Correlation of Absolute Configurations with Stabilities of Molecular Complexes

by

Wayne Myron Stalick

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University of Oregon

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LeRoy H. Klemm, Adviser for Thesis

ACKNOWLEDGEMENTS

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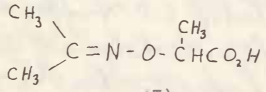
HISTORY AND INTRODUCTION

Many methods have been used for the optical resolution of racemic mixtures of compounds bearing no functional group capable of salt formation with an optically active acid or base.[1] None of these methods appeared particularly promising, however, for the resolution of polycyclic aromatic hydrocarbons in which molecular asymmetry is due to intramolecular overcrowding.[2]

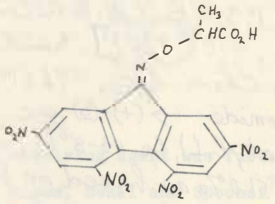
Racemic and optically active polynitrobiphenylcarboxylic acid and esters were reacted with synthetic 1-phenyl-1-(2-naphthyl)ethane, 1-phenyl-1-(1-naphthyl)ethane, 2-naphthylbutane, 7-methylacenaphthene and 7-phenylacenaphthene.[3] Only 7-methylacenaphthene successfully yielded a molecular compound with racemic dimethyl 4,6,4',6'-tetranitrobiphenate. However, no solid compounds were formed with optically active acids or esters. These optically active polynitrobiphenyl derivatives have proved unsuitable for resolution because of their poor complexing ability.

In 1956 Newman and Lutz[4] reported the synthesis of racemic 2-(isopropylideneaminoöxy)propionic acid (I) and its resolution into the enantiomers (-)-I and (+)-I by treating the racemic compound with (-)-ephedrine in a 1:1 benzene-Skellysolve B solution. The resulting salt was dissociated

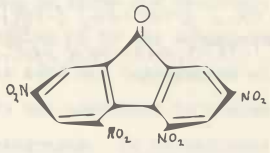
with hydrochloric acid to give (+)-I in crystalline form. After removal of (+)-I, (-)-I was obtained from the filtrate. When the (-)-I and (+)-I enantiomers were treated with 2,4,5,7-tetranitrofluorenone (III), they yielded the respective optically active molecular complexing agents (+)- and (-)-2-(2,4,5,7-tetranitro-9-fluorenylidene-aminoöxy)propionic acids (II).



(I)



(II)



(III)

This strong complexing agent (II) has been used to resolve, by means of fractional crystallization or precipitation from solution, several compounds lacking any functional group capable of salt formation.[4,5] Specifically, the compounds were 1-naphthyl 2-butyl ether (IV), methyl

↑ First reported in M. S. Newman, W. B. Lutz, + D. Lednicer, J. Am. C. S., 77, 3420 (1955).

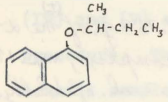
Literature survey on chiral

$C_{10}H_{14}O$

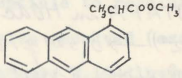
P. A. Spanninger & J. L. von Rosenberg, J. Am. Chem. Soc., 94, 1973 (1972).

2-Butanol was resolved via the half phthalate ester [J. W. Kantor and C. R. Hauser, J. Am. Chem. Soc., 75, 1744 (1953)]. Active alcohols were separately carried to the corresponding 2-Br butanes w. PBr_3 to give (-)-(R)-2-bromobutane, $[\alpha]_D^{24}$ -20.09 ± 0.02° (neat), 51.0% opt. pure, & (+)-(S)-2-bromobutane, $[\alpha]_D^{25}$ +11.80 ± 0.02° (neat), 30% opt. purity [P. S. Skell, R. G. Allen, & G. K. Helmkemp, J. Am. Chem. Soc., 82, 410 (1960)]. Used method of E. D. Hughes & C. K. Ingold, J. Chem. Soc., 1196 (1937) for alcoholysis of the bromides. (-)-(R)-bromide ⟶ (+)-(S)-sec.-butyl phenyl ether, α_D^{25} +27.27 ± 0.02° (neat, l 1), bp 46-8° (1.1 mm.), n_D^{23} 1.4942, assumed opt. purity of 51.0% as based on bromide [Hughes & Ingold claim >98% bimolecular rx. for this process.] (-)-(R)-ether had α_D -15.41 ± 0.2° (neat, l 1), n_D^{24} 1.4973, assumed opt. purity 30%.

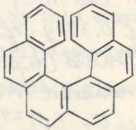
2-(1-anthryl)propionate (V), and phenanthro(3,4-c)phenanthrene (VI). Partial resolution of racemic (VI) with optically active (II) was the first example of the resolution of an underivatized hydrocarbon which owes its asymmetry to intramolecular overcrowding.



(IV)



(V)



(VI)

$C_{14}H_{16}O$

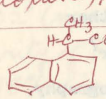
Checked C.A. formula indices, vols. 14-79, also Beilstein formula index,

The application of II as a resolving agent was further extended by Klemm and Reed[6] and Klemm, Desai and Spooner[7] by adapting it to use in molecular complexation chromatography. Silicic acid was impregnated with optically active II and used as the adsorbent in ordinary liquid-solid adsorption chromatography. It is believed that the adsorption of an aromatic hydrocarbon or of its simple derivatives involves the formation of a molecular complex between II and the substrate on the surface of the silicic acid. The chromatographic column was operated under conditions believed to represent virtual equilibrium so that the enantiomer (of the racemic substrate added to the column) which forms the

M. S. Newman & W. B. Lutz, J. Am. Chem. Soc., 78, 2469 (1956).

Hot soln of 0.589 g. of (±) 1-naphthyl 2-butylether and 0.944 g. of (-)TAPA in 1 ml. HOAc gave (on cooling) a pasty mass. Trituration w. 4 ml. of Skellysolve B of the purplish complex, filtration, & washing with 4 ml. of Skellysolve B, & drying in vacuo → 0.819 g. (94%) of complex, mp 137-141°. Washing complex & filt. (separately) w. NaHCO_3 soln removed TAPA → crude ether 0.158 g. $[\alpha]_D^{31}$ -7.8 ± 0.2° (c, 6.4, EtOAc) & 0.0508 g. $[\alpha]_D^{29}$ -7.4 ± 0.5° (c, 2.03, EtOAc), obtained thru evap. dist. filt. → ether, $[\alpha]_D^{32}$ +6.4 ± 0.09° (c, 11, EtOAc), (-)TAPA was recovered fr. the HCO_3^- extracts.

Hot soln of 0.330 g. of (+)TAPA in HOAc & 0.368 g. of the (±) α-(1-anthryl)propionate (mp 91-2°) → 0.521 g. of complex, mp 196-200°. Washing w. HCO_3^- removed TAPA. Residue cryst. fr. 2 ml. of Skellysolve B → 0.126 g. of ester, $[\alpha]_D^{29}$ +36.8 ± 0.1° (c, 4.3, dioxane). Residue fr. filt. → 0.150 g. of tan ~~filt~~ solid, mp 85-9°, $[\alpha]_D^{27}$ -66.0 ± 0.1° (c, 5, dioxane).



A. Fredga, Arkiv Kemi, 8, 463 (1956).

Prep. of racemic acid by method of Widequist [Arkiv Kemi, Mineral. Geol. 24B, No. 14 (1947).]

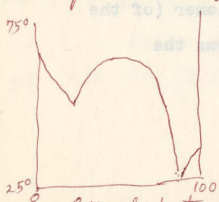
1-RphCH_2CN → 1-Rph-$CH(CN)CO_2Et$ → 1-Rph-$C(CH_3)(CN)CO_2Et$ → 1-Rph-$CH(CH_3)CO_2H$

Resolved by means of brucine and cinchonidine.

(+)-acid → small prisms or 4-sided plates, mp 69-69.5°, $[\alpha]_D^{25}$ (0.2025 g./10 ml. $CHCl_3$) +180.5°; $[\alpha]_D^{25}$ (0.2076 g./10 ml. abs. EtOH) +120.3°.

