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Stereochemistry of the Primary Carbon. III. Optically Active 1-Aminobutane-1-*d*[1,2]

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Optically active 1-butanol-1-*d* was converted to 1-aminobutane-1-*d* by reaction of 1-butyl-1-*d* brosylate with sodium azide followed by reduction with lithium aluminum hydride. Arguments are presented that this reaction sequence is accompanied by little or no racemization. By an analogous reaction sequence, 2-octanol was converted to 2-aminoöctane with >97% retention of optical purity.

The study of the stereochemistry of several reactions of an optically active primary carbinylamine required the conversion in a completely stereospecific manner of optically active 1-butanol-1-*d* to 1-aminobutane-1-*d*. None of the methods previously described for effecting this transformation with simple alcohols has been shown to proceed in a completely stereospecific manner. The Gabriel synthesis as it has been applied to sulfonate esters[4] and to alkyl halides[5] did not appear attractive. Not only are long periods of heating at elevated temperatures frequently required, but the use of alkyl halides may involve additional stereochemical uncertainties in establishing relative optical purity. Also there is danger of racemization by the halide ion produced in the reaction. The procedure actually adopted was a modification of the method of Levine and Rother[6] who treated *sec*-butyl iodide with sodium azide, followed by hydrogenation of the resulting *sec*-butyl azide to the optically active *sec*-butylamine. The modifications involved the use of a sulfonate ester in the sodium azide displacement step and the use of lithium aluminum hydride in the reduction of the azide to the amine.[7]

For use in stereochemical studies of a number of reactions a large homogeneous amount of optically active 1-butanol-1-*d* was required. One obvious advantage of such a procedure is that the direct interrelationship of the optical activities of the compounds used in the various studies is facilitated. Consequently, a large quantity of (−)-1-butanol-1-*d* was prepared by a modification of the procedure previously used.[2] Instead of a partially stereospecific reduction of butyraldehyde with optically active 2-octyloxymagnesium-2-*d* halide, butyraldehyde-1-*d* was reduced with optically active 2-octyloxymagnesium halide.

1-Butanol-1,1-d_2 was prepared by the reduction of a *n*-butyrate ester with deuteroacetic acid and sodium.[8] Oxidation with potassium dichromate and sulfuric acid gave butyraldehyde-1-*d*. The optically active 2-octanol used in the reduction of the butyraldehyde-1-*d* was obtained by the standard resolution.[9] Sufficient 2-octanol was resolved that only one enantiomer, (−)2-octanol, was employed in the partially asymmetric reduction. The (−)1-butanol-1-*d* resulting from several runs was combined and distilled several times through a small column to constant rotation. A sample was used for the preparation of the crystalline hydrogen phthalate. After several recrystallizations, hydrolysis regenerated 1-butanol-1-*d* having a rotation identical with that of the main batch. In this way a total of 95 grams of 1-butanol-1-*d* was prepared having $[\alpha]^{25}\mathrm{D}$ $-0.0434 \pm 0.0012°$. It is interesting to note that although 2-octanol-2-*d* yields 1-butanol-1-*d* having the opposite sign of rotation, the use of 2-octanol with butyraldehyde-1-*d*, as expected, yields 1-butanol-1-*d* having the same sign of rotation.

Part of this optically active 1-butanol-1-*d* was converted to the corresponding *p*-bromobenzenesulfonate by reaction with *p*-bromobenzenesulfonyl chloride in pyridine.[2] The resulting 1-butyl-1-*d* brosylate was treated with an excess of sodium azide in aqueous methanol. The product 1-butyl-1-*d* azide was not isolated but was reduced directly in ether solution with lithium aluminum hydride. A 70% over-all yield was obtained of 1-aminobutane-1-*d* having $[\alpha]^{25}\mathrm{D}$ $-0.009 \pm 0.003°$. This material was used in stereochemical studies of the amine–nitrous acid reaction and of the thermal decomposition of N-nitrosoamides which will be reported separately.

