Table III. Rates of Solvolysis of Bridgehead Chlorides 1b–4b in 80% Aqueous Dioxane

Compound	k_{25} (sec^{-1})	k_{rel}	k_{rel}	$\Delta\Delta G^{\ddagger}$, kcal/mol	$E_{(\varphi)}/E_{(\varphi=0)} = \cos^2\varphi$
1b	$\approx 2.6 \times 10^{-13}$ [a]	1.0		11.5	0.223
2b	6.87×10^{-5}	2.7×10^{8}			
3b	5.81×10^{-8} [b]	2.2×10^{5}	1.0	9.0	0.164
4b	2.24×10^{-1}	8.6×10^{11}	3.9×10^{6}		

[a] Estimated from the experimental solvolysis rate of 1-bromobicyclo[2.2.2]octane[16] in 80% aqueous ethanol, the known rate ratio of *tert*-butyl chloride and *tert*-butyl bromide,[15] and the Y value from ref 15b. [b] Taken from ref 17.

most 10^{12} times faster than **1b**, by this **4b** is the most reactive bridgehead chloride known to date, being 1.6×10^{5} times more reactive than *tert*-butyl chloride.[18] However, only part of this high reactivity of **4b** is due to cyclopropyl stabilization of the intermediate carbenium ion **4c**, the other part originates in a normal strain effect,[19] since the 1-hexahydrobullvalyl chloride **3b** also solvolyzes 2.2×10^{5} faster than **1b**. In fact, the three cyclopropyl groups in **4b** cause a rate enhancement of only 3.9×10^{6} over **3b**, whereas the same three cyclopropyl groups in **2b** enhance the rate by a factor of 2.7×10^{8} over that of **1b**.

This remarkable difference in cation stabilizing power of the three cyclopropyl groups in **2c** and **4c** must be attributed to the second important structural difference between the skeletons **2a** and **4a**, i.e., the difference in the dihedral angles between the axis of a bridgehead orbital and that of an adjacent cyclopropyl p orbital (angle φ in Table I). Since the stabilization energy of a cation by a neighboring electron donating group should be proportional to the overlap between the two interacting orbitals and this overlap for two adjacent p orbitals is proportional to $\cos^2$ of the dihedral angle φ between the two orbital axes,[20] it can be assumed that the relative stabilization of the two tricyclopropyl carbinyl cations **2c** and **4c** can be expressed by

$$E_{(\varphi)}/E_{(\varphi=0)} = \cos^2\varphi$$

With φ(**2a**) = 61.8° and φ(**4a**) = 66.1° this gives 0.223 and 0.164 (see Table III), meaning that the cyclopropyl groups should exhibit 22.3 and 16.4% of their maximum stabilizing ability in **2c** and **4c**, respectively. From the difference in orientation of the cyclopropyl groups in **2c** and **4c** alone one would conclude that **4c** experiences only 74% of the cyclopropyl stabilization effective in **2c**. Experimentally it is observed that the difference in the free energies of activation between **4b** and **3b** is only 78% of the one between **2b** and **1b** (see $\Delta\Delta G^{\ddagger}$ in Table III). This almost perfect agreement between the experimental ratio and the one predicted on the basis of structural differences excludes the possibility that a "leveling effect"[21] might be responsible for the decreased stabilizing ability of the three cyclopropyl groups in **4c**.

The results presented here strongly corroborate the conclusions drawn from CNDO calculations[22] by which the energy change of a cyclopropyl carbinyl cation upon rotation of the cationic center follows a function very similar to a $\cos^2\varphi$ relationship (with φ being the angle of rotation). It should be pointed out, however, that only the comparison of symmetrical systems such as **1–4** can yield a significant structure reactivity relationship for the cyclopropyl carbinyl system. In unsymmetrical systems such as 1-tricyclo[3.2.2.0^{2,4}]nonyl cation[4] distortion of the bridgehead geometry may play an important role.[23]

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Concerning the Role of 4β-Methyl Sterols in Cholesterol Biosynthesis[1]

