(m, 2 H), 1.4 (m, 1 H), 0.91 (d, 3 H); mass spectrum, m/z (relative intensity) 223 (M^+, 63.4), 167 (100), 164 (49.3), 122 (44.2), 108 (55), 94 (82), 80 (60.9).

Hydrolysis of 11 To Give Compound 9. (a) With Sodium Hydroxide. To compound 11 (0.112 g, 0.5 mmol) in methanol (5 mL) was added aqueous sodium hydroxide solution (1.2 equiv, 24 mg of NaOH in 1 mL of water). After the reaction mixture was refluxed overnight, the mixture was cooled to room temperature and then poured to 10 mL of water. This solution was washed with ether and the aqueous layer was then acidified with diluted HCl to pH 3 and extracted with ether. The combined ethereal layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give quantitatively a pale yellowish solid: mp 74–77 °C; $[\alpha]_D$ −16.4° ($CDCl_3$); ^1H NMR ($CDCl_3$) δ 11 (br, 1 H), 9.48 (s, 1 H), 7.17 (br, 1 H), 6.98 (d,d, 1 H), 6.32 (dd, 1 H), 6.05 (t, 1 H), 2.0 (m, 2 H), 1.4 (m, 1 H), 0.91 (d, 3 H), 0.88 (d, 3 H); mass spectrum, m/z (relative intensity) 209 (M^+, 52.7), 180 (75.4), 138 (63.6), 122 (66), 108 (71.3), 94 (78.1), 80 (62.2), 41 (100); IR (KBr) 3250–2400, 1740, 1610 cm^{-1}; $[\alpha]_D$ −16.4° ($CDCl_3$). Anal. Calcd: C, 63.1; H, 7.2. Found: C, 63.2; H, 7.3.

When quite excess aqueous sodium hydroxide solution was used, compound 9 showed no optical activity.

(b) With Trimethyliodosilane. This reaction was carried out according to Jung's method.[11] To compound 11 (0.112 g, 0.5 mmol) in dry $CHCl_3$ (5 mL) was added trimethyliodosilane (0.143 mL, 1 mmol). The solution was stirred overnight at room temperture while protected from light. The mixture was then poured into 5% aqueous $NaHCO_3$. The aqueous layer was washed with ether, acidified with diluted HCl to pH 3, and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give yellowish solid 9 (55%). The physical data was identical with that of method a.

Acknowledgment. We thank NSERC and FCAC for financial support of this research.

Registry No. 1, 696-59-3; 2, 86428-38-8; 3a, 100-46-9; 3b, 623-33-6; 3c, 3182-93-2; 3d, 56-40-6; 4a, 2051-97-0; 4b, 5145-67-5; 4c, 86436-62-6; 4d, 19167-98-7; 5, 66967-05-3; 6, 957-68-6; 7, 86436-63-7; 8, 551-16-6; 9, 86436-64-8; 10, 86436-65-9; 11, 86436-66-0; 12, 86436-67-1; Amberlyst A-21, 9049-93-8; L-leucine methyl ester hydrochloride, 7517-19-3.

(11) M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).

Intramolecular Addition of Enolates to Pyridinium Ions: Formation of Spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines]

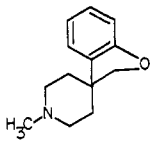
Dwight D. Weller,* Glenn R. Luellen, and Doreen L. Weller

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

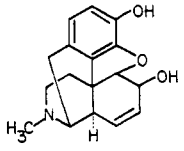
Received October 13, 1982

Intramolecular addition of ketone and ester enolates to *N*-alkylpyridinium species produced spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines] in 82–93% yields. When the ketone adducts were treated with hydriodic acid in ethanol at room temperature and the ester adducts treated with triethylammonium iodide in refluxing ethanol, the original pyridinium salts were produced in excellent yields. An attempt to extend the intramolecular pyridinium enolate addition to the synthesis of the 4a-phenylisoquinoline system failed but produced instead the 4-phenylquinoline system. The addition of enolates to *N*-acylpyridinium salts was moderately successful when the ketone enolates were generated with the hindered base 2,6-dimethyl-4-(1-piperidyl)pyridine.

The spiro[benzofuran-3(2*H*),4′-piperidines] **1**, represent an interesting substructure of the morphine molecule (**2**).

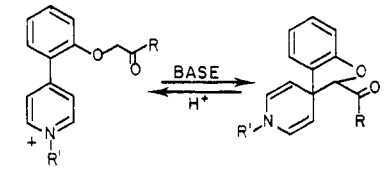


1



2

Although known for some time, this fragment has not been extensively explored since no exceptionally active analgesics have been found in this series.[1] Recently, it has reappeared as an early intermediate in a general route to the morphine system.[2] It is well suited to this role in that it is a relatively simple fragment which contains the important quaternary carbon of the morphine skeleton. Thus, the question of stereochemistry can be addressed early in the synthesis. We wished to explore the applicability of the derivative fragment, the spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines], **4**, toward the total synthesis of the morphine alkaloids.[3] We expected that these derivatives would be available by the intramolecular addition of enolates to pyridinium ions of type **3** (eq 1). This



3 R = OEt, CH_3

3 R′ = Alkyl, Acyl

4

(1)

addition reaction is well documented for both the intra- and intermolecular modes[4] and has found utility in the synthesis of several alkaloid systems such as ajmalicine,[5] yohimbine,[6] and sesbanine.[7]

(1) (a) Bergel, F.; Haworth, J. W.; Morrison, A. L.; Rinderknecht, H. *J. Chem. Soc.* **1944**, 261. (b) Barltrop, J. *Ibid.* **1946**, 958. (c) Kagi, H.; Miescher, K. *Helv. Chim. Acta* **1949**, *32*, 2489. (d) Spielman, M. A. U.S. Patent 2 500 714, 1950; *Chem. Abstr.* **1950**, *44*, 5922. (e) Gervais, C.; Anker, D.; Carret, G.; Pacheco, H. *Tetrahedron* **1979**, *35*, 745. (f) Gervais, C.; Anker, D.; Chareire, M.; Pacheco, H. *Bull. Soc. Chim. Fr.* **1979**, II-241. (g) Ong, H. H.; Agnew, M. M. *J. Heterocycl. Chem.* **1981**, *18*, 815. (h) Macdonald, A. D.; Woolfe, G.; Bergel, F.; Morrison, A. L.; Rinderknecht, H. *Br. J. Pharmacol.* **1946**, *1*, 4.

(2) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064.

(3) Weller, D. D.; Luellen, G. R. *Tetrahedron Lett.* **1981**, *22*, 4381.

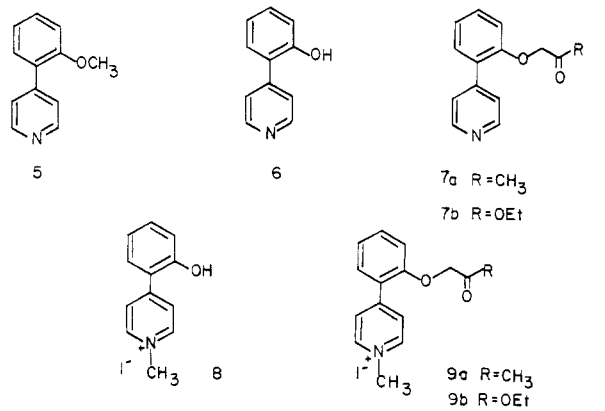
(4) (a) For a review covering the formation of dihydropyridines by addition of carbanions see: Eisner, V.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Kröhnke, F.; Ellegast, K. *Ann. Chem.* **1956**, *600*, 175. (c) Ahebrecht, H.; Kröhnke, F. *Ann. Chem.* **1967**, *704*, 133.

