Notes

Synthetic Applications of *N*-(Acylamino)-1,3-dienes. Control of Endo Stereoselectivity by the Acyl Substituent. Stereospecific Synthesis of the Analgesic Tilidine

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Received June 18, 1979

Recent publications from our laboratory have described the preparation[2] and Diels–Alder reactions[3] of *trans*-1-*N*-(acylamino)-1,3-dienes and have illustrated the utility of these dienes for alkaloid total synthesis.[4] In this note we report that the stereochemical outcome of cycloadditions of (acylamino)-1,3-dienes with atropate dienophiles is sensitively controlled by the nature of the acyl substituent and significantly that these 1-(acylamino)-1,3-dienes exhibit endo stereoselectivities *opposite* to those of the closely related 1-(dialkylamino)-1,3-dienes.

In 1969 Satzinger reported[5a] that the clinically used analgesic Tilidine (**2**, ethyl *trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate) was the minor stereoisomer formed from the cycloaddition of *trans*-1-(dimethylamino)-1,3-butadiene (**1**) and ethyl atropate. It was also shown that the 1:3 ratio of **2** and **3** which was produced in this cycloaddition was unaffected by large changes in the solvent dielectric.[5a] In marked contrast, we find that

1, $R^1 = R^2 = Me$
4, $R^1 = H$; $R^2 = CO_2CH_2Ph$
7, $R^1 = H$; $R^2 = CO_2CH_2CCl_3$

2, $R^1 = R^2 = Me$
5, $R^1 = H$; $R^2 = CO_2CH_2Ph$
8, $R^1 = H$; $R^2 = CO_2CH_2CCl_3$
9, $R^1 = R^2 = H$

3, $R^1 = R^2 = Me$
6, $R^1 = H$; $R^2 = CO_2CH_2Ph$

the cycloaddition (110 °C, 3.5 h) of benzyl *trans*-1,3-butadiene-1-carbamate (**4**)[2c] with ethyl atropate occurs in the opposite stereochemical sense and affords the crystalline adducts **5** and **6** in yields of 71 and 20%, respectively. The stereochemistry of adduct **5** was determined by single-crystal X-ray diffraction and is shown in Figure 1. Bond lengths and bond angles are summarized in Table I. It is interesting to note that the preferred conformation of **5** in the crystalline state has the carboethoxy and acylamino substituents in the axial and pseudoaxial positions, respectively,[6] a result not unexpected in light of the reduced conformational preferences of cyclohexene allylic substituents.[7]

Remarkably, the cycloaddition (80 °C, 4 days) of 2,2,2-trichloroethyl *trans*-1,3-butadiene-1-carbamate (**7**) with ethyl atropate was stereospecific and afforded a single crystalline cycloadduct **8**, mp 145–146 °C, in 84% yield. High-pressure LC analysis failed[8] to detect the presence

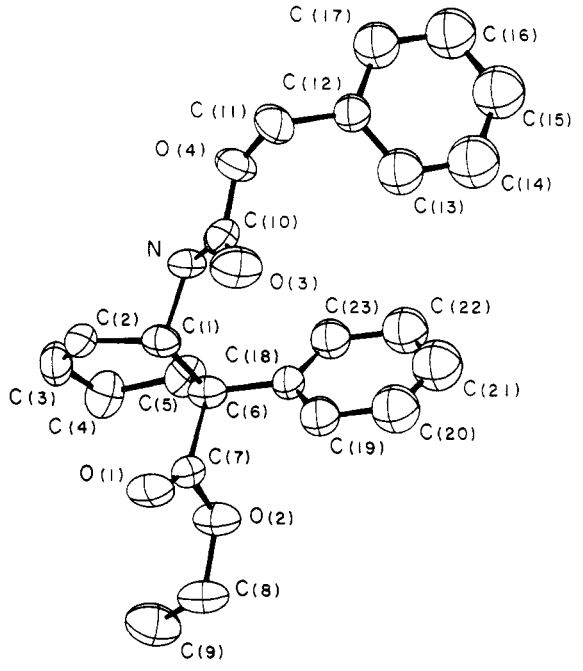

Figure 1. A view of the structure of **5**.

