Double Inversion of the Secondary Nitrogens in *cis*-Diaziridinocyclopentane

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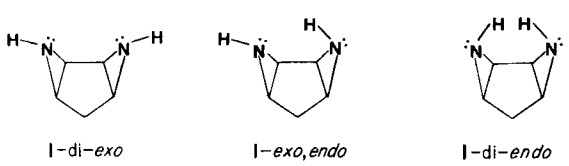
1α,2α,4α,6α-3,7-Diazatricyclo[4.1.0.0^{2,4}]heptane (*cis*-diaziridinocyclopentane) (1) has been prepared from the analogous *cis*-diepoxycyclopentane. Ring opening of the diepoxide with sodium azide produced a pair of regioisomeric azido alcohols. Tosylation and treatment with lithium aluminum hydride produced 1. The dibenzoyl derivative possessed the di-*exo* stereochemistry for the tertiary aziridine nitrogens. The ^{1}H spectrum of 1 was temperature dependent. Both the CH and NH resonances underwent decoalescence as the temperature was lowered. Because the rate was independent of concentration, the mechanism is probably inversion of the secondary nitrogen, the first such example to occur by the interchange of two diastereotopic, secondary (NH) amine nitrogens within the same molecule. The free energy of activation at coalescence (0 °C) was measured to be 12.8 kcal mol^{-1}. The unsymmetrical slow exchange of 1 is clearly consistent with the *exo,endo* stereochemistry for the secondary aziridine nitrogens, possibly stabilized by intramolecular attraction.

INTRODUCTION

Nitrogen inversion is commonly examined by NMR coalescence from diastereotopic protons on carbon, for example CH_2 or $C(Me)_2$, whose equivalence is determined by the stereochemical stability of a tertiary amine center.[1] Few examples exist of slow inversion of secondary nitrogen centers, RR'NH.[2] Many examples, of course, are known of various types of exchange in tertiary amines.[1] We exclude amide-type nitrogens in this context. To our knowledge, no example exists of the exchange between two diastereotopic protons on an amine nitrogen within the same molecule. Such an exchange requires either two non-equivalent protons on a primary nitrogen, NH_2, or two non-equivalent secondary nitrogens, NH and N'H'. We report here the first example in the second category.

To bring nitrogen inversion into an easily accessible kinetic range, we placed both secondary NH groups in aziridine rings. The *cis*-diaziridinocyclopentane molecule offers such a structure, provided that the stereochemistry of the two nitrogen centers is different, i.e. *exo,endo* rather than di-*exo* or di-*endo* (Scheme 1).

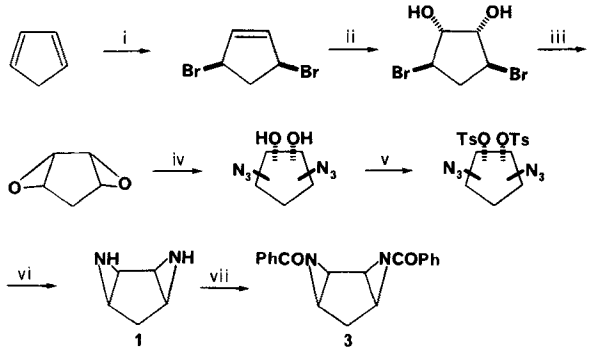


Scheme 1

We have prepared *cis*-diaziridinocyclopentane in six steps from cyclopentadiene. We report here the stereochemical analysis of this interesting molecule and of its precursors. The molecule exists as the *exo,endo* modification, and exhibits the first example of the interconversion of two diastereotopic amine NH groups within the same molecule.

RESULTS

The synthesis of 1α,2α,4α,6α-3,7-diazatricyclo[4.1.0.0^{2,4}]heptane followed the route illustrated in Scheme 2. (Our nomenclature corresponds to that used by Prinzbach and co-workers for analogous epoxycyclopentanes.[3] The prefix α denotes substituents on one side of the ring and β on the other.[4]



i, Br_2–$CHCl_3$– –35 °C; ii, $KMnO_4$–$MgSO_4$; iii NaOH; iv, NaN_3–NH_4Cl; v, TsCl–pyridine; vi, $LiAlH_4$; vii, $(PhCO)_2O$–Et_3N

