The Preparation of ^{2}H- and ^{3}H- Tertiary Amines. Catalytic Hydrogenation in the Presence of the N-Cyclopropylmethyl Group.

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During the study of the pharmacology and metabolism of the series of oripavine analgesics (1) methods for labelling these compounds have been developed and reported [1]. Introduction of an N-cyclopropylmethyl function into an analgesic is a frequently used method of increasing the narcotic antagonist character and hence such functionalisation is common [2]. A typical example of such a compound is buprenorphine (1; R_1 = CH_2·c-C_3H_5, R_2 = ^{t}Bu) a partial agonist which has a low dependence liability in animals [3].

As previously reported [1], the method of choice for the labelling of these compounds is the catalytic hydrogenation of the readily synthesised enamines (2) with tritium gas. Reductive ring opening of the cyclopropane ring is well documented [4] and this method was not considered generally applicable to compounds with N-cyclopropylmethyl substitution, especially as the ring opened butyl analogues (1; R_1 = ^{n}Bu or ^{s}Bu, R_2 = ^{t}Bu) are chromatographically very similar to the parent cyclopropylmethyl compound.

In order to investigate the preparation of labelled buprenorphine under catalytic hydrogenation conditions, the products of the reaction of the precursor (2; R_1 = CH_2·c-C_3H_5, R_2 = ^{t}Bu) with deuterium gas were examined by mass spectrometry.

When a solution of 15,16-didehydrobuprenorphine (2; $R_1 = CH_2 \cdot \underline{c}\text{-}C_3H_5$, $R_2 = \underline{t}$ Bu) was exposed to an atmosphere of deuterium in the presence of 10% palladised charcoal, one molar equivalent of the gas was taken up. The crude product, after trimethylsilylation, was examined by GC-MS, when two components were detected. On the basis of the mass spectrum of its TMS derivative [Fig (1)] and retention time, the major component (A, Fig 2) was identified as a mixture of mono, di, tri and tetradeuterobuprenorphine. In a similar fashion the minor

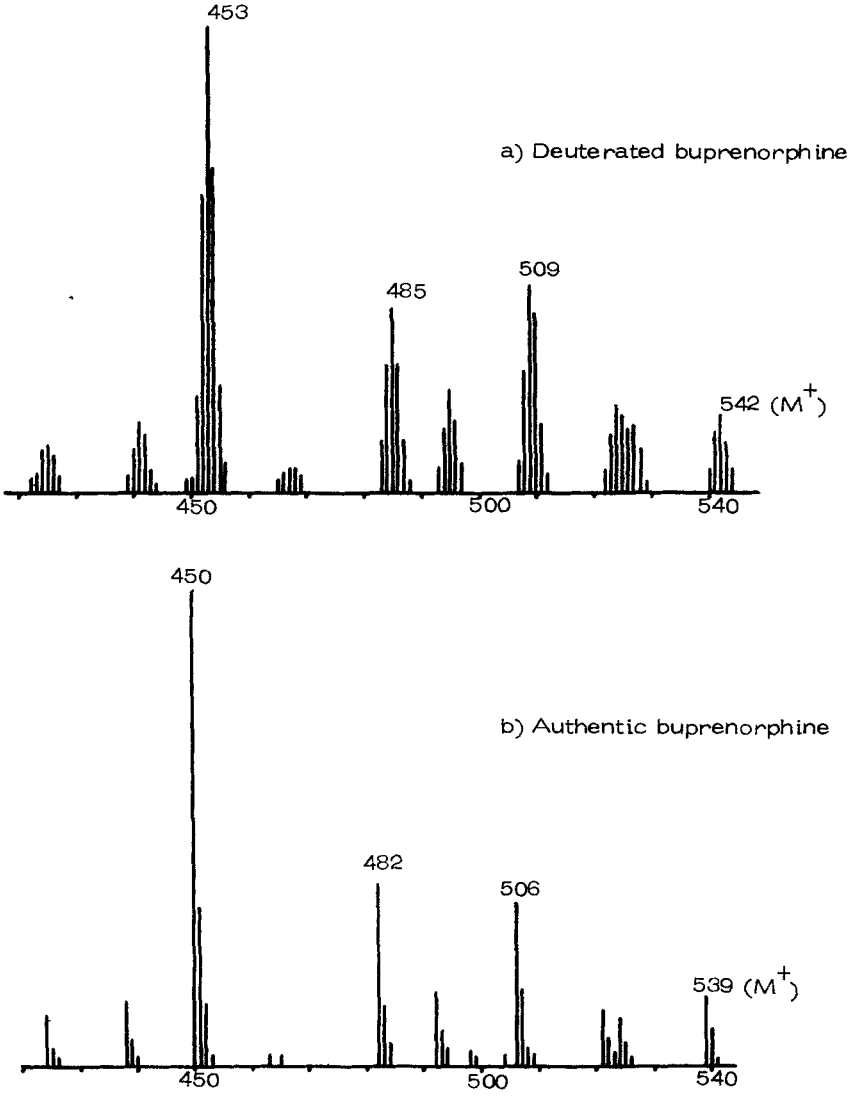
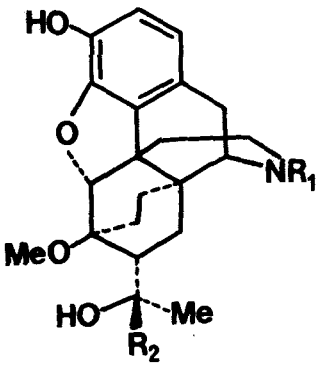
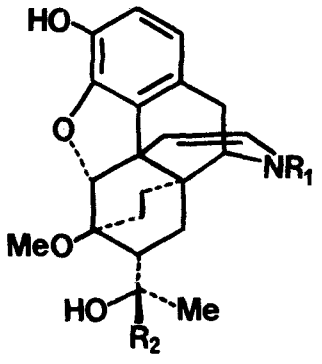


