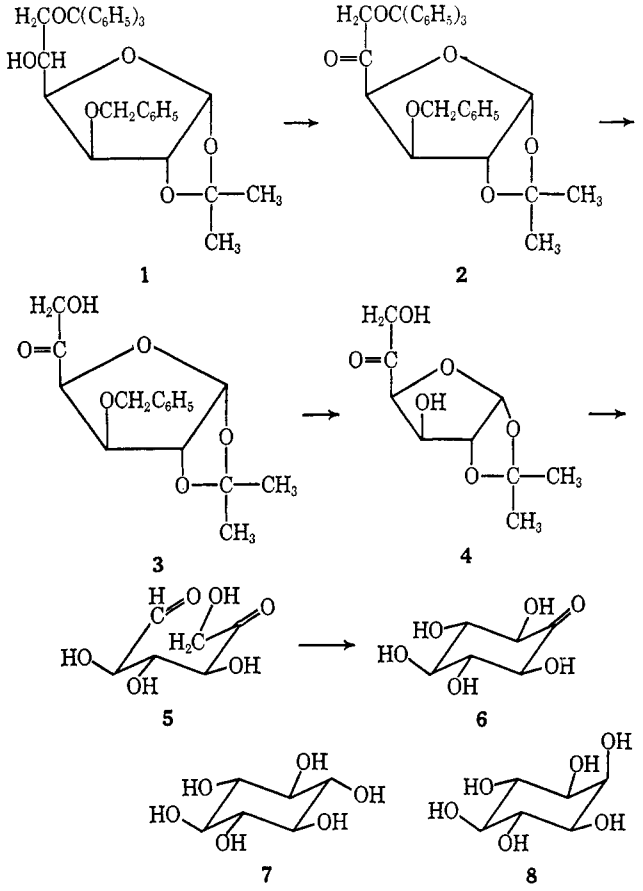
Cyclization of D-*xylo*-Hexos-5-ulose, a Chemical Model for the Biosynthesis of *myo*- and *scyllo*-Inositols

Sir:

It is now well established that D-glucose[1-3] and D-glucose 6-phosphate[3,4] are incorporated without fragmentation in the synthesis of *myo*-inositol by several biological systems. In at least one system,[5] the process is NAD^+–NADH dependent, and it has been suggested[2,6] that D-*xylo*-hexos-5-ulose 6-phosphate ("5-ketoglucose 6-phosphate") may be an intermediate in this cyclization. While this hypothesis has not, as yet, been confirmed, we wish to report a related transformation which we have carried out by purely chemical means.

D-*xylo*-Hexos-5-ulose (**5**) was first prepared by Helferich and Bigelow[7] through a complex series of reactions leading to a derivative from which **5** was made under alkaline conditions. We have developed an alternative pathway in which the dicarbonyl sugar is released in mildly acidic medium. 3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose[8] (**1**) was oxidized with dimethyl sulfoxide–acetic anhydride[9] to give crystalline 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuranos-5-ulose (**2**) in 91% yield.[10] The trityl group in **2** was removed by hydrolysis with warm aqueous acetic acid, and the crystalline hemihydrate of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**3**) was obtained in 57% yield. This substance served as an intermediate in the synthesis of D-*xylo*-hexos-5-ulose 6-phosphate which will be described elsewhere;[11] for the present purposes, **3** was debenzylated by catalytic hydrogenolysis over palladium, and the crystalline product, 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**4**, 71% yield), was hydrolyzed in aqueous solution at 38–40° by Dowex 50W X-8 (H^+). D-*xylo*-Hexos-5-ulose (**5**)[12] thus prepared was a chromatographically homogeneous syrup which decomposed on standing at room temperature. Aqueous solutions of **5**, however, may be stored in the frozen state at −5° for several months without detectable change. On reduction with sodium borohydride and subsequent acetylation with acetic anhydride–pyridine, **5** gave only two products; these were indistinguishable from the hexaacetates of D-glucitol and L-iditol when chromatographed isothermally at 190–200° on 3% ECNSS-M on Gas-Chrom Q.[13] The formation of glucitol and iditol derivatives from **5** confirms the structure of the dicarbonyl sugar.

