possible complexity in the quantitative analysis of these CIDNP intensities.

Polarizations from the carbons of olefin **2** were not observed during irradiation of **2**. Likewise, CIDNP signals were not detected during the photolysis of acid chloride **3** or chloride **4** under the reaction conditions.

Experimental Section

All chemicals were commercially available and were used without further purification. Solutions were deaerated by a stream of high-purity nitrogen. The products of the photolysis were identified with a Hewlett-Packard Model 5700A/5930A GC–MS system in addition to carbon-13 chemical shifts.

Carbon-13 NMR Measurements. Carbon-13 NMR spectra were obtained at 25.15 MHz on a Varian HA-100 spectrometer modified for pulsed operation and equipped with an external fluorine-19 field-frequency lock.[13] Free induction decays were accumulated and Fourier transformed with a NIC-80 data system. Typically, 100 free induction decays were accumulated using a pulse interval of 10 sec. A 90° pulse took 130 μsec. The probe temperature was 44 ± 2° and 7.5 mm o.d. quartz sample tubes were used. Identical phase corrections were applied to spectra obtained before, during, and after irradiation. Chemical shifts were assigned by comparison with spectra of authentic compounds, which were run as 25% solutions in CCl_4. Chemical shifts were converted to the Me_4Si scale using $\delta_{Me_4Si} = \delta_{CCl_4} + 96.0$.

Photolysis Experiments. Light from a 600-W Hg–Xe arc source was focused through a water filter, Corning filters no. CS-056 and CS-954, and onto the polished end of a quartz rod which terminated 1 mm from the bottom of the sample tube. The combined Corning filters had a measured transmittance of greater than 50% at wavelengths longer than 290 nm and less than 1% at wavelengths shorter than 250 nm. Deaerated 25% solutions of DTBK in CCl_4 were used in the photolysis experiments. For the photolysis of compounds **1**, **2**, **3**, and **4**, 10% solutions were used.

INDO Calculations. The signs of the electron–carbon hyperfine interaction constants for the pivaloyl and *tert*-butyl radicals were obtained using the INDO semiempirical method.[14] Standard geometries were assumed and QCPE program 142 was used for the calculations. All the $A(C^{13})$'s for the pivaloyl radical were calculated to be positive while for the *tert*-butyl radical $A(C^{\alpha})$ is positive and $A(C^{\beta})$ is negative. The $A(C^{13})$ for the trichloromethyl radical is positive.[15]

Registry No.—**1**, 630-19-3; **2**, 115-11-7; **3**, 3282-30-2; **4**, 507-20-0; **5**, 56087-10-6; DTBK, 815-24-7; $CHCl_3$, 67-66-3.

References and Notes

(1) Presented in part at the 9th Middle Atlantic Regional Meeting of the American Chemical Society, Wilkes-Barre, Pa., April 1974.
(2) (a) C. Brown, R. F. Hudson, and A. J. Lawson, *J. Am. Chem. Soc.*, **95**, 6500 (1973); (b) H. Iwamura, M. Iwamura, M. Imanari, and M. Takeuchi, *Tetrahedron Lett.*, 2325 (1973); (c) R. Kaptein, R. Freeman, H. D. W. Hill, and J. Bargon, *Chem. Commun.*, 953 (1973); (d) A. V. Kessenikh, P. V. Petrovskii, and S. V. Rykov, *Org. Magn. Reson.*, **5**, 227 (1973); (e) S. Berger, S. Hauff, P. Niederer, and A. Rieker, *Tetrahedron Lett.*, 2581 (1972).
(3) (a) B. Blank, A. Henne, and H. Fischer, *Helv. Chim. Acta*, **57**, 920 (1974); (b) M. Tomkiewicz, A. Groen, and M. Cocivera, *J. Chem. Phys.*, **56**, 5850 (1972); *Chem. Phys. Lett.*, **10**, 39 (1971).
(4) See A. R. Lepley and G. L. Closs, Ed., "Chemically Induced Magnetic Polarization", Wiley, New York, N.Y., 1973.
(5) (a) R. A. Cooper, R. G. Lawler, and H. R. Ward, *J. Am. Chem. Soc.*, **94**, 552 (1972); (b) R. Kaptein, *ibid.*, **94**, 6262 (1972).
(6) R. Kaptein, *Chem. Commun.*, 732 (1971).
(7) H. Fischer and G. P. Laroff, *Chem. Phys.*, **3**, 217 (1974).
(8) G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, **39**, 1276 (1974).
(9) N. C. Yang, E. D. Feit, M. H. Hui, N. J. Turro, and J. C. Dalton, *J. Am. Chem. Soc.*, **92**, 6974 (1970).
(10) See also (a) N. A. Porter and P. M. Iloff, Jr., *J. Am. Chem. Soc.*, **96**, 6200 (1974); (b) J. A. Den Hollander, R. Kaptein, and P. A. T. M. Brand, *Chem. Phys. Lett.*, **10**, 430 (1971); (c) J. O. Pavlik, P. I. Plooard, A. C. Somersall, and J. E. Guillet, *Can. J. Chem.*, **51**, 1435 (1973).
(11) The existence of the DTBK–CCl_4 exciplex is supported by the quenching of DTBK fluorescence by CCl_4. See ref 3b.
(12) The proton CIDNP from the photolysis of **1** has been studied: H. E. C. Chen, A. Groen, and M. Cocivera, *Can. J. Chem.*, **51**, 3032 (1973), and ref 3a.
(13) W. B. Moniz and S. A. Sojka, Abstracts, 14th Experimental NMR Conference, University of Colorado, Boulder, Colo., April 15–18, 1973, Session 8.
(14) J. A. Pople and D. L. Beveridge, "Appriximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(15) L. J. Aarons, I. A. Hillier, and M. F. Guest, *J. Chem. Soc., Faraday Trans. 2*, **70**, 167 (1974).
(16) H. Paul and H. Fischer, *Helv. Chim. Acta*, **56**, 1575 (1973).
(17) A. Hudson and H. A. Hussain, *Mol. Phys.*, **16**, 199 (1969).