(5) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Kazuhiko, O. *J. Am. Chem. Soc.* **1976**, *98*, 3645.

0022-3263/83/1948-3061$01.50/0

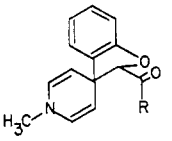
The dihydropyridines undergo elimination of the enol moiety with regeneration of the pyridinium species, upon treatment with acids.[3,4] In our scheme, this results in the return of chiral **4** into achiral **3**. Since the stereochemistry of the remaining asymmetric centers of the morphine skeleton will be determined relative to C-2 and C-3 in **4**, the interconversion of **3** and **4** would allow close control of the absolute stereochemistry. Two uncertainties arise in this sequence. The first is absence of a stabilizing electron-withdrawing group at the β position of the dihydropyridine. Also, in very few pyridinium enolate additions have quaternary carbons been generated in the addition reaction.[8] To test this sequence we wished to prepare the pyridinium salts **3** having either *N*-alkyl or *N*-acyl activating groups and either ketone or ester enolates as the nucleophilic species.

The key intermediate for the preparation of the phenylpyridines **3** was the phenol **6**, prepared in 99% yield by demethylation of 4-(2-methoxyphenyl)pyridine (**5**). This phenylpyridine was easily prepared in 54% from 2-methoxybenzaldehyde by a process described in detail elsewhere.[9] The initial goal was to prepare the O-alkylated materials **7**, which would be N-alkylated or N-acylated as required. Under optimum conditions, the ester **7b** was prepared in 69% yield from the phenol and ethyl bromoacetate by using sodium ethoxide in ethanol. On the basis of recovered phenol, the yield was 81% with the remainder of the material consisting of N-alkylated salts. Reaction of the phenol with the more reactive and less selective chloroacetone using potassium carbonate in dimethylformamide gave only 53% of the ketone **7a** with 33% recovered phenol. Attempts to use a more naked phen-



oxide ion (potassium carbonate in hexamethylphosphoramide) did not result in improved yields. Attempts to achieve selective O-alkylation by reaction of **6** with ethyl diazoacetate in the presence of rhodium acetate,[10] copper-bronze, or boron trifluoride etherate were unsuccessful. Alkylation of **8** using potassium carbonate in dimethylformamide provided the required N-alkylated salts **9** in high yield.

The *N*-alkylpyridinium salts **9** were cleanly converted into the corresponding dihydropyridines by base treatment. Reaction of **9a** with ethanolic sodium ethoxide caused immediate solution of the sparingly soluble salt, but surprisingly, no product was isolated after pouring the reaction mixture into water and extracting with chloroform. Additionally, the water layer had adopted the typical yellow color of the pyridinium salts. Saturation of this solution with sodium hydroxide and extraction returned the pure dihydropyridine **10a**. These observations accord



10a R=CH3
10b R=OEt

with the results of Kröhnke, who found that adducts from ketones readily dissociate in aqueous media.[4c] A more satisfactory procedure for obtaining the ketone adduct was to add aqueous sodium hydroxide to the salt dissolved in a stirred solution of dimethyl sulfoxide and benzene, whereby **10a** was obtained in 93% yield. More practically, **10a** was available in 91% yield directly from methiodide **8** by treatment of the O-alkylation reaction mixture with sodium hydroxide.

The ester dihydropyridine **10b** was prepared in 87% yield by heating the salt in anhydrous ethanol containing 1 equiv of sodium ethoxide for several minutes. In this case, a standard aqueous workup was satisfactory. Alternatively, the reaction proceeded at room temperature in 83% yield if the salt was first dissolved in dimethyl sulfoxide and treated with ethanolic sodium ethoxide. An interesting feature of the ring closure of **9b** to **10b** in ethanol at reflux is that the reaction achieves an equilibrium which heavily favors the dihydropyridine. The reverse reaction is dependent on the presence of the sodium cation. Compound **10b** can be heated in pure ethanol without effect, but when sodium iodide (or lithium bromide) is added, a pyridinium species was readily observable in the ^{1}H NMR spectrum and comprised roughly 10% of the mixture. Significantly, tetrabutylammonium iodide did not catalyze the equilibration process. This suggested that use of a tetraalkylammonium ethoxide should allow complete conversion of **9b** to **10b**. However, when the ring closure was attempted with trimethylanilinium ethoxide, there was no significant improvement in the product distribution. This may be due to traces of sodium ions remaining from the preparation of the quaternary ammonium base.

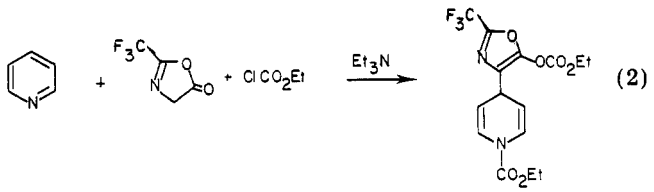
The characterization of the dihydropyridines **10a** and **10b** rests on the striking changes observed in the ^{1}H and ^{13}C NMR spectra attending ring closure. The proton spectrum of **10a** shows the dihydropyridine ring protons as four distinct doublet of doublets at chemical shifts expected for the enamine protons. The most outstanding features of the carbon spectrum are the appearances of a singlet at δ 48.4 due to the quaternary C-4′ of the dihydropyridine and also the C-2 methine resonance at δ 99.6. The ester **10b** shows analogous NMR spectra. Both **10a** and **10b** are stable indefinitely at −20 °C but will polymerize at 25 °C. The ester **10b** could be distilled provided chlorinated solvents were not used in the workup procedure. Although **10a** converts to the yellow pyridinium salt soon after spotting on a thin layer silica gel plate, **10b** may be chromatographed on silica provided the silica remains moistened with solvent. Both compounds may be chromatographed on neutral alumina.

The reversal of the *N*-alkyldihydropyridine formation to give the pyridinium salts was easily accomplished.

(6) Wenkert, E.; St. Pyrek, J.; Vesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.*, **1982**, *104*, 2244.
(7) (a) Wanner, M. J.; Koomen, G.-J.; Pandit, U. K. *Heterocycles* **1980**, *14*, 643. (b) Wanner, M. J.; Koomen, G.-J.; Pandit, U. K. *Ibid.* **1981**, *15*, 377.
(8) For examples see (a) Sainsbury, M.; Uttley, N. C. *J. Chem. Soc., Perkin Trans 1* **1977**, 2109. (b) Naito, T.; Ninomiya, I. *Heterocycles* **1980**, *14*, 959.
(9) Weller, D. D.; Luellen, G. R.; Weller, D. L. *J. Org. Chem.* **1982**, *47*, 4803.
(10) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.*, **1974**, 607.

