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The origin of MDMA ("Ecstasy") – separating the facts from the myth

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MDMA (3,4-methylenedioxy-*N*-methylamphetamine), better known as "Ecstasy", is a synthetic drug with psychedelic and stimulant effects which has gained great popularity. It is closely tied to the underground scene, but has also been used therapeutically as an adjunct to psychotherapy. Both scientific as well as newspaper articles communicate faulty or incomplete information on the origin of MDMA and the role of the German pharmaceutical-chemical company Merck in its development. One of the most common misconceptions is that the substance was synthesized with the goal of creating an anorectic but was not marketed by Merck because of side effects. It was our aim to clarify the circumstances of MDMA's discovery at Merck. An interdisciplinary working group conducted a comprehensive analysis of the original documents in Merck's historical archive in Darmstadt, Germany. It could be revealed that MDMA was in fact mentioned for the first time in files from 1912, but not under this name. In the lab journals it was called "*Methylsafrylamin*". In a patent certificate it was mentioned only with its chemical structure. Merck applied for this patent to protect an alternative chemical method for synthesizing the styptic hydrastinine, not appetite suppressants. MDMA was not the key substance in this patent, only a precursor. Archive documents revealed that Merck's scientists did not perform basic pharmacological tests with MDMA (now called "*Safrylmethylamin*") before 1927. These tests were halted for economic reasons. In the 1950s, primitive toxicological studies were conducted but MDMA was not tested in humans.

1. Introduction

3,4-Methylenedioxy-*N*-methylamphetamine (MDMA, "Ecstasy") is a synthetic amphetamine derivative with psychedelic and stimulant effects (Freudenmann and Spitzer 2004). In the "Ecstasy" literature – which covers more than 100 years – a large number of synonyms can be found for the substance, which complicates the complete coverage of its history.[1]

Table: Synonyms for MDMA

- Metyl-safryl-amin
- Safryl-methyl-amin
- β-3,4-Methylendioxy-phenylisopropyl-methylamin
- 3,4-Methylendioxy-*N*-methylamphetamin
- 1-(2-Methylaminopropyl)-3,4-methylendioxybenzol
- 2-Methylamino-1-(3,4-methylendioxyphenyl)-propan
- *N*-Methyl-α-Methylhomopiperonylamin
- 3,4-Methylenedioxymethamphetamine
- *N*-Methyl-3,4-methylenedioxyamphetamine
- *N*,α-Dimethyl-3,4-methylenedioxyphenetyleamine
- *N*,α-Dimethyl-homopiperonylamine
- *N*,α-Dimethyl-β-(3,4-methylenedioxyphenyl)-ethylamine
- *N*-Methyl-β-(3,4-methylenedioxyphenyl)-isopropylamine
- 2-Methylamine-1-(3,4-methylenedioxyphenyl)-propane
- *N*,α-Dimethylbenzodioxole-5-ethylamine
- "Ecstasy", "Adam", "XTC", "MDM, "E." ...

MDMA belongs to the arylalkylamine group like phenylethylamine, ephedrine or norephedrine with the parent substance amphetamine.[2] It is a psychoactive compound with structural similarities to both the stimulant amphetamine and the psychedelic phenethylamine mescaline.

Because of the unique combination of stimulant and psychotomimetic properties MDMA has been classified as an "entactogen" (Nichols 1986). MDMA (and some of its analogs) produced a state of increased energy, reduced anxiety, lowered defensiveness, and a feeling of "closeness" to other persons, particularly after intake in music clubs and larger crowds. MDMA's effects mainly result from an increased synaptic availability of serotonin (5-HT) based on serotonin re-uptake inhibition and serotonin release from presynaptic storages. The "stimulant" and emotional effects are mainly produced by the acute release of 5-HT, while the "hallucinogenic" effects of MDMA are mainly evoked by direct interactions with postsynaptic 5-HT_{2A} receptors (similar to LSD, mescaline, DOM). In 1986, MDMA, methylenedioxymetamfetamine or (1-(1,3-benzodioxol-5-yl)-propan-2-yl)(methyl)azane,[3] became an illegal substance according to the "United Nations' Commission on Narcotic Drug Laws". In Germany and most other countries it is listed in the most restrictive category of narcotics today.[4]

It seems necessary to give rise to a scientific debate about the history of MDMA, a substance which has been

at the centre of a virulent controversy since the early 1980s, a substance which has created its own subculture in the Techno Music and clubbing scene: In 1997, Matthew Collin and John Godfrey described that ecstasy subculture offers the "best" entertainment, which is up for grabs in the market at the moment. It is a combination of technologies – musical, chemical and computer based – providing a changed awareness, providing experiences, which change the way of thinking, feeling, acting, living (Collin and Godfrey 1997). "Ecstasy" has gained great popularity worldwide as a substance of abuse, but has also been used by experimental psychologists as an adjunct to psychotherapy in the 1970s (i.e. before it became a federally controlled substance). Even today, it pits proponents of its use as an adjunctive psychiatric treatment against those who argue that it poses a grave threat to public health and safety, e.g. because of MDMA's toxic effects to central nervous serotonergic neurotransmission and fatal intoxications. It is an illegal drug and cannot be prescribed. On the other hand, the US-based organisation MAPS[5] still wants to get MDMA approved by the FDA as an augmentation to psychotherapy in post-traumatic stress disorder. Both the scientific community as well as the public are still grappling with the perception of MDMA twenty years after it first became popular in the streets (Johnston et al. 2003; Freudenmann and Spitzer 2004).