Secondary Deuterium Isotope Effects and the Conformation of Transition States in the Solvolyses of 3α- and 3β-Cholestanyl Brosylates

Marko Tarle,[1] Stanko Borčić, and D. E. Sunko*[2]

Rugjer Bošković Institute, 41001 Zagreb, Croatia, Yugoslavia

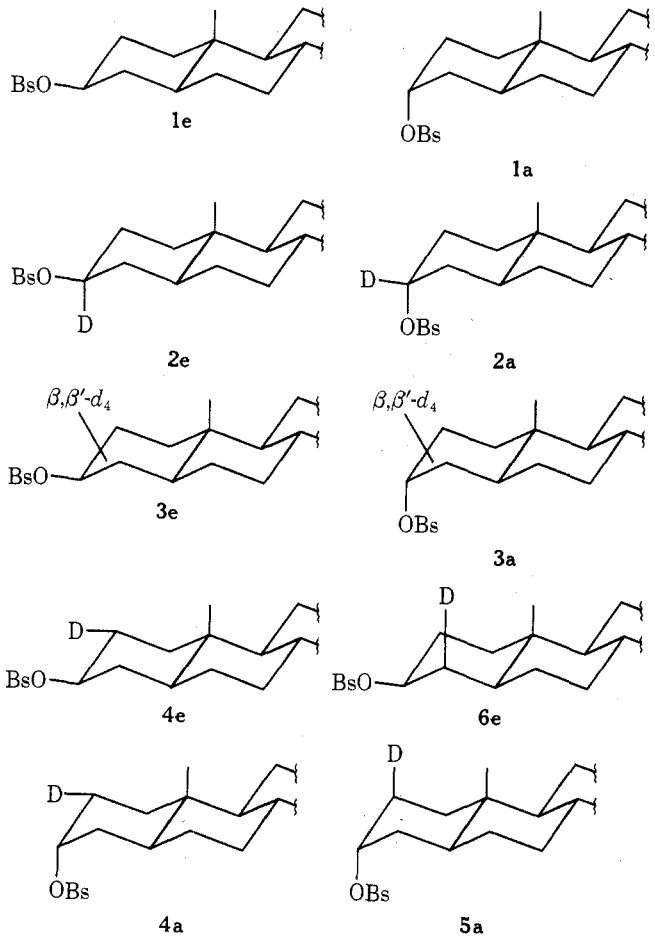
Received March 3, 1975

Secondary deuterium isotope effects in ethanolysis of 3β-cholestanyl-3-d_1 brosylate (**2e**), 3α-cholestanyl-3-d_1 brosylate (**2a**), 3β-cholestanyl-2,2,4,4-d_4 brosylate (**3e**), 3α-cholestanyl-2,2,4,4-d_4 brosylate (**3a**), 3β-cholestanyl-2α-d_1 brosylate (**4e**), 3α-cholestanyl-2α-d_1 brosylate (**4a**), and 3α-cholestanyl-2β-d_1 brosylate (**5a**) were measured. The solvolysis products of unlabeled epimeric brosylates (**1e** and **1a**) were also determined. The deuterium content analyses of olefinic fraction obtained in acetolyses of **3e**, **3a**, **4a**, and **5a** were carried out. The magnitude of the β isotope effects obtained in solvolysis of **3e** (k_H/k_D = 1.30), **4e** (k_H/k_D = 0.95), and **6e** (k_H/k_D = 1.18) leads to the conclusion that the 3β-cholestanyl arensulfonates solvolyze via a chair-like rate-determining transition state. On the other hand, the solvolysis products indicate a half-chair conformation for a product-forming transition state. The isotope effects measured on axial derivatives **3a** (k_H/k_D = 2.30), **4a** (k_H/k_D = 1.13), and **5a** (k_H/k_D = 1.60) discussed together with acetolysis products and the deuterium content of olefins from **3a**, **4a**, and **5a** suggest a partitioning between k_Δ and k_s processes.

