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The specific epimerisation of phthalideisoquinoline alkaloids

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Abstract

1*R*,9*S* α-Narcotine has been converted to 1*S*,9*S* β-narcotine by reaction with thiophosgene, followed by sodium acetate in acetic acid. Conversion to 1*R*,9*R* β-narcotine was achieved by sequential reaction of α-narcotine with α-chloroethyl chlorothionoformate, followed by aqueous sodium hydroxide. Finally, 1*R*,9*R* β-narcotine was converted to 1*S*,9*R* α-narcotine by reaction with thiophosgene, followed by sodium acetate in acetic acid. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: thiophosgene; chlorothionoformate; benzylic cleavage of amines; phthalideisoquinolines.

Members of the phthalideisoquinoline family of alkaloids are known in both the *R* and *S* configurations at both the chiral centres,[1,2] but the biological activity is not equal for each of the four isomers with a particular aromatic substitution pattern. For example, bicuculline (**1**) is a powerful convulsant that has found widespread application as a pharmacological probe for convulsants acting at the $GABA_A$ neuroreceptor,[3] while the enantiomer and its epimers are considerably less active.[4] It has long been regarded as desirable to find a procedure for the specific epimerisation of these alkaloids. Robinson and coworkers[5] have described the partial conversion of narcotine (**2**) and hydrastine into epimers, among other products, by prolonged heating with sodium methoxide, and have postulated that epimerisation is occurring at C-9; CD studies have confirmed these conclusions.[2]

As part of a programme aimed at probing some of the synthetic applications of phenyl chlorothionoformate as a dealkylating agent of tertiary amines,[6] we investigated the analogous use of thiophosgene. This reagent does not appear to have been used to achieve dealkylation of tertiary amines, but several reports of such reactions with phosgene have.[7] α-Narcotine (**2**), a readily available member of the phthalide isoquinoline alkaloids, was used as the test compound, since these compounds have previously been reported to react with chloroformates to give three different reaction pathways.[8–10] α-Narcotine reacted readily with thiophosgene at 20°C in dichloromethane, giving a single compound, as judged by its ^1H and ^{13}C NMR spectra, to which was assigned structure **3**, implying retention of configuration in the cleavage of the benzyl group. On treatment with water, this compound formed the hydrochloride **4** very

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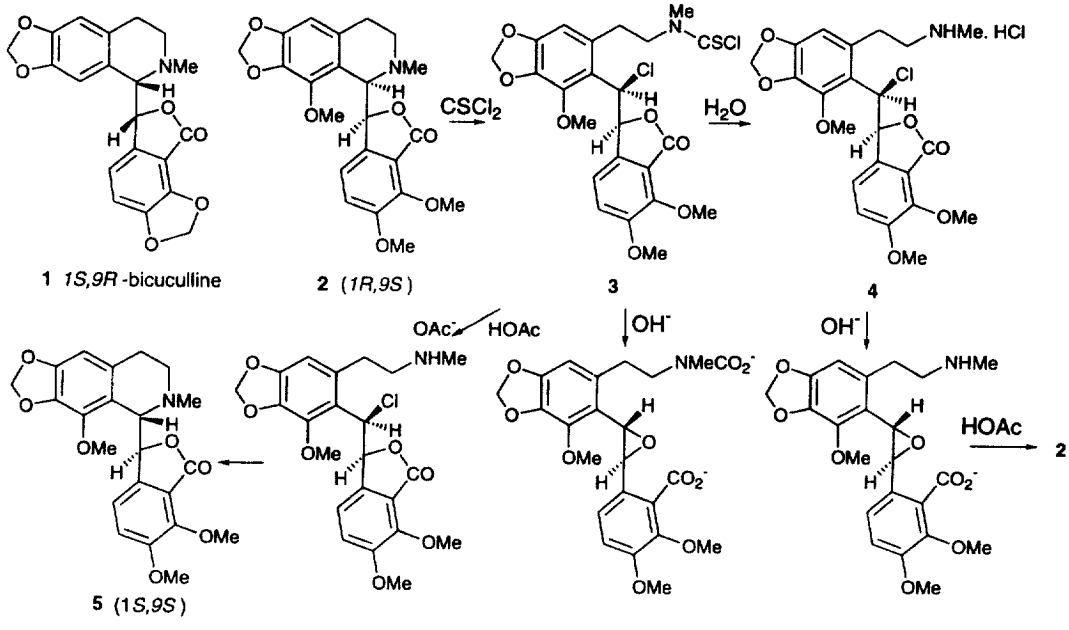
rapidly, and reaction of either **3** or **4** with sodium hydroxide at 20°C returned α-narcotine. When the free base from **4** was chromatographed on alumina, it gave a ca. 1:1 mixture of α- and β-narcotine (**5**) readily separable by chromatography. On the other hand, when **3** was treated with sodium acetate in acetic acid at 20°C for 12 h, the sole product, isolated in 90% yield, was (+)-β-narcotine, mp 176°C, $[\alpha]_D^{27}$ +99 (lit.[5] 176°C, $[\alpha]_D^{27}$ +101). The rotation of the isolated **5** was the opposite to that reported from the reaction of α-narcotine with base,[5] confirming that epimerisation had occurred at C-1 and not C-9. The interpretation of these observations is summarised in Scheme 1.

