tained by using radii suggested by Pauling[23] together with a simplification of Beveridge and Schnuelle's[19] concentric shell model of electrostatic hydration suggested by Abraham and Liszi.[18] This was also considered to be the most intellectually satisfactory procedure and was adopted throughout.

The magnitudes of the derived ionic-group contributions were largely comprehensible in terms of specific hydrogen-bonding interactions to the solvent. From these data approximate hydration energy changes accompanying protonation or alkylation of certain functional groups were tabulated and applied to the rationalization of solvent effects on product ratios in the benzylation of adenosine and guanosine.

Interactions between functional groups in the same molecule can lead to significant modifications in hydration behavior explicable in terms of parallel modification of the strengths of hydrogen bonding to the solvent.

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**Registry No.** 1, 58-61-7; 2, 118-00-3; 3a, 100-44-7; 3b, 100-39-0; 3c, 1024-41-5; 4, 85649-98-5; 5, 85649-98-5; 6, 71171-61-4; 7, 85649-99-6; 8, 85650-00-6; $MeOH_2$, 17836-08-7; $EtOH_2$, 18639-79-7; $Me_2OH$, 17009-82-4; $Et_2OH$, 17009-83-5; MeEtOH, 52067-06-8; $(CH_2)_4OH$, 27659-93-4; $(CH_2)_5OH$, 27659-94-5; $MeNH_3$, 17000-00-9; $EtNH_3$, 16999-99-8; *n*-$PrNH_3$, 17033-39-5; *i*-$PrNH_3$, 16999-98-7; $BuNH_3$, 16999-97-6; *sec*-$BuNH_3$, 34755-45-8; *t*-$BuNH_3$, 22534-19-6; $C_6H_5NH_3$, 17032-11-0; 3-$MeC_6H_4NH_3$, 18971-81-8; 4-$MeC_6H_4NH_3$, 17112-11-7; $Me_2NH_2$, 17000-01-0; $(CH_2)_3NH_2$, 66203-35-8; $(CH_2)_4NH_2$, 55526-39-1; $(CH_2)_5NH_2$, 17523-59-0; $Et_2NH_2$, 19497-23-5; $Pr_2NH_2$, 29384-47-2; $PhMeNH_2$, 17456-49-4; $Me_3NH$, 16962-53-1; $Me_2EtNH$, 71467-09-9; $MeEt_2NH$, 85649-95-2; $Et_3NH$, 17440-81-2; $Pr_3NH$, 50985-90-5; $(CH_2)_4MeNH$, 66203-36-9; $PhMe_2NH$, 17835-98-2; $Me_4N$, 51-92-3; $Et_4N$, 66-40-0; $Me_2COH$, 43022-03-3; $(CH_2)_4COH$, 64725-64-0; *t*-BuMeCOH, 68706-39-8; *i*-$Pr_2COH$, 18639-86-6; *c*-$C_6H_{11}MeCOH$, 75031-99-1; PhMeCOH, 39922-13-9; *c*-PrMeCOH, 70058-20-7; *c*-$Pr_2COH$, 70058-21-8; Me(OMe)COH, 39014-36-3; Me(OEt)COH, 39014-41-0; Ph(OMe)COH, 59137-82-5; *c*-Pr(OMe)COH, 85649-96-3; $Me(NMe_2)COH$, 52754-55-9; PyH, 16969-45-2; 2-Me(py)H, 16969-46-3; 3-Me(py)H, 17203-41-7; 4-Me(py)H, 16950-21-3; 4-$NMe_2$(py)H, 55277-36-6; 4-OMe(py)H, 33613-95-5; 4-Cl(py)H, 37449-65-3; 2,4-$Me_2$(py)H, 17126-11-3; 2,5-$Me_2$(py)H, 64343-93-7; 2,6-$Me_2$(py)H, 17033-11-3; 2,5-$Me_2$-(py)H, 19495-57-9; 4-*t*-Bu(py)H, 40569-37-7; 2,6-*t*-$Bu_2$(py)H, 62907-61-3; $MeNH_2$, 74-89-5; $Me_2O$, 115-10-6; $H_2O$, 7732-18-5.

**Supplementary Material Available:** Tables for calculating molecular volumes and electrostatic hydration free energies (9 pages). Ordering information is given on any current masthead page.