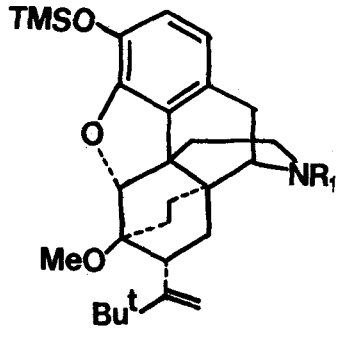
Fig. 1. Mass spectra of authentic and deuterated buprenorphine (as their TMS derivatives)



(1)

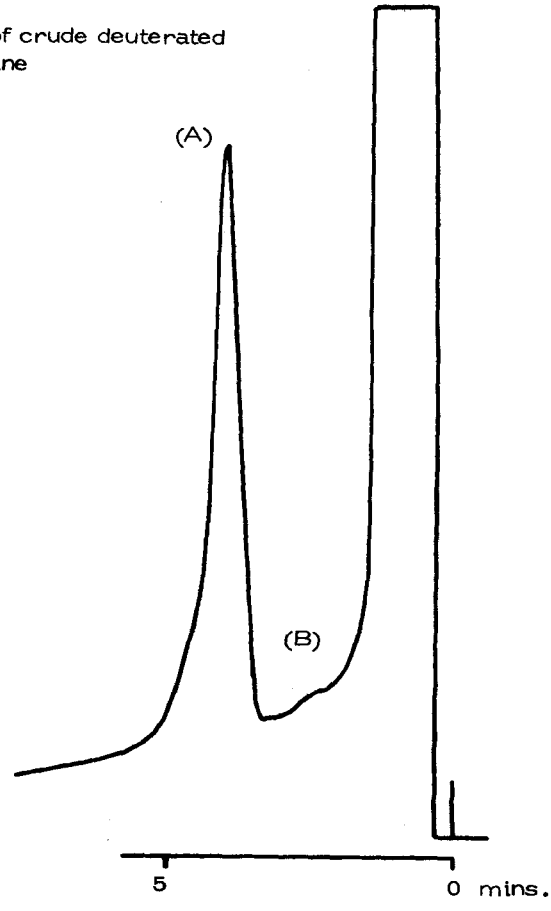


(2)



(3)

