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SYNTHESIS OF (+)-(3*S*,7*S*,10*S*)- AND (+)-(3*S*,7*S*,10*R*)-3,7,10-TRIMETHYLBORATRANE. AMPLIFICATION OF ENANTIOMERIC PURITY IN THE REACTION BETWEEN AMMONIA AND PROPYLENE OXIDE

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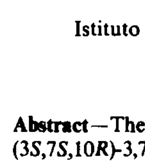
Abstract—The synthesis is described of the two enantiomerically pure isomers (+)-(3*S*,7*S*,10*S*)- and (+)-(3*S*,7*S*,10*R*)-3,7,10-trimethylboratrane. The structures were determined by ^{1}H- and ^{13}C-NMR spectroscopy. A method for increasing the enantiomeric purity by trimerization reactions of partially-resolved (*S*) propylene oxide is proposed. The reaction was studied from the kinetic viewpoint and interpreted according to a binomial probability scheme. The experimental findings point to a rapid growth in enantiomeric purity for the (*SSS*) trimer compared with the starting material, whilst no increase was found for the (*SSR*) trimer.

Amongst the as yet unresolved issues reported in a survey of chiral molecules of high symmetry,[1] our attention was attracted by 3,7,10-trimethylboratrane (triisopropanolaminoborate), **1**, a triptych molecule with C_3 symmetry. This compound had at that time been obtained only in the racemic form, and almost always mixed with considerable quantities of the unsymmetrical stereoisomer **2**.[2]



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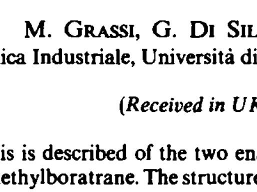

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The tricyclic structure of **1** and **2**, with a dative N → B bond, had been suggested by analogy with the structure of the corresponding non-methylated compound, on the basis of its considerable resistance to hydrolysis compared with that of common boric esters.[2,3] Measurement of the dipole moment[4,5] and a study of the ^{11}B-NMR spectrum[6] were also in agreement with such a structure. Confirmation was obtained by X-ray examination carried out on triethanolaminoborate.[7–9] The N–B distance was found to be 1.683 Å, comparable with the sum of the covalent bond radii. A further feature of this molecule is the marked non-planarity of the pentaatomic rings: the angle of torsion around the C—C bond was found to be about 40°.

The attribution of structure **1** to the minor product of the reaction between boric acid and triisopropanolamine (nitrilo-2-propanol) was made by Steinberg and Hunter on statistical considerations:[2] the ratio between the two products was found to be 38 : 62, not far from the 25 : 75 foreseen for the case of a completely random reaction between NH_3 and racemic propylene oxide. These authors also succeeded in obtaining small quantities, presumably in the pure state, of racemic compound **1** (and of the corresponding amine). The structure has more recently been confirmed by a study of the ^{1}H-NMR spectra of the mixture of the two compounds **1** and **2**.[10]

In pursuance of a study of chiral molecules possessing symmetry elements, an attempt was made to overcome the difficulties involved in separating diastereoisomers **1** and **2** and in resolving **1**, by preparing (+)-(*S*,*S*,*S*)-**1** in optically pure form starting from (−)-(*S*)-propylene oxide. A second method of synthesis made it possible to obtain (+)-(*S*,*S*,*R*)-**2** in an enantiomeric purity of over 92%.

The second part of this paper deals with a study of the amplification of enantiomeric purity in the synthesis of (+)-(*S*,*S*,*S*)-**1** and of the corresponding amine, starting from partially enriched (−)-(*S*)-propylene oxide. Amplification of the enantiomeric purity in dimerization or "duplication" reactions has already been observed and discussed by Horeau *et al.*[11] and Lahav *et al.*[12]; a substantially similar case has also been reported by Brown *et al.*[13] In their turn, Himmele and Siegel observed the same phenomenon during trimerization of 3-formylpinane.[14]

The very limited number of examples known in this field led us to undertake a detailed examination of the phenomenon, both from an experimental and from a theoretical point of view, using a probabilistic approach.