Sir:

The enzymatic conversion of lanosterol to cholesterol involves the removal of two methyl groups attached to C-4 of the sterol nucleus. Studies of the metabolism of 4,4-dimethyl sterols have indicated initial removal of the equatorial 4α-methyl substituent.[2] This process has been proposed to involve successive oxidations to yield the 4β-methyl-4α-car-

Table I

Compound	Mp, °C	[α]D	NMR C-3α-H (δ)	NMR C-4-CH_3 (J, Hz)	TLC (R_f, silica gel H, $CHCl_3$, 2 developments)	GLC[e] 3% OV-1	GLC[e] 3% OV-17
4α-Methyl-5α-cholest-8-en-3β-ol[15] (VIIa)	136.5–137.5[15]	+55.2°[15]	3.14[a]	6.5[a]	0.23[a]	2.13[a]	2.98[a]
4α-Methyl-5α-cholest-8-en-3β-ol[16] (VIIb)	138–140[a]	—	3.12[a]	6.5[a]	0.23[a]	2.12[a]	2.96[a]
4β-Methyl-5α-cholest-8-en-3β-ol (VI)	155–156.5[a]	+41.6°[a]	3.75[a]	>7[c]	0.19[a]	2.47[a]	3.63[a]
Suspected 4β-methyl-5α-cholest-8-en-3β-ol (VIII)	134–134.5[4]	+50.6°[b]	3.05[b]	6[d]	—	—	—

[a] Experimentally determined in this laboratory. [b] These values are those reported[4,5] for "4β-methyl-5α-cholesta-8,24-dien-3β-ol". The Δ^{24}-double bond has a negligible effect on the magnitude of these parameters. [c] In this particular case the chemical shift of the upfield wing of the C-4-methyl doublet could not be determined accurately due to overlapping resonances. However, the J value was definitely in excess of 7 Hz. [d] Value measured from the partial spectrum published by Sanghvi.[4] [e] These values are retention times relative to cholestane.

boxy-3β-hydroxysterol which, upon dehydrogenation to the 3-ketone in an NAD-dependent reaction, undergoes decarboxylation.[2] The nature of the primary product of this decarboxylation has not been unequivocally established. Gaylor and coworkers[2] have proposed that the initial product is the equatorial 4α-methyl-3-ketone which is then reduced in an NADPH-dependent reaction to give the 4α-methyl-3β-hydroxysterol. An alternative scheme can be envisaged in which the primary product of the decarboxylation reaction is the 4β-methyl-3-ketone which could then undergo epimerization to give the more stable 4α-methyl-3-ketone or be reduced to yield the 4β-methyl-3β-hydroxysterol. The latter possibility or a variant of it has been supported by the reported isolation of 4β-methyl-5α-cholesta-8,24-dien-3β-ol from the skins of rats treated with triparanol[3-5] and the reported isolation of 4β-methyl-5α-cholest-8-en-3β-ol from rat liver homogenates incubated with [^{14}C]mevalonic acid in the presence of cholestan-3β,5α,6β-triol.[6] Moreover, the efficient conversion of this sterol to cholesterol upon incubation with rat liver homogenates has been reported.[6]

The purpose of this communication is to report the chemical synthesis of 4β-methyl-5α-cholest-8-en-3β-ol and to present comparisons of its properties with those of its 4α-methyl isomer and of 4-methyl sterols, isolated from animal tissues, to which an assignment of the 4β-methyl configuration has been made. In addition, an assessment of the enzymatic convertibility of 4β-methyl-5α-cholest-8-en-3β-ol to cholesterol is reported herein.