Numerous publications deal with the history and development of this illegal drug, not only scientific articles and reviews, but also newspapers and websites.

But what is said about the first synthesis of MDMA and the pioneering pharmacological research on the substance? The most often repeated statements about the origin of MDMA in the literature are:

1. MDMA was first synthesized/patented in 1912/4 at the German pharmaceutical company Merck in order to create an anorectic or a psychoactive substance but was not marketed because of side effects. 2. MDMA was intended for use by soldiers in World War I. 3. MDMA was discovered by Fritz Haber, a German Nobel Prize winner for chemistry, while working on his doctoral thesis. 4. MDMA was discovered by the German chemists Carl Mannich and Willy Jacobsohn at Merck in Darmstadt.[6]

Obviously, these statements are contradictory, and the "Ecstasy" literature appears to communicate faulty or incomplete information about the origin of MDMA. Many authors apparently repeated "historical facts" from other publications uncritically and without checking the original sources. This resulted in the formation of the above mentioned "myths about the origin of MDMA". Many errors can be also attributed to the confusion of substances, misspelling of names, places, dates and historical facts.

Exceptions are works by Charles Grob and Russell Poland (Grob and Poland 2005), Julie Holland (Holland 2001) and the paper by Christian Beck (Beck 1997/98). The latter is pioneering but rarely cited by the scientific community because it was published in German. Many sources mentioning the use of MDMA as an appetite suppressant point to a publication by Alexander Shulgin in 1990, called 'History of MDMA' (Shulgin 1990). However, Shulgin explicitly stated that the patent by the company Merck which first mentioned MDMA in 1912 does not specify any pharmacological use at all. In conclusion, it was our aim to clarify the circumstances of the discovery of MDMA and to separate the facts from the myths by checking the original sources.

2. Investigations and results

For this purpose an interdisciplinary working group searched the historical archives at Merck in Darmstadt, Germany, for original information about the discovery of MDMA. All available documents (including memoirs and personal communications) between 1910 and 1960 were included in our comprehensive analysis of documents, many of which had not been reviewed for decades. These works were performed by a pharmacist (SBR), a chemist (FÖ), a physician (RWF) and an international patent lawyer.[7] It was part of the project to make important historical material more accessible for the scientific community. Accordingly, we digitalized all of the relevant certificates and laboratory notes of the chemists who first worked with MDMA. They are available at request at Merck's historical archive for further studies.

In addition to our analysis of files in Merck's historical archive, we collected and reviewed many original documents often referred to or mentioned in association with the discovery of MDMA. Some of them dated back to the 1890s. We set out to confront the most common statements about the origin of MDMA point by point with our analysis of the primary document sources.

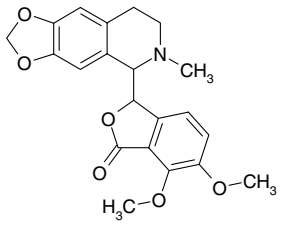
It was easy to reject statement 3 about the origin of MDMA (see above). Fritz Haber's thesis from 1891 work does not at all mention MDMA, only a substance close to MBDB, another ring-substituted amphetamine. Similarly, myth number 4 was easily disproved. According to Merck's historical personnel files it could be established that Carl Mannich never worked with the company. In a work from 1910, co-authored by Willy Jacobsohn, he described the "valuable pharmacological effects" of "organic phenol-like basic substances", in particular those of "hordenin". He tried to synthesize related substances and characterized 3,4-methylendioxyphenyl-isopropylamine as MDA, not MDMA (Mannich and Jacobsohn 1910). Apart from the similarity of the acronyms MDA and MDMA the two substances are also chemically and pharmacologically closely related which might explain the mix-up in some publications. MDA differs from MDMA only by a single CH_3 group in the side chain of the molecule. It has comparable psychotropic effects and is an abused substance, too (called "Love (Drug)" in the streets). Moreover, MDA is the active metabolite of MDMA.

The documents in Merck's historical archive were used to reconstruct the true circumstances of the first description of MDMA at Merck. Our findings did not support the abovementioned statements no. 1 and 2 about the origin of MDMA. In the following, the background of the first specification of arylalkylamines in general and MDMA in particular at Merck is given:

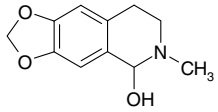
Since the earliest experiments with isoquinoline alkaloids, scientists had been interested in the properties of hydrastine and hydrastinine. These substances seemed to be promising treatments for abnormal bleeding, styptics: *„Die Base Hydrastinin ($C_{11}H_{13}NO_3$) ist ein Oxidationsproduct des [...] Alkaloids Hydrastin ($C_{21}H_{21}NO_6$) und entsteht aus diesem nach [Martin] Freund und Will (Bericht[e] d[er] chem[ischen] Ges[ellschaft] 1886, 2797 u. 1887, 89) durch Erwärmen mit verdünnter Salpetersäure"*.[8]

Several styptic drugs were in the Merck pipeline in the very late 19th century: "*Stypticin*" (Cotarninum hydrochloricum for medical use) was well known since 1896.[9] The important hydrastinine was isolated from *Radix Hydrastis Canadensis* based on a method developed by Prof. Martin Freund in Frankfurt.[10] Merck started working with the sub-

Scheme 1



Hydrastine



Hydrastinine [1-hydroxy-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline]

