retention time, 20–28 min). The nmr spectrum was essentially the same as that of the monodeuterated compound obtained upon irradiation of carvonecamphor in deuterium oxide followed by treatment with diazomethane. If the methoxyl group is taken as 3.0 protons, the region from \( \tau 7.4 \) to 8.36 contains 6.3 protons (compared to 7.0 for 4), while the total number of protons appears as 17.1 (16 is theoretical). No trace of any peak appears between the doublet peaks at \( \tau 8.90 \) and 9.00, indicating the nearly complete absence of deuterium atoms at C-5.

Barbier–Wieland Degradations. Degradations of the methyl esters 4 and 9 were carried out as described by Lane and Wallis.\(^4\)

Stereochemistry of the Cyclization of 5-Methoxy-2-pentyl Bromosylate to 2-Methyltetrahydrofuran\(^1\)

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Abstract: 5-Methoxy-2-pentanol has been resolved and its configuration correlated with that of 1-penten-4-ol, 4-methoxy-1-pentene, 2-methoxypentane, 1,4-pentanediol, and 2-methyltetrahydrofuran. Treatment of 5-methoxy-2-pentyl bromosylate with lithium chloride gives about 4% of 2-methyltetrahydrofuran, with complete inversion of configuration; an optically active mixture consisting of 80% 2-chloro-5-methoxypentane and 20% of 5-chloro-2-methoxypentane was also formed. Use of lithium bromide on the bromosylate yields the tetrahydrofuran, formed with 50% inversion, and a mixture of optically inactive bromomethoxypentanes. The mechanism proposed to account for these observations involves the formation of a methoxonium ion with inversion, followed by attack of nucleophiles on this at the methyl group, at C-2 and at C-5. An open carbonium ion is considered unlikely; lack of optical activity in the bromomethoxypentanes must be due to direct displacement by bromide ion and reversibility of most steps in the scheme.

During structural elucidation of the antibiotic fumagillin,\(^3\) we observed several examples of the formation of a perhydrobenzofuran ring, from a cyclohexane containing a hydroxyl group in the side chain and a methoxyl group on the cyclohexane ring adjacent to the side chains. A study of simpler compounds,\(^4\) of type 1, where the hydroxyl was primary, secondary, or tertiary and the substituents on the cyclohexane ring were either cis or trans, showed that the reaction was a general one, and gave some information concerning the reaction mechanism.

\[
\text{CH}_3\text{O} - \text{R} \xrightarrow{\text{OSiCl}_3} \text{O} - \text{R} \quad \text{CH}_3\text{O} - \text{H} \quad \text{R} \quad \text{R} \end{align}
\]

1, \( \text{R} = \text{CH}_3 \) or \( \text{H} \)

It was shown by O\(^{18}\)-tracer studies that the oxygen lost in the cyclization was that in the hydroxyl group;\(^4\) it was obviously significant, for the general problem of methoxyl participation, and for the specific problem of syntheses in the fumagillin series,\(^6\) to define the stereochemistry of the cyclization with respect to the carbon carrying the hydroxyl group.

Compound 1 contains two asymmetric carbon atoms, in addition to the one carrying the hydroxyl, when \( \text{R} = \text{CH}_3 \) and \( \text{R}' = \text{H} \). It was therefore experimentally much more feasible to study the problem in a compound containing a single asymmetric carbon. In the present paper, we have shown that the transformation of 5-methoxy-2-pentyl bromosylate (3b) to 2-methyltetrahydrofuran (4) takes place with 100% inversion of configuration. Further results allow a correlation of the absolute configurations of a number of open-chain compounds with 2-methyltetrahydrofuran. The results, therefore, give some insight into the stereochemistry of methoxyl participation.

Racemic 5-methoxy-2-pentyl bromosylate in pyridine with lithium chloride gave a few percent of 4, as was anticipated from earlier work,\(^3\)\(^4\)\(^5\) in addition to a mixture of halomethoxypentanes.

5-Methoxy-2-pentanol was therefore resolved,\(^6\)

(1) Aided by Grant AI-06328 from the National Institutes of Health.
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three crystallizations of the brucine salt of the acid phthalate were sufficient to give the (+) alcohol optically pure, $\alpha_{D}^{20}$ (+)12.38 $\pm$ 0.01°. The optically active brosylate 3b of 5-methoxy-2-pentanol was readily prepared with brosyl chloride in pyridine for a few hours at 0°, and it melted at 31-32°.

(R)-5-Methoxy-2-pentyl brosylate of 25% optical purity was allowed to stand 12 hr in pyridine at room temperature with 150 mole % of lithium chloride, and yielded 37.7% of (S)-2-methylenetetrahydrofuran (4): the optical purity was 26%, and the configuration was 102 $\pm$ 2% inverted. (The basis for the assignment of absolute configurations is given below; the per cent optical purity is based on the rotation of optically pure 2-methylenetetrahydrofuran, as calculated from the conversion of (S)-1-penten-4-ol to (S)-2-methylenetetrahydrofuran.)