Scheme 2

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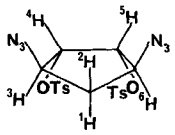
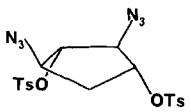
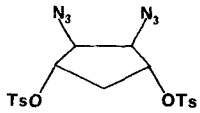


2a



2b



2c

An alternative trivial name would be *cis*-1,3-cyclopentadienediimine.) Reaction of the known *cis*-diepoxycyclopentane[4,5] with sodium azide followed by treatment of the azido alcohols with tosyl chloride yielded a mixture of tosyl azides. Ring opening of the epoxides was stereospecific, but not regiospecific. There are three possible doubly *trans* azido alcohol and azido tosylate structures (**2a–2c**) that can come from the *cis*-diepoxide. Column chromatography and fractionation revealed that the reaction produced two of the azido ditosylates, and one azido monotosylate containing an unreacted hydroxyl group. The monotosylate was easily separated by chromatography or was eliminated by a longer reaction time.

The structures of the azido tosylates were evident from the ^1H and ^{13}C NMR spectra. Isomers **a** and **c** have planes of symmetry and only three types of carbon, whereas isomer **b** lacks such symmetry and has five different carbons. The higher melting isomer has a less complex ^1H spectrum (Fig. 1a) and a three-carbon ^{13}C spectrum, indicative of one of the symmetrical isomers. The CH_2 resonance (H-1 and H-2 in **2a**) contains an AB quartet (δ 1.49 and 2.67, $J = -14.8$ Hz) with each component split into a triplet by coupling to the adjacent pair of CH protons, $J =$ 5.0 Hz in the higher field half of the AB and 8.6 Hz in the lower field half. The lowest field resonance, δ 4.50, is a doublet and must derive from the CH protons labeled H-4 and H-5 in **2a**, since these protons can couple only to a single adjacent proton. The coupling between the equivalent H-4 and H-5 might be determined from an AA'BB'XY analysis but may be indeterminate. The multiplet at δ 4.12 then must be from the CH protons labeled H-3 and H-6, with coupling to both the CH and CH_2 protons. Because the H-4 and H-5 signals are at lower field than H-3 and H-6, the more electron-withdrawing tosyloxy groups must be attached to C-4 and C-5, as in isomer **2a**, rather than **2c**.

The lower melting isomer has a more complex ^1H spectrum (Fig. 1b) and a five-carbon ^{13}C spectrum, indicative of isomer **2b**. Spectral simulation yielded all the ^1H–^1H coupling constants. The geminal coupling (1, 2) was calculated to be -15 Hz. Most of the *trans* couplings (1,6, 3,4, 4,5 and 5,6) were close to 5.2 Hz, although J(23) was about 7 Hz. The *cis* couplings (1,3 and 2,6) were about 7 Hz. Some distortion from symmetry is indicated by the unequal *trans* couplings.

The non-aromatic region of the ^1H spectrum for the dibenzoyl derivative of the diaziridinocyclopentane (**3**) bears a close resemblance to that of the *cis*-diepoxycyclopentane precursor, suggesting a similarity

