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TRANSFORMATIONS OF 2-(ISOPROPYLIDENEAMINOÖXY)PROPIONIC ACID

THE ABSOLUTE CONFIGURATION OF 2-(2,4,5,7-TETRANITRO-9-FLUORENYLIDENEAMINOÖXY)-PROPIONIC ACID

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Abstract—The carboxylic acid group in 2-(isopropylideneaminoöxy)propionic acid (Ia) has been transformed into a number of other functional groups. Conversion of (−)-Ia to (+)-1,2-propanediol established the absolute configuration of the former as S and, secondarily, that of (−)-2-(2,4,5,7-tetranitro-9-fluorenylideneaminoöxy)propionic acid (+)-II, as S. Correlation of configurations of II and of 9,10-dihydrodibenzo[*c*,*g*]phenanthrene (III) was made on the basis of earlier results.

NEWMAN and Lutz[4] reported the synthesis of racemic 2-(isopropylideneaminoöxy)-propionic acid (Ia) and its resolution into the enantiomers (−)-Ia and (+)-Ia. Treatment of these enantiomers with 2,4,5,7-tetranitrofluorenone gave the respective optically active molecular complexing agents (+)-II and (−)-II, with which several compounds lacking any functional group capable of salt formation were resolved by means of fractional crystallization or precipitation from solution.[4,5] Klemm *et al.*[6,7] used silicic acid impregnated with optically active II as an adsorbent to effect optical resolution of similar racemates, particularly the hydrocarbon (±)-9,10-dihydrodibenzo[*c*,*g*]phenanthrene (III), by means of molecular complexation chromatography. We report here studies on transformations of racemic Ia and of optically active Ia which have culminated in the assignment of absolute configurations to Ia and II and in configurational correlation between II and III.

Procedures were first developed on racemic compounds. Fischer esterification of Ia produced the methyl ester Ib in 78% yield. When Ib was treated with a two-molar quantity of lithium aluminum hydride in refluxing tetrahydrofuran, the ester was reductively degraded directly to 1,2-propanediol, isolated in 67% yield. However, under milder conditions (molar ratio of $LiAlH_4$:Ib of 0·6:1·0, ether as solvent and a maximum temperature equal to that of the room) there resulted a crude liquid mixture which showed by V.P.C. the presence of both a major and a minor component (in the ratio 9:1 by volume). In contrast to the IR spectrum of Ib, that of the reduction mixture showed no carbonyl absorption. The major component, isolated by fractional

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[1] John Simon Guggenheim Foundation fellow, Eidg. Tech. Hochschule, 1958–1959.

[2] National Science Foundation Undergraduate Research Participant.

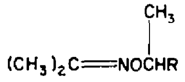
[3] Where inquiries concerning this paper should be sent.

[4] M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.* **78**, 2469 (1956).

[5] M. S. Newman and D. Lednicer, *Ibid.* **78**, 4765 (1956).

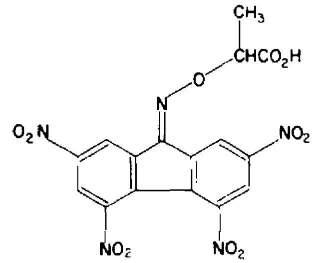
[6] L. H. Klemm and D. Reed, *J. Chromatog.* **3**, 364 (1960).

[7] L. H. Klemm, K. B. Desai and J. R. Spooner, *Ibid.* In press (1964).

