of CH_2Cl_2 was added 220 mL of dry methanol saturated with potassium carbonate. After 40 h at room temperature the reaction mixture still contained 7% of the original mixture of 8 and 9. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, water was added to dissolve the K_2CO_3, and the mixture was extracted five times with methylene chloride. The organic layer was dried ($MgSO_4$) and reduced in volume and the products were separated by preparative TLC (benzene) on four 50 × 20 × 0.2 cm silica gel plates. The following three compounds were isolated: 3-chloro-2-phenylindole (7), 5%; 3,3-dimethoxy-2-phenyl-3*H*-indole (12), 51%; 6-chloro-3-methoxy-2-phenylindole (13), 12%. The evidence on which these structures were based is given below.

3-Chloro-2-phenylindole (7). The solid obtained by TLC (R_f 0.74) was recrystallized three times from petroleum ether (bp 60–80 °C) and was identical in all respects with that prepared synthetically.

3,3-Dimethoxy-2-phenyl-3*H*-indole (12). The oil obtained by TLC (R_f 0.34) solidified after 2 h and was recrystallized twice from petroleum ether (bp 60–80 °C) and then sublimed three times at 50 °C (1 mm): mp 80 °C; IR (KBr) 2940, 2830, 1545 (C=N), 1452, 1440, 1235, 1170, 1130, 1090, 990, 890, 770, 760, 695, 652 cm^{-1}; UV (MeOH) λ_{max} 232 (log ϵ 4.25), 240 (4.29), 248 (4.26), 322 (4.12) nm; ^1H NMR ($CDCl_3$) δ 3.20 (s, 6 H), 7.10–8.57 (m, aromatic, 9 H).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.98; N, 5.53; 0, 12.63. Found C, 75.75; H, 5.99; N, 5.51; O, 12.75.

6-Chloro-3-methoxy-2-phenylindole (13). The material obtained by TLC (R_f 0.60) was chromatographed (methylene chloride) on silica gel and the solid eluted as a yellow band was recrystallized three times from *n*-hexane: mp 165–176 °C dec; IR (KBr) 3410, 2920, 1625, 1445, 1255, 1200, 1164, 1112, 823, 811, 804, 761, 690 cm^{-1}; UV (MeOH) λ_{max} 206 (log ϵ 4.17), 224 (4.08), 260 (sh, 3.70), 322 (4.04) nm; ^1H NMR (CD_3COCD_3) δ 3.83 (s, 3 H), 6.73–8.03 (m, aromatic, 8 H, NH); mass spectrum, *m/e* (relative abundance) 259 (M + 2, 35), 258 (M + 1, 17), 257 (M, 100), 244 (M + 2 - 15, 36), 242 (M - 15, 100), 214 (M - 15 - 28, 15), 128.5 (M^{2+}, 13).

There was also isolated by TLC a band (R_f 0.25) which represented 13% of the crude reaction mixture. This material was extremely unstable and all attempts at further purification resulted in decomposition. The NMR spectrum indicated at least two components and the possibility that one component contained two different methoxy groups. A broad band (R_f 0.03–0.12) was also obtained which accounted for 10% of the crude reaction mixture and contained at least three components. No pure material was obtained from this mixture.

5-Chloro-3-methoxy-2-phenylindole.[26] To 1.80 g (12.6 mmol) of *p*-chlorophenylhydrazine, obtained from its hydrochloride salt (Aldrich), were added 2.00 g (13.2 mmol) of α-methoxyacetophenone and 20 mL of glacial acetic acid. This solution turned red and was refluxed for 3 h. The reaction mixture was added to 200 mL of water, kept at 0 °C for 12 h, and filtered. The solid was washed with hot *n*-hexane and the filtrate was let cool whereupon a yellow solid formed. It was recrystallized by adding hot *n*-hexane and dried under vacuum and a 30% yield of 5-chloro-3-methoxy-2-phenylindole was obtained. This indole was heat sensitive and discolored during recrystallization. It had the following properties: mp 112–115 °C; IR (KBr) 3370, 3060, 2930, 1600, 1485, 1320, 1240, 1170, 1055, 810, 765, 690 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 3.97 (s, 3 H), 6.97–8.10 (m, 8 H), 10.68 (s, 1 H); high-resolution mass spectrum calcd for $C_{15}H_{12}NCl^{35}O$ 257.0606, found 257.0576.

Acknowledgment. This investigation was supported in part by Grant No. 31-26-S1-0641 from the Consejo Nacional de Investigaciones Cientificas y Tecnológicas (CONICIT). We thank Professors A. Rojas and B. Mendez, Departamento de Química, Facultad de Ciencias, Universidad Central de Venezuela, for the ^{13}C NMR spectra and Dr. J. D. Medina, Lic. V. Sanchez, and Lic. C. Cabello of the Instituto Venezolano de Investigaciones Cientificas (IVIC) for the mass spectra.

Registry No. 1, 95-20-5; 2, 76794-13-3; 3, 7164-92-3; 4, 76794-14-4; 5, 76794-15-5; 6, 948-65-2; 7, 76794-16-6; 8, 76794-17-7; 9, 76794-18-8; 10, 76794-19-9; 11, 76794-20-2; 12, 76794-21-3; 13, 76794-22-4; *p*-chlorophenylhydrazine, 1073-69-4; α-methoxyacetophenone, 4079-52-1; 5-chloro-3-methoxy-2-phenylindole, 76794-23-5; sodium hypochlorite, 7681-52-9.

Synthesis of Functionalized Quinoline Derivatives by Annulation of Pyridines

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Thiophenyl and sulfonylphenyl groups were introduced on each methyl group of 2,3-lutidine (1), and the reactivity of the adjacent carbanions has been examined. When both methyl groups of 1 were substituted with sulfur groups, regioselective alkylation of the vicinal 2,3 side chains could be performed. The bromosulfones 18 and 19 can be selectively prepared from 1 and were used for an annulation route leading to 6-oxo and 7-oxo derivatives of 5,6,7,8-tetrahydroquinolines.

There is widespread occurrence in nature of compounds which contain structural moieties derived from quinolines and isoquinolines. Most synthetic routes leading to these bicyclic structures consist of cyclization reactions starting from benzene (or cyclohexane) derivatives substituted with nitrogen functions[2] and are subject to the resulting reactivity and isomer restraints. The alternate route, involving the synthesis of quinolines by the annulation of pyridines, has been rarely utilized, and the reported examples are of limited synthetic value. The limitations of

(1) Experimental work done in these laboratories.

(2) See: Jones, G. *Chem. Heterocycl. Compd.* **1977**, *32*, 93.

0022-3263/81/1946-2059$01.25/0

Chart I

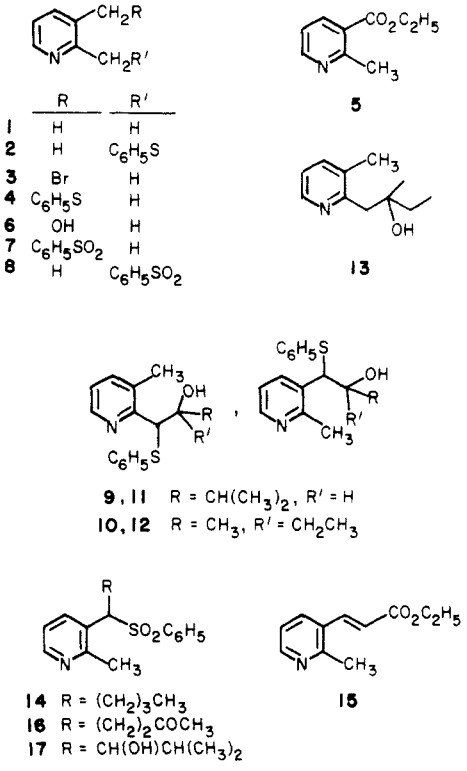
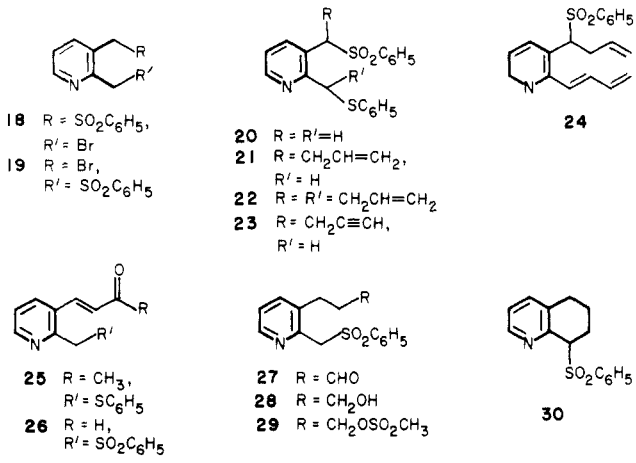


