67673-33-0; **5**, 67673-34-1; 2-bromoacetanilide, 614-76-6; diethyl methylphosphinite, 15715-41-0.

Supplementary Material Available: Tables of thermal parameters, refined atomic coordinates, bond distances and angles, least-squares mean planes, and crystal data and a stereodrawing of compound **2a** (6 pages). Ordering information is given on any current masthead page.

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Synthesis and Absolute Stereochemistry of *cis*- and *trans*-1,2-Indandiols: Metabolites of Indene and 2-Indanone

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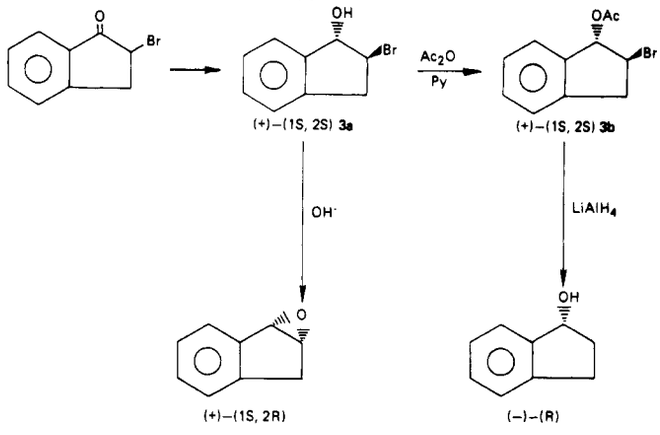
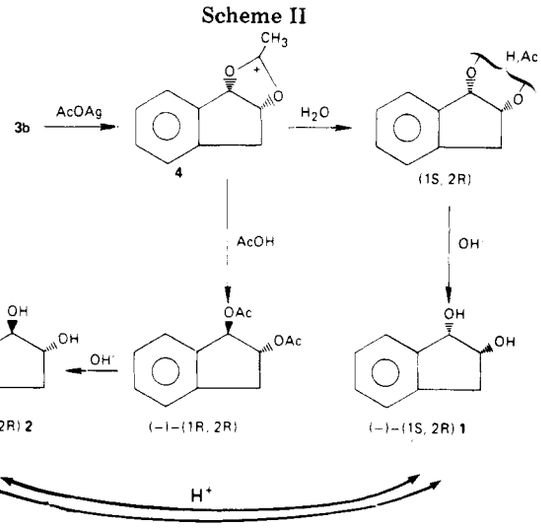
Systematic studies of the mammalian metabolism of aromatic hydrocarbons by Boyland,[1] Jerina,[2] and others[3] have established that these compounds are oxidized to arene oxides, which in turn are enzymatically hydrated to *trans*-dihydrodiols. The reported metabolism by animals of indene[3a] and acenaphthylene[3b] differs from that of other aromatic hydrocarbons in that both *cis*- and *trans*-dihydrodiols are formed. In studying the metabolism of indene, Brooks and Young[3a] introduced the compound into the animals through a stomach tube and isolated from urine the metabolites formed. The small quantities of optically active *cis*- and *trans*-1,2-indandiols obtained in this manner precluded chemical studies. Since the presence of cis and trans diols as animal metabolites is unusual, we wanted to determine which centers (i.e., C-1 or C-2) in these compounds have the same configuration. This information can be used to support or refute proposed biosynthetic schemes for formation of these metabolites. We elected to prepare both compounds by asymmetric synthesis and to determine their absolute stereochemistry.

Although several strategies have been devised to determine the absolute stereochemistry of dihydrodiols, most approaches depend upon a reduction step in which the diol is converted to a β-hydroxy hydroaromatic compound; the latter is synthesized, resolved, and its configuration established.[2a] The absolute stereochemistry of the diol is then logically deduced. Since all approaches that proceed via symmetric 2-indanol are doomed, we chose a synthetic approach utilizing the stereospecific reduction of a 1-indanone derivative. Earlier experiments[4] with *Cryptococcus macerans* demonstrated that this microbe reduces 1-indanone to (1*S*)-indanol. Our projected