Since no completely stereospecific method is known for converting an amine of this type to the corresponding alcohol, no direct check could be made on the optical purity of the 1-aminobutane-1-*d* relative to 1-butanol-1-*d*. Nevertheless, it was important to know whether any racemization accompanied the preparation of the amine. Examination of the individual steps involved in the synthesis, however, leads to the conclusion that the amine should have the same optical purity as the starting alcohol. The preparation of 1-butyl-1-*d* brosylate should not result in any racemization because the asymmetric center is not involved. The direct displacement reaction of 1-butyl-1-*d* brosylate with azide ion is closely analogous to the similar reaction with acetate ion in methanol. The latter reaction has been demonstrated to proceed with complete inversion of configuration.[10] Hence, the azide ion displacement is expected to

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[1] Taken in part from the dissertation submitted by William D. Schaeffer in partial fulfillment of the degree of Doctor of Philosophy, University of California, June, 1956.

[2] Part II: This Journal, **77**, 1117 (1955).

[3] General Electric Fellow, 1955–1956.

[4] E. Sakellarios, *Helv. Chim. Acta*, **29**, 1675 (1946).

[5] J. C. Sheehan and W. A. Bolhofer, This Journal, **72**, 2786 (1950); H. Ing and R. Manske, *J. Chem. Soc.*, 2348 (1926).

[6] P. A. Levine and A. Rother, *J. Biol. Chem.*, **115**, 415 (1936).

[7] J. H. Boyer, This Journal, **73**, 5865 (1951).

[8] D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, *ibid.*, **74**, 5599 (1952).

[9] A. W. Ingersoll in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 400.

[10] Ref. 2 and additional experiments of W. D. Schaeffer which will be published separately.

proceed with complete inversion. The reduction of 1-butyl-1-*d* azide with lithium aluminum hydride should proceed with complete retention of configuration because, again, the asymmetric center is not involved. However, the slight possibility of salt formation with the azide was investigated. A reaction of this sort with lithium aluminum hydride would result in a resonance stabilized carbanion, $\mathrm{R\overset{\ominus}{C}H{-}\overset{\oplus}{N}{=}N{=}\overset{\ominus}{N}} \longleftrightarrow \mathrm{RCH{=}N{-}N{=}\overset{\ominus}{N}}$, which, of course, would lead to a partially racemic product. This possibility was checked by converting 1-butanol-1,1-d_2 having 1.88 ±0.03 deuterium atoms per mole into 1-aminobutane-1,1-d_2 having 1.92 ±0.03 deuterium atoms per mole by the same sequence of steps used above. If any salt formation had taken place in the lithium aluminum hydride reaction, the product amine would have lost deuterium. Within experimental error no loss of deuterium was observed. Hence, salt formation is not a significant factor in the lithium aluminum hydride reduction of the azide.

Finally, the procedure for converting an alcohol to an amine was applied to optically active 2-octanol; the stereochemical relationship to 2-octylamine is known. 2-Octanol having $\alpha^{23}\mathrm{D}$ +5.79 ± 0.01° ($l = 2$) (36.0% of optical purity)[11] was converted to the tosylate in the usual way. The 2-octyl tosylate was allowed to react with sodium azide in aqueous methanol and the product, 2-octyl azide, without isolation was treated with lithium aluminum hydride in ether solution. The 2-octylamine produced in 59% yield (based on the tosylate) had $\alpha^{23}\mathrm{D}$ −3.70 ± 0.02° ($l = 2$) (34.9% of optical purity).[14] Consequently, the conversion went with 97%[16] of optical purity. These results strongly suggest that little or no racemization accompanied the transformation of alcohol to amine in the 1-butanol-1-*d* case.

Experimental

Optical rotations were taken on a Rudolph precision polarimeter on which readings could be made to the nearest 0.001°. Optical rotations of liquids were taken on the homogeneous liquid in wide bore center-fill tubes. The precision of such rotations is about ±0.003°.

1-Butanol-1,1-d_2.—The procedure of Hauser, *et al.*,[8] was followed in the reduction of a butyrate ester with sodium and deuteroacetic acid in the preparation of 1-butanol-1,1-d_2. The best yield (85%) was obtained with *n*-octyl butyrate using 3.33 moles of deuteroacetic acid and 3.83 atoms of sodium per mole of ester. In the infrared spectrum of 1-butanol-1,1-d_2, the C–D stretching doublet occurred at 4.52 and 4.74 μ.

1-Butanal-1-*d*.—1-Butanol-1,1-d_2 was oxidized to butanal-1-*d* with potassium dichromate and sulfuric acid following essentially the procedure described in "Organic Syntheses"[17] for the oxidation of propyl alcohol to propionaldehyde. In each of several runs 1.7 moles of 1-butanol-1,1-d_2 was allowed to react with a mixture containing 0.56 mole of potassium dichromate and 2.2 moles of sulfuric acid in one liter of water. The best yield was obtained when the oxidizing solution was added over a period of two hours. Under these conditions 7% of the alcohol was converted to ester and 46% of the alcohol was oxidized to butanal-1-*d*. In the infrared spectrum of butanal-1-*d* the C–*D* stretching band occurred at 4.82 μ.