Chart II



this latter approach are attributed to the inaccessibility of suitable 2,3-disubstituted pyridine derivatives[3] and to the electron-withdrawing properties of the pyridine ring nitrogen which inhibits cyclization by electrophilic attack on the ring, with the exception of attack on nitrogen. However, if suitably substituted pyridines could be made available, effective annulation reactions of pyridines might provide new routes for the preparation of less readily available quinoline derivatives functionalized in the carbocycle, thus contributing to the development of new synthetic methodology for such heterocyclic compounds.

In the present work we report on the elaboration of such pathways by the utilization of reactions of carbanions activated by sulfur groups in the pyridine side chains. In the absence of these groups, the metalation of 2,3-lutidine (1; see Chart I), chosen as the starting material, occurs only at the more acidic C-2 methyl group.[4] Our preliminary attempts to bring about concomitant metalation of the C-3 methyl under various conditions similar to those used for the metalation of 3-picoline[5] also were unsuccessful. Sulfur groups were therefore introduced successively on the methyl groups of 1, and the nucleophilic reactivity of the anions then formed was examined.

First, sulfide **2** was prepared by metalation of 1 with butyllithium and subsequent quenching with diphenyl disulfide. The regioisomeric sulfide **4** was prepared via the 3-bromomethyl derivative **3**, which is the major product of radical monobromination of 1 with *N*-bromosuccinimide (NBS). Preferential bromination of the C-3 methyl was surprising in view of results reported for monomethylated pyridines where 2-picoline was found to be much more reactive than 3-picoline toward NBS bromination.[6] The location of halogen in **3** was established by an independent synthesis starting from ethyl 2-methyl-3-nicotinate (**5**),[7] which was reduced to alcohol **6**, and the latter was further converted to the bromide **3**.

The presence of anion-stabilizing sulfur groups led to smooth metalation of **2** and **4** with lithium diisopropylamide (LDA) at low temperature, and the reactivity of the anions thus formed was demonstrated in aldol condensations with isobutyraldehyde and 2-butanone. β-Hydroxy sulfides **9–12** were obtained in good to excellent yields in diastereomeric ratios of about 1/1. The thiophenyl group can be reductively removed with Raney nickel (e.g., **10** → **13**) or may be used for other transformations on the pyridine side chains.

Next, functionalization of the unsubstituted methyl groups of **2** and **4** was attempted via the halides, but radical bromination failed to give the desired selectivity.[8] The sulfides were then converted to the corresponding sulfones **7** and **8** by successive treatment with sodium periodate and potassium permanganate.[9] In contrast to the α-thiophenyl anions from **2** and **4**, the α-sulfonyl carbanions of **7** and **8** differed significantly in their reactivities.

The α-sulfonyl anion of **7**, obtained by metalation with LDA, was useful in various C–C bond-forming reactions. Alkylation with butyl iodide gave **14**, and in the reaction with ethyl bromoacetate (*E*)-**15** was obtained when alkylation was followed by treatment with 1,5-diazabicyclo[5.4.2]undecene (DBU). With 1-buten-3-one, 1,4-addition occurred to give γ-sulfonyl ketone **16**, and with isobutyraldehyde one of the diastereomers of **17** was formed preferentially (84/16 ratio). This is in contrast to the equal amounts of diastereomers formed in analogous aldol reactions of the less hindered α-thiophenyl carbanions. The anion of sulfone **8**, though readily formed under analogous conditions as demonstrated by D_2O quenching, was unreactive under similar conditions with the above reagents. This difference in reactivity may arise from the greater stabilization of the C-2 sulfonyl carbanion due to additional resonance interaction with the pyridine nitrogen making C–C bond-forming reactions thermodynamically less favorable.

(3) Ref. 2, pp 243–245.
(4) Lochte, H. L.; Cheavens, T. H. *J. Am. Chem. Soc.* **1957**, *79*, 1667. Barringer, D. F., Jr.; Berkelhammer, G.; Carter, S. D.; Goldman, L.; Lanzilotti, A. E. *J. Org. Chem.* **1973**, *38*, 1933.
(5) Kaiser, E. M.; Petty, J. D. *Synthesis*, **1975**, 705.
(6) Kutney, J. P.; Cretney, W.; Tabata, T.; Frank, M. *Can. J. Chem.* **1964**, *42*, 698.
(7) Baumgarten, P.; Dornow, A. *Chem. Ber.* **1939**, *72*, 563.
(8) Klemm, L. H.; Johnson, W. O.; White, D. w. *J. Heterocycl. Chem.* **1972**, *9*, 873. Direct preparation of 2,3-bis(chloromethyl)pyridine as reported by these authors could be useful for the introduction of identical sulfur groups on both methyl groups, but the stepwise halogen substitution we have developed permits the introduction of nonidentical sulfur groups with more selective carbanion reactivity.
(9) Other direct methods of oxidation to sulfones were less effective and resulted in the partial formation of *N*-oxides.

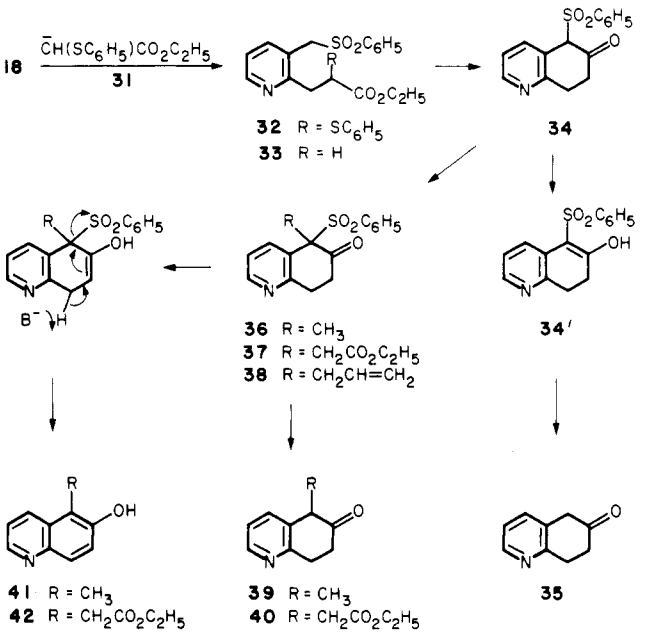
In view of these differences in reactivity, the synthetic exploitation of sulfone **7** was first explored. In a remarkably selective bromination with NBS, bromo sulfone **18** (see Chart II) was prepared in 84% yield. This compound, with reactive sites in the vicinal side chains, was considered a useful intermediate for annelation schemes such as the addition–alkylation sequence.[10] We found, however, that the pyridine ring in **18** is cleaved spontaneously on exposure to various alkaline conditions, even at very low temperature, as evidenced by the absence of low-field aromatic protons in the NMR spectrum of the products. Replacement of the halogen with a thiophenyl group was then effected by treating **18** with potassium thiophenoxide. The resulting sulfide–sulfone **20** could be regioselectively monometalated with 100 mol % LDA to form the α-sulfonyl anion.

