Oxoammonium Salts. 5.[1] A New Synthesis of Hindered Piperidines Leading to Unsymmetrical TEMPO-Type Nitroxides. Synthesis and Enantioselective Oxidations with Chiral Nitroxides and Chiral Oxoammonium Salts

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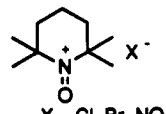
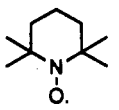
A new synthesis of unsymmetrical 2,2,6,6-tetraalkyl-4-piperidones from acetonin (2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine) and several ketones is described. When the ketone was a naturally occurring optically active ketone, the piperidones were optically active. The piperidones were converted to unsymmetrical TEMPO-type nitroxides and chiral nitroxides. The optically active nitroxides were used as catalysts for oxidations or converted to chiral oxoammonium salts. The structures of the chiral compounds were determined by 2D ^1H and ^{13}C NMR, and the cyclic voltammetric properties of the various nitroxides were measured. Several other pyrrolidine oxoammonium salts were prepared, and both types were used as oxidizing agents. Preliminary results of chiral oxidations are presented.

For several years, we have been interested in the use of oxoammonium salts such as **1**, as oxidants in organic chemistry.[1] Since these salts are almost completely organic in structure, it should be possible to construct oxidants with any desired steric or oxidation potential properties. The oxoammonium salts are normally derived from nitroxides, such as **2**, by a one-electron oxidation. In this



1 X = Cl, Br, NO_3, ClO_4, BF_4, etc.[1a]



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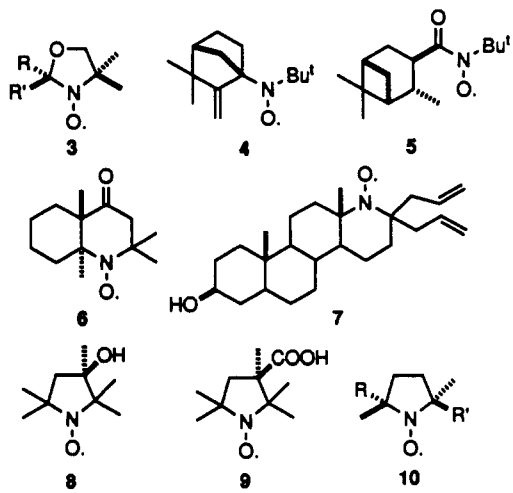
paper, we describe a new route to unsymmetrical piperidones and their conversion to unsymmetrical nitroxides. These nitroxides can be used in catalytic reactions or to prepare optically active oxoammonium salts.

Nitroxides of many types have been prepared for various probe experiments in which the unique radical character of the nitroxide is used.[2] We have found that the TEMPO-type radicals, that is, the materials containing a 2,2,6,6-tetraalkylpiperidine ring (**1** and **2**), are the most useful for making oxoammonium salts, although we have also investigated one pyrrolidine compound, **9**. A number of optically active nitroxides are known. The most common ones are the so-called DOXYL compounds such as **3**,[2] which can be derived from optically active ketones. However, these materials decompose on oxidation and cannot be converted to oxoammonium salts.[3] Several chiral nitroxides or groups of nitroxides have been prepared that would



3 **4** **5** **6** **7** **8** **9** **10**

R, R' = alkyl

be useful for conversion to oxoammonium salts, namely compounds **4**,[4] **5**,[5] **6**,[6] **7**,[7] **8**,[8] **9**,[9] and **10**.[10] However, all are difficult to prepare, and only one, **9**, has been converted to an oxoammonium salt (see Experimental Section).

The reaction of acetonin (2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine), **11**, with acetone to form triacetonamine (2,2,6,6-tetramethyl-4-oxopiperidine, **12**,[2b] has been the subject of many patents and may be a major industrial method for the synthesis of this compound (eq 1). The sterically hindered compound **12** can be easily oxidized to a nitroxide and is generally considered to be the starting material for many of the TEMPO-derived

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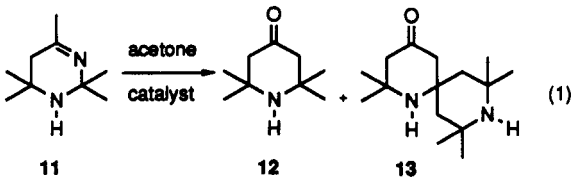
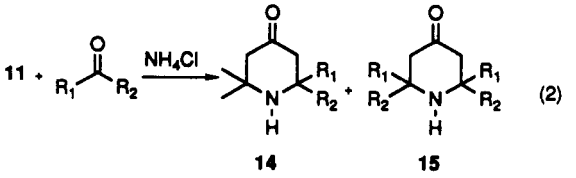


(1)

nitroxides. No attempts appear to have been made to substitute other ketones for acetone in the reaction. However, formation of a byproduct, **13**, isolated in 0.5% yield,[11] might indicate that another ketone may be inserted, in this case, another molecule of the piperidone **12**.

We have used this reaction to introduce one molecule of a ketone to give compounds such as **14** or even to introduce two molecules of ketone, as in **15** (eq 2).



(2)

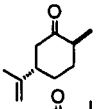
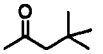
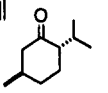
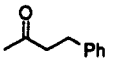
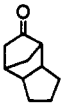
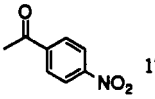
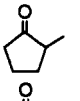
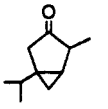
Specifically, cyclohexanone was used to prepare **14** and **15**, R_1 and R_2 = $-(CH_2)_5-$ in a combined yield of about 60%. The relative amounts of **14** and **15** depended on the ratio of cyclohexanone and **11** and are given in the Experimental Section. A number of other ketones were used in preliminary experiments with product determination by gas chromatography–mass spectrometry (GC/MS). These data are given in Table I, but may be misleading, since products were successfully isolated only from entries 6, 9, 11,[12] and 12.[12] The isolated yield of **17a–d** (entry 9) was 65%, and the isolated yields of product-type **14** for entries 11 and 12 were 42 and 45% respectively.[12] No products could be isolated from camphor, entry 13, despite many attempts, nor could products be isolated from entry 5. No attempts were made to isolate the other products. The derivatives of cyclohexanone, **14** and **15**, are known compounds, prepared in a multistep synthesis.[13a] In all cases, the major additional product was the acetone-derived material, **12**. Although the yields are not high, the starting material, acetonin, is easily made from acetone and ammonia.[13b]

The distribution of the several product yields (GC/MS) depends on the steric hindrance around the carbonyl of the ketones, with the best yields (of **14**) for cyclic ketones. Several catalysts were tried, namely methylammonium chloride, acetic acid, *p*-toluenesulfonic acid, and ethanol, but anhydrous, powdered ammonium chloride gave the best results.

