Table II. Free-Radical Diazo Coupling by Ketones, Peroxides,[a] and *p*-Chlorobenzendiazonium Sulfate[b]

$$R_1COR_2 + H_2O_2 + p\text{-}ClArN_2^+ \xrightarrow{M^{n+}} R_1N{=}NAr\text{-}p\text{-}Cl + R_2N{=}NAr\text{-}p\text{-}Cl$$

entry	R_1	R_2	[peroxide],[c] M	ratio peroxide/ diazonium salt	% yield[d] $R_1N{=}NAr$	% yield[d] $R_2N{=}NAr$
8	CH_3	CH_3	*e*	1:1	15	
				2:1	26	
9	C_2H_5	C_2H_5	6.0	1:1	36	
				2:1	60	
10	i-C_3H_7	CH_3	6.1	1:1	56	1.8
				2:1	87	3.0
11	i-C_3H_7	i-C_3H_7	4.0	1:1	50	
12	t-C_4H_7	CH_3	2.3	1:1	67	0.4
				2:1	90	0.7
13[f]	CH_2Ph	CH_3	4.1	1:1	38	0.5

[a] The peroxide solutions were prepared by addition of 36% H_2O_2 to ketone (1:1 molar ratio) and a few drops of 50% H_2SO_4; the organic phase was washed with H_2O and dried on Na_2SO_4. In experiment 12 the peroxide was prepared as previously but at an initial temperature of 50 °C. [b] All the reactions were carried out as follows. The peroxide solution (7.8 mmol) was added in 15 min to a mixture of *p*-chlorobenzendiazonium sulfate (7.8 mmol, 17 mL) and $FeSO_4 \cdot 7H_2O$ (32 mmol) in water (40 mL) and acetic acid (30 mL) at −5 °C. Pentane (3 × 30 mL) extracts after 15 min give the azo derivatives which were isolated and quantitatively analyzed by GLC. [c] Peroxide molarity was determined by iodometric titration. [d] Yields are based on the diazonium salt. [e] The peroxide was prepared by addition of 59% H_2O_2 (0.45 and 0.9 mL, respectively, for the 1:1 and 2:1 experiments) to acetone (7 mL) over Na_2SO_4 (3 g) for 0.5 h. [f] Bibenzyl (12%) was also detected.

liquid was isolated and was an analytically pure sample of 1 (R = cyclohexyl): 0.606 g (70% yield based on reaction 3); bp 90–91 °C (0.5 mmHg); n^{20}_D 1.5134; UV (EtOH) λ_{max} 403 (log ϵ 2.28), 268 (4.19); NMR ($CDCl_3$) δ 3.62 (m, 1 H, CH), 1.2–2.0 (m, 10 H), 7.0–7.4 (A_2B_2 system, 4 H); mass spectrum, *m/e* 222 ($M^{+\cdot}$), 139, *111*, 83, 55.

The results reported in Table I were obtained under the same conditions with the exception of the entries 2 and 5; spectral (UV, NMR, and mass spectra) and analytical data are in good agreement with all the diazene structures of the products obtained by purification of the reaction mixtures as mentioned above.

Reactions of Ketone Peroxides with 4-Chlorobenzenediazonium Salt. A typical experimental procedure was as follows. H_2O_2 (36%, 18. mL, 0.2 mol) was added to 3-methyl-2-butanone (17.2 g, 0.2 mol) under stirring at 20 °C. H_2SO_4 (50%, 0.5 mL) was added, and the temperature increased to 50 °C. The mixture was stirred for 30 min, the organic phase was washed with saturated NaCl solution, and the peroxide was determined by iodometric titration (70% conversion of the ketone to peroxides). The crude peroxide (15.6 mmol) was added under stirring at −5 to 0 °C within 15 min to a mixture of 4-chlorobenzenediazonium sulfate (15.6 mmol, prepared as above) and $FeSO_4 \cdot 7H_2O$ (16 g, 62 mmol) in water (80 mL) and acetic acid (60 mL). After being stirred 15 min, the mixture was extracted with pentane, and the solution was washed with water and concentrated. The residue was purified by column chromatography on silica gel with pentane as the eluent. (4-Chlorophenyl)isopropyldiazene [n^{20}_D 1.5017; UV (EtOH) λ_{max} 402 nm (log ϵ 2.26), 266 (4.10); NMR ($CDCl_3$) δ 3.91 (septet, 1 H, CH), 1.31 (d, 6 H), 7.0–7.4 (A_2B_2 system, 4 H, Ar); mass spectrum, *m/e* 182, 139, *111*, 43] was isolated in 87% yield as the diazonium salt. (4-Chlorophenyl)methyldiazene was also isolated in 1.8% yield.

