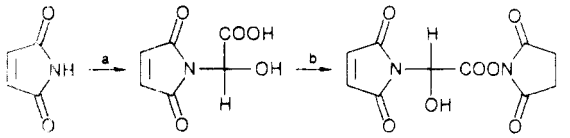
Scheme I[a]

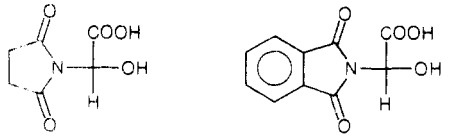


3 4

[a] Reagents: (a) glyoxylic acid·H_2O, 1.5 equivs, acetone, reflux, 90% based on recovered maleimide; (b) *N*-hydroxysuccinimide, DCC, DME, 4 °C, 51%.

bamato glycolic acids in moderate to good yields.[1] Described herein is an extension of this reaction to five-membered cyclic imides which allows for the preparation of 2-imidoglycolic acids as potential ligands for biologically interesting metals[2] and, in one case, as a precursor to a new heterobifunctional cross-linking agent, *N*-succinimidyl 2-maleimidoglycolate, MGS.

Succinimido, phthalimido, and maleimidoglycolic acids **1**, **2**, and **3**, respectively, are produced by the reaction of the corresponding cyclic imide with glyoxylic acid monohydrate in refluxing acetone. The former two are isolated as crystalline solids while the latter is afforded only as a heavy syrup. Characteristic to all three, however, is the presence of a clean singlet at 5.69–5.90 ppm in the ^1H NMR spectrum which is attributable to the α proton resonance of the product.[3]



1 2

Conversion of the syrupy 2-maleimidoglycolic acid to its crystalline *N*-hydroxysuccinimide ester **4** was easily achieved by the reaction of **3** with *N*-hydroxysuccinimide in the presence of DCC in DME at 4 °C (Scheme I).

Very much like *m*-maleimidobenzoyl *N*-hydroxysuccinimide ester, MBS,[4] in its ability to cross-link drugs, enzymes, etc., to proteins, MGS has the added potential for the pH-dependent controlled release of a drug or enzyme from the protein to which it is coupled. Precedent for this behavior can be found in a study by Bundgaard and Buur involving the pH-dependent hydrolysis of amidoglycolic acids and amidoglycolates.[5] Pseudo-first-order rate constants for decomposition with U-shaped pH-dependent curves indicative of both specific acid and base catalysis as well as a spontaneous or water-catalyzed reaction were observed, with minimal decomposition occurring at pH 3–4. In preliminary experiments designed to test the feasibility for controlled release, *p*-nitroaniline (pNA) was coupled to bovine albumin via MGS, utilizing methodology described by Kitagawa and co-workers,[6] and was found to release pNA gradually with time at physiological pH and temperature.[7] This characteristic is critical to therapy in which a controlled or prolonged release of a drug or enzyme into the serum or at the surface of a targeted cell is desired.

(1) Ben-Ishai, B.; et al. *Tetrahedron* **1976**, *32*, 1571–1573.
(2) For an interesting application of this, see: Serino, A. J. U.S. Pat. Appl. 084 037, August 11, 1987.
(3) All new compounds have been fully characterized by IR, ^1H NMR, and combustion analysis.
(4) (a) Kitagawa, T.; Aikawa, T. *J. Biochem.* **1976**, *79*, 233–236. (b) Kitagawa, T.; Fujitake, T.; Tamiyama, H.; Aikawa, T. *Ibid.* **1978**, *83*, 1493–1501.
(5) Bundgaard, H.; Burr, A. *Int. J. Pharm.* **1987**, *37*, 185–194.
(6) Kitagawa, T.; Kawasaki, T.; Munechika, H. *J. Biochem.* **1982**, *92*, 585–590.
(7) Details of this experimentation will be reported at a later date elsewhere.

Acknowledgment. Special thanks to Ms. Candace Keene for obtaining the combustion analyses.

Supplementary Material Available: Experimental procedures for the preparation of 1–4 and complete spectral data (3 pages). Ordering information is given on any current masthead page.

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1,7-Methanohomopentaprismane:[1] A [2.2.1]Propellane

Summary: The intramolecular cycloaddition of 11-methylene-8-pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanylidene to the olefinic bond leads to 1,7-methanohomopentaprismane, a highly elusive [2.2.1]propellane, which spontaneously abstracts two hydrogen atoms from its environment, yielding 1,3-bishomopentaprismane.

Sir: We report strong evidence for the transient existence of 1,7-methanohomopentaprismane[1] (**6**) a [2.2.1]propellane. This is the first report of a [2.2.1]propellane being produced by the simultaneous formation of *two* carbon–carbon bonds.

