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One-pot N-dealkylation and acid-catalyzed rearrangement of morphinans into aporphines

Sándor Berényi [a], Zsuzsanna Gyulai [a], Antal Udvardy [b], Attila Sipos [a,c,*]

[a] Department of Organic Chemistry, University of Debrecen, H-4010, PO Box 20, Debrecen, Hungary
[b] Department of Physical Chemistry, University of Debrecen, H-4010, PO Box 7, Debrecen, Hungary
[c] Department of Pharmaceutical Chemistry, University of Debrecen, H-4010, PO Box 70, Debrecen, Hungary

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Dedicated to Professor Mihály Beck on the occasion of his 80th birthday

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ABSTRACT

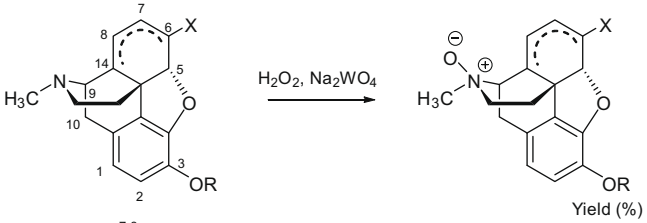
The one-pot N-demethylation and acid-catalyzed rearrangement of morphinan-*N*-oxides offers a new, shorter and more efficient route to neuropharmacologically important N-substituted aporphines. An improved procedure is described for the preparation of the starting alkaloid *N*-oxides using Na_2WO_4 as catalyst. The transetherification during the rearrangement of codeinone into 2-*O*-alkyl-norapocodeines is documented.

The efficient synthesis of N-substituted aporphines is one of the main research fields of dopamine- and/or serotonin-active compounds.[1] The need for high yielding synthetic routes to 2-substituted-noraporphines emerged when extended neuropharmacological studies of the most active compounds were reported.[2] This raised the issue of the preparation of multi-gram batches which in turn required large amounts of expensive starting morphinans which are difficult to obtain.

Currently the main method for the preparation of 2-substituted-*N*-alkyl-noraporphines is via the three-step N-substitution of the starting morphinans, acid-catalyzed rearrangement into aporphines and further chemical modifications on this sensitive backbone.[3] Here we present a one-pot method for the N-dealkylation and rearrangement of previously oxidized morphinan into the noraporphine derivative.

The *N*-oxides of morphinans are well known[4] with the exception of oripavine *N*-oxide (**8**).[5] Their syntheses were accomplished in accordance with our recently developed method (Scheme 1).[2]

All the synthesized *N*-oxides were investigated in a new, one-pot procedure for the N-deprotection and rearrangement. The morphinan *N*-oxides (**6**–**10**, 1 equiv) and iron(II) sulfate monohydrate (2.5 equiv) were suspended in anhydrous alcohol and cooled to 0 °C. Cold methansulfonic acid (99.5% purity, 84% of the total volume) was added dropwise to the suspension under an argon atmosphere. The mixture was stirred at 0 °C for 15 min before being heated at 90 °C for 30 min under argon. The resulting mixture was poured into ice-water, the alcohol and some of the water were removed under reduced pressure until extensive precipitation of the mesylate salt occurred. The solution was cooled to 5 °C for 30 min after which the salt was filtered off. The extent of rearrangement during the heating period was checked by thin layer



1 morphine $\Delta^{7,8}$, R=H, X=α-OH
2 codeine $\Delta^{7,8}$, R=CH_3, X=α-OH
3 oripavine $\Delta^{6,7}\Delta^{8,14}$, R=H, X=$OCH_3$
4 thebaine $\Delta^{6,7}\Delta^{8,14}$, R=$CH_3$, X=$OCH_3$
5 codeinone $\Delta^{7,8}$, R=CH_3, X=O

	Yield (%)
6	64
7	71
8	56
9	58
10	72

Scheme 1. Formation of morphinan *N*-oxides **6**–**10**.

* Corresponding author. Tel.: +36 52 512 900/22478; fax: +36 52 453 836.
E-mail address: asipos@puma.unideb.hu (A. Sipos).