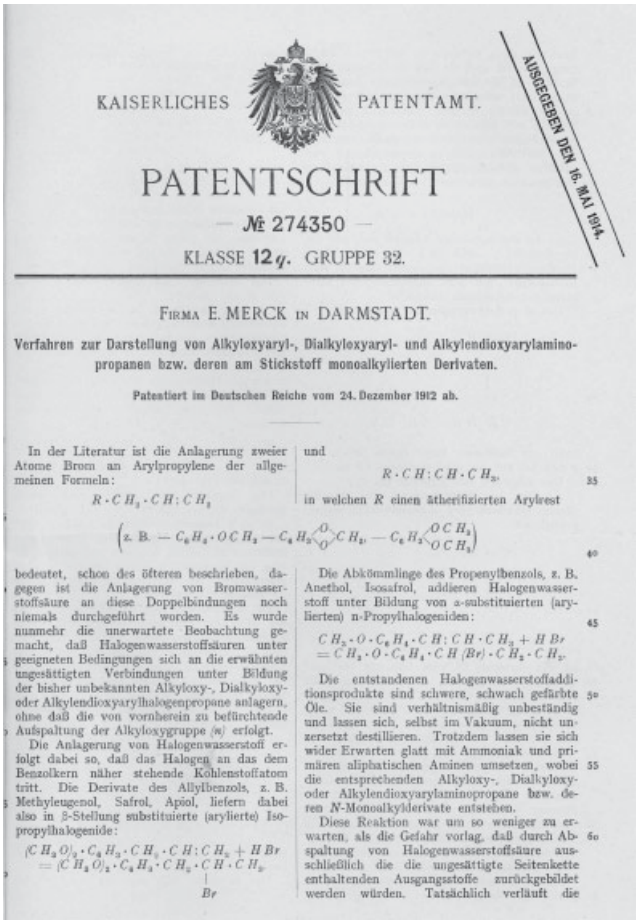
stance in 1892, as could be shown by the company's 1892 report concerning new pharmaceutical products which mentioned "Hydrastininum hydrochloricum Merck-Freund".[11]

The drug hydrastinine became more and more expensive because the naturally occurring plant became rare and cultivation attempts failed.[12] Therefore, Merck was interested in finding new ways for a chemical synthesis. Already in 1907 Merck tried to use narcotine for producing hydrastine from which the desired substance hydrastinine can be obtained in a second step: *„Eine äusserst rentable Veredlung würde in der Verwandlung des Narcotins in Hydrastin bestehen; das Hydrastin kostet ungefähr das zwanzigfache des Narcotins. Beide Körper stehen chemisch in naher Beziehung, da das Narcotin methoxyliertes Hydrastin ist […] Die Anstellung von Versuchen [ist] gewiss empfehlenswert"*.[13] In 1910, Dr. Hermann Decker at the organic laboratory of the Königlich Technische Hochschule Hannover offered Merck a new procedure for synthetic production of both hydrastine and hydrastinine: *„[Ich] bekomme ein vollkommen mit dem Ihrigen identisches Produkt. Das sich zu einem Preise herstellen lassen wird, der ganz erheblich nicht nur unter denjenigen [!] des Hydrastinins, sondern auch unter demjenigen des Hydrastins sich stellen wird. Das Verfahren ist zum Patent angemeldet."*[14] For some reason, Decker did not sign the contract with Merck but with Bayer/Farbenfabriken Elberfeld, another German pharmaceutical company.[15] The competition with Bayer forced Merck's scientists to try and find patentable ways to synthesize hydrastinine or to find new styptic agents. In Merck's historical archives we were able to discover the annual reports of the scientific laboratory from 1911 and 1912. They provide information about the endeavours to establish Merck in this area. Here we cite interesting passages from these annual reports: „*Beide Verfahren, sowohl das Bayer-Decker'sche wie das Freund'sche arbeiten billiger als die Herstellung des Hydrastinins aus der Droge möglich ist. […] Bayer geht vom Piperonal aus, dieses zum Hydrastinin aufbauend, während Freund von dem Berberin zum Hydrastinin abbaut. Wie zu erwarten wurde durch beide Synthesen als erstes natürlich Hydrastinin vom Markt verdrängt während als weitere Konsequenz sodann der Kampf zwischen den beiden neuen Verfahren entbrennen musste. Das umso mehr, als Bayer sein Hydrastinin mit grosser Reklame auf den Markt bringt, nicht nur unser Produkt verdrängend, sondern auch scheinbar mit der Absicht, das Hydrastinin an Stelle des Stypticins zu setzen. Ein Gegenzug der Fa. Merck erschien daher dringend geboten […* um] *patentrechtlich einwandfreie Verbesserungen oder Umgehungen des Decker'schen Verfahrens zu finden.*"[16]

