# 1,13-Diazabicyclo[11.1.1]pentadecane-14,15-dione and 1,12-Diazabicyclo[10.1.1]tetradecane-13,14-dione. Two Novel Aliphatic Diisocyanate Dimers

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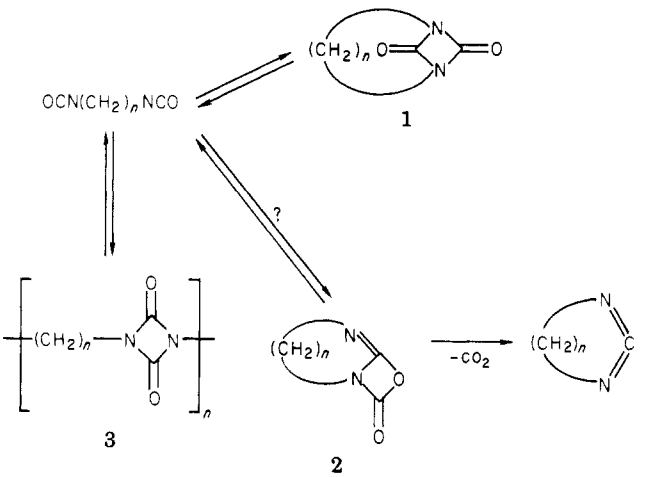
The intramolecular cyclodimerization of aliphatic diisocyanates with the general formula $OCN(CH_2)_nNCO$, in which the two isocyanate moieties are separated by a sufficient number of $CH_2$ groups, could theoretically lead to products of type **1** and/or **2** (Scheme I). All dimerizations of aliphatic and aromatic monoisocyanates known to date have been found to yield only 1,3-diazetidinediones ("symmetric dimers" **1**).[1] The formation of "asymmetric dimers" **2** in which the C=O group of an isocyanate participates in the ring formation is not known, although compounds of this type are believed to be intermediates in the uncatalyzed formation of carbodiimides from isocyanates.[2]

Although it is unlikely that 1,3-diazetidinediones of type **1** can be obtained directly in reasonable yields from the parent diisocyanates as formation of polymeric products (**3**) would predominate, their synthesis is of interest as they constitute potentially useful building blocks of polyurethanes with commercial value. In fact, they are the simplest form of masked aliphatic diisocyanates which could be converted back into diisocyanates by being heated above their dissociation point.

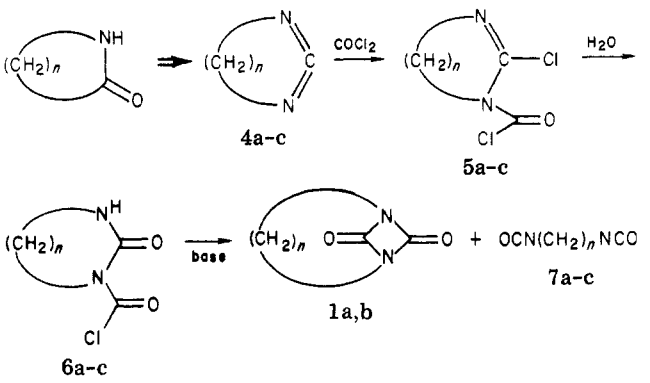
A promising route leading to **1** involves the dehydrohalogenation of allophanyl chlorides. Compounds of this type are best prepared by a method reported recently involving the addition of phosgene to carbodiimides (prepared by ring expansion of lactams)[3] followed by mild hydrolysis of the formed *N*-(chlorocarbonyl)chloroformamidine intermediates.[4] This method of preparing allophanyl chlorides is superior to the one based on reacting ureas with phosgene since attack of the latter at the carbonyl oxygen of the urea can lead to chloroformamidinium salts as side products.[5] Allophanyl chlorides have been converted successfully into 1,3-dialkyl or 1-alkyl-3-aryl-1,3-diazetidinediones.[4,6-8] Reacting 1,3-diazacyclotetradeca-1,2-diene (**4a**, $n$ = 11) with excess phosgene in methylene chloride solution (Scheme II) leads cleanly to the *N*-(chlorocarbonyl)chloroformamidine **5a** [not isolated; IR 1740, 1670 $cm^{-1}$ (C=O, C=N)] which on hydrolysis in acetone/water gives a 96% yield of allophanyl chloride **6a**.

