agents (acetophenone, benzophenone, phenanthrene, naphthalene, and piperylene) in ether. Each solution was irradiated in a Pyrex tube at room temperature for 70 min and submitted to GLC after removal of solvent. Irradiation of **9** in the presence of acetophenone or benzophenone led to complete disappearance of starting material within 10 min and formation of a new product, which was identical on the GLC retention time with a product obtained from irradiation of **14a** in the presence of acetophenone or benzophenone; thus, the new compound is a secondary product from **14a**. The nature of this compound is presently under investigation. Phenanthrene and naphthalene completely quenched the cycloaddition, and piperylene partially quenched by the concentration used.

Energy Transfer Experiments on 12. Energy transfer experiments on **12** using benzophenone and piperylene as transfer agents were carried out in a similar manner described above for **9**. Benzophenone has no effect on the product distribution and yields, and piperylene gave results as shown in Figure 2.

Registry No.—**3**, 126-81-8; **4**, 107-11-9; **5**, 627-37-2; **6**, 124-02-7; **7**, 589-09-3; **8**, 55800-10-7; **9**, 55800-11-8; **10**, 55800-12-9; **11**, 55800-13-0; **12**, 55800-14-1; **13**, 55800-15-2; **14a**, 37914-13-9; **14a** HCl, 55869-62-0; **15**, 55869-63-1; **16**, 55800-16-3; **17**, 55800-17-4; **18**, 55869-64-2; **19**, 55800-18-5; **20**, 55869-65-3; **21a**, 37914-12-8; **21a** HCl, 55800-19-6; **22a**, 55800-20-9; **23**, 37910-73-9; **24**, 37910-74-0; **25a**, 37910-75-1; **26**, 55800-21-0; **27**, 37914-08-2; **27** HCl, 37910-76-2; **29**, 55800-22-1; **31**, 55800-23-2; **32**, 55869-66-4; **33**, 55800-24-3; **34**, 55800-25-4; **35**, 55800-26-5; **36**, 31928-99-1; **37a**, 55869-67-5; **38**, 37914-09-3; **39**, 37914-10-6; **40**, 55800-27-6; **41**, 37914-11-7; **43**, 55800-28-7; **44**, 55800-29-8.

References and Notes

(1) Portions of this work have appeared as preliminary communications; see Y. Tamura, Y. Kita, H. Ishibashi, and M. Ikeda, *Chem. Commun.*, 167 (1971); *Tetrahedron Lett.*, 1977 (1972).
(2) For a review and leading references, see (a) W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966); (b) J. W. Gibson and W. F. Erman, *J. Org. Chem.*, **37**, 1148 (1972); (c) J. R. Scheffer and R. A. Wostradowski, *ibid.*, **37**, 4317 (1972).
(3) At the same time, Paquette and coworkers reported a synthesis of 1,4-dimethyl-2-azabicyclo[2.1.1]hexan-3-one by the reaction of 1,3-dimethylbicyclo[1.1.0]butane with chlorosulfonyl isocyanate; see L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Am. Chem. Soc.*, **93**, 4503 (1971).
(4) For the 2-oxabicyclo[2.1.1]hexane ring system, see (a) E. P. Blanchard, Jr., *Chem. Abstr.*, **67**, 108316e (1967); (b) D. G. Farnum and A. J. Mostashari, *Org. Prep. Proced. Int.*, **2**, 5 (1971).
(5) The stereochemistry of **17** was assigned on the basis of the coupling pattern of >CHOH (quartet, J = 3.0 Hz) and the mode of the formation of **17** (an approach of hydride is expected to occur exclusively from the outer face of the folded molecule).
(6) The long-range coupling between H_b and H_f in the bicyclo[2.1.1]hexane system is as yet unrecorded.
(7) J. K. M. Sanders and D. H. Williams, *J. Am. Chem. Soc.*, **93**, 641 (1971), and references cited therein.
(8) (a) J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961); (b) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1594 (1962).
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(10) N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.*, **80**, 4959 (1958).
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(13) (a) K.-H. Grellmann, G. M. Sherman, and H. Linschits, *J. Am. Chem. Soc.*, **85**, 1881 (1973); (b) H. Linschitz and K.-H. Grellmann, *ibid.*, **86**, 3030 (1964); (c) K. Yamada, T. Konakahara, and H. Iida, *Bull. Chem. Soc. Jpn.*, **46**, 2504 (1973).
(14) Although it has been reported in a preliminary paper[1] that two products were obtained in a ratio of ca. 4:1, careful reinvestigation indicated that the reaction proceeds with high stereoselectivity.
(15) E. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. de Mayo, *J. Org. Chem.*, **34**, 794 (1969).
(16) (a) E. J. Corey, J. D. Base, R. Lemahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964); (b) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969); (c) P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971); (d) P. G. Bauslaugh, *Synthesis*, 287 (1970).
(17) We have not been able to detect phosphorescence from $n \rightarrow \pi^*$ excited **9** in methylcyclohexane at 77 K and thus there is no direct evidence for the generation of $n \rightarrow \pi^*$ triplets. However, since there are ample examples in which phosphorescence was not observed from $n \rightarrow \pi^*$ triplets of α,β-unsaturated ketones, and since most of the photoaddition reaction of α,β-unsaturated ketones is known to involve $n \rightarrow \pi^*$ triplets, it is reasonably assumed that this excited state is also $n \rightarrow \pi^*$ in nature.
(18) M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967), and references cited therein.
(19) That the dimethyl group on the cyclohexenone ring has no effect on the stereochemical consequence was shown by the stereospecific transformation of 3-(*N*-methylallylamino)-2-cyclohexen-1-one to the corresponding 2-azabicyclo[2.1.1]hexane, whose structure was deduced from comparison of the NMR spectrum of the crude photoproduct with that of **14a**. However, attempts to isolate it in a pure form were unsuccessful because of its lability, thus precluding elemental analysis (unpublished results).
(20) G. Büchi and H. Wüest, *J. Am. Chem. Soc.*, **87**, 1589 (1965).
(21) The different slopes in Figure 2 may be attributed to the experimental error.
(22) Y. Tamura, Y. Kita, M. Shimagaki, and M. Terashima, *Chem. Pharm. Bull.*, **69**, 571 (1972).
(23) R. D. Desai, *J. Chem. Soc.*, 1079 (1932).

The Chemistry of Hindered Systems. Syntheses and Properties of Tetramethylazacycloheptanes and Related Acyclic Amines

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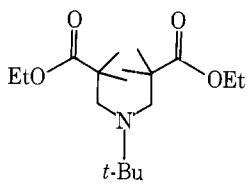
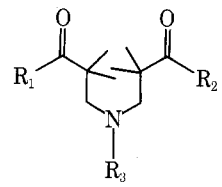
Received May 21, 1975

Hindered acyclic *N-tert*-butyl amines **1–5** have been synthesized to determine the relative importance of steric and electronic factors in these systems. The syntheses of the acyclic amines, which involved manipulation of a common intermediate, namely tetramethylazacycloheptane acyloin **9**, (formed from diester **1**), are discussed. The reduction of acyloin **9** was studied in detail and the stereochemistry of the critical diol intermediates formed, **12a** and **12b**, was established using chemical and spectroscopic techniques. One of the spectroscopic approaches utilized ^{1}H NMR chiral shift reagents to distinguish between the diol meso and *dl* diastereomers. Low-temperature dynamic ^{1}H NMR techniques were used to measure $\Delta G^{\ddagger}$ (free energy for inversion–rotation processes about the N–CH_2 bonds; e.g., 9.1 kcal/mol for parent amine **4**) for the acyclic amines. Similarities in $\Delta G^{\ddagger}$ for **1–4** indicate that steric factors and not electronic factors best account for the inversion–rotation barrier found in these molecules. Studies of favorable conformations for amines **1–3**, however, suggested that these systems might be capable of some nitrogen–carbonyl interaction. Comparisons of uv spectra obtained for the diketone **3**, dialdehyde **2**, and cyclic ketone **23** provide evidence that interaction (i.e., mixing of the nitrogen and carbonyl orbitals) does occur in the examples cited.

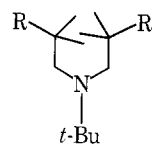
Our reports[1,2] on the synthesis of the hindered *N-tert*-butyl-3,3′-imino diester **1**, and on the possibility that intramolecular 1,4-nitrogen–carbonyl interactions[3,4] resulting as a consequence of preferred conformations[5] might account for some of the unusual properties of this molecule (and other hindered systems we have now synthesized as part of this study), prompted us to synthesize dialdehyde **2** and diketone **3**.



1

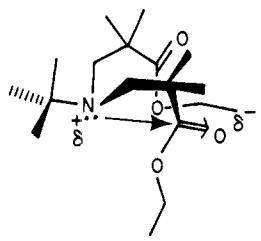


2, $R_1 = R_2 = H$; $R_3 = t$-Bu
3, $R_1 = R_2 = CH_3$; $R_3 = t$-Bu
5, $R_1 = H$; $R_2 = CH_3$; $R_3 = t$-Bu
8, $R_1 = R_2 = H$; $R_3 = CH_3$

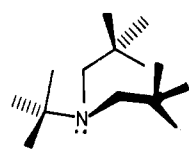


4, R = CH_3
6, R = CH_2-OH

We expected that the increased reactivity toward nucleophiles of the aldehyde and ketone groups, compared to the ester group, would enhance any potential or existing interactions. If 1,4-nitrogen–carbonyl interactions were important in these hindered systems, they would be expected to increase inversion–rotation barriers related to the CH_2–N bonds relative to the parent amine 4[6] (compare **1a** with **4a**).



1a



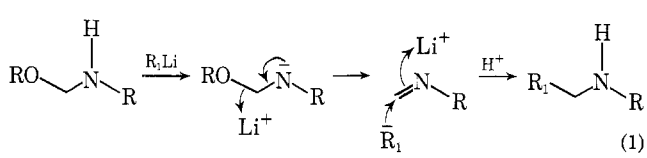
4a

On the other hand, if steric factors were mainly responsible for the chemistry of these systems, the inversion–rotation barriers about the CH_2–N bonds of these molecules should be similar.

The CH_2–N rotation or nitrogen inversion barriers can be estimated by low-temperature ^1H or ^{13}C dynamic magnetic resonance techniques. Our efforts directed toward the synthesis of **1**, **2**, **3**, and a mixed system, **5**, as well as estimates of $\Delta G^{\ddagger}$ for inversion–rotation at the CH_2–N bonds of **1** through **5**, will be discussed.

