylpiperidines. A series of 4-*tert*-butyl-*N*-alkylpiperidines was prepared by combinations of known methods.[4,5] Each compound was oxidized according to eq 1. The yields are in the range of 90–95% when the reaction was allowed to proceed to the point of disappearance of the amine (TLC).



a (trans)

b (cis)

(1)

R = Me, Et, *i*-Pr, *t*-Bu, $PhCH_2$

Table I. NMR and Product-Distribution Data of 4-*tert*-Butyl-*N*-alkylpiperidine 1-Oxides

compd	R[b]	shift,[a] δ trans	shift,[a] δ cis	multiplicity	% trans
1[3]	CH_3	3.60	3.38	singlet	95
2	CH_2CH_3	3.59	3.22	quartet	95
3	$CH(CH_3)_2$	3.58	3.15	septet	95
4	$PhCH_2$	4.46	4.34	singlet	91
5	$C(CH_3)_3$				100

[a] NMR was measured with an HA 100-MHz spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard. [b] Italic atoms are those α to the N atoms.

The relative concentrations of the two diastereomeric amine oxides was determined by integrating the appropriate NMR signals of the crude reaction mixture with a precision of ±3%. The NMR and product-distribution data are presented in Table I.

The configurational assignment techniques were described in our previous paper on this subject.[3] It was established unequivocally that the axial *N*-methyl protons in 1-methylpiperidine 1-oxide resonate at higher field than the equatorial ones. It is logical to assume that similar anisotropy affects operate in the other *N*-alkylpiperidines of Table I. Therefore, the relative chemical shifts of the group of protons α to the N atoms (italic in Table I) served as configurational indicators; i.e., the high-field signal in each diastereomeric pair indicated the axial configuration of the *N*-alkyl group (or cis configuration). However, to further secure the configurational assignments, we have resorted to additional NMR proofs. It should be stated here that each isomeric reaction mixture was resolved either by chromatography or crystallization. Large shifts of the *ring protons* were observed where the NMR spectra of the individual isomers were analyzed. These shifts and the coupling constants were consistent with each and every pair of isomers of compounds 1–5. The axial protons at C-3 and C-5 are shifted downfield (ca. 2 ppm) in the trans isomer relative to the cis and lose their fine structure. Since exactly the same spectral behavior is manifested by 1, for which the configurational assignment was secured independently,[3] we are justified in using this spectral behavior for configurational assignments for the rest of the isomeric pairs in Table I. The observed differential shift is most probably due to anisotropy of the axial oxygen which in the trans isomer is in 1,3-diaxial disposition with respect to the 3- and the 5-position axial protons.

From Table I it is evident that the diastereomeric ratio is not very sensitive to the structure of the N substituents. In all cases, axial oxidation predominates. Such behavior may be traced to the energetics of the equilibrium I ⇄ II, where the conformer with the axial oxygen (I) is the more stable one ($\Delta G°$ = 0.65 kcal/mol). The source of the energy difference must be the differential nonbonding interaction of the oxygen atom and the methyl group with the 1,3 ring hydrogens. It is therefore concluded that very similar interactions must operate in the transition state of the oxidation reaction leading to the observed predominance of the trans isomer. An increase in the steric bulk of R is anticipated to accelerate axial oxidation relative to equatorial oxidation. This is realized in the case of 5 (R = *t*-Bu) where the cis isomer could not be detected at all. Analogous trends were also observed in the alkylation reactions of *N*-alkylpiperidines.[5a]

The effects of temperature, solvent, and oxidant were briefly examined with 1 and 4. The stereoselectivity diminishes from 95% at 25 °C to 80% at 75 °C for 1, as could be anticipated from kinetic considerations. The increase

