Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 443–445

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Photochemical *N*-Demethylation of Alkaloids

Justin A. Ripper,[a] Edward R. T. Tiekink[b] and Peter J. Scammells[a,*]

[a]*School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria 3217, Australia*
[b]*Department of Chemistry, The University of Adelaide, Adelaide 5005, Australia*

Received 4 April 2000; accepted 22 November 2000

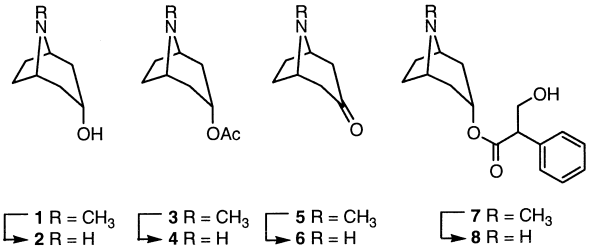
Abstract—Certain alkaloids were observed to undergo *N*-demethylation processes under photochemical conditions. Tropine, acetyltropine, tropinone, and atropine were cleanly *N*-demethylated upon treatment with tetraphenylporphin, oxygen, and light. Dextromethorphan also underwent a *N*-demethylation reaction, but reacted further to afford an imine. In contrast, 14-acyloxycodeinones underwent a photochemically induced tandem *N*-demethylation–acyl migration. © 2001 Elsevier Science Ltd. All rights reserved.

N-Demethylation of tertiary amines was traditionally achieved using cyanogen bromide in the von Braun reaction.[1] Limited yields and the toxicity of cyanogen bromide have seen this reaction largely replaced by chloroformate reagents.[2] Certain chloroformates, such as vinyl chloroformate, generally *N*-demethylate in high yield and the resultant carbamates are readily cleaved to afford the corresponding secondary amines. Unfortunately this reagent is very expensive,[3] limiting its applicability to larger scale processes. Some photochemical procedures have been developed for the cleavage of *N*-methyl amines,[4–6] but these methods have not seen widespread use.

We now wish to report a simple, inexpensive, and efficient photochemical method for the *N*-demethylation of alkaloids that requires no specialized apparatus. Tropine (**1**) was dissolved in dichloromethane in the presence of the photosensitizing catalyst, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphin (TPP) and oxygen was bubbled through the reaction mixture while irradiating with a 300 watt lamp (standard sunlamp).[7] The desired *N*-demethylated product was precipitated as the hydrochloride salt in 79% yield (Scheme 1, Table 1). No chromatography was required as the nortropine hydrochloride precipitated in a pure form. Similar high yields were obtained when Rose Bengal was used instead of TPP as the photosensitizing agent in a *tert*-butanol-water solvent system. These yields are comparable to those obtained using vinyl chloroformate (77% over two steps; carbamate formation and hydrolysis[8]) and have the advantage of proceeding in one simple, inexpensive step. This procedure is clearly superior to the *N*-demethylation using the more common, cheaper chloroformates such as ethyl chloroformate which gave a 16% yield[9] for this transformation.

The *N*-demethylation of acetyltropine (**3**), tropinone (**5**), and atropine (**7**) using the TPP procedure also proceeded in reasonable yield (isolated yields of 57, 54, and 66%, respectively). *N*-Demethylation of these alkaloids using simple chloroformate reagents has proven problematic due to difficulty in cleaving the intermediate carbamates.[10]

When dextromethorphan (**9**) was irradiated in the presence of TPP using the reaction conditions described above, a complex mixture of products resulted. The use of Rose Bengal in aqueous alcohol gave a cleaner reaction. In this case, the imine **10** was isolated in 55% yield (Scheme 2). The mechanism of *N*-demethylation is believed to involve an electron transfer to produce an α-amino radical that loses an electron to afford an iminium



Scheme 1. Photochemical *N*-demethylations.

*Corresponding author. Tel.: +61-3-5227-1439; fax: +61-3-5227-1040; e-mail: scam@deakin.edu.au

0960-894X/01/$ - see front matter
PII: S0960-894X(00)00690-9

ion. This iminium ion is hydrolyzed upon work-up to afford the corresponding secondary amine (Scheme 2).[5,11] In this case, the imine **10** presumably resulted from in situ hydrolysis of the intermediate iminium ion in the aqueous solvent, followed by further reaction of the resultant secondary amine. A repeat of this process would yield another iminium ion that could lose a proton to give the isolated product **10**.

