Synthesis and Structural Analysis of a 2,5-Diazabicyclo[4.1.0]heptane

Michal W. Majchrzak* and Antoni Kotelko

Institute of Drug Research, Pharmaceutical Faculty of the Medical Academy,
Narutowicza 120a, 91037 Łódź, Poland

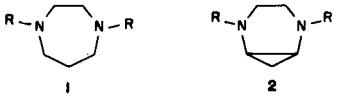
Joseph B. Lambert

Department of Chemistry, Northwestern University,
Evanston, Illinois 60201
Received December 9, 1982

Synthesis of a new heterocyclic system, 2,5-diazabicyclo[4.1.0]heptane, substituted on nitrogen, has been achieved by the reaction of the disodium or dipotassium salt of *cis*-1,2-(arenesulfonamido)cyclopropane with ethylene bromide. Analysis of the ^1H magnetic resonance spectrum demonstrated that this bicyclic system exists as a mixture of interconverting enantiomeric half-chair conformers.

J. Heterocyclic Chem., **20**, 815 (1983).

A substituted *cis*-1,2-diaminocyclopropane has recently been shown to exhibit anticancer activity (1,2). Another arrangement of a vicinal pair of amine groups that exhibits physiological activity is found in the seven-membered ring perhydro-1,4-diazepine (**1**) (3,4). The diamine elements of these two ring systems can be combined in the unknown ring system, 2,5-diazabicyclo[4.1.0]heptane, (**2**). In order to explore its physiological properties, we have now prepared the first examples of the bicyclic system **2**.



1 **2**

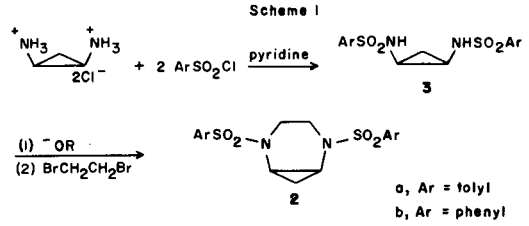
Introduction of a double bond or a three-membered ring into a seven-membered ring alters the conformation and internal dynamics of the larger ring. The double bond in cycloheptene prevents pseudorotation and causes the chair form to be favored. Thus cycloheptene resembles cyclohexane conformationally (5). The major conformational process is a relatively high energy chair/chair ring reversal. On the other hand, the three-membered ring within a seven-membered framework, as in norcarane, cyclohexene oxide, or **2**, causes the half-chair conformation to be favored (6). In this sense, the bicyclo[4.1.0]heptanes resemble cyclohexene conformationally. Here the major conformational process should be a relatively rapid half-chair/half-chair ring reversal. The dominance of the half-chair conformation has been well established for cyclohexenes (7), cyclohexene oxide (8), cyclohexene sulfide (9), and some norcaranes (10).

We report herein the synthesis of the first 2,5-diazabicyclo[4.1.0]heptane systems and the analysis of their ^1H nmr coupling constants, which demonstrate the rapid interconversion of half-chair conformations.

Results and Discussion.

Synthesis of the 2,5-diazabicyclo[4.1.0]heptane was carried out by the sequence shown in Scheme I. Because of

Scheme I

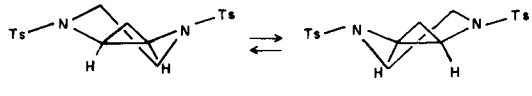


3 **2**

the need for basic conditions and because of the instability of *cis*-1,2-diaminocyclopropane as the free base, the sulfonylation was carried out by reverse addition of the diamine to a chilled solution of the sulfonyl chloride in pyridine. The disodium or dipotassium salt of the disulfonamide reacted smoothly with 1,2-dibromoethane to give the desired product, **2** (R = SO_2Ar).

The structures of **2** and **3** are confirmed by their nmr spectra. The aliphatic ^{13}C nmr region for the monocyclic **3** contained resonances with the appropriate off-resonance decoupling multiplicities for the CH, CH_2, and CH_3 groups (see Experimental). The bicyclic compounds **2** in addition had the resonance for the ethylene bridge. The ^1H nmr spectrum for the monocyclic **3** exhibited a doublet of doublets for the methinyl proton, unequally coupled to the two methylene protons, which in turn gave a multiplet. The ^1H nmr spectrum of **2a** (Figure 1) contained a similar doublet of doublets for the CH resonance at δ 2.95. The CH_2 protons gave individual doublets of triplets at high field and the ethylene bridge gave an AA'BB' spectrum at δ 3.20.

