hydroxide solution. The yield after recrystallization from water was 76% crystals having mp 143–147°, mmp 144–147° (lit.[21] mp 147°). In another run the crude product was chromatographed in cyclohexane–benzene on Florisil. N-*p*-tolylmaleisoimide (5%) was isolated having mp 70–72° (lit.[14b] mp 74°).

N-Phenylmaleimide, N-Phenylmaleisoimide, and Acetanilide.—The dehydration reaction of **1c** was carried out as described above. The crude product was dissolved in benzene and the solution was dried with magnesium sulfate. The dried benzene solution was chromatographed on Florisil and 12% N-phenylmaleisoimide and 11% N-phenylmaleimide were isolated. Nmr indicated that each compound was contaminated with about 10% of the other. Later fractions gave 35% acetanilide, mp 112–114°, mmp 112–115° (lit.[21] mp 114°).

N-*p*-Chlorophenylmaleimide and *p*-Chloroacetanilide.—The reaction was run as above and the crude mixture was poured into saturated sodium bicarbonate solution. The precipitate formed was dried in air and chromatographed on Florisil with cyclohexane–benzene to yield 33% N-*p*-chlorophenylmaleimide [mp 107–109°, mmp 107–109° (lit.[2] mp 108–110°)] and in a later fraction 37% *p*-chloroacetanilide, mp 176–177° (lit.[21] mp 179°).

N-*p*-Acetylmaleimide.—In a similar manner 40% N-*p*-acetylmaleimide was obtained, mp 152–155° (lit.[22] mp 151°).

***endo*-Norbornene-*cis*-5,6-dicarboxylic Acid Monomethyl Ester.**—A third run of the dehydration reaction of **1b** in acetic anhydride alone was treated with excess cyclopentadiene.[23] After the exothermic reaction had subsided, an equal volume of methanol was added and the solution was heated at reflux for 2 hr. The solvents were removed by distillation and the residue was poured into water and extracted with ether. The ether extracts were combined and extracted with saturated sodium bicarbonate solution. The aqueous solution was acidified with concentrated hydrochloric acid to pH 3 and extracted with ether. After drying (magnesium sulfate) the ether was removed by evaporation. The residue, a clear colorless oil, solidified on standing to a white solid, mp 79–82° (lit.[24] mp for *endo*-norbornene-*cis*-5,6-dicarboxylic acid monomethyl ester, 76–78.5°). The nmr was identical with that of an authentic sample.

(22) B. Matkovics, L. Ferenezi, and Gy. Selneczi, *Acta Univ. Szgeded. Acta Phys. Chem.*, **4**, 134 (1958); *Chem. Abstr.*, **53**, 14934 (1959).

(23) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, p 83.

(24) M. S. Morgan, R. S. Tipson, A. Lowy, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944).

Registry No.—**2a**, 1081-17-0; **2b**, 1631-28-3; **2c**, 941-69-5; **2d**, 1631-29-4; **2e**, 1082-85-5; **3a**, 19990-24-0; **3b**, 19990-25-1; **3c**, 19990-26-2; **3d**, 19990-27-3; **3e**, 19990-28-4; acetic anhydride, 108-24-7.

Acknowledgments.—I am indebted to The Society of Sigma Xi and The Rutgers Research Council for financial support of this work and to Professor Benjamin Carroll of the Rutgers Computer Center for assistance in obtaining the computer results. The Varian A-60A nuclear magnetic resonance spectrometer was purchased with the aid of a grant to the Chemistry Department of Douglass College from the National Science Foundation.

Stereochemistry of Microbiological Hydroxylation. II. Oxygenation of 1-Benzoylalkylpiperidines

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The microorganism *Sporotrichum sulfurescens* has been found to oxygenate a series of 1-benzoylalkylpiperidines. Oxygenation of 1-benzoyl-4-*n*-propylpiperidine (**2**) gives 1-benzoyl-4-(2-oxo)propylpiperidine (**3**); of 1-benzoyl-4-methylpiperidine (**4**) gives 1-benzoyl-4-hydroxymethylpiperidine (**5**) and 1-benzoyl-4-methyl-4-piperidinol (**6**); of (±)-1-benzoyl-3-methylpiperidine (**7**) gives 1-benzoyl-3-methyl-3-piperidinol (**8**) and (−)-1-benzoyl-3-methyl-4-piperidinol (**9**); of (±)-1-benzoyl-2-methylpiperidine (**12**) gives (2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol (**13**), (2*R*,4*S*)-1-benzoyl-2-methyl-4-piperidinol (**14**), and (2*R*-)1-benzoyl-2-methyl-4-piperidinone (**16**); and of 1-benzoyl-*cis*-2,6-dimethylpiperidine (**32**) gives 1-benzoyl-*cis*-2,6-dimethyl-3-piperidinol (**33**). The substrates, 1-benzoyl-2-ethylpiperidine (**19**) and 1-benzoyl-2-*n*-propylpiperidine (**25**), also are oxygenated.

The hydroxylation of organic compounds by microbial enzyme systems is a valuable reaction for the introduction of functionality into a saturated molecule. Of additional interest is the fact that enzymatic reactions, when performed upon the substrate specific to the enzyme, generally are highly stereoselective. Enzymatic reactions upon foreign substrates may also be stereoselective in which case they are particularly valuable in synthesis. Stereoselectivity may be of two types in the case of hydroxylation reactions. First, the introduction of a hydroxyl group in the place of a particular hydrogen atom in the substrate molecule may result in the formation of a single alcohol epimer. As examples, the hydroxylation of steroids usually gives either the α- or the β-hydroxy product rather than a mixture of the two.[1] The second potential result, which is a consequence of the first, is the formation of an optically active product, either through the introduction of asymmetry into the molecule or through resolution of a racemate.[2] Examples in which both hydroxylation and introduction of optical activity occur are few, largely because most substrates used for this reaction have been naturally occurring steroids. Two notable exceptions are the hydroxylation and resolution of a racemic intermediate by the mold *Ophiobolus herpotrichus* in the total synthesis of *d*-aldosterone[3] and of a series of synthetic gonanes by the microorganism *Aspergillus ochraceus*.[4]

We have recently described the microbial hydroxylation of molecules other than steroids by the microorganism *Sporotrichum sulfurescens* in which both the stereospecific introduction of hydroxyl[5] and the intro-

(1) *Cf.* C. Tamm, *Angew. Chem. Intern. Ed. Engl.*, **1**, 178 (1962).