Table I. Selected Bond Distances (Å) and Bond Angles (degrees)[a]

C(1)-N	1.462 (7)	C(4)-C(5)	1.532 (10)
C(1)-C(2)	1.512 (9)	C(5)-C(6)	1.550 (7)
C(1)-C(6)	1.544 (8)	C(6)-C(7)	1.546 (8)
C(2)-C(3)	1.313 (9)	C(6)-C(18)	1.521
C(3)-C(4)	1.487 (10)		
C(6)-C(1)-C(2)	112.1 (5)	C(5)-C(6)-C(1)	108.3 (5)
N-C(1)-C(2)	109.0 (5)	C(5)-C(6)-C(7)	108.4 (5)
N-C(1)-C(6)	112.0 (4)	C(1)-C(6)-C(7)	107.4
C(3)-C(2)-C(1)	124.4 (6)	C(1)-C(6)-C(18)	112.0
C(4)-C(3)-C(2)	123.0 (5)	C(5)-C(6)-C(18)	112.8
C(5)-C(4)-C(3)	112.7 (6)	C(7)-C(6)-C(18)	107.6
C(6)-C(5)-C(4)	111.2 (5)		

[a] Complete tables are available in the supplementary material.

(1) Camille and Henry Dreyfus Teacher-Scholar Award Recipient, 1976–81.

(2) (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8295. (b) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089. (c) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

(3) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182.

(4) Overman, L. E.; Jessup, P. J. *Tetrahedron Lett.* **1977**, 1253; *J. Am. Chem. Soc.* **1978**, *100*, 5179.

(5) (a) Satzinger, G. *Justus Liebigs Ann. Chem.* **1969**, *728*, 64. (b) Satzinger, G. *Ibid.* **1972**, *758*, 43.

(6) A similar conformation has been suggested for Tilidine in carbon tetrachloride solution on the basis of ^1H NMR spectra.[5b]

(7) Cf. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1967**, 1417.

(8) A 30 cm × 4 mm μ Porasil column and the eluent 9:1 hexane–ethyl acetate were used for this analysis. Adducts **5** and **6** were clearly resolved by high-pressure LC.

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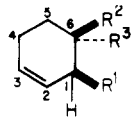
Table II. ^{13}C NMR Spectra for Substituted Cyclohexenes



compd no.	R^1	R^2	R^3	chemical shift[a] C_1	C_4	C_5	C_6
5	$NHCO_2CH_2Ph$	Ph	CO_2Et	49.7	23.0*	24.0*	53.5
6	$NHCO_2CH_2Ph$	CO_2Et	Ph	53.7	23.5	30.9	54.7
8	$NHCO_2CH_2CCl_3$	Ph	CO_2Et	50.3	23.3*	24.2*	53.6
9	NH_2	Ph	CO_2Et	50.9	22.4*	23.7*	54.5
2	$N(Me)_2$	Ph	CO_2Et	62.9	23.8*	24.3*	55.2
3[b]	$N(Me)_2$	CO_2Et	Ph	61.2	22.1	27.8	56.3

[a] In $CDCl_3$; chemical shifts are given in ppm from internal Me_4Si; assignments are consistent with the results of off-resonance decoupled spectra; assignments with an asterisk may be reversed. [b] Prepared by the method of ref 5.

of other adducts in the crude cycloaddition product. The structural assignment for 8 follows from ^{13}C NMR data (Table II) which show nearly identical ring carbon shifts for 8 and 5. This assignment was confirmed by the two-step conversion of cycloadduct 8 to Tilidine. Cleavage[9] of the amino protecting group in 8 with zinc dust in acetic acid yielded bis(normethyl)Tilidine 9, which was methylated by treatment with formaldehyde and sodium cyanoborohydride[10,11] to give Tilidine 2 in 64% overall yield from 8. To our knowledge, this represents the first stereospecific synthesis of the analgesic Tilidine.

