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THERMAL BEHAVIOUR OF FENTANYL AND ITS ANALOGUES DURING FLASH PYROLYSIS

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Flash pyrolysis of fentanyl and its analogues has been studied on pyrolysis-gas chromatograph-mass spectrometer (Py-GC-MS) system. Initial pyrolytic fragmentation of these compounds led to the formation of N-substituted-1,2,5,6-tetrahydropyridine and N-phenylpropanamide as the primary pyrolytic products. Moreover, depending up on the furnace temperature, these pyrolytic products can also undergo further fragmentation to give different compounds. We, herein, discuss the probable fragmentation routes of parent as well as pyrolytic products. This study will be useful while developing technologies for thermal aerosol generation of fentanyl and related compounds.

Keywords: *fentanyl, flash pyrolysis, N-phenylpropanamide, N-phenethyl-1,2,5,6-tetrahydropyridine, Py-GC-MS*

Introduction

Fentanyl, N-(1-phenethyl-4-piperidinyl)propionanilide (**1**) is the representative member of 4-anilidopiperidine class of narcotic analgesics and classified as Schedule-II controlled drug. It is characterized by relatively short duration of action and good overall safety margin during surgical anesthesia [1]. It was introduced in clinical practice in 1960's as an analgesic [2] and its application as anesthetic agent represented a major increase in its potency in comparison to other contemporary opiate agonists. It can be administered to the human body through a variety of ways including injection, oral intake and transdermal route [3]. However, rapid delivery of the drug via inhalation route is more advantageous because the aerosol particles of the inhaled drug can reach the body and brain in less than a minute. Hence, substantial efforts have been devoted to develop technologies for the systemic delivery of the drug via inhalation route [4]. These technologies require the generation of aerosol containing drug particles which can be inhaled. It could be achieved either by forcing the liquid solutions of drugs through small holes [5] or by dispersing them as dry powders [6]. As an alternate, generation of fentanyl aerosols by thermal means has also been reported [3] which involved the heating of small amount of fentanyl at high temperature in a very short period of time under nitrogen flow. This thermal mean of producing aerosol was found to be a low cost and convenient method being capable of producing small-sized particles and enabling simple, additive-free formulation of both hydrophobic and hydrophilic medications. However, it is quite probable that application of heat for aerosol generation may sometimes lead to the formation of the toxic degradation products due to decomposition of the drug, especially at higher temperatures. It is a very undesirable feature for the administration of a drug through inhalation route and hence, it is very essential to know the effect of temperature on the stability of fentanyl so that danger of its degradation can be avoided. At the same time, it is also desirable to know about the possible routes of its fragmentation so that the nature of the degradation products formed under thermal stress can be predicted. In this paper, we describe the results of flash pyrolytic studies of fentanyl and its analogues carried out at different furnace temperatures on pyrolysis-gas chromatograph-mass spectrometer (PY-GC-MS). Also, after comparing the pyrolytic products of fentanyl and its analogues, their probable fragmentation route was proposed.

Experimental

Fentanyl and its analogues were synthesized in the laboratory by the procedures developed in our laboratory and reported elsevier [7]. Flash pyrolysis of all the compounds was carried out on Py 2020iD (Frontier Lab) pyrolyzer at specified temperatures for 10 ms. Separation and analysis of the pyrolysate components was accomplished using Agilent 6890 GC system coupled to a 5973 MSD. The analytical column used was an Ultra Alloy Capillary Column (UA-5); 30 m×0.25 mm ID, 0.25 μm film thickness. The chromatograph was programmed from an initial temperature of 50°C, held for 2 min and then increased at a rate of 10°C min^{-1} to a final temperature 280°C, kept isothermal for 15 min (total run time 40 min). The tem-

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perature of the MS interface, MS source and MS quadrupole were kept at 300, 230 and 150°C, respectively. Helium was used as the carrier gas at a flow rate of 1.0 mL min^{-1}. The mass spectrometer was operated in the electron impact ionisation mode at 70 eV. Sample mass taken for pyrolysis was approximately 5 mg. The products formed were characterized by analyzing and comparing their mass spectra with NIST MS library (matching>95%) and then confirmed them using authentic chemicals of >98% purity by comparing their retention times and mass spectral data under same GC-MS operating conditions.

