erican Scientific). Melting points were determined in a Mettler machine and are uncorrected.

General Method of Isomerization of Polycyclic Precursors to Cage Hydrocarbons. To a solution of 5.0 mmol of precursors (0.68 g of **1**, 0.92 g of **2**, 1.2 g of **3**) in 50 mL of Freon-113 or CH_2Cl_2 was added an equimolar amount of acid under dry argon with constant stirring. Aliquots were taken and analyzed by gas chromatograph after appropriate workup.[5] When the starting isomer was found to react completely (as in the case of adamantane or diamantane) or other intermediate isomers were found not to react any further (as in the case of triamantane), the reaction mixture was quenched in ice–bicarbonate and extracted in CH_2Cl_2 and the products were precipitated/crystallized according to literature procedures[5,13,17] and characterized by melting points and ^{13}C NMR spectra. Reactions in solvent-free systems were carried out according to our previous procedure.[5] Reactions under the influence of ultrasound were similarly carried out in a Schlenk flask in the ultrasonic bath for different lengths of time (Table I).

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Registry No. **1a**, 2825-83-4; **1b**, 2825-82-3; **2f**, 51966-17-7; **3c**, 74999-13-6; **3d**, 74999-14-7; $B(OSO_2CF_3)_3$, 64371-01-3; CF_3SO_3H, 1493-13-6; SbF_5, 7783-70-2; adamantane, 281-23-2; diamantane, 2292-79-7; triamantane, 13349-10-5; 1-bromoadamantane, 768-90-1; 1-chloroadamantane, 935-56-8; 1-fluoroadamantane, 768-92-3.

Keto–Enol Tautomerism of Phloroglucinol and the Formation of the Tris(sodium bisulfite) Addition Complex

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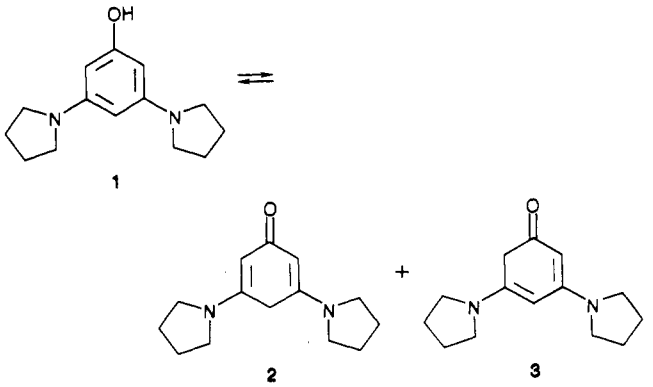
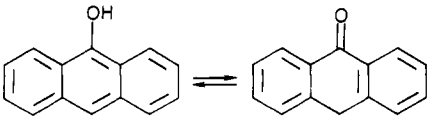
Factors governing the equilibrium between keto and enol forms continue to arouse substantial interest.[1] Recently, a study of the position of this equilibrium between the phloroglucinol analogue **1** and its keto forms, **2** and **3**, showed that the aromatic "enol" form **1** is favored by the ability of the solvent to accept a hydrogen bond, while the keto forms, **2** and **3**, are favored by the ability of the solvent to donate a hydrogen bond.[2,3] A detailed study of the



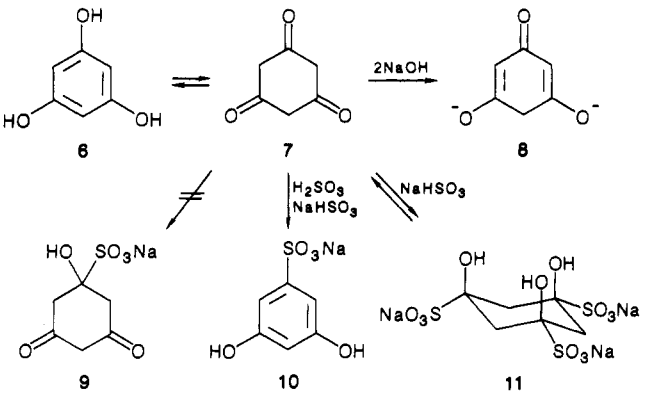
contributions of the various properties of solvents to such equilibria has concluded that, in the absence of the possibility of intramolecular hydrogen bonding, it is the ability of the solvent to enter into intermolecular hydrogen bonds which determines the position of the equilibrium.[4] In particular, the ability of the solvent to accept a hydrogen bond dominates the situation. The anthrol–anthrone pair, **4** and **5**, show such behavior, with a similar formation and



disruption of an aromatic system. Since the ketonic and phenolic forms of phloroglucinol, **6** and **7**, are believed to be similar to each other in stability,[5] they should behave similarly. Indeed, the dianion of phloroglucinol exists exclusively in the alicyclic form, **8**.[6] Nonetheless, ^1H or ^{13}C NMR spectra of solutions of phloroglucinol in water or trifluoroethanol reveal no alicyclic form, although this latter solvent has essentially no ability to accept a hydrogen bond.[7]