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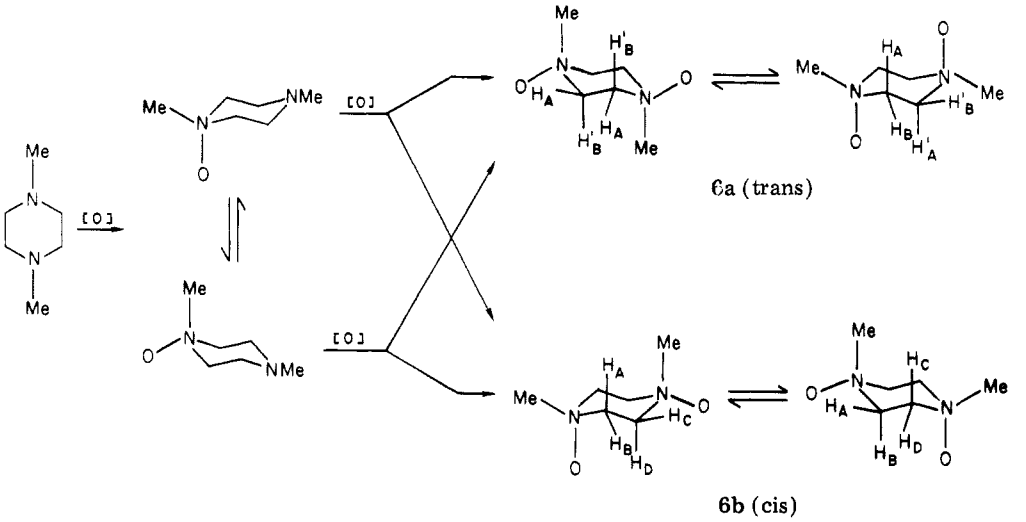
(3) Shvo, Y.; Kaufman, E. D. *Tetrahedron* **1972**, *28*, 573.
(4) Kawazoe, Y.; Tsuda, M. *Chem. Pharm. Bull.* **1967**, *15*, 1405.
(5) (a) House, H. O.; Tefertiller, B. A.; Pitt, C. G. *J. Org. Chem.* **1966**, *31*, 1073. (b) Brown, H. C.; Murphy, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3308. (c) Perlowski, E. F.; Troscianiec, H. J.; Lyle, G. G. *J. Org Chem.* **1955**, *20*, 1761. (d) Craig, J. C.; Yorg, R. G. *Org. Synth.* **1962**, *42*, 19. (e) Cook, N. J.; Katritzky, A. R.; Mauas, M. M. *J. Chem. Soc. B*, **1971**, 1330. (f) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.

Scheme I



in the rate of formation of the less stable cis isomer with an increase in temperature is consistent with our configurational assignment. A slight increase in stereoselectivity to 99% for 1 is obtained by using *m*-chloroperbenzoic acid at 25 °C.

(II) Oxidation of 1,4-Dimethylpiperazine. It was reported, over 40 years ago, that oxidation of 1,4-dimethylpiperazine yields only one isomer.[6] Indeed, we have confirmed these results. However, in order to discover the second isomer, we carried out the oxidation reaction at 100 °C. The NMR spectra of the crude reaction mixture indicated the rpesence of two isomers in the ratio of 91/9 ± 3%. After several dry-column chromatographies, the minor component was isolated in a pure state.

The configurational assignment was based on the observed polarity difference and NMR data. From chromatographic and solubility behavior it was noted that the major isomer is the less polar one. It was assigned the trans configuration **6a** on the basis of previous findings. It should also be noted that **6a** possesses a point of symmetry.

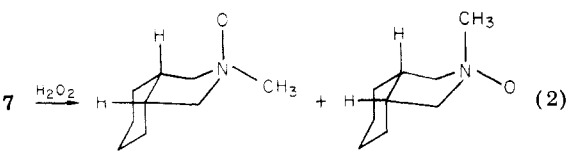
The NMR data of the two isomers corroborate the above conclusion. The trans configuration (**6a**) was assigned to the major isomer which exhibited a clear AB quartet, while the minor one (*cis*-**6b**) exhibited a broad singlet with unresolved couplings (see Scheme I).

Although very small (0.02 ppm), the finite differential shifts of the average Me signals are in agreement with our previous observation; i.e., equatorial Me in 1-alkylpiperidine 1-oxides resonates at lower field than an axial one. Similar differential shifts were observed in several solvents. No limiting NMR spectrum could be attained at −80 °C.

It is logical to assume that the oxidation of 1,4-dimethylpiperazines occurs in two steps (Scheme I). Therefore, the net stereochemical outcome would be determined by the second step. The experimental results clearly indicate that the axial approach is the predominating stereochemical path in the second oxidation step. Furthermore, an increase in the stereoselectivity with respect to the oxidation of *N*-methylpiperidine is noted. Similar steric factors which control the axial approach of the oxidant in *N*-alkylpiperidine and were discussed before must operate also in the piperazine systems. It was noted, however, that the overall reaction rate with the latter system is slower than with the former one. This may account for the higher stereoselectivity observed with the piperazine system. We suggest that the slower oxidation rate of 1,4-dimethylpiperazine is associated with the second oxidation step (Scheme I) and is due to a through-bond or an electrostatic effect generated by the partial positive charge on the oxidized N atom and induced at the nonoxidized N atom. In other words, the generation of two proximally charged N atoms in the transition state generates a larger activation energy compared to that of a system devoid of such interaction, i.e., *N*-alkylpiperidines.

