SYNTHESIS OF ^{14}C-LABELLED FLUPHENAZINE ESTERS

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SUMMARY

Fluphenazine labelled with ^{14}C at the 3-propyl position was prepared. Starting from K^{14}CN, 3-chloropropyl p-toluenesulfonate (7) was synthesized via 3-chloropropionic acid (4) intermediate and coupled with 2-trifluoromethylphenothiazine. The phenothiazine derivative (8) obtained was converted into 1a, from which various long acting esters (1b, 1c, 1d) of labelled fluphenazine were prepared for comparative pharmacokinetic studies.

Key Words: Phenothiazine, Fluphenazine, long acting tranquilizer, ^{14}C-labelling

INTRODUCTION

Yale and coworkers (1) synthesized a number of esters of 4-{3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazine-ethanol (fluphenazine; 1a) searching long acting tranquillizing agents. One of these, the ester with heptanoic acid, was labelled with ^{14}C in the ethyl group, introducing the labelling by 2-bromo-ethanol. Dreyfuss et al. reported the biological disposition and metabolic fate of fluphenazine-^{14}C labelled in the propyl group (2) as well as the excretion and biotransformation of its enanthate ester by the dog (3), but the text is in contradiction with the formula concerning the position of labelling, and the synthesis of the labelled compound does not appear to have been published so far.

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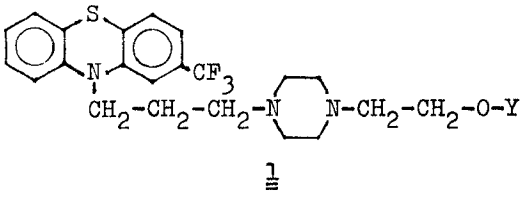

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	Y
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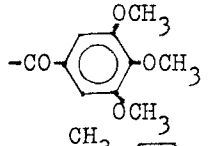
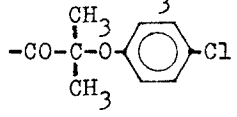
b	-CO-$(CH_2)_8$-CH_3
c	
d	

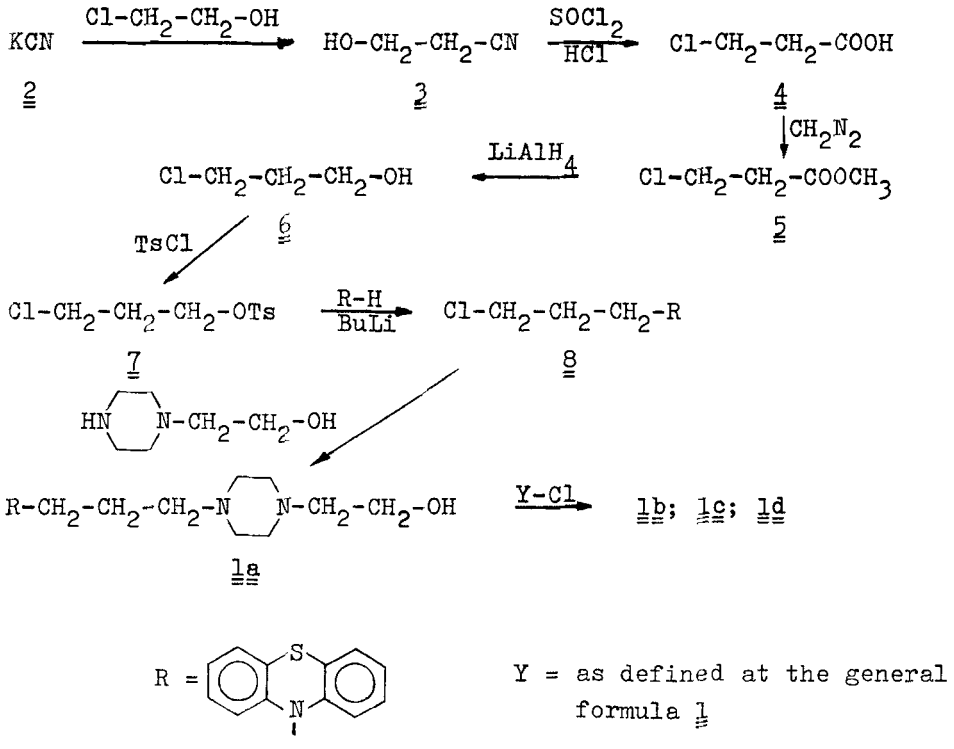
Toldy and coworkers (4) synthesized a number of new compounds of general formula 1 and two of them (1c, 1d) together with the decanoate ester (1b) were selected to be labelled with ^{14}C for comparative pharmacokinetic studies.