1-Butanol-1-*d*.—The preparation was essentially that of Streitwieser[2] except that butanal-1-*d* and 2-octyloxymagnesium bromide were used. The 2-octyloxymagnesium bromide was prepared from 2-octanol, which was almost optically pure, and propylmagnesium bromide. The resulting ether solution was 2 *M* in 2-octyloxymagnesium bromide and 2 *M* in butanal-1-*d* and was allowed to stand for three hours at room temperature before the reaction was stopped by the addition of dilute hydrochloric acid. The yield was 44 to 49% and did not vary significantly with a change in the molar ratio of the reagents. The product from four such runs was distilled four times through a small glass spiral column rated at 5 plates. The distillate from the third distillation had $\alpha^{25}\mathrm{D}$ −0.145 ± 0.004° ($l = 4$) and $\alpha^{25}{}_{5461}$ −0.176 ± 0.004° ($l = 4$), whereas the distillate from the fourth distillation had $\alpha^{25}\mathrm{D}$ −0.143 ± 0.004° ($l = 4$) and $\alpha^{25}{}_{5461}$ −0.173 ± 0.005° ($l = 4$) and b.p. 116.5 117.5°.

The 17 g. of 1-butanol-1-*d* boiling outside the above boiling range was converted into the hydrogen phthalate using phthalic anhydride.[2] The solid derivative was recrystallized four times from cyclohexane–benzene. After the second recrystallization the material had $[\alpha]^{25}\mathrm{D}$ +0.062 ± 0.004° (*c* 25, acetone). After the fourth recrystallization the ester had $[\alpha]^{25}\mathrm{D}$ +0.063 ± 0.004° (*c* 25, acetone). This material was saponified giving 1-butanol-1-*d* (5.1 g.) having $\alpha^{25}\mathrm{D}$ −0.140 ± 0.005° ($l = 4$) and $\alpha^{25}{}_{5461}$ −0.176 ± 0.008° ($l = 4$). This was combined with the main batch of 1-butanol-1-*d* which had $n^{25}\mathrm{D}$ 1.4008, $d^{25}{}_4$ 0.8170 (corresponds to 1.0 atoms D per molecule, assuming constancy of molecular volume), $\alpha^{25}\mathrm{D}$ −0.142 ± 0.004° ($l = 4$) and $\alpha^{25}{}_{5461}$ −0.176 ± 0.005° ($l = 4$). These rotations are the unweighted averages of all the rotations taken on the pure alcohol. The total quantity prepared was 95.0 g.

Optically Active 1-Aminobutane-1-*d*.—Eighteen and eight-tenths grams (0.25 mole) of 1-butanol-1-*d* prepared above was converted to the *p*-bromobenzenesulfonate using *p*-bromobenzenesulfonyl chloride in pyridine.[2] The 1-butyl-1-*d* brosylate was transferred to a flask which contained 24.0 g. (0.369 mole) of sodium azide dissolved in 250 ml. of methanol and 65 ml. of water. The flask was immersed in a thermostat at 65° and the mixture was stirred magnetically. Shortly after the solution of the brosylate was complete, solid sodium brosylate began to precipitate. After stirring and heating for 24 hr. the reaction mixture was allowed to cool to room temperature and the solid sodium brosylate was filtered. The filtrate was added to a flask which contained 700 ml. of a calcium chloride solution (prepared by dissolving 800 g. of calcium chloride in 2000 ml. of water) and 300 ml. of *n*-butyl ether. After thorough mixing the organic phase was separated and the aqueous phase was re-extracted three times with 100-ml. portions of *n*-butyl ether. The combined extracts were dried with anhydrous calcium chloride. The infrared spectrum of this solution showed a strong absorption band at 4.67 μ which is attributed to the azide grouping.