Consequently, selective alkylation at the C-3 side chain of **20** was now possible, although two-centered cyclization attempts with compounds possessing two vicinal electrophilic centers were sluggish and gave at best low yields of regioisomeric mixtures of bicyclic products. The reaction of **20** with allyl bromide resulted in the formation of the monoalkylated product **21** or dialkylated product **22**, depending on the amount of LDA used. The selective formation and alkylation of the α-sulfonyl anion in **20** were unambiguously proved by oxidation of the sulfide group in **21** and **22** to the sulfoxide followed by exposure of the latter to thermolytic conditions (refluxing toluene). While the sulfoxides from **21** remained unchanged on being heated, the sulfoxide mixture from **22** was readily converted into the triene **24**. Similarly, reaction of **20** with propargyl bromide gave **23** as the sole product.

The C-3 side chain in compounds **21** and **23** provided the potential for formation of a carbonyl at the correct site for an intramolecular aldol condensation. Thus, acid hydration of the acetylene group in **23** gave directly the α,β-unsaturated ketone **25** by a rather unusual elimination of the phenylsulfonyl group under acidic conditions. The α-thiophenyl anion in the C-2 side chain, although effective in intermolecular aldol additions, could not be utilized for intramolecular condensations because the trans double bond in **25** withstood hydrogenation and isomerization. The *E*, unsaturated aldehyde **26** was then prepared by the oxidative cleavage of the double bond in **21** ($NaIO_4/OsO_4$) followed by treatment with DBU. During this reaction the sulfide group in the C-2 side chain underwent oxidation to the sulfone.[11] Now hydrogenation to aldehyde **27** was not inhibited. Treatment of the latter with 100 mol % of LDA afforded selectively the α-sulfonyl anion, but no addition to the carbonyl group occurred. Nonetheless, the anion at C-2 did undergo irreversible intramolecular reactions; e.g., the mesylate **29** obtained via the alcohol **28** was readily cyclized to the bicyclic derivative **30** in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol.

Although the reactions described above have opened new routes for regioselective substitution of vicinal side chains in substituted pyridines, they still do no provide the desired annulation pathways. This target has been effectively reached by using the regioisomeric bromo sulfones **18** and **19** as key intermediates in C–C bond formation via halide displacement. In view of the earlier observed instability of bromo sulfone **18** under alkaline conditions, we utilized its electrophilic site for alkylation by an independently generated carbanion. Thus **18** was added to the anion **31**

Scheme I. Conversion of 2,3-Disubstituted Pyridines to 6-Oxo-5,6,7,8-tetrahydroquinolines and 6-Hydroxyquinolines



of ethyl (phenylthio)acetate, and alkylation via halide displacement resulted in the formation of **32**. Treatment with Raney nickel in 1/1 acetone/ethanol led to the selective desulfurization of the latter to ester **33** which underwent intramolecular acylation on treatment with sodium hydride in THF/Me_2SO, to give ketone **34** as the sole isolated product in 51% overall yield from **18** (Scheme I).

The spectral properties of the quinoline derivative **34** show the presence of a keto–enol equilibrium: the IR spectrum has an absorption at 1718 cm^{-1} (C=O) but the UV spectrum, which shows λ_{max} 266, 274, and 299 nm (as compared with λ_{max} 265 and 272 nm of the nonenolic **36**), and the δ 4.64 signal in the ^1H NMR spectrum (in $CDCl_3$, exchangeable with D_2O) indicate the presence of the enol tautomer. The sulfonyl group in **34** is easily removed by Raney nickel (9/1 acetone/ethanol)[12] to afford 6-oxo-5,6,7,8-tetrahydroquinoline (**35**) in 31% overall yield from 2,3-lutidine (**1**), previously obtained in 8.5% overall yield from 6-methoxyquinoline.[13] The ketone **35** is readily polymerized in air, and attempts to perform its regioselective alkylation gave poor results.

In contrast, the phenylsulfonyl derivative **34** was successfully alkylated at C-5 by reactive halides by utilizing K_2CO_3 in acetone to afford compounds **36–38** in good yields. The latter, when treated with Raney nickel, afforded the corresponding 5-substituted 6-oxotetrahydroquinolines **39** and **40**. The bicyclic sulfonyl derivatives, substituted at C-5, also provide a synthetically convenient entry into 5-substituted 6-hydroxyquinolines: compounds **36** and **37** were converted in high yield into hydroxyquinolines **41** and **42** on treatment with potassium *tert*-butoxide. This conversion can be rationalized to occur via an enol as shown in Scheme I.

Bromo sulfone **19** also could be utilized in an analogous alkylation–acylation pathway leading to the regioisomeric 7-oxo derivatives of 5,6,7,8-tetrahydroquinolines. The ester–sulfone **43** was obtained, analogously to **33**, from the

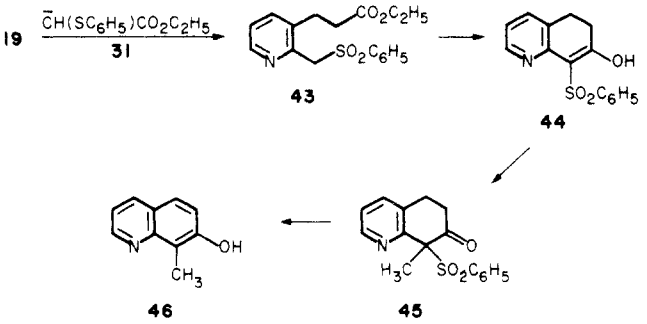
(10) E.g.: Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772.

(11) The presence of catalytic amounts of OsO_4 did not necessarily result in the direct oxidation of other sulfides to sulfones.

(12) Use of more ethanol resulted in the partial reduction of the ketone.

(13) (a) Remers, W. A.; Gibs, G. J.; Weiss, M. J. *J. Heterocycl. Chem.* **1971**, *8*, 1083. (b) Remers, W. A.; Gibs, G. J., Pidacks, C.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 279.

Scheme II. Conversion of 2,3-Disubstituted Pyridines to 7-Oxo-5,6,7,8-tetrahydroquinolines and 7-Hydroxyquinolines



reaction of **19** with anion **31**, followed by desulfurization. From the evidence described above, the α-sulfonyl anion at the pyridine C-2 methyl group would be less reactive than the C-3 regioisomeric anion. When **43** was submitted to the acylation conditions successful with ester **33** (NaH in THF/Me_2SO), most of the starting material was indeed recovered. Successful cyclization to **44**, however, was achieved in 71% yield by using potassium *tert*-butoxide in THF (Scheme II). As could be expected from the greater acidity of α- as compared to β-alkyl hydrogens of pyridines, the equilibrium in **44** is totally displaced toward the enolic form. This has been deduced from the complete absence of C=O absorption in the IR spectrum (in $CHCl_3$ and KBr) and from the UV λ_{max} at 293 and 359 nm in ethanol. The structure of **44** has been unambiguously confirmed by C-alkylation with methyl iodide which resulted in the formation of the 7-oxo derivative **45**. On treatment with alkali, **45** was converted to the 7-hydroxy-8-methylquinoline (**46**) by an elimination analogous to that described for the 6-oxo derivatives.

In summary, the bromo sulfones **18** and **19**, which can be obtained selectively and conveniently from 2,3-lutidine, have been shown to be useful intermediates for the regioselective introduction of substituents into the 2,3 side chains of pyridine. By exploitation of the presence of both nucleophilic and electrophilic termini in these compounds, an annulation route, leading to a series of quinoline derivatives functionalized in the carbocycle, has been developed.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$, by using tetramethylsilane as internal standard, with Varian T-60 or Bruker 90 spectrometers. IR spectra were recorded on a Perkin-Elmer 467 spectrometer and UV spectra on a Cary 118 spectrophotometer. Flash chromatography[14] with silica gel (234–400 mesh) was used for the purification, and precoated Merck Kieselgel 60 F_{254} plates were used for TLC analyses. Final organic solutions were dried over Na_2SO_4, and air-sensitive reactions were carried out in flame-dried, argon-flushed, two-necked flasks sealed with rubber septa, and the reagents were introduced with a syringe.