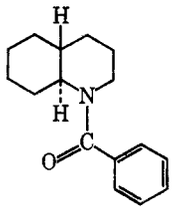
(2) Resolution may be accomplished upon either the substrate or the product. Resolution of the latter requires further degradation of one enantiomer of the product.

(3) E. Vischer, J. Schmidlin, and A. Wettstein, *Experientia*, **12**, 50 (1956).

(4) L. L. Smith, G. Greenspan, R. Rees, and T. Foell, *J. Amer. Chem. Soc.*, **88**, 3120 (1966).

(5) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968); (b) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3195 (1968); (c) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3201 (1968); (d) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3207 (1968).

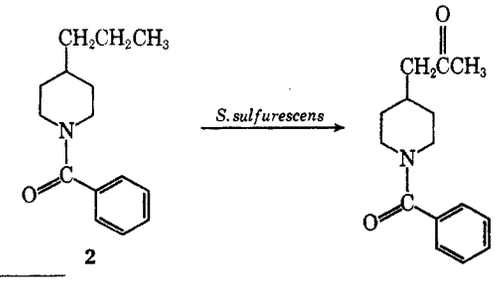
duction of optical activity were observed.[5a,b] Of particular interest was the hydroxylation of (±)-1-benzoyl-*trans*-decahydroquinoline (**1**). We have also



1

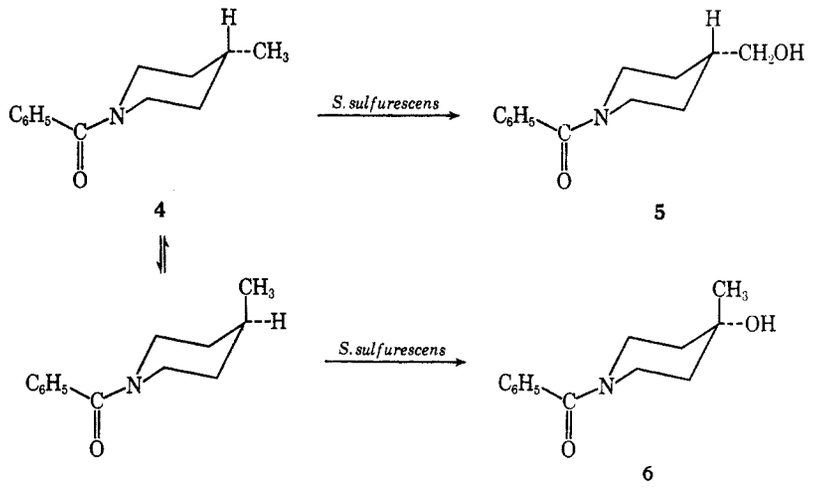
observed[6a] that 1-benzoylpiperidine is hydroxylated at the 4 position, whereas the piperidine ring contained in the nucleus of **1** is not hydroxylated. It became of interest therefore to investigate the microbial hydroxylation of a series of 1-benzoyl-*x*-alkyl-substituted piperidines to determine (1) if these compounds could be hydroxylated, (2) if hydroxylation might occur in the alkyl protions of the molecules, and (3) if stereoselectivity, with respect to both introduction of the hydroxyl group and introduction of optical activity, would be observed in these molecules. In the following discussion, the successful hydroxylation of such a series of substrates is described and structural and stereochemical assignments are made on the basis of the spectral data of the hydroxylated products and their ketonic oxidation derivatives.

1-Benzoyl-4-*n*-propylpiperidine (**2**) was the first compound in this series used as a substrate for the hydroxylation reaction with *Sporotrichum sulfurescens*. A single oxygenated product (**3**) was obtained and was shown to be a ketone by its infrared spectrum. The product was easily identified as 1-benzoyl-4-(2-oxo)-propylipiperidine (**3**) by examination of its nmr spectrum, which had a doublet at 146 Hz and a singlet at 127 Hz corresponding to the methylene and methyl groups adjacent to the carbonyl group, respectively. The formation of **3**, which very recently has been prepared by chemical synthesis,[7] is noteworthy in several respects. First it provides an as yet unusual example of hydroxylation in an acyclic portion of a molecule by *S. sulfurescens*. Secondly, it is the only example of a major ketonic product obtained in the present series of substrates and as such is in agreement with the notion of further oxidation of conformationally mobile substrates, which has been outlined previously.[6]



2

Hydroxylation of 1-benzoyl-4-methylpiperidine (**4**) with *S. sulfurescens* gave two hydroxylated products. These were readily identified by their nmr spectra as 1-benzoyl-4-methyl-4-piperidinol (**6**) and 1-benzoyl-4-hydroxymethylpiperidine (**5**), the 4-methyl group of the former appearing as a singlet at 72 Hz and the 4-methylene group of the latter as a doublet at 203 Hz (J = 5 Hz). While the exact reaction paths leading to products **5** and **6** cannot easily be determined, we suggest the possibility that **5** arises through hydroxylation of the conformer of **4** having the equatorial methyl group and **6** from hydroxylation of the conformer of **4** having the axial methyl group. Such a pathway to **6** is consistent with the observation that in rigid systems the hydroxyl group is introduced in a *trans* orientation with respect to the amide functional group,[6] assuming that the benzoyl function occupies predominately an equatorial configuration in the present case.

