Pergamon

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Photochemical Hydroxymethylation of Protoberberine Alkaloids. Total Synthesis of (±)-Solidaline.

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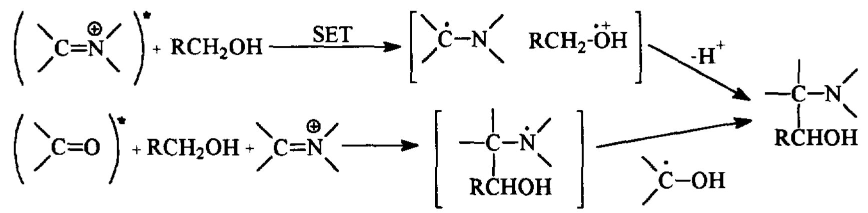
Abstract: The introduction of a hydroxymethyl group at the C-8 position of berberinium salts was readily achieved by photoaddition of methanol. The resulting photoproducts were isolated as tetrahydroprotoberberine derivatives. By combining this photochemical reaction with the oxidation of the photoproduct, the synthesis of (±)-solidaline starting from palmatine chloride was accomplished for the first time.

The presence of a hydroxymethyl group as a substituent at position 1 of the isoquinoline nucleus is common structural feature among isoquinoline alkaloids.[1] Typical examples include simple tetrahydroisoquinolines[2] such as the widespread calycotomine, the more complex benzophenanthridines,[3] and three protoberberine alkaloids that share the same structural characteristics, with the substituent at either C-8, as in (+)-malacitanine[4] and (±)-solidaline (**1**),[5] or at C-14, as in zijinlongine.[6] These berbines, of unknown biosynthesis,[7] are minor alkaloids in their respective plants. It was of interest to study the introduction of the hydroxymethyl group at these positions in the previously formed berbines or berberinium salts, which are readily available from natural sources.[8]

Position 8 in berberinium salts is sufficiently electrophilic as to allow the addition of carbon nucleophiles such as Grignard reagents or the anion of acetone.[9] Consequently, hydroxymethyl anion equivalents prepared from *t*-butyl methyl ether,[10] methyl 2,4,6-triisopropylbenzoate,[11] (tributylstannyl) methanol[12] or (chloromethyl)isopropoxydimethylsilane[13] should react in a similar manner. Nevertheless, a more simple and expeditious synthetic option would be to use the photoaddition of methanol to the corresponding iminium salts.[14] This Letter demonstrates that under appropriate conditions, 8-hydroxymethyl berbine alkaloids can be prepared photochemically from the corresponding berberinium salts in good yields. This synthetic approach has been used to accomplish the first total synthesis of (±)-solidaline (**1**) and to confirm its tentative structure.[5]

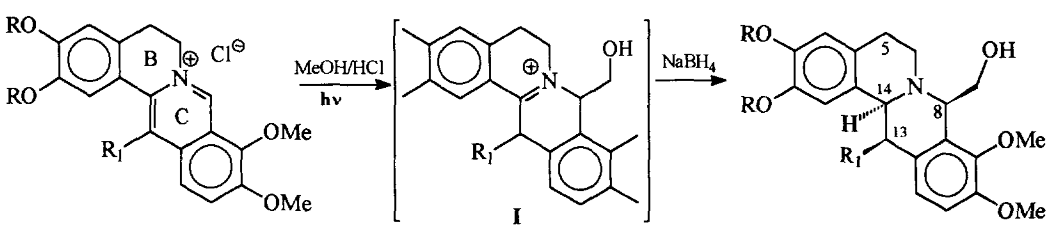
While electronically excited iminium ions are ineffective in direct hydrogen abstraction processes, two major mechanisms are operative in the photoaddition of alcohols to iminium salts: chemical sensitization and single electron transfer (SET).[14] The acetone or benzophenone sensitized irradiation of a methanol solution of berberine chloride (**2a**) exhibited very slow disappearance of the alkaloid,



leading to an intractable complex mixture. This result is in contrast with the reported formation of bocconoline, a 6-hydroxymethyl benzophenanthridine alkaloid obtained by acetone sensitized irradiation of chelerithrine chloride in methanol.[15] Probably, the unsuccessful photoaddition to **2a** can be partially attributed to the dark reactivity of the enamine intermediate. Under identical conditions, N-methyl-(6,7-dimethoxy)-isoquinolinium chloride and N-methyl papaverinium chloride also failed to give the products resulting from the photosensitized addition of methanol.