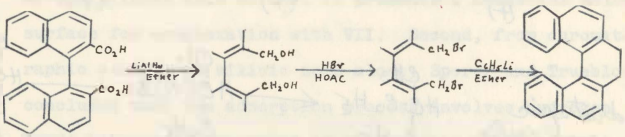
(-)acid → elongated prisms, mp 69-69.5°, $[\alpha]_D^{25}$ (0.2021 g./10 ml. abs. EtOH) -120.1°.

m.m.p. curve of (-)acid) taken with (+)hydratropic acid shows so the (-)acid & (-)hydratropic acid have the same config. See Kleinholdt's method [J. prakt. Chem., [2] 111, 242 (1925)] & apparatus of Friedrichs [Z. angew. Chem., 34, 61 (1921)]. Other combination was not tried. There is strong evidence that (+)hydratropic acid has config. (+)S



(see back of next p.)

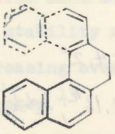
stronger complex with the optically active impregnant should be the one which is more strongly retained on the column. It was then believed that one might be able to adapt the chromatographic procedure to the determination of the absolute configurations of the enantiomeric pairs of racemates resolvable in this manner. Klemm and Reed[6] found (IV) and (V) susceptible to resolution by this chromatographic procedure. They also resolved (essentially completely for a small sample) racemic 9,10-dihydrodibenzo(c,g)phenanthrene (VII) for the first time.



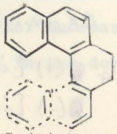
(VII)

Scheme I

The pure enantiomers of VII had been prepared previously by Hall and Turner,[9] from optically active 1,1'-binaphthyl-2,2'-dicarboxylic acids (Scheme I). The absolute configurations of the enantiomers were determined by Mislow and McGinn[10] (VII-a) and (VII-b).



R-(-)-VII-a



S-(+)-VII-b

Refs. to abs. config. of (+) hydratropic acid:

C. L. Arcus & J. Kenyon, J. Chem. Soc., 916 (1939).

A. Campbell & J. Kenyon, " , 25 (1946).

K. Mislow & M. Heffler, J. Am. Chem. Soc., 74, 3668 (1952).

A. Fredga, Arkiv Kemi, 7, 241 (1954).

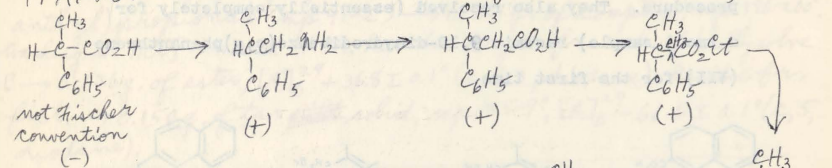
B. Sjöberg, Arkiv Kemi, 9, 295 (1956).

prep. by method of Widequist. Resolved.

$[\alpha]_D^{25} = +68.8°$ (abs. EtOH) & $[\alpha]_D^{25} = -68.6°$ (abs. EtOH)

No determination made of abs. config.

P. A. Levine and R. E. Marker, J. Biol. Chem., 93, 749 (1931).

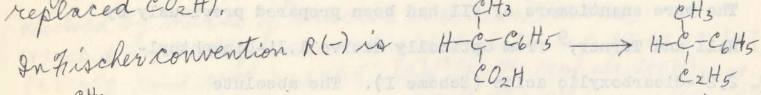


not Fischer convention (−)

(+) (+) (+)

So R(−) hydratropic acid has same config. in space as (+) s-butylbenzene (where Et has replaced CO_2H).

In Fischer convention R(−) is



R(−) S(+)

(−) $[\alpha]_D^{24} = -1.92°$

See also P. A. Levene and R. E. Marker, J. Biol. Chem., 97, 563 (1932).

Heilbron, 1965 gives (+) [i.e. S(+)] of $[\alpha]_D^{25}$ 24.2°

(−) [i.e. R(−)] of $[\alpha]_D^{20}$ −0.16°; $[\alpha]_{5461}^{23}$ −21.65°.

Seem consistent with above.

L. Lardicci, R. Menicagli, & P. Salvadori, Gazz. Chim. Ital., 98, 738-59 (1968); [C. A., 69, 96089j (1968)] gives (+)(S)-2-φbutane $[\alpha]_D^{25}$ 28.40°

Using silicic acid impregnated with (+)-II as absorbent, Klemm and Reed[6] found that R(-)-VII (or VII-a) is more strongly retained than S(+)-VII (or VII-b) on this column, so that (+)-II·R(-)-VII should be a more stable complex than (+)-II·S(+)-VII. A molecular model was presented for the preceding complexes.[11] This model allows one to predict the absolute configuration of (+)-II as S before performing any chemical configurational relationship studies. The model is based on the following considerations. First, it is assumed[8] that the complexing agent II is held flatwise on the surface of the silicic acid so that II presents a broadside molecular surface for complexation with VII. Second, from chromatographic studies on silicic acid alone, Sporer and Trueblood[12] concluded that the adsorption process involves hydrogen bonds between oxygen atoms in the surface layer of the silicic acid and electronegative atoms present in the adsorbate. Moreover, the hydrogen atoms in these bonds are furnished primarily by the silicic acid. Third, it is rationalized that any out-of-plane projection by a bulky, non-polar group (such as the methyl group on the asymmetric carbon in II) will be directed away from the effectively flat, polar silicic acid surface. Fourth, it is accepted that in general the stability of the molecular complex increases with increasing overlap of the π-systems in the donor and the acceptor.[13]

Note: a literature search was made in Chem. Abstr., vols. 51- [redacted] in formula indices to search for:

$C_9H_{10}O_2$ hydratropic acid (later known as benzeneacetic acid, α-methyl)

$C_{10}H_{12}O_2$ methyl ester of above

$C_{10}H_{14}$ (+)&(-)-s-butylbenzene, also given in subject index under benzene, (+) & (-)-s-butyl or methylpropyl.

$C_{13}H_{12}O_2$ naphthaleneacetic acid, α-methyl

$C_{14}H_{14}O_2$ methyl ester of above

$C_{14}H_{16}$ naphthalene, s-butyl

$C_{17}H_{14}O_2$ anthraceneacetic acid, α-methyl
also phenanthreneacetic " , "

$C_{18}H_{16}O_2$ methyl ester of above

$C_{18}H_{18}$ anthracene, s-butyl
phenanthrene, s-butyl

References

Fifth, it is conceded that insofar as optical resolution is concerned, one need consider only those orientations of the donor and the acceptor molecules which bring the immediate chemical environment of the asymmetric center of the latter into intimate contact with some portion (especially an asymmetric center if present) of the former. Using Stuart-Briegleb molecular models and orienting them in accordance with these five considerations, one is lead to the pertinent geometric relationships shown in Fig. 1 (schematic, broadside and edgewise views) for these two complexes. Although the hydrogen atom on the carboxylic acid group of S-II is appropriately located for facile hydrogen bonding to the oximino nitrogen, the illustration of such intramolecular hydrogen bonding in Fig. 1 is made for simplicity only. It is evident from Fig. 1 that maximal overlap of one naphthalene moiety of the donor R(-)-VII with the tetranitrofluorene ring system of the acceptor S-II is possible with little or no steric compression of the second naphthalene moiety of the donor against the protruding H- and CH_3-groups of the acceptor. However, in Fig. 1(b) one sees that the protruding methyl group of the acceptor S-II compresses against the second naphthalene moiety of the donor S(+)-VII while the first naphthalene moiety of the donor has only partially overlapped the tetranitrofluorene system of the