3β-Acetoxy-4β-methyl-cholest-5-ene (I) was prepared by the method of Julia and Lavaux.[7] Allylic bromination of I with dibromodimethylhydantoin followed by dehydrobromination with collidine in xylene yielded, after two recrystallizations from ether-methanol, 3β-acetoxy-4β-methyl-cholesta-5,7-diene (II).[8] Treatment of diene (II) with a refluxing mixture of HCl-benzene-95% ethanol (1:4:10) yielded, after purification of the crude product by preparative TLC on 12% silver nitrate on silica gel G[9] and crystallization from methanol-water, 4β-methyl-5α-cholesta-8,14-dien-3β-ol (III).[10] Alternative work-up of the crude reaction mixture by acetylation followed by purification by column chromatography (12% silver nitrate on alumina) and two recrystallizations from ether-methanol gave 3β-acetoxy-4β-methyl-5α-cholesta-8,14-diene (IV).[11] Catalytic reduction (Raney nickel; 40 psi) of III in benzene yielded a crude product which gave, after acetylation and purification on an alumina-Super Cel-silver nitrate column[12] and crystallization from methanol-water, 3β-acetoxy-4β-methyl-5α-cholest-8-ene (V).[13] Catalytic reduction (Raney nickel; 40 psi) of IV and purification of the crude product on an alumina-Super Cel-silver nitrate column[12] and crystallization from methanol yielded 3β-acetoxy-4β-methyl-5α-cholest-8-ene (V).[13] Reduction of V with lithium aluminum hydride in ether yielded 4β-methyl-5α-cholest-8-en-3β-ol (VI)[14] as needles from methanol-water.

Table I provides data collected and reported for 4β-methyl-5α-cholest-8-en-3β-ol (VI), its 4α-methyl isomer (VII), and the suspected "4β-methyl-5α-cholesta-8,24-dien-3β-ol" (and its 24,25-dihydro derivative (VIII)).[3-5] VI and VII can be distinguished from each other by melting point, optical rotation, NMR,[17] TLC, GLC, and IR (vide infra). The mass spectra of VI and VII are essentially identical. The cited data published by Sanghvi et al.[3-5] do not support the assignment of the 4β-methyl configuration for the 4-methyl sterol isolated from skins of triparanol-treated rats. Assignment of the 4β-methyl configuration to the sterol isolated from liver (IX)[6] was based largely on the identity of its ir spectra with the spectra presented for VIII by Sanghvi.[5] The ir spectra of VIIa, VIIb, VIII, and IX are essentially indistinguishable. The spectrum of VI differs markedly from those of VIIa, VIIb, VIII, and IX in the 1350–700-cm^{-1} region. It is concluded that the 4-methyl sterols[3-6] previously assigned the 4β-methyl configuration most probably represent 4α-methylsterols.

In further studies we have prepared [3α,4α-^{3}H]-4β-methyl-5α-cholest-8-en-3β-ol (X) by chemical synthesis from [3α,4α-^{3}H]-4β-methyl-cholest-5-en-3β-ol[18] using the same synthetic approach outlined above. No conversion of labeled X to cholesterol upon incubation with a 10,000*g* supernatant fraction of a rat liver homogenate could be detected,[19] a finding in variance with the results reported by Scallen et al.[6] for labeled IX.

In summary, the evidence presented herein does not support a significant role of 4β-methyl-3β-hydroxysterols in the biosynthesis of cholesterol.

References and Notes

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(8) Compound II, mp 144–145°; single component on TLC and GLC; uv, λ_{max} 263 nm (log ε 3.63), 274 (log ε 4.03), 283 (log ε 4.03), 296 (log ε 3.52); MS 440 (M; 100%), calcd for $C_{30}H_{48}O_2$: 440.3654, found: 440.3663; NMR 1.15 (d, J = 7.2 Hz, 3 H, 4β-CH_3), 2.04 (s, 3 H, methyl of acetate), 2.87 (m, 1 H, C-4α-H), 4.87 (m, 1 H, C-3α-H), and 5.61 (m, 2 H, C-6-H and C-7-H).
(9) Solvent system, 5% acetone in chloroform.
(10) Compound III, mp 140–141°; purity in excess of 95% as judged by TLC and GLC; uv, λ_{max} 251 nm (log ε 4.26); MS 398 (M; 100%), calcd for $C_{28}H_{46}O$: 398.3548, found: 398.3561; NMR 0.92 (d, 3 H, J = 6–8 Hz, 4β-CH_3), 3.81 (m, 1 H, C-3α-H), 5.44 (m, 1 H, C-15-H).