# Deuterium and Tritium Labeling with the Zinc–Sodium Iodide Method

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Primary and secondary hydroxyl groups can be replaced by deuterium or tritium when the corresponding sulfonate esters are reduced with zinc, sodium iodide, and deuterium or tritium oxide in 1,2-dimethoxyethane. The method tolerates a variety of other reducible functionalities, namely, $\alpha,\beta$-enone, ketone, and ester. The labeling can be conducted with a high regiospecificity in the presence of enolizable hydrogens. The method is less satisfactory for a stereospecific replacement of secondary hydroxyl groups, yielding mixtures of stereoisomers and olefins as byproducts. The distribution of the stereoisomers depends on the rate of configurational inversion in the intermediary iodides arising by displacement of the original tosyloxy group. Deuterium NMR spectra and their use in the configurational assignment are discussed.

The reductive removal of the hydroxyl group is a standard method of deuterium labeling.[1] The hydroxyl to be removed is first converted to an activated form (a sulfonate ester, halide, or thiocarbonate) and then reduced with a suitable reagent, e.g., $LiAl^2H_4$,[1,2] $NaB^2H_3CN$,[3] $Li(C_2H_5)_3B^2H$,[4] $(n\text{-}C_4H_9)_3Sn^2H$,[5] $Zn–Cu/^2H_2O$,[6] $Li/THF–t\text{-}C_4H_9O^2H$,[7,8] or $Zn/CH_3COO^2H$.[9,10] While the reduction utilizing metal deuterides can be conducted with a high regio- and stereospecificity, the cost may become prohibitive when scaling up the preparation. Especially tritium introduction may pose a problem, for the corresponding

(1) Thomas, A. F. "Deuterium Labelling in Organic Chemistry"; Appleton: New York, 1971.
(2) Strating, J.; Backer, H. J. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 639.
(3) Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82. Lane, C. F. *Synthesis* **1975**, 135.
(4) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669.
(5) Albert, H.-J.; Neumann, W. P. *Synthesis* **1980**, 942.
(6) Stephenson, L. M.; Gemmer, R. V.; Current, S. P. *J. Org. Chem.* **1977**, *42*, 212.
(7) Bruck, P.; Thompson, D.; Winstein, S. *Chem. Ind. (London)* **1960**, 405.
(8) Tureček, F.; Hanuš, V. *Org. Mass Spectrom.* **1980**, *15*, 4.
(9) Corey, E. J.; Howell, M. G.; Boston, A.; Young, R. L.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 5036.
(10) Hanson, J. R.; Wadsworth, H. J.; Huel, W. E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1381.

