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 τ 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 τ 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.[14]

1-*exo*-5-Dimethyl-*syn*-2-methoxycarbonylbicyclo[2.1.1]hexane (11) was produced in 45% over-all yield; bp 54° (5 mm); nmr spectrum (τ), a singlet at 6.43 (3 H), a series of peaks between 7.3 and 8.4 (5 H), and a series of peaks between 8.6 and 9.2 (8 H) including two peaks at 8.89 and 8.99 interpreted as a singlet at 8.99 (3 H) and a doublet at 8.94 (3 H, J = 6 cps); $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.76 (s), 6.90 (m), 6.99 (m), 7.24 (w), 7.38 (m), 7.81 (m), 8.40 (s), 8.51 (s), 8.60 (s), 9.40 (m), and 10.85 (m) μ.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.61; H, 9.57.

1-*exo*-5-Dimethyl-*syn*-2-methoxycarbonylbicyclo[2.1.1]hexane-5-*d* (10). The nmr spectrum is identical with that of **11** for τ values <8.6. Between 8.6 and 9.3 (7 H) lies predominantly one major singlet at 8.98 which has a second singlet on its side at 8.94 and a small peak at 8.89 appearing as a shoulder near the base.

---

[14] J. L. Lane and E. S. Wallis, *J. Am. Chem. Soc.*, **63**, 1674 (1941).

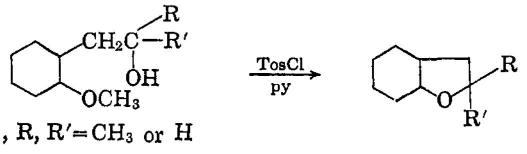
Stereochemical Consequences of Methoxyl Participation. The Stereochemistry of the Cyclization of 5-Methoxy-2-pentyl Brosylate to 2-Methyltetrahydrofuran[1]

Ernest R. Novak[2] and D. Stanley Tarbell

Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627. *Received August 11, 1966*

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 brosylate with lithium chloride in pyridine 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 brosylate 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.



1, R, R'=CH_3 or 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,[5] 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 R = CH_3 and R' = 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 brosylate (**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 brosylate in pyridine with lithium chloride gave a few per cent of **4**, as was anticipated from earlier work,[3,4,6] in addition to a mixture of halomethoxypentanes.

5-Methoxy-2-pentanol was therefore resolved;[7]

---

[1] Aided by Grant AI-06328 from the National Institutes of Health.

[2] National Science Foundation Summer Teaching Fellow, 1966.

[3] D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961).

[4] S. E. Cantor and D. S. Tarbell, *ibid.*, **86**, 2902 (1964).

[5] S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, **28**, 928 (1963); D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *ibid.*, **31**, 2192 (1966).

[6] S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958); E. L. Allred, Ph.D. Dissertation, University of California, Los Angeles, 1959 (private communication from Professor Winstein).

[7] General method of R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, **91**, 1973 (1907).

three crystallizations of the brucine salt of the acid phthalate were sufficient to give the (+) alcohol optically pure, $\alpha^{25}\text{D}$ (+)12.38 ± 0.01°.[8] 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°.

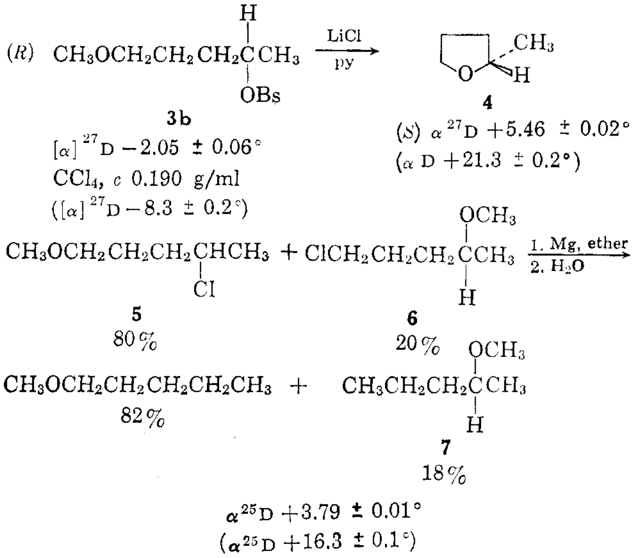
(*R*)-5-Methoxy-2-pentyl brosylate of 25% optical purity was allowed to stand 12 hr in pyridine at room temperature with 150 mole % of lithium chloride, and yielded 3.7% of (*S*)-2-methyltetrahydrofuran (**4**); the optical purity was 26%, and the configuration was 102 ± 2% inverted. (The basis for the assignment of absolute configurations is given below; the per cent optical purity is based on the rotation of optically pure 2-methyltetrahydrofuran, as calculated from the conversion of (*S*)-1-penten-4-ol to (*S*)-2-methyltetrahydrofuran.)

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 ± 1% inverted, somewhat less than the 100% inversion in the formation of the 2-methyltetrahydrofuran.

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 work-up of the reaction of (*R*)-5-methoxy-2-pentyl brosylate with lithium chloride had a rotation of $\alpha^{25}\text{D}$(+)0.08° (l = 2 dm). This rotation did not change after five extractions with ether, indicating that the rotation was caused by some water-soluble, but ether-insoluble, compounds, probably 5-methoxy-2-pentyl- and perhaps 2-methoxy-5-pentylpyridinium salts.

Chart I



Treatment of the free alcohol, (*R*)-5-methoxy-2-pentanol (**3a**), of 41% optical purity with brosyl chloride in pyridine for 3 days at room temperature gave results analogous to those in Chart I. (*S*)-Methyltetrahydrofuran (3.1% yield) which had been inverted 101 ± 2% was obtained. The mixture of halomethoxy compounds consisted of 78% of the 2-chloro compound **5** and 22% of the 5-chloro isomer **6**. Removal of the chlorine as above gave a mixture of 20% of the 2-methoxy and 80% of the 1-methoxy compound. Separation of the pure 2-methoxypentane by vpc gave the (*S*) enantiomer of 38.5 ± 0.4% optical purity, 93 ± 1% inverted with respect to the 5-methoxy-2-pentanol.

It has been shown by Doering and Young[9] that on reduction through the Grignard, (+)-5-chloro-2-methoxypentane, $[\alpha]^{25}\text{D}$ (+)1.55°, gave (+)-2-methoxypentane, $[\alpha]^{30}\text{D}$ +2.52°, d^{30} 0.750, *i.e.*, $\alpha^{25-30}\text{D}$ +3.36°. From the correlations of configurations (below) we calculated that optically pure (*S*)-(+)-2-methoxypentane has a rotation of $\alpha^{25}\text{D}$ +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 $[\alpha]^{25}\text{D}$ +7.4° or $\alpha^{25}\text{D}$ +7.1° since d^{25} 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 $\alpha^{25}\text{D}$ +2.7°. The 78:22 mixture of 5-chloro and 2-chloro compounds had a rotation of $\alpha^{25}\text{D}$ +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 $\alpha^{25}\text{D}$ +12.08° to $\alpha^{25}\text{D}$ +12.98°.