The application of Hammond's postulate[3] to SN1 type reactions implies structural similarities of the cationic intermediate with both ionization and product-forming transition states. One of the best probes of the rate-determining ionization transition state structure are kinetic isotope effects,[4] in particular, owing to their strong conformational dependence, the secondary β-deuterium isotope effects. Product studies, on the other hand, furnish information regarding the structure of the product-forming transition state which, being of lower energy than the rate-determining transition state, resembles the intermediate even more closely.

Recently,[5] we applied both kinetic isotope effects and product analysis in our studies of menthyl tosylate solvoly-

sis. In the present paper we wish to report a case where different structures seem to be involved in the rate-determining transition state and the product-forming intermediate cation, respectively. The reaction studied was the solvolysis of cholestanyl derivatives **1e–6e** and **1a–5a.**



Results

Preparations. The epimeric 3β-cholestanyl brosylate (**1e**) and 3α-cholestanyl brosylate (**1a**) as well as their labeled analogs **2e, 2a, 3e, 3a, 4e, 4a,** and **5a,** were synthesized by the procedures described in the Experimental Section. All compounds except **3e** and **3a** have been known and described previously. The last two were prepared by a modified Djerassi method for the preparation of Δ^4-cholestene-3,6-dione-2,2,7,7-d_4.[6] The configuration of all parent alcohols and their derivatives was determined by NMR spectra and mass spectral and the TLC data, which were compared with either authentic samples or with data reported in the literature. Brosylate esters were obtained by the treatment of alcohols with *p*-bromobenzenesulfonyl chloride in anhydrous pyridine following described procedures. The stereochemistry of C–D bonds in labeled compounds was determined by the ir spectra, which exhibited characteristic streching frequencies for axial or equatorial C–D bonds.[7] The deuterium content and distribution in all labeled compounds came from mass spectral data. The synthesis of **6e** was described in our previous work.[8]

Rates. The rate measurements were performed by the potentiostatic technique at a constant pH of 6.8 for ethanolyses and 2.3 for acetolysis. The liberated acid was titrated with 0.03 *M* sodium ethoxide solution or sodium acetate solution, respectively. Infinity titers were checked and were found to be in accordance with the theoretical values. The solvolysis course was followed in each experiment to 75–80% completion in the case of ethanolysis and to 50–60% in acetolysis. More detailed descriptions about kinetic measurements are given in the Experimental Section. The rate data and calculated isotope effects are listed in Table I.

Solvolysis Products. Although acetolysis products from both **1e** and **1a** have been reported previously,[9] the product composition was checked twice. Slight differences from Baker's results were found in the first experiment so that the product studies were repeated. The data given in Table II are the average values obtained from these two experiments. For a comparison products of **1e** in 89% aqueous acetone were also recorded.

From the acetolysis of tetradeuterated brosylates **3e** and **3a** and monodeuterated 3α-cholestanyl derivatives **4a** and **5a** only the olefinic fraction was isolated. The deuterium content and distribution in alkenes was determined by means of mass spectrometry (Table III). The detailed procedure used in product studies is given in the Experimental Section.

Discussion

The equatorial brosylate **1e** solvolyses in 96% ethanol 6.8 times slower than the axial epimer **1a,**[10] which compares well with the 4.35 rate ratio for epimeric 2-decalyl tosylates.[11] The secondary α isotope effects differ only slightly for the two epimers **2e** and **2a** and are of identical magnitude with those observed in the solvolysis of epimeric cholesteryl tosylates.[8] This can be taken as evidence for similar degrees of bond breaking and/or solvent or neighboring-group participation in the rate-determining transition states.[12]

However, the β-d_4 isotope effect in **3e** (k_H/k_D = 1.30) is significantly smaller in comparison with the d_4 isotope effect in **3a** (k_H/k_D = 2.31). Such small β-d_4 isotope effects have been observed only in solvolysis of menthyl-β,β'-d_3 tosylate[5] and have been explained in terms of a rigid chair-like conformation of the rate-determining ionization transition state. On this basis we exclude for this transition state[13] other conformations of C_2 or C_s symmetry in the cyclohexane ring A[5], which is also in accordance with the suggestion "that equatorial tosylates do not have to assume an axial orientation (either in another chair form or twist form) for solvolyses".[14] This rigidity, which cannot be found in other related cyclohexyl derivatives,[15] must be due to the trans fusion of rings A and B in **1e.** In this respect this ring fusion in positions 3 and 4 relative to the reaction center probably plays a similar role as the two alkyl groups in positions 2 and 5 in menthyl tosylate.[5] Further support for a chair-like transition state in solvolysis of **1e** is furnished from rate data in the solvolysis of **4e** and **6e.** While conformationally flexible cyclohexyl derivatives show very similar normal (k_H/k_D > 1) isotope effects[15a,16–18] for both axial and equatorial deuteriums in β positions,[7] the effect observed with **4e** is inverse (k_H/k_D = 0.944). This can only be caused by a dihedral angle of ca. 90° between the developing p orbital at C-3 and the equatorial C–D bond on carbon atom 2.[19] At the same time this orientation allows a good hyperconjugative overlap with the axial C–D bond on C-4 as demonstrated by the effect in **6e** (k_H/k_D = 1.20).