Scheme I



Scheme II



synthesis involved preparing a single compound whose absolute stereochemistry could conveniently be determined, and which could be transformed to **1** and **2**, thus circumventing the need to transform **1** and **2** to compounds of known absolute stereochemistry. *trans*-1-Hydroxy-2-bromoindan (**3a**) fulfills these requirements and it was prepared by reduction of 2-bromoindan-1-one by *C. macerans*. The stereochemistry of the bromoindanol was assigned by comparison of its NMR spectrum with that of authentic racemic material. The absolute stereochemistry of (+)-**3a** was established as 1*S*,2*S* by conversion to (1*R*)-indanol of known configuration[5] as shown in Scheme I. The cis diol, (−)-**1**, was prepared from **3b** by treatment with silver acetate in wet acetic acid followed by hydrolyses under basic conditions (see Scheme II). Since Woodward[6a] and Winstein[6b] have shown that these solvolyses proceed by neighboring group participation, as shown for **4**, the absolute stereochemistry of (−)-**1** is 1*S*,2*R*. Although it is possible to convert **3b** to the trans diol diacetate, an assignment of the absolute stereochemistry of the latter compound appeared equivocal. The intermediate **4** could react with acetate at C-1, C-2 or in a non-regioselective manner. In the latter case attack by acetate yields a racemic product. Solvolyses of **3b** in glacial acetic acid in the presence of silver acetate yielded a trans diacetate, which had a large specific rotation ($[\alpha]_D$ −52.4°) demonstrating that the reaction was regioselective. Although the factors that determine the relative ease with which a benzylic vs. a saturated carbon atom of an acyloxonium ion is attacked have not been studied in the detail as they have been in aryloxirans,[7] the acyloxonium's reactivity should parallel that of the aryloxirans. The argument that regioselective attack occurred primarily at C-1 was proved by equilibrating **1** and **2** with dilute acid. This equilibration

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which Berti et al.[8a] have shown also yields 2-indanone proceeds via the C-1 carbonium ion. The configuration at C-2 is unaffected in the equilibration, and therefore according to our assignments (−)-(1*R*,2*R*)-**2** should yield (−)-(1*S*,2*R*)-**1**. A sample of (−)-**2** was treated with dilute sulfuric acid in dioxane–water (7:3) for 1 h and the resulting mixture of diols separated. An examination of their specific rotations showed that (−)-**1** formed, and thus (−)-**1** and (−)-**2** have the same configuration at C-2.

In addition to serving as a valuable intermediate for the preparation of **1** and **2**, (+)-**3a** was also used to prepare optically active (+)-(1*S*,2*R*)-indene oxide. Although there are many possible uses for optically active oxiranes, their asymmetric synthesis by chemical methods has not been particularly successful.[9] The microbial reduction route employed here thus offers a promising entry to these compounds.[10]

Brooks and Young[3a] isolated (+)-**2** and (+)-**1** from the urine of rabbits dosed with indene. Therefore the metabolites have 1*S*,2*S* and 1*R*,2*S* configurations, respectively. Both (+)-**1** and (+)-**2** were also isolated by Lewis[3c] from the urine of rats which had been subcutaneously injected with 2-indanone. Although the mechanisms by which these diols are produced from either substrate are unknown, proposed mechanisms must account for the observed absolute stereochemistry.

Experimental Section

General Procedure. Melting points were determined using a hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian HR-220 MHz instrument using FT technique and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (J) in hertz. Optical rotations were recorded on a Cary 60 spectropolarimeter. Chemical ionization mass spectra were taken with a Hitachi RMS-4. Preparative and analytical TLC work was performed on plates coated with Kieselgel silica gel F-254.

Microbial Reduction of 2-Bromoindan-1-one. 2-Bromoindan-1-one was prepared from 1-indanone and bromine by the method of House and McDaniel.[11]

A liter Erlenmeyer flask containing 250 mL of a sterile solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was innoculated with a culture of *C. macerans*. The flask was shaken at 30 °C for 2 days and to the optically dense culture was added 100 mg of 2-bromoindan-1-one. Shaking was continued for 7 days and the suspension was then extracted three times with 250-mL portions of ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Analysis of the crude mixture by NMR indicated *trans*-1-hydroxy-2-bromoindan (**3a**) was produced in ~55% yield and no significant amount of the cis isomer was detected. The mixture was separated by thick layer chromatography (silica gel, ethyl acetate–hexane (1:9)) to yield (+)-**3a**: 34 mg; mp 132–133 °C (recrystallized from 95% EtOH); $[\alpha]^{25}_D$ +29.0° (c 0.530, EtOH). The NMR spectrum of this material was identical with racemic material prepared from indene and NBS according to the method of Berti et al.:[3a] NMR ($CDCl_3$) δ 2.47 (1 H, OH, d, J = 5.6 Hz), 3.21 (1 H, dd, J = 16.2, 7.5 Hz), 3.57 (1 H, dd, J = 16.2, 7.0 Hz), 4.26 (1 H, m), 5.31 (1 H, dd, J = 5.6, 5.6 Hz), 7.24–7.41 (4 H, m).