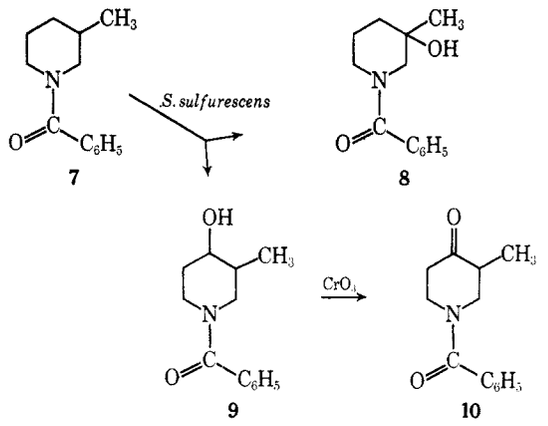


4 **5** **6**

When (±)-1-benzoyl-3-methylpiperidine (**7**) was used as a substrate, two hydroxylated compounds (**8** and **9**) were obtained as the products. The first alcohol obtained from chromatography of the products was readily identified as the tertiary alcohol, 1-benzoyl-3-methyl-3-piperidinol (**8**). The nmr spectrum of **8** contained a singlet at 69 Hz for the uncoupled tertiary methyl group at C-3. In addition, the axial proton at C-2 was a sharp doublet as a result of being coupled only with the geminal C-2 equatorial hydrogen. The second alcohol (**9**) could be oxidized to a ketone (**10**) with chromic acid. Only positions C-4 and C-5 of the 3-methylpiperidine nucleus can accommodate a ketone carbonyl group and, from the lack of a characteristic nmr signal attributable to a methylene group isolated at C-6 by a C-5 carbonyl, the position of the oxygen in

(6) (a) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968); (b) *ibid.*, **33**, 3217 (1968).

(7) R. J. Sundberg, *ibid.*, **33**, 487 (1968).

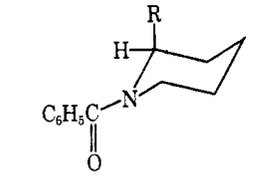


ketone **10**, and therefore in alcohol **9**, is assigned to C-4. The configuration of the C-4 hydroxyl group in **9** can be assigned on the basis of the nmr spectrum of the trichloroacetylurethan derivative (**11**) of **9**. The splitting of the C-4 signal, now shifted downfield, by two adjacent axial protons and one adjacent equatorial proton is consistent with an assignment of an axial configuration to the C-4 proton. The configuration of the hydroxyl group is therefore equatorial.

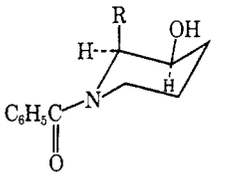
It now was necessary to consider the question of optical activity in this series of compounds since substrate **7** contains an asymmetric carbon and a second such center has been introduced in the formation of product **9**. The crystalline alcohol **9** was optically active ($[\alpha]_D$ −21°) but the crystalline alcohol **8** was optically inactive at the sodium D line. The lack of optical activity in **8** may be due to the fact that only the racemate was obtained in crystalline form in this case, since the amount of crystalline material (7% yield) obtained was only a small part of the crude fraction of **8**. Similarly, crystalline **9** (6% yield) may represent the preferential crystallization of the enantiomer.

The homologous series of 2-methyl-, 2-ethyl-, and 2-*n*-propyl-substituted piperidine substrates was submitted to the microbial oxygenation reaction and similar products were obtained from each. In considering the hydroxylation of these substrates as well as the structures of the products, it should be pointed out that the preferred conformation of these substrate molecules is the one in which the 2-alkyl group is in an axial configuration.[8] Similarly, the methyl groups in the substrate 1-benzoyl-2,6-dimethylpiperidine, discussed later below, also are found in axial configurations.[8]

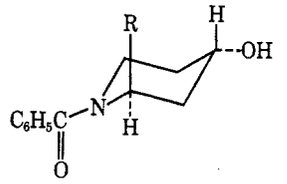
Three products, two major and one minor in terms of quantity, were isolated from the oxygenation of (±)-1-benzoyl-2-methylpiperidine (**12**). Obtained in largest quantity was a hydroxylated product (**14**), whose chromic acid oxidation product (**16**) was identical with the minor reaction product. The position of the ketone group in **16** was determined to be at C-4, since in its nmr spectrum (see Experimental Section) the C-2 proton and the C-6 protons all are split by the protons of adjacent saturated carbons, *i.e.*, C-3 and C-5. The hydroxyl group of **14** therefore is also at C-4 and it is assigned an equatorial configuration on the basis of the splitting of the C-4 proton in the nmr spectrum of the trichloroacetylurethan derivative (**17**).



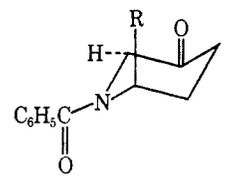
12, R = CH_3
19, R = C_2H_5
25, R = *n*-C_3H_7



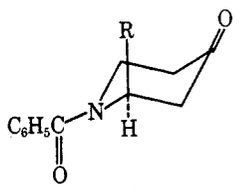
13, R = CH_3
20, R = C_2H_5
26, R = *n*-C_3H_7



