Absolute Configuration of (−)-2-Chloro- and (−)-2-Bromo-3,3-dimethylbutanoic Acids

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The absolute configuration of (−)-2-chloro-3,3-dimethylbutanoic acid has been assigned as *R* on the basis of chemical correlation, g.l.c. separation of diastereomers, c.d. measurements, and Freudenberg's rules. Application of the same methods allows assignment of the *R*-configuration to (−)-2-bromo-3,3-dimethylbutanoic acid; this is a reversal of an earlier assignment which was based on the incorrect configuration of (+)-α-t-butylglycine.

Abderhalden and his co-workers [1] assigned the *R*-configuration to (+)-2-bromo-3,3-dimethylbutanoic acid (Ia) in the light of the following observations. Treatment of (+)-α-t-butylglycine (Ib) with nitrosyl bromide gave the (−)-bromo-acid (Ia), which was then treated with (*S*)-tyrosine methyl ester. The *N*-acyl-(*S*)-tyrosine methyl ester produced (IIa; X = Br), when treated with trypsin, was hydrolysed to a greater extent than the corresponding acyl-ester derived from (−)-α-t-butylglycine. Either 2-bromo-acid could be reconverted into the original amino-acid, presumably with complete retention of configuration during both bromination and amination. These results [1] indicated that (+)-α-t-butylglycine and the (−)-bromo-acid (Ia) were both of the natural or *S* absolute configuration.

More recently Izumiya and his co-workers [2] resolved (*RS*)-α-t-butylglycinamide with hog kidney-amidase, an (*S*)-amino-acid amidase. The product of hydrolysis was laevorotatory α-t-butylglycine. Consequently, they [2] assigned the *S*-configuration to (−)-α-t-butylglycine (Ib), the reverse of that suggested earlier.[1] The *S*-configuration for (−)-Ib has since been verified independently by Schlott [3] and by Pracejus and Winter.[4]

$Bu^t \cdot CHX \cdot CO_2H$ (I)

a; X = Br
b; X = NH^2
c; X = Cl

$Bu^tCHX \cdot CO \cdot NH \cdot CHR \cdot CO_2Me$ (II)

a; R = p-$HO \cdot C_6H_4 \cdot CH_2$
b; R = Pr^i

This unequivocal assignment [2-4] allows for speculation as to the absolute configuration of the 2-bromo-analogue. In an attempt to explain the enzymic reactivity of the bromo-amides (IIa) of (*S*)-tyrosine, Izumiya and his co-workers,[2] suggested that two consecutive Walden inversions occur in the sequence amino-acid (Ib) → 2-bromo-acid (Ia) → amino-acid (Ib). This could indeed explain the results of Abderhalden and his co-workers,[1] but other evidence [5] indicates that in such instances when chain branching occurs *alpha* to the halogen atom, this series of conversions goes with complete retention of configuration and not by two Walden inversions. For example treatment [6] of (*R*)-(−)-valine with nitrosyl bromide gives (*R*)-(+)-2-bromoisovaleric acid, which then gives the original (*R*)-(−)-valine upon reaction with aqueous ammonia. Furthermore, no inversion occurs during these transformations in the cases of both isoleucine [7,8] and alloisoleucine.[7,8] Since α-t-butylglycine also contains chain branching *alpha* to the amino- or potential bromo-group, inversion of configuration upon bromination is unlikely, and the original [1] assignment of configuration to (Ia) is questionable.

The direct conversion of α-amino-acids into α-halogeno-acids according to Renard [9] and Karrer and his co-workers [10] with nitric acid and hydrobromic or hydrochloric acids has been shown [11,12] to proceed with retention of configuration and with little loss of optical purity. We have used this reaction to obtain a direct chemical comparison of the absolute configuration and sign of optical rotation of halogeno-acids (Ia) and (Ic) with the (*R*)-(+)-amino acid (Ib). Both resulting halogeno-acids (Ia) and (Ic) were laevorotatory at the wavelength of the sodium D-line.

The relative retention times of their diastereomeric amides can be used to correlate the absolute configurations of aliphatic α-chloro-acids.[11-13] The *R*-acid *S*-amides consistently have smaller retention times in this series. Our g.l.c. investigations show that amide (IIb; X = Br) prepared from (−)-(Ia), and amide (IIb; X = Cl) prepared from (−)-Ic both have retention times corresponding to the faster emerging diastereomers (see Experimental section). This indicates that the laevorotatory halogeno-acids are of *R*-configuration. Halpern and his co-workers [13] have reported g.l.c. data on the diastereomeric α-chloro-amides (IIb; X = Cl) but they did not indicate the sign of rotation of the *R*- or *S*-acids involved.