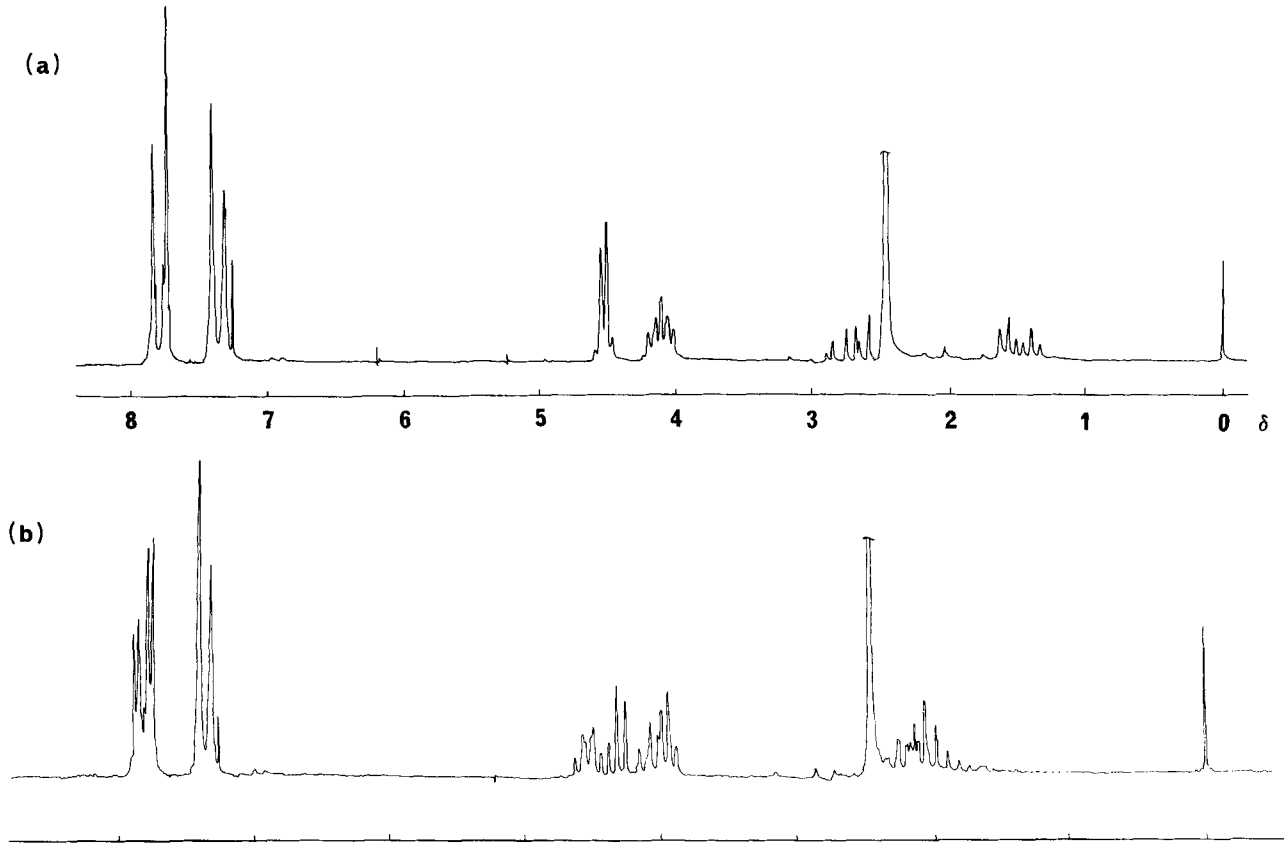


Figure 1. (a) 90 MHz ^1H spectrum of 1,2-ditosyloxy-3,5-diazido-1α,2α,3β,5β-cyclopentane (**2a**); (b) 90 MHz ^1H spectrum of 1,3-ditosyloxy-2,5-diazido-1α,2β,3α,5β-cyclopentane (**2b**).