The potential to control endo stereoselectivity in cycloadditions of *N*-(acylamino)-1,3-dienes by modifications of the acyl substituent further enhances the synthetic utility of these useful dienes.

Experimental Section[12]

2,2,2-Trichloroethyl *trans*-1,3-butadiene-1-carbamate (7) was prepared from *trans*-2,4-pentadienoic acid and 2,2,2-trichloroethanol following the in situ trapping procedure described[2c] for the preparation of diene 4. In a typical preparation, 5.7 g (58 mmol) of *trans*-2,4-pentadienoic acid[2c] was converted to a yellow solid residue which was recrystallized from hexane–ether to give 5.3 g of nearly pure 7, mp 66–68 °C. Column chromatography (silica gel; 9:1 hexane–ethyl acetate) of the recrystallization residue afforded an additional 3.7 g of pure 7, mp 70–71 °C. The combined yield of 7 was 9.0 g (63%). One recrystallization from hexane–ethyl acetate yielded material of analytical purity: mp 70–71 °C; IR (KBr) 3350, 1710, 1660, 1540, 710 cm^{-1}; ^1H NMR (CCl_4) δ 7.0–5.3 (m, vinylic and NH), 5.2–4.8 (m, $=CH_2$), 4.68 (s, CH_2CCl_3); ^{13}C NMR ($CDCl_3$) δ 150.7 (C=O), 132.8 (C-3), 124.9 (C-1), 113.3 (C-2), 112.7 (C-4), 93.8 (CH_2), 73.5 (CCl_3); mass spectrum (isobutane CI), *m/z* 248 (27), 246 (100), 244 (97), 212 (2), 210 (5), 208 (4). Anal. ($C_7H_8Cl_3NO_2$) C, H, N.

Cycloaddition of Benzyl *trans*-1,3-Butadiene-1-carbamate (4) and Ethyl Atropate. Preparation of Benzyl *trans*-6-(Ethoxycarbonyl)-*cis*-6-phenyl-2-cyclohexene-1-carbamate (5) and Benzyl *cis*-6-(Ethoxycarbonyl)-*trans*-6-phenyl-2-cyclohexene-1-carbamate (6). A solution of 4 (1.44 g, 7.09 mmol), ethyl 2-phenylacrylate[13] (ethyl atropate, 1.19 g, 6.75 mmol), 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (50 mg), and 2.3 mL of toluene was heated at reflux for 3.5 h. As the solution was cooled to room temperature, crystals of the major adduct 5 separated and were recrystallized to give 1.34 g (52%) of 5, mp 92–95 °C. Column chromatography (silica gel; 9:1 hexane–ethyl acetate) of the residue afforded two fractions. The first fraction yielded 506 mg (20%) of the minor adduct 6 (TLC R_f 0.4, 3:1 hexane–ethyl acetate), and a second fraction (TLC R_f 0.3, 3:1 hexane–ethyl acetate) gave an additional 475 mg (19%) of pure 5.

Three recrystallizations from hexane afforded an analytical specimen of the major adduct 5: mp 98–99 °C; IR (KBr) 3370, 1730, 1700, 1540, 1265, 1240, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–6.9 (m, two Ph), 6.0–5.8 (m, CH=CH), 5.3–4.9 (m, NH), 4.84 (s, CH_2Ph), 4.5–4.3 (m, CHNHCOX), 4.3–3.8 (m, nonequivalent CH_2CH_3), 1.15 (t, J = 7 Hz, CH_2CH_3); mass spectrum (isobutane CI), *m/z* 380 (18), 229 (100), 203 (20), 177 (5), 91 (71). Anal. ($C_{23}H_{25}NO_4$) C, H, N.

Three recrystallizations from hexane afforded an analytical specimen of the minor adduct 6: mp 87–88 °C; IR (KBr) 3360, 1735, 1725, 1520, 1255, 1240, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 7.3 (apparent singlet, two Ph), 5.7 (apparent singlet, CH=CH), 4.96 (s, CH_2Ph), 4.8–4.5 (m, CHNHCOX), 4.14 (q, J = 7 Hz, CH_2CH_3), 1.17 (t, J = 7 Hz, CH_2CH_3); mass spectrum (isobutane CI), *m/z* 380 (32), 229 (100), 203 (20), 152 (5). Anal. ($C_{23}H_{25}NO_4$) C, H, N.

