LABELLED COMPOUNDS OF POTENTIAL BIOLOGICAL INTEREST

III. Tritium labelling of 1-butyl-3-piperidyl 2-methyl-6-chloro-carbanilate with high specific activity.*

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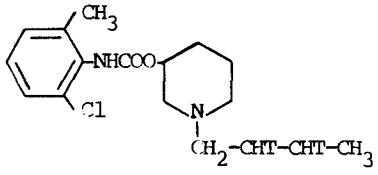
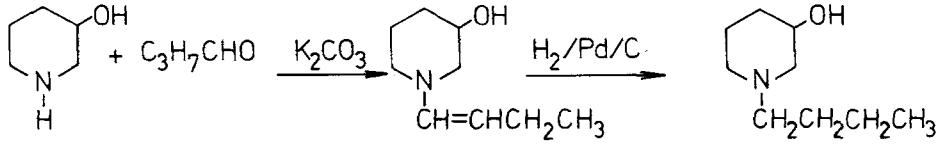
The synthesis and the local anesthetic potency of a number of carbanilic acid esters of cyclic amino alcohols has been reported (1). One of these compounds 1-butyl-3-piperidyl 2-methyl-6-chloro-carbanilate showed especially good local anesthetic properties, characterized by a long duration of action. The compound was found interesting enough to warrent further pharmacological and toxicological investigations. For this purpose it was synthesized labelled at a high specific activity with tritium (I).



I

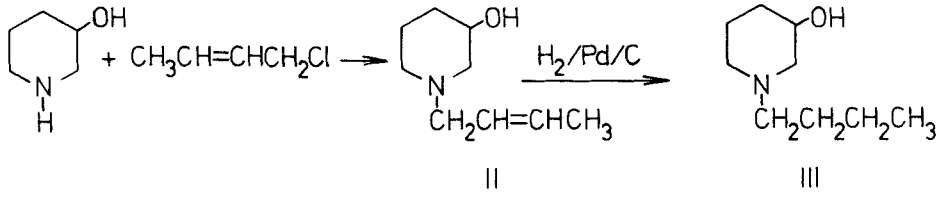
The preparation of unlabelled I in 43 % yield by treating 1-butyl-3-piperidinol with 2-methyl-6-chlorophenylisocyanate in toluene has been reported (1). Thus, performing this reaction with tritium labelled butylpiperidinol seemed to be a feasible route to compound I. As a high specific activity was required, catalytic tritiation of an unsaturated precursor had to be chosen. At first an attempt was made to prepare an enamine by the reaction of 3-piperidinol with n-butyraldehyde, which on catalytic reduction with tritium gas should give 1-butyl-3-piperidinol according to equation 1:



(equation 1)

* Part II: A. Telc, B. Brunfelter, T. Gosztonyi, J. Lab. Comp. 8, 13-23 (1972)

However, difficulty in separating the intermediate enamine from excess 3-piperidinol made this reaction of little value. Much more promising results were obtained on alkylation of 3-piperidinol with 1-chloro-2-butene and subsequent catalytic hydrogenation of the unsaturated intermediate according to equation 2. The alkylation step gave II in 73 % yield and the catalytic hydrogenation of II in ethyl acetate to give III was rapid and nearly quantitative.

