

N-Quaternary Compounds

Part XIII. Partial Asymmetric Synthesis

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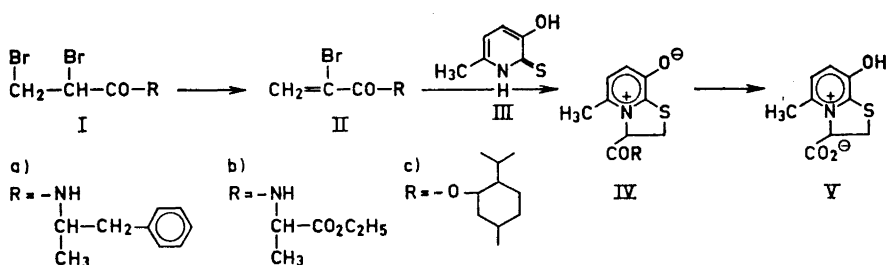
Addition of 3-hydroxy-6-methylpyrid-2-thione to the L-(-)-menthyl ester of α -bromoacrylic acid followed by cyclisation of the adduct first formed, led to 8-hydroxy-5-methyldihydrothiazolo [3,2-a]pyridinium-3-carboxylate in 27 % optical yield. The asymmetric induction observed in the addition to chiral α -bromoacrylamides was negligible.

Prelog's rule, used to rationalize the observed steric induction in additions to the carbonyl-oxygen double bond of the α -keto group in the acid moiety of esters derived from chiral alcohols, has been further extended to carbon-carbon double bonds in α,β -unsaturated acid derivatives. Thus, partial asymmetric synthesis has been realized in cycloadditions of Diels-Alder type and cyclopropane formation, in Michael type additions, in reductions of the carbon-carbon double bond and in amine additions to α,β -unsaturated acid derivatives of chiral alcohols or amines. The optical yield varies considerably and the steric result is not always in agreement with the Prelog rule for a transoid conformation of the α,β -unsaturated acid.^{1,2} We have previously found³ that a substituted 2-thiolactam (III) will add to α -bromoacrylic acid derivatives in the *trans* sense. The cyclisation of the resulting adduct proceeds by an S_N2 mechanism as judged from the relative stereochemistry of the reaction products and the fact that only one isomer is obtained from β -substituted α -bromoacrylic acids. Since both the addition and the cyclisation are mechanistically homogeneous, it should be possible in this system to study

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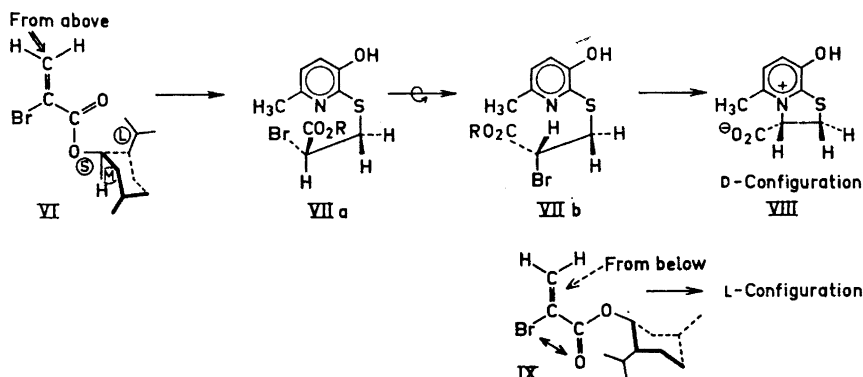
asymmetric induction during sulphur addition to α -bromoacrylic acid derivatives of optically active alcohols or amines.

