On the C-25 Chirality of 26-Hydroxycholesterol[1]

Chang-Yon Byon, Marcel Gut,* and Voldemar Toome[2]

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

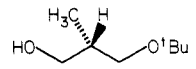
Received May 19, 1981

The stereospecific synthesis of (25*S*)-26-hydroxycholesterol with a chiral synthon derived from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid is described and the Cotton effects of the CD spectra were found not to be a general means for distinguishing epimers of monohydric secondary alcohols or for distinguishing epimers in which the chiral center is in the α position to the primary alcoholic function.

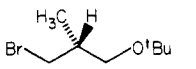
Our interest in the catabolism of cholesterol in the liver and, specifically, the claim of stereospecific microsomal "26"-hydroxylation in the bile acid biosynthesis[3-5] led us to develop methods for the separation and identification of the two 25-epimers of 26-hydroxycholesterol.

The description of the synthesis of chiral synthons derived from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid by Cohen et al.[6] allowed for the syntheses of (25*R*)- and (25*S*)-26-hydroxycholesterol and thereby an easy testing for the difficult separation of these two epimers by HPLC.[7,8]

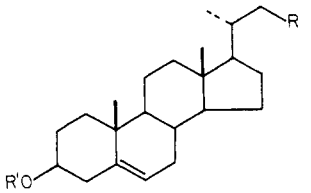
The briefly mentioned 3β-(tetrahydropyranyloxy)-23,24-bisnorchol-5-en-22-ol[9] (**3**) was tosylated (*p*-TsCl/Py)

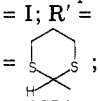


1
(*S*)-(−)-3-*tert*-butoxy-2-methyl-1-propanol

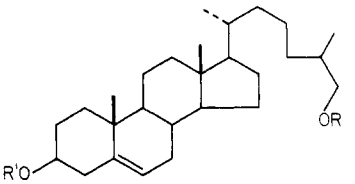


2
(*R*)-(−)-3-*tert*-butoxy-2-methyl-1-bromopropane



3, R = OH; R′ = THP
4, R = $OSO_2C_6H_4CH_3$; R′ = THP
5, R = I; R′ = THP
6, R =  ; R′ = THP
7, R = CHO; R′ = H
8, R = CHO; R′ = THP
9, R = CH_2OH; R′ = THP
10, R = CH_2OTs; R′ = THP

and the tosyloxy group displaced by iodine (NaI/acetone, reflux) to give 3β-(tetrahydropyranyloxy)-22-iodo-23,24-bisnorchol-5-ene (**5**). 1,3-Dithiane was alkylated (*n*-butyllithium) with this iodide to give the dithiane product (**6**), which upon hydrolysis (mercuric oxide), reprotection with THP ether, and reduction gave 3β-(tetrahydropyranyloxy)-24-norchol-5-en-23-ol (**9**). The alcohol was tosylated and this ester reacted with the Grignard solution prepared from (*R*)-(−)-3-*tert*-butoxy-2-methyl-1-bromopropane (**2**). This bromide was prepared from (*S*)-(−)-3-*tert*-butoxy-2-methylpropan-1-ol (**1**) by displacement with triphenylphosphine/NBS. The resulting (25*S*)-3β-(tetrahydropyranyloxy)-26-hydroxycholesterol 26-*tert*-butyl ether (**11**) was hydrolyzed with trifluoroacetic acid to give the desired (25*S*)-26-hydroxycholesterol (**13**).



11, R = *t*-Bu; R′ = THP
12, R = *t*-Bu; R′ = H
13, R = H; R′ = H
14, R = $COCF_3$; R′ = H
15, R = *t*-Bu; R′ = $COCH_3$
16, R = H; R′ = $COCH_3$
17, R = $COCF_3$; R′ = $COCH_3$
18, R = CO-*p*-BrC_6H_4; R′ = $COCH_3$

This 25*S* epimer was acetylated and showed identical retention (on HPLC) with the less polar diacetate, obtained from the transformation[10] of kryptogenin to 26-hydroxycholesterol (25-isomeric mixture). The investigation of the material obtained from several reductions of kryptogenin indicated a variable content of 3–10% of the 25*S* epimer, while the material obtained, according to Varma et al.[11] by hydroboration of 3β-hydroxycholesta-5,25-diene 3β-tetrahydropyranyl ether, gave ~1:1 mixture of epimers.

