THE SYNTHESIS OF [4,6-^{2}H] SALICYLATES

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Summary

[4,6-^{2}H] Salicylic acid, salicyluric acid and methyl salicylate are prepared by hydrogenolysis of 3,5-dichlorophenol followed by carboxylation with sodium ethyl carbonate.

Key Words

[4,6-^{2}H] Salicylic acid, [4,6-^{2}H] salicyluric acid, [4,6-^{2}H] methyl salicylate.

Introduction

Most of any absorbed dose of methyl salicylate MS, salicylic acid SA or acetyl salicylic acid AcSA is excreted in the urine as free salicylic acid or one of its conjugates[1]. Since the relative amounts of these vary with the size of the dose, route of application, urine pH, individual etc[1,2], urine analysis is preferably preceded by an acid hydrolysis step which converts the conjugates back to the free acid.

The widespread use of MS, SA and AcSA as flavouring agents in food, drink, toothpaste etc, and as therapeutic agents in man and animals means that the background level in man tends to be high, for example, a study of eleven individuals, none of whom were using salicylate medication, revealed levels of 0.5 to 32 μg/ml total salicylate in their urine[3]. Recognition of small applied doses can therefore be difficult. One solution is to use labelled material; however any label must survive both metabolic action and any acid workup used.

The preparation of [3,5-^{2}H] salicylates from the corresponding 3,5-dibromo compounds by catalytic exchange with Raney Ni-Al in $NaO^2H/^2H_2O$ has been described. Deuterium substitution in these positions does not however

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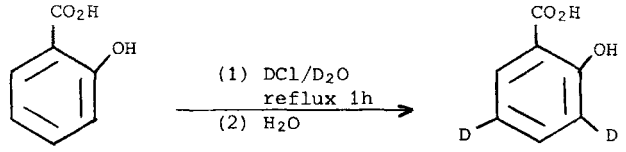
survive mild acid hydrolysis and indeed [3,5-^{2}H] salicylates are easily prepared by boiling a solution of SA in dilute ^{2}HCl/^{2}H$_2$O (Scheme 1).



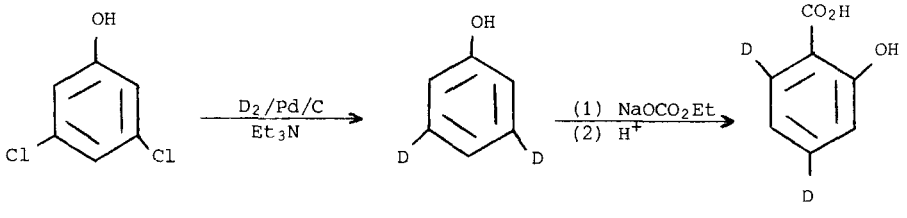
Scheme 1 where D = ^{2}H

In this paper the synthesis of [4,6-^{2}H] salicylic acid, which is stable to prolonged treatment with acid is reported.

Results

We initially investigated the high temperature ^{1}H/^{2}H exchange between SA and ^{2}H$_2$O in the presence or absence of palladium/charcoal or platinum black. In every case the rate at each aromatic position decreased in the series: 3,5 >> 4 > 6. Significant exchange at position 6 only occurred after several hours at 180°C and was competitive with decarboxylation. Although a yield of 50% [3,4,5,6-^{2}H]SA was obtained in this way the procedure was unreliable.

A more useful route is outlined in Scheme 2.

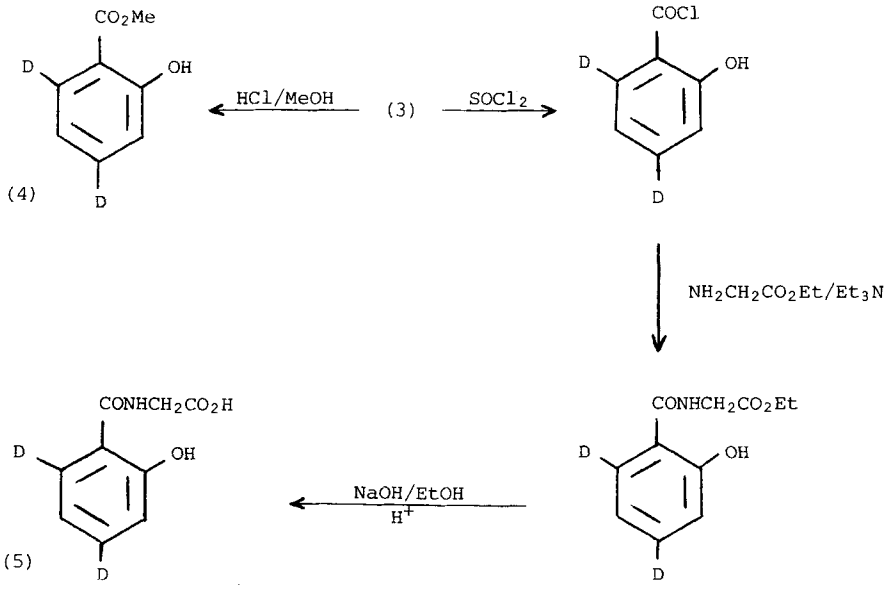


(1) (2) (3)

