

SYNTHESIS OF [¹⁴C] STANZOLOL

D. R. Duncan and D. Johnston

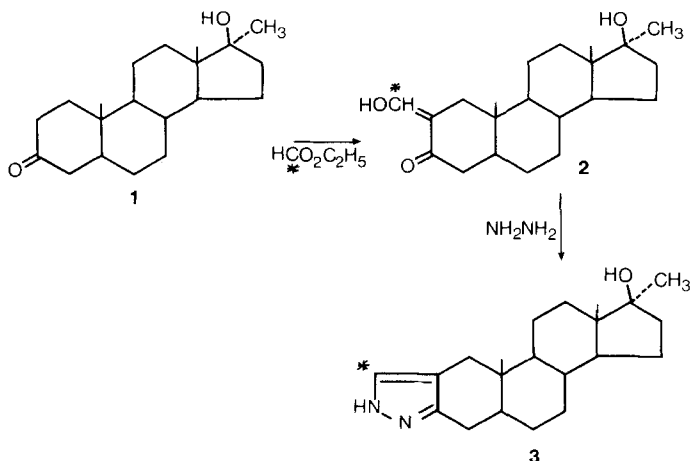
Sterling-Winthrop Research and Development Division, Alnwick, Northumberland.

SUMMARY

The anabolic steroidal pyrazole derivative stanozolol has been labelled with ¹⁴C in the pyrazole ring. The overall chemical yield of the synthesis was 62%.

INTRODUCTION

Stanozolol¹ (17 α -methyl-2'H - 5 α -androst-2-eno [3,2c] - pyrazol-17 β -ol) is an anabolic steroid well established in the management of such disorders as post menopausal and senile osteoporosis and in the treatment of lipodermato-sclerosis. As part of our interest in the drug^{2,3} we required a quantity of ¹⁴C-labelled material for use in metabolic studies. The method used involved firstly the reaction of 17 α -methylandrostanolone (1) with ethyl [¹⁴C] formate to give (2) followed by reaction of this intermediate with hydrazine hydrate to give the desired product (3) as shown in the synthetic route below.



EXPERIMENTAL

Ethyl [¹⁴C] formate (10 m Ci) was obtained from Amersham INTERNATIONAL plc with a nominal activity of 724 mCi/g.

[¹⁴C]Stanozolol

To a solution of 17 α -methylandrostan-17 β -ol-3-one (5 g, 16.4 mmol) in dry freshly distilled pyridine (50 ml) was cautiously added, with stirring, sodium hydride (50% dispersion in oil, 3.78 g). The mixture was cooled to 0°C and ethyl formate (0.7 ml) and ethyl [¹⁴C]formate (10 mCi) were added, the containers being washed into the reaction vessel with dry freshly distilled pyridine (10 ml) and ethyl formate (0.7 ml). The reaction mixture was stirred at 0°C for 75 min under a phosphorus pentoxide trap after which additional ethyl formate (1.4 ml) was added and the reaction mixture was allowed to warm to room temperature and left to stand for 24 h.

The reaction mixture was cooled in an ice water bath and distilled water (100 ml) was added cautiously. The solution was made just acid by the addition of concentrated hydrochloric acid and allowed to stir for 1 h. The yellow crystalline solid which separated was collected by filtration, washed with distilled water until the washings were neutral and then dried in vacuo. The crude hydroxymethylene compound (2) was dissolved in absolute ethanol (150 ml) and hydrazine hydrate (1.81 g) added. The solution was heated under reflux for 6 h. treated with charcoal (0.5 g) and then heated under reflux for a further 15 min. The charcoal was removed by filtration and the solution was concentrated under reduced pressure to give the crude product. Recrystallisation of this solid from absolute ethanol gave [¹⁴C]stanozolol with a weight of 3.31 g (62%) m.p. 234.8 - 238.2°C. The specific activity of the product was 1.53 mCi/g.

The chemical and radiochemical purity of at least 99% was confirmed by TLC on silica gel using chloroform/methanol (9:1 v/v) and chloroform/ethyl acetate (1:1 v/v). The product migrated as a single spot in both of these systems (Rf 0.42 and 0.25 respectively) and ∞ -chromatographed with an authenticated sample of stanozolol.

REFERENCES

1. R.O. Clinton, A.J. Manson, F.W. Stonner, A.L. Beyler, G.O. Potts and A. Arnold
J. Amer Chem. Soc. 81, 1513 (1959)
2. O. Lantto, I. Björkhem, H. Ek and D. Johnston,
J. Steroid Biochem. 14, 721 (1981)
3. K. Henderson and D. Johnston in press.