The product composition in the acetolysis of **1e** is practically identical with the results reported by Baker et al.[9] The amount of inverted substitution product (39.7%) is solvent dependent as it was shown in the solvolysis of **1e** in 89% aqueous acetone (Table II). Under these conditions 64% of inverted cholestanol was formed.

From the magnitude and practical identity of β-d_4 isotope effects in both acetolysis and ethanolysis of **3e** we as-

Table I
Deuterium Isotope Effects in the Solvolysis of the Cholestanyl Brosylates

Compd	Solvent	Deuterium content, %	Temp, °C	k, sec^{-1} [a]	k_H/k_D
2e	96 E[b]	0.99	60.1	$(2.771 \times 10^{-5}) \pm 0.020$[c] $(2.460 \times 10^{-5}) \pm 0.013$	1.130 ± 0.010
2a	96 E	0.99	60.0	$(1.890 \times 10^{-4}) \pm 0.012$[c] $(1.720 \times 10^{-4}) \pm 0.009$	1.099 ± 0.009
3e	96 E	0.89	60.0	$(2.670 \times 10^{-5}) \pm 0.027$[c] $(2.060 \times 10^{-5}) \pm 0.016$	1.296 ± 0.022[d]
	AcOH		70.5	$(3.310 \times 10^{-5}) \pm 0.145$[c] $(7.230 \times 10^{-5}) \pm 0.201$	1.288 ± 0.045
3a	96 E	0.89	60.0	$(1.890 \times 10^{-4}) \pm 0.017$[c] $(0.858 \times 10^{-4}) \pm 0.026$	2.307 ± 0.019[e]
4e	96 E	0.98	60.0	$(2.644 \times 10^{-5}) \pm 0.029$[c] $(2.799 \times 10^{-5}) \pm 0.011$	0.944 ± 0.016
4a	96 E	0.98	60.3	$(2.134 \times 10^{-4}) \pm 0.014$[c] $(1.888 \times 10^{-4}) \pm 0.142$	1.130 ± 0.019
5a	96 E	0.98	60.3	$(2.134 \times 10^{-4}) \pm 0.014$[c] $(1.334 \times 10^{-4}) \pm 0.044$	1.599 ± 0.013
6e	96 E	0.88	60.3	$(3.040 \times 10^{-5}) \pm 0.015$[c] $(2.590 \times 10^{-5}) \pm 0.028$	1.174 ± 0.020[f,g]

[a] Uncertainties are standard errors. [b] 96% v/v EtOH. [c] The values correspond to undeuterated compound. [d] Isotope effect corrected to 100% deuterium content is 1.36. [e] Isotope effect corrected to 100% deuterium content is 2.56. [f] Isotope effect corrected to 100% deuterium content is 1.195. [g] Reference 8.

Table II
Products in the Solvolysis of Epimeric Cholestanyl Derivatives [a]

Compd	1e	1e	1a	
Solvent	AcOH	89% (v/v) aq acetone	AcOH	Products, %
	39.70	63.94	6.00	3α-Cholestanol
	2.03	0.22	7.91	3β-Cholestanol
	0.45			2α-Cholestanol
			0.99	2β-Cholestanol
	55.92	33.73	82.29	Δ^2- + Δ^3-Cholestene
	98.10	97.99	97.19	Total

[a] From the acetolysis of tetradeuterated brosylates **3e** and **3a** and monodeuterated 3α-cholestanyl derivatives **4a** and **5a** only the olefinic fraction was isolated. The deuterium content and distribution in alkenes was determined by means of mass spectrometry (Table III). The detailed procedure used in product studies is given in the Experimental Section.

sume that, in these solvents, the ionization step is rate determining. Despite the large olefin fraction (56% in ethanol, Table II) these effects are clearly too small for a rate-determining elimination and are more characteristic for an ionization transition state.[5,15]

A comparison of the product composition found in the acetolysis of **1e** with the solvolytic product of menthyl tosylate[5] reveals a significant difference with respect to the configuration of substitution products. While the identity of kinetic β isotope effects data for both systems indicates similar chair-like transition states, the stereochemical outcome from the product-determining step in solvolysis of **1e** suggests that the geometry of the latter is half-chair or bent chair.[5] Such a conformation is required for a back-side solvent attack leading to products of inverted configuration on the C-3 atom.

The small amount of rearranged 2β product probably arises from a 1,2-hydrogen migration in a half-chair product transition state. This migration can be detected by the deuterium content of olefins formed from **3e** which show 2.29% of d_4 molecules (Table III).

