SYNTHESIS AND CHARACTERIZATION OF CARBON-14 LABELLED 4,4'-DIAMINODIPHENYL SULFONE (DAPSONE-^{14}C; DDS-^{14}C).

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SUMMARY

*4,4'-Diaminodiphenyl-^{14}C sulfone *(DDS-^{14}C) was synthesized in four steps. Uniformly carbon-14 labelled aniline hydrochloride was first acetylated to yield acetanilide (phenyl-^{14}C). This was coupled with $SOCl_2$ and $AlCl_3$ in a Friedel-Crafts reaction to yield 4,4'-diacetamidodiphenyl-^{14}C sulfoxide. Oxidation with hydrogen peroxide yielded 4,4'-diacetamidodiphenyl-^{14}C sulfone (DADDS-^{14}C. Hydrolysis of DADDS-^{14}C in HCl yielded DDS-^{14}C. Characterization data are included.*

INTRODUCTION

During an intensive study of the metabolic disposition of DDS in laboratory animals, tracer experiments were carried out with the sulfur-35 labelled compound [1,2]. Although DDS-^{35}S has been used in human subjects [3], we investigated the feasibility of synthesizing the carbon-14 labelled compound for metabolic studies in man. The 4,4'-diacetamidodiphenylsulfone (DADDS) prepared as an intermediate in the synthesis of DDS has also been used successfully as a repository formulation in the treatment of leprosy [4].

* Named as 4,4'-sulfonyldianiline in *Chemical Abstracts*.

SYNTHESIS

The sequence of reactions used to synthesize DDS-^{14}C are outlined in Figure 1.

Acetanilide (phenyl-^{14}C) (II):

Acetanilide (phenyl-^{14}C) (II) was synthesized from 2.19 g (16.90 mmoles) of uniformly carbon-14 labelled aniline hydrochloride (I) with a specific activity of 156.4 μCi/mmole, according to the method of Searle and Cupery as described by Murray and Williams [5]. The yield was 2.17 g of white crystalline II (95.0%), m.p. 105-112°C, with a specific radioactivity of 151.6 μCi/mmole. Thin layer chromatography (TLC) (Appendix - system A) detected II with an estimated radiochemical purity of ≥ 98.5%; no I (< 0.1%) was detected.

4,4'-diacetamidodiphenyl-^{14}C sulfoxide (III):

4,4'-diacetamidodiphenyl-^{14}C sulfoxide (III) was synthesized from II using a modification of the procedure described by Sugasawa and Sakurai [6] for non-radioactive preparations of III. To a slurry of 2.17 g (16.05 mmoles) of II (151.6 μCi/mmole) in 30 ml of carbon disulfide was added with stirring 0.58 ml (8.05 mmoles) of thionyl chloride and then 4.43 g (33.2 mmoles) of aluminum chloride in small portions. The reaction mixture, which darkened very quickly, was refluxed for 3 days. While still warm, the reaction solvent was decanted from the reaction flask leaving a black residue. This residue was cooled to 30°C and decomposed with 40 ml of 2 N HCl yielding a suspension of tan solids. The solids were collected by filtration to yield 2.09 g of tan crystalline III (82.3% yield), m.p. 260-263°C (dec), with a specific radioactivity of 293.7 μCi/mmole. TLC (Appendix - system A) detected III with an estimated radiochemical purity of ≥ 94.3%; II was detected as a radiochemical impurity in the amount of < 0.5%. The chemical purity of III was estimated as 93.5% by ultraviolet analysis in methanol (λ = 270; ε = 32100).