Cycloaddition of 2,2,2-Trichloroethyl *trans*-1,3-Butadiene-1-carbamate and Ethyl Atropate. Preparation of 2,2,2-Trichloroethyl *trans*-6-(Ethoxycarbonyl)-*cis*-6-phenyl-2-cyclohexene-1-carbamate (8). A solution of 7 (201 mg, 0.818 mmol), ethyl 2-phenylacrylate (ethyl atropate, 217 mg, 1.23 mmol), 4-*tert*-butylcatechol (5 mg), and 0.8 mL of benzene was heated at 80 °C in a sealed glass ampule for 4 days. High-pressure LC[8] and ^{13}C NMR analysis of the crude product indicated that no starting diene 7 remained and that a single cycloadduct had been formed. Concentration afforded a light yellow crystalline solid which was recrystallized from hexane–ether to give 58 mg of adduct 8, mp 142–144 °C. Column chromatography (silica gel, 4:1 hexane–ethyl acetate) of the crystallization residue yielded an additional 233 mg of pure 8, mp 143–145 °C. The combined yield of 8 was 291 mg (84%). One recrystallization from hexane–ether yielded an analytical specimen: mp 145–146 °C; IR (KBr) 3360, 1740, 1709, 1530, 1235 1030, 720, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.0 (m, Ph), 5.9 (broad s, CH=CH), 5.0–5.2 (m, NH), 4.4–4.7 (m, CHNHCOX), 4.47 and 4.40 (two lines of AB q), nonequivalent CH_2CCl_3), 4.3–3.9 (m, nonequivalent CH_2CH_3), 1.16 (t, J = 7.2 Hz, CH_2CH_3); mass spectrum (isobutane CI), *m/z* 424 (1), 422 (3), 420 (3), 230 (16), 229 (100), 155 (10). Anal. ($C_{18}H_{20}Cl_3NO_4$) C, H, N.

Ethyl *trans*-2-Amino-1-phenyl-3-cyclohexene-1-carboxylate (9). A mixture of 8 (126 mg, 0.299 mmol), activated zinc dust (200 mg, 3.0 mmol, prewashed with 2% HCl, H_2O,

(9) Windholz, T.; Johnston, P. *Tetrahedron Lett.* **1967**, 2555.
(10) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.
(11) In our hands, classical Eschweiler–Clarke methylation of 9 proceeded in lower yield.
(12) Toluene and benzene were purified by distillation from CaH_2. 4-*tert*-Butylcatechol was purified by sublimation [50 °C, (0.1 mm)] and recrystallization from hexane. ^1H NMR spectra were determined with a Varian EM 360 or Brucker WH-90 spectrometer. ^{13}C NMR spectra were determined at 22.62 MHz with a Brucker WH-90 spectrometer. ^1H NMR shifts are reported as δ valves in ppm relative to internal tetramethylsilane. Coupling constants (J) are reported in Hz and refer to apparent multiplicities and not true coupling constants; abbreviations used are: s, singlet; d, doublet; t, triplet; m, complex multiplet. Infrared spectra were determined with a Perkin-Elmer Model 283 spectrophotometer. Mass spectra were determined on a Finnigan Model 4000 GC/MS/DS. Combustion analyses were obtained at Galbraith Laboratories, Knoxville, Tenn.
(13) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180. Schinz, H.; Hinder, M. *Helv. Chim. Acta* **1947**, *30*, 1349.

ethanol, and ether), and 1.5 mL of acetic acid was stirred at room temperature for 24 h and filtered; the filter cake was washed with 5 mL of acetic acid. The filtrate was concentrated, 5 mL of 2 N NaOH was added, and the amine product isolated by $CHCl_3$ extraction was dried over Na_2SO_4. Concentration afforded 67 mg (91%) of pure **9**: mp (HBr salt) 240–241 °C dec; IR (film) 3380, 1730, 1260, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (apparent s, Ph), 6.3–5.5 (m, CH=CH), 3.6–4.4 (m, $CHNH_2$ and nonequivalent CH_2CH_3), 1.10 (t, J = 7 Hz, CH_3), 0.6–1.1 (broad s, NH_2); mass spectrum (isobutane CI), m/z 246 (100), 229 (31), 155 (7).