The head of Merck's laboratory, Dr. Walter Beckh (1870–1915) and his co-worker Dr. Otto Wolfes (1895–1942) came up with the idea to synthesize and use 3-methyl-hydrastinine as a replacement for hydrastinine; they believed that the methylated analog of hydrastinine might be similarly effective. In the newly developed synthetic pathway to 3-methyl-hydrastinine MDMA was mentioned as one of several key precursors under the name of "*Methylsafrylamin*". Importantly, the company was interested in the new styptic 3-methyl-hydrastinine, not the precursor MDMA. The third lab member Dr. Anton Köllisch (?–1916) was requested to develop patentable syntheses: „*Aus dem Hydrastinin-Gebiet. Die Arbeiten fallen in zwei Categorien: 1. Die Herstellung von Körpern des Hydrastinin- und Cotarnintypus, welche jedoch vermöge ihrer Konstitution soweit von dem Hydrastinin selbst verschieden sind, dass die Patente der Farbenfabriken Elberfeld und Decker nicht mehr als fabrikationshindernd im Wege stehen. [Hierzu] gehören alle die Wege und Substanzen, welche nicht über das Homopiperonylamin sondern über dessen im Phenylrest oder vorzugsweise in der Seitenkette anders substituierte Homologe führen. Es hat sich […] gezeigt, dass man von Phenoläthern mit ungesättigten Seitenketten ausgehend, beispielsweise vom Safrol, oder Isosafrol oder auch vom Eugenoläthyläther, durch Anlagern von Bromwasserstoff an die Doppelbindung und darauf folgende Umsetzung mit Ammoniak oder Methylamin sehr bequem zu Phenylalkylaminen gelangen kann, die dann im weiteren Verfolg der Synthese zu am Kohlenstoff methyliertem Hydrastinin oder dessen im Phenylrest anderweitig substituierten Derivaten führen. Die erste, vollständig nach diesen Gesichtspunkten ausgeführte Synthese wurde, vom Safrol ausgehend, von Herrn Dr. Köllisch bearbeitet, und führte […] zum Methylhydrastinin. Die Substanz wurde inzwischen sowohl in unserem eigenen Laboratorium wie auch bei Herrn Professor Heinz auf ihre styptische Wirkung untersucht und sowohl dem Hydrastinin als auch dem Cotarnin gleichwertig befunden […]. Die Reaktion selbst, ebenso wie die Herstellung der letzten Zwischenprodukte, wurde zum Patent angemeldet.*"[17]

As soon as possible, the new compound 3-methyl-hydrastinine was tested at Merck's laboratory and also externally. It proved to be equivalent to the reference haemostyptic substances hydrastinine and cotarnine. Therefore, it was also tested in human subjects in a hospital in Berlin the same year. No results were reported. However, they must have been promising, because Köllisch tried to increase the yield of the synthesis. In 1912, Merck applied for two patents (Figs. 1 and 2).

The first and more important patent with the No. 274 350 is entitled *„Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylaminopropanen bzw. deren am Stickstoff monoalkylierten Derivaten"*. It was assigned to the company E. Merck by the German Imperial Patent Office in Berlin. It started on December 24, 1912, when the patent application was filed. It is a procedural patent for



KAISERLICHES PATENTAMT.

AUSGEGEBEN DEN 16. MAI 1914.

PATENTSCHRIFT

— № 274350 —

KLASSE 12 *q*. GRUPPE 32.

FIRMA E. MERCK IN DARMSTADT.

Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylaminopropanen bzw. deren am Stickstoff monoalkylierten Derivaten.

Patentiert im Deutschen Reiche vom 24. Dezember 1912 ab.

In der Literatur ist die Anlagerung zweier Atome Brom an Arylpropylene der allgemeinen Formeln:

$$R \cdot C H_2 \cdot C H : C H_2$$

und

$$R \cdot C H : C H \cdot C H_3,$$

in welchen R einen ätherifizierten Arylrest

(z. B. $-C_6H_4 \cdot O C H_3$, $-C_6H_3\langle{}^{O}_{O}\rangle C H_2$, $-C_6H_2\langle{}^{O C H_3}_{O C H_3}$)

bedeutet, schon des öfteren beschrieben, dagegen ist die Anlagerung von Bromwasserstoffsäure an diese Doppelbindungen noch niemals durchgeführt worden. Es wurde nunmehr die unerwartete Beobachtung gemacht, daß Halogenwasserstoffsäuren unter geeigneten Bedingungen sich an die erwähnten ungesättigten Verbindungen unter Bildung der bisher unbekannten Alkyloxy-, Dialkyloxy- oder Alkylendioxyarylhalogenpropane anlagern, ohne daß die von vornherein zu befürchtende Aufspaltung der Alkyloxygruppe *(u)* erfolgt.

Die Anlagerung von Halogenwasserstoff erfolgt dabei so, daß das Halogen an das dem Benzolkern näher stehende Kohlenstoffatom tritt. Die Derivate des Allylbenzols, z. B. Methyleugenol, Safrol, Apiol, liefern dabei also in β-Stellung substituierte (arylierte) Isopropylhalogenide:

$$(C H_3 O)_2 \cdot C_6 H_3 \cdot C H_2 \cdot C H : C H_2 + H Br = (C H_3 O)_2 \cdot C_6 H_3 \cdot C H_2 \cdot \underset{Br}{C H} \cdot C H_3.$$

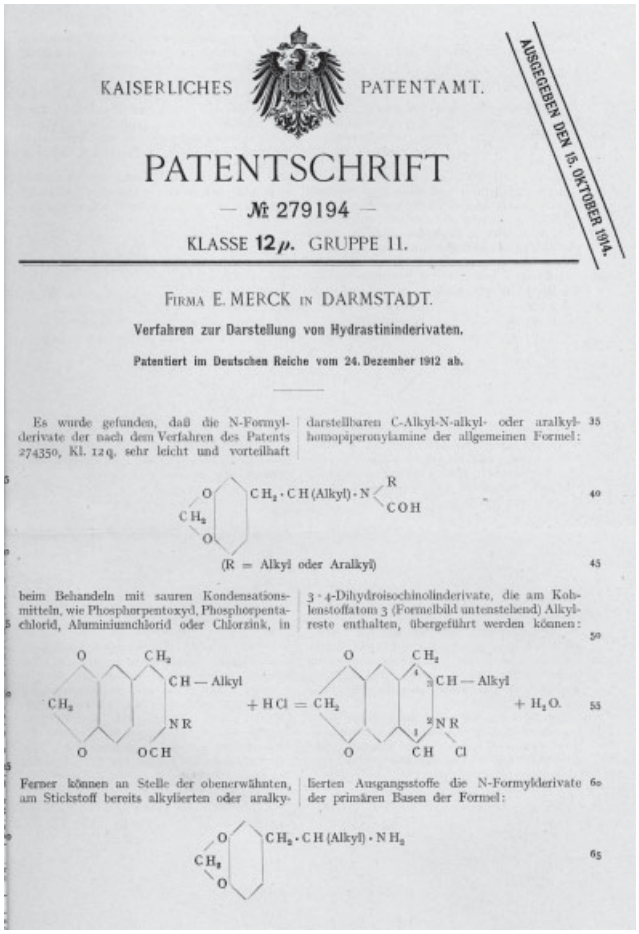
Die Abkömmlinge des Propenylbenzols, z. B. Anethol, Isosafrol, addieren Halogenwasserstoff unter Bildung von α-substituierten (arylierten) n-Propylhalogeniden:

