

Fluorescent indolium dyes for applications in aqueous halide sensing—part 2: the repeated alkylation of Harmane post quaternisation

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Abstract

The repeated alkylation of Harmane, 1-methyl-9*H*-pyrido[3,4-*b*] indole, post quaternisation has been observed during fusion with primary alkyl acid halides. This can be explained by two possible competing mechanisms, the electrophilic addition of alkylating agent to the resonance enamine form of the quaternised product and/or polyester formation between the quaternised product and the primary alkyl acid halide. The mechanisms are supported by ¹H NMR, FTIR and mass spectrometry analysis. The possibility for controlling the repeated alkylation in nanometre size silica pores, in essence restricted geometry nanometre size reaction vessels, is discussed. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The betacarboline Harmane (sometimes also referred to as Harman or Aribine in the research literature) (Fig. 1) is the parent compound of an important class of heterocyclic compounds that are the basic structural unit of some indole alkaloids possessing a wide range of bioactive effects [1]. At present, the precise mechanisms of biological action of these drugs are unknown although it is thought that they interact with their biological targets by forming association complexes. In addition to its biological importance this hallucinogen

alkaloid is a useful indicator for the fluorometric determination of small acidities in the physiological pH range [2] as well as possessing useful fluorescence characteristics for aqueous halide sensing [3–5]. To improve its aqueous solubility or even provide reactive functional groups for further chemistries, several authors have quaternised the nitrogen heteroatom of Harmane, (Fig. 1, ring position 2), but have not hitherto reported its repeated alkylation post quaternisation.

In this paper, the observation of the repeated alkylation of Harmane after its quaternisation with the primary alkyl halides 8-bromooctanoic acid, 11-bromoundecanoic acid and 15-bromopentadecanoic acid is reported (Fig. 2). Mass spectrometry, ¹H NMR and FTIR data of the three

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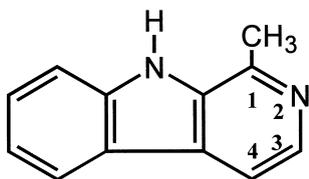


Fig. 1. Harmane, 1-methyl-9*H*-pyrido[3,4-*b*] indole. Harmane is sometimes also referred to as Aribine or Harman in the research literature.

mentioned reactions enable one to realise that repeated alkylation occurs during the fusion of Harmane with primary alkyl halide, due to two competing reactions, the electrophilic addition of alkylating agent to the resonance enamine form of the quaternised product (Figs. 3 and 4) and/or polyester formation between the quaternised product and the primary alkyl acid halide, *mechanism 2* (Fig. 4).

2. Experimental

All reagents were purchased from the Aldrich Chemical Company and were used as received except for 15-bromopentadecanoic acid which was a gift from Dr. John Maud, University of Wales, Swansea.

¹H NMR spectra were recorded on a Varian Unity plus (400 MHz) spectrometer. All IR spectra were recorded on a Perkin-Elmer PE2000R NIR FT-Raman spectrometer. Positive and negative ion

electrospray mass spectrometry (piems and niems, respectively) were performed by both Crosfield Ltd, Warrington (now Ineos Silicas Ltd) and Kodak Ltd, Harrow, London.

Quaternisation of the Harmane heterocyclic nitrogen base was achieved by separately using 8-bromooctanoic acid, 11-bromoundecanoic acid and 15-bromopentadecanoic acid (Fig. 2). Each of the required starting materials (1.65 mmol) was heated under reflux for 1 h at 120 °C. After cooling for 1 h the resulting yellow solids were treated with 50 ml diethyl ether and vigorously stirred for a further 1 h. The yellow products were then recovered and slowly dried under vacuum. This procedure was in accordance with previous work by the author and co-workers [5] although column chromatography, which was previously used to separate the components before recrystallisation, was not undertaken here enabling the mixture of products to be studied.