Propellanes containing six or fewer bridge carbons have been of considerable recent interest, both experimental[2-10] and theoretical.[11] They possess two inverted carbon atoms and are highly reactive toward free radicals and electrophiles, but entirely inert toward nucleophiles. Such chemical behavior as well as recent experimental and theoretical studies indicates a significant electron density outside the inverted carbon atoms and, consequently, a reduced electron density between them compared with that between tetrahedral carbons. Whereas [1.1.1]-,[3]

(1) Heptacyclo[5.4.1.$0^{1,7}$.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane.
(2) Reviews: Wiberg, K. B. *Acc. Chem. Res.* **1984**, *17*, 379–386. Ginsburg, D. *Propellanes*; Verlag Chemie: Weinheim, 1975. Its sequels I and II, Department of Chemistry, Technion: Haifa, 1981 and 1985, respectively.
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(7) Wiberg, K. B.; Walker, F. H.; Pratt, W. E.; Michl, J. *J. Am. Chem. Soc.* **1983**, *105*, 3638–3641. Reference 4e.
(8) (a) Walker, F. H.; Wiberg, K. B.; Michl, J. *J. Am. Chem. Soc.* **1982**, *104*, 2056–2057. (b) Carroll, W. F., Jr.; Peters, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 4127–4134. Carroll, W. F., Jr.; Peters, D. G. *Tetrahedron Lett.* **1978**, 3543–3546. (c) Wiberg, K. B.; Bailey, W. F.; Jason, M. E. *J. Org. Chem.* **1976**, *41*, 2711–2714. References 5c,d.
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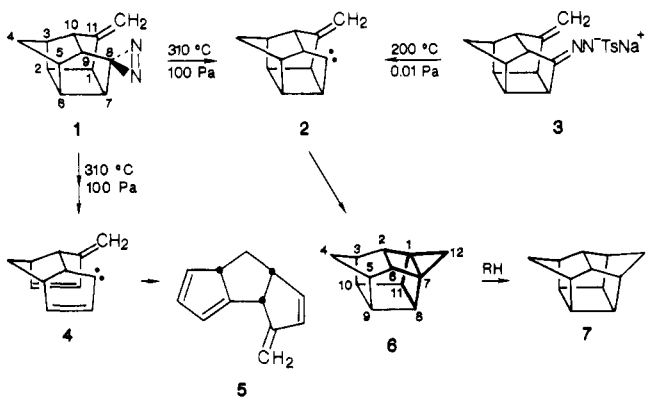
0022-3263/88/1953-2662$01.50/0

Scheme I



[3.1.1]-,[4] [3.2.1]-,[5] and [4.1.1]propellanes[6] are now easily accessible, [2.1.1]-,[7] [2.2.1]-,[8] and [2.2.2]propellanes[9] are still quite elusive compounds.

All evidence for the existence of [2.2.1]propellane has been obtained from chemical or electrochemical reductions of 1,4-dihalonorbornanes.[8] This approach, however, is not as straightforward as it appears to be. The formation of [2.2.1]propellane followed by rapid reactions of its extremely weak central bond[8a] can easily be mistaken for possible substitution reactions of the starting 1,4-dihalonorbornane.[8] Nevertheless, Wiberg, Walker, and Michl recently detected [2.2.1]propellane in a nitrogen matrix isolated product mixture of the gas-phase dehalogenation of 1,4-diiodonorbornane with potassium vapor.[8a] In the present work, we have used a different approach to the [2.2.1]propellane system: intramolecular carbene cycloaddition to a suitably located olefinic bond. This approach involves the simultaneous formation of *two* carbon–carbon bonds; hence, any reactions of the propellane central bond can lead only to products having structures entirely different from that of the starting material.

We chose 11-methylene-8-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanylidene (**2**) as a potential precursor of the [2.2.1]propellane. Its vacant p orbital should be close to the olefinic bond and favorably directed for the cycloaddition. In addition, 11-methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**8**), the logical precursor of **2**, is easily accessible.[12] Carbene **2** was generated by pyrolyses of both 11-methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-spiro-3′-diazirine (**1**) and the related tosylhydrazone sodium salt **3** (Scheme I).