A mechanism has been proposed for the reaction of **11** with acetone,[11] which is essentially the dismantling of the pyrimidine ring and its reassembly as a piperidine. We suggest the more concerted mechanism shown in Scheme I. For the addition of the second molecule of ketone (to form **15**), we can think of no logical and simple mechanism.

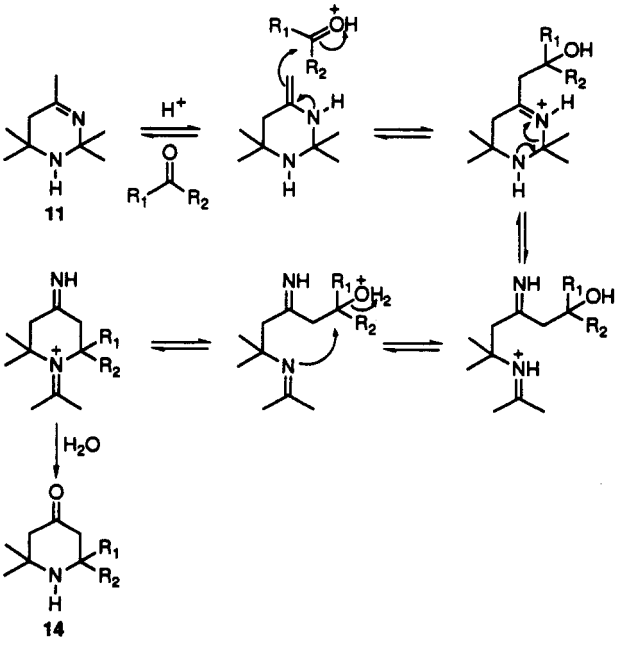
Preparation of Chiral Piperidones. Optically active piperidones were prepared by reaction of acetonin, **11**, with commercial, natural dihydrocarvone, **16** (entry 9 in Table I), in the presence of ammonium chloride and in excess ketone as a solvent. The product was a mixture of isomers having the general structure **17**, 4-oxo-2,2,7-trimethyl-10-isopropenyl-1-azaspiro[5.5]undecane (eq 3). The stereochemistry at position 10 of all products was (*R*) due to the stereochemistry of the dihydrocarvone. The stereochemistry at position 7 was variable since it is not pure in commercial dihydrocarvone and would be prone

Table I. Reaction of Acetonin (11) and Various Ketones[a]

entry	ketone	12 (%)	14 (%)	15 (%)[b]	entry	ketone	12 (%)	14 (%)	15 (%)[b]
1		56	44	0	9		18	82	0
2		54	46	0	10		100	0	0
3		63	27	0	11		28	72	0
4		22	52	26	12		34	66	0
5		17	78	5	13		84	16	0
6		4	37	59	14		14	62	14
7		25	63	12	15		21	46	33
8		18	82	0	16		90	10	0

[a] All reactions were carried out in a similar manner to that described in the Experimental Section with an acetonin (**11**), ketone, and NH_4Cl ratio of 1:5:1. [b] Analyses were carried out by GC-MS and the results represent the GC area percentage.

Scheme I



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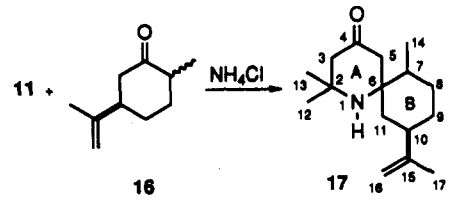


(3)

to isomerization in the conditions of the reaction. Further, a new chiral center at position 6 is formed in the reaction. Although the GC/MS yield was about 65%, the actual isolated yields of the four pure isomers totaled only about 34%, due to the extensive column chromatography involved in the separations. The ratio of the four isomers, **17a–d**, was 49:26:14:11 (based on increasing polarity according to chromatography).

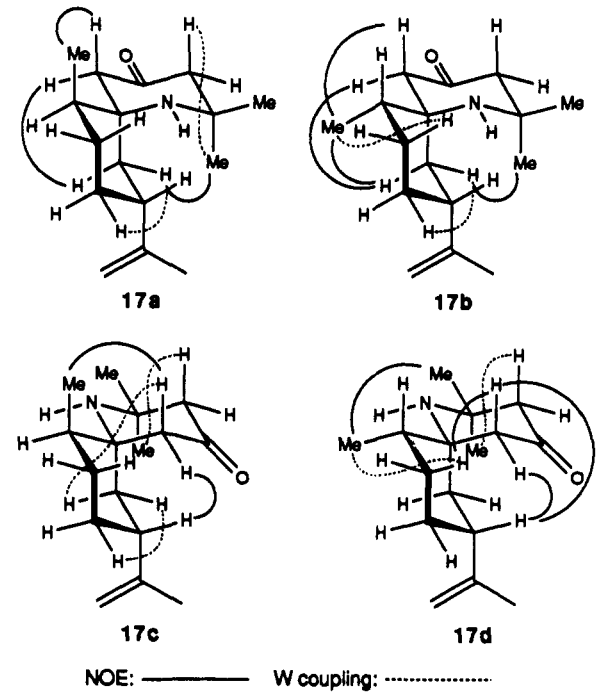
The structures of compounds **17a–d** are shown in Scheme II and were established by two-dimensional nuclear magnetic resonances (2D NMR) spectroscopy. Proton and ^{13}C chemical shifts for the four isomers are given in Tables II and III. The proton chemical shift assignments are based on those of standard compounds and coupling constants, but mainly on 2D COSY spectra, and are tabulated in Table II. The actual structure assignments are based upon the so-called "W coupling"[14] and nuclear Overhauser enhancement (NOE) effects. These effects are illustrated in Scheme II as solid lines (NOE as measured by NOESY) and dotted lines (W coupling as measured by COSY). Other important relationships, shown in Table II establish the structures of the four isomers beyond a reasonable doubt. The reasoning is as follows.