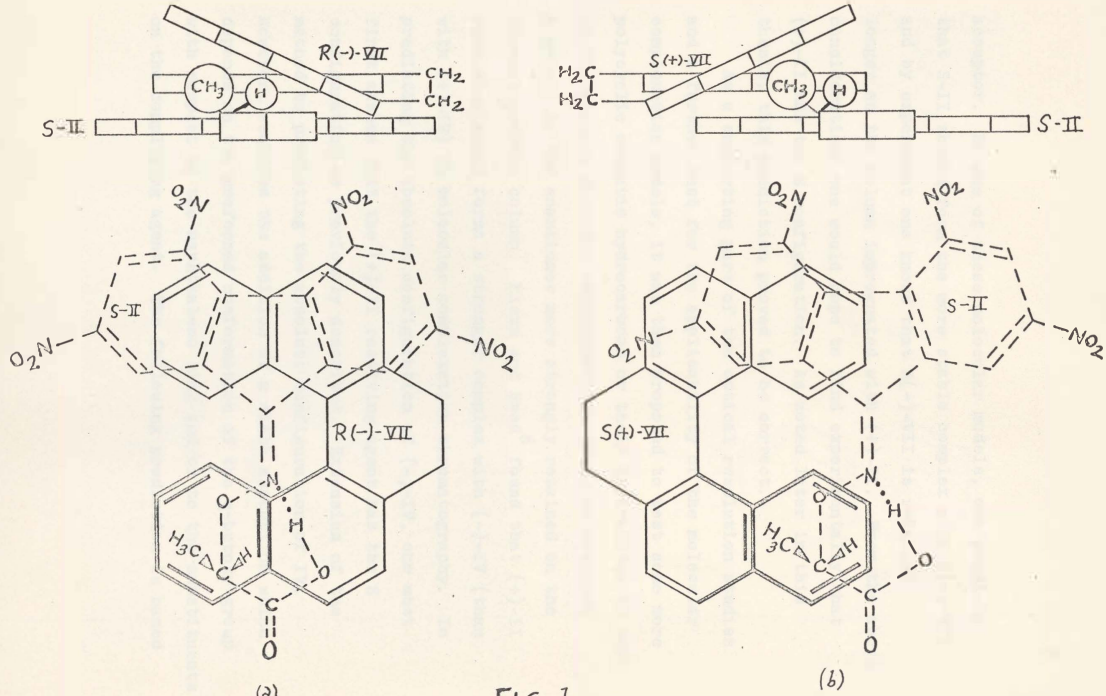
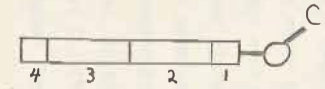
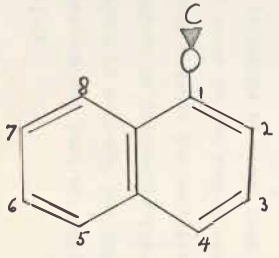

R(-)-VII
CH3
H
CH2
CH2
S-II
O2N
NO2
S-II
O2N
NO2
R(-)-VII
N
H
O
H3C
C
H
O
C
O
(a)
S(+)-VII
H2C
H2C
CH3
H
S-II
O2N
NO2
S-II
O2N
NO2
S(+)-VII
N
H
O
H3C
C
H
O
C
O
(b)

FIG. 1

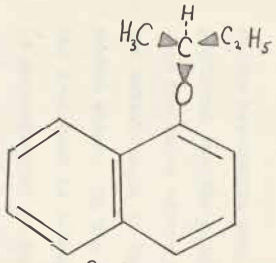
acceptor. By use of these molecular models, one predicts that S-II should form the more stable complex with R(-)-VII and by experiment one knows that R(-)-VII is retained longer on the column impregnated with (+)-II. From the above considerations one would hope to find experimentally that (+)-II has the S configuration. As noted later in this thesis, this prediction proved to be correct.

As a supporting part of the optical resolution studies and a further test for the applicability of the molecular complexation models, it was then proposed to test some more polycyclic aromatic hydrocarbons or their derivatives to see if the correct absolute configurations could be assigned a priori to the enantiomer more strongly retained on the chromatographic column. Klemm and Reed[6] found that (+)-II resolving agent forms a stronger complex with (-)-IV (than with (+)-IV) in molecular complexation chromatography. In predicting the absolute configuration of (-)-IV, one must first assume that the (+)-II resolving agent has the S configuration as previously described. Extension of the method to predicting the absolute configuration of IV, however, requires the addition of a sixth assumption which depends on the preferred conformation of the s-butoxy group with respect to the naphthalene ring and/or to the substituents on the complexing agent. The following prediction is based

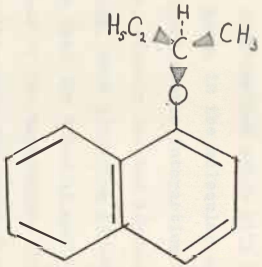




(a)



S - IV

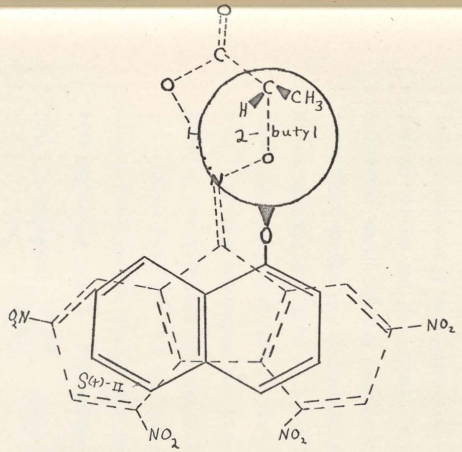


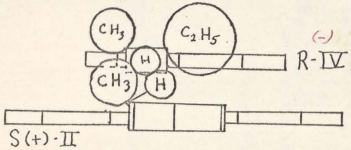
R - IV

(b)

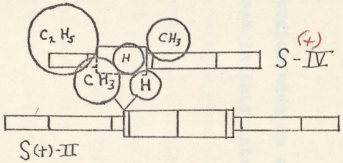
FIG. 2

on the assumption that the conformation which will be preferred for the s-butoxy group in the molecular complex is that one which offers the least steric interaction between the substituents on the two, closely located asymmetric carbon atoms. In the complex, this situation arises when the Ar-O bond is rotated so that the dihedral angle Ar-O-C is perpendicular to the plane of the naphthalene ring (Fig. 2-a). In order to fit the ether onto the complexing agent with the asymmetric carbons in close proximity and to still have minimal steric interaction, the sec-butyl group must point upwards away from the resolving agent (Fig. 2-b). Then the hydrogen atom (nearly horizontal) can be directed back toward the asymmetric carbon of the resolving agent. There are now two possibilities for formation of a complex. Considering the ether in the R-configuration, one then has C_2H_5- over H- and CH_3- over CH_3- (Fig. 3-a). Now considering the ether in the S-configuration, one finds CH_3- over H- and C_2H_5- over CH_3- (Fig. 3-b). It should be clear that the least steric interaction will occur in the former case where one compresses the largest group against the smallest and an intermediately-sized group against an intermediately-sized one. If the aforementioned model is correct, one should find that (-)-IV has the R configuration and that the stronger complex formed is S(+)-II·R(-)-IV.


CH3
H
2- butyl
O
N
O
O2N
NO2
S(+)-II
NO2
NO2


CH3
C2H5
H
CH3
H
(-)
R-IV
S(+)-II

(a)


C2H5
CH3
H
CH3
H
(+)
S-IV
S(+)-II

(b)

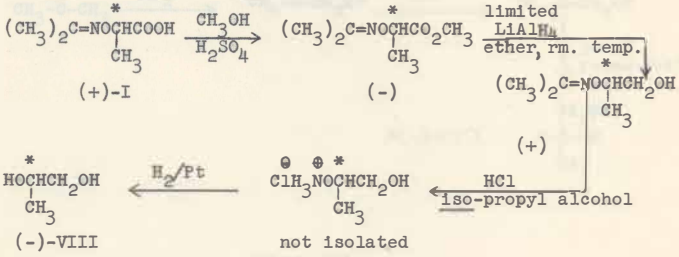
FIG. 3

This thesis describes experimental studies made in an effort to test the two predictions discussed in this introduction.

GENERAL APPROACH

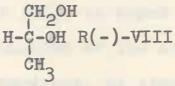
Klemm and Reed[6] found by experiment that R(-)-VII was retained longer than its isomer S(+)-VII on a column impregnated with (+)-II. By use of the molecular model described in the introduction, R(-)-VII should form a more stable complex with S-II, so that one would predict that (+)-II has the S configuration. The essential thing to be proved before one can debate the validity of the proposed molecular model is the absolute configuration of 2-(2,4,5,7-tetranitro-9-fluorenylideneaminoöxy)propionic acid (II). Since optically active II is obtained without a change in absolute configuration by treating optically active I with III,[4] one may determine the absolute configuration of II by knowing the absolute configuration of I.

Diane Bradway[14] in her tenure at the University of Oregon developed a method for determining the absolute configuration of I. Her method is shown in scheme II.

