

# 4-Dimethylaminopyridine as a catalyst in heroin synthesis

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## Abstract

In this paper, we describe an acetylating method for fast synthesis of heroin from morphine in the presence of 4-dimethylaminopyridine (4-DMAP) as a catalyst. In the reaction which led to heroin formation, the morphine base was subjected to a solution made up of 4-DMAP (catalyst), methylene chloride (solvent) and acetic anhydride (acetylating agent). We showed that in comparison with classic acetylating procedures, reaction time can be reduced from at least several hours at elevated temperatures to <10 min at room temperature. In general, reaction time is dependant on the molar concentration ratio between morphine and 4-DMAP.

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## 1. Introduction

Diacetylmorphine has had a long history since it was first synthesized by C.R.A. Wright in 1874 in the reaction where morphine was brought into a contact with an excess of acetic anhydride [1]. In Wright's original work, the substance was termed as tetracetylmorphine. Later, in 1898, the substance was commercially produced by Bayer Company in Eberfeld, Germany, and marketed under the name of Heroin [2]. Nowadays heroin is generally not used as a pharmaceutical (with some exceptions, i.e. heroin prescription programmes for dependent users which have been pioneered in Switzerland). Anyway, at the global level, due to high illicit production, it is one of the most significant illicit drugs in terms of treatment demand, hospitalisation, overdose, drug related mortality, involvement of organized crime and drug related violence [3]. So, it is not surprising that this drug is forensically (and toxicologically) still very interesting. Regardless of this fact, heroin synthesis has not changed much within a century. Some general ways of heroin synthesis that we have found in the literature were acetylation of morphine at elevated temperatures with an excess of acetic anhydride [1,4–8] or with acetic anhydride in combination with pyridine [9,10], benzene [11] or sodium acetate [12]. It

has been reported that the time needed for the acetylation to be completed is from several hours to a few days.

In this work, we describe a method of fast heroin synthesis, where 4-dimethylaminopyridine was used as a catalyst. 4-Dimethylaminopyridine, which has already been applied in some forensic investigations [13,14], has been reported as an excellent catalyst for acetylation of alcoholic and phenolic hydroxy groups [15]. A recent review on catalysis by 4-dialkylaminopyridines is given in [15].

## 2. Materials and methods

### 2.1. Chemicals

4-Dimethylaminopyridine (99%+, Aldrich, Steinheim, Germany) was used as a catalyst, morphine base was from Alkaloid (Skopje, Macedonia), acetic anhydride (Kemika, Zagreb, Croatia) and dichloromethane (Merck, Darmstadt, Germany) were of the analytical reagent grade.

### 2.2. Acetylation of morphine

To study acetylation of morphine by acetic anhydride in the presence of 4-dimethylaminopyridine, morphine base was subjected to a solution made up of 4-DMAP (catalyst), dichloromethane (solvent) and acetic anhydride (acetylating

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agent). Three experiments where reagents were mixed in different proportions were done. The prepared reaction mixtures were of the following composition:

*Mixture 1:* Morphine base (28.5 mg, 0.1 mmol); 4-dimethylaminopyridine (29.4 mg, 0.24 mmol); 1 ml of dichloromethane; 0.1 ml (1.06 mmol) of acetic anhydride ( $\text{Ac}_2\text{O}$ ).

*Mixture 2:* Morphine base (28.5 mg, 0.1 mmol); 4-dimethylaminopyridine (29.4 mg, 0.24 mmol); 1 ml of dichloromethane; 0.025 ml (0.26 mmol) of acetic anhydride ( $\text{Ac}_2\text{O}$ ).

*Mixture 3:* Morphine base (28.5 mg, 0.1 mmol); 4-dimethylaminopyridine (29.4 mg, 0.24 mmol); 1 ml of dichloromethane; 0.1 ml (1.06 mmol) of acetic anhydride ( $\text{Ac}_2\text{O}$ ).

