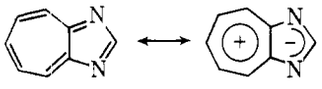
Comparison of the individual carbon chemical shifts of X with those of azulene indicates a definite transfer of electron density from the seven- to the five-membered ring. While the $C_{4,8}$ shifts are similar, those of $C_6$ and $C_{5,7}$ are 3.0 and 11.6 ppm further downfield for X than for azulene. This is consistent with the 4.05 D dipole moment of X[17] and a charge-distribution structure such as that drawn below. The tropylium-like character of the seven-membered ring of X is further enhanced by protonation of the imidazole ring. For benzimid-



azole in $HCl/Me_2SO$, the peaks of the 2 and 8,9 carbons are moved upfield by 1.9 and 8.1 ppm, respectively, while the 4,7 peak remains unchanged and the 5,6 peak moves downfield 4.4 ppm. Under the same conditions, the 2 and 9,10 peaks of X are also moved upfield (11.9 and 6.9 ppm, respectively). All of the remaining carbon peaks of the seven-membered ring, however, are shifted downfield by 6.4–9.3 ppm, a much greater average shift than for I. The average chemical shift of carbons 4–8 of X is 136.3 and of protonated X, 143.6 ppm. Both of these values are closer to the chemical shift of tropylium ion (155.3 ppm[19]) than the average for azulene of 131.2 ppm. The series of seven-membered ring derivatives azulene, X, protonated X, and tropylium ion is one of gradually decreasing average electron density in the carbocyclic ring. As expected from the dipole measurement, X exhibits a greater electron transfer from the seven- to the five-membered ring than azulene.

## Conclusions

The determination of long-range $^{13}C$–$^{1}H$ and $^{13}C$–$^{13}C$ coupling constants is extremely useful for peak assignment in $^{13}C$ NMR spectroscopy. Observation of exocyclic coupling to methyl hydrogens allows assignment of the ipso and ortho carbons of methyl compounds, while the $^{3}J_{^{13}C-^{13}C}$ of 2-$^{13}C$-enriched imidazole derivatives identifies carbons three bonds distant. For 5(6)-substituted benzimidazoles, correlations of $^{13}C$ chemical shifts with various Hammett $\sigma$ parameters are observed, the most useful of which should be the relationship of $\delta(C_2)$ to $pK_a$. The chemical shifts of carbons in the carbocyclic ring of 1,3-diazaazulene indicate qualitatively a lower average electron density for this ring than in azulene. Protonation of the imidazole ring further decreases the average electron density and makes the seven-membered ring even more tropylium-like for this azulene analogue.

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# Preparation and Absolute Stereochemistry of Isomeric Pyridylethanols and *threo*-Di(2-pyridyl)ethanediol

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Optically active isomeric pyridylethanols have been prepared by microbial (*C. macerans*) reduction of the corresponding acetyl derivatives. The absolute stereochemistry of each alcohol was determined as *S* by conversion to (+)-(*S*)-methyl *O*-acetyllactate. Reduction of 2,2′-pyridil by the same organism yielded (−)-di(2-pyridyl)ethanediol, whose configuration was established as *R,R* by conversion to (*S,S*)-dimethyl diacetyltartrate. The stereospecificity of these reductions is discussed with reference to Prelog's rule for predicting their absolute stereochemistry.

In a recent study of asymmetric cathodic reduction, Kopilov, Kariv and Miller[1] examined the reductions of 2-, 3- and 4-acetylpyridines in the presence of alkaloids known to adsorb on the cathode under the reduction conditions. Since Miller et al. obtained high optical yields (40 and 48% for **1a** and **1b**, respectively), additional studies employing this technique for the synthesis of a wide variety of medicinal compounds can be expected. Although a detailed mechanism was not proposed, it is apparent that any mechanism proposed must account for the absolute stereochemistry of the products. The configurations of (−)-**1a**, (−)-**1b**, and (−)-**1c** were assigned

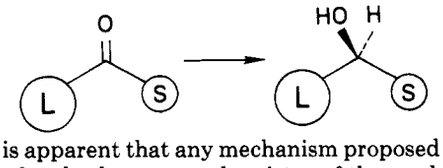
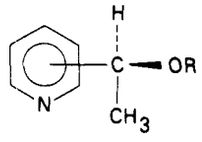


