Regioselective O-Demethylation in the Aporphine Alkaloid Series

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Sodium benzylselenolate in refluxing dimethylformamide has been found to be a superior reagent for the O-demethylation of aryl methyl ethers, as evidenced by a study of its reaction with a number of representative nonphenolic aporphine alkaloids, including nuciferine (**3**), apomorphine dimethyl ether (**6**), ocopodine (**11**), *O*-methylbulbocapnine (**9**), and thalicarpine (**13**). Good yields of monophenolic bases are obtained owing to regioselective demethylation at positions 1, 8, and 11 of the aporphine nucleus; methylenedioxy functions survive the reaction.

The demethylation of aryl methyl ethers under nonacidic conditions has been accomplished by the use of a wide variety of nucleophiles, including iodide, diphenylphosphide, amide, hydroxide, alkoxide, sulfite, and thiolate anions.[1] The most convenient reagents reported have been thioethoxide in hot dimethylformamide (DMF)[2] and *p*-thiocresolate in hot toluene containing hexamethylphosphoramide.[3] At a lower temperature (80 °C) and in the less polar solvent 2-butanone, several methoxylated quaternary alkaloids were cleanly N-demethylated by thiophenoxide ion to tertiary bases without any O-demethylation.[4] A virtual repetition of the latter study using selenophenoxide ion led to exactly the same results with much shorter reaction times.[5]

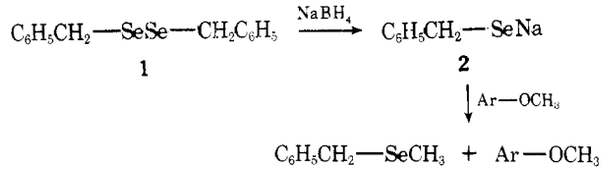
We now report the results of a study of the reaction of benzylselenolate ion in hot DMF with a number of representative nonphenolic aporphine bases containing from two to seven methoxy functions. As described below, the reactions proceeded smoothly and with a remarkable degree of regiospecificity.

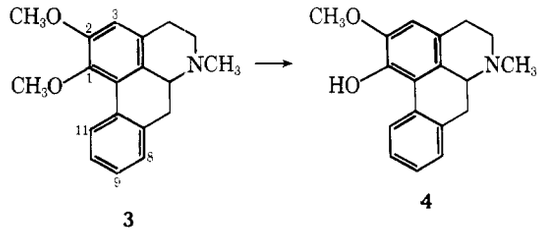
Results

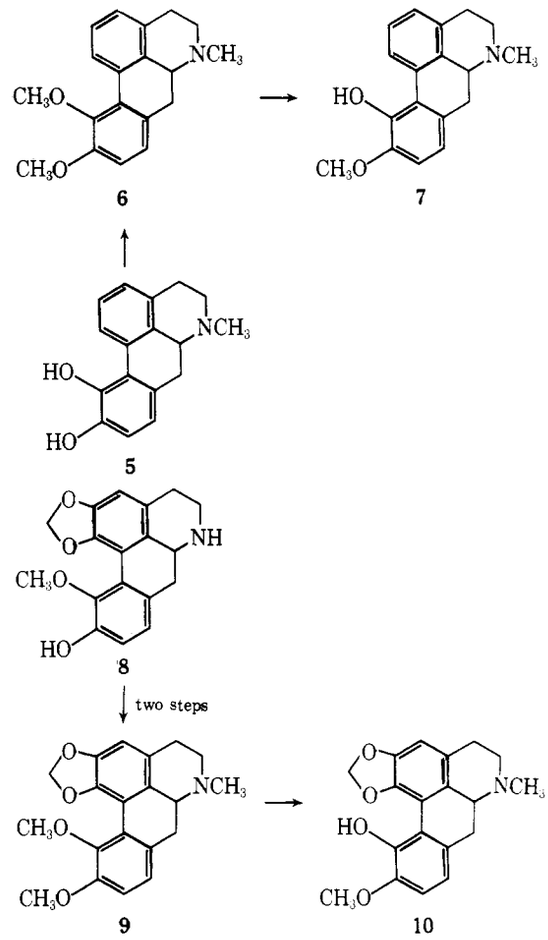
The reagent employed in this study was a solution of sodium benzylselenolate (**2**) in refluxing DMF. The readily oxidized selenolate **2** was prepared in situ by the reaction of excess sodium borohydride in DMF with the easily prepared,[6] stable, and odorless dibenzyl diselenide (**1**). A ratio of 1.3/1.0 molar equiv of selenolate ion to alkaloid was employed, and the reaction mixture was refluxed under nitrogen until almost complete disappearance of the original alkaloid was observed (30–120 min).