Treatment of methylene ketone **8** with *freshly prepared* hydroxylamine-*O*-sulfonic acid in methanolic ammonia at −33 °C yielded 85% of the expected diaziridine, which was readily oxidized (72%) with silver oxide to the respective diazirine **1**. Diazirine **1** (200 mg) was subjected to flash pyrolysis at 310 °C in a gentle stream of nitrogen in a moderate vacuum (100 Pa).[13a] The volatile products (130 mg) were collected in a liquid nitrogen cooled trap. The ^{13}C NMR spectrum of the crude product showed 16 significant signals indicating the presence of at least two components.[13b] Attempted separations by column chromatography led only to a 15% yield (25 mg) of a colorless highly volatile solid, which was identified as 1,3-bishomopentaprismane[14] (**7**) by comparison of its ^{13}C NMR, ^{1}H NMR, IR, and mass spectra with the spectral data reported for this hydrocarbon.[15]

The other component oligomerized or polymerized on the chromatographic column. It was identified as the tetraolefin **5** on the basis of its spectra[16] and the expected[17] chemical behavior of 1-seco-3-homopentaprismane derivatives,[18] such as **1**, under the pyrolytic conditions employed. Tetraolefin **5** is probably formed by the thermal [2 + 2] cycloreversion of the C_1–C_7 and C_2–C_6 bonds[19] in **1** followed by pyrolysis of the diazirine group and insertion of the resulting tricyclic carbene **4** into the adjacent bridgehead C–H bond. In contrast to carbene **2**, carbene **4** should be rather flat, and hence, its vacant p orbital may be favorably aligned[20] for the insertion into the adjacent bridgehead C–H bond.

1,3-Bishomopentaprismane (**7**) can only arise from the [2.2.1]propellane **6** formed by the intramolecular cyclo-

(10) (a) Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. *J. Am. Chem. Soc.* **1985**, *107*, 7247–7257. (b) Hedberg, L.; Hedberg, K. *J. Am. Chem. Soc.* **1985**, *107*, 7257–7260. (c) Chakrabarti, P.; Seiler, P.; Dunitz, J. D.; Schlüter, A.-D.; Szeimies, G. *J. Am. Chem. Soc.* **1981**, *103*, 7378–7380. (d) Wiberg, K. B.; Burgmaier, G. J.; Shen, K.; La Placa, S. J.; Hamilton, W. C.; Newton, M. D. *J. Am. Chem. Soc.* **1972**, *94*, 7402–7406. (e) Honegger, E.; Huber, H.; Heilbronner, E.; Dailey, W. P.; Wiberg, K. B. *J. Am. Chem. Soc.* **1985**, *107*, 7172–7174. (f) Eckert-Maksič, M.; Mlinarič-Majerski, K.; Majerski, Z. *J. Org. Chem.* **1987**, *52*, 2098–2100. (g) Majerski, Z.; Mlinarič-Majerski, K. *J. Org. Chem.* **1986**, *51*, 3219–3221. (h) Gassman, P. G.; Armour, E. A. *Tetrahedron Lett.* **1971**, 1431–1434. (i) Belzner, J.; Szeimies, G. *Tetrahedron Lett.* **1986**, *27*, 5839–5842. (j) Wiberg, K. B.; Waddell, S. T.; Laidig, K. *Tetrahedron Lett.* **1986**, *27*, 1553–1556. (k) Wiberg, K. B.; Waddell, S. T. *Tetrahedron Lett.* **1987**, *28*, 151–154. (l) Baumgart, K.-D.; Harnisch, H.; Szeimies-Seebach, U.; Szeimies, G. *Chem. Ber.* **1985**, *118*, 2883–2916. (m) Wiberg, K. B.; Connon, H. A.; Pratt, W. E. *J. Am. Chem. Soc.* **1979**, *101*, 6970–6972.

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(12) (a) Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1983**, *48*, 5392–5395. Marchand, A. P.; Allen, R. W. *J. Org. Chem.* **1974**, *39*, 1596. (b) We prepared methylene ketone **8** in 55% overall yield by starting from pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione[12a] by monoketalization followed by a modified Wittig methylenation[12c] and formic acid catalyzed deketalization. (c) Dauben, W. G.; Cunningham, A. F., Jr. *J. Org. Chem.* **1983**, *48*, 2842–2847.

(13) (a) The flash pyrolysis was performed in a 22-cm-long horizontal glass tube (8-mm i.d.) heated by an external nichrome ribbon wrapping insulated with asbestos. (b) The total amount of "impurities" was less than 10%.

(14) Hexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane.

(15) Marchand, A. P.; Wu, A. *J. Org. Chem.* **1986**, *51*, 1897–1900. de Vries, L.; Winstein, S. *J. Am. Chem. Soc.* **1960**, *82*, 5363–5376. We are grateful to Dr. T. Fukunaga for providing us with a copy of the ^{13}C NMR spectrum of an authentic sample of **7** in 1984.