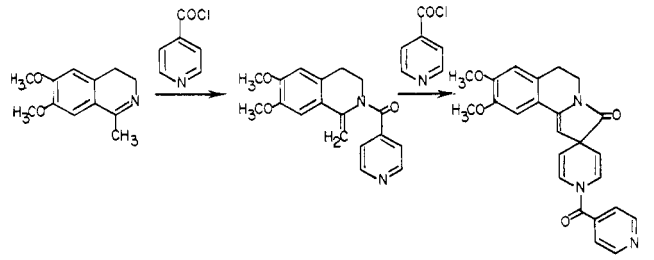
Dissolution of the adduct **10a** in a minimum amount of ethanol followed by treatment with concentrated hydriodic acid resulted in precipitation of **9a** in 95% yield. The reversal of **10a** to **9a** may be accomplished even with the usual carboxylic acids. Addition of a stoichiometric quantity of acetic acid to **10a** in ethanol led to complete reversal to **9a**, as evidenced by ^{1}H NMR of the reaction mixture. The reaction of **10b** with hydriodic acid gave initially a protonated species (loss of the enamine resonance in the ^{1}H NMR), which only slowly yielded impure **9b** in refluxing ethanol. A more efficient reversal was effected by reaction of **10b** with triethylammonium iodide in hot ethanol. Here, no protonated species form, and 82% of **9b** may be recovered by cooling the reaction solution after 2 h of heating. The ready reversibility of the ester dihydropyridine in the presence of metal ions can be employed to utilize otherwise inefficient proton donors such as phenol, but the reaction appears to have no advantage over the process using the amine salt.

The formation of the *N*-acyldihydropyridines represents a significant departure from the *N*-alkyl analogues because the reactive intermediate, the *N*-acylpyridinium ion, is a potent acylating reagent. Literature examples suggest the addition is most successful for enolates that may be generated under mild conditions,[11] as for the oxazolidinone in eq 2.[12] In eq 3, the presence of the in situ formed



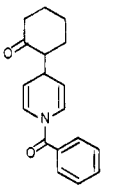
(2)

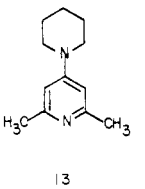
enamide allowed ready ring closure to the *N*-acylspirodihydropyridine, analogous to our compounds.[8] The *N*-



(3)

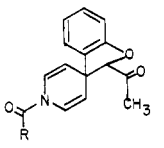
acylpyridinium species are very electrophilic and are also reactive toward indole and dimethylaniline.[13,14] However, in simple ketones, where the reactive enol is less accessible, few successful examples have been reported. In one case, the reaction of cyclohexanone with pyridine and benzoyl chloride gave 40% of the 1,4 adduct **12** after 30 days at room temperature.[15] Thus, a general method for the direct reaction of ketones with *N*-acylpyridinium salts is not available. Reaction of **7a** with benzoyl chloride or methyl chloroformate immediately produced a solid complex.


12

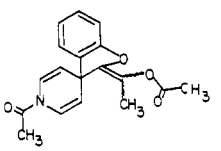


13

Treatment with a variety of bases (potassium carbonate, disodium hydrogen phosphate, triethylamine, diethylisopropylamine) gave only small amounts of dihydropyridines as evidenced by the ^{1}H NMR spectra of the crude reaction mixtures. The most consistent results were obtained with the tertiary amines, but it appeared that decomposition of the amine by the acylpyridinium species was the major competing reaction. The use of hindered pyridines such as 2,4,6-collidine failed, but in this case no decomposition was noted. Introduction of a dialkylamino substituent at C-4 of 2,6-lutidine would create a suitably hindered, yet significantly more basic, pyridine. A search of the literature uncovered 2,6-dimethyl-4-(1-piperidyl)pyridine (**13**), an excellent candidate compound.[16] Addition of this amine to the solid complex from **7a** and benzoyl chloride and heating the melt to 110 °C for 5 min resulted in smooth preparation of the *N*-benzoyldihydropyridine **14a**,



14a R = C6H5
14b R = CH3

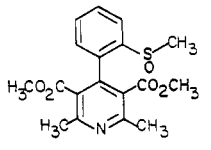


15

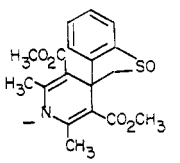
but as a roughly 50/50 mixture with the starting pyridine. Addition of excess benzoyl chloride or **13** or running the reaction in 2,4,6-collidine or in the presence of disodium hydrogen phosphate had little effect on the product distribution. To increase the conversion of **7a** to **14a**, the reaction mixture was worked up and the basic fraction, consisting of **7a** and **13**, was resubmitted to the reaction conditions. This process was repeated. At this stage, no **7a** was present in the reaction mixture and chromatography returned **14a** in 56% yield.

Acylative ring closure of **7a** could also be accomplished with acetic anhydride by prolonged reaction at 100 °C in the presence of triethylamine or sodium acetate. Under these conditions the *N*-acetyl derivative **14b** was isolated in 37% yield accompanied by 8% of a minor isomer that, according to the mass spectrum, was a bisacetylated derivative. The absence in the ^{1}H NMR spectrum of the methine proton adjacent to the ketone of **14b** and appearance of a vinylic methyl at δ 1.8 suggested the enol ether **15**. The IR spectrum provided confirmatory evidence showing the ester absorption at 1750 cm^{-1}.

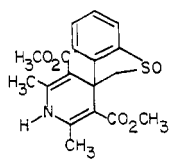
The attempted formation of *N*-acylspirodihydropyridines in the ester series followed closely the recently reported example of the spiro[benzothiophene-3(2*H*),4′(1′*H*)-pyridine] **18**.[17] In this case,



16



17



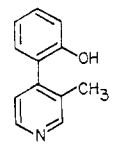
18

(11) Recently, Akiba has found that boron enolates are capable of adding to *N*-acylisoquinolinium salts in good yield: Akiba, A.; Araki, K.; Nakatani, M.; Wada, M. *Tetrahedron Lett* **1981**, *22*, 4961.
(12) Steglich, W.; Höfle, G. *Chem. Ber.* **1969**, *102*, 1129.
(13) (a) V. Dobeneck, H.; Deubel, H.; Heichele, F. *Angew. Chem.* **1959**, *71*, 310. (b) V. Dobeneck, H.; Goltzsche, W. *Chem. Ber.* **1962**, *95*, 1484. (c) Bergmann, J. *J. Heterocycl. Chem.* **1970**, *7*, 1071. (d) Bailey, A. S.; Chum, N. C.; Wedgewood, J. J. *Tetrahedron Lett.* **1968**, *5953*. (e) Deubel, H.; Wolkenstein, D.; Jokisch, H.; Messerschmitt, T.; Brodka, S.; V. Dobeneck, H. *Chem. Ber.* **1971**, *104*, 705.
(14) McEwen, W. E.; Terss, R. H.; Elliot, I. W. *J. Am. Chem. Soc.* **1952**, *74*, 3605.
(15) Doering, W. E.; McEwen, W. E. *J. Am. Chem. Soc.* **1951**, *73*, 2104.
(16) Anker, R. M.; Cook, A. H. *J. Chem. Soc.* **1946**, 117.

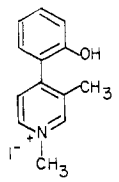
treatment of sulfoxide **16** with lithium diisopropylamide at −78 °C gave the α-lithio derivative, which underwent intramolecular addition to the free pyridine, yielding anionic intermediate **17**. Quenching gave the spirocycle **18** in 74% yield. The success of the addition to the free pyridine in this case undoubtedly arises from the presence of the electron-withdrawing groups at C-3 and C-5 and from the resultant highly stabilized anion **17**. When **7b** was treated with lithium diisopropylamide at −78 °C and quenched with triethylamine hydrochloride in ethanol, no spirocyclic products were found. Analysis of the reaction mixture by TLC revealed that extensive decomposition had taken place, with only traces of starting material remaining. Attempts to trap anionic addition products with trimethylsilyl chloride or acetic anhydride were likewise unsuccessful.