(+)-(1*S*,2*S*)-*trans*-1-Acetoxy-2-bromoindan (3b). A solution of (+)-**3a** (21 mg) in acetic anhydride (5 mL) and pyridine (1 mL) was stirred at room temperature for 10 h. Water (20 mL) was added and the mixture was extracted with benzene, washed with 5% HCl and 10% sodium bicarbonate, dried over anhydrous Na_2SO_4, and concentrated to yield **3b**, which was purified by thick-layer chromatography on silica gel (ethyl acetate–hexane (1:9)): 23 mg (92% yield); mp 56 °C (recrystallized from 95% EtOH); $[\alpha]^{25}_D$ +79.2° (c 4.80, EtOH). The NMR spectrum of this sample was identical with that of racemic material: NMR ($CDCl_3$) δ 2.09 (3 H, s), 3.25 (1 H, dd, J = 16.5, 4.0 Hz), 3.70 (1 H, dd, J = 16.5, 7.0 Hz), 4.48 (1 H, m), δ 6.29 (1 H, d, J = 3.8 Hz), 7.23–7.41 (4 H, m).

Conversion of (+)-3b to (−)-(1*R*)-Indanol. To a slurry of $LiAlH_4$ (38 mg) in 10 mL of dry THF was added (+)-**3b** (51 mg) and the solution was refluxed under N_2 for 5 h. The reaction mixture was decomposed using cold water and worked up as usual to yield a colorless oil which was purified by thick-layer chromatography (silica gel, ethyl acetate–hexane (1:4)) to give (−)-(1*R*)-indanol: 18 mg (69% yield); colorless oil; $[\alpha]^{25}_D$ −18.0° (c 0.40, $CHCl_3$). The NMR of this sample was identical with that of racemic material and the optical purity was 78% based on its reported[5] specific rotation.

(+)-(1*S*,2*R*)-Indene Oxide. A solution of (+)-**3a** (42 mg) in $CHCl_3$ (25 mL) and 2 N KOH (25 mL) was stirred at 50 °C for 2 h. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue purified by distillation (78 °C (1.0 mmHg)) to give (+)-(1*S*,2*R*)-indene oxide: 21 mg (82% yield); colorless oil; $[\alpha]^{25}_D$ +17.5° (c 3.33, $CHCl_3$). The NMR and mass spectra of this sample were identical with those of racemic material which was prepared according to the method[8a] of Berti et al.

(−)-(1*S*,2*R*)-*cis*-1,2-Indandiol (1). A solution of (+)-**3b** (128 mg) and silver acetate (125 mg) in 10 mL of glacial acetic acid containing 0.1 mL of water was refluxed for 4.5 h. After cooling, the reaction mixture was filtered and the precipitated salts were washed with ethyl acetate. The solvent was removed in vacuo to leave an oily residue, which was treated with 200 mg of KOH in methanol (10 mL) containing 1 mL of water. After refluxing for 1 h, the solvent was removed in vacuo and the residue was extracted with $CHCl_3$, washed with water, and dried over anhydrous Na_2SO_4. The NMR spectrum of this crude reaction mixture showed that the corresponding cis diol was formed almost quantitatively. The reaction mixture was purified by thick-layer chromatography (silica gel, ethyl acetate–hexane (3:7)) to give (−)-**1**: 66 mg (89% yield); mp 99–100 °C (recrystallized from cyclohexane); $[\alpha]^{25}_D$ −51.0° (c 0.40, $CHCl_3$) (reported **3c**, $[\alpha]^{25}_D$ +41° ($CHCl_3$)). The NMR spectrum of this sample was identical with that of racemic material prepared from indene and osmium tetraoxide: NMR (pyridine-d_5) δ 3.12 (1 H, dd, J = 15.9, 5.6 Hz), 3.24 (1 H, dd, J = 15.9, 3.8 Hz), 4.74 (1 H, m), 5.09 (2 H, OH, broad s), 5.29 (1 H, d, J = 4.9 Hz), 7.21–7.71 (4 H, m).

