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SYNTHESIS OF *ERYTHRO*- AND *THREO*-α-BROMO-α'-FLUOROSUCCINIC ACIDS

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SUMMARY

erythro- and threo-α-Bromo-α'-fluorosuccinic acids have been prepared from their corresponding dimethyl esters. Because of the extreme readiness of elimination of hydrogen fluoride in basic medium, a special method of acid hydrolysis had to be applied. Hydrogen and fluorine NMR spectra are reported.

INTRODUCTION

Dimethyl and diethyl esters of α-bromo-α'-fluorosuccinic acids were found to eliminate hydrogen fluoride in preference to hydrogen bromide when treated with base [1,2]. For a kinetic study of such eliminations free α-bromo-α'-fluorosuccinic acids were desirable. Since the elimination of hydrogen fluoride by base is faster than the hydrolysis of the ester groups alkaline hydrolysis had to be avoided. Simple acid hydrolysis with dilute sulfuric acid gave disappointing results [2]. Other ways of synthesizing the two diastereomeric acids were therefore attempted.

RESULTS AND DISCUSSION

Addition of bromine and fluorine to maleic anhydride using N-bromoacetamide and hydrogen fluoride failed when tried by Bose et al. [1] and by the author. Equally negative was the result of treatment of free maleic and fumaric acids with the same reagents. The reaction of meso-α,α'-dibromosuccinic acid with silver fluoride in acetonitrile gave bromomaleic acid, and treatment of 2-bromo-3-hydroxybutanoic acid with DAST (dimethylaminosulfur trifluoride) did not give the expected bromofluoro acid.

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Attempts to obtain bromofluorosuccinic acids by hydrogenolysis of their benzyl esters were equally unsuccessful. Dibenzyl maleate and fumarate treated with N-bromoacetamide and hydrogen fluoride underwent, instead of addition of bromine and fluorine, ring bromination, and the p-nitrobenzyl maleate and p-nitrobenzyl fumarate suffered resinification and hydrolysis, respectively. Di-(pentafluorobenzyl)esters resisted hydrogenolysis: catalytic hydrogenation of di-(pentafluorobenzyl) maleate gave di-(pentafluorobenzyl) succinate.

When all the above experiments failed the author modified his original method of acid hydrolysis. Under controlled conditions dimethyl α-bromo-α'-fluorosuccinates were hydrolyzed by brief refluxing with 5% hydrobromic acid, or, better still, with 5% sulfuric acid, and the unreacted esters were subjected to two more successive refluxings until a major part of them was hydrolyzed. Under these conditions the elimination of hydrogen fluoride was cut to a minimum. However, the hydrolysis gave, in addition to the free bromofluoro acids, also products of incomplete hydrolysis, the monomethyl esters. Additional refluxing of the water-soluble mixtures with 5% sulfuric acid followed by ether extraction gave practically pure acids with only small amounts of the monomethyl esters and bromobutenedioic acids resulting from dehydrofluorination.

The final purification by chromatography over silica gel proved impractical, and crystallization extremely tedious. Both erythro- and threo-α-bromo-α'-fluorosuccinic acids are extremely soluble in ether and acetone, and very sparingly soluble in benzene and halogenated methanes. When dissolved in boiling mixtures of the solvents they usually did not crystallize on cooling even after seeding. The best way of purifying both the acids was to spread the crude crystalline products containing still some mono esters over a porous plate which absorbed the liquid mono esters and gave sufficiently pure acids according to NMR. Both acids, especially the erythro isomer, are hygroscopic and must be kept in desiccators.

EXPERIMENTAL

Melting points were taken in Thomas-Hoover Unimelt apparatus and are uncorrected. Gas-liquid chromatography was carried out on Varian 920 Aerograph with thermal conductivity detection and helium as a carrier gas at a flow rate of approximately 100 ml/min. ^{1}H and ^{19}F NMR spectra were taken on Varian EM 390 NMR Spectrometer at 90 MHz and 84.6 MHz, respectively, using TMS and HFB as internal standards and carbon tetrachloride and acetone-d_6 as the solvents. The solvents and chemicals used were of commercial grade.