Each reaction mixture was allowed to react at room temperature for approximately 5–6 min. Then a 100  $\mu\text{l}$  aliquot of mixture was washed with water (200  $\mu\text{l}$ ) and diluted (to approximately 1 ml) with dichloromethane. Water layer was discarded. Dichloromethane layer was dried by small amount of sodium sulphate. An amount of 1  $\mu\text{l}$  of dichloromethane fraction was analysed by capillary gas chromatograph hyphenated with a mass selective detector (GC–MS).

For the blank experiment, we prepared a mixture without a catalyst (4-DMAP) while other ingredients were the same as in mixture 3.

### 2.3. Identification of reaction products

The acetylation products were identified by GC–MS. The analyses were performed on a HP 5890 capillary gas chromatograph equipped with a mass selective detector (MSD) HP 5972 and an auto sampler. Detailed instrumental parameters were described in our previous work [16]. For this particular research only the modification of an oven temperature programming was applied. The temperature programme was 260  $^{\circ}\text{C}$  for 1 min, then to 280  $^{\circ}\text{C}$  with the rate of 13  $^{\circ}\text{C}/\text{min}$  and isothermal for 6 min.

## 3. Results and discussion

The reaction of heroin synthesis in the presence of acetic anhydride as the acetylating agent can be schematically presented as shown in Fig. 1. The reaction goes from morphine through 3-acetylmorphine to 3,6-diacetylmorphine—heroin ([7] and references herein). Acetylation of

the 3-hydroxy (phenolic) group of morphine which leads to the formation of 3-monoacetylmorphine is a relatively fast process, while additional acetylation of 6-hydroxy group which leads to heroin formation is a slower process.

In heroin synthesis, various experimental conditions have been applied (or reported) by different authors. Some data that we have found in the literature are collected in Table 1, where references are noted in the first column. In the second column (Table 1), the molar concentration ratio (given in rounded integer numbers) between morphine and acetic anhydride applied in the acetylation reaction is shown. Calculations of the molar ratios were done by the author of this article from data available in the original texts. Other information, i.e. reaction temperature, reaction time and use of additional solvents and/or chemicals, was taken from original works.

From Table 1, one can see that what almost all procedures have in common are elevated temperatures, while the reported time needed for acetylation to be completed is from several hours (except [12]) to a few days. From the same table a great diversity in the molar concentration ratios between morphine and acetic anhydride applied in the acetylation reaction can be noted. Pyridine and benzene are organic bases which force the acetylation reaction. Sodium acetate acts as a drying agent on one hand, while on the other hand in further processing (when the addition of water is involved) the appropriate amount of sodium acetate acts as a buffer.

Since literature data did not give a unique starting point regarding the molar concentration ratio between morphine and acetic anhydride, we arbitrarily decided to start our experiment with molar concentration of morphine in relation to acetic anhydride in the approximate ratio of 1:10 (i.e. acetic anhydride is five times over stoichiometric demands). The next question was to find the appropriate molar concentration of catalyst 4-dimethylaminopyridin. The supposed reaction mechanism of 4-DMAP acetylation catalysis is schematically presented in Fig. 2. The nucleophilic attack of 4-DMAP on a carbonyl group of acetic anhydride leads to intermediates marked as **A** and **B**. Due to resonant stabilization (structures **A**, **A<sub>res</sub>**; electron movements are shown by non-bold arrows), a lot of **A** is present in equilibrium. Interactions (marked by bold arrows and a dotted line) between intermediates **A**, **B** and substrate **C** lead through **D** to the final reaction products which are acetate ester, acetic acid and regenerated 4-DMAP.

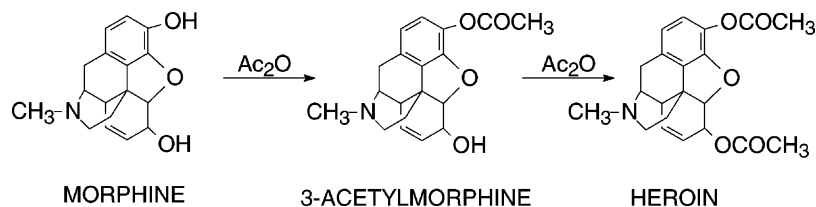


Fig. 1. Schematic reaction of heroin synthesis.