Fig. 2. TIC Trace of crude deuterated buprenorphine



component (B, Fig 2) was assigned the structure (3) and was again a mixture of partially deuterated analogues. The olefin (3) is presumably formed by the thermal elimination of water from the 7-substituent. The homogeneity of the major peak was established by the identity of a number of mass spectra obtained by repetitive scanning of the GC peak as it eluted. Reductive ring opening would lead to the incorporation of two deuterium atoms into the N-alkyl group which would result in a cluster of ions similar to that obtained for buprenorphine but displaced by 4 a.m.u. to higher mass. No such pattern was obtained (Fig 1) and thus no detectable ring opening had taken place. Confirmation of this observation was obtained in three ways. Firstly, during hydrogenation a single equivalent of deuterium gas was taken up. Secondly, using chromatographic system (A), a partial separation of the two authentic butyl analogues from buprenorphine could be obtained but no ring opened products were observed. Finally, the nmr spectrum of the deuterated product showed the presence of a complex signal (δ 0-1) due to the hydrogens attached to the cyclopropyl ring, although quantitation of the spectrum was not possible.

Directly analogous mass spectral results were obtained after the reduction of 15,16-didehydrodiprenorphine (2; $R_1 = CH_2 \cdot \underline{c}\text{-}C_3H_5$, R_2=Me) and we conclude that the hydrogenation route for the labelling of tertiary amines, previously reported [1], is generally applicable to compounds containing the N-cyclopropylmethyl group.

Experimental

Chromatography was carried out on Kieselgel $60F_{254}$ plates (5 x 20 cm) supplied by Merck Ag using the following solvent systems:-

i) n-butanol : acetic acid : water (20:5:8)
ii) ethyl acetate : methanol (9:1)

or on Kieselgel GF_{254} plates (5 x 20 cm) supplied by Anachem Ltd. using chloroform - ether (1:1) as solvent (System A).

Deuterium gas (99.5% D_2) was supplied by B.D.H. Ltd. GC-MS was carried out using an LKB 2091 mass spectrometer. The total ion current (TIC) trace was obtained at an ionising electron energy of 20eV, whilst spectra were recorded at 70eV, with a trap current of 50 μA and accelerating potential of 3.5 KV. A glass (3ft x 4 mm) GC column, packed

with 1% Dexil on Diatomite C-AW, was used and the separation was achieved at an oven temperature of 275° with a helium flow-rate of 30 ml min^{-1}. The separator and ion source were both maintained at 250°. Nmr spectra were determined using a Varian T60 spectrometer.

Experimental details are given for buprenorphine only.

15,16-Didehydrobuprenorphine (2; $R_1 = CH_2 \cdot \underline{c}\text{-}C_3H_5$, $R_2 = \overset{t}{-}Bu$)

15,16-Didehydrobuprenorphine was prepared from the parent tertiary base by the method of Haddlesey et. al. [5]

Reduction of 15,16-didehydrobuprenorphine by deuterium gas

Palladium on charcoal (10 mg, 10%) was stirred in anhydrous dioxan (distilled from lithium aluminium hydride) in an atmosphere of deuterium, until equilibrium was reached. 15,16-Didehydrobuprenorphine (102 mg, 0.22 moles) was added and the mixture stirred for 30 min during which time ca 1.0 equivalent (4.8 mls., 0.214 moles) of deuterium was taken up. The catalyst wes removed by filtration through celite and the filtrate taken to dryness to yield the deuterated buprenorphine (100 mg) as a colourless solid. The product co-chromatographed with authentic buprenorphine on silica plates in three different solvent systems and its infra-red spectrum was essentially identical to that of an authentic sample.

The sample to be subjected to GC-MS was dissolved in 1M-hydrochloric acid which was basified (sodium carbonate) and extracted with chloroform. The chloroform solution was washed several times with water, dried (sodium sulphate) and taken to dryness to yield deuterated buprenorphine free from readily exchangeable deuterium. The mono TMS derivative was prepared by treatment of the crude deuterated product (0.5 mg) with bis-trimethylsilylacetamide (200 µl) in ethyl acetate (1 ml).

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