Synthesis and structural determination of (+)-(*S*,*S*,*S*)-**1** *and* (+)-(*S*,*S*,*R*)-**2** *and their precursors*

The reaction between NH_3 and (−)-(*S*)-propylene oxide in a 1 : 3 stoichiometric ratio proceeded quantitatively with the formation of (+)-(*S*,*S*,*S*)-triisopropanolamine (Scheme 1), together with small

$$NH_3 \xrightarrow{3\underline{S}} N\underline{S}_3 \xrightarrow{H_3BO_3} (\underline{S},\underline{S},\underline{S})\text{-BORATRANE} \qquad (1)$$

(S̲ represents the (S̲) enantiomer of propylene oxide)

Scheme 1.

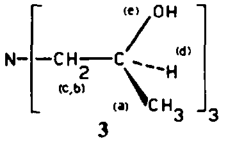
Table 1. ^{1}N-NMR spectrum of (+)-(*S,S,S*)-*triisopropanolamine*

	δ,ppm	J_{bc},Hz	J_{cd}	J_{bd}	J_{ad}
a)	1.12				6.0
b)	2.22	13.0	2.2		
c)	2.38	13.0		10	
d)	3.89		2.2	10	6.0
e)	4.9$^{+)}$				

+) broad resonance

quantities of the (+)-(*S,S,R*) isomer arising from the enantiomeric impurity of the propylene oxide. The presence of the secondary product was detectable in the NMR spectrum, but its quantitative determination could be achieved easily by GLC only at the borate stage.

After crystallization the amine had m.p. 96°, $[\alpha]_D^{25°} = +136°$ ($CHCl_3$, 4%). Its ^{13}C-NMR spectrum showed only three signals, at 20.20 (CH_3), 63.20, 63.64 (CH_2,CH) ppm. The ^1H-NMR spectrum, recorded at 200 MHz (Table 1), is in full agreement with the formula 3.



3

By reaction with boric acid the amine was converted in high yield into (+)-(*S,S,S*)-1, which after purification had m.p. 151° (with a solid–solid transition around 105° detected by DSC) and $[\alpha]_D^{25°} = +162°$ ($CHCl_3$, 1%). The sample must be taken to be 100% optically pure (see Table 2). The ^{13}C-NMR spectrum consists of only three signals, at 18.94 (CH_3), 65.82 (CH_2) and 67.62 (CH) ppm.

The isomer (+)-(*S,S,R*)-2 was obtained in a two-stage synthesis (Scheme 2): first the racemic propylene oxide was reacted with a large excess of NH_3, yielding the racemic monoisopropanolamine, which was then treated with two moles of (−)-(*S*)-propylene oxide, yielding an equimolecular mixture of (+)-(*S,S,S*)-1 and (+)-(*S,S,R*)-2. Separation of the two isomers was achieved by flash chromatography. A sample of pure 2 has $[\alpha]_D^{25°} = +58.5°$ ($CHCl_3$, 1%) corrected for 92% optical purity (see below). Its ^{13}C-NMR spectrum consists of eight signals assigned as follows, 19.43, 19.92, 21.99 (CH_3); 67.23, 67.32, 68.42 (CH_2); 70.33, 72.35, 72.35 (CH) ppm. It can be seen that, among each group of carbon atoms (particularly CH_3 and CH), one of the signals differs sharply from the others. This suggests that one of the arms of the triptych is in a different steric environment.

The ^1H-NMR (300 MHz) spectra of compounds 1 and 2 in the pure state are substantially in agreement with those recorded by Tandura *et al.*[10] on the diastereoisomer mixture. However, whilst the attribution of 1 is immediate, we do not feel that these authors' interpretation of the spectrum of 2 is unequivocal. They suggested that the configurational inversion of one of the three asymmetric carbons involves the passage of a CH_3 group from an equatorial to an axial position leaving the geometry of the triptych structure unchanged. Such behaviour would not be in agreement with the observed J values. In our opinion the spectrum of 2 can reasonably be interpreted on the basis of a significant modification in the geometry of the skeleton involving distortion of the angle of torsion O—C—C—N. To clarify this point, we are presently undertaking a crystallographic and conformational analysis of 1 and 2.