0022-3263/83/1948-2233$01.50/0 

Table I. Label Content in the Products of Reductive Deuteriation and Tritiation

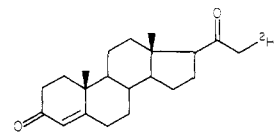
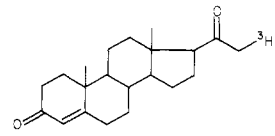
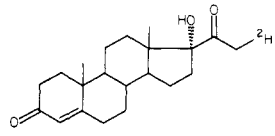
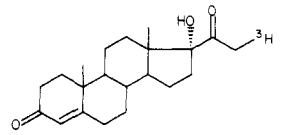
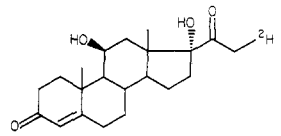
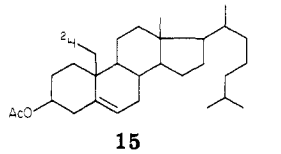
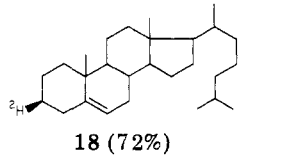
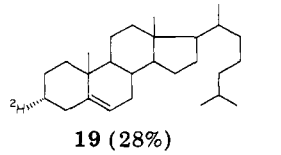
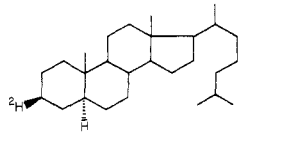
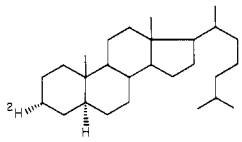
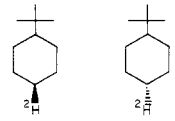
| entry | starting compound | product(s) | yield, % | label content | label distribution[b] |
|---|---|---|---|---|---|
| 1 | 1 |  **10** | 39[a] | 12% $^2H_0$, 74% $^2H_1$, 11% $^2H_2$, 3% $^2H_3$ | C-21 (92%), C-2 (4%), C-6 (4%) |
| 2 | 1 |  **11** | 45[a] | 83%[c] | |
| 3 | 2 |  **12** | 52[a] | 6% $^2H_0$, 80% $^2H_1$, 13% $^2H_2$, 1% $^2H_3$ | C-21 (95%), C-2 + C-6 (5%) |
| 4 | 2[d] | **12** | 54[a] | 19% $^2H_0$, 43% $^2H_1$, 28% $^2H_2$, 7% $^2H_3$, 3% $^2H_4$ | C-21 (92%), C-2 + C-6 (8%) |
| 5 | 2[e] | **12** | 52[a] | 17% $^2H_0$, 58% $^2H_1$, 20% $^2H_2$, 4% $^2H_3$, 1% $^2H_4$ | C-21 (94%), C-2 + C-6 (6%) |
| 6 | 2[f] | **12** | 54[a] | 19% $^2H_0$, 44% $^2H_1$, 28% $^2H_2$, 8% $^2H_3$, 1% $^2H_4$ | C-21 (86%), C-2 + C-6 (14%) |
| 7 | 2 |  **13** | 48[a] | 80%[c] | |
| 8 | 3 |  **14** | 67[a] | 9% $^2H_0$, 78% $^2H_1$, 13% $^2H_2$ | C-21 (94%), C-2 + C-6 (6%) |
| 9 | 4 |  **15** | 48[a] | 13% $^2H_0$, 86% $^2H_1$, 1% $^2H_2$ | C-19 (>98%), $CH_3COO^-$ (<2%) |
| 10 | 5 |  **18** (72%) | | | |
| | |  **19** (28%) | 75[a] | 89% $^2H_1$, 11% $^2H_0$ | C-3 |
| 11 | 6 |  **16** (57%) | | | |

Table I (*Continued*)

| entry | starting compound | product(s) | yield, % | label product | label distribution[b] |
|---|---|---|---|---|---|
| | |  17 (43%) | 72[a] | 3% $^2H_0$, 97% $^2H_1$ | C-3 |
| 12 | 7 | **16** (86%), **17** (14%) 78 | 78[a] | 2% $^2H_0$, 98% $^2H_1$ | C-3 |
| 13 | 8 |  **20** (24%) **21** (76%) | 46 | 3% $^2H_0$, 97% $^2H_1$ | C-4 |
| 14 | 9 | **20** (67%) **21** (33%) | 52 | 2% $^2H_0$, 98% $^2H_1$ | C-4 |

[a] After recrystallization; yields of crude products were 80–90%. [b] From the relative abundance of $(M - C(H, {}^2H)_3CO)^+$, $(M - C(H, {}^2H)_2CO)^{+\cdot}$, and $C_8$ $(H, {}^2H)_{12}O^{+\cdot}$ ions. [c] Total label content determined from specific activity. [d] 10% solution of $^2H_2O$ in 1,2-dimethoxyethane. [e] 5% $^2H_2O$. [f] 1% $^2H_2O$.

reagents are commercially unavailable and their laboratory preparation necessitates special equipment. In addition, metal deuterides often do not tolerate other reducible functionalities (namely, carbonyl groups), so that the labeling step must be accompanied by protection and subsequent removal of the protective group. A less expensive source of the label is used in dissolving metal reductions; however, converting an alcohol to a halide represents an additional synthetic step that may prove to be a nuisance. A labeling method of choice would (a) proceed in a minimum number of steps with a high specificity, (b) tolerate other functional groups, and (c) use an inexpensive source of the label.

Recently it has been shown[11] that reduction of sulfonate esters (tosylates or mesylates) with zinc and sodium iodide in moist 1,2-dimethoxyethane, originally developed by Fujimoto and Tatsuno,[12] can be selectively conducted in the presence of a number of reducible groups such as keto, $\alpha,\beta$-enone, $\alpha,\beta$-epoxy keto, $\alpha$-hydroxy keto, isolated epoxide ring, ester, nitrile, or isolated double bonds. The method thus appeared promising for labeling purposes, and this prompted us to examine the regio- and stereospecificity of the label introduction.