2-[(Phenylthio)methyl]-3-methylpyridine (2). To a stirred solution of 34 mL of 1.5 M butyllithium/hexane (51 mmol) in anhydrous ether (50 mL) at 0 °C was added dropwise under argon 3.65 g (34 mmol) of 2,3-lutidine (**1**; Columbia Organics). A yellow precipitate was formed and the temperature was allowed to rise to 10 °C. After 3 h, Ph_2S_2 (7.5 g, 34 mmol) in anhydrous ether (35 mL) was added to the mixture which was stirred for an additional hour at 5 °C, poured into cold aqueous $NaHCO_3$, and extracted with ether. The organic layer was dried and filtered, the filtrate was evaporated, and the volatile fractions were removed up to 80 °C (0.3 mm). Chromatography of the residue (4/1 pentane/ether) afforded 5.84 g (80%) of **2** as an oil: bp 98 °C (0.1 mm); NMR δ 2.36 (s, 3), 4.26 (s, 2), 6.20–8.30 (m, 8). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.6; H, 6.1. Found: C, 72.4; H, 6.1.

2-Methyl-3-[(phenylthio)methyl]pyridine (4). A mixture of 2,3-lutidine (**1**; 9.63 g, 90 mmol), azobis(isobutyronitrile) (3 g) and NBS (19.2 g, 108 mmol) in CCl_4 (800 mL) was refluxed for 1.5 h with lamp irradiation until almost all of **1** had reacted (TLC). The mixture after concentration at reduced pressure contained mainly 3-(bromomethyl)-2-methylpyridine (**3**) [NMR (CCl_4) δ 2.52 (s, 3), 4.24 (s, 2), 6.80–8.24 (m, 3)] and small amounts of less polar brominated products (TLC). The concentrated mixture was diluted with EtOH (100 mL) and added to PhSK, prepared from KOH (5.2 g, 94 mmol) and PhSH (10 g, 90 mmol) in 120 mL of EtOH. The mixture was refluxed for 1 h, poured into ice–aqueous $NaHCO_3$, and then extracted and chromatographed as described for **2** to give 11.2 g (58%) of **4** as an oil: bp 112 °C (0.1 mm); NMR δ 2.58 (s, 3), 4.00 (s, 2), 6.92–8.43 (m, 8). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.6; H, 6.1. Found: C, 72.3; H, 6.2.

Preparation of 3-(Bromomethyl)-2-methylpyridine (3) from Ethyl 2-Methylnicotinate (5). A solution of 0.165 g of nicotinate **5** (1 mmol)[7] in dry ether (5 mL) was added to a suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry ether (3 mL). After being stirred for 1 h at room temperature, the mixture was diluted with ether, treated with 0.5 mL of aqueous Na_2SO_4, dried, and filtered, and the filtrate was evaporated to give crude alcohol **6** as an oil: NMR δ 2.42 (s, 3), 4.62 (s, 2). To the ether solution (5 mL) of **6** was added PBr_3 (0.15 mL), and the mixture was stirred for 1 h, poured into cold aqueous Na_2CO_3, and extracted (20% $CHCl_3$/ether). The crude product obtained from extraction (112 mg) was identical by ^1H NMR and TLC with the bromide **3**.

Preparation of Sulfones 7 and 8. A solution of 2.15 g (10 mmol) of **4** in methanol (50 mL) was added to an aqueous (20 mL) solution of excess $NaIO_4$ (4 g). After being stirred for 6 h at room temperature, conversion to the more polar sulfoxide was complete (TLC). The precipitate was filtered and washed with $CHCl_3$, and the organic layer from the filtrate was separated, dried, and evaporated. To the residue dissolved in methanol (100 mL) was added $KMnO_4$ (1.73 g, 11 mmol) in water (30 mL), the dark mixture was stirred for 30 min at room temperature and then filtered, and the precipitate was thoroughly washed with $CHCl_3$. The filtrates were washed with saturated aqueous $NaHCO_3$ and with brine, dried, and evaporated to give 2.20 g (89%) of crystalline **7**: mp 113–134 °C (hexane/chloroform); NMR δ 2.26 (s, 3), 4.32 (s, 2), 7.0–8.45 (m, 8). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.2; H, 5.3. Found: C, 63.3; H, 5.3.

Sulfide **2** was converted by the same procedure to sulfone **8** in 91% yield: mp 81–82 °C (hexane/chloroform); NMR δ 2.31 (s, 3), 4.60 (s, 2), 6.95–8.20 (m, 8). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.2; H, 5.3. Found: C, 63.3; H, 5.4.

Reaction of Sulfides 2 and 4 with Carbonyl Compounds. General Procedure. To a solution of LDA prepared at 0 °C from diisopropylamine (0.21 mL, 1.5 mmol) in THF (1.5 mL) and 2 M BuLi/hexane (0.65 mL, 1.3 mmol) were added 0.2 mL (1.3 mmol) of tetramethylethylenediamine (TMEDA) and the sulfide (0.215 g, 1 mmol) in THF (3 mL). After being stirred for 1 h at 0 °C, the mixture was cooled to −78 °C, and the carbonyl compound (2 mmol) was added dropwise with strirring. After 1 h the mixture was poured into ice and aqueous NH_4Cl and extracted with ether/chloroform (8/2), after addition of aqueous $NaHCO_3$. The organic layer was dried and filtered, and the filtrate was evaporated under reduced pressure to a residue which was purified by chromatography.

2-[1-(Phenylthio)-2-hydroxy-3-methylbut-1-yl]-3-methylpyridine (9) was obtained from **2** and isobutyraldehyde as consecutively eluting (6/1 pentane/ether) diastereomers (1/1 ratio), 0.287 g (100%).

Isomer a: mp 76–77 °C; NMR δ 1.02 (d, 3), 1.09 (d, 3), 1.84–2.40 (m, 1), 1.86 (s, 3), 3.68 (dd, 1), 4.41 (d, 1), 6.65–8.20 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 71.3; H, 7.2.

Isomer b: mp 44–45 °C; NMR δ 0.80 (d, 3), 0.94 (d, 3), 1.24–1.86 (m, 1), 2.06 (s, 3), 3.64 (dd, 1), 4.41 (d, 1), 6.76–8.24 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 71.3; H, 7.3.

2-[1-(Phenylthio)-2-hydroxy-2-methylbut-1-yl]-3-methylpyridine (10) was obtained from **2** and 2-butanone as an inseparable mixture of diastereomers in a 1/1 ratio as deduced from

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

the NMR signals δ 4.33 (s, 1) and 4.36 (s, 1) of equal size. After short column chromatographic purification (4/1 pentane/ether), the oily product was dissolved in 1/1 acetone/ethanol (5 mL) and treated with Raney nickel (1 g) with refluxing and stirring for 30 min to give 0.168 g (94%) of **2-(2-hydroxy-2-methyl-but-1-yl)-3-methylpyridine (13)**: bp 82 °C (0.3 mm); NMR δ 0.93 (t, 3), 1.15 (s, 3), 1.55 (q, 2), 2.28 (s, 3), 2.85 (s, 2), 6.98–8.34 (m, 3). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.5. Found: C, 73.5; H, 9.6.

2-Methyl-3-[1-(phenylthio)-2-hydroxy-3-methylbut-1-yl]-pyridine (11) was obtained from **4** and isobutyraldehyde (0.166 g, 58%) as consecutively eluting (2/1 entane/ether) diastereomers (55:45 ratio).

Isomer a: mp 110–111 °C (hexane/chloroform); NMR δ 0.88 (d, 3), 1.24–1.98 (m, 1), 2.01 (d, 3), 2.40 (s, 3), 3.69 (dd, 1), 4.40 (d, 1), 6.83–8.32 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 70.9% H, 7.4.