14, R = CH_3
21, R = C_2H_5
27, R = *n*-C_3H_7



15, R = CH_3
22, R = C_2H_5
28, R = *n*-C_3H_7



16, R = CH_3
23, R = C_2H_5
29, R = *n*-C_3H_6

The second major product, alcohol **13**, obtained in the oxygenation of **12**, also had a secondary hydroxyl group, which was oxidized to a ketone (**15**). The ketone carbonyl may be at C-3 or at C-5 in **15**. Again, the nmr spectrum of the ketone allows assignment of structure to this compound. The C-2 proton signal is found as a quartet (J = 7 Hz) at 290 Hz in the spectrum of **15**, indicating that it is being split only by the protons of the axial C-2 methyl group. The ketone group must therefore be placed at the C-3 position to account for the lack of further splitting of the C-2 proton. The hydroxyl group of **13**, therefore also at C-3, is assigned an equatorial configuration by analogy with the similar 1-benzoyl-2-ethyl-3-piperidinol (**20**) obtained by hydroxylation of the 2-ethylpiperidine substrate and discussed below. The nmr spectra of the two alcohols, **13** and **20**, and their trichloroacetylurethan derivatives, **18** and **24**, are very similar between 100 and 300 Hz; however, only in the spectrum of **24** is the C-3 proton shifted downfield sufficiently to allow assignment of an axial configuration (half band width = 19 cps)[9] and therefore an equatorial configuration to the hydroxyl group. The question of optical activity in these products is discussed below.

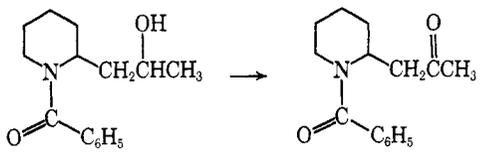
Oxygenation of (±)-1-benzoyl-2-ethylpiperidine (**19**) gave two hydroxylated products. Purification of these by chromatography gave first a compound (**20**) analogous to the C-3 hydroxylated product **13**, as discussed above, which was oxidized by Jones reagent to a ketone (**22**). The similarity of the nmr spectrum of **22** to the spectrum of **15** (see Experimental Section) is convincing evidence that the ketone carbonyl in **22** is also at C-3. The assignment of an equatorial configuration to the hydroxyl group at C-3 in **20** was

(8) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); also Y. L. Chow, C. J. Colon, and J. N. S. Tam, *Can. J. Chem.*, **46**, 2821 (1968); H. Paulsen, K. Todt, and H. Ripperger, *Chem. Ber.*, **101**, 3365 (1968); F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(9) *Cf.* R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

discussed above. The second product **21** was also oxidized by Jones reagent to a ketone (**23**). Both had nmr spectra very similar to the 4-hydroxy and 4-keto products in the 2-methyl series and therefore are assigned the analogous structures.

Oxygenation of the third member of the 2-alkyl series, 1-benzoyl-2-*n*-propylpiperidine (**25**), gave a mixture of three oxygenated products. Two of these (**26** and **27**) are similar to compounds **13** and **14**, derived from the 2-methylpiperidine substrate, and are assigned the analogous structures. The third product (**30**) has a hydroxyl group at the 2′ position of the *n*-propyl side chain as shown by the nmr spectra of it and of the ketone **31** obtained from it after oxidation. The



30 **31**

presence of a signal for the methyl group in the spectrum of **30** as a doublet (J = 6 Hz) at 74 Hz and as a singlet at 131 Hz in the spectrum of **31** requires this assignment of structure. Formation of compound **30** and oxidation to **31** represent a microbial synthesis of the N-benzoyl derivatives of the alkaloids sedridine and isopelletierine, respectively.

Several points of similarity of the products from the above homologous series of substrates should be noted. First, the two major products isolated from each bioconversion are a 3-hydroxy and a 4-hydroxy compound in which the configuration of the hydroxyl group is equatorial in each case. This configuration places the hydroxyl groups nearest to a 1,3- or a 1,4-diequatorial relationship that is possible in these molecules and is consistent with the previously observed *trans* relationship between the hydroxyl group and the electron-rich benzamide group in microbial hydroxylation products. Secondly, a similarity of the products can be seen in their optical activities, which are summarized in Table I. These results suggest that

TABLE I

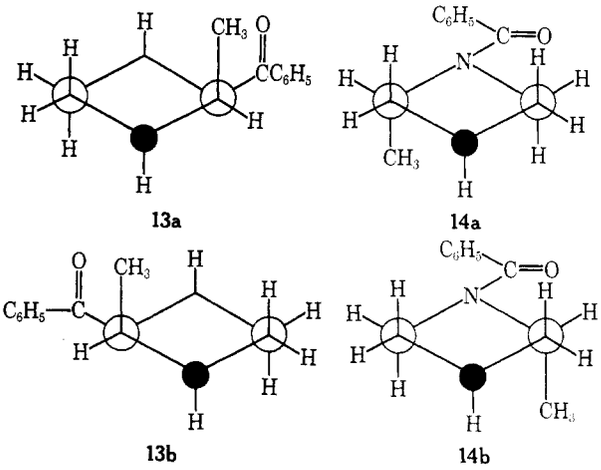
SPECIFIC ROTATIONS OF OXYGENATED 1-BENZOYL-2-ALKYLPIPERIDINES

Alkyl derivative	[α]D, deg 3-OH	4-OH	3 C=O	4 C=O
2-Methyl	+35	−29	+74	−19
2-Ethyl	+51	−22[a]	+50	
2-*n*-Propyl	+51	−26[a]		

[a] Measured on filtrates of crystalline, optically inactive analytical samples.

analogous reaction pathways are followed in the hydroxylation of each substrate. The formation of optically active products from these racemic substrates may result from either the preferential hydroxylation of one enantiomer of the substrate at a single position or the further preferential metabolism (and loss) of one enantiomer of the product molecules. In other experiments similar to these the total yield of optically active products exceeded 50%, which can best be interpreted as preferential hydroxylation of the enantiomers of the substrate at different positions. It seems probable that this is the case with the present substrates as well.