Enantiomeric amplification in the synthesis of triisopropanolamine

The reaction between ammonia and propylene oxide may be described as a series of parallel and consecutive reactions governed by six rate constants (Scheme 3).

This scheme is reduced to a simple problem of binomial probability if all the elementary reactions are of the first order with respect to *R* or *S* and there is no enantiomeric recognition at any stage (i.e. $k_2 = k_3$, $k_4 = k_5 = k_6$.

Taking x to be the molar fraction of the enantiomer *S* in the original propylene oxide, and p(= 2x − 1) to be its enantiomeric purity, the quantity of trimers is found (using an obvious abbreviated notation) to be:

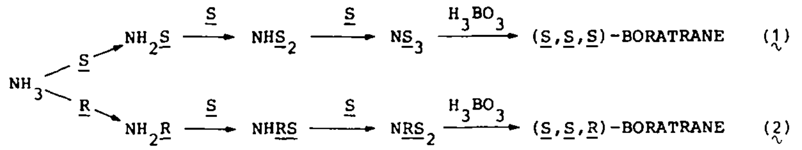
$$S_3 = x^3;\ R_3 = (1-x)^3;$$
$$S_2R = 3x^2(1-x);\ SR_2 = 3x(1-x)^2. \quad (1)$$

Table 2. Amplification of enantiomeric purity (optical activity measured at 25° at the D-line)

	1	2	3	4	5
α (propylene oxide)¶	− 2.363°	− 1.421°	− 1.036°	− 0.328°	0
p %	96.1	57.8	42.1	13.3	0
Γ_{T1} (exptl) %	94.3	51.3	40.2	27.9	26.5
F_{T1} (calcd, eq. 2) %	94.3	50.0	38.3	26.3	25.0
[α] (exptl)	+ 155.0	+ 95.9	+ 73.5	+ 23.9	0
[α] (calcd, eq. 6)	+ 155.9	+ 94.9	+ 69.4	+ 22.5	0
[α] (calcd, eq. 5)†	+ 155.9	+ 96.4	+ 71.6	+ 22.8	0
p_{T1} (calcd, eq. 3) %	> 99.9	96.2	87.4	38.2	0
p_{T2} (calcd, eq. 4) %	96.1	57.8	42.1	13.3	0

¶ Direct polarimetric reading in a 0.2 dm cell.

† Using experimental values for F_{T1} and calculated ones (eqs. 2 and 4) for p_{T1} and p_{T2}.



Scheme 2.

The symmetric trimer fraction is then:

$$F_{T1} = (1+3p^2)/4 \qquad (2)$$

the optical purity of the symmetric trimer:

$$p_{T1} = p(3+p^2)/(1+3p^2) \qquad (3)$$

that of the non-symmetric trimer:

$$p_{T2} = p \qquad (4)$$

the optical activity of the borate mixture:

$$[\alpha] = ([\alpha]_{SSS}p_{T1} - [\alpha]_{SSR}p_{T2})F_{T1} + [\alpha]_{SSR}p_{T2} \qquad (5)$$

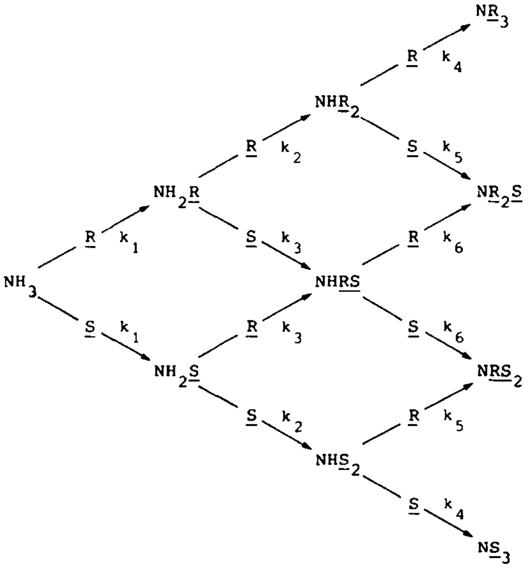
and also:

$$[\alpha] = (p/4)([\alpha]_{SSS}(3+p^2) + [\alpha]_{SSR}(3-3p^2)). \qquad (6)$$

It may be observed that this expression reduces to a linear relationship: $[\alpha] = [\alpha]_{SSS}p$, when $[\alpha]_{SSR} = [\alpha]_{SSS}/3$; i.e when the optical activity of the two trimers can be expressed as the sum of independent contributions from the three chiral carbons.