DISCUSSION

In the present paper we report the preparation of fluphenazine labelled with ^{14}C at the 3-propyl position, starting from $K^{14}CN$, and its conversion to esters according to the scheme given below.

We are aware of the fact that this sequence of the reaction steps is unfavourable because of incorporating the radioactive starting material at the beginning of the synthesis. Previously we investigated two other synthesis routes, which had been widely used in the phenothiazine chemistry; both of them, however, proved to be unsuitable for labelling. The first one was based on an N-acylated 2-trifluoromethylphenothiazine intermediate, but on reducing it with $LiAlH_4$, 2-trifluoromethylphenothiazine was obtained instead of the alkyl derivative required. In the second case 2-(2-trifluoromethylphenothiazin-10-yl)ethyl chloride was reacted with KCN. The formation of 3-(2-trifluoromethylphenothiazin-10-yl)-propionitrile could be detected by TLC, but in the presence of cyanide ion the reversal of cyanoethylation took place resulting in 2-trifluoromethylphenothiazine and acrylonitrile.

Scheme



The procedure for synthesis of labelled 1a involved the preparation of 3-chloro-1-propanol-1-^{14}C starting from K^{14}CN * which was carried out essentially as described (6), with the exception that hydracrylonitrile was converted into 3-chloropropionic acid by the method of Yakubovich and Merkulova (7). 3-Chloropropyl p-toluenesulfonate was prepared in accordance with Rossander and Marvel (8), and coupled with 2-trifluoromethyl-10-lithio-phenothiazine in a manner analogous to preparation of 10-phenothiazinyl-propyl chloride described by Gilman and Shirley (9). The compound obtained was then converted into 1a according to Toldy et al. (10), and the latter gave 1b, 1c and 1d respectively, on treatment with the corresponding acyl chloride.

* K^{14}CN was prepared by Bánfi's method (5).

EXPERIMENTAL

Melting points are determined on a Boëtius hot stage and are uncorrected. Radioactivities were measured with a Packard TRI-CARB liquid scintillation spectrometer. TLC was carried out on silica gel $HF_{254-360}$ (Merck) and a Berthold TLC scanner was used for evaluation. All evaporations were carried out under reduced pressure.

3-Chloropropionic-1-^{14}C acid (4)

A solution of 0.419 g (6.43 mmole) of $K^{14}CN$ (13.31 GBq, 2.07 GBq/mmole) and 1.302 g (13.57 mmole) inactive KCN in water (4 ml) was added dropwise to a boiling solution of 3.22 g (40 mmole) of freshly distilled 2-chloroethanol in EtOH (16 ml). The mixture was refluxed for 5 hours, then left to stand overnight, and diluted with acetone (40 ml). The solution was dried over a large amount of anhydrous $MgSO_4$, which was filtered off and washed with acetone (2x10 ml). The filtrate was evaporated and the residue was distilled to give 1.415 g of colourless oil. B.p. 102-120°C at 12 Torr or 1.6 kPa. To this oil, thionyl chloride (2 ml) was added dropwise under cooling, and the mixture was stirred for 30 min. at 40°C. After cooling, 14 ml of conc. HCl was added, and the mixture was refluxed for 3 hours, while HCl gas was bubbled through the liquid. The solution was diluted with water (14 ml) and extracted with ether (6x15 ml). The ethereal solution was dried over anhydrous $MgSO_4$, evaporated, and the residue was sublimed in vacuum at 0.4 Torr or 53 Pa to give 1.576 g (14.5 mmole; 72.5 %) pure 3-chloropropionic acid.