As in the case of several other epimeric benzoic acid esters of acyclic secondary alcohols,[12] the CD spectra of both epimers (25*R*)- and (25*S*)-3β-acetoxy-26-[(*p*-bromobenzoyl)oxy]cholest-5-ene in methanol exhibit positive Cotton effects at around 244–240 nm (Table I) due to the *p*-bromobenzoyl chromophore. Therefore, it seems that the sign of the Cotton effects of the CD spectra are not a general means for distinguishing epimers of monohydric secondary alcohols or for distinguishing epimers in which the chiral center is in α position to the primary alcoholic function, as claimed in the literature.[11] The positive and negative Cotton effects observed by Varma et al.[11] in the case of the two C-25 epimeric (25*S*)- and (25*R*)-cholest-4-ene-3β,26-diol 26-*p*-bromobenzoates could not be reproduced by us.

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The UV spectra were determined

(1) This study was supported, in part, by U.S. Public Health Service Grant AM-03419 from the Institute of Arthritis and Metabolic Diseases and by a grant from the National Science Foundation (PMC 78-19594).
(2) Research Division of Hoffmann-La Roche, Inc., Nutley, NJ.
(3) O. Berseus, *Acta Chem. Scand.*, **19**, 325 (1965).
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(12) In the series of the following benzoylated steroids: (22*R*)- and (22*S*)-22-(benzoyloxy)-3β-hyroxycholest-5-ene and (20*R*)- and (20*S*)-3β,21-diacetoxy-20-(benzoyloxy)pregn-5-ene, both *R* and *S* isomers were found to exhibit negative CD bands at around 230 nm; V. Toome, unpublished observations.

0022-3263/81/1946-3901$01.25/0

Table I

compound	chirality	origin of sample	CD in methanol Δε	CD in methanol λ, nm
3β-acetoxy-26-[(*p*-bromobenzoyl)oxy]cholest-5-ene	25*S*	synthesis **18**	+0.55	242
	25*S*	kryptogenin	+0.39	240/242
	25*R*	kryptogenin	+0.46	242/244
(25*R*)-26-[(*p*-bromobenzoyl)oxy]cholest-4-en-3β-ol	25*R*	kryptogenin[11]	−0.80	244
(25*S*)-26-[(*p*-bromobenzoyl)oxy]cholest-4-en-3β-ol	25*S*	microbial transformation[11]	+0.78	244

in methanolic solutions on a Cary Model 14 recording spectrophotometer. The IR spectra were determined as KBr pellets. The NMR spectra were obtained in deuteriochloroform solution, using tetramethylsilane as an internal reference, and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane. The CD curves were recorded in methanol on a JASCO J-20 automatic recording spectropolarimeter.

23,24-Bisnorchol-5-ene-3β,22-diol 3β-Tetrahydropyranyl Ether (3). To the stirred mixture of 10 g of 3β-hydroxy-23,24-bisnorchol-5-en-22-oic acid and 200 mg of *p*-toluenesulfonic acid in 100 mL of tetrahydrofuran was added 7 mL of dihydropyran. After 20 min all solids were in solution, and after 2 h the solution was poured into a saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, washed with water, dried, and evaporated. The crude residue (7.45 g) was directly reduced with excess lithium aluminum hydride in tetrahydrofuran (4 h reflux). The crude product, after recrystallization from methanol, gave 6.85 g of 23,24-bisnorchol-4-ene-3β,22-diol 3β-tetrahydropyranyl ether (**3**): mp 155–157 °C; IR ν 3500 (OH), 1090 and 980 cm^{-1} (THP-ether); NMR δ 0.73 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.05 (d, 3 H, J = 6 Hz, 21-CH_3), 3.47 (m, 2 H, CH_2OH), 5.35 (m, 1 H, 6-H).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.94; H, 10.82.