However, it has long been known that phloroglucinol, **6**, reacts readily as the keto form, **7**. A hundred years ago Baeyer showed that the compound forms a trioxime with hydroxylamine,[8] subsequently shown by its infrared and ultraviolet spectra to be a true trioxime, rather than the isomeric trinitrosobenzene.[9]

Among earlier studies of such reactions is the observation by Fuchs that phloroglucinol forms a bisulfite addition compound, to which he assigned the structure **9**.[10] The characterization then possible was limited to elemental analysis, a positive ferric chloride test, and the observation that the material was water soluble and surprisingly stable to acid and base. Contemporary critics objected that such stability was not characteristic of bisulfite addition compounds,[11] but the question has not been further investigated.



The earlier method of forming **9** relied on the formation of sodium bisulfite by passing sulfur dioxide into a solution of sodium bicarbonate to the point of saturation, followed by extensive reflux. However, the solution so prepared is substantially more acidic than a solution prepared directly from sodium bisulfite, and the prolonged reflux seemed anomalous; the sodium bisulfite addition compound of

(1) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186.
(2) Highet, R. J.; Chou, F. E. *J. Am. Chem. Soc.* **1977**, *99*, 3538.
(3) Highet, R. J. *J. Org. Chem.* **1986**, *51*, 3231.
(4) Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216.
(5) Wheland, G. *Resonance in Organic Chemistry*; Wiley: New York, 1955.
(6) Highet, R. J.; Batterham, T. J. *J. Org. Chem.* **1964**, *29*, 475.
(7) Kamlet, M. J.; Abboud, J. L. M.; Abrahame, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877.
(8) Baeyer, A. *Ber.* **1886**, *19*, 159.
(9) Farmer, V. C.; Thomson, R. H. *Chem. Ind. (London)* **1956**, 86.
(10) Fuchs, W. *Ber.* **1921**, *54*, 245.
(11) Bucherer, H. T. *Ber.* **1921**, *54*, 1457.

cyclohexanone forms at room temperature in 30 min.[12]

Repetition of this preparation afforded material shown by ^{13}C NMR to be aromatic, with peaks at 157.5, 144.4, 106.1, and 104.8 ppm. In context, the chemical shifts and implied symmetry suggest that the product might well be sodium 3,5-dihydroxybenzenesulfonate, **10**. Preparation of this material by the sodium hydroxide fusion of 1,3,5-benzenetrisulfonic acid provided identical material.[13] The anomalous stability of the product is thus readily explained. Inasmuch as the molecular formulae of **9** and **10** differ by 1 mol of water, the elemental analysis implies that the material is isolated as a hydrate.

The question remains of whether or not phloroglucinol actually forms a sodium bisulfite addition compound. A solution of phloroglucinol in 4 M sodium bisulfite shows only two resonances in the ^{13}C spectrum, at 35.5 and 87.7 ppm, which appear in a coupled spectrum as a triplet and singlet respectively. The observation shows complete conversion to the tris addition compound, **11**. Addition of ethanol produced an oily layer which crystallized from aqueous ethanol. Combustion analysis showed that this material was grossly contaminated with sodium bisulfite, but the preparation allowed spectral examination in D_2O.

Attempts to prepare conventional derivatives of the material were frustrated by its insolubility in organic solvents and the ready reversibility of the formation in water. A D_2O solution of this material shows the carbon spectrum observed of the sodium bisulfite solution and, at proton frequencies, the AB system of the methylene group, observable at 300 MHz, δ 2.24 and 2.28, $J = -14.3$ Hz. The spectra gradually decreased in intensity as the result of exchange of the protons with the solvent, the process being essentially complete after about 45 min. The observation of the discrete methylene peaks and the slow exchange with solvent makes it clear that the peaks observed must therefore correspond to a single species, rather than the averaged resonances of rapidly exchanging species. Thus, within the limits of detection by the NMR spectra, only a single isomer of **11** is formed. It must be the all-cis isomer, for the ^{13}C spectrum of the cis-trans isomer must show four peaks. It seems reasonable to suppose that the conformation adopted must be that with the mutually repulsive sulfonic anions in the equatorial position.

Experimental Section

NMR spectra were run on a Varian XL200 and XL300 spectrometers. ^{13}C chemical shifts of aqueous solutions are relative to internal dioxane, $\delta = 67$ ppm; those of organic solutions are relative to $(CH_3)_4Si = 0$. Infrared spectra were run on KBr pellets on a Perkin-Elmer 1420 spectrometer.

