Synthesis of Pharmacologically Active Apomorphines by Direct N-Substitution on the Aporphine Backbone

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Abstract: A method has been developed for the direct N-substitution of aporphines comprising the N-oxidation–N-deprotection–N-alkylation sequence. This methodology was found to be insensitive to the change in the substitution pattern of rings A or D, therefore it is presumed to be applicable also for aporphines derived from total synthesis and natural sources.

Key words: alkaloids, transition metals, protecting groups, medicinal chemistry, oxidations

Aporphines are isolated in increasing number from natural sources.[1] This group of isoquinoline alkaloids can be prepared by total synthesis,[2] and by semisynthesis from natural-occurring morphinans via acid-catalyzed rearrangement of the morphinan ring.[3]

Aporphines display a variety of interesting pharmacological properties.[4] The SAR studies indicate that in particular substituents at N-6 influences binding affinity and selectivity to dopamine D1- and D2-agonist receptors.[5] Selected D2-receptor agonists are shown in Table 1.

Apomorphine (**1**) itself displays dopaminergic properties and it is used in certain pharmaceuticals. Compounds **2**, **4**, **6**, **8**, and **10** are even more potent.

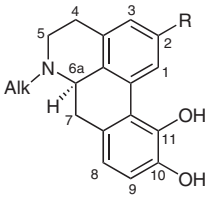
N-Methyl aporphines can be prepared by acid-catalyzed rearrangement of *N*-methyl morphinandienes.[6] Other *N*-alkyl groups can be introduced by demethylation followed by re-alkylation. However, the N-demethylation requires so harsh conditions that a C8=C14 bond in the morphinandiene skeleton usually does not survive.[7]

Hence, there is a demand for a more efficient approach. The present paper describes a new protocol, which gives access to a series of important N-alkylated aporphines by demethylation of *N*-methylaporhines followed by re-alkylation.

There has been no practical method for the direct N-demethylation and consequent N-alkylation of aporphines,[8] however, some successful attempts were published regarding the synthesis of noraporphines. Begtrup's group applied the cleavage of N–Bn bond by catalytic hydrogenation.[9] They performed N-deprotection of an aporphine obtained by the rearrangement of the previously N-benzylated morphinan. Garrido and co-workers studied the oxidative behavior of apomorphine in aqueous media giving raise to some norapomorphines as a result of anodic oxidation.[10] This investigation aimed the better understanding of the biological interactions of apomorphine rather than providing some practical procedure for the N-substitution.

We explored the possibilities of adoption of the oxidation–cleavage-alkylation sequence of Scammells et al., originally developed for morphinans, to aporphine backbone to obtain pharmacologically more interesting *N*-propyl congeners.[11]

Table 1 Some Important D2 Agonists



1–10

Compd	R	Alk	D_2 Binding affinity (nM)
1	H	Me	11.1
2	H	Pr	0.80
3	OH	Me	0.38
4	OH	Pr	0.05
5	OMe	Me	1.12
6	OMe	Pr	0.17
7	F	Me	6.45
8	F	Pr	0.071
9	Br	Me	17.7
10	Br	Pr	0.89

Table 2 Oxidation of 2-Bromoapocodeine (**14**)

Procedure	Temp (°C)	Time (h)	Yield (%)[a]
H_2O_2	r.t.	18	11
MCPBA	60	7	6
H_2O_2, $Mg(OH)_2$, PhCN	60	24	36
H_2O_2, Na_2WO_4	r.t.	3.5	61

[a] Isolated yields after column chromatography, averages of three runs.

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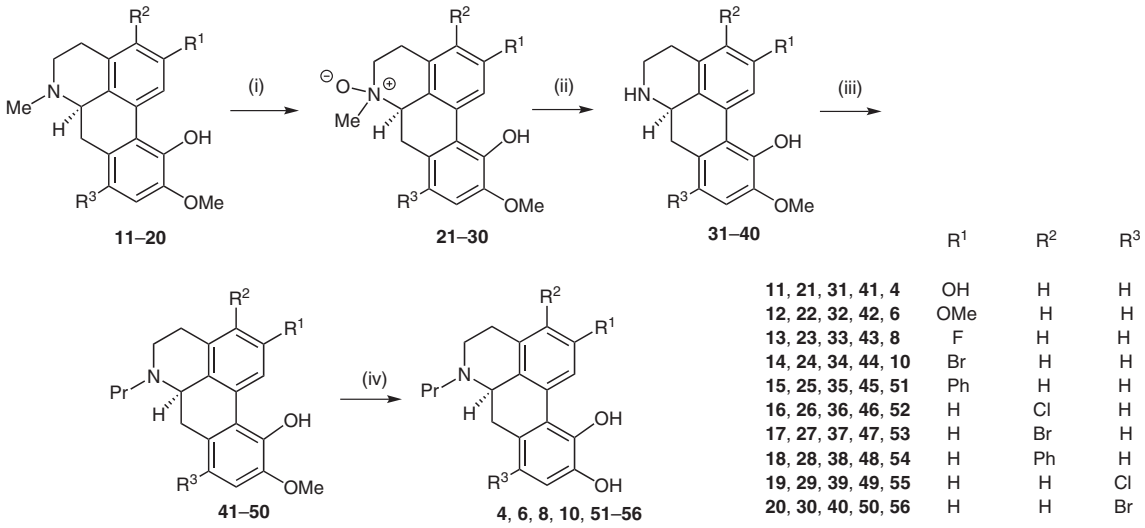