The results reported in Table II were obtained under the same experimental conditions with the appropriate ketone.

Reaction of Di-*n*-propyl Sulfoxide with Hydrogen Peroxide and 4-Chlorobenzenediazonium Salt. H_2O_2 (36%, 0.002 mol) was dropped at 0 °C under stirring to a mixture of 0.006 mol of di-*n*-propyl sulfoxide (from EGA), 4-chlorobenzenediazonium tetrafluoborate (0.001 mol) and $FeSO_4 \cdot 7H_2O$ (0.002 mol) in 50 mL of water. After stirring 10 min, the mixture was extracted with pentane (5 × 10 mL), the solution was washed with water and concentrated. The residue was purified by column chromatography as above. (4-Chlorophenyl)-*n*-propyldiazene was isolated as the first component in 31% yield based on the diazonium salt: bp 58–59 °C (1mmHg), n^{20}_D 1.5211; UV (EtOH) λ_{max} 4.05 nm (log ϵ (2.11), 261 (4.18); NMR ($CDCl_3$) δ 3.85 (t, 2 H, CH_2N=), 1.2–2.0 (m, 4 H), 0.8 (t, 3 H, CH_3), 7.0–7.4 (A_2B_2 system, 4 H, Ar); mass spectrum, *m/e*: 182 ($M^{+\cdot}$), 181, 165, 139, 111, 76, 43.

Registry No. 1 (R = CH_3), 80227-98-1; 1 (R = C_2H_5), 80227-99-2; 1 (R = cyclohexyl), 80228-00-8; 1 (R = t-C_4H_9), 80228-01-9; 1 (R = CH_2Ph), 80228-02-0; 1 (R = i-C_3H_7), 80228-03-1; 1 (R = n-C_3H_7), 80228-04-2; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; cyclohexyl iodide, 626-62-0; *tert*-butyl iodide, 513-38-2; benzyl iodide, 620-05-3; 2-propanone, 67-64-1; 3-pentanone, 96-22-0; 3-methyl-2-butanone, 563-80-4; 2,4-dimetyl-3-pentanone, 565-80-0; 3,3-dimethyl-2-butanone, 75-97-8; 1-phenyl-2-propanone, 103-79-7; di-*n*-propyl sulfoxide, 4253-91-2; 4-chlorobenzenediazonium tetrafluoborate, 673-41-6; 4-chlorobenzenediazonium sulfate, 53486-30-9.

Resolution of Dextro- and Levomethorphan via Their Quaternary Ammonium Salts. 1. Stereoselectivity of the Quaternization[1]

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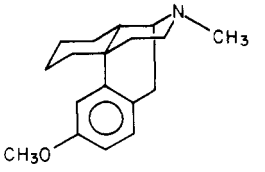
Dextromethorphan (1) and levomethorphan constitute an example of an enantiomorphic pair with drastically different pharmacological actions—the former is a widely used nonprescription antitussive, whereas the latter is a potent narcotic. This difference creates the need to



monitor and control the level of the levo isomer in pharmaceutical products containing 1. No official method of analysis for dextromethorphan is included in the U.S.

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, Mar 1980; Abstract No. ORGN 015.

Pharmacopeia (USP) although the specific rotation of the bulk drug substance and the USP reference standard for dextromethorphan must agree to within 1.0%.

In addition to being an important regulatory problem, the development of a suitable assay for the determination of levomethorphan in the presence of dextromethorphan is also a challenging chemical problem since the methorphans are not amenable to standard approaches such as the synthesis and separation of diastereoisomeric esters and amides. The presence of a tertiary nitrogen atom in a conformationally fixed piperidine ring suggests another possible route: the use of optically pure alkyl halides to convert the methorphans into diastereoisomeric quaternary ammonium salts, followed by the resolution of these salts. The stereochemical course of the reaction is the key to the development of the assay since the piperidine ring can be alkylated by axial and equatorial routes. Complete axial alkylation or complete equatorial alkylation results in the desired diastereoisomers; however, a mixture of axial and equatorial alkylation results in two sets of diastereoisomers, and this complicates the assay.

