NOTES

Synthesis and characterization of three ^{14}C-labelled derivatives of 4-chloro-3-sulfamoylbenzoic acid

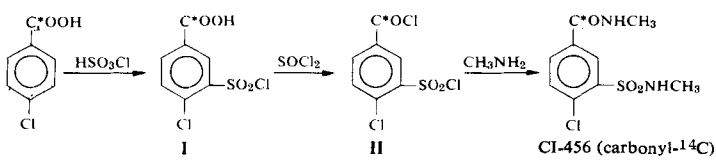
Received on 8th August 1966

This paper describes the synthesis and characterization of three ^{14}C labelled compounds prepared for use in drug metabolism studies of certain 4-chloro-3-sulfamoylbenzoic acid derivatives possessing diuretic and antihypertensive activity. [1, 2] The compounds prepared were : 4-chloro-*N*-methyl-3-(methylsulfamoyl)-benzamide(carbonyl-^{14}C) ; 4-chloro-3-sulfamoylbenzoic acid 2,2-dimethylhydrazide(carbonyl-^{14}C) ; 4-chloro-3-sulfamoylbenzoic acid 2,2-dimethylhydrazide(methyl-^{14}C). These compounds will hereinafter be referred to by the code numbers of CI-456 (carbonyl-^{14}C), CI-546 (carbonyl-^{14}C) and Cl-546 (methyl-^{14}C), respectively.

CI-456 (carbonyl-^{14}C) and CI-546 (carbonyl-^{14}C) were synthesized from *p*-chlorobenzoic acid (carbonyl-^{14}C). The carbonyl-^{14}C label was introduced by reacting *p*-chlorophenylmagnesium bromide with carbon dioxide-^{14}C. The procedure, scale, and reaction conditions used followed closely those described in Murray and Williams [3] for the synthesis of benzoic acid (carbonyl-^{14}C) from bromobenzene. In our experience, the highest yields of carbonyl labelled *p*-chlorobenzoic acid were obtained using a 50% excess of the Grignard reagent (yields based on Ba $^{14}CO_3$ ranged from 53% to 79%).

Synthesis of CI-456 (Carbonyl-^{14}C)

Several synthetic routes to CI-456 have been described. [4] The reaction sequence used in the synthesis of CI-456 (carbonyl-^{14}C) is indicated below :

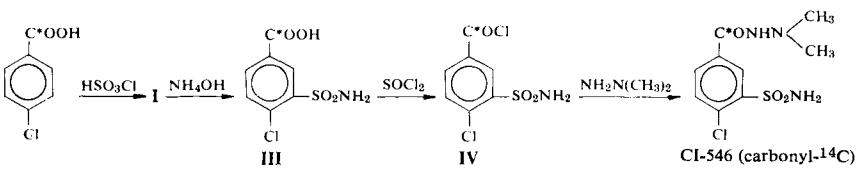


Chlorosulfonation was accomplished by adding 1.65 g (10.5 mmoles, 7.15 mc ^{14}C) *p*-chlorobenzoic acid (carbonyl-^{14}C) to 30 ml chlorosulfonic acid and

heating at 143-145 °C for 5 hours. The reaction mixture was poured over an ice-water mixture (to decompose the excess chlorosulfonic acid) and then extracted with ether. The ether phase was dried with anhydrous $MgSO_4$, treated with Norite, and filtered. Ether was removed by distillation leaving an oil residue[1] to which was added 25 ml thionyl chloride. This mixture was heated at gentle reflux for 4 hours and then allowed to cool. The excess thionyl chloride was removed by distillation leaving an oil residue (II). This oil was dissolved in 5 ml tetrahydrofuran (THF) and then added to 10 ml of chilled 40% aqueous methylamine. This mixture was allowed to stand at 0 °C for one hour. The excess methylamine was removed by vacuum distillation and the residue was neutralized with acetic acid. The resultant solid was crystallized twice from 50% aqueous acetone to yield 1.21 g CI-456 (carbonyl-^{14}C), m.p. 166-167 °C, with a specific activity of 2.41 μc/mg. Weight and ^{14}C yields based on *p*-chlorobenzoic acid were 44% and 41% respectively. Characterization data are in the appendix.