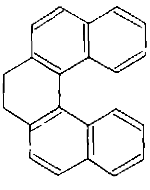


$(CH_3)_2C{=}NOCH(CH_3)R$

I



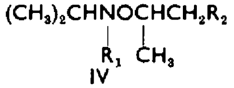
II



III

a: $R = CO_2H$
b: $R = CO_2CH_3$
c: $R = CH_2OH$
d: $R = CH_2OTs$
e: $R = CH_2N(CH_3)_2$
f: $R = CH_2N^+(CH_3)_3I^-$

distillation (57% yield), was identified as the compound Ic by means of its IR spectrum (bands for OH and C=N groups), its elemental analysis and its conversion to two crystalline derivatives (a tosylate Id and a dinitrobenzoate). It is apparent that under the milder conditions used, the carbomethoxy group is far more susceptible to reduction by lithium aluminum hydride than is the carbon-nitrogen double bond. However, efforts to avoid the formation of the minor component (believed to be the amino alcohol IVa derived from reductions of both of these functional groups, *vide infra*) by decreasing the molar ratio of $LiAlH_4$:Ib to the theoretical value of 1:2 (for reduction of the carbomethoxy group only) led to incomplete reaction of Ib.



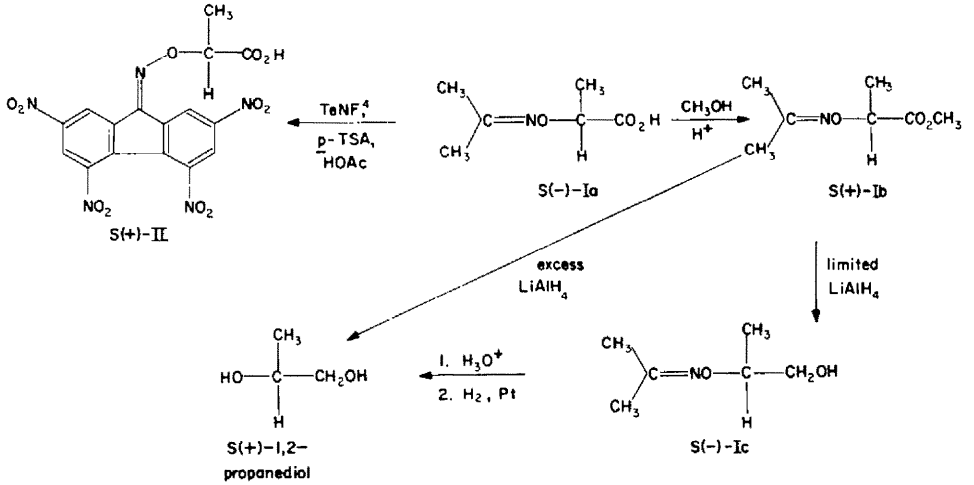
$(CH_3)_2CHN(R_1)OCH(CH_3)CH_2R_2$

IV

a: $R_1 = H, R_2 = OH$
b: $R_1 = Ts, R_2 = OTs$
c: $R_1 = Ts, R_2 = N(CH_3)_2$
d: $R_1 = Ts, R_2 = N^+(CH_3)_3I^-$

Indirect structural determination on the preceding minor component was obtained by first tosylating the crude, mixed reduction product (containing Ic) with pyridine and excess *p*-toluenesulfonyl chloride and then warming the crude mixed tosylates with excess anhydrous dimethylamine. In the first step, NH and OH groups should be converted to NTs and OTs, respectively, while in the second step only the OTs function should react, to give $N(CH_3)_2$. The aminolysis reaction mixture was readily separated into two liquid products by fractional distillation. The lower boiling, major product was identified as the expected Ie by its IR spectrum (C=N band) and its elemental analysis as well as by the elemental analysis of its crystalline methiodide If. The IR spectrum of the higher boiling fraction showed the presence of a benzenesulfonyl group but not of a C=N function. Its crystalline methiodide gave an elemental analysis consistent with the formula IVd. It thus seems clear that the minor component of the reduction product is, indeed, IVa, transformed subsequently to IVb (not isolated) by tosylation and, thence, to IVc (obtained in molar ratio of Ie:IVc of 12:1) by aminolysis.

A flow diagram showing the transformations of the enantiomer (—)-Ia and the absolute configurations of the compounds involved (as based on Fischer and R,S-conventions) is presented in Scheme 1. In this series the acid (−)-Ia was converted to the methyl ester (+)-Ib which was then degraded to the glycol (+)-1,2-propanediol.



