Synthesis of (*R*)- and (*S*)-2-Aminobutane from (*S*)- and (*R*)-2-Aminobutanol

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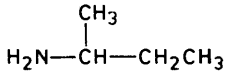
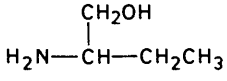
(*R*)-(−)- and (*S*)-(+)-2-Aminobutane (**1**) can be synthesized in good yield and high optical purity from (*S*)-(+)- and (*R*)-(−)-2-aminobutanol (**2**) respectively.

2-Aminobutane (s-butylamine) (**1**) is the simplest primary amine which can exist as an enantiomeric mixture and is of interest as the (*R*)-(−)-compound (**1**) is present in pharmacologically active species such as β-blockers [1] or central analgesics.[2]

Although 75% optically pure (*R*)-(−)-compound (**1**) has been prepared *via* hydroboration of *cis*-but-2-ene,[3] the only method available for the preparation of the single enantiomers of (**1**) is still based on the resolution of the racemate.† Repeated crystallizations of the diastereoisomeric salt prepared from compound (**1**) with natural L-(+)-tartaric acid are reported to afford pure (*S*)-(+)-compound (**1**), $[\alpha]_D$ +7.4° (neat).[4] It is possible to obtain the pure (*R*)-(−)-enantiomer of (**1**) by using as the resolving reagent the much more expensive, unnatural D-(−)-tartaric acid.[2] Alternatively, (*R*)-(−)-(**1**) can be obtained from the mother-liquor of the salt prepared from racemic amine and L-(+)-tartaric acid after several crystallizations.[5]

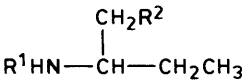


(**1**)



(**2**)

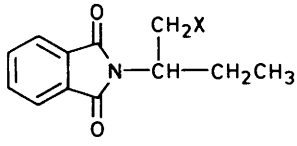
We report here the first enantioselective synthesis of (*S*)-(+)- and (*R*)-(−)-(**1**) starting from the commercially available and relatively inexpensive (*R*)-(−)- and (*S*)-(+)-2-aminobutanol (**2**). For this transformation, which is simple in principle, it was essential to find a suitable nitrogen protecting group and to establish the best route for the conversion of the CH_2OH moiety into the methyl group in order to avoid the participation of vicinal groups during the conventional synthetic steps. For instance, starting from compound (**2**), protected as its benz-



(**3**)

a; R^1 = PhCO, R^2 = OH
b; R^1 = PhCO, R^2 = OTs
c; R^1 = PhCO, R^2 = Br
d; R^1 = Ts, R^2 = OTs
e; R^1 = Ts, R^2 = H

amido derivative (**3a**), it was not possible to prepare the corresponding tosylate (**3b**) or the bromo derivative (**3c**) in acceptable yields, presumably because of the formation of cyclization products. In another approach,‡ the *N*,*O*-ditosylate (**3d**) was prepared from (*R*)-(−)-(**2**) ($[\alpha]_D$ −10.5, 70% optically pure) and reduced to the tosylamide (**3e**) ($LiAlH_4$ in THF, reflux, 3 h, 50% yield§). Cleavage of the *N*-protecting group (aqueous 48% HBr or liquid ammonia[6]) afforded (*S*)-(+)-(**1**) {$[\alpha_D]$ +3.5° (neat), 50% optical purity}. The ^1H n.m.r. spectrum of the amine so obtained, however, showed that the final product was a mixture of (*S*)-(+)-(**1**) and an aziridine, which could not be removed even after careful distillation.



(**4**)

a; X = OH
b; X = OTs
c; X = I
d; X = H

As an alternative approach, 2-phthalimidobutanol (**4a**) was prepared, either by the reaction of compound (**2**) with phthalic anhydride at 150—160 °C (50% yield) or by the method of Nefkens [7] (*N*-ethoxycarbonylphthalimide, aqueous sodium carbonate, 40% yield¶). The phthalimido alcohol (**4a**) could be transformed into the tosylate (**4b**) (TsCl in pyridine, room temperature, 70% yield of isolated product), which was in turn converted into the corresponding iodide (**4c**) with potassium iodide, either in dimethyl sulphoxide (140 °C, 3 h, 82%) or polyethylene glycol (PEG) 400 (120 °C, 2 h, 95%).[8] Reduction of the iodide (**4c**) with lithium aluminium hydride gave only a complex mixture of products, whereas with $NaBH_4$ in PEG 400 [9] a mixture (3:2 ratio) of the two oxazolidines (**5a**) and (**5b**) was formed.‖ The formation of the above products could be easily rationalized assuming reduction at one carbonyl of the phthalimido group†† and displacement of iodine by the