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_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, or n-C_7H_{15} and where X = OH, OMe, OEt, Cl, Br, I, or NH_2.[10] Furthermore, (*S*)-5-bromo-2-methoxypentane, (*S*)-5-methoxy-2-pentanol, and (*S*)-1,4-pentanediol are also dextrorotatory.

---

[8] Throughout this paper, the symbol αD refers to rotations taken neat in a 1-dm tube.

[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 5-chloro-2-methoxypentane contained no appreciable amounts of the 2-chloro isomer.

[10] *Cf.* J. A. Mills and W. Klyne, *Advan. Stereochem.*, **1**, 195 (1954).

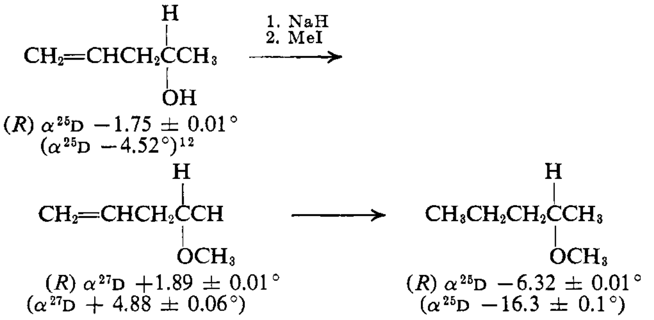
Treatment of the brosylate of (*S*)-5-methoxy-2-pentanol (28% optical purity) with *lithium bromide* in pyridine for 5 days gave a 5% yield of (*R*)-2-methyltetrahydrofuran, of 13.6 ± 0.2% optical purity. A 48% yield of a mixture consisting of 88% of 2-bromo-5-methoxypentane and 12% of the 5-bromo isomer 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

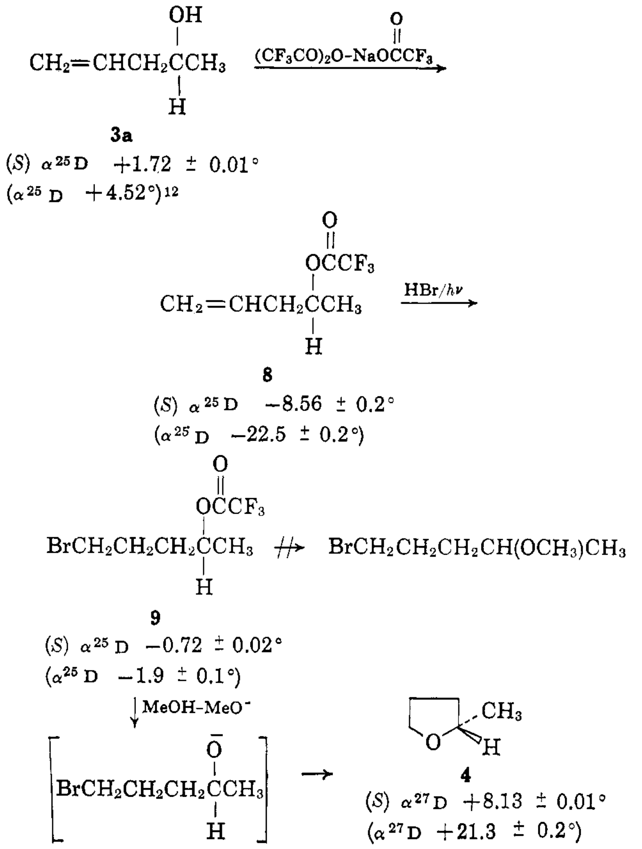
It has been shown that hydrogenation of (−)-1-penten-4-ol yields (−)-2-pentanol[11,12] and that oxidation of (−)-1-penten-4-ol gives (−)-3-hydroxybutyric acid.[13] In the present paper (Chart II), (−)-1-penten-4-ol[14] was converted to (+)-4-methoxy-1-pentene, which yielded upon hydrogenation (−)-2-methoxypentane. (−)-2-Pentanol, (−)-3-hydroxybutyric acid, and (−)-2-methoxypentane have (*R*)-absolute configurations.[15] It follows that (−)-1-penten-4-ol is also of (*R*) configuration.

Chart II. Correlation of (−)-1-Penten-4-ol with Methoyxpentane (values of rotations given in parentheses are those for optically pure materials)



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.

Chart III. Stereospecific Synthesis of (*S*)-2-Methyltetrahydrofuran from (*S*)-1-Penten-4-ol (values in parentheses are the calculated rotations for the optically pure materials)



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 carbonium 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-

---

(11) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).

(12) P. A. Levene and A. Rothen, *J. Chem. Phys.*, **5**, 982 (1937).

(13) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **81**, 425 (1929).

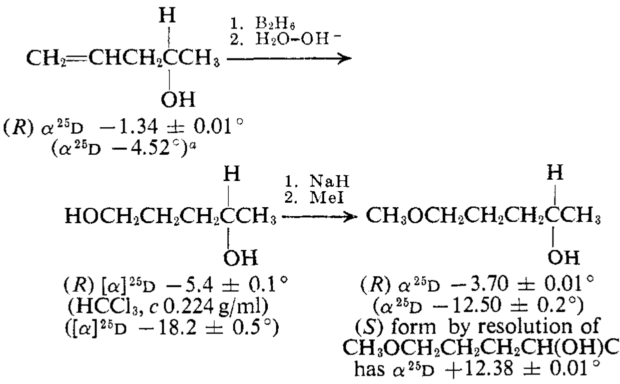
(14) The resolution was carried out by Miss Barbara Bartusek, working under a National Science Foundation Undergraduate Research Participation Program. The procedure of ref 13 was employed.

(15) Correlations of these compounds with each other and with lactic and tartaric acids are summarized by ref 10, pp 183 and 195, and by R. U. Lemieux and J. Giguere, *Can. J. Chem.*, **29**, 678 (1951).

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[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.[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 $[\alpha]^{25}\text{D}$ −5.4 ± 0.1° ($CHCl_3$, *c* 0.224 g/ml). Since the starting material was of 29.6 ± 0.3% optical purity, the minimum rotation for the optically pure (*R*)-1,4-pentanediol is $[\alpha]^{25}\text{D}$ −18.2 ± 0.5° ($CHCl_3$, *c* 0.224 g/ml), which is significantly higher than the $[\alpha]^{22}\text{D}$ −4.90° (EtOH, *c* 0.36 g/ml) reported by Levene[18] and the $[\alpha]^{20}\text{D}$ −13.4° (CH_3OH, *c* 1.05 g/ml) given by Bolton.[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; *a*, calculated from the data in ref 12)



(*R*) $\alpha^{25}\text{D}$ −1.34 ± 0.01°
($\alpha^{25}\text{D}$ −4.52°)^a

(*R*) $[\alpha]^{25}\text{D}$ −5.4 ± 0.1°
($HCCl_3$, *c* 0.224 g/ml)
($[\alpha]^{25}\text{D}$ −18.2 ± 0.5°)

(*R*) $\alpha^{25}\text{D}$ −3.70 ± 0.01°
($\alpha^{25}\text{D}$ −12.50 ± 0.2°)
(*S*) form by resolution of
$CH_3OCH_2CH_2CH_2CH(OH)CH_3$
has $\alpha^{25}\text{D}$ +12.38 ± 0.01°

The (*R*)-1,4-pentanediol was treated with 1.09 mole equiv of sodium hydride in tetraethyleneglycol dimethyl ether, and the resulting mixture of alkoxides 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 $\alpha^{25}\text{D}$ −3.70 ± 0.01°. Since the starting (*R*)-1-penten-4-ol was of 29.6 ± 0.4% optical purity, the minimum rotation for optically pure (*R*)-5-methoxy-2-pentanol is $\alpha^{25}\text{D}$ −12.5 ± 0.2°, which is in good agreement with the $\alpha^{25}\text{D}$ −12.38 ± 0.01° for the (*S*) enantiomer obtained from the resolution of racemic 5-methoxy-2-pentanol described above.