The four isomers of **17** can be divided into two groups, according to the NOE effect between the protons on carbon 5 and the protons on the B ring. The first two isomers, **17a** and **17b** show an NOE effect between H5 and H11, resulting from an (*R*) configuration at carbon 6. The second two isomers, **17c** and **17d**, show an NOE effect between H5 and H8-axial and H10-axial, resulting from an (*S*) configuration at carbon 6.

Isomers **17a** and **17b** can be distinguished by a W coupling between H14 and H8-axial. Since only an axial methyl group can show such a coupling, and **17b** has such a coupling, the structures must be as drawn. Using the same approach, **17c** and **17d** can be distinguished, since only **17d** has such a W coupling. Many other NOE effects and couplings, shown in the structures and tables, support the structures as drawn.

The COSY and NOESY experiments also provided useful information about the conformations of **17a–d**. The W couplings between H3-axial and H12, between H8-axial and H14, and between H9-equatorial and H11-equatorial, suggest that both the A ring and the B ring are in chair conformations, as shown in Scheme II. When the methyl group and the isopropenyl groups on the B ring are *trans* to one another (**17a** and **17c**), both are equatorial. In this case the molecules are very rigid, and the A ring must adopt such a conformation that the interactions between methyl-13 and methyl-14 are minimum. When the methyl and the isopropenyl groups on the B ring are *cis* to one another, however, the isopropenyl group must occupy the

Scheme II



equatorial position and force the methyl to be axial. In these cases, **17b** and **17d**, ring A can be present in the alternate chair conformation. This is only apparent in **17d**, where there is a clear NOE effect between methyl-13 and methyl-14.

We are mainly interested in the 4-aminopiperidine nitroxides since they can be easily attached to electrodes[15] and since they are easily acetylated to give compounds that are useful in other oxidizing systems.[1b] Thus, the four isomeric piperidone derivatives, after separation, were converted to the 4-aminonitroxides by the reactions shown in Scheme III. Hydrogenation was carried out at atmospheric pressure over a Pt catalyst to give **18a–d** in near quantitative yields. Oxidation with *m*-chloroperbenzoic acid[16] gave the nitroxides **19a–d**, which were converted by reductive amination[17] to **20a–d**. Formation of the 4-amino group introduces another chiral center, and its configuration is unknown. However, compounds **20a–c** gave only one peak in GC/MS. Compound **20d** gave two. NMR spectra could not be determined because of the paramagnetism of the oxygen radical. Compounds **20a–c** are probably pure stereoisomers, although the stereochemistry at carbon 4 is not known. The chiral amines have been attached to electrode surfaces and are under further study.[15] Amines **20a–d** were acetylated to amides, **21a–d** for use as catalysts and for the preparation of oxoammonium salts.

Chiral and Achiral Pyrrolidine Nitroxides and Oxoammonium Salts. Nitroxides **22–24** and **9** are known compounds and were prepared by known methods.[18]

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Table II. ^{1}H NMR Data for Compounds 17a–17d[a,b]

proton	17a	17b	17c	17d
$H3_{ax}$	2.21 (1H, d, 14.0)	2.26 (1H, d,14.6)	2.26 (1H, d, 15.7)	2.25 (1H, d, 13.0)
$H3_{eq}$	2.29 (1H, dd, 14.0, 1.4)	2.27 (1H, d, 14,6)	2.27 (1H, d, 15.7)	2.24 (1H, d, 13.0)
$H5_{ax}$	2.58 (1H, d, 13.8)	2.20 (1H, s)	2.31 (1H, dd, 11.9, 2.0)	2.63 (1H, dd, 13.5, 0.9)
$H5_{eq}$	1.98 (1H, dd, 13.8, 1.4)	2.20 (1H, s)	2.32 (1H, d, 11.9)	2.29 (1H, d, 13.5)
H7	1.32 (1H, m)	1.65 (1H, m)	1.33 (1H, m)	1.83 (1H, m)
$H8_{ax}$	1.49 (1H, m)	2.14 (1H, m)	1.14 (1H, m)	1.68 (1H, m)
$H8_{eq}$	1.48 (1H,m)	1.36 (1H, m)	1.58 (1H, m)	1.48 (1H, m)
$H9_{ax}$	1.24 (1H, m)	1.36 (1H, m)	1.14 (1H, m)	1.45 (1H, m)
$H9_{eq}$	1.68 (1H, m)	1.50 (1H, m)	1.68 (1H, m)	1.34 (1H, m)
H10	2.31 (1H, m)	2.41 (1H, m)	1.96 (1H, m)	2.00 (1H, dddd, 13.5, 13.5, 3.8, 3.8)
$H11_{ax}$	1.03 (1H, dd, 13.5, 12.4)	1.28 (1H, dd, 11.0, 11.0)	1.14 (1H, ddd, 12.7, 12.7, 2.0)	1.47 (1H, dd, 13.5, 13.5)
$H11_{eq}$	1.95 (1H, ddd, 13.5, 2.1, 2.1)	1.64 (1H, m)	2.03 (1H, ddd, 12.7, 2.8, 2.8)	1.39 (1H, m)
$H12_{ax}$	1.20 (3H, s)	1.20 (3H, s)	1.20 (3H, s)	1.18 (3H, s)
$H13_{eq}$	1.27 (3H, s)	1.28 (3H, s)	1.20 (3H, s)	1.20 (3H, s)
H14	0.92 (3H, d, 6.5)	0.94 (3H, d, 7.0)	0.92 (3H, d, 6.6)	0.99 (3H, d, 7.0)
H16(Z)	4.65 (1H, s)	4.65 (1H, s)	4.63 (1H, s)	4.64 (1H, s)
H16(E)	4.65 (1H, s)	4.65 (1H, s)	4.63 (1H, s)	4.64 (1H, s)
H17	1.68 (3H, s)	1.68 (3H, s)	1.65 (3H, s)	1.66 (3H, s)