Later we shall demonstrate a new method by which a drastic change in the stereoselectivity of oxidation of 1,4-dimethylpiperazine can be effected.

(III) Oxidation of *cis*-8-Methyl-8-azabicyclo-[4.3.0]nonane (7). Next, we have examined the stereoselectivity of the oxidation of the bicyclic heterocycle **7**, which was prepared by a known method.[7] Oxidation with H_2O_2 in acetone at 25 °C resulted in a mixture of two isomers (12:88 ratio) as was indicated by NMR; the mixture was separated by crystallization of the picrates. Since the N–Me is now substituted on a five-membered ring, we are not justified in applying our previous correlations of chemical shifts and configuration. However, aside from the doubling of the N–Me peaks, we have observed two NMR signals at δ 3.50 and 2.62 in a ratio of 12:88, respectively; the combined integration accounts for two hydrogens. In accordance with our previous assignments, the low-field signal must be associated with protons which are diamagnetically deshielded by the oxygen atom. The two cis bridge H atoms in **8a** (eq 2), which are equivalent



(2)

8a **8b**

by virtue of the dynamic chair–chair interconversion process of the cyclohexane ring, are in a geometrical disposition, which may account for such deshielding ($\Delta\delta$ =

(6) Polonovsky, Max; Polonovsky, Michel *Bull. Soc. Chim. Fr.* **1926**, *39*, 1161.

(7) Sample, J. E.; Hatch, L. F. *J. Chem. Educ.* **1968**, *45*, 55: Culberson, C.; Wilder, P., *J. Org. Chem.* **1960**, *25*, 1358; Mitchell, E. D., Jr.; Tolbert, N. E. *Biochemistry* **1968**, *7*, 1019.

(8) Ottenberger, R.; Lipkowitz, K.; Mundy, B. P. *J. Org. Chem.* **1974**, *39*, 319.

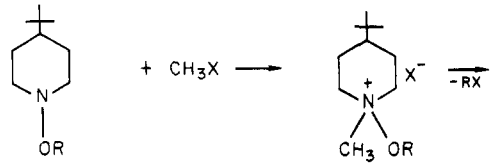
Table II. Isomeric Distribution Data of 4-*tert*-Butyl-1-methylpiperidine 1-Oxide

compd	methylation reagent	yield, %	ratio of 1a/1b
9a	CH_3I	15	50/50 ± 5
9b	CH_3I	40	50/50 ± 5
9c	CH_3OSO_2F	80	35/65 ± 3

0.88 ppm). This implies that the low-energy oxidation path is correlated with **8b** (88%). Again, it is concluded that the preferred oxidation of the N atom is from the direction which is sterically more shielded.

(IV) Modulation of the Stereoselectivity in the Synthesis of Amine Oxides. The experimentally observed stereoselectivity in the oxidation reaction of *N*-alkylpiperidines is kinetically controlled. To the best of our knowledge no chemical reaction is known which leads to direct equilibration of diastereomeric amine oxides differing in the nitrogen configuration. We therefore pursued investigating possible modulation of stereoselectivity in kinetically controlled reactions.

On the basis of the accumulated data and our conclusions regarding the stereoselectivity of oxidation of *N*-alkylpiperidines, we inferred that reversing the substitution sequence of the N atom would lead to inversion of the stereoselectivity, i.e., predominance of equatorial oxidation. The reaction sequence which was studied is depicted in eq 3. 4-*tert*-Butyl-1-hydroxypiperidine (**9a**) was prepared



9a, R = H
b, R = CH_2Ph
c, R = COPh

10a, R = H
b, R = CH_2Ph
c, R = COPh

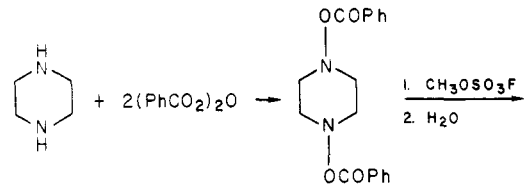
1a (trans) + **1b** (cis) (3)

