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Synthesis of *S*- and *R*-4-Amino-3-hydroxybutyric Acid (GABOB) and *S*- and *R*-Carnitine from Arabinose or Ascorbic Acid

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Through a simple series of reactions D- and L-arabinose have been converted into the optically pure forms of *S*- and *R*-4-amino-3-hydroxybutyric acid, (GABOB), respectively, and of *S*- and *R*-carnitine. *R*-GABOB and *R*-carnitine have also been prepared from L-ascorbic acid.

Reaction of hexono- or pentono-lactones with hydrogen bromide in acetic acid (HBA) has been shown to give bromodeoxy- or dibromodideoxy-lactones, which have subsequently been converted into deoxylactones, deoxysugars, or into simpler, optically active compounds.[1,2,3] In the present work the reaction of salts of erythronic and threonic acid with HBA has been studied and the resulting dibromoderivatives have been converted into optically pure *R*- and *S*-4-amino-3-hydroxybutyric acid (GABOB) and into *R*- and *S*-carnitine. *R*-GABOB and *R*-carnitine have been prepared from L-glutamic acid *via* an enzymatic decarboxylation [4] and, recently, *R*-GABOB has been synthesized from L-ascorbic acid.[5] The latter synthesis did not, however, produce an optically pure product.

Reaction of potassium D-erythronate (*1*) with HBA for 24 h followed by treatment with methanol gave the crystalline methyl ester of 2,4-dibromo-2,4-dideoxy-D-threonic acid (*2*) in 76 % yield. Selective hydrogenolysis of *2* subsequently yielded the 2,4-dideoxy-4-bromo ester (*3a*) in ~85 % yield. Reaction of *3a* with sodium azide in dimethylformamide gave the azide (*3b*) which was hydrogenated in acidic solution in the presence of platinum to give the aminoester (*3c*). Neither *3b* nor *3c* were isolated in a pure state, but were only characterized through their ^{13}C NMR spectra. Hydrolysis of *3c* and purification on an ion exchange resin gave *S*-(+)-GABOB (*4c*) in 58 % yield, calculated from the dibromoester (*2*). By the same procedure, *R*-(−)-GABOB (*8c*) was prepared from potassium L-erythronate (*5*) *via* the dibromoester (*6*), the 2,4-dideoxy-4-bromoester (*7a*), the azide (*7b*) and the aminoester (*7c*). The optical rotations of *4c* and *8c* were in close agreement with those reported previously on products obtained by resolution of derivatives of racemic GABOB.[6]

Treatment of the bromocompound (*3a*) with trimethylamine in methanol gave the trimethylammonium derivative (*3d*) as the hydrobromide. Subsequent hydrolysis and purification on an ion exchange resin yielded *S*-(+)-carnitine (*4d*), isolated as the hydrochloride. Similarly, *R*-(−)-carnitine (*8d*) was prepared from (*7a*). Comparison of the optical rotations of the two products with those reported [4,7] indicates that they are optically pure.

The potassium salts of D- and L-erythonic acid (*1* and *5*) are readily prepared from D- and L-arabinose, respectively.[8] Oxidation of L-ascorbic acid with hydrogen peroxide gives L-threonic acid which can be easily isolated as its crystalline calcium salt (*9*).[9] Treatment of *9* with HBA followed by reaction with methanol gave the methyl ester of 2,4-dibromo-2,4-dideoxy-L-erythronic acid (*10*). Selective hydrogenolysis of *10* gave *7a*, identical with the product obtained from *6*. Since, however, *10* could not be induced to crystallize it was found most convenient to prepare *7a* from the crystalline *6*.