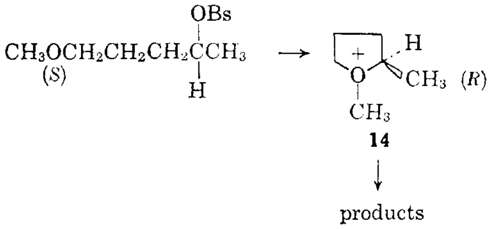
The results just described, therefore, relate the relative and absolute configurations of 2-methyltetrahydrofuran, 5-methoxy-2-pentanol, 1-penten-4-ol, and several other compounds. In particular, the results show that the conversion of 5-methoxy-2-pentanol and its brosylate to 2-methyltetrahydrofuran 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,[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-methoxypentane; this was reduced, with lithium aluminum 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



14

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 $CH_3OCH_2CH_2CH_2O^+$-HCH_3, is inferred from Winstein's results[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 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

---

(16) E. J. Bourne, A. J. Huggard, and J. C. Tatlow, *J. Chem. Soc.*, 735 (1953).

(17) *Cf.* G. Zweifel and H. C. Brown, *Org. Reactions*, 13, 1 (1963).

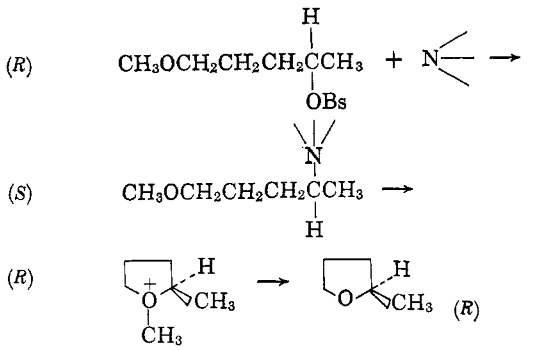
(18) P. A. Levene, H. L. Haller, and A. Walti, *J. Biol. Chem.*, 72, 591 (1927).

(19) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, 4835 (1961).

(20) D. Gagnaire and A. Bull, *Bull. Soc. Chim. France*, 312 (1961).

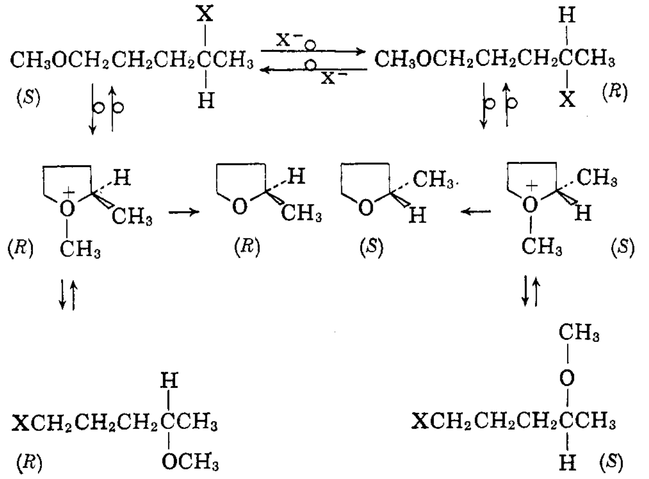
chloride at C-5 to give the 5-chloro compound is slower by a factor of 2–4, and attack at the methyl group to form the tetrahydrofuran is slower by another factor of 6–8. It may be noted that chloride ion in pyridine is thus either a better nucleophile than pyridine, or else the reactions with pyridine 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 stereochemistry 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 racemized 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[21] that aliphatic oxonium ions, such as **15**, are opened up by back side displacement, the SN2 attack on the brosylate is more probable.

Chart V. Mechanism of Racemization of the Halo Compounds



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 ion 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

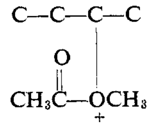
Elementary analyses are by Microtech Laboratories; nmr spectra were taken on a Varian A-60 spectrometer under the direction of Dr. L. D. Colebrook. Infrared spectra were taken on a Perkin-Elmer 421 spectrometer. Rotations were taken on an O. C. Rudolph and Son No. 465 polarimeter, neat in a 1-dm tube, 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. 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); $n^{24}\text{D}$ 1.4349; lit.[23] $n^{20}\text{D}$ 1.4360.

5-Methoxy-2-pentanone was prepared in 41% yield by the method of Favorskaia and Sergievskaia.[24] Dimethyl sulfate (360 g) and

---

[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 acetyl chloride–stannic chloride, presumably *via*



15

[22] Alternative procedures investigated were: (1) acetylbutyrolactone → 5-chloro-2-pentanone → 2-ethylene ketal → 5-methoxy-2-pentanone; (2) ethyl acetoacetate → ethyl 2-methoxyethylacetoacetate → 5-methoxy-2-pentanone; (3) valerolactone → 1,4-pentanediol → 5-methoxy-2-pentanol. All gave the desired product but were less satisfactory than the procedure described.

[23] T. E. Londergan, N. L. Hause, and W. R. Schmitz, *J. Am. Chem. Soc.*, **75**, 4456 (1953).

[24] *Cf.* T. A. Favorskaia and O. V. Sergievskaia, *J. Gen. Chem. USSR*, **28**, 92 (1958).

40% aqueous potassium hydroxide were added to 5-hydroxy-2-pentanone (260 g) at such a rate that the reaction temperature rose and stayed between 70 and 80° and that the reaction mixture was moderately basic. (A 1% solution of phenolphthalein in acetone, added at a very slow rate, was used as indicator.) The product (121 g) had identical properties with those of the samples prepared by methods 1 and 2, ref 22.

5-Methoxy-2-pentanone (60 g) in 400 ml of methanol in an ice bath was treated 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 extracts were combined and dried over $MgSO_4$. After filtering, ether was distilled off, and the residue was distilled to give 47.8 g (75%) of product, bp 84–86° (30 mm), $n^{22}\mathrm{D}$ 1.4210. The reported[25] values are: bp 171–172°; $n^{20}\mathrm{D}$ 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 sublimed phthalic anhydride (452 g, 3.02 moles), and 500 ml of anhydrous pyridine were heated on a steam bath for 3 hr.[26] The resulting viscous oil was cooled in an ice bath and acidified by the addition of ice-cold 6 *N* HCl. The oily precipitate was separated from the aqueous layer, which was extracted with three portions of chloroform. The combined organic layers were washed with three portions of ice-cold 6 *N* HCl and two portions of water, and the chloroform layer was filtered through a layer of anhydrous sodium sulfate. The chloroform was removed under vacuum; the resulting viscous, slightly yellowish oil was dissolved in ice-cold saturated sodium bicarbonate. The solution was extracted with ether (to remove unreacted alcohol and neutral phthalate ester) and passed through a wet filter. A slight excess of cold hydrochloric acid was added, and the oil precipitate of 5-methoxy-2-pentyl hydrogen phthalate was taken up in chloroform. The chloroform solution was filtered through anhydrous sodium sulfate and dried. Chloroform was removed under vacuum. All attempts at crystallization of the product (601 g) from several solvents failed. Titration with 0.1 *N* sodium hydroxide to a phenolphthalein end point in aqueous ethanol gave neut equiv 273 (calcd 266).