In our initial study D-(-)-amphetamine was used. The amine was acylated with 2,3-dibromopropionyl chloride in cold dioxane in the presence of triethylamine. The resultant amide (Ia) was dehydrobrominated in cold methanol by slow addition of methanolic sodium methoxide: $[\alpha]_D = +9^\circ$ (EtOH). Heating the acrylamide (IIa) with the thiolactam (III) in benzene solution furnished the desired condensation product (IV): $[\alpha]_D = -41^\circ$ (EtOH). Chromatography showed that the product consisted of about equal amounts of the two diastereomers. These could be separated by preparative TLC chromatography on silica. The apparent lack of steric induction control in the reaction was further confirmed by acid hydrolysis. The acid (V) obtained was optically



inactive. In another series the ethyl ester of alanine was acylated by 2,3-dibromopropionyl chloride and dehydrobrominated as above adding the sodium alkoxide very slowly to minimize any base induced racemisation: $[\alpha]_D = -24^\circ$ (EtOH). The condensation with the thiolactam was done in ethyl acetate. The product (IVb), $[\alpha]_D = -76^\circ$ (MeOH) was hydrolysed by heating overnight in 6 N HCl. The acid (V) thus obtained was weakly levorotatory, $[\alpha]_D = -3^\circ$ (NaOH), and therefore has the L-configuration.⁴ On the basis of the highest rotation we have obtained,⁵ $[\alpha]_D = -153^\circ$ (NaOH), by synthesis from L-cysteine, this corresponds to an optical yield of 2 %. Acid hydrolysis of the amides (IVa,b) was used since the acid (V) is optically stable under acidic conditions.

The poor optical yield in these addition-cyclisation reactions could in part be due to low optical stability of the corresponding amides under the experimental conditions used to effect the reactions. We therefore decided to investigate an ester condensation choosing L-(-)-menthyl ester (IIc). L-(-)-Menthol was esterified with 2,3-dibromopropionyl chloride in methylene chloride. The dehydrobromination was again carried out in ethanolic sodium ethoxide: $[\alpha]_D = -76^\circ$ (EtOH). The addition-cyclisation reaction with the thiolactam (III) was done by heating in ethyl acetate: $[\alpha]_D = +8.5^\circ$ (MeOH). The same ester (IVc) prepared from L-(-)-menthol and the racemic acid (V) with acid catalysis was levorotatory: $[\alpha]_D = -37^\circ$ (MeOH). The latter would be expected to contain about equal amounts of the diastereomers.



The condensation between the thiolactam (III) and the methyl acrylate in ethyl acetate required 16 days, the yield being 79 %. Similarly, the amphetamine reaction required several days for completion while the alanine derivative (IVb) was obtained in 68 % yield after one day. α -Bromoacrylic acid itself and simple esters react in the course of a few hours. Large substituents on the carboxy group therefore decrease the rate of the reaction because of steric reasons as do substituents on the olefinic β -carbon.³ Acid hydrolysis of the menthyl ester (IVc) furnished the acid with the D-configuration: $[\alpha]_D = +35.5^\circ$ (NaOH) corresponding to an optical yield of about 27 %.

If steric approach control as defined in the Prelog rule is to be used to explain the observed D-configuration of the acid the menthyl ester cannot have a transoid conformation (IX) since this would lead to the L-enantiomer. 1,3-Dienes and compounds with 1,2-dicarbonyl groups prefer a transoid conformation. This does not hold when the conjugated system becomes strongly polarized. Thus *trans*-3-penten-2-one for example may exist in both cisoid and transoid conformations.⁶ Furthermore, in a transoid conformation of the α -bromoacrylate one would expect a strong dipole-dipole interaction between the bromine atom and the carbonyl oxygen. It is therefore not unreasonable in the case of the bromoacrylate to assume a cisoid conformation (VI) in which case Prelog's rule is applicable.

EXPERIMENTAL

D-(−)-2-(2,3-Dibromopropionamido)-1-phenylpropane (Ia). 2,3-Dibromopropionyl chloride (22.0 g, 0.088 mole) in dioxane (25 ml) was added dropwise over 30 min at 10° to a stirred solution of D-(−)-amphetamine (10.8 g, 0.08 mole) and triethylamine (8.9 g, 0.088 mole) in dioxane (150 ml). The addition completed, the reaction mixture was stirred at room temperature for 30 min, the precipitated triethylamine hydrobromide removed by filtration, the filtrate evaporated, and the residue suspended in water (50 ml). The insoluble oil was extracted into ethyl acetate (3×100 ml), dried and evaporated. The residual oil was extracted with petroleum ether (3×30 ml) under heating, the petroleum ether decanted and the residual oil dried *in vacuo*; yield 21.1 g (75 %). The oil, on standing, solidified to a white material, m.p. $71-75^\circ\text{C}$. This material was used in the next step without further purification. $[\alpha]_D = -13^\circ$ ($c=1.0$ in EtOH). An analytical sample was recrystallized thrice from ligroin; m.p. $79-81^\circ$. (Found: C 41.26; H 4.20; N 4.17.