The major fraction from the reaction consisted of a 58% yield of a mixture of 2-chloro-5-methoxypentane (5) and 5-chloro-2-methoxypentane (6) in a 4:1 ratio, as determined by nmr. A portion of the mixture was converted to the Grignard reagents, which were treated with water. The resulting mixture of methoxypentanes, obtained in 72% yield, consisted of 18% 2-methoxypentane (7) and 82% 1-methoxypentane, as determined by vpc. The 2-methoxypentane, separated from the mixture by vpc, was of (S) configuration, and was 23% optically pure. In relation to the starting alcohol 3a, the 2-methoxypentane obtained in this way was 93 $\pm$ 1% inverted, somewhat less than the 100% inversion in the formation of the 2-methylenetetrahydrofuran.

A portion of the above mixture of 2-chloro-5-methoxypentane and 5-chloro-2-methoxypentane was allowed to stand in pyridine for 18 hr with 150 mole % of lithium chloride. The reaction yielded 82% of a mixture of the 5-chloro-2-methoxypentane (6) and 2-chloro-5-methoxypentane (5) in a 1:5 ratio. The mixture was converted to the Grignards and then to the methoxypentanes, as above. The 2-methoxypentane (isolated by vpc) had optical activity 10% lower than that of the sample above; this difference is greater than the experimental uncertainty, and means that 2-chloro-5-methoxypentane is racemized appreciably by lithium chloride in pyridine in 18 hr.

The relationships indicated are given in Chart I; values of rotations given in parentheses are those for optically pure materials. The aqueous layer from the reaction of (+)-5-chloro-2-methoxypentane, [a]$_D^{20}$ (+)1.55°, gave (+)-2-methoxypentane, [a]$_D^{20}$ +2.52°, d$_D^{20}$ 0.750, i.e., $\alpha_{D}^{20}$ $\pm$ 3.36°. From the correlations of configurations (below) we calculated that optically pure (S)-(+)-2-methoxypentane has a rotation of $\alpha_{D}^{20}$ +16.3°. Thus, the above (+)-2-methoxypentane had 21% optical purity. Consequently, based on our data and on the data previously given, 9 optically pure (+)-5-chloro-2-methoxypentane should have a rotation of [a]$_D^{20}$ +7.4° or $\alpha_{D}^{20}$ +7.1° since $\alpha_{D}^{20}$ 0.957.

Since (S)-(+-)2-methoxypentane from the reaction of (R)-5-methoxy-2-pentanol with brosyl chloride was 38.5% optically pure, the rotation of 5-chloro-2-methoxypentane should have been $\alpha_{D}^{20}$ +2.7°. The 78:22 mixture of 5-chloro and 2-chloro compounds had a rotation of $\alpha_{D}^{20}$ +12.08°; therefore, 2-chloro-5-methoxypentane was dextrorotatory. Additional evidence for this conclusion was obtained from the observation that when one-half of the 5-chloro compound was removed from the 78:22 mixture, the rotation increased from $\alpha_{D}^{20} +12.08^\circ$ to $\alpha_{D}^{20} +12.98^\circ$.

Although there is no direct evidence that bears on the configuration of (+)-2-chloro-5-methoxypentane, it is probable that it is of (S) configuration, since compounds of the type RR'CHX, having (S) configuration, are all dextrorotatory, where R = Me, R' = C$_2$H$_5$, n-C$_3$H$_7$, n-C$_4$H$_9$, n-C$_5$H$_{11}$, n-C$_6$H$_{13}$, or n-C$_7$H$_{15}$ and where X = OH, OMe, OEt, CF$_3$Br, I, or NHz.H$_2$. Furthermore, (S)-5-bromo-2-methoxypentane, (S)-5-methoxy-2-pentanol, and (S)-1,4-pentanediol are also dextrorotatory.

(9) W. von E. Doering and R. W. Young, J. Am. Chem. Soc., 74, 2997 (1952). They prepared (+)-5-chloro-2-methoxypentane by treatment of (+)-2-methoxy-5-pentanol with thionyl chloride in pyridine. Since in this reaction the intermediate contains the easily replaceable chlorosulfite, it is possible that in addition to 5-chloro-2-methoxypentane some 5-methoxy-2-chloropentane was formed via methoxy participation. In the calculations it was assumed that 2-chloro-5-methoxypentane contained no appreciable amounts of the 2-chloro isomer.

Treatment of the brosylate of (S)-5-methoxy-2-pentanol (28% optical purity) with lithium bromide in pyridine for 5 days gave a 5% yield of (R)-2-methyltetrahydrofuran, of 13.6 ± 0.2% optical purity. A 48% yield of a mixture consisting of 88% of 2-bromo-5-methoxypentane and 12% of the 5-bromo isomer was obtained; the mixture was devoid of optical activity. Reductive removal of the bromine by lithium aluminum hydride, followed by vpc separation, gave optically inactive 2-methoxypentane.

The mixture of the bromomethoxypentanes was allowed to stand 3 days in a pyridine–lithium bromide solution of the same concentration as the reaction mixture. Analysis by vpc showed that 3–4% of the bromomethoxypentanes had been converted to 2-methyltetrahydrofuran.

Correlations of Configurations

It has been shown that hydrogenation of (−)-1-penten-4-ol yields (−)-2-pentanol11,12 and that oxidation of (−)-1-penten-4-ol gives (−)-3-hydroxybutyric acid.12 In the present paper (Chart II), (−)-1-penten-4-ol14 was converted to (+)-4-methoxy-1-pentene, which showed that 0.1% yield would have been detected.

