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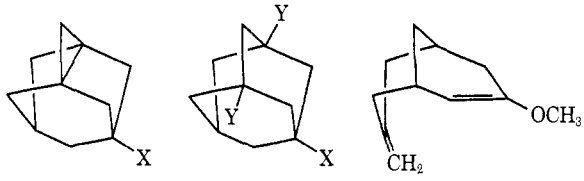
Compounds Containing Inverted Carbon Atoms. Synthesis and Reactions of Some 5-Substituted 1,3-Dehydroadamantanes

Sir:

Small ring propellanes[1] and polycyclic compounds containing "inverted carbon"[2,3] atoms present interesting theoretical questions with regard to hybridization, p–σ bonding, and strain energies.[3-6] The few known examples of inverted carbon compounds show that they possess unusual chemical reactivity; *e.g.*, [3.2.1]propellane[3,7] and 1,3-dehydroadamantane[8,9] react spontaneously with oxygen in solution at room temperature. We present here the synthesis and some reactions of 5-substituted 1,3-dehydroadamantanes (**1**) together with some thermochemical data bearing on



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strain energy. These compounds, derivatives of [3.3.1]-propellane, are now the most accessible type of inverted carbon compound.

1,3,5-Tribromoadamantane (**2**, X = Y = Br)[10] reacts with *n*-butyllithium at −35° in ether containing hexamethylphosphoramide (25:1 v/v) to give 1,3-dehydro-5-bromoadamantane (**1**, X = Br). Unlike the known[9] unsubstituted compound **1** (X = H), which is readily isolated by glpc or by sublimation from a similar reaction of 1,3-dibromoadamantane with *n*-butyllithium–HMPA, the high reactivity of the bromo derivative has prevented its isolation. However, the presence of **1** (X = Br) was shown, after removal of ether solvent below 0°, by treatment with iodine in pentane to yield 1,3-diiodo-5-bromoadamantane (**2**, X = Br, Y = I), mp 113.5–114°, δ (benzene) 2.95 ($ICCH_2CI$, s), 2.87 (two of $ICCH_2CBr$, s), 1.92 (two of $ICCH_2C$, d, J = 3 Hz), 1.82 ($BrCCH_2C$, d, J = 3 Hz), and 1.15 (bridgehead H, m). *Anal.* Calcd for $C_{10}H_{13}BrI_2$: C, 25.69; H, 2.78; Br, 17.13; I, 54.39. Found: C, 25.97; H, 2.88; Br; 17.00; I; 54.18.

Unusual reactivity for bromide substitution and a driving force for subsequent ring opening in **1** (X = Br) is shown by its rapid hydrolysis between −35° and room temperature to yield 7-methylenebicyclo[3.3.1]-nonan-3-one. Initial substitution by hydroxyl is followed by a fragmentation of the 2-hydroxy-1-cyclopropyl moiety of **1** (X = OH) to give this known[11] methylene ketone. Similar ring opening occurs even when X is methoxyl since addition of methanol to a solution of bromide yields the methyl vinyl ether **3**, δ (benzene) 4.95 (CH_2=C, s), 4.8 (other CH_2=C, s), 4.65 (OC=CH, d, J = 6 Hz), 3.4 (OCH_3, s), and 2.7–1.6 (complex multiplets). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.47; H, 9.91. However, after initial reaction of the bromide **1** (X = Br) with methanol in diethyl ether at −35°, the unstable methyl ether (**1**, X = OCH_3) may be trapped at −20° by addition of iodine to produce (*R,S*)-1-iodo-3-ethoxy-5-methoxyadamantane,[12] separated by glpc, δ (CCl_4) 3.43 and 1.1 (q and t of ethoxyl group), 3.20 (CH_3O, s), 2.42 (two of $ICCH_2CO$–, s), 2.3 (three H's of a CH_2 bridge and CH bridgehead), 1.69 (three other CH_2 units, broad s). *Anal.* Calcd for $C_{13}H_{21}O_2I$: C, 46.43; H, 6.25; I, 37.80. Found: C, 46.19; H, 6.39; I, 37.56.

An isolable derivative of the 1,3-dehydroadamantane system is produced when the group X in structure **1** has neither electron donor nor solvolytic capabilities. Reaction of a solution of **1** (X = Br) with sodium cyanide in hexamethylphosphoramide at −35 to 20° over 3 hr gave 5-cyano-1,3-dehydroadamantane[13] (**1**, X = CN) separated by sublimation and glpc, δ (benzene) 2.45 (bridgehead H, broad s), 1.45–2.05 (eight hydrogens, complex multiplets), and two pairs of doublets at 1.35 and 0.85 (two of CH_2CCN, J_{ab} = 11 Hz). *Anal.* Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.88; H, 8.44; N, 8.63. An X-ray structural determination[15] of this solid compound shows that the two bridgehead carbon atoms of the cyclopropyl ring are "inverted"; *i.e.*, that all attached atoms lie within a hemisphere around each bridgehead carbon atom. These carbon atoms are 0.1 Å above the plane of the three attached methylene carbon atoms and the 1,3-cyclopropyl carbon–carbon bond length is a remarkably long 1.64 Å.[16] High σ bonded p character of the central cyclopropyl bond in **1** is apparent from this bond length.