Calc. for $C_{12}H_{11}Br_2NO$: C 41.29; H 4.23; N 4.02). IR (KBr): Amide carbonyl at 1660 cm^{-1} . NMR in $CDCl_3$: 8.82 (3H, doublet, $J=7.0$ cps, CH_3), 7.18 (2H, triplet, unresolved CH_2 -phenyl), 5.5–6.3 (4H, multiplet, remaining aliphatic protons), and 2.73 τ (5H, singlet, phenyl group).

D-(+)-2-(2-Bromoacrylamido)-1-phenylpropane (IIa). D-(–)-2-(2,3-Dipromopropionamido)-1-phenylpropane (10.47 g, 0.03 mole) was dissolved in methanol (250 ml) and N methanolic sodium methoxide (30 ml, 0.03 mole) added dropwise over 2 h with stirring at room temperature. The reaction mixture was then evaporated at reduced pressure, water (50 ml) added to the residue and the oily suspension extracted with ethyl acetate (4×60 ml), the extracts dried, evaporated, the residue dried *in vacuo*, extracted with boiling petroleum ether (3×75 ml), treated with a little charcoal, filtered and evaporated leaving a white solid (5.1 g, 63 %, m.p. $50-54^\circ$. $[\alpha]_D = +9$ ($c=3.1$ in EtOH). An analytical sample, recrystallized twice from small volumes of petroleum ether, had m.p. $53-56^\circ$. (Found: C 53.98; H 5.26; N 5.10. Calc. for $C_{12}H_{11}Br_2NO$: C 53.74; H 5.26; N 5.22). IR (KBr): Amide carbonyl at 1650 cm^{-1} . NMR in $CDCl_3$: 8.80 (3H, doublet, $J=7.0$ cps, CH_3), 7.18 (2H, triplet, unresolved CH_2 -phenyl), 5.73 (1H, multiplet, $-CH-$), 3.98 and 3.05 (2H, doublets, $J=1.5$ cps. $=CH_2$, and 2.73 τ (5H, singlet, phenyl group).

3-Carboxamido[N-2-(1-phenyl)propyl]-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (IVa). A solution of the above D-(+)-2-(2-bromoacrylamido)-1-phenylpropane (2.68 g, 0.01 mole) dissolved in benzene (25 ml) was added dropwise to a boiling, stirred solution of 3-hydroxy-6-methylpyrid-2-thione (1.41 g, 0.01 mole) in benzene (150 ml). Greyish-white solid was slowly precipitated. The reaction mixture was heated under reflux overnight, allowed to cool and the crystalline precipitate collected by filtration (2.97 g, 27 %); m.p. $202-220^\circ$. $[\alpha]_D^{25} = -41^\circ$ ($c=2.9$ in EtOH). Recrystallisation twice from isopropanol and once from acetic acid gave m.p. $213-236^\circ$. $[\alpha]_D^{25} = -45^\circ$ ($c=2.0$ in MeOH). (Found: C 52.51; H 4.99; N 6.53. Calc. for $C_{18}H_{20}N_2O_2S \cdot HBr$: C 52.82; H 5.17; N 6.84).

The yield in this reaction could be increased to 60–70 % by heating for several days but the diastereomer ratio appeared to be the same as in the first product filtered off. On prolonged heating the product becomes coloured.