Scheme 2 where D = ^{2}H

The hydrogenolysis of haloaromatic compounds is well documented[5] and in the case of the conversion of 3,5-dichlorophenol (1) into [3,5-^{2}H] phenol (2) occurs in high (> 95%) yield. Carboxylation of (2) with sodium ethyl carbonate is less favourable (yields ≈ 35%) but much of the phenol (≈ 50%) can be recovered and recycled[6].

[4,6-^{2}H] salicylic acid (3) can readily be converted into its methyl ester (4) using HCl/MeOH and into its glycine conjugate, [4,6-^{2}H] salicyluric acid (5) by way of the acid chloride (Scheme 3).



where D = ^{2}H Scheme 3

Those carbon atoms bonded directly to ^{2}H resonate as triplets in the proton decoupled ^{13}C nmr spectra of (3), (4) and (5). Comparison with the spectra of authentic unsubstituted material revealed that in each case the percentage label at positions 3 and 5 was $\approx$ 95%. The corresponding mass spectra were consistent with this degree of purity.

Experimental

^{1}H and proton decoupled ^{13}C nmr spectra were measured for C^2HCl_3 solutions. Shifts are quoted in ppm downfield from tetramethylsilane.

[3,5-^{2}H] Phenol (2) - In order to exchange the phenolic proton, 3,5-dichlorophenol (9.8 g) was dissolved by warming in ^2H_2O (50 ml) then recovered by extraction with ether and concentration to dryness. Ethyl acetate (100 ml), triethylamine (25 ml), and 10% palladium on charcoal (0.3 g) were added and the mixture was stirred under an atmosphere of ^{2}H until uptake ceased (24 h). The solution was filtered, reduced to dryness, the residue dissolved in ether,

and the ethereal solution washed with dilute aqueous acid. Concentration of the solution and distillation of the residue gave (2) (5.68 g, 98%), δ_{1H} 6.79 (H-2,H-6), 6.86 (H-4).

[4,6-^{2}H] Salicylic acid (3) - An excess of solid carbon dioxide was added to a solution of sodium (1.35 g) in ethanol (40 ml). A solution of the phenol (2) (5.6 g) in ethanol (25 ml) was then added. The solvent was removed by distillation and the residue heated to 175°C. Unreacted phenol (3) (2.86 g, 51%) was then recovered under reduced pressure. The residue was dissolved in aqueous sodium carbonate and the solution washed with ether. The aqueous layer was acidified and again washed with ether. Concentration of the ether solution and crystallisation of the residue from water gave (3) (2.85 g, 35%), δ_{1H} 6.92, 6.99 (H-3,H-5), δ_{13C} 111.3 (C-1), 117.7 (C-3), 119.4 (C-5), 130.5 (triplet, C-6), 136.7 (triplet, C-4), 162.3 (C-2), 175.0 (CO_2H).

[4,6-^{2}H] Methyl salicylate (4) - A solution of the acid (3) (0.87 g) in methanol (20 ml) was saturated with hydrogen chloride then boiled under reflux for 4 h. The solution was concentrated and the residue was dissolved in ether. The ether was washed with dilute sodium carbonate solution then concentrated and the residue distilled [100°(bath) 13 mmHg] to give the ester (4) (0.75 g, 78%), δ_{1H} 3.89 (Me), 6.85, 6.95 (H-3,H-5), δ_{13C} 51.9 (Me), 112.7 (C-1), 117.6 (C-3), 119.0 (C-5), 130.1 (triplet, C-6), 135.5 (triplet, C-4), 162.0 (C-2), 170.6 ($\underline{C}O_2Me$).

[4,6-^{2}H] Salicyluric acid (5) - A solution of the acid (3) (0.35 g) in thionyl chloride (2 ml) was boiled under reflux for 1 h then the thionyl chloride was removed under vacuum. The residue was dissolved in benzene (5 ml) and added to a suspension of glycine hydrochloride ethyl ester (0.4 g) in triethylamine (0.5 ml) and benzene (5 ml). After 24 h the solution was filtered, washed with water, then concentrated. The residue was hydrolysed by warming in a dilute solution of sodium hydroxide in aqueous ethanol. Conventional processing gave the acid (5) (0.27 g, 55%), δ_{1H} 4.15 (CH_2), 6.87, 6.91 (H-3,H-5).

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