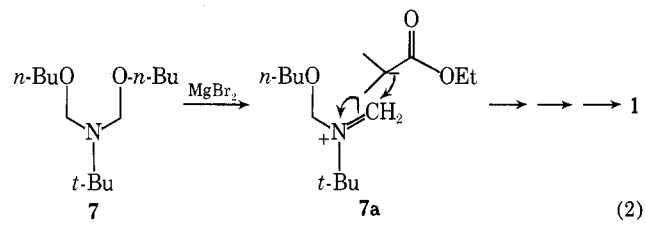
Synthesis and Reactions of Diester 1. It appeared that **1** would represent a good starting material for the synthesis of **2** (and possibly **3**), since partial reduction of **1**, or complete reduction of **1** to diol **6**[6] followed by partial oxidation of **6**, could yield **2**.

Diester **1** was obtained via a dialkylation procedure which involved reaction of the Grignard reagent generated from ethyl 2-bromoisobutyrate with bis(*n*-butoxymethyl)-*tert*-butylamine (**7**) under mild conditions. This approach was employed after more conventional approaches employing Reformatsky reagents[7] were shown to give only monoalkylated products. Interestingly, amine **7** was reasonably stable to organolithium reagents[8] which seem to react, under mild conditions, with molecules containing the $-OCH_2NR_2$ linkage (other than possible acid–base reactions) only when the nitrogen contains a proton.[8e,h] In these cases the "displacement" reaction is believed to be an "elimination–addition" reaction not possible with tertiary amines (eq 1).



(1)

We believe that the Lewis acid ($MgBr_2$)[9] generated in the course of the Grignard reaction is important in catalyzing the formation of dialkylmethyleneimmonium ion **7a**,[10] which we feel is the actual species attacked by the organomagnesium reagent (eq 2).



(2)

Treatment of diester **1** with diisobutylaluminum hydride under conditions which effect the reduction of ethyl isobutyrate[11] gave no reduction. Similarly, reduction with lithium tri-*tert*-butoxyaluminum hydride was also ineffective. In contrast, treatment of **1** with lithium aluminum hydride in refluxing ether gave diol **6** in good yield. Reaction of **6** with oxidizing agents known to convert alcohols to aldehydes (e.g., CrO_3–pyridine,[12] CrO_3–graphite,[13] DMSO–DCC,[14] or methyl phenyl sulfide–Cl_2 complex[15]) failed to give **2** in our hands. In most cases **6** could be recovered. We were also unable to synthesize **2** via either direct or indirect procedures employing the Mannich reaction, which had proved fruitful in the synthesis of the less hindered N-CH_3 dialdehyde **8**.[16]

Synthesis of Dialdehyde 2. Taking a different approach, we found that we were able to synthesize **2** using the sequence outlined in Scheme I. Reaction of **1** under acyloin conditions, sodium in refluxing toluene, gave 80% yield of acyloin **9**. Treatment of ketol **9** with acetic acid–acetic anhydride gave acetate **10** in 85% yield. The high yield of tetramethylated **9** is not surprising, since alternate base condensation reactions are not possible in these systems.[17] Steric compression also favors ring formation (see **1a**). Oxidation of **9** using lead tetraacetate in refluxing pyridine for at least 24 hr gave dione **11** in 60–70% yield. Reduction of **9**, **10**, or **11** gave cis–trans mixtures of diol **12** as shown in Table I.

Scheme I

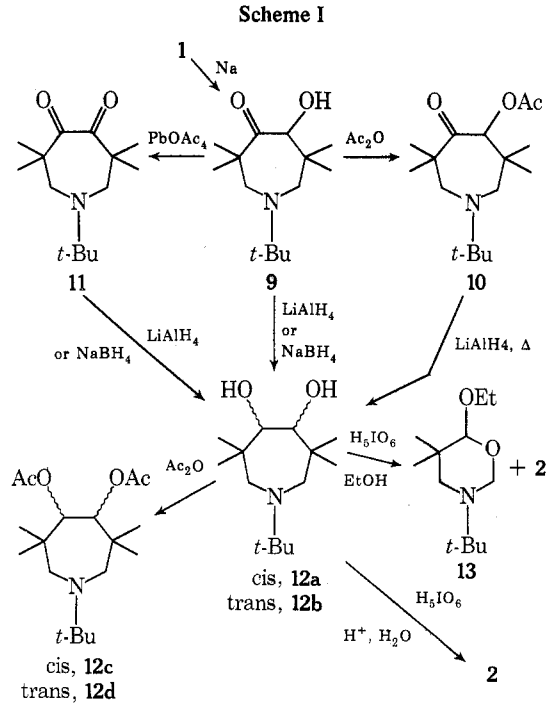


Table I
Reduction of 9, 10 and 11

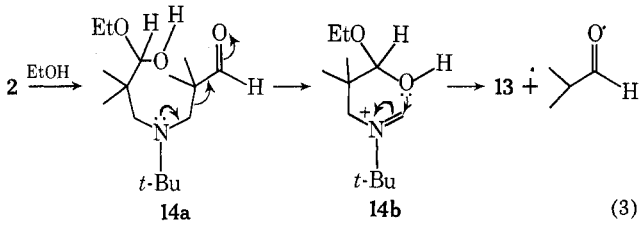
Run	Starting material	Reducing agent	Solvent	Ratio[a] of 12a:12b
A	9	$NaBH_4$	EtOH (25–50°)	80:20[b]
B_1	9	$LiAlH_4$	THF (–78–50)	83:17
B_2	9	$LiAlH_4$	THF (80°)	74:26
C	11	$NaBH_4$	EtOH (25–50°)	80:20[b]
D	11	$LiAlH_4$	Pentane (–78 to 50°)	85:15[b]
E	11	$LiAlH_4$	THF (–78 to 50°)	75:25[b]
F	10	$LiAlH_4$	THF (25–80°)	100:0

[a] Ratios were determined by ^1H NMR integration of the N–CH_2 protons. [b] Average of several runs.

While we were unable to separate the cis and trans diols by GLC (SE-30, SE-52, UCON columns), they were readily analyzed by ^1H NMR or TLC (the minor component having the larger R_f value) and separated by column chromatography using silicic acid with hexane–ether elution. The diols, which have nearly identical melting points (**12a,** mp 140–141°; **12b,** mp 140–142°), were readily converted to their respective diacetates **12c** and **12d** but different approaches were required.

While cis diol **12a** was readily converted to its diacetate **12c** using acetic acid–acetic anhydride, several products were isolated when **12b** was treated in a similar manner. Treatment of **12b** with acetic anhydride in pyridine gave **12d,** however, in 82% yield. The stereospecific acylation–rearrangements observed for **12b,** but not **12a,** under acid conditions (these will be discussed elsewhere) appear to be related to preferred conformations.[18]

Oxidation of **12a** with paraperiodic acid in ethanol for 24 hr at 25° gave two products in a 60:40 ratio. These were identified as the desired dialdehyde **2** and 6-ethoxytetrahydro-3-*tert*-butyl-5,5-dimethyl-2*H*-1,3-oxazine (**13**).[19] We have now shown that tetrahydrooxazine **13** results from the decomposition of **2** in the alcoholic solvents. Stirring pure **2** in anhydrous ethanol for 24 hr at 25° leads to its quantitative (by ^1H NMR, 82% isolated yield) conversion to **13.** This interesting reaction appears to involve loss of isobutyraldehyde (readily detected by ^1H NMR) from **2** or hemiacetal **14a** via a reverse Mannich[20] reaction followed by ring closure of hemiacetal **14b** to give **13** (eq 3). Dialdehyde **2** was found to be stable when stored neat or in nonpolar solvents (CCl_4).

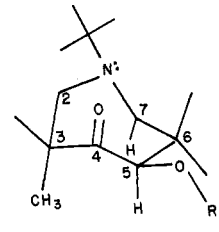


(3)

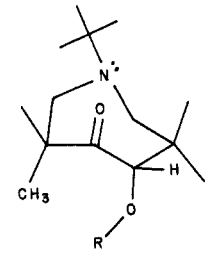
To circumvent participation by the nitrogen lone pair in this reaction, oxidation of **12a** was carried out in aqueous hydrochloric acid at 25°. Under these conditions **2** could be isolated in 62–77% yield depending on the scale of the reaction.

Stereochemistry of Diols 12a and 12b. We have studied the reduction of **9** and **11** and the stereochemistry of diols **12a** and **12b** using semiempirical, chemical, and physical techniques.[21] Since the rapidity and exothermicity (E_{act} = 8–15 kcal/mol)[22] of hydride reactions indicates in many cases that they proceed via "steric approach control"[23] (i.e., little bond breaking and making has occurred at the transition state), the stereoselectivity of the hydride reactions is expected to be reflected by the geometries of the ground state of the starting materials.[24]

Assuming that this is the case for the hindered mesocyclic acyloins, such as **9,** predictions about their ground-state geometries might allow predictions concerning the cis:trans ratios of diols expected from their reduction by hydride.[25c,26] Studies of models[18] of acyloin **9** show that there appears to be two preferred conformations for this molecule, namely, **15a** and **15b.** Because nitrogen can undergo inversion, conformations **15a** and **15b** can be "viewed" as epimers and their relative populations calculated using free-energy differences ($\Delta G_{E/A}$) between conformations involving equatorial and axial C_5 substituents.[25] Assigning a value[25a,b] of 0.9 kcal/mol for the C_3, C_5 ($CH_3 \rightarrow$ H) diaxial interaction in **15a,** and values of 2.0–2.2 kcal/mol for the C_3, C_5 ($CH_3 \rightarrow$ OH) diaxial interaction and 0.2–0.4 kcal/mol for the C_5, C_7 (OH $\rightarrow$ H) diaxial interaction in **15b,** a $\Delta G_{E/A}$ ranging from 1.3 to 1.7 kcal/mol can be calculated. Using the relationship $\Delta G_{E/A} = -RT \ln K_{E/A}$ and solving for $K_{E/A}$ at 25° gives a value for $K_{E/A}$ which indicates that the more stable conformer, **15a,** should comprise 90–95% of the acyloin mixture.