† Recent improvements in the asymmetric hydroboration of *cis*-but-2-ene using either (+)- or (−)-α-pinene of nearly 100% o.p. (H. C. Brown and B. Singaram, *J. Am. Chem. Soc.*, 1984, **106**, 1797) should afford an alternative and convenient route to (*R*)- and (*S*)-2-aminobutane of very high optical purity.

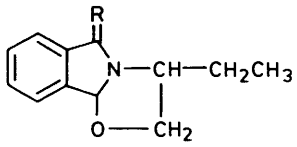
‡ Reactions were first carried out on racemic (**2**) and were only repeated on enantiomerically pure (**2**) if the synthetic path enabled us to prepare (**1**).

§ Throughout the work yields were not optimized and refer to isolated and purified products.

¶ Other authors have experienced side reactions and modest yields in the preparation of *N*-phthaloylamino alcohols. For pertinent references, see: P. W. Worster, C. L. Leznoff, and C. R. McArthur, *J. Org. Chem.*, 1980, **45**, 174.

‖ Apparently compound (**5b**) is the product of the reduction of compound (**5a**), since when the reduction was carried out at 60 °C, the ratio of (**5a**) to (**5b**) was 5:1 (60% yield of products of reduction along with unchanged starting material).

†† Simple phthalimides are reduced in a similar manner by $NaBH_4$, but generally the reduction affords a complex mixture of products derived from the hydroxyphthalimidines formed. See: K. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, 1961, **26**, 2273.

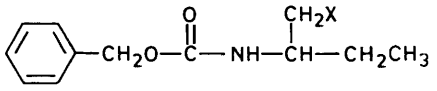


(5)

a; R = O
b; R = H,OH

resulting negatively charged oxygen. Hydrogenation on 10% Pd–C in the presence of triethylamine was the alternative to hydride reduction of the iodide (**4c**), and 2-aminobutane (**1**) was obtained from 2-phthalimidobutane (**4d**) by treatment with aqueous hydrazine.

As the overall yield of compound (**1**) from the above synthetic procedure was modest (less than 10%),* the benzyloxycarbonyl group was chosen for the *N*-protection of compound (**2**). 2-Amino-*N*-benzyloxycarbonylbutanol (**6a**) and the corresponding tosylate (**6b**) were easily prepared in good yields. Treatment of the tosylate (**6b**) with lithium iodide in acetone[9] satisfactorily afforded the iodide (**6c**) [63% yield from (**2**)]. The above iodide (**6c**) was reductively cleaved (H_2/Pd–C, AcOEt, Et_3N) affording the protected amine (**6d**). Alternatively, the hydroiodide of compound (**1**) could be directly obtained if triethylamine was omitted from the hydrogenolysis reaction.



(6)

a; X = OH
b; X = OTs
c; X = I
d; X = H

The availability of the *N*-benzyloxycarbonylamine (**6d**) was useful, as this compound could be purified to the correct elemental analysis and aided the evaluation of the optical purity of the final amine (**1**). In order to determine the optical rotation of the pure compound (**6d**), we prepared (*S*)-(+)-(**1**) by the resolution procedure † and obtained a 76% optically pure amine ($[\alpha]_D$ +5.4°); (*S*)-(+)-compound (**6d**) was prepared and showed $[\alpha]_D$ +15.1°, and an optical rotation of +20° was therefore attributed to pure (*S*)-(+)-(**6d**). This was confirmed by the optical rotation of the benzamido derivative of (*S*)-(+)-(**1**) ($[\alpha]_D$ +5.4°) which exhibited $[\alpha]_D$ +23.5°, corresponding to an optical purity of 76% (literature value[10] for optically pure benzamide, $[\alpha]_D$ +31°).