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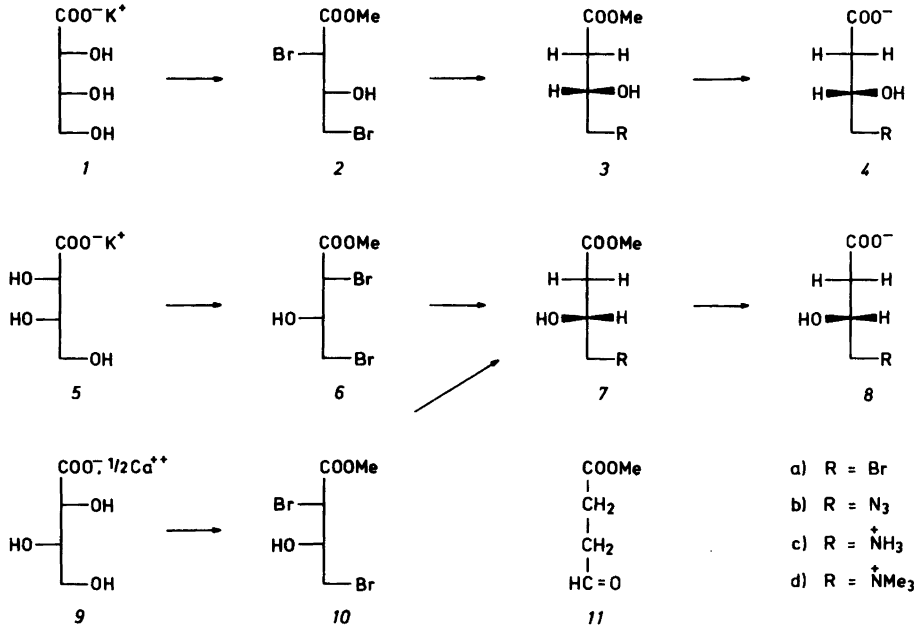

The configuration at C–2 of *2*, *6*, and *10* was not proved, but was assumed to be as indicated, since reactions of aldonic acids [1,2,3] and of diethyl tartrate [10] with hydrogen bromide in acetic acid in all cases give 2-bromo-derivatives with inversion of the configuration at C–2.

The selective removal of the 2-bromine from *2*, *6* or *10* was performed by hydrogenolysis using palladium on carbon as catalyst and sodium acetate–acetic acid as the acid acceptor, whereas in previous work on dibromolactones [2,3] triethylamine was used as the acid acceptor. Attempts to used triethylamine in the hydrogenolysis of *2* or *6* resulted in formation of *ca.* 10 % of methyl 4-oxo-butanoate (*11*) in addition to *3a* or *7a*. With the weaker base, sodium acetate–acetic acid, only traces of *11* were observed.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. NMR spectra were obtained on Bruker WH-90 and HX-90 instruments. For ^{1}H and ^{13}C NMR spectra measured in $CDCl_3$ solution TMS was used as internal reference whereas 1,4-dioxane (67.4 ppm) was used for ^{13}C NMR spectra measured in D_2O solution. Microanalyses were performed by NOVO microanalytical laboratory.

Potassium D- and L-erythronate (*1* and *5*) were prepared by treatment of D- and L-arabinose, respectively, with oxygen in potassium hydroxide solution at 40 °C.[8] The products were recrystallized from methanol–water. Yields in a series of preparations varied from 50–60 %.

Calcium L-threonate, monohydrate (*9*) was obtained in 79 % yield by oxidation of L-ascorbic acid with hydrogen peroxide.[9]

Methyl 2,4-dibromo-2,4-dideoxy-D-threonate (2). Potassium D-erythronate (*1*) (20 g) was stirred with 140 ml of a 32 % solution of hydrogen bromide in acetic acid for 24 h at room temperature. Methanol (500 ml) was then added and the mixture was kept overnight. The potassium bromide was filtered off and the solution was evaporated; the residue in methanol (200 ml) was boiled for 2 h and the methanol was evaporated. The residue thus obtained was dissolved in ethyl acetate (100 ml) and washed twice with water, the solution was dried and evaporated leaving 28.5 g (90 %) of crude, crystalline *2*, m.p. 68–71 °C. Recrystallization from ether–pentane gave 24.0 g (76 %) of a product with m.p. 75–77 °C. Further recrystallization gave an analytical sample, m.p. 76–77 °C, $[\alpha]_D^{20}$ −44.4° (c 3.4, $CHCl_3$). Anal. $C_5H_8Br_2O_3$:C, H, Br. ^{13}C NMR ($CDCl_3$): 169.0 ppm (C–1); 70.5 (C–3); 53.4 (OMe); 48.5 (C–2); 32.9 (C–4).