22-(Tosyloxy)-23,24-bisnorchol-5-en-3β-ol 3β-Tetrahydropyranyl Ether (4) from 3. A solution of 6.0 g of the alcohol **3** and 7.0 g of *p*-toluenesulfonyl chloride in 50 mL of pyridine was left standing for 18 h at 22 °C. Then water was added and the precipitate was filtered off and washed with water. Two recrystallizations from methanol gave 6.75 g of tosylate **4**: mp 185–187 °C; IR ν 1160 (tosylate), 1020 and 930 cm^{-1} (THP–ether); NMR δ 0.73 (s, 3 H, 18-CH_3), 0.97 (d, 3 H, J = 6 Hz, 21-CH_3), 0.98 (s, 3 H, 19-CH_3), 2.43 (s, 3 H, $C_6H_4CH_3$) 5.33 (m, 1 H, 6-H), 7.20–7.80 (m, 4 H, aromatic H).

Anal. Calcd for $C_{34}H_{50}O_5S$: C, 71.55; H, 8.33; S, 5.61. Found: C, 71.47; H, 8.66; S, 5.64.

3β-(Tetrahydropyranyloxy)-22-iodo-23,24-bisnorchol-5-ene (5) from 4. A solution of 4.5 g of tosylate **4** and 3 g of sodium iodide in 150 mL of dry acetone was heated under reflux for 17 h. Most of the solvent was evaporated in vacuo, the residue was extracted with methylene chloride, and the solution was dried over anhydrous sodium sulfate and evaporated. Recrystallization from acetone gave 4.1 g of pure iodide **5**: mp 136–139 °C; NMR δ 0.73 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 3.28 (m, 2 H, CH_2I), 4.73 (m, 1 H, OCHO), 5.38 (m, 1 H, 6-H).

Anal. Calcd for $C_{27}H_{43}IO_2$: C, 61.59; H, 8.23; I, 24.10. Found: C, 61.93; H, 8.26; I, 23.82.

(*R*)-(−)-3-*tert*-Butoxy-2-methyl-1-bromopropane (2). This compound was prepared from (*S*)-(−)-3-*tert*-butoxy-2-methylpropan-1-ol as described.[6]

3β-Hydroxy-23-(1,3-dithianyl)-24-norchol-5-ene 3-Tetrahydropyranyl Ether (6). To a solution of 2.3 g of 1,3-dithiane in 30 mL of tetrahydrofuran, which was cooled in a dry ice-acetone bath, was added dropwise 8.4 mL of *n*-butyllithium (2.4 M in hexane). The mixture was stirred for 2.5 h at −25 °C. Then a solution of 3.4 g of iodide **5** in 30 mL of tetrahydrofuran was added dropwise at −10 °C and the mixture was stirred for 1 h at −15 °C and stirred an additional 15 h at 3 °C. The mixture was poured into water and extracted with methylene chloride. The extract was washed with a 3% aqueous sodium bisulfite solution, 2 N sodium hydroxide, and saline, dried, and evaporated to give 4.7 g of crude dithiane. Recrystallization from acetone–hexane gave 3.06 g of **6**: mp 147–148 °C; NMR δ 0.70 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 2.82 (m, 6 H, $SCH_2CH_2CH_2S$), 4.68 (m, 1 H, OCHO), 5.33 (m, 1 H, 6-H).

Anal. Calcd for $C_{31}H_{50}O_2S_2$: C, 71.78; H, 9.72; S, 12.34. Found: C, 71.35; H, 9.64; S, 12.36.