## Result and Discussion

A series of polyfunctional steroids, 21-[(methylsulfonyl)oxy]pregn-4-ene-3,20-dione (**1**), 17$\alpha$-hydroxy-21-[(methylsulfonyl)oxy]pregn-4-ene-3,20-dione (**2**), 11$\beta$,17$\alpha$-dihydroxy-21-[(methylsulfonyl)oxy]pregn-4-ene-3,20-dione (**3**), 3$\beta$-acetoxy-19-[(methylsulfonyl)oxy]-cholest-5-ene (**4**), and 3$\beta$-[(*p*-tolylsulfonyl)oxy]cholest-5-ene (**5**), were chosen to examine the efficiency and site specificity of labeling. The deuterium content and label distribution were determined by mass spectrometry; the relevant data are summarized in Table I. In accordance with the postulated mechanism of the reduction,[11,12] monodeuterated ($^2H_1$) species predominate in the products obtained from **1** to **5**. The content of $^2H_0$ species varies slightly, depending on the amount of light water in the reagents used. Rigorous drying of zinc and sodium iodide reduced the content of $^2H_0$ to 2% (Table I, entries 10–14), which is comparable to the results obtained in metal deuteride reductions. The exchange of enolizable hydrogen atoms for deuterium takes place to a small extent in **1–3** giving rise to $^2H_2$- and $^2H_3$-containing products. As follows from the label distribution in **10** and **12–14**, the exchange occurs predominantly at C-21, preserving the regiospecificity of the labeling. Blank experiments showed that deuterium was not incorporated into the products **10** and **12–14** under the reaction conditions, so that the exchange must have occurred either in the readily enolizable mesyloxy ketones **1–3** or in the intermediate iodo ketones. Lowering the amount of deuterium oxide in the reaction mixture both increases the abundance of non-deuterated products and slows down the reduction rate. As a result, the proportion of $^2H_2$ and $^2H_3$ species due to exchange rises and, to a small extent, the label enters positions C-2 and C-6 as well (Table I).

The reductive tritiation[13] of **1** yielded [$^3$H]progesterone **11** containing 83% of the available label. Although the distribution of tritium in **11** could not be determined by mass spectrometry, an analogous deuteriation carried out with the same label concentration showed that 86% of deuterium was contained in the C-21 methyl group (Table I). The reduction of **2** gave a similar result (Table I, entry 7). It should be noted here that the exchange of the hydroxyl hydrogen for tritium lowers the actual concentration of the label available for the reduction. Hence, the concentration of tritium oxide, normally kept as low as possible for practical reasons, should be adequately increased when reducing a mesyloxy group in compounds that contain a large number of exchangeable hydrogens such as in sugars, peptides, nucleosides, and antibiotics.

**Stereochemistry.** The stereochemistry of the labeling was examined with the complementary pairs of *p*-toluenesulfonates, 3$\beta$-[(*p*-tolylsulfonyl)oxy]-5$\alpha$-cholestane (**6**), [3$\alpha$-$^2$H]-3$\beta$-[(*p*-tolylsulfonyl)oxy]-5$\alpha$-cholestane[9] (**7**), *trans*-4-*tert*-butyl[(*p*-tolylsulfonyl)oxy]cyclohexane (**8**), and *trans*-4-*tert*-butyl-[1-$^2$H]-[(*p*-tolylsulfonyl)oxy]cyclohexane (**9**), (Table I). The configuration of the label was determined by $^2$H NMR spectroscopy. Although the configurational assignment of equatorial and axial protons is normally achieved by means of their different chemical shifts,[14] we have also used the bandwidths of well-separated

(11) Kočovský, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1979**, *44*, 246.
(12) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325.
(13) Vereš, K.; Fajkoš, J.; Kočovský, P. Czech. *Pat.* 217 028.

