Radiosynthesis of Dextroamphetamine-^{14}C Sulfate

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A high yield radiosynthesis of *dl*-amphetamine-7-^{14}C was developed using 0.5 c. of benzoic-7-^{14}C acid as the starting material. The *dl*-amphetamine-7-^{14}C was resolved in 84 per cent yields by the successive crystallization of *d*-amphetamine-^{14}C *d*-bitartrate and *l*-amphetamine-^{14}C *l*-bitartrate salts.

IT BECAME necessary to prepare relatively large quantities (80–90 mc.) of ^{14}C-tagged *d*-amphetamine sulfate[1] for metabolic and pharmaceutical dosage form studies. In 1950, Wilson (1) prepared 0.28 Gm. of a ^{14}C-tagged *dl*-amphetamine sulfate[2] using a microsynthetic approach from phenylacetic-2-^{14}C acid. A more direct radiosynthetic approach from a readily available starting material such as benzoic-7-^{14}C acid was necessary to prepare the large amounts of *dl*-amphetamine-^{14}C necessary for the resolution of optical isomers. One of the most direct methods for preparing 1–10-Gm. quantities of phenylethylamines is the use of the intermediate nitrölefin prepared by the base-catalyzed condensation of the appropriate aryl aldehyde and nitroalkane.

A number of microchemical syntheses are available for the preparation of benzaldehyde-7-^{14}C (2); however, the reduction of benzoyl-7-^{14}C chloride with lithium aluminum tritertiarybutoxy hydride appeared to be the simplest method for the 100 mmolar scale contemplated. Brown's procedure (3, 4) for the low-temperature reduction of acid chlorides in diglyme gave 55–60% of a crude benzaldehyde. Significant amounts of benzaldehyde were lost in the extractive purification due to its solubility in aqueous diglyme. The use of tetrahydrofuran as the reaction medium gave consistent 75% yields of benzaldehyde. A number of condensation reactions between benzaldehyde and nitroethane were explored using nitroethane, benzene, or glacial acetic acid as the solvent and *n*-butylamine, piperidine, or ammonium acetate as the basic catalyst. The best yields were obtained by refluxing the aldehyde with excess nitroethane in benzene and removing the water formed in the reaction with a Dean Stark trap (5). The resulting crude 1-phenyl-2-nitropropane was then converted to *dl*-amphetamine in 80–85% yields by reduction with lithium aluminum hydride (6).

The crude reaction intermediates were partially purified by extraction, and the vapor phase chromatograph was used to determine relative purities and to follow the reaction sequence. The *dl*-amphetamine was purified by an acid-base extraction to remove neutral side products formed in the reaction sequence.

The two methods that were considered for quantitative resolution of *dl*-amphetamine-^{14}C were: (*a*) isotope carrier dilution of *d*-amphetamine-^{14}C *d*-bitartrate and (*b*) cyclic crystallization of *d*-amphetamine-^{14}C *d*-bitartrate and *l*-amphetamine-^{14}C *l*-bitartrate from the enriched *d*-isomer and *l*-isomer mother liquors, respectively. The latter resolving method was applied to the hot run since a 97% optical purity could be realized with a single crystallization with rigid temperature control. It was thus possible to obtain an 85–90% recovery of the optical isomers.

EXPERIMENTAL

Benzaldehyde-7-^{14}C.—The benzoic-7-^{14}C acid (6.867 Gm., 525 mc.)[3] was diluted to 12.272 Gm. (100.1 mmoles) with reagent grade benzoic acid. The benzoic-7-^{14}C acid dissolved in 60 ml. of benzene was refluxed for 3 hr. with 22.6 ml. (0.3 mole) of thionyl chloride. An additional 5.0 ml. of thionyl chloride was added, and the reaction mixture was refluxed 1 additional hour. The solvent and excess thionyl chloride then were removed by distillation, and the residue was treated with three 20-ml. portions of benzene with successive distillation to remove traces of thionyl chloride.