Our initial attempts to *N*-demethylate 14-hydroxycodeinone (**11a**) using the TPP procedure produced negligible yields of the desired product (Scheme 3, Table 2). However, after protecting the 14-hydroxy group as an acetate, *N*-demethylation and acetyl transfer occurred giving *N*-acetyl-14-hydroxycodeinone (**12b**). Intramolecular O→N acyl transfers have been previously observed for opiates of this type when the secondary amine is present as the free base.[12] An appreciable amount of the byproduct **13b** (R = Ac) was also isolated from this reaction. This compound presumably resulted from the formation of an iminium ion at C16, conversion to the corresponding enamine, addition of oxygen and finally fragmentation of the resultant endoperoxide. A slightly higher yield of the major product (**13b**) was obtained when air was used as the oxygen source. The yields of related photochemical *N*-demethylation reactions have been improved by the addition of salts such as lithium perchlorate.[5] These salts are thought to stabilize the α-amino radical, favoring the *N*-demethylation pathway over alternatives such as recombination with an oxygen centered radical. In this case, the addition of lithium perchlorate (0.25 mol equiv) had little effect on the outcome of the reaction. It was reasoned that this could be due to the low solubility of lithium perchlorate in dichloromethane. However, when the reaction was repeated in acetonitrile, the addition of salt failed to improve the yield. In this case, Rose Bengal gave significantly inferior results to TPP.

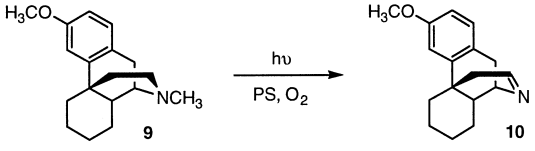
The photochemical *N*-demethylation reaction of oxycodone (**14a**) and analogues proceeded in similar fashion. Once again, when the 14-hydroxy was unprotected, a negligible yield was obtained. The acetyl protected analogue (**14b**) gave a 34% yield of the *N*-demethylation–acyl transfer product **15b**. This was accompanied by the formation of an appreciable amount of the oxidation byproduct **16b** (29%). The structure of this compound was initially determined by NMR and confirmed by X-ray crystallography (Fig. 1).[13]

It was thought that the introduction of other acyloxy substituents into the 14-position may offer advantages in the synthesis of commercially important opiate antagonists, such as naltrexone and nalbuphine. The use of a cyclopropyl ester (compound **14c**) allowed *N*-demethylation and *N*-acylation to be effected in one

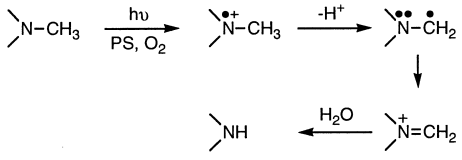
Table 1.

Reactant	Conditions	Purification	Yield (%)
1	TPP, O_2, light	A[a]	79
1	Rose Bengal, O_2, light	A	79
3	TPP, O_2, light	B[b]	57
5	TPP, O_2, light	B	54
7	TPP, O_2, light	B	66

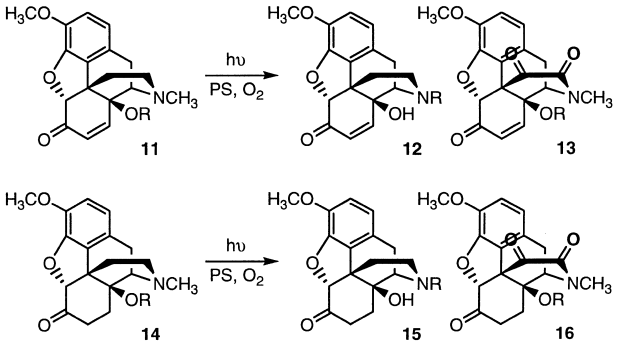
[a]Precipitation of HCl salt from ethanol and diethyl ether.
[b]Column chromatography using EtOAc/MeOH/NH_3 (90:10:1→70:30:1).



Proposed Mechanism:[5]



Scheme 2. Photolysis of dextromethophan.



Scheme 3. Photochemical *N*-demethylation of various opiates.

Table 2.

Reactant	Conditions	Yield (%)
11a (R = H)	TPP, O_2, light	—
11b (R = Ac)	TPP, O_2, light	33 (**12b**):17 (**13b**)
11b (R = Ac)	TPP, air, light	38 (**12b**)
11b (R = Ac)	TPP, O_2, light, $LiClO_4$	32 (**12b**)
11b (R = Ac)	Rose Bengal, O_2, light	11 (**12b**)
14a (R = H)	TPP, O_2, light	—
14b (R = Ac)	TPP, O_2, light	34 (**15b**):29 (**16b**)
14c (R = )	TPP, O_2, light	38 (**15c**):24 (**16c**)