3β-(Tetrahydropyranyloxy)-24-norchol-5-en-23-ol (9). To the mixture of 520 mg mercuric oxide in 4.8 mL of 15% aqueous tetrahydrofuran and 0.4 mL of boron trifluoride etherate was added 600 mg of dithiane **6** in 6 mL of tetrahydrofuran in the course of 10 min. The mixture was stirred for 15 min at 25 °C and refluxed for 20 min and then cooled to 25 °C. Ether was added to this mixture which was filtered through Celite. The filtrate was washed with 2 N sodium carbonate solution and saline and dried.

A solution of 447 mg of crude hydroxy aldehyde **7** and 30 mg of *p*-toluenesulfonic acid and 0.4 mL of dihydropyran in 3 mL of tetrahydrofuran was left standing for 30 min. Then the mixture was poured into salt water, extracted with methylene chloride, dried, and evaporated to give 500 mg of crude tetrahydropyranyl ether aldehyde **8**.

A solution of 500 mg of crude aldehyde **8** in 2 mL of anhydrous ether was added dropwise to the solution of 30 mg of lithium aluminum hydride in anhydrous ether and stirred under reflux for 15 min. Excess lithium aluminum hydride was destroyed with 2 N sodium hydroxide by dropwise addition. Then the mixture was filtered through Celite, dried, and evaporated. The residue was purified by preparative TLC (25% acetone in hexane) to give 206 mg of **9**. An analytical sample was prepared by recrystallization from acetone: mp 140–143 °C; NMR δ 0.68 (s, 3 H, 18-CH_3), 0.94 (d, 3 H, J = 6 Hz, 21-CH_3), 0.99 (s, 3 H, 19-CH_3), 4.70 (m, 1 H, OCHO), 5.32 (m, 1 H, 6-H).

Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 77.87; H, 10.74.

3β-(Tetrahydropyranyloxy)-23-(tosyloxy)-24-norchol-5-ene (10). The tosylate **10** was prepared by treating **9** with *p*-toluenesulfonyl chloride in the same manner as described for **8**. An analytical sample was prepared by recrystallization from hexane: mp 137–138 °C; NMR δ 0.63 (s, 3 H, 18-CH_3), 0.85 (d, 3 H, J = 6 Hz, 21-CH_3), 0.99 (s, 3 H, 19-CH_3), 2.44 (s, 3 H, $C_6H_4CH_3$), 4.70 (m, 1 H, OCHO), 5.32 (m, 1 H, 6-H), 7.33 and 7.78 (d, 4 H, J = 8 Hz, aromatic protons).

Anal. Calcd for $C_{35}H_{52}O_5S$: C, 71.90; H, 9.0; S, 5.50. Found: C, 72.15; H, 9.25; S, 5.88.

(25*S*)-3β-(Tetrahydropyranyloxy)-26-hydroxycholesterol 26-*tert*-Butyl Ether (11). To a solution of 620 mg of tosylate **10** in 2 mL of dry tetrahydrofuran was added a Grignard solution (40 mg of Mg powder, 300 mg of bromide **2** in 1.5 mL of dry tetrahydrofuran) dropwise at −70 °C followed by 0.05 mL of a 0.1 M $LiCuCl_4$[6] solution in dry tetrahydrofuran. The resulting mixture was stirred at −70 °C for 10 min, then in an ice bath for 2 h, and at 25 °C for 16.5 h. Then 20 drops of 1 N aqueous sulfuric acid were added to this mixture which was extracted with ether. The residue, after evaporation of solvent, was purified by preparative TLC to give 135 mg of desired product **11** and 173 mg of starting material and 232 mg of undetermined byproduct, which was less polar than **11**.

An analytical sample was prepared by recrystallization from acetone: mp 74–76 °C; NMR δ 0.65 (s, 3 H, 18-CH_3), 0.85 (d, 3 H, J = 6 Hz, 27-CH_3), 0.89 (d, 3 H, J = 6 Hz, 21-CH_3), 0.98 (s, 3 H, 19-CH_3), 1.14 (s, 9 H, CMe_3), 4.70 (m, 1 H, OCHO), 5.32 (m, 1 H, 6-H).

