Analytical Profiles of Drug Substances

Volume 12

Edited by

Klaus Florey

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PREFACE

The compilation of *Analytical Profiles of Drug Substances* to supplement the information contained in the official compendia is now a well-established activity.

That we are able to publish one volume per year is a tribute to the diligence of the editors to solicit monographs and even more so to the enthusiastic response of our authors, an international group associated with pharmaceutical firms, academic institutions, and compendial authorities. I would like to express my sincere gratitude to them for making this venture possible.

Over the years, we have had queries concerning our publication policy. Our goal is to cover all drug substances of medical value, and therefore, we have welcomed any monographs of interest to an individual contributor. We also have endeavored to solicit profiles of the most useful and used medicines, but many in this category still need to be profiled.

In the preface to the eleventh volume, I announced that we would try to supplement previously published profiles with new data. Unfortunately, most of the original contributors are no longer available to undertake this task, and it has proven to be difficult to find other volunteers. We shall continue to pursue the updating program, but it will not be as comprehensive as originally envisioned.

Again, I would like to request of all those who have found these profiles useful to contribute monographs of their own. We, the editors, stand ready to receive such contributions.

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AMANTADINE

Joel Kirschbaum

ISBN 0-12-260812-7

1. Introduction

1.1 History, Therapeutic Use and Mechanism of Action

Amantadine is an orally active antiviral agent (1,2). It was discovered by workers at DuPont via an empiric screening program (3). Other than vaccination, it is the only prophylactic drug presently useful against many viral infections, especially influenza A and C. Once administered, its effect is immediate to reduce signs of infection among 50% to 70% of individuals exposed to the virus. A use panel recommended (4) it for individuals with a high risk of serious morbidity or mortality due to cardiovascular, immunodeficiency, metabolic, neuromuscular or pulmonary diseases, the elderly, and the unvaccinated and the important (5). It is 91% effective in preventing influenza. The antiviral activity of amantadine hydrochloride appears at an early phase of the infection (6). The mode of action appears to be the inhibition of the uncoating of the virus (7) once it has penetrated the host cell. Such a failure prevents replication. Gene 7, coding for the virus matrix protein, carries the property of amantadine resistance (8), and can be transferred by recombination between influenza viruses. It was conjectured (9) that other highly symmetrical hydrocarbons, perhaps in the shapes of the Platonic solids like cubane and dodecahedrane, when derivatized like amantadine, might have similar properties to pass through the membrane of a cell and destroy virus particles inside it (10).

Amantadine is also useful in treating Parkinson's disease (2). This use was found by a chance observation of a significant improvement in such a patient taking 200 mg of amantadine daily for flu prophylaxis. It also appears clinically effective in the treatment of drug-induced extrapyramidal symptoms (11).

Amantadine relieves Parkinson's disease (including drug-induced Parkinsonism by neuroleptics), apparently by a mechanism involving dopamine (12); indeed, amantadine enhances *L*-dopa activation (2).

As expected, various investigators found amantadine to have other uses; not only against other

viruses (12), but also in treating cancer (13), aiding priapus (14), and inhibiting rust (15).

Rimantadine, an amino group analogue [1-(1-aminoethyladamantane)] is also active against virus (2,16). Rimantadine is 4-8 times more effective than amantadine hydrochloride to protect against influenza A virus infection, but it is more toxic (17).

1.2 Nomenclature, Molecular Weight and Structure

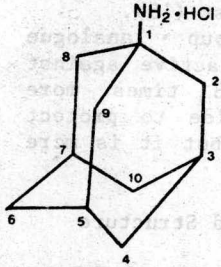
Amantadine hydrochloride is the United States adopted name (18). The preferred chemical name is tricyclo [3.3.1.$1^{3,7}$]decan-1-amine, hydrochloride. Other names include 1-adamantanamine hydrochloride, 1-aminotricylo[3.3.1.$1^{3,7}$]decane hydrochloride, 1-adamantylamine hydrochloride, adamantylamine hydrochloride, and 1-aminoadamantane hydrochloride, and, less correctly, midantane and dimantane hydrochloride (19). Its molecular weight is 187.71 daltons. Amantadine hydrochloride was given the chemical abstracts service systematic number 665-66-7; the free base, amantadine, was numbered CAS-768-94-5. It is currently marketed under the name Symmetrel (Endo Laboratories). Other names include EXP-105-1, Mantadix, Matadan, Mydantan and Virafral. In Wiswesser notation it is L66 B6 A B- C 1B ITJ BZ &GH.