Dimethyl α-bromo-α'-fluorosuccinates (threo and erythro)

Preparation of both dimethyl threo and erythro-α-bromo-α'-fluorosuccinates from dimethyl maleate and fumarate, respectively, as described by Bose et al. using hydrogen fluoride and N-bromoacetamide in a mixture of dichloromethane and tetrahydrofuran [1], gave results inferior to the procedure of Gershon et al. using N-bromoacetamide and anhydrous hydrogen fluoride alone [3]. Since the latter procedure is not fully described in the literature [3] it is reported in detail.

In a 100 ml polyethylene flask fitted with a magnetic stirring bar and immersed in a dry ice-acetone bath, 14.4g (0.1 mol) of dimethyl maleate or dimethyl fumarate was dissolved in 20-25 ml (27-35 ml in the case of dimethyl fumarate) of anhydrous hydrogen fluoride by portionwise addition over a period of 3-5 minutes at -60° to -50°. N-bromoacetamide (16.5g 0.12 mol, 20% excess) was added portionwise over a period of 15-20 minutes at temperatures of -50° to -30°. The mixtures were allowed to warm slowly to room temperature and after 12-15 hours poured into polyethylene or Teflon dishes to let the hydrogen fluoride evaporate. The bromofluoro esters were isoisolated by extraction with dichloromethane. Vacuum distillation of the oily residues (20-22g) and redistilation of the foreruns containing dimethyl fumarate afforded dimethyl threo-α-bromo-α'-fluorosuccinate in 61%, yield and the erythro isomer in 49% yield. B.p. of dimethyl erythro-α-bromo-α'-fluorosuccinate was 50-53°/0.015 mm or 57-63°/0.05 mm, that of dimethyl threo-α-bromo-α'-fluorosuccinate 61-66°/0.025 mm or 65-70°/0.05 mm. The ^{1}H NMR chemical shifts of both esters are in agreement with the literature [1]. However considerable differences were noticed in coupling constants [1], probably owing to different concentrations in the solvents.

NMR spectra of dimethyl erythro-α-bromo-α'-fluorosuccinate: ^{1}H NMR (neat): $\underline{CH_3}O$ 3.82 (s,3); -$\underline{CH}$Br- 4.89 (dd,1) ($J_{H'F}$vic 18 Hz, $J_{HH'}$ 4.5 Hz); -$\underline{CH}$F- 5.33 (dd,1) (J_{HF}gem 45 Hz, HH' 4.5 Hz). In CCl_4: $\underline{CH_3}O$ 3.80 (s,3); -$\underline{CH}$Br- 4.57 (dd,1) ($J_{H'F}$vic 13.5 Hz, $J_{HH'}$ 7 Hz); -$\underline{CH}$F- 5.13 (dd,1) (J_{HF}gem 46.5 Hz, $J_{HH'}$ 7 Hz). Lit. [1]: -$\underline{CH}$Br$\underline{CH}$F- 4.94, 5.41; $J_{H'F}$vic 18.45 Hz, J_{HF}gem 45.95 Hz, $J_{HH'}$ 4.62 Hz).

^{19}F NMR (CCl_4): 21.8 (upfield from HFB) (dd, J_{HF}vic 13.5 Hz, J_{HF}gem 46.5 Hz).

NMR spectra of dimethyl threo-α-bromo-α'-fluorosuccinate: ^1H NMR (CCl_4): CH_3O 3.81(s,3); -CHBr- 4.66 (dd,1) (J_{HF}vic 19.0 Hz, $J_{HH'}$ 5Hz); -CHF- 5.22 (dd,1) (J_{HF}gem 46.0 Hz, $J_{HH'}$ 5 Hz); Lit. [1]: -CHBrCHF- 5.00, 5.55; $J_{H'F}$vic 23.69 Hz, J_{HF}gem 45.99, $J_{HH'}$ 3.66 Hz).
^{19}F NMR (CCl_4): 32.9 (upfield from HFB) (dd, $J_{H'F}$vic 19Hz, J_{HF}gem 46 Hz).