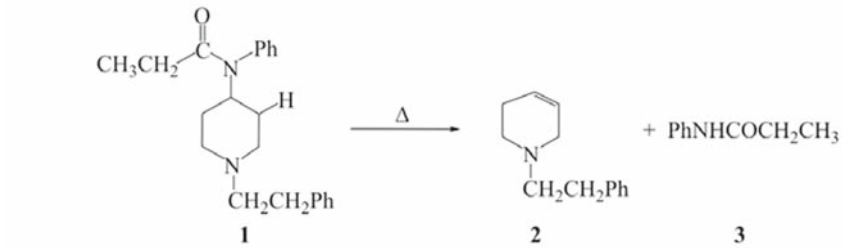
Results and discussion

During present course of work, fentanyl (**1**) was subjected to flash pyrolysis at furnace temperatures ranging from 250 to 900°C which led to the formation of different decomposition products depending on the pyrolysis temperature. Up to 350°C, corresponding pyrogram showed only one peak corresponding to the parent compound which revealed that fentanyl was quite stable up to this temperature. However, further increase in the pyrolysis temperature resulted in the decomposition of the analyte and at 500°C, two extra peaks, in addition to that due to the parent molecule, were also became apparent. Mass spectral analysis of these peaks revealed that these peaks appeared due to N-phenethyl-1,2,5,6-tetrahydropyridine (**2**) and N-phenylpropanamide (**3**) and their formation was supposed to take place by the elimination of propionanilide moiety and a β-hydrogen of piperidine ring of fentanyl molecule (Scheme 1).

The initial fragmentation route of fentanyl proposed above was also supported by flash pyrolysis of fentanyl analogues (**1.1**–**1.4**) differing in the substituent at piperidino ring nitrogen. The analogues **1.1**–**1.4**, on flash pyrolysis at the same furnace temperature (500°C), led to the formation of N-phenylpropanamide (**3**) and corresponding N-substituted-1,2,5,6-tetrahydropyridines (**2.1**–**2.4**) as the pyrolytic compounds (Scheme 2).

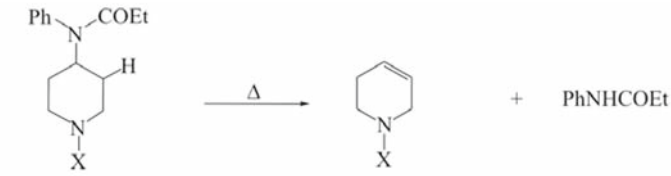
The fragmentation mechanism for fentanyl class of compounds, as proposed above, was further substantiated by flash pyrolysis of 4-substituted-N-phenethylpiperidine derivatives, viz., 4-hydroxy-N-phenethylpiperidine (**4**) and 4-anilino-N-phenethylpiperidine (**5**) to flash pyrolysis under similar experimental conditions. The corresponding pyrogram also contained the peak due to N-phenethyl-1,2,5,6-tetrahydropyridine (**2**) thereby confirming the proposed fragmentation route for fentanyl class of compounds (Scheme 3).

Further increase in the temperature of flash pyrolysis of fentanyl to 750°C resulted in extensive degradation of the parent compound leading to the appearance of a number of peaks in the pyrogram. At this point, it was quite reasonable to consider the pyrolytic products formed at this temperature as the result of thermal degradation of the parent compound fentanyl as well as that of primary pyrolytic products (**2**) and (**3**). Formation of these secondary pyrolytic products could be explained after studying possible routes of fragmentation of primary pyrolytic products. These routes were worked out by comparing the pyrogram of N-phenethyl-1,2,5,6-tetrahydropyridine (**2**) and N-phenylpropanamide (**3**) obtained