(16) ^{13}C NMR ($CDCl_3$): δ 163.4 (s), 161.7 (s), 150.0 (d), 128.4 (d), 126.3 (d), 124.1 (d), 118.2 (d), 103.2 (t), 51.8 (d), 40.6 (d), 35.3 (d), 28.2 (t). ^{1}H NMR ($CDCl_3$): δ 6.46 (dd, J = 6, 2 Hz, 1 H), 6.34 (d, J = 6 Hz, 1 H), 5.8–5.5 (m, 3 H), 4.86 (d, J = 5 Hz, 2 H), 3.5–3.0 (m, 2 H), 2.8–1.4 (m). IR (neat): 3055 (w), 3020 (m), 2940 (s), 2840 (m), 1620 (w), 1610 (s), 1440 (m), 1330 (m), 860 (s), 785 (w), 755 (w), 700 (m) cm^{-1}. Mass spectrum: m/z (relative intensity) 156 (M^+, 55), 155 (40), 141 (70), 129 (45), 128 (83), 115 (100), 91 (44), 77 (38), 63 (37), 51 (47). These data are obtained from a pyrolysis product sample containing 85–90% of **5** (by ^{13}C NMR).

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(18) Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane derivatives.

(19) For a review on [2 + 2] cycloreversions, see: Schaumann, E.; Ketcham, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 255–247.

(20) (a) The dihedral angles between the vacant carbene p orbital and the adjacent bridgehead C–H bond in **4** and **2** were estimated to be 25° and 80°, respectively, by inspection of the molecular models. (b) Nickon, A.; Huang, F.-C.; Weglein, R.; Matsuo, K.; Yagi, H. *J. Am. Chem Soc.* **1974**, *96*, 5264–5265. Nickon, A.; Bronfenbrenner, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 2022–2023. Altmann, J. A.; Tee, O. S.; Yates, K. *J. Am. Chem. Soc.* **1976**, *98*, 7132–7138. Press, L. S.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 509–510.

addition of carbene **2** to the olefinic bond.[21] In order to confirm the intermediacy of **2** in the pyrolysis of diazirine **1**, we prepared the tosylhydrazone sodium salt (**3**) of methylene ketone **8** and generated **2** by pyrolysis of **3**. Pyrolysis of the dry salt **3** at 200 °C and 0.01 Pa yielded 5% of 1,3-bishomopentaprismane (**7**) along with a polymeric material and small amounts of unidentified olefins (by ^{13}C NMR and ^{1}H NMR). This is consistent with the formation of norbornane and its dimer in the gas-phase dehalogenation of 1,4-diiodonorbornane to the highly unstable parent [2.2.1]propellane.[8a] The central bond in [2.2.1]propellanes is extremely weak (≤20 kcal/mol[8a]) and may easily dissociate to the respective diradicals, which then react further. Consequently, at high temperatures, propellane **6** will rapidly polymerize or abstract two hydrogen atoms from its environment, yielding the stable hydrocarbon **7**. The latter reaction should be more significant when a reasonably good hydrogen donor, such as tetraolefin **5**, is present.

(21) We have shown that pyrolysis of a diazirine possessing a suitable olefinic bond leads to the desired propellane provided that it is reasonably thermally stable. Thus, pyrolysis of 4-methyleneadamantane-2-spiro-3′-diazirine (**9**) at 320 °C and 100 Pa yielded 2,4-methano-2,4-didehydroadamantane, **10** (a [3.1.1]propellane), as the major product in addition to some unreacted diazirine and small amounts of unidentified byproducts. Propellane **10** was identified by comparison of the ^{13}C NMR and ^{1}H NMR spectra of the crude product mixture with the spectral data reported[4b,c] for this propellane. The presence of **10** was confirmed by its conversion to 2-chloro-4-(trichloromethyl-2,4-methanoadamantane[4b,c] by treatment with carbon tetrachloride.

In conclusion, the formation of 1,3-bishomopentaprismane (**7**) by pyrolysis of both diazirine **1** and tosylhydrazone salt **3** provides strong evidence for the transient existence of highly elusive [2.2.1]propellane. It should be noted, finally, that [2.2.1]propellane **6** is the only small ring propellane not containing the bicyclobutane unit, which has been produced by intramolecular carbene cycloaddition to an olefinic bond.

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Registry No. **1**, 114095-89-5; **2**, 114095-90-8; **3**, 114130-42-6; **5**, 114095-91-9; **6**, 114095-92-0; **7**, 704-02-9; **8**, 87830-51-1; **8** (diaziridine deriv), 114095-93-1; **9**, 114095-94-2; **10**, 114130-41-5; hydroxylamine-*O*-sulfonic acid, 2950-43-8; pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione, 2958-72-7.

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