The crude benzoyl-7-^{14}C chloride was dissolved in 40 ml. of dry redistilled tetrahydrofuran and cooled to −78°. Lithium aluminum tritertiarybutoxy hydride (27.5 Gm., 103 mmoles) was dissolved in 80 ml. of tetrahydrofuran and added to the stirred solution of benzoyl-7-^{14}C chloride over a period of 70 min. The reaction mixture was stirred 1 additional hour and slowly brought to room temperature by removing the freeze bath. The reaction mixture was poured into 200 Gm. of crushed ice and extracted with eight 50-ml. portions of ether. The ether and tetrahydrofuran were removed *in vacuo*. The crude benzaldehyde-7-^{14}C was dissolved in ether and washed with water to remove excess tetrahydrofuran. The ether was removed *in vacuo*, and 9.10 Gm. of 80% benzaldehyde-7-^{14}C (15% benzyl-7-^{14}C alcohol and 5% tetrahydrofuran by vapor phase chromatography) was obtained for a 68.8% yield from benzoic-7-^{14}C acid. The benzyl-7-^{14}C alcohol did not interfere

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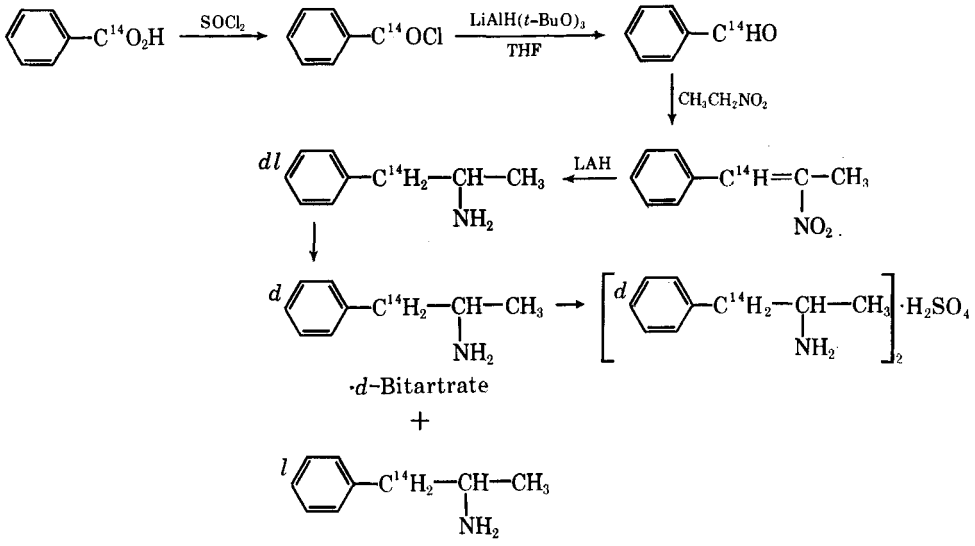
[1] Marketed as Dexedrine Sulfate by Smith Kline & French Laboratories, Philadelphia, Pa.

[2] Marketed as Benzedrine Sulfate by Smith Kline & French Laboratories, Philadelphia, Pa.

[3] Purchased from the New England Nuclear Corp., Boston, Mass.



Flow Sheet for the Radiosynthesis of *d*-Amphetamine-^{14}C Sulfate

with the remainder of the chemical sequence and was removed in the acid-base extraction of *dl*-amphetamine-^{14}C. A total of 68.8 mc. (13.1%) of benzoic-7-^{14}C acid was recovered from the aqueous layers.

l-Phenyl-2-nitropropene-1-^{14}C.—The 9.10 Gm. (68 mmoles) of benzaldehyde-7-^{14}C was diluted to 100 mmoles with carrier and dissolved in 50 ml. of benzene. The benzaldehyde-7-^{14}C was reacted with 10.7 ml. of nitroethane in the presence of 0.75 ml. of piperidine and 0.5 ml. of *n*-butylamine. The reaction mixture was refluxed for 12 hr. and the water formed in the condensation was removed with a Dean Stark trap. The theoretical quantity of water (2.1 ml.) was formed in 9 hr. The excess nitroethane and benzene were evaporated *in vacuo*. The residual tan residue was dissolved in ether and washed thoroughly with water. The ether was removed *in vacuo* and the crude 1-phenyl-2-nitropropene-1-^{14}C weighed 15.5 Gm. The vapor phase chromatograph of the material showed a purity of 85% so that the chemical yield was 81%.