Ethyl *trans*-2-(Dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate (Tilidine) (2). The general procedure of Borch was followed.[10] Sodium cyanoborohydride (45 mg, 0.72 mmol) was added in one portion to a stirred solution of **9** (110 mg, 0.45 mmol), formaldehyde (0.18 mL, 37% aqueous solution), and 1.4 mL of acetonitrile at room temperature. After being stirred at room temperature for 12 h, the solution was neutralized by adding acetic acid dropwise and concentrated, 5 mL of 2 N KOH was added, and the mixture was extracted (3 × 10 mL) with ether. The ether extracts were washed with 5 mL of 0.5 N KOH and extracted (3 × 5 mL) with 1 N HCl. The combined acid extracts were basified by adding solid KOH, extracted (3 × 10 mL) with chloroform, and dried (K_2CO_3). Concentration gave 86 mg (70%) of **2**: a colorless liquid which was pure by TLC and ^{13}C NMR; mp (HCl salt) 158.5–159 °C (lit.[5a] mp 159 °C).

Crystallography. Single crystals were prepared by slow crystallization from hexane–ethyl acetate. A small crystal measuring approximately 0.5 mm × 0.2 mm × 0.6 mm was cut from a larger one and mounted for data collection. The crystal was found to belong to the orthorhombic system with unit cell dimensions at 23 °C: a = 20.000 (4), b = 11.092 (2), c = 9.231 (1) Å. Systematic absences indicated that the space group was either $P2_1ab$ or $Pmab$. Intensity statistics suggested a noncentrosymmetric structure and thus indicated the space group $P2_1ab$. The measured density, 1.23 g/cm^3, agrees favorably with the calculated value of 1.22 g/cm^3 for Z = 4 molecules per unit cell. Three-dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer, using monochromatized Mo Kα radiation (λ = 0.70930 Å). The θ–2θ scan technique was used to measure the intensities of 1867 independent reflections within the range $0° < 2\theta < 50°$.[14] Of these, 1295 had $F^2 > 3\sigma(F^2)$ and were used in subsequent calculations.

The structure was solved, with considerable difficulty, by direct methods, using the MULTAN 77 system of programs.[15] The central atoms, excluding hydrogens, were anisotropically refined, using full-matrix least-squares methods. The phenyl substituents were treated as groups[16] with individual isotropic temperature factors for the carbon atoms. Phenyl hydrogen atoms were included in the groups with fixed thermal parameters at 6.5 $Å^2$; nongroup hydrogens were included at their idealized positions with fixed isotropic temperature factors. The final unweighted and weighted R values were 0.062 and 0.075, respectively. A final difference map showed no significant residual features.

Acknowledgment. This work was generously supported by a grant from the National Institutes of Health (NS-12389).

Registry No. **2**, 51931-66-9; **2**·HCl, 35481-00-6; **3**, 20380-56-7; **4**, 71616-72-3; **5**, 71616-73-4; **6**, 71616-74-5; **7**, 71616-75-6; **8**, 71616-76-7; **9**, 71656-78-5; **9**·HBr, 71656-79-6; *trans*-2,4-pentadienoic acid, 21651-12-7; 2,2,2-trichloroethanol, 115-20-8; ethyl atropate, 22286-82-4.

Supplementary Material Available: Tables I–VII of atomic positional and thermal parameters, bond distances, and bond angles (8 pages). Ordering information is given on any current masthead page.