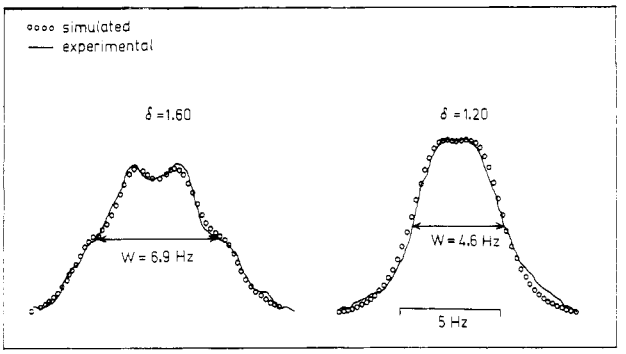
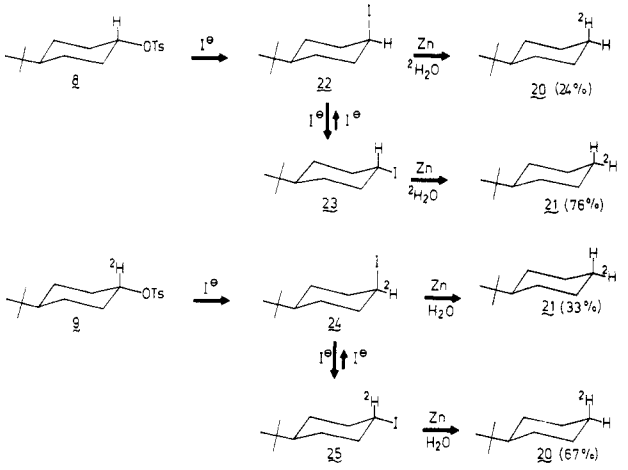



**Figure 1.** 3α-$^2$H and 3β-$^2$H peak profiles in the $^2$H NMR spectrum of **16** and **17**.

$^2$H signals as a check. Non-deuterated tosylates **6** and **8** were reduced in the presence of deuterium oxide, while water was employed in reduction of labeled tosylates **7** and **9**. Both **8** and **9** gave mixtures of isomeric [4-$^2$H]*tert*-butylcyclohexanes **20** and **21**. The assignment of deuterium signals on the basis of the chemical shift[10,15] agrees with the experimental bandwidths: the broader signal of axial deuteron ($\delta$ = 1.07 ± 0.01 ppm, $W$ = 6.4 Hz) appears at a higher field than that of the equatorial isomer ($\delta$ = 1.61 ± 0.02, $W$ = 4.2 Hz). In contrast, in labeled cholestanes **16** and **17**, the signal of the axial deuteron appears at a *lower* field ($\delta$ = 1.62 ± 0.02, $W$ = 6.9 Hz) than that of the equatorial 3β-isomer ($\delta$ = 1.20, $W$ = 4.6 Hz). This points out that the configuration assignment of deuterium may be erroneous if based only on chemical shifts obtained from proton decoupled $^2$H NMR spectra, and it should be confirmed by the relevant coupling constants. Figure 1 shows the fit of the experimental peak shapes with those simulated by using the experimental line width Δ(0.5) = 1.8 Hz (from $CDCl_3$) and $^1$H–$^2$H coupling constants $|J_{gem}|$ = 1.9 Hz, $J_{ax,ax}$ = 1.8 Hz, and $J_{eq,ax} = J_{eq,eq}$ = 0.6 Hz.[14] The broader signal at a lower field was observed independently at 30.74 and 46.075 MHz, although at the lower frequency the peaks had to be separated by deconvolution.

The formation of mixtures of isomers from configurationally homogeneous starting tosylates can be explained by multiple inversion of configuration at the reaction center occurring prior to the reduction step (Scheme I). Should we suppose a fast exchange reaction **22** ⇄ **23**, **24** ⇄ **25** and retention of configuration in the reduction step, the distribution of the products would be controlled by the equilibrium constant of the former reaction: 33% **22**, **24** and 67% **23**, **25** for $\Delta G$ = 0.43 kcal mol$^{-1}$ at 298 K.[16] Although the experimental distribution (Table I) is close to that calculated from the $\Delta G$ value of iodine,[16] it should be mentioned that the fraction of the isomers arising from axial iodides **22** and **24** could be decreased by the competing elimination of hydrogen iodide, the products of which amount to 30–40% of the total yield. The reduction of 3β-(tosyloxy)cholestanes **6** and **7** gives a different distribution of isomeric products than that observed for *tert*-butylcyclohexanes. This can be attributed to the steric effect of the C-19 methyl group, which hinders the approach of the iodide ion from the β-side of the skeleton. This slows down the iodide exchange in intermediate 3α-iodocholestanes and leads to an increased formation of **16** from **6**. On the other hand, reduction of **7** also yields

Scheme I




[3β-$^2$H] isomer **16** as a main product (Table I). The preferential formation of **16** from **7** may be in part due to the secondary isotope effect on configurational inversion in deuterated iodocholestanes, provided the reduction step becomes competitive with the iodide exchange. It should be noted, however, that isotope effects alone cannot account for the high percentage of **16**, as also pointed out by a referee, and that there must be other, yet undisclosed factors.