dl-Amphetamine-7-^{14}C.—The procedure for the reduction of the nitrölefin is similar to that employed by Erne and Ramirez (6). A solution of 15.5 Gm. (81 mmoles) of *l*-phenyl-2-nitropropene-1-^{14}C in 170 ml. of ether was added over a 2-hr. period to a stirred solution of 10.6 Gm. (280 mmoles) of lithium aluminum hydride. The reaction mixture was refluxed for 2 hr. and cooled to 5°. The reaction then was quenched by the cautious slow addition of 6 ml. of water, 6 ml. of 10% sodium hydroxide, and finally 10 ml. of water. The aluminum salts were filtered and washed thoroughly with warm ether. The ether solution of *dl*-amphetamine-7-^{14}C was concentrated *in vacuo* to a volume of 45 ml., and the *dl*-amphetamine-^{14}C was extracted into 65 ml. of 1.89 *N* sulfuric acid. The acidic extract was washed with ether and made alkaline with 10 ml. of 10 *N* sodium hydroxide. The pale yellow oil of *dl*-amphetamine-^{14}C was extracted into ether and dried over anhydrous magnesium sulfate.

The ether was evaporated *in vacuo*, and the *dl*-amphetamine-^{14}C weighed 10.1 Gm. (85% pure by vapor phase chromatography). An additional 2 mmoles of material was recovered from the magnesium sulfate for a yield of 81%.

dl-Amphetamine-7-^{14}C Sulfate.[2]—The 85% *dl*-amphetamine-7-^{14}C (251 mg.) was dissolved in 5 ml. of ethanol, and 83 mg. of sulfuric acid diluted with 3 drops of water was added. The suspension of *dl*-amphetamine-^{14}C sulfate was diluted with 2.5 ml. of ether and refrigerated overnight. The salt was filtered and washed with 1:1 ethanol–ether and ether. The dry *dl*-amphetamine-^{14}C sulfate weighed 224 mg. and had a specific activity of 6.04 mc./mmole. The identity by infrared and radiochemical purity by scanning a paper chromatogram were satisfactory.

The over-all chemical yield from benzoic-7-^{14}C acid was 44.3%, and the radiochemical yield was 37.7%.

Resolution of dl-Amphetamine-7-^{14}C.—The 62 mmoles of *dl*-amphetamine-7-^{14}C was diluted to 165 mmoles with carrier and dissolved in 250 ml. of 91% (v/v) isopropanol. The solution was warmed, and 25.5 Gm. (170 mmoles) of *d*-tartaric acid was added. The tartaric acid dissolved with the aid of heat, and the solution was placed in a constant-temperature bath set initially at 75–80°. The solution was allowed to cool slowly to 59° and maintained at that temperature (±0.02°) overnight. The mother liquor was decanted through a 59° jacketed sintered-glass Büchner funnel and the crystalline *d*-amphetamine-^{14}C *d*-bitartrate was filtered with the aid of 50 ml. of a 91% isopropanol rinse. Even though more than 97% optically pure *d*-amphetamine *d*-bitartrate was obtained in cold runs, a recrystallization was applied to all labeled *d*-bitartrates. The *d*-amphetamine-^{14}C *d*-bitartrate was recrystallized from 150 ml. of 91% isopropanol and 13.5 Gm. (57.4% of the *d*-isomer) was obtained. The melting point was 180–181°[4]

[4] Corrected melting points were obtained with a capillary tube apparatus.

TABLE I.—SUCCESSIVE RESOLUTION OF *dl*-AMPHETAMINE-^{14}C

	d-Amphetamine-^{14}C *d*-bitartrate		*l*-Amphetamine-^{14}C *l*-bitartrate		
	Wt., Gm.	mc.	Wt., Gm.	mc.	M.p., °C.
1	13.5	52.6	...	...	180–181
2	...	...	13.5	52.7	180–181.5
3	5.0	19.5	...	...	180–181
4	...	...	4.7	18.3	181–182
5	1.3	5.1	...	...	180–181
6	...	...	1.1	4.3	178–180
7	0.43	1.7	...	...	178–180
Total	20.23	78.9 (86% recovery)	19.2	75.3 (82% recovery)	