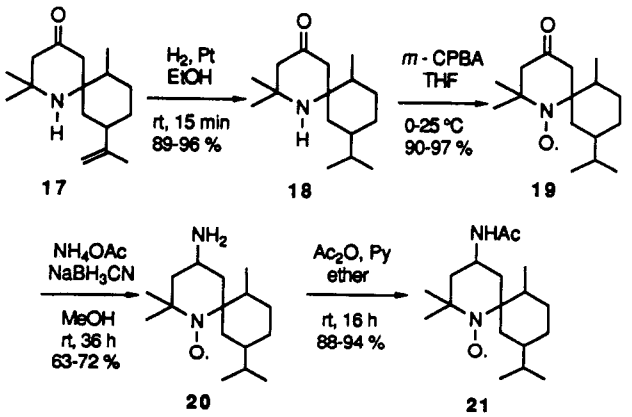
[a] Chemical shifts (δ) in ppm at 270 MHz with TMS as internal standard and coupling constants in hertz. [b] Solid line for NOEs and dotted line for W couplings.

Table III. ^{13}C NMR Data for Compounds 17a–d[a]

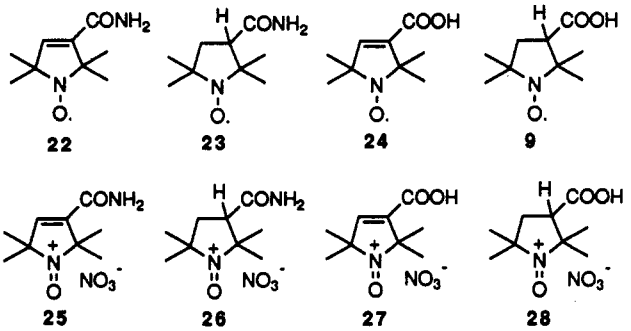
carbon	17a	17b	17c	17d
2	53.8	55.2	52.9	54.7
3	54.2	54.7	53.5	54.7
4	211.3	211.3	211.5	211.1
5	51.0	52.9	47.2	50.1
6	58.8	60.6	59.2	60.0
7	44.2	41.0	42.2	40.9
8	34.4	34.3	34.3	33.5
9	31.6	25.1	31.5	24.6
10	41.8	40.1	41.9	41.0
11	40.0	36.4	41.5	36.8
12	30.2	28.5	31.2	29.0
13	30.2	30.1	30.8	30.8
14	15.3	14.8	15.7	14.7
15	149.8	150.1	149.4	149.5
16	108.4	108.4	108.7	108.7
17	20.8	20.9	20.8	20.7

[a] Chemical shifts in ppm downfield from TMS using $CDCl_3$ as solvent.

Scheme III



Compound **9** has been resolved.[19] However, almost nothing is known about pyrrolidine oxoammonium salts. Only two such compounds have been prepared,[20] and in only one case was an alcohol (ethanol) oxidized by an oxoammonium salt of this type.[20a] In related work, however, Moutet[21] and co-workers attached pyrrolidine radicals to electrode surfaces and used the catalytic surfaces for alcohol oxidation.



Most of the known oxoammonium salts of the pyrrolidine series are halide salts. However, we found halides to be quite hygroscopic and hard to work with. The pyrrolidine nitroxides also failed to give tetrafluoroborates or perchlorates by the disproportionation reaction.[22] Using the procedure of Spencer,[3] we treated the nitroxides with nitrogen dioxide in nitrogen to obtain the oxoammonium nitrates in good yields. The materials were not hygroscopic and seemed quite stable. They have structures **25–28**. The oxoammonium salts had all of the properties expected and were used for the oxidation of several alcohols.[12] However, only one example, the oxidation of piperonyl alcohol to piperonal, is given in the Experimental Section. The enantiomers of **28** were prepared from resolved **9** and probably constitute the first examples of optically active oxoammonium salts.

Asymmetric Oxidations. The cyclic voltammetry of each of the chiral nitroxides **21a–d** was studied to determine whether they were stable as oxoammonium salts.[23] Normally, TEMPO gives a reversible wave showing that the oxidation product, the oxoammonium salt, is stable enough to be reduced back to nitroxide.

(19) Flohr, K.; Paton, R. M.; Kaiser, E. T. *J. Am. Chem. Soc.* **1975**, *97*, 1209.

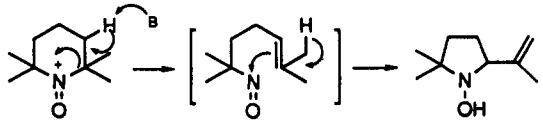
(20) (a) Golubev, V. A.; Voronina, G. N.; Rozantsev, É. G. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* **1970**, *19*, 2449. (b) Golubev, V. A.; Voronina, G. N.; Rozantsev, É. G. *Ibid.* **1972**, *21*, 146.

(21) Deronzier, A.; Limosin, D.; Moutet, J.-C. *Electrochim. Acta* **1987**, *32*, 1643.

(22) Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* **1990**, *30*, 1131.

(23) Reference 1a and Shchukin, G. I.; Ryabinin, V. A.; Grigor'ev, I. J.; Volodarski, L. B. *J. Gen. Chem. U.S.S.R* **1986**, *56*, 753.