Resolution of 5-Methoxy-2-pentyl Hydrogen Phthalate. 5-Methoxy-2-pentyl hydrogen phthalate (266 g, 1 mole) and brucine (394 g) were refluxed in 1000 ml of 80% acetone–20% benzene (by volume); more solvent was added until the reagents dissolved. On cooling for 5 hr in a cold room (*ca.* 7°) some of the brucine salt of the half ester precipitated out. A portion of the precipitated brucine salt was decomposed by treatment with hydrochloric acid. The recovered phthalate had a rotation of $[\alpha]^{27}\mathrm{D}$ +10° (*c* 20.0 g/100 ml, benzene). The precipitated brucine salt from the first crystallization was recrystallized twice more from acetone; the mother liquors from these recrystallizations were united with the original mother liquor. After the third recrystallization, the recovered phthalate (purified through the sodium salt) had a rotation of $[\alpha]^{29}\mathrm{D}$ +19.2 ± 0.3° (*c* 20.0 g/100 ml, benzene). Three more recrystallizations of the precipitated brucine salt did not increase the rotation of the phthalate. The pure brucine salt of (+)-5-methoxy-2-pentyl hydrogen phthalate melted at 119–120°. The strychnine salt of the above resolved hydrogen phthalate was also prepared and crystallized twice from acetone, but this did not increase the rotation of the phthalate either.

The hydrogen phthalate from the precipitated brucine salt was recovered by treatment with dilute hydrochloric acid. The precipitated oil (+)-hydrogen phthalate was separated, the aqueous layer extracted twice with chloroform, and the combined organic layers were washed twice with dilute hydrochloric acid. Chloroform was removed under vacuum, and a portion of the residue was purified through the sodium salt for taking the rotations. The major portion of the (+)-hydrogen phthalate was dissolved in 25% aqueous sodium hydroxide (three times the theoretical amount), and the alcohol was removed by steam distillation. The alcohol was extracted out of the distillate with five portions of ether. The combined ether layers were dried, and the solvent was removed by distillation. Distillation of the residue gave (+)-5-methoxy-2-pentanol, 18.3 g (30%), bp 84–85° (25 mm), $n^{20}\mathrm{D}$ 1.4215, $\alpha^{25}\mathrm{D}$ +12.38 ± 0.01°. Redistillation of the alcohol did not alter the rotation.

The (−)-5-methoxy-2-pentanol obtained from the mother liquors of the recrystallizations of the brucine salts had a rotation of $\alpha^{25}\mathrm{D}$ −5.11°.

5-Methoxy-2-pentyl Brosylate (3b) The optically active brosylate was prepared from 3.0 g of (*S*)-5-methoxy-2-pentanol, $\alpha^{25}\mathrm{D}$ +3.41 ± 0.01° (27.5% optical purity), in 12.5 ml of dry pyridine in an ice–salt bath. Brosyl chloride (7.2 g in 12.5 ml of pyridine) was added during 45 min. The reaction mixture was stirred at 0° for an additional 3 hr, then poured into excess ice-cold 3 *N* HCl, and extracted with three portions of 1:1 ether–petroleum ether (bp 30–60°). The organic layers were washed twice with ice-cold 3 *N* HCl and with three portions of cold distilled water. After drying and removing the solvent, the crude product, 8.0 g, mp 29–31°, was recrystallized twice from 1:1 ether–petroleum ether (bp 30–60°) at −30 to −20°. The recrystallized material, 6.6 g (78%), mp 31–32°,[27] had an infrared spectrum identical with that of the brosylate from racemic alcohol; the brosylate had $[\alpha]^{27}\mathrm{D}$ +2.27 ± 0.04° (CCl_4, *c* ±0.2626 g/ml).

Two other samples of the sulfonate ester prepared separately from the above alcohol gave rotations of $[\alpha]^{27}\mathrm{D}$ +2.29 ± 0.04° and $[\alpha]^{27}\mathrm{D}$ +2.32 ± 0.04° (CCl_4, *c* 0.2273 and 0.2500 g/ml, respectively). Since the starting alcohol was of 27.5 ± 0.1% optical purity, the minimum rotation for the optically active sulfonate ester should be $[\alpha]^{27}\mathrm{D}$ +8.3 ± 0.2° (CCl_4, *c* 0.25 g/ml).

Analytical data was obtained on a racemic sample prepared as above from racemic 5-methoxy-2-pentanol. The nmr spectrum was consistent with the proposed structure; except for the absence of hydroxyl and presence of aromatic protons, it was similar to that of 5-methoxy-2-pentanol. The ultraviolet spectrum had a maximum at 233 mμ (ε 15,700 in ethanol).

Anal. Calcd for $C_{12}H_{17}BrO_4S$: C, 42.74; H, 5.08; Br, 23.70; S, 9.51. Found: C, 42.64; H, 5.23; Br, 23.47; S, 9.37.

Reaction of (*S*)-5-Methoxy-2-pentyl Brosylate (3b) with Lithium Bromide in Pyridine. Anhydrous lithium bromide (dried in a vacuum oven at 120° for 5 hr (15 mm) and stored in a P_2O_5 vacuum desiccator), 40.0 g (0.465 mole), was dissolved in 300 ml of anhydrous pyridine. To this solution was added 85 g (0.251 mole) of the brosylate, $[\alpha]^{27}\mathrm{D}$ +2.32 ± 0.04° (CCl_4, *c* 0.2273 g/ml), prepared from (*S*)-5-methoxy-2-pentanol of 27.5 ± 0.1% optical purity. The resulting homogeneous reaction 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 acid. 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 distilled water. 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 the ether was removed on an all-glass Todd column (~45 theoretical plates, reflux ratio 3:1). Further distillation of the residue on a small Vigreux column yielded a fraction, 3.6 g, bp 50–95°, and a 21.8-g fraction boiling at 78–80° (20 mm).

Vpc analysis on a 13 ft × 0.25 in. 20% Dow 11 column (60°, He, 90 cc/min) showed that the 50–95° fraction contained ether, 1.1 g (5.1% 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 coinjection. The two other small peaks overlapped and were not investigated further.

Some of the 2-methyltetrahydrofuran was collected by preparative vpc. The collected material, $n^{26}\mathrm{D}$ 1.4020 (known sample $n^{26}\mathrm{D}$ 1.4018), had infrared and nmr spectra identical with a known sample. It had a rotation of $\alpha^{27}\mathrm{D}$ −2.90 ± 0.02°, was of (*R*) configuration and of 13.6 ± 0.2% optical purity.