Isomer b: mp 123–134 °C (from hexane/chloroform); NMR δ 0.84 (d, 3), 0.98 (d, 3), 1.66–2.12 (m, 1), 2.42 (s, 3), 3.58 (t, 1), 4.39 (d, 1), 6.93–8.30 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 71.3; H, 7.3.

2-Methyl-3-[1-(phenylthio)-2-hydroxy-2-methylbut-1-yl]-pyridine (12) obtained from **4** and 2-butanone (0.240 g, 84%) consisted of diastereomers with identical R_f values which were partly separable by crystallization, after chromatography (5/1 pentane/ether).

Isomer a: mp 125–126 °C; NMR δ 0.96 (t, 3), 1.34 (s, 3), 1.65 (q, 2), 2.40 (s, 3), 4.55 (s, 1), 7.10–8.32 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 71.4; H, 7.2.

Isomer b: mp 88–90 °C; NMR δ 0.97 (t, 3), 1.12 (s, 3), 1.79 (q, 2), 2.34 (s, 3), 4.99 (s, 1), 7.10–8.35 (m, 8). Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.1; H, 7.3. Found: C, 71.2; H, 7.3.

Reactions of Sulfone 7. The general procedure described for sulfides **2** and **4** was utilized, unless otherwise specified. An excess of 50 mol % of LDA was used in the reaction of sulfone **7** with BuI and of 100 mol % of LDA in other reactions. Hexamethylphosphoric triamide (HMPT, 150 mol %) was used instead of TMEDA in the reaction with BuI.

2-Methyl-3-[1-(phenylsulfonyl)pent-1-yl]pyridine (14) was obtained from **7** and BuI (0.242 g, 80%) as an oil: NMR 0.82 (t, 3), 1.15–1.38 (m, 4), 2.10 (s, 3), 1.90–2.42 (m, 2), 4.35 (dd, 1), 7.01–8.44 (m, 8). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.3; H, 6.9. Found: C, 67.5; H, 6.8.

2-Methyl-3-[2-(ethoxycarbonyl)-(*E*)-ethen-1-yl]pyridine (15) was obtained from **7** and ethyl bromoacetate. Elution with 4/1 ether/pentane gave a mixture of two compounds which was left overnight in an ether solution to which a few drops of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) were added. The ether solution was washed with aqueous NaCl, dried, and evaporated to give **15** as an oil: 0.137 g (72% overall yield); NMR δ 1.35 (t, 3), 2.58 (s, 3), 4.18 (q, 2), 6.22 (d, J = 16 Hz, 1), 6.98 (dd, J = 4, 2 Hz, 1), 7.62 (dd, J = 4, 1 Hz, 1), 7.72 (d, J = 16, 1), 8.25 (dd, J = 2, 1 Hz, 1). Anal. Calcd for $C_{11}H_{13}O_2N$: C, 69.1; H, 6.8. Found: C, 68.9; H, 6.9.

2-Methyl-3-[1-(phenylsulfonyl)-4-oxopent-1-yl]pyridine (16), from **7** and 1-buten-3-one, was obtained by chloroform extraction followed by chromatography (eluting with ethyl acetate/2% MeOH) to give, successively, unchanged **7** and then the ketone **16**: 0.155 g (49%); mp 124–125 °C (from hexane–chloroform); IR ($CHCl_3$) 1710 cm^{-1}; NMR δ 2.04 (s, 3), 2.11 (s, 3), 2.10–2.74 (m, 4), 4.60 (dd, 1), 7.02–8.44 (m, 8). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.3; H, 6.0. Found: C, 64.1; H, 6.1.

2-Methyl-3-[1-(phenylsulfonyl)-2-hydroxy-3-methylbut-1-yl]pyridine (17), from **7** and isobutyraldehyde (0.236 g, 74%), consisted of two diastereomers in a 84/16 ratio. Elution with 4/1 ether/pentane gave first the major isomer: mp 204–206 °C (from chloroform/hexane); NMR δ 0.69 (d, 3), 1.02 (d, 3), 1.06–1.47 (m, 1), 1.95 (s, 3), 4.38–4.75 (m, 2), 7.07–8.45 (m, 8). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 64.0; H, 6.6. Found: C, 64.1; H, 6.6.

The minor isomer had the following: mp 172–173 °C (chloroform/hexane); NMR δ 0.78 (d, 3), 0.96 (d, 3), 1.54–1.71 (m, 1), 2.06 (s, 3), 4.40–4.49 (m, 2), 7.08–8.50 (m, 8). Anal. Calcd for $C_{17}H_{21}SO_3S$: C, 64.0; H, 6.6. Found: C, 64.1; H, 6.5.

2-(Bromomethyl)-3-[(phenylsulfonyl)methyl]pyridine (18). A mixture containing 1.976 g (8 mmol) of **7**, 2.136 g of NBS (12 mmol), and 0.8 g of azobis(isobutyronitrile) in 180 mL of CCl_4 was refluxed with lamp irradiation. After 2 h the conversion was complete (TLC), and the mixture was concentrated under reduced pressure at room temperature. Chromatographic purification (2/1 pentane/ethyl acetate, avoiding evaporation of fractions to dryness) yielded 2.19 g (84%) of crystals (stable if kept cold under pentane): mp 126–128 °C (chloroform/hexane); NMR δ 4.50 (s, 2), 4.53 (s, 2), 7.06–8.32 (m, 8). Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.8; H, 3.7. Found: C, 47.6; H, 3.8.

1-[(Phenylsulfonyl)methyl]-3-(bromomethyl)pyridine (19) was prepared from **8** and purified in the manner described for **18**: 1.62 g (62%); mp 148–150 °C (hexane/chloroform); NMR δ 4.61 (s, 2), 4.63 (s, 2), 7.01–8.20 (m, 8). Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.8; H, 3.7. Found: C, 47.5; H, 3.5.

2-[(Phenylthio)methyl]-3-[(phenylsulfonyl)methyl]-pyridine (20). The concentrated reaction mixture containing the crude bromo sulfone **18** from 1.2 g of **7** was dissolved in EtOH (25 mL) and added to a solution of PhSK prepared from 3.8 mL of thiophenol (37 mmol) and 2 g of KOH (37 mmol) in 35 mL of EtOH. After being stirred for 1 h at room temperature, the mixture was poured into ice–water and extracted with chloroform. The organic layer was dried and filtered, the filtrate was evaporated, and the residue was chromatographed (eluting with ether) to give 1.38 g of **20**: mp 82–84 °C (80% from **7**); NMR δ 4.11 (s, 2), 4.38 (s, 2), 7.02–8.52 (m, 13). Anal. Calcd for $C_{19}H_{17}NO_2S_2$: C, 64.2; H, 4.8. Found: C, 64.0; H, 4.7.

Deuteration of 20. A solution of LDA (1.2 mmol) in THF (2 mL) was added to a stirred solution of **20** (0.355 g, 1 mmol) in THF (3 mL) at 0 °C. After 1 h, D_2O (0.2 mL) was added, and the mixture was diluted with ether and washed with brine. The organic layer was dried and filtered and the filtrate evaporated. The NMR spectrum of the residue was identical with that of **20**, with the exception of a decreased δ 4.38 (s, 1) signal.

2-[(Phenylthio)methyl]-3-[1-(phenylsulfonyl)-3-buten-1-yl]pyridine (21). To a solution of **20** (1.49 g, 4.2 mmol) in THF (8 mL) was added allyl bromide (0.57 g, 4.6 mmol) and TMEDA (0.8 mL). The mixture was cooled to −78 °C, and a solution of LDA (4.6 mmol) in THF (4 mL), prepared as described before, was added dropwise, via syringe, with stirring. After 1 h at −78 °C the conversion of **20** was complete (TLC), the mixture was poured into ice–aqueous NH_4Cl, and the product was isolated as described before. The residue was chromatographed (1/1 pentane/ether) to give **21** as an oil: 1.32 g (80%); bp 205 °C (2.5 mm); NMR δ 2.80–3.13 (m, 2), 3.96 (s, 2), 4.69–5.09 (m, 3), 5.33–5.58 (m, 1), 7.12–8.44 (m, 13). Anal. Calcd for $C_{22}H_{21}NO_2S_2$: C, 66.8; H, 5.3. Found: C, 66.4; H, 5.5.