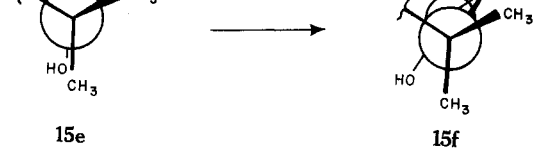


15a, R = H
15c, R = AlH_3

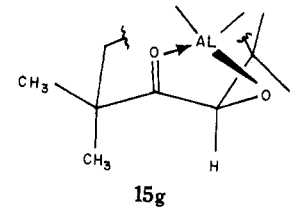


15b, R = H
15d, R = AlH_3

Distortion of the cycloheptanoid half-boat, half-chair conformations (**15a** and **15b**) to half-twist boat, half-chair conformations, while possibly creating C_3, C_7 and C_2, C_5 interactions, relieves the C_3, C_5 diaxial interaction.[18] We feel that this distortion is probably important for **15a,** and especially for **15b,** and estimate that a 30° twist (i.e., **15e** → **15f**) between C_3, C_5 substituents would result in ca. 40% re-



15e **15f**



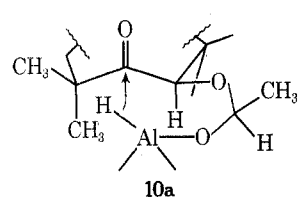
15g

duction (based on dihedral angle–rotational barrier relationships) of their interaction. Given the assumptions,[24] reduction of **9** with sodium borohydride ($NaBH_4$) in ethanol at 25° (attack by hydride at the least hindered face of the carbonyl) would be expected to give cis (from **15a**) and trans (from **15b**) diols **12a** and **12b** in ca. 80–90:20–10 ratios, respectively. These predictions appear to agree reasonably well with experimental results (see run A, Table I).[27] Reduction of either acyloin **9** or dione **11** by lithium aluminum hydride ($LiAlH_4$) might be expected to give, after initial acid–base reaction in the case of **9** or partial reduction in the case of **11**, aluminate esters **15c** and **15d**. Aluminate ester **15c**, but not **15d**, is capable of forming a cyclic cyclopentanoid species such as **15g** where the acyloin acts as a bidentate ligand for the metal atom.

The effect of **15g** on the equilibrium of **15** would be expected to be more important in less polar solvents where the carbonyl oxygen does not have to compete with solvent for complexation.[26b]

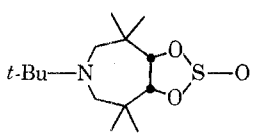
Since conformers **15c** and **15g** should yield cis diol **12a** while **15d** would give trans diol **12b**, reduction of **9** or **11** with $LiAlH_4$ in THF (polar solvent) would be expected to yield about the same cis:trans ratio as observed with $NaBH_4$.[28] In less polar solvents, such as pentane, the yield of cis diol should increase upon $LiAlH_4$ reduction of **9** or **11** owing to the increased importance of **15g** in this poorly solvating solvent. The stereoselectivity of the $LiAlH_4$ reduction of **9** in THF at higher temperature would be expected to decrease owing both to decreased importance of **15g** at the higher temperature and the change expected in $K_{E/A}$ due to the change in temperature. At 80° the more stable conformer, **15a**, would be expected to comprise only 75 to 85%[25a] of the mixture. Reduction of **9**, by adding it to THF and $LiAlH_4$ at reflux (80°), gave a 74:26 ratio of **12a** to **12b** (run B_2, Table I). In general, the experimental results agree well with prediction (see runs B–E, Table I).

The complete stereoselectivity noted in the $LiAlH_4$ reduction of acetate **10** (run F, Table I) is believed to result from the initial reduction of the acetate group in preference to the hindered ketone to give **10a** followed by directed delivery of hydride[29] to give **12a**.

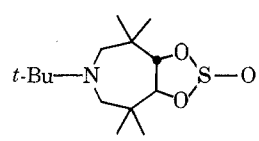


10a

The predicted cis stereochemistry of the major diol was established unambiguously by classical techniques. Examination of the ^1H NMR spectrum of the sulfite ester **16a**, formed from **12a**, showed a singlet occurring at δ 4.63 due to the protons α to the oxygen while sulfite ester **16b** showed an AB pattern at δ 4.30 (J = 11 Hz) for its C-4, C-5 protons.



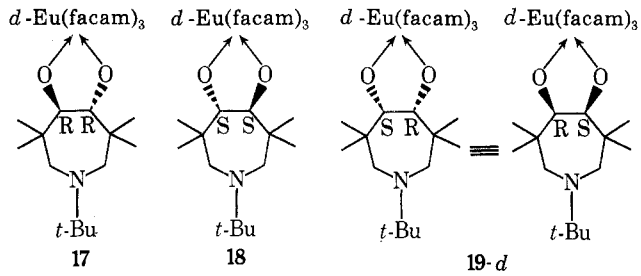
16a



16b

As the chemical–spectroscopic techniques require fair amounts of diol, other simple physical methods for determining the stereochemistry of **12** (and related systems)[21] were studied. Comparison of the mass spectra of **12** indicated that the cis and trans diols could be identified on the basis of their ability to lose water upon electron impact. Comparison of ions occurring at m/e 228 ($M^+ - CH_3$) and 210 (228 − H_2O) for **12a** and **12b** indicates that the loss of water is considerably more favorable from the trans than the cis diol. This seems to be a general property of the cyclic tetramethylated 1,2-diols we have studied and is in agreement with the observation that water is eliminated preferentially via cis elimination processes only available to the trans diol upon electron impact.[30] While extremely dependable in our systems, mass spectra of both isomers are required for comparative purposes (both isomers are not always available; see run F, Table I).

A much more interesting approach to diol stereochemistry, which we believe will prove to be generally applicable to symmetrical diols and related systems, and which should allow isomer assignment in most cases even when only one isomer is available, involves the use of chiral lanthanide shift reagents.[31] Cis diol **12a** (meso) and trans diol **12b** (*dl* racemate) are diastereomers[32] which would be expected to exhibit predictably different ^1H NMR patterns in the presence of chiral shift reagents such as tris(3-trifluoroacetyl-*d*-camphonato)europium (III) [Eu(facam)$_3$]. Trans diol **12b** should show two (probably similar) sets of ^1H NMR signals resulting from formation of "pseudo-contact" diastereomers[33] **17** and **18**[34,35] in the presence of the chiral shift reagent. On the other hand, cis diol **12a** should show ^1H NMR signals resulting from the formation of "pseudo-contact" enantiomer[33] **19-*d***. For **19-*d*** induced asymmetries,



17 **18** **19-*d***

caused by the presence of the chiral center and which should diminish with distance from it, would be expected. Specifically for **12a** and **12b**, only **12b** can show two *tert*-butyl signals in the presence of chiral shift reagents. Comparison of spectra C and E (Figure 1) shows that this point alone is sufficient, in this case, to assign structures to diols **12a** and **12b** (spectra A and D, Figure 1).

Other aspects of spectra C and E (Figure 1) are completely in agreement with the above general predictions, including the induced asymmetries expected for **12a** in the presence of the chiral shift reagent.[34] A spectrum of **12a** in the presence of 0.45 equiv of tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionatoeuropium [Eu(fod)$_3$],[31] an achiral shift reagent, is included for comparative purposes (spectrum B, Figure 1).

Synthesis of Diketone 3, Ketone Aldehyde 5, and Monoketone 23. Diketone **3** (57% yield) and ketone aldehyde **5** (77% yield) were synthesized from diols **22** and **20** using oxidative procedures similar to those employed in the synthesis of **2**. The syntheses of diols **20** and **22** are shown in Scheme II along with synthesis of ketone **23**.

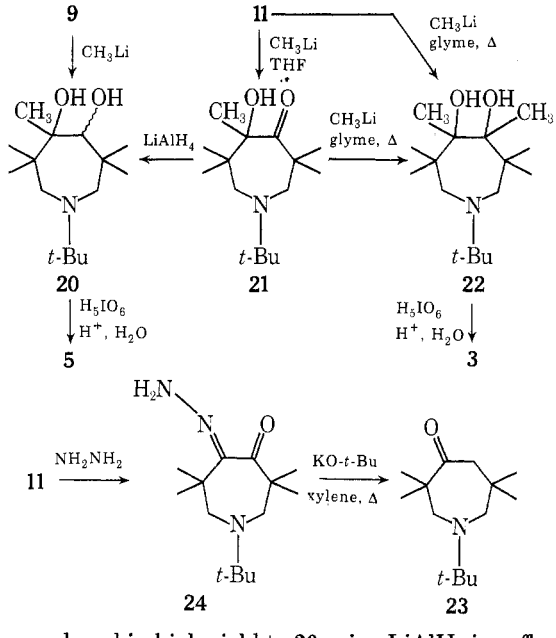
Treatment of acyloin **9** with 4 equiv of methyllithium in THF at −78° followed by warming to 35°[36] gave, after work-up, pentamethyl diol **20** of unknown stereochemistry in 81% yield. Treatment of dione **11** under similar conditions led to formation of acyloin **21** in 87% yield. While we were able to convert dione **11** to hexamethyl diol **22** in 81% yield by treating it with excess (4 equiv) methyllithium in glyme under reflux conditions, we were unable to convert either **11** or **21** to **22** using excess methyllithium in THF, even when vigorous (35°) conditions[36] were used. Acyloin

Table II

Starting material	T_c, °C	T_c, K	$\Delta\nu$, Hz	ΔG^*, kcal/mol	A value
1[a]	−88	185	67	8.8[b]	1.3 (CO_2Et)[42a]
2[d]	−97	176	78	8.3	1.3 (COH)[42b]
3	−102	171	29	8.4	1.2 ($COCH_3$)
4[d]	−81	192	79	9.1	1.7 (CH_3)
5 (aldehyde CH_2)	−100	173	60	8.2[c]	
5 (ketone CH_2)	−100	173	24	8.4[c]	

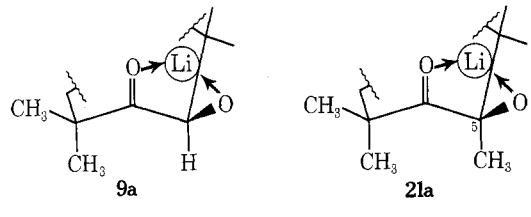
[a] Ca. 5% v/v in vinyl chloride. [b] Error is estimated at ±3°, ±5 Hz = ±0.3$\Delta G^\ddagger$. [c] Overlapping AB patterns make these values less reliable. [d] See Figure 4 for representative dynamic ^1H NMR spectra (i.e., 2 and 4).

Scheme II



21 was reduced in high yield to 20 using $LiAlH_4$ in refluxing THF.

Literature precedent[25,26] suggests that the successful reaction of 9 with methyllithium (in THF) occurs via a lithium alkoxide–ketone complexed cyclopentanoid half-chain conformer such as **9a**. The front face of complex **9a** would be partially obstructed by the lithium cation. Since we feel this interaction might also exist in complex **21a**, it seems



likely that steric hindrance due to the added methyl group at C_5, and not electronic factors, accounts for the relative reactivities of 9 and 21 with methyllithium (in THF). While not unambiguously established, we believe that only *cis*-**22**,[37] the product expected from attack of conformer **21a**, was obtained from the reactions of either 11 or 21 with excess methyllithium in hot glyme [^1H NMR spectra of 22 taken in the presence of Eu(facam)$_3$ (0.25–0.7 equiv) show only one *tert*-butyl signal indicating "pseudo-contact" diastereomers were not formed].

Ketone 23 was prepared from dione 11 via reaction of its monohydrazone 24 with potassium *tert*-butoxide in refluxing xylene.

