6   7

→ 4–5

8
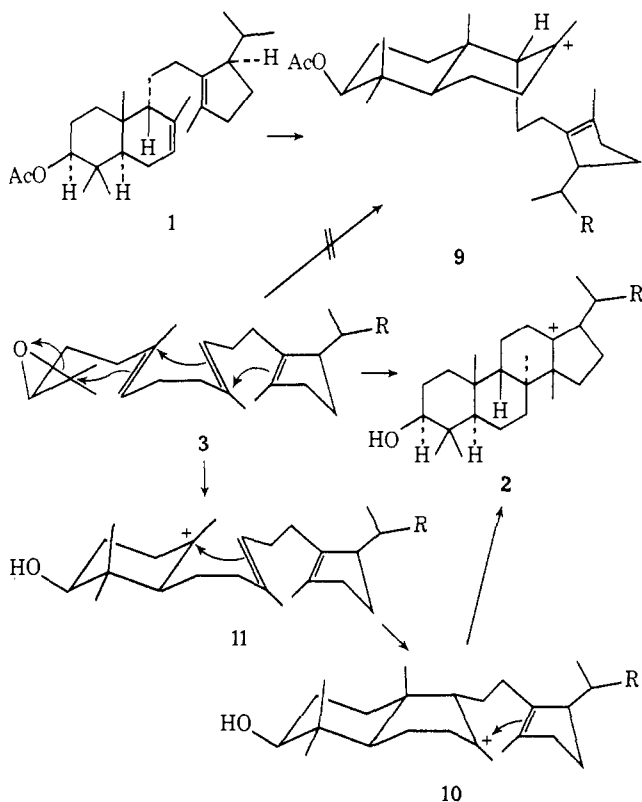
= CH₃). In the nonenzymic formation of sterol from polyene epoxide 3, therefore, the B–C portion of the cyclization must proceed in concert with the remainder of the overall process or must utilize a "frozen," less stable, ring B boat-like conformation, 10, which does


1

9

3

11

2

10

not equilibrate with the conformationally isomeric 9 (R = (CH₂)₃CH(CH₃)₂). Taken together with previous conclusions regarding the synchronousness of the cyclization pathway by which the A–B rings are built up from acyclic terminal epoxide,[9] this new result allows the view that the entire A–B–C elaboration also is either wholly concerted or involves intermediate frozen mono- or bicyclic carbonium ion entities (10–11). Assuming that biological systems can, in a suitable environment, avail themselves of any purely organic behavior, one may surmise that, especially with the help of an enzyme system, this same mechanistic characterization applies to the formation of sterol from squalene 2,3-oxide.[10,11] In order to detect a stable ground-state bicyclic inter-

(9) E. E. van Tamelen and J. P. McCormick, J. Amer. Chem. Soc., 91, 1847 (1969).

(10) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, Helv. Chim. Acta, 38, 1890 (1955).

(11) G. Stork and A. W. Burgstahler, J. Amer. Chem. Soc., 77, 5068 (1955).

mediate in lanosterol synthesis, radioactive 10[1] was assayed as a substrate for the cyclase system, both in whole animal experiments and with isolated enzyme, using procedures already described.[12] Lack of conversion of 12 to radiolabeled lanosterol, under condi-

12
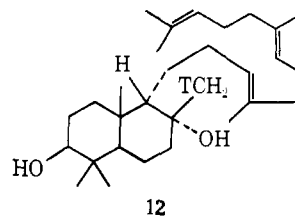
tions where a variety of unnatural squalene oxide variants are transformed to lanosterol-like products, is consistent with the mechanistic views presented herein.

(12) J. D. Willett, K. B. Sharpless, K. E. Lord, E. E. van Tamelen, and R. B. Clayton, J. Biol. Chem., 242, 4182 (1967).