Nuciferine (**3**) was found to be demethylated in a highly selective manner at C-1 to give 1-hydroxy-2-methoxyaporphine (**4**)[7] in 75% yield.

In the case of apomorphine dimethyl ether (**6**) the internally situated methoxy (in this case at C-11) was also selectively demethylated, giving apocodeine (**7**)[8] in high yield (79%). Since a good conversion of apomorphine (**5**) to its dimethyl ether has been described,[8] a simple and practical conversion





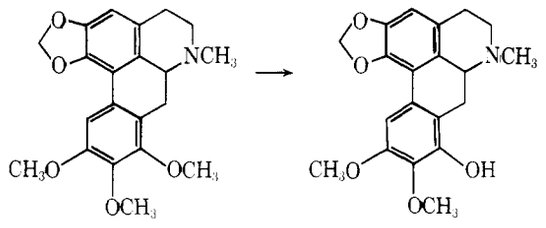


of apomorphine into apocodeine (**7**) is now available for the first time.

In a similar manner, selective demethylation of *O*-methylbulbocapnine (**9**) took place also by attack of the nucleophile on the C-11 methoxyl to give bulbocapnine (**10**) in 65% yield. Since methyl ether **9** is also the *O,N*-dimethyl derivative of nandigerine (**8**), selective demethylation of **9** provides a simple means of preparing bulbocapnine from nandigerine, which is a major alkaloid from the bark of the widely distributed tree *Hernandia ovigera*.[9]

Ocopodine (**11**) illustrates a different type of methoxyl substitution pattern, its three methoxyls being situated vicinally at C-8, C-9, and C-10. Demethylation again took place selectively, yielding leucoxine (**12**)[10] in 68% yield.

The most interesting results were obtained with the more complex antitumor alkaloid thalicarpine (**13**). Despite the presence of seven methoxyls in thalicarpine, the C-1 methoxyl of the aporphine nucleus was preferentially attacked to give, in 51% yield, the rare natural base thalictropine (**14**);[11] this degradation has made thalictropine available for the first time



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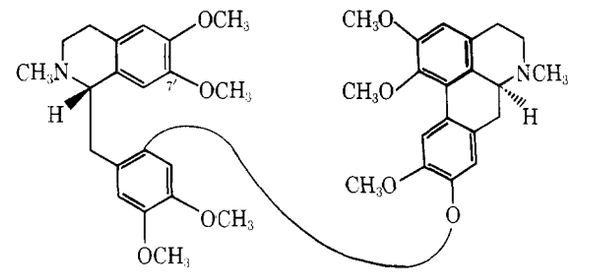
in amounts necessary for biological evaluation.

The most abundant by-product of the thalicarpine demethylation was an amorphous base (*m/e* 668), obtained in 22% yield, which was assigned the structure of 1,4″-dide-



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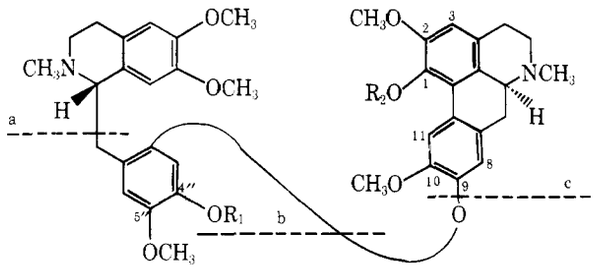
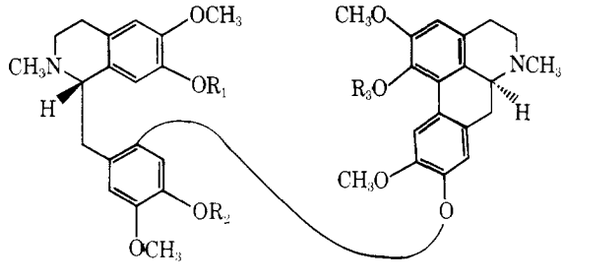


