

The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents*

Roland W. Freudenmann¹, Florian Öxler² & Sabine Bernschneider-Reif²

Department of Psychiatry, University of Ulm, Ulm, Germany¹ and Department of Corporate History, Merck KGaA, Darmstadt, Germany²

ABSTRACT

Background Little is known about the origin of methylenedioxymethamphetamine (MDMA, ecstasy). The most commonly repeated statement in the medical literature is that MDMA was synthesized by the German pharmaceutical company Merck in 1912 in order to develop an appetite suppressor. **Aim** To reconstruct the true story of the first known description of MDMA at Merck using the original documents. **Methods** A systematic analysis of the original documents in Merck's historical archive in Darmstadt, Germany, was conducted (years 1900–60). **Results** There were no indications for plans to develop an appetite suppressant at Merck between 1900 and 1960. Although MDMA was, in fact, first synthesized at Merck in 1912, it was not tested pharmacologically because it was only an unimportant precursor in a new synthesis for haemostatic substances. The new pathway was patented in order to evade an existing patent by a local competitor. MDMA was called 'Methylsafrylamin' in 1912. In 1927 and 1959, the pharmacological effects of MDMA were studied at Merck, but not in humans. **Discussion** A systematic analysis of the original documents in the company's archive revealed that uncritical copy-paste procedures may have contributed to the famous myth that MDMA was patented as an appetite suppressor in 1912.

Keywords Ecstasy, history, MDMA, ring-substituted amphetamines.

Correspondence to: Roland Freudenmann, Department of Psychiatry, University of Ulm, Leimgrubenweg 12, 89075 Ulm, Germany.

E-mail: roland.freudenmann@uni-ulm.de

Submitted 4 January 2006; initial review completed 20 February 2006; final version accepted 17 March 2006

INTRODUCTION

The ring-substituted amphetamines methylenedioxymethamphetamine (MDMA) and its analogues, better known as 'ecstasy', have been among the most popular illegal psychotropic drugs since the mid-1980s [1–3]. Contrary to expectation, MDMA was discovered much earlier.

In the medical literature it is usually maintained that MDMA was first synthesized and patented by the German pharmaceutical company Merck in Darmstadt around 1912, with plans to market an 'anorectic drug' or 'appetite suppressor'. This statement has been repeated almost verbatim in reviews [1,4–9], textbooks [10], original articles [11] and also in American Federal sources such as websites of the US Drug Enforcement Administration [12]. Only a few authors have questioned the 'Merck story' [13–16]. These works, however, as well as the

small number of papers that deal specifically with the history of MDMA, do not provide detailed information about the substance's first known description [14,15,17–19].

It was our aim to reconstruct the true story about the origin of MDMA by means of the first systematic analysis of the original documents in Merck's historical archive in Darmstadt, Germany. (An unsystematic search of the Merck archive was performed around 1996 by the student Christian Beck. Some of his findings were published in German a few years later [18]. We would like to credit him for the idea to examine the Merck archive for MDMA-related material.)

METHODS

For the analysis, an interdisciplinary work group comprising a pharmacist specialized in the history of pharmacy (S. B. R.), a chemist (F. Ö.) and a physician (R. W. F.)

*This paper is based on a lecture given at the International Congress for the History of Pharmacy in Edinburgh in June 2005 and a poster presented at the DGPPN Congress in Berlin in November 2005.

was set up. All available documents in Merck's archive from 1900 to 1960 (patents, laboratory journals, annual laboratory reports, letters, interviews, memoirs, etc.) were searched systematically for MDMA-related information by hand-search or digitally (e.g. using internal databases). The search took into account that MDMA had several other names at Merck (see Results). All retrieved documents were evaluated in the context of the history of pharmacy. For patent law-related issues we collaborated with an international patent lawyer (Sabine Schoen, Merck). The archive work was conducted between February 2004 and March 2005. It was part of our project to digitize important documents in order to make them more accessible for the scientific community.