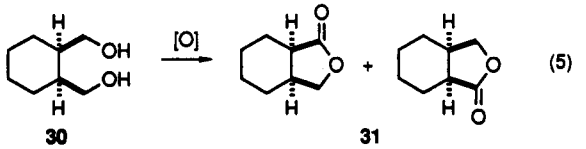
Of the various chiral 4-acetamido nitroxides, only two, **21b** and **21c**, gave reversible waves. The decomposition of the other nitroxide-derived oxoammonium salts is probably similar to the Hoffmann-like elimination shown in eq 4. This was first described by Moad and co-workers



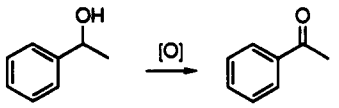
1 29 (4)

for the decomposition of the oxoammonium chloride derived from TEMPO, **1**, $X^- = Cl^-$.[24] In Moad's case, the olefin recondenses to form the hydroxy amine **29**. In the case of compounds **21a** and **21d**, the tertiary proton on C7 is *anti*-periplanar to the NO bond and would be in a favored position for β-elimination. This is not true in structures **21b** and **21c**. The relief of steric strain may also play a role.

Two reactions were investigated using the chiral reagents **21a–d**. The first was the asymmetric oxidation of *cis*-1,2-cyclohexanedimethanol, **30**, to its chiral lactones, **31**, as explored by Jones with horse liver alcohol dehydrogenase (eq 5).[25] The second was the kinetic resolution of



30 31 (5)



32 33 (6)

racemic 1-phenylethanol, **32**, by enantioselective oxidation to acetophenone, **33** (eq 6). In the latter case, a portion of the starting alcohol was oxidized, and the remaining alcohol was analyzed for optical activity.

The oxidation of *cis*-1,2-cyclohexanedimethanol was carried out using *m*-chloroperbenzoic acid as a secondary oxidant and the chiral nitroxides as catalysts. The nitroxide–peracid system on achiral systems has been explored by several groups.[26] The enantioselectivity was determined by optical rotation. All isomers of **21** gave some enantioselectivity, even those that decomposed on conversion to oxoammonium salts, presumably due to the fact that decomposition is slower than the desired oxidation. The degrees of selectivity for **21a–d** were as follows: for **21a**, a product yield of 36% with 38% enantioselectivity; for **21b**, a product yield of 84% with a 14% enantioselectivity; for **21c**, a product yield of 85% with 16% enantioselectivity, and for **21d**, a product yield of 50% with an enantioselectivity of 6%. In the cases of **21b** and **21c**, the starting nitroxides could be isolated. For **21a**, which gave the best selectivity, the nitroxide was destroyed.

The kinetic resolution of 1-phenylethanol was carried out using **21a** and **21b** and the same catalytic conditions described above for the diol **30**, with only half of the peracid oxidant. However, no optical activity was observed in the unreacted alcohol.

When the oxoammonium salt was prepared by disproportionation of nitroxide **21c** in *p*-toluenesulfonic acid,[1b] the remaining alcohol was partially active. Specifically, **21c** yielded a mixture of 30% acetophenone with 70% alcohol. The optical activity of the alcohol corresponds to a selectivity of 20%, indicating that the (*S*) isomer reacts about 5 times faster than the (*R*) isomer. Molecular models using the transition state suggested earlier by us[1b] are in accord with this result. In this experiment, the nitroxide was recovered and reused in an identical experiment with the same result.

Similar experiments with the enantiomers of **28** failed to yield optically active products, undoubtedly because the chiral center is too far removed from the oxidation site.

Experimental Section[27]

Acetonin Monohydrate (2,2,4,4,6-Pentamethyl-2,3,4,5-tetrahydropyrimidine, 11. Modified Procedure.[13b] Anhydrous ammonia was slowly bubbled into a solution of 0.33 g (4.3 mmol) of NH_4SCN in 60 mL (1.03 mol) of acetone for 5 h. During the first hour, the solution was cooled in an ice bath; afterward, it was kept at about 25 °C. The solution was then stirred for 1 h. The colorless solution was extracted with 30 mL of 50% aqueous NaOH. The layers were carefully separated, and the organic phase was filtered through a paper filter to remove the last droplets of aqueous base. The solution was concentrated under vacuum below 35 °C to a thick viscous liquid. When placed in a freezer overnight, the mass solidified. When allowed to warm to room temperature, the mass became semisolid and was placed in a glass dish in a current of air until it completely solidified.[28] The white crystals (43.0 g, 70%) melted at 42–44 °C, lit.[13] 42–43 °C.

Reaction of 11 with Cyclohexanone. Acetonin monohydrate, 11 (6.88 g, 40.0 mmol), cyclohexanone (19.6 g, 200 mmol) and finely divided anhydrous NH_4Cl (2.12 g, 40.0 mmol) were mixed and stirred at 60 °C for 10 h. The acetone byproduct which distilled was collected in a Dean–Stark tube. The solution was cooled, treated with 80 mL of 10% HCl, and washed with three 50-mL portions of ether to remove the cyclohexanone. The aqueous phase was basified with 80 mL of 20% NaOH and extracted with three 50-mL portions of ether. The ether extracts were combined, dried (saturated NaCl and K_2CO_3), and evaporated. The residue was chromatographed on a silica gel column (3 × 20 cm) using ethyl acetate as eluant.

Two compounds were obtained. The less polar compound was **15** (R_1, R_2 = $-(CH_2)_5-$): 3.40 g, 36%; mp 100–101 °C, lit.[12] mp 100–101 °C. The next more polar compound was **14** (R_1, R_2 = $-(CH_2)_5-$): 1.90 g, 24%; mp 47–48 °C, lit.[12] mp 50–51 °C. Finally, about 3% of **12** was obtained.

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(26) (a) Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860. (b) Ganem, B. *Ibid.* **1975**, *40*, 1998.