The correlation of the configurations of 1-penten-4-ol and 2-methyltetrahydrofuran was accomplished (Chart III) by conversion of (S)-(−)-1-penten-4-ol to the trifluoroacetate ester 8, followed by free radical addition of HBr, to yield a mixture consisting of 92% of the 5-bromo-2-trifluoroacetoxy compound 9 and 8% of the 4-bromo isomer. The structure of the 5-bromo compound (obtained pure by vpc) was established conclusively by its elementary analysis and infrared and nmr spectra.

Attempted hydrolysis of 5-bromo-2-trifluoroacetoxypentane to 5-bromo-2-pentanol in ethanol–water in the presence of sodium bicarbonate yielded only 2-methyltetrahydrofuran. When the reaction was carried out in ethanol–water, the product, which was allowed to stand for 2 days in ether over anhydrous sodium sulfate, was 1,4-dibromopentane. This was identified by infrared and nmr spectroscopy. When the reaction was carried out in the presence of sodium bicarbonate, no 1,4-dibromopentane was obtained, indicating that it was formed by the attack of hydrogen bromide (but not bromide ion) on the trifluoroacetate, on 5-bromo-2-pentanol, or on 2-methyltetrahydrofuran. The hydrogen bromide was probably formed by the hydrolysis of the trifluoroacetate to 5-bromo-2-pentanol, which cyclized to give 2-methyltetrahydrofuran and hydrogen bromide.

Since all attempts at isolating 5-bromo-2-pentanol failed, and since the hydrolysis of the trifluoroacetate ester in the presence of sodium bicarbonate yielded 2-methyltetrahydrofuran, it was decided to convert 5-bromo-2-trifluoroacetoxypentane into 2-methyltetrahydrofuran directly. Treatment of the trifluoroacetoxy compound 9 with sodium methoxide–methanol gave a reaction complete in 10 min (judging by vpc tests), giving no detectable amount of 5-bromo-2-methoxypentane, which would be expected if there was alkyl-oxygen cleavage of the trifluoroacetate. Control experiments, including putting a “known amount of 5-bromo-2-methoxypentane into the reaction mixture, showed that 0.1% yield would have been detected.

While the above experiment does not entirely exclude the possibility of alkyl–oxygen cleavage, it nevertheless is rather unlikely that it occurred to any significant extent. Furthermore, even if it did take place and the carboxonium ion did not get trapped by methoxide but eliminated a proton to give the olefin, this would not effect the rotation of the 2-methyltetrahydrofuran, be-
cause 1-bromo-4-pentene or 1-bromo-3-pentene would not be converted into 2-methyltetrahydrofuran under the basic conditions present in the reaction. One possible way for racemization to take place in this step would be the formation of 5-bromo-2-pentyl carbonium ion and trifluoroacetate ion pair, followed by collapse of the ion pair to 5-bromo-2-trifluoroacetoxypentane. However, the formation of an ion pair so tight that the stronger nucleophile methoxide would not trap the carbonium ion is very unlikely. Furthermore, it has been shown\(^\text{16}\) that the hydrolysis of trifluoroacetates in basic solution is not accompanied by inversion or racemization.

The correlation of the configuration of (R)-1-penten-4-ol with (–)-5-methoxy-2-pentanol is shown in Chart IV; the unsaturated alcohol was hydroborated and oxidized with alkaline peroxide.\(^\text{17}\) The product was a 9:1 mixture of 1,4-pentanediol and (presumably) 2,4-pentanediol; the latter was not identified, but the former was characterized by spectral and other physical properties and by a known solid derivative. The 1,4-diol purified by vpc had \([\alpha]^{25D} -5.4 \pm 0.1^o\) (CHCl\(_3\), c 0.224 g/ml). Since the starting material was of 29.6 \pm 3.9% optical purity, the minimum rotation for the rotation for the optically pure (R)-1-pentanol was \([\alpha]^{25D} -18.2 \pm 0.5^o\) (CHCl\(_3\)), c 0.224 g/ml, which is significantly higher than the \([\alpha]^{25D} -4.90^o\) (EtOH, c 0.36 g/ml) reported by Levene\(^\text{18}\) and the \([\alpha]^{25D} -13.4^o\) (CH\(_3\)OH, c 1.05 g/ml) given by Bolton.\(^\text{19}\) Both groups of workers were interested in the direction of rotation, and not its magnitude.

**Chart IV.** Configurational Correlation of (+)-5-Methoxy-2-pentanol with (R)-1-Penten-4-ol (the values in parentheses are the calculated minimum rotations; \(\alpha\), calculated from the data in ref 12)

\[
\begin{align*}
\text{CH}=\text{CHCHCH}_{2} & \xrightarrow{1. \text{HBr}} \text{CH}_{2} \text{CHCHCH}_{2} \text{OH} \\
\text{(R)} \quad \alpha^{25D} -1.34 \pm 0.01^o & \quad (\alpha^{25D} -4.52^o)^\text{obs} \\
\text{OH}
\end{align*}
\]

The (R)-1,4-pentanediol was treated with 1.09 mole equiv of sodium hydride in tetrahydrofuran dimethyl ether, and the resulting mixture of alcohols was treated with 1.07 mole equiv of methyl iodide. 5-Methoxy-2-pentanol (3a) was obtained in 58% yield, in addition to two other compounds, presumably 1,4-dimethoxypentane and 4-methoxy-1-pentanol. 5-Methoxy-2-pentanol, collected by preparative vpc, had a rotation of \(\alpha^{25D} -3.70 \pm 0.01^o\). Since the starting (R)-1-penten-4-ol was of 29.6 \pm 0.4% optical purity, the minimum rotation for rotationally pure (R)-5-methoxy-2-pentanol is \(\alpha^{25D} -12.5 \pm 0.2^o\), which is in good agreement with the \(\alpha^{25D} -12.38 \pm 0.01^o\) for the (S) enantiomer obtained from the resolution of racemic 5-methoxy-2-pentanol described above.