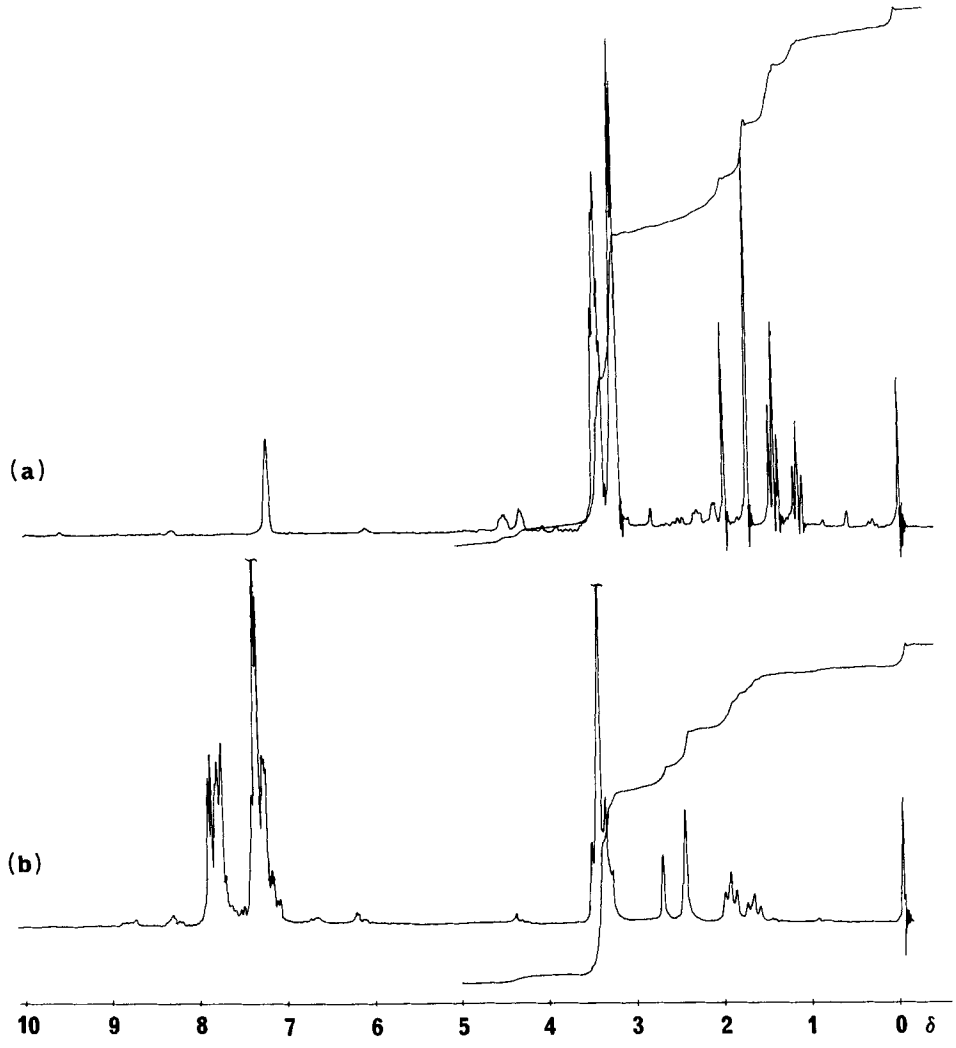


Figure 2. (a) 60 MHz ^{1}H spectrum of 1α,2α,4α,6α-3,7-dioxatricyclo[4.1.0.0^{2,4}]heptane; (b) 60 MHz ^{1}H spectrum of 3,7-dibenzoyl-1α,2α,4α,6α-3,7-diazatricyclo[4.1.0.0^{2,4}]heptane (**3**).

in symmetry (Fig. 2). The large size of the benzoyl groups prohibits population of the *endo* position, so that the dibenzoyl derivative must have the *exo,exo* structure (see **1**). Indeed, the primary spectral resemblance is in the CH_2 resonances, which in both cases consist of an AB quartet in which the lower field doublet is unsplit and the higher field doublet is split into triplets.

The ^{1}H spectrum of the diaziridinocyclopentane (**1**) in undried $CDCl_3$ at room temperature contains three singlets at δ 2.60 (CH), 1.70 (CH_2) and 1.35 (NH). The ^{1}H resonances pass through a coalescence (T_c = 0 °C for the CH resonance) and at −60 °C (Fig. 3) produce a pair of triplets for NH, a singlet with a shoulder for CH_2 and a pair of doublets for CH. The NH triplets show couplings of 8.75 Hz (higher field) and 5.2 Hz (lower field). The larger coupling, characteristic of *cis* geometry in a cyclopropane ring, defines the *exo* NH geometry; the smaller coupling, characteristic of *trans* geometry, defines the *endo* geometry. The spectrum is simplified by an almost zero coupling between the CH_2 protons and the adjacent CH protons, by the near coincidence of the CH_2 resonances and by the coincidence of some CH resonances.

Analysis of the CH coalescence yielded $\Delta G^{\neq}$ = 12.8 kcal mol^{-1}. In $CDCl_3$ that had been dried over and distilled from phosphorus pentoxide, the coalescence temperature was independent of solute concentration down to 10^{-4} M. In undried $CDCl_3$, T_c was lower. The concentration independence in dried $CDCl_3$ suggests an intramolecular process.