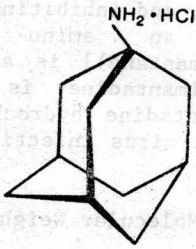
Amantadine hydrochloride can be represented a variety of ways, as shown below:

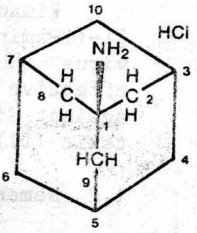
Amantadine hydrochloride possesses a unique, rigid, relatively unstrained ring system that is composed of three fused cyclohexane rings in the chair conformation (20). Amantadine is considered to be the smallest repeating unit of the diamond lattice (21). The symmetrical cage structure causes the infrared, nuclear magnetic resonance and mass spectra to be comparatively simple, as will be illustrated later. As expected from this lack of asymmetry, there is no observable optical rotation (22) using the D lines of sodium, at a concentration of 1% in water.

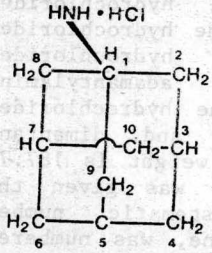
1.3 Appearance, Color, Odor and Precautions

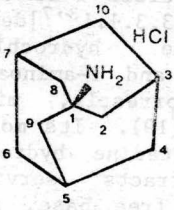
Amantadine hydrochloride is a white, odorless, free-flowing crystalline powder. No precautions are given for this relatively non-toxic compound.

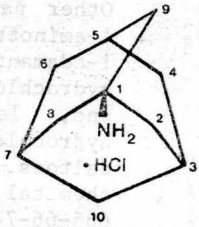












1.4 Synthesis

Adamantane is found naturally at low concentrations (approximately 0.02%) in various petroleum fractions (23). However, it may be synthesized by isomerization of ten carbon cyclic hydrocarbons, the probable basis of the naturally formed adamantane. A convenient starting material, dicyclopentadiene (I) was hydrogenated quantitatively to *endo*-trimethylnorbornane (II, *endo*-tetrahydrodicyclopentadiene). After refluxing overnight with such Lewis acids as aluminum trichloride or tribromide, adamantane (III) was found. The possible mechanism (24) is shown below.

Bromination to 1-bromoadamantane, an ionic process, can be followed by a sequence of reactions with either ammonia, methylcyanide, urea or thiourea as sources of the amino group, to give amantadine (25-30). More complicated reactions of the 1-bromo-compound involve dehalogenation, reaction with methylcyanide and saponification (31,32). Other syntheses utilize the 1-carboxylic acid (33) and the 1-nitrate (34).

Direct amination (35) of adamantane or introduction of a source of an amino group during the rearrangement of II (also known as tricyclo[5.2.1.$0^{2,6}$]decane) gives a yield of 75% amantadine (36) The reaction precedes (37) the bridgehead carbon via  Various other combinations of isomerization and conversion to amantadine have been described (38,39). Amantadine can also be synthesized by the photochemical reaction of chloramine with adamantane (40).

1.5 Reactions, Stability and Metabolism

Possible reactions are substitution at the amino group of amantadine, replacement of the amino group, rearrangement of the cage structure or replacement of the cage hydrogens, and have been discussed elsewhere (20). A vast number of derivatives of the amino group have been prepared (41). The amino group can undergo all of the typical reactions of primary amines, such as Schiff base formation (42), alkylation (43,44), halogenation (45) and amination (46). Deamination with sodium nitrite and acetic

acid or nitrous acid gives 1-hydroxyadamantane in 97% yield (20). The *in situ* reaction with trichloroacetyl isocyanate in NMR tubes was used to analyze for the amino function (47). As expected, various compounds like acid chlorides were reacted with amantadine (48,49) to create potential drugs with new properties. The relative stability of the 1-adamantyl cation (50) permits conversion of the amino group to nitro, and then to a large series of derivatives (51).