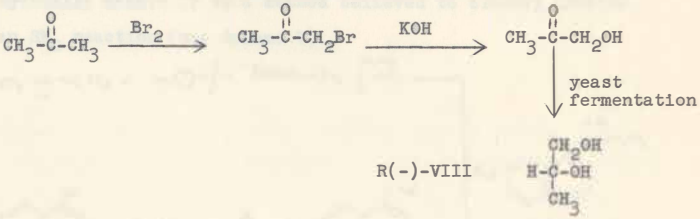


Scheme II

The product obtained had $[\alpha]_D = -2.7^\circ$, as compared to a reported value of $[\alpha]_D = -15.0^\circ$[15] for propylene glycol from yeast fermentation with a known absolute configuration R(-)-VIII, as related to (-)-lactic acid[16] (Scheme V).



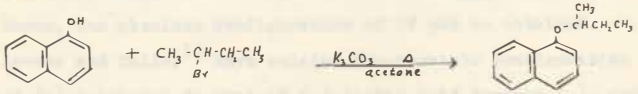
As a first part of the present project, it was proposed to confirm the results of Diane Bradway by going through the transformations from (-)-I to propylene glycol (if possible, by a more direct and simplified route) and then to make an optically active crystalline derivative of the resultant glycol. It was planned to work out a suitable scheme on racemic I first and then to apply this scheme to use with the optically active forms.



Scheme III

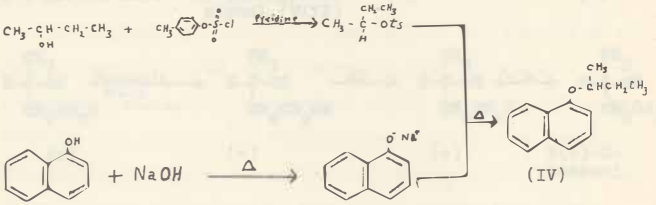
For comparison purposes, optically active propylene glycol was needed. It was planned to prepare this by yeast fermentation.[15] The procedure is outlined in Scheme III.

After determining the absolute configuration of Newman's resolving agent (II), we hoped to be able to extend the study to the determination of the absolute configuration of IV. For comparison purposes, we planned to prepare racemic IV first by the known procedure[17] shown below (Scheme IV).



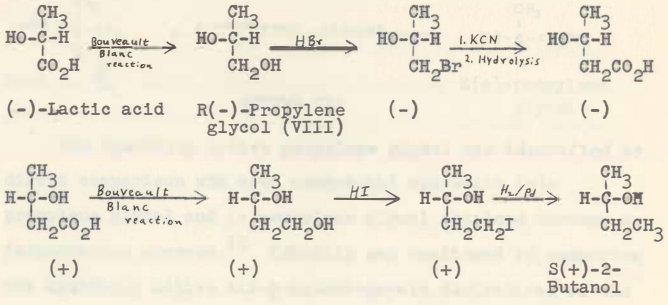
SCHEME IV

For use in further studies, however, it was then proposed to investigate the syntheses of both racemic and optically active IV by a method believed to clearly involve an SN_2 reaction (see Scheme V).



SCHEME V

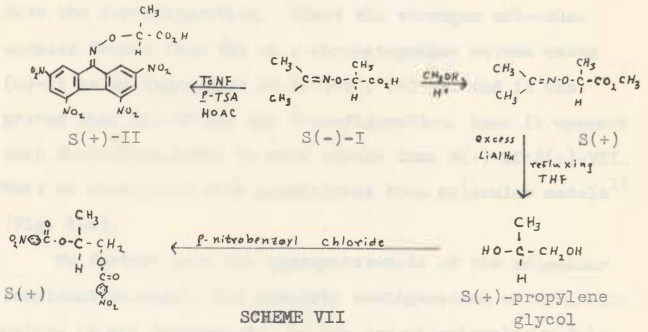
For formation of optically active IV by Scheme V, one needs optically active sec-butanol. It was planned to obtain this by a known procedure[18] wherein racemic sec-butanol is resolved by going through the half ester, sec-butyl hydrogen phthalate, and using brucine as a resolving agent. By tosylating the optically active sec-butanol and reacting this with sodium α-naphthoxide, one should obtain an inversion of configuration. Therefore, since the absolute configuration of optically active sec-butanol is known, the absolute configuration of IV can be obtained. Levene and Haller[16] have related the absolute configuration of (+)-2-butanol to that of (-)-lactic acid through (-)- and (+)-β-hydroxybutyric acids as shown in Scheme VI.



Scheme VI

RESULTS AND DISCUSSION

Degradation of (-)-I in a two-step process, as shown in Scheme VII, by first methylating the acid and then treating the methyl ester with excess lithium aluminum hydride in refluxing tetrahydrofuran gave the optically active (+)-propylene glycol.

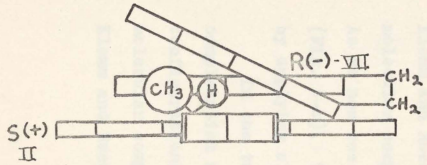


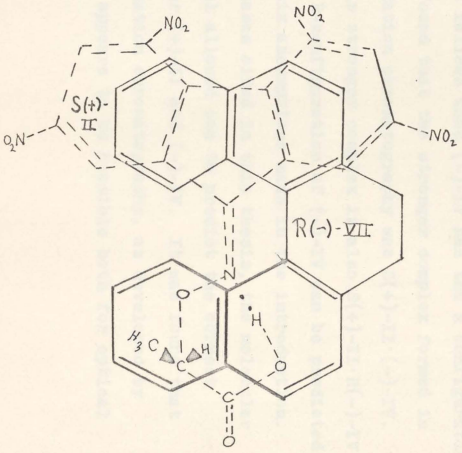
SCHEME VII

The optically active propylene glycol was identified by direct comparison with both commercial synthetic (±)-propylene glycol and (-)-propylene glycol obtained through a fermentation process.[15] Identity was confirmed by comparing the optically active bis-p-nitrobenzoate derivatives of the known glycols with the same derivative of the reduction product glycol. Since the absolute configuration of (-)-propylene glycol is known to be R by direct correlation with

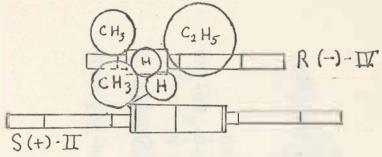
(-)-lactic acid,[19] it follows that (+)-propylene glycol has the S[20] configuration, as shown in Scheme VII. Since the transformations in Scheme VII do not serve to alter either the relative spatial relationships of the four groups attached to the asymmetric carbon atom or their relative priority ratings in the R,S-nomenclature, it follows that (-)-I and therefore (+)-II (derivable from (-)-I and III)[4] have the S-configuration. Since the stronger molecular complex formed from VII on a chromatography column using (+)-II as an impregnant is R(-)-VII·(+)-II, and it was proved that (+)-II has the S configuration, then it appears that S(+)-II·R(-)-VII is more stable than S(+)-II·S(+)-VII. This is consistent with predictions from molecular models[11] (Fig. 4-a).

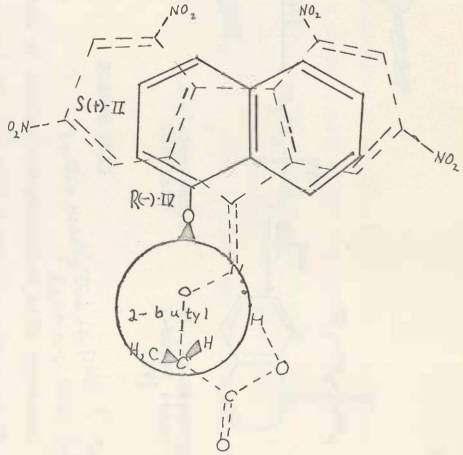
To further test the appropriateness of the molecular complexation model, the absolute configuration of optically active IV was determined. By the use of molecular models, it was predicted that the stronger complex should be formed between S(+)-II and R-IV and therefore, one should find that R-IV has a (-)-rotation. By resolving 2-butanol,[18] tosylating the S(+)-enantiomer and reacting the tosylate with sodium α-naphthoxide, (-)-IV was obtained (Scheme VIII).