2-[1-(Phenylthio)-3-buten-1-yl]-3-[1-(phenylsulfonyl)-3-buten-1-yl]pyridine (22). To the above reaction mixture at −78 °C was added an additional amount of allyl bromide (0.57 g, 4.6 mmol) followed by LDA (4.6 mmol) in THF (4 mL), and the temperature of the stirred mixture was slowly allowed to rise to −30 °C during 2 h (TLC). Isolation as for **21** and chromatography (2/1 pentane/ether) gave 1.20 g (66%) of **22** as an oil: bp 156 °C (0.05 mm); NMR δ 2.52–3.01 (m, 4), 4.18 (t, J = 7 Hz, 1), 4.67–5.15 (m, 5), 5.29–5.65 (m, 2), 7.18–8.42 (m, 13). Anal. Calcd for $C_{25}H_{25}NO_2S_2$: C, 69.0; H, 5.8. Found: C, 68.8; H, 5.8.

Preparation and Thermolysis of Sulfoxides from 21 and 22. Compound **22** (0.2 g, 0.46 mmol) was treated with excess $NaIO_4$ in methanol–water, as described for the oxidation of **4**. After 4 h the conversion to a mixture of isomeric sulfoxides was complete (TLC). The usual isolation gave a residue which was dissolved in toluene (10 mL) and boiled for 1 h. The residue after evaporation of the solvent was purified on a silica column (1.5/1 pentane/ether) to give **24**: 0.112 g (75%); bp 148 °C (0.05 mm); UV λ_{max} (EtOH) 274 nm (ε 32400), 305 (16000); NMR δ 2.88–3.27 (m, 2), 4.58 (dd, J = 4 Hz, 11 Hz, 1), 4.91–5.56 (m, 5), 6.10–6.51 (m, 2), 6.84–8.50 (m, 9); mass spectrum, m/e 325 (M^+), 234, 184. Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.2; H, 5.8. Found: C, 70.3; H, 5.7.

Compound **21** was treated similarly with $NaIO_4$, and a mixture of two sulfoxides was obtained. Refluxing in toluene for 2 h resulted in recovery of the unchanged sulfoxide mixture.

2-[(Phenylthio)methyl]-3-[1-(phenylsulfonyl)-3-butyn-1-yl]pyridine (23). To a solution of 1.952 g (5.5 mmol) of **20** in dry THF (15 mL) were added propargyl bromide (0.5 mL, 6.3 mmol) and TMEDA (1.5 mL). The mixture was cooled to −78 °C, and LDA (6.6 mmol), prepared separately as described before,

was added dropwise. After the mixture was stirred for 0.5 h at −78 °C, additional LDA (3 mmol) was added. After another 0.5 h, isolation as described for **21** afforded 1.706 g (78%) of **23** as an oil: bp 160 °C (0.1 mm); NMR δ 1.84 (t, J = 2.5 Hz, 1), 3.00–3.18 (m, 2), 4.09 (s, 4), 4.95 (dd, J = 5 Hz, 10 Hz), 7.16–8.48 (m, 13). Anal. Calcd for $C_{22}H_{19}NO_2S_2$: C, 67.2; H, 4.8. Found: C, 67.3; H, 4.8.

2-[(Phenylthio)methyl]-3-(3-oxo-1(*E*)-buten-1-yl)pyridine (25). A solution of **23** (0.79 g, 2.01 mmol) in acetone (30 mL) was added to a mixture containing 70% aqueuous acetone (215 mL), 14 mL of aqueous 10% H_2SO_4, and 0.45 g of $HgSO_4$. The mixture was stirred for 3 h at 60 °C, part of the acetone was evaporated at reduced pressure, and the concentrated mixture was poured into ice and aqueous Na_2CO_3 and extracted with chloroform. The organic layer was washed with brine, dried, and filtered, and the filtrate was evaporated to a residue which was chromatographed (1.5/1 ether/pentane) to give 0.378 g (70%) of **25**: mp 80 °C (from hexane/chloroform); IR ($CHCl_3$) 1670 cm^{-1}; NMR δ 2.31 (s, 3), 4.37 (s, 2), 6.54 (d, J = 16 Hz, 1), 7.68 (d, J = 16 Hz, 1), 7.14–8.55 (m, 8). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.4; H, 5.6. Found: C, 71.5; H, 5.6.

Hydrogenation attempts with **25** in methanol or ethyl acetate, using Pd or Pt catalsyts, gave back unchanged starting material.

2-[(Phenylsulfonyl)methyl]-3-(3-oxo-1(*E*)-propen-1-yl)-pyridine (26). To a cooled (0 °C) solution of **21** (0.5 g, 1.26 mmol) in 2/1 THF/water (30 mL) was added 60 mg (0.23 mmol) of OsO_4 in ether (3 mL). After the mixture was stirred for 15 min, 1.25 g of $NaIO_4$ was added and stirring continued for 1 h at room temperature. Cyclohexene (2 mL) was then added, and the mixture was stirred for 2 h, poured into ice–aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and filtered, and the filtrate was evaporated. The residue was dissolved in THF (20 mL) containing 0.2 mL of DBU, and the solution was kept overnight at room temperature, diluted with ethyl acetate, and washed with brine. The usual isolation gave, after chromatography (ether/2% MeOH), 0.295 g (81%) of **26**: mp 142–143 °C; IR ($CHCl_3$) 1680 cm^{-1}; NMR δ 4.78 (s, 2), 6.49 (dd, J = 16 Hz, 7 Hz, 1), 7.20–8.47 (m, 9), 9.74 (d, J = 7 Hz, 1). Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.7; H, 4.5. Found: C, 62.7; H, 4.5.

2-[(Phenylsulfonyl)methyl]-3-(3-oxoprop-1-yl)pyridine (27). To a solution of 0.272 g of **26** in methanol (40 mL) was added 0.15 g of 5% Pd on charcoal, and the mixture was stirred for 1 h under hydrogen at room temperature. The catalyst was separated by filtration and washed with chloroform. Evaporation of the filtrates and chromatography of the residue (ether/5% MeOH) gave 0.2 g (44%) of **27** as an oil: IR ($CHCl_3$) 1720 cm^{-1}; NMR δ 2.77–3.18 (m, 4), 4.73 (s, 2), 7.09–8.29 (m, 8), 9.78 (s, 1). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.3; H, 5.2. Found: C, 62.3; H, 5.3.

Further chromatographic elution gave alcohol **28**: 0.055 g (20%); an oil; NMR δ 1.79–2.10 (m, 2), 2.79–2.98 (m, 2), 3.67 (t, 2), 4.72 (s, 2), 7.09–8.30 (m, 8). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.8; H, 5.8. Found: C, 61.7; H, 5.9.

8-(Phenylsulfonyl)-5,6,7,8-octahydroquinoline (30). To the alcohol **28** (0.1 g, 0.34 mmol) dissolved in CH_2Cl_2 (1.5 mL) were added at 0 °C triethylamine (0.2 mL) and methanesulfonyl chloride (0.2 mL), and the mixture was stirred for 1 h, poured into ice and aqueous $NaHCO_3$, and extracted (CH_2Cl_2). The organic layer was dried and filtered, the filtrate was evaporated in vacuo, and the residual **29**, homogeneous on TLC, was dissolved in dry THF (2 mL) and added to a solution of *t*-BuOK freshly prepared from 0.1 g of K and *tert*-butyl alcohol (4 mL). After being stirred 1 h at room temperature, the mixture was poured into aqueous NaCl and extracted ($CHCl_3$). Isolation as above gave a residue which on chromatography (1/1 ethyl acetate/pentane) afforded 62 mg (66%) of **30**: mp 140–141 °C (hexane/chloroform); mass spectrum, m/e 209 ($M^+ - SO_2$), 132 ($M^+ - PhSO_2$); NMR δ 1.70–2.85 (m, 6), 4.56 (br, 1), 7.04–8.28 (m, 8). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.9; H, 5.5. Found: C, 65.8; H, 5.4.