The cage structure can be rearranged (52) in a reversal of the synthesis. The cage hydrogens can be replaced by fluorine, as induced by light (53) or by perfluoridation (54; ^{19}F-NMR, infrared and mass spectra discussed), as well as by tritium (55).

The amantadine structure has been characterized as being extremely stable, as predicted from the equatorial position of the amino group and the facile rearrangement of ten carbon hydrocarbons to adamantane (20).

After oral administration, amantadine was found in the heart, kidney, liver and lungs (56). Concentration of the drug in the lungs may be part of its prophylactic action. After an oral dose of 2.5 mg/kg, maximum concentration of 0.3 µg/mL was reached in 1-4 hours (57), with a plasma half-life of 9-15 hours (58). The rate of excretion depends of the pH of the urine; *i.e.*, at pH 5.0, 5-7% per hour of body content was excreted, but at pH 8 the excretion rate was 4% per hour (59). As expected, with patients having negligible renal function, excretion was impaired, with plasma concentrations reaching 4.4 µg/mL, and accompanied by toxic manifestations of the drug (60).

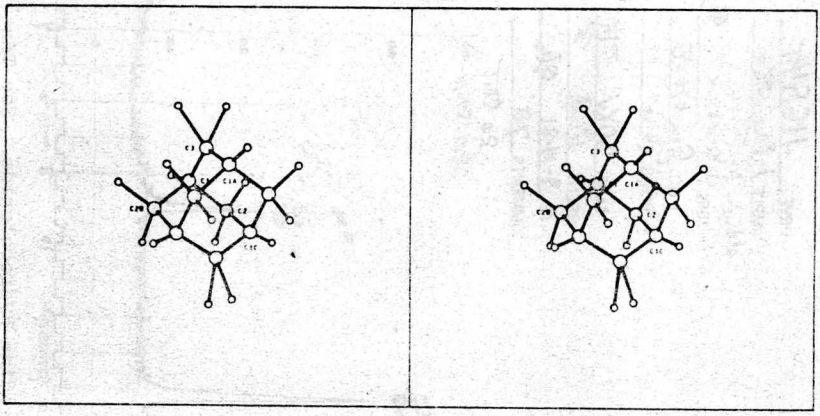
In hepatic microsomal preparations, N-hydroxy-1-aminoadamantane and 1-nitrosoadamantane were identified as metabolites (61). Approximately 0.1% of the administered amantadine was found in urine in the form of 1-amino-3-hydroxyadamantane (62).

2. Physical Properties of Crystalline Amantadine

2.1 Single Crystal X-Ray Diffraction

Although the x-ray structure of amantadine hydrochloride was not determined, the structure of the parent compound adamantane was elucidated (63).

The three-dimensional representation below is reproduced with the permission of the Crystallographic Data Centre, Cambridge (64).



Electron diffraction data (65) for adamantane agreed with the x-ray crystallography. The band length of C-H and C-C (1.54 ± 0.01Å) appear normal, and the C-C-C angles are tetrahedral (109.5 ± 1.5°).

2.2 X-Ray Powder Diffraction

To observe x-ray diffraction patterns, a Philips powder diffraction unit emitting Cu$K\alpha$ radiation at 1.54Å was used with a scintillation counter detector (66). The relative lack of peaks seen in Figure 1 was expected from the highly symmetrical structure of amantadine hydrochloride. Below are the sorted data based on highest intensity of 1.00 using Cu$K\alpha$ radiation.

2θ(Degrees)	'd'(Angstroms)	Relative Area
18.2	4.88	1.000
15.9	5.58	0.739
27.4	3.26	0.499
14.4	6.17	0.405
23.9	3.72	0.344