Table 1  
Esterification conditions by different authors

Reference	Molar concentration ratio (morphine:Ac <sub>2</sub> O)	Reaction temperature (°C)	Reaction time	Additional substances
[1]	Excess of Ac <sub>2</sub> O (exact proportions not given)	Ordinary temperature	Several days	None
[1]	Excess of Ac <sub>2</sub> O (exact proportions not given)	38–60	Several hours	None
[4] <sup>a</sup>	Not given	Elevated temperature (mixture was refluxed)	5 h	None
[5]	1:10	90	3 h (+3 days at room temperature)	None
[6] <sup>b</sup>	1:40	80	2 h	None
[7]	1:100	Boiling temperature	Approximately 2 h	None
[8] <sup>c</sup>	1:60	Elevated temperature (mixture was refluxed)	2 h	None
[8] <sup>c</sup>	1:3	Elevated temperature (mixture was refluxed)	20 h	None
[9]	1:280	50	30 min (+24 h at room temperature)	Pyridine
[10]	1:30	Room temperature	6 h	Pyridine
[11]	1:7	Near boiling point	3 h	Benzene
[12] <sup>d</sup>	1:(15–40)	Near boiling point	20 min	Sodium acetate

<sup>a</sup> General description of illicit heroin production.

<sup>b</sup> Deuterated acetic anhydride was used.

<sup>c</sup> Simulation of illicit heroin synthesis, crude morphine was used.

<sup>d</sup> As a part of analytical procedure, heroin was further purified by HPLC.

Thus, when the substrate **C** (see Fig. 2) is morphine (it has two OH groups in a molecule) it can be expected that the acetylation reaction can go fast and smoothly if at the starting point of the reaction the concentration of intermediate **A** is high enough to enable simultaneous (at least theoretically) acetylation of both OH groups of morphine. In the excess of acetic anhydride, this can theoretically be true when the molar concentration ratio between 4-DMAP and morphine is at least 2 (or more):1. Hence, for our first experiment, we decided to set the molar concentration of 4-DMAP 20% over the theoretical value, which means 2.4 mol 4-DMAP per 1 mol of morphine.

For the first experiment, a reaction mixture was prepared as described in Section 2.2 (see mixture 1). After the components were mixed, the reaction was allowed to proceed for approximately 5–6 min at room temperature. The colourless solution was obtained. It was washed with water to remove the bulk of the 4-DMAP (to stop the catalysis and to prevent possible column deterioration [13]) and diluted by dichloromethane (to avoid the column overloading). An amount of 1 µl of dichloromethane layer was injected into GC-MS. In Fig. 3, gas chromatogram and mass spectrum of the product obtained by acetylation of morphine with acetic anhydride in the presence of 4-DMAP at room temperature

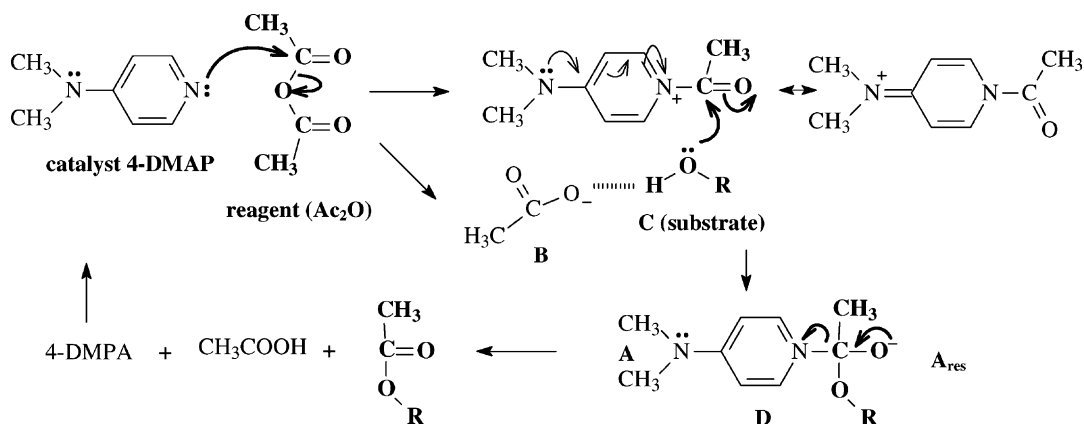


Fig. 2. The supposed reaction mechanism of acetylation catalysis in the presence of 4-DMAP.

