SYNTHESIS OF ^{3}H-LABELLED DL-TETRAHYDROPALMATINE METHANE SULFONATE (12-^{3}H).

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Tetrahydropalmatine (2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo-[a,g]-quinolizine) (THP) has been found to have analgetic and sedative effect[1,2]. Tetrahydropalmatine methane sulfonate (THP-MS), which is soluble in water, is interesting in application as a tranquilizer.

In order to obtain detailed knowledge of the biotransformation of THP-MS in animals, radioactive THP-MS was required. The present paper is concerned with the synthesis of ^{3}H-labelled THP-MS.

THP was brominated with bromine in acetic acid. The i.r. and n.m.r. spectra of the brominated THP was identical with that of 2,3,9,10-tetramethoxy-12-bromo-5,6,13,13a-tetrahydro-8H-dibenzo-[a,g]-quinolizine (THP-Br) reported by Kametani and Ihara[3]; calcd. for $C_{21}H_{24}O_4NBr$: C,58.07; H,5.57; N,3.22%, Found: C,58.26; H,5.73; N,3.40%, m.p. 158-9°C (lit. 161-2°C[3], 162°C[4]).

100 mg of THP-Br in 20 ml of methanol was reduced by tritium (5 Ci) and then hydrogen gas in the presence of 10 mg of 10% palladium on charcoal under atmospheric pressure at room temperature. After removal of the catalyst, the filtrate was evaporated in vacuo. The pale yellow crystals obtained were dissolved in methanol and evaporated 3 times to remove the exchangeable tritium. The product and tetrahydropalmatine hydrobromide (THP-HBr) were indistinguishable by thin-layer chromatography, as shown in Fig. 1.

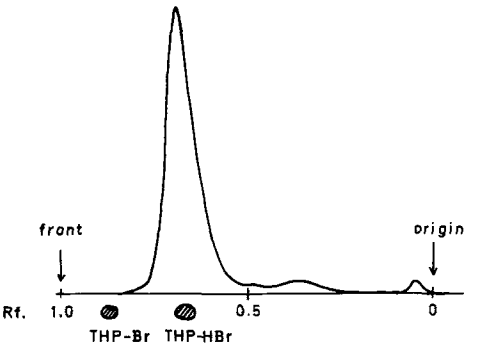

Fig. 1. Radioscan of thin-layer chromatography of ^{3}H-THP-HBr

Thin-layer chromatography : Kieselgel G plate (Merk), (0.25 mm thick); solvent system, $CHCl_3$-MeOH (30 : 1); Dragendorff reagent for detection.
Radio-scanner : Aloka thin-layer chromatogram scanner model TLC-2B

A solution of ^{3}THP-HBr in 30 ml of water was made alkaline (pH 10) with NH_4OH and extracted with 60 ml of chloroform 3 times. The chloroform solution was washed with water, dried with anhydrous Na_2SO_4 and then evaporated in vacuo. The admixture of the residual gum with 120 mg of the authentic THP was recrystallized from methanol.

0.03 ml of methane sulfonic acid, anhydrous, was added to a suspension of 98.0 mg of ^{3}H-THP in 2 ml of isopropanol under stirring at room temperature. After 20 minutes, the solution was left in the cold chamber ; a pale yellow solid then precipitated. The separated solid was recrystallized twice from a mixture of methanol and ethylacetate; 64.3 mg of ^{3}H-THP-MS was obtained as colourless needles, m.p. 226-230°C, 2.35 mCi/mg. The melting point in admixture with the authentic sample, THP-MS, was 226 -230°C.

The product was also recognized as pure ^{3}H-THP-MS by means of radioscans of thin-layer chromatography (Fig. 2).

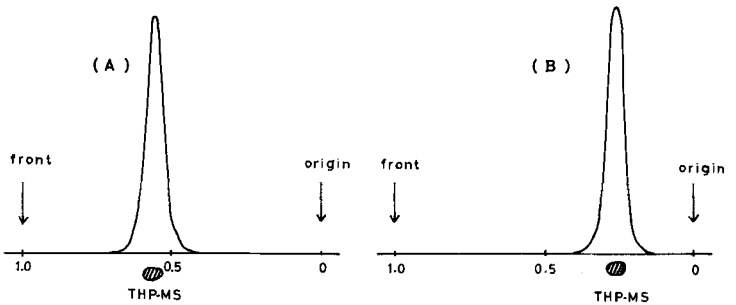

Fig. 2. Radioscans of thin-layer chromatography of ^{3}H-THP-MS

Solvent system : upper phase of n-BuOH - AcOH - H_2O (4:1:5), (A) ; $CHCl_3$-MeOH (30:1), (B)

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