House and co-workers[2] demonstrated that both axial and equatorial alkylation take place during the quaternization of a series of 4-*tert*-butylpiperidines. The reaction of *N*-methyl-4-*tert*-butylpiperidine with trideuteriomethyl *p*-toluenesulfonate and ethyl *p*-toluenesulfonate yielded two sets of diastereoisomers. For the trideuteriomethyl derivative, the ratio of axial to equatorial substitution was 9:1; the ethyl derivative yielded an axial to equatorial substitution ratio of 4:1. The ratios were determined from the *N*-methyl ^{1}H NMR signal. In the methyl derivative, the equatorial *N*-methyl group exhibits a singlet at δ 3.09; the same group in the axial position is found at δ 2.97. In the ethyl derivative, the *N*-methyl group in the equatorial or axial position is found at δ 2.92 or 2.84, respectively.

The stereochemical course of the quaternization of a number of other piperidines has been reviewed.[3] It was found that, in general, the stereoselectivity of the quaternization of *N*-methylpiperidines varies from slight (axial/equatorial ratio of 2–5:1) to none (1:1). This is not the case, however, for the sterically hindered and strained tropane ring system, which is an excellent model for the methorphans.

A number of papers have reported a high degree of stereoselectivity in the quaternization of a series of substituted tropanes.[3-6] Fodor and co-workers[4] demonstrated that the quaternization of tropane by trideuteriomethyl iodide favors an axial attack by a 4:1 ratio. When 3α-hydroxy-6β,7β-epoxytropane was allowed to react with the same halide, the reaction favored an equatorial attack by a 9:1 ratio. The quaternization of 3β-hydroxytropane with methyl iodide follows an axial stereochemical course in a 5:1 ratio, whereas the quaternization with ethyl iodide results in 100% equatorial addition.[4] A later paper by Fodor et al.[5] postulates that equatorial attack is the preferred and predominant steric course in the quaternization of tropanes. Szendey and Mutschler,[6] on the other hand, reported that the quaternizations of 3β-hydroxytropane with benzyl bromide and *p*-phenylbenzyl bromide follow an axial stereochemical course that is favored by ratios of 49:1 and 24:1, respectively. These latter results may be due to the reaction of the tropane with the benzyl carbonium ion rather than with the benzyl halide.

Table I. Stereoselectivity of the Quaternization of Dextromethorphan by a Series of *n*-Alkyl Iodides

n-alkyl iodide	chemical shift, δ		stereoselectivity, axial/equatorial ratio
	CH_3(axial)	CH_3(equatorial)	
methyl	3.64	3.78	
methyl-d_3	3.68	3.78	1/7
ethyl	3.41	3.44	3/1
ethyl-d_5	3.40	3.44	4/1
propyl	3.45	3.50	3.5/1
butyl	3.42	3.48	3/1

In order to elucidate the stereochemical course of the quaternization of methorphan, dextromethorphan was quaternized by using a series of *n*-alkyl iodides. The results of this study are reported below.

Results and Discussion

The distribution of the axial and equatorial *N*-methyl ^{1}H NMR signals for the various quaternary ammonium salts studied is shown in Table I. The axial and equatorial positions were assigned by using the generally accepted criterion that in epimeric compounds the signals for the axial *N*-methyl groups are at higher field than those for the corresponding equatorial *N*-methyl groups. In the compounds studied, the *N*-methyl peaks appeared as sharp singlets with chemical shifts ranging from δ 3.40 to 3.78. The corresponding methylene peaks appeared as multiplets with chemical shifts ranging from δ 3.80 to 4.60. These assignments were confirmed by a series of decoupling experiments and by ^{13}C NMR studies. In the latter experiments, the ^{13}C NMR spectrum of the ethyl iodide salt of dextromethorphan was obtained, and the positions of the *N*-methyl absorptions were assigned by using "insensitive nuclei enhanced by polarization transfer reversed" (INEPTR)[7] techniques for multiplicity assignment. The axial and equatorial *N*-methyl signals, which appear at 50.2 and 55.0 ppm, respectively, are consistent with the findings of Eliel and Vierhapper,[8] who reported that, in the case of the hydrochloride salt of *N*-methyl-*trans*-decahydroquinoline, the equatorial *N*-methyl signal at 40.35 ppm is upfield from the axial ^{1}H NMR *N*-methyl signal at 32.77 ppm.

