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A rapid and convenient method for the synthesis of labelled tertiary amines

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SUMMARY

A rapid and simple procedure is described for synthesizing a wide range of tritium and ^{14}C-labelled tertiary amines in millimolar quantities with good yields by melting together alkylhalides and secondary amines.

1. — INTRODUCTION.

To study the excretion, the distribution and the metabolism of various drugs [1-5] (Table I), each was specifically labelled with tritium or ^{14}C. The last step in the synthesis of the tertiary amine is the reaction of an alkylhalide with a secondary amine.

The alkylhalide was selected for labelling as this permitted the synthesis of several different drugs from the same precursor halide.

These tertiary amines are commonly synthesized by refluxing the secondary amines for 48-60 hours with excess alkylhalide in methylisobutylketone with KI and anhydrous Na_2CO_3.

This practice could not be adopted for two reasons. Firstly, it would have been uneconomic to use an expensive labelled reagent in excess when the excess cannot be recovered. Secondly, when refluxing for a long time in millimolar quantities, darkly coloured products are formed which can only be purified with difficulty and at a loss rate that is prohibitively high.

A search was therefore made for an alternative method of synthesizing such tertiary amines, and haloperidol was selected for the initial investigation.

These studies form the basis of the present paper.

2. — *Methods.*

Choice of an HHal scavenger is greatly restricted as γ-chloro-4-fluoro-2-tritio butyrophenone, which is normally used in the synthesis, readily loses HCl in the presence of strong bases and is converted to cyclopropyl-4-fluoro-2-tritio phenylketone. The following scavengers were tried : anhydrous

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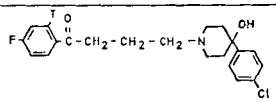
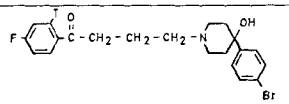
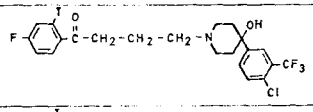
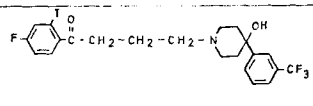
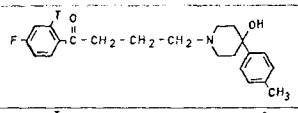
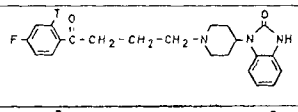
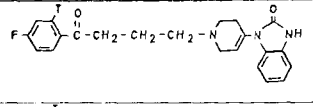
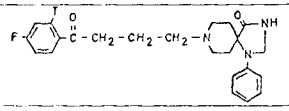
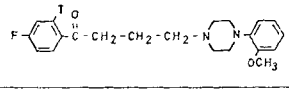
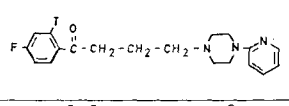
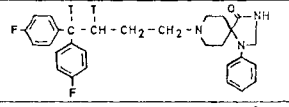
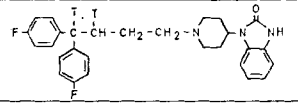
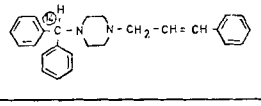
R 1625	HALOPERIDOL	
R 11.333	BROMOPERIDOL	
R 9298	CLOFLUPEROL	
R 2498	TRIFLUPERIDOL	
R 1658	MOPERONE	
R 4584	BENPERIDOL	
R 4749	DROPERIDOL	
R 5147	SPIPERONE	
R 2028	FLUANISONE	
R 1929	AZAPERONE	
R 6218	FLUSPIRILENE	
R 6238	PIMOZIDE	
R 516	CINNARIZINE	

TABLE I. Serial numbers, generic names and chemical structures of the synthesised drugs.

K_2CO_3, anhydrous Na_2CO_3 in the presence of drierite, triethanol amine, diisopropylamine and the secondary amine itself.

The following solvents were used for 1-8 hours reaction (temperature in brackets) : carbontetrachloride (77 °C), chloroform (61 °C), anisole (155 °C), dioxane (40 °C, 101 ° C), *n*-butanol (80° C, 118° C), dimethylformamide (80° C) and dimethylsulfoxide (40° C).

The yield was similar in most cases, rarely exceeding 40 % except for dioxane where it was 60 % when the alkylhalide and the secondary amine were in a molar ratio of 1 : 2.

The HCl yield was always quantitative, indicating that the formation of cyclopropyl-4-fluorophenyl ketone was a faster reaction than the formation of the tertiary amine.

Better yields were subsequently obtained by omitting the solvent completely, and melting the alkylhalide and the secondary amine together in a molar ratio of 1 : 2, in the presence of a trace of KI. After preliminary experiments in which rate and duration of heating and final temperature were varied, the best results (75-85 % yield) were obtained as described below (3.5).

3. — Results.

3.1. — m-*tritio-fluorobenzene.*

Specifically labelled *m*-tritio-fluorobenzene was synthesized at the C. E. N. Mol Belgium by catalytic dehalogenation of *m*-fluoro-bromobenzene with tritium gas.

6 ml *m*-fluoro-bromobenzene and 200 mg of 10 % Pd/C under 15 C tritium gas absorbed 2 C tritium in 24 hours. After diluting with unlabelled fluorobenzene and drying over $CaCl_2$, the mixture was distilled at atmospheric pressure. The crude *m*-tritio-fluorobenzene was redistilled twice and yielded 2.69 g pure *m*-tritio-fluorobenzene with a specific activity of 25 mC/mM.