The same sequence of reactions could be repeated starting from 80% optically pure (*R*)-(−)-compound (**2**), giving (*S*)-(+)-compound (**1**) ($[\alpha]_D$ +5.8°, 78% o.p.). The optical purity of the final amine was confirmed by the optical rotation observed for (*S*)-(+)-compound (**6d**) prepared during the synthesis ($[\alpha]_D$ + 15.6°).

The (*R*)-(−)-enantiomer of (**1**) could be obtained from (*S*)-(+)-compound (**2**), which is also commercially available but at a higher price than the corresponding (*R*)-(−)-isomer. Fortunately, the optical purity of (*S*)-(+)-compound (**2**) is higher (95%) and from this amino alcohol (*R*)-(−)-(**1**) can be obtained in 92% optical purity ($[\alpha]_D$ −6.8°). Again, the optical purity of the final amine was confirmed by the optical rotation of (*R*)-(−)-(**6d**) ($[\alpha]_D$ −18.8°).

The optical purities of both enantiomeric amines (**1**) were confirmed by converting them into the corresponding benzamides {$[\alpha]_D$ +24° and −28° for benzamides of (*S*)-(+)- and (*R*)-(−)-(**1**), respectively}.

In conclusion, both enantiomers of compound (**1**) can be prepared from (*R*)-(−)- and (*S*)-(+)-(**2**) by a synthetic route which preserves the stereochemistry and the optical purity of the starting material, which is commercially available.

Experimental

All m.p.s are uncorrected. I.r. spectra were recorded for solutions in chloroform or for Nujol mulls. ^1H N.m.r. spectra were recorded on a Varian 360 L spectrometer for solutions in $CDCl_3$ using Me_4Si as internal standard. The progress of all reactions and column chromatographies (silica 230—400 mesh, unless otherwise stated) was monitored by t.l.c. on E. Merck silica gel HF_{254} plates visualized by spraying with 5% or 10% ethanolic phosphomolybdic acid followed by heating or exposure of the plates to iodine vapour.

1-*Iodo*-2-*phthalimidobutane* (**4c**).—To a solution of potassium iodide (13.3 g, 0.08 mol) in PEG 400 (160 ml), the tosylate (**4b**) (10 g, 0.027 mol) was added and the solution stirred at 120 °C for 2 h. When the reaction was complete, the solution was poured into water (200 ml) and the product extracted with ethyl acetate (4 × 50 ml). The organic solution was washed with water (100 ml), aqueous sodium thiosulphate (2 × 100 ml), dried and evaporated. A nearly pure product was recovered in 95% yield (8.44 g) and crystallized from hexane (cold) to give the *iodide* (**4c**); m.p. 57—60 °C; δ 0.95 (t, 3 H, CH_3), 2.10 (q, 2 H, CH_2), 3.50—4.50 (m, 3 H, CH_2I and CHN), and 7.90 (s, 4 H, aromatic) (Found: C, 43.9; H, 3.9; N, 4.15. $C_{12}H_{12}INO_2$ requires C, 43.76; H, 3.65; N, 4.25%).

Reduction of the Iodide (**4c**) *by* $NaBH_4$ *in* PEG 400.—A mixture of sodium borohydride (90.7 mg, 2.4 mmol) and PEG 400 (1.92 g, 4.8 mmol) was heated at 80 °C until the evolution of hydrogen was complete (2 h). To the above solution, a solution of iodide (**4c**) (0.395 g, 1.2 mmol) in tetrahydrofuran (reagent grade, 1 ml) was added at 80 °C. After 10 min a precipitate was formed and the starting material disappeared. Tetrahydrofuran was evaporated at reduced pressure and water (5 ml) was added to the mixture. The products were extracted with diethyl ether (3 × 10 ml) and the organic layer was washed with water, dried, and evaporated to dryness. The mixture of the two products (**5a**) and (**5b**) (350 mg) was purified by silica gel column chromatography. The fractions eluted with hexane–ethyl acetate, 8:2, contained 3-ethyl-2,3-dihydro-[1,3]oxazolo[2,3-*a*]isoindol-5(9b*H*)-one (**5a**) (140 mg); δ 1.10 (t, 3 H, CH_3), 1.65 (q, 2 H, CH_2), 3.70—4.70 (m, 3 H, CH_2O and CHN), 5.90 (s, 1 H, CHO), and 7.60—8.00 (4 H, aromatic); *m/z* 203 (M^+), 173 (M^+ − 30). Fractions eluted with hexane–ethyl acetate, 7:3, contained 3-ethyl-5-hydroxy-2,3,5,9b-tetrahydro-[1,3]oxazolo[2,3-*a*]isoindole (**5b**) (210 mg); *m/z* 205 (M^+), 176 (M^+ − 30), 133.