The 78–80° (20 mm) fraction contained 5-bromo-2-methoxypentane 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, shoulder), 975 (w), 880 (w), and 755 (w) cm^{-1}. All attempts at separating the

---

[25] O. S. Stepanova, *J. Gen. Chem. USSR*, **32**, 3236 (1962).

[26] *Cf.* A. W. Ingersoll, *Org. Reactions*, **2**, 376 (1944).

[27] The reported value (Allred'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 τ): a doublet at 8.90, area 6 ($\mathrm{HC(OCH_3)}$-$\mathit{CH_3}$); a doublet at 8.34 ($\mathrm{HCBr}\mathit{CH_3}$) 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 ($\mathit{H_2}\mathrm{COCH_3}$ and $\mathit{H}\mathrm{C(OCH_3)CH_3}$), area 81; and a multiplet at 5.8 ($\mathit{H}\mathrm{CBrCH_3}$), area 16. From the above nmr it was estimated that the ratio of 2-bromo-5-methoxypentane to 5-bromo-2-methoxypentane is 8:1.

Anal. Calcd for $C_6H_{13}BrO$: C, 39.80; H, 7.24; Br, 44.13. Found: C, 40.25; H, 7.47; Br, 43.56.

The total yield of isomeric bromomethoxypentanes was 21.8 g (48%). The mixture had a rotation of $\alpha^{27}\mathrm{D}$ 0.00 ± 0.01°. Reduction with lithium aluminum hydride (following the procedure used for the reduction of (*R*)-5-bromo-2-methoxypentane) of 8.0 g gave 3.2 g (71%), bp 90–100°, of 1-methoxypentane and 2-methoxypentane. Analysis by vpc on a 15 ft × 0.25 in. 20% Ucon Polar (80°, He 80 cc/min) showed that the 90–100° fraction contained 20% 2-methoxypentane and 80% 1-methoxypentane; no 3-methoxypentane was detected. The 2-methoxypentane was optically inactive.

5-Bromo-2-methoxypentane and 2-bromo-5-methoxypentane, obtained from the reaction, were allowed to stand in a pyridine–lithium bromide solution of the same concentration as the reaction mixture. Vpc analysis indicated that in 3 days 3–4% of the bromopentyl methyl ethers were converted to 2-methyltetrahydrofuran.

Reaction of (*R*)-5-Methoxy-2-pentyl Brosylate (3b) with Lithium Chloride in Pyridine. (*R*)-5-Methoxy-2-pentyl brosylate, $[\alpha]^{27}\mathrm{D}$ −2.05 ± 0.06° (CCl_4, *c* 0.190 g/ml) (prepared from (*R*)-5-methoxy-2-pentanol of 25.0 ± 0.1% optical purity), 80.0 g (0.238 mole), was treated with lithium chloride, 15.3 g (0.36 mole), in 300 ml of pyridine for 12 hr. After the usual work-up, the yield of 2-methyltetrahydrofuran was 0.77 g (3.7%) and that of the chloromethoxypentanes **5** and **6** was 18.3 g (58%), as determined by vpc analysis.

After preliminary separation by distillation, 0.2800 g of 2-methyltetrahydrofuran was isolated by preparative vpc. This was diluted with 0.0870 g of racemic material; the diluted sample had a rotation of $\alpha^{27}\mathrm{D}$ +4.15 ± 0.01°. The 2-methyltetrahydrofuran from the reaction, therefore, had a rotation of $\alpha^{27}\mathrm{D}$ +5.46 ± 0.02° and was of 25.6 ± 0.3% optical purity. It was of (*S*) configuration and was 102 ± 2% inverted in relation to the starting (*R*)-5-methoxy-2-pentanol.

The high boiling fraction, 54–56° (25 mm), from the distillation contained a 4:1 ratio of 2-chloro-5-methoxypentane and 5-chloro-2-methoxypentane, as determined by nmr. The nmr spectrum contained the following peaks (in τ): doublet at 8.92, area 7 ($\mathrm{C(OCH_3)}\mathit{CH_3}$); doublet at 8.53, area 29 ($\mathrm{CCl}\mathit{CH_3}$); multiplet at 8.2, area 49 ($\mathit{CH_2CH_2}$); sharp singlet at 6.77 on top of a multiplet centered at 6.5, total area 61 ($\mathit{CH_3OCH_2}$, $\mathit{CH_3OCH}$, and $\mathrm{Cl}\mathit{CH_2}$); and a multiplet at 6.0, area 9 ($\mathrm{ClC}\mathit{H}$). The peak areas of $\mathrm{C(COCH_3)}\mathit{CH_3}$ and $\mathrm{CCl}\mathit{CH_3}$ were used to determine the ratio of the two chloro compounds. The above mixture had a rotation of $\alpha^{25}\mathrm{D}$ +7.20 ± 0.01°. A portion, 9.4 g (0.075 *m*), of these ethers were converted to the corresponding Grignards, which were treated with water. After the usual work-up, the resulting mixture, 5.4 g (72%), contained an 18:82 ratio of 2-methoxypentane and 1-methoxypentane, as determined by vpc. The 2-methoxypentane isolated by vpc had a rotation of $\alpha^{25}\mathrm{D}$ +3.79 ± 0.01°; it was of (*S*) configuration and 23.3 ± 0.2% optically pure. In relation to the starting alcohol, 2-methoxypentane was 93 ± 1% inverted.

A portion of the above mixture of 2-chloro-5-methoxypentane and 5-chloro-2-methoxypentane, 4.6 g (0.32 mole), was allowed to stand in a solution of 6.2 g (0.145 mole) of lithium chloride in 120 ml of pyridine for 18 hr. After work-up, 3.6 g (82%) of 2-chloro-5-methoxypentane and 5-chloro-2-methoxypentane in a 5:1 ratio were recovered. They were converted through the Grignards to 1-methoxypentane and 2-methoxypentane, 2.3 g (85%). The final product contained 15% 2-methoxypentane and 85% 1-methoxypentane. 2-Methoxypentane was isolated by vpc; it had a rotation of $\alpha^{25}\mathrm{D}$ +3.38 ± 0.01°.

The reaction of (*R*)-5-methoxy-2-pentanol ($\alpha^{25}\mathrm{D}$ −5.11 ± 0.01°, 41.3 ± 0.1% optical purity) with brosyl chloride in pyridine for 3 days at room temperature was worked up as above, and the products were essentially identical. 2-Methyltetrahydrofuran (3.1%) had a rotation of $\alpha^{27}\mathrm{D}$ +8.88 ± 0.08°. It was of 41.7 ± 0.7% optical purity and was 101 ± 2% inverted in relation to the starting alcohol. The yield of the chloro compounds was 43%. From the nmr it was estimated that the ratio of 2-chloro-5-methoxypentane to 5-chloro-2-methoxypentane was 3.5:1 (based on the area of $\mathrm{CH(Cl)}\mathit{CH_3}$ and $\mathrm{CH(OCH_3)}\mathit{CH_3}$). This mixture had a rotation of $\alpha^{25}\mathrm{D}$ +12.08 ± 0.01°. When about one-half of the 5-chloro-2-methoxypentane was removed from the mixture, the rotation increased to $\alpha^{25}\mathrm{D}$ +12.98 ± 0.01°. 2-Methoxypentane, obtained by reduction, had a rotation of $\alpha^{25}\mathrm{D}$ +6.27 ±0.03° (38.5 ± 0.4% optical purity) and was 93 ± 1% inverted in relation to the 5-methoxy-2-pentanol.