3-Chloropropyl-1-^{14}C p-toluenesulfonate (7)

1.576 g (14.5 mmole) 3-chloropropionic-1-^{14}C acid was dissolved in ether, and freshly prepared ethereal diazomethane solution was added at 0°C until the yellow colour persisted. After 3 hours the solution was dried over anhydrous $MgSO_4$ and the ether was distilled off through a short column. The residue was taken up in dry

ether (40 ml) and added dropwise to a solution of 0.600 g (16.0 mmole) of $LiAlH_4$ at -30°C. After being stirred for 2 hours at 0°C the mixture was cooled to -15°C and hydrolysed by addition of 5 N HCl (10 ml). The mixture was then continuously extracted with ether for 14 hours, the ethereal solution was dried over anhydrous $MgSO_4$, and the ether was distilled through a short column. To the residue 5.529 g (29 mmole) of p-toluenesulfonyl chloride and 5 N NaOH (12 ml) was added, and the mixture was stirred vigorously for 4 hours. Then it was diluted with water (12 ml), and extracted with ether (4x20 ml). The combined ethereal extract was washed successively with 5 N NaOH solution (10 ml) and water (2x10 ml), dried over anhydrous $MgSO_4$, evaporated, and the residue was distilled in vacuum. B.p. 170-190°C at 0.4 Torr or 53 Pa. Yield: 1.755 g (7.05 mmol, 48.6 %) of yellowish oil. The residue was mixed with 0.870 g of unlabelled 7 and distilled in vacuum to give a second crop (0.758 g).

3-[2-(Trifluoromethyl)phenothiazin-10-yl]-3-^{14}C-propyl chloride (8)

2.5 g (10.1 mmole) of the above 7 (calculated activity: 4.69 GBq, 464 MBq/mmole) was dissolved in anhydrous ether (50 ml) and added to an ethereal solution (100 ml) of 5.75 g (15 mmole) of 2-trifluoromethylphenothiazine. To this mixture a solution of n-butyllithium in n-hexane (9.2 ml) containing 20 mmole of organometallic compound was added slowly under nitrogen, and the mixture was stirred for 20 hours at room temperature. After cooling, the mixture was hydrolysed by slow addition of water (60 ml). The ether layer was separated, dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by chromatography on silica gel using cyclohexane/chloroform 4:1 eluent. Yield: 2.486 g (7.24 mmole).

4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]-3-^{14}C-propyl}-1-piperazineethanol (Fluphenazine-^{14}C; 1a)

To a stirred solution of the above 8 (2.486 g, 7.24 mmole) in 2-butanone (50 ml) 1.086 g (7.24 mmole) of sodium iodide and

3.770 g (29 mmole) of 1-piperazineethanol were added, and the mixture was refluxed for 12 hours. The solution was evaporated and the residue was taken up in 1 N HCl (100 ml) and washed with ether (2x20 ml). The aqueous solution was made alkaline by addition of saturated Na_2CO_3 solution and extracted with ether (4x20 ml). The combined ethereal extract was dried over anhydrous $MgSO_4$ and evaporated. The residue (2.590 g) was dissolved in dry benzene (30 ml) and 1.393 g (12 mmole) of maleic acid dissolved in boiling 2-propanol (20 ml) was added to the solution with stirring. After standing overnight the solid was filtered off and recrystallized from 50 ml of anhydrous 2-propanol to give 3.368 g (5.03 mmole, 69.5 %) of pure maleate (checked by TLC using ethyl acetate/ethanol/water 10:3:2 solvent system). M.p. 158-160°C; a mixture m.p. with authentic compound was 158-160°C. Total activity: 2.23 GBq at a specific activity of 443.0 MBq/mmole. Overall radiochemical yield: 16.7 % based on $K^{14}CN$.