The availability of a method for the resolution of 2-methylpiperidine[10] and knowledge of the absolute configuration of (2*S*)-(+)-2-methylpiperidine[11] and its conversion to (2*S*)-(+)-1-benzoyl-2-methylpiperidine[12] enabled us to determine the absolute configuration of the optically active products **13** and **14**. A sample of (2*S*)-(+)-1-benzoyl-2-methylpiperidine ([α]D +38°, lit.[12] +41°) was prepared and used as a substrate with *S. sulfurescens*. Before examining the reaction product, an attempt was made to predict the structures of **13** and **14** with the use of a spatial orientation model, outlined previously.[6b] Four structures are possible for these products, two arising from each enantiomer of the substrate. These four structures appear as shown in the following projection formulas when oriented as defined previously.[6b]



13a **14a**

13b **14b**

Hydroxylation at C-3 of the *S* form of the substrate would give **13a**, whereas hydroxylation of the *R* form at C-3 would give **13b**. Likewise, hydroxylation at C-4 of the *S* form would give **14a** while hydroxylation of the *R* form at C-4 would give **14b**. From previous examples, a preference for an orientation of unsymmetrical molecules having the bulk of the molecule in the upper right rear octant was observed.[6b] In the present examples such preference predicts that hydroxylation of the *S* form of the substrate will give **13a** as the major product. Indeed, the major product isolated from hydroxylation of (2*S*)-1-benzoyl-2-methylpiperidine with *S. sulfurescens* was **13a**, identical with compound **13** isolated from bioconversion of racemate **12**. It can be expected that hydroxylation of the *R* form of the substrate would give **14b** as the product. The methyl group of structure **14b** is seen to lie slightly in the lower right octant, suggesting that this area of space is available to substrate molecule when in contact with the hydroxylating enzyme.

Finally, oxygenation of 1-benzoyl-*cis*-2,6-dimethylpiperidine (**32**) gave a single major product (**33**, [α]D −5°). The optical activity of **33** shows that it cannot be symmetrical (*i.e.*, a 4-hydroxy derivative) and the secondary character of the hydroxyl group, shown by oxidation to a ketone, leaves only C-3 as the position

(10) W. Marckwald, *Chem. Ber.*, **29**, 43 (1896).
(11) H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).
(12) O. Cervinka, A. Fabryova, and V. Novak, *Collect. Czech. Chem. Commun.*, **30**, 1742 (1965).

of hydroxylation in this product. Compound **33** could not be obtained as a sharp-melting solid; yet it was found homogeneous by tlc, vpc, and paper chromatography. This leads us to conclude that the product is optically impure, having an excess of the (−) enantiomer present as indicated by its optical rotation. A minor product (**34**) from this bioconversion had the empirical formula $C_{14}H_{19}NO_2$ suggesting that it was a dihydroxylated product. We were unable to obtain a satisfactory nmr spectrum of this material owing to its insolubility in the usual solvents.

Experimental Section[13]

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* V. Beyma (ATCC 7159). The biotransformation procedure has been described previously,[6a] the only variation being that the dispersing agent Ultrawet DS-30 (2.5 ml/l.) was added to the fermentations.

Isolation of Products from the Microbiological Oxygenations.—The following general procedure was followed in the separation of the oxygenated products. The methylene chloride extracts of the fermentation beers were allowed to evaporate to dryness. The residues were redissolved in methylene chloride and chromatographed on Florisil (ratio of substrate to adsorbent 1:100) chromatography columns which were dry packed in Skellysolve B. Elution of the column with increasing proportions of acetone in Skellysolve B generally resulted in removal of the products in the range of 10–25% (v/v) acetone in Skellysolve B. Purity of the fractions could be determined by tlc on silica gel plates developed in 20% methanol–benzene with detection by uv, Dragendorff reagent, or iodine vapor. The appropriate fractions were combined in acetone and usually decolorized with activated charcoal. The products were then crystallized from acetone–Skellysolve B, unless indicated otherwise. The products from each substrate are described in the order in which they were eluted from the column.

Oxygenation of 1-Benzoyl-4-*n*-propylpiperidine (2).—Oxygenation of **2** (25.0 g, 0.108 mole) gave an oil product which was distilled (bp 168–172°, 0.15 mm), giving 7.91 g (0.0323 mole, 30%) of 1-benzoyl-4-(2-oxo)propylpiperidine (**3**). The distillate crystallized after standing 8 months giving colorless crystals, mp 69–71°. Two recrystallizations gave an analytical sample of **3**: mp 69–71°, lit.[7] mp 63–65°; $\nu_{C=O}$ 1715, 1630, $\nu_{C=C}$ 1600, 1575, 1525, 1495, ν_{Ph} 790, 735, 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$), 247 (2- and 6-H_{eq}, broad, 2 H), 174 (2- and 6-H_{ax}, broad triplet, J_{gem} = 13 Hz, 2 H), 146 (CH_2CO, doublet, J = 5 Hz, 2 H), 127 (CH_3, singlet, 3 H).

Oxygenation of 1-benzoyl-4-methylpiperidine (4) (25.0 g, 0.123 mole) gave a total of 18.6 g of crude oxygenated product. Two crops of **1-benzoyl-4-methyl-4-piperidinol (6)**, 1.342 g, mp 105–110°, and 2.239 g, mp 93–106° (total 16.3 mmoles, 13%), were obtained. Two recrystallizations gave an analytical sample of **6** as colorless crystals: mp 109–111°; ν_{OH} 3320, $\nu_{C=O,C=C}$ 1605, 1575, 1500, ν_{Ph} 785, 710 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$), 260–184 (2- and 6-H, 4 H), 108–82 (3- and 5-H, 4 H), 72 (CH_3, singlet, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.24; H, 7.77; N, 6.53.