(−)-(1*R*,2*R*)-*trans*-1,2-Indandiol (2). A solution of silver acetate (125 mg) in acetic acid (10 mL) containing 2 mL of acetic anhydride was refluxed for 2 h under N_2. To this solution was added 128 mg of (+)-**3b** and the reaction mixture was refluxed for another 3 h under N_2. After cooling, the reaction mixture was filtered and the precipitated salts were washed with ethyl acetate. The solvent was removed in vacuo to leave an oily residue and the NMR spectrum of this crude mixture showed *trans*-1,2-diacetoxyindan was produced. This was purified by distillation (123–125 °C (1.0 mmHg)) to give (−)-(1*R*,2*R*)-*trans*-1,2-diacetoxyindan: 98 mg (84% yield); colorless oil; $[\alpha]^{25}_D$ −52.4° (c 1.13, $CHCl_3$). The NMR spectrum of this sample was identical with that of racemic material prepared from (±)-*trans*-1,2-indandiol and acetic anhydride–pyridine: NMR ($CDCl_3$) δ 2.06 (3 H, s), 2.10 (3 H, s), 2.89 (1 H, dd, J = 16.6, 4.6 Hz), 3.52 (1 H, dd, J = 16.6, 7.2 Hz), 5.46 (1 H, m), 6.25 (1 H, d, J = 3.5 Hz), 7.22–7.38 (4 H, m).

The (−)-(1*R*,2*R*)-*trans*-1,2-diacetoxyindan was then hydrolyzed to (−)-**2**. A solution of 58 mg of (−)-(1*R*,2*R*)-*trans*-1,2-diacetoxyindan in 10 mL of methanol containing 1 mL of water and 200 mg of KOH was refluxed for 2 h. The solvent was removed in vacuo; the residue was extracted with hot ethyl acetate, washed with water, dried over sodium sulfate, and concentrated to yield (−)-**2** which was recrystallized from toluene: mp 182–184 °C; 33 mg (88% yield); $[\alpha]^{25}_D$ −10.7° (c 0.93, EtOH) (reported[3c] $[\alpha]^{25}_D$ +30° (ethanol)). The NMR spectrum of this sample was identical with that of racemic material prepared by the known method:[8a] NMR (pyridine-d_5) δ 3.12 (1 H, dd, J = 15.4, 7.6 Hz), 3.41 (1 H, dd, J = 15.4, 7.2 Hz), 4.92 (1 H, m), 5.17 (2 H, OH, broad s), 5.58 (1 H, d, J = 5.4 Hz), 7.22–7.73 (4 H, m).

Isomerization of (−)-2 Diol to (−)-1. A solution of (−)-**2** (50 mg) in dioxane (7 mL) and water (3 mL) containing 1 mL of 1 N H_2SO_4 was refluxed for 1 h. After cooling, the reaction mixture was made alkaline with $NaHCO_3$, saturated with NaCl, and extracted with ethyl acetate. Analysis of the crude reaction mixture by NMR (pyridine-d_5) indicated that *trans*-1,2-indandiol, *cis*-1,2-indandiol, and 2-indanone were produced in the ratio of 67:23:10. These three compounds were separated by thick-layer chromatography (silica gel, ethyl acetate–hexane (3:7)).

(−)-**2**: 29 mg; purified as described above; $[\alpha]^{25}_D$ −8.9° (c 0.56, EtOH).

(−)-**1**: 12 mg; purified as described above; $[\alpha]^{25}_D$ −41.3° (c 0.42, $CHCl_3$).

2-Indanone: 3 mg; mp 54–56 °C; the NMR spectrum of this sample was identical with that of authentic material prepared from 2-indanol by Jones oxidation.

Registry No.—**1**, 67528-22-7; **2**, 67528-23-8; **3a**, 67528-24-9; **3b**, 67528-25-0; 2-bromoindan-1-one, 1775-27-5; (−)-(1*R*)-indanol, 697-64-3; (+)-(1*S*,2*R*)-indene oxide, 67528-26-1; (−)-(1*R*,2*R*)-*trans*-1,2-diacetoxyindan, 67528-27-2.