Low-Temperature Dynamic ^1H NMR Studies of 1, 2, 3, 4, and 5. The free energies of activation, $\Delta G^\ddagger$, for inversion–rotation related to the CH_2–N[38] bonds for 1, 2, 3, 4, and 5 were determined using low-temperature dynamic proton magnetic resonance techniques. Measurement of T_c (coalescence temperature for the CH_2–N protons) and $\Delta\nu$ [the chemical shift difference between H_A and H_B (CH_AH_B–N) well below T_c] allows estimation of $\Delta G^\ddagger$[39] from the Eyring equation.[40]

$$\Delta G^\ddagger = RT_c \ln (\sqrt{2}\, KT_c/h\pi\Delta\nu)$$

Table II shows the measured ^1H NMR parameters and estimated $\Delta G^\ddagger$ for 1–5. *A* values[41,42] are included in Table II as a possible measure of substituent size in order that the various steric and electronic factors responsible for conformational preferences and possibly CH_2–N inversion–rotation barriers might be separated and compared.

Examination of the various conformations possible for a generalized amine **25** (Chart I), taking into account nitrogen inversion, CH_2–N rotation, and concerted inversion–rotation processes,[38] reveals that six conformers, **26–31**, can be drawn (Newman projection down the CH_2–N bond of **25**). Since, to a first approximation, R on **25** can be viewed as a *tert*-butyl group (more will be said about this point), conformers **26, 31** and **27, 30** can be considered unimportant because of the high vicinal nonbonded repulsions due to *tert*-butyl–*tert*-butyl–neopentyl interactions in the former case and *tert*-butyl–*tert*-butyl interactions in the latter. Conformers **28** and **29** suffer from *tert*-butyl–neopentyl nonbonded interaction but studies of models[18] show that because of free rotation about the CH_2–$C(CH_3)_3$ bond in the neopentyl group, this interaction can be considered about equivalent to a *tert*-butyl–methyl vicinal interaction[43] and consequently should be of considerably lower energy than the other two types of vicinal nonbonded repulsions existing in these systems. For these reasons we believe that only conformations **28** and **29** are populated below the coalescence temperature. While H_A and H_B are nonequivalent for each of the conformers, in **28** and **29** they have exchanged environments. Consequently the CH_2–N dynamic ^1H NMR spectrum of **28** and **29** should be the same under static conformation conditions and only one AB pattern due to the CH_2–N protons should exist for each of the amines (**1–4**). The near-perfect symmetry[38] below the coalescence temperature of the different AB patterns resulting from the CH_2–N protons of 1–4 supports these conclusions (see Figure 4). Having demonstrated that only conformations **28** and **29** appear to be populated under static conformation conditions, the effect of the various R groups (**25**, R_M, R_A, R_K, R_E, Chart I) can be analyzed. Amines **1–3** can be looked at as conformers **32–34** (Newman projections down the C_3–C_2 bond, Chart I) formed via a threefold rotation process. If *A* values are used as a criteria for deciding the magnitude of nonbonded interaction, it would seem that **32** and **33**, which have the smaller (Table II) sp^2 hybridized carbon as one of the two groups gauche to the bulky nitrogen, would be preferred over **34**. These steric arguments tend to indicate that 1,4-nitrogen–carbonyl interactions seem at least conformationally feasible as

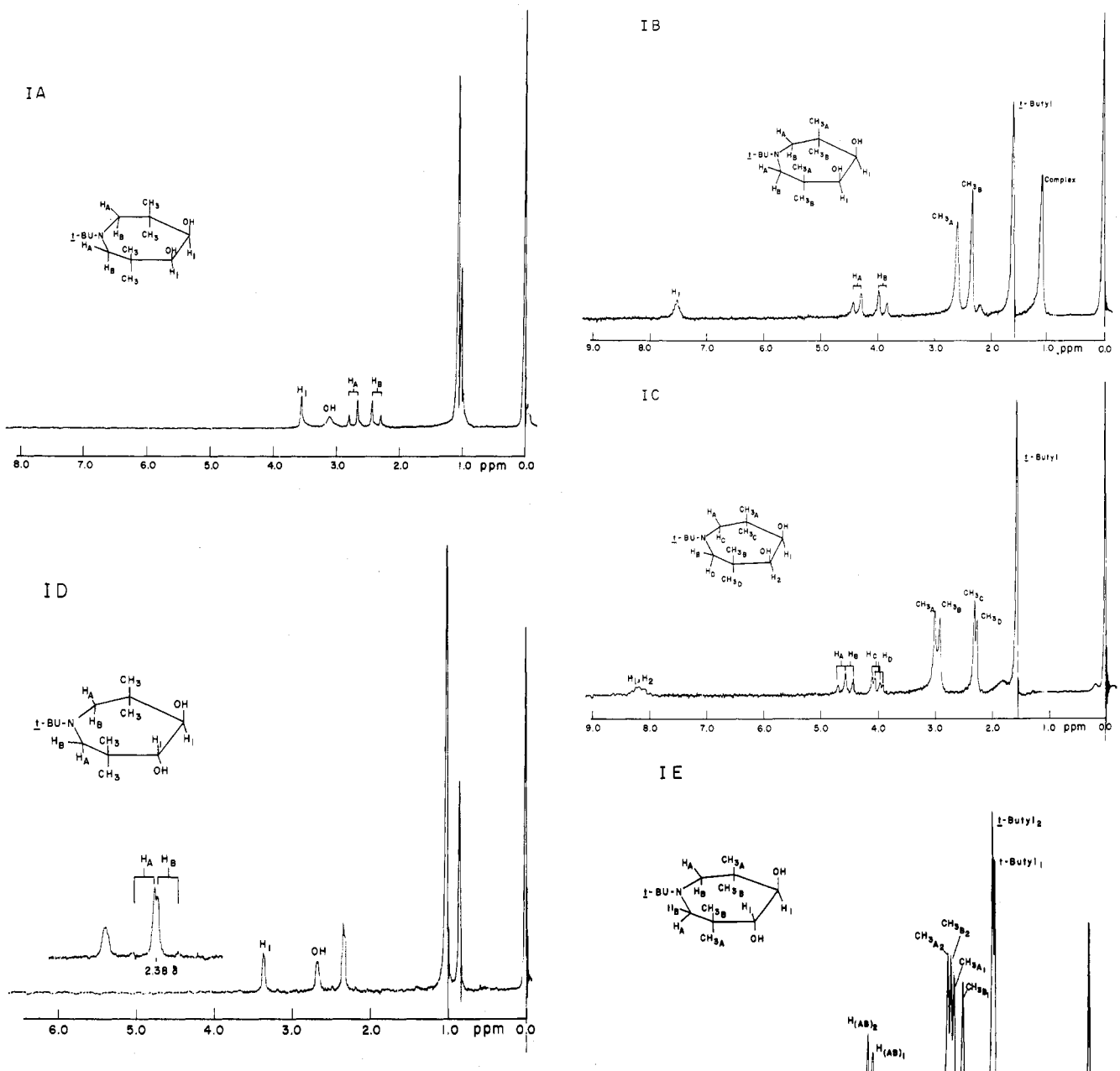


Figure 1. ^{1}H NMR spectra of diols **12**: A, **12a** (ca. 5% in $CDCl_3$); B, **12a** [ca. 5% in $CDCl_3$ containing 0.45 equiv of $Eu(fod)_3$]; C, **12a** [ca. 5% in $CDCl_3$ containing 0.45 equiv of $Eu(facam)_3$]; D, **12b** (ca. 5% in $CDCl_3$); E, **12b** [ca. 5% in $CDCl_3$ containing 0.45 equiv of $Eu(facam)_3$].

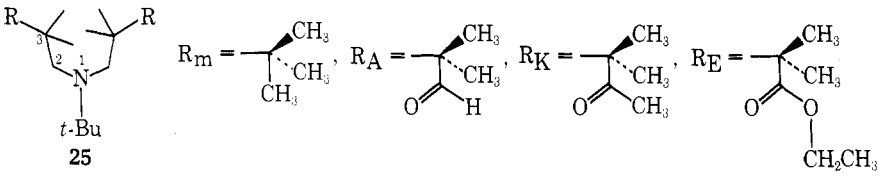
was postulated. Efforts to stop C_2–C_3 rotation in order to look for a nonequivalence of the aldehyde protons of **2** under static conditions resulted in 60 Hz broadening at −150 to −160° of the aldehyde signal but no nonequivalence was noted.

While it is perhaps dangerous to compare ground-state (A values) and transition ($\Delta G^{\ddagger}$) parameters[25] for amines **1–4**, we feel they should show similar trends for these similar systems if steric factors tend to dominate but that they might show divergent trends if electrostatic interaction (e.g., **1a**) were important for the carbonyl containing systems (i.e., **1–3**). It is interesting to note, then, that the former case is observed and that A values do generally parallel the $\Delta G^{\ddagger}$ values obtained for **1–3** (sp^2) and **4** (sp^3), ruling out the likelihood that strong 1,4-nitrogen–carbonyl interactions are important in these systems.

Comparison of $\Delta G^{\ddagger}$ for **4** (9.1 kcal/mol) and for *tert*-butyldiethylamine[38] (**35**, $\Delta G^{\ddagger}$ = 7.2 kcal/mol) is somewhat instructive. While calculations and studies of models show that some sp^2 character at nitrogen relieves nonbonded interactions in the ground state of **35**, thus raising the energy of its ground state relative to its transition state for inversion–rotation (pure sp^2 character) processes, similar sp^2 character in the ground state of **4** would seem unfavorable. While it might relieve CH_2–CH_2–*N*-*tert*-butyl interactions, the increased planarity at nitrogen would cause serious 1,7 alkyl–alkyl interactions. The planar transition state for inversion–rotation of **4** appears to be considerably more crowded than that of **35**. We feel that both of these factors account for the 2 kcal/mol difference between the $\Delta G^{\ddagger}$ of **4** and **35**.