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Selective Reduction of the Benzene Ring in Quinolines and Isoquinoline

Sir:

It is generally known[1] that partial hydrogenation of quinolines and isoquinolines involves preferentially the nitrogen-containing ring giving rise to 1,2,3,4-tetra-hydroquinolines and -isoquinolines. Only when the pyridine ring is substituted is there some concomitant, but by no means predominant, reduction of the benzene ring.[2]

We now wish to report a selective reduction of the benzene moiety in quinolines and isoquinoline leading to the 5,6,7,8-tetrahydro compounds in yields ranging from 53 to 98%. The method calls for use of a strongly acid medium (such as concentrated hydrochloric acid), a platinum oxide catalyst, and long hydrogenation times.[3] A typical experiment is as follows. The quinoline or isoquinoline (50 mmol) was dissolved in 40 ml of cold concentrated (37–38%) hydrochloric acid, 750 mg of PtO₂ (83%, Engelhard Inc.) was added, and the mixture was hydrogenated at room temperature and 50 psi H₂ in a Parr apparatus. When the theoretical amount of hydrogen had been consumed,[4] the catalyst

(1) (a) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, p 385; (b) M. Frei-felder, "Practical Catalytic Hydrogenation," Wiley-Interscience, New York, N. Y., 1971, p 601; (c) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 106.

(2) J. von Braun, W. Gmelin, and A. Schultheiss, Ber., 56, 1338 (1923); see also ref 1b.

(3) The same recipe has previously been reported to lead to cis-deca-hydroquinoline when even longer reduction times were employed: H. Booth and A. H. Bostock, J. Chem. Soc., Perkin Trans. 2, 615 (1972).

(4) Reduction time varies between 30 (quinoline) and 130 hr (6- and 8-methylquinoline). Much longer reduction times and elevated temperatures (~70°) lead to high yields of cis-decahydroquinolines (see also ref 3).

was filtered off, the acidic solution was cooled and carefully made strongly basic with NaOH and extracted with ether, the ether extract was dried over KOH, and the solvent was evaporated. The yields of products were determined by vpc (columns: 20% Carbowax 20 M + 10% KOH on Chromosorb W or 30% SE 30 on Chromosorb W). Decahydro and 1,2,3,4-tetrahydro compounds were separated, if necessary (see Table I), by

Table I

Starting Material	Yield of 5,6,7,8-tetrahydro product, %	Mp of picrate, °C, (lit.)
Quinoline	70[a]	159–160 (158–159[b])
2-Methylquinoline	95	158–159 (154[c])
3-Methylquinoline	98	182–183 (182–183[b])
6-Methylquinoline	53[d]	161–162 (159.5–160.5[e])
8-Methylquinoline	55[f]	126–127 (125–126[e])
Isoquinoline	95	143–144 (144[g])

[a] 6% $\Delta^{1,9}$-octahydroquinoline, 24% cis-decahydroquinoline. [b] E. Breitmaier and E. Bayer, *Tetrahedron Lett.*, 3291 (1970). [c] See ref 2. [d] 8% starting material, 15% octa- and decahydro, and 24% 1,2,3,4-tetrahydro product. [e] T. Ishiguro, Y. Morita, and K. Ikushima, *Yakugaku Zasshi*, 79, 1073 (1959). [f] 10% starting material, 12.5% octa- and decahydro, and 22.5% 1,2,3,4-tetrahydro product. [g] R. Grewe and A. Mondon, *Ber.*, 81, 279 (1948).

dissolving the mixture of products in 100 ml of dry acetone, adding acetic anhydride and potassium carbonate, and refluxing overnight. After dilution with ether, the salts were filtered off, the solvents were evaporated, and the residue was dissolved in 6 N HCl and extracted with ether. (From the ether solution the amides can be recovered and cleaved with concentrated HCl.) The aqueous solution was made strongly basic, and the 5,6,7,8-tetrahydroquinoline or -isoquinoline was extracted with ether, dried, distilled under reduced pressure, and characterized by nmr spectrum and melting point of picrate.

Using this procedure, yields of 5,6,7,8-tetrahydroquinolines shown in Table I were attained.

When the reaction time is sufficient to reduce all starting material, the by-products are readily removed by acetylation, as described above.