The subsequent treatment of a chloroform solution of **6a** with excess triethylamine at room temperature yields a mixture of 1,11-diisocyanatoundecane (**7a**) and 1,13-diazabicyclo[11.1.1]pentadecane-14,15-dione (**1a**). The reaction take approximately 7-15 days for completion, depending on the amount of base used. On following the reaction by infrared spectroscopy, formation of **1a** is indicated by appearance of a band at 1765 $cm^{-1}$ (C=O of the 1,3-diazetidinedione) while **7a** shows a N=C=O band at 2180 $cm^{-1}$; at the same time, the carbonyl band characteristic of **6a** at 1725 $cm^{-1}$ disappears. The reaction is accompanied by formation of a small amount of a brown, resinous material (approximately 7%) which can be separated by treatment of the product mixture with *n*-hexane. VPC analysis showed that **1a** and **7a** are formed in a ratio of 1:2, although complete separation of both products proved difficult. Most of the solid dimer can be isolated by filtration; however, some **1a** remains dissolved in the diisocyanate and cannot be removed. Attempted distillative separation resulted in co-distillation of both products.

Scheme I




Scheme II




The reaction of the allophanyl chloride **6b** ($n$ = 10) derived from 1,3-diazacyclotridecane-1,2-diene (**4b**) with triethylamine under similar conditions affords the corresponding 1,12-diazabicyclo[10.1.1]tetradecane-13,14-dione (**1b**) in an isolated yield of 6%. The major product in this case is also the corresponding alkylene diisocyanate **7b** ($n$ = 10). When the reaction is followed by IR spectroscopy over a period of 10 days, it can be seen that the dimer **1b** and the diisocyanate **7b** are formed at a constant rate. It became apparent that smaller ring allophanyl chlorides favored formation of diisocyanate over dimer. The ten-membered-ring carbodiimide **4c**, derived from 2-azacyclononanone, was converted into the corresponding allophanyl chloride **6c** and treated with triethylamine. This reaction gave only diisocyanate **7c** (aside from small amounts of brown resin) which could be isolated in 84% yield; IR spectra taken during the reaction gave no evidence for the formation of **1c**. This result was expected; Dreiding models easily show that a bicyclic system having a nearly planar 1,3-diazetidinedione ring is difficult to

(1) For a review see: Richter, R.; Ulrich, H. In "The Chemistry of Cyanates and Their Thio Derivatives", Patai, S., Ed.; Wiley: Chichester, England, 1977; pp 667-674.
(2) Campbell, T. W.; Monagle, J. J.; Foldi, V. S. *J. Am. Chem. Soc.* **1962**, *84*, 3673.
(3) A description of the synthesis and chemistry of several cyclic carbodiimides will be published at a later date.
(4) White, D. K.; Greene, F. D. *J. Org. Chem.* **1978**, *43*, 4530.
(5) Ulrich, H.; Tilley, J. N.; Sayigh, A. A. R. *J. Org. Chem.* **1964**, *29*, 2401.
(6) Koenig, K. H.; Fischer, A.; Zeeh, B.; to BASF A-G. German Offen. 2027345, 1971; *Chem. Abstr.* **1972**, *76*, 72500.
(7) Johnson, H. E.; to Union Carbide. U.S. Patent 3671500, 1972; *Chem. Abstr.* **1972**, *77*, 75833.
(8) D. S. Gilmore Laboratories, unpublished results.