SCHEME 1

This degradation was effected either in one step using excess lithium aluminum hydride in refluxing tetrahydrofuran or in two separate steps involving (a) initial reduction of the ester to the isolable intermediate (−)-Ic using limited lithium aluminum hydride and (b) subsequent hydrolysis-hydrogenolysis. The optically active propanediol was identified by direct comparison with both commercial synthetic (±)-1,2-propanediol and (−)-1,2-propanediol obtained through a fermentation process.[15] Optically active Ib and Ic were identified by comparison with the corresponding racemic compounds described previously. In as much as the absolute configuration of (−)-1,2-propanediol is known to be R by direct correlation with (−)-lactic acid[8] it follows that (+)-1,2-propanediol has the S-configuration[9] as shown in Scheme 1. Since the various transformations in Scheme 1 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 (−)-Ia, (+)-Ib (−)-Ic, and also (+)-II (derivable from (−)-Ia and 2,4,5,7-tetranitrofluorenone)[4] have the S-configuration. The exactly analogous enantiomeric R-series (based on (+)-Ia) for Scheme 1 was also investigated. A fortunate experimental aspect of these series is that a change in sign of optical rotation accompanies each chemical change (except that of Ib → propanediol directly).

The absolute configurations of the enantiomeric 9,10-dihydrodibenzo[*c*,*g*]-phenanthrenes (III) were determined as R(−) and S(+) by Mislow and McGinn.[10] According to Klemm *et al.*[6,11] optical resolution of III by means of molecular complexation chromatography, using silicic acid impregnated with S(+)-II as adsorbent, results from a difference in the relative stabilities of the two molecular complexes

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[8] P. A. Levene and H. L. Haller, *J. Biol. Chem.* **67**, 329 (1926).

[9] See E. Baer and H. O. L. Fischer, *J. Amer. Chem. Soc.* **70**, 609 (1948).

[10] K. Mislow and F. A. McGinn, *Ibid.* **80**, 6036 (1958).

[11] L. H. Klemm, D. Reed and C. D. Lind, *J. Org. Chem.* **22**, 739 (1957).

S(+)-II·R(−)-III and S(+)-II·S(+)-III which form on the column during the chromatographic separation. Since R(−)-III is more strongly retained than S(+)-III on this column,[6] it follows that S(+)-II·R(−)-III should be the more stable complex of the two.

For the preceding complexes we present now a molecular model which successfully allowed us to predict an S-configuration for (+)-II before the experiments described in this paper were performed. In future studies we plan to test this model further.