The results just described, therefore, relate the relative and absolute configurations of 2-methyltetrahydrofuran, 5-methoxy-2-pentanol, 1-penten-4-ol, and several other compounds. In particular, the results show that the conversion of 5-methoxy-2-pentanol and its brosylate to 2-methyltetrahydrofuran under the conditions specified earlier proceeds with inversion.

If it is accepted, as seems highly probable, that the reactions in Chart III proceed stereospecifically, the rotation of optically pure 2-methyltetrahydrofuran can be calculated. This value was used for the calculations of the per cent inversion given above for the conversion of 5-methoxy-2-pentyl brosylate to the tetrahydrofuran. Our configurational assignments agree with and supplement those of Gagnaire and Bull,\(^\text{20}\) who ring-opened 2-methyltetrahydrofuran with acyl halides.

A further configurational correlation, which did not prove essential to our purpose, may be recorded briefly. (R)-(+)-4-Methoxy-1-pentene was converted by free radical HBr addition to (R)-(–)-5-bromo-2-methoxy-pentane; this was reduced, with lithium aluminium hydride, to (R)-(-)-2-methoxypentane. In view of the instability of the bromo compounds it is not surprising that the 2-methoxypentane obtained by this method was 5% racemized in comparison to the one obtained by hydrogenation of 4-methoxypentene.

**Discussion of Results**

The results described above indicate that the (S) brosylate with lithium chloride gives the (R) methoxonium ion 14 with inversion; there is no evidence that this step is reversible. Attack of chloride ion, or of pyridine, removes the methyl group from the methoxonium ion to yield the (R)-2-methyltetrahydrofuran 4. Attack of chloride ion on the methoxonium ion at C-2 of the ring, presumably with inversion, yields the (S)-2-chloro-5-methoxypentane (5), and attack at C-5 of the methoxonium ion yields the 5-chloro-2-methoxypentane, the latter with (R) configuration, because removal of the chlorine yields (R)-2-methoxypentane.

The intermediacy of the oxonium ion 14, instead of an open carbonium ion such as CH\(_2\)O\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)O\(^+\)
HCH\(_3\), is inferred from Winstein's results\(^\text{6}\) on the rate increase in solvolysis due to neighboring group participation by methoxyl. From the stereospecificity of cyclization to 2-methyltetrahydrofuran, the possibility of open carbonium ion formation before cyclization to the oxonium ion, or of opening of the cyclic oxonium ion to an open carbonium ion, are eliminated.

The quantities of products formed indicate that the most rapid reaction of the oxonium ion is its conversion to the 2-chloro-5-methoxy compound; the attack of


chloride at C-5 to give the 5-chloro compound is slower by a factor of 2-4, and attack at the methyl group to form the tetrahydrofuran is slower by another factor of 6-8. It may be noted that chloride ion in pyridine is thus either a better nucleophile than pyridine, or else the reactions with pyridine are reversible and take place stereospecifically.

Reaction sequences involving pyridine would require an odd number of inversions in going from the brosylate to the tetrahydrofuran, in order to give the demonstrated stereospecificity in this step. Schemes such as the following, on the other hand, have only two inversions. Thus, it is unlikely that a quaternary pyridinium compound is involved in the reaction. If any of it is formed, it is probably stable and stays in the aqueous layer during work-up, but does not eliminate pyridine to give the oxonium ion.

The observation that the mixture of chloromethoxy compounds was racemized slowly by lithium chloride in pyridine can be explained by direct displacement of chloride by chloride in the 2-chloro compound, followed by cyclization to the oxonium ion, which in turn reacts with chloride ion to give the various products described above and shown in Chart V. By this sequence of reactions 2-chloro-5-methoxypentane is racemizes and is slowly converted to 5-chloro-2-methoxypentane, and vice versa. The net result is the slow racemization of the 5-chloro compound. The small amount of slightly racemized 2-methyltetrahydrofuran, formed by the reaction of the chloride outlined in Chart V, would have not been detected, since the experimental error, 2%, was larger than the 0.3% (7% of 3.7%) racemization. If it is accepted, as is very likely, that the reaction of (R)-5-methoxy-2-pentanol with brosyl chloride gave (S)-2-chloro-5-methoxypentane, then the major portion of this compound must have arisen either by direct SN2 displacement of brosylate by chloride ion or by front side opening of the oxonium ion by chloride. Since it has been shown that alliphatic oxonium ions, such as 15, are opened up by back side displacement, the SN2 attack on the brosylate is more probable.

The reaction of the brosylate with lithium bromide in pyridine further supports the conclusion that 5-chloro-2-methoxypentane was formed with 100% inversion (in addition to 2-methyltetrahydrofuran) via the methoxonium ion 14, but was racemized to a small extent under reaction conditions. In the reaction with bromide the yield of 2-methyltetrahydrofuran was significantly higher (5%), but it was 50% racemized; the bromo compounds were completely racemic.

