termediate. The species has been proposed by Howe and Franz as an intermediate in the decomposition of 1,3,4-oxathiazol-2-ones.[6] The second involves nucleophilic attack on sulfur.[7] Several ring openings of isothiazoles have been shown to involve attack on the ring sulfur.[8-11] At this point it is not possible to decide between the two mechanisms.

## Experimental Section

**3-(4-Methyl-1-piperazino)-2-nitroacrylonitrile (3a).** To 5.00 g of 3-chloro-4-nitroisothiazole[1] in 25 ml of isopropyl alcohol at 0°, 3.25 g of *N*-methylpiperazine in 10 ml of isopropyl alcohol was added dropwise. The solution was kept at room temperature overnight. A pale yellow solid (mp 119°, sulfur, 600 mg) was filtered. The solution was concentrated and cooled, giving 3.32 g of **3a:** mp 83–85°; NMR ($CDCl_3$) δ 2.33 (3 H, s), 2.55 (2 H, t), 2.61 (2 H, t), 3.70 (2 H, t), 4.00 (2 H, t), 8.50 ( 1 H, s); ir, see text. Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.98; H, 6.17; N, 28.56. Found: C, 48.80; H, 5.90; N, 28.37; S, 0.0.

**3-(1-Morpholino)-2-nitroacrylonitrile (3b).** To 5.00 g of 3-chloro-4-nitroisothiazole in 25 ml of benzene at 0°, 2.80 g of morpholine in 5 ml of benzene was added slowly followed by 3.16 g of triethylamine. An exothermic reaction occurred and a solid formed. After 1 hr the solution was treated with dilute HCl and benzene, and the solid was filtered and crystallized from dimethoxyethane to give sulfur (mp 118°, insoluble in DME), and 3.02 g of **3b,** mp 143–145°. Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.90; N, 22.94. Found: C, 45.76; H, 4.82; N, 22.84.

**3-(1-Piperidino)-2-nitroacrylonitrile (3c).** 3-Chloro-4-nitroisothiazole (5.00 g) and piperidine (2.80 g) were allowed to react as above. The product was soluble in benzene but was crystallized from isopropyl alcohol and then methanol to give 3.54 g of **3c,** mp 116–118°. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.80; H, 6.16; N, 23.48.

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**Registry No.**—1, 14217-68-6; **3a,** 54062-82-7; **3b,** 54062-83-8; **3c,** 54062-84-9; *N*-methylpiperazine, 109-01-3; morpholine, 110-91-8; piperidine, 110-89-4.

## References and Notes

(1) R. Williams, U.S. Patent 3,285,930 (1967); *Chem. Abstr.*, **66,** 28766r (1967).
(2) L. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd ed, Methuen, London, 1958, p 299.
(3) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron,* **25,** 2023 (1969).
(4) G. Descotes, Y. Bahurel, M. Bourillot, G. Pingeun, and R. Rostaing, *Bull. Soc. Chim. Fr.*, 282 (1970).
(5) J. Clark, I. Gelling, I. Southon, and M. Morton, *J. Chem. Soc. C,* 494 (1970).
(6) R. K. Howe and J. E. Franz, *J. Org. Chem.*, **39,** 962 (1974); *J. Chem. Soc., Chem. Commun.*, 524 (1973).
(7) The author thanks one of the referees for pointing out this possibility.
(8) W. R. Hatchard, *J. Org. Chem.*, **29,** 660 (1964).
(9) W. D. Crow and I. Gusney, *Aust. J. Chem.*, **19,** 1693 (1966); **20,** 2729 (1967).
(10) M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 4616 (1964).
(11) K. R. H. Wooldridge, *Adv. Heterocycl. Chem.*, **14,** 19 (1972).