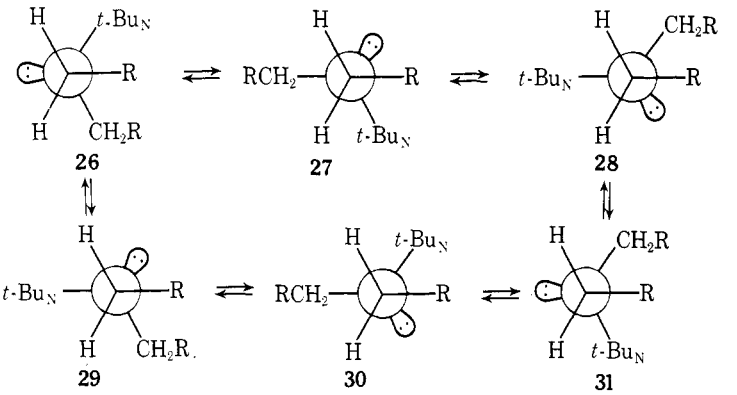
Ultraviolet Studies of 11, 23, and 3. Since the data and discussions presented above indicate that, even though there appear to be no strong ground-state electrostatic (N–C=O) interactions in amines **1–3**, the nitrogen lone pair and carbonyl π orbitals (especially the larger π^* orbit-

Chart I
Newman Projections of 25



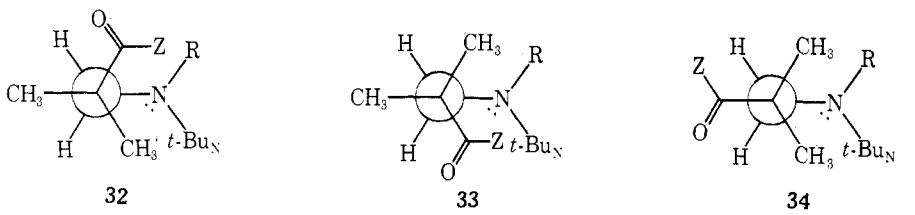
25

A. Down the C_2–N Bond



26 27 28 29 30 31

B. Down the C_3–C_2 Bond



32 33 34

Z = H, CH_3, OEt

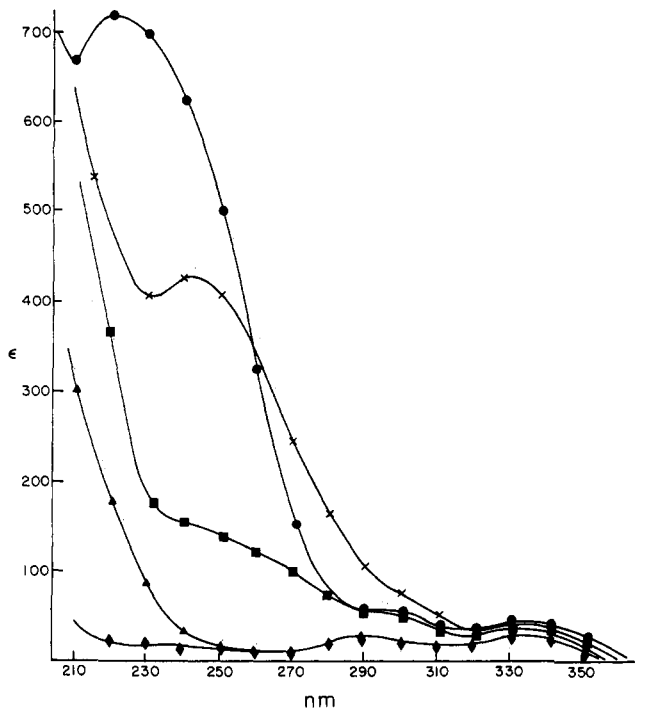
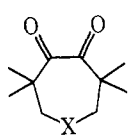
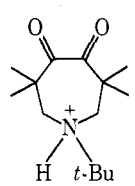


Figure 2. Uv spectra (EtOH) of **36**, ●; **11**, ×; **11** plus 40 μmol AcOH, ■; **37**, ▲; **38**, ♦.

als) should be in close proximity much of the time (see conformers **32** and **33**, Z = H, CH_3), uv studies were undertaken to add support to our conclusions. We felt that the uv spectra of the restricted linear systems should resemble those of cyclic systems if they contained similar structural features. Figure 2 shows uv spectra (EtOH) of tetramethylcycloheptane-4,5-diones **36**,[44] **11**, **37**,[45] and **38**.[46]





36, X = S
11, X = N-*t*-Bu
37, X = O
38, X = CH_2

39

It can be seen that both **36** (219 nm, ε 720) and **11** (242 nm, ε 420) show charge-transfer[47] (C-T) bands in their uv spectra as a consequence of the close proximity of the heteroatom and the carbonyl orbitals while **37** and **38** show spectra typical of normal mesocyclic α-diones. When the spectra of **11** is looked at in the presence of added acetic acid, the C-T absorption decreases significantly because protonation of the nitrogen lone pair (see **39**) prevents nitrogen–carbonyl interaction. Comparing the uv spectra of **11**, **23**, and **3** (see Figure 3), one notices that all three of these molecules show C-T absorption near 240 nm. We believe the strong similarities between the uv spectra of **3** and **23** reflect the fact that their most favored conformations at 25°, **40a**, **40b** (same as **40a** but nitrogen inverted), and **41**, respectively, contain similar important geometric relationships supporting the conformational arguments based on steric factors presented earlier. The lower intensity of the C-T absorption of **3** can be accounted for by the greater

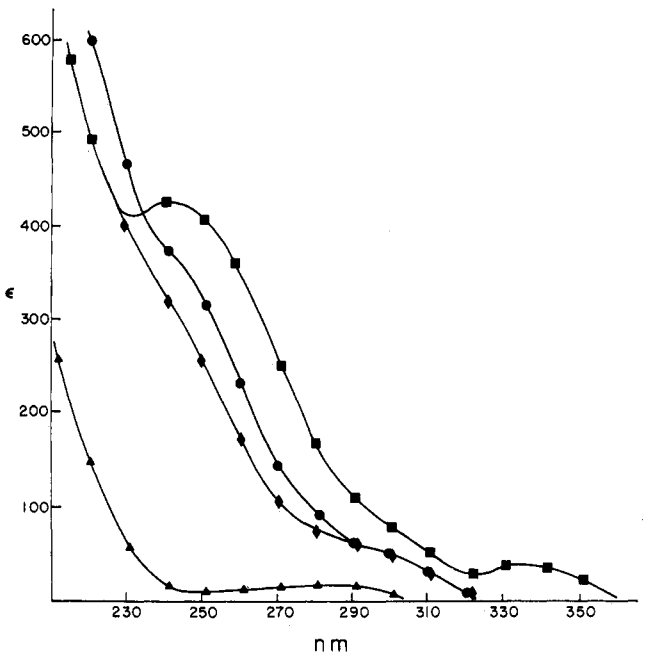
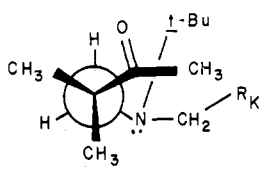
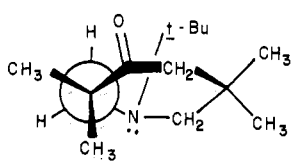


Figure 3. Uv spectra (EtOH) of **23**, ●; **3**, ♦; **42**, ▲; **11**, ■.

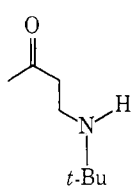
flexibility of the acyclic system at 25° [i.e., conformer **34**, Z = CH_3 (Chart I) would not permit nitrogen–carbonyl interaction].



40a (b)



41



42

To make certain that similar C-T phenomena do not occur in "anti" oriented systems, the uv spectra of **42** was taken (see Figure 3). No evidence for nitrogen–carbonyl interaction was noted in this case.

In conclusion, it seems that while steric considerations dominate the chemistry of these amines, some mixing of the nitrogen and carbonyl orbitals as determined by uv studies does exist.

Further studies on the chemistry and physical properties of these hindered amines are currently underway in our laboratories.

Experimental Section

Melting points were taken on a calibrated Mel-Temp apparatus. Infrared spectra were taken on a Perkin-Elmer 337 or 457A spectrometer; ^1H NMR spectra were recorded on a Varian A-60 or JeOL MH-100 spectrometer using Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer. Ultraviolet spectra were recorded on a Cary 14 instrument. VPC analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Bis(*n*-butoxymethyl)-*N*-*tert*-butylamine (7). Amine **7** was synthesized in 79% yield using a modification of a general procedure developed by Gaines and Swanson.[10a] Into a flask was placed

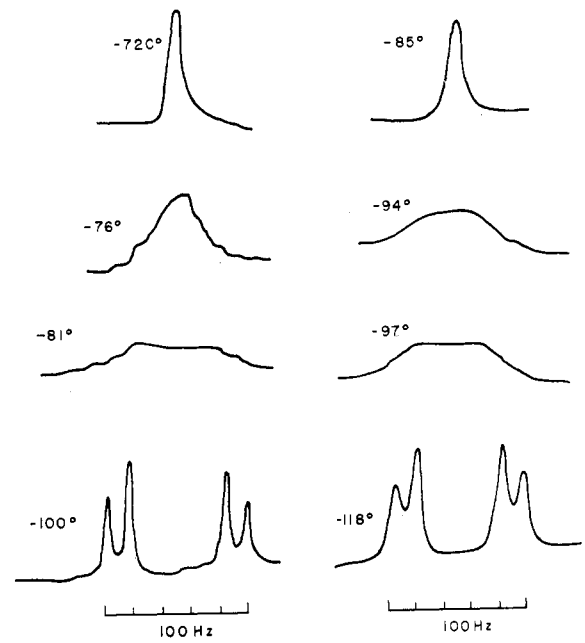


Figure 4. The dynamic ^1H NMR spectra (100 MHz) of the CH_2 groups of (A) amine **4** and (B) dialdehyde **2** (~5% v/v in vinyl chloride).

paraformaldehyde (60.0 g, 2.0 mol, CH_2=O), 1-butanol (149.7 g, 2.02 mol), and 200 ml of benzene. The mixture was warmed gently with stirring under N_2 while *tert*-butylamine (74.2 g, 1.0 mol) was added dropwise over 15 min. A Dean-Stark trap was added to the flask and the mixture was heated to reflux. After the theoretical amount of water was removed as an azeotrope (ca. 6 hr), the benzene was distilled off at 760 mm and the remaining oil was vacuum distilled to give 193.0 g of pure **7**: bp 80–83° (0.5 mm); ir (CCl_4) 2955, 2940, 2870, 1465, 1360, 1278, 1231, 1094, 1043, and 998 cm^{-1}; ^1H NMR (CCl_4) δ 0.91 (t, 6), 1.19 (s, 9), 1.42 (m, 8), 3.29 (t, 4), and 4.32 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 245 (M^+, trace), 230 (1), 173 (5), 172 (5), 159 (15), 101 (8), 100 (26), 87 (8), 86 (60), 72 (30), 70 (20), 57 (40), 56 (10), 44 (100), 43 (40), 42 (35), and 41 (70).