Anal. Calcd for $C_{36}H_{62}O_3$: C, 76.64; H, 11.51. Found: C, 79.23; H, 11.84.

(25*S*)-26-Hydroxycholesterol (13). To a solution of 90 mg of butyl ether **11** in 0.7 mL of tetrahydrofuran was added dropwise 0.72 mL of precooled trifluoroacetic acid. The mixture was stirred for 4 h in an ice bath. Then 7 mL of 5% methanolic sodium hydroxide was added to the mixture and the mixture was stirred

for 15 min at 25 °C. The alkaline solution was diluted with water and extracted with ethyl acetate. After drying, the solvent was evaporated to give 71 mg of crude hydroxy *tert*-butyl ether **12**: NMR δ 0.65 (s, 3 H, 18-CH_3), 0.85 (d, 3 H, J = 6 Hz, 27-CH_3), 0.89 (d, 3 h, J = 6 Hz, 21-CH_3), 0.98 (s, 3 H, 19-CH_3), 1.14 (s, 9 H, -CMe_3), 3.11 (m, 2 H, OCH_2), 5.32 (m, 1 H, 6-H).

To 20 mg of hydroxy *tert*-butyl ether **12** was added dropwise 0.6 mL of precooled trifluoroacetic acid in an ice bath and stirring was continued for 4 h; then the solution was concentrated in vacuo. To the residue was added 1 mL of 5% methanolic sodium hydroxide and the reaction was worked up in the same manner as described above. Purification by TLC (20% acetone in hexane) gave 4 mg of **13** and 3.7 mg of hydroxy ester **14** and some undetermined byproducts. The diol **13** had a smaller R_f value than that of the ester. **13**: mp 171-174 °C; NMR δ 0.66 (s, 3 H, 18-CH_3), 0.90 (d, 6 H, J = 6 Hz, 21,27-CH_3), 1.00 (s, 3 H, 19-CH_3), 3.54 (m, 3 H, 3,26-H), 5.32 (m, 1 H, 6-H); mass spectrum calcd for $C_{27}H_{46}O_2$ 402.349 78, found 402.349 65.

(25*S*)-3β-Acetoxy-26-[(*p*-bromobenzoyl)oxy]cholest-5-ene (18). A solution of 40 mg of crude **12** and 0.1 mL of acetic anhydride in 0.5 mL of pyridine was left standing overnight. The mixture was poured into water and extracted with methylene chloride. The combined extracts were washed with 2 N aqueous hydrochloric acid, saturated sodium bicarbonate, and water, then dried, and evaporated to give 41 mg of crude ester **15**: NMR δ 0.67 (s, 3 H, 18-CH_3), 0.91 (d, 6 H, J = 6 Hz, 21,27-CH_3), 1.01 (s, 3 H, 19-CH_3), 4.19 (m, 2 H, CH_2O).

To 40 mg of crude **15** was added dropwise 0.7 mL of precooled trifluoroacetic acid, and the mixture was stirred for 4 h in an ice bath and worked up in the same manner as described before. The crude mixture was purified on TLC (15% acetone in hexane) to give 4 mg of desired hydroxy ester **16** and diester **17**. NMR of **16**: δ 0.67 (s, 3 H, 18-CH_3), 0.91 (d, 6 H, J = 6 Hz, 21,27-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.03 (s, 3 H, $COCH_3$), 3.45 (m, 2 H, CH_2O), 4.63 (m, 1 H, 3-H), 5.40 (m, 1 H, 6-H). NMR of **17**: δ 0.67 (s, 3 H, 18-CH_3), 0.91 (d, 6 H, J = 6 Hz, 21,27-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.03 (s, 3 H, $COCH_3$), 4.19 (m, 2 H, CH_2O), 4.63 (m, 1 H, 3-H), 5.40 (m, 1 H, 6-H).