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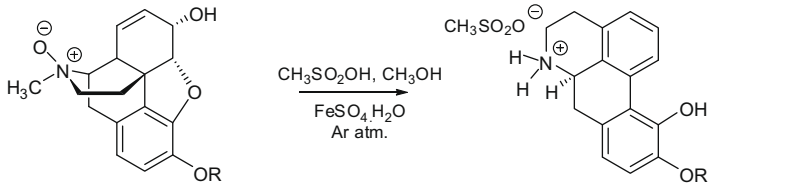


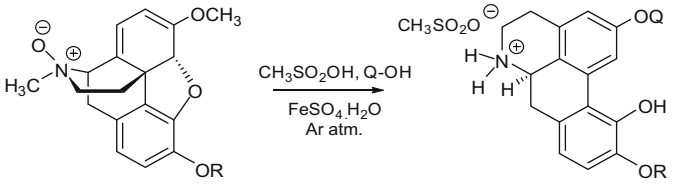
6 morphine *N*-oxide, R=H

7 codeine *N*-oxide, R=CH_3

11 norapomorphine.$HOSO_2CH_3$, R=H

12 norapocodeine.$HOSO_2CH_3$, R=CH_3

Scheme 2. Transformation of morphine- and codeine-*N*-oxides **6** and **7**.



8 oripavine *N*-oxide, R=H

9 thebaine *N*-oxide, R=CH_3

	Yield (%)*
13 2-methoxynorapomorphine.$HOSO_2CH_3$, R=H, Q=CH_3	48
14 2-ethoxynorapomorphine.$HOSO_2CH_3$, R=H, Q=C_2H_5	51
15 2-propoxynorapomorphine.$HOSO_2CH_3$, R=H, Q=C_3H_7	47
16 2-methoxynorapocodeine.$HOSO_2CH_3$, R=CH_3, Q=CH_3	64
17 2-ethoxynorapocodeine.$HOSO_2CH_3$, R=CH_3, Q=C_2H_5	60
18 2-propoxynorapocodeine.$HOSO_2CH_3$, R=CH_3, Q=C_3H_7	67

*reported yields are the average of 3 runs

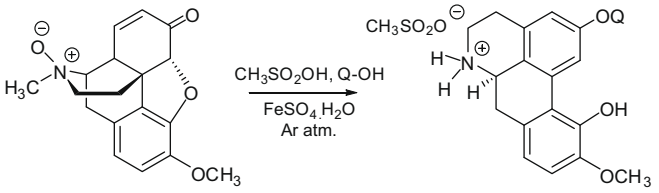
Scheme 3. Versatile rearrangements of oripavine and thebaine *N*-oxides **8** and **9**.

chromatography (dichloromethane–methanol-*c*. NH_3 = 80:19:1) and by using Dragendorff's reagent which provided primary information on the depth of colour of the visualized spots on interaction with tertiary/quaternary amine functions. Morphinans appear as brown spots, *N*-oxides are usually grey, while noraporphines are black. During preliminary reactions, it was noted that in accordance with previous observations,[6] a reduction in the amount of water had a crucial effect on the homogeneity of the product. Therefore, absolute alcohols were used and commercially available iron(II) sulfate heptahydrate was partially dehydrated to the monohydrate at 120 °C under a nitrogen atmosphere for 5 h prior to use.[7]

In the case of morphine- and codeine-*N*-oxides (**6** and **7**) absolute methanol was used and the yields of products **11** and **12** were 47% and 59%, respectively (Scheme 2). This difference was commonly noticed for apomorphine- and apocodeine-type products which could be the result of the higher oxidative sensitivity of apomorphines. The physical and spectral data for the free base forms of compounds **11** and **12** conformed with those of authentic samples.

The unique diene structure of the C ring of oripavine and thebaine *N*-oxides (**8** and **9**) offers possibilities of extended transformation in comparison to other morphinans.[8,9] In addition, the C6-ether function gives the opportunity for in situ transetherification during rearrangement into aporphine.[6b] Combination of this strategy with the simultaneous iron-mediated N-deprotection led to a variety of noraporphines in 47–67% yields (Scheme 3). In the case of norapomorphines **13**–**15**, the products were obtained after recrystallization from methanol.[10] The physical and spectral data for the free base forms of compounds **13**–**18** were in accord with those obtained via different synthetic routes.[2,3a]

Codeinone (**5**) is known to produce 2-methoxyapocodeine on acid-catalyzed rearrangement.[11] However, a systematic investigation of the acid-catalyzed rearrangement of **5** has not yet been carried out. Here we present the first examples of the rearrangement in the presence of anhydrous alcohols and an iron(II) salt (Scheme 4). The electronic structure of the C ring and the C6-oxo function also offer the opportunity for transetherification. As a proof of concept, products **16**, **17** and **18** were obtained in 67%, 71% and 63% yields, respectively.



10 codeinone *N*-oxide

16, Q=CH_3
17, Q=C_2H_5
18, Q=C_3H_7

Scheme 4. Novel rearrangements of codeinone *N*-oxide (**10**).

