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REDUCTIVE CLEAVAGE OF 1-METHYLTRICYCLO[4.4.0.$0^{2,6}$]DECAN-3-ONE AND RELATED COMPOUNDS WITH LITHIUM IN LIQUID AMMONIA[1]

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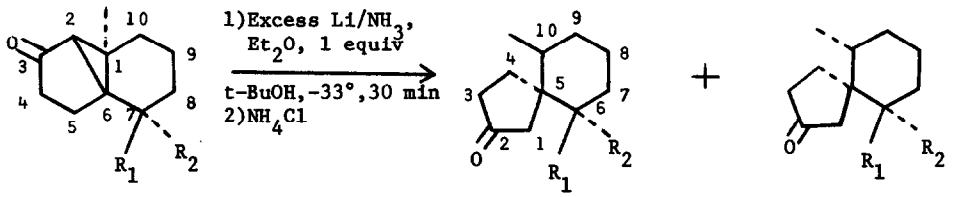
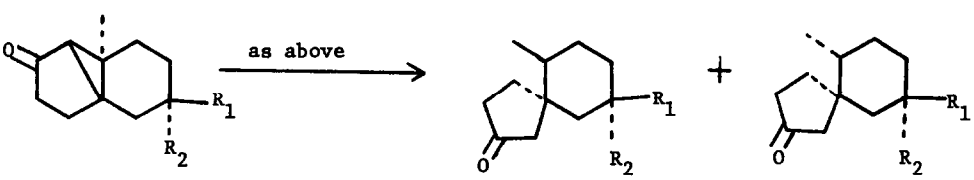
Reductive cleavage of the external(α,β) bond of the cyclopropane ring in tricyclo[x.y.0.$0^{2,x+2}$]-alkan-3-ones with lithium in liquid ammonia provides a general method of synthesis of spirocyclic ketones.[2,3] Piers and Worster have recognized that the stereochemical fate of the β carbon atom is an important feature of these reactions.[3] They conducted a detailed study of the reaction of cis-1,7-dimethyltricyclo[4.4.0.$0^{2,6}$]decan-3-one (1a) with lithium in liquid ammonia and found that the trans dimethyl ketone 2a (inversion of configuration at the β carbon) was favored over the cis isomer 3a (retention at the β position) under a variety of conditions. At -78° and with no added proton donor or up to 5 equiv of an added alcohol the 2a:3a ratio was 9:1 or greater. We have performed lithium-ammonia reductions of tricyclodecanones 1b,[5] 1c,[5] 4a,[5] and 4b[5] which are related to 1a and observed that the stereochemistry of these reactions is highly dependent upon the location and stereochemistry of the alkyl substituents.



1a. R_1 = H, R_2 = CH_3 — 2a — 3a
b. R_1 = CH_3, R_2 = H — 2b (80%) — 3b ≡ 2a (20%)
c. R_1 = R_2 = H — 2c (55-60%) — 3c (40-45%)



4a R_1 = i-Pr, R_2 = H — 5a (0%) — 6a (100%)
b R_1 = H, R_2 = i-Pr — 5b (100%) — 6b (0%)

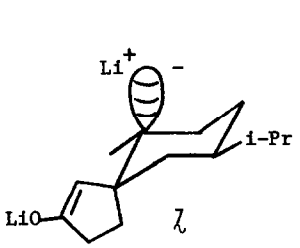
The reductions were carried out by dropwise addition of a solution of the cyclopropyl ketone in anhydrous ether containing 1 equiv of t-butyl alcohol to a stirred solution containing ca. 10 g.-atom of lithium in liquid ammonia at -33°. After 30 min, solid ammonium chloride was added and the ketonic products were isolated in the usual way. The total yields of spirocyclic ketones were in the 80-85% range for the four compounds studied. The percentages of the cleavage products are indicated in parenthesis beside the structure numbers. The percentages of the trans dimethyl ketone 2a[3,6] and the cis isomer 2b[6] were determined by GLC.[7a] Pure samples of these compounds, collected by GLC,[7b] exhibited spectral properties identical with those reported.[6] The mixture of 2c and 3c could not be separated by GLC on several columns, although fractions enriched in each of the components were obtained by low pressure liquid chromatography on silica gel. Ketone 3c [nmr (CCl_4) δ 0.94 (d, J=6.1 Hz, 3H, 6-CH_3) and 2.05 (s, 2H, 1-CH_2)] is known[8] and it could be distinguished from its isomer 2c [nmr (CCl_4) δ 0.91 (d, J=6.1 Hz, 3H, 6-CH_3) and 2.01 (AB quartet, J = ~18 Hz, 2H, 1-CH_2)] by nmr spectroscopy. Therefore, the 2c/3c ratio was estimated from integration of the nmr spectrum of the mixture of isomers.