Diethyl *N*-*tert*-Butyl-3,3′-imino-2,2,2′,2′-tetramethyldipropionate (1). Into a dried flask containing 100 ml of dry ether under N_2 at 10° was added 8 g (0.30 mol) of Mg. While the mixture was stirred at high speed, ethyl α-bromoisobutyrate (50 g, 0.25 mol) in 200 ml of dry ether was added dropwise over 0.5 hr and the mixture was stirred at 10° until the bromo ester had reacted. Maintaining a 10° temperature, amine **7** (26.2 g, 0.11 mol) in 50 ml of ether was added to the reaction mixture over 0.5 hr. After stirring for 2 hr, allowing warming to 35° over the last 1 hr, the reaction mixture was quenched with cold aqueous ammonium chloride. An acid–base work-up gave a small amount of neutral product (ethyl isobutylisobutyrate) and 31 g of crude amine products. Careful distillation of the amine products gave 1 g of a mixture of ethyl *N*-*tert*-butyl-3-imino-2,2-dimethylpropionate and ethyl *N*-methyl-*tert*-butyl-3-imino-2,2-dimethylpropionate[7] and 29 g (83%) of amino diester **1**: bp 96–98° (0.1 mm); ir (CCl_4) 2980, 1728, 1465, 1393, 1367, 1268, 1150, 1111, 1062, and 1032 cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (s, 9), 1.09 (s, 12), 1.21 (t, 6), 2.73 (s, 4), 4.03 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 329 (M^+, trace), 328 (1), 314 (2), 214 (34), 158 (95), 112 (42), 84 (45), 57 (25), 41 (100), and metastable peaks at *m/e* 116.9 ($158^2/214$), and 79.5 ($112^2/158$).

Anal. Calcd for $C_{18}H_{35}NO_4$: C, 65.75; H, 10.65; N, 4.25. Found: C, 66.00; H, 10.93; N, 4.57.

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol (9).** Into a dry three-neck Morton flask equipped with an overhead stirrer and condenser was added 600 ml of toluene. After removal of 50 ml of toluene from the flask by distillation under a N_2 atmosphere, 3.0 g (0.13 mol) of sodium metal was added to the hot toluene and converted to a fine sand using high-speed stirring. Diester **1** (9.87 g, 0.03 mol) was then added dropwise into the flask over 1 hr and the mixture was refluxed for an additional 1 hr, at which time it was cooled and 50 ml of 5% NH_4Cl was added. The organic layer was washed with water until the water wash was neutral and the aqueous layer was backwashed with ether. The combined organic washes were dried with $MgSO_4$ and evaporated to

give 5.8 g (80%) of solid hydroxy ketone **9**, which was further purified by sublimation: mp 55–56°; ir (CCl_4) 3430, 2965, 1700, 1465, 1390, 1365, 1266, 1200, and 1039 cm^{-1}; ^1H NMR (CCl_4) δ 0.60 (s, 3), 0.91 (s, 3), 0.97 (s, 3), 1.05 (s, 9), 1.20 (s, 3), 2.56 (AB, 2, J = 12 Hz), 2.61 (AB, 2, J = 14 Hz), 3.57 (s, 1, absent in D_2O), and 4.01 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 241 (M^+, 9), 226 (43), 154 (14), 126 (14), 100 (14), 98 (14), 86 (20), 85 (40), 84 (39), 83 (20), 70 (67), 57 (100), 56 (26), 55 (36), and 41 (91); uv λ_{max} (EtOH) 290 nm (shoulder, ϵ 50), 245 (shoulder, 360).

***N-tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-5-acetoxy-4-one (10).** A mixture of 4 g (0.0165 mol) of hydroxy ketone **9**, 25 ml of acetic acid, and 25 ml of acetic anhydride was refluxed for 3 hr. Most of the solvent was evaporated from the reaction mixture under reduced pressure and the remaining liquid was poured into ice water. The aqueous solution was made basic with NaOH and extracted with ether which was dried with K_2CO_3, filtered, and evaporated, giving 4.4 g of brownish solid. The solid was sublimed, giving 4.0 g (85%) of pure **10** as a white solid: mp 86–88°; ir (CCl_4) 2960, 1740, 1710, 1470, 1360, 1240, and 1033 cm^{-1}; ^1H NMR (CCl_4) δ 0.75 (s, 3), 0.90 (s, 3), 0.96 (s, 3), 1.02 (s, 9), 1.05 (s, 3), 1.93 (s, 3), 2.49 (AB, 2, J = 12 Hz), 2.61 (AB, 2, J = 14 Hz), and 4.82 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 283 (M^+, 35), 269 (18), 268 (96), 225 (18), 224 (96), 189 (15), 168 (70), 100 (30), 98 (100), 84 (37), 70 (37), 57 (83), 56 (25), 55 (30), 43 (58), and 41 (63), with metastable ions at m/e 254 ($268^2/283$), 126, and 57; uv λ_{max} (EtOH) 288 nm (shoulder, ϵ 60), 240 (shoulder, 360).

Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.32; N, 4.95. Found: C, 68.11; H, 10.03; N, 4.80.

***N-tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptane-4,5-dione (11).** A mixture of 5.7 g (0.024 mol) of hydroxy ketone **9**, 50 ml of pyridine, and 10.5 g (0.024 mol) of lead tetraacetate was refluxed for 24 hr under N_2. The pyridine was evaporated in vacuo, leaving a brown residue. Water and ether were added to the residue and the pH of the aqueous layer was adjusted to **10.** The aqueous phase was extracted several times with ether which was dried with K_2CO_3, filtered, and evaporated. The resulting residue, a pale yellow oil, was distilled to give 3.9 g (68%) of diketone **11**, which solidified on standing: bp 73–74° (0.1 mm); ir (CCl_4) 2970, 1725 (shoulder 1700), 1475, 1390, and 1375 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (s, 12), 1.09 (s, 9), 2.62 (s, 4); mass spectrum (70 eV) m/e (rel intensity) 239 (M^+, 44), 224 (26), 196 (2), 183 (3), 168 (3), 154 (11), 139 (8), 112 (18), 100 (100), 99 (19), 85 (25), 70 (34), 57 (95), 56 (75), 55 (24), and 41 (55); uv λ_{max} (EtOH) 335 nm (ϵ 40), 300 (shoulder, 80), 242 (425).

Amino dione **11** was characterized as its quinoxaline derivative, **29**, which was synthesized in the following manner. A mixture of 0.120 g (0.5 mmol) of diketone **11** and 0.054 g (0.5 mmol) of *o*-phenylenediamine in 5 ml of acetic acid was refluxed for 3 hr. The solution was diluted with ice water, made basic with sodium hydroxide, and extracted with ether. The ether solution was dried over potassium carbonate, and the solvent was evaporated. The brown residue was recrystallized from 95% ethanol to give 0.065 g (43% yield) of **29** as yellowish-white needles: mp 109–110°; ^1H NMR (CCl_4) δ 1.20 (s, 9), 1.45 (s, 12), 2.84 (s, 4), and 7.72 (m, 4).

Anal. Calcd for $C_{20}H_{29}N_3$: C, 77.20; H, 9.39; N, 13.50. Found: C, 76.97; H, 9.27; N, 13.42.

Reduction of 9 with $NaBH_4$–EtOH. 12a and 12b. A mixture of 0.85 g (3.5 mmol) of acyloin **9**, 0.13 g (3.5 mmol) of sodium borohydride, and 20 ml of ethanol were stirred under N_2 at 25° for 2 hr and then warmed to 50° over an additional 2 hr. The ethanol was removed in vacuo and water and ether were added to the residue. The aqueous layer was extracted with ether which was dried with K_2CO_3, filtered, and evaporated to give 0.88 g (100%) of a crude solid which was shown by ^1H NMR to be a mixture of cis (**12a**) and trans (**12b**) diols (see Table I, run A). Separation of the diols by column chromatography using silicic acid with hexane–ether elution allowed isolation of pure trans and cis material. For trans diol **12b:** mp (sublimed) 140–142°; ir ($CHCl_3$) 3500, 2980, 1468, 1390, 1360, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 6), 1.02 (s, 15), 2.34 (AB, 4), 2.80 (s, 2, absent in D_2O), 3.39 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 243 (M^+, 3), 228 (38), 210 (42), 170 (7), 156 (48), 114 (10), 100 (12), 99 (10), 98 (10), 86 (37), 85 (11), 84 (28), 72 (10), 71 (14), 70 (40), 57 (72), 56 (22), 55 (37), 44 (41), 43 (87), 42 (66), and 41 (100).

Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01. Found: C, 68.72; H, 11.98.

For cis diol **12a:** mp (hexane) 140–141°; ir ($CHCl_3$) 3480, 2980, 1470, 1385, 1365, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 6), 1.07 (s, 15), 2.52 (AB, 4, J = 12 Hz) 3.41 (s, 2), and 3.50 (br s, 2, absent in D_2O); mass spectrum (70 eV) m/e (rel intensity) 243 (M^+, 10), 228 (100), 210 (4), 170 (16), 156 (47), 114 (17), 86 (28), 84 (18), 70 (18), 57 (34), 55 (12), 44 (22), 43 (25), and 41 (26).

Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01. Found: C, 69.25; H, 12.02.

Other reductions were run by adding the appropriate substrate to the appropriate solvent at the temperature specified in Table I. In run B_2, solid **9** was added to the refluxing mixture through the condenser top.

Reduction of Acetate 10 with $LiAlH_4$–THF. To 10 ml of THF containing 2 equiv of $LiAlH_4$ was added 0.28 g (0.001 mol) of **10** and the mixture was heated to reflux for 1 hr and cooled.

Standard work-up gave a near quantitative yield of cis diol **12a.**

Cis Diacetate 12c. Diol **12a** (90 mg) was refluxed for 3 hr in a 1:1 mixture of acetic acid–acetic anhydride and poured onto ice. Acid–base work-up gave 115 mg (95%) of a solid which could be sublimed or recrystallized from hexane: mp 91.5–92.5°; ir (CCl_4) 2885, 1745, 1458, 1248, and 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 6), 1.04 (s, 9), 1.06 (s, 6), 2.06 (s, 6), 2.52 (AB, 4, J = 13 Hz), 5.01 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 327 (6, M^+), 312 (100), 284 (2), 267 (22), 252 (7), 208 (5), 152 (40), 138 (5), 123 (8), 102 (7), 84 (10), 70 (22), 57 (30), 55 (10), 44 (14), 43 (49), 42 (27), and 41 (21).

Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16. Found: C, 66.27; H, 10.23.

Trans Diacetate 12d. Diacetate **12d** could not be synthesized using the procedure described to make **12c.** The following procedure was employed. Diol **12b,** 120 mg (0.5 mmol), was refluxed for 20 min in 5 ml of pyridine containing 5 ml of acetic anhydride. After cooling, the mixture was made basic with aqueous KOH and extracted with ether. Purification of the crude material by column chromatography after evaporation of solvents gave diacetate **12d** as a white solid (82% yield): mp (sublimed) 79–82°; ir (CCl_4) 2965, 1748, 1391, 1370, 1250, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 6), 0.98 (s, 6), 1.03 (s, 9), 2.02 (s, 6), 2.42 (AB, 4) and 4.97 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 327 (5, M^+), 312 (100), 284 (3), 268 (58), 252 (19), 208 (10), 152 (54), 84 (19), 70 (27), 57 (44), 56 (27), 55 (24), 44 (20), 43 (72), 42 (41), and 41 (58).