3. Results and discussion

The piems, niems, ¹H NMR and FTIR for all three reactions showed the expected quaternised products but also showed evidence for higher molecular weight species. For example, piems analysis of the recovered product for the preparation of 1-methyl-2-(8-octanoic acid)-9*H*-pyrido[3,4-*b*] indolium bromide (Fig. 2, $x=7$), identified the quaternised Harmane product at m/z 325.2 (M^+) and additional products at m/z 467.2,

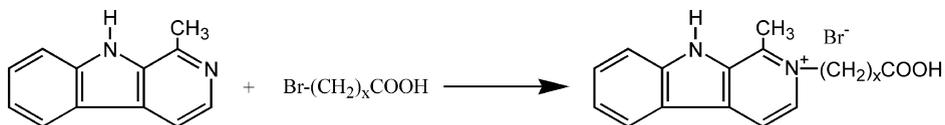


Fig. 2. Quaternisation of the Harmane heterocyclic nitrogen base with the primary alkyl halides, 8-bromooctanoic acid ($x=7$), 11-bromoundecanoic acid ($x=10$) and 15-bromopentadecanoic acid ($x=14$).

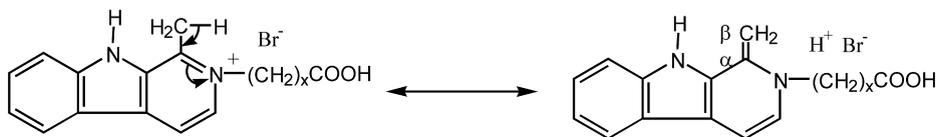


Fig. 3. Enamine formation of 1-methyl-2-($x+1$ -octanoic acid/undecanoic acid/pentadecanoic acid)-9*H*-pyrido[3,4-*b*] indolium bromide, where $x=7, 10$ or 14 .