NMR in DMSO- d_6 : The protons attached to the same carbon have slightly different shifts in the two diastereomers. Therefore the spectrum is not clear. 8.85 (doublet, $J=7.0$ cps, CH_3-CH), 7.88 and 7.52 (singlets, pyridyl- CH_3 in the two modifications); 7.28 (broad doublets, CH_2 -phenyl), 6.2–5.8 (multiplet, $-CH_2-S$, $-CH-$), 3.8 multiplet, ($H-C-N^+ \equiv$), 2.73 (singlet, phenyl group), 2.7–2.2 (pyridine protons).

On TLC chromatography on silica gel in BuOH:AcOH:H₂O (100:22:50) the above product gave rise to two spots of equal intensity at R_F 0.5–0.55 and R_F 0.55–0.6. The product, therefore, consists of about equal amounts of the two diastereomers. These could be partially separated by preparative TLC chromatography on silica coated plates using the above developer. Thus 600 mg of the above product was dissolved in methanol (3 ml) and applied onto 3 glass plates (20×20 cm) coated with a 1 mm thick layer of silica gel. The bands at R_F 0.5 and 0.6 were scraped off separately, leaving the overlapping region at R_F 0.55, eluted with methanol and the eluates evaporated. Isopropanol extraction of the solid residue, evaporation and repetition of this procedure left 40 mg of the substance with $R_F=0.5$ about 95 % pure, $[\alpha]_D^{25} = -70^\circ$ (MeOH). Likewise the other geometrical isomer (50 mg) was obtained in about the same purity, m.p. $210-215^\circ$, $[\alpha]_D = +4^\circ$ ($c=2.0$ in MeOH).

D-(+)-8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (V). A solution of 3-carboxamido[N-2-(1-phenyl)propyl]-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (500 mg) in 6 N HCl (20 ml) was refluxed for 5 days. Chromatography showed that 60 % of the material had then been hydrolyzed. Some decarboxylation had also occurred. The mixture was then evaporated, the residue dissolved in water (60 ml), the pH adjusted to 4.2, the solution extracted with 90 % phenol (3×20 ml), the combined phenol extracts washed with water (2×15 ml), ether (180 ml) added to the phenol, the separated aqueous phase collected, the organic phase washed with water (3×30 ml), and the aqueous phase and the aqueous washings combined and washed with ether. Finally the aqueous solution was concentrated to about 5 ml and left in the cold when the desired acid, contaminated with some decarboxylated material, crystallized out. The decarboxylated material was removed by preparative paper chromatography on Whatman No. 17 paper using the system BuOH:EtOH:NH₃:H₂O

(4:1:2:1). The acid band was eluted with water, the eluates concentrated to about 3 ml and the pH brought to 3.5 when 38 mg of the desired acid crystallized out, m.p. 160–162°C. $[\alpha]_D^{25} = +0.5^\circ$ ($c = 1.7$ in 0.1 N NaOH).

L-(-)-2,3-Dibromopropionyl-alanine ethyl ester (Ib). To a stirred suspension of L-alanine ethyl ester hydrochloride (15.4 g, 0.1 mole) in dioxane (200 ml) was added triethylamine (11.0 g, 0.11 mole). After stirring for $\frac{1}{2}$ h the suspension was cooled down to 10°, more triethylamine (11.0 g, 0.11 mole) added, and 2,3-dibromopropionyl chloride (27.5 g, 0.11 mole), dissolved in dioxane (50 ml), added dropwise over 1 h to the stirred suspension at 10°. After stirring for an additional 2 h at room temperature the precipitated triethylamine hydrochloride was removed by filtration, washed with dioxane (100 ml), the combined washings and filtrate evaporated, and the residual oily material (41 g) extracted with boiling ligroin several times (in all 450 ml). On cooling a crystalline material (13.4 g, 41%), white needles, separated from the extracts, m.p. about 85°. Further recrystallisation from ligroin gave m.p. 84–87°, (partial sublimation). (Found: C 29.46; H 4.09; N 4.36. Calc. for $C_8H_{13}Br_2NO_3$: C 29.02; H 3.96; N 4.09). $[\alpha]_D^{25} = -38^\circ$ ($c = 2.7$ in EtOH). IR (KBr) 1730 cm^{-1} (CO-ester) 1660 cm^{-1} (CO-amide), 3290 cm^{-1} (NH).