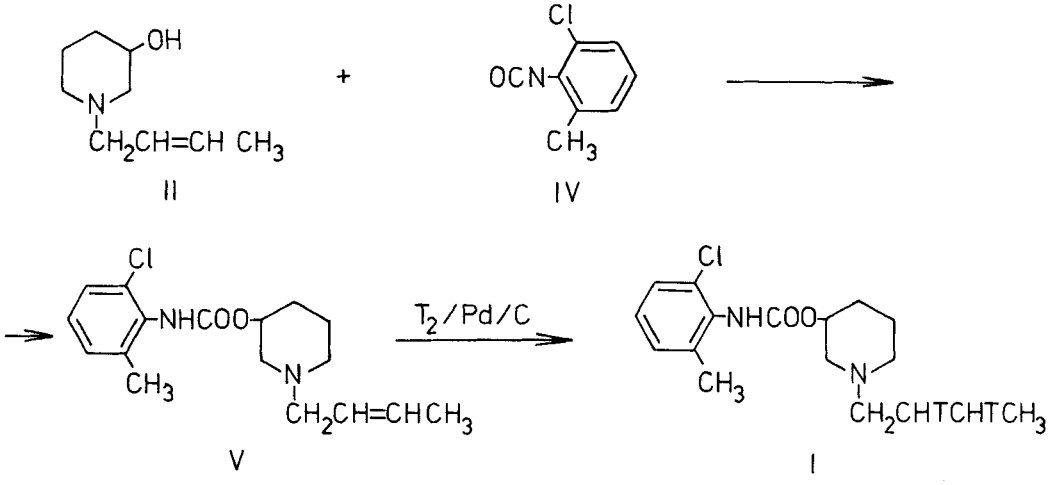


II III

(equation 2)

It is worth mentioning here that an attempt to prepare II by acylating 3-piperidinol with crotonyl chloride and subsequent reduction of the amide with $LiAlH_4$ was unsuccessful. The amide was obtained in 60 % yield by performing the acylation in chloroform in the presence of triethylamine, but the subsequent reduction with $LiAlH_4$ in ether resulted in saturation of the double bond with the amide function remaining intact as verified by the IR spectrum.

However, in order to avoid losses of the incorporated radioactivity during coupling with 2-methyl-6-chlorophenylisocyanate (yield 43 % according to ref. 1), II was first treated with the isocyanate and the possibility of catalytic reduction of the coupled unsaturated product was also investigated (equation 3):



II IV V I

(equation 3)

The conditions of the coupling reaction were somewhat modified and V was formed in a yield of 58 %. Catalytic hydrogenation of V gave I in a rapid reaction without any dehalogenation, so this reaction sequence could be used advantageously for the tritiation of I. On performing the tritiation in ethyl acetate with carrier free tritium gas, I was formed in a yield of nearly 80 %, having a specific activity of 62 mCi/mg = 20 Ci/mM.

At room temperature the labelled product suffered severe self-decomposition quite rapidly. Within 48 hours the white crystalline substance became brownish and smeary.

Purification of this product was accomplished by acidic extraction of its benzene solution, followed by alkalization of the water extract and reextraction with benzene. The purity was then checked by thin-layer chromatography on silica in benzene–acetone (1:1). The radiochemical purity of the purified product was >96 %. On storing in benzene solution (1.5 mCi/ml) the purity was unchanged for about two weeks, but after this time repurification was necessary.

Experimental

Melting and boiling points reported are uncorrected.
Specific radioactivities were measured in a Packard Liquid Scintillation Spectrometer (Model 3320) using internal standardization (Hexadecane-1,2-^{3}H).
Scanning of the chromatograms was carried out in a Packard paper chromatogram scanner (Model 7200) using an adapter for thin-layer plates.

1-(1-Butenyl)-3-piperidinol. - 3-Piperidinol (10.1 g, 100 mmoles) was dissolved in 50 ml of benzene and anh. K_2CO_3 (3 g, 217 mmoles) was added. A solution of 3.6 g (50 mmoles) freshly distilled butyraldehyde in 25 ml of benzene was added dropwise to the mixture keeping the temperature at 5–8°C. After stirring at room temperature for 3.5 hours, the solution was filtered and fractionated. The fraction boiling at 98–100°/10 mm Hg was collected (7.6 g). GLC analysis showed that the product was considerably contaminated with 3-piperidinol.