(reported 181–182°) and the specific activity was 1.11 mc./mmole. The mother liquors and rinses were combined, and the isopropanol was removed *in vacuo*. The concentrate was made alkaline with 40 ml. of 10 *N* sodium hydroxide and the *l*-rich amphetamine-^{14}C was extracted into ether. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed cautiously on a steam bath. The *l*-rich amphetamine-^{14}C residue was dissolved in 200 ml. of 91% isopropanol. The solution was heated and 17.56 Gm. (117 mmoles) of *l*-tartaric acid was added. Crystallization at 59° was carried out as with the *d*-bitartrate; however, the *l*-bitartrate was not recrystallized. The *l*-amphetamine-^{14}C *l*-bitartrate also weighed 13.50 Gm. (57.4% of the *l*-isomer). The melting point of the *l*-bitartrate was 180–181.5°, and the specific activity was 1.11 mc./mmole. The resolution was continued by crystallization of the *d*-amphetamine-^{14}C *d*-bitartrate from the *d*-rich ^{14}C-amphetamine mother liquors followed by the crystallization of *l*-amphetamine-^{14}C *l*-bitartrate from the *l*-rich ^{14}C-amphetamine mother liquors. A total of seven successive crystallizations gave the results shown in Table I.

The residual *l*-rich ^{14}C-amphetamine after the seventh crystallization had a purity of approximately 60% by vapor phase chromatography.

Racemization of l-Amphetamine-^{14}C.—In order to increase the total amount of *d*-amphetamine-^{14}C *d*-bitartrate, the *l*-amphetamine-^{14}C from 15.41 Gm. (60.4 mc.) of *l*-amphetamine-^{14}C *l*-bitartrate was racemized. The *l*-amphetamine-^{14}C was saturated with ammonia, and 2.5 Gm. of commercial Raney nickel catalyst was added. The reaction mixture was stirred and heated at 110–115° for 3 hr. The racemized ^{14}C-amphetamine was resolved into 16.9 mc. each of *d*-amphetamine-^{14}C *d*-bitartrate and *l*-amphetamine-^{14}C *l*-bitartrate. Weight recoveries of the tartrates indicated that only partial racemization had occurred. Preliminary nonradioactive attempts at racemization showed that extensive decomposition occurred with forcing conditions such as 130°.

d-Amphetamine-7-^{14}C Sulfate.—An aliquot of each of the crystal crops of *d*-amphetamine-^{14}C *d*-bitartrate (total of 24.25 Gm., 94.6 mc.) was combined and a micro-optical rotation determined. The specific rotation of the *d*-bitartrate was $[\alpha]_D^{25}$ + 29.03 (2% in water), and a standard sample gave a specific rotation of +30.19 under the same conditions. The minimum optical purity was therefore 97%.

The specific rotation sample and the remainder of the *d*-amphetamine-^{14}C *d*-tartrate were dissolved in 200 ml. of water and made alkaline by the addition of 27 ml. of 10 *N* sodium hydroxide. The free base which separated was extracted into 200 ml. of ether and dried over anhydrous magnesium sulfate. The ether was removed on a steam bath and the *d*-amphetamine-^{14}C was diluted with 11.66 Gm. of carrier. The diluted *d*-amphetamine-^{14}C (172.7 mmoles) was dissolved in 200 ml. of 91% isopropanol and acidified (pH 6.8) with 86.4 mmoles of a 50% sulfuric acid solution.

The mixture was refluxed and cooled to 5°. The crystalline *d*-amphetamine-^{14}C sulfate was filtered, washed, and dried *in vacuo*. The *d*-amphetamine-^{14}C sulfate weighed 27.01 Gm., and the specific activity was 1.08 mc./mmole (2.92 μc./mg.). An additional 2.73 Gm. was recovered from the mother liquor and drying agent for a total yield of 29.75 Gm. (86.9 mc.).

The identity and radiochemical purity as determined by scanning a chromatogram were satisfactory. The purity of the *d*-amphetamine-^{14}C sulfate was 98.4% by ultraviolet absorption, and the optical rotation was $[\alpha]_D^{25}$ + 22.4.

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