Spirodecanones 6a[9] [bp 89-94°/0.09 mm (bath temperature); ir(CCl_4) 1745 cm^{-1} (cyclopentanone); nmr (CCl_4) δ 0.85 (bd, 5.8 Hz, 9H, >$CHCH_3$ and -$CH(CH_3)_2$), and 1.99 (AB quartet, J_{AB} = 19.0 Hz, 2H, 1-CH_2)] and 5b[9] [bp 85-92°/0.08 mm (bath temperature); ir (CCl_4) 1745 cm^{-1} (cyclopentanone); nmr (CCl_4) δ 0.86 (bd, J=5.6 Hz, 9H, >$CHCH_3$ and -$CH(CH_3)_2$) and 1.98 (AB quartet, J_{AB} = 19.0 Hz, 2H, 1-CH_2] which have a trans relationship between the methyl and isopropyl groups were the only products obtained from the reductive cleavages of cyclopropyl ketones 4a and 4b, respectively.

A 7:3 mixture of spirodecanones 6a and 5a[9] [ir (CCl_4) 1739 cm^{-1} (cyclopentanone); nmr (CCl_4) δ 0.98 (d, J=7.3 Hz, 3H, >$CHCH_3$), 0.87 δ (d, J=5.9 Hz, 6H, -$CH(CH_3)_2$], which was purified by preparative GLC,[7c] was prepared by treatment of the 4,5-dehydro derivative of 4a with hydrogen bromide in glacial acetic acid to obtain the 10α-bromo-4,5-dehydro derivative of 5a followed by catalytic hydrogenation of the double bond and hydrogenolysis of the tertiary bromide over 5% palladium on carbon in 95% ethanol containing 1 equiv of triethylamine. Also, a 45:55 mixture of 5b and 6b[9] [ir (CCl_4) 1748 cm^{-1} (cyclopentanone); nmr (CCl_4) δ 0.85 (bd, J=7.0 Hz and 5.8 Hz, 9H, >$CHCH_3$ and -$CH(CH_3)_2$], which was purified by preparative GLC,[7b] was prepared by dehydrohalogenation of the 10α-bromo derivative of 5b[10] with tetra-n-butylammonium bromide in acetone to obtain the 9,10-dehydro derivative of 5b followed by catalytic hydrogenation.

In ketones 6a and 5b the 10-methyl groups would be expected to be equatorial to the more stable chair conformations of the six-membered rings while in the isomers 5a and 6b these groups should be axial. Three pieces of spectral evidence provided support for the structural assignments of these four compounds. (1) The ^{13}C absorptions for the 10-methyl groups in 6a and 5b occurred at δ ($CDCl_3$) 16.5 and 16.4, respectively, while those for 5a and 6b occurred at δ 11.1 and 11.5, respectively. Methyl groups which are equatorial with respect to cyclohexane rings normally absorb at lower field than the corresponding axial methyl groups which have a larger number of γ-interactions.[11] (2) In the presence of the nmr shift reagent Eu(fod)$_3$ the ^1H absorptions for the equatorial methyl groups in 6a and 5b which are relatively close to the carbonyl oxygen atoms were shifted further downfield than the absorptions for the more remote axial methyl groups in 5a and 6b. (3) The ^1H coupling constants, which were observable in the presence of Eu(fod)$_3$, were smaller for the equatorial 10-methyl groups in 6a and 5b than for the corresponding axial methyl groups in 5a and 6b.[12]

In the reductive cleavage of cyclopropyl ketones with lithium in liquid ammonia, it is generally considered that intermediates having carbanionic character at the β carbon (perhaps formed via intermediates with radical character at this position) are protonated by ammonia to give lithium enolates which are converted into ketones by protonation with ammonium chloride or water during workup.[13] Thus equilibration at the β carbon might be expected to occur faster than protonation and the more thermodynamically stable product might be expected to be produced when a chiral center is generated.[14] This appears to be the case for the reductions of the isopropyl substituted ketones 4a and 4b. Apparently, carbanionic species 7 and 8 which lead to the products of retention (6a) and inversion (5b) of configuration at C-10 are highly preferred. Spiro ketones with cis relationships between the methyl and isopropyl groups, which were not observed, would have to be formed (1) via protonation of carbanions with conformations analogous to 7 and 8, but with the electron pairs equatorial to the cyclohexane rings, or (2) via protonation of carbanions with the lone pairs and the isopropyl groups axial to chair conformations of the cyclohexane rings. The former intermediates would be destabilized by charge repulsions between the enolate moieties and the carbanionic centers while the latter would be of relatively high energy because 1,3-diaxial interactions would exist between the isopropyl groups and the carbon atoms of the five-membered rings.