Anal. Calcd for: $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16. Found: C, 66.02; H, 10.12.

Cis Sulfite Ester 16a. To a mixture of 0.125 g (0.52 mmol) of diol **12a,** 0.107 g (1.21 mmol) of dry pyridine, and 25 ml of ether under N_2 at 0° was added dropwise 80 mg (0.68 mmol) of thionyl chloride in 5 ml of ether. After allowing the mixture to stir at 0° for 1 hr and 25° for an additional 1 hr it was poured into cold aqueous K_2CO_3 which was extracted with ether to give, after evaporation of the solvents, a crude solid. Column chromatography on silicic acid using hexene–ether elution gave pure **16a** in good yield: mp (sublimed) 85–87°; ^1H NMR ($CDCl_3$) δ 1.08 (s, 15), 1.12 (s, 6), 2.44 (AB, 4, J = 14 Hz), and 4.63 (s, 2).

Anal. Calcd for $C_{14}H_{27}NO_3S$: C, 58.09; H, 9.40. Found: C, 58.18; H, 9.41.

Trans Sulfite Ester 16b. Sulfite ester **16b** was synthesized using the procedure described to make **16a.** For **16b:** mp (sublimed) 131–132°; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 1.01 (s, 3), 1.04 (s, 9), 1.08 (s, 3), 1.11 (s, 3), 2.49 (AB, 4), 4.30 (AB, 2, J = 11 Hz).

Anal. Calcd for $C_{14}H_{27}NO_3S$: C, 58.09; H, 9.40. Found: C, 9.67; H, 58.33.

***N-tert*-Butyl-3,3'-imino-2,2,2',2'-tetramethyldipropanal (2).** A mixture of 4.31 g (0.017 mol) of diol **12a,** 4.17 g (0.018 mol) of paraperiodic acid, 100 ml of water, and 4 ml of 1 *N* hydrochloric acid was stirred for 40 hr at 25°. The solution was made basic with cold concentrated sodium hydroxide solution and extracted with chloroform. The chloroform was dried with $MgSO_4$ and evaporated, giving, after distillation, 2.64 g (62%) of dialdehyde **2:** bp 95–96° (0.25 mm); ir (CCl_4) 2965, 2680, 1726, 1467, 1390, and 1365 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (s, 9), 1.01 (s, 12), 2.75 (s, 4), and 9.60 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 241 (M^+, trace), 240 (1), 239 (1), 238 (2), 198 (5), 154 (7), 142 (5), 86 (21), 79 (10), 72 (59), 70 (58), 58 (22), 57 (79), 56 (20), 55 (19), 43 (95), and 41 (100); uv λ_{max} (EtOH) 290 nm (ϵ 55), 235 (shoulder, 320).

Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.48; H, 11.42; N, 5.73.

***N-tert*-Butyl-3,3,4,6,6-pentamethylazacycloheptane-4,5-diol (20).** A mixture of 0.75 g (3.1 mmol) of acyloin **9** in either 15 ml of dry ether or THF and 9 mmol of methyllithium was stirred for 10 hr at 25°, at which time a few milliliters of water were added and the organic layer separated. The solvent was evaporated and the crude solid remaining was recrystallized from hexane–ether, giving 0.63 g (81%) of diol **20** as a white solid: mp 122–123°; ir (CCl_4) 3300, 2965, 1470, 1391, 1368, and 1020 cm^{-1}; ^1H NMR

($CDCl_3$) δ 0.92 (s, 3), 1.02 (s, 3), 1.06 (s, 3), 1.09 (s, 9), 1.12 (s, 3), 1.17 (s, 3), 2.54 (AB, 2, J = 14 Hz), 2.57 (AB, 2, J = 13 Hz), 3.41 (broad, sharp in D_2O, 1); mass spectrum (70 eV) m/e (rel intensity) 257 (M^+, 14), 242 (100), 200 (11), 170 (52), 156 (59), 140 (21), 128 (37), 114 (17), 86 (66), 84 (43), 70 (23), 57 (49), 43 (63), and 41 (38).

Anal. Calcd for $C_{15}H_{31}NO_2$: C, 69.99; H, 12.14. Found: C, 70.17; H, 12.26.

***N*-*tert*-Butyl-3,3,4,6,6-pentamethylazacycloheptan-4-ol-5-one (21).** A mixture of 1.0 g (4.2 mmol) of dione **11**, 4.6 mmol of methyllithium, and 25 ml of dry tetrahydrofuran was stirred at 35° for several hours. After cooling, water and ether were added. The ether was dried with K_2CO_3 and filtered, and the solvents were removed in vacuo, leaving a solid which was sublimed to give 1.0 g (87%) of acyloin **21**: mp 57–60°; ir (CCl_4) 3440, 2960, 1685, 1465, 1385, 1370, 1050, and 1024 cm^{-1}; ^1H NMR (CCl_4) δ 0.71 (s, 3), 0.92 (s, 3), 1.03 (s, 3), 1.07 (s, 9), 1.24 (s, 3), 1.32 (s, 3), 2.70 (m, 4), and 4.25 (s, 1, absent in D_2O); mass spectrum (70 eV) m/e (rel intensity) 225 (M^+, 11), 240 (100), 226 (7), 171 (10), 156 (10), 154 (27), 140 (23), 126 (18), 86 (63), 85 (56), 84 (64), 71 (15), 70 (53), 57 (88), 56 (15), 55 (20), 43 (44), and 41 (38). The addition of excess methyllithium to the THF mixture did not allow isolation of diol **22** in our hands.

Reduction of 21 with $LiAlH_4$. Acyloin **21** was reduced by $LiAlH_4$ in refluxing THF to give after work-up a near quantitative yield of diol **20**.

***N*-*tert*-Butyl-3,3,4,5,6,6-hexamethylazacycloheptane-4,5-diol (22).** Into a solution of 0.15 g (0.5 mmol) of acyloin **21** (or dione **11**) in dried glyme under N_2 was added 4 equiv of methyllithium. The mixture was heated slowly to reflux over several hours and refluxed for an additional 1 hr, cooled, and quenched with cold water. The basic aqueous layer was extracted with ether which was dried with $MgSO_4$ and evaporated to give a solid residue. Sublimation gave 0.13 g (81%) of **22** as a white solid: mp 91–94°; ir (CCl_4) 3300 and 2985 cm^{-1}; ^1H NMR (CCl_4) δ 0.91 (s, 6), 1.08 (s, 6), 1.10 (s, 9), 1.14 (s, 6), 2.25 (d, 2, J = 13 Hz), and 2.99 (d, 2, J = 13 Hz); mass spectrum (70 eV) m/e (rel intensity) 271 (M^+, 6), 256 (31), 242 (31), 170 (76), 156 (24), 140 (28), 128 (57), 100 (10), 86 (100), 84 (46), 70 (20), 57 (46), 55 (15), and 43 (73).

***N*-*tert*-Butyl-4,4′-imino-3,3,3′,3′-tetramethyldibutane-2,2′-dione (3).** Diketone **3** was synthesized from diol **22** in 57% yield using the same procedure described to make dialdehyde **2**. For **3**: mp (sublimation) 60–62.5°; ir (CCl_4) 2970, 1705, 1470, 1390, 1365, 1352, 1254, and 1100 cm^{-1}; ^1H NMR (CCl_4) δ 0.94 (s, 9), 1.07 (s, 12), 2.10 (s, 6), and 2.76 (s, 4); mass spectrum (70 eV) m/e (rel intensity) 269 (M^+, trace) 183 (5), 168 (39), 156 (6), 112 (5), 110 (3), 86 (36), 84 (12), 70 (26), 57 (23), 43 (100), and 41 (33); uv λ_{max} (EtOH) 285 nm (ε 69), 235 (shoulder, 370).

Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.40; H, 11.56; N, 5.20.

***N*-*tert*-Butyl-3-imino-2,2-dimethylpropanal-4′-imino-3′,3′-dimethyl-2′-butanone (5).** Aldehyde ketone **5** was synthesized from diol **20** in 77% yield using the same procedure described to make dialdehyde **2**. For **5**: mp (sublimation) 18–19°; ir (CCl_4) 2960, 2680, 1728, 1705, 1470, 1423, 1390, 1390, 1365, 1352, 1245, and 1103 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (s, 12), 1.08 (s, 9), 2.12 (s, 3), 2.80 (s, 4), and 9.58 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 255 (M^+, none), 183 (6), 168 (23), 156 (21), 112 (5), 86 (57), 72 (24), 70 (84), 57 (72), 43 (100), and 41 (86).

Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.35; H, 11.35; N, 5.66.

Synthesis of Monohydrazone 24. To 1.2 g (5.3 mmol) of amino dione **11** in 10 ml of a 1:2 mixture of ethanol–benzene containing a few drops of acetic acid was added 2.0 g (6.2 mmol) of 98% hydrazine. The reaction mixture was heated at reflux for 10 hr at which time water was removed from the reaction mixture as an azeotrope using a Dean-Stark trap. The reaction mixture was then cooled and water was added. The resulting mixture was extracted with ether which was dried with $MgSO_4$, filtered, and evaporated to give a solid material. Recrystallization of the solid from methanol gave 0.53 g (42%) of pure hydrazone **24**: mp 78–80°; ir ($CHCl_3$) 3473, 3418, 2973, 2860, 2810, 1735, 1693, 1625, and 1032 cm^{-1}.

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-one (23).** Monohydrazone **24** (0.48 g, 1.9 mmol) was dissolved in 15 ml of dry xylene. Potassium *tert*-butoxide (0.24 g, 2.1 mmol) was added to the mixture, which was refluxed under N_2 for 5 hr. After cooling, the mixture was poured onto 50 ml of ice. The organic layer was separated and the aqueous layer was washed with ether. The combined organic washes were dried over $MgSO_4$, filtered, and evaporated to give a residue which was further purified by column chromatography using 100 mesh silicic acid. Elution with hexane–ether gave a white solid which was sublimed to give 0.20 g (42% yield) of pure **23**: mp 37–38°; ir (CCl_4) 2960, 1702, 1465, 1390, 1370, 1260, 1188, 1068, and 1042 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (s, 6), 0.97 (s, 6), 1.05 (s, 9), 2.28 (s, 2), 2.47 (s, 2), and 2.63 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 225 (M^+, 21) 211 (19), 210 (100), 154 (13), 152 (14), 140 (25), 126 (12), 125 (9), 114 (28), 85 (34), 97 (12), 84 (42), 70 (41), 57 (68), 56 (20), 55 (30), 44 (28), 43 (30), and 41 (60) (a metastable peak appears at m/e 196.5); uv λ_{max} (EtOH) 290 nm (shoulder, ε 58), 240 (shoulder, 375).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.66; H, 12.06; N, 6.22. Found: C, 74.56; H, 12.04; N, 6.14.