The large β,β′-d_4 isotope effect in the solvolysis of **3a** can be attributed to a primary isotope effect due to rate-determining hydrogen participation and/or β-elimination.[15a,20-22] According to Streitwieser[23] "the tendency for participation by an axial hydrogen adjacent to an axial leaving group appears to be general". A chair-like transition state of ring A in the solvolysis of **1a** fulfills this requirement. It has been shown that even more flexible axial cyclohexyl derivatives solvolyze via a chair-like transition state.[5a]

Table III
Mass Spectral Analysis of Olefins Formed in the Acetolysis of Specifically Deuterated 3α- and 3β-Cholestanyl Brosylates

Substrate		
Compd	Deuterium content	Deuterium content in olefinic products
3e	70.30 d_4	2.29 d_4
	19.35 d_3	70.46 d_3
3a	70.30 d_4	48.56 d_4
	19.35 d_3	13.24 d_3
4a	0.98 D	0.67 D
5a	0.98 D	0.83 D

The isotope effect observed in the solvolysis of **5a** (k_H/k_D = 1.60) is too large to be of hyperconjugative origin only,[22] and is, as in neomenthyl tosylate,[21] likely due to hydrogen participation. The β effect observed with **4a** (k_H/k_D = 1.13)

has to be considered as an α effect with the migrating hydrogen as the leaving group.

The observation of 1% of the rearranged 2β-substitution product and the fact that 69% of deuterium originally present in **3a** remains in the isolated olefin(s) is indicative of a hydrogen-bridged cationic intermediate. This intermediate is probably also the precursor of the retained substitution product. Thus, a 1,2-hydrogen shift probably occurs from this intermediate in one of the subsequent steps. Unfortunately, the incomplete deuteration of **3a** precludes a more detailed mechanistic interpretation. Also, here the situation is less clear because product studies were made in a different solvent than the rate studies.

Additional information can, to a certain extent, be gained by inspecting the elimination products in the solvolysis of **4a** and **5a** (Table III). Here deuteration of the starting ester was complete (0.98 atom D per molecule). The olefin from **4a** showed only 0.67 atom D per molecule, while 83% of deuterium remained in the alkene formed from **5a**. The loss of deuterium from the equatorial position probably occurs in a k_s process (competitive solvent-promoted elimination and back-side substitution on the intimate ion pair).

The relatively smaller loss of the axial deuterium in **5a** during the elimination process implies that an E2-type elimination does not play a substantial role.

The best rationalization of these results is, in our opinion, the formation of a hydrogen-bridged intermediate in the k_Δ process in competition with the k_s solvolytic pathway.

The ratio of inverted to retained unrearranged substitution products from **1a** (1.33) is slightly lower than that reported by Baker et al.[9] (3.53) and can also be explained in terms of two separate paths, i.e., k_Δ, yielding the retained product, and k_s, proceeding with inversion on the C-3 atom.

Experimental Section

General. Melting points were taken on a Kofler block and are uncorrected. Mass spectra were measured on a Bell and Howell CEC-21-110C spectrometer. Infrared spectra were recordered on a Perkin-Elmer 211 spectrophotometer using KBr pellets. The NMR spectra were taken on a Varian A-60A spectrophotometer in $CDCl_3$ solutions with internal Me_4Si. Optical rotations were determined with a Carl Zeiss polarimeter in chloroform solutions. Thin layer chromatography was carried out with silica gel G (Merck) and spots were located with uv light or by spraying plates with dilute H_2SO_4. Column chromatography was performed on silica gel (Merck) or alumina activity II/III (Merck). In chromatographic separations on silica gel benzene–ethyl acetate (9:1 v/v) was used as eluent.

All chemicals used were reagent grade.

3β-Cholestanyl Brosylate (1e). Commercial 3β-cholesterol was converted to 3β-cholestanol as described in the literature[24] (94%). The saturated alcohol was oxidized using a known procedure and gave cholestan-3-one[25] (88%): mp 127–129.5° (lit.[25] mp 128–129°); $[\alpha]_D$ +41.4° (lit.[25] $[\alpha]_D$ +41.5°); ir ν 1720 cm^{-1} (C=O). The reduction of the ketone with lithium aluminum hydride gave a mixture of 3β-cholestanol and 3α-cholestanol[26] (93%) in the ratio 87.4:9.3. The epimers were separated and purified by column chromatography over silica gel:[27] 3β-cholestanol, mp 143–144° (lit.[26] mp 140–141°); $[\alpha]_D$ +23.3° (lit.[28] $[\alpha]_D$ +22°); NMR δ 1.67 (s, 1, –OH), 3.63 (m, 1, >CHOH); ir ν 3500 cm^{-1} (O–H); 3α-cholestanol, mp 183–185.5° (lit.[29] mp 184–185°); $[\alpha]_D$ +24.2° (lit.[29] $[\alpha]_D$ +24°); NMR δ 1.48 (s, 1, –OH), 4.05 (m, 1, >CHOH); ir ν 3500 cm^{-1} (O–H). 3β-Cholestanyl brosylate (**1e**) was prepared[30] by treatment of the corresponding alcohol in anhydrous pyridine with BsCl at 0° for 48 hr (81%): mp 123–124° (lit.[28] mp 120–122°); NMR δ 4.41 (m, 1, >CHOBs), 7.62 (m, 4, C_6H_4). According to TLC analysis the product was free from both unreacted alcohol and brosyl chloride.

3α-Cholestanyl Brosylate (1a). The axial alcohol was converted to the corresponding brosylate in the usual manner[31] (54%): mp 133–135 (lit.[31] mp 132–133°); NMR δ 4.45 (m, 1, >CHOBs), 7.65 (m, 4, C_6H_4). The NMR spectrum and TLC analysis did not show the presence of alkenes, free alcohol, or BsCl.