Erythro-α-bromo-α'-fluorosuccinic acid (nc)

Dimethyl erythro-α-bromo-α'-fluorosuccinate (9.35g, 0.0385 mol) and 1 ml of methanol were stirred and refluxed with 40 ml of 5% sulfuric acid for 30 minutes. After cooling, the heavier layer of the unreacted dimethyl ester was separated (4.95g), the aqueous layer was extracted with two 10 ml portions of dichloromethane, the extract was combined with the separated unreacted ester and all was evaporated at 40° at 60 mm to give 6.76g of the recovered dimethyl ester containing some monomethyl esters. This mixture was diluted with 1 ml of methanol and stirred and refluxed with 30 ml of 5% sulfuric acid for 30 minutes. After cooling, the unreacted ester was recovered in the way described above (2.73g), and subsequently stirred and refluxed with 10 ml of 5% sulfuric acid. Extraction with two 10 ml portions of dichloromethane followed by evaporation of the extract yielded 1.07g (11.5%) of the recovered unreacted dimethyl erythro-α-bromo-α'-fluorosuccinate.

Each of the three aqueous layers containing erythro-α-bromo-α'-fluorosuccinic acid and its monomethyl esters was evaporated at 40° at 40 mm to about one fourth of its volume, extracted with 50+40+30 ml of ether, the ether extracts were evaporated at 40° at 60 mm, and combined to give 8.72g of crude oily erythro-α-bromo-α'-fluorosuccinic acid. Its solution in 18 ml of 5% sulfuric acid was extracted with two 1 ml portions of hexane and the aqueous layer was refluxed for 30 minutes. After cooling the solution was extracted with two 10 ml portions of dichloromethane, the aqueous layer was evaporated at 40° at 30 mm to a small volume and extracted consecutively with 50+40+30 ml of ether. The combined ether extracts were dried with absorbent cotton and evaporated to dryness at 40° at 30 mm. The residue was heated for three hours at 40° at 0.5-0.01 mm and gave ultimately 5.84g (70.7%) of a white solid, crude erythro-α-bromo-α'-fluorosuccinic acid containing, according to NMR, only small amounts of its monomethyl esters and of bromofumaric acid. Purification was carried out by adding 10-15 volume % of acetone to a boiling mixture of 1 part of the acid and 20 weight parts of chloroform until all the acid dissolved. Evaporation at 40° at

30-60 mm to about one fifth of the original volume and allowing the solution to stand overnight afforded crystals, m.p. 146-147°.

^{1}H NMR (CCl_4-CD_3COCD_3): $CO_2\underline{H}$ 8.93 (broad s); -$\underline{CH}$Br- 4.88 (dd,1), J_{HF}vic 17.0 Hz, HH' 4.8 Hz); -$\underline{CH}$F- 5.31 (dd,1) (J_{HF}gem 45.0 Hz, HH' 4.8 Hz).

^{19}F NMR (CCl_4-CD_3COCD_3): 25.1 (upfield from HFB) (dd) ($J_{H'F}$vic 17.0 Hz, J_{HF}gem 45.0 Hz).

Analysis: Found: 21.96%, 21.97%C; 2.14%, 2.18%H. Calcd. for $C_4H_4BrFO_4$ (215.0): 22.35%C, 1.88%H.

Threo-α-bromo-α'-fluorosuccinic acid (nc)

The hydrolysis of dimethyl threo-α-bromo-α'-fluorosuccinate was carried out analogously to that of the erythro isomer. The ester (6.74g, 0.0277 mol) diluted with 1 ml of methanol was stirred and refluxed for 30 minutes with 30 ml of 5% sulfuric acid. The unreacted ester (2.95g) was refluxed for 30 minutes with 12 ml of 5% sulfuric acid, and the recovered unreacted ester (1.30g) was refluxed for 30 minutes with 5 ml of 5% sulfuric acid. Only 0.48g (7.1%) of the ester remained after the third hydrolysis. The individual aqueous layers were worked up in the same way as in the case of the erythro acid giving 3.97g (66.7%) of crude threo-α-bromo-α'-fluorosuccinic acid containing only small amounts of its monomethyl esters and bromofumaric acid. Repeated recrystallization from chloroform with 10-15% of acetone gave the pure product, m.p. 145.5-146.5°. Mixed m.p. with the erythro isomer was 116-122°.

^{1}H NMR (CCl_4-CD_3COCD_3): $CO_2\underline{H}$ 7.52 (s): -$\underline{CH}$Br- 4.88 (dd,1) ($J_{H'F}$vic 23.7 Hz, $J_{HH'}$ 3.6 Hz); -$\underline{CH}$F- 5.40 (dd,1) (J_{HF}gem 45.6 Hz, $J_{HH'}$ 3.6 Hz).

