The Synthesis and Chemistry of Some bis-Aziridinylketones and Their Spectral Study

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The synthesis and spectral characteristics of certain bis(1-alkyl-3-phenyl-2-aziridinyl)ketones are reported. The reactions of 1,2,4,5-tetrabromo-1,5-diphenyl-3-pentanone (**2**) with primary amines are assumed to have a mechanism similar to that of a simple dibromo-ketone. The so-called *cis, cis-* or *trans, trans*-configurations of the bis-aziridinylketones were determined by ^1H and ^{13}C nmr spectra.

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Results and Discussion.

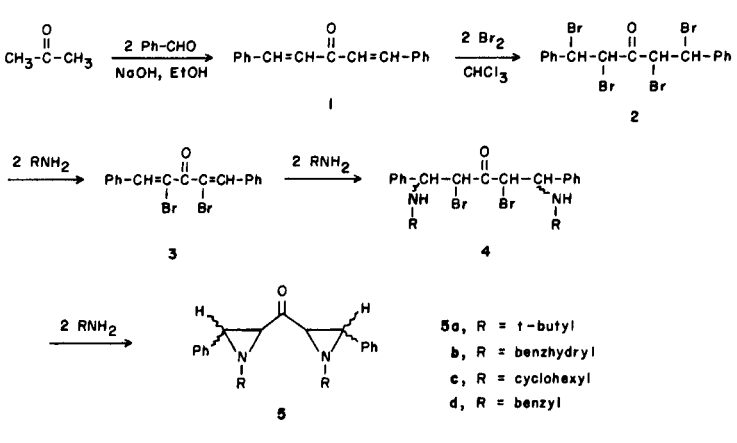
The purpose of this investigation is to develop a synthesis of several new bis-aminocarbonyl compounds which are to be tested biologically. To extend previous studies in aziridine compounds [2,3,4], we now wish to report the synthesis of a series of bis-aziridinylketones which are under investigation for anti-tumor activity [5]. It has been considered possible that such compounds might function as dialkylating agents toward DNA [6], or as diaminocarbonyl immunomodulating agents similar to the Tilorones [7].

I) The Chemistry of bis-Aziridinylketones.

Previous work has dealt with the cyclization of α,β-dibromoketones with primary amines to form aroylaziridines. By extension of our previously proposed mechanism [2,3,4] (*cf.* Scheme I), two moles of amine are believed to act as a base on the tetrabromide **2** causing two eliminations to form the bis-unsaturated ketone **3**. The next steps involve the addition of the second two moles of amine to the bis-α,β-unsaturated ketone **3** forming the bis-amino bromide **4**, which cyclizes to form the bis-aziridine **5**. Compounds **5c** and **5d** possess photochromism [8], *i.e.* they develop a pink color when exposed to light, and that coloration fades on standing in the dark.

Three possible isomers exist for each bis-aziridinylketone, however, only one isomer was found in each instance. When R is *t*-butyl, only the *cis,cis*-bis-aziridinylketone **5a** was isolated. When R is either benzyl, or cyclohexyl, or benzhydryl, the *trans,trans*-bis-aziridinylketone **5b,5c,5d** is the only product. Tarburton *et al.* [4] and Soriano [9] indicated that the 1,4-conjugate addition is not stereospecific in the system studied since both *cis-* and *trans*-α-bromochalcones produced a mixture of the *erythro* and *threo* isomers. Ring closure of a given *erythro* or *threo* diastereomer (similar to **4**) to a *cis* or *trans* isomer (similar to **5**) is believed to be stereospecific [4,9]. However, the aziridines may later isomerize under the influence of base to the most stable product. From a deuterium exchange study, Tarburton *et al.* [10] concluded that the *cis* isomer of mono-aziridinylketones is of greater thermodynamic stability. However, the attempt to convert *trans*-**5b**, **5c**, or **5d** to the *cis* isomer failed and resulted in the recovery of *trans* isomer. In the present system, a deuterium exchange study resulted in incorporation of deuterium in the carbonyl activated ring positions, under base catalysis. However, no isomerization of the starting *trans,trans*-bis-aziridine **5c** was observed. Thus, either the intermediate carbanion fails to yield epimerized product, or else starting

Scheme I



structure already is the thermodynamically stable product. The latter interpretation seems more likely. Walborsky, *et al.* found that unstabilized cyclopropyl carbanions are able to maintain their stereochemical integrity, but that activated cyclopropanes rapidly racemize under basic conditions [11].