3β-Cholestanyl-3-d_1 Brosylate (2e) and 3α-Cholestanyl-3-d_1 Brosylate (2a). Monodeuterated brosylates **2e** and **2a** were synthesised by methods described for the preparation of unlabeled compounds. The reduction of cholestan-3-one was performed using lithium aluminum deuteride instead of $LiAlH_4$.[26] The NMR spectra of both brosylates did not show signals corresponding to protons on the C-3 atom. According to TLC both compounds were more than 98% pure. From mass spectral data the deuterium content in both esters was calculated as 0.99 atom D per molecule.

3β-Cholestanyl-2,2,4,4-d_4 Brosylate (3e) and 3α-Cholestanyl-2,2,4,4-d_4 Brosylate (3a). According to Djerassi's procedure for the preparation of β-tetradeuterio ketones,[6] cholestan-3-one[25] (5.0 g, 12.5 mmol) was dissolved in AcOD (100 ml) and D_2O (180 ml) and the mixture was refluxed for 4 hr under a slight stream of dry nitrogen. Solvent was removed under high vacuum and this operation was repeated three times. The residue was dissolved in ether (previously saturated with D_2O) and the organic solution was washed with D_2O (2 × 50 ml), a saturated solution of $NaHCO_3$ in D_2O (2 × 50 ml), and again with heavy water (2 × 25 ml). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed in vacuo. The crude cholestan-3-one-2,2,4,4-d_4 was subjected to low-temperature recrystalization from MeOD. The yield was 4.60 g (91.5%): mp 129–130.5;[25] $[\alpha]_D$ +41.7°;[25] ir ν 2140, 2175 cm^{-1} (axial and equatorial C–D bond streching frequencies[7]). The deuterium distribution was determined by mass spectral analysis: d_4, 70.30%; d_3, 19.35%; d_2, 7.55%; d_1, 1.36%; total 3.56 atoms D per molecule. Reduction of β-perdeuteriocholestan-3-one with $LiAlH_4$ in anhydrous ether[26] gave a mixture (95.4%) of 3β-cholestanol-2,2,4,4-d_4 and 3α-cholestanol-2,2,4,4-d_4 in the ratio 87.4:9.2. Separation over silica gel[27] yielded the pure epimeric tetradeuterioalcohols. Mass spectra of both compounds were in full accordance with the deuterium content and distribution found in the parent ketone. The perdeuterio alcohols were converted to the corresponding brosylates in a manner used for the preparation of unlabeled esters **1e**[30] and **1a**.[31] Both **3e** and **3a** did not show the change in the deuterium content in respect with the data obtained from the epimeric alcohols. According to TLC analysis and NMR spectra **3a** and **3e** were 98% pure.

3α-Cholestanyl-2β-d_1 Brosylate (5a). A sample of 3β-cholestanol[24] was treated with TsCl in anhydrous pyridine in a usual manner,[30] yielding 3β-cholestanyl tosylate (62.6%), mp 135–137.5° (lit.[28] mp 135–137°). The purity of the tosylate was checked by NMR and TLC techniques. A sample of 3β-cholestanyl tosylate was kept in benzene over basic Al_2O_3 for 2 days.[32] After filtration benzene was removed under high vacuum. The crude product was recrystallized from acetone, yielding 2-cholestene (69%): mp 74.5–75° (lit.[33] mp 73–75°); $[\alpha]_D$ +69.1° (lit.[32] $[\alpha]_D$ +64°).

2α,3α-Epoxycholestane was prepared by treatment of 2-cholestene with perbenzoic acid[34] in chloroform at −10° for 20 hr.[35] The mixture was then worked up as usual.[35] The crude product was recrystallized (86%) from ether–ethanol mixture: mp 102–104° (lit.[35] mp 105–106°); $[\alpha]_D$ +36.2° (lit.[35] $[\alpha]_D$ 36.0–36.9°). The epoxide was refluxed with lithium aluminum deuteride in spectrograde dioxane for 90 hr.[36] The excess of deuteride was destroyed with water. The usual work-up[36] gave a white solid which showed on TLC several spots. By column chromatography on alumina (II/III) unindentified impurities were removed with petroleum ether (bp 45–60°). Pure 3α-cholestanol-2β-d_1 (53%) was obtained using petroleum ether–benzene (90:10) as eluent: mp 184–186° (lit.[36] mp 184–186°); $[\alpha]_D$ +24.2° (lit.[29] $[\alpha]_D$ +24°). The mass spectrum showed 0.98 atom D per molecule. The corresponding brosylate was prepared by a standard procedure[31] (59%): mp 132.5–134° (lit.[31] mp 132–133°); ir ν 2140 cm^{-1} (axial C–D bond frequency[7]). The deuterium content was the same as in the parent alcohol.