The aqueous phase, left over from the extraction of the original reaction mixture, $\alpha^{25}\mathrm{D}$ +0.08 ± 0.01° (*l* = 2 dm), was reextracted with five portions of ether. The ether layer was washed, dried, and distilled in the customary fashion, 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-methoxypentane or 2-chloro-5-methoxypentane. The rotation of the aqueous phase was not changed by the extraction.

Anal. Calcd for $C_6H_{13}OCl$: C, 52.75; H, 9.59; Cl, 25.95. Found: C, 52.83; H, 9.44; Cl, 25.81.

(*R*)-4-Methoxy-1-pentene. (*R*)-1-Penten-4-ol, $\alpha^{25}\mathrm{D}$ −2.01 ± 0.01° (optical purity 44.5 ± 0.2%), 17.2 g (0.2 mole), was dissolved in 75 ml of purified diglyme and treated with small clean pieces of sodium, 4.6 g (0.2 g-atom). The mixture was maintained at 70° for 2 days, by which time all of the sodium had dissolved. After cooling to room temperature, the reaction mixture was treated with 30.0 g of methyl iodide and stirred at room temperature for 1 day. The product was distilled, and the fraction of bp 60–130° was collected. The distillate was redistilled from sodium and the fraction boiling between 86 and 88° was 16.8 g, 84%, ∼98% pure.

A portion of it was collected on vpc (10 ft × 0.5 in., 30% Ucon Polar on Chromosorb W; 85°; He 160 cc/min; retention time 7.5 min). The material purified by vpc had $\alpha^{27}\mathrm{D}$ +2.19 ± 0.01°, $n^{27}\mathrm{D}$ 1.3932. The infrared spectrum in CCl_4 had the following absorption peaks in cm⁻¹: 3000 (s), 2940 (s, broad), 1830 (w, overtone of 915), 1640 (m), 1450 (m, broad), 1380 (m), 1350 (m), 1280 (w), 1230 (w), 1195 (m), 1110 (s, very broad), 990 (m), 950 (w), 915 (s), 630 (m). The nmr in carbon tetrachloride (τ) showed a methyl doublet at 8.92, a multiplet at 7.83 (methylene protons), a sharp singlet at 6.75 (methoxy protons) on top of a multiplet at 6.70 (H on carbon bearing the methoxy), multiplet at 5.00 (terminal vinylic protons), and a multiplet at 4.30 (nonterminal vinylic proton).

Since the starting alcohol was of 44.5 ± 0.2% optical purity, optically pure (*R*)-4-methoxypentene should have a minimum rotation of $\alpha^{27}\mathrm{D}$ +4.92 ± 0.05°. In another run, starting with alcohol of 38.7 ± 0.2% optical purity ($\alpha^{25}\mathrm{D}$ −1.75 ± 0.01°), the methyl ether obtained had a rotation of $\alpha^{22}\mathrm{D}$ +1.89 ± 0.01. The calculated rotation for the optically pure ether is $\alpha^{27}\mathrm{D}$ +4.88 ± 0.06°.

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.93; H, 12.19.

(*R*)-2-Methoxypentane. (*R*)-4-Methoxypentene, $\alpha^{27}\mathrm{D}$ +1.89 ± 0.01° (prepared from the corresponding alcohol of 38.7 ± 0.2% optical purity, sodium hydride, and methyl iodide), 1.8 g (0.018 mole), was hydrogenated in 20 ml of diglyme using 5% Pd–C on a Parr shaker. After filtering off the catalyst the filtrate was distilled to obtain 1.6 g (87%) of (*R*)-2-methoxypentane, bp 90–91°. Since vpc analysis indicated that the above sample was contaminated to the extent of 1–2% with starting material, the analytical sample was obtained by preparative vpc. The collected material, $n^{25}\mathrm{D}$ 1.3813,[28] had the same vpc retention time as the known sample, but different from the starting material. It had an infrared spectrum identical with a known sample and a rotation of $\alpha^{25}\mathrm{D}$ −6.32 ± 0.01°. The calculated rotation for the optically pure ether is $\alpha^{25}\mathrm{D}$ −16.3 ± 0.1°.

(*S*)-4-Trifluoroacetoxy-1-pentene (8). (*S*)-1-penten-4-ol (6.9 g, 0.08 mole, $\alpha^{27}\mathrm{D}$ +1.72 ± 0.01°, of 38.1 ± 0.2% optical purity) and sodium trifluoroacetate (17.7 g, 0.13 mole) were cooled to 0°. With stirring, trifluoroacetic anhydride (21.0 g, 0.10 mole) was added dropwise during 1 hr at temperatures below 10°. The stirring was continued at room temperature for 1.5 hr after completion of addition. The reaction mixture was poured into 150 ml of ice-cold saturated sodium bicarbonate solution and extracted with five portions of ether; the ether layer was dried, and the ether was removed by distillation. The fraction boiling at 110–111° (11.9 g, 82%), $n^{27}\mathrm{D}$ 1.3523, was collected. The infrared spectrum showed the absence of hydroxyl, but a strong band at 1780 cm⁻¹ showed the presence of the trifluoroacetate; absorptions at 1645, 990, 915, and 1420 (shoulder) cm⁻¹ indicated that the terminal double bond was still present. Analysis by vpc on a 15 ft × 0.25 in. 20% Carbowax 20M on 30–60 Chromosorb P (75°, He 120 cc/min) showed only one peak (retention time 5 min). The trifluoroacetate

---

[28] The known sample, prepared by the action of sodium hydride and methyl iodide on 2-pentanol, had $n^{25}\mathrm{D}$ 1.3816, bp 90–91°.

of (*S*)-1-penten-4-ol had a rotation of $\alpha^{25}\text{D}$ −8.56 ± 0.02°. Since the starting material was of 38.1 ± 0.2% purity, an optically pure sample should have a rotation of $\alpha^{25}\text{D}$ −22.5 ± 0.2.

Anal. Calcd for $C_7H_9F_3O_2$: C, 46.16; H, 4.98. Found: C, 46.30; H, 5.23.

(*S*)-5-Bromo-2-trifluoroacetoxypentane (9). Anhydrous hydrogen bromide was bubbled through permanganate-purified ligroin, which was being irradiated with a Sylvania sun lamp. The distillation fraction, bp 50–60°, was collected. (*S*)-4-Trifluoroacetoxy-1-pentene, $\alpha^{25}\text{D}$ −8.56 ± 0.02° (38.1 ± 0.2% optical purity, 10 g, 0.055 mole), was added to 60 ml of the above purified ligroin in a Vycor flask. Anhydrous hydrogen bromide was passed through the solution during irradiation with a Sylvania sun lamp. In about 1 hr, 1 mole equiv of hydrogen bromide was taken up (determined by weighing the flask). Ligroin was distilled off, and the residue was distilled under reduced pressure. The fraction boiling at 87–89° (20 mm), 13.6 g (94%), was collected.