(*S*)-(+)-2-Chloro- and (*S*)-(−)-2-bromo-3-methylbutanoic acids were prepared [9,10] from (*S*)-(+)-valine; both gave positive Cotton effects at 213—215 nm. Since negative Cotton effects were observed at 220—222 nm. for both (−)-(Ia) and (−)-(Ic), the *R*-configuration is suggested for these laevorotatory isomers. We have also found, in the (−)-(Ic) acid series, a considerable

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shift (*ca.* 80°) towards a more negative rotation in going from the methyl ester to the *NN*-dimethylamide. According to Freudenberg's 'rule of shift'[14,15] the (−)-chloro-acid (Ic) has the *R*-configuration.

EXPERIMENTAL

Elemental analyses were carried out by L. M. White, M. Long, and G. E. Secor. I.r. absorption spectra were measured with a Beckman IR 8 spectrophotometer. G.l.c. was carried out with either a Loenco model 70 Hi-Flex with a thermo-conductivity detector or a Varian Aerograph 660 with a flame detector. C.d. measurements were performed with a Cary 6001 instrument. Optical rotations were measured with a Carl Zeiss polarimeter for solutions in a 1 dm. tube.

(RS)-*α-t-Butylglycine* (Ib).—This amino-acid was prepared[16] by oxidation of pinacolone with permanganate to 3,3,3-trimethylpyruvic acid. Conversion of the keto-acid into its oxime with hydroxylamine hydrochloride followed by reduction with aluminium amalgam gave (Ib) (25% overall), which sublimed at 285—295° (Found: C, 55·1; H, 9·93; N, 10·7. Calc for $C_6H_{13}NO_2$: C, 54·9; H, 10·0; N, 10·7%). Attempts to reduce the oxime with zinc dust and acetic acid were unsuccessful.

Resolution of (RS)-*α-t-Butylglycine*.—The amino-acid was resolved by fractional crystallisation of the brucine salts of its *N*-formyl derivative.[1] In a typical experiment (Ib) (5·03 g.) was dissolved in 88% formic acid (75 ml.), and acetic anhydride (25 ml.) was added dropwise at a rate such as to keep the temperature at 55—60°. After 1·5 hr. at room temperature, water (12·5 ml.) was added and the solution was concentrated to *ca.* 25 ml. and placed in a refrigerator. The *N*-formyl-(*RS*)-α-t-butylglycine obtained (4·98 g., 81%) had m.p. 208—210° (lit.,[2] 210°). It was treated with anhydrous brucine and the product fractionally crystallised[1] to give formyl-(*R*)-α-t-butylglycine brucine salt, m.p. 194—195° (lit.,[1] 195°). Hydrolysis and deformylation gave (*R*)-(+)-(Ib), $[\alpha]_D^{27}$ +8·4 (*c* 0·910 in H_2O) (82·7% optically pure) (Found: C, 54·4; H, 9·84; N, 10·6. Calc. for $C_6H_{13}NO_2$: C, 54·9; H, 10·0; N, 10·7%).

(R)-(−)-2-*Chloro*-3,3-*dimethylbutanoic acid* (Ic).—(*a*) Racemic (Ic), prepared by chlorination of t-butylacetic acid[17] in the presence of phosphorus trichloride, had m.p. 56—57° (lit.,[18] 62—63°), b.p. 80—82°/1·0—2·0 mm. (lit.,[18] 80—84°/5 mm.). When resolved[12] by fractional crystallisation of its cinchonidine salts, it had m.p. 67—70°, b.p. 83—84°/1·5—2·0 mm., $[\alpha]_D^{27}$ −9·9° (*c* 0·323, MeOH).

(*b*) (+)-α-t-Butylglycine (Ib) (82·7% optically pure, 1·62 g.) was dissolved in concentrated hydrochloric acid (40 ml.) and concentrated nitric acid (20 ml.) was added dropwise[9] with stirring during 0·5 hr. The mixture was then cooled and extracted with ether (4 × 50 ml.). The extracts were water washed, dried (Na_2SO_4), and vacuum distilled to give (Ic), identical (i.r., g.l.c., m.p., and b.p.) with the product from (*a*), $[\alpha]_D^{27}$ −14·3° (*c* 0·203 in MeOH), c.d. (*c* 0·203 in MeOH) $[\theta]_{222}$ −2120 (max.) (Found: C, 47·3; H, 7·31. Calc. for $C_6H_{11}ClO_2$: C, 47·8; H, 7·36%). Correction for the optical purity of the starting material gives $[\alpha]_D^{27}$ −17·3 (MeOH), c.d. (MeOH) $[\theta]_{222}$ −2560 (max.).

