SYNTHESIS OF 5-NITROFURAN-2-[^{14}C]ALDEHYDE DIACETATE AND THE ANTIBACTERIAL AGENT [^{14}C]-NIFUROXAZIDE

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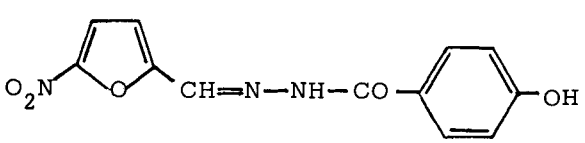
SUMMARY

Furan-2-[^{14}C]carboxylic acid has been prepared in 74% yield by carbonation of 2-furyllithium. Furan-2-[^{14}C]aldehyde was isolated as the diacetate after catalytic reduction of the corresponding acid chloride. Nitration gave 5-nitrofuran-2-[^{14}C]aldehyde diacetate and after hydrolysis to the aldehyde was condensed with 4-hydroxybenzhydrazide to give 5-nitrofuran-2-[^{14}C]-aldehyde 4'-hydroxybenzoylhydrazone, [^{14}C]-nifuroxazide, in an overall radiochemical yield of 15% from barium [^{14}C]-carbonate.

Key words: Carbon-14, Carbonation,
5-nitrofuran-2-aldehyde diacetate,
nifuroxazide.

INTRODUCTION

5-Nitrofuran-2-aldehyde 4'-hydroxybenzoylhydrazone (nifuroxazide) has been shown to possess significant antibacterial activity against numerous gram positive and gram negative bacteria[1].



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Nifuroxazide

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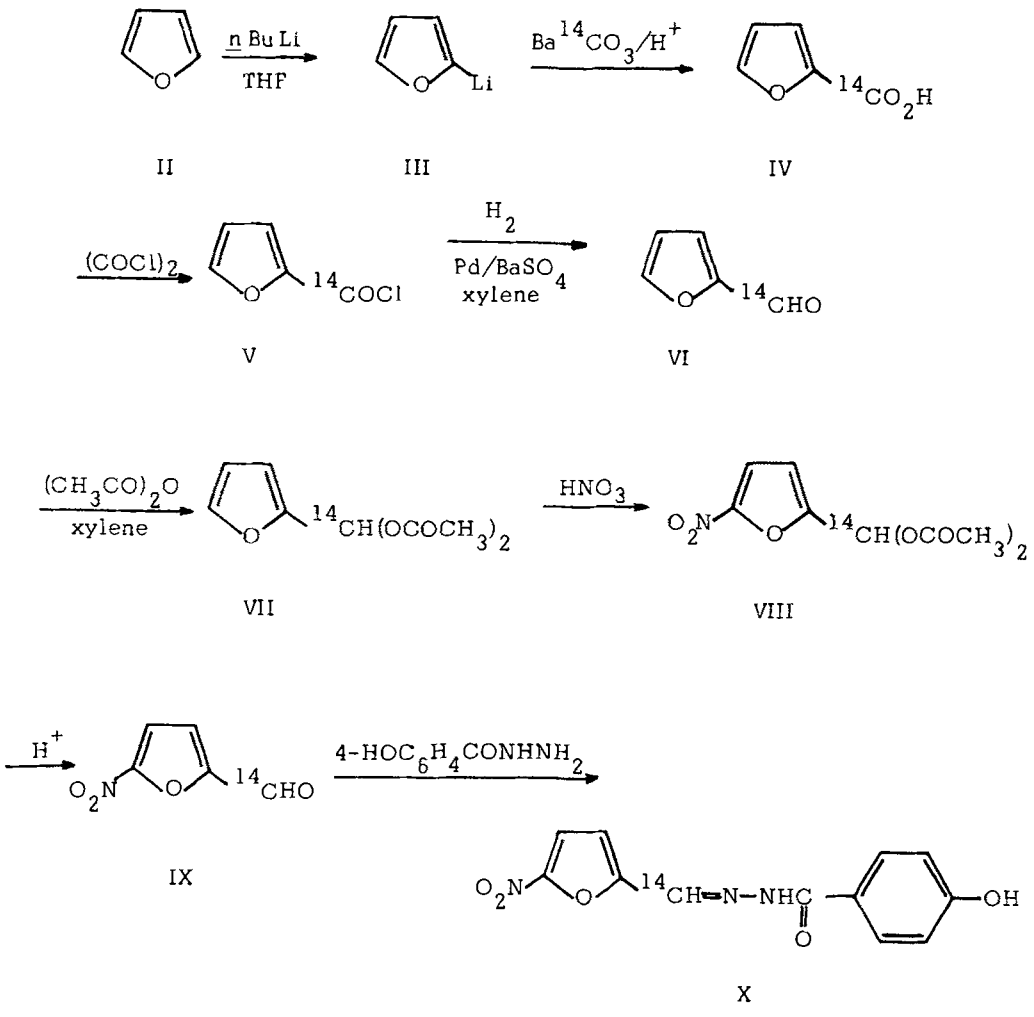
As part of the development of this drug it was necessary to synthesise a radiolabelled form for use in metabolism studies. It was considered that the nitrofurfuryl group was the biologically important part of the molecule and accordingly a synthetic route has been developed with the incorporation of a carbon-14 radiolabel in this group.