The reversal of dihydropyridine formation in the *N*-acyl series was studied with **14b**. Unlike **10a**, **14b** is stable to a 3/1 water/ethanol solution. However, addition of concentrated hydrochloric acid resulted in rapid conversion to the pyridine **7a**, isolated in 95% yield after neutralization and extraction. In addition to their greater hydrolytic stability, the *N*-acyldihydropyridines may be stored at 25 °C and can be chromatographed without difficulty on silica.

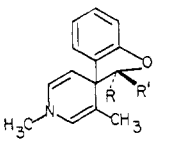
To explore the formation of dihydropyridines containing a substituent at C-3′, readily available 4-(2-hydroxyphenyl)-3-methylpyridine **19** was converted to the pyridinium salt **20** by the methods described above.[9] Alkylation and direct ring closure yielded 82% of dihydropyridines **21** as a mixture of epimers. Although we expected the anti isomer to predominate by a large margin, the ratio of anti to syn epimers was 60/40. The assignment of structure and the determination of isomer ratio was done by ^{1}H NMR. In the minor (syn) isomer the C-3′ methyl appears significantly upfield at δ 1.20, an affect ascribed to the adjacent side chain carbonyl. The observed isomer ratio is reflective of the equilibrium composition. Treatment of the isomer mixture with sodium ethoxide in ethanol caused no change in the ratio of products.



19



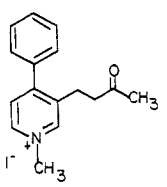
20



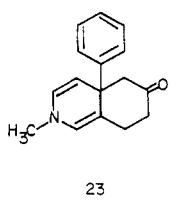
21 SYN R′ = $COCH_3$, R = H

21 ANTI R′ = H, R = $COCH_3$

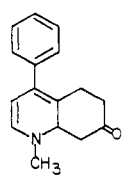
Finally, the applicability of the intramolecular pyridinium enolate addition toward the formation of a related morphine fragment, the 4a-phenyldecahydroisoquinoline ring system, was investigated. In the example chosen, pyridinium salt **22** can undergo ring closure in a 1,4 mode to produce **23**. However, **22** may also cyclize via the 1,2 pathway, giving the isomeric quinoline **24**. α-Methylstyrene was converted into 4-phenylpyridine-3-carboxaldehyde (**25**) in 87% yield by reaction with excess Vilsmeier reagent followed by treatment with aqueous ammonium chloride.[18] The requisite ketonic side chain was introduced by reaction of **25** with acetylmethylenetriphenylphosphorane in a melt at 115 °C, giving enone **26** in 92% yield. Reduction of the double bond produced the saturated ketone **27**, and quaternization yielded the key salt **22**. When **22** was treated with 4 N sodium hydroxide in dimethyl sulfoxide, a single, unstable dihydropyridine was formed in 97% yield. The ^{1}H NMR spectrum is consistent only with the quinoline derivative **24** and shows only two vinyl protons (δ 5.93 and 4.65, doublets, J = 7 Hz) and a broad triplet (δ 4.35, J = 7 Hz) arising from the C-8a proton. In the intermolecular reactions of enolates with unsubstituted pyridinium ions the 1,4 adducts generally predominate.[4] In this instance, a number of features apparently outweigh the tendencies toward formation of the 1,4 adduct. Firstly, the formation of **23** would require the generation of a quaternary carbon at the ring junction while the corresponding carbon in **24** is tertiary. Secondly, the diene system is conjugated with the benzene ring in the 1,2 adduct **24**. For these reasons it is not possible to generalize the predominance of the 1,2 adduct in this case to other intramolecular pyridinium enolate additions.



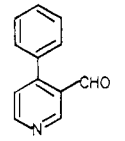
22



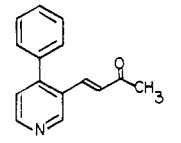
23



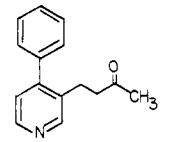
24



25



26



27

Experimental Section[19]

4-(2-Hydroxyphenyl)pyridine (6). Methyl ether **5**[9] (19.1 g, 0.103 mol) and concentrated HBr (191 mL) were heated at reflux for 11 h. The reaction was cooled to 0 °C, at which time **6**·HBr crystallizes. The crude reaction mixture was treated with H_2O (380 mL) and the solution cooled to 0 °C and then basified to pH 12 with 4 N NaOH. After the addition of Na_2HPO_4 (200 mg), concentrated HBr was added until pH 7. The precipitated phenol was collected, washed with water, and dried, yielding **6** (17.2 g, 98%) as an off-white powder, mp 210–215 °C. An analytical sample was sublimed, mp 216–217 °C.

^{1}H NMR (Me_2SO-d_6) δ 9.82 (1 H, br s), 8.55 (2 H, AA′), 7.55 (2 H, XX′), 7.35–6.75 (4 H, m); IR (KBr) 3200–2200 (br), 1600, 1450, 1420, 1290 cm^{-1}; MS, m/z 171 (M^+, 100), 170, 144, 115.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.7; H, 5.16; N, 7.69.

4-[2-(2-Oxopropoxy)phenyl]pyridine (7a). The phenol **6** (1.71 g, 10 mmol) and crushed anhydrous K_2CO_3 (2.76 g, 20 mmol) were stirred in DMF (14 mL) for 30 min. Chloroacetone (Aldrich, 92%, 925 mg, 10 mmol) was added and the solution immediately developed a red color. The mixture was stirred at 25 °C for 1 h, then added to 1 N HCl, and extracted with $CHCl_3$. The aqueous layer was made basic (pH 12) with 4 N NaOH and extracted with benzene. The aqueous basic layer was treated with concentrated

(17) Goldmann, S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 779.

(18) Jutz, C.; Müller, W.; Muller, E. *Chem. Ber.* **1966**, *99*, 2479.

(19) Low-resolution mass spectra were obtained on a Varian MAT CH-7 mass spectrometer. High-resolution mass spectra were performed by Richard Wielesek at the University of Oregon Micro-Analytical Lab. Combustion analyses were performed by Richard Wielesek at the University of Oregon Micro-Analytical Lab and by MicAnal, Tucson, AR. Proton NMR analyses were performed on Varian spectrometers, Models HA-100, FT-80, and EM-360, and carbon NMR analyses were performed on the FT-80. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane for proton spectra while carbon spectra are referenced to the residual solvent signal. Infrared spectra were recorded on Perkin-Elmer infrared spectrophotometers, Model 727B and 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. All temperatures are given in degrees centigrade.

H_3PO_4 (1 mL) and then with concentrated HCl (to pH 7). The precipitated phenol was filtered and dried, yielding 573 mg (33.5%) of recovered starting phenol. The combined benzene layers were washed with brine, dried (Na_2SO_4), evaporated, and chromatographed on SiO_2 (50 g, 80/20 $CHCl_3$/acetone). The recovered ketone (1.21 g, 53%) was a colorless mobile oil, which spontaneously crystallized. An analytyical sample was prepared by recrystallization from benzene/hexane, mp 100.5–102 °C.

^1H NMR ($CDCl_3$) δ 8.61 (2 H, AA'), 7.45 (2 H, XX'), 7.40–6.70 (4 H, m), 4.51 (2 H, s), 2.17 (3 H, s); IR (KBr) 1725, 1600, 1405, 1270 cm^{-1}; MS, m/z 227 (M^+), 184 (100), 155, 127.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 74.1; H, 5.78; N, 6.18.