Concentration of the filtrate from the ligroin extracts after filtering off the desired dibromopropionyl derivative left an oily material (11.8 g), which was extracted with boiling petroleum ether (100 ml), and the petroleum ether evaporated yielding an oily material (4.6 g) which was found to be mainly 2-bromoacryl-alanine ethyl ester.

L-(-)-2-Bromoacryl-alanine ethyl ester (IIb). 0.1 N Methanolic sodium methoxide (20 ml, 0.02 mole) diluted with methanol (50 ml) was added dropwise over 2 h at room temperature to a solution of 2,3-dibromopropionyl-L-alanine ethyl ester (6.62 g, 0.02 mole) in methanol (100 ml). The mixture was then concentrated to dryness at reduced pressure, the residue extracted several times with hot petroleum ether (b.p. 40–60, in all 350 ml) and the extracts evaporated yielding the desired substance as a pale yellow oil (5.1 g, 100%). This material was chromatographically homogeneous and was used in further synthetic work without any additional purification. $[\alpha]_D^{25} = -24^\circ$ ($c = 1.7$ in EtOH).

3-Carboxamido[N-1-(1-carbethoxy)ethyl]-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (IVb). A solution of L-2-bromoacryl-alanine ethyl ester (5.0 g, 0.02 mole) in 50 ml of ethyl acetate) was added dropwise to a boiling solution of 3-hydroxy-6-methylpyrid-2-thione (2.52 g, 0.02 mole) in ethyl acetate (100 ml). A solid was gradually precipitated. After refluxing with stirring for 24 h, the mixture was allowed to reach room temperature and filtered; (5.3 g, 68%), m.p. 218–222°. Recrystallization from acetic acid gave white crystalline material, m.p. 225–228°. (Found: C 42.99; H 4.77; N 7.20. Calc. for $C_{14}H_{18}N_2O_4S \cdot HBr$: C 42.95; H 4.90; N 7.16). $[\alpha]_D^{25} = -76^\circ$ ($c = 1.4$ in MeOH). IR (KBr): 1740 cm^{-1} (CO-ester), 1700 (CO-amide). NMR in DMSO- d_6 : 5.88 and 8.80 (O-CH₂CH₃), 8.59 (doublet, $J = 7.0$ cps, CH₃-CH), 7.45 (singlet, CH₃-pyridine), 5.55–6.05 (multiplet), CH₂-S, -CH-), 3.65 (multiplet, CH-N⁺≡), 2.2–2.6 (2 nearly coinciding AB systems of pyridine protons).

L-(-)-3-Carboxy-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium chloride (V). The above crude 3-carboxamido[N-1-(1-carbethoxy)ethyl]-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (500 mg) dissolved in 6 N HCl (25 ml) was refluxed overnight and then evaporated to dryness. The residual solid was redissolved in 2 N HCl (10 ml) by heating. On standing in the cold 173 mg of the acid hydrochloride crystallized out, m.p. 183° (decomp.). $[\alpha]_D^{25} = -3^\circ$ ($c = 1.1$ in 0.1 N NaOH aq.).

L-(-)-Menthyl-2,3-dibromopropionate (Ic). A solution of 2,3-dibromopropionyl chloride (25.0 g, 0.10 mole) and L-(-)-menthol (15.6 g, 0.10 mole), in methylene chloride (100 ml) was kept at room temperature for 24 h. The solvent was then evaporated and the residual oil distilled, b.p. 122–126°/0.15 mm Hg; colourless liquid (29.4 g, 79%), which solidifies on cooling; m.p. 32–34°. (Found: C 42.21; H 5.82; Calc. for $C_{13}H_{22}Br_2O_3$: C 42.18; H 6.00). $[\alpha]_D^{25} = -35^\circ$ ($c = 2.1$ in MeOH). IR spectrum (liquid film): Ester carbonyl at 1740 cm^{-1} . NMR in CDCl₃: 5.5–6.5 (unresolved multiplet, -CH₂-CH-) besides unresolved menthol spectrum.