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# Monoesters of Cyclohexane-1β,3β,5β-triol

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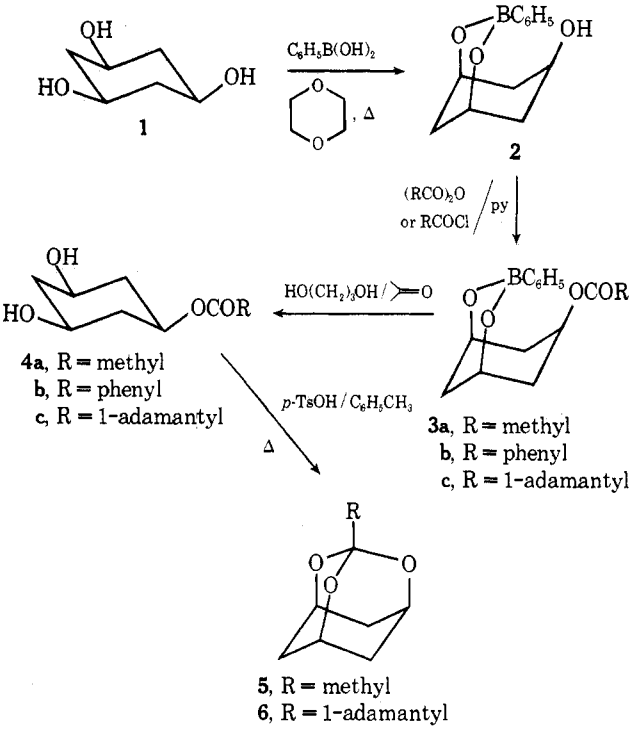
We required a series of the title compounds in order to study their cyclization to the corresponding trioxaadamantanes. This ring system, hitherto prepared[2] from cyclohexane-1β,3β,5β-triol (α-phloroglucitol, **1**) (Scheme I) and a trialkyl ortho ester, is reported[3] to be stable toward Grignard reagents and has seen limited use as a carboxylic acid protecting group.[4] We describe herein the synthesis of three monoesters of **1** and some preliminary cyclization results.

**Scheme I**




Starting triol **1** was obtained highly stereoselectively by high-pressure hydrogenation[2] of 1,3,5-trihydroxybenzene (phloroglucinol) over a rhodium catalyst. Efforts to conveniently prepare monoesters of **1** by direct acylation with 1 equiv of acylating agent in pyridine were thwarted by the qualitative observation that partially acylated phloroglucitols appeared to be more susceptible to further acylation than **1** itself. Likewise, partial saponification of fully acylated derivatives (for example, α-phloroglucitol tribenzoate) with 2 equiv of base produced mixtures in which the desired monoacyl product did not predominate.

Success was achieved through reaction of **1** with phenylboronic acid[5] in refluxing dioxane, producing α-phloroglucitol phenylboronate (**2**) in 99% yield. This last substance was treated with 1 equiv of the acid chloride or anhydride in pyridine, leading to the corresponding acyl derivatives **3** in good yields (79–99%). The phenylboronate group was then cleaved using propane-1,3-diol in acetone,[5] affording the title compounds **4** in yields of ca. 80%.

While monoacetate **4a** could be cyclized to trioxaadamantane **5** in 40% yield with refluxing toluene containing toluenesulfonic acid, esters **4b** and **4c** proved much more resistant to cyclization. For example, reaction of **4c** with toluenesulfonic acid in boiling xylene afforded trioxaadamantane **6** [mp 142–144°, tentative assignment based on a high-resolution mass spectrum, *m/e* 276.176 (calcd, 276,173)] in less than 1% yield.

## Experimental Section

Melting points were determined on a Kofler hot stage or in a sealed capillary in an oil bath and are uncorrected. Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. NMR spectra were recorded on a Varian A-60, HA-100, or XL-100 high-resolution spectrometer. Chemical shifts are reported in parts per million downfield from internal $Me_4Si$. Mass spectra (70 eV) were determined on a CEC 110-2B double-focusing mass spectrometer equipped with a direct inlet. Elemental analyses were performed at the University of Oregon by Dr. S. Rottschaefer.

**Cyclohexane-1β,3β,5β-triol (1).** A mixture of 10.9 g of phloroglucinol (Aldrich), 5 g of 5% rhodium on alumina (Engelhard), and 70 ml of 95% ethanol (distilled from Raney nickel) was shaken in an atmosphere of hydrogen at 2900 psi and 98° for 18 hr. Filtration of the hot mixture and concentration of the filtrate afforded 6.55 g (58%) of crystalline **1** as a hydrate, mp 110–112° (lit.[2] mp 110°). Anhydrous **1**, mp 185° (lit.[2] mp 184°), used in subsequent experiments, was obtained by heating the hydrate overnight at 50° (10 mm). The NMR spectrum of the original mother liquors of **1** revealed only the presence of **1** and unreacted phloroglucinol.