3β-Cholestanyl-2α-d_1 Brosylate (4e). Deuterioboration of 2-cholestene with $LiAlD_4$ and freshly distilled BF_3-Et_2O complex in dry ether was carried out over dry and oxygen-free nitrogen for 15 hr.[36] After usual treatment with H_2O_2,[36] the crude product was chromatographied over Al_2O_3 (II/III).[36] The unreacted alkene (12%) was eluted with petroleum ether. Pure 3α-cholestanol-2α-d_1[36] (21.7%) was obtained using petroleum ether–benzene (40:60): mp 183–185°; ir ν 2150, 2175 cm^{-1} (equatorial C–D bond frequency[7]). The mass spectrum showed 0.98 atom D per molecule. Elution with petroleum ether–benzene (30:70) gave 2α-cholestanol-3α-d_1 (12.6%), mp 177–180° (lit.[36] mp 177–180°). Using benzene–ether (80:20) 3β-cholestanol-2α-d_1 (18.0%) was isolated: mp 142–144°; ir ν 2150, 2175 cm^{-1} (equatorial C–D bond frequency[7]). The mass spectral data showed 0.98 atom D per molecule. Using the

standard procedure,[30] 3β-cholestanol-2α-d_1 was converted to the brosylate (54%). Deuterium content in **4e** was the same as determined in the parent alcohol. According to NMR and TLC analysis ester was 98% pure.

3α-Cholestanyl-2α-d_1 Brosylate (4a). Treatment of 3α-cholestanol-2α-d_1 with BsCl in dry pyridine at 0° for 5 days gave the corresponding brosylate[31] (44%), mp 132–134° (lit.[31] mp 132–133°). According to mass spectrum 0.98 atom D per molecule was found.

Kinetic Measurements. Reagent grade acetic acid was redistilled over $KMnO_4$ and P_2O_5, respectively, prior to use as a solvolytic solvent. Spectrograde ethanol, 96% v/v (Merck), was redistilled. The middle fraction was used as solvent in solvolyses.

Measurements of the titrimetric rates were carried out by means of a pH-stat, Radiometer, Copenhagen, SBR 2c titrigraph with PHM 25 and TTT 11. The titrimetric cell with solvent was allowed to stabilize at the desired temperature prior to addition of substrate. The concentration of arensulfonate esters was 1.5–2.0 mmol in all experiments. Six to nine kinetic measurements were performed for each compounds alternating the solvolysis of labeled and unlabeled substance. Rate data were evaluated by a nonlinear least-squares sum-fitting program. The rate constants did not exhibit any trend between 15 and 75% of the solvolysis completion.

Solvolysis Products. In a typical acetolysis run, the brosylate **1a** or **1e** (3.7 g, 6.04 mmol) was dissolved in anhydrous acetic acid (600 ml) containing anhydrous sodium acetate (5.85 g, 3.75 mmol). The resulting solution was refluxed for 36 hr. After removal of solvent under high vacuum the residue was dissolved in petroleum ether (bp 30–45°). The organic solution was washed repeatedly with aqueous $NaHCO_3$ until neutral reaction and dried over $MgSO_4$. Evaporation of the solvent gave crude product, which after the usual treatment with lithium aluminum hydride gave a mixture of alkenes and alcohols. Products were separated over alumina (II/III); elution with petroleum ether yielded the olefinic fraction; petroleum ether–benzene (85:15) gave 2β-cholestanol (if present); the use of petroleum ether–benzene (70:30) resulted in the collection of 3α-cholestanol; elution with petroleum ether–benzene (50:50) gave 2α-cholestanol (if present); the last elution using pure benzene yielded 3β-cholestanol. The products were identified by TLC, NMR, and ir spectra, as well as by measurements of their optical rotations and melting points.

Olefinic products (mp 72–74°, $[\alpha]_D$ +64.8°) were almost pure 2-cholestene, compared with data from the literature (mp 73–75°,[33] $[\alpha]_D$ +64°[32]). Mass spectral analysis, with respect to previously reported results,[9] supported this conclusion. The low-pressure hydrogenation of the isolated olefinic products from both **1a** and **1e** gave pure cholestane: mp 78–80° (lit.[37] mp 79.5–80°); $[\alpha]_D$ +25.1° (lit.[37] $[\alpha]_D$ +25°); NMR spectrum of the hydrogenated product did not show a signal corresponding to olefinic protons. By this experiment the absence of 4-cholestene in the solvolysis products was confirmed.[38]

Isolated alkenes treated under identical solvolytic conditions as described above in AcOD (0.97 atom D per molecule) did not show after reisolation any deuterium incorporation. This experiment was performed to show that olefins formed in acetolysis of both **1e** and **1a** are primary solvolytic products.

The mass spectra made on olefinic products isolated in solvolysis of labeled substrates gave the amount and distribution of deuterium.

The hydrolysis in 89% aqueous acetone was run in the same manner as the acetolysis using 4000 ml of solvent together with 15 g of $CaCO_3$ as a base. Brosylate **1e** (8.0 g, 13.1 mmol) was refluxed for 72 hr. The resulting mixture gave olefins and alcohols as products. Separation over alumina (II/III) and product identification were performed in a manner described for the acetolysis.