3.2. — γ-*chloro*-4-*fluoro*-2-*tritio butyrophenone.*

2.6 ml *m*-tritio-fluorobenzene was mixed with 3.6 g of powdered anhydrous $AlCl_3$ at 0° C. 2.94 ml 4-chlorobutyroylchloride was added slowly and the mixture cooled and stirred throughout. Crystallisation occurred after about one hour, 10 ml of carbontetrachloride was added and cooling and stirring continued for another hour.

The complex was decomposed with ice and conc. HCl (2 : 1) and the γ-chloro-4-fluoro-2-tritio butyrophenone extracted with carbon tetrachloride. The combined organic layers were washed with water. $NaHCO_3$ solution and water again. They were then dried over $MgSO_4$ and filtrated.

After evaporation to dryness *in vacuo*, the yield was 4.07 g (75 %) of crude γ-chloro-4-fluoro-2-tritio butyrophenone as a faintly yellow-coloured

oil. It was possible to purify the crude product by distillation ($bp_{12\,mm}$ = 121° C), giving a very small fore-run of acylchloride.

Alternatively it could be used directly for N-alkylation, but the tertiary amine yield was lower (ca 65 %) than for the distilled product (75-85 %).

3.3. — 4-4, *bis* p-*fluorophenyl* 3.4 *ditritio-butyrylchloride.*

0.7 ml 1.1 bis *p*-fluorophenyl-4-chlorobutene-1.2 was tritiated at C. E. N. using 40 C tritiumgas with 40 mg of 10 % Pd/C as a catalyst.

No solvent was used and after a 24 hour exposure the tritium gas was replaced with hydrogen. Fresh Pd/C, suspended in isopropyl alcohol was added and the hydrogenation was carried to completion. After filtration the isopropylalcohol was evaporated off *in vacuo.*

The residual 4.4 bis *p*-fluorophenyl-3.4 ditritio butyrylchloride (spec. act. 1.2 C/mM) was diluted with dry benzene for storage, without purification by distillation.

3.4. — *^{14}C-benzhydrylbromide.*

A mixture of 184 mg ^{14}C-benzhydrol (methylene ^{14}C, spec. act. 1 mC/mM) and 130 mg acetylbromide in 3 ml dry benzene, was refluxed for 45 minutes. After cooling, the benzene, acetic acid and excess acetyl bromide were evaporated off, initially by warming under a current of nitrogen and finally *in vacuo.* The ^{14}C-benzhydrylbromide (yield 90 %) could be used immediately for the N-alkylation.

3.5. — *General procedure for the N-alkylation.*

1 mM of secondary amine, powdered in a mortar with a few crystals of KI was added to 0.5 mM alkylhalide in a pearshaped 5 ml flask. The stoppered vessel was placed with the tip in an oil-bath. After 15 minutes at room temperature, the bath was heated slowly until the mass began to shrink. After about 15 minutes at this temperature the mass melted and crystallisation of the HCl salt of the secondary amine often began spontaneously or could be induced by seeding the melt. The bath temperature was then gradually raised to 130-150° C over about 15 minutes.

After 5 minutes at this temperature the reaction mixture was cooled and distributed between chloroform and water. The latter was again extracted with chloroform and the combined organic layers were washed once with water. After drying, the chloroform was evaporated, firstly under a current of nitrogen and secondly *in vacuo.*

The oily residue was made to crystallise under a small volume of secondary butylalcohol or isopropylalcohol. The product was recrystallised from isopropyl alcohol or absolute alcohol.

After one crystallisation the product was undistinguishable from the pure drug by thin layer chromatography and did not contain radiochemical impurities.

With high melting secondary amines, good results were obtained by a combined reflux-melting procedure. After reflux of the reactants in peroxide-free, dry dioxane for 1-2 hours, the solvent was evaporated off at reflux temperature under a current of nitrogen. The temperature was then raised quickly to 140° C. After 5 minutes the mixture was cooled and extracted according to the General Procedure.

For exothermic reactions, as for example with cinnarizine, brief heating at moderate temperatures (60-70° C) was sufficient for good yields of the drug.

The melting procedure can be successfully applied in miniscale synthesis (1-2 mM) and when the reactants do not decompose or evaporate appreciably during the melting process. It is a simple, rapid and reliable method of synthesizing a wide range of labelled drugs at good yields in a short time.

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REFERENCES

1. SOUDIJN, W., VAN WIJNGAARDEN, I. and ALLEWIJN, F. — *European J. Pharmacol.*, **1** : 47 (1967).
2. BRAUN, G. A., POOS, G. I. and SOUDIJN, W. — *European J. Pharmacol.*, **1** : 58 (1967).
3. JANSSEN, P. A. J. and ALLEWIJN, F. — *Arzneimittel-Forsch* **18** : 279 (1968).
4. JANSSEN, P. A. J., SOUDIJN, W., VAN WIJNGAARDEN, I. and DRESSE, A. — *Arzneimittel-Forsch* **18** : 282 (1968).
5. SOUDIJN, W. and VAN WIJNGAARDEN, I. — *Life Sci.* **7** : 231 (1968).