SYNTHESIS OF CI-546 (CARBONYL-^{14}C)

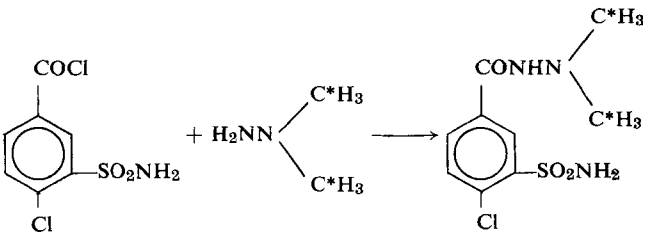
Several synthetic routes to CI-546 have been described. [5] The reaction sequence used in the synthesis of CI-546 (carbonyl-^{14}C) is indicated below :



I was prepared from 2.24 g (14.3 mmoles) *p*-chlorobenzoic acid (carbonyl-^{14}C) as described above. The product (I) was added to 20 ml chilled concentrated NH_4OH and allowed to stand overnight. Subsequently, the mixture was heated on a steam bath for 10 minutes, then treated with charcoal, filtered, and finally acidified with HCl. The product (III) was collected by filtration, dried (yield = 2.40 g), and then refluxed in 30 ml thionyl chloride with stirring for 4 hours. The excess thionyl chloride was removed by vacuum distillation at 60 °C leaving a residue which was purified by crystallizing from ether, then filtering, and finally washing with cyclohexane to yield 1.87 g IV, m.p. 165-170 °C. Recrystallized IV must be used in the next reaction to avoid difficulty in crystallizing CI-546 (carbonyl-^{14}C). The 1.87 g (7.35 mmoles) of purified IV was dissolved in 10 ml THF and then added dropwise to an ice bath chilled solution of 1.5 ml (19.7 mmoles) *unsym.* dimethylhydrazine (UDMH) in 15 ml THF. The reaction mixture was stirred for 30 minutes. THF was removed by vacuum distillation at 60 °C leaving a gummy residue which was mixed with 20 ml water, seeded with non-radioactive CI-546, and allowed to crystallize overnight at — 2 °C. The product was collected by filtration and recrystallized from methanol

to yield 0.89 g CI-546 (carbonyl-^{14}C), m.p. 192-193 °C, with a specific activity of 4.71 μc/mg. The weight yield based on *p*-chlorobenzoic was 22%.

SYNTHESIS OF CI-546 (METHYL-^{14}C)



IV

CI-546 (methyl-^{14}C)

To conserve UDMH-^{14}C, the reaction conditions were modified from those described above such that an excess of IV was reacted with UDMH-^{14}C to yield CI-546 (methyl-^{14}C). To an ice bath chilled mixture of 273 μl UDMH-^{14}C (3.60 mmoles, 946 μc ^{14}C obtained from New England Nuclear Corp.) and 0.50 ml (3.60 mmoles, an exactly equivalent amount) triethylamine (TEA) in 10 ml THF was added dropwise with stirring a solution of 1.37 g (5.40 mmoles) IV in 15 ml THF. Stirring was continued for 6 hours at room temperature. THF was removed by vacuum distillation leaving a residue to which was added 5 ml methanol and 0.2 ml 50% NaOH (measured pH = 8.5). This mixture was evaporated to dryness under a nitrogen stream overnight (to remove TEA). The residue was acidified with 5 ml 1*N* HCl and stirred for one hour (white precipitate formed). This aqueous mixture was extracted with 15 ml ethyl acetate (to remove precipitate), then adjusted to exactly pH 8.5 with 0.5 ml 50% NaOH, and finally stirred in an ice bath for 2 hours. The product was collected by filtration, dried, and recrystallized once from methanol to yield 580 mg CI-546 (methyl-^{14}C), m.p. 191-193 °C, with a specific activity of 0.71 μc/mg. Weight and ^{14}C yields based on UDMH-^{14}C were 58% and 44% respectively. Characterization data are in the appendix.

ACKNOWLEDGEMENT

We gratefully acknowledge Dr. J.M. Vandenbelt and his group for the ultraviolet and infrared analyses and Mr. C.E. Childs and his group for the elemental analyses.