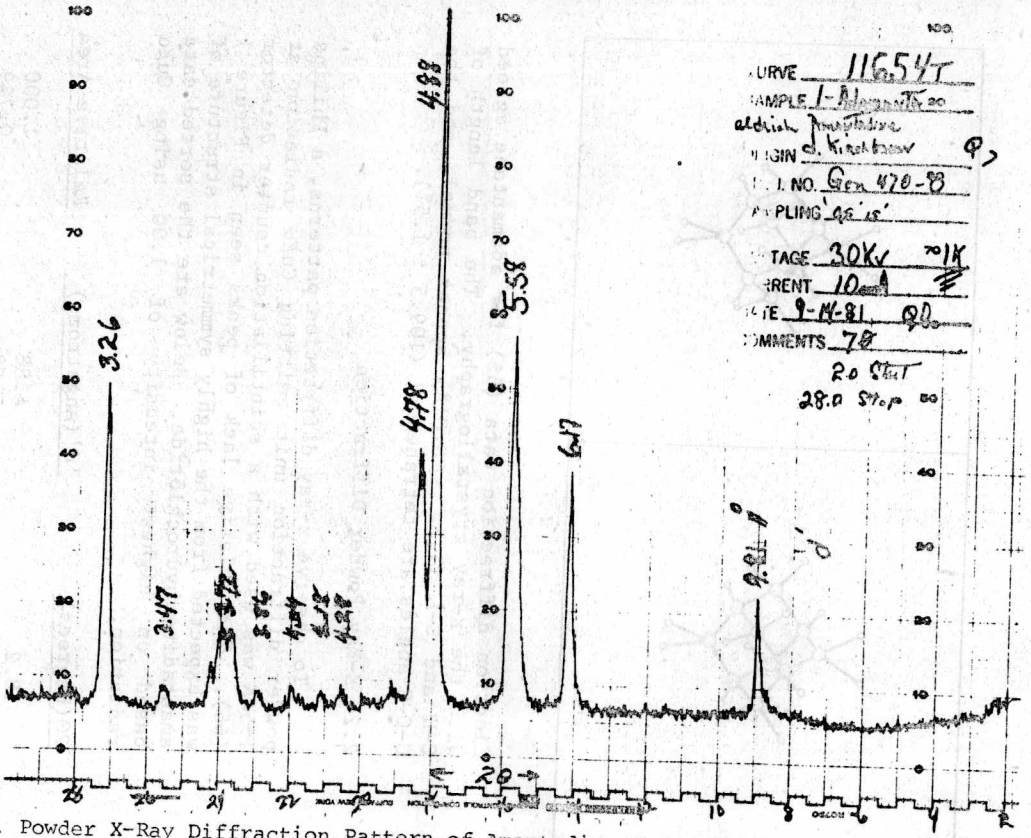
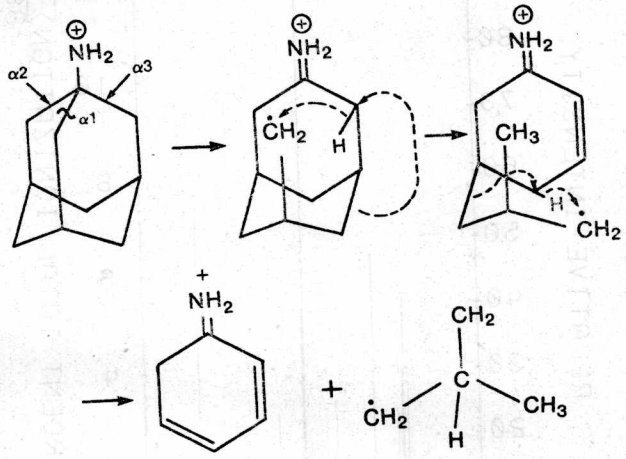


Figure 1. Powder X-Ray Diffraction Pattern of Amantadine Hydrochloride. See Text for Details

18.6	4.78	0.298
9.0	9.81	0.235

2.3 Mass Spectrometry

The mass spectrum (67) of amantadine hydrochloride (Figure 2) shows that the amino substituent was present as a major ionic species (68). The molecular peak was at m/e 151, with an intensity as great as 60% (69). Below is the suggested fragmentation pathway (62).



Secondary ion mass spectrometry (70) using silver showed $(M + H)^+$ and $(Ag + M)^+$ adducts. Protonated amantadine gave rise to the fragment ion $(M + H - NH_3)^+$.

Mass spectrometry combined with gas chromatography has been used to determine amantadine in biological tissues and fluids, *cf.* section 5.5.

2.4 Infrared Spectrometry

Figure 3 shows the infrared spectra of a commercial preparation of amantadine hydrochloride using mineral oil and potassium bromide (71). The instrument used was a Perkin-Elmer Model 983 Fourier transform infrared spectrometer. The minor differences in band intensities of the two spectra could be due to either pressure effects in the preparation of the potassium bromide pellet or