As pointed out by Dewar[10b] and by Lischka and Köhler,[11] MINDO/3 often provides remarkably good results in such comparisons between small classical and nonclassical cations as judged from experimental data or from high-level ab initio calculations.[12,13] Although the MINDO/3 estimate of the energy difference favoring **6** over **7**, 5.0 kcal/mol (eq 5), is in satisfactory agreement with the experimental barrier to methyl scrambling in **6**, 3.5 kcal/mol, the trends in the MINDO/3 results (Scheme I) probably are more significant. Thus, the bridged classical ion energy difference in the secondary case (eq 6) is 4.0 kcal/mol less than that in the tertiary (eq 5). This contradicts the assumption of Fărcaşiu that **5** should lie about 3 kcal/mol *higher* in energy than **4**. We conclude that **4** and **5** probably are comparable in energy in nonnucleophilic media. No correction of the measured activation energy for methyl equilibration in **3** is thus needed, and this value is given in eq 4.

Equations 3 and 4 can now be compared in order to provide a corrected estimate, 6 ± 1 kcal/mol, for the extra stabilization associated with the secondary 2-norbornyl cation in stable ion media. This value is in good agreement with other differently based estimates under such conditions[9c] and with the energy expected from solution solvolysis data (compare the Goering–Schwene diagram[9b] and the finding of Arnett, Petro, and Schleyer[14] that nearly 90% of the total ionization energy of a carbocation in stable ion media is reflected in the corresponding solvolysis transition state). This extra stabilization, in principle, might be due to effects other than bridging. However, if the structure of the norbornyl cation is established to be nonclassical by other methods, it is reasonable to attribute the 6 ± 1 kcal/mol stabilization to the energy gained on bridging.

The experimental evidence favoring the bridged structure of the 2-norbornyl cation in nonnucleophilic media, where direct spectroscopic observations can be made, is now overwhelming. The ESCA spectrum has been determined a third time, with the same results as before.[15] Theoretically calculated ESCA spectra for the classical and nonclassical species firmly support the nonclassical assignment.[16] Detailed analysis of the ^{13}C NMR chemical shifts of the 2-norbornyl cation, in comparison with numerous other carbocations, demonstrates its bridged nature.[8] Finally, Saunders' isotopic perturbation probe[10c] shows the structure of the 2-norbornyl cation to be bridged.[17] The time has come to ask the question, "Are remaining doubts concerning the bridged structure of the 2-norbornyl cation resonable or unreasonable?"

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(13) Whatever the deficiencies of MINDO/3 in other contexts may be, comparisons within limited reaction series such as eq 5–7 reduce or eliminate possible errors by cancellation. Ab initio results show the same trends, also, for the related energy differences reflecting 1,2-hydride (instead of methide) shifts along the cation series, ethyl, 2-butyl, and 2,3-dimethyl-2-butyl.[10-12] In stable ion media, the experimental hydride shift barrier in the classical 2,3-dimethyl-2-butyl cation is 3.1 kcal/mol,[7] but the latest evidence shows the 2-butyl cation to be hydrogen-bridged (Saunders, M.; Hehre, W. J., private communications). The indicated secondary–secondary vs. tertiary–tertiary energy difference is thus >3.1 but <3.1 ± 2.4[7] = 5.5 kcal/mol, in reasonable agreement with MINDO/3 results[10c] and the related 4.0 kcal/mol difference between eq 5 and 6.
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A Brief Total Synthesis of *N*-Benzoyl-D,L-daunosamine

Summary: A brief regioselective total synthesis of *N*-benzoyl-D,L-daunosamine [(±)-**7a**] from chlorosulfonyl isocyanate (**2**) and (*E*)-1,3-pentadiene (**1**) is described.

Sir: $[_2\pi_s + _2\pi_a]$ cycloadditions of chlorosulfonyl isocyanate to alkenes have been widely employed to synthesize β-lactam antibiotics and structurally related systems.[1,2] We have extended the preparative utility of this reaction to the biologically important 2,3,6-trideoxy-3-aminohexoses and have accomplished short regioselective syntheses of the *N*-benzoyl derivative [(±)-**7a**] of D,L-daunosamine [2,3,6-trideoxy-3-amino-D,L-*lyxo*-hexose, (±)-**7b**] and the corresponding derivative of the D,L-*xylo*-isomer (±)-**8a**.