Acknowledgment. This investigation was supported by the Research Council of Croatia and by Grant 02-011-1 (PL 480) administered by the National Institutes of Health. The authors are grateful to Mrs. Sanja Hiršl-Starčević, who carried out some of the preliminary experiments in this study, and to Professor V. J. Shiner, Jr., for numerous helpful discussions.

Registry No.—**1e,** 35596-32-8; **1a,** 56083-04-6; **2e,** 55925-56-9; **2a,** 56083-05-7; **3e,** 55925-57-0; **3a,** 55954-88-0; **4e,** 55954-89-7; **4a,** 55954-90-0; **5a,** 56083-06-8; **6e,** 55954-49-9; 3β-cholestanol, 80-97-7; 3α-cholestanol, 516-95-0; cholestan-3-one, 15600-08-5; lithum aluminum deuteride, 14128-54-2; cholestan-3-one-2,2,4,4-d_4, 13976-58-4; 2α,3α-epoxycholestane, 1753-61-3; 2-cholestene, 570-73-0.

References and Notes

(1) Taken in part from the Ph.D. Thesis of M. Tarle, University of Zagreb, Yugoslavia, 1972.
(2) Correspondence should be addressed to this author at University of Zagreb, Faculty of Natural Sciences and Mathematics, Laboratory of Organic Chemistry, 41000 Zagreb, Yugoslavia.
(3) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(4) For a comprehensive review of this subject see "Isotope Effects in Chemical Reactions", ACS Monograph 167, C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, New York, N.Y., 1970.
(5) S. Hirsl-Starcevic, Z. Majerski, and D. E. Sunko, *J. Am. Chem. Soc.*, **96**, 3659 (1974).
(6) C. Djerassi, J. Karliker, and T. A. Aplin, *Steroids*, **6**, 1 (1965).
(7) R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Am. Chem. Soc.*, **81**, 2818 (1959).
(8) M. Tarle, S. Borcić, and D. E. Sunko, *J. Org. Chem.*, following paper in this issue.
(9) R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. B*, 1446 (1970).
(10) Kosower, quoting unpublished results, reported a ratio of 6.6 in acetic acid at 50°: E. M. Kosower, "An Introduction to Physical Organic Chemistry", Wiley, New York, N.Y., 1968, p 114.
(11) H. Tanida, S. Yamamoto, and K. Takeda, *J. Org. Chem.*, **38**, 2792 (1973).
(12) See ref 4, p 184, and also S. R. Hartshorn, "Aliphatic Nucleophilic Substitution", Cambridge University Press, New York, N.Y., 1973, p 139.
(13) A. Komornicky and J. W. McIver, *J. Am. Chem. Soc.*, **95**, 4512 (1973).
(14) D. J. Pasto and D. R. Rao, *J. Am. Chem. Soc.*, **92**, 5151 (1970).
(15) (a) V. J. Shiner, Jr., and J. G. Jewitt, *J. Am. Chem. Soc.*, **87**, 1382, 1383 (1965); (b) J. B. Lambert, G. J. Putz, and C. E. Mixan, *ibid.*, **94**, 5132 (1972); (c) J. B. Lambert and G. J. Putz, *ibid.*, **95**, 6313 (1973); (d) J. E. Nordlander and T. J. McCrary, Jr., *ibid.*, **94**, 5133 (1972); (e) M. Pankova, J. Sicher, M. Tichý, and M. C. Whiting, *J. Chem. Soc. B*, 365 (1968).
(16) W. H. Saunders, Jr., and K. T. Finley, *J. Am. Chem. Soc.*, **87**, 1384 (1965).
(17) N. A. LeBel and R. J. Maxwell, *J. Am. Chem. Soc.*, **91**, 2307 (1969).
(18) M. Tichý, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739 (1969).
(19) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **85**, 2416 (1963).
(20) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).
(21) S. Hirsl-Starcević, M.S. Thesis, University of Zagreb, 1973.
(22) V. J. Shiner, Jr., ref 4, Chapter II.
(23) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 143.
(24) "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1963, p 195.
(25) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, **75**, 1718 (1953).
(26) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 678 (1950).
(27) R. S. Rosenfeld, D. K. Fukushima, L. Hellman, and T. F. Gallagher, *J. Biol. Chem.*, **211**, 301 (1954).
(28) G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 1720 (1959).
(29) J. R. Bull, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965).
(30) E. S. Wallis, E. F. Fernholz, and F. T. Gephardt, *J. Am. Chem. Soc.*, **59**, 137 (1937).
(31) D. Kovacevic, Z. Majerski, S. Borcic, and D. E. Sunko, *Tetrahedron*, **28**, 2469 (1972).
(32) T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. Pharm. Bull.*, **11**, 465 (1963).
(33) D. Levy and R. Stevenson, *Tetrahedron Lett.*, **6**, 341 (1965).
(34) M. Vilkas, *Bull. Soc. Chim. Fr.*, 1501 (1959).
(35) A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).
(36) R. C. Cookson, D. P. G. Hamon, and R. E. Parker, *J. Chem. Soc.*, 5014 (1962).
(37) I. Scheer, M. J. Thomson, and E. Mosetting, *J. Am. Chem. Soc.*, **78**, 4733 (1956).
(38) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).