R(-)-VII
CH3
H
CH2
CH2
S(+)
II


NO2
NO2
S(+)-
II
O2N
NO2
R(-)-VII
N
O
H
H3C
C
H
O
C
O

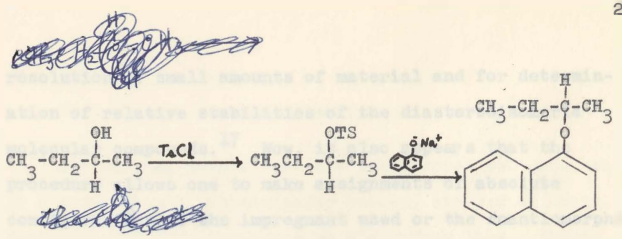
(a)


CH3
C2H5
H
CH3
H
R(-)-IV
S(+)-II


NO2
NO2
S(+)-II
O2N
NO2
R(-)-II
O
2-butyl
H
H3C
C
H
O
C
O

(b)

FIG. 4



S(+)-Sec-butanol S(+)-Sec-butyl tosylate R(-)-1-Naphthyl 2-butyl ether (IV)

SCHEME VIII

Is this really true in DMF? Could one have an S_Ni-type?

Since the reaction of sodium α-naphthoxide with sec-butyl tosylate is a typical SN_2 reaction involving attack at the asymmetric carbon in the sec-butyl group, with displacement of the tosylate ion, an inversion of configuration takes place. Hence, it follows that (-)-IV has the R configuration. Klemm and Reed[6] found that the stronger complex formed in molecular complexation chromatography was S(+)-II·(-)-IV. As we now see this stronger complex is also S(+)-II·R(-)-IV (Fig. 4-b). The R-configuration of (-)-IV can be predicted by applying all six assumptions made in the introduction.

In the two cases cited in this thesis, the molecular complexation model allowed one to predict the correct configurations for (+)-II and (-)-IV. It was found that molecular complexation chromatography, as developed by Klemm and Reed[6], appears to be feasible both for optical

resolution of small amounts of material and for determination of relative stabilities of the diastereoisomeric molecular compounds.[17] Now, it also appears that the procedure allows one to make assignments of absolute configurations to the impregnant used or the enantiomorphs separated.

EXPERIMENTAL

All melting points here are uncorrected and were taken in a conventional, electrically heated, stirred oil bath. Microanalyses were performed by Micro-Tech Labs., Skokie, Illinois. I.R. spectra were determined by means of a Perkin-Elmer Model 137 Infracord Spectrophotometer or by a Beckman Model IR-5 Infrared Spectrophotometer. NMR spectra were taken with a Varian Associates A-60 instrument. Optical rotations were measured by means of a Hilger Polarimeter using the sodium D-line or by means of a Perkin-Elmer Model 141 Polarimeter using light of shorter wavelengths. The gas chromatograph used was an F and M Model 202 with a 5'x3/8" carbowax 20 M column at 175°.

Purification of Ethyl Formate

Approximately 500 g. of technical grade ethyl formate was washed three times in a separatory funnel with 3% aqueous sodium carbonate solution and then once with cold distilled water. It was dried with magnesium sulfate, filtered, and distilled to yield a clear, colorless liquid, b.p. 54.5° at room pressure.

Purification of α-Naphthol

To a boiling solution of 900 ml. of 65-110° petroleum ether, was added 80 g. of technical grade α-naphthol, brown color, m.p. 68-82°. Enough acetone was then added to the boiling solution to dissolve all of the α-naphthol not yet in solution. Activated charcoal was then added to the solution, and it was boiled for an additional five minutes. The hot solution was filtered through a layer of Celite. The filtrate was concentrated to a thin past on a rotary evaporator, and then filtered by suction. The crystals obtained were dark tan. When dried in the dark they had a m.p. of 88-90°. The crystals were again dissolved in 900 ml. of 65-110° petroleum ether, and the above process repeated. Upon evaporation of the solvent and filtration, the crystals obtained were tan-pink, m.p. 95-96°, wt. 45 g. (56%).

Purification of Tetrahydrofuran

One liter of tetrahydrofuran (THF) was put into a flask (equipped with a calcium chloride tube) containing 75 g. of Baker's reagent grade potassium hydroxide and the mixture was refluxed overnight on a steam bath. Solid material was removed by filtration and the filtrate was distilled from a flask containing 10 g. of lithium aluminum hydride. The THF distilled at 65.5-66°. Approximately 750 ml. of THF was

distilled. The residue was reacted first with ethanol and then with hydrochloric acid before it was discarded.

Bromoacetone

Bromoacetone was prepared following a procedure described by Levene and Walti.[21] A 5-l., 3-necked round-bottom flask was provided with a mechanical stirrer, an Allihn reflux condenser, a thermometer, a long-stemmed separatory funnel, and a calcium chloride tube. The apparatus was assembled in a water bath (galvanized pail, ca. 14 qt.). Since bromine was used and the liquid formed was lachrymatory, the experiment was conducted in a hood.

Through the separatory funnel was introduced 1.6 l. of distilled water, 500 ml. of reagent grade acetone, and 372 ml. of glacial acetic acid. The stirrer, controlled by means of a transformer, was operated at a speed just slow enough so as to prevent splashing. The bath temperature was raised to about 70° and 354 ml. (7.3 moles) of bromine was added slowly (over ca. 2 hours) from the separatory funnel in order to prevent accumulation of excessive unreacted bromine in the reaction mixture. Stirring was continued until the solution was decolorized (ca. 20 minutes). The solution was then diluted with 800 ml. of cold, distilled water, cooled to 10° in an ice bath, and finally made neutral

to Congo red by means of sodium carbonate (ca. 0.5 kg.). An orange-brown oil which precipitated was collected, dried with anhydrous calcium chloride, and distilled to yield a clear, colorless liquid (lachrymatory), b.p. 37-43°/11 mm. (reported[21] b.p. 38-45°/12 mm.), yield 380 g. (40.8%).

Acetol

A procedure of Levene[22] was used to prepare acetol. A solution of 210 g. of potassium hydroxide (Baker, reagent) in 1.5 l. of anhydrous methanol was placed in a 3-l. flask fitted with a condenser and calcium chloride tube. The solution was cooled to below 50°. Then 300 g. of purified ethyl formate was added and the mixture was refluxed for two hours. To this mixture was added 380 g. (2.8 moles) of bromoacetone, and the entire mixture was refluxed in a hood for 16 hours by means of a heating mantle. The solution was cooled to 0° in an ice-salt bath and the potassium bromide which formed was removed by filtration on a cooled suction filter. The filtrate was distilled to give a first fraction (ca. 1.5 l.) of b.p. 25-38°/15 mm., n_D^{26} = 1.3324, believed to be methanol. The second fraction, a clear, colorless liquid, b.p. 39-45°/15 mm., (reported[22] b.p. 35-47°/12 mm.), was collected as the product, yield 119 g. (54%).

(-)-Propylene Glycol

A sample of Eastman Kodak White Label propylene glycol was checked out of a stockroom and used for comparison purposes. A procedure of Levene and Walti[15] was used for preparing a sample of (-)-propylene glycol. A solution of one kg. of sucrose in 9 l. of water was placed in a 5-gal. drum. A paste, made by breaking up one kg. of baker's yeast (Fleischmann's cake yeast) and gradually stirring it into 1 l. of water, was added to the sugar mixture and another 0.5 l. of water was added. This final mixture was allowed to stand at room temperature until a lively evolution of gas developed (ca. 1 hour). An addition of 118 g. of acetol was made after the yeast had ceased to react. After six days in a thermostated water bath at 32°, the yeast mixture still yielded a positive test for reducing sugars, as checked by Fehling's solution and also by Benedict's solution. A new active mixture was prepared from a solution of 350 g. of sugar in 3.06 l. of water and a paste of 0.8 lb. of yeast in 0.34 l. of water. This new mixture was allowed to react and was then added to the old yeast mixture in the drum. The reaction subsided for a couple of hours, but then it started again. The 5-gal. drum was again returned to the heated water bath for a couple of days, whereupon a check with Benedict's solution was negative (liquid remained blue and

a white precipitate settled out). The mixture was taken out of the bath and divided into two portions. The first portion, about 2.5 gal., was mixed with about 50 g. of asbestos fibers and the yeast removed by suction filtration. The green-yellow liquid remaining after filtration was evaporated on the rotary evaporator at 50-55° to a brown syrupy residue. The residue was taken up in a mixture of 200 ml. of absolute ethanol and 50 ml. of dry ether, and the precipitate which formed, a dark gummy sludge, was removed by filtering the solution through a layer of Celite. The precipitate was then extracted with a mixture of 200 ml. of 95% ethanol and 100 ml. of dry ether. The two ethanol-ether layers were combined and concentrated on the rotary evaporator to a thick, clear, brown syrup. The residue was again taken up in a mixture of 200 ml. of absolute ethanol and 50 ml. of dry ether, and filtered through Celite. The filtrate was again concentrated on the rotary evaporator. The crude filtrate was distilled to yield about 30 g. of crude (-)-propylene glycol, b.p. 91-97°/20 mm. The crude product was again distilled to yield 27.3 g. of clear, colorless liquid, b.p. 92-95°/23 mm., $[\alpha]_D^{25}$ = -12.75° (neat), (reported[15] 88-90°/12 mm. and $[\alpha]_D$ = -15.0° (neat)).