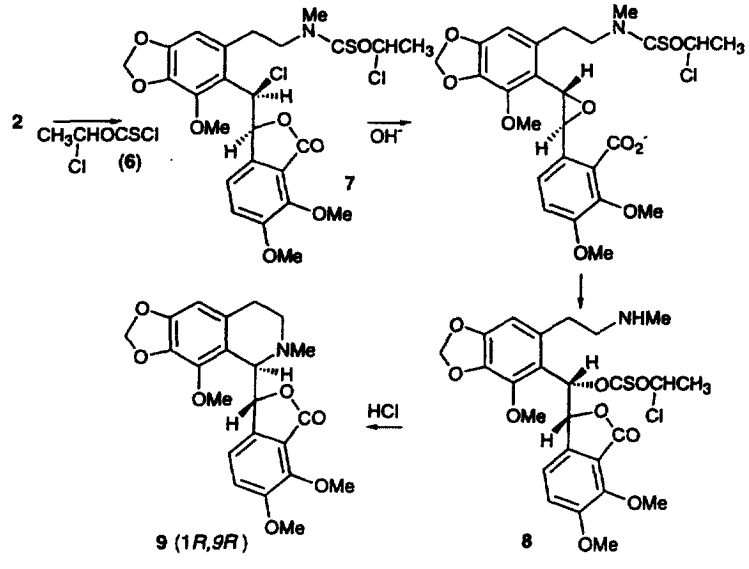


Scheme 1.

The key features of the reactions above are that the thiocarbamoyl chloride **3** is extremely readily decomposed with water in a few minutes at 20°C. It can be reasonably supposed that the intramolecular displacement of the chloride, being stereospecific, is an S_N2 reaction, hence the reaction with hydroxide ion must involve opening of the lactone at a rate faster than chloride displacement by the amine, leading to formation of the epoxide, with inversion at C-1. Opening of the epoxide by amine now occurs more rapidly, resulting in a second inversion at C-1, and the reformation of 1*R*,9*S* α-narcotine, **2**. Alternatively, if the carbamoyl chloride **3** is treated with sodium acetate in acetic acid, the carbamoyl chloride is converted into the amine without affecting the phthalide, and inversion at C-1 then leads to 1*S*,9*S* β-narcotine (**5**).

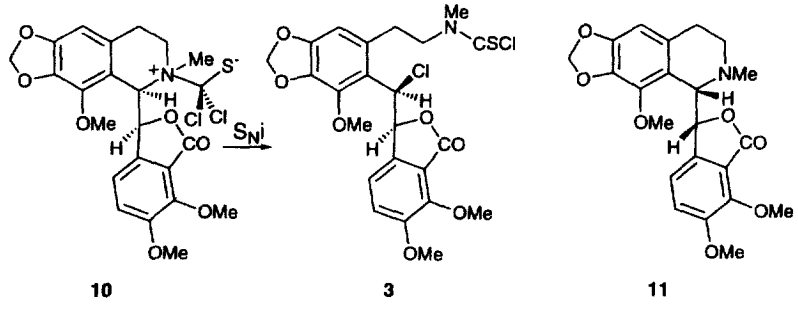
When thiophosgene is treated with acetaldehyde in dichloromethane, the formation of the novel chlorothionoformate (**6**) required 24 h for completion at 20°C, but in the presence of a trace of benzyltributylammonium chloride[11] reaction was rapid, and **6** could be isolated by distillation, bp 65°C/760 mm. 1*R*,9*S*-(−)-α-Narcotine (**2**) reacted with **6** within 1 h at 20°C to give a single product **7** with retention of configuration at C-1. Brief treatment of **7** with aqueous NaOH gave the thiocarbonate (**8**), in which the NMe group had changed from the typical amide environment (δ_H 3.5) to the amine environment (δ_H 2.5), but the chloroethyl thionocarbonate group was present, as was the phthalide moiety. The stereochemistry of **8** was deduced from the observation that when **8** was refluxed in THF/dil. HCl, it gave 1*R*,9*R*-(−)-β-narcotine (**9**), mp 175–176°C, $[\alpha]_D^{27}$ −99 (lit.[5] 176°C, $[\alpha]_D^{27}$ −101). The ^1H

and ^{13}C NMR spectra of **9** were identical with those of **5**. The pathway proposed for the formation of **9** is shown in Scheme 2.



Scheme 2.

The crucial reaction for the success of these epimerisations is the retention of configuration at C-1 on cleavage of the tertiary amine with the chlorothionoformates to form **3** and **7**. This outcome could be due either to the fact that the thermodynamically most stable product from a carbocation intermediate is **3**, or that the formation of **3** reflects an S_Ni reaction, e.g. **10** goes to **3**[12] (Scheme 3). The question was resolved when 1*R*,9*R*-β-narcotine **9** was treated with thiophosgene, followed by sodium acetate in acetic acid, to give 1*S*,9*R*-(+)-α-narcotine (**11**). The properties of this compound were identical with those cited in the literature,[5] and the stereospecificity of the reactions are inconsistent with a carbocation intermediate.



Scheme 3.

In summary, we have shown that any of the four stereoisomers of narcotine can be selectively converted to any other isomer in good yield, and this has considerable implications for stereoselective transformations of other benzylic amines. The above reactions appear to be general. We have carried out similar sequences with bicuculline and hydrastine, and although the initial dealkylation reactions gave a ca. 4:1 mixture (retention:inversion), the isomers were readily separable by chromatography.

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