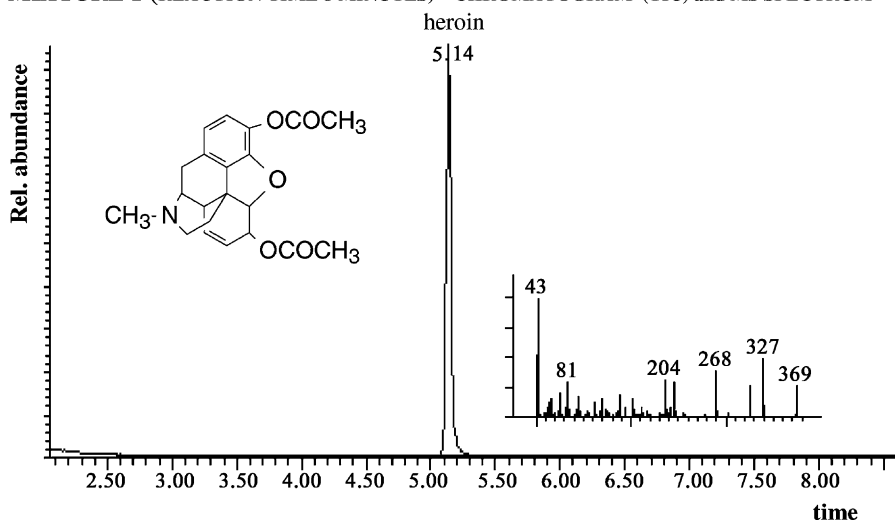
**MIXTURE 1 (REACTION TIME 8 MINUTES) – CHROMATOGRAM (TIC) and MS SPECTRUM**

Fig. 3. Gas chromatogram and mass spectrum of the acetylation product obtained in the acetylation reaction of morphine (0.1 mmol) by the solution made up of 4-DMAP (0.24 mmol), dichloromethane (solvent) and acetic anhydride (1.06 mmol), at room temperature—reaction time 8 min.

is shown. The product, which has peak maximum at the retention time of 5.14 min, was identified as heroin. Identification was done on the basis of characteristic mass spectrum (molecular ion of 369) which matched the library spectrum with the quality of 99%. As can be seen in Fig. 3, all morphine was converted to diacetylmorphine—in the reaction time of approximately 8 min at room temperature.

In the second experiment, molar concentration of acetic anhydride was lowered (it was set to 30% over stoichiometric demand—see mixture 2 in Section 2.2), while the concentration of the catalyst was the same as in the first experiment. As expected, the obtained results were the same as in the first experiment. It can be deduced that the quantity of acetic anhydride is not a critical parameter for the reaction

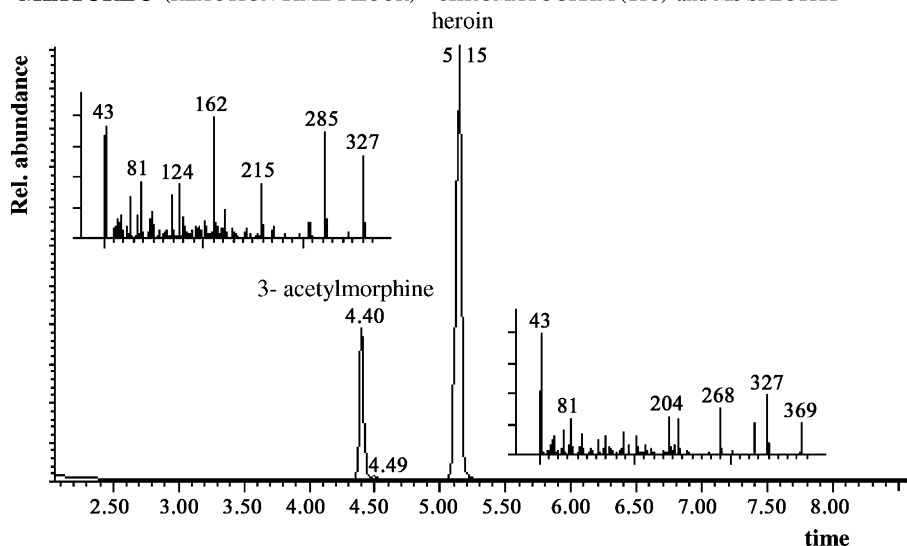
**MIXTURE 3 (REACTION TIME 1 HOUR) – CHROMATOGRAM (TIC) and MS SPECTRA**