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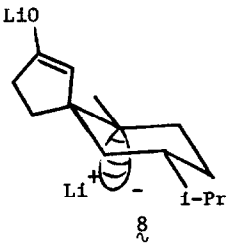

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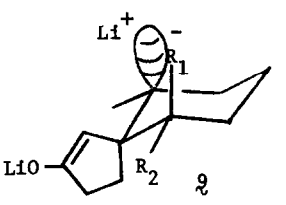

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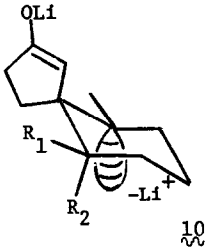

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a. $R_1 = H, R_2 = CH_3$; b. $R_1 = CH_3, R_2 = H$;

c. $R_1 = R_2 = H$

The course of the reductions of ketones 1b and 1c can be explained reasonably well if it is assumed that carbanions such as 9 and 10 achieve conformational equilibrium prior to protonation. In the cleavage of 1b where there is a 4:1 preference for the inversion product 2b, carbanion 10b with the 7β-methyl group equatorial should be favored over 9b (7β-methyl group axial) by perhaps as much as 1.0 kcal/mole considering non-bonded interactions. In the case of 1c, the slight preference for carbanion 10c may be because the sp^2 hybridized carbon atom of the enolate, which should be slightly smaller than the 5-methylene group, is axial to the cyclohexane ring.

However, the stereochemical results for the reduction of 1a do not seem to be readily accounted for in terms of equilibration of carbanions 9a and 10a. On the basis of non-bonded interactions there should be a slight preference for 9a which on protonation would give the retention product 3a, yet the inversion product 2a is favored by 9:1 or greater in the absence of a large excess of proton donor.[3] A possible explanation for this result is that the carbanion intermediate which gives 2a is formed kinetically and protonated faster than conformational equilibrium is achieved. Examination of models of the two conformations of 1a with the cyclohexane rings in a chair shows that a rather severe esclipsed interaction which is present when the 7α-methyl group is equatorial may cause the conformation with the 7α-methyl group axial to be more stable. If this factor is also important in the transition state for the ring opening process, the carbanion 10a leading to 2a could be formed more rapidly than carbanion 9a which would lead to 3a.

As noted above the results for the cleavages of 1b and 1c are consistent with the achievement of conformational equilibrium among carbanionic intermediates prior to protonation, but they also could be consistent with rapid protonation of kinetically generated carbanion mixtures.

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References and Notes

1. a. This investigation was supported by Public Health Service Grant No. CA 12193 from the National Cancer Institute. b. The investigation was also assisted by an Institutional Research Grant from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform nmr spectrometer.
2. a. W. G. Dauben and E. J. Diviny, J. Org. Chem., 31, 3794 (1966). b. S. B. Laing and P. J. Sykes, J. Chem. Soc. C, 937 (1968). c. J. D. White, S. Torii, and J. Nogami, Tetrahedron Lett., 2879 (1974). d. J. F. Ruppert and J. D. White, J. Chem. Soc. Chem. Commun., 976 (1976). e. J. F. Ruppert, M. A. Avery, and J. D. White, ibid., 978 (1976).
3. E. Piers and P. M. Worster, J. Am. Chem. Soc., 94, 2895 (1972).
4. D. Caine, A. A. Boucugnani, and W. R. Pennington, J. Org. Chem., 41, 3632 (1976).
5. As was the case for ketone 1b,[4] ketones 1c, 4a, and 4b were prepared starting with the appropriate bicyclic enone and using the sequence: enone→cross-conjugated dienone→tricyclodecenone→tricyclodecanone. Full experimental details will be presented later in a full paper. The enantiomer of 4b was actually employed but the indicated structure is given for clarity.
6. J. A. Marshall and P. C. Johnson, J. Org. Chem., 35, 192 (1970).
7. a. A 1/8" x 6' stainless steel column containing 10% Apiezon L on Chromosorb W HMDS was employed. b. A 1/4" x 10' stainless steel column containing 20% Carbowax K-20 M on Chromosorb W HMDS was employed. c. A 1/4" x 10' stainless steel column containing 10% silicone SE-30 on Chromosorb W HMDS was employed.
8. R. D. Clark and C. H. Heathcock, Tetrahedron Lett., 529 (1975). We are grateful to Professor Heathcock for copies of the nmr and ir spectra of an authentic sample of 3c.
9. Correct elemental analysis and/or exact mass data has been obtained for this compound.
10. D. Caine, A. A. Boucugnani, C-Y. Chu, S. L. Graham, and T. L. Smith, Jr., Tetrahedron Lett., 0000 (1978).
11. J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, pp. 60-69.
12. N. S. Blacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, 1964, pp. 49-54.
13. a. W. G. Dauben and R. E. Wolf, J. Org. Chem., 35, 374, 2361 (1970). b. S. A. Monti, D. J. Bucheck, and J. C. Shepard, ibid, 34, 3080 (1969). c. A. J. Bellamy, E. A. Campbell, and I. R. Hall, J. Chem. Soc., Perkin II, 1347 (1974).
14. A. Tahara, M. Shimagaki, S. O'Hara, T. Tanaka, and T. Nakata, Chem. Pharm. Bull., 23, 2329 (1975).