(27) The general experimental procedures are the same as those given in ref 2b. Column chromatography was carried out on silica gel 32–63, obtained from Universal Scientific Inc., Atlanta, GA, and activated aluminum oxide, Brockmann, I, 150 mesh, from Aldrich Chemical Co. TLC was carried out on E. Merck Kieselgel 60 F_{254} layers. The various oils were purified by molecular distillation for microanalyses, which were carried out by Galbraith Laboratories, Inc., Memphis, TN. Optical rotations were measured on an O. C. Rudolph polarimeter, no. 119, with an accuracy of about 0.005°. All rotations were checked by a second person. Solvents were commercial grades used without purification or drying.
(28) This entire experient should be carried out without delay. If the solutions become yellow, the product will normally not crystallize and should be discarded. The thick viscous liquid obtained after acetone evaporation is probably a mixture of anhydrous acetonin (a liquid), acetonin monohydrate (mp 42–43 °C), and a little acetone. The semisolid mass partially dries in air and probably also hydrates to the crystalline monohydrate. The monohydrate is stable only for about 1 week, even when kept in a freezer.

When the ratio of cyclohexanone to **11** was 1:1, the yields were as follows: **15**, 30%; **14**, 52%; and **12**, 16%.

General Procedure for Compounds in Table I. The general procedure was the same as that used for cyclohexanone. The ether solution was analyzed by GC/MS, and the component percentages were estimated by peak areas.

Reaction of 11 With (+)-Dihydrocarvone. Acetonin monohydrate, **11** (3.44 g, 20.0 mmol), dihydrocarvone, **16** (15.2 g, 100 mmol), and finely divided anhydrous NH_4Cl (1.06 g, 20.0 mmol) were mixed and stirred at temperatures between 90 and 100 °C for 5 h. The acetone byproduct which distilled was collected in a Dean–Stark tube. The solution turned brown. It was cooled, treated with 50 mL of 10% HCl, and washed with three 50-mL portions of ether to remove the dihydrocarvone. The aqueous phase was basified with 50 mL of 20% NaOH and extracted with three 50-mL portions of ether. The ether extracts were combined, dried (saturated NaCl and K_2CO_3), and evaporated. The residual orange oil (by GC/MS) contained about 25% dihydrocarvone, 10% of **12**, and 65% of the isomeric mixture **17a–d**. The mixture was separated on a silica gel column (3 × 30 cm) using petroleum ether–ethyl acetate mixtures as eluant (400 mL of 90:10, 600 mL of 80:20, and then 400 mL of 50:50). About 56 25-mL fractions were collected and monitored by thin-layer chromatography (TLC, petroleum ether–ethyl acetate, 8:2 on silica gel).[29]

The first component (R_f 0.65, fractions 18–28) consisted of 775 mg of **17a** as a light yellow oil: $[\alpha]^{20}_D$ −6.47° (*c* = 10.0, EtOH); IR (neat) 1709 (C=O), 1643 (C=C) cm^{-1}; MS (EI) *m/e* 249 (M^+), 234, 206, 192, 165, 153, 139, 124. Anal. Calcd for $C_{16}H_{27}NO$: C, 77.05; H, 10.91; N, 5.62. Found: C, 77.25; H, 10.67; N, 5.39. Complete NMR data are given Tables II and III and in the supplementary material.

The second component (R_f 0.40, fractions 28–34) consisted of 407 mg of **17b** as slightly yellow crystals: mp 66–68 °C $[\alpha]^{20}_D$ + 6.61° (*c* = 9.3, EtOH); IR (neat) 1705 (C=O), 1643 (C=C) cm^{-1}; MS (EI) *m/e* 249 (M^+), 234, 206, 192, 178, 166, 139, 124. Anal. Found: C, 77.23; H, 10.93; N, 5.69. Complete NMR data are given in Tables II and III and in the supplementary material.

The third component (R_f 0.30, fractions 35–38) consisted of 219 mg of **17c** as a slightly yellow oil: IR (neat) 1707 (C=O), 1644 (C=C) cm^{-1}; HRMS (EI) *m/e*, calcd for $C_{16}H_{27}NO$ 249.2094, found 249.2097. Complete NMR data are given in Tables II and III, and in the supplementary material.

The fourth component (R_f 0.25, fractions 39–47) consisted of 171 mg of **17d** as a slightly yellow oil: IR (neat) 1707 (C=O), 1644 (C=C) cm^{-1}; HRMS (EI) *m/e*, found 249.2097. Complete NMR data are given in Tables II and III and in the supplementary material.

Catalytic Hydrogenation of Compounds 17a–d to 18a–d. Compound **17a** (1.36 g) was dissolved in 100 mL of ethanol, and 100 mg of platinum oxide was added. The hydrogenation was carried out at atmospheric pressure and room temperature. One equivalent of H_2 was absorbed in 15 min. The catalyst was removed by filtration and washed with EtOH. The washing and filtrate were concentrated and chromatographed on silica gel using 90:10 petroleum ether–ethyl acetate as eluant. Compound **18a** (1.32 g, 96%) was obtained as a yellow oil: IR (neat) 1711 (C=O) cm^{-1}; MS (EI) 251 (M^+) *m/e* 251, 236, 208, 194, 166. Anal. Calcd for $C_{16}H_{29}NO$: C, 76.43; H, 11.63; N, 5.57. Found: C, 76.09; H, 11.65; N, 5.77.

In an analogous manner, **17b** gave **18b** as slightly yellow crystals; mp 57–59 °C in 91% yield; IR (neat) 1704 (C=O) cm^{-1}. Anal. Found: C, 76.50, H, 11.79; N, 5.52.

In an analogous manner, **17c** gave **18c** as a light yellow oil in 89% yield: IR (neat) 1712 (C=O) cm^{-1}; HRMS (EI) *m/e*, calcd for $C_{16}H_{29}NO$ 251.2249, found 251.2243.

In an analogous manner, **17d** gave **18d** as a light yellow oil in 92% yield: IR (neat) 1707 (C=O) cm^{-1}; HRMS (EI) *m/e*, found 251.2246.