To 70 ml. of *n*-butyl ether and 8.5 g. (0.224 mole) of lithium aluminum hydride the above solution of 1-butyl-1-*d* azide in *n*-butyl ether was added dropwise and with stirring. The addition which was made over a period of 2 hr. was accompanied by evolution of nitrogen. When addition was complete, the mixture was stirred at room temperature for 1 hr. and water was added to destroy the excess lithium aluminum hydride and to precipitate the inorganic salts. The organic phase was decanted, the inorganic salts were dissolved in concentrated potassium hydroxide solution and the aqueous solution was extracted three times with 50-ml. portions of *n*-butyl ether. The combined organic phases were dried over anhydrous sodium sulfate and were slowly distilled through a 24-in. Vigreux column. The first 150 ml. of distillate, b.p. 75–140°, was redistilled through a small glass spiral column to give 13.5 g. (73% yield based on starting alcohol) of 1-aminobutane-

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(11) The highest recorded rotation, $\alpha^{16}{}_{5461}$ +19.45° ($l = 2$)[12] corresponds to $\alpha^{23}\mathrm{D}$ +16.08° ($l = 2$).[13]

(12) T. S. Patterson and C. Buchanan, *J. Chem. Soc.*, **125**, 1475 (1924).

(13) M. K. Hargreaves, *ibid.*, 2953 (1953).

(14) The maximum recorded rotation for 2-octylamine is $\alpha^{19}\mathrm{D}$ 5.30° ($l = 1$).[15]

(15) F. G. Mann and J. Reid, *J. Chem. Soc.*, 3384 (1950).

(16) This is a minimum figure. Our 2-octylamine was not scrupulously dried and probably contained traces of water. Traces of water are known to lower the rotation of 2-octylamine by about 3%.[15]

(17) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 541.

1-*d*, b.p. 77–80°. In another run the yield was 10.9 g. (60%). The combined materials were redistilled to yield 21.0 g. of 1-aminobutane-1-*d* having b.p. 77–79°, $\alpha^{25}{}_D$ $-0.013 \pm 0.004°$ ($l = 2$), $\alpha^{25}{}_{5461}$ $-0.015 \pm 0.005°$ ($l = 2$), $n^{25}{}_D$ 1.3967, $d^{25}{}_4$ 0.7471. The infrared spectrum showed a doublet in the C—D region at 4.63 and 4.72 μ.

1-Aminobutane-1,1-d_2.—A portion of the 1-butanol-1,1-d_2 used in this experiment, which had $d^{25}{}_4$ 0.8255 (corresponding to 1.82 ± 0.1 atoms D per molecule), was converted to hydrogen 1-butyl-1,1-d_2 phthalate, which after two crystallizations from benzene–hexane had m.p. 73.0–73.4°. A deuterium analysis[18] showed 1.88 ± 0.03 atoms D per molecule. The alcohol was converted to 1-aminobutane-1,1-d_2 following the procedure described above, in an over-all yield of 69%. A portion of the 1-aminobutane-1,1-d_2 was treated with phenyl isothiocyanate and the resulting N-1-butyl-1,1-d_2-N-phenylthiourea obtained had, after two crystallizations from benzene–heptane, m.p. 64.0–64.3°. Deuterium analysis[18] showed 1.92 ± 0.03 atoms D per molecule. The infrared spectrum of the amine showed a doublet at 4.57 and 4.79 μ.

2-Octyl Tosylate.—To a 500-ml. flask equipped with a calcium chloride drying tube and arranged for magnetic stirring was added 300 ml. of dry pyridine and 33.0 g. (0.25 mole) of 2-octanol, $\alpha^{23}{}_D$ $5.79 \pm 0.01°$ ($l = 2$). The mixture was placed in an ice-bath and 80.0 g. (0.42 mole) of *p*-toluenesulfonyl chloride was added in 40-g. portions, made 15 min. apart. The mixture was stirred in the cold for 1 hr. and placed in a refrigerator for 2 hr. The reaction mixture was poured into 300 ml. of concentrated hydrochloric acid and 500 ml. of water and ice. The organic phase was separated and dried with anhydrous sodium sulfate, yield 56 g. (76% yield) of 2-octyl tosylate.

2-Aminoöctane.—To a solution containing 20.0 g. (0.308 mole) of sodium azide in 260 ml. of methanol and 58 ml. of water pre-heated in a thermostat held at 70° was added 52 g. (0.178 mole) of 2-octyl tosylate. The addition of the tosylate resulted in a small phase separation. After heating and stirring for 24 hr. the mixture was allowed to cool to room temperature and was diluted with 150 ml. of water and poured into 200 ml. of ether. The resulting mixture was treated with 250 ml. of a calcium chloride solution (prepared by dissolving 800 g. of calcium chloride in 2 l. of water). After separating the phases the aqueous phase was extracted three times with 100-ml. portions of ether. The combined ether solutions were dried with calcium chloride.