RESULTS

We identified MDMA-related documents in Merck's archive dating back to the years 1912, 1927, 1952 and 1959.

Our archive analysis confirmed that MDMA was, in fact, first synthesized at Merck as early as 1912, as proved by two documents which described explicitly the making of MDMA. The first is a German patent with the number 274350, from which both the original patent instrument ('Patent-Urkunde') and the patent specification ('Patentschrift') were retrieved (Fig. 1). The second is the *Annual Report for 1912 (Jahresbericht für 1912)* of Merck's 'Scientific Laboratory' (the German phrases are direct quotes from the documents, and English citations are direct translations from the German originals).

However, in these documents there were *no indications for plans to develop an appetite suppressant*. MDMA was mentioned only casually and without being called 'MDMA'. In the patent specification, MDMA appeared only as a chemical formula and in the annual report it was referred to as 'Methylsafrylamin'. The accurate background for the first synthesis of MDMA was that Merck wanted to find and patent pathways leading to haemostatic substances, not appetite suppressors. The company tried to evade an existing patent for the synthesis of a clotting agent called 'Hydrastinin' held by the German competitor Farbenfabriken Elberfeld und Decker or Bayer/Elberfeld, as stated explicitly by the head of Merck's laboratory, Dr Walter Beckh (1870–1915) in the *Annual Report for 1912*.

Beckh and his coworker, Dr Otto Wolfes (1895–1942), believed that the methylated analogue of hydrastinin, methylhydrastinin, might be similarly effective. They requested the third laboratory member, Dr Anton Köllisch (?–1916), to develop syntheses for methylhydrastinin and new patentable syntheses for hydrastinin. Once available, methylhydrastinin was tested at Merck's laboratory and externally (Dr Gustav Landmann, Frank-

furt, and Professor Robert Heinz, Erlangen). It proved to be equivalent to the reference haemostatics hydrastinin and cotarnin. Methylhydrastinin was also tested in humans in 1912 in a Berlin hospital. Results must have been promising, because Köllisch later worked on a higher yield of the synthesis. The new syntheses were then secured by patent 274350 and a second patent filed on Christmas Eve 1912 (patent 279194, 'Verfahren zur Darstellung von Hydrastinin-Derivaten').

According to the patent instrument the patent 274350 was assigned 'to the company E. Merck in Darmstadt' by the German Imperial Patent Office in Berlin (Fig. 1). It began on 24 December 1912, when the application for the patent was filed. The patent specification described the newly developed chemical reactions starting from different basic compounds with examples. In the fourth example, MDMA was mentioned without a name as one of many chemical intermediates ($\text{CH}_2 \cdot \text{O}_2 : \text{C}_6\text{H}_3 \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{NH} \cdot \text{CH}_3$) with some chemical properties [e.g. colourless oil, boiling point 155° (Celsius) at 20 mm pressure, its salt forms white crystals which boil at 148–150°]. There were no signs of a particular interest in MDMA. The reaction leading to MDMA results from the addition of aqueous hydrobromic acid (HBr) to safrole and goes via MDA. The patent stated explicitly that the products of the synthesis were 'important intermediates for the manufacturing of therapeutically effective compounds', but the main background for the new syntheses (clotting agents) was not mentioned. Instead, Merck protected the whole group of reactions leading to the 'alkyloxyaryl-, dialkyloxyaryl- and alkylendioxyarylamino-propanes' described in the patent specification.

For the next 15 years MDMA was not mentioned in the archive files. In 1927, Merck's laboratory was interested in adrenaline- or ephedrine-like substances on the basis of safrole. Merck's chemist, Dr Max Oberlin (1896–?), noted MDMA's structural similarity to ephedrine and adrenaline and probably rediscovered patent 274350 because it also began from safrole and expired in 1927. After some basic chemical studies he compared MDMA, now called 'Safryl-methyl-amin', and its two analogues 'Eugenyl-methyl-amin' and 'Methyl-eugenyl-methyl-amin' with ephedrine according to the *Annual Report for 1927*. As far as is known, these investigations were the *first proven pharmacological tests* with MDMA. MDMA was transformed from a free base to a hydrochloride salt for the testing. Unfortunately, no further details about the experimental setting could be found. MDMA's effects on blood glucose levels were comparable to high doses of ephedrine. MDMA was as effective as ephedrine at vascular smooth muscle tissue and stronger at the uterus, but devoid of a 'local effect at the eye'. Oberlin concluded that the substance does not have 'pure