Ethyl 2-(4-Pyridinyl)phenoxyacetate (7b). Phenol **6** (1.00 g, 5.84 mmol) was added to EtOH (10 mL) containing NaOEt (5.84 mmol). The solution was treated with ethyl bromoacetate (0.65 mL, 5.84 mmol) and stirred at 25 °C for 13 h. H_2O (40 mL) was added, and the mixture was extracted with benzene. Aqueous workup as for **7a** and distillation (125–140 °C (0.1 mmHg)) yielded the ester **7b** (1.03 g, 69%).

^1H NMR ($CDCl_3$) δ 8.60 (2 H, AA'), 7.52 (2 H, XX'), 7.45–6.75 (4 H, m), 4.63 (2 H, s), 4.17 (2 H, q, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz); IR (neat) 1750, 1600, 1195 cm^{-1}; MS m/z 257 (M^+), 256, 184 (100).

Anal. Calcd for $C_{15}H_{15}NO_3$: M_r, 257.105. Found: M_r, 257.105.

The combined NaOH washes from the workup above returned 109 mg of the phenol.

4-(2-Hydroxyphenyl)-1-methylpyridinium Iodide (8). To a solution of phenol **6** (8.55 g, 50 mmol) in DMF (50 mL) was added CH_3I (14.2 g, 100 mmol). After stirring 2 h at 25 °C the solution was added slowly to benzene/hexane (50/50, 160 mL). After several hours of vigorous stirring, the powdered precipitate was filtered and dried yielding 15.45 g (99%) of the pure salt **8**. An analytical sample was prepared by recrystallization from H_2O, mp 231–234 °C.

^1H NMR (Me_2SO-d_6) δ 8.90 (2 H, AA'), 8.33 (2 H, XX'), 7.70–7.25 (2 H, m), 7.85–6.85 (2 H, m), 4.29 (3 H, s); IR (KBr) 3300–2900 (br), 1630, 1605, 1440, 1185 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}INO$: C, 46.03; H, 3.86; N, 4.47. Found: C, 45.93; H, 3.88; N, 4.29.

1-Methyl-4-(2-(2-oxopropoxy)phenyl)pyridinium Iodide (9a). A. From 7a. To the ketopyridine **7a** (450 mg, 1.98 mmol) in benzene (2 mL) was added CH_3I (4.51 g, 10 mmol). The reaction was heated at reflux for 1 h and then stirred for 12 h at 25 °C. After filtration and drying, 506 mg (69%) of **9a** was obtained. The analytical sample was obtained by recrystallization from H_2O, mp 199–200° C dec.

^1H NMR (Me_2SO-d_6) δ 8.96 (2 H, AA'), 8.35 (2 H, XX'), 7.75–7.35 (2 H, m), 7.30–7.00 (2 H, m), 5.01 (2 H, s), 4.34 (3 H, s), 2.18 (3 H, s); IR (KBr) 1720, 1640 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}INO_2$: C, 48.80; H, 4.37; N, 3.79. Found: C, 48.43; H, 4.43; N, 3.47.

B. From 8. The phenol **8** (313 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) were reacted in DMF to form a bright red solution, from which a red precipitate appeared after several minutes. Chloroacetone (Aldrich, 92%, 139 mg, 1.5 mmol) was added. The solid soon dissolved, and the solution changed from a bright red to a brown-red over the course of 90 min. No further change appeared and the reaction was filtered quickly with minimum exposure to the atmosphere. The filtrate was slowly added to benzene/hexane (50/50, 12 mL) and vigorously stirred until the precipitate had formed a fine powder. The recovered product (339 mg, 91%) had an ^1H NMR spectrum identical with that of the material prepared in procedure A.

1-Methyl-4-(2-(2-ethoxy-2-oxoethoxy)phenyl)pyridinium Iodide (9b). A. From 7b. The ester **7b** (310 mg, 1.21 mmol) and methyl iodide (4 mL) were refluxed for 1 h. The solid was filtered, washed with benzene, and dried to give 472 mg (98%) of **9b** as a yellow powder, mp 180–182 °C. An analytical sample was prepared by recrystallization from EtOH, mp 182–182.5 °C.

^1H NMR (Me_2SO-d_6) δ 8.96 (2 H, br d, AA'), 8.36 (2 H, br d, XX'), 7.75–7.40 (2 H, m), 7.30–7.05 (2 H, m), 4.96 (2 H, s), 4.36 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 1.23 (3 H, t, J = 7 Hz); IR (KBr) 1735, 1640, 1295, 1240 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}INO_3$: C, 48.14; H, 4.54; N, 3.51. Found: C, 48.06; H, 4.51; N, 3.44.

B. From 8. The salt **8** (4.70 g, 15 mmol) was mixed with crushed, anhydrous K_2CO_3 (3.11 g, 22.5 mmol) in DMF (30 mL) and alkylated with ethyl bromoacetate (3.76 g, 22.5 mmol) as for **9a**. The yield was 5.98 g (99%). Although the ^1H NMR was indistinguishable from the material prepared in procedure A, recrystallization from H_2O gave a salt of lower melting point (179–181 °C).

Spiro[(2-(1-oxoethyl)benzofuran)-3(2*H*),4′(1′*H*)-(1′-methylpyridine)] (10a). A. From 9a. The salt **9a** (372 mg, 1 mmol) was suspended in 4 N NaOH (2 mL) and overlayed with benzene (2 mL). The mixture was vigorously stirred, but no reaction occurred until Me_2SO (2 mL) was added, at which time the salt rapidly went into solution and the aqueous layer became orange. Hexane (2 mL) was added and after 1 min of stirring the organic layer was removed by pipet. Additional benzene (2 mL) and hexane (2 mL) were added, and the extraction process was repeated twice. There was recovered 226 mg (94%) of pure dihydropyridine after the combined organic phases were washed with 4 N NaOH/brine (50/50, 2 mL), dried (Na_2SO_4), and evaporated.

^1H NMR ($CDCl_3$) δ 7.35–6.70 (4 H, m), 6.07 (1 H, dd, J = 8, 2 Hz), 5.80 (1 H, dd, J = 7, 2 Hz), 4.50 (1 H, dd, J = 7, 3 Hz), 4.22 (1 H, dd, J = 8, 3 Hz), 2.84 (3 H, s), 2.22 (3 H, s); IR (neat) 1725, 1675, 1595, 1470, 1460 cm^{-1}; MS, m/z 241 (M^+), 198 (100), 169, 168; ^{13}C NMR ($CDCl_3$) δ 209.9 (s), 153.7 (s), 134.8 (s), 129.6 (d), 127.8 (d), 126.4 (d), 123.9 (d), 119.7 (d), 107.5 (d), 98.3 (d), 98.1 (d), 96.5 (d), 48.4 (s), 38.2 (q), 26.0 (q).

Anal. Calcd for $C_{15}H_{15}NO_2$: M_r, 241.110. Found: M_r, 241.110.

B. From 8. The methiodide **8** (313 mg, 1 mmol) was O-alkylated with chloroacetone exactly as in procedure B of **9a** except that Me_2SO was used instead of DMF. Under these conditions no initial red precipitate appears. At the end of the alkylation, the entire reaction mixture was added to a stirred mixture of 4 N NaOH (4 mL) and benzene (4 mL) and then worked up as above. There was isolated 219 mg (91%) of the pure dihydropyridine.

Reversal of 10a into 9a. Ketodihydropyridine **10a** (241 mg, 1 mmol) was dissolved in EtOH (0.5 mL) and concentrated HI (3 drops) was added. The initially clear solution began to precipitate the salt **9a** after several seconds. Cooling (0 °C, 2 h) and filtration gave pure **9a** (350 mg, 95%).

