RADIOSYNTHESIS OF (-)-COCAINE AND NOR-(-)-COCAINE USING TRITIUM-LABELLED METHANOL

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

SUMMARY

(-)-Cocaine and nor-(-)-cocaine both were labelled on the methyl ester group with tritium. The synthesis was performed by partial hydrolysis of the parent compounds and reesterification of them using tritium-labelled methanol.

Key Words:(-)-Cocaine, Nor-(-)-cocaine, Tritium-Methanol, Esterification

INTRODUCTION

One of the first steps in (-)-cocaine metabolism is the formation of nor-(-)-cocaine by oxidative N-demethylation[1]. Recent experiments in this laboratory have demonstrated the potent pharmacological activity of this (-)-cocaine metabolite. To study the formation of nor-(-)-cocaine and also follow the metabolism of this drug an easy radioactive synthesis was developed labelling the (-)-cocaine and the nor-(-)-cocaine molecule in the methyl ester group.

Comparative autoradiographic studies between both of these drugs were intended requiring a certain specific radioactivity of the drugs to avoid long times of exposure. Therefore, the polytopical labelling of (-)-cocaine and nor-(-)-cocaine as described by Schmidt and Werner[2] and Werner and Schmidt[3] could not be used due to low specific radioactivities which resulted.

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Esterification of O-benzoyl-(-)-ecgonine in the presence of ^{14}C-labelled diazomethane (also described by Schmidt and Werner[4]) was not applicable for the esterfication of O-benzoyl-nor-(-)-ecgonine since attack on the nitrogen also resulted. Therefore, the following route of synthesis was chosen. Preparation of O-benzoyl-(-)-ecgonine and O-benzoyl-nor-(-)-ecgonine by hydrolysis of (-)-cocaine and nor-(-)-cocaine respectively. This was followed by the synthesis of the acid chlorides and reesterification by means of tritium-labelled methanol.

EXPERIMENTAL

NMR spectroscopy: The spectra of (-)-cocaine and nor-(-)-cocaine were obtained with a Varian T-60 NMR spectrometer. The compounds were dissolved in deuteriochloroform. TMS served as the internal standard.

Mass spectroscopy: The spectra were obtained with a Varian CH-5 mass spectrometer equipped with a direct input.

Melting points were determined on a Leitz melting point apparatus which was equipped with both a hot plate and a microscope. They were reported uncorrected. A thin layer scanner (Berthold, Wildbad) was used to detect radioactivities after thin layer chromatography was performed.

O-Benzoyl-(-)-ecgonine: Hydrolysis of (-)-cocaine was carried out according to Einhorn[5].

O-Benzoyl-(-)-ecgonyl chloride: According to F.Hoffmann-La Roche & Co.[6] 450 mg (1.38 mmole) O-benzoyl-(-)-ecgonine.HCl were dissolved in 0.8 ml (11.1 mmole) freshly distilled thionyl chloride and stirred for 15 min at room temperature. The temperature was increased then to 63-65°C and was maintained at this level for 20 min. For the esterification which followed

the acid chloride was used without further isolation.

(-)-Cocaine (OC^3H_3): To the synthesized O-benzoyl-(-)-ecgonyl chloride 6.25 mg (0.195 mmole) tritium-labelled methanol (NEN Chemicals, 90 mCi/mmole) dissolved in 1.4 ml acetonitrile were added. The mixture was stirred for two hrs at room temperature. After evaporation of the solvent the residue was dissolved in water and extracted a few times with diethyl ether. To the aqueous phase diluted ammonia was added until alkaline reaction was reached. The solution was again extracted with diethyl ether. (-)-Cocaine was purified by preparative thin layer chromatography (silica gel G, Merck, cyclohexane-acetone-conc. ammonia, 100:40:0.2). The yield was 52.0 mg (0.172 mmole) (-)-cocaine (free base) (88%). The chromatographically pure substance (silica gel G, cyclohexane-diethylamine, 9:1, Rf.0.58) was crystallized in methanol/acetone. Mp. 191-192°C ((-)-cocaine. HCl). The specific radioactivity was 90 mCi/mmole. The NMR-values were identical with those reported by Sinnema et al.[7].

Nor-(-)-cocaine (unlabelled): The procedure reported by Werner et al.[8] was followed with slight modifications. The $KMnO_4$-oxidation of (-)-cocaine was controlled chromatographically (silica gel G, acetone-methyl acetate-conc.ammonia, 40:20:0.2). The reaction was normally completed after 6 hrs. Acetonitrile was partially removed and the aqueous solution was then frozen and lyophilized. Using the solvent system mentioned above, the residue was purified chromatographically yielding 40 % nor-(-)cocaine. Mp.80-82°C.

O-Benzoyl-nor-(-)-ecgonine: The substance was prepared either by $KMnO_4$-oxidation of O-benzoyl-(-)-ecgonine according to Einhorn[5] or by hydrolysis of nor-(-)-cocaine in water or borate buffer (pH 7.0). The substance was purified by column chromatography (silica gel 60, Merck, acetone-methanol,3:2). MS (280°C/70 eV). m/e 275(12%), 257(2%), 154(100%), 136(38%),

122(20%), 110(45%), 108(39%), 105(66%), 93(16%), 82(24%), 80(32%), 77(54%), 68(68%).