A separate run showed that the mixture of bromomethoxy compounds was converted to the tetrahydrofuran with lithium bromide and pyridine, indicating that the bromides can revert to the oxonium ion more rapidly than the chlorides (Chart V, X = Br). This rapid reconversion of the bromides to the methoxonium ion causes a rapid racemization of the two isomeric bromo compounds, and also causes a significant increase in the amount, and decrease in the optical purity, of 2-methyltetrahydrofuran. Since bromide is both a better leaving group and a better nucleophile than chloride, it is not surprising that the bromomethoxy compounds are completely racemized.

Since neither the intervention of pyridine nor an open carbonium ion was of any importance in the formation of the methoxonium ion from the brosylate, it is very unlikely that they are of any significance in racemization since both chloride and bromide are a poorer leaving group, than brosylate.

**Experimental Section**

Elementary analyses are by Microtech Laboratories; nmr spectra were taken on a Varian A-60 spectrometer under the direction of Dr. L. D. Colebrook. Infrared spectra were taken on a Perkin-Elmer 421 spectrometer. Rotations were taken on an O. C. Rudolph and Son No. 465 polarimeter, neat in a 1-dm tube, unless otherwise noted.

5-Methoxy-2-pentanol (3a) was prepared best from 5-methoxy-2-pentanone,22 best obtained in turn from 5-hydroxy-2-pentanone.22 Best obtained in 75% yield. 2-Methylfuran (100 g) was hydrogenated in acetone containing aqueous acid to yield 68.3 g of 5-hydroxy-2-pentanone, bp 115-117° (33 mm); nD 1.4360. 14-Methyl furoate (360 g) and Dimethyl sulfate (360 g) and

![Chart V. Mechanism of Racemization of the Halo Compounds](chart_v)

(21) R. L. Burwell, Jr., L. M. Melkin, and L. G. Mury, *J. Am. Chem. Soc.*, 73, 2428 (1951), have shown that sec-butyl methyl ether is inverted during cleavage by aliphatic chloride-stannic chloride, presumably via

![Diagram](diagram)

(22) Alternative procedures investigated were: (1) acetylbutoxyacetone → 5-chloro-2-pentanone → 2-ethyleneketals → 5-methoxy-2-pentanone; (2) ethyl acetooacetate → ethyl 2-methoxyethylacetooacetate → 5-methoxy-2-pentanone; (3) valerolactone → 1,4-pentanediol → 5-methoxy-2-pentanone. All gave the desired product but were less satisfactory than the procedure described.


5-Methoxy-2-pentanol (60 g) in 400 ml of methanol in an ice
bath was distilled with a solution of 8 g of sodium borohydride in
12 ml of 2 N sodium hydroxide, diluted with 100 ml of water, added
at such a rate that the temperature did not exceed 25°. Methanol
was removed by distillation, and the residue treated with 400 ml of
water. The solution was extracted with ether and the ether ex-
tracts were combined and dried over MgSO4. After filtering, ether
was removed from the residue until the residue weighed to give 47.8 g (75%)
of product, bp 84-86° (30 mm). nD19 1.4210. The reported values are:
bp 84-86° (30 mm), nD19 1.4220. The nmr spectrum and elementary
analysis were in agreement with the structure.

5-Methoxy-2-pentyl Hydrogen Phthalate. 5-Methoxy-2-pentanol
(356 g, 3 moles), freshly distilled phthalic anhydride (452 g, 3.02
moles), and 500 ml of anhydrous pyridine were heated on a steam
bath for 3 hr. The resulting viscous oil was cooled in an ice bath and
acidified by the addition of ice-cold 6 N HCl. The oily precipi-
tate was separated from the aqueous layer, which was extracted with
six 150-ml portions of ether. During extractions the temperature of both
aqueous and ether phases was kept below 70° and 80° respectively, and
the ether layer was filtered through a layer of anhydrous sodium sulfate.
The chloroform layer was filtered through a layer of anhydrous hydroxyl
sulfate. The chloroform solution was washed with ether, 1.16
portion of water, and the chloroform layer was filtered through a layer
of anhydrous sodium sulfate. The chloroform layer was filtered through a
layer of anhydrous sulfate, then with three 100-ml portions of cold distilled
water. After drying with acid and water, the chloroform layer was filtered
through a layer of anhydrous sodium sulfate. The chloroform layer was
filtered through a layer of anhydrous sulfate, then with three 100-ml portions
of water, and the chloroform layer was filtered through a layer of
anhydrous sodium sulfate. The chloroform layer was filtered through a
layer of anhydrous sulfate, then with three 100-ml portions of water.
The residue was dried and filtered, and the ether was removed on an all-glass
Toddl. The collected material, bp 195-196° (0.25 mm) and stored in a
P2O5 vacuum desiccator. 40.0 g (446 mg), which contained 300 ml of anhydrous
pyridine. To this solution was added 8S g (0.251 mole) of the bro-
sylate, [aD] +2.32 = 0.04° (CCl4, e 0.2273) and prepared from (S)-5-methoxy-2-pentanol (37.5 g, 0.1% optical purity). The
resolved homogeneous fraction mixture was allowed to stand in the
dark at room temperature for 3 days. The mixture was cooled in
ice, 200 ml of ether was added, and the mixture was poured into
500 ml of 3 N ice-cold hydrochloric acid containing ice. The
aqueous phase was made slightly acidic by addition of more cold
ice. The organic layer was separated: 100 g of sodium chloride
was added to the aqueous layer, and it was extracted with six 150-ml
portions of ether. During extractions the temperature of both
phases was maintained below 5°. The combined organic layers
were washed with two 100-ml portions of cold 0.5 N hydrochloric
acid, then with three 100-ml portions of cold 95% ethanol; the
aqueous washings were extracted twice with 50-ml portions of
ether. This 100 ml of ether was washed with acid and water
and combined with the original layer. The combined organic phase
was dried and filtered, and ether was removed on an allglass
Toddl. Further distillation of the residue on a small Vigreux column
yielded a fraction, 3.6 g, bp 30-35°, and a 21.8% enantiomeric
fraction boiling at 78-80° (20 mm). Vpc analysis on a 13 ft x 0.25 in. 20° Dow 11 column (60°, He, 90 cc/min) showed that the
50-95° fraction contained ether, 1.1 g (51.5% yield) of 2-methyltetrahydrofuran (determined by peak area
calibration), and four other minor peaks amounting to less than 1% of the total peak area. One of the minor peaks had the same retention
time as 5-methoxy-1-pentene prepared from 5-hydroxy-1-
pentene (Columbia Organic Chemicals), sodium hydride, and methyl
iodide, and another of the small peaks corresponded to 4-methoxy-
1-pentene, as determined by comparison. The two other small
peaks overlapped and were not investigated further.