(14) General procedures for data collection and processing have been given in Sams, D. B.; Doedens, R. J. *Inorg. Chem.* **1979**, *18*, 153. Details specific to the current analysis include: scan rate, 2.0 deg/min in 2θ; scan range, −0.9 deg from the Kα_1 peak to +0.9 deg from the Kα_2 peak; stationary background counts at each end of the scan, each for half of the scan time; p factor in the calculation of standard deviations, 0.05.

(15) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P., MULTAN 77, University of York, York, England, 1977.

(16) Doedens, R. J. In "Crystallographic Computing"; Ahmed, F. R., Ed.; Munksgaard: Copenhagen, 1970; pp 198–200.

Stereochemistry of the Protonolysis of Organoboranes

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Received June 21, 1979

The hydroboration of alkenes coupled with the protonolysis of the resultant organoboranes affords a convenient alternative to catalytic hydrogenation.[2] This sequence is particularly useful in instances in which sulfur, halogens, or nitrogen substituents are present in the alkene.

The protonolysis reaction is thought to occur with retention of configuration at the carbon attached to boron. This belief is based primarily on the facts that deuteriolysis of chiral dibutyl 1-phenylethylboronate produces chiral α-deuterioethylbenzene[3] and that the hydroboration–deuteriolysis of norbornene yields 2-*exo*-deuterionorbornane.[4] Unfortunately, the absolute configuration of the deuterioethylbenzene was not determined and consequently the question of retention vs. inversion was not decided; in addition, the use of rigid bicyclic systems in stereochemical investigations is subject to uncertainties.[5] We felt that the protonolysis of organoboranes was of sufficient importance to warrant the unambiguous determination of its stereochemistry. Nuclear magnetic resonance spectroscopy was chosen as the appropriate analytical method due to its proven utility in stereochemical investigations.[6-8]

We recently demonstrated that the hydroboration reaction proceeds via the syn addition of the boron–hydrogen moiety to an alkene.[6] Knowledge of the stereochemistry of the hydroboration reaction permits a straightforward determination of the stereochemistry of the protonolysis reaction. Thus, retention of configuration during the protonolysis of an organoborane would produce an overall syn hydrogenation of an alkene which has been submitted to the hydroboration–protonolysis sequence. Inversion of configuration during the protonolysis reaction would result in overall anti hydrogenation.

Results and Discussion

(*Z*)- and (*E*)-1-phenyl-3,3-dimethyl-1-butenes-*1,2-d_2* (**1** and **2**, respectively) were hydroborated and the intermediate organoboranes were protonolyzed. An overall syn hydrogenation (retention of configuration during protonolysis) would produce *erythro*- and *threo*-1-phenyl-3,3-dimethylbutane-*1,2-d_2* (**3** and **4**), respectively. An overall anti

(1) (a) University of Tennessee. (b) Tulane University.

(2) H. C. Brown, "Organic Synthesis via Boranes", Wiley, New York, 1975.

(3) A. C. Davies and B. P. Roberts, *J. Chem. Soc. C*, **27**, 1474 (1968).

(4) H. C. Brown and K. J. Murray, *J. Org. Chem.*, **26**, 631 (1961).

(5) Rigid bicyclic systems possess stereochemical biases which can affect the stereochemistry of the product. As an example, Larock reports that the mercuration of tri-*exo*-norbornylborane produces 93% of the *exo*-mercurial product [R. C. Larock and H. C. Brown, *J. Organomet. Chem.*, **26**, 35 (1971)]. However, Gielen reports that mercuration of an (*erythro*-3,3-dimethyl-1-butyl-*1,2-d_2*)borane proceeds with inversion of configuration [M. Gielen and R. Fosty, *Bull. Soc. Chim. Belg.*, **83**, 333 (1974)].

(6) G. W. Kabalka, R. J. Newton, Jr., and J. Jacobus, *J. Org. Chem.*, **43**, 1567 (1978).

(7) D. A. Dougherty, K. Mislow, J. F. Blount, J. B. Wooten, and J. Jacobus, *J. Am. Chem. Soc.*, **99**, 6149 (1977).

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0022-3263/79/1944-4185$01.00/0