^{19}F NMR (CCl_4-CD_3COCD_3): 32.1 (upfield from HFB) (dd) ($J_{H'F}$vic 23.7 Hz, J_{HF}gem 45.6 Hz).

Analysis: Found 22.43%, 22.42%C; 1.91%, 1.89%H. Calcd. for $C_4H_4BrFO_4$ (215.0); 22.35%C, 1.88%H.

Di(pentafluorobenzyl) maleate (nc)

Maleic acid (1.14g, 0.01 mol) was dissolved in 36 ml of hexamethylphosphoramide (HMPA), 1.71g (0.0124 mol, 24% excess) of finely powdered potassium carbonate (predried at 150°) was added, and the mixture was stirred at room temperature for 1 hour. Thereafter 5.22g (0.02 mol) of pentafluorobenzyl bromide was added and the stirring was continued while the contents of the flask warmed up to 25-30°. After sixteen hours of stirring at room

temperature the off-white emulsion showing pH 8 was transferred into a separatory funnel, diluted with 75 ml of water and, after cooling, 25 ml of ether was added to dissolve the solid deposited in the separatory funnel. The aqueous layer was separated, extracted with 25 ml of ether, the combined ether solutions were washed with 35 ml of water, dried with anhydrous magnesium sulfate, the ether was evaporated at 45° at 20 mm, and the white crystalline residue (4.21g) was recrystallized from 10 ml of hexane giving 3.73g (78.3%) of a pure product of m.p. 65.5-66.5°.

^{1}H NMR (CCl_4): $C_6F_5\underline{CH_2}O$ 5.22 (s,2); -$\underline{CH}$= 6.18 (s,1).
^{19}F NMR (CCl_4)(downfield from HFB): $\underline{o}$-, 20.4 (m,2); p-, 9.6 (t,1) (J_{FF} 21Hz); m-, 0 (m,2).

Analysis: Found: 45.27%C, 1.39%H. Calcd. for $C_{18}H_6F_{10}O_4$ (476.2): 45.40%C, 1.27%H.

Di(pentafluorobenzyl) fumarate (nc)

Di(pentafluorobenzyl) fumarate was prepared analogously to the maleate from 1.14g (0.01 mol) of fumaric acid, 1.52g (0.011 mol, 10% excess) of dry potassium carbonate and 5.22g (0.02 mol) of pentafluorobenzyl bromide in 35 ml of anhydrous HMPA. The reaction mixture was shaken with 250 ml of water and 250 ml of ether. Evaporation of the ether layer at 45°/20 mm gave 3.00g of white shiny crystals. An additional 1.02g of the same product was obtained by suction filtration of an obstinate emulsion which accumulated at the interface of the aqueous and ether layers. The total yield of di(pentafluorobenzyl) fumarate was 4.02g (84.5%), m.p. 124-124.5° (126.5-127.5° after recrystallization from a mixture of equal parts of benzene and hexane).

^{1}H NMR (CCl_4): $C_6F_5\underline{CH_2}O$ 5.48 (s,2); -$\underline{CH}$= 6.87 (s,1).
^{19}F NMR (CCl_4) (downfield from HFB): o-, 21.0 (m,2); p-, 9.0 (t,1) (J_{FF} 22.5Hz); m-, 0 (m,2).

Analysis: Found: 45.52%C, 1.38%H. Calcd. for $C_{18}H_6F_{10}O_4$ (476.2): 45.40%C, 1.27%H.

Di(pentafluorobenzyl) succinate (nc)

Hydrogenation of 0.119g (0.25 mmol) of di(pentafluorobenzyl) maleate in 2 ml of carbon tetrachloride over 0.060g of 10% palladium on activated charcoal, or in 8 ml of ether over a mixture of 0.035g of platinum dioxide and 0.067g of 10% palladium on charcoal after 16 hours at room temperature and atmospheric pressure afforded 0.076g (63.6%) of di(pentafluorobenzyl) succinate, m.p. 91-92°, unchanged on recrystallization from a mixture of benzene and hexane.

^{1}H NMR (CCl_4): $C_6F_5C\underline{H}_2O$ 5.24 (s,1); $-C\underline{H}_2-$2.65 (s,1).

Analysis: Found: 45.27%C, 1.80%H. Calcd. for $C_{18}H_8F_{10}O_4$ (478.2): 45.21%C, 1.69%H.

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