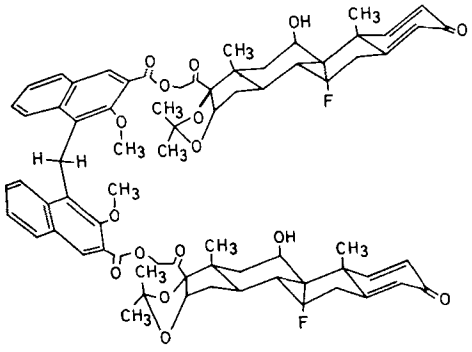
SYNTHESIS OF ^{3}H-LABELLED FLUPAMESONE

V. RIMBAU AND J. FORN
DEPARTMENT OF RADIOISOTOPES, PHARMACOKINETICS AND METABOLISM
J. URIACH & CÍA. S.A. DECANO BAHÍ, 59 - BARCELONA.26 - SPAIN

INTRODUCTION

4-4'-Methylene-bis-[(9α-fluor-11β,21-dihydroxy--16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione) 3-methoxy-2-naphthoate] (flupamesone) is a triamcinolone derivative with a metembonic bridge between two steroid radicals. Its molecular structure is :



Flupamesone has a high molecular weight and a very poor solubility in polar solvents (1). These properties explain its long duration in skin (2) and the absence of systemic effects (3-7). In man, the amount of flupamesone eliminated in urine after topical application is very low (8).

Experimental findings in pigs showed a good penetration of the drug into the skin (2). These results are consistent with a very slow removing of flupamesone from the skin layers. However, percutaneous absorption studies with other fluorinated corticoids have shown that the penetration rate is unpredictable (9, 10). It depends on factors such as molecular size

0362-4803/82/060721-04$01.00

Received December 10, 1981

and liposolubility of the corticoid, stratum corneum thickness, hydration of the skin, etc (11).

In a previous study (8), flupamesone had been labelled at random with tritium by heterogeneous catalytic interchange. The crude obtained by this method presented an extensive radiolysis, and the isolation of ^{3}H-flupamesone was difficult and gave a very low yield. We have developed a method to prepare ^{3}H-labelled flupamesone based on the industrial procedure for the preparation of this drug. This method is much more satisfactory than the one using catalytic interchange ; moreover, it gives a compound with physicochemical properties similar to those of the commercially available product and, consequently, more adequate for pharmacokinetic studies.

EXPERIMENTAL

1. ANALYTICAL METHODS

Thin layer chromatography (TLC) was conducted with precoated silica gel glass plates (E. Merck) and solvent systems :

a) ethylacetate-cyclohexane (10 : 1)
b) ethylacetate-chloroform-water (85 : 15 : 1)
c) chloroform-methanol-water (180 : 15 : 1)

Radiolabelled zones were visualized by autoradiography with Agfa X-ray film. The radiochemical purity of ^{3}H-labelled flupamesone was estimated by liquid scintillation counting of the silica scraped from the plates. The chemical purity was tested by U.V. absorption in methylene chloride (λ_1=340 nm; λ_2=290 nm; λ_3=280 nm) and by I.R. spectrophotometry. Melting points are uncorrected.

2. SYNTHESIS

2.1. Dimethoxypamoyl chloride

In a screw capped Sovirel type centrifugation tube (34 x 110 mm, 50 ml), attached through a Sovirel point (SVL-30) to a condenser, the upper end of which is protected with a calcium chloride drying tube, 1 g of dimethoxypamoic acid is refluxed with 3,1 ml of freshly distilled thionyl choride for 2,75 hours. The excess of Cl_2SO is eliminated in vacuum and the residue dissolved in 4 ml of boiling anhydrous benzene. After a new evaporation to dryness under reduced pressure, the crude is recrystallized from 4 ml of anhydrous benzene and the solid separated by centrifugation. After removing the benzene and drying, 0.90 g (yield 83%) of dimethoxypamoyl chloride are obtained as a yellow solid, m.p. 177-178° C.

2.2. ^{3}H-flupamesone

1 mCi of $\left[1,2,4\ (n)\text{-}^3H\right]$ Triamcinolone acetonide (Amersham International, Amersham) and 0.5 g of cold triamcinolone acetonide were dissolved in ethanol. The solvent was removed under stream of dry nitrogen at room temperature, and 0.40 g of dimethoxypamoyl chloride and 3 ml of pyridine were added. The mixture was vigorously stirred with a magnetic bar and heated at 50-55° C during 3 hours. Afterwards, 4 ml added of 96° ethanol and solid formed was separated by centrifugation and washed with 5 ml of 96° ethanol and 5 ml of methanol. The ^{3}H-flupamesone was collected by centrifugation and dried under vacuum. The yield was 0.59 g (82%) of a white solid, m.p. 235°-237° C. U.V. and I.R. spectra corresponded to those of standard flupamesone. TLC and scintillation counting indicated that the radiochemical purity was superior to 99%. The specific activity was 1.67 mCi/mM, representing an overall radiochemical yield of 79%.

REFERENCES

1. Bachs, J. and Rimbau, V., Drugs of Today, 11 (8), 311 (1975).

2. Rimbau, V. and Lleonart, F., Arzneim. Forsch., 25, 1040 (1975).

3. Corominas, F. and Goday, A., Actual. Dermatol., 14 (4), 21 (1974).

4. Rodriguez Moreno, T., and Rodriguez Cañas, T., Rev. Clín. Esp., 142 (3), 255 (1976).

5. Rodriguez Moreno, T., Rodriguez Cañas, T. and Morell, J., Curr. Ther. Res., 21, 183 (1977).

6. Gajate, A., Rev. Clín. Esp., 144 (4), 287 (1977).

7. Ferrandiz, L., Rev. Clín. Esp., 149 (5), 495 (1978).

8. Rimbau, V. and Forn, J., Europ. J. Drug Metab. Pharmacokin., 1, 206 (1976).

9. Lewis, I.D., Cameron, B.D., Hawkins, D.R., Chasseaud, L.F. and Franklin, E.R., Arzneim. Forsch., 25, 1646 (1975).

10. James, M., Marty, J.P. and Wepierre, J., Europ. J. Drug Metab. Pharmacokin., 1, 69 (1976).

11. Rimbau, V., Antol. Dermatol., 4 (4), 11 (1974)