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(13) This ready exchange of bromide by cyanide in dehydroadamantane (**1**) may be contrasted with the preparation of 1-cyanoadamantane by reaction of 1-bromoadamantane with sodium cyanide in pyridine where temperatures up to 230° are used for the exchange.[14] A homoconjugative effect of the p orbitals in the 1,3-bond of dehydroadamantanes toward the five position in **1** (X = Br) is apparent from the fast rates of hydrolysis, methanolysis, and cyanide exchange; see R. M. Coates and J. L. Kirkpatrick, *J. Amer. Chem. Soc.*, **92**, 4883 (1970), and references therein.
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The strain energy in 1,3-dehydroadamantanes is not especially great however; scanning calorimetric measurements on 5-cyanodehydroadamantane show endotherms at 69–71° (2.08 ± 0.05 kcal/mol), 99–102° (1.41 ± 0.02 kcal/mol), and a relatively large exotherm (28.6 ± 1.2 kcal/mol) at *ca.* 120–145° (heating rate 10°/min under nitrogen). These correspond respectively to a phase transition into a mesomorphic plastic-crystal,[19] then melting at 99–102°, and finally 1,3 polymerization to a hard clear solid (mp > 300°, the ir cyano band at 2250 cm^{-1} is retained in the polymer). Heats of polymerization have been directly related to strain energies,[20] and assuming that the polyadamantane is relatively free from conformational strain, the strain of near 28.6 kcal/mol in **1** (X = CN) is close to that of cyclopropane (28 kcal/mol,[21] calculated heat of polymerization 27 kcal/mol at 25° [22]). Special stability in p–σ bonding of two inverted carbon atoms such as in 1,3-dehydroadamantanes has been described theoretically.[23] Even if the unusual bonding in **1** and related compounds results in no great increase in energies, the reactivities of these propellane compounds are much greater than that of any simple cyclopropane. This is shown by the reactions at low temperatures with oxygen or iodine, the ring opening reactions of **1** (X = OH or OCH_3), and the polymerization of **1** (X = CN). The ring openings of **1** (X = OH or OCH_3), which are apparently made possible by the electron donor capabilities of the oxygen atom, may be aided by the predicted polar ("zwitterionic"[23]) character of this type of cyclopropane carbon–carbon bond.

Acknowledgment. This work was supported by the National Research Council of Canada.

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Conformation of Angiotensin II in Aqueous Solution. Evidence for the γ-Turn Model

Sir:

We wish to report nmr data supporting the proposed γ-turn model[1] for the conformation of Asn_1Val_5 angiotensin II in aqueous solution. Two possible models were suggested based on the finding of two abnormally slowly exchanging hydrogens[2] and dialysis data.[3] The β-turn model had two intramolecular hydrogen bonds involving the amide protons of Val_3 and His_6, while the previously undescribed γ turn involved the Val_3 and Val_5 amide protons in hydrogen bonds. Energy minimization calculations indicate that the γ turn has a potential energy minimum equal to or less than that expected for the β turn.[4] A γ turn was recently identified in thermolysin based on X-ray diffraction analysis.[5]

In the experiments reported here we simultaneously followed the spectral changes in the α region as the disappearance of the amide resonances was observed in deuterium oxide. This technique allows simultaneous measurement of the rates of exchange of the amide protons and the identification of their corresponding α protons since the coupling between α and amide protons disappears as deuterium replaces amide hydrogen. The subsequent assignment of the α-proton resonances is then achieved by conventional spin decoupling in deuterium oxide.

The Asn_1Val_5 angiotensin II was synthesized by the solid phase method[6] and was homogeneous by high voltage electrophoresis at pH 1.7, paper chromatography in three systems, and amino acid analysis. It was digested down to proline by aminopeptidase M. Nmr spectra were recorded at a probe temperature of 17 ± 1° on a Varian HR 220 spectrometer operated by a consortium at Rockefeller University. The deuterium exchange experiments were done at pH 2.5 adjusted with trifluoroacetic acid.

The half-lives for the exchange of the amide resonances in angiotensin II are listed in Table I. The rates

Table I. Exchange Data and Resonance Assignments for Angiotensin II

Resonance line	Half-life, min (pH 2.3, 17°)	Residue	Evidence
A	Fast[a]	Arg_2	Exchange rate
B	5.3 ± 0.5	His_6	pH profile
C	15.9 ± 0.6	Tyr_4	
D	5.8 ± 0.8	Phe_8	pH profile
E	28.7 ± 1.2		
F	30.2 ± 0.9	Val_3, Val_5	Decoupling

[a] Not observed after 4.5 min.

were obtained from a least-squares fit of a semilogarithmic plot of the resonance amplitudes *vs.* time. After 20 min of exchange only the amides associated with resonances E and F are still protonated to a significant extent. From Figure 1, the collapse of the α resonances at 4.04 and 4.13 ppm to two doublets after 23 min of exchange is therefore entirely due to the two slowly exchanging amide protons, E and F. The spin-decoupling experiments gave the results shown in Figure 2. In each case the β-proton resonances were irradiated while the α and γ resonances were recorded. Since the resonance near 0.8 ppm can be uniquely assigned to the γ protons of valine, the slowly exchanging amide protons must also be assigned to the two valine residues.

The pH and temperature dependences of the amide region have also been studied and will be reported elsewhere in greater detail. The results of these studies permit the assignment of the remaining amide resonances of angiotensin II. Resonance A shows an en-

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