Figure 1 Patent instrument no. 274350 ('Patent-Urkunde') from 1912. The text states: 'Subject of the patent is: Procedure for the manufacturing of alkyloxyaryl-, dialkyloxyaryl- and alkylendioxyarylaminoopropanes and their at the nitrogen monoalkylated derivatives' ('Gegenstand des Patentees ist: Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylaminoopropanen bzw. deren am Stickstoff monoalkylierten Derivaten'). 'Beginning of the patent: December 24th 1912' ('Anfang des Patentees: 24. Dezember 1912'). The document refers to the patent law from April 7th 1891 and June 6th 1911



sympathetic effects'. MDMA showed the highest toxicity of the three bases and ephedrine. Despite these 'partly remarkable results of the pharmacological testing' the research was halted, 'particularly due to a strong price increase of Safryl-Methyl-Amin (intermediate in the synthesis of methylhydrastinin) in the meantime'. Oberlin recommended 'to keep an eye on this field'. He also provided the oldest structural formula of MDMA known today.

The next records of MDMA were detected in the archive material from 1952. Chemist Dr Albert van Schoor (?–1995) conducted a simple toxicological experiment documented only by a short note in his personal laboratory book (volume XVII, experiment 123a): '[...] After 30' 6 flies †', 'Flies lie in supine position, then death'. He called MDMA 'Methylsafrylamin' or

'IT61'. On a 'confidential' substance data card from 2 September 1952, MDMA was also referred to as '1-(2-Methylaminpropyl)-3,4-methylenedioxybenzol' along with some chemical properties (EMD 002640, formula $C_{11}H_{15}NO_2$, MW 193.25).

In 1959, Merck's chemist Dr Wolfgang Fruhstorfer (1926–) worked with MDMA and similar substances according to another 'confidential' substance data card (formula $C_{11}H_{15}NO_2$, MW 193.25, salt hydrochlorid, MW salt 229.71, date 03.08.1959, chemist Dr Fruhstorfer, remainder 3700 mg). Fruhstorfer was interested in the production of new stimulants. There were some insinuations of a cooperation with an institute for aviation medicine. Despite all efforts, it remains unclear whether he also investigated MDMA effects in humans.

Table 1 Milestones from the history of MDMA/ecstasy.

| Year | Event | Literature |
|--------|---|------------|
| 1912 | First synthesis of MDMA by Köllisch at Merck (Darmstadt, Germany), secured by German patent 274350 | |
| 1927 | First pharmacological tests with MDMA by Oberlin at Merck | |
| 1952 | Basic toxicological tests with MDMA by van Schoor at Merck | |
| 1953/4 | First formal animal study in five species using MDMA and seven other psychotropic drugs (University of Michigan); secret, US army-sponsored study, unpublished until 1973 | [14,17,23] |
| 1959 | Re-synthesis of MDMA by Fruhstorfer at Merck | |
| 1960 | First regular scientific paper on MDMA (in Polish) describing an MDMA synthesis | [24] |
| 1970 | First detection of MDMA in tablets seized in the streets of Chicago | [25] |
| 1978 | First MDMA studies in humans by Shulgin and coworkers reporting on chemistry, dosage, kinetics and psychotropic effects | [26,27] |
| 1984 | MDMA's street name 'ecstasy' was coined in California | |
| 1985–8 | MDMA became a Schedule I controlled substance in the United States and banned in most others soon thereafter | |

DISCUSSION

The true story about the origin of MDMA at the German pharmaceutical company Merck was reconstructed by the first systematic analysis of the original documents in the company's archive. Many important files, such as the oldest proven records of MDMA (patent 274350, *Annual Report for 1912*), were discovered, digitized and made accessible for the community.