DISCUSSION

The first structural question concerning the diaziridinocyclopentane is whether the two three-membered rings are *cis* or *trans* to each other. The *cis* relationship, of course, is required by the expected stereospecific ring opening and ring closing steps in Scheme 2. The methylene group provides a useful monitor for this structural distinction. In all the *cis* forms, the two protons in the methylene group must be diastereotopic. In the dibenzoyl derivative of the formed compound, these two protons indeed are very different, with $\Delta\nu$ = 0.75 ppm, comparable to 0.65 ppm for the diepoxy analogue. Of the *trans*

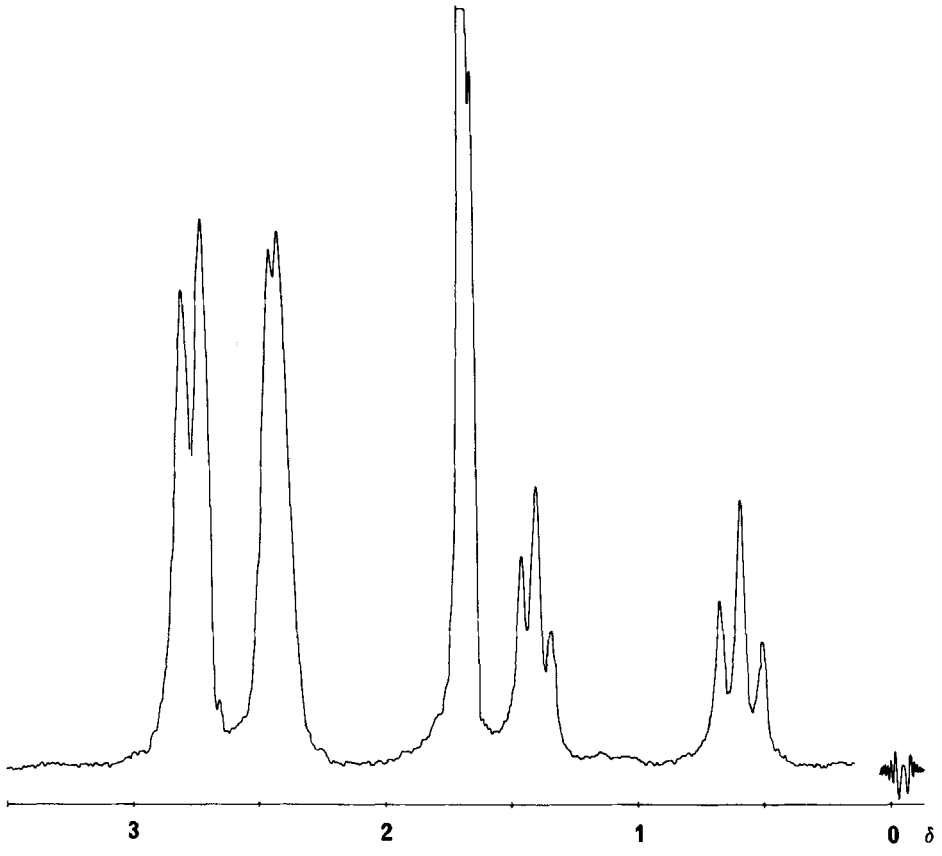


Figure 3. 100 MHz ^{1}H spectrum of 1α,2α,4α,6α-3,7-diazatricyclo[4.1.0.0^{2,4}]heptane (**1**) at −60 °C.

forms, the di-*exo* and di-*endo* have equivalent methylene protons and are excluded. Although the *exo,endo trans* form does have non-equivalent methylene protons, it is excluded as a possibility in the dibenzoyl derivative because of the steric impossibility of placing the large benzoyl group in the *endo* position. Thus, the dibenzoyl derivative **3** must be *cis* and di-*exo*. Because benzoylation should not affect the covalent bonds of the aziridine rings, it also follows that the parent NH compound **1** must be *cis*, even though the methylene protons appear fortuitously equivalent in the spectrum (Fig. 3).

The NH protons of **1** give a pair of triplet resonances at slow exchange in thoroughly dried $CDCl_3$. Apparently the vicinal couplings of each NH to the two non-equivalent CH protons are very similar, as would be expected for a rigid three-membered ring. That the NH protons give distinct resonances proves the *exo,endo* stereochemistry. Further, the higher field triplet has the larger vicinal coupling, characteristic of a *cis* HNCH relationship within the three-membered ring. The *cis* HNCH stereochemistry is possible only when the NH proton is *exo*. Similarly, the lower field, smaller coupled NH proton must have a *trans* HNCH relationship and hence be *endo*. The *exo,endo* stereochemistry may be stabilized by intramolecular hydrogen bonding, although the di-*endo* and di-*exo* forms also may be destabilized by H–H non-bonded repulsions and by dipolar repulsions.