Fig. 4. Gas chromatogram and mass spectra of the acetylation products obtained in the acetylation reaction of morphine (0.1 mmol) with the solution made up of 4-DMAP (0.024 mmol), dichloromethane (1 ml solvent) and acetic anhydride (1.06 mmol), at room temperature—reaction time 1 h.

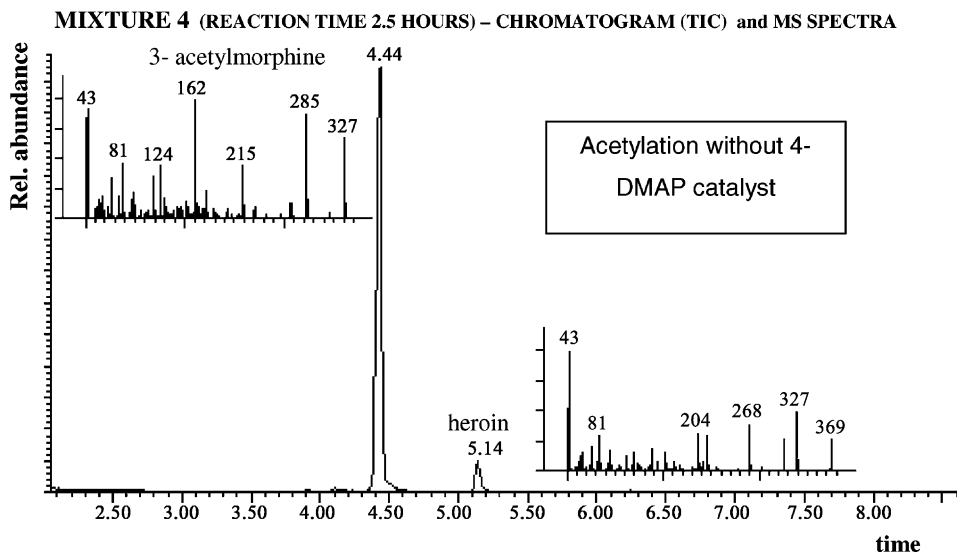


Fig. 5. Gas chromatogram and mass spectra of the acetylation products obtained in the acetylation reaction of morphine (0.1 mmol) in dichloromethane (1 ml solvent) and acetic anhydride (1.06 mmol), 2 h at room temperature plus 10 min at 50 °C—reaction time 2.5 h.

rate, of course, if we keep in mind that the minimum amount is defined by the reaction stoichiometry.

In the third experiment, the mixture 3 described in Section 2.2 was used. In this experiment, we lowered (10 times) the molar concentration of 4-DMAP catalyst. It was expected that a longer reaction time will be needed for acetylation to be completed. As can be seen in Fig. 4, where chromatogram (as well as mass spectra) of the acetylation products obtained in third experiment is presented, there was still a considerable amount of 3-monoacetylmorphine in the reaction mixture after 1 h. Further measurements showed that the reaction was completed in approximately 7 h. Results of this experiment infer to the conclusion that the acetylation reaction rate is dependant on the molar concentration ratio between morphine and 4-DMAP.