A solution of 4 mg of the alcohol **16** and 5 mg of *p*-bromobenzoyl chloride in 0.2 mL of pyridine was allowed to stand overnight and worked up as described above. The crude ester was purified on TLC (CH_2Cl_2 as eluant) to give 5 mg of *p*-bromobenzoate **18**: NMR δ 0.67 (s, 3 H, 18-CH_3), 0.91 (d, 3 H, J = 6 Hz, 21-CH_3), 1.00 (d, 3 H, J = 6 Hz, 27-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.03 (s, 3 H, $COCH_3$), 4.17 (m, 2 H, CH_2O), 4.63 (m, 1 H, 3-H), 5.40 (m, 1 H, 6-H); mass spectrum, m/e 566 (M^+ - 60), 551 (M^+ - 75), 366 (M^+ - 260), 351 (M^+ - 275).

Acknowledgment. We are most grateful to Drs. Noal Cohen and Milan R. Uskokovič of Hoffmann-La Roche, Inc., Nutley, NJ, for helpful discussions and for the donation of a generous amount of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid and to the Northeast Regional NSF-NMR Facility at Yale University for the registration of high-resolution NMR spectra.

Reverse Anomeric Effect of the Carbamoyl Group of 2,6-Anhydroheptonamides

Marek Chmielewski,[1] James N. BeMiller,* and Douglas Pat Cerretti

Department of Chemistry and Biochemistry, Southern Illinois University at Carbondale, Carbondale, Illinois 62901

Received March 26, 1981

Photoaddition of formamide–acetone to 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol yields seven products; of these 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*ido*-heptonamide and 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptonamide, which can be converted into *C*-glycosyl compounds of α-D-gluco- and α-D-mannopyranoses, respectively, are of particular interest. In the same way, photoaddition of formamide–acetone to 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol gave six products, including 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*gluco*-heptonamide, a precursor of *C*-glycosyl compounds of α-D-galactopyranose. Analysis of the ^{1}H NMR spectral data of these formamide addition products revealed that all compounds in the "α-D" configuration existed predominantly in the $^2C_5$ conformation in $CDCl_3$ despite extensive 1,3-diaxial nonbonded interactions. However, when the more polar solvent Me_2SO-d_6 was used, these compounds existed only in the $^5C_2$ conformation. Anhydroheptonamides of the "β-D" configuration existed only in the $^5C_2$ conformation in either solvent. A polar effect that is a combination of a large reverse anomeric effect and other polar interactions is used to explain the shift in conformational equilibria.

Glycosides, oligosaccharides, and polysaccharides with the α-D configuration are important in nature, and their corresponding *C*-glycosyl analogues are of interest because of their potential as competitive inhibitors of glycohydrolases and glycosyltransferases. However, synthesis of *C*-glycosyl compounds of hexopyranoses (2,6-anhydroheptitols) in which the "glycosidic bond"[2] has the α-D configuration is more difficult than the synthesis of *C*-glycosyl compounds with the β-D configuration owing to two factors: (i) thermodynamic (the substituent group on the "anomeric"[2] carbon atom prefers the equatorial position over the axial position) and (ii) kinetic (participation of a 2-O-substitutent favors the relative trans configuration at the C-1 and C-2 carbon atoms, i.e., the β-D configuration in the case of those C-glycosyl compounds with the D-gluco and D-galacto configurations at C-3, -4, -5, and -6).[3] The purpose of this work was to find an efficient route to substituted 2,6-anhydroheptitols with the α-D configuration at C-1–C-2 which can then be transformed into a variety of *C*-glycosyl compounds.

Known methods based on displacement of the halogen atom of glycosyl halides by carbanions yield compounds with the β-D configuration of the anomeric carbon atom.[4]

(1) Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland.

(2) The same nomenclature used with ordinary *O*-glycosides is used to describe the configuration of *C*-glycosyl compounds. Thus, a *C*-glycosyl compound with the α-D configuration is the compound with the same configuration as an α-D-hexopyranoside but with a methylene group in place of O-1, and what would be the central carbon atom in the O–C–O acetal linkage if the compound were an *O*-glycoside is still referred to as the anomeric carbon atom.

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0022-3263/81/1946-3903$01.25/0