Analysis by vpc on a 15 ft × 0.25 in., 25% di-*n*-decylphthalate on Chromosorb P, 152° (He 135 cc/min), showed two peaks in the approximate ratio of 9:1. The major peak (retention time 16 min) was collected. The nmr of the vpc-purified material showed (in τ) a doublet at 8.65 (methyl protons), a multiplet at 8.15 (nonterminal methylenes), a multiplet at 6.68 (protons of bromomethylene), and a multiplet at 5.00 (*H*COOCCF₃). The infrared spectrum showed the presence of carbonyl (1780 cm⁻¹) and the absence of the carbon–carbon double bond. The vpc purified sample, $n^{25}\text{D}$ 1.4040, had a rotation of $\alpha^{25}\text{D}$ −0.72 ± 0.02°. Optically pure material should have a rotation of $\alpha^{25}\text{D}$ −1.9 ± 0.1°.

Anal. Calcd for $C_7H_{10}BrF_3O_2$: C, 31.96; H, 3.83; Br, 30.38. Found: C, 32.22; H, 3.90; Br, 30.49.

Attempted Hydrolysis of 5-Bromo-2-trifluoroacetoxypentane. 5-Bromo-2-trifluoroacetoxypentane (13.16 g, 0.05 mole) was dissolved in an ethanol-water (100:20) solution. After 2 hr 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 solvent was removed by distillation, and the fraction boiling at 91–94° (14 mm) was collected. The collected material was further purified by preparative vpc on 13 ft × 0.15 in. 20% Dow 11 (110°; He 100 cc/min; retention time 22 min). The infrared spectrum showed no hydroxyl in the purified sample. The nmr showed the following peaks (in τ): doublet at 8.28, three protons ($CHCH_3$); multiplet at 8.0, four protons (protons on C-4 and C-3); triplet at 6.6, two protons ($BrCH_2$); and multiplet at 6.0, one proton ($CH(Br)CH_3$).

This compound,[29] $n^{25}\text{D}$ 1.5053, was 1,4-dibromopentane, obtained in 34% yield (3.95 g).

When the reaction was repeated in the presence of 0.055 mole of sodium bicarbonate, 2-methyltetrahydrofuran was the only detectable product by vpc analysis. Attempts at hydrolysis or ester interchange in anhydrous methanol, methanol–dioxane, and dioxane–water, both in the presence and in the absence of sodium bicarbonate, failed to give 5-bromo-2-pentanol.

(*S*)-2-Methyltetrahydrofuran. To a solution of 2.3 g of sodium in anhydrous methanol was added 70 ml of purified triethyleneglycol dimethyl ether and most of the methanol was removed under vacuum. (*S*)-5-Bromo-2-trifluoroacetoxypentane (12.0 g, $\alpha^{25}\text{D}$ −0.72 ± 0.02°) was added to the methoxide. Some evolution of heat occurred and sodium bromide precipitated. Vpc analysis on a 13 ft × 0.25 in. 20% Dow 11 column (85°, He 100 cc/min) showed that there was no 5-bromo-2-methoxypentane formed. (Analysis could detect 0.1% yield, as shown by control experiments.) Distillation of the reaction mixture yielded 7.2 g of material, bp 63–82°. Analysis by vpc on 13 ft × 0.25 in. 20% Dow 11 (55°, He 80 cc/min) showed that of the 7.2 g, 3.1 g (79%) was 2-methyltetrahydrofuran; the rest was methanol and less than 0.1 g of other compounds. The 2-methyltetrahydrofuran collected from vpc had identical retention time and infrared spectrum with a known sample (Eastman Kodak Co., White Label, redistilled). The collected material, $n^{26}\text{D}$ 1.4016 (known: $n^{26}\text{D}$ 1.4018), had a rotation of $\alpha^{27}\text{D}$ +8.13 ± 0.02°. Since the starting material was of 38.1 ± 0.2% purity, the rotation of optically pure (*S*)-2-methyltetrahydrofuran is $\alpha^{27}\text{D}$ +21.3 ± 0.2°; the data of Gagnaire and Bull[20] give the values α_{5780} +25.2 ± 2.5° and α_{5461} +31.6°.

(*R*)-1,4-Pentanediol. (*R*)-1-Penten-4-ol, $\alpha^{25}\text{D}$ −1.34 ± 0.01°, of 29.6 ± 0.3% optical purity (calculated from the data in ref 10), 11.0 g, dissolved in 600 ml of anhydrous tetrahydrofuran, was treated with excess diborane generated externally from 200 ml of 1 *M* 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.[17] 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 saturated with sodium chloride; 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 119–122° (18 mm, 10.5 g, 79%) was collected; the reported[30] value is bp 221° (753 mm).

Vapor-phase chromatography on a 15 ft × 0.25 in. 20% Carbowax 20 M column (155°, He 200 cc/min) indicated that the product contained 90% 1,4-pentanediol (by coinjection, retention time 28 min) and 10% of another compound that had higher retention time (32 min). The compound with the higher retention time is probably 2,4-pentanediol. A small portion of the 1,4-pentanediol, collected by vpc, had $n^{25}\text{D}$ 1.4452 (lit.[30] $n^{20}\text{D}$ 1.4470) and an infrared spectrum that was identical with that given by Bolton.[19] The nmr spectrum (in τ) had a doublet at 8.82 (3 H), multiplet at 8.42 (4 H), multiplet at 6.3 (2 H), and singlet at 5.9 (2 H). The bisphenylurethan melted at 129–130° (lit.[30] mp 129–131°). The diol had $[\alpha]^{25}\text{D}$ −5.4 ± 0.1° ($CHCl_3$, *c* 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 $[\alpha]^{25}\text{D}$ −18.2 ± 0.5° ($CHCl_3$, *c* 0.224 g/ml) [lit.[18] $[\alpha]^{22}\text{D}$ −4.90 (ethanol, *c* 0.316 g/ml), lit.[19] $[\alpha]^{20}\text{D}$ −13.4° (CH_3OH, *c* 1.05 g/ml)].

(*R*)-5-Methoxy-2-pentanol. (*R*)-1,4-pentanediol, $[\alpha]^{25}\text{D}$ −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 tetraethyleneglycol 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 tetraethylene glycol dimethyl ether. The resulting alkoxide was treated dropwise with 10.5 g (0.074 mole) of methyl iodide; the reaction mixture was stirred at room temperature for 11 hr after the completion of addition. Distillation yielded the following fractions: 43–45° (15 mm), 1.730 g; 73–75° (15 mm), 3.28 g; and 76–79° (15 mm), 2.60 g. The two higher boiling fractions contained 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 × 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. The vpc purified material had $\alpha^{25}\text{D}$ −3.70 ± 0.01°. If the starting material was optically pure, the rotation of (*R*)-5-methoxy-2-pentanol would be $\alpha^{25}\text{D}$ −12.5 ± 0.2°.