(R)-(−)-2-*Bromo*-3,3-*dimethylbutanoic Acid* (Ia).—(+)-α-t-Butylglycine (82·7% optically pure) was treated[10] with concentrated hydrobromic acid and concentrated nitric acid as in the preparation of (Ic). The product (Ia), purified by preparative g.l.c. (¼ in. × 6 ft. 10% Apiezon column at 170°), had m.p. 70—72° (lit.,[1] 66°), $\nu_{max.}$ (CCl_4) 1710 (CO) cm.$^{-1}$, $[\alpha]_D^{27}$ −10·0 (*c* 0·05 in MeOH) [lit.,[1] $[\alpha]_D$ −14·4 (EtOH)], c.d. (*c* 0·05 in MeOH) $[\theta]_{220}$ −1130 (max.). Correction for the optical purity of the starting material gives $[\alpha]_D^{27}$ −12·0 (MeOH), c.d. (MeOH) $[\theta]_{220}$ −1370 (max.).

Preparation and Separation of Diastereoisomeric α-Chloro- and α-Bromo-amides by G.l.c.—The racemic α-chloro- and α-bromo-acid chlorides were treated[12] with (*S*)-valine methyl ester to give the (*RS*)-halogeno-acid mixture. The optically active α-chloro- and α-bromo-acid chlorides were treated with (*S*)-valine methyl ester to give the halogeno-acid diastereoisomers (IIb; X = Cl or Br) which were 82·7% optically pure at the halogeno-acid asymmetric centre. The procedure used for the g.l.c. separation of diastereoisomers is that of Halpern and Westley[11] and is discussed in detail elsewhere.[12] The conditions used were: 20% Carbowax 20M column, ⅛ in. × 8 ft., nitrogen carrier gas at 50 ml./min., temperature 220°. The results were: (IIb X = Cl) retention time *R,S*-diastereoisomer 411 sec., *S,S*-diastereoisomer 501 sec.; (IIb, X = Br) retention time *R,S*-diastereoisomer 440 sec., *S,S*-diastereoisomer 529 sec.

Preparation and C.d. of (S)-(+)-2-*Chloro- and* (S)-(−)-2-*Bromo*-3-*methylbutanoic Acids*.—(*S*)-(+)-2-Chloro- and (*S*)-(−)-2-bromo-3-methylbutanoic acids were prepared[9,10] from (*S*)-(+)-valine. (*S*)-(+)-2-Chloro-3-methylbutanoic acid had b.p. 76—80°/1·5 mm., $[\alpha]_D^{27}$ +1·0 (*c* 1·36 in MeOH), c.d. (*c* 1·36 in MeOH) $[\theta]_{215}$ +2070 (max.) (Found: Cl, 26·5. Calc. for $C_5H_9ClO_2$: Cl, 26·0%). (*S*)-(−)-2-Bromo-3-methylbutanoic acid had b.p. 83—87°/1·3 mm., $[\alpha]_D^{27}$ −16·8 (*c* 0·65 in MeOH) [lit.,[6] $[\alpha]_D^{30}$ +22·6 (C_6H_6)], c.d. (*c* 0·65 in MeOH) $[\theta]_{213}$ +3210 (max.).

(S)-(+)-*Methyl* 2-*Chloro*-3,3-*dimethylbutyrate*.—(*S*)-(+)-(Ic), $[\alpha]_{578}^{27}$ +2·2 ($CHCl_3$) (9·4% optically pure by g.l.c.), was treated with ethereal diazomethane until a yellow colour persisted. The mixture was concentrated and purified by preparative g.l.c. (¼ in. × 10 ft. SE-30 column), and the product was characterised only by the following data: $\nu_{max.}$ (CCl_4) 1735 cm. (ester CO), n_D^{22} 1·4300, $[\phi]_D^{22}$ +31° (*c* 7·26 in CCl_4).

(S)-(+)-2-*Chloro*-3,3,NN-*tetramethylbutanamide*.—(*S*)-(+)-(Ic), $[\alpha]_{578}^{27}$ +2·2° ($CHCl_3$) (9·4% optically pure by g.l.c.), was refluxed for 1 hr. with thionyl chloride. Excess of reagent was distilled off and an excess of anhydrous dimethylamine in ether was added at 0°. After concentration of the mixture, the amide was purified by preparative g.l.c. (¼ in. × 10 ft. SE-30 column) and characterised only by the following data: $\nu_{max.}$ (CCl_4) 1652 cm.$^{-1}$ (tertiary amide CO), n_D^{22} 1·4702, $[\phi]_D^{22}$ +110° (*c* 7·31 in CCl_4).

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