The presence of only one methinyl resonance indicates that the ring is undergoing a rapid half-chair/half-chair ring reversal, equation (1). The methinyl protons are unequally coupled to the cyclopropyl methylene protons (J



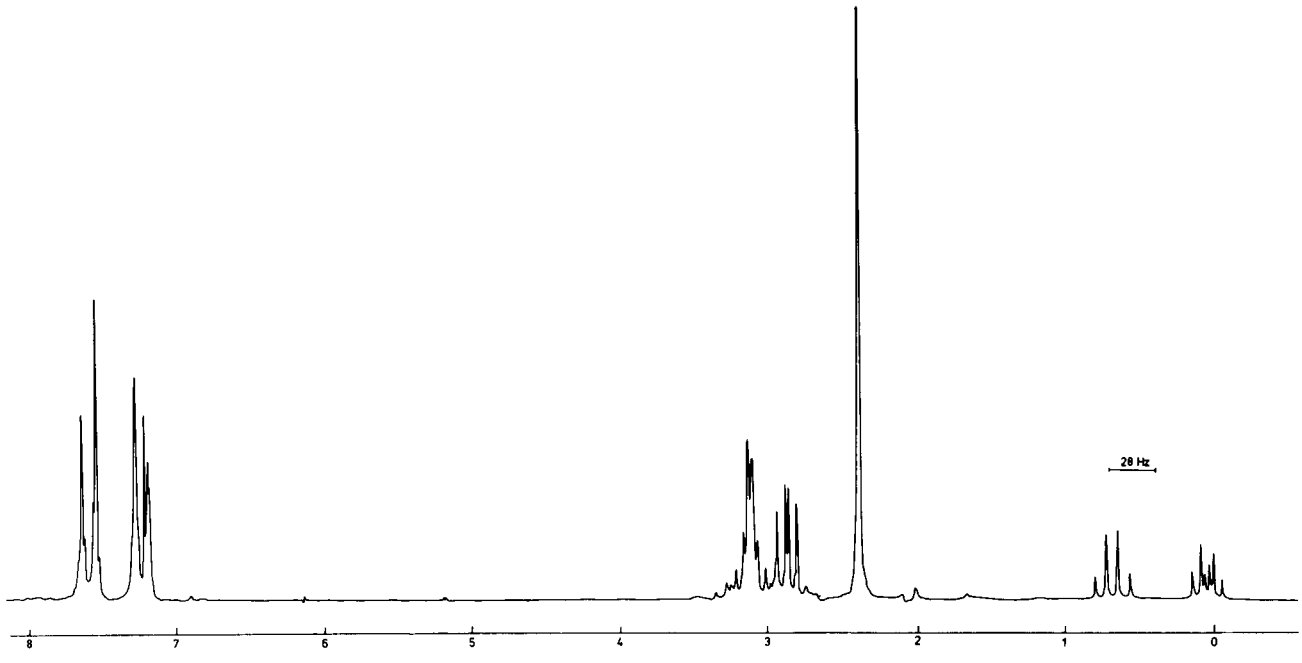


Figure 1. The 90 MHz ^{1}H nmr spectrum of 2,5-di-*p*-toluenesulfonyl-2,5-diazabicyclo[4.1.0]heptane (**2a**).

= 10.0 and 13.9 Hz), the lower value being associated with the *trans* vicinal coupling. This difference in magnitude permits the higher field methylene resonance to be assigned to the proton that is *trans* to the methinyl proton. This proton then is the one that is directed toward the inner part of the molecule and must be subjected to additional shielding, in comparison with the *cis* proton. The accidental equivalence (13.9 Hz) of the *cis* vicinal coupling and the geminal coupling causes the lower field doublet of triplets to have the appearance of a first order quartet. The coupling constants were determined by computer simulation.

In summary, we have synthesized the first example of the 2,5-diazabicyclo[4.1.0]heptane system. The molecule exists as a rapidly interconverting pair of enantiomeric half-chairs. The near planarity of the nitrogen center, as expected for a tosyl- or benzenesulfonyl-substituted amine, probably lowers the barrier to ring reversal, equation (1).

EXPERIMENTAL

Proton spectra were recorded on a Varian EM 360 (60 MHz) or a Bruker HFX-72 (90 MHz) spectrometer. Carbon-13 spectra were recorded on the Bruker HFX-72 at 22.63 MHz. Theoretical spectra were computed on a Nicolet BNC-12 microcomputer. Infrared spectra were recorded on a Pye Unicam SP 200G spectrophotometer, and mass spectra were obtained on an LKB 2091.

cis-1,2-Di-*p*-toluenesulfonylamidocyclopropane (**3a**).

To a stirred solution of 0.3 mole of arylsulfonyl chloride in 50 ml of pyridine at 0° was added 2 g (0.014 mole) of *cis*-1,2-diaminocyclopropane dihydrochloride (**2**) in portions. The solution was allowed to stand for 40 hours and was poured onto ice water. The resulting precipitate was filtered off, dried, and crystallized from methanol, 3.8 g (71%), mp 166-169°; ^{1}H nmr (deuteriochloroform): δ 0.90 (m, 2H, CH_2), 2.25 (d of d (J = 10, 14 Hz), 2H, CH), 2.43 (s, 6H, CH_3), 5.33 (s, 2H, NH), 7.60 (q, 8H, aryl); ^{13}C nmr (deuteriochloroform): δ 13.97 (CH_2), 21.58 (CH_3), 28.79 (CH), 127.54, 129.88, 136.64, 143.98 (aryl); ir (potassium bromide): 3250 (NH), 1320, and 1160 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{20}N_2S_2O_4$: C, 53.66; H, 5.29; N, 7.36. Found: C, 53.20; H, 5.20; N, 7.49.

cis-1,2-Dibenzenesulfonylamidocyclopropane (**3b**).