(11) Compound IV, mp 134.5–135.0°; purity in excess of 99% as judged by TLC and GLC; MS 440 (M; 100%), calcd for $C_{30}H_{48}O_2$: 440.3654, found: 440.3663; NMR 0.99 (d, J = 8 Hz, 4β-CH_3), 2.03 (s, 3 H, methyl of acetate), 4.78 (m, 1 H, C-3α-H).

(12) Prepared and developed as described previously (W.-H. Lee, R. Kammereck, B. N. Lutsky, J. A. McCloskey, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **244**, 2033 (1969).

(13) Compound V, mp 128.5–130°; purity in excess of 98% as judged by TLC and GLC; MS 442 (M; 100%), calcd for $C_{30}H_{50}O_2$: 442.3790, found: 442.3810; NMR 0.89 (d, 3 H, J = 7.2 Hz, 4β-CH_3), 2.07 (s, 3 H, methyl of acetate), 4.82 (m, 1 H, C-3α-H).

(14) Compound VI, mp 155–156.5°; purity in excess of 99% as judged by TLC and GLC; MS 400 (M; 100%), calcd for $C_{26}H_{48}O$: 400.3702, found: 400.3704; NMR, 0.92 (d, 3 H, J = 7–8 Hz, 4β-CH_3), 3.75 (m, 1 H, C-3α-H); $[\alpha]_{589}$ +41.6° ($CHCl_3$).

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(17) In a separate study (F. F. Knapp, Jr., and G. J. Schroepfer, Jr., manuscript submitted for publication) of a large number of synthetic 4α-methyl- and 4β-methyl-3β-hydroxysterols, it has been established that the 3α-proton resonance is consistently further downfield (0.57–0.61 ppm) and the C-4-methyl group coupling constant (J) is larger (1.2–1.8 Hz) for the 4β-methyl sterols.

(18) Prepared by the specific approach utilized for the preparation of [3α,4α-$^2H_2$]-4β-methyl-cholest-5-en-3β-ol (F. F. Knapp, Jr., and G. J. Schroepfer, Jr., *J. Org. Chem.*, **39**, 3247 (1974)).

(19) Over 90% of the incubated radioactivity was extracted into petroleum ether from saponified incubation mixtures, values comparable to those of boiled enzyme controls. The only labeled component recovered showed the chromatographic mobility of the incubated substrate. Under the incubation conditions employed, the label of [3α-^{3}H]-14α-methyl-5α-cholest-7-en-3β-ol was efficiently (40–60%) incorporated into cholesterol.

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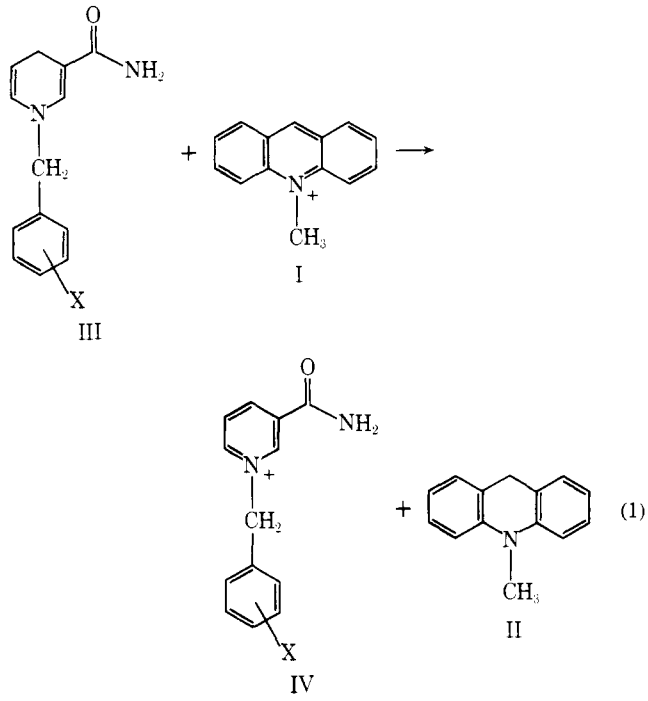
Model Dehydrogenase Reactions. Neighboring Group Effects in Dihydronicotinamide Reductions