1-Crotonyl-3-piperidinol. - A solution of crotonyl chloride (10.5 g = 100 mmoles) in 15 ml of chloroform was added dropwise at 5–10°C to a solution of 3-piperidinol (10.1 g = 100 mmoles) and triethylamine (10.1 g = 100 mmoles) in 100 ml of chloroform. The mixture was stirred at room temperature for 3 hours. The chloroform solution was washed with saturated $NaHCO_3$ and saturated Na_2SO_4 solution, dried and distilled. The fraction boiling at 142–3°C/0.3 mm Hg was collected. Yield: 10.1 g (60 mmoles; 60 %) n_D^{25}: 1.5283. An IR spectrum of the product verified the unsaturated amide structure (ν_{max} = 1610, 1660 cm^{-1}).
N: found 8.20 % ($C_9H_{15}NO_2$ requires 8.28 %)

1-(2-Butenyl)-3-piperidinol (II). - Freshly distilled 1-chloro-2-butene (10 g, 110 mmoles) was added dropwise at 25–30°C to a solution of 3-piperidinol (20.2 g, 200 mmoles) in 175 ml of benzene. After stirring at room temperature overnight the mixture was heated under reflux for 1 hour. The salt formed was removed by filtration, washed with benzene and the filtrate was fractionated. The fraction boiling at 105–106°C/8 mm Hg was collected. Yield 12.5 g (80 mmoles, 73 %). n_D^{25}: 1.4913. On GLC analysis the product gave one major peak (99.9 %).

1-Butyl-3-piperidinol (III). - Compound II. (220 mg, 1.4 mmoles) was dissolved in 15 ml of ethyl acetate, 10 % Pd on charcoal (30 mg) was added and the mixture was stirred in an atmosphere of H_2. The theoretical amount of hydrogen was taken up within 25 minutes. After removal of the catalyst and solvent the residue was distilled at 10 mm Hg in a microdistillation apparatus. Yield: 200 mg (1.3 mmoles, 91 %) n_D^{25}: 1.4700. The product had the same retention time as an authentic sample of 1-butyl-3-piperidinol on GLC.

1-(2-Butenyl)-3-piperidyl 2-methyl-6-chlorocarbanilate (V). - A mixture of II. (1 g, 6.7 mmoles) and 2-methyl-6-chlorophenylisocyanate (1.12 g, 6.7 mmoles)

was heated at 100°C in an oil bath for 3 hours. After cooling, the mixture was dissolved in 10 ml ether. The ethereal solution was filtered to remove a small amount of insoluble material and extracted with 4 ml of 2 M HCl. The aqueous phase was then made alkaline with 30 % aqueous NaOH solution (pH = 10) and extracted with ether. After drying the ether was removed in vacuo. The crystalline residue was repeatedly recrystallized from ligroin giving 1.25 g white crystalline product (3.9 mmoles, 58 %), which melts at 97.5-99°C.
N: found 8.63 % ($C_{17}H_{23}N_2O_2Cl$ requires 8.68 %).

1-(Butyl-2,3-^{3}H)-3-piperidyl 2-methyl-6-chlorocarbanilate (I). - Compound V. (160 mg, 0.5 mmole) was dissolved in 2 ml of ethyl acetate, 10 % Pd on charcoal (20 mg) was added and the mixture was stirred at room temperature in an atmosphere of 36 Ci carrier-free tritium gas. The uptake of tritium ceased after 60 minutes and the reaction was stopped. After removal of the catalyst and solvent any labile tritium was removed by addition of several portions of methanol and repeatedly removing the solvent by evaporation. The crystalline residue was recrystallized twice from ligroin giving white crystals (130 mg, 0.4 mmole, 80 %).
Mp: 72.5-73.5°C.
Specific activity: 62 mCi/mg = 20.1 Ci/mmole.
Radiochemical purity by TLC on silica in benzene acetone (1:1) was better than 96 % (R_f: 0.56).

The substance was stored in benzene solution (1.5 mCi/ml) at room temperature. After about two weeks of storage, the solution became coloured and was purified as described above.

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References

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