Figures 1 and 2 show the variation of F_{T1} and p_{T1} with p. For the sake of comparison Fig. 1 also shows the chiral dimer fraction $F_D = \frac{1}{2}(1+p^2)$ and Fig. 2 its enantiomeric purity $p_D = 2p/(1+p^2)$ determined by Horeau and co-workers[11] for the duplication reaction.

We carried out a series of trimerization experiments starting from propylene oxide at various optical purities. Evaluation of F_{T1} and optical activity was achieved after conversion of the amine into boratrane; the findings were compared with those computed according to eqns (2) and (6) respectively (Table 2). Agreement was found to be quite satisfactory; nonetheless a few observations are necessary before drawing any final conclusions.



Scheme 3.

The propylene oxide used in these experiments was not quite enantiomerically pure. The presence of 5.7% of the unsymmetrical trimer made it possible to determine the optical purity of the reactant using eqn (2). The error introduced in this way, due to the possibly incomplete validity of the statistical approach, is in any case negligible, the optical purity of propylene oxide being close to 100%. From eqn (3) it can be shown that a small fraction of enantiomer *R* has no practical influence on the enantiomeric purity of **1**.

Equation (6) enables us to calculate the values of [α] according to the probabilistic scheme. A better fit is achieved if [α] is computed using experimental values of F_{T1} and eqn (5). Direct determination of p_{T1} and p_{T2} however, requires an independent experiment.

Flash chromatography on silica gel was used to fractionate the mixture of borates derived from propylene oxide of p = 0.421 (Table 2, column 3); fractions were obtained having different F_{T1} but constant p_{T1} and p_{T2}. The fractionation data were interpreted by means of eqn (5) (Fig. 3). Since $[\alpha]_{SSS}$ and $[\alpha]_{SSR}$ were known independently, p_{T2} was obtained from the intercept and p_{T1} from the slope.

Linear regression analysis yielded the following values: $p_{T1} = 0.863$ and $p_{T2} = 0.464$, whence we obtain [α] = 72.4°. Agreement on p_{T1} (Table 2) is excellent; we can thus consider the values of p_{T1} computed by eqn (3) as being truly representative of the state of the system. Agreement on p_{T2} is less good, but to an extent which we feel is still within the experimental error allowed for in determining [α], p and F_{T1}.

It may thus be concluded that the reaction between ammonia and propylene oxide fits well into a simple probability scheme, at least at this level of accuracy. A slight but systematic excess of stereoisomer **1** with respect to the computed value can nonetheless be

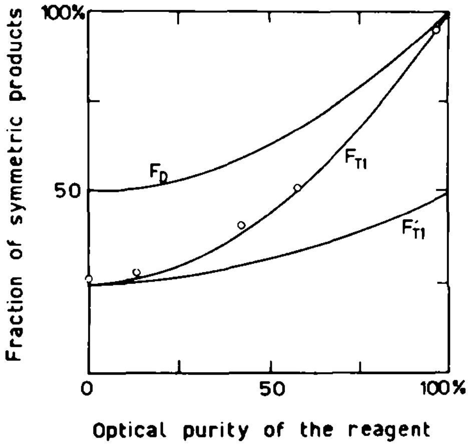


Fig. 1. Dependence of the yield of symmetric products on the optical purity of the reagent. For the meaning of F_{T1}, F'_{T1} and F_D, see the text.