(*R*)-5-Bromo-2-methoxypentane. Anhydrous hydrogen bromide was bubbled through a solution of 15 g of (*R*)-4-methoxy-1-pentene, $\alpha^{27}\text{D}$ +1.03 ± 0.01°, optical purity 20.9 ± 0.4%, in 200 ml of purified ligroin in a Vycor flask. Two Blak-Ray[31] lamps and 0.5 g of benzoyl peroxide were used as initiators. After approximately 9 g (~75% of theoretical) of hydrogen bromide was taken up, the reaction mixture was distilled; 3.4 g of starting material, bp 86–88°, was recovered. The desired material, 14.3 g (68%, based on unrecovered starting material), boiled at 72–74° (20 mm). Analysis by vpc (on 15 ft × 0.25 in. 20% Carbowax 20M, 100°, He 135 cc/min) showed two peaks in the approximate ratio of 92:8. The major peak (retention time 30 min) had $n^{26}\text{D}$ 1.4474 and $\alpha^{27}\text{D}$ −1.37 ± 0.01°. The minimum rotation of optically pure (*R*)-5-bromo-2-methoxypentane should be $\alpha^{27}\text{D}$ −6.56 ± 0.2°. The infrared spectrum of the material collected from vpc showed the absence of the carbon–carbon double bond; its nmr spectrum (in τ) had a methyl doublet at 8.90, a multiplet at 8.3 (protons on C-3 and C-4), and a sharp singlet at 6.75 (methoxy protons) on top of a multiplet centered at 6.7 ($BrCH_2$ and CH_3OCH).

Anal. Calcd for $C_6H_{13}BrO$: C, 39.80; H, 7.24. Found: C, 39.92; H, 7.35.

(*R*)-2-Methoxypentane. (*R*)-5-Bromo-2-methoxypentane, 9.0 g (0.0497 mole), from the above preparation, was added drop-

---

[29] The reported constants are: $n^{20}\text{D}$ 1.5087, bp 74–80° (9 mm) (N. I. Shuikin and I. F. Belskii, *Dokl. Akad. Nauk SSSR*, **111**, 1048 (1956); *Chem. Abstr.*, **51**, 9569*a* (1957)).

[30] G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 188 (1962).

[31] Long-wavelength ultraviolet lamp from Ultraviolet Products, Inc., South Pasadena, Calif.

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 ice-cold 1 *N* hydrochloric acid. The usual work-up gave 3.6 g (71%) of a fraction, bp 90–91°. Preparative vpc on a 15 ft × 0.25 in. 20% Carbowax 20M on Chromosorb P column (70°, He 80 cc/min) yielded pure (*R*)-2-methoxypentane (the fraction obtained from distillation was approximately 98% pure). The vpc purified sample, $n^{25}\text{D}$ 1.3814 (known sample: $n^{25}\text{D}$ 1.3816), had retention time and infrared spectrum identical with a known sample.[28] It had $\alpha^{25}\text{D}$ $-3.24 \pm 0.01°$. 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 $\alpha^{25}\text{D}$ $-15.5 \pm 0.3°$, to be compared with $\alpha^{25}\text{D}$ $-16.3 \pm 0.1°$ 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[1]

J. E. Anderson[2a] **and J. M. Lehn**

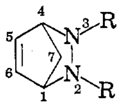
Contribution from the Institut de Chimie, Université de Strasbourg, Strasbourg 67, France.[2b] *Received August 19, 1966*

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. Solvent effects on the barrier height have been observed.

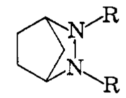
Of the different types of rate processes amenable to quantitative study by means of variable temperature nuclear magnetic resonance, nitrogen inversion is among the most fascinating for both physical and chemical reasons. Nitrogen inversion is usually very fast on the nmr time scale, but in certain compounds structural features may so slow down inversion that its effects are visible in the nmr spectrum. The first reported study was in the aziridine series,[3] where ring strain leads to a high barrier to inversion. Temperature changes in the nmr spectrum of a sterically hindered benzoquinoline have been attributed to hindered nitrogen inversion.[4] Recently, studies of an open-chain hydroxylamine ether[5] and a perfluorohydroxylamine ether[6] have provided further examples of hindered nitrogen inversion, which has also been observed in diaziridine derivatives[7] and in a fluorinated oxazetidine.[8]

In the course of an investigation of rate processes in nitrogen-containing heterocycles,[1,9–11] we have become interested in the analogous bicyclic systems.[11]

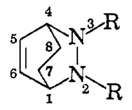
Several compounds of this type have been found to display temperature-dependent nmr spectra. We report here our studies of *double nitrogen inversions* in compounds of the 2,3-diazabicyclo[2.2.1]heptane and 2,3-diazabicyclo[2.2.2]octane series.



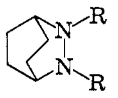
1, R = $COOC_2H_5$
2, R = CH_3
3, R = CD_3



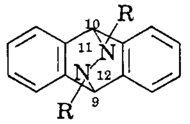
4, R = $COOC_2H_5$
5, R = CH_3
6, R = H



7, R = $COOC_2H_5$
8, R = CH_3



9, R = $COOC_2H_5$
10, R = CH_3



11, R = $COOCH_3$
12, R = CH_3

Results

Preparation of the Substrates. Diels–Alder addition of diethyl azodicarboxylate to cyclopentadiene[12] gives an adduct **1** 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′-di(trideuteriomethyl) derivative **3**. Hydrogenation of adduct **1** produces the dihydro adduct[13] **4** which by treatment with LAH gives N,N′-dimethyl-

---

[1] Part IV: J. M. Lehn and F. G. Riddell, *Chem. Commun.*, in press.

[2] (a) Salters' Co. Postdoctoral Research Fellow 1964–1966; (b) laboratory associated with the Centre National de la Recherche Scientifique.

[3] (a) For a recent review see J. P. Engstrom in Massachusetts Institute of Technology Seminars in Organic Chemistry, Cambridge, Mass., first semester 1965–1966, p 255; (b) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5126 (1956); **80**, 5203 (1958); (c) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960); (d) A. L. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964); (e) H. S. Gutowsky, *Ann. N. Y. Acad. Sci.*, **70**, 786 (1958); (f) T. J. Bardos, C. Szantay, and C. K. Navada, *J. Am. Chem. Soc.*, **87**, 5796 (1965); (g) A. T. Bottini, R. L. Van Etten, and A. J. Davidson, *ibid.*, **87**, 755 (1965).

[4] W. M. Speckamp, U. K. Pandit, and H. O. Huismann, *Tetrahedron Letters*, 3279 (1964).

[5] D. L. Griffith and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 4089 (1965).

[6] R. E. Banks, M. G. Barlow, R. N. Haszeldine, and M. K. McCreath, *J. Chem. Soc.*, 7203 (1965).

[7] K. Deutsch, *Ann. Physik*, **16**, 300 (1965).

[8] J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **61**, 2342 (1965).

[9] J. C. Brelière and J. M. Lehn, *Chem. Commun.*, 426 (1965).

[10] F. G. Riddell and J. M. Lehn, *ibid.*, 375 (1966).

[11] J. E. Anderson and J. M. Lehn, *Bull. Soc. Chim. France*, 2402 (1966).

[12] J. C. J. McKenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.*, **17**, 1666 (1952).

[13] O. Diels, J. H. Blom, and W. Koll, *Ann.*, **443**, 242 (1925).