A solution of **5** in 0.1 *N* sodium hydroxide was held at room temperature under nitrogen for 30–60 min, becoming during this period pale brown in color. Deionization with a mixture of Amberlite IR-120 (H^+) and Duolite A-4 (CO_3^{2-}) gave a colorless solution which strongly reduced Fehling solution. A sample which



was concentrated to a syrup and then trimethylsilylated was examined by glpc on 3% SE-52 on Gas-Chrom A at 150°. A component which was chromatographically indistinguishable from the TMS derivative of *myo*-inosose-2 (**6**) was detected.

The deionized solution from the alkaline treatment of **5** was reduced with sodium borohydride, and a white precipitate which formed was collected and dried. The infrared spectrum (KBr disk) of this product very closely matched that of an authentic specimen of *scyllo*-inositol diborate.[14,15] On acetylation with hot acetic anhydride containing a little sulfuric acid, the material gave *scyllo*-inositol hexaacetate, identified by its melting point and infrared spectrum and by comparison with authentic material. Deacetylation of the hexaacetate, followed by conversion to the TMS derivative, gave a product which was indistinguishable, on glpc, from the TMS derivative of authentic *scyllo*-inositol (**7**).

The solution from which the insoluble *scyllo*-inositol diborate had been removed was decationized and con-

(1) F. Eisenberg, Jr., A. H. Bolden, and F. A. Loewus, *Biochem. Biophys. Res. Commun.*, **14**, 419 (1964).
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(7) B. Helferich and N. M. Bigelow, *Z. Physiol. Chem.*, **200**, 263 (1931).
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(10) All new crystalline compounds reported here gave satisfactory elemental analyses.
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(12) The actual form of **5** is not known; doubtless it exists, at least in part, in one or more of the possible cyclic acetal structures.
(13) J. S. Sawardeker, J. H. Sloneker, and A. Jeanes, *Anal. Chem.*, **37**, 1602 (1965).
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centrated to a residue from which boric acid was removed *in vacuo* as its methyl ester. Acetylation with acetic anhydride–pyridine then gave crystalline *myo*-inositol hexaacetate which was identified by its melting point and infrared spectrum and by comparison with an authentic specimen. A sample of the hexaacetate was deacetylated and converted into the TMS derivative which proved to be indistinguishable, on glpc, from an authentic sample of the TMS derivative of *myo*-inositol (**8**).

The formation of *scyllo*-inositol (**7**) and of *myo*-inositol (**8**) unequivocally identifies the product from the alkaline treatment of **5** as *myo*-inosose-2 (**6**). The ease with which **5** cyclizes to **6** lends support to the proposed pathway for the biosynthesis of *myo*-inositol, and it is interesting to note that, while *scyllo*-inositol was first discovered in nature 110 years ago, the presence of *myo*-inosose-2 in a biological system was first reported only this year, Sherman and his coworkers[16] finding it, together with *scyllo*-inositol, in rat sciatic nerve and calf brain.

Acknowledgment. We are indebted to Dr. F. Eisenberg, Jr., of this Institute for a sample of authentic *scyllo*-inositol and to Dr. A. J. Fatiadi of the National Bureau of Standards for a specimen of *myo*-inosose-2.

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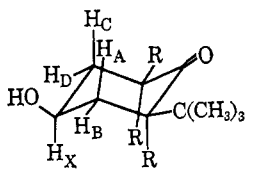
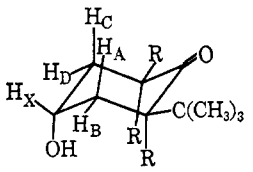
Conformational Studies. X. Census of Nonchair Conformations of 2-*t*-Butylcyclohexanones[1]

Sir:

Optical rotatory dispersion[2] and circular dichroism[3] studies of 2-*t*-butylcyclohexanone have been interpreted without invoking nonchair conformations.[2,3] However, Allinger[4] has concluded from estimates of nonbonded group interactions that "the amount of compound in the boat form in 2-*t*-butylcyclohexanone is ... appreciable," implying a need for reinterpretation of the optical results.[2,3] We wish to report infrared and nmr studies of *cis*- and *trans*-2-*t*-butyl-4-hydroxycylohexanone (**1** and **2**) which allow limits to be set upon nonchair populations of **1** and **2** and from which we infer by analogy that nonchair populations are *not* appreciable for 2-*t*-butylcyclohexanone.