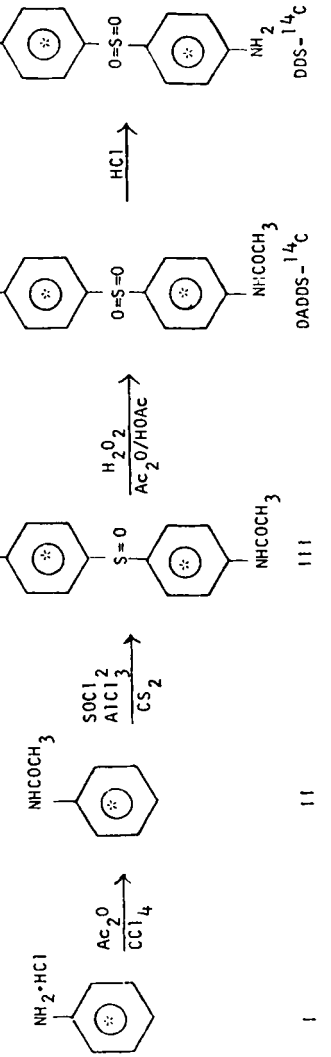


Fig. 1. Synthesis of Carbon-14 Labelled 4,4'-Diaminodiphenyl Sulfone (DDS-^{14}C)

4,4'-diacetamidodiphenyl-^{14}C sulfone (DADDS-^{14}C):

Oxidation of III with hydrogen peroxide to yield 4,4'-diacetamidodiphenyl-^{14}C sulfone (DADDS-^{14}C) was performed in a solvent mixture of acetic acid and acetic anhydride. The presence of acetic anhydride was found necessary to prevent partial hydrolysis of the acetyl groups. The 2.09 g (6.60 mmoles) yield of crude III (293.7 μCi/mmole) was slurried in 150 ml of acetic anhydride and heated to 100°C. To this mixture was added 60 ml of acetic acid. A clear red solution was obtained. While stirring at 100°C, 30 ml of 30% hydrogen peroxide was added dropwise. A pale yellow solution was obtained immediately which refluxed spontaneously at 110-120°C for about 15 minutes. Heating at reflux was continued for an additional 45 minutes. The reaction mixture was cooled, diluted with water, and made basic with 50% sodium hydroxide, causing precipitation of the product. Collection by filtration yielded 1.37 g of tan DADDS-^{14}C (62.5% yield), m.p. 266-268°C (dec), with a specific radioactivity of 287.2 μCi/mmole. Radiochromatographic analysis (Appendix - system B) detected DADDS-^{14}C with a radiochemical purity of $\geq$ 88.3%. To purify the product, the yield of crude DADDS-^{14}C was dissolved in boiling ethanol, treated with charcoal and Celite, and crystallized at -20°C to yield 1.02 g of white DADDS-^{14}C, m.p. 278-280°C, with a specific radioactivity of 310.5 μCi/mmole. TLC (Appendix - system B) detected DADDS-^{14}C with an estimated radiochemical purity of $\geq$ 97.6%.

4,4'-diaminodiphenyl-^{14}C sulfone (DDS-^{14}C):

4,4'-Diaminodiphenyl-^{14}C sulfone (DDS-^{14}C) was obtained from DADDS-^{14}C by hydrolysis in aqueous HCl using methods previously described [6,7] for non-radioactive preparations of DDS. The 1.02 g (3.07 mmoles) of IV (310.5 μCi/mmole) was refluxed in 10 ml of 6 N HCl for 2 hours, yielding a clear light orange solution. This solution was diluted with 20 ml of water, warmed to 70°C, decolorized with charcoal and Celite and made basic with

NaOH, causing precipitation of DDS-^{14}C. The white flocculent precipitate was collected by filtration and washed with water to yield 0.59 g of DDS-^{14}C (77.5% yield), m.p. 169.5-172°C, with a specific radioactivity of 306.7 μCi/mmole.

PURIFICATION AND CHARACTERIZATION

This preparation of DDS-^{14}C was characterized extensively to determine its chemical and radiochemical purity. The chemical purity of DDS-^{14}C, as indicated by ultraviolet and elemental analyses, appeared to be ≥ 98%. The radiochemical purity, as indicated by TLC (Appendix - system B, C, D, E and F) was found to be only ≥ 94.3%; an unidentified radiochemical impurity that was found not to be any of the synthesis intermediates (see Figure 1) or other likely by-products (see analogues in Table 2), was detected in the amount of approximately 5.7%.