Solutions of phloroglucinol in trifluoroethanol (ca. 1%) showed ^{13}C resonances at 159.39 and 97.50 ppm. Aqueous solutions (1%) showed peaks at 158.26 and 95.70 ppm. Neither solution had changed after 2 weeks.

Conversion of Phloroglucinol to 3,5-Dihydroxybenzenesulfonic Acid.[10] Ten grams of sodium bicarbonate was suspended in 30 mL of water while sulfur dioxide was bubbled through until the suspended solid dissolved and exit gases gave a strong acid reaction. The solution so prepared showed a pH of 1.2. A 5-g sample of phloroglucinol dihydrate was added and the solution was refluxed 3.5 days. A ^{13}C spectrum now showed peaks at 157.5, 144.4, 106.1, and 104.8 ppm. The solution was diluted with ethanol, allowed to stand overnight, and filtered, to provide 5.2 g of solid. An analytical sample was prepared by crystallization from ethanol. The infrared spectrum (KBr) was identical with that of material prepared by fusion of 1,3,5-benzenetrisulfonic acid:[13] 3608, 3450, 3370, 3240, 1630, 1596, 1515, 1495, 1380, 1305, 1220, 1195, 1167, 1110, 1052, 1003, 990, 837, 677, 645 cm^{-1}. Anal. Calcd for $C_6H_5SO_3Na \cdot 2H_2O$: C, 29.04; H, 3.66; S, 12.92. Obsd: C, 29.17; H, 3.48; S, 12.31.

Trisodium *cis,cis*-1,3,5-Trihydroxycyclohexane-1,3,5-trisulfonate. Phloroglucinol dihydrate, 2 g, was added to 40 mL of 4 M sodium bisulfite solution and stirred at room temperature for 3 h. The solution was transferred to a separatory funnel and diluted with 2 volumes of ethanol. The lower layer was separated, dissolved in 40 mL of ethanol–water (7:3), and chilled overnight. The solid was separated by filtration, washed with cold ethanol–water, and dried to afford 5.2 g of a white powder. Material so prepared showed strong absorption at 1130, 637, and 620 cm^{-1}, with small peaks at 1625 and 1511 cm^{-1} corresponding to phloroglucinol. The ^{13}C spectrum of an aqueous solution of this material showed peaks corresponding to phloroglucinol immediately, which increased with time.

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(12) Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman, Greene and Company: London, 1956; p 342.
(13) Suter, C. M.; Harrington, G. W. *J. Am. Chem. Soc.* **1937**, *59*, 2575.

Multigram Preparation of 1,8-Diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic Acid, a Phenolic Metabolite of the Analgesic and Antiinflammatory Agent Etodolac

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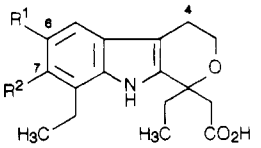
The hydroxypyranoindoles **2** and **3** are oxidative metabolites of the analgesic and antiinflammatory drug etodolac (**1**).[1,2] We recently required large amounts of 7-hydroxyetodolac (**2**). Although **2** is available through a



1(etodolac), $R^1 = H$; $R^2 = H$
2, $R^1 = H$; $R^2 = OH$
3, $R^1 = OH$; $R^2 = H$

nonselective microbial hydroxylation of **1** using *Cunninghamella blackesleeama*,[2] the low yields in this biotransformation make this process impractical. We now report a synthesis of **2** that utilizes as the key step the condensation of the lithio anion of *tert*-butyl acetate with isatin **9**. The twelve-step synthesis proceeds in 17% yield from *N*-(trimethylacetyl)-3-methoxyaniline (**4**)[3] and is readily adaptable to multigram quantities of **2** as demonstrated herein.

As shown in Scheme I, orthometalation of **4** with *n*-butyllithium[3] at 0 °C followed by an acetaldehyde quench at −78 °C provided crystalline alcohol **5** in 74% yield. Catalytic hydrogenation[4] and hydrolysis gave 2-ethyl-3-methoxyaniline (**6**), isolated as its HCl salt, in 86% yield. Aniline **6** was elaborated to tryptophol **11** via isatin **8**,

(1) Humber, L. *Med. Res. Rev.* **1987**, *7*(1), 1.
(2) Ferdinandi, E. S.; Sehgal, S. N.; Demerson, C. A.; Dubuc, J.; Zilber, J.; Dvornik, D.; Cayen, M. N. *Xenobiotica* **1986**, *16*, 153.
(3) Fuhrer, W.; Gschwend, H. *J. Org. Chem.* **1979**, *44*, 1133.
(4) Horn, A. S.; Kaptein, B.; Mulder, T. B. A.; DeVries, J. B.; Wynberg, H. *J. Med. Chem.* **1984**, *27*(10), 1340.

0022-3263/88/1953-2844$01.50/0