Inspection of molecular models does suggest that unusual steric interactions are likely in the present bis-aziridines that were not present in previously studied simple aziridines. Assuming that both aziridine rings in *cis,cis*-**5b-d** occupy the bisected geometry with respect to carbonyl, models show that the β-phenyl substituents strongly interfere with one another, with the other aziridine ring, or with carbonyl, depending on the torsional state actually present (*cf.* Figure 2). In the *trans,trans*-isomers, this effect is alleviated. However, for the *N-t*-butylaziridine (**5a**), the extreme steric demands of the *t*-butyl function override other considerations. The presence of any group *cis* to *t*-butyl is prohibited, and thus phenyl and carbonyl lie *cis* to one another, and *trans* to *t*-butyl. The bisected geometry is probably not at hand in this compound.

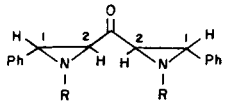


Figure 1

II. Spectral Determinations.

The structural assignments of compounds **5** were based on ^{1}H and ^{13}C nmr spectra. Previous work has shown that vicinal coupling constants lie in the ^3J = 6.5-7.5 Hz range for the *cis* isomers; in contrast to this ^3J = 2.0-3.5 Hz is found for the *trans* compounds. The ^3J of **5a** is 6.8 Hz, and thus it is a *cis,cis*-isomer. The coupling constants of the remaining three compounds **5b-d** were not resolved. The resonances for H-1 and for H-2 were somewhat broadened, possibly due to the fact that the fast exchange limit for the *N*-alkyl inversion was not present at ambient temperature (peak widths at half-height, 10, 20 and 35 Hz respectively). These broadened peaks mask the small ^3J believed to be present for these putative *trans* isomers.

Table I

^{1}H NMR Chemical Shifts

Compound	R	H-1 (ppm)	H-2 (ppm)
5a	*t*-Butyl	3.2	2.62
5b	Benzhydryl	2.97	3.33
5c	Cyclohexyl	3.19	3.35
5d	Benzyl	3.16	3.38

The structural assignments were confirmed by ^{13}C spectral determinations (Table II). Previous work showed that an additivity relationship governed the ^{13}C chemical shift of the N-Cα carbon. The existence of a steric shift term for the *trans* isomer (in which N-Cα is *cis* to the C-1 or else the C-2 substituent no matter which state of inversion of nitrogen exists) but not for the *cis* isomer (in which the N-Cα is *trans* to both C-1 and C-2 major substituents) permits facile identification of the state of isomerism. To obtain the calculated ^{13}C chemical shift value for the N-C carbon, the following equation is applied:

$$C\ (calcd) = B_C + \alpha N1 + \beta N2 + S$$

where B_C is the base value, 49.2 ppm, N1 and N2 are the numbers of carbons α or β to N-C respectively; the constant α is 6.2, and β is 3.65. The steric compression factor, S (-10.4 ppm), is applied for the *trans* isomer only [10,13]. As Table II shows, the calculated and observed chemical shifts are in good agreement for **5b-d**, thus corroborating their assignment as *trans*.

Table II

The ^{13}C Chemical Shift of Compounds **5**

Compound	R	-C=O	C-1	C-2	Cα(exp)	Cα(calcd)
5a	*t*-Butyl	201.8	42.7	44.5	53.3	—
5b	Benzhydryl	200.7	51.6	50.6	67.1	65.8
5c	Cyclohexyl	201.7	50.0	49.1	57.2	58.5
5d	Benzyl	—	49.4	48.8	53.9	52.3

The steric shift of the ring carbons should be most pronounced for *N-t*-butyl aziridines [15]. The narrow C-N-C bond angle of the aziridine ring imparts a strong conformational preference for the exocyclic *N*-alkyl substituent. Only the smallest group possible (usually hydrogen) exists gauche to the ring atoms C-1 and C-2 (*cf.*Figure 2). The similarity of the chemicals shifts of C-1 and C-2 for **5b-d** indicates that hydrogen at Cα is preferentially in the sterically constrained gauche position, and that the major substituents and N-Cα are *anti* to C-1 or C-2. However, for the *N-t*-butyl compound, **5a**, one methyl of *t*-butyl must lie in the gauche position, and a substantial steric shift for C-1 and C-2 is then observed (*cf.* Table II).