**Cyclohexane-1β,3β,5β-triol Phenylboronate (2).** A mixture of 220 ml of dioxane (distilled from $LiAlH_4$), 3.0 g (0.023 mol) of anhydrous **1**, and 2.8 g (0.023 mol) of phenylboronic acid (Aldrich) was refluxed while the dioxane–water azeotrope was slowly removed by fractional distillation over a 90-min period. Removal of the remaining solvent (ca. 150 ml) in vacuo afforded 4.9 g (99%) of **2**, mp 109–111°. Two successive sublimations (100°, 0.25 mm) gave the analytical specimen as colorless prisms: mp 114–115°; ir ($CHCl_3$) 1441 (m, B–Ar stretch[6]), 1312 $cm^{-1}$ (s, B–O stretch[6]); NMR ($CDCl_3$) δ 1.58 (m, 3, axial methylene protons), 2.19 (m, 3, equatorial methylene protons), 4.24 (m, 3, methine protons), 7.0–7.9 (m, 5, aromatic protons); mass spectrum *m/e* 218 ($M^+$), 210, 186, 177.

Anal. Calcd for $C_{12}H_{15}BO_3$: C, 66.10; H, 6.93. Found: C, 66.13; H, 7.09.

**Acylation of 2.** The synthesis of **3b** is representative. To a solution of 1.35 g (6.2 mmol) of **2** in 15 ml of dry pyridine was added 710 μl (6.2 mmol) of benzoyl chloride. After a 2-hr period at 25° the solvents were removed *in vacuo*, and the residual solid was extracted with hot benzene. Evaporation of the extract afforded 1.95 g (99%) of crystalline **3b**, mp 125–127°. Two recrystallizations from benzene–hexane gave the analytical specimen as colorless pentagonal clusters: mp 137–137.5°; ir ($CHCl_3$) 1447 (m, B–Ar stretch), 1309 $cm^{-1}$ (s, B–O stretch); NMR ($CDCl_3$) δ 1.5–2.8 (m, 6, $-CH_2-$), 4.48 (m, 2, –CHOB–), 5.45 (m, 1, –CHOCO), 6.5–7.9 (m, 10, aromatic protons); mass spectrum *m/e* 322 ($M^+$), 245, 200, 172.

Anal. Calcd for $C_{19}H_{19}BO_4$: C, 70.84; H, 5.94. Found: C, 70.82; H, 5.93.

Similarly prepared using acetic anhydride was **3a**, mp 74–75° (hexane).

Anal. Calcd for $C_{14}H_{17}BO_4$: C, 64.65; H, 6.59. Found: C, 64.64; H, 6.69.

Similarly prepared using adamantane-1-carbonyl chloride was **3c**, mp 149–151° (hexane).

Anal. Calcd for $C_{23}H_{29}BO_4 \cdot H_2O$: C, 69.36; H, 7.84. Found: C, 69.06; H, 7.69.

**Monoesters 4a–c of Cyclohexane-1β,3β,5β-triol.** The synthesis of **4b** is representative. To a solution of 504 mg (1.56 mmol) of **3b**, mp 125–127°, in 5 ml of dry acetone was added 1.0 ml (14 mmol) of propane-1,3-diol. The solution was stirred at 25° for 2.5 hr and then the volatiles were removed under vacuum (1 mm) overnight. The residue was taken up in 5 ml of ethyl acetate and washed with water. The organic phase was dried and evaporated, affording 306 mg (83%) of **4b**, mp 110–116°. Recrystallization from toluene gave the analytical specimen as colorless, chunky prisms: mp 114°; NMR (acetone-$d_6$) δ 1.35 [q, $J$ = 11.5 Hz, 1, axial methylene proton –CHOHCH$_2$(a,e)CHOH–], 1.50 [q, $J$ = 11.5 Hz, 2, axial methylene protons CH$_2$(a,e)CHOCOC$_6$H$_5$CH$_2$(a,e)–], 2.28 (m, 3, equatorial methylene protons), 3.83 (t of t, 2, –CHOH–), 3.93 (brs, 2, OH), 5.02 (t of t, 1, –CHOCOC$_6$H$_5$), 7.3–8.1 (m, 5, aromatic protons); mass spectrum *m/e* 236 ($M^+$), 218, 200, 123.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.90; H, 6.71.