Alternatively, if the reaction was repeated and CH_3CO_2H (60 mg, 1 mmol) was substituted for the concentrated HI, no precipitate formed. However, ^1H NMR of the reaction mixture showed the complete absence of the dihydropyridine α protons and the appearance of the pyridinium α and β protons.

1′-Methylspiro[benzofuran-3(2*H*),4′(1′*H*)-pyridine]-2-carboxylic Acid Ethyl Ester (10b). A. From NaOEt/EtOH. The salt **9b** (399 mg, 1 mmol) was heated (80 °C) in anhydrous EtOH (2 mL) containing NaOEt (1.5 mmol) for 5 min. After cooling to 25 °C, the reaction mixture was added to benzene and H_2O. Workup gave 228 mg (83%) of pure dihydropyridine **10b**. An anlytical sample was prepared by distillation (115–125 °C (0.1 mmHg)). An ^1H NMR of the crude reaction mixture gave a 9/91 ratio of **9b** to **10b**.

^1H NMR ($CDCl_3$) δ 7.25–6.25 (4 H, m), 6.07 (1 H, dd, J = 8, 2 Hz), 5.87 (1 H, dd, J = 7, 2 Hz), 4.60 (1 H, s), 4.51 (1 H, dd, J = 7, 3 Hz), 4.33 (1 H, dd, J = 8, 3 Hz), 4.30 (2 H, q, J = 7 Hz), 2.98 (3 H, s), 1.25 (3 H, t, J = 7 Hz); IR (neat) 1750, 1680, 1600, 1470 cm^{-1}; MS m/z 271 (M^+), 198 (100), 169, 168; ^{13}C NMR ($CDCl_3$) δ 169.0 (s), 156.1 (s), 136.6 (s), 131.1 (d), 129.8 (d), 128.4 (d), 125.8 (d), 121.7 (d), 109.6 (d), 100.2 (d), 98.4 (d), 94.2 (d), 60.6 (t), 50.7 (s), 40.2 (q), 14.2 (q).

Anal. Calcd for $C_{16}H_{17}NO_3$: M_r 271.121. Found: M_r, 271.122.

B. From Trimethylanilinium Ethoxide in EtOH. In the same fashion as for procedure A, 399 mg (1 mmol) of **9b** was converted into **10b** (230 mg, 85%) by reaction with trimethylanilinium ethoxide[20] in refluxing EtOH. An ^1H NMR directly of the crude reaction mixture revealed a ratio of salt **9b** to product **10b** of 7/93.

C. From NaOEt/EtOH/Me_2SO. To a solution of salt **9b** (399 mg, 1 mmol) in Me_2SO (1.11 mL) was added 0.89 mL (1.5 mmol) of a 1.69 N solution of NaOEt/EtOH. The reaction was

(20) Rodionov, W. *Bull. Soc. Chim. Fr.* **1926**, *39*, 305.

completed (^{1}H NMR) within 5 min. The solution was added to benzene/hexane (50/50, 10 mL) and the mixture washed with H_2O and brine, dried over Na_2SO_4, and evaporated to yield 234 mg (86%) of pure dihydropyridine.

Reversal of 10b into 9b. Triethylammonium iodide (458 mg, 200 mmol) was generated by adding concentrated HI (180 μL) to EtOH (5 mL) containing Et_3N (202 mg, 2.00 mmol) and evaporating to dryness. Additional EtOH (2.0 mL) was added and reevaporated. Dissolution of the salt in EtOH (2 mL) and addition to dihydropyridine **10b** (212 mg, 0.78 mmol) gave a clear solution. Heating to 80 °C for 1 h and cooling caused formation of yellow crystals. Removal of the solvent left 254 mg (82%) of **9b**.

Reaction of 10b with Salts. Dihydropyridine **10b** (54 mg, 0.20 mmol) was heated at reflux in EtOH (400 μL) containing either LiBr, NaI, or tetrabutylammonium iodide. The resultant reaction mixture was analyzed directly by ^{1}H NMR by comparing the relative amounts of pyridinium α or β protons of the salt vs. the dihydropyridine α protons.

NaI: 0.2 mmol, **9b/10b** = 14/86 after refluxing 10 min. Additional heating resulted in the appearance of additional pyridinium protons.

LiBr: 0.2 mmol, **9b/10b** = 10/90 (10 min).

$(Bu)_4NI$: 0.1 mmol, no reaction was observed.

Addition of *p*-cresol (21.6 mg, 0.2 mmol) to a solution of NaI (0.2 mmol) and **10b** (54 mg, 0.2 mmol) in EtOH (400 μL) and heating to 80 °C for 20 min caused complete conversion of the dihydropyridine into the salt as evidenced by ^{1}H NMR.

Spiro[(2-(1-oxoethyl)benzofuran)-3(2*H*),4′(1′*H*)-(1-(phenyloxomethyl)pyridine)] (14a). A mixture of 61.2 mg (0.270 mmol) of **7a** and 33.0 μL (0.284 mmol) of benzoyl chloride was heated at 120 °C for 30 s. When the mixture was cool, 71.8 mg (0.378 mmol) of **13**[16] was added, and the reaction mixture was then heated at 120 °C for 1 min. Benzene and 2 N HCl were added to the resulting solid. The acidic layer was extracted twice more with benzene. The combined extracts were washed twice with 2 N HCl, once with 2 N NaOH, and once with brine, then dried over Na_2SO_4, and evaporated to a reddish brown oil containing **14a**. The combined acidic layers were neutralized with 2 N NaOH and extracted twice with benzene. The extracts were washed with brine, dried over Na_2SO_4, and evaporated to a residue of **7a** and **13**. To this was added another 33.0 μL of benzoyl chloride, and the mixture was heated for 1 min at 120 °C. Workup proceeded as above, and a second fraction containing **14a** was isolated. Again, unreacted **7a** and **13** were recovered. To this was added 20 μL of benzoyl chloride, and the mixture resubmitted to the reaction conditions. Workup as above yielded a third dihydropyridine fraction. These combined fractions were purified by silica gel chromatography ($CHCl_3$) to give 49.6 mg (56%) of **14a** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.84–7.63 (9 H, m), 5.14 (1 H, dd, J = 2, 8 Hz), 4.82 (1 H, dd, J = 2, 8 Hz), 4.79 (1 H, s), 2.28 (3 H, s); IR (KBr) 1720, 1660, 1330 cm^{-1}; MS, m/z 331 (M^+), 288, 105 (100), 77.

Anal. Calcd for $C_{21}H_{17}NO_3$: M_r 331.121. Found: M_r 331.119.

Spiro[(2-(1-oxoethyl)benzofuran)-3(2*H*),4′(1′*H*)-(1-(1-oxoethyl)pyridine)] (14b). Ketopyridine **7a** (325 mg, 1.43 mmol) and Et_3N (441 mg, 4.37 mmol) were heated at reflux in Ac_2O (4 mL) for 12 h. At this point, considerable starting material remained, but addition of more Et_3N did not cause significant further conversion. The reaction mixture was evaporated, and standard workup provided an oil, which was chromatographed on SiO_2 (50 g, 2.5% acetone/$CHCl_3$) to return two materials. Eluted last was the expected *N*-acetyldihydropyridine **14b** (151 mg, 37%).

^{1}H NMR ($CDCl_3$) δ 7.60–6.40 (6 H, m), 5.25–4.60 (3 H, br m, with br s at 4.72), 2.27 (3 H, br s), 2.22 (3 H, s); IR (KBr) 1710, 1695 (sh), 1675, 1625 cm^{-1}; MS, m/z 269 (M^+), 184 (100). The analytical material was recrystallized from benzene/hexane, mp 136–137 °C.