**Table I. Summary of Optical Properties of 1a, 1b, 1c, and 2b and Ozonolysis Products**

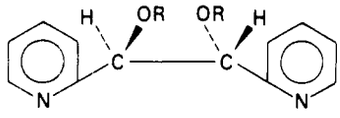
| compd. | registry no. | specific rotation, deg observed | specific rotation, deg reported[2] | specific rotation of acetate | registry no. | specific rotation of ozonolysis product $3^{a,b}$ | specific rotation of ozonolysis product $4^{c,d}$ |
|---|---|---|---|---|---|---|---|
| 1a | 59042-90-9 | −56.7 (*c* 3.88, EtOH) | −56.1 (*c* 0.5, EtOH) | −98 (*c* 2.31, EtOH) | 66842-20-4 | −35.7 (*c* 2.81, acetone), ee 85% | |
| 1b | 5096-11-7 | −30 (*c* 4.92, EtOH) | −40.2 (*c* 0.87, MeOH) | −102 (*c* 3.37, EtOH) | 66842-21-5 | −34.5 (*c* 2.32, acetone), ee 82% | |
| 1c | 54656-96-1 | −29.5 (*c* 1.60, $CHCl_3$) | −43.4 (*c* 0.5, EtOH) | −74.7 (*c* 5.57, EtOH) | 66842-22-6 | −32.0 (*c* 3.54, acetone), ee 79% | |
| 2a | 66900-45-6 | −51.7 (*c* 2.44, EtOH) | | −17.4 (*c* 0.78, EtOH) | 66842-23-7 | | +19.1 (*c* 1.39, $CHCl_3$), ee 81% |

[a] Authentic sample prepared from (+)-(*S*)-lactic acid has specific rotation −42 (*c* 2.13, acetone). [b] Registry no. 14031-88-0. [c] Authentic sample prepared from (−)-(*S,S*)-tartaric acid has specific rotation +23.7 (*c* = 1.52, $CHCl_3$). [d] Registry no. 6304-92-3.



1

(a) 2-pyridyl, R = H (d) 2-pyridyl, R = $-COCH_3$
(b) 3-pyridyl, R = H (e) 3-pyridyl, R = $-COCH_3$
(c) 4-pyridyl, R = H (f) 4-pyridyl, R = $-COCH_3$



2

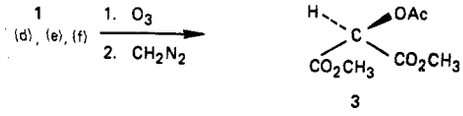
(a) R = H (b) R = $-COCH_3$

by Gottarelli and Samori[2] using Horeau's method, which is known to have exceptions.[3] Cervinka[4] independently assigned the absolute stereochemistry of the isomeric pyridylethanols; however, his assigned configuration for (−)-**1a** differed from that of Gottarelli and Samori. The latter investigators used the absorption spectra and the chiroptical properties of these compounds to interpret the spectral properties of the pyridine chromophore. Since the configurations of **1a, 1b,** and **1c** appear critical in at least two studies, we transformed optically active samples of these compounds into compounds of known absolute stereochemistry. In addition to the alcohols (+)-**1a,** (+)-**1b,** and (+)-**1c** Miller et al. also obtained dimeric reduction products from 2-acetylpyridine. In order to distinguish between *erythro*- and *threo*-1,2-di(2-pyridyl)ethanediols we have examined the microbial and chemical reduction of 2,2′-pyridil.

In addition to our interest in determining the absolute stereochemistry of the alcohols obtained from microbial reduction of the corresponding ketones, we were interested in the asymmetric syntheses of these compounds. While chiral reducing agents have recently been successfully used for asymmetric synthesis,[5] the presence of a basic nitrogen atom in the acetyl pyridines introduces many complications.[6a] In the course of examining the chiral reduction by microorganisms of several tetrahydro polycyclic ketones, we found that the chemical and optical yields in these reductions were frequently high and that the method had the distinct advantage of producing alcohols of a consistent configuration.[6b] As there were no analogous examples of the reduction of heterocyclic ketones, we were interested in determining the effect of a heteroatom, nitrogen, on the course of the reduction.

