SYNTHESIS OF TRITIUM-LABELLED d.l-CONIINE

Wilhelm W.Just, Volker Böhnisch and Gottfried Werner
Max-Planck-Institut für Hirnforschung, Arbeitsgruppe Neurochemie, Frankfurt/Main, GFR.

Received on November 10, 1975
Revised on December 12, 1975

SUMMARY

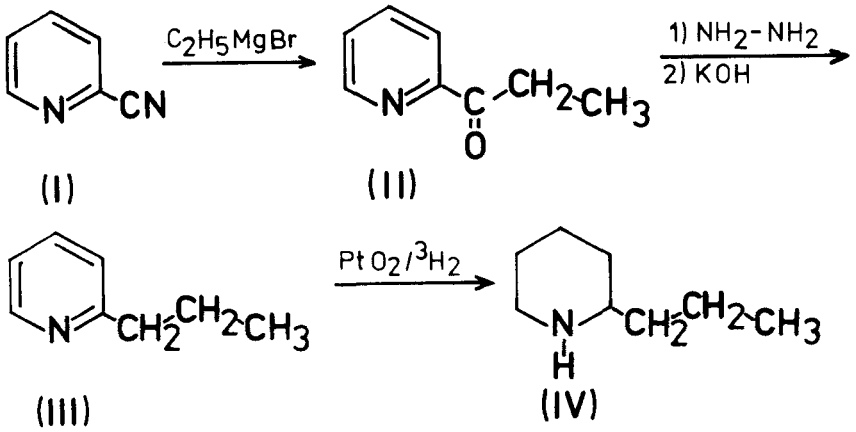
d.l-Coniine was labelled with tritium in the ring by catalytic hydrogenation of 2-propylpyridine using Adams-catalyst in the presence of acetic acid.

Key Words:d.l-Coniine, 2-propylpyridine, Tritium, catalytic hydrogenation, Adams-Catalyst

INTRODUCTION

During the last few decades the pharmacological effects of coniine have been of great interest to many pharmacologists. Investigations in different laboratories have demonstrated neuromuscular as well as ganglonic blockades[1-4]. For further pharmacological studies, especially concerning metabolic and autoradiographic investigations, radioactive labelling of the drug was desirable.

Starting from the first synthesis of d.l-coniine by Ladenburg[5] several other possibilities to synthesize d.l-coniine were described[6-10]. Of them the route suggested by Prasad and Shaw[11] seemed to be most suitable to introduce tritium into the molecule. The synthesis starts from 2-cyanopyridine (I) which is converted into 2-propionylpyridine (II) by means of the Grignard-reaction. 2-Propionylpyridine is further transformed to 2-propylpyridine (III) by a modified



Wolff-Kishner reduction[12]. The catalytic hydrogenation of (III) in the presence of Adams-catalyst yields racemic 2-propylpiperidine (IV). The use of tritium gas in the last step of synthesis enabled the radioactive labelling.

In most cases the catalytic hydrogenations utilizing Adams-catalyst were performed in glacial acetic acid solutions. Although preceding studies demonstrated the rapid hydrogenation of pyridine to piperidine in methyl acetate as a solvent in the absence of acetic acid, no reaction was observed when 2-propylpyridine was used instead of pyridine. On the other hand, the addition of acetic acid decreases the yield of specific radioactivity. Therefore, several catalytic hydrogenations with different amounts of catalyst and various concentrations of acetic acid were achieved from which the following procedure was finally adopted for the radioactive synthesis.

Experimental

The NMR spectra were obtained with a Varian T-60 NMR spectrometer. The substance was dissolved in deuteriochloroform. TMS served as the internal standard. Mass spectra were obtained with a Varian 311 A mass spectrometer. The samples

were introduced by direct input. The melting point which is reported uncorrected was determined on a Leitz apparatus equipped with a hot plate and a microscope. The radioactivity on thin layer plates was located by a thin layer scanner (Berthold, Wildbad).

2-Cyanopyridine was purchased from EGA-Chemie, Steinheim. 2-Propionylpyridine and 2-propylpyridine were synthesized according to the method of Prasad and Shaw[11].

d.l-2-Propylpiperidine (^3H): In a thermostated 5 ml vessel (32°C) which was connected to a vacuum pump, a hydrogen reservoir and the tritium vial by a threeway stopcock were placed in 50 mg (0.256 mmole) PtO_2, 0.06 ml (1.05 mmole) glacial acetic acid and 200 mg (1.64 mmole) 2-propylpyridine dissolved in 2 ml methyl acetate. The total applied radioactivity was 1.0 Ci. First the catalyst was reduced with normal hydrogen. After evacuation of the reaction vessel, the tritium vial was opened and during the following two hours period the vial was rinsed a few times with normal hydrogen. The reaction was stopped after 36 hrs. Within that time 110.7 ml hydrogen were consumed (theoretical consumption 121.4 ml).