Two crops of **1-benzoyl-4-hydroxymethylpiperidine (5)**, 4.721 g, mp 90–94°, and 1.557 g, mp 88–94° (total 28.6 mmoles, 23%), were obtained. Two recrystallizations gave an analytical sample of **5** as colorless crystals: mp 92–95°; ν_{OH} 3440, $\nu_{C=O,C=C}$ 1630, 1615, 1600, 1575, 1495, ν_{Ph} 800, 725, 715 cm^{-1} in Nujol; nmr (in Hz 60°, $CDCl_3$), 251 (2- and 6-H_{eq}, broad doublet, J_{gem} = 13 Hz, 2 H), 203 (CH_2O, doublet, J = 5 Hz, 2 H), 172 (2- and 6-H_{ax}, six-line pattern, J_{gem} = 13 Hz, 2 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.37; H, 7.94; N, 6.43.

Oxygenation of (±)-1-benzoyl-3-methylpiperidine (7) (25.0 g, 0.123 mole) gave, following chromatography, a crude weight of 15.6 g of oxygenation products. Two crops of **1-benzoyl-3-methyl-3-piperidinol (8)**, 1.350 g, mp 91–3°, and 0.415 g (total 8.10 mmoles, 7%), were obtained. Two recrystallizations gave an analytical sample of **8**: mp 92–94°; $[\alpha]_D$ 0° (chloroform); ν_{OH} 3410, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1580, 1505, ν_{Ph} 790, 740, 730, 700 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 225 (2- and 6-H_{eq}, doublet, J_{gem} = 13 Hz, 2 H), ~188 (6-H_{ax}, multiplet, 1 H), 184 (2-H_{ax}, doublet, J_{gem} = 13 Hz, 1 H), 69 (CH_3, singlet, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.12; H, 8.12; N, 6.59.

(−)-1-Benzoyl-3-methyl-4-piperidinol (9) was obtained as colorless crystals, mp 119–135°, 1.762 g (8.04 moles, 6%). Three recrystallizations gave an analytical sample of **9**: mp 141–143°; $[\alpha]_D$ −21° (*c* 0.628, chloroform); ν_{OH} 3330, $\nu_{C=O}$ 1610, $\nu_{C=C}$ 1575, 1530, 1495, ν_{Ph} 795, 745, 720, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 242 (2- and 6-H_{eq}, broad singlet, 2 H), 210–158 (2- and 6-H_{ax}, multiple signals, 2 H), 56 (CH_3, doublet, J = 6 Hz, 3 H); trichloroacetylurethan derivative (**11**) of **9** nmr (in Hz, 60°, $CDCl_3$) 285 (4-H, triplet of doublets, J_{aa} = 8.5, J_{ae} = 4 Hz, 1 H), 242 (2- and 6-H_{eq}, doublet, J = 13 Hz, 1 H), 209–155 (2- and 6-H_{aa}, multiple signals, 1 H), 58 (CH_3, doublet, J = 6 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.24; H, 7.95; N, 6.39.

Oxidation of 9 with Jones reagent[14] gave ketone **10** as a viscous oil which failed to crystallize: nmr (in Hz, 37°, $CDCl_3$) 263 (2- and 6-H_{eq}, broad doublet, J = 13 Hz, 2 H), 222–180 (2- and 6-H_{ax}, multiple signals, 2 H), 174–140 (3- and 5-H, multiple signals, 3 H), 62 (CH_3, doublet, J = 6 Hz, 3 H).

Oxygenation of (±)-1-benzoyl-2-methylpiperidine (12) (25.0 g, 0.123 mole) gave a crude weight of 16.5 g of oxygenated products. A first crop, 0.252 g, and second crop, 0.061 g (1.44 mmoles, 1%), of **(2*R*)-1-benzoyl-2-methyl-4-piperidone (16)**, mp 111–116°, was obtained. Two recrystallizations gave an analytical sample of **16**: mp 117–118°; $\nu_{C=O}$ 1715, 1700, 1620, ν_{Ph} 790, 740, 700 cm^{-1} in Nujol; nmr (in Hz, $CDCl_3$) 298 (2-H, quartet, J_{CH_3} = 7 Hz, 1 H), 265 (6-H_{eq}, doublet, J_{gem} = 14 Hz, 1 H), 204 (6-H_{ax}, eight-line pattern, 1 H), 175–123 ($COCH_2$, multiple signals, 4 H), 75 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.21; H, 7.07; N, 6.46.

Two crops, 1.225 g, mp 125–130°, and 1.533 g, mp 120–125° (total 12.6 mmoles, 10%), of **(2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol (13)** were obtained. Two recrystallizations gave an analytical sample of **13**: mp 127–129°; $[\alpha]_D$ +35° (*c* 0.864, $CHCl_3$); ν_{OH} 3380, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1575, 1500, ν_{Ph} 745, 715, 705 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 268 (2-H, multiplet, 1 H), 234 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 171 (6-H_{ax}, six-line pattern, 1 H), 67 (CH_3, doublet, J = 6 Hz, 3 H); trichloroacetylurethan derivative (**18**) of **13** nmr (in Hz, 60°, $CDCl_3$) 291 (2-H and –OCH, multiplet, 2 H), 241 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 179 (6-H_{ax}, six-line pattern, 1 H), 75 (CH_3, doublet J = 6.5 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.26; H, 8.00; N, 6.68.

Two crops 4.277 g, mp 127–130°, and 1.303 g, mp 110–120° (total 25.5 mmoles, 21%), of **(2*R*,4*S*)-1-benzoyl-2-methyl-4-piperidinol (14)** were obtained. Two recrystallizations gave an analytical sample of **14**: mp 128–130°; $[\alpha]_D$ −29° (*c* 0.365, $CHCl_3$); ν_{OH} 3340, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1595, 1575, 1530, 1495, ν_{Ph} 795, 740, 715 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 274 (2-H, broad, 1 H), ~242 (6-H_{eq}, doublet, $J \simeq$ 13 Hz, 1 H), 236 (4-H, seven-line pattern, $J_{aa} \simeq$ 11 Hz, $J_{ac} \simeq$ 5.5 Hz, 1 H), 178 (6-H_{ax}, triplet of doublets, J_{gem} = 13 Hz, J_{aa} = 3 Hz, 1 H), 72 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.25; H, 7.83; N, 6.65.