(R)-2-*Benzyloxycarbonylaminobutan*-1-*ol* (**6a**).—To a solution in water (40 ml) of (*R*)-(−)-(**2**) {$[\alpha]_D$ −11.6° (*c* 2, water)} (35.6 g, 0.4 mol), anhydrous sodium carbonate (42.4 g, 0.4 mol) and benzyl chloroformate (68.2 g, 0.4 mol) were sequentially added at 0—5 °C. The addition of the chloroformate was carried out dropwise in order to keep the internal temperature at 5—10 °C. A white precipitate was formed (2 h) which was filtered off with suction and recrystallized from ethyl acetate–hexane to give the *alcohol* (**6a**) (71.36 g, 80%); m.p. 61—63 °C;

* When the synthesis was attempted on a multigram scale on (*R*)-(**2**), low yields of (*R*)-(**4a**) were obtained after column chromatography. Furthermore, (*R*)-(**4a**) had a low optical rotation (α_D −0.5°).

† As footnote † on preceding page.

$[\alpha]_D$ −12° (*c* 2, ethanol); δ 0.9 (t, 3 H, CH_3), 1.90 (q, 2 H, CH_2), 3.40—3.60 (m, 3 H, CH_2OH), 5.10 (s, 2 H, CH_2 benzyl), 5.40 (d, 1 H, NH), and 7.40 (m, 5 H, aromatic) (Found: C, 64.7; H, 7.7; N, 6.4. $C_{12}H_{17}NO_3$ requires C, 64.57; H, 7.62; N, 6.28%).

(R)-2-*Benzyloxycarbonylamino*-1-*tosyloxybutane* (**6b**).—To a solution of the above protected amino alcohol (**6a**) (27.2 g, 0.122 mol) in pyridine (80 ml), tosyl chloride (23.2 g, 0.122 mol) was added in portions at 0—5 °C. The reaction mixture was then kept at room temperature (15 h). When the reaction was complete, the mixture was poured into cooled water and the oil was decanted, washed several times with water, and dissolved in chloroform. The organic solution was repeatedly washed with water, dried and evaporated. The oily residue (39.1 g, 85%) was used as such for the next step; δ 0.85 (t, 3 H, CH_3), 1.45 (q, 2 H, CH_2), 2.40 (s, 3 H, CH_3 tosyl), 3.70 (m, 1 H, CH), 4.05 (d, 2 H, CH_2OTs), 5.05 (s, 2 H, CH_2 benzyl), 5.40 (d, 1 H, NH), 7.20—7.60 (m, 7 H, aromatic), and 7.80 (d, 2 H, tosyl).

(R)-2-*Benzyloxycarbonylamino*-1-*iodobutane* (**6c**).—To a solution of the above tosylate (**6b**) (36.2 g, 0.096 mol) in acetone (500 ml), lithium iodide (40.2 g, 0.3 mol) was added and the solution refluxed (4 h). Acetone was evaporated under reduced pressure and the residue treated with water (100 ml) and extracted with ethyl acetate (3 × 100 ml). After a few washings with aqueous thiosulphate and water, the solution was dried and evaporated. The residue of the iodide (**6c**) (28.8 g, 90%) was nearly pure and was recrystallized from dichloromethane–hexane to give pure *product* (**6c**); m.p. 79—81 °C; $[\alpha]_D$ −1.2° (*c* 2, ethanol); δ 0.85 (t, 3 H, CH_3), 1.45 (q, 2 H, CH_2), 3.20 (m, 2 H, CH_2I), 3.75 (m, 1 H, CH), 5.10 (s, 2 H, CH_2 benzyl), 5.40 (d, 1 H, NH), and 7.20 (m, 5 H, aromatic) (Found: C, 43.6; H, 5.1; N, 4.3. $C_{12}H_{16}INO_2$ requires C, 43.44; H, 4.90; N, 4.20%).