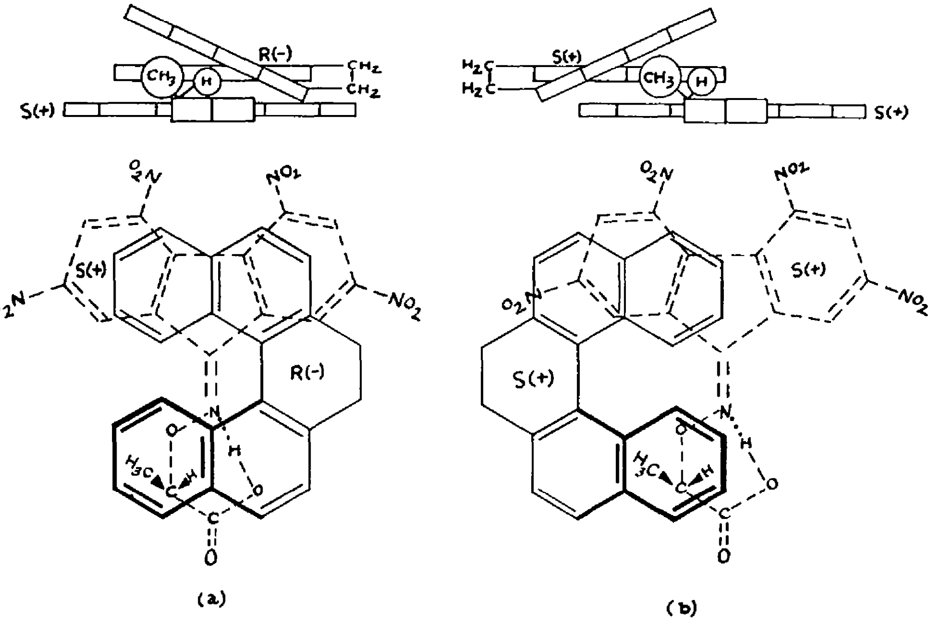

FIG. 1

The model is based on the following considerations. First, it is assumed[11] 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 III. 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. These concepts are retained in our model. 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 molecules,[13] which approach one another to van der Waals distances. Using Stuart–Briegleb molecular models and orienting them in accordance with these four considerations lead one to the geometric relationships shown in Fig. 1 (schematic, broadside and edgewise views) for these two complexes. Although the hydrogen atom on the carboxylic acid

[12] A. H. Sporer and K. N. Trueblood, *J. Chromatog.* **2**, 499 (1959).

[13] L. H. Klemm and J. W. Sprague, *J. Org. Chem.* **19**, 1464 (1954); J. Landauer and H. McConnell, *J. Amer. Chem. Soc.* **74**, 1221 (1952).

group of S(+)-II is appropriately located for facile hydrogen bonding to the oximino nitrogen, the illustration of such intramolecular hydrogen bond in Fig. 1 is made for simplicity only. From Fig. 1(a), it is readily apparent that maximal overlap of one naphthalene moiety of the donor R(−)-III with the tetranitrofluorene ring system of the acceptors (+)-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. In Fig. 1(b), however, one sees that the protuding methyl group of the acceptor S(+)-II compresses against the second naphthalene moiety of the donor S(+)-III while the first naphthalene moiety of the donor has only partially overlapped the tetranitrofluorene system of the acceptor. Clearly (a), *i.e.* S(+)-II·R(−)-III, should represent the more stable complex.

EXPERIMENTAL

IR spectra were determined by means of a Perkin–Elmer model 137 Infracord spectrophotometer. 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. Elemental analyses were performed in the microanalytical laboratory at the E.T.H. or by Micro-Tech Labs., Skokie, Illinois.

2-(*Isopropylideneaminoöxy*)*propionic acid* (Ia). (±)-Ia was prepared and resolved by the procedure of Newman and Lutz[4] using (−)-ephedrine. However, irregularity was found in the melting point and in the sign and magnitude of the optical rotation of the salt which crystallized first or in greater abundance. In some cases, a salt of m.p. 85–88°, $[\alpha]_D^{26}$ −19·8° (*c* 2·8, water), was obtained. Processing of this salt gave crystals of (−)-Ia, m.p. 83–85°, $[\alpha]_D^{25}$ −28·5° (*c* 3·7, water).

Methyl 2-(*isopropylideneaminoöxy*)*propionate* (Ib). A mixture of 63·4 g. of (±)-Ia, 200 ml of methanol and 10 ml of conc. H_2SO_4 was refluxed for 4 hr. The solvent was evaporated *in vacuo* at 40° and the residue was treated with water. Combined ethereal extracts of this mixture were washed with $NaHCO_3$ aq and then with water, dried and distilled, yield 54·3 g. (78%) of liquid, b.p. 73–76° (10 mm). For analysis a sample was re-distilled once at 731 mm (b.p. 183–184°) and then twice at 10 mm, n_D^{23} 1·4313; IR bands (neat) at 1770 (very strong, C=O) and 1670 (weak, C=N) cm^{-1}. (Found: C, 52·89; H, 8·42; N, 8·87. $C_7H_{13}NO_3$ requires: C, 52·81; H, 8·23; N, 8·80%).