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Carbon-13 and Proton Nuclear Magnetic Resonance Spectroscopic Evidence for a Molecular Complex of Actinomycin D and 10,11-Dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol

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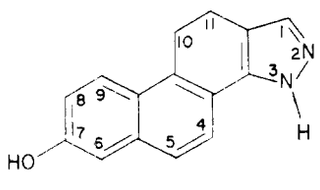
The role of molecular complexation in the activity of actinomycin D in the presence of heterosteroid-type substances has been recently investigated[1-3] by a variety of spectrometric methods, including fluorescence and proton magnetic resonance spectroscopy. While ^{1}H NMR studies have proven to be useful in the study of molecular complexes,[4,5] the complexity of the spectra of large biomolecular complex systems is a limiting factor except in those cases in which a well-resolved signal is available or the system is a highly symmetrical molecule.[6]

It has been recognized for many years that the application of ^{13}C NMR analysis to large, unsymmetrical molecular complexes could be instructive in that the chemical shifts of most of the carbon atoms of the acceptor and donor may be examined simultaneously. With the advent of pulse Fourier transform techniques, examination of molecular complexation of the charge transfer type has become feasible, and recent work on some known charge transfer systems[7,8] has provided advances in this area.

It has been reported that a combination of actinomycin D, a clinical anticancer agent, and 10,11-dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol (**1**) readily inhibited growth of selected microorganisms and the L–M cell line to a greater extent than the individual compounds alone.[1,2] The later report[1] gave evidence for the hypothesis that this potentiation in activity could be due to the formation of a molecular complex between the two compounds in solution. A tentative structure for the complex was also postulated on the basis of ^{1}H NMR spectral analysis.[1] However, the data did not permit unequivocally the elimination of alternative structures and did not have the benefit of ^{13}C NMR analysis.



This paper describes additional evidence for the formation of a molecular complex between actinomycin D and **1** as well as a postulated orientation of the complex under the stipulated conditions. All spectrometric determinations were done with D_3COD as the solvent to attain the concentrations necessary for ^{13}C NMR. Although the previous complexation studies for this system[1] were done in D_2O, unfortunately, low solubility of **1** in D_2O prevented a practical ^{13}C spectral analysis in this solvent, and also some decompostion of the actinomycin D occurred during the extremely long acquisition times. Thus, the concentrations used in the D_2O study were less than those used in the D_3COD study by a factor of 10 (1.3 mM vs. 12.7 mM).

Results and Discussion

The ^{13}C NMR spectrum of actinomycin D had been previously analyzed in $DCCl_3$.[9,10] Assignments in D_3COD were made by direct comparison with this published work. However, not every carbon atom could be identified due to the low solubility of the actinomycin D as well as the low intensity of some of the slower relaxing carbons.[10] No assignments were made of the carbon signals in the polypeptide chains, as several resonances were partially obscured by a large ^{13}C signal from the solvent and the high resonance density of carbon signals. Partial obscuring of ^{13}C signals by a large ^{13}C solvent signal was avoided in the previous study[10] by using $D^{12}CCl_3$. Unfortunately, isotopically pure $D_3{}^{12}COD$ is not available.

In the case of **1**, chemical shifts were identified for appropriate carbons on the basis of model compounds, as well as by use of an off-resonance, broad-band, proton-decoupled spectral analysis. The assignments for the ^{13}C shifts for the individual solutions of actinomycin D, **1**, and the complex are given in Table I.

The striking feature of the ^{13}C NMR spectrum of the complex is that *all* identifiable signals for carbon atoms in the phenoxazine ring of actinomycin D displayed a *negative* (*upfield*) shift in the spectrum relative to the corresponding signals in the ^{13}C spectrum of pure actinomycin D in D_3COD. In contrast, the ^{13}C chemical shifts in the complexed indazole **1** displayed *both* upfield and downfield shifts. A more graphic representation of these results can be seen in Figures 1 and 2, where the numerical differences between the ^{13}C chemical shifts of the free and complexed actinomycin D (Figure 1) and the free and complexed indazole **1** (Figure 2) are given.

As can be seen in Figure 1, the largest ^{13}C shift differences in the spectrum of complexed actinomycin D occur with carbons in the quinoid portion of the phenoxazine ring. Such differences are reduced for the carbon atoms furthest removed from this part of the ring system. This strongly implies that the primary interaction between the compounds in the complex occurs at the quinoid end of the phenoxazine ring behaving as the acceptor.

The observation of solvent-induced shifts for substituted aromatic systems for carbons several atoms removed from the site of substitution has been shown to correlate in a nearly quantitative manner with electronic perturbations in the ring.[11] Similar electronic perturbations can be postulated as the cause of the "tapering off" effect observed in the phenoxazine ring of actinomycin D, although it is impossible to judge the degree of perturbation for any one carbon atom

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