$$C H_3 \cdot O \cdot C_6 H_4 \cdot C H : C H \cdot C H_3 + H Br = C H_3 \cdot O \cdot C_6 H_4 \cdot C H (Br) \cdot C H_2 \cdot C H_3.$$

Die entstandenen Halogenwasserstoffadditionsprodukte sind schwere, schwach gefärbte Öle. Sie sind verhältnismäßig unbeständig und lassen sich, selbst im Vakuum, nicht unzersetzt destillieren. Trotzdem lassen sie sich wider Erwarten glatt mit Ammoniak und primären aliphatischen Aminen umsetzen, wobei die entsprechenden Alkyloxy-, Dialkyloxy- oder Alkylendioxyarylaminopropane bzw. deren *N*-Monoalkylderivate entstehen.

Diese Reaktion war um so weniger zu erwarten, als die Gefahr vorlag, daß durch Abspaltung von Halogenwasserstoffsäure ausschließlich die die ungesättigte Seitenkette enthaltenden Ausgangsstoffe zurückgebildet werden würden. Tatsächlich verläuft die

Fig. 1: Patent instrument and patent specification 274 350, 1912



KAISERLICHES PATENTAMT.

AUSGEGEBEN DEN 15. OKTOBER 1914.

PATENTSCHRIFT

— № 279194 —

KLASSE 12 *p*. GRUPPE 11.

FIRMA E. MERCK IN DARMSTADT.

Verfahren zur Darstellung von Hydrastininderivaten.

Patentiert im Deutschen Reiche vom 24. Dezember 1912 ab.

Es wurde gefunden, daß die N-Formylderivate der nach dem Verfahren des Patents 274350, Kl. 12 q, sehr leicht und vorteilhaft darstellbaren C-Alkyl-N-alkyl- oder aralkyl-homopiperonylamine der allgemeinen Formel:

(R = Alkyl oder Aralkyl)

beim Behandeln mit sauren Kondensationsmitteln, wie Phosphorpentoxyd, Phosphorpentachlorid, Aluminiumchlorid oder Chlorzink, in 3·4-Dihydroisochinolinderivate, die am Kohlenstoffatom 3 (Formelbild untenstehend) Alkylreste enthalten, übergeführt werden können:

Ferner können an Stelle der obenerwähnten, am Stickstoff bereits alkylierten oder aralkylierten Ausgangsstoffe die N-Formylderivate der primären Basen der Formel:

Fig. 2: Patent instrument and patent specification 279 194, 1912

compounds which are important key precursors for therapeutics.[18] However, no specific purpose or medical indication such as the use as an appetite suppressant was mentioned. The second patent No. 279 194 *„Darstellung von Hydrastininderivaten“* is closely related to the first and described syntheses of hydrastinine derivatives. A thorough analysis of the patent specification No. 274 350 showed that MDMA was not the purpose of the patent. It was mentioned only as a by-product and chemical intermediate in one the pathways which started from safrole (Scheme).

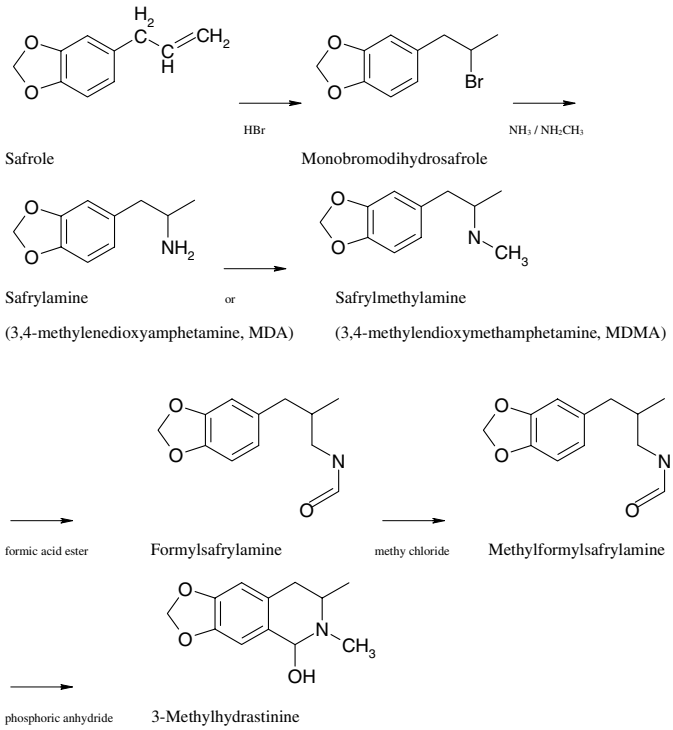
In the patent specification MDMA appeared as a chemical formula and not under the name “MDMA”: $CH_2{-}O_2 : C_6H_3{-}CH_2{-}CH(CH_3){-}NH{-}CH_3$.