X = I, OSO_2F

(25%) by the Cope elimination of 4-*tert*-butyl-1-ethylpiperidine 1-oxide. Compound **9b** was made by the Meisenheimer rearrangement (80%) of 4-*tert*-Butyl-1-benzylpiperidine 1-oxide, while the benzoate derivative (**9c**) was synthesized (88%) by oxidation of the parent base with dibenzoyl peroxide. Compounds **9a** and **9b** were methylated with methyl iodide, resulting in the direct formation of the amine oxides **1a,b**, most probably via nucleophilic attack of the iodide anion on the R group of **10**. However, **10c** was isolated and characterized. Its water hydrolysis products were benzoic acid and *trans*- (**1a**) and *cis*-4-*tert*-butyl-1-methylpiperidine 1-oxide (**1b**). The chemical yields and the isomeric distribution ratios are listed in Table II. From a synthetic standpoint the benzoate method resulted in the highest overall yield (80%) and constitutes a new and efficient chemical method for the preparation of amine oxides. The change in the isomer ratio (cis/trans) from 5/95 in the previously described direct oxidation reaction to 65/35 in the above sequence is impressive. It reflects the differential nonbonded interaction of the bonded OCOPh vs. the approaching methylation reagent in the transition state. Obviously the latter is smaller than the former when axial interactions are concerned.

The extent of stereoselectivity (65%) is smaller than in the direct oxidation reaction, although optimization of the reaction conditions with respect to the stereoselectivity was not attempted. However, the importance of this novel reaction sequence is in providing an access to the thermodynamically and kinetically less stable isomer encountered in the direct oxidation reaction. Indeed, the extent of predominance of the less stable isomer in the reaction mixture (65%) secures its facile separation and purification.

In order to test the generality of the above idea, we employed the benzoate reaction sequence with piperazine (eq 4). Recalling that direct oxidation of 1,4-dimethyl-



11

6a (trans 45%) + **6b** (cis 55%) (4)

piperazine (H_2O_2) at 25 °C generated only one isomer (NMR detectability) and 9% of the cis isomer at 100 °C, one can see that the extent of predominance, 55% (above), is indeed significant.

Although applied only to two N heterocycles, this approach may be of general nature and useful in generating substantial quantities of the thermodynamically less stable heterocyclic amine oxides.

Experimental Section

Melting points were determined in a capillary melting point apparatus, and infrared spectra were recorded with a Perkin-Elmer spectrometer, Model 257. NMR spectra were recorded on Varian HA-100 and JEOL JNM-C-60HL spectrometers.

Amine Oxides: General Method for Oxidation of Amines. If not otherwise specified, the oxides were prepared as follows: to a solution of the amine in acetone (0.25 M) there was added a 30% aqueous solution of H_2O_2. The molar ratio of amine to H_2O_2 was 1:2.5. Usually the oxidation was complete after 24 h at 25 °C (disappearance of amine as monitored by TLC). Excess oxidant was decomposed with MnO_2 to negative KI test. The solvents were removed under vacum (60 °C), and the residue was flash evaporated several times with benzene. The crude product was washed with pentane to remove residual amine and dissolved in chloroform, and the mixture was dried ($MgSO_4$), filtered, and evaporated (crude yields were 90–95%). Picrates were prepared in aqueous solutions and usually crystallized from chloroform. Separations of isomers were effected either by fractional crystallization of the picrates or by chromatography on basic alumina (II-III) as described in ref 2. The isomer mixture of 1,4-dimethylpiperazine 1,4-dioxide (0.5 g) was separated by dry chromatography on neutral alumina (III, 150 g) with methanol–ethyl acetate solution (1:1).