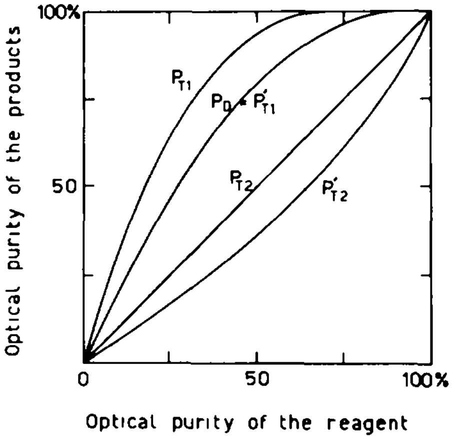


Fig. 2. Variation of the optical purity of the products as a function of the optical purity of the reagent. For the meaning of p_{T1}, p'_{T1}, p_{T2}, p'_{T2} and p_D, see the text.

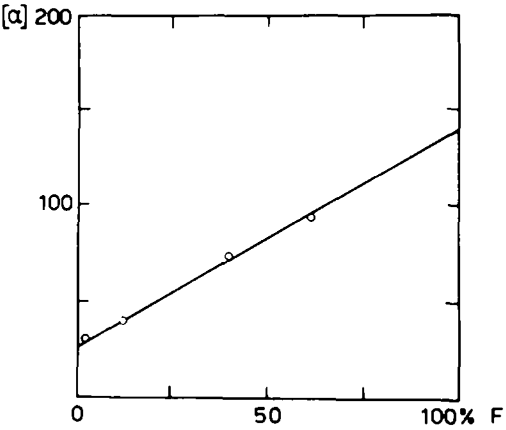


Fig. 3. Fractionation data expressed according to eqn (5).

observed. In particular it should be borne in mind that the ratio F_{T1}(exp)/F_{T1} (calc) lies between 1.05 and 1.06 for p between 0 and 0.5, whilst it is close to unity for higher initial purities (Table 2). This fact can be interpreted as indicating a small degree of enantiomeric recognition ($k_2 > k_3$ and/or $k_4 > k_5$ and/or $k_4 > k_6$). The ratio between these constants would in any case be between 1.02 and 1.06.

An analogous probability treatment was also applied to the reaction conducted according to Scheme 2. The optical purity of the symmetric trimer is expressed by

$$p'_{T1} = 2p/(1+p)^2 \qquad (7)$$

identical to Horeau's finding for the duplication reaction;[11] the optical purity of the unsymmetrical trimer is:

$$p'_{T2} = 2p/(3-p^2) \qquad (8)$$

and the symmetric trimer fraction:

$$F'_{T1} = (1+p^2)/4. \qquad (9)$$

These curves are also given in Figs 1 and 2.

It should be noted that the unsymmetrical trimer undergoes a reduction of enantiomeric purity ($p'_{T2} < p$). Formula (8) has been used above to evaluate the maximum optical activity of (+)-(*S*,*S*,*R*)-**2**.

In conclusion, trimerization of partially enriched reagents should be considered as a process endowed with a higher power of amplification of enantiomeric purity than dimerization. Tetramerization and, in general, oligomerization reactions seem at first glance to be even more attractive; however, their use is limited in practice by the huge number of side-products, i.e. of diastereoisomers containing differing ratios and/or disposition of *R* and *S* units.

EXPERIMENTAL

The products are very hygroscopic, and wherever possible manipulations were performed under nitrogen or in a dry-box. GLC analyses were performed on a Dani 3800 gas chromatograph equipped with 20–50 m capillary columns and OV-17, OV-1, SE-52 as stationary phases. M.ps were recorded on a Mettler TA-2000 DSC instrument. Polarimetric measurements were performed on a Perkin–Elmer 241 polarimeter using 1–5% $CHCl_3$ solns at 25°. Titrations were performed on a Metroohm E-576 potentiograph.

^1H-NMR spectra were recorded on Varian XL-200 and Bruker CXP-300 spectrometers, ^{13}C-NMR spectra on a Varian XL-100 FT spectrometer (10% soln, $CDCl_3$ as solvent, TMS as internal standard, at room temp).

Flash chromatography was performed on a 70 cm h, 3 cm i.d., silica gel (230–400 mesh) column, working pressure 1.5 atm, eluent $CHCl_3$–MeOH (85:15), with 200–300 mg samples: 50–60 fractions (20 ml each) were collected and analysed by GLC.