When *Cryptococcus macerans,* a microorganism which reduces acetophenone quantitatively to optically pure (*S*)-phenylethanol,[6b] is used to reduce the three isomeric acetylpyridines, the resulting alcohols are formed in good chemical and optical yields (Table I). The absolute stereochemistries of the alcohols were then determined by first acetylating the hydroxyl group, followed by ozonolysis of the pyridine derivative to a mixture of acids (Scheme I). The latter were methylated and pure methyl *O*-acetyllactate (**3**) was isolated and its specific rotation measured. The optical properties of the alcohols, acetates, and **3** formed are summarized in Table I. *These results clearly establish that C. macerans reduced each of the ketones to the S alcohol.* Thus, with the configurations of the isomeric pyridylethanols established, it is clear that Cervinka's assignment of the (*R*) configuration to (−)-2-pyridylethanol[2] was in error and that Horeau's method *correctly* predicted the absolute stereochemistry of (−)-**1a,** (−)-**1b,** and (−)-**1c.**

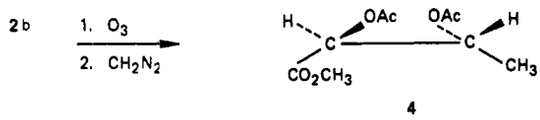
Scheme I



The configurations of **1a, 1b,** and **1c** are those expected from Prelog's rule[7] (shown in Figure 1) which states that if the ketone is placed with the larger group on the observer's left as shown, the hydroxyl group formed is closer to the observer. Thus the rule predicts that the alcohols formed from reduction of acetophenone and the isomeric acetylpyridines each have the same absolute stereochemistry, as is observed. The simplicity of predicting the configuration of alcohols formed by *C. macerans* using Prelog's rule contrasts with the difficulties associated in interpreting the weak and complex CD bands exhibited by these compounds. The latter are very difficult to use in assigning the absolute stereochemistry of a pyridine derivative whose configuration is not known.

While studying the asymmetric cathodic reduction of acetylpyridines, Kopilov, Kariv, and Miller[1] isolated small quantities of the corresponding pinacols. The pinacols were optically inactive in every case. However, the authors did not specify whether the observed pinacols were the erythro or threo isomers or mixtures. In an earlier study[8] on the reduction of a series of benzil derivatives we had shown that *C. macerans* provided optically active threo diols. Samples enriched in the erythro isomers, which are meso, were prepared by hydride reduction of the appropriate benzil. When 2,2′-pyridil was used as a substrate for *C. macerans* an optically active diol was isolated whose NMR spectrum differed from the spectrum of the major isomer formed by hydride reduction of 2,2′-pyridil. These results enable us to assign threo and erythro configurations to the microbial and chemical reduction products, respectively. The absolute stereochemistry of (−)-di(2-pyridyl)ethanediol was determined by conversion to (*S,S*)-(+)-dimethyl diacetyltartrate **4** as shown in Scheme

Scheme II




4

II. The absolute stereochemistry of (−)-di(2-pyridyl)ethanediol was thus established as (*R,R*).

The observation that the threo (*R,R*)-diol is the predominant product while the erythro isomer forms to less than 5% of the threo isomer requires some comment. Since the erythro isomer is present only to a small extent, it is apparent that the enzyme responsible for reducing the carbonyl group of the half-reduced 2,2′-pyridil distinguishes between *R* and *S* configurations, stereoselectively and preferentially reducing the former. The surprising sensitivity of the enzyme to the differences between α carbons bearing a hydrogen, a hydroxyl, and a pyridyl ring in an [*R*] or [*S*] arrangement indicates the necessity of accumulating additional experimental data before it is possible to order the effective size of substituents. The observation that the presence of a heteroatom (nitrogen) in these compounds does not alter the stereochemical course of the reduction from that of the carbon analogue is consistent with Prelog's rule, if in the half-reduced pyridil the 2-pyridyl ring is considered to be the larger substituent while $CHOHC_5H_5N$ is the smaller, which emphasizes steric effects over electronic considerations. These results strongly suggest that configurations assigned to alcohols as a result of microbial reduction have general applicability and therefore deserve more attention than they have received.