This material was prepared by a procedure identical to that used for **3a**, 3.6 g (73%), mp 158-160°; ^{1}H nmr (perdeuterioacetone): δ 0.90 (m, 2H, CH_2), 2.33 (d of d (J = 10, 14 Hz), 2H, CH), 3.15 (s, 2H, NH), 7.80 (m, 10H, aryl); ir (potassium bromide): 3300 (NH), 1160, and 1315 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}N_2S_2O_4$: C, 51.12; H, 4.57; N, 7.95. Found: C, 51.05; H, 4.24; N, 7.81.

2,5-Di-*p*-toluenesulfonyl-2,5-diazabicyclo[4.1.0]heptane (**2a**).

A mixture of 0.0065 mole of **3a** and 0.88 g (0.013 mole) of sodium ethoxide or 1.45 g (0.013 mole) of potassium *t*-butoxide in ethanol (50 ml) was heated to reflux for 0.5 hour. The solvent was evaporated, and the dry residue was dissolved in 100 ml of dry dimethylformamide and 80 ml of toluene. To this solution was added dropwise with stirring and heating (boiling water bath) 1.22 g (0.065 mole) of 1,2-dibromoethane in 20 ml of toluene. Stirring and heating were continued for an additional 5 hours. The mixture was poured onto ice water. The resulting precipitate was filtered, dried, and crystallized from methanol to give **2a**, 1.0 g (38%), mp 185-187°; ^{1}H nmr (deuteriochloroform): δ 0.05 (m, 1H, half of CH_2), 0.75 (q (J = 13.9), 1H, half of CH_2), 2.45 (s, 6H, CH_3), 2.95 (d of d (J = 10 and 13.9), 2H, CH), 3.20 (m, 4H, CH_2CH_2), 7.40 (q, 8H, aryl); ^{13}C nmr (deuteriochloroform): δ 10.92 (C7), 21.51 (CH_3), 28.34 (Cl, C6), 43.42 (C3, C4), 127.73, 129.81, 134.75, 144.05 (aryl): ir (potassium bromide): 1320 and 1160 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}N_2S_2O_4$: C, 56.13; H, 5.46; N, 6.89. Found: C, 56.03; H, 5.73; N, 6.96.

2,5-Dibenzenesulfonyl-2,5-diazabicyclo[4.1.0]heptane (**2b**).

This material was prepared from **3b** by a procedure identical to that used for **2a**, 1.0 g (40%), mp 169-171°; ^{1}H nmr (deuteriochloroform): δ 0.05 (m, 1H, half of CH_2), 0.70 (q (J = 14 Hz), 1H, half of CH_2), 2.95 (d of d (J = 10, 14 Hz), 2H, CH), 3.23 (s, 4H, CH_2CH_2), 7.80 (m, 10H, aryl); ir (potassium bromide): 1310 and 1160 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_2O_4S_2$: C, 53.95; H, 4.79; N, 7.40. Found: C, 53.85; H, 4.59; N, 7.32.

Acknowledgments.

This work was supported by the Polish Academy of Sciences (M. W. M. and A. K.) (Problem I.12.1) and by the National Institutes of Health (J. B. L.) (Grant No. GM26124). We are indebted to Dr. K. Wróblewski for the computer simulation program.

REFERENCES AND NOTES

(1) D. T. Witiak, H. J. Lee, H. D. Goldman and B. S. Zwilling, *J. Med. Chem.*, **21**, 1194 (1978).

(2) M. W. Majchrzak, A. Kotelko and R. Guryn, *Syn. Commun.*, **11**, 493 (1981).

(3) M. Majchrzak, A. Kotelko and R. Guryn, *Pol. J. Chem.*, **53**, 2135 (1979).

(4) M. W. Majchrzak, A. Kotelko, R. Guryn, J. B. Lambert and S. W. Wharry, *Tetrahedron*, **37**, 1075 (1981).

(5) J. Dale, "Stereochemie und Konformationsanalyse", Verlag Chemie, Weinheim, Germany, 1978, pp 149-151.

(6) J. A. Hirsch, "Concepts in Theoretical Organic Chemistry", Allyn and Bacon, Boston, Massachusetts, 1975, pp 263-264.

(7a) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. France*, 1366 (1965); (b) N. L. Allinger, J. A. Hirsch, M. A. Miller and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968); (c) F. A. L. Anet and M. Z. Haq, *ibid.*, **87**, 3147 (1965).

(8a) T. Ikeda, R. Kewley and R. F. Curl, Jr., *J. Mol. Spectrosc.*, **44**, 459 (1972); (b) V. A. Naumov and V. M. Bezzubow, *J. Struct. Chem.*, **8**, 466 (1967).

(9) R. Kewley, *Can. J. Chem.*, **51**, 529 (1973).

(10) R. Perraud and J-L. Pierre, *Bull. Soc. Chim. France*, 2615 (1974).