Oxidation of Compounds 18a–d to Compounds 19a–d. Compound **18a** (1.29 g, 5.14 mmol) was dissolved in 30 mL of tetrahydrofuran (THF) and cooled in ice. A solution of *m*-chloroperbenzoic acid (1.99 g, 9.25 mmol, 80% pure) in 20 mL of THF was added dropwise over 30 min with stirring. The mixture was stirred at room temperature for 4 h. Ether (100 mL) was added, and the solution was extracted with four 50-mL portions of 10% $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a silica gel column with 90:10 petroleum ether–ethyl acetate to give 1.32 g (97%) of **18a** as a red oil: IR (neat) 1723 (C=O) cm^{-1}; MS (EI) *m/e* 266 (M^+), 221, 193, 166, 137, 136, 109. Anal. Calcd for $C_{16}H_{28}NO_2$: C, 72.13; H, 10.59; N, 5.26. Found: C, 72.06; H, 10.40; N, 5.42.

In an analogous manner, **18b** gave **19b** as a red oil in 90% yield: IR (neat) 1723 (C=O) cm^{-1}; MS (EI) *m/e* 266 (M^+). Anal. Found: C, 72.12; H, 10.86; N, 5.63.

In an analogous manner, **18c** gave **19c** as a red oil in 90% yield: IR (neat) 1720 cm^{-1}; HRMS (EI) *m/e*, calcd for $C_{16}H_{28}NO_2$ 266.2120, found 266.2116.

In an analogous manner, **18d** gave **19d** as a red oil in 91% yield: IR (neat) 1722 (C=O) cm^{-1}; HRMS (EI) *m/e*, found 266.2116.

Reductive Amination of Compounds 19a–d to 20a–d. Compound **19a** (994 mg, 3.74 mmol), NH_4OAc (2.88 g, 37.4 mmol), and $NaBH_3CN$ (176 mg, 2.80 mmol) were dissolved in 100 mL of absolute ethanol and stirred at room temperature for 36 h. The solvent was evaporated, and the residue was taken up in 50 mL of H_2O. The solution was acidified to pH 2–4 with 1 M HCl and washed with three 60-mL portions of $CHCl_3$. The aqueous phase was then basified to pH 12 with 10% NaOH and extracted with three 60-mL portions of $CHCl_3$. The extracts were combined, dried (Na_2SO_4), and concentrated. The residue was chromatographed on an alumina column with ethanol as eluant to give 695 mg (70%) of **20a** as a red oil: IR (neat) 3360 (NH), 3287 (NH_2) cm^{-1}, no C=O; MS (EI) *m/e* 267 (M^+), 250, 225, 211, 204, 177, 138. Anal. Calcd for $C_{16}H_{31}N_2O$: C, 71.85; H, 11.68; N, 10.48. Found: C, 71.77; H, 11.51; N, 10.11.

In an analogous manner, **19b** gave **20b** as a red oil in 63% yield: MS (EI) *m/e* 267 (M^+). Anal. Found: 71.41; H, 12.16; N, 11.09.

In an analogous manner, **19c** gave **20c** as a red oil in 72% yield: HRMS (EI) *m/e*, calcd for $C_{16}H_{31}N_2O$ 267.2436, found 267.2426.

In an analogous manner, **19d** gave **20d** as a red oil in 66% yield: HRMS (EI) *m/e*, found 267.2426.

Acetylation of 20a–d to 21a–d. Compound **20a** (95 mg, 0.36 mmol) was dissolved in 10 mL of anhydrous ether, and 0.50 mL of pyridine and 0.50 mL of acetic anhydride were added. The mixture was stirred at room temperature for 16 h and washed successively with 10-mL portions of 5% HCl, water, 5% $NaHCO_3$, and saturated aqueous NaCl. The ether solution was dried (Na_2SO_4) and evaporated to give slightly red crystals, mp 140–142 °C. The crude product was chromatographed on silica gel with ethyl acetate as eluant to give 104 mg (94%) of **21a** as slightly red needles from hexane: mp 140–142 °C; $[\alpha]^{20}_D$ +129.6° (*c* = 0.746, $CHCl_3$); IR (KBr) 3254 (NH), 1639 (C=O) cm^{-1}; MS (EI) *m/e* 309 (M^+) 250, 223, 177, 164, 150. Anal. Calcd for $C_{18}H_{33}N_2O_2$: C, 69.86; H, 10.75; N, 9.05. Found: C, 69.97; H, 10.93; N, 8.98.

In an analogous manner, **20b** was converted to **21b**, a red oil, in 94% yield: $[\alpha]^{20}_D$ +32.4° (*c* = 0.705, $CHCl_3$); IR (KBr) 3283 (NH), 1649 (C=O) cm^{-1}; MS (EI) *m/e* 309 (M^+). Anal. Found: C, 69.63; H, 10.71; N, 8.94.

In an analogous manner, **20c** was converted to slightly red crystals of **21c** in 89% yield: mp 130–132 °C (from hexane) $[\alpha]^{20}_D$ +5.2° (*c* = 0.801, $CHCl_3$); IR (KBr) 3286 (NH), 1643 (C=O) cm^{-1}; MS (EI) *m/e* 309 (M^+). Anal. Found: C, 70.16; H, 10.75; N, 8.92.

In an analogous manner, **20d** was converted to slightly red crystals of **21d** in 88% yield: mp 180–183 °C (from hexane); $[\alpha]^{20}_D$ +38.1° (*c* = 0.724, $CHCl_3$). IR (KBr) 3263 (NH), 1649 (C=O) cm^{-1}; MS (EI) *m/e* 309 (M^+). Anal. Found: C, 69.94; H, 10.97; N, 8.85.

Preparation of the Oxoammonium Salts 25–28. Nitrogen dioxide (1% in nitrogen gas)[30] was passed through a solution of 1.00 g of 3-carbamoyl-2,2,5,5-tetramethyl-3-pyrrolin-1-yloxyl, **22**,[18] dissolved in 140 mL of CH_2Cl_2 until no more precipitate formed. Nitrogen gas was passed through for 5 min to remove the last traces of NO_2. The precipitate was collected by filtration to give 0.84 g (63%) of the oxoammonium salt **25** as orange crystals: mp

(29) When larger amounts were separated, it was neseccary to rechromatograph the fractions containing **17b–d**.