From the 5,6,7,8-tetrahydroquinolines it is easy to prepare, by means of sodium–ethanol reduction,[2,5] the otherwise not very readily available trans-decahydroquinolines. The products can be isolated by crystallization, if solid, or by preparative gas chromatography, using the columns described above. The trans-decahydroquinolines so prepared are listed in Table II. Configurational assignments are evident from the pmr spectra[6] and are confirmed by the cmr spectra;[7] a complete discussion of these data will be given in the full paper.

We are presently studying variations in catalyst and reaction medium designed to optimize yields and to reduce reaction times if possible. Preliminary results in reduction of quinoline over platinum oxide using 12 N sulfuric acid as a solvent indicate that 5,6,7,8-tetrahydroquinoline may be obtained in 74% yield in 4.5 hr;

(5) R. L. Augustine, "Reduction," Marcel Dekker, New York, N. Y. 1968, p 135.

(6) Cf. ref 3 for trans-decahydroquinoline.

(7) Cf. H. Booth and D. V. Griffiths, *J. Chem. Soc., Perkin Trans. 2*, 842 (1973) for trans-decahydroquinoline.

Table II

Starting 5,6,7,8-tetrahydroquinoline	Product trans-decahydroquinoline	Yield,[a] %
Unsubstituted	Unsubstituted[b]	90
3-Methyl	3-α-methyl (equatorial)[c,d]	60
	3-β-methyl (axial)[c]	30
8-Methyl	8-α-methyl (equatorial)[c,e]	50
	8-β-methyl (axial)[c,e]	40

[a] Determined by vpc. [b] Mp 48° (petroleum ether) (lit.[3] 48–48.5°). [c] β means "on the same side as the hydrogen at the proximal ring junction," α "on the opposite side from this hydrogen;" cf. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 89. [d] Mp 81° (petroleum ether); a melting point of 70–71° is reported for an unspecified mixture of 3-methyldecahydroquinolines (ref 2). [e] Elemental analysis agreed with theory.

use of trifluoroacetic acid leads to 5,6,7,8-tetrahydroquinoline in 84% yield after only 45 min.

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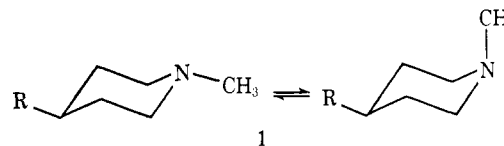University of North Carolina
Chapel Hill, North Carolina 27514*

High Equatorial Preference of the N-Methyl Group in N-Methyl-trans-decahydroquinoline

Sir:

Comparison of the conformational equilibrium of the N-methyl group in an N-methylpiperidine (Scheme I,

Scheme I

1

R = H) with the known equilibrium in methylcyclohexane ($\Delta G° = 1.7$ kcal/mol[1]) is of considerable interest. The $\Delta G°$ value for **1** was originally assessed[2] by a dipole moment measurement on 4-p-chlorophenyl-N-methylpiperidine (Scheme I, R = p-ClC₆H₄) as 1.6–1.7 kcal/mol, essentially identical with the methylcyclohexane value. However, it later appeared[3] that, because of an error in the measurement of the reference moment (p-chlorophenylcyclohexane), the calculated value was too high, and recent dipole measurements, using p-chlorophenyl and p-nitrophenyl (Scheme I, R = p-O₂NC₆H₄) 4-substituted N-methylpiperidines, have yielded a value for $\Delta G°$ of 0.53–0.81 kcal/mol;[4] this value seems to have been accepted by others,[5] even though it appears surprisingly small and even though interpretation of Bohlmann band measurements in the

(1) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.

(2) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Amer. Chem. Soc.*, 87, 1232 (1965); R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc., London*, 257 (1964).

(3) R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc. B*, 493 (1967).

(4) R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc. B*, 122 (1970). The most recently published value—I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J. Chem. Soc., Perkin Trans. 2*, 332 (1973)—based on "optimized geometry" is 0.65 kcal/mol.

(5) See, e.g., J. B. Lambert, D. S. Bailey, and B. F. Michel, *J. Amer. Chem. Soc.*, 94, 3812 (1972).