The position of the *N*-methyl ^{1}H NMR signals and their sharpness permitted the direct determination of the axial methyl/equatorial methyl product ratio from the peak heights. These ratios were determined by using twice-recrystallized samples of the salts. For determination of whether recrystallization affects the product ratio, a sample of the ethyl iodide salt was studied before recrystallization and after each of two successive recrystallizations; the axial methyl/equatorial methyl ratios were 2.6:1, 3:1, and 2.9:1, respectively. In addition, another sample of dextromethorphan was quaternized with ethyl iodide; after completion of the reaction, the sample was evaporated to dryness under reduced pressure and redissolved in deuteriochloroform, and the product ratio was determined. In this case, the axial methyl/equatorial methyl ratio was 3.1:1, which is consistent with the data from the recrystallizations.

(2) House, H. O.; Tefertiller, B. A.; Pitt, C. G. *J. Org. Chem.* **1966**, *31*, 1073–1079.
(3) McKenna, J. *Top. Stereochem.* **1970**, *5*, 275.
(4) Fodor, G.; Medina, J. D.; Mandava, N. *Chem. Commun.* **1968**, 581–583.
(5) Fodor, G.; Chastain, R. V.; Frehel, D.; Cooper, M. J.; Mandava, N.; Gooden, E. L. *J. Am. Chem. Soc.* **1971**, *93*, 403–413.
(6) Szendey, G. L.; Mutschler, E. *Arch. Pharm. (Weinheim, Ger.)* **1974**, *307*, 647–652.
(7) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760–762.
(8) Eliel, E. L.; Vierhapper, F. W. *J. Am. Chem. Soc.* **1975**, *97*, 2424–2430.

Table II. Kinetic Data and Arrhenius Parameters for the Quaternization of Dextromethorphan by *n*-Alkyl Iodides

n-alkyl iodide	temp, °C	10^3k, L mol^{-1} min^{-1}	E_a, kcal	$H^{\ddagger}$, kcal mol^{-1}	$S^{\ddagger}$, cal mol^{-1} deg^{-1}
methyl iodide	−10	18.1 ± 1.6	11.3	10.7	−57.0[a]
	0	35.4 ± 2.3			
	10	77.0 ± 5.4			
ethyl iodide	38	3.43 ± 0.11	13.2	12.6	−59.2[b]
	50	6.77 ± 0.10			
	60	14.1 ± 0.80			
propyl iodide	50	1.04 ± 0.00	15	14.4	−63.1[b]
	60	2.06 ± 0.16			
	70	4.25 ± 0.27			
butyl iodide	60	1.74 ± 0.13	14.7	14.1	−63.4[b]
	70	2.90 ± 0.20			
	80	6.11 ± 0.16			

[a] Calculated at 0 °C. [b] Calculated at 60 °C.

The quaternization of dextromethorphan by methyl iodide produces a dimethyl salt, and the stereochemical course of this reaction is not discernible. However, the product distribution arising from the quaternization of dextromethorphan by trideuteriomethyl iodide can be measured; the equatorial route of attack was found to predominate over the axial by a ratio of 7:1. It appears that, in the case of the methyl moiety, equatorial attack is the preferred stereochemical course.

The quaternization of dextromethorphan by larger alkyl iodides, i.e., by ethyl, ethyl-d_5, *n*-propyl, and *n*-butyl iodides, proceeds by axial attack (see Table I). While this route of attack predominates, the stereoselectivity of the reaction is low, with the axial/equatorial approach favored by a ratio of only 3–4:1. The size of the alkyl group does not appear to affect the product ratio because each member of the series displays the same general stereoselectivity. The deformation of the piperidine ring resulting from the quaternization by the various alkyl iodides also appears equivalent throughout the series. This conclusion is inferred from the fact that the *N*-methyl signals from the *N*-methyl alkyl salts are all shifted upfield from that of the dimethyl salt by 0.2–0.3 ppm.