L-(-)-Menthyl- α -bromoacrylate (IIc). L-(-)-Menthyl-2,3-dibromopropionate (22.2 g 0.06 mole) was dissolved in dry ethanol (60 ml) and ethanolic sodium ethoxide (31.9 ml, 1.88 N, 0.06 mole) was added dropwise with stirring at room temperature. Sodium bromide was slowly precipitated. The reaction mixture was stirred at room temperature for 22 h, a few mg of hydroquinone added and the salt quickly removed by filtration. The filtrate

was evaporated and the residue distilled, b.p. 82–86°/0.1 mm Hg. Yield 14.4 g (82 %). A few mg of hydroquinone was also placed in the receiving flask during the distillation to reduce the polymerisation tendency. Without added stabilizer the distillate was polymerized in a few hours. The compound was not sent for elementary analysis but spectroscopic data are in agreement with the postulated structure.

This compound is extremely harmful to the skin and the slightest contact can cause serious allergic reactions. $[\alpha]_D^{25} = -76^\circ$ ($c=2.1$ in EtOH). IR spectrum (liquid film): Ester carbonyl at 1720 cm^{-1} and double bond at 1600 cm^{-1} . NMR in CDCl_3 : Vinyl protons at 3.09 and 3.76 τ ($J=1.5$ cps) besides unresolved menthol spectrum.

8-Hydroxy-3-L-menthylcarboxy-5-methyldihydrothiazolo[3,2-a]pyridinium bromide (IVc). a) A solution of 3-hydroxy-6-methylpyrid-2-thione (2.8 g, 0.02 mole) and the above L-(–)-menthyl-2-bromoacrylate (6.0 g, 0.021 mole) in ethyl acetate (120 ml) was refluxed for in all 16 days. The solid precipitate which slowly formed was filtered off at two day intervals and washed well with ethyl acetate. The total yield was 6.59 g (79 %); $[\alpha]_D = +8.5^\circ$ ($c=1.2$ in MeOH). To avoid any fractionation on purification the crude product was hydrolysed as such to the acid below.

b) DL-8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (2.14 g, 0.01 mole) was dried at 70° *in vacuo* to remove water of crystallization. A suspension of this material in L-(–)-menthol (6.3 g, 0.04 mole) was stirred at 100° while dry gaseous HCl was passed into the reaction flask for 45 h. Chromatography showed that about 60 % of acid had been esterified at that time. The reaction mixture was then dissolved in the minimum amount of methanol, and water was then added until the solution separated into 2 layers. The top menthol layer which contained some ester was separated and added to ether (200 ml). After stirring for 15 min the insoluble ester was collected by filtration (0.10 g), m.p. 230–232°. The aqueous layer which contained considerable amounts of the ester was washed with a little ether and left in the cold. The ester precipitate (0.35 g) was collected, dried and triturated with ether, m.p. 231–232°. (Found: C 58.75; H 7.05; N 3.88; S 8.39. Calc. for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{S}\cdot\text{HCl}$: C 59.13; H 7.31; N 3.63; S 8.31). $[\alpha]_D^{25} = -37^\circ$ ($c=2.0$ in MeOH).

D-(+)-3-Carboxy-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium chloride (V). 8-Hydroxy-3-L-menthylcarboxy-5-methyldihydrothiazolo[3,2-a]pyridinium bromide (1.0 g) $[\alpha]_D^{25} = 8.5^\circ$ (MeOH), in 6 N HCl (30 ml) was refluxed for 20 h. The hydrolysis was then complete as shown by chromatography. Insoluble and polymeric materials were removed by filtration, the filtrate extracted with ether (3 × 20 ml) and the aqueous phase evaporated. The residual solid was dried and triturated with ether. There remained 0.40 g of the desired acid hydrochloride, chromatographically pure. $[\alpha]_D^{25} = +35.5^\circ$ ($c=1.0$ in 0.1 N NaOH aq.). Recalculated for the zwitterion this corresponds to $[\alpha]_D = +41.5^\circ$, $p=27\%$.

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