14, $R_1 = CH_3$; $R_2 = H$
15, $R_1 = R_2 = H$
16, $R_1 = R_2 = COCH_3$



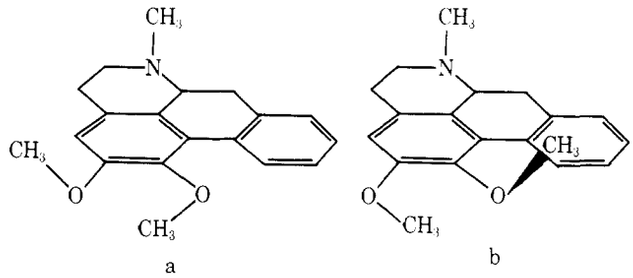
17, $R_1 = R_3 = H$; $R_2 = CH_3$
18, $R_1 = R_2 = CH_3$; $R_3 = H$

methylthalicarpine (**15**). The position of the hydroxyl functions in **15** was revealed by a combination of mass spectroscopic and NMR data, as compared with those reported for the closely related natural bases thalictropine (**14**),[11] thalictrogamine (**17**),[11] and thalidoxine (**18**).[12] Thus, significant mass spectral peaks corresponding to fragments of *m/e* 462 (M − a), 326 (M − b), 296 (M − c), and 206 (a) indicated that one hydroxyl must be in the aporphine moiety of the molecule, while the second must be located on the benzyl unit of the benzylisoquinoline moiety. A comparison of the NMR of **15** with that of its diacetate (**16**) revealed an upfield shift of the C-11 proton from δ 8.09 to δ 7.61, indicative of the presence of a phenolic hydroxyl at C-1 in the parent base.[11] A further change in the NMR spectrum of **15** upon acetylation was the upfield shift of the C-8 proton singlet from δ 6.52 to 6.22, an effect attributable to shielding by an acetoxyl at C-4″ but not by such a function at C-5″.[12]

Discussion

A very recent study of the reaction of *p*-thiocresolate ion with a number of polymethoxybenzaldehydes has shown that demethylation of a 2-methoxy or 4-methoxy group takes place selectively in the presence of a 3-methoxy group;[3] this observation is consistent with carbonyl resonance stabilization of the phenoxide leaving group when ortho or para to the aldehyde function.

In the examples of selective demethylation reported in the present paper, similar resonance effects are not operative, and the observed regioselectivity must be attributed to steric factors. In the case of the *O*-dimethoxyaporphines **3**, **6**, and **9**, the internally situated methoxyls (at C-1 or C-11) are selectively attacked by the selenolate ion; these same methoxyls appear in the NMR at positions from 0.15 to 0.22 ppm upfield from their neighbors, indicating that their methyl components are pushed above the plane of the adjacent aromatic ring. If one makes a rough "conformational analysis" of the two methoxyls of one of these compounds, i.e., nuciferine (**3**), the selective demethylation at C-1 can be rationalized. Assuming that maximum conjugation in an aryl methyl ether requires coplanarity of the methoxyl C–O with the arene ring, the two energy minima for the rotation of the C-2 methoxyl of **3** are the syn and anti structures (a and b). In a, the C-1 methoxyl also achieves maximum conjugation, but in b it is directed out of the plane of its aromatic ring by the repulsion of the C-11 hydrogen. Since attack of a selenolate anion on a methoxyl methyl must take place on a trajectory of 180° from the methoxyl oxygen, only *one* trajectory is possible for attack on each *O*-methyl in conformational minimum a. In the less favorable minimum b, only *one* trajectory can be drawn for attack at the C-2 methoxyl, but a whole arc of trajectories above (or below) the ring can be drawn for attack on the unconjugated out-of-plane C-1 methoxyl. An extension of this type of entropy argument also predicts the stability of the methylenedioxy group of **9** and **11** to nucleophilic attack, since only *one* anionic 180° trajectory is allowed for the displacement of each oxygen of this function owing to its rigidity as part of a ring.



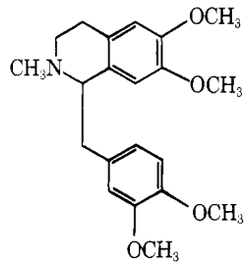
a b

In the case of ocopodine (**11**), all three methoxyls appear in the NMR within the narrow range of 0.05 ppm and a similar compression of the readily attacked C-8 methoxyl is not observed. Models reveal, however, that the methyl of the C-8 methoxyl can in fact be pushed above the adjacent nonaromatic ring, a position which would not reveal itself by an aromatic shielding effect.