The stereochemical course of the reaction is not temperature dependent. Average yields for the axial adduct from a number of quaternizations of dextromethorphan by *n*-propyl iodide at 60 and 70 °C were 76% and 79%, respectively. The diastereoisomers also are not interconvertible by heating. Heating the *n*-propyl quaternary salt at 100 °C in chloroform-*d* for 24 h did not noticeably change the product ratio.

The kinetic data and the calculated Arrhenius parameters for the reaction are presented in Table II. The rate constants were calculated as second-order constants and were determined by using a 10- to 30-fold excess of the alkyl iodide at a variety of temperatures. The enthalpy of activition ($\Delta H^{\ddagger}$) values are consistent with previously reported values for the quaternization of various piperidines.[9] The entropy of activation ($\Delta S^{\ddagger}$) values, however, are double those reported for the quaternization of a series of 4-phenyl- and 4-*tert*-butylpiperidines with methyl iodide.[9] The free-energy differences between the transition states leading to axial and equatorial substitutions were calculated by using the product ratios. At 60 °C, axial attack by the ethyl, *n*-propyl, and *n*-butyl moieties is favored by 0.80, 0.84, and 0.76 kcal, respectively.

Conclusions

The quaternization of dextromethorphan by ethyl and larger alkyl iodides proceeds by a predominantly axial stereochemical course. The stereoselectivity of this reaction, which ranges from 3:1 to 4:1, arises from an energy difference between the transition state that leads to axial substitution and the one that leads to equatorial substitution. This difference, which averages 0.8 kcal, appears to be due to steric effects. These results are consistent with the observed stereoselectivity of a number of *N*-methylpiperidines but differ from those of the equatorial attack postulated for the quaternization of tropane. The source of this difference is not readily discernible from the structure of the two molecules and is currently under further investigation.

Experimental Section

Determination of Product Ratios. The ratios of the equatorial and axial isomers were determined from the comparison of the peak heights of the respective ^{1}H NMR signals. Samples of the quaternary salts were recrystallized twice from methanol–ether and analyzed at 200 MHz with a Varian XL-200 NMR spectrometer. ^{13}C NMR spectra were obtained with the same instrument.

Determination of Kinetic Data. The observed rate constants were determined by following the disappearance at δ 2.4 of the *N*-methyl peak associated with the tertiary nitrogen atom of dextromethorphan. The reactions were carried out in chloroform-*d* with 20 μL of chloroform added as an internal standard. The reactions were followed with an R12B Perkin-Elmer 60-MHz NMR spectrometer equipped with a variable-temperature probe.

The dextromethorphan base was prepared from the hydrobromide salt according to the procedure outlined in the literature.[10] The *n*-alkyl iodides were used as purchased. The quaternization reactions were carried out with a 10- to 30-fold excess of the alkyl iodide which ensured the determination of the second-order rate constant. The molar concentration of dextromethorphan ranged from 0.10 to 0.16, and the molar concentration of the alkyl iodides ranged from 2.0 to 3.2. Each reaction was monitored in a standard 5-mm NMR tube with 0.6 mL of solution.

Rate constants were determined by standard mathematical procedures, and the Arrhenius parameters were calculated in the normal manner.[11]

Acknowledgment. We thank Dr. J. D. Weber of the Food and Drug Administration for his help in the acquisition and intrepretation of the ^{13}C and ^{1}H NMR spectra.

Registry No. 1 methyl iodide, 80629-94-3; 1 trideuteriomethyl iodide (isomer 1), 80584-69-6; 1 trideuteriomethyl iodide (isomer 2), 80584-70-9; 1 ethyl iodide (isomer 1), 80584-71-0; 1 ethyl iodide (isomer 2), 80584-72-1; 1 ethyl-d_5 iodide (isomer 1), 80584-73-2; 1 ethyl-d_5 iodide (isomer 2), 80584-74-3; 1 propyl iodide (isomer 1), 80584-75-4; 1 propyl iodide (isomer 2), 80584-76-5; 1 butyl iodide (isomer 1), 80584-77-6; 1 butyl iodide (isomer 2), 80584-78-7; 1, 125-71-3; levomethorphan, 125-70-2.

(9) Imbach, J. L.; Katritzky, A. R.; Kolinski, R. A. *J. Chem. Soc. B* **1966**, 557–562.

(10) "National Formulary XIV"; Mack Publishing Co.: Easton, PA, 1975; p 193.

(11) Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism"; Wiley: New York, 1961; p 16.