The other 1.5 gal. of the yeast fermentation product was worked up as before to yield 16.4 g. of clear, colorless

liquid, b.p. 96-102°/18-20 mm., $[\alpha]_D^{26}$ = -12.30 (neat). The two samples of propylene glycol were combined and distilled to yield a clear, colorless liquid, b.p. 92-95°/23 mm., $[\alpha]_D^{27}$ = -14.2 (neat), $[\alpha]_D^{27}$ = -11.2 (c 16.7, acetone), I.R. spectrum (neat) identical with that of a commercial, synthetic, racemic propylene glycol (Eastman Kodak White Label).

α-(Isopropylideneaminoöxy)propionic Acid (I)

α-(Isopropylideneaminoöxy)propionic acid (IPAPA) was prepared following a procedure of Newman and Lutz.[4] A mixture of 530 g. of α-bromopropionic acid and 390 g. of ice was carefully neutralized with 325 g. of 40% aqueous sodium hydroxide. Additional ice, about 400 g., was added periodically to keep the temperature below 15°. To the neutralized acid mixture was added a suspension of 200 g. of acetone oxime in 325 ml. of 40% aqueous sodium hydroxide. Ice was again added to keep the temperature below 20°. The mixture was then allowed to come to room temperature, and the almost clear solution was then dropped slowly (5.5 hours) through a series of three 30" Liebig condensers inclined at about a 22° angle from the horizontal. The two upper condensers were heated with steam and the lower condenser cooled with tap water. The clear, colorless reaction product was then

extracted three times with 350-ml. portions of ether to remove the unreacted acetone oxime. The aqueous layer was made acid to Congo red with concentrated hydrochloric acid. The acidified solution was then saturated with sodium sulfate. The saturated solution was extracted with ether for four hours by means of a continuous extraction apparatus. The ether layer was put on the steam bath to remove the volatile solvents. The residue was distilled under water vacuum up to a temperature of 110°. This material was discarded. The desired acid was obtained in a fraction of b.p. 80-93°/1 mm. By passing steam through the condenser and employing a heat lamp for the rest of the apparatus, the acid crystals were prevented from crystallizing before reaching the receiving vessel. The colorless liquid which came off was diluted with 72 ml. of petroleum ether (60-90°) and 48 ml. of acetone. The solution was then seeded and allowed to stand overnight to crystallize at room temperature. The resulting large, colorless crystals were suction filtered, washed with 4:1 petroleum ether-acetone mixture and dried in vacuo to yield 74.6 g. of crystals. Upon concentration of the filtrate and additional recrystallizations, an extra 80.4 g. was obtained. The total amount of IPAPA crystals obtained was 155 g. (39%), m.p. 57-60° (reported[4] m.p. 57-61°).

Resolution of IPAPA

The general method outlined by Newman and Lwtz[4] was followed for the resolution of IPAPA. To a solution of hot benzene (1125 ml.) was added a mixture of 135 g. of (-)-ephedrine from Inland Alkaloid Inc. (m.p. 38-44°) and 61 g. of (-)-ephedrine from Merck (hydrous N.F., m.p. 33-40°, total of 196 g. (1.07 moles)) and 206.5 g. (1.42 moles) of racemic IPAPA. The solution was then diluted with 1 l. of cyclohexane and allowed to stand for two days at room temperature, at which time the crystallized ephedrine salt was filtered and dried. The yield was 309.8 g. of salt, m.p. 85-88°, $[\alpha]_D^{26}$ = -19.8° (c 2.8, water). Upon concentration, the mother liquor yielded another batch of crystals, 19 g., m.p. 110-114°, $[\alpha]_D^{26}$ = -21.6° (c 2.8, water). To free the acid, 640 ml. of water was mixed with 80 g. of sodium chloride and 200 g. of the (-19.8°) ephedrine salt was added. This was then acidified to Congo red with concentrated sulfuric acid. It was extracted continuously for four hours with ether. The ether extract was then percolated through anhydrous sodium sulfate and concentrated in an airstream. The concentrate was put into a cold room to crystallize. The crystals were filtered, dried, and recrystallized three times from acetone-Skelly-solve B mixture. Three recrystallizations yielded 31 g.

of colorless needle-like crystals, m.p. 83-85°, $[\alpha]_D^{26}$ = -28.5° (c 3.7, water) (reported[4] m.p. 83-84.5°, $[\alpha]_D^{26}$ = +30.8° (c 7.57, water)). The acetone-Skellysolve B mother liquor was evaporated to about 50 ml. and placed in a cold room. Two crops of crystals which formed were collected by filtration. The two samples of crystals were combined and recrystallized from a Skellysolve B-acetone mixture to furnish 5.82 g. of clear, colorless, needle-like crystals, m.p. 82-85°, $[\alpha]_D^{24}$ = +25.6° (c 3.13, water). The remaining mother liquor from recrystallizations was combined with the original ethereal mother liquor and about 20 g. more of IPAPA was obtained, but the optical activity decreased with each recrystallization.

Methyl 2-(Isopropylideneaminoöxy)propionate

Into a 200-ml. round-bottom flask, fitted with a West condenser, and calcium chloride tube, were placed 25 g. (0.172 mole) of racemic IPAPA, 55 ml. of methanol and 3 ml. of concentrated sulfuric acid. The mixture was refluxed on the steam bath for four hours, and then the volatile solvent removed at 45° by means of a rotary evaporator. The residue was extracted four times with ether. The combined ethereal extracts were washed first with excess aqueous sodium bicarbonate solution and then with water. The ethereal

solution was dried with magnesium sulfate, filtered, and evaporated. The residue was distilled, yield 16.4 g. (60.2%) of clear, colorless liquid, b.p. 82-85°/15 mm., $n_D^{23.4}$ = 1.4308 (reported[23] b.p. 73-76°/10 mm., n_D^{23}= 1.4313).

Esterification of 17.3 g. of (-)-IPAPA, m.p. 83-85°, $[\alpha]_D^{26}$ = -29.4° (c 3.76, water), with 40 ml. of methanol and 2.2 ml. of concentrated sulfuric acid, in a manner similar to that used for the racemic IPAPA gave 9.46 g. (49.5%) of the (+)-methyl ester, b.p. 83-85°/16 mm., $[\alpha]_D^{27}$= +14.6° (neat), I.R. bands (neat) at 1770 (very strong, C=O) and 1670 (weak, C=N) cm^{-1}.

Propylene Glycol from Methyl 2-(Isopropyledeneaminoöxy)-propionate

To a well-stirred mixture of 8.1 g. (0.2 mole) of lithium aluminum hydride and 200 ml. of purified tetrahydrofuran in a three-neck round-bottom flask was slowly added (over a period of 1.5 hours) a solution of 16.2 g. (0.1 mole) of preceding racemic methyl ester in 50 ml. of tetrahydrofuran. The gray mixture was heated on a steam bath for 2 hours after the addition was complete and was then treated, in succession, with 8 ml. of water, 8 ml. of 20% aqueous sodium hydroxide solution, and 18 ml. of water. The white suspension was filtered by means of a sintered glass funnel

and the residue was washed with 400 ml. of tetrahydrofuran. The filtrate was dried with magnesium sulfate and distilled, yield 5.2 g. (67%) of racemic propylene glycol, b.p. 93-95°/13 mm., n_D^{24} = 1.4314, I.R. spectrum (neat) identical with that of a commercial synthetic sample. The bis-p-nitrobenzoate derivative (vide infra) melted at 123-125°, undepressed on admixture with the same derivative made from the commercial propylene glycol, m.p. 126-127°.