Nitrogen inversion in **1** is slow on the NMR time scale at −60 °C. Raising the temperature brings about rapid inversion, with coalescence of the CH protons at 0 °C and of the NH protons at higher temperatures. The rate process is independent of concentration in dried $CDCl_3$. Thus the process must be nitrogen inversion, rather than intermolecular exchange. The process constitutes the first example of interchange of diastereotopic, secondary amine groups within the same molecule.

EXPERIMENTAL

Routine ^{1}H NMR spectra were obtained at 60 MHz on a Varian EM-360 spectrometer. Routine 90 MHz ^{1}H spectra, all ^{13}C spectra and spectral simulations were obtained on a Bruker HFX-72 spectrometer equipped with a Nicolet B-NC-12 computer. Variable-temperature spectra were obtained on a JEOL INM-100 spectrometer at 100 MHz. Temperatures were calibrated with the methanol standard.

1α,2α,4α,6α-3,7-Dioxatricyclo[4.1.0.0^{2,4}]heptane

3,5-Dibromo-1α,2α,3β,5β-cyclopentane-1,2-diol was prepared according to the method of Young[5] and was converted into the *cis* diepoxide by the method of Tolbert *et al.*[4]

1,2-Ditosyloxy-3,5-diazido-1α,2α,3β,5β-cyclopentane (2a) and 1,3-Ditosyloxy-2,5-diazido-1α,2β,3α,5β-cyclopentane (2b)

To 4.2 g (0.043 mol) of the *cis*-diepoxide were added 14 g (0.22 mol) of sodium azide and 23 g (0.43 mol) of ammonium chloride in 350 ml of 90% ethanol with stirring. The mixture was heated at reflux for 18 h, concentrated by rotary evaporation, dissolved in 200 ml of water, extracted with 4×70 ml of diethyl ether, dried over $MgSO_4$ and again concentrated. The oily residue of azido alcohols (7 g, 0.038 mol; 88%) was dissolved directly in 100 ml of pyridine. At 0 °C, 21.7 g (0.11 mol) of tosyl chloride were added in portions and the mixture was allowed to stand for 7 days. It was then poured on to ice water and the precipitate was filtered off, dried and chromatographed on silica gel ($CHCl_3$–EtOAc, 9:1). Two fractions were obtained with R_F 0.62 and 0.42.

The second fraction (6 g, 41%) contained only one tosyloxy group, 1-tosyloxy-3,5-diazido-1α,2α,3β,5β-cyclopentan-2-ol, and could be minimized by longer reaction times: n_D^{20} 1.5479; ^{1}H NMR ($CDCl_3$), δ 7.50 [q (J = 10 Hz), 4, arom], 4.55 (m, 1, CHOTs), 3.75 (m, 4, CHOH), 2.35 (s, 3, CH_3), 2.00 (m, 2, CH_2); IR (film), 3480 (OH), 2120 (N_3), 1360, 1200 (SO_2) cm^{-1}. Analysis for $C_{12}H_{14}N_6O_4S$: calcd., C 42.59, H 4.17, N 24.84; found, C 42.85, H 4.20 N 24.31%.