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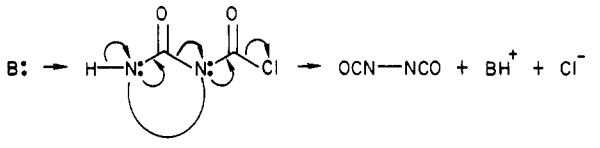
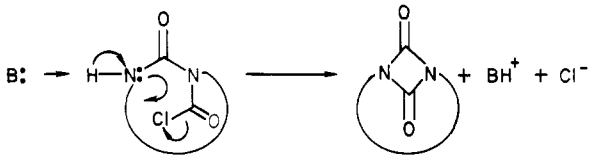
accomodate with an alkylene bridge consisting of only seven carbon atoms. These models also show that the formation of four-membered rings of type 1 from allophanyl chloride precursors requires a fair amount of flexibility in the alkylene chain. Only rotation of the alkylene chain into a favorable conformation in relationship to the chlorocarbonyl group will allow the formation of a four-membered ring, other rotamers favor formation of diisocyanate. A simplified representation of allophanyl chloride isomers, A and B, as shown below, illustrates the

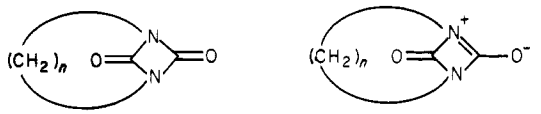


A



B

experimental results. These models show that restricted rotation due to shorter alkylene chains connecting the two nitrogens will force the molecule to assume a conformation as represented by A. Furthermore, it can be argued that a shortening of the alkylene chain will cause a destabilization of these bicyclic ureas due to limitations in the formation of resonance forms such as 1′ with double bonds



1 1′

shifted into the four-membered ring. Aspects of the stability of bicyclic lactams, urethanes, and ureas with bridgehead nitrogen atoms have been studied in the context with the Bredt rule.[9-13]

The novel aliphatic diisocyanate dimers are crystalline compounds which are stable at room temperature. Heating of **1a** in *o*-dichlorobenzene at 160–165 °C produced the diisocyanate **7a** cleanly, although the reaction requires 7.5 h to be complete. This indicates that the dimers, once formed, are relatively stable. The unbridged 1,3-diethyl-1,3-diazetidine-2,4-dione dissociates under comparable conditions (6 h, 165–170 °C, *o*-dichlorobenzene) to give ethyl isocyanate as the sole product.

The monomeric structure of **1a** was confirmed by X-ray analysis, details of which will be published elsewhere. The $^1$H NMR spectra of **1a,b** show unresolved broad multiplets for the methylene protons between $\delta$ 1.2 and 1.8 in addition to triplets centered around 3.2 ppm for the methylene protons adjacent to the nitrogens. The $^{13}$C NMR spectrum of **1a** shows a signal for the carbonyl carbon at $\delta$ 158.16 downfield from $Me_4Si$. This position is nearly identical with the one recorded for 1,3-diethyl-1,3-diazetidine-2,4-dione at 158.04 ppm.[8] IR spectra of **1a,b** show the $\nu$(CO) bands at 1755 cm$^{-1}$ (strongest bands in the spectra), a position which is not very much different from that for other monocyclic 1,3-dialkyl-1,3-diazetidine-2,4-diones, which generally show bands between 1763 and 1750 cm$^{-1}$; only the 1,3-dimethyl (1778 cm$^{-1}$) and several 1,3-dibenzyl derivatives (1770–1775 cm$^{-1}$) have been reported to absorb at higher frequencies.[4,14,15]

## Experimental Section[16]

**General Procedure for the Preparation of *N*-(Chlorocarbonyl)-*N*,*N*′-alkylene Ureas (Allophanyl Chlorides) 6a–c.** To an ice-cold solution of 0.05 mol of **4** (**a–c**) in 20 mL of methylene chloride is added over a period of 5 min a solution of 10.0 g (0.1 mol) of phosgene in methylene chloride. An exothermic reaction ensues which is complete within a few minutes as indicated by disappearance of the band at 2160 cm$^{-1}$ (N=C=N) in the IR spectra of the reaction solutions. Solvent and excess phosgene are removed in vacuo, leaving colorless oils of **5a–c** which show characteristic IR bands in the double bond region at 1740 and 1670 cm$^{-1}$ ($CHCl_3$). The crude products are taken up in 30 mL of acetone. After water (3–4 mL) is added to the onset of turbidity, the solutions are set aside for 18–20 h. Removal of solvent and drying the solid residues in vacuo over calcium chloride leaves crude **6a–c**, which are further purified for analysis by recrystallization from *n*-hexane. This occasionally leaves small amounts of impurities (yellowish oil) undissolved.