In a summary, the present method allows an expedient and regiospecific introduction of deuterium or tritium into multifunctional molecules without need of protection and with the use of an inexpensive source of the label. The method appears especially advantageous for the specific labeling of isolated methyl groups attached to a quaternary carbon, in which the sulfonate elimination is avoided and the products are obtained in good yields and high purity.

## Experimental Section

The $^2$H NMR spectra were measured on Bruker WH-300 (46.075 MHz) and Varian XL-200 (30.47 MHz) spectrometers (FT-mode, pulse width 80 μs, unlocked, $^1$H coupled) in chloroform at 22 °C. The chemical shifts are related to the $CDCl_3$ signal (internal reference) and recalculated by using $\delta(CDCl_3)$ = 7.25 ppm. The mass spectra were obtained on a JEOL JMS D-100 spectrometer (direct inlet, 75 eV, 300 μA).

**Materials.** Zinc powder and sodium iodide (Lachema, analytical grade) were used as received or dried at 100 °C (0.1 torr) for 20 h. 1,2-Dimethoxyethane (Fluka) was dried over lithium aluminum hydride and distilled. The starting mesylates **1**, **2**, and **3** were prepared according to standard procedures.[11]

**1**: mp 127–129 °C. Anal. Calcd for $C_{22}H_{32}O_5S$ (408.6): C, 64.68; H, 7.90; S, 7.85. Found: C, 64.32; H, 7.49; S, 7.49.

**2**: mp 180–182 °C dec; 1H NMR δ 0.62 (s, 3 H, 18-H), 1.12 (s, 3 H, 19-H), 3.13 (s, 3 H, $CH_3SO_3$), 4.93 (d, $J$ = 18 Hz, 1 H, 21-H), 5.42 (d, $J$ = 18 Hz, 1 H, 21-H), 5.70 (br s, 1 H, 4-H).

Anal. Calcd for $C_{22}H_{32}O_6S$ (424.6): C, 62.24; H, 7.60; S, 7.55. Found: C, 62.12; H, 7.54; S 7.71.

**3**: mp 187-189 °C dec; $^1$H NMR δ 0.92 (s, 3 H, 18-H), 1.42 (s, 3 H, 19-H), 3.17 (s, 3 H, $CH_3SO_3$), 4.43 (m, $W$ = 12 Hz, 1 H, 11-H), 4.95 (d, $J$ = 18 Hz, 1 H, 21-H), 5.43 (d, $J$ = 18 Hz, 1 H, 21-H), 5.65 (br s, 1 H, 4-H).

Anal. Calcd for $C_{22}H_{32}O_7S$: C, 59.98; H, 7.32; S, 7.28. Found: C, 59.73; H, 7.21; S, 7.36.

**Reduction of Mesylates and Tosylates (General Procedure for Deuteration).** To a flame-dried flask fitted with a magnetic stirrer, dry tosylate or mesylate (500 mg), 1,2-dimethoxyethane (8 mL), zinc powder (500 mg), sodium iodide (580 mg), and deuterium oxide (99%, 0.5 mL) were added, and the mixture was refluxed under argon. After 6 h the reaction mixture was diluted with ether (100 mL), filtered, washed successively with 2 M HCl, water, saturated $KHCO_3$ solution, sodium thiosulfate, and water, and dried over sodium sulfate, and the solvent was evaporated.

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The residue was crystallized from ethyl acetate–heptane or acetone–methanol–water.

**Reductive Tritiation.** The mesylate (**1**, **2**, respectively) (0.05 mmol), zinc powder (20 mg), sodium iodide (20 mg), and 1,2-dimethoxyethane (2 mL containing 10 mg of tritium oxide, activity 6 Ci) were heated in a sealed tube at 80 °C for 6 h. The cooled tubes was opened, and the reaction mixture worked up as described for deuteriation (vide supra). The crude product was purified by column chromatography by using silica gel (Merck, 1 g) and a mixture of light petroleum ether–acetone–diethyl ether (90:5:5). The specific activity of tritiated compounds, **11** (5.49 Ci/mmol) and **13** (5.3 Ci/mmol), was detd. by a conventional liquid scintillation technique.