(S)-2-*Benzyloxycarbonylaminobutane* (**6d**).—A solution of the above iodide (**6c**) (28.6 g, 0.086 mol) and triethylamine (24 ml) in ethyl acetate (250 ml) was hydrogenated at atmospheric pressure in the presence of 10% Pd on charcoal (2 g). When the reaction was complete, the catalyst was filtered off and the organic solution washed with water. The usual work-up left a residue of compound (**6d**) (16 g, 90%), which could be crystallized from cold hexane to give pure *product* (**6d**); m.p. 51—53 °C; $[\alpha]_D$ +15.6° (*c* 2, ethanol); δ 1.20 (t, 6 H, CH_3), 1.40 (q, 2 H, CH_2), 3.75 (m, 1 H, CH), 5.10 (s, 2 H, CH_2 benzyl), and 7.40 (m, 5 H, aromatic) (Found: C, 69.7; H, 8.3; N, 6.8. $C_{12}H_{17}NO_2$ requires C, 69.56; H, 8.21; N, 6.76%).

(S)-2-*Aminobutane* (**1**).—A solution of the above compound (**6d**) (15.73 g, 0.076 mol) in ethanol (150 ml) was hydrogenated at ambient pressure in the presence of 10% Pd on charcoal (1.7 g). When the reaction was complete, the catalyst was filtered off and 2M-HCl was added until the solution became acidic. The solution was then evaporated and water was added (2 ml) to enable the transfer of the hydrochloride of (**1**) into a flask for distillation. An excess of solid KOH was added and the amine was collected at 60—65 °C (4.99 g, 90%); $[\alpha]_D$ +5.8° (neat). In order to prepare the benzoylamide of (*S*)-(+)-(**1**), the freshly distilled amine (1.43 g, 19.6 mmol) was dissolved in pyridine (10 ml) and benzoyl chloride (3.45 ml) was added dropwise at 0—5 °C. After 4 h at ambient temperature, work-up as described [10] afforded the desired *benzoylamide* of (**1**), which was crystallized from hexane (m.p. 94—95 °C) to constant elemental analysis, $[\alpha]_D$ +24° (*c* 2, ethanol) (Found: C, 74.5; H, 8.3; N, 7.8. $C_{11}H_{15}NO$ requires C, 74.58; H, 8.47; N, 7.91%).

(R)-(−)-*Compound* (**1**).—The whole procedure was exactly as described for the (*S*)-isomer. Starting from (*S*)-(+)-(**2**) ($[\alpha]_D$ +13.8°), (*R*)-(−)-(**6d**) was prepared ($[\alpha]_D$ −18.4°). Hydrogenolysis of (*R*)-(−)-(**6d**) afforded (*R*)-(−)-(**1**) ($[\alpha]_D$ −6.8°), the benzoylamide of which showed $[\alpha]_D$ −28°.

Acknowledgements

We thank Dr. Morteza Nasr Azadani for valuable experimental assistance during some stages of the work and the Ministero della Pubblica Istruzione for financial support for the studies on polyethylene glycols.

References

1 C. Casagrande and G. Ferrari, *Farmaco, Ed. Sci.*, 1966, **21**, 229.
2 D. Chiarino, D. Della Bella, G. Jommi, and C. Veneziani, *Arzneim. Forsch.*, 1978, **28**, 1554.
3 L. Verbit and P. J. Hefforn, *J. Org. Chem.*, 1967, **32**, 3199.
4 L. G. Thomè, *Chem. Ber.*, 1903, 582.
5 A. Fleury-Larsonneau, *Bull. Chem. Soc. Fr.*, 1939, **6**, 1576.
6 V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, 1937, **117**, 27; J. Kovacs and U. R. Ghatak, *J. Org. Chem.*, 1966, **31**, 119.
7 G. H. L. Nefkens, *Nature (London)*, 1960, **185**, 309.
8 E. Santaniello, A. Manzocchi, and P. Sozzani, *Tetrahedron Lett.*, 1979, 4581.
9 E. Santaniello, A. Fiecchi, A. Manzocchi, and P. Ferraboschi, *J. Org. Chem.*, 1983, **48**, 3229.
9 K. Mori, *Tetrahedron*, 1975, **31**, 3011.
10 P. Bruck, J. N. Denton, and A. H. Lamberton, *J. Chem. Soc.*, 1956, 921.

Received 11*th June* 1984; *Paper* 4/964