The most important finding was that Merck did not want to produce and patent an appetite suppressor when MDMA was first synthesized in 1912, in clear contrast to what is usually claimed by the 'ecstasy' literature. MDMA was neither studied in animals nor humans at Merck around 1912. The first basic pharmacological tests using MDMA were performed by the company's chemists decades later (1927, 1952), but there was no indication of MDMA testing in humans until 1960. In 1912, the substance was merely a precursor in a new chemical pathway which was patented in order to avoid an existing patent for the synthesis of the clotting agent hydrastinine. MDMA, like other intermediates, became patented inadvertently because they were covered by the patent claim in the patent specification 274350. From a legal perspective, patent 274350 was a procedure patent. Substance patents were unknown in the German Empire in 1912.

An explanation for the erroneous association of MDMA with appetite suppressors might be that MDMA's analogue MDA was studied for its potential as an antidepressant and appetite suppressor by Smith, Kline and French between 1949 and 1957 [20,21].

Dr Anton Köllisch can be regarded as the person who first described a synthesis for MDMA. Accordingly, our archive search disproved that MDMA was discovered by German chemists Mannich and Jacobsohn around 1900 [10] or German Nobel Prize winner for Chemistry Fritz Haber (1868–1934) [22], as reported by some authors.

For a better overview on the history of MDMA/ecstasy we have summarized briefly the major milestones from the 'Merck era' and beyond in Table 1.

CONCLUSIONS

Uncritical 'copy-paste' procedures in the ecstasy literature may have contributed to the formation of the myth that MDMA was developed as an appetite suppressor at the German pharmaceutical company Merck just before World War I. The true story about the origin of MDMA was reconstructed by checking primary sources in the company's archive.

Declaration of interest

Sabine Bernschneider-Reif is Head of the Department Corporate History at Merck KGaA, Darmstadt, Germany.

References

- Kalant H. The pharmacology and toxicology of 'ecstasy' (MDMA) and related drugs. *Can Med Assoc J* 2001; **165**: 917–28.
- Freudenmann R. W., Spitzer M. The neuropsychopharmacology and toxicology of 3,4-methylenedioxy-N-ethylamphetamine (MDEA). *CNS Drug Rev* 2004; **10**: 89–116.
- Freudenmann R. W. ['Ecstasy', the drug of the techno generation: clinical aspects]. *Nervenheilkunde* 2005; **24**: 557–72.
- Climko R. P., Roehrich H., Sweeney D. R., Al-Razi J. Ecstasy: a review of MDMA and MDA. *Int J Psychiatry Med* 1986; **16**: 359–72.
- Steele T. D., McCann U. D., Ricaurte G. A. 3,4-Methylenedioxyamphetamine (MDMA, 'ecstasy'): pharmacology and toxicology in animals and humans. *Addiction* 1994; **89**: 539–51.
- Gouzoulis-Mayfrank E., Hermlle L., Kovar K. A., Sass H. [Entactogenic drugs 'ecstasy' (MDMA), 'eve' (MDE) and other ring-substituted methamphetamine derivatives. A new class of substances among illegal designer drugs?]. *Nervenarzt* 1996; **67**: 369–80.