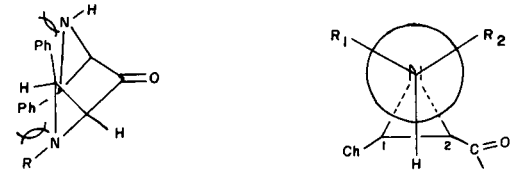


Figure 2. The effect of steric compression shift.

EXPERIMENTAL

Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analysis were performed by the Micro Tech Laboratory, Skokie, Illinois. The ^1H magnetic resonance spectra were performed by the Colorado State University NMR Regional Center using a Nicolet 360 MHz instrument. The ^{13}C spectra were determined in deuteriochloroform solution employing a Varian XL-200 spectrometer. Chemical shifts are referenced to internal chloroform-d taken as 76.9 ppm downfield from tetramethylsilane and are accurate to 0.1 ppm. Infrared spectra were obtained on a Perkin-Elmer model 283 Infrared Spectrophotometer. The high resolution mass spectra were performed by Dr. Issenberg of the University of Nebraska-Medical Center, Omaha, NE. The mass spectrometer consisted of an MS9 analyzer and solid state electronics console (Model 200, Mass Spectrometry Service). The mode of analysis was electron impact by direct insertion of sample. Ultraviolet spectra were obtained using a Hewlett-Packard 8450A UV/Vis spectrophotometer with anhydrous methanol as solvent.

1,5-Diphenyl-1,4-pentandien-3-one (**1**).

We were unable to locate a suitable reference for this synthesis, so the process reported below is based on our best estimation of the Garland and Reid [17] method.

A solution which contained 2 moles of benzaldehyde in 5 moles of ethanol was added to a one liter beaker which contained one mole of acetone. The beaker was then placed in an ice bath. Then 100 ml of 5% (w/w) of sodium hydroxide was added slowly. The beaker remained on the ice bath for 10 minutes after the completion of the sodium hydroxide addition. After it stood for another hour, 200 ml of ethyl ether was added. Filtration of this mixture was followed by washing the crystals a few times with 100 ml portions of ethyl ether giving 147 g (55%) of the yellow product, mp 118°.

1,2,4,5-Tetrabromo-1,5-diphenyl-3-pentanone (**2**).

Again, the process reported below is based on our best estimation of the literature report of Poggi and Guastalla's [18] method.

A solution which contained 41 g (0.26 mole) of bromine in 200 ml of chloroform was added dropwise into a one liter flask which contained 40.0 g of **1** in 200 ml of chloroform. After the completion of the addition, the mixture was stirred for another hour. An amount of 200 ml of ethyl ether was added and the solution was cooled to 0°. Filtration gave 60.0 g (61%) of **2** as white crystals, mp 184°.

bis(1-*t*-Butyl-3-phenyl-2-aziridinyl)ketone (**5a**).

To a suspension of 25.0 g (0.045 mole) of **2** in 200 ml of benzene was added 20.0 g (0.27 mole) of *t*-butylamine. The mixture was placed in a refrigerator. After one week, the salts formed were removed by filtration. Benzene was then evaporated from the filtrate under reduced pressure and 200 ml of the petroleum ether was added to precipitate the unreacted tetrabromide **2** or the *t*-butylamine hydrobromide which was supersaturated in benzene. The dark-brown substance was filtered and the petroleum ether filtrate was cooled for 2 days in the ice-chest. Filtration gave white crystals which were then dissolved in a 200 ml amount of ethanol. The solvent was reduced to about 50 ml by using a vacuum pump, and the residue stood for a couple of days to allow the crystals to form. Filtration gave 1.5 g (8.8%) of **5a**, mp 123°; ir (nujol): 1671 cm^{-1} (carbonyl -C=O); uv (methanol): 271 nm, 293 nm; nmr (deuteriochloroform): 7.2-7.4 (c, 10, Ph), 3.2 (d, 2, -C(C=O)H-), 2.6 (d, 2, -CH-), 0.84 (s, 18, *t*-butyl); ms: (50 eV), m/e Calcd. for $C_{25}H_{32}N_2O$: 376.251; Found: 376.252.