	R^1	R^2	R^3
11, **21**, **31**, **41**, **4**	OH	H	H
12, **22**, **32**, **42**, **6**	OMe	H	H
13, **23**, **33**, **43**, **8**	F	H	H
14, **24**, **34**, **44**, **10**	Br	H	H
15, **25**, **35**, **45**, **51**	Ph	H	H
16, **26**, **36**, **46**, **52**	H	Cl	H
17, **27**, **37**, **47**, **53**	H	Br	H
18, **28**, **38**, **48**, **54**	H	Ph	H
19, **29**, **39**, **49**, **55**	H	H	Cl
20, **30**, **40**, **50**, **56**	H	H	Br

Scheme 1 Direct N-substitution of aporphines. *Reagents and conditions*: (i) H_2O_2, Na_2WO_4, 52–67%; (ii) $FeSO_4{\cdot}7H_2O$, 82–91%; (iii) PrI/K_2CO_3, 75–82%; (iv) $MeSO_2OH$, methionine, 77–87%.

The main concern regarding the oxidative N-deprotection of aporphine skeleton was its sensitivity to this kind of chemical effect. It is well known that the nondegradative oxidation of aporphines leads to 7-oxoaporphines with several oxidizing agents ranging from chromium trioxide in pyridine[12a] to manganese(III) acetate.[12b] Since the modification of the N-substituent was planned on apocodeines having semiprotected catechol motifs, the oxidation of ring D was considered a minor issue under mild conditions. Scammells' method offered the choice between the application of large excess of hydrogen peroxide (11 equiv) and almost quantitative amount of *m*-chloroperbenzoic acid (MCPBA, 1.1 equiv). Both oxidizing agents were tested according to the original methods[11] in terms of the potency of formation of the desired *N*-oxide and unfavorable oxidation products. In these test reactions and further optimization steps 2-bromoapocodeine (**14**) was used.[13] It was found that these long-term oxidation procedures produced *N*-oxide in low yield and considerable amount of side product was obtained in the form of insoluble dark tar in the crude product mixture (Table 2).

After reviewing recent literature we identified two promising catalytic procedures offering significantly milder conditions. The first one suggested the application of heterogeneous catalysis with H_2O_2, basic minerals, and benzonitrile as an additive in water–methanol solvent.[14] During workup it was noted that the amount of the dark, overoxidized side product decreased, however, the isolated yield for *N*-oxide remained under 40%. Therefore our attention turned to the application of a shorter, room-temperature procedure utilizing Na_2WO_4 as a catalyst.[15] In order to increase the solubility of our apocodeine **14** the original aqueous media was changed to water–1,4-dioxane (1:2). The yield of the reaction remarkably increased and the amount of the side product remained at an acceptable level.

After this optimization step the method was expanded to a variety of apocodeines **11**–**20** in order to synthesize *N*-oxides (Table 3) leading either to previously highlighted *N*-propyl norapomorphines **4**, **6**, **8**, and **10** or other, hitherto unknown, apomorphines **51**–**56** (Scheme 1) with potential pharmacological interest.[16,17]

The HCl salts of *N*-oxides **21**–**30** were N-deprotected according to Scammells' procedure applying $FeSO_4{\cdot}7H_2O$ in methanol at 0 °C.[11] Noraporphine hydrochlorides **31**–**40** were then re-alkylated with propyl iodide in the presence of three equivalents of potassium carbonate in methanol. Finally, the O-demethylation of norapocodeines **41**–**50** into the pharmacologically more interesting norapomorphines **4**, **6**, **8**, **10**, and **51**–**56** was carried out by methanesulfonic acid and methionine[18] reagent mixture. The neuropharmacological characterization of the stable HCl salts of novel apomorphines **51**–**56** is still in progress.

Table 3 Yields of the N-Deprotection Steps

Compd	Isolated yield (%)[a]	
	N-Oxide formation	N-Deprotection
11	52	85
12	54	82
13	63	87
14	61	82
15	67	90
16	55	91
17	59	82
18	63	84
19	60	87
20	59	84

[a] Reported yields are averages of 3 runs.

In conclusion we have presented a procedure for direct N-substitution of aporphines comprising the N-oxidation–N-deprotection–N-alkylation sequence. This methodology was found to be insensitive to the change in the substitution pattern of rings A or D, therefore it is presumed to be applicable for aporphines also from total synthesis and natural sources.