In Merck’s laboratory reports, the substance was referred to as “*Metyl-safryl-amin* (*Metylsafrylamin*)”, “*Safryl-methyl-amin”* or “*N-Methyl-α-Methylhomopiperonylamin”*.

In the early 20th century the German Empire did not issue patents for single chemical substances, only procedural patents which protect new syntheses: *„Unser Patentgesetz nimmt von der Patentierung aus die unsittlichen Erfindungen, sowie die chemischen Stofferfindungen […]; ein chemischer Stoff ist als Naturstoff nicht menschliche Schöpfung und darum nicht Gegenstand des Erfinderrechts. [Auch] Arzneimittel […] sind der Patentierung entzogen. […] Der Ausschluss der Patentes […] bezieht sich nicht auf das Verfahren, so dass nur das Stoffpatent, nicht das Verfahrenspatent ausgeschlossen ist“*.[19] Accordingly, Merck’s patent No. 274 350 does not patent MDMA as a substance (although the compound appeared in the patent specification), but all the new pathways described in the specification. The patents and also all other archive documents did not provide any evidence of a specific pharmacological interest in the precursor MDMA or of plans to create an anorectic.[20] Obviously, it was never intended for sale. MDMA was not tested pharmacologically in 1912. Therefore, no one was able observe side effects which stopped the marketing of the substance.

On the other hand, methylsafrylamine remained a key chemical precursor. In 1927 – the procedural patent was about to expire that year – Dr. Max Oberlin (1896-?) at Merck resumed the work in this field. He was looking for new substances with adrenaline-like or ephetonine-like effects. MDMA has a structure similar to ephetonine (Merck launched this synthetic ephedrinum in 1927). Oberlin believed that it would be desirable to learn more about MDMA, now called “*Safryl-Methyl-Amin*”. That is why he performed studies on the properties of three chemically similar substances (“*Safryl-Methyl-Amin*”, “*Eugenyl-Methyl-Amin*”, “*Methyl-Eugenyl-Methyl-Amin*”) and noted that “*Safryl-Methyl-Amin*” (MDMA) was as effective as ephetonine at vascular smooth muscle tissue, was stronger at the uterus, but was devoid of a “local effect at the eye”. He concluded correctly that the substance did not only have “pure sympathetic effects”. Its effects on blood glucose levels were comparable to those of high doses of ephetonine. Safrylmethylamine was the most toxic of the four substances. Despite these “partly remarkable results of the pharmacological testing” the research was halted “particularly due to a strong price increase of safrylmethylamine (intermediate in the synthesis of methylhydrastinine) in the meantime”. Oberlin recommended “to keep an eye on this field”.[21] His simple experiments only aimed at exploring the substances potential pharmacological action. The files from 1927 (not 1912) were the first indications

Scheme 2



for pharmacological tests with MDMA at Merck. We were not able to reconstruct the methods Oberlin used (Animal experiments? Isolated organs?), but as far as we can tell he did not perform studies in humans. Nothing was said about psychotropic effects. Research on the substance was stopped for economic reasons and the substance was buried in oblivion for some decades.

Statements in the literature saying that the synthesis of MDMA in 1912 was intended for soldiers in World War I are false. This misconception might originate from a mix-up with a research project in the 1950s when the U.S. Army tested MDMA and other psychotropic agents (Hardman et al. 1973; Shulgin 1986, 1990). In that period, the German Bundeswehr was also interested in stimulants, particularly for jet fighter pilots. There was a basic increasing interest in amphetamine derivaties in the 1950s. Most probably scientists at Merck re-synthesized the substance while searching for stimulants and circulatory medications. Initially, primitive toxicological studies were conducted as part of a test series by the chemist Dr. Albert van Schoor (?-1995) in 1952 (Fig. 3). He wrote in his personal laboratory journal: *"After 30 minutes 6 flies †", "Flies lie in supine position, then death"*.[22] No data about MDMA dosage and the route of administration was found. Pharmacological studies were performed as well, but no reason for additional work in this area was seen. On a "confidential" substance data card dated "02. 09. 1952", MDMA was also found under the name of "*1-(2-Methylaminpropyl)-3,4-methylendioxybenzol*" along with some of its chemical key properties ("EMD 002640, Formula $C_{11}H_{15}N0_2$, MW 193.25").

In 1959, Merck's chemist Dr. Wolfgang Fruhstorfer (*1926) worked with MDMA and similar substances, as revealed by another "confidential" substance data card dated "03.08.1959" which mentioned the substance together with its formula and some basic chemical properties ("Formula $C_{11}H_{15}N0_2$, MW 193.25, Salt Hydrochlorid, MW Salt 229.71, Date 03. 08. 1959, Chemist Dr. Fruhstorfer, Remainder 3700 mg") and a laboratory journal (Fig. 4). Fruhstorfer was interested in the development of new stimulants. He synthesized "*1-(3,4-Methylendioxyphenyl)-2-methylaminopropan*" (biographical reference: "*DRP 274 350"* and *"Friedlaender 12; 768*"), numbered "*H 671 (lfd. Nr. 5709) 30. 7. 1959*" and brought this product to pharmacological testing. H 671 was identified to be MDMA.