Anal. Calcd. for $C_{25}H_{32}N_2O$: C, 79.74; H, 8.57; N, 7.40. Found: C, 79.39; H, 8.50; N, 7.31.

bis(1-Benzhydryl-3-phenyl-2-aziridinyl)ketone (**5b**).

To a suspension of 14.5 g (0.026 mole) of **2** in 200 ml of benzene was added a mixture which contained 30.0 g (0.157 mole) of benzhydrylamine in 200 ml of benzene. The mixture was stirred at room temperature for five days. After removal of the salts formed, the benzene solution was evaporated under reduced pressure and the trace of volatile materials were removed using a vacuum pump. A 75 ml amount of anhydrous ethyl ether was added to remove benzhydrylamine hydrobromide which was supersaturated in benzene. After removal of salts, the filtrate was cooled overnight in the ice chest. Filtration gave 2 g of white crystals which was the crude product **5b**. The crude product was then recrystallized by using hot hexane to produce 1.4 g (9.0%) of pure product, mp 152-153°; ir (nujol): 1678 cm^{-1} (carbonyl -C=O); uv (methanol): 273 nm; nmr (deuteriochloroform): 6.95-7.40 (c, 30, Ph), 5.06 (d, 2, -NCH-), 3.33 (s, 2, -C(C=O)H-), 2.97 (s, 2, -CH-); ms: (50 eV), m/e Calcd. for $C_{43}H_{36}N_2O$: 596.283; Found: 596.282.

Anal. Calcd. for $C_{43}H_{36}N_2O$: C, 84.54; H, 6.08; N, 4.69. Found: C, 84.59; H, 6.15; N, 4.78.

bis(1-Cyclohexyl-3-phenyl-2-aziridinyl)ketone (**5c**).

At room temperature tetrabromo-di-benzalacetone (**2**) was allowed to stand with 6 moles of cyclohexylamine using benzene as the solvent, for two days. After removal of the salts formed, the benzene solution was concentrated under reduced pressure and the traces of volatile materials were removed using a pump.

Isolation of **5c** was accomplished by addition of petroleum ether to the residue above followed by crystallization of the solid obtained from methanol affording 1.2 g (15%) of colorless crystals (unstable in light), mp 120°; mp (nujol): 1662 cm^{-1} (carbonyl -C=O); nmr (deuteriochloroform): 7.29 (s, 10, Ph), 3.35 (s, 2, -(C=O)-CH-), 3.19 (s, 2, -CH-), 2.76 (b, 2, -CH-N-), 1.22-1.76 (c, 20, cyclohexyl); ms: (50 eV), m/e Calcd. for $C_{29}H_{36}N_2O$: 428.283; Found: 428.286.

Anal. Calcd. for $C_{29}H_{36}N_2O$: C, 81.26; H, 8.47; N, 6.54. Found: C, 81.47; H, 8.52; N, 6.35.

bis(1-Benzyl-3-phenyl-2-aziridinyl)ketone (**5d**).

The same procedure as for the synthesis of **5c** was applied. Isolation of **5d** was accomplished by addition of methanol, to the residue followed by recrystallization of the solid obtained from methanol giving 1.47 g (17%) of colorless crystals (unstable in light), mp 120°; ir (nujol): 1659 cm^{-1} (carbonyl -C=O); uv (methanol): 272 nm, 312 nm; nmr (deuteriochloroform): 7.22-7.34 (s, 20, Ph), 4.02, 4.25 (d, 4, -N-CH-), 3.38 (s, 2, -(C=O)-CH-), 3.16 (s, 2, -CH-); ms: (50 eV), m/e Calcd. for $C_{31}H_{28}N_2O$: 444.220; Found: 444.219.

Anal. Calcd. for $C_{31}H_{28}N_2O$: C, 83.75; H, 6.35; N, 6.30. Found: C, 83.94; H, 6.36; N, 6.20.

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[13a] This equation and all the parameters were copied from Tarburton *et al.*, see reference [10] for detail; [b] This equation is not suitable for a *t*-*N*-alkyl substituent.

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