The first fraction was recrystallized from methanol to give two crops of crystals. One crop was 1,2-ditosyloxy-3,5-diazido-1α,2α,3β,5β-cyclopentane (**2a**) (4.5 g, 21.3%), m.p. 151–153 °C; ^{1}H NMR ($CDCl_3$), δ 7.50 [q (J = 12 Hz), 8, arom], 4.50 [d (J = 4 Hz), 2, CHOTs], 4.12 (m, 2, CHN_3), 2.67 [d of t (J = 5.0, 8.6, 14.8 Hz), 1, half of CH_2], 2.45 (s, 3, CH_3), 1.49 [d of t (J = 5.0, 8.6, 14.8 Hz), 1, half of CH_2]; ^{13}C NMR ($CDCl_3$), δ 145.7, 132.7, 130.1, 128.3 (arom), 80.93 (d, C-1 and C-2), 61.56 (d, C-3 and C-5), 32.69 (t, C-4) 21.71 (CH_3); IR (KBr), 2120 (N_3), 1360, 1190 (SO_2) cm^{-1}. The other crop was 1,3-ditosyloxy-2,5-diazido-1α,2β,3α,5β-cyclopentane (**2b**) (5.5 g, 26%), m.p. 103–105 °C: ^{1}H NMR ($CDCl_3$), δ 7.50 [q (J = 12 Hz), 8, arom], 4.30 (m, 4, CH), 2.45 (s, 3, CH_3), 2.10 (m, 2, CH_2); ^{13}C NMR ($CDCl_3$), δ 145.8, 133.2, 133.0, 130.3, 128.3, 128.1 (arom), 86.13, 80.73 (d, C-1 and C-3), 69.36, 62.59 (d, C-2 and C-5), 34.84 (C-4), 21.78 (CH_3); IR (KBr), 2120 (N_3), 1360, 1190 (SO_2). Analysis for $C_{19}H_{20}N_6O_6S_2$: calcd., C 46.33, H 4.09, N 17.06; found for 151–153 °C isomer, C 46.52, H 4.15, N 16.88%; found for 103–105 °C isomer, C 46.60, H 4.17, N 16.82%.

1α,2α,4α,6α-3,7-Diazatricyclo[4.1.0.0^{2,4}]heptane (1)

To 2.07 g (0.055 mol) of $LiAlH_4$ in 50 ml of tetrahydrofuran (THF) was added a solution of **2a** or **2b** or both (9 g, 0.018 mol) in 60 ml of THF below 10 °C. Stirring was continued at this temperature for 2 h and then at room temperature for 2 h. The complex was decomposed by the addition of 10% aqueous NaOH. The inorganic salts were filtered off and washed several times with THF and diethyl ether. The combined organics and the filtrate were dried over solid KOH, concentrated by rotary evaporation and distilled to give 0.8 g (47%) of the diazidocyclopentane, b.p. 78–84 °C (15 mmHg). An analytical sample was purified by preparative gas chromatography: n_D^{20} 1.5082; ^{1}H NMR ($CDCl_3$), δ 2.60 (s, 4, CH), 1.70 (s, 2, CH_2), 1.35 (s, 2, NH); ^{13}C NMR ($CDCl_3$), δ 41.66 (C-1, C-2) 31.26 (C-4, C-6), 26.64 (C-5); IR (film), 3210 (NH) cm^{-1}. Analysis for $C_5H_8N_2$: calcd., C 62.46, H 8.39, N 29.15; found, C 62.40, H 8.29, N 29.10%.

3,7-Dibenzoyl-1α,2α,4α,6α-3,7-diazatricyclo-[4.1.0.0^{2,4}]heptane (3)

To 0.04 g (0.0004 mol) of the diaziridine **1** at 0 °C in 5 ml of dry CH_2Cl_2 containing 0.1 ml of triethylamine were added 0.18 g (0.0008 mol) of benzoic anhydride. The mixture was allowed to stand in a refrigerator overnight, concentrated by rotary evaporation and chromatographed on silica gel ($CHCl_3$–EtOAc, 9:1). The fraction at R_F 0.35 was collected (0.1 g, 83%), m.p. 139–141 °C (recrystallized from $CHCl_3$–light petroleum); ^{1}H NMR ($CDCl_3$), δ 7.85 (m, 4, arom), 7.30 (m, 6, arom), 3.40 (s+m, 4, CH), 2.55 [d (J = 16 Hz), 1, C-5H], 1.75 [d of t (J = 3, 16 Hz), 1, C-5H]; ^{13}C NMR ($CDCl_3$), δ 176.55 (CO), 133.45, 132.54, 128.90, 128.45 (arom), 52.00 (d, C-1 and C-2), 41.08 (d, C-4 and C-6), 26.26 (t, C-5); IR (KBr), 3050 (CH), 1680 (C=O) cm^{-1}. Analysis for $C_{19}H_{16}N_2O_2$: calcd., C 74.97, H 5.29, N 9.20; found, C 74.85, H 5.25, N 9.15%.

Acknowledgments

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