**6a** (***n*** **= 11**): 97% yield; mp 65–67 °C; IR ($CHCl_3$) 1725 cm$^{-1}$ (C=O). Anal. Calcd for $C_{13}H_{23}ClN_2O_2$: C, 56.82; H, 8.44; N, 10.19; Cl, 12.90. Found: C, 57.06; H, 8.26; N, 10.16; Cl, 13.10.

**6b** (***n*** **= 10**): 82% yield; mp 72 °C; IR ($CHCl_3$) 1725 cm$^{-1}$ (C=O). Anal. Calcd for $C_{12}H_{21}ClN_2O_2$: C, 55.28; H, 8.11; N, 10.74; Cl, 13.60. Found: C, 55.24; H, 8.17; N, 10.74; Cl, 13.56.

**6c** (***n*** **= 7**): 93% yield; mp 147–148 °C dec; IR ($CHCl_3$) 1720 cm$^{-1}$ (C=O). Anal. Calcd for $C_9H_{15}ClN_2O_2$: C, 49.43; H, 6.91; N, 12.80; Cl, 16.21. Found: C, 49.18; H, 7.03; N, 12.74; Cl, 16.36.

**(1) 1,13-Diazabicyclo[11.1.1]pentadecane-14,15-dione (1a) and 1,11-Diisocyanatoundecane (7a).** A solution of 8.25 g (0.03 mol) of allophanyl chloride **6a** and 10 g (0.1 mol) of triethylamine in 100 mL of chloroform is kept at room temperature for 4 days after which an additional 5.0 g (0.05 mol) of triethylamine is added. During the course of the reaction, the solution turns pale brown. IR spectra indicate the disappearance of starting material while bands appear that are characteristic of **1a** (1760 cm$^{-1}$) and **7a** (2280 cm$^{-1}$). After a total of 7 days, the solvent is removed in vacuo, and the obtained residue is treated with 100 mL of *n*-hexane, leaving triethylamine hydrochloride and a brown resinous material undissolved. After filtration, the pale yellow filtrate is concentrated in vacuo, yielding a mixture of crystals and liquid totaling 6.7 g (93%) of **1a** and **7a**. VPC analysis (glass column, 50 °C) of the mixture gave a ratio of approximately 65% of **7a** and 35% of **1a**. This determination allows for a 9–10% dissociation of **1a** to **7a** which occurs during the analysis. In order to partially isolate **1a** from the product, the material is cooled in an ice bath an filtered quickly, leaving 1.15 g (15%) of colorless crystals of **1a**. A sample is recrystalled for analysis from *n*-hexane; colorless crystals, mp 93–94 °C; mol wt (by vapor pressure osmometry in $CHCl_3$) 240 (calcd 238). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.66; H, 9.43; N, 11.76.

The filtrate consists of a mixture of **1** and **7a**. Vacuum distillation at 114–115 °C (0.01 mm) gave **7a** which was contaminated by codistilling **1a**. Repeated distillation finally gave a small sample of **7a** free of dimer; bp 112–114 °C (0.01 mm). This material was identical on IR comparison with a sample obtained according to a literature procedure[17] from 1,11-diaminoundecane.