Ketone **16** was also obtained when **14** was oxidized with chromic acid[14] in acetone. Recrystallization from acetone–Skellysolve B gave colorless crystals, mp 116–119°, $[\alpha]_D$ −19° (*c* 0.651, $CHCl_3$); the infrared spectrum in Nujol is identical with the spectrum of ketone **16** obtained above.

(2*S*)-1-Benzoyl-2-methyl-3-piperidone (15).—Oxidation of **13**

(13) Melting points were determined on a Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60A spectrometer, using tetramethylsilane as an internal standard. Trichloroacetylurethan derivatives for determination of nmr spectra were prepared by the addition of a slight excess of trichloroacetylisocyanate to the deuteriochloroform solution of the alcohol in the nmr sample tube.

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(0.352 g, 1.60 mmoles) with chromic acid in acetone gave 0.214 g (0.986 mmole, 62%) of crystalline ketone, mp 102–104°. Recrystallization from acetone–Skellysolve B gave colorless plates of **15**: mp 103–105°; $[\alpha]_D$ +74° (*c* 0.657, $CHCl_3$); $\nu_{C=O}$ 1715, 1620, $\nu_{C=C}$ 1600, 1575, 1495, ν_{Ph} 795, 730, 725 cm^{-1} in Nujol; nmr (in Hz, $CDCl_3$) 290 (2-H, quartet, J_{CH_3} = 7 Hz, 1 H), 248 (6-H_{eq}, doublet of triplets, J_{gem} = 14 Hz, $J_?$ = 4 Hz, 1 H), 197 (6-H_{ax}, five-line pattern, J_{gem} = 14 Hz, J_{aa} = 7 Hz, J_{ae} = 7 Hz, 1 H), 155 (4-H, triplet J = 7 Hz, 1 H), 154 (4-H, triplet, J = 6 Hz, 1 H), 121 (5-H, quintuplet, $J \simeq 6$ Hz, 2 H), 84 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.99; H, 7.09; N, 6.25.

Oxygenation of (2*S*)-1-Benzoyl-2-methylpiperidine.—The methylene chloride extract from the oxygenation of 2*S*-1-benzoyl-2-methylpiperidine (2.0 g, 0.00985 mole) was chromatographed on Florisil. A total of 0.778 g (0.00355 mole, 36%) of colorless crystals, mp 125–127, was obtained from crystallization from acetone–Skellysolve B. Two recrystalizations from acetone–Skellysolve B gave colorless crystals of **(2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol**, mp 129–131°, $[\alpha]_D$ + 37° (*c* 0.608, chloroform), infrared spectrum in Nujol identical with the spectrum of **13** above.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.32; H, 7.67; N, 6.27.

Oxygenation of (±)-1-benzoyl-2-ethylpiperidine (19) (25.0 g, 0.115 mole) gave a crude weight of 17.0 g of oxygenated products. **(+)-1-Benzoyl-2-ethyl-3-piperidinol (20)** was obtained as an oil, which crystallized after long standing (8 months). Colorless crystals (5.399 g, 0.0232 mole, 20%), mp 109–111° were obtained. Two recrystallizations gave an analytical sample of **20**: mp 111–113°; $[\alpha]_D$ +51° (*c* 0.564, chloroform); ν_{OH} 3390, 3320, $\nu_{C=O,C=C}$ 1625 s, 1610 s, 1600, 1575, 1495 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 261 (2-H, broad singlet, 1 H), 247–210 (6-H_{eq}, 3-H, OH, 3 H), 167 (6-H_{ax}, six-line pattern, J_{gem} = 13 Hz, 1 H), 51 (CH_3, triplet, J = 7 Hz, 3 H); trichloroacetylurethan derivative (**24**) of **20** nmr (in Hz, 60°, $CDCl_3$) 299 (3-H, six-line pattern with ~5.5-Hz peak separation, 1 H), 276 (2-H, broad singlet, 1 H), 241 (6-H_{eq}, doublet, J_{gem} = 13 Hz, 1 H), 173 (6-H_{ax} six-line pattern, J_{gem} = 13 Hz, 1 H), 53 (CH_3, triplet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.25; H, 8.43; N, 6.06.

Three crops of crystalline **1-benzoyl-2-ethyl-4-piperidinol (21)**, 2.049 g (8.79 mmoles, 8%), mp 104–106°, were obtained. Two recrystallizations of the first crop gave an analytical sample of **23**: mp 107–109°, $[\alpha]_D$ 0°; ν_{OH} 3330, $\nu_{C=O,C=C}$ 1605 s, 1600 s, 1575, 1520, 1495, ν_{Ph} 790, 730, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 234 (4-H, seven-line pattern, 1 H), 175 (6-H_{ax}, broad triplet, $J_{gem,aa}$ = 13 Hz, 1 H), 50 (CH_3, triplet, J = 7 Hz 3 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.06; H, 8.39; N, 6.03.

The third crop of **21** had $[\alpha]_D$ −22° (chloroform).

Oxidation of 20 with Jones reagent gave (+)-1-benzoyl-2-ethyl-3-piperidone (**22**) as colorless crystals, mp 61–63°, following three recrystallizations from acetone–Skellysolve B: $[\alpha]_D$ +50° (*c* 0.637, chloroform); $\nu_{C=O}$ 1720, 1615, $\nu_{C=C}$ 1600, 1575, 1495, ν_{Ph} 795, 725, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 284 (2-H, broad, 1 H), 245 (6-H_{eq}, broad, 1 H), 197 (6-H_{ax}, five-line pattern, J_{gem} = 14 Hz, J_{ae} = 7 Hz, J_{aa} = 7 Hz, 1 H), 153 (4-H, triplet, J = Hz, 1 H), 152 (4-H, triplet, J = 6 Hz, 1 H), 118 (5-H, quintuplet, $J \simeq 7$ Hz, 2 H), 54 (CH_3, triplet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.33; N, 5.91.