Fluphenazine-^{14}C decanoate ester (1b)

0.560 g (0.85 mmole) of above purified maleate of 1a was suspended in ether (30 ml) and carefully shaken with a solution of 1.5 g of $NaHCO_3$ and 0.68 g of NaCl in water (5 ml) until no solid remained. The organic phase was separated, dried over anhydrous $MgSO_4$ and evaporated. To the residue 0.39 g (2.05 mmole) of decanoyl chloride dissolved in dry chloroform (10 ml) was added and the mixture was refluxed for 12 hours. After cooling, the solution was poured into saturated $NaHCO_3$ solution (20 ml), the mixture was shaken for 10 min. and the organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated. To this residue 0.197 g (1.7 mmole) of fumaric acid dissolved in EtOH (15 ml) was added, the solution was evaporated to dryness, and the remaining solid was washed with dry ether (3x10 ml). After the third portion of ether was decanted, an additional portion of ether (20 ml) was added and the suspension was shaken with a saturated solution of $NaHCO_3$

until no solid remained. The ethereal solution was separated, dried over anhydrous $MgSO_4$ and evaporated to give 0.397 g (0.67 mmole, 79.1 %) of decanoate ester, which was shown to be identical with the authentic material and homogeneous by radiochromatography using ethyl acetate/ethanol/water 10:3:1 solvent system for TLC.

Fluphenazine-^{14}C 3,4,5-trimethoxybenzoate ester (1c)

1a base was prepared as described above from 1.138 g (1.70 mmole) of pure maleate, and it was added to a solution of 3,4,5-trimethoxybenzoyl chloride (0.945 g, 4.1 mmole) in dry chloroform (20 ml). The mixture was refluxed for 15 hours and after cooling was poured into saturated $NaHCO_3$ solution (40 ml). The mixture was shaken for 10 min., the organic phase was separated, dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel using ethyl acetate/ethanol 3:2 eluent. After evaporation, the homogeneous compound was dissolved in MeOH (10 ml) and 3 ml of this solution was evaporated to give 0.317 g (0.5 mmole) of pure ester; 7.0 ml of the methanolic solution was diluted with 13 ml of MeOH, and 0.278 g (2.4 mmole) of fumaric acid was added. The mixture was heated until a clear solution was obtained, then cooled, and the precipitated solid was filtered off, washed with cold MeOH (2x2 ml) and dried; 0.859 g (0.995 mmole) of fumarate of 1c was obtained as white crystalline product. M.p. 175-177°C.

Fluphenazine-^{14}C 4-chlorophenoxy-isobutyrate ester (1d)

To a mixture of 1a base prepared from 1.400 g (2.08 mmole) of pure maleate, 0.75 ml of triethylamine and 1,2-dichloroethane (8.0 ml), a solution of 0.630 g (2.7 mmole) of 4-chlorophenoxy-isobutyryl chloride in dichloroethane (1 ml) was added dropwise at 0°C. After being stirred for one hour, the mixture was refluxed for 10 hours, cooled and the solid was filtered off. The filtrate was washed with water (10 ml), dried and evaporated. The residue was chromatographed on silica gel using ethyl acetate/

ethanol 3:2 eluent, to give after evaporation 1.085 g (1.71 mmole) of semi-solid homogeneous compound.

0.477 g (0.76 mmole) of this compound was converted into fumarate by adding 0.196 g (1.68 mmole) of fumaric acid dissolved in a hot mixture of ethanol (2.2 ml) and water (2.0 ml). After cooling, a white crystalline product (the fumarate of 1d) precipitated, which was filtered off, washed with cold EtOH and dried. Yield: 0.513 g (0.59 mmole). M.p. 166-167°C.

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