After removing the catalyst by centrifugation the reaction mixture was brought to alkaline reaction by adding methanolic potassium hydroxide. The alkaline mixture was layered on a chromatographic column (silica gel 60, Merck, gel bed 25/60 mm) and separated by elution with a mixture of methyl acetate-methanol, starting with a ratio of 5:1 and increasing the methanol content during the separation. The final elution was performed using pure methanol. The pooled fractions containing d.l-coniine were concentrated after the addition of etheric hydrogen chloride. Aqueous potassium hydroxide was added to the residue and the radioactive d.l-coniine was extracted with ether. The substance which was again transformed into the

hydrochloride was obtained yielding 140 mg (54%) in crystalline form.

The specific radioactivity was 385.0 mCi/mmole. After dissolution in water and lyophilization this specific activity remained constant. Mp. 214-216°C, Rf. 0.23 (silica gel G, methyl acetate-acetone-conc.ammonia, 50:50:0.2). NMR ($CDCl_3$). δ3.08 (m/1H), 2.53 (m/2H), 1.81 (s/1H/exchangeable with D_2O), 1.41 (m/8H), 0.96 (m/5H). For the interpretation of the NMR-spectrum see Weitkamp and Korte[13]. MS (70 eV/200°C). m/e 127 (3%), 112 (2%), 97 (3%), 84 (100%), 70 (8%), 56 (20%), 43 (16%). Also see Spiteller-Friedman and Spiteller[14].

1-N-Dimethylaminonaphthalene-5-sulfonyl-d.l-coniine-^{3}H (Dns-coniine-^{3}H): The derivatization was performed according to Seiler and Wiechmann[15]. Chromatography on silica gel G using the solvent system cyclohexane-ethyl acetate, 4:1 showed one single peak of radioactivity on the scannogram with Rf 0.52. The mass spectrum of Dns-coniine-^{3}H is shown in Fig.1.

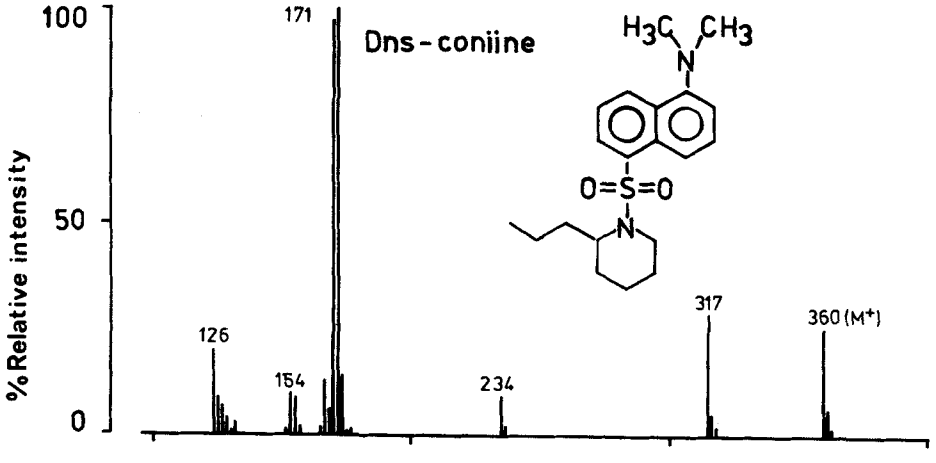


Fig.1. Mass spectrum of Dns-d.l-coniine-^{3}H (70 eV/80°C).

REFERENCES

1. Kölliker,A., Arch.path.Anat., 10,235(1856).

2. Langley,J.N., and Dickinson,W.C., J.Physiol., 11.509(1890).
3. DeBoer,J., Arch.int.Pharmacodyn., 83,473(1950).
4. Sampson,S.R., Esplin,D.W., and Zablocka,B., J.Pharmacol. Exp.Ther., 152,313(1966).
5. Ladenburg,A., Ber.dtsch.chem.Ges., 40,3734(1907).
6. Diels,O., and Alder,K., Ann.Chem. 498,1(1932).
7. Gallinovsky,F., and Mulley,H., Mh.Chem., 79,426(1948).
8. LeMen,J., Bull.Soc.chim.France, 1950,599.
9. Urry,W.H., Juveland,O.O., and Stacey,F.W., J.amer.chem.Soc. 74,6155(1952).
10. Hill,R.K., J.amer.chem.Soc., 80,1609(1958).
11. Prasad,K.B., and Shaw,S.C., Ber.dtsch.chem.Ges., 98, 2822(1965).
12. Lock,G., Mh.Chem., 85,802(1954).
13. Weitkamp,H., and Korte,F., Mh.Chem., 95,2896(1962).
14. Spiteller-Freidmann,M., and Spiteller,G., Mh.Chem., 96, 104(1965).
15. Seiler,N., and Wiechmann,M., Progress in thin layer chromatography and related methods. Vol.1., London: Ann Arbor-Humphry Science Publishers, 1970.