7. Rochester J. A., Kirchner J. T. Ecstasy (3,4-methylenedioxyamphetamine): history, neurochemistry, and toxicology. *J Am Board Fam Pract* 1999; **12**: 137–42.
8. O'Leary G., Nargiso J., Weiss R. D. 3,4-Methylenedioxyamphetamine (MDMA): a review. *Curr Psychiatry Rep* 2001; **3**: 477–83.
9. Montoya A. G., Sorrentino R., Lukas S. E., Price B. H. Long-term neuropsychiatric consequences of 'ecstasy' (MDMA): a review. *Harvard Rev Psychiatry* 2002; **10**: 212–20.
10. Morgan J. P. Designer drugs. In: Lowinson J. H., Ruiz P., Millman R. B., Langrod J. G., editors. *Substance abuse. A comprehensive textbook*, ch. 21. Philadelphia: Lippincott, Williams & Wilkins; 2005, p. 367–73.
11. Schreckenberger M., Gouzoulis-Mayfrank E., Sabri O., Arning C., Zimny M., Zeggel T. *et al.* 'Ecstasy'-induced changes of cerebral glucose metabolism and their correlation to acute psychopathology. An 18-FDG PET Study. *Eur J Nucl Med* 1999; **26**: 1572–9.
12. Drug Enforcement Administration (DEA). Available at: <http://www.dea.gov/concern/mdma/mdma020700.htm> (accessed 22 October 2005).
13. Cohen R. S. 1995 Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; **19**: 1137–45.
14. Shulgin A. T. History of MDMA. In: Peroutka S. J., editor. *Ecstasy: the clinical, pharmacological and neurotoxicological effects of the drug MDMA*. Boston: Kluwer; 1990, p. 1–20.
15. Green A. R., Mechan A. O., Elliott J. M., O'Shea E., Colado M. I. The pharmacology and clinical pharmacology of 3,4-methylenedioxyamphetamine (MDMA, 'ecstasy'). *Pharmacol Rev* 2003; **55**: 463–508.
16. Grob C. S., Poland R. E. MDMA. In: Lowinson J. H., Ruiz P., Millman R. B., Langrod J. G., editors. *Substance abuse. A comprehensive textbook*, ch. 22. Philadelphia: Lippincott, Williams & Wilkins; 2005, p. 374–86.
17. Shulgin A. T. The background and chemistry of MDMA. *J Psychoact Drugs* 1986; **18**: 291–304.
18. Beck C. MDMA—Die frühen Jahre [MDMA—the early years]. In: Rättsch C., Baker J. R., Müller-Ebeling C., editors. *Jahrbuch für Ethnomedizin und Bewußtseinsforschung 1997/98*. Berlin, Germany: Verlag für Wissenschaft und Bildung; 2000, p. 95–125.
19. Green A. R., Cross A. J., Goodwin G. M. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxyamphetamine (MDMA or 'ecstasy'). *Psychopharmacology (Berlin)*, 1995; **119**: 247–60.
20. Smith Kline & French Laboratories. Report on clinical evaluation of SKF #5 (Amphedoxamine). Philadelphia, PA: Smith Kline & French Laboratories; 1957.
21. Yensen R., Di Leo F. B., Rhead J. C., Richards W. A., Soskin R. A., Turek B. *et al.* MDA-assisted psychotherapy with neurotic outpatients: a pilot study. *J Nerv Ment Dis* 1976; **163**: 233–45.
22. Poethko-Müller C. Ecstasy. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 1999; **42**: 187–95.
23. Hardman H. F., Haavik C. O., Seevers M. H. Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. *Toxicol Appl Pharmacol* 1973; **25**: 299–309.
24. Biniński S., Krajewski E. [Production of d,1-N-methyl-beta-(3,4-methylenedioxyphenyl)-isopropylamine and d,1-N-methyl-beta-(3,4-dimethoxyphenyl)-isopropylamine]. *Acta Polon Pharm* 1960; **17**: 421–5.
25. Gaston T. R., Rasmussen G. T. Identification of 3,4-methylenedioxyamphetamine. *Microgram* 1972; **5**: 60–3.
26. Shulgin A. T., Nichols D. E. Characterization of three new psychotomimetics. In: Stillman R. C., Willette R. E., editors. *The psychopharmacology of the hallucinogens*. New York: Pergamon Press; 1978, p. 74–83.
27. Anderson G. M. III, Braun G., Braun U., Nichols D. E., Shulgin A. T. Absolute configuration and psychotomimetic activity. 'QuaSAR' Research Monograph. *Natl Inst Drug Abuse* 1978; **20**: 8–15.