Some of the 2-methyltetrahydrofuran was collected by prepara-
tive vpc. The collected material, nD19 1.4020 (known sample nD19
1.4018), had infrared and nmr spectra identical with a known sample. It
had a rotation of [αD] +2.90 = 0.02°, was of (R) configuration
and of 13.6 = 0.2% optical purity. The residue, containing 5-bromo-2-methoxy-
and 2-bromo-5-methoxypentane. The infrared spectrum of this fraction had the following absorptions: 2900 (s, broad),
2740 (w), 1450 (m), 1380 (m), 1250 (w), 1120 (s), 1090 (s), 975 (w), 880 (w), and 755 (w) cm⁻¹. All attempts at separating the

(27) The reported value (Alfred's Ph.D. thesis, ref 6) is 31.5-32° for
the racemic brosylate.
two isomeric compounds by vpc failed. The nmr spectrum showed the following peaks (in δ): a doublet at 8.92, area 6 (H(COCH3)-
CH3); a doublet at 8.54 (H(CBrCH3)) on top of a multiplet centered at 8.2 (protons on C-3 and C-4), area 114; a sharp singlet at 6.77 (methoxy protons) on top of a multiplet centered at 6.6 (H(OCCH3) and H(OC(CH3)CH3)), area 81; and a multiplet at 5.8 (H(BCBrCH3)), area 16. From the above nmr it was estimated that the ratio of 2-bromo-5-methoxytetrachloro to 5-bromo-2-methoxytetrachloro is 8:1. The nmr spectrum of 2-bromotetrahydrofuran showed a doublet at 8.90, a multiplet at 7.83 (methylene protons), a sharp singlet at 6.75 (methoxy protons) on top of a multiplet at 6.70 (H(OCH3)) in 38.1 (optical purity), 17.1 g (0.2 mole), was distilled in 75 mL of purified diglyme and treated with small pieces of sodium, 4.6 g (0.2 g-atom). The mixture was maintained at 70°C for 2 days, by which time all of the sodium had dissolved. After cooling to room temperature, the reaction mixture was treated with 30 mL of methyl iodide and stirred at room temperature for 1 day. The product was distilled, and the fraction of bp 60-130°C was collected. The distillate was redissolved in sodium and the fraction boiling between 66 and 88°C was 16.8% 85% (absolute purity) and was obtained by preparative vpc. The collected material, 4.6 g (0.018 mole), was redissolved in sodium hydroxide, and methyl iodide (38.7% 85% 1.8 g (0.018 mole), was added dropwise during 1 hr at temperatures below 10°C. The stirring was continued for 1 hr after completion of addition. The reaction mixture was poured into 150 mL of ice-cold saturated sodium carbonate solution and extracted with portions of ether. The ether layer was washed, dried, and distilled in the customary manner, until 10 mL remained in the distilling flask. Vpc analysis indicated that it contained less than 0.008 g of 2-methyltetrahydrofuran and no detectable amounts of 5-chloro-2-methoxytetrachloro or 5-chloro-5-methoxytetrachloro. The nmr spectrum of the aqueous phase was not changed by the extraction. Anal. Calcd for C15H22O2: C, 71.95; H, 9.59; Cl, 24.55. Found: C, 72.83; H, 9.44; Cl, 25.81.