(30) The original authors used pure NO_2.[3] We found it much more convenient to use a commercial mixture of 1% NO_2 in nitrogen.

128–130 °C. Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 44.14; H, 6.15; N, 17.36.

Compound **26** was prepared in an analogous manner and in 85% yield as yellow crystals: mp 138–140 °C. Anal. Calcd for $C_9H_{17}N_3O_5$: C, 43.72; H, 6.93; N, 16.99. Found: C, 43.78; H, 7.21; N, 16.85.

Compound **27** was prepared in an analogous manner and in 86% yield as yellow crystals: mp 111–112 °C. Anal. Calcd for $C_9H_{14}N_2O_6$: C, 43.90; H, 5.73; N, 11.38. Found: C, 44.21; H, 5.82; N, 11.33.

Racemic **28** was prepared in an analogous manner and in 88% yield as yellow crystals: mp 111–112 °C. Anal. Calcd for $C_9H_{16}N_2O_6$: C, 43.55; H, 6.50; N, 11.29. Found: C, 43.70; H, 6.54; N, 11.07.

The (+) isomer of **28** was prepared from (+)-3-carboxyl-2,2,5,5-tetramethylpyrrolidin-1-yloxyl[9] in an analogous manner and in 87% yield as yellow crystals; mp 111–112 °C; $[\alpha]^{23}_D = +105.5°$ (c = 1, CH_3CN). The other properties were identical to those of the racemic compound.

The (−) isomer of **28** was prepared from (−)-3-carboxyl-2,2,5,5-tetramethylpyrrolidin-1-yloxyl[9] in an analogous manner and in 89% yield as yellow crystals: mp 111–112 °C; $[\alpha]^{23}_D = -107.2°$ (c = 1, CH_3CN). The properties were identical to those of the racemic compound.

Oxidation of Piperonyl Alcohol with Oxoammonium Salt 25. Piperonyl alcohol (456 mg, 3.00 mmol) and 732 mg (3.00 mmol) of **25** were dissolved in 40 mL of CH_3CN and stirred at 0 °C for 30 min and at room temperature for 5 h or until the solution no longer gave a positive test with starch–iodide paper. The solution was evaporated to dryness, and the residue was dissolved in 50 mL of CH_2Cl_2, washed with water, 10% $NaHCO_3$ solution and saturated NaCl. The solvent was evaporated to give 422 mg (94%) of piperonal: mp 34–36 °C (lit.[31] mp 35–37 °C). The compound was pure by GC/MS.

The *m*-Chloroperbenzoic Acid Oxidation of *cis*-1,2-Cyclohexanedimethanol, 30, Catalyzed by Nitroxides 21a–d. A solution of *m*-chloroperbenzoic acid (472 mg, 80% peracid, 2.20 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a solution of **30** (144 mg, 1.00 mmol) and **21a** (31 mg, 0.10 mmol) in 5 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 1 h and then at room temperature for 72 h. After 48 h, a white precipitate (*m*-chlorobenzoic acid) formed. This precipitate was removed by filtration, and the filtrate was concentrated and separated on a silica gel column with CH_2Cl_2 as eluant, to give 51 mg (36%) of *cis*-8-oxobicyclo[4.3.0]nonan-7-one, **31**, as a colorless liquid. The observed rotation of a solution of 31.4 mg in 1.00 mL of $CHCl_3$ was +0.594°, corresponding to a specific rotation of $[\alpha]^{25}_D$ = +18.9° and an enantioselectivity of 38.8%. The literature rotation for the pure isomers is 48.8°.[25] The major product formed was the (1*S*,6*R*) isomer of **31**. In the case of nitroxide **21a**, the catalyst was not recoverable.

In identical experiments, isomers **21b**, **21c**, and **21d** gave yields of 84, 85, and 50% and with enantioselectivities of 14.4, 16.1, and 5.9%, respectively. In the cases of **21b** and **21c**, the catalysts could be recovered.

Kinetic Resolution of 1-Phenylethanol Using an Oxoammonium Salt Generated from Nitroxide 21c by Disproportionation.[1b] 1-Phenylethanol (106 mg, 0.87 mmol) was dissolved in 2 mL of CH_2Cl_2 and cooled to 0 °C. Solid *p*-toluenesulfonic acid monohydrate (165 mg, 0.87 mmol)[32] was suspended in the solution. During 5 min, a solution of 185 mg (0.60 mmol) of **21c** in 2 mL of CH_2Cl_2 was added, and the mixture was stirred at room temperature for 5 h, after which the ratio of alcohol–ketone did not change. The mixture was separated on a silica gel column using CH_2Cl_2 as eluant to give 81 mg of 1-phenylethanol. The observed rotation of 51.2 mg of the alcohol in 1 mL of CH_2Cl_2 was +0.537°, corresponding to a specific roation of $[\alpha]^{25}_D = +10.5°$. The enantiomeric excess was 20.0%, based on a literature rotation of +52.5° for (*R*)-(+)-1-phenylethanol.[33] Thus, the less reactive enantiomer of 1-phenylethanol is the (*R*)-(+)-isomer.

The catalyst was recovered in 92% yield during the chromatography, and, when the experiment was repeated with the recovered catalyst, the identical result was obtained.

Acknowledgment. We would like to thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Connecticut Research Foundation for partial support of this research. We would also like to thank Dr. Thomas Leipert of this department for help with the NMR experiments.

Supplementary Material Available: Two-dimensional proton and ^{13}C NMR spectra for compounds **17a–d** and CV data for compounds **21a–d** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(31) Feugeas, P. C. *Bull. Soc. Chim. Fr.* **1964**, 1892.

(32) This generates only enough oxidant for 34% of the alcohol since 2 equiv of nitroxide and acid are required for the oxidation of 1 equiv of alcohol.[1b]

(33) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.