***N*-*tert*-Butyl-4-iminobutan-2-one (42).** *tert*-Butylamine (0.75 g, 0.011 mol) and methyl vinyl ketone (0.70 g, 0.01 mol) were stirred in 10 ml of methanol at 25° for 24 hr. The solvent was removed by careful evaporation and the crude material was distilled to give **42** as a clear oil in good yield. For **42**: bp 33–34° (2 mm); ir ($CHCl_3$) 3300, 2850, 1715, 1370, 1230, and 1168 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (s, 9), 2.08 (s, 3), 2.65 [m, 5, becomes 4 (2 partially overlapping triplets), J = 6 Hz, in D_2O]; mass spectrum (70 eV) m/e (rel intensity) 143 (1, M^+), 97 (3), 70 (3), 58 (100), 56 (20), 43 (28), 42 (22), and 41 (27); uv (EtOH) 288 nm (ε 25).

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Registry No.—**1**, 37489-09-1; **2**, 55886-30-1; **3**, 55886-31-2; **4**, 53934-35-3; **5**, 55886-32-3; **7**, 37489-08-0; **9**, 55886-33-4; **10**, 55886-34-5; **11**, 55886-35-6; **12a**, 55886-36-7; **12b**, 55886-37-8; **12c**, 55886-38-9; **12d**, 55886-39-0; **16a**, 55886-40-3; **16b**, 55923-87-0; **20**, 55886-41-4; **21**, 55886-42-5; **22**, 55886-43-6; **23**, 55886-44-7; **24**, 55886-45-8; **29**, 55886-46-9; **42**, 55886-47-0; 1-butanol, 71-36-3; *tert*-butylamine, 75-64-9; ethyl α-bromoisobutyrate, 600-00-0; o-phenylenediamine, 95-54-5; thionyl chloride, 7719-09-7; methyllithium, 917-54-4; potassium *tert*-butoxide, 865-47-4; methyl vinyl ketone, 78-94-4.

References and Notes

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(3) 1,4-Nitrogen–carbonyl interaction might be expected to vary from "not measureable" to "interaction resulting in the formation of a covalent bond". While we are unable to find specific examples of 1,4-tertiary nitrogen–carbonyl interaction in acyclic systems, it should be noted that the formation of β-lactams from β-amino acids proceeds via tetrahedral intermediates (R_3N^+–C–O^-) formed as a result of reaction of nitrogen at the carbonyl carbon.
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heptane acyloins [see N. J. Leonard et al., *J. Am. Chem. Soc.*, **76**, 630 (1954)], more recent reports on acyloin reactions involving the use of chlorotrimethylsilane as an anion trapping agent indicate that nitrogen-containing acyloins can be obtained in 90% yield: K. Ruhlmann, *Synthesis*, 236 (1971).
(18) Ground-state conformations were decided by careful examination of Buchi and space filling models and the conclusions drawn checked against experimental results obtained for related systems. (a) Cycloheptanes: J. B. Hendrickson et al., *J. Am. Chem. Soc.*, **95**, 494 (1973). (b) Azacyclooctanes: J. B. Lambert and S. A. Khan, *J. Org. Chem.*, **40**, 369 (1975).
(19) This molecule, which has been demonstrated to show activity against leukemia, has been previously synthesized by another route: P. Y. Johnson and R. Silver, *J. Heterocycl. Chem.*, 1029 (1973).
(20) Mannich and reverse Mannich reactions involving 2,2-disubstituted ketones (but not aldehydes) have been the subject of considerable debate and controversy. A discussion of this problem has been treated by G. L. Buchanan, A. C. Curran, and R. T. Wall, *Tetrahedron*, **25**, 5503 (1969), and references cited therein. *N*-Methyl dialdehyde **8** does not undergo this interesting reaction: P. Y. Johnson, unpublished results.
(21) While the particular problem of the stereochemistry of **12** could be solved using combination wet chemical–spectroscopic techniques, the frequent reoccurrence of the cis/trans diol problem in our research prompted us to seek a general, more facile approach to this problem.
(22) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962).
(23) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(24) This statement is not a violation of the Curtin–Hammett principle,[25] which states that the ratios of products from one starting material depends only on the free energy differences of the transition states, but rather reflects the cases where E_{act} is not necessarily much larger than rotational barriers [compare an E_{act} of 8–15 kcal/mol for reduction of a carbonyl with a $\Delta G^{\ddagger}$ of 9 kcal/mol for rotation in acyclic analogs of our systems (Table II)] and where the geometry of the transition state resembles that of the ground state.
(25) For a general introduction to free-energy calculations and the Curtin–Hammett principle see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965; (b) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962; (c) N. L. Allinger and E. L. Eliel, *Top. Stereochem.*, **1**, 1 (1967). For specific application of these principles to the reduction of acyclic acyloins see G. J. Karabatsos, *J. Am. Chem. Soc.*, **89**, 1367 (1967).
(26) While studies of hydride reductions of acyclic acyloins have been made [see (a) S. B. Bowlus and J. A. Katzenellenbogen, *J. Org. Chem.*, **39**, 3309 (1974); (b) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); (c) D. R. Boyd and M. A. McKervey, *Q. Rev., Chem. Soc.*, **22**, 95 (1968), and references cited therein] we are unable to find a similar treatment of hindered alicyclic acyloins.
(27) The reduction of 3,3,6,6-tetramethyl-2-hydroxycyclohexanone by $NaBH_4$ has been reported to give 82% cis diol: D. E. Applequist et al., *J. Am. Chem. Soc.*, **94**, 4272 (1972). Our approach predicts this result.
(28) Because of the geometries involved, a change in mechanism from least hindered attack to directed attack[29] would not alter this conclusion.
(29) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966).
(30) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Molecules", Holden-Day, San Francisco, Calif., 1967.
(31) (a) M. D. McCreary, D. W. Lewis, D. L., Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974); (b) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *ibid.*, **96**, 1493 (1974). For a review of this subject see R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N.Y., 1973.
(32) While shift reagents have been used for direct determination of enantiomeric composition,[31] we have found only one report, involving epoxides, concerning the use of these reagents to distinguish meso and *dl* diastereomers: M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Am. Chem. Soc.*, **94**, 5924 (1972).
(33) We have chosen to introduce this general nomenclature, since it provides a picture of our systems from which ^1H NMR spectra taken in the presence of chiral shift reagents can be predicted. Descriptions of our multifunctional systems in terms of enantiotopic and diastereotopic [K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967)] relationships are unwieldly when seeking fast, qualitative (cis or trans?) information.
(34) A more quantitative study of the application of chiral shift reagents as a method of determining the stereochemistry of diol systems is under study in our laboratories. Spectra presented (Figure 1) for **12a** and **12b** are included to demonstrate the feasibility and utility of this approach.
(35) Structures **17**, **18**, and **19**-*d* should be considered averages and do not imply knowledge of the exact nature of binding for these systems.
(36) Since the half-life of alkyllithium reagents in THF is ca. 10 min at 35° [R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972), and references cited therein], this solvent is only appropriate for alkyllithium addition reactions when the rate of addition is much faster than the rate of decomposition due to reaction with THF.
(37) The addition of methyllithium to cyclodecane-1,3-dione has been shown to give 98% cis diol: A. E. Runquist and J. A. Marshall, Northwestern University, Evanston, Ill., unpublished results.
(38) For a more quantitative treatment of related, but less hindered, *N*-*tert*-butyl-*N*,*N*-dialkylamines see (a) C. H. Bushweller et al., *J. Am. Chem. Soc.*, **96**, 3892 (1974), and references cited therein; (b) see S. Brownstein, E. Horswill, and K. U. Ingold, *J. Am. Chem. Soc.*, **92**, 7217 (1970), for a discussion of several mononeopentylamines.
(39) For comparisons of related compounds, in particular for investigations of substituent effects, measurements of $\Delta G^{\ddagger}$ are usually adequate. See L. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, **4**, 71 (1971).
(40) For the use and limitations of this approximation of $\Delta G^{\ddagger}$ see (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959; (b) for a more precise expression, see S. Alexander, *J. Chem. Phys.*, **37**, 967 (1963).
(41) See ref 25c, p 199.
(42) (a) F. Jensen et al., *J. Am. Chem. Soc.*, **91**, 344 (1969); (b) G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967).
(43) This contention is supported in part by the lower $\Delta G^{\ddagger}$ (7.6 kcal/mol) ($T_c = -112°$) (P. Y. Johnson, unpublished results) found for trineopentylamine. For the synthesis of trineopentylamine see ref 6.
(44) (a) J. Strating, S. Reiffers, and H. Wynberg, *Synthesis*, 209 (1971); (b) P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972).
(45) P. Y. Johnson, J. Zitsman, and C. Hatch, *J. Org. Chem.*, **38**, 4087 (1973).
(46) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).
(47) For examples of C-T phenomena in related systems see (a) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960); (b) N. J. Leonard, *Rec. Chem. Prog.*, **17**, 243 (1956); (c) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949); (d) C. G. Overgerger, P. Barkan, A. Lusi, and H. Ringsdorf, *J. Am. Chem. Soc.*, **84**, 2814 (1962); (e) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967); (f) G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962); (g) P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970).

Synthesis and Properties of 3-Amino-3-pyrazolin-5-ones

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The enamines, 1-amino-1-trichloromethyl-2,2-dicarboxyalkylethenes, reacted with hydrazine in DMF to yield 1-amino-1-hydrazino-2,2-dicarboxyalkylethenes (**2**) at 25° or 3-amino-3-pyrazolin-5-ones (**3**) at 100°. These heterocyclics react with acid halide and phenyl isocyanate to give mono (3-amino) or di (3-amino,5-hydroxy) derivatives. With isatoic acid, a 3-(*o*-aminobenzamido) compound can be made. Infrared and mass spectral data indicate considerable intra- and intermolecular hydrogen bonding in most of these compounds.

In a program concerned with the synthesis and pharmacological activities of certain enamines,[2,3] one of us converted these compounds into mono- and diaminopyrazoles.[3] Here we report on the synthesis and properties of several 3-aminopyrazole-5-ones, or in *Chemical Abstracts* terminology, 3-amino-3-pyrazolin-5-ones (**3**).[4a] Among the numerous patterns of substitution in this ring system, a few N-unsubstituted pyrazol-5-ones[4b] and 3-aminopyrazoles[4c] have been reported. Recently, Gillis and Weinkam have oxidized tautomers of 3,4-disubstituted pyrazolin-5-ones and