There has been intense synthetic *N*-benzoyl-D,L-daunosamine in daunosamine (L_S-**7b**) because it is the glycosidic residue of a number of anthracycline anticancer antibiotics[3] and contributes significantly to their biological activity. Elegant chiral preparations of both the natural L_S[4] and unnatural D_R[5] isomers have been reported. Several shorter total syntheses of (±)-**7b** have also been reported.[6]

Our short total synthesis of *N*-benzoyl-D,L-daunosamine

(1) For a recent example, see: Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313.
(2) For a recent review on β-lactam synthesis see: Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *5*, 181 and references therein.
(3) (a) Daunorubicin: Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334; Arcamone, F.; Cassinelli, G.; Franceschi, G.; Mondelli, R.; Orezzi, P.; Penco, S. *Gazz. Chim. Ital.* **1970**, *100*, 949. (b) Adriamycin: Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, 1007; DiMarco, A.; Arcamone, F.; Zunio, F. *Antibiotics* **1975**, *3*, 101–128. (c) Carminomycin: Brazhnikova, M. G.; Zbarsky, V. B.; Potapova, V. L. *J. Antibiot.* **1974**, *27*, 254; Gause, G. F.; Brazhnikova, M. G.; Shorin, V. B. *Cancer Chemother. Rep.* **1974**, *58*, 255; Wani, M. C.; Taylor, H. L.; McPhail, A. T.; Onan, K. D. *J. Am. Chem. Soc.* **1975**, *97*, 5955. (d) 11-Deoxydaunorubicin, 11-deoxydoxorubicin (11-deoxyadriamycin): Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, C. M.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *Ibid.* **1980**, *102*, 1462. (e) Nogalamycin: Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; Mackellar, F. A.; Mizsak, S. A. *Ibid.* **1977**, *99*, 542.
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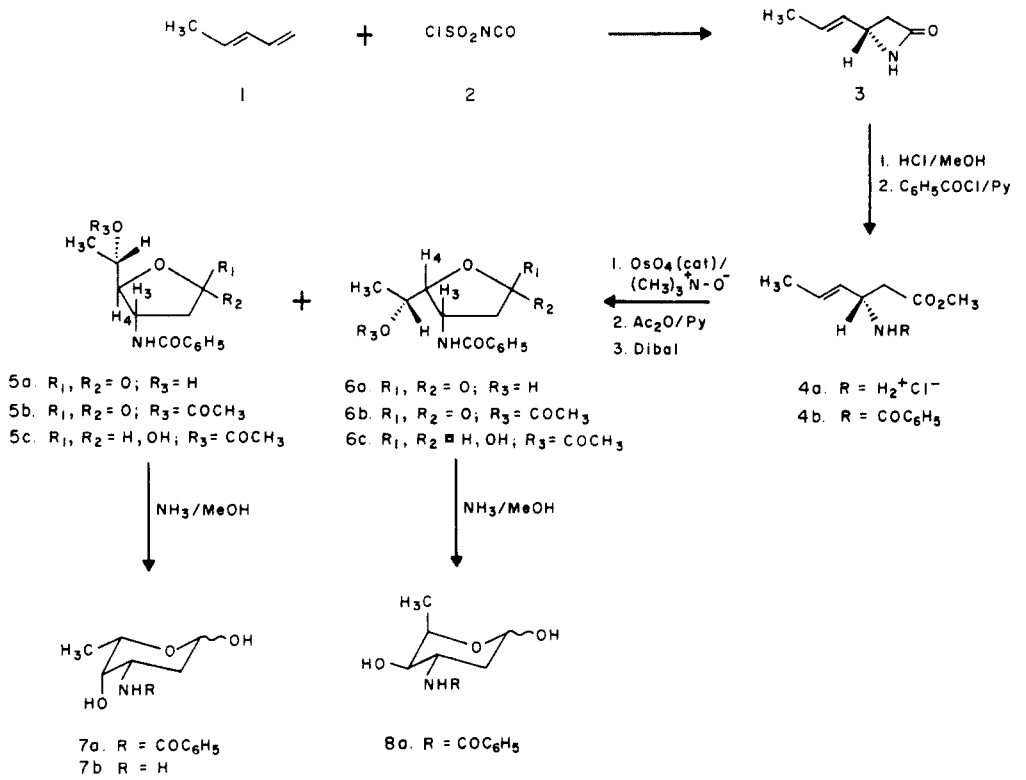
(6) Wong, C. M.; Ho, T. L.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144. Dyong, I., Wiemann, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 682. Iwataki, I.; Nakamura, Y.; Takahashi, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. Uskokovic, M. R.; Wovkulick, P. Twenty-sixth National Organic Chemistry Symposium of the American Chemical Society, Tuscon, AZ, June 1979; p 41.