2-[2-(Ethoxycarbonyl)eth-1-yl]-3-[(phenylsulfonyl)-methyl]pyridine (33). To a solution of 20 mmol of LDA in 20 mL of THF, prepared at 0 °C as described before, was added ethyl phenylthioacetate (**31**; 4.41 g, 22 mmol) in 20 mL of THF and 8 mL of HMPT. After 1 h at 0 °C, the stirred mixture was cooled to −78 °C, 4.70 g of bromo sulfone **18** (14.4 mmol) in 50 mL of THF was added dropwise via syringe, and the reaction was continued for 0.5 h at this temperature. The mixture was then poured into ice–aqueous $NaHCO_3$ and extracted with ether/20% $CHCl_3$. The organic layer was dried, filtered, and evaporated to a residue which was chromatographed (2/1 ether/pentane) to give **32** as an oil, homogeneous on TLC: 4.51 g (71%); NMR δ 1.06 (s, 3), 2.84–3.08 (m, 2), 4.00 (q, 2), 4.22 (t, 1), 4.35 (dd, J = 14 Hz, 2), 7.01–8.48 (m, 13).[15] The product was dissolved in 1/1 ethanol/acetone (300 mL), Raney nickel (12 g) was added, and the mixture was vigorously stirred for 1 h at 60 °C, poured into ice–water, acidified with aqueous HCl, and made slightly alkaline with aqueous Na_2CO_3. Extraction with $CHCl_3$ (3×) in the usual manner gave a residue which crystallized at once, affording 3 g (62.5% from **18**) of **33**: mp 72–74 °C (from hexane/chloroform); IR ($CHCl_3$) 172 cm^{-1}; NMR δ 1.20 (t, 3), 2.72–2.83 (m, 4), 4.06 (q, 2), 4.48 (s, 2), 7.03–8.53 (m, 8); mass spectrum, m/e 333 (M^+) 288, 260, 257, 192. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.3; H, 5.7. Found: C, 61.0; H, 5.7.

2-[(Phenylsulfonyl)methyl]-3-[2-(ethoxycarbonyl)-ethyl]pyridine (43) was prepared from bromo sulfone **19** and **31** under the same conditions as described for **33**. After desulfurization, **43** was obtained in 61% overall yield from **19**: mp 70 °C (hexane/chloroform); IR 1720 cm^{-1}; NMR δ 1.22 (t, 3), 2.56–2.72 (m, 2), 3.03–3.18 (m, 2), 4.10 (q, 2), 4.73 (s, 2), 7.08–8.30 (m, 8). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.3; H, 5.7. Found: C, 61.3; H, 5.7.

5-(Phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline (34). Sodium hydride (0.9 g, 55% dispersion in oil, 20 mmol) was washed (2×) with dry pentane via syringe in an argon flushed flask, and 1.5 g of **33** (4.5 mmol) dissolved in 95/5 THF/Me_2SO (55 mL) was added. After being stirred for 1 h at room temperature, the mixture was poured into ice–water, slightly acidified (aqueous HCl), made alkaline to pH 8 with aqueous Na_2CO_3, and extracted (3×) with $CHCl_3$. The residue obtained by the usual isolation crystallized on washing with pentane–10% ether to give 1.04 g (81%) of **34**: mp 169–170 °C (chloroform/hexane); IR ($CHCl_3$) 1718 cm^{-1}; UV (EtOH) λ_{max} 266 nm (ε 6200), 274 (6300), 299 (7000);[16] NMR δ 2.60–3.55 (m, 4), 4.64 (s, 1), 7.11–8.62 (m, 8); mass spectrum, m/e 287 (M^+), 146, 118. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.7; H, 4.5. Found: C, 62.9; H, 4.5.

6-Oxo-5,6,7,8-tetrahydroquinoline (35). To 0.287 g (1 mmol) of **34** dissolved in 9/1 acetone/ethanol (10 mL) was added Raney nickel (1 g), and the mixture was refluxed with vigorous stirring for 1 h. Filtration and washing with ether of the black precipitate followed by evaporation gave a residue which on chromatography (ether/2% methanol) afforded **35** (0.105 g, 72%) as an oil, unstable in air, which can be preserved for several weeks in cold solution under nitrogen: NMR δ 2.60–2.75 (m, 2), 3.20–3.36 (m, 2), 3.61 (s, 2), 7.15 (dd, J = 4 Hz, 8 Hz, 1), 7.42 (d, J = 8 Hz, 1), 8.43 (d, J = 4 Hz, 1); mass spectrum, m/e 147 (M^+), 118; other spectral and physical data were in agreement with those reported.[13a]

Alkylation of 34. General Procedure. To a solution of 0.1 g (0.35 mmol) of **34** in dry acetone (6 mL) were added anhydrous K_2CO_3 (40 mg), DBU (0.1 mL), and the halide in excess (350 mol %). After being stirred 1–2 h at 60 °C, the mixture was poured into aqueous NaCl and extracted with $CHCl_3$. After the usual isolation the residue was purified by chromatography (ether/2% MeOH).

5-Methyl-5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline (36) was obtained from **34** and MeI: 65%; mp 128–129 °C (hexane/chloroform); IR ($CHCl_3$) 1720 cm^{-1}; UV λ_{max} 265 nm (ε 6700), 272 (5500); NMR δ 1.80 (s, 3), 2.60–3.50 (m, 4), 7.17–8.61 (m, 8). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 5.0. Found: C, 63.7; H, 5.0.

5-[(Ethoxycarbonyl)methyl]-5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline (37) was obtained from **34** and $BrCH_2CO_2Et$: 68%; mp 105 °C (hexane/chloroform); IR (KBr) 1720, 1735 cm^{-1}; NMR δ 1.04 (t, 3), 2.85–3.46 (m, 4), 3.56 (d, 2),

(15) In compound **32** the NMR signal of the α-sulfonyl methylene is split (dd, δ 4.35) due to hindered rotation. After removal of the sulfide, the methylene group is a singlet in **33**.

(16) The relative intensity of λ_{max} in the UV spectrum of **34** in ethanol changed after 24 h to λ_{max} 266 nm (ε 6700), 272 (6600), 299 (6100), probably due to changes in the keto–enol ratio.

3.89 (q, 2), 7.14-8.58 (m, 8). Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 51.5; H, 5.1. Found: C, 51.6; H, 5.0.

5-(2-Propen-1-yl)-5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline (38) from 34 and allyl bromide (85%): mp 96-97 °C (hexane/chloroform); IR ($CHCl_3$) 1720 cm^{-1}; NMR δ 2.25-3.40 (m, 6), 4.82-5.21 (m, 3), 7.20-8.60 (m, 8). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 69.5; H, 5.2. Found: C, 69.5; H, 5.1.

5-Methyl-6-oxo-5,6,7,8-tetrahydroquinoline (39) and 5-[(ethoxycarbonyl)methyl]-6-oxotetrahydroquinoline (40) were obtained from **36** and **37**, respectively, as described for **35**, by treatment with Raney nickel. Compound **39** was obtained as an oil, unstable in air: bp 78 °C (0.3 mm); 98%; IR 1718 cm^{-1}; NMR δ 1.49 (d, J = 7 Hz, 3), 2.55-2.98 (m, 3), 3.22-3.59 (m, 2), 7.20 (dd, J = 3 Hz, 4 Hz, 1), 7.51 (d, J = 4 Hz, 1), 8.44 (J = 3 Hz, 1); mass spectrum, m/e 161 (M^+), 132.