O-Benzoyl-nor-(-)-ecgonyl-chloride: O-Benzoyl-nor-(-)-ecgonine, 400 mg (1.29 mmole), were dissolved in 1.4 ml (19.0 mmole) thionyl chloride which had been freshly distilled. The solution was kept for 15 min at room temperature and was then heated to 65-70°C under simultaneous stirring for another 25 min. The procedure which followed was the same as described for O-benzoyl-(-)-ecgonyl chloride.

Nor-(-)-cocaine (OC^3H_3): To the crude O-benzoyl-nor-(-)-ecgonyl chloride 21 mg (0.6 mmole) tritium-labelled methanol (NEN Chemicals, 38.1 mCi/mmole) dissolved in 1.4 ml acetonitrile were added. The reaction mixture was stirred for 1 hr at room temperature. The procedure which followed was the same as

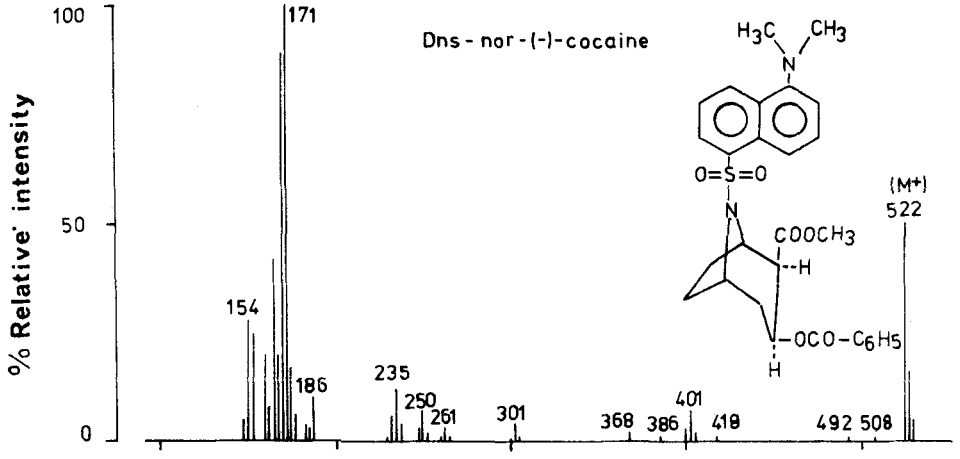

Fig.1. Mass spectrum of Dns-nor-(-)-cocaine (230°C/70 eV).

described for (-)-cocaine (OC^3H_3). The yield was 121 mg (64%). The obtained radioactive nor-(-)-cocaine was chromatographically pure (cyclohexane-diethylamine,9:1, Rf. 0.32). The specific radioactivity determined by liquid scintillation counting was 38.0 mCi/mmole.

NMR ($CDCl_3$). δ 7.9 (m/2H/aromatic protons), 7.38 (m/3H/aromatic protons), 5.42 (m/1H/C-3 proton), 3.81 (s broad/2H/C-1,C-5 protons), 3.61 (s/1H/N-H proton, D_2O-exchangeable), 1.85 (m/6H/C-4,C-6,C-7 protons). MS (100°C/70 eV). m/e 289 (21%), 258(3%), 245(0.7%), 230(1.5%), 222(4%), 184(13%), 168(100%), 152(4%), 141(6%), 136(61%), 122(5%), 108(45%), 105(66%), 82(23%), 80(26%), 77(42%), 68(72%).

1-N-Dimethylaminonaphthalene-5-sulfonyl nor-(-)-cocaine (OC^3H_3) (Dns-nor-(-)-cocaine, OC^3H_3): The derivatization of nor-(-)-cocaine was performed according to Seiler and Wiechmann[9]. Chromatography was carried out on silica gel G using n-heptane-ethyl acetate,7:3 as a solvent system (Rf. 0.3). The mass spectrum of Dns-nor-(-)-cocaine is shown in Fig.1.

ACKNOWLEDGEMENT

The technical assistance of M.Nazirizade is greatfully acknowleged.

REFERENCES

1. Schmidt,H-L., and Werner,G., Neuropsychopharmacol., 3,427(1964).
2. Schmidt,H-L., and Werner,G., Ann.Chem., 656,149(1962).
3. Werner,G., and Schmidt,K-H., J.labelled Comp., 5,200(1969).
4. Schmidt,H-L., and Werner,G., Ann.Chem., 653,184(1962).
5. Einhorn,A., Ber.dtsch.chem.Ges., 21,47(1888).
6. F.Hoffmann-La Roche & Co., Ber.dtsch.chem.Ges., 26,1482 (1893).
7. Sinnema,A., Maat,L., van der Gugten,A.J., and Beyerman, H.C., Rec.Trav.Chim., 87,1027(1968).
8. Werner,G., Hackel,R., Mohammad,N., Seiler,N., and Störr, K-H., Ann.Chem., 708,210(1967).
9. Seiler,N., and Wiechmann,M., Progress in thin layer chromatography and related methods. Vol.1., London: Ann Arbor-Humphry Science Publishers. 1970.