**(2) 1,12-Diazabicyclo[10.1.1]tetradecane-13,14-dione (1b) and 1,10-diisocyanatodecane (7b)** are prepared by the same method. From 6.90 g (0.026 mol) of **6b** is obtained 0.39 g (6.5%)

(9) (a) Hall, H. K., Jr.; El-Shekeil, Ali *J. Org. Chem.* **1980**, *45*, 5325. (b) Hall, H. K., Jr.; Shaw, R. G., Jr.; Deutschmann, A. *Ibid.* **1980**, *45*, 37.
(10) (a) Pracejus, H. *Chem. Ber.* **1959**, *92*, 988. (b) Pracejus, H. *Ibid.* **1965**, *98*, 2987.
(11) Pracejus, H.; Kehlen, M.; Kehlen, H.; Matschiner, M. *Tetrahedron* **1965**, *21*, 2257.
(12) Yakhontov, L. N. *Usp. Khim.* **1969**, *38*, 1038.
(13) Yakhonton, L. N.; Rubtsov, M. V. J. *Zh. Obshch. Khim.* **1957**, *27*, 72; *Chem. Abstr.* **1957**, *51*, 12085.
(14) Kuhn, N.; Schwarz, W.; Schmidt, A. *Chem. Ber.* **1977**, *110*, 1130.
(15) Richter, R.; Ulrich, H. *Synthesis* **1975**, 463.
(16) Melting points were taken with a Fisher-Johns melting point apparatus, and elemental analyses were by Galbraith Laboratories. Spectra were recorded by using the following instruments: Beckman Acculab 4 (IR), Varian T-60 ($^1$H NMR), and Varian CFT-20 ($^{13}$C NMR).
(17) Siefken, W. *Justus Liebigs Ann. Chem.* **1949**, *562*, 75.

of **1b**: mp 98–99 °C (*n*-hexane); colorless needles; IR ($CHCl_3$) 1755 $cm^{-1}$; mol wt (by vapor pressure osmometry in $CHCl_3$) 226 (calcd 224). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.52; H, 9.07; N, 12.51. The liquid fraction consisted mainly of **7b** and small amounts of **1b**.

**1,7-Diisocyanatoheptane (7c)** was obtained in 84% yield [11.5 g; bp 75–78 °C (0.01 mm); identical on IR comparison with an authentic sample prepared according to a published procedure[17]] from 16.45 g (0.525 mol) of **6c** and 20 g (0.2 mol) of triethylamine in 200 mL of chloroform within 18 h at room temperature.

**Registry No. 1a**, 79568-33-5; **1b**, 79568-34-6; **4a**, 72995-04-1; **4b**, 79568-35-7; **4c**, 6543-91-5; **5a**, 79568-36-8; **5b**, 79568-37-9; **5c**, 79568-38-0; **6a**, 79568-39-1; **6b**, 79568-40-4; **6c**, 79568-41-5; **7a**, 78980-33-3; **7b**, 4538-39-0; **7c**, 18020-78-5.

## Synthesis and Structural Assignments for ("1*R*-*anti*")- and ("1*R*-*syn*")-1-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.1.1]heptan-7-ol

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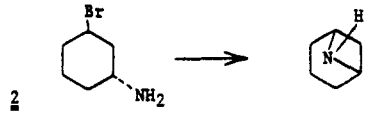
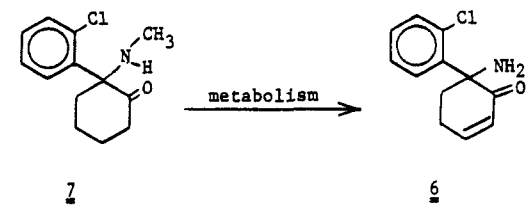
The only reported example of the 6-azabicyclo[3.1.1]-heptane ring system is the parent compound 1 reported by von Braun et al. in 1928.[1] It was prepared by an intramolecular displacement of bromine from *trans*-3-bromocyclohexanamine (2, eq 1).