Compound **40** was obtained as an oil: bp 102 °C (0.2 mm); 71%; IR ($CHCl_3$) 1720 cm^{-1}; NMR δ 1.22 (t, 3), 2.60-2.83 (m, 2), 3.04 (d, J = 6 Hz, 2), 3.27-3.44 (m, 2), 3.85-4.26 (m, 3), 7.20 (dd, J = 4, 7 Hz, 1), 7.46 (d, J = 7 Hz, 1), 8.44 (d, J = 4 Hz, 1); mass spectrum, m/e 233 (M^+), 187.

5-Methyl-6-hydroxyquinoline (41) and 5-[(Ethoxycarbonyl)methyl]-6-hydroxyquinoline (42). To a solution of 33 mg (0.3 mmol) of t-BuOK in 1.5 mL of dry t-BuOH was added under nitrogen 0.1 mmol of **36** or **37**, respectively, dissolved in 3 mL of dry THF, and the mixture was stirred at room temperature for 1 h, poured into ice and brine, and extracted with chloroform (3×). The usual isolation gave **41** in 88% yield: mp 173-174 °C (chloroform/hexane); IR (KBr) 1575, 1500, 1405, 1330, 1260 cm^{-1}; λ_{max} 288 nm (ϵ 2500), 335 (3600); NMR δ 2.54 (s, 3), 7.26-8.24 (m, 5); mass spectrum, m/e 159 (M^+),]30. Anal. Calcd for $C_{10}H_9NO$: C, 74.5; H, 5.7. Found: C, 74.6; H, 5.8.

Compound **42** was isolated in 84% yield: mp 181 °C (chloroform/hexane); IR (KBr) 1730, 1580, 1510, 1330, 1270, 1180 cm^{-1}; UV λ_{max} 285 nm (ϵ 3000), 335 (4300); NMR δ 1.25 (t, 3), 4.08 (s, 2), 4.18 (q, 2), 7.18-8.76 (m, 5); mass spectrum, m/e 231 (M^+), 185, 157, 130. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.6. Found: C, 67.8; H, 5.6.

7-Oxo-8-(phenylsulfonyl)-5,6,7,8-tetrahydroquinoline (44). To a stirred mixture of t-BuOK (0.15 g) in dry THF (10 mL) under argon was added 0.15 g (0.45 mmol) of ester **43** dissolved in 15 mL of THF. After being stirred for 1 h at room temperature, the mixture was poured into water, and the aqueous solution was acidified with dilute aqueous HCl and then brought to pH 8 with aqueous Na_2CO_3. Extraction with chloroform (3×) and isolation in the usual manner gave 92 mg (71% yield) of **44** which crystallized directly on being washed with pentane/20% ether: mp 236-238 °C dec; UV λ_{max} 295 nm (ϵ 10500), 359 (16000); IR (KBr) 1560-1580 cm^{-1} (vs); NMR δ 2.31-2.47 (m, 2), 2.68-3.09 (m, 2), 6.64 (t, 1), 7.21-8.09 (m, 7); mass spectrum, m/e 287 (M^+), 223, 222, 146, 118. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.7; H, 4.5. Found: C, 62.6; H. 4.6.

7-Hydroxy-8-methylquinoline (46). Keto sulfone **44** (60 mg, 0.21 mmol) was treated with MeI as described for the preparation of **36** by adding 600 mol % of MeI in several portions during 1 h at which time all the **44** had been converted to the less polar **45**. The residue from isolation was dissolved in THF (4 mL) and added to a solution of t-BuOK (50 mg) in t-BuOH (2 mL). After being stirred for 1 h at room temperature, the mixture was poured into ice-water and extracted with chloroform, and the residue was purified on a silica column (eluting with ether) to give 15 mg of **46** (46% from **44**): mp 189 °C; IR (KBr) 1610, 1580, 1480, 1320, 1270 cm^{-1}; UV λ_{max} 270 nm (ϵ 2500), 333 (4500); NMR δ 2.69 (s, 3), 7.11-7.30 (m, 2), 7.57 (d, J = Hz, 1), 8.03 (dd, J = 9, 2 Hz, 1), 8.87 (dd, J = 4, 2 Hz, 1); mass spectrum, m/e 159 (M^+), 131, 130. Anal. Calcd for $C_{10}H_9NO$: C, 74.5; H, 5.7. Found: C, 74.8; H, 5.7.

Ketone **45** was isolated from a separate experiment by omitting the *tert*-butoxide treatment and concluding with chromatography and ether/2% methanol elution: mp 135 °C (hexane/chloroform); IR 1712 cm^{-1}; UV λ_{max} 266 nm (ϵ 6500); NMR δ 1.86 (s, 3), 2.48-3.90 (m, 4), 7.26-8.43 (m, 8); mass spectrum, m/e 301 (M^+), 160. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 5.0. Found: C, 63.9; H, 5.1.

Registry No. **1**, 583-61-9; **2**, 76915-52-1; **3**, 76915-53-2; **4**, 76915-54-3; **5**, 1721-26-2; **6**, 56826-61-0; **7**, 73843-36-4; **8**, 76915-55-4; **9** (isomer 1), 76915-56-5; **9** (isomer 2), 76915-57-6; **10** (isomer 1), 76915-58-7; **10** (isomer 2), 76915-96-3; **11** (isomer 1), 76915-59-8; **11** (isomer 2), 76915-60-1; **12** (isomer 1), 76915-61-2; **12** (isomer 2), 76915-62-3; **13**, 76915-63-4; **14**, 76915-64-5; **15**, 76915-65-6; **16**, 76915-66-7; **17** (isomer 1), 76915-67-8; **17** (isomer 2), 76915-68-9; **18**, 76915-69-0; **19**, 76915-70-3; **20**, 76915-71-4; **21**, 76915-72-5; **22**, 76915-73-6; **23**, 76915-74-7; **24**, 76915-75-8; **25**, 76915-76-9; **26**, 76915-77-0; **27**, 76915-78-1; **28**, 76915-79-2; **29**, 76915-80-5; **30**, 76915-81-6; **31**, 7605-25-6; **32**, 76915-82-7; **33**, 76915-83-8; **34**, 76915-84-9; **35**, 27463-91-8; **36**, 76915-85-0; **37**, 76915-86-1; **38**, 76915-87-2; **39**, 76915-88-3; **40**, 76915-89-4; **41**, 76915-90-7; **42**, 76915-91-8; **43**, 76915-92-9; **44**, 76915-93-0; **45**, 76915-94-1; **46**, 76915-95-2; azobis(isobutyronitrile), 78-67-1; isobutyraldehyde, 78-84-2; 2-butanone, 78-93-3; ethyl bromoacetate, 105-36-2; 1-buten-3-one, 78-94-4; allyl bromide, 106-95-6; propargyl bromide, 106-96-7.

Bis Heteroannulation. 2. Oxazole Alcohols from the Interaction of Lithiomethyl Isocyanide with Lactones. A Novel Synthesis of Evodone

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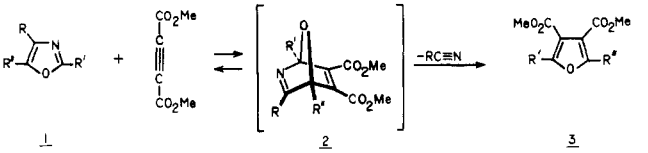
Oxazole alcohols may be readily obtained through the interaction of lithiomethyl isocyanide with lactones. Acetylenic oxazoles of proper design have been shown to undergo a facile intramolecular Diels-Alder reaction, leading directly to fused-ring furan derivatives of the type found in the furanosesquiterpenes ("bis heteroannulation"). A novel synthesis of evodone is presented.

The extraordinary reactivity of the oxazoles in Diels-Alder reactions has led to their widespread use in natural product synthesis. Reaction with alkenes, for example, leads directly to highly substituted pyridine derivatives,[1] a transformation extensively utilized in the synthesis of pyridoxine derivatives[2] and recently applied in a novel synthesis of the antitumor agent ellipticine.[3] Alternatively, reaction with acetylenic dienophiles provides an

Scheme I



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