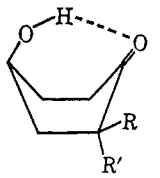


1, R = H
3, R = D



2, R = H
4, R = D

No evidence of intramolecular hydrogen bonding was detected by infrared spectroscopy for either **1** or **2**.[5] We conclude that the populations of boat conformations $\mathbf{1b}_0$ and $\mathbf{2b}_0$ are negligible.[6] However, for **1** and **2**,



$\mathbf{1b}_0$, R = $C(CH_3)_3$; R' = H
$\mathbf{2b}_0$, R = H; R' = $C(CH_3)_3$

there are five other boat ($\mathbf{b}_\psi$) and six twist ($\mathbf{t}_\psi$) conformations to be considered in which significant intramolecular hydrogen bonding is *not* possible. Defining boat conformation $\mathbf{b}_0$ as the $\psi = 0°$ (and 360°) point of the nonchair pseudo-rotational cycle, each nonchair conformation may be identified.

Examination of Dreiding molecular models suggests that steric strain is severe for **1** when ψ is 210–330° and for **2** when ψ is 30–90°.[7] Nonchair conformations within these ψ ranges for **1** and **2** undoubtedly have negligible populations.[7] In estimating population limits for the remaining possible conformations, nmr studies of **1** and **2** as their 2,6,6-d_3 derivatives (**3** and **4**) have been most informative.[8] These compounds afford ABCDX spin systems. The *cis* isomer **3** gives a first-order-like triplet of triplets for the C_4 X-proton resonance, band width, W (separation between the outer lines of the multiplet), 29.6 ± 0.1 Hz in benzene and 30.2 ± 0.2 Hz in methanol-d_4. Computer analysis shows the spectrum of **3** in methanol-d_4 solution to be consistent with $J_{AX} = J_{CX} = 10.7$, $J_{BX} = 4.3$, and $J_{DX} = 4.5$ Hz.[9]

Compare **3** with *cis,cis*-2,6-dimethyl-4-hydroxycyclohexanone (**5**), for which conformations other than the chair with all three substituents equatorial would be populated negligibly.[10] For **5**, the C_4 X-proton band width is 29.5 ± 0.2 Hz in benzene and 30.2 ± 0.2 Hz in methanol-d_4 solution, the same as for **3** within experimental error. For **3**, the conformations consistent with its observed W and J values are the chair illustrated for **3**, above, and $\mathbf{3b}_{180}$, with nearly the same dihedral angles

(1) We wish to thank the National Science Foundation for support of this work.
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(7) Boat conformations $\mathbf{1b}_{210}$ and $\mathbf{2b}_{60}$ have the *t*-butyl group in the most strained position; their adjacent twist conformations, $\mathbf{1t}_{210}$, $\mathbf{1t}_{270}$, $\mathbf{2t}_{30}$, and $\mathbf{2t}_{90}$, are also severely strained. In these conformations, *t*-butyl would occupy the C_6-B or C_6-TB 1β(a) positions described for methylcyclohexane by J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7043 (1967). A *t*-butyl group at these positions would experience much more severe repulsive interactions than a methyl group. The 1,3-diaxial-type *t*-butyl–hydroxyl interaction, which would severely destabilize $\mathbf{1b}_{300}$, is only partially relieved in $\mathbf{1t}_{330}$.
(8) We are deeply indebted to Dr. Kenneth Williamson and to Dr. David Nelson for recording spectra of **3** and **4** at 100 MHz by use of Varian HA-100 spectrometers. The hydroxyl proton was observed in each case as a sharp singlet (rapid exchange).
(9) Estimated probable error ±0.2 Hz. LAOCOON I and II and NMRIT programs were used. See J. D. Swalen, *Progr. Nucl. Magnetic Resonance Spectry.*, **1**, 205 (1966). The sum of the vicinal coupling constants equals the experimental X-proton band width. Expected changes in vicinal coupling constants with changes in HCCH dihedral angle (ω) were estimated taking $J = A\cos^2\omega - B\cos\omega + C$; $A = 10$, $B = 1$, and $C = 0$. See C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967).
(10) M. Litchman prepared **5**, mp 65.8–66.2°, by Jones oxidation of *cis,cis,cis*-2,6-dimethyl-1,4-cyclohexanediol,[11] mp 139.5–140°.
(11) R. D. Stolow and R. R. Krikorian, unpublished work.