(R)-4-Methoxy-1-pentene. (R)-1-Penten-4-ol, [d]~+2.01 ± 0.01° (optical purity 44.5 ± 0.2%, 17.2 g (0.2 mole), was distilled in 75 mL of purified diglyme and treated with small pieces of sodium, 4.6 g (0.2 g-atom). The mixture was maintained at 70°C for 2 days, by which time all of the sodium had dissolved. After cooling to room temperature, the reaction mixture was treated with 30 mL of methyl iodide and stirred at room temperature for 1 day. The product was distilled, and the fraction of bp 60-130°C was collected. The distillate was redissolved in sodium and the fraction boiling between 66 and 88°C was 16.8% 85% (absolute purity) and was obtained by preparative vpc. The collected material, 4.6 g (0.018 mole), was redissolved in sodium hydroxide, and methyl iodide (38.7% 85% 1.8 g (0.018 mole), was added dropwise during 1 hr at temperatures below 10°C. The stirring was continued for 1 hr after completion of addition. The reaction mixture was poured into 150 mL of ice-cold saturated sodium carbonate solution and extracted with portions of ether. The ether layer was washed, dried, and distilled in the customary manner, until 10 mL remained in the distilling flask. Vpc analysis indicated that it contained less than 0.008 g of 2-methyltetrahydrofuran and no detectable amounts of 5-chloro-2-methoxytetrachloro or 5-chloro-5-methoxytetrachloro. The nmr spectrum of the aqueous phase was not changed by the extraction. Anal. Calcd for C15H22O2: C, 71.95; H, 9.59; Cl, 24.55. Found: C, 72.83; H, 9.44; Cl, 25.81.

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(S)-1-Penten-4-ol had a rotation of $\alpha_{D} = -8.56 \pm 0.02^\circ$. Since the starting material was of $38.1 \pm 0.2\%$ purity, an optically pure sample should have had a rotation of $\alpha_{D} = -22.5 \pm 0.2^\circ$.

An attempt at hydrolysis with 1 mole equiv of hydrogen bromide was taken up ($\alpha_{D}^{0} = 1.0040$, had a rotation of $\alpha_{D}^{0} = -0.72 \pm 0.02^\circ$). Optically pure material should have had a rotation of $\alpha_{D}^{0} = 1.9 \pm 0.1^\circ$.

An analysis by vpc on a 15 ft x 0.25 in., 25% divinyl-derivate on Chromosorb P, 152° (He 155 cc/min), showed two peaks in the approximate ratio of 9:80.

The reported constants are: $n_{D} = 1.5087$, bp 74-80° (9 mm) (N. I. Shuklin and I. F. Belski, Dokl. Akad. Nauk SSSR, 111, 1048 (1956); Chem. Abstr., 51, 9566a (1957)).

| (S)-5-Bromo-2-trifluoroacetoxy pentane | 9.0 g (0.0497 mole), from the above preparation, was added dropwise to Anhydrous hydrogen bromide was bubbled through the solution during irradiation with a Sylvania sun lamp.

The reaction mixture was saturated with sodium chloride and dried. The residue was distilled at atmospheric pressure and the distilled residue was 2-4-pentanediol. A small portion of the 1,4-pentanediol, collected by vpc, had $\alpha_{D}^{0} = 1.4452$ (lit. $\alpha_{D}^{0} = 1.4470$) and an infrared spectrum that was identical with that given by Boltz. The nmr spectrum (in $\eta$) had a doublet at 8.55 (3H), multiplet at 8.42 (4H), multiplet at 6.3 (2H), and singlet at 5.9 (2H). The phosphorylurea had a tetrahydrofuran band at $\nu = 1309$ cm$^{-1}$. [a]$_{D}^{0}$ = 5.4 ± 0.1° (CHCl$_3$, 0.224 g/ml). Since the starting material was of 29.6 ± 0.3% optical purity, the minimum rotation of optically pure (R)-1,4-pentanediol is [a]$_{D}^{0} = -18.2 ± 0.5^\circ$ (CHCl$_3$, 0.224 g/ml) (lit. $\alpha^{0}_{D} = -4.90$ (ethanol, c 0.316 g/ml), lit. $\alpha^{0}_{D} = -13.4$ (CH$_3$OH, c 1.05 g/ml).

1.4-Pentanediol, [a]$_{D}^{0}$ = 5.4 ± 0.1° (CHCl$_3$, c 0.224 g/ml, optical purity 39.6 ± 0.3%, 7.20 g dissolved in 30 ml of purified trithyleneglycol dimethyl ether was slowly added to a well-stirred mixture of sodium hydride, 3.50 g of 51.5% NaH dispersion in mineral oil (0.075 mole), in 100 ml of tetrahydrofuran and 5% water. The resulting alkoxide was treated with excess diborane generated externally from 200 ml of triethylamine and 10% of another compound that had higher retention time (52 min). The compound with the higher retention time was identified as 2,4-pentanediol.

The major peak (retention time 16 min) was collected. The mnr of the vpc-purified material showed (in $\eta$) a doublet at 8.65 (methyl protons), a multiplet at 8.15 (terminal methyls), a multiplet at 6.68 (protons of bromomethylene) and a multiplet at 5.00 (HCOOCCF$_3$). The ir spectrum showed the presence of carbonyl (1780 cm$^{-1}$) and the absence of the carbon-carbon double bond. The vpc purified sample, $n_{D} = 1.4040$, had a rotation of $\alpha_{D}^{0} = -0.72 \pm 0.02^\circ$. Optically pure material should have had a rotation of $\alpha_{D}^{0} = 1.9 \pm 0.1^\circ$.