Esterification of (−)-Ia, m.p. 83–85°, $[\alpha]_D^{26}$ −29·4° (*c* 3·76, water), in the foregoing manner gave (+)-Ib, b.p. 83–85° (16 mm), $[\alpha]_D^{27}$ +14·6° (neat), IR spectrum (neat) identical with that of (±)-Ib.

Similarly, (+)-Ia gave (−)-Ib, b.p. 68–69° (10 mm), $n_D^{24 \cdot 8}$ 1·4298, $[\alpha]_D^{24}$ −9·0° (*c* 2·5, acetone). (Found: C, 52·81; H, 8·28; N, 8·76). Ester of the same optical purity was obtained on methylation of (+)-Ia with diazomethane.

2-(*Isopropylideneaminoöxy*)-1-*propanol* (Ic). A rapidly stirred solution of 57·3 g of (±)-Ib in 300 ml of anhydrous ether was treated (in a cold water bath) with 1540 ml of 0·15M (28% excess over that needed for exclusive reduction of the carbomethoxy group) $LiAlH_4$ in ether added in a fine stream. The mixture was allowed to stand overnight and then was treated in succession with a few ml of glacial acetic acid, water, dil. H_2SO_4 (until acid to litmus) and solid NaCl (until saturated). The organic layer was separated, combined with ethereal extracts of the aqueous layer, dried and distilled, yield 32·8 g of impure liquid, b.p. 75–78° (16 mm). V.P.C.[14] of this product at 200° using Emulphor-O as stationary phase showed the presence of two major components of relative retention times V_R = 1·00 (82 vol%, apparently (±)-Ic) and V_R = 1·12 (9%, presumably (±)-IVa). For analysis of (±)-Ic, a sample of the crude liquid was re-distilled once at 740 mm (b.p. 176–179°) and four times at 10 mm, $n_D^{21 \cdot 7}$ 1·4440; IR bands (neat) at 3400 (broad, strong; bonded OH) and 1650 (weak, C=N) cm^{-1}. (Found: C, 54·86; H, 10·07; N, 10·51. $C_6H_{13}NO_2$ requires: C, 54·94; H, 9·99; N, 10·68%).

The 3,5-*dinitrobenzoate*, prepared from the analytically pure alcohol, formed faintly yellow nacreous platelets from absolute ethanol, m.p. 91·5–92·5°. (Found: C, 47·92; H, 4·68; N, 13·14. $C_{13}H_{15}N_3O_7$ requires: C, 48·00; H, 4·65; N, 12·92%).

Reduction of (−)-Ib in the preceding manner (except that only 10% excess of $LiAlH_4$ was used)

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[14] Conducted by Dr. W. Simon.

gave (+)-Ic, b.p. 75–78° (15 mm), $n_D^{24\cdot5}$ 1·4430, $[\alpha]_D^{24}$ +4·6° (neat); IR spectrum (neat) identical with that of (±)-Ic.

Similarly, (+)-Ib [b.p. 79–80° (14 mm), $[\alpha]_D^{24}$ +9·0° (*c* 3·2, water)] when treated with 30% excess of 0·23M $LiAlH_4$ in an atmosphere of nitrogen gave (−)-Ic $[\alpha]_D^{24}$ −6·0° (*c* 9·2, acetone).

(±)-2-(*Isopropylideneaminoöxy*)-1-*propyl* p-*toluenesulfonate* (Id). A solution of 8·2 g of crude, once-distilled preceding (±)-Ic and 12·0 g of *p*-toluenesulfonyl chloride in 100 ml of anhydrous pyridine was allowed to remain at room temp for 2 days. It was diluted with 200 ml of ether, allowed to stand for 1 hr and filtered. The filtrate was washed with dil. HCl aq. and then water, dried and evaporated. Agitation of the amber, viscous residue gave 15·3 g of light tan crystals, m.p. 42–46°. For analysis, a sample was washed with ether and acetone, treated (in acetone) with decolorizing charcoal, and recrystallized from ether to give white prisms, m.p. 47–50°; IR bands ($CHCl_3$) at 1680 (weak, C=N), 1600 and 1500 (weak, aromatic C=C), and *ca.* 1365 and 1180 cm⁻¹ (strong $—SO_2—$). (Found: C, 54·58; H, 6·74; N, 4·81; S, 11·30. $C_{13}H_{19}NO_4S$ requires: C, 54·72; H, 6·71; N, 4·91; S, 11·23%).