In the case of the more complex aporphine–benzylisoquinoline base thalicarpine (**13**), preferential demethylation of the crowded aporphine C-1 methoxyl (δ 3.71) is still observed, although the most shielded methoxyl (δ 3.58) in the molecule is that at C-7′.[12] Shielding of the latter methoxyl, however, is probably not a result of steric compression, but rather a shielding by the aporphine moiety of the molecule.

Laudanosine (**19**) represents not only the nonaporphine portion of thalicarpine, but it is an example of a typical ben-

zyltetrahydroisoquinoline alkaloid. Attempted selective demethylation of laudanosine afforded a complex mixture of phenolic bases which was not further investigated. This result is not unexpected, since all four methoxyls of **19** are in a similar steric environment owing to the relatively free rotation of the lower ring.



19

Experimental Section

Melting points are uncorrected. NMR spectra ($CDCl_3$ containing tetramethylsilane as internal standard), infrared spectra (KBr), and mass spectra were determined using Varian A-60 and Perkin-Elmer 202 and 270 spectrometers, respectively. TLC and PLC were carried out on silica plates with 1:9 methanol–chloroform as developer.

General Procedure for Alkaloid Demethylations. To a stirred solution of 0.222 g (0.65 mmol) of dibenzyl diselenide in 10 ml of dry DMF was added excess $NaBH_4$ (ca. 200 mg) under N_2. After 15 min 1 mmol of alkaloid in 10–15 ml of DMF was introduced. The mixture was refluxed under nitrogen until all the alkaloid was consumed (monitored by TLC). The mixture was cooled and solvent was evaporated under reduced pressure. The residue was taken up in 5% H_2SO_4 and the nonalkaloidal components were extracted with benzene. The acid solution was basified with 10% NH_4OH (pH 8–9) and exhaustively extracted with chloroform. The combined chloroform extracts were dried (anhydrous Na_2SO_4) and evaporated. The product was further purified in the usual manner.

The free bases were identified as such or as their derivatives. The experimental data are summarized in Table I.

Table I

Registry no.	Starting material	Product	Refluxing time, min	Yield, %
475-83-2	3	4	120	75
38291-33-7	6	7	30	79
2490-83-7	9	10	45	65
19893-95-9	11	12	90	67.8
5373-42-2	13	(a) 14	50	51
		(b) 15		22

1-Hydroxy-2-methoxyaporphine (**4**) was crystallized as the hydrochloride, mp 223 °C dec (MeOH/ether) (lit.[7] mp 220 °C dec). The NMR and mass spectra were identical with those reported.

The hydrochloride of apocodeine (**7**) was crystallized from MeOH/ether: mp 258–260 °C (lit.[8] mp 255 °C). The spectroscopic data were identical with those reported.

Bulbocapnine hydrochloride (**10**), leucoxine (**12**), and the acetate of thalictropine (**14**) were identified by comparison with authentic samples.

The demethylation mixture from thalicarpine was separated by pH-gradient countercurrent distribution using citrate–phosphate buffer solutions, to give 51% of thalictropine (**14**) and 22% of dihydroxy compound (**15**).

The 1,4″-didemethylthalicarpine (**15**) was amorphous: $[\alpha]D$ +105° (MeOH, *c* 0.5); mass spectrum *m/e* (rel intensity) 668 (M^+, 15), 462 (M − a, 60), 326 (M − b, 88), 296 (M − c, 35), 206 (a, 100); NMR δ 2.50 (s, 6 H, 2 NCH_3), 3.54 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.14 (s, 1 H), 6.52 (s, 1 H), 6.58 (s, 4 H), 8.09 (s, 1 H).

The acetate of **15** was prepared using acetic anhydride in pyridine. Its NMR spectrum showed δ 2.27 (s, 3 H, $CH_3C{=}O$), 2.34 (s, 3 H, $CH_3C{=}O$), 2.52 (s, 6 H, 2 NCH_3), 3.58 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.86 (s, 6 H, 2 OCH_3), 6.11 (s, 1 H), 6.22 (s, 1 H), 6.59 (s, 2 H), 6.65 (s, 2 H), 7.61 (s, 1 H).

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Registry No.—**1**, 1482-82-2; **15**, 61193-40-6; **16**, 61193-41-7.

References and Notes

(1) See ref 2 for specific references to and a critical comparison of these reagents.
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