Repetition of this procedure but with preceding (+)-methyl ester, $[\alpha]_D^{27}$ = +14.6° (neat), gave a liquid product, b.p. 93-95°/15 mm., $[\alpha]_D^{26}$ = +11° (c 13, acetone). The I.R. spectrum and the V.P.C. retention time (run at 175° using Carbowax-20 M as stationary phase) were identical with those of the commercial, synthetic sample of racemic propylene glycol.

In one other trial, (+)-methyl ester, $[\alpha]_D^{26}$ = +4.7° (neat), gave a product of b.p. 94-95°/15 mm., $[\alpha]_D^{26}$ = +4.0° (neat), converted to a bis-p-nitrobenzoate derivative, (vide infra), m.p. 122-125° $[\alpha]_{436}^{25}$ = +55.5°, $[\alpha]_{546}^{25}$ = +27.4°, $[\alpha]_{578}^{25}$ = +23.7° (c 0.98, acetone).

Bis-p-nitrobenzoate of Propylene Glycol

Following the general procedure of Shriner, Fuson, and Curtin,[24] a bis-p-nitrobenzoate derivative of commercial,

synthetic propylene glycol was prepared. One ml. of propylene glycol was dissolved in 3 ml. of anhydrous pyridine and 2 g. of p-nitrobenzoyl chloride was added. A spontaneous exothermic reaction took place. The solution was heated further over a low flame for a minute and then poured into 10 ml. of distilled water. The water was separated by decantation and the precipitate washed with 5 ml. of 5% aqueous sodium sulfate, and separated by decantation. The precipitate was dissolved in 95% ethanol and placed in a coldroom for three hours. The mixture was filtered to yield 0.705 g. of cream-colored needle-like crystals of racemic bis-p-nitrobenzoate, m.p. 126-127° (reported[25] m.p. 126-127°).

Repetition of this procedure but with (-)-propylene glycol from yeast fermentation and four recrystallizations gave cream-colored needles of (-)-bis-p-nitrobenzoate from 95% ethanol, m.p. 107.5-108.5°; $[\alpha]_{436}^{23.8} = -108°$, $[\alpha]_{546}^{23.8} = -59.2°$ $[\alpha]_{578}^{23.8} = -45.1°$ (c 0.70, acetone).

Anal. Calcd. for $C_{17}H_{14}N_2O_8$: C, 54.55; H, 3.77; N, 7.48%. Found: C, 54.62; H, 3.66; N, 7.70%.

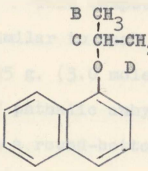
The same procedure was used in making a derivative of (+)-propylene glycol, $[\alpha]_D^{26} = +4.0°$ (neat). The (+)-bis-p-nitrobenzoate derivative, obtained from 95% ethanol, occurred as cream-colored crystals, m.p. 119-121°,

$[\alpha]_{436}^{23}$ = +36.6°, $[\alpha]_{546}^{23}$ = +18.3°, $[\alpha]_{578}^{23}$ = +15.7° (c 0.31, acetone).

Anal. Calcd. for $C_{17}H_{14}N_2O_8$: C, 54.55; H, 3.77; N, 7.48%. Found: C, 54.61; H, 4.20; N, 7.77%.

(±)-1-Naphthyl 2-Butyl Ether. A. From 2-Butyl Bromide

This compound was prepared following a procedure described in Dave Reed's doctoral thesis.[17] A mixture of 30.3 g. (0.2 mole) of α-naphthol, 30.0 g. (0.22 mole) of 2-butyl bromide, 28 g. of anhydrous potassium carbonate and 200 ml. of dry acetone (dried over potassium carbonate), contained in a 1-l. round-bottom flask, was refluxed on a steam bath for 48 hours. The acetone was removed by distillation, 200 ml. of water was added to the residue, and the resulting mixture was extracted with two 100-ml. portions of benzene. The two benzene extracts were combined and washed with three 100-ml. portions of 10% aqueous sodium hydroxide solution. The benzene was removed with a rotary evaporator, and the residual oil was distilled under reduced pressure to yield 20.1 g. (50%) of a light yellow liquid, b.p. 97-102°/0.25 mm.; I.R. band (neat) at 1090 cm^{-1}, (very strong, C-O-C), other strong bands at 765, 1215, 1230, and 1400 cm^{-1}; NMR absorptions (in CCl_4) as follows:



Assignment	δ ppm vs. TMS	Multiplicity
A- 0.9		triplet
B- 1.25		doublet
C- 4.3		sextet
D- 1.7		multiplet

J_{AD} 8 cps J_{BC} 6 cps

(+)-2-Butyl p-Toluenesulfonate

Into a 2-l. round-bottom flask immersed in an ice bath, were placed 143 g. (0.75 mole) of p-toluenesulfonyl chloride, 50 g. (0.75 mole) of 2-butanol and 465 g. of anhydrous, reagent-grade pyridine. The solution was allowed to stand at room temperature for 3 hours at which time a tan precipitate had formed. After another hour the solution was poured into 1 l. of ice water. The tan precipitate disappeared and a yellow oil precipitated. The solution was extracted four times with ether. The ethereal layers were combined and washed four times with 5% hydrochloric acid and then with water. The ether was evaporated and a light yellow, clear liquid was obtained, yield 110 g. (64%); I.R. bands (neat) at 1360, 1170 and 1180 cm^{-1} (strong, $-OSO_2-$).

(±)-2-Butyl Hydrogen Phthalate

This compound was prepared following a procedure similar to that of Pickard and Kenyon.[26] A mixture of 225 g. (3.0 mole) of racemic 2-butanol and 450 g. (3.0 mole) of phthalic anhydride was stirred magnetically for 13 hours in a round-bottom flask immersed in an oil bath at 110-115°. The solution was cooled, a concentrated aqueous solution of sodium carbonate was added, and the mixture was allowed to stand for a few hours. The clear solution was extracted three times with ether. The half ester was then precipitated by addition of concentrated hydrochloric acid to the aqueous solution. The yellow liquid which formed was extracted from the aqueous layer with three portions of chloroform. Combined chloroform layers were evaporated on a rotary evaporator and the product was obtained as a yellow liquid which crystallized upon cooling and scratching, yield 593 g. (2.6 mole, 85.3%), m.p. 57-59° (reported[26] 56-57°).

Sodium α-Naphthoxide

A mixture of 50 g. (0.35 mole) of α-naphthol and 35 g. (0.35 mole) of 40% aqueous sodium hydroxide was heated until all of the α-naphthol had dissolved. The solution was cooled and the precipitated sodium salt was collected by suction-filtration. The precipitate was added to 100 ml. of

absolute ethanol, and the solution was concentrated on a rotary evaporator to yield 59 g. (0.33 mole, 94%) of brown crystals, m.p. 78-80°.

(±)-1-Naphthyl 2-Butyl Ether B. From (±)-2-Butyl p-Toluenesulfonate

Into a 300-ml. flask were placed 59 g. (0.33 mole) of sodium α-naphthoxide, 150 ml. of reagent-grade N,N-dimethylformamide, and 61 g. (0.27 mole) of (±)-2-butyl p-toluenesulfonate. The mixture was warmed on the steam bath for 70 hours and then allowed to cool. It was diluted with 200 ml. of water and then extracted with three 100-ml. portions of benzene. The benzene layers were combined and washed with three 100-ml. portions of 10% aqueous sodium hydroxide and then with 100 ml. of water. The benzene was removed on the rotary evaporator, and the reddish-brown residual liquid was distilled under reduced pressure to yield 8.9 g. (0.05 mole, 17%) of a dark yellow liquid, b.p. 83-84°/0.15 mm. The liquid was redistilled to yield 8.6 g. (0.045 mole, 16%) of light-yellow liquid, b.p. 84-85°/0.15 mm. The I.R. and NMR spectra are identical with those taken on the (±)-1-naphthyl 2-butyl ether from part A.