An outline of the synthetic route used for [^{14}C]-nifuroxazide (X) is shown in the Scheme 1. The synthesis involved the preparation of 5-nitrofuran-2-[^{14}C]aldehyde which is a precursor in the synthesis of many other well-known pharmacologically active nitrofuran derivatives[2]. 2-Furyllithium (III), prepared from furan (II) and n-butyllithium, was carbonated with [^{14}C]-carbon dioxide to give furan-2-[^{14}C]carboxylic acid (IV) in a 74% radiochemical yield. This acid was converted to the acid chloride (V) with oxalyl chloride. Oxalyl chloride was used in preference to thionyl chloride since this gave a crude acid chloride (V), uncontaminated with sulphur compounds, which could be used in a catalytic reduction without purification. Furan-2-[^{14}C]carboxylic acid chloride (V) was reduced with hydrogen on a palladium-barium sulphate catalyst in refluxing xylene to give furan-2-[^{14}C]aldehyde. The aldehyde could not be isolated efficiently from the xylene solution due to the difficulty in performing fractional distillation on a small scale. However, by a modification of the published synthesis of furan-2-aldehyde diacetate[3] it was possible to prepare the diacetate in a yield of 76% by acetylation of a solution of furan-2-aldehyde in xylene with acetic anhydride. Furan-2-[^{14}C]-aldehyde diacetate (VII) was prepared in an overall radiochemical yield of 68% from furan-2-[^{14}C]carboxylic acid without isolation of the aldehyde. Nitration of furan-2-[^{14}C]aldehyde diacetate (VIII) by the method of Gilman and Wright[4] gave the 5-nitroderivative (VIII) in 38% yield. 5-Nitro-furan-2-[^{14}C]aldehyde (IX) was prepared *in situ* from the diacetate by

Scheme 1


n Bu Li
THF
Li
Ba 14CO3/H+
14CO2H
II
III
IV
(COCl)2
14COCl
H2
Pd/BaSO4
xylene
14CHO
V
VI
(CH3CO)2O
xylene
14CH(OCOCH3)2
HNO3
O2N
14CH(OCOCH3)2
VII
VIII
H+
O2N
14CHO
4-HOC6H4CONHNH2
O2N
14CH=N-NHC
O
OH
IX
X

acid hydrolysis and condensation of the aldehyde with 4-hydroxybenzhydrazide gave [^{14}C]-nifuroxazide (X). The radiochemical purity was greater than 99% as determined by thin-layer chromatography and liquid scintillation counting and the specific activity was 6.8 mCi/mmole.

The overall radiochemical yield of 5-nitrofuran-2-[^{14}C]-aldehyde diacetate from furyllithium and barium [^{14}C]-carbonate was 19%. The corresponding yield of [^{14}C]-nifuroxazide was 15%. This method provides a convenient, economic synthesis of 5-nitrofuran-2-[^{14}C]aldehyde diacetate which is an important intermediate used in the synthesis of many biologically active compounds.

EXPERIMENTAL

Synthesis of [^{14}C]-nifuroxazide

2-Furyllithium (III)

Furan (40 mmoles, 2.72g) was added dropwise to a solution of n-butyllithium (36 mmoles, 2.4M solution in hexane) in tetrahydrofuran (60 ml) at -25°C. The mixture was stirred for a further 4 hr at -15°C and then left to stand overnight at -20°C. Acidimetric titration of this solution showed it to be 0.48M furyllithium.

Furan-2-[^{14}C]carboxylic acid (IV)

2-Furyllithium (ca. 5 mmoles) in tetrahydrofuran was carbonated at -10°C with [^{14}C]-carbon dioxide, prepared from barium [^{14}C]-carbonate (116 mCi, 442mg, 2.2mmoles, Radiochemical Centre, Amersham). The resulting solution was diluted with 5% (v/v) sulphuric acid (25 ml) and extracted with ether (5 x 30 ml). The combined ether extracts were then extracted with 5% (w/v) sodium hydroxide solution (3 x 15 ml) and the ether layer discarded. The alkaline extract was acidified with sulphuric acid, extracted with ether, and the organic phase evaporated to give the crude acid (187mg, 86 mCi, 74%).