To a stirred suspension of 50 ml. of dry ether and 7.0 g. (0.184 mole) of lithium aluminum hydride was added dropwise, the ether solution of 2-octyl azide prepared above. The addition was carried out over a period of 1.5 hr. and was accompanied by evolution of nitrogen. The mixture was then refluxed for 1 hr., cooled to room temperature, and treated with an excess of dilute hydrochloric acid. The aqueous phase was separated and was extracted once with 75 ml. of ether. The aqueous phase was then made strongly alkaline with concentrated potassium hydroxide solution and was heated on a steam-bath until all of the inorganic salts dissolved. After cooling to room temperature the mixture was extracted three times with 75-ml. portions of ether. The combined organic phases were dried over magnesium sulfate. After removal of the ether distillation yielded 13.6 g. (59% based on 2-octyl tosylate) of 2-aminoöctane, b.p. 163–164°, $\alpha^{23}{}_D$ $-3.70 \pm 0.02°$ ($l = 2$).

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[18] We are grateful to Dr. N. R. Treuner of Merck and Co. for the deuterium analyses.

[Contribution from the Department of Chemistry, Massachusetts Institute of Technology]

Proximity Effects. III. *trans*-1,4-Cyclohexanediol from Cyclohexene and Performic Acid

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Hydroxylation of cyclohexene with performic acid has been shown to yield *trans*-1,4-cyclohexanediol (0.03%) and the two stereoisomeric 2,2′-dihydroxydicyclohexyl ethers in addition to 85% of the normal product, *trans*-1,2-cyclohexanediol.

The isolation of *cis*-1,4-cycloheptanediol in 2.4% yield from the products of solvolysis of cycloheptene oxide with dilute hydrochloric acid[2] led us to investigate the hydroxylation of cyclohexene with performic acid, to determine whether products other than the normal *trans*-1,2-glycol were formed. Cyclohexene was treated with a mixture of formic acid and hydrogen peroxide under conditions similar to those described by Roebuck and Adkins.[3] The products isolated were *trans*-1,2-cyclohexanediol (85%), *trans*-1,4-cyclohexanediol (0.03%), 1-methyl-*trans*-1,2-cyclopentanediol (0.37%) and a high-boiling residue (approximately 8%) containing the two stereoisomeric 2,2′-dihydroxydicyclohexyl ethers. These compounds were separated from the mother liquors from crystallization of *trans*-1,2-cyclohexanediol by chromatography on alumina. No other pure compounds were isolated.

trans-1,4-Cyclohexanediol was identified by comparing its infrared spectrum with the spectrum of an authentic sample, and by mixed melting point of the two samples. 1-Methyl-*trans*-1,2-cyclopentanediol was identified by comparison with an authentic sample[4] (infrared spectra and mixed m.p.), and by comparison of the monophenylurethans of the two samples. Vapor phase chromatography of the cyclohexene employed on a column containing silicone oil (Dow Corning 550) and 100–200 mesh Celite in a ratio of 3:7 showed that it contained 0.66% of 1-methylcyclopentene, thus accounting for the formation of 1-methyl-*trans*-1,2-cyclopentanediol derived from this impurity.[5] A second impurity present in the cyclohexene to the extent of 0.20% according to the vapor-phase chromatogram is believed to be methylenecyclopentane; an authentic sample of that hydrocarbon showed identical behavior on vapor-phase chromatography. The structures of the stereoisomeric 2,2′-dihydroxydicyclohexyl ethers are assigned on the basis of elemental analyses, and the isolation of a homolo-

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[1] National Institutes of Health Postdoctoral Fellow, 1955–1956.

[2] A. C. Cope, T. A. Liss and G. W. Wood, *Chemistry and Industry*, 823 (1956).

[3] A. Roebuck and H. Adkins, *Org. Syntheses*, **28**, 35 (1948).

[4] C. J. Maan, *Rec. trav. chim.*, **48**, 332 (1929).

[5] Dehydration of cyclohexanol and isomerization of cyclohexene are known to result in the formation of 1-methylcyclopentene; see H. Adkins and A. K. Roebuck, This Journal, **70**, 4041 (1948).