0022-3263/81/1946-0227$01.00/0

Scheme I



[(±)-7a] is shown in Scheme I. The brevity of the sequence was achieved by using azetidinone intermediate **3** which has both the requisite disposition of amino and carbonyl groups and contains an olefinic fragment with the inherent regio- and stereochemistry for controlled introduction of hydroxyl groups. Efficient regiospecific construction of propenylazetidinone **3**[7] was accomplished by cycloaddition of chlorosulfonyl isocyanate (**2**) to (*E*)-1,3-pentadiene (**1**). Methanolysis (HCl/CH_3OH) of **3** gave the hydrochloride salt of methyl (*E*)-3-amino-4-hexenoate (**4a**, mp 117–20 °C) which was subsequently converted to the *N*-benzoyl derivative **4b**[8] with benzoyl chloride in pyridine in 80% overall yield.

Cis hydroxylation of the olefinic fragment of **4b** with trimethylamine *N*-oxide and a catalytic amount of osmium tetroxide[9,10] afforded the lyxo and xylo lactone isomers **5a** and **6a** (92% yield, 62:38 ratio) which were readily separated by chromatography on silica gel. Subsequently, it was discovered that acetylation of the lactone mixture (90% yield) permitted direct separation of acetates **5b** (mp 158–159 °C) and **6b** (mp 158–159 °C) by crystallization.

The five-membered lactone structures for **5a** and **6a** were indicated by infrared absorptions at 1779 and 1787 cm^{-1}, respectively. Decoupling of the individual ^1H NMR spectra permitted definitive determination of the stereochemistry of the individual isomers.[8] Isomer **5a** exhibited a smaller H_3–H_4 coupling constant (J = 3.52 Hz at 4.39 ppm) since the dihedral angle between the coupling protons approaches 90°[11] and was therefore assigned the lyxo configuration. The xylo configuration was assigned to isomer **6a** which had a larger coupling constant (J = 7.26 Hz at 4.38 ppm) due to the near 0° dihedral angle between the corresponding protons.[11]

Diisobutylaluminum hydride reduction (3.0 equiv, THF, −100 °C) of the individual acetates **5b** and **6b** afforded the lactols **5c** and **6c** in 80 and 58% yields, respectively. Ammonolysis (NH_3/MeOH/23 °C/1 h) of **5c** gave *N*-benzoyl-D,L-daunosamine [(±)-**7a**], while corresponding treatment of **6c** furnished the xylo isomer **8a**, both in quantitative yield.

The potential of this approach for general synthesis of the configurational isomers of 2,3,6-trideoxy-3-aminohexoses in their optically active form is under study.

Acknowledgment. This work was generously supported by the National Institutes of Health of the Department of Health Education and Welfare (GM 26754).

(7) Vinyl azetidinone **3** has previously been prepared but only as a mixture of *E* and *Z* isomers. Goebel, P.; Clauss, K. *Justus Liebigs Ann. Chem.* **1969**, *722*, 122. Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, *36*, 2841.

(8) **4b**: mp 74–76 °C; ^1H NMR (CCl_4) δ 1.59 (d, J = 5 Hz, 1 H), 2.58 (d, J = 6 Hz, 2 H), 3.58 (s, 3 H), 4.70–5.0 (m, 1 H), 5.20–5.80 (m, 2 H), 7.20–7.50 (m, 5 H), 7.66–7.85 (br, 1 H). **5a**: mp 134–137 °C; ^1H NMR (acetone-d_6/D_2O) δ 1.22 (d, J = 6.59 Hz, 3 H), 2.60 (d'd, J = 18, 8.79 Hz, 1 H), 4.10 (m, 1 H), 4.39 (d'd, J = 2.64, 3.52 Hz, 1 H), 4.78 (m, 1 H), 7.4–7.97 (m, 6 H). **6a**: mp 155–156 °C; ^1H NMR (acetone-d_6/D_2O) δ 1.27 (d, J = 6.59 Hz, 3 H), 2.76 (d'd, J = 18, 7.47 Hz, 1 H), 3.00 (d'd, J = 18, 8.35 Hz, 1 H), 4.06 (m, 1 H), 4.38 (d'd, J = 2.86, 7.26 Hz, 1 H), 5.09 (m, 1 H), 7.46–7.95 (m, 6 H).

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