**Purification of 16 and 17.** The olefin containing products **16** and **17** were dissolved in chloroform and treated with *m*-chloroperoxybenzoic acid at 20 °C overnight. After a standard workup, the mixture of **16** and **17** was separated from the epoxides on a silica gel column (elution with light petroleum ether).

The labeled compounds **10–15**, **16** + **17**, and **18** + **19** were identified by mixture melting points with the corresponding unlabeled derivatives. **20** + **21** were identified by comparing the retention time and mass spectrum of each with those of *tert*-butylcyclohexane (column SE-30, 3% on Chromosorb, 70 °C).

**Registry No.** **1**, 20576-45-8; **2**, 82427-84-7; **3**, 6677-96-9; **4**, 23712-51-8; **5**, 1182-65-6; **6**, 3381-52-0; **7**, 85749-83-3; **8**, 7453-05-6; **9**, 53042-75-4; **10**, 55487-61-1; **11**, 35481-45-9; **12**, 85749-84-4; **13**, 85749-85-5; **14**, 85749-86-6; **15**, 62743-60-6; **16**, 54482-38-1; **17**, 20810-53-1; **18**, 85749-87-7; **19**, 85749-88-8; **20**, 17553-36-5; **21**, 53042-76-5; Zn, 7440-66-6; NaI, 7681-82-5; T, 10028-17-8.

# Benzo[*f*]isobenzofuran. Mechanistic Aspects of Isobenzofuran Formation from Acetals and Ortho Esters

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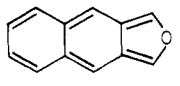
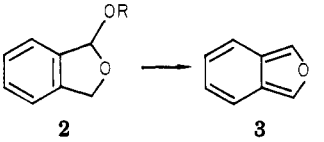
Benzo[*f*]isobenzofuran (**1**) is generated as a reactive intermediate by using the acetal **8** (R = Me, Et) with carboxylic acid catalysts, as shown by the formation of Diels–Alder adducts when the reaction is carried out in the presence of dienophiles ranging in reactivity from maleic anhydride to norbornene. Results with **8** generally parallel those observed earlier with 1-alkoxy-1,3-dihydroisobenzofuran (**2**). In contrast to the lower homologue 1,1-dialkoxy-1,3-dihydroisobenzofuran (**4**), which like the acetals gives Diels–Alder reactions, the ortho ester **9** fails to yield cycloadducts. With acetal **2**, various kinetic parameters were explored. The rate of loss of **2** is half-order in mesitoic acid catalyst and follows second-order behavior with *N*-phenylmaleimide (NPM); i.e., the rate is proportional to the concentrations of **2** and NPM. The reaction of **2** appears to be zero order in dienophile with the less reactive norbornene. An alternative product must be formed reversibly under these conditions, and an oligomeric structure is suggested for this material. In the absence of dienophile a similar rate is observed, leading eventually to the presumed polymer in an irreversible reaction. Deuterium incorporation in recovered **2** when treated for a short time with $CH_3OD$ and acid catalyst provides evidence for the rapid reversible formation of isobenzofuran under the usual reaction conditions. This was further substantiated by deuterium incorporation in the Diels–Alder adducts from a reaction of **2** with norbornene in the presence of $CH_3OD$. Ortho ester **4** reacts with various acids to give phthalide and ring-opened diesters, and these pathways are shown to dominate the reactions of **9**. The different behavior of **4** and **9** in attempted Diels–Alder reactions is shown to be due to a higher barrier for formation (or lower stability) of 1-alkoxybenzo[*f*]isobenzofuran, rather than more facile ring opening of **9** relative to **4**.

Although several years have passed since Cava's report of the isolation of the reactive 1,3-diphenyl derivative[1] and although the unsubstituted thia[2,3] and aza[4] analogues have been generated and trapped in situ, the parent linearly fused isonaphthofuran (**1**; INF, benzo[*f*]isobenzofuran, or naphtho[2,3-*c*]furan) remains unknown. Given suitable



**1**

precursors, **1** is in principle accessible through the elegant flash vacuum pyrolysis technique,[5] but this approach has apparently not been attempted. We have reported[6] that the cyclic acetal **2** can be converted to isobenzofuran (IBF, **3**) in two ways. Treatment with lithium diisopropylamide allows the isolation of solutions of **3**, or heating **2** in the presence of a carboxylic acid catalyst and dienophile gives Diels–Alder adducts, implicating **3** as the reactive intermediate. Both the base-induced and acid-catalyzed pro-




**2** **3**

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