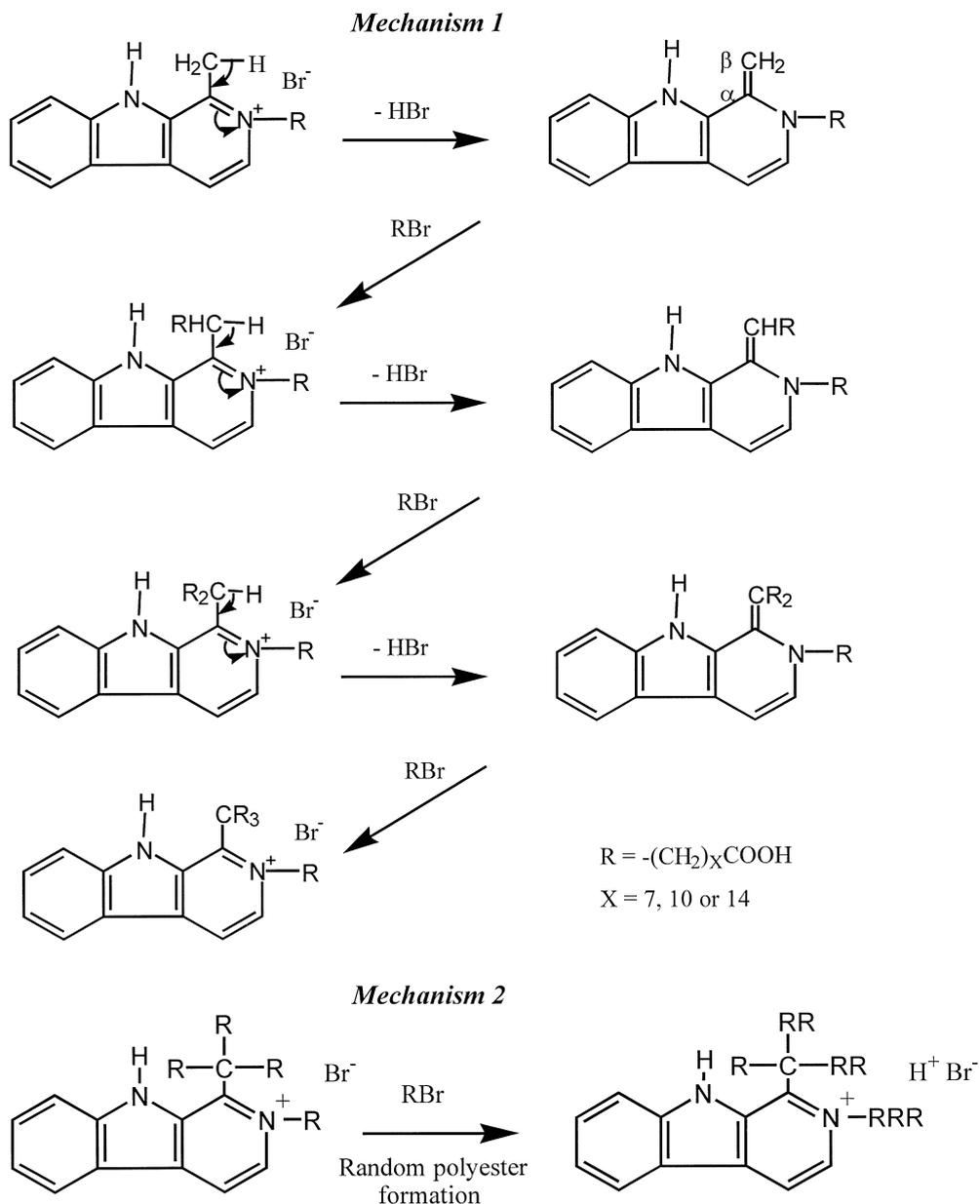


Fig. 4. Repeated alkylation of the quaternised product. *Mechanism 1*— $\text{R} = -(\text{CH}_2)_x\text{COOH}$, $x = 7, 10$ or 14 . *Mechanism 2*—random polyester formation.

609.3, 751.4, 893.6, 1035.6, 1177.0 and 1319.0 (M^+), which appears consistent with the further addition of seven $-(\text{CH}_2)_7\text{COOH}$ groups. The niems revealed the bromide counter-ion at m/z 80.9 (M^-). The IR spectra also showed evidence for polyester formation.

This repeated alkylation can be explained by two competing reactions, the first reaction of which can also be explained in two steps, *mechanism 1*. Firstly, the spontaneous and rapid loss of a proton from the methyl group on C1 of the quaternised product makes the β -carbon atom of

the resultant enamine a nucleophilic site (Fig. 3). Secondly, the nucleophilicity of the β -carbon atoms affords its rapid electrophilic addition by primary alkyl halide until the thrice addition has occurred (Fig. 4).

A second competing reaction, *mechanism 2*, is also evident, whereby polyester chains are formed by the further addition of the primary alkyl acid halide to the quaternised product, although it is not possible to say in which order the mechanisms compete, but the polyester constituents are minor. The complete alkylation mechanism proposed is shown in Fig. 4.

To further investigate polyester formation post quaternisation 6-methoxyquinoline (6MQ) was quaternised with 8-bromooctanoic acid under similar reaction conditions (Fig. 5). The 6MQ heterocyclic nitrogen base is also readily quaternised by primary alkyl acid halides but cannot undergo further alkylation proposed by mechanism 1. The piems identified the quaternised product at m/z 302.1 (M^+) and two further minor products at 444.2 and 586.3. It was also confirmed by 1H

NMR and FTIR that polyester formation is possible but produces only small quantities of polyester products.

Due to the fact that the piems for the quaternisation of Harmane with 8-bromooctanoic acid identifies the addition of seven further $-(CH_2)_7COOH$ groups and the fact that the polyester products are minor, then the quaternisation reaction is thought to proceed via the two competing mechanisms described here (Fig. 4). All three reactions produced similar products respectively although it was not possible to distinguish any relationships between the reaction yields and the primary alkyl acid halide used.

Quaternisation reactions have been used previously as a quick and simple means of improving the aqueous solubility and hence compatibility of the Harmane nucleus within plastic films [3] as well as providing additional functional groups for further chemistries, such as the linkage and therefore immobilisation of Harmane within polymers [6]. Such criteria are important considerations for aqueous halide sensors based on Harmane [4].