Sir:

Recent X-ray crystallographic studies of an abortive ternary complex of the NAD^+-dependent lactate dehydrogenase from dogfish have revealed that the carboxylate of a glutamyl residue is in close proximity to the nitrogen of the bound coenzyme's nicotinamide moiety.[1] We wish to report a nonenzymic reaction which suggests the catalytic function of this residue. Specifically, we have found that dihydronicotinamide derivatives in which a carboxylate is adjacent to the nicotinamide moiety reduce nonenzymic oxidants in anhydrous media much more rapidly than homologous dihydronicotinamides in which the carboxylate is absent. The acceleratory effect of the neighboring carboxylate group in acetonitrile is most likely due to the stabilization of the developing positive charge on the nicotinamide ring in the transition state. By analogy, the role of the active site glutamate may be to stabilize the partial positive charge which develops in the nicotinamide moiety of the coenzyme in the transition state during its reversible oxidation and reduction by pyruvate and lactate. These studies provide the first example of a noncovalent interaction capable of enhancing the reactivity of a dihydronicotinamide that is of potential importance in the mechanism of action of $NAD^+/NADP^+$-dependent dehydrogenases. Previous nonenzymic studies have focused on mechanisms of enhancing the reactivity of the hydride acceptors.[2-4]

Our most important observation, reported in Table I, is that the second-order rate constant for the reduction of N-methylacridinium ion by N-2′-carboxybenzyldihydronicotinamide (IIIh) in acetonitrile is two orders of magnitude greater than the corresponding rate constant for N-benzyldihydronicotinamide (IIIa) or any of its other 2′- or 4′-substituted derivatives (IIIa-g). The observed kinetic isotope effect for this reduction using monodeuterio-N-2′-carboxybenzyldihydronicotinamide (IIIh) is 1.11. The ratio of undeuterated N-methylacridan (m/e, 195) to monodeuterio-N-methylacridan (m/e, 196) formed, using the monodeutero form of IIIh as reductant, is 3.8. Similar isotope effects have been observed for the reduction of N-methylacridinium ion[5] and trifluoroacetophenone[6] by N-propyldihydronicotinamide in aqueous solution. They suggest the formation of a noncovalent complex between the "hydride donor" and "hydride acceptor" during the course of the reaction.[5,6]



Since the various neutral dihydronicotinamides react with I considerably faster in water than in acetonitrile, a significant amount of positive charge must develop on the nicotinamide ring in the transition state at the expense of the larger acridinium cation. As noted above, we propose that the ability of the negatively charged carboxylate of IIIh to stabilize this positive charge in acetonitrile is primarily responsible for the efficiency of IIIh as a reductant compared to the neutral dihydronicotinamides. Comparable rate accelerations are not observed in aqueous solution because water is probably better able to stabilize the incipient positive charge and the hydration of the carboxylate group in aqueous solution would restrict its access to the dihydronicotinamide ring. In acetonitrile, the carboxylate is less effectively solvated[7] and therefore able to approach the nicotinamide ring more readily. Moreover, electrostatic interactions would be greater in acetonitrile because of the lower dielectric constant. Consistent with the presence of a negative charge at the nitrogen of the dihydronicotinamide in acetonitrile, we have found a red shift in the characteristic dihydronicotinamide absorption of IIIh in acetonitrile.[8]

Inductive effects are not responsible for the enhanced reactivity of IIIh because the rate constants for the reduction by other N-benzyldihydronicotinamides exhibit little sensitivity to substituents on the phenyl ring. The possibility that the carboxylate group permits the formation of a reactive