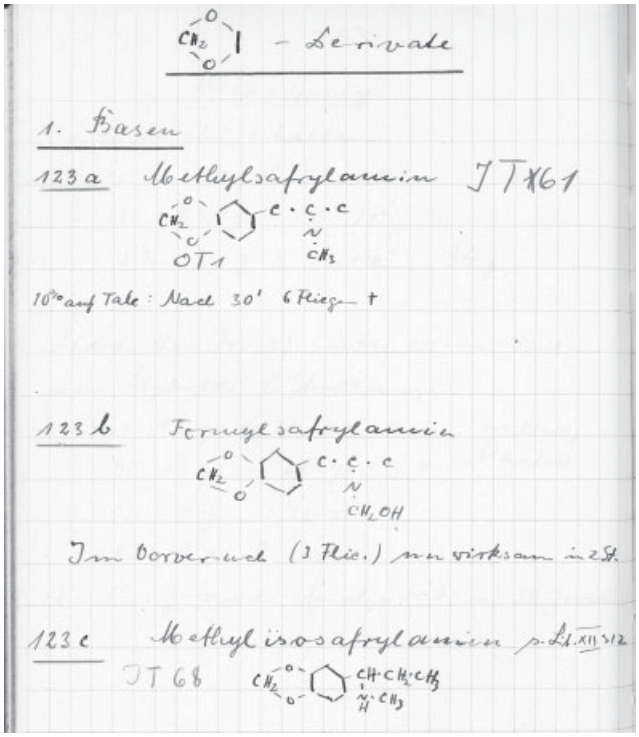


Fig. 3: MA Laboratory journal XVII Dr. van Schoor 1952, S. 122

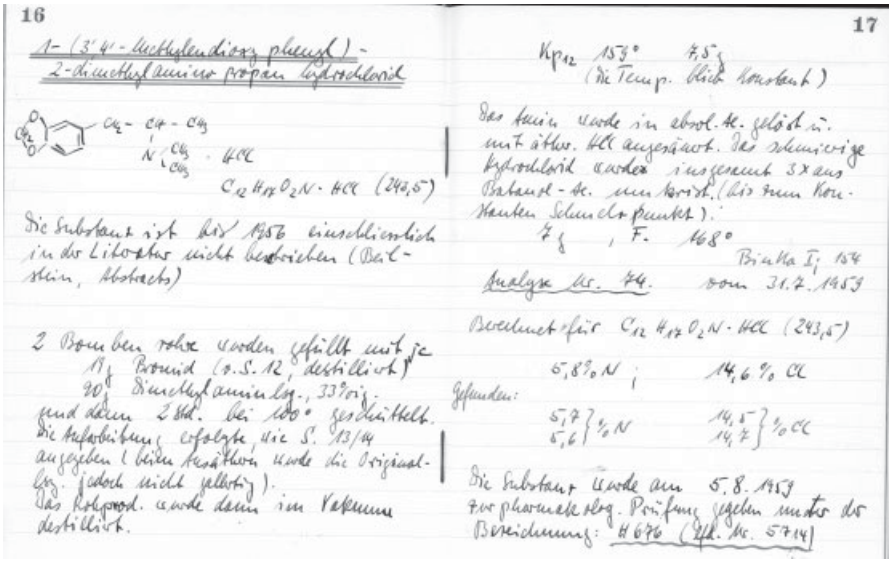


Fig. 4:
MA Laboratory journal X Dr. Wolfgang Fruhstorfer 1959, p. 16/17

A series of very similar substances such as *"H 676, 1-(3′,4′-Methylendioxyphenyl)-2-dimethylaminopropanhydrochlorid"* was also tested pharmacologically[23]. In the archive material from the 1950s there were some insinuations of a co-operation with an institute for aviation medicine but we did not find any proof that MDMA was administered to humans. Substituted phenylethylamines seemed to be more useful in these areas. As a psychotropic stimulant, Reaktivan® was finally launched in 1960. Its chemical structure is not related to that of MDMA.

The first regular scientific paper on MDMA was published in 1960 and described a synthesis for MDMA. It is written in Polish and almost unknown (Biniecki and Krajewski 1960). Alexander Shulgin re-synthesized the substance around 1965 while working at Dole Pharmaceutical Company. Although he was not the first to conduct pharmacological studies with MDMA, he did publish the first scientific article on the drug's *psychotropic* effect in *humans* in 1978 (Shulgin and Nichols 1978).

MDMA became available world-wide during the 1980s and the street name "Ecstasy" was coined. Since the mid 1980s it is an illegal substance which is listed in the most restrictive category of narcotics in most countries (e.g. Schedule 1 controlled in the United States). Recently, MDMA is being studied as an adjunct treatment in the psychotherapy of post-traumatic stress disorder (Check 2004). Both the history and future of this substance will continue to fascinate scientists and the general public for years to come.