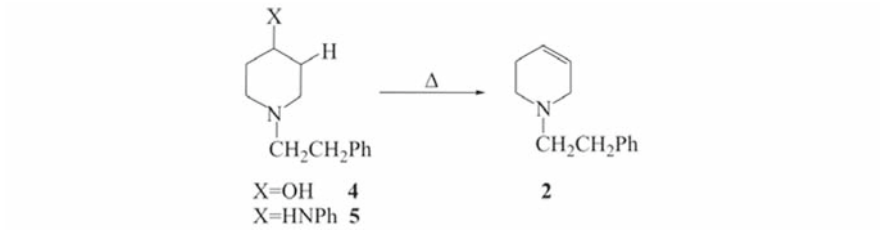
1 **2** **3**

Scheme 1

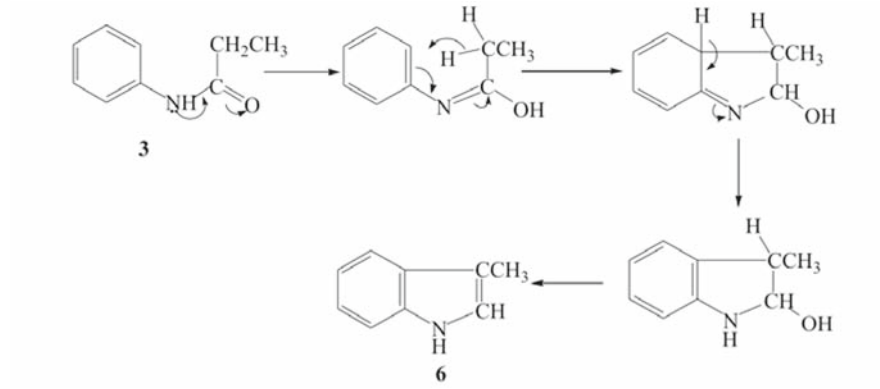


1.1 X=CH_2CH_2OPh **2.1** X=CH_2CH_2OPh **3**
1.2 X=CH_2CH_2CN **2.2** X=CH_2CH_2CN
1.3 X=$CH_2CH_2CH_3$ **2.3** X=$CH_2CH_2CH_3$
1.4 X=CH_2Ph **2.4** X=CH_2Ph

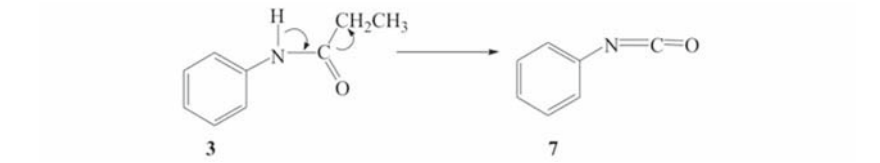
Scheme 2



Scheme 3



Scheme 4

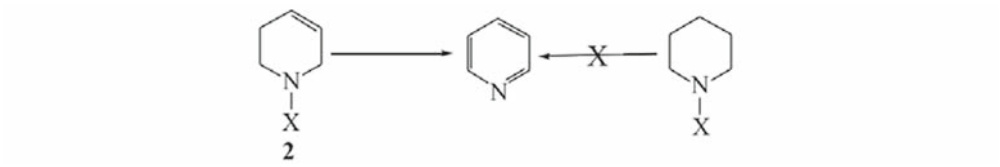


Scheme 5

after their flash pyrolysis at 750°C under similar experimental conditions.

Flash pyrolysis of N-phenylpropanamide (**3**) at 750°C yielded two major compounds, viz., 3-methylindole (**6**) and phenylisocyanate (**7**). These compounds are believed to be formed as a result of intramolecular rearrangement in the parent molecule as shown below (Schemes 4 and 5). These compounds (**6**) and (**7**) were also obtained during the flash pyrolysis of fentanyl at 750°C. At high temperature (750°C), phenylisocyanate may lead to the formation of hydrogen cyanide [8] which may be responsible for the toxicity of the smoke of the fentanyl.

The second primary pyrolytic product, N-phenethyl-1,2,5,6-tetrahydropyridine (**2**), also underwent tandem pyrolytic reactions during flash pyrolysis at 750°C. Corresponding pyrogram was rich in peaks only in the early region indicating the formation of volatile low molecular mass compounds, most of them were identified as aromatic hydrocarbons. The important product arising from the pyrolysis of this compound was pyridine which was supposed to arise from the dehydrogenation of the unsaturated piperidine ring of N-phenethyl-1,2,5,6-tetrahydropyridine (**2**). Presence of double bond in the piperidine ring of (**2**) facilitated the dehydrogenation of the molecule to form pyridine. Pyridine was found in the pyrolysis of all the 4-anilidopiperidines studied but not in that of unsubstituted N-phenethylpiperidine. In latter case, no unsaturation is present in the piperidine ring to assist the dehydrogenation and pyridine was not detected in the pyrolysis of the N-phenethylpiperidine (Scheme 6).



Scheme 6

Conclusions

We have investigated the thermal behavior of fentanyl at different temperatures by flash pyrolysis. This study can be useful while developing technologies for the generation of fentanyl aerosol by thermal means. As these studies revealed that fentanyl is stable up to 350°C, temperature should never be exceeded above this point for the aerosolization of fentanyl. Although, this study does not give a full account of the pyrolytic products of fentanyl, it still gives new information on the thermal decomposition reactions and products of fentanyl which may contribute to the toxicity of the thermally generated fentanyl aerosols. Thus, while administering fentanyl in the form of thermally generating aerosols to the humans, toxicity of the pyrolytic products should always be kept in mind. This study will also be useful for understanding the toxicity of the fentanyl smoke which is used by abusers for fentanyl administration.

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