Anal. Calcd for $C_{16}H_{15}NO_3$: M_r, 269.105. Found: M_r, 269.105.

Eluted first from the column was a bis acetylated material, which is best formulated as the enol acetate **15**.

^{1}H NMR (Me_2SO-d_6) δ 7.70–6.70 (6 H, m), 4.79 (2 H, br d of AA′XX′), 2.31 (3 H, s), 2.17 (3 H, s), 1.88 (3 H, s); IR (KBr) 1750, 1695 (sh), 1670 cm^{-1}; MS, m/z 311 (M^+), 269, 226, 184, 43 (100).

Anal. Calcd for $C_{18}H_{17}NO_4$: M_r, 311.116. Found: M_r, 311.115.

Reversal of 14b to 7a. Adduct **14b** (102 mg, 0.33 mmol) dissolved in EtOH/H_2O (25/75, 4 mL) was treated with four drops of concentrated HCl. Workup and chromatography on SiO_2 (10 g, 20% acetone/$CHCl_3$) yielded 64 mg (85%) of the pyridine **7a**.

3-Methyl-4-(2-hydroxyphenyl)pyridine (19). To 3.89 g (19.6 mmol) of 3-methyl-4-(2-methoxyphenyl)pyridine[9] was added 40 mL of concentrated HBr and the mixture refluxed for 11 h. After cooling to 0 °C, 120 mL of water was added to the clear, pink–orange solution, and the pH was brought to 12 with 4 N NaOH. After the addition of Na_2HPO_4 (200 mg) the pH was lowered to 7 with concentrated HBr. From the clear solution **19** precipitated as a white solid that was isolated by filtration (3.48 g, 96%), mp 189–190 °C.

^{1}H NMR (Me_2SO-d_6) δ 2.12 (3 H, s), 6.70–7.32 (5 H, m), 8.34 (1 H, d, J = 6 Hz), 8.38 (1 H, s), 9.55 (1 H, s); IR (KBr) 3040–2560 (br), 1600, 1440 cm^{-1}; MS, m/z 185 (M^+, 100), 184, 170, 158.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.8; H, 6.00; N, 7.56. Found: C, 77.7; H, 5.98; N, 7.45.

1,3-Dimethyl-4-(2-hydroxyphenyl)pyridinium Iodide (20). The phenol **19** (2.00 g, 10.8 mmol) was dissolved in 10 mL of dry DMF, and 2.69 mL (43.2 mmol) of CH_3I was introduced by syringe. The resulting amber solution was stirred for 1 h and then added dropwise to 80 mL of stirring benzene. The product oiled out, the solvent layer was removed, and fresh benzene was added. After 10 min of stirring, the solvent was replaced again. The oil solidified upon further stirring, and 3.49 g (99%) of the methiodide **20** was isolated by filtration as a pale yellow solid, mp 90 °C dec.

^{1}H NMR (Me_2SO-d_6) δ 2.29 (3 H, s), 4.31 (3 H, s), 6.79–7.45 (4 H, m), 7.89 (1 H, d, J = 6 Hz), 8.76 (1 H, d, J = 6 Hz), 8.89 (1 H, s); IR (KBr) 3170 (br) cm^{-1}.

1′,3′-Dimethylspiro[(2-(1-oxoethyl)benzofuran)-3-(2*H*),4′(1′*H*)-pyridine] (21). Finely ground anhydrous K_2CO_3 (0.32 g, 2.32 mmol) was added to a solution of 0.50 g (1.53 mmol) of **20** in 3 mL of Me_2SO. Chloroacetone (0.20 mL, 2.29 mmol) was then added and the red mixture was stirred for 1 h at 25 °C. The resulting amber-colored reaction mixture was poured into a rapidly stirring solution of 12 mL each of 4 N NaOH, benzene, and hexane. Workup as for **10a** gave 0.3192 g (82%) of **21** as an off-white solid as a mixture of isomers, mp 96–101 °C.

^{1}H NMR ($CDCl_3$) 60/40 mixture of anti/syn isomers; anti: δ 1.53 (3 H, s), 2.18 (3 H, s), 2.91 (3 H, s), 4.10 (1 H, d, J = 8 Hz), 5.03 (1 H, s), 5.87 (1 H, dd, J = 8, 2 Hz), 5.90 (1 H, m); syn: δ 1.20 (3 H, d, J = 1 Hz), 2.29 (3 H, s), 2.94 (3 H, s), 4.50 (1 H, d, J = 8 Hz), 4.62 (1 H, s), 5.68 (1 H, m), 6.17 (1 H, dd, J = 8, 2 Hz), 6.76–7.36 (total intensity 4 H, m); IR (KBr), 1720, 1680, 1595, 1205 cm^{-1}; MS, m/z 255 (M^+), 240, 212, 182 (100).

Anal. Calcd for $C_{16}H_{17}NO_2$: M_r 255.126. Found: M_r 255.127.

To a solution of 0.25 g (0.98 mmol) of **21** in 1.0 mL THF was added 1.0 mL of 1 M NaOEt in EtOH. After stirring for 1 h at 25 °C, the solution was worked up. ^{1}H NMR showed no change in isomer ratio. Heating with ethoxide at 60 °C also caused no change.

4-(4-Phenyl-3-pyridinyl)-3-buten-2-one (26). 4-Phenyl-3-pyridinecarboxaldehyde (**25**)[18] (992 mg, 5.42 mmol) and (acetylmethylene)triphenylphosphorane (1.73 g, 5.43 mmol) were heated to a melt at 115 °C. After 15 min, the cooled reaction mixture was filtered through SiO_2 (25 g, 20% acetone/$CHCl_3$) and distilled (110–120 °C (0.1 mmHg)) to give 1.11 g (92%) of the enone **26**.

^{1}H NMR ($CDCl_3$) δ 8.84 (1 H, s), 8.58 (1 H, d, J = 6 Hz), 7.70–7.40 (7 H, m), 6.81 (1 H, d, J = 16 Hz), 2.27 (3 H, s); IR (neat) 1685, 1608, 1585 cm^{-1}; MS, m/z 223 (M^+), 208, 180 (100).

Anal. Calcd for $C_{15}H_{13}NO$: M_r, 223.100. Found: M_r, 223.100.

4-(4-Phenyl-3-pyridinyl)-2-butanone (27). The enone **26** (1.00 g, 4.48 mmol) was hydrogenated (40 psi) in EtOH (20 mL) with Pd/C (10%, 100 mg) for 14 h. The catalyst was removed by filtration through Celite, the solvent evaporated, and the residue chromatographed on SiO_2 (50 g, 20% acetone/$CHCl_3$). The resultant material was distilled (110–120 °C (0.1 mmHg)) to provide 900 mg (89%) of the pure ketone **27**.

^{1}H NMR ($CDCl_3$) δ 8.45 (1 H, s), 8.42 (1 H, d, J = 6 Hz), 7.60–7.15 (5 H, m), 7.06 (1 H, d, J = 6 Hz), 3.05–2.75 (2 H, m), 2.65–2.30 (2 H, m), 2.01 (3 H, s); IR (neat) 1720, 1580 cm^{-1}; MS, m/z 225 (M^+), 226, 210, 207, 182 (100).

Anal. Calcd for $C_{15}H_{15}NO$: M_r, 225.115. Found: M_r, 225.115.