Analytical values of optical purity (calculated from the data in ref 10), 11 g, dissolved in 600 ml of anhydrous tetrahydrofuran, was treated with excess diborane generated externally from 200 ml of sodium borohydride in diglyme and 46 ml of boron trifluoride etherate. The organoborane was oxidized by the dropwise addition of 32 ml of 30% hydrogen peroxide, while the solution was maintained slightly basic by controlled addition of 3 N aqueous sodium hydroxide. After completion of addition, the solution was heated at 45-50° for 1 hr, then stirred at room temperature for 3 hr. The reaction mixture was on anhydrous calcium sulfate, the organic layer was separated and the aqueous phase extracted with six portions of tetrahydrofuran. The combined organic layers were stirred with sodium chloride and dried. The tetrahydrofuran was removed by distillation at atmospheric pressure and the residue distilled. The fraction boiling at 0.185 (18 mmol, 7.5%, was collected; the reported value is bp 221° (753 mm).

Vapor-phase chromatography on a 5x 0.25 in. Carbowax 20 M column (155°, He 200 cc/min) indicated that the product contained 90% 1,4-pentanediol (by co-injection, retention time 28 min) and 10% of another compound that had higher retention time (52 min). The compound with the higher retention time was identified as 2,4-pentanediol.

The two higher boiling fractions combined approximately 80% of 5-methoxy-2-pentanol, as estimated by vpc (total yield of 5-methoxy-2-pentanol was 4.70 g, 58%). The 5-methoxy-2-pentanol was collected on vpc (15 ft x 0.25 in. Carbowax 20M, 125°, He 125 cc/min; retention time 17 min). The collected material had vpc retention time, physical constants, and infrared spectrum identical with those of an authentic sample. Material had $\alpha_{D}^{0} = 0.01$ (C$_2$H$_5$OH, 0.2%). If the starting material was optically pure, the rotation of (R)-5-methoxy-2-pentanol would be $\alpha_{D}^{0} = 12.5 ± 0.2^\circ$.

The reaction mixture was stirred for 30 min with 30 g of sodium sulfate. It was extracted with five portions of ether; the ether layer was dried; the 5-methoxy-2-pentanol was collected on vpc (15 ft x 0.025 in. 25% Dow 11 column (155°, He 200 cc/min) indicated that the product was 5-methoxy-2-pentanol, as estimated by vpc (total yield of 5-methoxy-2-pentanol was 4.70 g, 58%). The 5-methoxy-2-pentanol was collected on vpc (15 ft x 0.25 in. Carbowax 20M, 125°, He 125 cc/min; retention time 17 min). The collected material had vpc retention time, physical constants, and infrared spectrum identical with those of an authentic sample. Material had $\alpha_{D}^{0} = 0.01$ (C$_2$H$_5$OH, 0.2%). If the starting material was optically pure, the rotation of (R)-5-methoxy-2-pentanol would be $\alpha_{D}^{0} = 12.5 ± 0.2^\circ$.

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wise to a dispersion of lithium aluminum hydride, 0.19 g in 100 ml of anhydrous ether, and the reaction mixture was refluxed for 8 hr. The excess lithium aluminum hydride was decomposed by careful addition of water. The precipitated hydroxide was dissolved in 0.25 ml of anhydrous ether, and the reaction mixture was refluxed for 8 hr. Ice-cold 1M hydrochloric acid. The usual work-up gave 3.6 g (71%) of a fraction, bp 90-91°C. Preparative vpc on a 15 ft x 0.25 in. 20% Carbowax column (70°C, He 80 cc/min) yielded pure (R)-2-methoxypentane (the fraction obtained from distillation was approximately 98% pure). The vpc purified sample, nD 1.3814 (known sample: nD 1.3816), had retention time and infrared spectrum identical with a known sample. It had αD 3.24 ± 0.01°. Since the starting (R)-4-methoxy-1-pentene was of 20.9 ± 0.4% optical purity, the minimum rotation of (R)-2-methoxypentane should be αD 15.5 ± 0.3°, to be compared with αD 16.3 ± 0.1° for the sample obtained by hydrogenation of (R)-4-methoxypentene.

Nuclear Magnetic Resonance Studies of Rate Processes and Conformations. V. Synchronous Inversion at Two Nitrogens

J. E. Anderson and J. M. Lehn

Contribution from the Institut de Chimie, Universite de Strasbourg, Strasbourg 67, France. Received August 19, 1966

Abstract: Temperature-dependent nmr spectra have been observed for compounds of the 2,3-diazabicyclo[2.2.1]-heptane and bicyclo[2.2.2]octane series. The activation parameters ΔF*, ΔH*, and ΔS* have been calculated from the spectral data; they lie in the range of 11.8-13.9, 12.4-16.2 kcal/mole, and 2.8-11.5 eu, respectively. The nature of the rate process giving rise to the spectral changes is discussed. The data are best rationalized on the basis of a consecutive inversion process at two nitrogens. The shape of the potential curve and the origin of the inversion barrier are discussed.

Several compounds of this type have been found to display temperature-dependent nmr spectra. We report here our studies of double nitrogen inversions in compounds of the 2,3-diazabicyclo[2.2.1]heptane and 2,3-diazabicyclo[2.2.2]octane series.

Results

Preparation of the Substrates. Diels–Alder addition of diethyl azodicarboxylate to cyclopentadiene gives an adduct which on reduction with lithium aluminum hydride (LAH) or lithium aluminum deuteride leads to N,N′-dimethyl-2,3-diazabicyclo[2.2.1]-5-heptene (2) or its N,N′-dip(trideuteriomethyl) derivative 3. Hydrogenation of adduct 1 produces the dihydro adduct 4 which by treatment with LAH gives N,N′-dimethyl-


Anderson, Lehn / Synchronous Inversion at Two Nitrogens