Reaction of crude Id *with dimethylamine.* A homogeneous mixture of 26·6 g of crude non-crystalline (±)-Id, prepared as in the preceding experiment, and *ca.* 25 g (excess) of anhydrous dimethylamine was heated in a sealed tube at 65° for 24 hr, whereupon two liquid phases were present. Cooling to room temp caused gradual disappearance of the less dense phase (temperature-dependent reversible process). The residue from evaporation of volatile components at room temp was treated with water and 40% NaOH aq. (to incipient precipitation) and extracted with ether. Distillation of the water-washed, dried ethereal solution gave 10·4 g of colorless *N,N-dimethyl-2-(isopropylideneaminoöxy)-1-propylamine* (Ie), b.p. 60–64° (11 mm), and 2 g of yellow, viscous *N,N-dimethyl-2-[N-isopropyl-N-*(p-*toluenesulfonyl*)-*aminoöxy*]-1-*propylamine* (IVc), b.p. 152–155° (0·5 mm).

For analysis, Ie was distilled thrice more, $n_D^{22\cdot5}$ 1·4328; IR band (neat) at 1650 cm⁻¹. (Found: C, 60·53; H, 11·74; N, 17·81. $C_8H_{18}N_2O$ requires: C, 60·72; H, 11·47; N, 17·70%). The *methiodide* (If) formed nacreous leaflets from methanol–ether, m.p. 184·5–185·5°. (Found: C, 36·13; H, 7·07; N, 9·38; I, 42·20. $C_9H_{21}IN_2O$ requires: C, 36·01; H, 7·05; N, 9·33; I, 42·28%).

IVc had IR bands (neat) at 1600 and 1500 (weak, aromatic C=C) and 1350 and 1175 cm⁻¹ (strong, $—SO_2—$), but none near 1650 cm⁻¹. The *methiodide* (IVd) formed prisms from methanol, m.p. 203·5–205·5°, IR bands (KBr) at 1590, 1490, 1340, and 1165 cm⁻¹. (Found: C, 42·27; H, 6·54; N, 6·11; S, 7·34; I, 28·28. $C_{16}H_{29}IN_2O_3S$ requires: C, 42·11; H, 6·40; N, 6·14; S, 7·03; I, 27·81%).

(−)-1,2-*Propanediol from fermentation.* For comparative purposes (−)-1,2-propanediol was prepared from acetone by a three-step process[15] involving fermentation as the last step. There resulted 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), IR spectrum (neat) identical with that of commercial, synthetic (±)-1,2-propanediol; lit[15], b.p. 88–90° (12 mm), $[\alpha]_D^{20}$ −15·0°.

A *bis*-p-*nitrobenzoate* of the fermentation product formed cream-colored needles from ethanol, m.p. 107·5–108·5°; $[\alpha]_{436}^{23\cdot8}$ −108°, $[\alpha]_{546}^{23\cdot8}$ −52·9°, $[\alpha]_{578}^{23\cdot8}$ −45·1° (*c* 0·70, acetone). (Found: C, 54·62; H, 3·66; N, 7·70. $C_{17}H_{14}N_2O_8$ requires: C, 54·55; H, 3·77; N, 7·48%).

The bis-*p*-nitrobenzoate of commercial (±)−1,2-propanediol (n_D^{21} 1·4309) melted at 126–127°, lit[16] 126–127°.

The *mono*-3,5-*dinitrobenzoate*[17] of commercial (±)-1,2-propanediol formed colorless needles from ethanol, m.p. 149—150°. (Found: C, 44·54; H, 3·71; N, 10·58. $C_{10}H_{10}N_2O_7$ requires: C, 44·45; H, 3·73; N, 10·37%).