The following compounds were obtained. *cis*-**2**, mp 193–195 °C. Anal. Calcd for $C_{17}H_{26}N_4O_8$: C, 49.27; H, 6.32; N, 13.52. Found: C, 49.64; H, 6.16; N, 13.48. *trans*-**2**, mp 150–151 °C. *cis*-**3**, mp 195–198 °C. Anal. Calcd for $C_{18}H_{28}N_4O_8$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.70; H, 6.71; N, 12.97. *trans*-**3**, mp 150–152 °C. *cis*-**4**, mp 180–182 °C. Anal. Calcd for $C_{22}H_{28}N_4O_8$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.63; H, 5.94; N, 11.67. *trans*-**4**, mp 167–168 °C. *cis*-**5**, mp 179–180 °C. Anal. Calcd for $C_{16}H_{24}N_4O_8$: C, 48.15; H, 6.07; N, 13.57. Found: C, 48.28; H, 6.07; N, 13.67. *trans*-**5**, mp 228–229 °C. Anal. Calcd for $C_{16}H_{24}N_4O_8$: C, 48.15; H, 6.07; N, 13.57. Found: C, 47.92; H, 5.99; N, 13.89. *cis*-**6**, mp 257–259 °C. *trans*-**6**·2HCl, mp 230 °C. Anal. Calcd for $C_6H_{16}N_2O_2Cl_2$: C, 32.93; H, 7.38; N, 12.29. Found: C, 32.96; H, 7.47; N, 12.62.

4-*tert*-Butyl-1-hydroxypiperidine (9a). 4-*tert*-Butyl-1-ethylpiperidine (30 g) was oxidized with H_2O_2 in the usual manner. The dried amine oxide was refluxed in toluene.[9] There was obtained **9a**: 10 g (25%); pale yellow oil; bp 100–102 °C (26 mm);

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NMR δ ($CDCl_3$) 0.85 (s, 9 H), 1–2 (m, 5 H), 2–2.6 (m, 2 H), 2.6–3.2 (m, 2 H).

1-(Benzyloxy)-4-*tert*-butylpiperidine (9b). *trans*-1-Benzyl-4-*tert*-butylpiperidine 1-oxide(**4**, 4.5 g) was pyrolyzed[10] at 170 °C. There was obtained an oil: 3.5 g (80%); bp 108–115 °C (2×10^{-3} mm); NMR δ (CCl_4) 0.85 (s, 9 H), 1.2 (m, 1 H), 1.45 (m, 4 H), 2.35 (m, 2 H), 3.3 (m, 2 H), 4.65 (s, 2 H), 7.25 (s, 5 H). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: 77.45; 10.01; 5.77.

1-(Benzoyloxy)-4-*tert*-butylpiperidine (9c). 4-*tert*-Butylpiperidine (10 g, 0.071 mol) and dibenzoyl peroxide (16.05 g, 0.071 mol) in ether (300 mL) were refluxed for 10 h.[11] The cold ether solution was washed with 15% H_2SO_4 (3 × 75 mL) followed by 15% NaOH (3 × 75 mL) and water (100 mL). The ether solution was dried ($MgSO_4$), and the residue which was left after evaporation was crystallized from hot methanol–water solution: 19.3g (74%); mp 121 °C; γ_{max} (KBr) 1730 cm^{-1}; NMR δ (CCl_4) 0.9 (s, 9 H), 1–1.5 (m, 1 H), 1.75 (m, 4 H), 2.7 (m, 2 H), 3.6 (m, 2 H), 7.5 (m, 3 H), 8.0 (m, 2 H). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 75.33; H, 8.89; N, 5.19.

Reaction of 4-*tert*-Butyl-1-hydroxypiperidine (9a) with Methyl Iodide. Compound **9a** (3.87 g, 24.6 mmol) and methyl iodide (3.7 g, 24.6 mmol) in ethanol (20 mL) containing sodium bicarbonate (25 mmol) were heated in a sealed glass ampule at 50 °C for 5 days. The solution was cooled, filtered, and evaporated to dryness, and the residue was taken up in a small volume of acetone. The product was precipitated by adding ether (1.8 g), dissolving the mixture in chloroform, and chromatographing on basic alumina (III). A 1:1 mixture of **1a** and **1b** was eluted with 5:95 methanol–chloroform (0.63 g, 15%).

Reaction of 1-(Benzyloxy)-4-*tert*-butylpiperidine (9b) with Methyl Iodide. 1-(Benzyloxy)-4-*tert*-butylpiperidine (2.5 g, 0.01 mol) and methyl iodide (1.4 g, 0.011 mol) in ethanol (25 mL) were heated in a sealed glass ampule at 75 °C for 3 days. The reaction mixture was worked up and chromatographed as described for **9a** to give 0.27 g (40%) of a 1:1 mixture of **1a** and **1b**.