Similarly prepared from **3a** was **4a**, mp 131–132° (acetone–hexane).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.96; H, 8.23.

Similarly prepared from **3c** was **4c**, mp 175–176° (toluene).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.50; H, 9.03.

**Cyclohexane-1β,3β,5β-triol Tribenzoate.** To a solution of 100 mg (0.75 mmol) of anhydrous **1** in 2 ml of pyridine was added 0.90 ml (7.7 mmol) of benzoyl chloride. After 1 hr at 25° the usual work-up gave 262 mg (78%) of the title compound which was recrystallized from chloroform–methanol, affording the analytical specimen as colorless prisms, mp 177–178°.

*Anal.* Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.79; H, 5.38.

**Cyclization of 4a.** A mixture of 69.5 mg of **4a** in 3 ml of toluene containing 7 mg of toluenesulfonic acid monohydrate was refluxed for 4 hr with continuous removal of water by means of a Dean-Stark trap. The solvent was removed and the residue was taken up in chloroform, washed with 2% $NaHCO_3$, dried, and the chloroform then evaporated. Sublimation (12 hr, 60°, 760 mm) of the residue afforded 24.5 mg (40%) of **5**, mp 126° (lit.[7] mp 126°).

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**Registry No.**—**1**, 50409-12-6; **2**, 53951-24-9; **3a**, 53951-25-0; **3b**, 53951-26-1; **3c**, 53951-27-2; **4a**, 53951-28-3; **4b**, 53951-29-4; **4c**, 53951-30-7; **5**, 27761-63-3; phloroglucinol, 108-73-6; phenylboronic acid, 98-80-6; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; adamantyl-1-carbonyl chloride, 2094-72-6; propane-1,3-diol, 504-63-2; cyclohexane-1β,3β,5β-triol tribenzoate, 53951-31-8.

## References and Notes

(1) Alfred P. Sloan Foundation Fellow, 1972–1974. Recipient of a NIH Research Career Development Award (1 K4 70156).
(2) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **85**, 451 (1952).
(3) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **87**, 205 (1954); R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives", Organic Chemistry, A Series of Monographs, Vol. 14, Academic Press, New York, N.Y., 1970.
(4) J. M. Osbond, P. G. Philpott, and J. C. Wickens, *J. Chem. Soc.*, 2779 (1961); F. Bohlmann and W. Sucrow, *Chem. Ber.*, **97**, 1839, 1846 (1964).
(5) R. J. Ferrier and D. Prasad, *J. Chem. Soc.*, 7425, 7429 (1965).
(6) L. J. Bellamy, W. Gerrard, and M. F. Lappert, *J. Chem. Soc.*, 2412 (1958).
(7) H. Stetter and K. H. Steinacker, *Chem. Ber.*, **86**, 790 (1953).

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## On the Specificity of Amine Solvation

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The question arose whether proton exchange of a cyclic amine obeys the mechanism now widely accepted for acyclic aliphatic amines:[2]

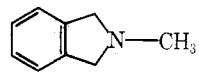
$$R_3NH^+\cdots OH_2 + HOH \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} R_3N\cdots HOH + H_3O^+$$

$$R_3N\cdots HOH \xrightarrow{k_H} R_3N + HOH$$

$$R_3N + H_3O^+ \xrightarrow{fast} R_3NH^+\cdots OH_2$$

Since the rate parameters, especially $k_H$, are sensitive to subtle interactions between the water and the alkyl groups,[3] it was by no means clear how incorporating the amine into a ring would perturb the exchange process.

Proton exchange rates of *N*-methylisoindoline conjugate acid were measured by NMR line-shape analysis of the



doublet-to-singlet transition of the $NCH_3$ signal as the pH increased from 0 to 2. In this pH range, bimolecular exchange[4] between $R_3NH^+$ and $R_3N$ was unimportant (the rate constants showed no dependence on amine concentration below the 0.15 *M* amine used in the experiments). Likewise, exchange catalyzed by hydroxide ion[4] did not contribute to the observed rates. If *N*-methylisoindoline exchanges by the mechanism shown above, then the corresponding rate equation (eq 1) predicts that a plot of $1/k_{obsd}$