In our fourth experiment, the reaction mixture 4 (without catalyst 4-DMAP) was used. After the preparation of the mixture, we left it standing at room temperature for 2 h. In that time dissolution was not completed yet. Hence, we forced dissolution by heating the sample at 50 °C for 10 min. After that the sample was analysed by GC–MS approximately 2.5 h after preparation. The obtained result is presented in Fig. 5. If we compare the results from Figs. 3–5, it is evident that the acetylation reaction without 4-DMAP catalyst is much slower. Even more within 2 days the reaction without catalyst did not proceed further.

#### 4. Conclusions

The synthesis of heroin in the acetylation reaction, where morphine is brought into a contact with an excess of acetic anhydride, is usually performed at elevated temperatures and

the time needed for the acetylation to be completed is from several hours to a few days. We showed that in the presence of the catalyst 4-dimethylaminopyridine reaction time can be reduced to <10 min at room temperature. The quantity of acetic anhydride is not a critical parameter for the reaction rate, of course, if we keep in mind that the minimum amount is defined by the reaction stoichiometry. The experiments showed that the reaction time is dependant on the molar concentration ratio between morphine and 4-DMAP.

#### References

- [1] C.R.A. Wright, On the action of organic acids and their anhydrides on the natural alkaloids, *J. Chem. Soc.* 27 (1874) 1031–1043.
- [2] United Nations, History of heroin, *Bull. Narcotics* 5 (2) (1953) 3–16.
- [3] United Nations International Drug Control Programme, World Drug Report 2000, Northamptonshire, UK, 2000, p. 33.
- [4] United Nations, Recommended Methods for Testing Heroin, United Nations, New York, 1986, p. 8.
- [5] S.E. Hays, L.T. Grady, A.V. Kruegel, Purity profiles for heroin, morphine, and morphine hydrochloride, *J. Pharm. Sci.* 62 (1973) 1509–1513.
- [6] S.T. Chow, Quantitative analysis of illicit heroin by selected ion monitoring, *J. Forensic Sci.* 27 (1982) 32–38.
- [7] H. Huizer, Analytical studies on illicit heroin. I. The occurrence of O<sup>3</sup>-monoacetylmorphine, *J. Forensic Sci.* 28 (1983) 32–39.
- [8] H. Neumann, T. Schönberger, in: Proceedings of International Symposium of Forensic Science, Tokyo, 1993/1994, pp. 117–119.
- [9] F. Besacier, R. Guilluy, J.L. Brazier, H. Chaudron-Thozet, J. Girard, A. Lamotte, Isotopic analysis of <sup>13</sup>C as a tool for

- comparison and origin assignment of seized heroin samples, *J. Forensic Sci.* 42 (1997) 429–433.
- [10] C.C. Clark, A study of procedures for the identification of heroin, *J. Forensic Sci.* 22 (1977) 418–428.
- [11] J. Schwyzer, *Die Fabrikation Pharmazeutischer und Chemisch-Technischer Produkte*, Verlag von Julius, Springer, Berlin, 1931, p. 364.
- [12] P.A. Hays, G.S. Remaud, E. Jamin, Y.L. Martin, Geographic origin determination of heroin and cocaine using site-specific isotopic ratio deuterium NMR, *J. Forensic Sci.* 45 (2000) 552–562.
- [13] J.M. Moore, A.C. Allen, D.A. Cooper, Determination of manufacturing impurities in heroin by capillary gas chromatography with electron capture detection after derivatization with heptafluorobutyric anhydride, *Anal. Chem.* 56 (1984) 646–646.
- [14] J.G. Guillot, M. Lefebvre, J.P. Weber, Determination of heroin, 6-acetylmorphine, and morphine in biological fluids using their propionyl derivatives with ion trap GC–MS, *J. Anal. Toxicol.* 21 (1997) 127–133.
- [15] D.J. Berry, C.V. Digiovanna, S.S. Metric, R. Murugan, Catalysis by 4-dialkylaminopyridines, *ARKIVOC* 2 (2001) 944–964.
- [16] S. Klemenc, In common batch searching of illicit heroin samples—evaluation of data by chemometrics methods, *Forensic Sci. Int.* 115 (2001) 43–52.