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(17) **General Procedure for the N-Substitution of Aporphines**
Apocodeine base (2.92 mmol) and Na_2WO_4 (300 mg, 1.02 mmol) was dissolved in H_2O–1,4-dioxane (1:2, 10 mL) and cooled to 0 °C for the dropwise addition of H_2O_2 (30% w/v, 12 mmol). The reaction mixture was stirred at r.t. for 3.5 h. The excess H_2O_2 was quenched by addition of small portions of MnO_2 at 0 °C and the presence of the peroxide determined by KI-starch paper. The reaction mixture, containing some overoxidized product as dark precipitation, was then vacuum filtered through a short pad of Celite. Solvent was removed in vacuo to give the crude product as a pale brown solid. It was immediately turned into hydrochloride salt by dissolving in a few drops of $CHCl_3$ and dropping some EtOH sat. with HCl gas. After filtration, the mixture of minor apocodeine·HCl and major apocodeine *N*-oxide·HCl was dissolved in MeOH (10 mL) followed by the addition of $FeSO_4·7H_2O$ (2 equiv) at 0 °C. The reaction mixture was then left to stir at r.t. for 1 h. Conversion was followed by TLC (80% CH_2Cl_2–20% MeOH). The reaction solvent was removed in vacuo and the residue redissolved in a 0.1 M EDTA solution adjusted to pH 10 by addition of NH_3 (70 mL). The aqueous phase was then extracted with $CHCl_3$ (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent removed in vacuo to give dark brown mixture of apocodeine and norapocodeine. Norapocodeine was isolated by means of silica column chromatography (eluent: 80% CH_2Cl_2–20% MeOH). Physical and spectral data of the products of the synthetic route from (–)-(*R*)-2-bromoapocodeine (**14**) to (–)-(*R*)-*N*-propyl-2-bromonorapomorphine (**10**) are detailed to represent the described method.
(–)-(*R*)-2-Bromoapocodeine *N*-Oxide Hydrochloride (24·HCl)
Off-white, plate-shape crystals; mp >250 °C (Et_2O); $[\alpha]_D^{25}$ –168 (*c* 0.1, DMSO); R_f base = 0.21 ($CHCl_3$–MeOH, 8:2). HRMS (EI): *m/z* (%) calcd for $C_{18}H_{18}BrNO_3^+$: 375.0470 [M^+]; found: 375.0482 (100) [M^+]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (1 H, s, C1–H), 7.14 (1 H, s, C3–H), 6.77–6.70 (2 H, 2 d, C8–H, C9–H, $J_{8\text{-}9}$ = 8.1 Hz), 6.14 (1 H, br s, OH), 5.32 (1 H, td, C6a–H, $J_{6a\text{-}7a}$ 9.4 Hz, $J_{6a\text{-}7b}$ 2.7 Hz), 3.77 (3 H, s, C10–OCH_3), 3.70–2.94 (6 H, m, C4–Ha, C4–Hb, C5–Ha, C5–Hb, C7–Ha, C7–Hb), 2.91 (3 H, s, NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.61 (C10), 144.43 (C9), 136.19–114.78 (10 C, arom.), 75.09 (C6a), 60.56 (C5), 56.23 (C10–OCH_3), 54.51 (N–CH_3), 37.39 (C7), 25.81 (C4).
(–)-(*R*)-2-Bromonorapocodeine Hydrochloride (34·HCl)
White, cubic crystals; mp >250 °C (Et_2O); $[\alpha]_D^{25}$ –78 (*c* 0.1, DMSO); R_f base = 0.17 ($CHCl_3$–MeOH, 8:2). HRMS (EI): *m/z* (%) calcd for $C_{17}H_{17}BrNO_2^+$: 346.0437 [M^+ + 1]; found: 346.0444 (100) [M^+ + 1]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.41 (1 H, s, C1–H), 7.07 (1 H, s, C3–H), 6.69–6.62 (2 H, 2 d, C8–H, C9–H, $J_{8\text{-}9}$ = 8.0 Hz), 6.09 (1 H, br s, OH), 4.13 (1 H, td, C6a–H, $J_{6a\text{-}7a}$ = 9.1 Hz, $J_{6a\text{-}7b}$ = 2.5 Hz), 3.83 (3 H, s, C10–OCH_3), 3.09–2.18 (7 H, m, C4–Ha, C4–Hb, C5–Ha, C5–Hb, C7–Ha, C7–Hb, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.12 (C10), 144.76 (C9), 137.28–113.19 (10 C, arom.), 56.47 (C10–OCH_3), 53.71 (C6a), 43.56 (C5), 37.18 (C7), 26.66 (C4).
(–)-(*R*)-*N*-Propyl-2-bromonorapocodeine (**44**) and (–)-(*R*)-*N*-propyl-2-bromonorapomorphine (**10**) are characterized in ref. 16a.

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