Methyl 2,4-dibromo-2,4-dideoxy-L-threonate

(6) was prepared in the same manner from potassium L-erythronate (5), m.p. 75–76.5 °C, $[\alpha]_D^{20}$ +43.8° (c 3.5, $CHCl_3$). Anal. $C_5H_8Br_2O_3$: C, H, Br. ^1H and ^{13}C NMR spectra were identical with those of *2*.

Methyl 2,4-dibromo-2,4-dideoxy-L-erythronate (10). Calcium L-threonate, monohydrate (*9*) (10 g) was stirred with HBA (70 ml) for 24 h followed by treatment with methanol and subsequent work-up as described above. This gave *10* as a crude syrup (15.0 g, 89 %) which could not be induced to crystallize. The product was virtually pure as seen from a ^{13}C NMR spectrum. Distillation in vacuum gave 11.0 g (65 %), b.p. 115–116 °C (2 mmHg), $[\alpha]_D^{20}$ −26.0° (c 17, $CHCl_3$). Anal. $C_5H_8Br_2O_3$: C, H, Br. ^{13}C NMR ($CDCl_3$): 168.7 ppm (C–1); 70.4 (C–3); 52.6 (OMe); 44.5 (C–2); 35.8 (C–4).

Methyl S-4-bromo-3-hydroxybutanoate (3a). The dibromoester (*2*) (8.0 g) in ethyl acetate (80 ml) and acetic acid (8 ml) was treated with hydrogen at 1 atm. pressure in the presence of anhydrous sodium acetate (8.0 g) and 5 % palladium on carbon (500 mg). After *ca.* 1 h 1 molar equivalent of hydrogen was consumed and the hydrogen uptake became much slower. The mixture was then filtered, the solution was washed with aqueous sodium hydrogencarbonate, dried and evaporated leaving 5.1 g (89 %) of *3a* as a colourless liquid which was almost pure as seen from a ^1H NMR spectrum. Distillation gave 4.67 g (82 %) of product, b.p. 79–80 °C (1 mmHg), $[\alpha]_D^{20}$ −16.2° (c 8, $CHCl_3$). Anal. $C_5H_9BrO_3$; C, H, Br. ^{13}C NMR ($CDCl_3$): 171.7 ppm (C–1); 67.2 (C–3); 51.7 (OMe); 39.0 (C–2); 37.1 (C–4).

Methyl R-4-bromo-3-hydroxybutanoate (7a) was prepared analogously from methyl 2,4-dibromo-2,4-dideoxy-L-threonate (*6*) in 86 % yield, b.p. 80–81 °C (1 mmHg), $[\alpha]_D^{20}$ +16.1° (c 9, $CHCl_3$). Anal. $C_5H_9BrO_3$: C, H, Br. A ^{13}C NMR spectrum was identical with that of the *S*-enantiomer.

Alternatively, methyl 2,4-dibromo-2,4-dideoxy-L-erythronate (*10*) was hydrogenolyzed as described above. This gave 70 % of *7a*, b.p. 79–80 °C (1 mmHg), $[\alpha]_D^{20}$ +16.0° (c 5, $CHCl_3$).

S-4-Amino-3-hydroxy-butanoic acid (4d). The dibromoester (*2*) (8.0 g) was hydrogenolyzed as described above to give 5.1 g (89 %) of crude 2-deoxy-ester (*3a*). This product was stirred with sodium azide (10 g) in DMF (30 ml) for 5 h at 65 °C. The DMF was then evaporated and the residue in water (25 ml) was extracted 4 times with ethyl acetate. The combined extract was washed once with water, dried and evaporated leaving 4.1 g (89 %) of crude, syrupy methyl *S*-4-azido-3-hydroxy-butanoate (*3b*). ^{13}C NMR ($CDCl_3$): 171.5 ppm (C–1); 66.6 (C–3); 55.1 (C–4); 51.1 (OMe); 38.1 (C–2).

The crude azide (*3b*) was dissolved in methanol and conc. hydrochloric acid (3 ml) and platinum oxide (100 mg) was added. The mixture was shaken with hydrogen for 5 h at 3 atm. pressure. Filtration and evaporation gave the crude, syrupy hydrochloride of methyl *S*-4-amino-3-hydroxy-butanoate (*3c*). ^{13}C NMR (D_2O): 173.6 ppm (C–1); 65.0 (C–3); 53.2 (OMe); 44.7 (C–4); 39.9 (C–2).