The N-propylation of noraporphines **11**–**18** was achieved in one step. A mixture of 1 equiv of noraporphine salt, 1.5 equiv of *n*-propyl iodide and 3.5 equiv of $NaHCO_3$, was allowed to reflux for 24 h in the presence of a catalytic amount of KI in CH_3CN. The mixture was cooled then filtered and the filtrate was evaporated to dryness. The crude product was purified on a silica gel column using ether as the solvent to afford *N*-propyl-noraporphines in 65–87% yield. To demonstrate the effectiveness of this methodology, *N*-propylnorapomorphine was obtained in 27% overall yield from morphine (**1**), which is at least fivefold higher in comparison to the best reported method.

The development of efficient synthetic routes to highly active and selective dopaminergic aporphines is important for discovering efficacious alternatives for the management of diseases related to the malfunction of the dopaminergic system (e.g., Parkinson's disease). One of our main intentions is to develop efficient solutions for the preparation of pharmacologically promising derivatives. The present one-pot method reduces the number of steps towards 2-substituted-*N*-alkylnoraporphines and significantly raises the overall yield.

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5. Oripavine *N*-oxide (**8**) was prepared from oripavine (**3**) according to the method described in Ref.[2] in 56% yield. White, plate-shape crystals; mp 198–200 °C (ether); $[\alpha]_D^{25}$ −198 (*c* 0.5, MeOH); R_f ($CHCl_3$–MeOH = 8:2) 0.45; HRMS (ESI) *m*/*z* (%) calcd for $C_{18}H_{19}NO_4Na^+$: 336.1212 ($M+Na^+$), Found: 336.1230 ($M+Na^+$, 100); δ_H (360 MHz DMSO-d_6) 9.76 (1H, br s, C3–OH), 6.62 (1H, d, C1–H, J_{1-2} 8.0), 6.59 (1H, d, C2–H, J_{1-2} 8.0), 5.68 (1H, d, C8–H, J_{7-8} 5.5), 4.93 (1H, d, C7–H, J_{7-8} 5.6), 4.70 (1H, s, C5–H), 4.54 (1H, dd, C9–H, *J* 12.9, *J* 5.7), 3.59 (3H, s, C6–OCH_3), 3.34–2.94 (4H, m, C10–Ha, C10–Hb, C16–Ha, C16–Hb), 2.91 (3H, s, NCH_3), 2.03–1.94 (2H, m, C15–Ha, C15–Hb); δ_C (90 MHz DMSO-d_6) 154.45 (C6), 147.61 (C4), 139.43 (C3), 132.19, 130.09, 128.64, 128.01, 122.99, 118.66 (6C, 4 aromatic, C8, C14), 95.01 (C7), 91.78 (C5), 77.49 (C9), 64.56 (C14), 56.68, 56.12 (C6–OCH_3, N–CH_3), 47.57 (C13), 36.39 (C10), 34.81 (C15).
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10. 2-Methoxy-norapocodeine mesylate (**16**) was prepared from thebaine *N*-oxide (**4**) or codeinone *N*-oxide (**10**) in 64% or 67% yields, respectively. Off-white, powder; mp 212–214 °C (ether); $[\alpha]_D^{25}$ −123 (*c* 0.1, DMSO); R_f for the base ($CHCl_3$–MeOH = 8:2) 0.18; HRMS (ESI) *m*/*z* (%) calcd for $C_{18}H_{19}NO_3Na^+$: 320.1263 ($M+Na^+$), Found: 320.1267 ($M+Na^+$, 100); δ_H (360 MHz DMSO-d_6 for the base) 9.59–9.10 (2H, br s, C11–OH, =N–H), 7.23 (1H, d, C1–H, J_{1-3} 1.2), 6.98 (1H, d, C3–H, J_{1-3} 1.2), 6.75 (1H, d, C8–H, J_{8-9} 8.3), 6.73 (1H, d, C9–H, J_{8-9} 8.3), 4.32 (1H, td, C6a–H, J_{6a-7a} 9.1, J_{6a-7b} 2.5), 3.93 (3H, s, C2–OCH_3), 3.86 (3H, s, C10–OCH_3), 3.35–2.84 (6H, m, C4–Ha, C4–Hb, C5–Ha, C5–Hb, C7–Ha, C7–Hb); δ_C (90 MHz DMSO-d_6) 159.31 (C2), 147.73 (C10), 144.31 (C11), 133.94, 132.20, 129.98, 124.62, 124.12, 123.49, 119.91, 117.34, 111.78 (9C, aromatic), 57.62, 57.56, 56.83 (C6a, C2–OCH_3, C10–OCH_3), 44.23 (C5), 37.94 (C7), 27.89 (C4).
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