2 1 (1)

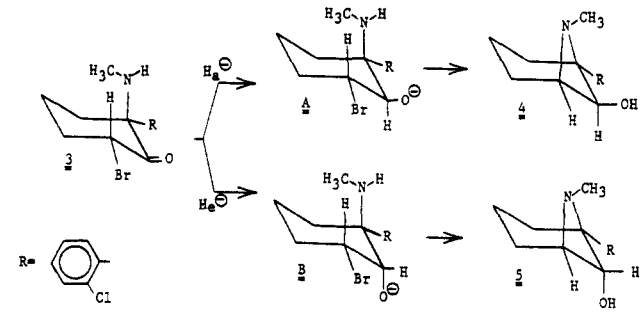
As part of our attempt to synthesize metabolite II (6)[6] of ketamine (7,[2] Scheme I), a sodium borohydride reduction was carried out on 2-bromo-6-(2-chlorophenyl)-6-(methylamino)cyclohexanone (3). This reaction gave a mixture of the title compounds (4 and 5). The bromine substituent of 3 had been previously established as having the equatorial conformation.[3] Therefore, the delivery of a hydride ion axial or equatorial at the carbonyl carbon

Scheme I




7 6

Scheme II

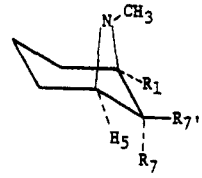



leads to the formation of the alkoxide anions A and B, respectively (Scheme II). The resulting change in hybridization at C-1 from $sp^2$ to $sp^3$ alters the overall conformation of the molecule, allowing the electrons on nitrogen to displace bromine in an intramolecular $S_N2$ reaction. Subsequent protonation of the anions afforded a mixture of the two isomers (4 and 5) which were separated by fractional crystallization.

Initial structural assignments can be made by analogy with the bicyclo[3.1.1]hept-2-ene[4] and bicyclo[3.1.1]heptane[5] ring systems which have been previously described. These workers have established that the coupling constant for $H_{5,7}$ is very small ($J \simeq 0$ Hz) while that of $H_{5,7'}$ is comparatively large ($J \simeq 6$ Hz). The parameters describing the pertinent protons of the two aza isomers of the bicyclo[3.1.1]heptane ring system are summarized in Table I.

A deuterium oxide exchange established the position of the labile hydroxy protons and their effect on the multiplicity of the other protons in the spectrum. This essentially established the structural assignments for the two isomers since the proton in 4 at $\delta$ 2.68 (d, 1 H, $J$ = 9 Hz) was exchanged and the proton at $\delta$ 4.63 (d, 1 H, $J$ = 9 Hz) collapsed to a singlet. This strongly indicated that the

Table I. Some $^1$H NMR Data of the Two Aza Isomers 4 and 5




| 4 ($R_{7'}$ = OH, $R_7$ = H) | | 5 ($R_{7'}$ = H, $R_7$ = OH) | |
|---|---|---|---|
| atom | shift, $\delta$ | atom | shift, $\delta$ |
| $H_5$ | 3.48 (unresolved m, 1 H) | $H_5$ | 3.73 (m, 1 H) |
| $R_7$ H | 4.63 (d, 1 H, $J$ = 9 Hz) | $R_{7'}$ H | 4.40 (d, 1 H, $J$ = 6 Hz) |
| $R_{7'}$ OH | 2.68 (d, 1 H, $J$ = 9 Hz) | $R_7$ OH | 2.67 (s, 1 H) |

(1) van Braun, J.; Haensel, W.; Zobel, F. *Justus Liebigs Ann. Chem.* **1928**, *462*, 283. Another report (Beck, I.; Rakoczi, J.; Bolla, K.; Porszasz-Gibiszer, K. German Offen. 2 528 194; *Chem. Abstr.* **1976**, *85*, 46439) discusses (benzhydryloxy)alkylamine derivatives and cites a 9-azabicyclo[3.1.1]heptan-9-yl derivative which may be another example.
(2) Stevens, C. L.; Belgian Patent 634 208, 1963; *Chem Abstr.* **1964**, *61*, 5569*d*.
(3) Parcell, R. F.; Sanchez, J. P., submitted for publication.
(4) Kaplan, F.; Schulz, C. O.; Weisleder, D.; Klopfenstein, C. *J. Org. Chem.* **1968**, *33*, 1728.
(5) Bates, R. B.; Thalacker, V. P. *J. Org. Chem.* **1968**, *33*, 1730.
(6) Chang, T.; Dill, W.; Glazko, A. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1965**, *24*, Abstract 770.

0022-3263/81/1946-5228$01.25/0 