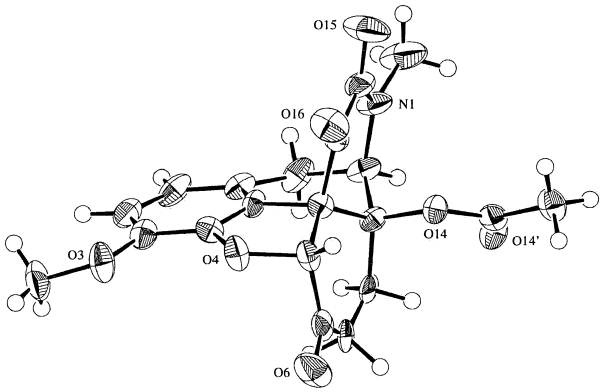


Figure 1. Crystal structure of oxidation byproduct **16b**.

step. *N*-Acyl 14-hydroxycodones of this type have been elaborated to the corresponding 14-hydroxymorphinan pharmaceuticals in high yield.[12] Unfortunately due to the low yield of the photolysis step this approach does not compare favorably with current syntheses where all steps proceed in high yield.[12,14]

In summary, a simple photochemical procedure involving an inexpensive catalyst and a sunlamp can be used for the *N*-demethylation of certain alkaloids. This procedure works well for simple substrates, but the formation of byproducts lowers the yield in the case of more complex structures. The reaction of 14-acyloxycodeinones gave rise to a tandem *N*-demethylation–acyl transfer to yield the corresponding *N*-acyl 14-hydroxy opiates. This process was accompanied by the formation of an interesting 1,2-dicarbonyl oxidation product.

References and Notes

1. von Braun, J. *Chem. Ber*. **1900**, *33*, 1438.
2. Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
3. Vinyl chloroformate was available in 5 and 10 mL pack sizes from Sigma-Aldrich for >$A 3500 per mole at the time this manuscript was written.
4. Lindner, J. H. E.; Kuhn, H. J.; Gollnick, K. *Tetrahedron Lett*. **1972**, *13*, 1705.
5. Santamaria, J.; Ouchabane, R.; Rigaudy, J. *Tetrahedron Lett*. **1989**, *30*, 2927.
6. Lopez, D.; Quinoa, E.; Riguera, R. *Tetrahedron Lett*. **1994**, *35*, 5727.
7. **TPP method**: Tropine (1.0 g, 7.1 mmol) and TPP (210 mg) were dissolved in dichloromethane (100 mL) in a water jacketed reaction vessel. The mixture was irradiated with a 300 W lamp (purchased from the local hardware store) while bubbling oxygen for 6 h.

Work up A: The reaction mixture was extracted with water (3×50 mL), the aqueous phase washed with ether (50 mL) and made acidic (pH ~1–2) with concd HCl. The water was removed in vacuo and the residue dissolved in a minimal amount of ethanol. A large excess of ether was added, and the mixture was left in the refrigerator overnight. Collection of the precipitate gave a 79% yield of pure nortropine hydrochloride.

Work up B: The reaction mixture was extracted with 1 M HCl (3×40 mL), the combined extracts were washed with dichloromethane (2×10 mL) and then evaporated under reduced pressure. The residual oil was taken up in saturated $NaHCO_3$ and extracted with ethyl acetate (3×50 mL). Ethyl acetate portions were combined, dried ($MgSO_4$) and evaporated to afford a crude oil. Pure product was obtained (free base) after column chromatography using an EtOAc/MeOH/NH_3 gradient (90:10:1 to 70:30:1).

Rose Bengal method: As above except Rose Bengal was used instead of TPP in *tert*-butanol/water (80:20).

8. Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett*. **1977**, *18*, 1567.
9. Kraiss, G.; Nador, K. *Tetrahedron Lett*. **1971**, *12*, 57.
10. Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett*. **1974**, *14*, 1325.
11. Lee, L. Y. C.; Ci, X.; Giannotti, C.; Whitten, D. G. *J. Am. Chem. Soc*. **1986**, *108*, 175.
12. Olofson, R. A.; Pepe, J. P. *Tetrahedron Lett*. **1977**, *18*, 1575.
13. Crystal data for $C_{20}H_{19}NO_7$, $M=385.4$, orthorhombic, $a=7.345(7)$, $b=7.673(4)$, $c=30.537(8)$ Å, $T=173$ K, space group $P2_12_12_1$, $Z=4$, μ(Mo-K_α)=1.13 cm^{-1}, 3638 reflections measured on a Rigaku AFC7R diffractometer, θ_{max} 27.5°, 2868 unique ($R_{int}=0.043$), 1457 with $I \geq 3.0\sigma(I)$ were used in subsequent calculations: final $R=0.047$ and $R_w=0.038$. The absolute structure was determined from the chemistry. The data has been deposited at the Cambridge Crystallographic Data Centre (deposition number 148944).
14. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfoot, T. *J. Org. Chem*. **1984**, *49*, 2081.