The product (*3c*) in water (20 ml) was boiled for 4 h and the solution was then poured on a column of ion exchange resin (Amberlite IR-120, H^+). The column was washed with water until the eluate was neutral. Subsequent eluation with 10 % aqueous ammonia (500 ml) and evaporation gave 2.9 g of crude product which was recrystallized from water–ethanol to give 2.0 g (58 %) of *S*-GABOB (*4c*), m.p. 213–214 °C (dec.), $[\alpha]_D^{20}$ +20.1° (c 2.3, H_2O), (reported [6] m.p. 210–212 °C, $[\alpha]_D$ +20.4°). ^{13}C NMR (D_2O): 179.3 ppm (C–1); 66.4 (C–3); 45.0 (C–4); 43.2 (C–3).

R-4-Amino-3-hydroxy-butanoic acid (*8c*) was prepared in the same way from the L-dibromoester (*6*) in a yield of 55 %, m.p. 213–214 °C; $[\alpha]_D^{20}$ −20.2° (c 4.0, H_2O), (reported [6] m.p. 210–212 °C, $[\alpha]_D$ −21.4°). Its ^{13}C NMR spectrum was identical with that of the *S*-form described above.

S-(+)-1-Propanaminium-3-carboxy-2-hydroxy-N,N,N-trimethyl chloride, [*S-(+)-carnitine, hydrochloride*], (4d). The bromoester (*3a*) (9.6 g) in methanol (40 ml) containing trimethylamine (6 g) was heated to 60 °C for 20 h in a closed container. The yellow solution was then evaporated and the crystalline residue was stirred with ether and filtered off yielding 11.0 g of crude methyl ester of *S*-carnitine (*3d*) as the hydrobromide. ^{13}C NMR (D_2O): 175.5 ppm (C=O); 70.5 (CHOH); 63.7 ($CH_2\overset{+}{N}\equiv$); 55.2 ($\overset{+}{N}Me_3$); 53.5 (OMe); 41.1 (CH_2). A small signal at 45.9 ppm showed that the product contained some trimethylammonium bromide.

The product was boiled for 3 h in 50 ml 2 M hydrochloric acid and the solution was evaporated. The residue in water was put on a column of ion exchange resin (Amberlite IR-120, H^+); the column was then eluted with water until the eluate was neutral then with 10 % aqueous ammonia (500 ml). The latter eluate was evaporated and coevaporated with water. The residue in water was acidified with hydrochloric acid and evaporated leaving a product which crystallized when stirred with acetone. Filtration and drying gave 6.2 g (65 %) of *S*-carnitine, hydrochloride (*4d*), m.p. 133–136 °C, $[\alpha]_D^{20}$ +22.9° (c 3.3,

H_2O). Recrystallization from 2-propanol gave 5.5 g (57 %) of product with m.p. 135–137 °C, $[\alpha]_D^{20}$ +23.2° (c 2.3, H_2O). These values were not changed on further recrystallization, (reported [7] m.p. 142 °C, $[\alpha]_D$ +23.7°). ^{13}C NMR (D_2O): 174.8 ppm (C=O); 70.4 (CHOH); 63.6 ($CH_2\overset{+}{N}\equiv$); 55.1 ($\overset{+}{N}Me$); 40.8 (CH_2).

R-*(−)-1-Propanaminium-3-carboxy-2-hydroxy*-N,N,N-*trimethyl chloride, (*R-*(−)-carnitine, hydrochloride), (8d)* was synthesized in the same manner from the bromoester (*7a*). The crude product was obtained in 64 % yield, m.p. 132–134 °C $[\alpha]_D^{20}$ −22.7° (c 3.1, H_2O). Recrystallization from 2-propanol gave 57 %, m.p. 135–137 °C, $[\alpha]_D^{20}$ −23.2° (c 1.9, H_2O), (reported [7] m.p. 142 °C, $[\alpha]_D$ −23.7°). Its ^{13}C NMR spectrum was identical with that of the *S*-enantiomer.

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