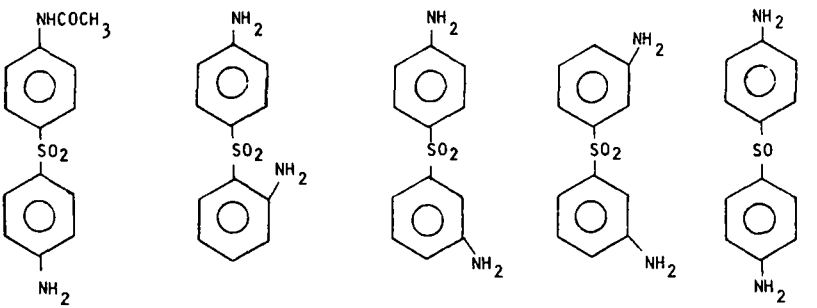
Initial attempts to purify this preparation by crystallization from aqueous ethanol and by column chromatography (neutral alumina; chloroform:methanol, 100:1) failed to remove the impurity. However, the product was purified as follows: the yield of DDS-^{14}C was dissolved in 40 ml of warm 1 N HCl and treated with charcoal and Celite. The treatment with charcoal and Celite was repeated two times. The resulting HCl solution of DDS-^{14}C was cooled and made basic with 50% NaOH, causing precipitation of a tan product which was collected by filtration and washed with water. This tan product was dissolved in boiling ethanol, treated again with charcoal and Celite, concentrated to approximately 15 ml, and diluted with hot water to 80 ml. Cooling to 0°C overnight yielded 270 mg of white needles of DDS-^{14}C, m.p. 174.5-175.5°C, with a specific activity of 328.7 μCi/mmole.

Radiochromatographic analyses (Appendix - systems B, C, E and F) detected DDS-^{14}C with an estimated radiochemical purity of ≥ 97%. The

TABLE 1. Summary of Characterization of DDS-^{14}C

Parameter	DDS-^{14}C
Color	White
Melting Point	174.5-175.5°C
Specific Activity	328.7 μCi/mmole
Elemental Analyses	
Calc C 58.04%	57.72%
H 4.87%	4.86%
N 11.28%	11.29%
Ultraviolet Analysis in MeOH	λ 294, 260 ϵ 39600, 24400
Infrared Analysis	Identical to IR of authentic DDS
Chromatography	Radiochemical Purity > 97% in four TLC systems

TABLE 2. Analogues of DDS



unidentified impurity of 5.7% was reduced to < 3.0%. None of the synthesis intermediates (Figure 1) or likely by-products (Table 2) was detected as impurities. The chemical purity, as established by ultraviolet, infrared and elemental analyses, was estimated to be nearly 100%. All of the characterization data are summarized in Table 1.

APPENDIX: Chromatographic Methods

DDS-^{14}C and each of the carbon-14 labelled intermediates were characterized to establish their radiochemical identity and purity by using at least one of the thin layer chromatography (TLC) systems shown in the Table below. The compounds were chromatographed on thin layers of silica gel or alumina until the solvent front was 15 cm from the origin. The chromatograms were scanned for carbon-14 by measuring amounts of carbon-14 on each of the 1 cm sections cut along the chromatographic lane from the origin to the solvent front. A Packard Model 3365 liquid scintillation spectrometer was used to measure amounts of carbon-14 on each of the 1 cm sections. Radiochromatographic profiles were constructed, and the radiochemical purity of each of the products was estimated.

THIN LAYER CHROMATOGRAPHY SYSTEMS

System	Medium	Solvent Composition
A	Silica Gel	benzene:methanol:acetic acid, 45:8:4
B	Silica Gel	ethyl acetate
C	Silica Gel	ethyl acetate:diethylamine, 30:1
D	Alumina	methanol
E	Alumina	chloroform:acetic acid, 30:1
F	Alumina	chloroform:methanol, 30:1

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