APPENDIX

CHARACTERIZATION DATA FOR CI-456 (CARBONYL-^{14}C): Elem. Anal. Calcd. for $C_9H_{11}ClN_2O_3S$: C, 41.14; H, 4.22; N, 10.66. Found : C, 41.26; H, 4.24; N, 10.65. Infrared Anal.: structure verified as CI-456. Ultraviolet Anal., in abs. ethanol. Authentic CI-456: λ 288, ε 1230; λ 278, ε 1550; Found : λ 288, ε 1230; λ 278, ε 1570. Chromatography (Jan., 1965, immediately after synthesis) : * a major ^{14}C spot having the same R_f as authentic CI-456 was detected in two PC solvent systems (*n*-BuOH saturated with 3% NH_4OH, R_f 0.88; *n*-BuOH saturated with 3% HOAc, R_f 0.88) and in two TLC solvent systems ($CHCl_3$: (abs) EtOH : Heptane, 1 : 1 : 1, R_f 0.55; $CHCl_3$: MeOH : H_2O, 3 : 2 : 1 (lower phase), R_f 0.78); a radiochemical impurity of $\leq$ 0.6% was detected; repeat chromatography (Feb., 1966, same four systems) detected a 2% radiochemical impurity.

CHARACTERIZATION DATA FOR CI-546 (CARBONYL-^{14}C) AND CI-546 (METHYL-^{14}C) : Elem. Anal. Calcd for $C_9H_{12}ClN_3O_3S$: C, 38.92; H, 4.36; N, 15.13. Found for CI-546 (Carbonyl-^{14}C) : C, 38.96; H. 4.45; N, 15.14. Found for CI-546 (methyl-^{14}C): C, 39.24; H, 4.32; N, 14.98. Infrared Anal. : structures verified as CI-546. Ultraviolet Anal. Authentic CI-546 in MeOH : λ 285, ε 1790; λ 277, ε 2310; λ 230, ε 12200; in MeOH-HCl : λ 288, ε 950; λ 279, ε 1230; λ 242, ε 13600. Found for CI-546 (carbonyl-^{14}C), in MeOH : λ 285, ε 1710; λ 276, ε 2210; λ 231, ε 11400. Found for CI-546 (methyl-^{14}C), in MeOH : λ 285, ε 1800; λ 276, ε 2320; λ 232, ε 12100; in MeOH-HCl; λ 288, ε 970; λ 279, ε 1250; λ 242, ε 13700. Chromatography. * CI-546 (carbonyl-^{14}C) : a single ^{14}C spot having the same R_f as authentic CI-546 was detected in two PC solvent systems (*n*-BuOH saturated with 3% NH_4OH, R_f 0.67; isoamyl alcohol saturated with 3% HOAc, R_f 0.41); no radiochemical impurity was detected. CI-546 (methyl-^{14}C) (July, 1965, immediately after synthesis) : a major ^{14}C spot having the same R_f as authentic CI-546 was detected in four TLC solvent systems (*n*-BuOH saturated with 3% NH_4OH, R_f 0.62; EtOAc : HOAc, 20 : 1, R_f 0.13; *n*-BuOH : HOAc, 20 : 1, R_f 0.21; $CHCl_3$: benzene; HOAc, 1 : 1 : 1, R_f 0.10) and in one PC solvent system (*n*-BuOH saturated with 3% NH_4OH, R_f 0.67); a radiochemical impurity of $\leq$ 0.5% was detected; repeat chromatography (June, 1966) in two TLC solvent systems (EtOH : HOAc : H_2O, 8 : 1 : 1, R_f 0.61; Et_2O : MeOH : HCl (0.03 *N*), 4 : 4 : 1, R_f 0.75) and in two PC solvent systems (*n*-BuOH : HOAc : H_2O, 2 : 2 : 1, R_f 0.94; isoamyl alcohol saturated with 3% HOAc, R_f 0.69) detected a radiochemical impurity of $\leq$ 0.3%.

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* The ^{14}C-labelled compounds were chromatographed on Whatman No. 1 paper (PC) and on Silica Gel GF (TLC). The chromatograms were scanned for ^{14}C by analyzing 1 cm sections using liquid scintillation techniques.