1-Methyl-3-(3-oxobutyl)-4-phenylpyridinium Iodide (22). Pyridine **27** (820 mg, 3.65 mmol) was stirred at 25 °C with CH_3I (1.529 g, 10.75 mmol) in benzene (1 mL) for 8 h. Filtration provided 1.27 g (95%) of pure methiodide **22**. After recrystallization from H_2O the analytical sample had mp 176–177.5 °C.

^1H NMR (Me_2SO-d_6) δ 9.01 (1 H, br s), 8.87 (1 H, br d, J = 6 Hz), 7.95 (1 H, d, J = 6 Hz), 7.75 (5 H, s), 4.37 (3 H, s), 2.88 (4 H, br s), 2.05 (3 H, s); IR (KBr) 3100, 1710, 1670 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}INO$: C, 52.33; H, 4.93; N, 3.81. Found: C, 52.37; H, 4.97; N, 3.76.

1-Methyl-4-phenyl-1,5a,8,8a-tetrahydroquinolin-7(6*H*)-one (24). The salt **22** (183 mg, 15 mmol) was treated with 4 N NaOH/Me_2SO/benzene (2 mL/1 mL/2 mL) exactly as for the preparation of **10a**, to give 116 mg (98%) of the 1,2-adduct **24** as an unstable, waxy solid, mp 80–82 °C dec.

^1H NMR ($CDCl_3$) δ 7.50–7.00 (5 H, m), 5.93 (1 H, d, J = 7 Hz), 4.65 (1 H, d, J = 7 Hz), 4.35 (1 H, br t, J = 7 Hz), 2.78 (3 H, s); IR (KBr) 1705, 1635, 1575 cm^{-1}; MS, m/z 239 (M^+), 210, 196 (100).

Anal. Calcd for $C_{16}H_{17}NO$: M_r, 239.131. Found: M_r, 239.132.

Acknowledgment. We wish to thank Kevin DeWhitt for the preparation of 4-phenylpyridine-3-carboxaldehyde and Ignatius M. Ejimadu for the synthesis of **13**. We are grateful to the Oregon State University Honors Program, the N. L. Tarter Fund, and the National Institutes of Health (DA-02708) for support of this research.

Registry No. **5**, 5958-00-9; **6**, 86610-20-0; **7a**, 81115-41-5; **7b**, 86610-21-1; **8**, 81115-40-4; **9a**, 81115-33-5; **9b**, 81115-34-6; **10a**, 81115-38-0; **10b**, 81115-39-1; **13**, 86610-22-2; **14a**, 86610-23-3; **14b**, 81115-42-6; **15**, 86610-24-4; **19**, 86610-25-5; **20**, 86610-26-6; *anti*-**21**, 86610-27-7; *syn*-**21**, 86610-28-8; **22**, 86610-29-9; **24**, 86610-30-2; **25**, 46268-56-8; **26**, 86610-31-3; **27**, 86610-32-4; chloroacetone, 78-95-5; ethyl bromoacetate, 105-36-2; benzoyl chloride, 98-88-4; (acetylmethylene)triphenylphosphorane, 1439-36-7; 3-methyl-4-(2-methoxyphenyl)pyridine, 83463-15-4.

(±)-3-Phenylhexahydrophthalides. Synthesis and Structural Assignments

Naser Pourahmady[1] and Edmund J. Eisenbraun*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078

Received March 1, 1983

The four racemic 3-phenylhexahydrophthalides **3a–3d** were synthesized by reducing the corresponding cis and trans γ-keto acids with a variety of metal hydride reducing agents as well as with platinum oxide catalyzed hydrogenation. The product ratio obtained by hydride reduction of an individual γ-keto acid depends on the reducing activity and the bulk of the hydride reagent. The greatest hydride reducing selectivity was observed with lithium trialkylborohydrides and lithium tri-*tert*-butoxyaluminohydride. The ratio obtained through metal–hydride reduction is reversed from that of platinum oxide catalyzed hydrogenation. The selectivity in the reduction of the corresponding methyl γ-keto esters is greatly diminished as compared to that in the reduction of the γ-keto acids.

As part of a continuation of stereochemical studies of γ-lactones,[2] we prepared the racemic 3-phenylhexahydrophthalides **3a–3d**. The synthesis, separation, and configurational assignments of these lactones, through use of ^1H and ^{13}C NMR studies, are reported.

The preparation of the cis γ-keto acid **1a** and its epimerization to the trans-isomer **1b** was accomplished as previously described.[3a,b] These acids were converted to the corresponding esters **1c** and **1d** with diazomethane.[4] The resulting γ-keto esters were used, as shown in Table I, in gas chromatography studies to establish the separation and purity of **1a** and **1b** and as model compounds in metal hydride reductions and catalytic hydrogenations.[3c]

Attempts to prepare the cis-fused γ-lactones **3a** and **3b** by $NaBH_4$ reduction of **1a** were frustrated by epimerization of **1a** to **1b**. Super-Hydride ($LiEt_3BH$) (Aldrich) reduction of **1a**,[5] however, proceeded with little epimerization regardless of order of addition[6a] of reactants to give cis γ-lactones **3a**/**3b** (94:6). We were unable to isolate the individual cis γ-hydroxy acids **2a** and **2b** as reduction products owing to their ease of lactonization. The ratios of products from various reductions of γ-keto acids **1a** are presented in Table II.

Table I. Reduction of Methyl γ-Keto Esters 1c and 1d

reagent	keto ester	rctn time, h	total lactone yield, %	product ratio after lactonization[a] 3a/3b	3c/3d
$Li(t\text{-}BuO)_3AlH$	1c	4	80	65:35	
$Li(t\text{-}BuO)_3AlH$	1d	4	78		54:46
PtO_2/H_2	1c	2.5	87	58:42	
PtO_2/H_2	1d	2.5	85		55:45

[a] These lactones were obtained from the corresponding methyl hydroxy esters in refluxing toluene containing 2% oxalic acid.

Reduction of **1b** with Super-Hydride and acidification at room temperature provided a mixture of trans γ-lactones **3c**/**3d** (55:45). The trans γ-hydroxy acids **2c** and

(1) Pourahmady, N. Ph.D. Thesis, Department of Chemistry, Oklahoma State University, Stillwater, OK, 1981.

(2) Eisenbraun, E. J.; Browne, C. E.; Irvin-Willis, R. L.; McGurk, D. J.; Eliel, E. L.; Harris, D. L. *J. Org. Chem.* **1980**, *45*, 3811.

(3) (a) Fieser, L. F.; Novello, C. F. *J. Am. Chem. Soc.* **1942**, *64*, 802. (b) Scribner, J. D.; Miller, J. A. *J. Chem. Soc.* **1965**, 5377. (c) GC analysis of trans ester **1d**, formed from **1b** with diazomethane, showed it to be free of cis γ-keto ester **1c** and 99.5% pure.

(4) Ruehle, P. H.; Browne, C. E.; Eisenbraun, E. J. *Chem. Ind.* **1979**, 255.

(5) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(6) (a) The ratio of products **3a**/**3b** and **3c**/**3d** is independent of the order of addition of reagents (hydride reducing agent to keto acid or the reverse mode of addition). (b) This ratio was determined by thermal lactonization at the melting point of the trans γ-hydroxy acids **2c** and **2d** and analysis by HPLC (silica column; dichloromethane/*n*-hexane, 4:1). (c) Formation of a carboxylate anion is assumed since rapid hydrogen evolution was observed upon addition of hydride reducing agent to the γ-keto acid.

0022-3263/83/1948-3067$01.50/0