[1] Shulgin spoke out on the history of MDMA in several publications. He falsely associated the patent from 1912 with the term "MDMA", although the patent does not mention the substance with this name see below). *"Here MDMA was synthesized in two steps from safrol"* (Shulgin 1986)

[2] Amphetamine was synthesized in 1887 by Lazar Edeleanu. Edeleanu L (1887) Berichte der Deutschen Chemischen Gesellschaft 20: 616–622. Cf. Terres E (1931) L[azar] Edeleanu [1861–1941] zum 70. Geburtstag, Angewandte Chemie 44: 749

[3] The substance has no INN (International Nonproprietary Name) notation. Therefore the short term or the IUPAC name is used in the "Betäubungsmittelgesetz"

[4] "Betäubungsmittelgesetz (BtMG), Fassung vom 1. März 1994 (BGBl. I S. 358, BGBl. III 2121-6-24), Anlage 1 zu § 1 Abs. 1, Änderung vom 28. 11. 2001 (16. BtMÄndG)". In appendix 1, MDA, MDMA, MDEA and MBDB can be found

[5] MAPS = The Multidisciplinary Association for Psychedelic Studies (www.maps.org)

[6] Exemplary cp: Szukaj M (1994) MDMA („Ecstasy") – gefährliche Droge oder Psychotherapeutikum? Der Nervenarzt 65: 802–805, p. 802: *„MDMA ist […] bereits 1914 von der deutschen Firma E. Merck aus den Stoffen Methamphetamin und Safrol (vermutlich als Appetitzügler) synthetisiert worden."* Keup W (1996) Ecstasy, Deutsche Apotheker Zeitung 136: 4503f.: *„[Die Substanz wurde] bereits 1912 bei Merck synthetisiert und 1914 als Anorektikum patentiert."* Morgan JP (2005) Designer Drugs (Chapter 21). In: Lowinson JH et al (ed) Substance Abuse. A Comprehensive Textbook, Philadelphia, p. 367–373. Poethko-Müller C (1999) Ecstasy. Bundesgesundheitsblatt. Gesundheitsforschung. Gesundheitsschutz 42: 187–195

[7] Sabine Schoen, Merck KGaA Darmstadt, Germany

[8] E. Merck's Jahresberichte über Neuerungen auf den Gebieten der Pharmakotherapie und Pharmazie 1889. Darmstadt: E. Merck 1890, p. 42f

[9] E. Merck's Jahresberichte über Neuerungen auf den Gebieten der Pharmakotherapie und Pharmazie 1895. Darmstadt: E. Merck 1896, p. 120–122

[10] In 1891, an agreement had been concluded with Prof. Dr. Martin Freund, Frankfurt a. M., concerning the profit participation on the sale of hydrastinine. Cf. MA R 5/23, especially letter of May 1, 1922

[11] E. Merck's Jahresberichte über Neuerungen auf den Gebieten der Pharmakotherapie und Pharmazie 1892. Darmstadt: E. Merck 1893. p. 74

[12] MA K 1/228 Betr. Decker, Dr., Hannover, Hydrastinin. Letter Gehe to Merck June 14, 1910

[13] MA F 3/11b Bericht über das Betriebsjahr vom 1. Januar bis 31. Dezember 1907 Abteilung I. C [Carl Scriba]. Cf. also MA F 6/8 (b) Tätigkeitsberichte und Laboraufzeichnungen Carl Scriba (1854–1929) [vor 1908] p. 27–35

[14] MA K 1/228 Betr. Decker, Dr., Hannover, Hydrastinin. Brief Decker to Merck May 10, 1910

[15] MA K 1/228 Betr. Decker, Dr., Hannover, Hydrastinin. Brief Decker to Merck June 27, 1910

[16] MA F 3/15(d) Jahresbericht 1911 Wissenschaftliches Laboratorium [Annual report 1911 Scientific Laboratory]. Gesamt-Bericht Dr. W. Beckh

[17] MA F 3/16(f) Jahresbericht 1912 Wissenschaftliches Laboratorium [Annual report 1912 Scientific Laboratory] p. 21–24 „Aus dem Hydrastinin-Gebiet", p. 105f. „Methylhydrastinin aus Safrol", p. 247f. „Methylhydrastinin". MA R 10 Patente Deutschland; cf. Chemisches Zentralblatt (1914), 2079. Prof. Robert Heinz worked at the University of Erlangen, Germany

[18] *„Die […] erhältlichen [Substanzen] sind wichtige Zwischenprodukte zur Herstellung therapeutisch wirksamer Verbindungen" – [„important intermediates for the manufacturing of therapeutically effective compounds"]*

[19] For the effective patent law in particular concerning „patentable inventions", „exceptions to patentable inventions" in detail, consult Kohler J (1900): Handbuch des Deutschen Patentrechts in rechtsvergleichender Darstellung. Mannheim, p. 171–176 and 657

[20] Most probably this rumor is based on confusing MDMA with MDA. The latter, and not MDMA, was tested for its anorectic effects by Smith Kline French in the 1950s

[21] MA F 3/31(i) Jahresbericht [annual report] 1927 Dr. [Max] Oberlin, p. 7f.

[22] MA Journal [Laboratory journal] XVII Dr. [A.] van Schoor 1952, p. 122

[23] MA Journal [Laboratory journal] X Dr. [Wolfgang] Fruhstorfer [1959], p. 10–26. In later journals of Fruhstorfer we see that he furthermore worked on the field of substituted phenylethylamines: e.g. MA Journal [Laboratory journal] XII Dr. [Wolfgang] Fruhstorfer XII [1960]

[24] E.g. „[Es wird auf] den schon lange gehegten Wunsch nach einem Stimulans, ähnlich der im Katovit enthaltenen Substanz [hingewiesen]. Die Suche nach einem solchen Stoff, der eher dem Pervitin als dem Ephedrin nahe stehen müsste (ohne sofort dem Opiumgesetz unterstellt zu werden) ist einer der Programmpunkte des Hauptlabors." [10. 7. 1958] MA K 16 Wiss[enschaftliche] Bespr[echungen]. Minutes 1. 1. 58–31. 12. 1959

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