Oxidation of 21 with Jones reagent gave ketone **23** as a viscous oil: nmr (in Hz, 37°, $CDCl_3$) 274 (2-H, broad, 1 H), 264 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 210–130 (6-H_{ax}, 3- and 5-H, multiple line, 5 H), 95 (ethyl CH_2, quintuplet, J = 7 Hz, 2 H), 54 (CH_3, triplet, J = 7 Hz, 3 H).

Oxygenation of (±)-1-benzoyl-2-*n*-propylpiperidine (25) (25.0 g, 0.108 mole) gave fractions as shown in Table II when the Florisil column was eluted with 20% acetone–Skellysolve B. Crystals in fraction 8 were washed with ether–Skellysolve B and collected by filtration, 0.524 g, mp 115–127°. Three recrystallizations from acetone–Skellysolve B gave **1-benzoyl-2-*n*-(2-hydroxy)propylpiperidine (30)** as colorless crystals: mp 128–131°; $[\alpha]_D$ 0° (chloroform); ν_{OH} 3460 w, 3400, 3300 w, $\nu_{C=O,C=C}$ 1625, 1605, 1590, 1580, 1525, 1495, ν_{Ph} 785, 745, 715 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 74 Hz (CH_3, doublet, J = 6.5 Hz, 3 H).

TABLE II

Fraction no.	Crude wt, g
7	1.12
8	3.98
9	7.02
10	4.99
11	3.10
12	2.18
13	1.57
14	0.60

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.64; H, 8.71; N, 5.42.

Fraction 9 was rechromatographed on a column of silica gel (500 g, 4.8 × 50 cm) packed as a slurry in benzene. Elution with 1% (v/v) methanol in benzene (500 ml) fractions gave pure (as detected by tlc on silica gel with 20% methanol–benzene development and Dragendorff spray) **(+)-1-benzoyl-2-*n*-propyl-3-piperidinol (26)** as a viscous oil (3.68 g) in fractions 21–27, $[\alpha]_D$ +51° (*c* 0.827, chloroform).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.15; H, 8.67; N, 5.82.

Crystals in fractions 11–14 of the Florisil column were washed with ether–Skellysolve and collected, 2.18 g, mp 110–118°. Three recrystallizations from acetone–Skellysolve B gave **1-benzoyl-2-*n*-propyl-4-piperidinol (27)** as colorless crystals: mp 122–123°; $[\alpha]_D$ −0.7° (chloroform); ν_{OH} 3360, $\nu_{C=O}$ 1600, $\nu_{C=C}$ 1575, 1525, 1500, ν_{Ph} 795, 735, 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 237 (4-H, six-line pattern, 1 H).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.09; H, 8.47; N, 5.59.

Oxidation of 30 with Jones reagent gave ketone **31**: nmr (in Hz, 37°, $CDCl_3$) 167 (CH_2CO, doublet, J = 7 Hz, 2 H), 131 (CH_3, singlet, 3 H).

Oxidation of 27 with Jones reagent gave ketone **29**: nmr (in Hz, 37°, $CDCl_3$) 287 (2-H, broad, 1 H), (6-H_{eq}, doublet, J = 13 Hz, 1 H), 198 (6-H_{ax}, multiple lines, 1 H), 175–130 (3- and 5-, multiple line, 4 H).

Oxygenation of 1-benzoyl-*cis*-2,6-dimethylpiperidine (32) (25.0 g, 0.115 mole) gave a total of 13.159 g (0.0565 mole, 49%) of crystalline **(−)-1-benzoyl-*cis*-2,6-dimethyl-3-piperidinol (33)**, mp 152–158°. Paper chromatography using the Bush B-3 system, tlc on silica gel with 20% (v/v) acetone in chloroform development, and vpc on 5% G.E. S. E. 52 on Gas Chrom Z and on 4% XE-60 on Haloport F columns all indicated only a single component in this product. Repeated recrystallizations from acetone–Skellysolve B gave an analytical sample of **33**: mp 147–157°; $[\alpha]_D$ −5 (*c* 0.913, chloroform); ν_{OH} 3360, $\nu_{C=O}$ 1630, $\nu_{C=C}$ 1610, 1595, 1515, 1495, V_{Ph} 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 274 (2- and 6-H, broad singlet, 2 H), 221 (3-H, four-line pattern having peak separation of 6 Hz, 1 H), 74 and 70 (CH_3, two doublets, J = 7 Hz, 6 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.86; H, 8.31; N, 6.33.

A second product, **34**, was obtained as 0.207 g (0.831 mmole, 0.7%) of colorless crystals, mp 263–265°, following two recrystallizations; $[\alpha]_D$ +2° (*c* 0.547, 95% ethanol); ν_{OH} 3400, 3240, $\nu_{C=O,C=C}$ 1615, 1585, 1530, 1490, ν_{Ph} 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.16; H, 7.65; N, 5.67.

Registry No.—**5**, 19980-00-8; **6**, 19980-01-9; **8**, 19980-02-0; **9**, 19980-03-1; **13**, 19980-04-2; **14**, 19980-05-3; **15**, 19980-06-4; **16**, 19980-07-5; **20**, 19980-08-6; **21**, 19980-09-7; **22**, 19980-10-0; **26**, 19980-83-1; **27**, 19990-84-2; **30**, 19990-85-3; **33**, 19990-86-4.

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