Reaction of 1-(Benzoyloxy)-4-*tert*-butylpiperidine (9c) with Methyl Fluorosulfonate. 1-(Benzoyloxy)-4-*tert*-butylpiperidine (15 g, 0.057 mol) and methyl fluorosulfonate (6.5 g, 0.06 mol) in methylene chloride (20 mL) were stirred at room temperature for 72 h. A sticky solid precipitated: 21 g; NMR δ ($CDCl_3$) 0.85 (s, 9 H), 1.85 (m, 5 H), 3.9–4.4 (m, 2 H), 4.0 (s, 3 H), 4.4–4.8 (m, 2 H); ν_{max} ($CDCl_3$) 1770 cm^{-1}.

The above product (5 g) in water (190 mL) was heated to 70 °C and left overnight at room temperature. The benzoic acid was filtered, and a saturated solution of picric acid (water) was added to the filtrate to the point of complete precipitation (4.25 g, 80%). The free amine oxide was obtained by decomposing the picrate salt on Amberlite 400 (BDH) in methanol solution. A mixture of **1a/1b** in the ratio of 35:65 was obtained.

1,4-Bis(benzoyloxy)piperazine (11). Dibenzoyl peroxide (48.4 g, 0.2 mol) in methylene chloride (150 mL) was added dropwise with stirring to a solution of dry piperazine (8.6 g, 0.1 mol) in methylene chloride (100 mL). The reaction mixture was refluxed for 4 h and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was crystallized from acetone: 30 g (93%); mp 142–5 °C; NMR δ ($CDCl_3$) 3.26 (s, 8 H), 7.3–7.7 (m, 6 H), 7.9–8.1 (m, 4 H); ν (KBr) 1735 cm^{-1}. Anal. Calcd for $C_{18}H_8N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.38; H, 5.61; N, 8.68.

Reaction of 1,4-Bis(benzoyloxy)piperazine (11) with Methyl Fluorosulfonate. 1,4-Bis(benzoyloxy)piperazine (16.3 g, 0.05 mol) and methyl fluorosulfonate (12.5 g, 0.11 mol) in methylene chloride (50 mL) were stirred at room temperature for 10 h: white precipitate; 32.5 g (100%); NMR δ ($CDCl_3$) 3.5 (s, 8 H), 7.5 (m, 6 H), 8.05 (m, 4 H).

The above product (30 g) was dissolved in water (30 mL) and the mixture stirred for 15 h at room temperature. After the benzoic acid was filtered off, the filtrate was treated in the manner described for **9c**. A mixture of **6a/6b** in the ratio of 45:55 was obtained (72%).

Preparation of 8. *cis*-8-Methyl-8-azabicyclo[4.3.0]nonane (0.70 g) was oxidized with H_2O_2 (30%, 3.0 mL) in acetone (10 mL) at room temperature. After the usual workup the ratio of the NMR *N*-methyl signals was determined (88:12). The oxide mixture was precipitated from an aqueous solution as the picrates and separated by fractional crystallization from acetone–petroleum ether. For **8a**: mp 172–175 °C; NMR δ (Me_2SO-d_6) 1.47 (m, 8 H), 3.50 (m, 2 H), 3.64 (s, 3 H), 3.95 (m, 4 H), 8.51 (s, 2 H). Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.25; N, 14.58. Found: C, 47.01; H, 5.28; N, 14.74.

Registry No. 1a, 35305-09-4; **1a** picrate, 35365-13-0; **1b**, 35365-10-7; **1b** picrate, 35365-14-1; **2a**, 76832-67-2; **2a** picrate, 76832-68-3; **2b**, 76832-69-4; **2b** picrate, 76832-70-7; **3a**, 76832-71-8; **3a** picrate, 76832-72-9; **3b**, 76832-73-0; **3b** picrate, 76832-74-1; **4a**, 76832-75-2; **4a** picrate, 76832-76-3; **4b**, 76832-77-4; **4b** picrate, 76832-78-5; **5a**, 76832-79-6; **5a** picrate, 76832-80-9; **5b** picrate, 76832-82-1; **6a** dihydrochloride, 76832-83-2; **6b** dihydrochloride, 76832-84-3; **7**, 76832-85-4; **8a**, 76832-86-5; **8a** picrate, 76832-87-6; **8b**, 76832-88-7; **8b** picrate, 76832-89-8; **9a**, 42164-97-6; **9b**, 76832-90-1; **9c**, 76832-91-2; **10c**, 76832-93-4; **11**, 76832-94-5; 4-*tert*-butyl-1-ethylpiperidine, 7576-03-6; 4-*tert*-butylpiperidine, 1882-42-4; piperazine, 110-85-0.

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