Two further carbonations were carried out using 107.2 and 58.1mCi of barium [^{14}C]-carbonate.

The acid obtained from the three carbonations was combined to give a total yield of furan-2-[^{14}C]-carboxylic acid of 610 mg, 209 mCi (74% radiochemical yield).

Furan-2-[^{14}C]carboxylic acid chloride

Furan-2-[^{14}C]carboxylic acid (610 mg, 209 mCi) and non-radioactive acid (1.104 g) were dissolved in dry benzene and then oxalyl chloride (1.5 ml) was added. To initiate the reaction dimethyformamide (10 µl) was added and the resultant mixture stirred at room temperature for 16hr. The excess oxalyl chloride and benzene were removed by evaporation in vacuo to yield a residue of the crude acid chloride (ca. 2g) which was used without purification for the next stage.

Furan-2-[^{14}C]aldehyde

The crude furan-2-[^{14}C]carboxylic acid chloride (ca. 2g) was dissolved in xylene (20 ml) and 5% Pd on $BaSO_4$ (300 mg) added. The mixture was stirred and heated to 140°C while a stream of hydrogen was bubbled through the solution. The reaction was followed by silica gel tlc using benzene as the developing solvent. This showed that there was complete reduction of the acid chloride after 6hr with the formation of a major component corresponding to furan-2-aldehyde. The resultant mixture was cooled and the catalyst filtered off to give a solution of furan-2-[^{14}C]aldehyde in xylene.

Furan-2-[^{14}C]aldehyde diacetate

Concentrated sulphuric acid (0.1 ml) was added to acetic anhydride (102g) and a sample of this solution (3 ml) was cooled to 10°C. Furan-2-[^{14}C]-aldehyde in xylene was added to the cooled solution at such a rate as to

keep the temperature at 15-20°C. The mixture was then allowed to warm to about 35°C and anhydrous sodium acetate (50 mg) was added. The mixture was evaporated to dryness on a rotary film evaporator (bath temperature 45°C). The furan-2-[^{14}C]aldehyde diacetate was distilled off at 138-145°C/ 20 mm. Yield of [^{14}C]-diacetate 2.1 g, 141.75 mCi (68% radiochemical yield from furan-2-[^{14}C]carboxylic acid).

5-Nitrofuran-2-[^{14}C]aldehyde diacetate

Fuming nitric acid (1.9 g, S.G. 1.5) was added dropwise to acetic anhydride (6.1 g) at 0°C. The nitrating mixture was cooled to -15°C and a solution of furan-2-[^{14}C]aldehyde diacetate (2.1 g) in acetic anhydride (2.3 ml) was added slowly so that the temperature did not rise above -5°C. After the addition was complete the reaction mixture was stirred for 3 hr and then poured onto 30 g of ice. Sodium hydroxide (40% w/v) was added with stirring until precipitation of the oil was complete. The product was extracted with chloroform (3 x 20 ml) and the combined extracts were evaporated to give a brown oil to which pyridine (5 ml) was added. After 5 min the reaction mixture was diluted with water (20 ml) and then extracted with chloroform (3 x 15 ml). The combined chloroform extracts were washed with dilute acetic acid and then water and finally evaporated to dryness to give a brown oily solid. Recrystallisation from alcohol-water gave a yellow crystalline solid of 5-nitro-furan-2-[^{14}C]aldehyde diacetate (970 mg, 54.3 mCi, 38.3%).

5-Nitrofuran-2-[^{14}C]aldehyde 4'-hydroxybenzoylhydrazone

5-Nitrofuran-2-[^{14}C]aldehyde diacetate (530 mg, 29.7 mCi) and 5-nitro-furan-2-aldehyde diacetate (530 mg) was added to a mixture of water (1.25 ml), ethanol (1.6 ml) and concentrated sulphuric acid (249 µl) and the resultant mixture heated to 60-70°C until solution was complete. A solution of

4-hydroxybenzhydrazide (632 mg) in a mixture of water (1.35 ml) and concentrated hydrochloric acid (416 µl) was added slowly during 0.5hr. After the addition was complete acetone (3 ml) was added and the resultant mixture heated at reflux for 4hr. The hot mixture was filtered and the bright yellow solid was washed successively with acetone and water, and then dried in a vacuum dessicator to give 5-nitrofuran-2-[^{14}C]aldehyde-4'-hydroxybenzoylhydrazone, [^{14}C]-nifuroxazide (956 mg, 23.6 mCi, 79.7%). The specific activity was 6.8 mCi/mmole, 24.7 µCi/mg. Thin-layer chromatography in ethyl acetate:propan-2-ol:ammonia (45:35:20, v/v) and liquid scintillation counting showed the product to have a radiochemical purity greater than 99%.

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