(+)-(S,S,S)-Triisopropanolamine. (−)-(*S*)-Propylene oxide ($\alpha_D^{25°} = -11.81°$ neat, 5 ml) was stirred with concentrated NH_3 soln (32%, 1.3 ml) at 0° for 24 hr. After removal of water under reduced pressure, the title compound (4.5 g) was obtained as a viscous oil (yield 95.5%). Colourless crystals melting at 96° were obtained by crystallization from anhydrous ether (yield 71.7%).

(+)-(S,S,S)-3,7,10-Trimethylboratrane (**1**). Reaction of (+)-(*S*,*S*,*S*)-triisopropanolamine and H_3BO_3 was performed as reported in Ref. 2. GLC analysis of the product from the oily amine showed 5.7% of isomer **2**, while boratrane obtained from the crystallized amine was 99.2% pure.

(+)-(S,S,R)-3,7,10-Trimethylboratrane (**2**). Racemic propylene oxide (1.3 ml) was stirred with NH_3 soln (32%, 40 ml) at 0° for 24 hr. The soln was concentrated under reduced pressure and residual water was azeotropically removed with toluene. The residue was distilled and the racemic monoisopropanolamine was obtained as viscous oil from the fraction 100–105°/20 mmHg. The product, b.p. 158°/1 atm, was characterized by GLC and titration with HCl. Its ^1H-NMR spectrum (10% in D_2O) was almost superimposable upon the spectrum of symmetric triisopropanolamine. The racemic monoisopropanolamine (0.5 g) and (−)-(*S*)-propylene oxide (0.93 ml) were stirred for 24 hr at 0°. (+)-(*S*,*S*,*S* and *S*,*S*,*R*)-Triisopropanolamine (1.17 g) was obtained (yield 92%). The presence of the two isomers of C_3 and C_1 symmetry was revealed by ^1H- and ^{13}C-NMR spectroscopy (very complex spectra with many overlapping lines), but no resolution of the compounds was achieved by GLC analysis.

Reaction of the amine with H_3BO_3 produced the expected equimolecular mixture of **1** and **2** (51 and 49% respectively, by GLC analysis, yield 80.6%). Flash chromatography of 320 mg of the mixture afforded **2** (32 mg, 95.2% pure, GLC) and **1** (68 mg, 100% pure, GLC).

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REFERENCES

[1] M. Farina and C. Morandi, *Tetrahedron* **30**, 1819 (1974).

[2] H. Steinberg and D. L. Hunter, *J. Am. Chem. Soc.* **82**, 853 (1960).

[3] H. C. Brown and E. A. Fletcher, *Ibid.* **73**, 2808 (1951).

[4] H. Lumbroso and A. Grau, *Bull. Soc. Chem. Fr.* 1866 (1961).

[5] J. M. Pugh and R. H. Stokes, *Aust. J. Chem.* **16**, 204 (1963).

[6] T. P. Onak, R. E. Williams and R. Swidler, *J. Phys. Chem.* **67**, 1741 (1963).

[7] Z. Taira and K. Osaki, *Inorg. Nucl. Chem. Letters* **7**, 509 (1971).

[8] R. Mattes, D. Fenske and K. F. Tebbe, *Chem. Ber.* **105**, 2089 (1976).

[9] M. Bonzeek and H. Follner, *Monatsh. Chem.* **107**, 283 (1976).

[10] S. N. Tandura, V. A. Pestunovich, M. G. Voronkov, G. I. Zelchan, V. P. Baryshok and Yu. A. Lukina, *Dokl. Akad. Nauk S.S.S.R.* (*Phys. Chem.*) (Engl. Trans.) **235**, 688 (1977).

[11] J. P. Vigneron, M. Dhaenes and A. Horeau, *Tetrahedron* **29**, 1055 (1973).

[12] M. Lahav, F. Laub, E. Gati, L. Leiserowitz and Z. Ludmer, *J. Am. Chem. Soc.* **98**, 1620 (1976).

[13] H. C. Brown, J. R. Schwier and B. Singaram, *J. Org. Chem.* **43**, 4395 (1978).

[14] W. Himmele and H. Siegel, *Tetrahedron Letters* 911 (1976).