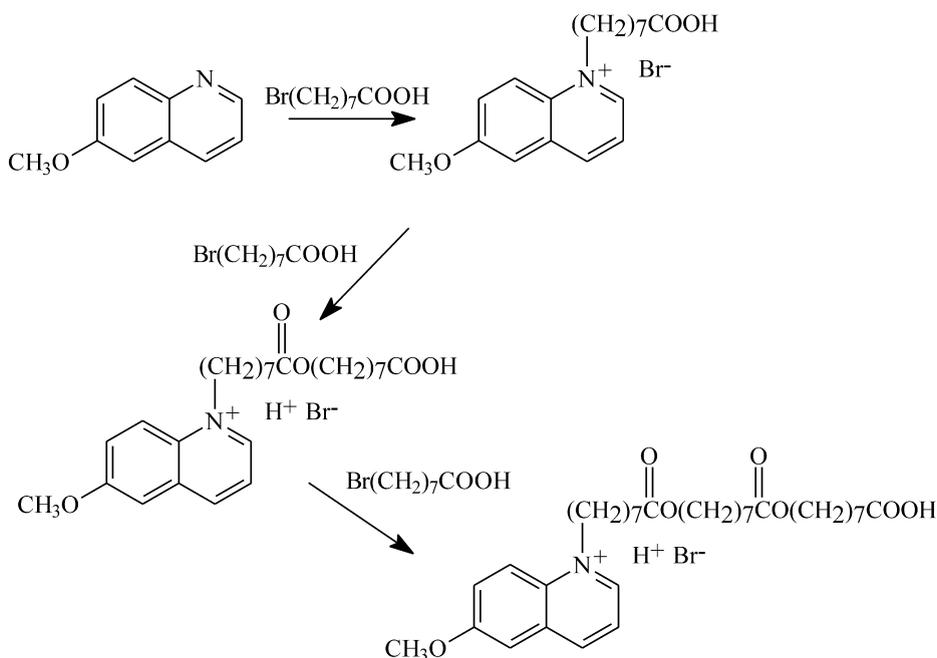


Fig. 5. The quaternisation of 6-methoxyquinoline (6MQ) with 8-bromooctanoic acid and the subsequent polyester formation of the quaternised product.

However the need for further product separation, e.g. using column chromatography, via this quaternisation route shrouds its simplicity, especially when quaternising with alkylating agents containing reactive functional groups capable of further chemistries during the quaternisation reaction. The use of protective groups to hinder further alkylation reactions may introduce, if not completely removed after the reaction, additional complications to the excited state halide quenching kinetics of Harmane, and hence should therefore be avoided. However, it may be possible to use the nanometre size of silica pores to control the alkylation process, where tailoring the size of pores may restrict the extent of alkylation. The use of molecular sieves for similar chemistries is by no means uncommon, but most molecular sieves, clathrates or inclusion compounds do not boast the pore size tuneability offered by silica hydrogels, which would be required for control of the alkylation processes described here. Recently, Geddes and Birch have developed a new technique which offers nanometre resolution for determining silica particle sizes [7], which are themselves tuned via the sodium silicate and proton concentrations during the hydrolysis and polycondensation reactions of the sol-gel process [8,9]. Given that pores are simply the voids between silica particles it is envisaged that by carefully tuning the silica particle size and therefore the pore size (also surface area), one may be able to control the extent of alkylation. This recent advance in silica particle metrology may therefore enable one to tune pore sizes in aqueous based systems, *hydrogels*, polymerised from sulphuric acid and lithium, sodium or potassium silicate solution, and in alcohol based systems, *alcogels*, using acid catalysed tetramethoxy or tetraethoxy silanes. The solvent flexibility offered by these sol-gels may therefore enable this suggested approach to be applied to other systems in general, where tailored restricted environments, in

essence nanometre size reaction vessels, offer future possibilities for controlling the extent of reaction.

4. Conclusions

It has been shown that the simple quaternisation of Harmane with primary alkyl acid halides can lead to multiple alkylated products. This has been interpreted as the repeated electrophilic addition of alkylating agent to the enamine form of the quaternised product and/or polyester formation between the quaternised product and the primary alkyl acid halide.

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