Complexation of (±)-1-Naphthyl 2-Butyl Ether with (±)-II

This complex was made following a procedure of Newman

and Lutz.[4] A solution containing 0.26 g. of (±)-1-naphthyl 2-butyl ether and 0.13 g. of racemic 2-(2,4,5,7-tetranitro-9-fluorenylideneaminoöxy)propionic acid (±)-II in 3 ml. of acetic acid deposited a gummy red solid. This solid was triturated with 2 ml. of Skellysolve B and allowed to dry. The residue was washed two times with 5-ml. portions of Skellysolve B. The complex was dried in vacuo at room temperature, yield 0.120 g., m.p. 156-159° (reported[4] 155-158°).

Optical Resolution of 2-Butanol

A procedure outlined by Ingersoll[18] was followed. A solution of 447 g. (2 moles) of pure (±)-2-butyl hydrogen phthalate in 2 l. of warm acetone was treated with 790 g. (2.01 moles) of anhydrous brucine (m.p. 171-174°, $[\alpha]_D^{24} = -90°$ (c 1, acetone), obtained from Inland Alkaloid Inc., Tipton, Ind.) and the mixture was heated at about 40° for three hours. The solution was then heated to boiling and filtered hot. The insoluble material nearly filled a 750-ml. Buchner funnel. The filtrate was kept in a cold room overnight, and then filtered to yield a first crop of crystals (A_1) of crude brucine 2-butyl hydrogen phthalate salt which was washed with about 300 ml. of acetone. The combined filtrate and washings were

concentrated to about 300 ml. and placed in a cold room to yield a small second crop of crystals (A_2). The final mother liquor was set aside.

Crop A_1 was recrystallized from 1.5 l. of acetone, and A_2 was recrystallized from the resultant mother liquor. This second mother liquor was then combined with the mother liquor set aside in the previous step.

The crystalline fractions were systematically recrystallized from methanol. The main crop was recrystallized from about 600 ml. of methanol, and the second crop always from the mother liquor. Crop A_1 was successively recrystallized from 150-, 250-, and 250-ml. portions of methanol. The crystals which had acquired an opalescent appearance were dried, m.p. 160-161.5°, $[\alpha]_D^{23} = +0.90 \pm 0.05°$, yield 32 g. Crop A_2, which had been recrystallized from the mother liquors and had also acquired an opalescent appearance was dried, yield 25 g., m.p. 160-162°, $[\alpha]_D^{23.5} = +0.63 \pm 0.05°$ (c 4, MeOH).

The residue from the first filtration in this procedure was dissolved in 1.5 l. of acetone. The solution was heated to boiling, filtered hot, and then placed in a cold room to yield another crop of crystals (B). The B crop was worked up exactly as the A crops to yield 27 g., m.p. 158-160°, $[\alpha]_D^{23.5} = +0.30 \pm 0.05°$ (c 4, MeOH).

Crops A_2 and B were combined and steam distilled from 600 ml. of 5% aqueous sodium hydroxide. The alcohol was salted out of the distillate with potassium carbonate. The ether extract of this distillate was dried with sodium sulfate and distilled to yield 3.31 g. of (+)-2-butanol, b.p. 86-89°/room pressure, $[\alpha]_D^{23.8}$ = +11.55 ± 0.01° (c 2, ether) (reported[18] $[\alpha]_D^{27}$ = +10.83° (neat)); I.R. (neat) identical with that of stockroom racemic 2-butanol.

b.p. 98°/750mm.

(+)-2-Butyl p-Toluenesulfonate

A solution of 3.1 g. (0.04 mole) of (+)-2-butanol and 8 g. (0.04 mole) of p-toluenesulfonyl chloride in 100 ml. of anhydrous pyridine was allowed to remain at room temperature for two days. It was diluted with 200 ml. of ether, allowed to stand for 1 hour, and filtered. The filtrate was washed with dilute aqueous hydrochloric acid and then water, dried with sodium sulfate, and evaporated. The tosylate was obtained as a light-yellow liquid, yield, 1.2 g. (13%), $[\alpha]_D^{27}$ = +14.6 ± .01° (c 2, ether) (reported[27] $[\alpha]_{5461}^{20}$ = +12.98° (neat)), I.R. bands (neat) identical with those of the racemic tosylate.

See refs. at end also.

Optical Resolution of 1-Naphthyl 2-Butyl Ether

Optically active 1-naphthyl 2-butyl ether was prepared

following the procedure of Newman and Lutz.[4] A hot solution of 0.595 g. of ether and 0.996 g. of (-)-II $[\alpha]_D^{24} = -76.6 \pm 0.2$ (c 1, dioxane)) in 1 ml. of acetic acid solidified to a pasty red mass on cooling. After trituration with 4 ml. of Skellysolve B, the purplish complex was collected, washed with four ml. of Skellysolve B, and dried in vacuo, m.p. 138-142° (reported[4] 137-141°). The 1-naphthyl 2-butyl ether from the complex and from the filtrate was recovered after removing the (-)-II by washing with aqueous 5% sodium bicarbonate solution. The crude ether obtained from the solid complex was purified by evaporative distillation with a molecular distillation apparatus at 0.15 mm. pressure, yield 0.0385 g., $[\alpha]_D^{23.8} = -7.5 \pm 0.1°$ (c 0.385, ethyl acetate). The ether obtained from the filtrate was purified in the same way, yield 0.121 g., $[\alpha]_D^{24} = +11.5 \pm 0.2$ (c 1.21, ethyl acetate) (reported[4] 0.158 g., $[\alpha]_D^{31} = -7.8 \pm 0.2$ (c 6.4, ethyl acetate), and no reported yield for $[\alpha]_D^{32} = +6.4 \pm 0.09$ (c 11, ethylacetate)).

(-)-1-Naphthyl 2-Butyl Ether from (+)-2-Butyl p-Toluene-Sulfonate

The procedure was the same as method B used for preparation of racemic 1-naphthyl 2-butyl ether. Into a

200-ml. round-bottom flask were placed 0.2 g. (0.11 mmole) of sodium α-naphthoxide (prepared in a nitrogen atmosphere) and a solution of 1.2 g. (0.053 mmole) of (+)-2-butyl p-toluenesulfonate in 100 ml. of dimethylformamide. The following reaction was then run in a nitrogen atmosphere. The mixture was warmed on a steam bath for 70 hours, and then allowed to cool. The mixture was diluted with 100 ml. of water and extracted with three 50-ml. portions of benzene. The benzene layers were combined and washed with three 50-ml. portions of 10% aqueous sodium hydroxide and then with 100 ml. of water. The benzene was removed on a rotary evaporator, and the reddish residual liquid was distilled under reduced pressure to yield 0.273 g. (0.014 mmole, 27%) of a yellow liquid, b.p. 104-106°/0.35 mm. The I.R. and NMR spectra were identical with the corresponding spectra of racemic 1-naphthyl 2-butyl ether. The optical rotation of the product was $[\alpha]_D^{23.8} = -64.4 \pm 0.2°$ (c 2, ethyl acetate).

mol. wt. 166.2

?

26

note that this is nearly 10x as large as for the Newman method on p. 42. Why?

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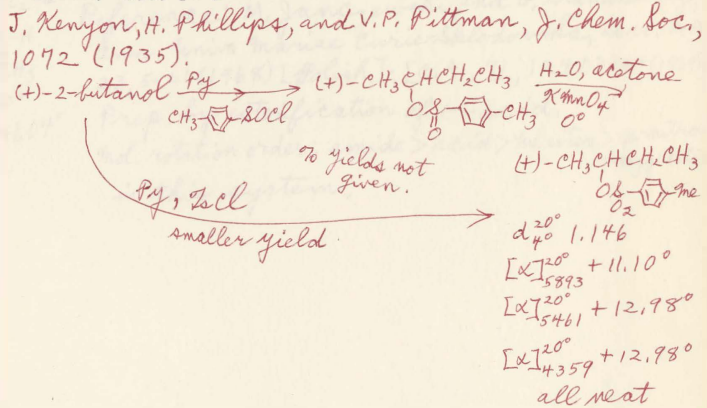
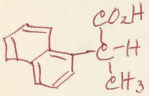


Some absolute configurations: Checked C.A. thru vol. 79.

Reference:

(+) S-hydratropic acid



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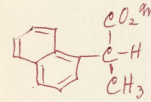

mp 48-50°

$[\alpha]_D^{20}$ -141.04°

(-) R

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