Conversion of Ib *to* 1,2-*propanediol.* To a well-stirred mixture of 8·1 g (0·2 mole) of $LiAlH_4$ in 200 ml of purified[18] tetrahydrofuran was slowly added (over a period of 1·5 hr) a solution of 16·2 g (0·1 mole) of (±)-Ib in 50 ml of the same solvent. The gray mixture was heated on a steam bath for 2 hr longer and then treated, in succession, with 8 ml of water, 8 ml of 20% NaOH aq, and 18 ml of water. The white suspension was filtered through a sintered glass funnel and the residue was washed with 400 ml of tetrahydrofuran. The filtrate was dried with anhydrous $MgSO_4$ and

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[15] P. A. Levene and A. Walti, *Org. Synth.* Coll. Vol. II, 5, 88, 545 (1943).

[16] H. Eklund and C. C. Price, *J. Amer. Chem. Soc.* **67**, 693 (1945).

[17] R. L. Shriner, R. C. Fuson and D. Y. Curtin, *The Systematic Identification of Organic Compounds* (4th Edition) pp. 212–213. J. Wiley, New York (1956).

[18] Refluxed with solid KOH for several hr, decanted and distilled from $LiAlH_4$.

distilled, yield 5·2 g (67%) of (±)-1,2-propanediol, b.p. 94–95° (13 mm), n_D^{24} 1.4314, IR spectrum identical with that of a commercial, synthetic sample. The *p*-nitrobenzoate derivative melted at 123–125°, undepressed on admixture with the aforementioned sample of m.p. 126–127°.

Repetition of this procedure but with (+)-Ib, $[\alpha]_D^{27}$ +14·6° (neat), gave a liquid product, b.p. 93–95° (15 mm), $[\alpha]_D^{26}$ +11° (*c* 13, acetone). The IR spectrum and the V.P.C. retention time (run at 175° using Carbowax-20 as stationary phase) were identical with those of a commercial, synthetic sample of (±)-1,2-propanediol.

In another case, (+)-Ib, $[\alpha]_D^{26}$ +4·7° (neat), gave a product of b.p. 94–95° (15 mm), $[\alpha]_D^{26}$ +4·0° (neat), converted to a *p*-nitrobenzoate derivative, m.p. 122–125°, $[\alpha]_{436}^{25}$ +55·5°, $[\alpha]_{546}^{25}$ +27·4°, $[\alpha]_{578}^{25}$ +23·7° (*c* 0·98, acetone).

Conversion of Ic *to* 1,2-*propanediol.* A solution containing 16·3 g of (+)-Ic, 150 ml of 2:1 (v/v) isopropanol–water and 11·5 ml of conc. HCl was first allowed to stand at room temp for 12 hr and then was shaken with 0·3 g of Adams' platinum oxide catalyst in the presence of hydrogen at 3–4 atm press for 24 hr, whereupon had occurred absorption of a quantity of hydrogen equimolar to the Ic used. The mixture was filtered, evaporated to a syrup, re-filtered, dissolved in 50 ml of 2:1 (v/v) ethanol–ether, dried, and distilled, yield 4·2 g (45%) of (−)-1,2-propanediol, b.p. 78–82° (18 mm), $[\alpha]_D^{24}$ −2·7° (*c* 1·36, ethanol), IR spectrum (neat) identical with that of commercial, synthetic (±)-1,2-propanediol and with that of (±)-1,2-propanediol prepared from (±)-Ic by the same method.

In another run a solution of 0·8 g (−)-Ic in 1 ml of conc. HCl and sufficient 60% isopropanol to make 5 ml of solution (α = −0·15°) was treated in the preceding manner except that the first filtrate (after hydrogenation) was merely re-diluted to 5 ml with additional 60% isopropanol for direct polarimetric measurement (α = +0·36°).

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