## Experimental Section

**Microbial Reduction.** A 1-L Erlenmeyer flask containing 250 mL of a sterile solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was inoculated with a culture of *C. macerans*. The flask was shaken at 30 °C for 2 days, and 100 mg of 2,2′-pyridil was added to the optically dense culture. Shaking was continued for 7 days and the suspension was then made alkaline with 10% KOH and 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. No starting material was detected in the NMR spectrum of the crude extract. The threo diol (**2a**) was formed in ~80% yield along with ~5% of the erythro isomer (detected by NMR). The mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (1:1)) to yield the threo diol (**2a**), 72 mg, which was recrystallized from 50% aqueous EtOH, mp 92–93 °C. The $[\alpha]^{25}_D$ data of this sample and the other optically active alcohols obtained from microbial reduction of the isomeric acetylpyridines are summarized in Table I.

Microbial reductions of the acetylpyridines were carried out in a similar manner.

**Ozonolysis of (−)-*S*-1d, (−)-*S*-1e, (−)-*S*-1f, and (−)-2b.** (*S*)-4-Pyridylethanol acetate **1f** was prepared by acetylating (−)-**1c** with acetic anhydride in pyridine in the usual manner. The crude acetate was purified by thick layer chromatography on silica gel (ethyl acetate:hexane (15:85)) and distilled in vacuo (colorless oil, NMR (in $CDCl_3$)): δ 1.50 (3 H, d, *J* = 6.7 Hz), 2.11 (3 H, s), 5.83 (1 H, q, *J* = 6.7 Hz), 7.24 (2 H, d, *J* = 5.7 Hz), 8.58 (2 H, d, *J* = 5.7 Hz). The $[\alpha]^{25}_D$ data of this sample and those of the other optically active acetates are summarized in Table I.

A solution of the acetate (151 mg) **1f** in 50 mL of dichloromethane was ozonized at 0 °C using a stream of ozone (2–4%) [from an Ozonator, Model 03V2]. When the ozonolysis was complete (~24 h) the solvent was removed in vacuo and 5 mL of 97% formic acid and 2 mL of 30% hydrogen peroxide were added. The solution was stirred at 50 °C for 1 h, at which time unreacted hydrogen peroxide was decomposed with sodium sulfite and the solvent was removed in vacuo. Excess saturated aqueous sodium bicarbonate was added to the residue and the solution was extracted with hexane. The aqueous layer was then acidified with hydrochloric acid, saturated with sodium chloride, and extracted several times with ether. The ether extract was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The NMR spectrum of the crude reaction mixture showed that **3** was produced in ~65% yield. An ether solution of this mixture was esterified with diazomethane. The solvent was removed and the residue distilled (bp 102–103 °C (99 mm)) to yield methyl (−)-(*S*)-**3**, 62 mg, 41% yield. The $[\alpha]^{25}_D$ of **3** formed from **1d** and **1e** is listed in Table I.

**(−)-Methyl *O*-Acetyllactate.** A solution of (+)-(*S*)-lactic acid (90 mg) in 5 mL of dry ether was esterified with diazomethane. The resulting methyl ester was treated with acetic anhydride (5 mL) and pyridine (1 mL) overnight at room temperature. The mixture was poured into water and extracted with ether and the ether solution was washed with 10% HCl and saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled (bp 102–103 °C (99 mm Hg)) to provide methyl (−)-**3** in an overall yield of 83%: 95 mg; $[\alpha]^{25}_D$ −42.0° (*c* 2.133, acetone); $^1H$ NMR (in $CDCl_3$) δ 1.47 (3 H, d, *J* = 7.1 Hz), 2.14 (3 H, s), 3.76 (3 H, s), 5.10 (1 H, q, *J* = 7.1 Hz). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.85; Found: C, 49.20; H, 6.91.

Ozonolyses of **1d, 1e,** and **2b** were carried out as described above. A sample of authentic (+)-**4** was previously prepared.[8] The $[\alpha]^{25}_D$ data and enantiomeric excess (ee) of products are given in Table I.

**Registry No.**—2,2′-Pyridil, 492-73-9; 2-acetylpyridine, 1122-62-9; 3-acetylpyridine, 350-03-8; 4-acetylpyridine, 1122-54-9; (+)-(*S*)-lactic acid, 79-33-4.

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