The major mechanism operating in the photoreaction of iminium salts and their N-heteroaromatic analogues with alcohols[14c] involves initial SET from the oxygen atom to the singlet exited state of the iminium salt leading to the radical-ion pair. Carbon deprotonation of the cation radical provides a route for generating the radical precursor of the addition products. Contrary to our expectations, a deoxygenated methanolic solution of **2a** remained unchanged after one week of irradiation at $\lambda > 300$nm.

Next, we thought that performing the reaction in a strong acid medium might favour the reaction in several ways: a) by facilitating the initial SET; b) by stabilizing the C-8 radical intermediate through extended conjugation; and c) preventing dark reactions of the photoadduct while keeping the enamine formed protonated. Thus, a deoxygenated hydrogen chloride-saturated methanolic solution of **2a** (450 mg in 150 ml) was irradiated at either 254 nm (quartz) or 300nm (Pyrex) and the reaction monitored via the disappearance of the low field signal of the H-8 proton in the ^1H NMR spectrum. After irradiation for 6 days, part of the solvent was removed and $NaBH_4$ slowly added to afford 8-hydroxymethyl canadine (3a)[16] in a 60% yield. The *trans* relationship between H-14 and the substituent at C-8 was inferred from the γ-gauche effects observed in the carbon-13 NMR spectrum relative to canadine and related systems,



2a-d

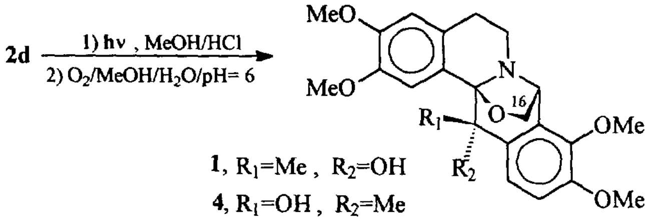
3a-d

a, R+R = CH_2, R_1 = H
b, R = Me, R_1 = H
c, R+R = CH_2, R_1 = Me
d, R = R_1 = Me

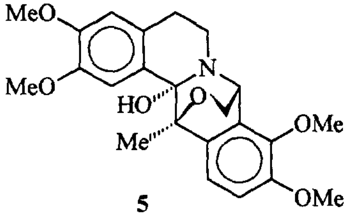
consistent with a *trans*-quinolizidine conformation.[4]

Similarly, the chloride salts of palmatine (**2b**), 13-methylberberine (**2c**) and dehydrocorydaline (**2d**),[17] were subjected to the photohydroxymethylation/reduction reaction sequence. Products **3b-d** were isolated in 56, 72 and 75% yields, respectively.[16] Both alkyl substituents at ring C in compounds **3c** and **3d** exhibited a *cis* arrangement, while the hydrogen at C-14 was *trans* to them, as inferred from the coupling constant between H-13 and H-14, and the strong nOe observed between H-8 and H-14, consistent with a *trans* B/C ring junction.

The easy access to **3d** moved our attention to the iminium intermediate precursor, which is one oxidation stage behind the one proposed for the structure of (±)-solidaline (**1**), a protoberberine alkaloid isolated from *Corydalis solida*, whose structure required synthetic confirmation. Since any attempt to isolate the photoadduct (**I**) as either iminium or enamine was unsuccessful, its direct oxidation was undertaken. The crude product obtained by irradiation of **2d** was oxidized with molecular oxygen at pH 6 to give a major compound (12%) that was characterized from its physical and spectroscopic data as solidaline (**1**)[5] and its epimer at C-13 (**4**)(5%).[18]



1, R_1=Me , R_2=OH
4, R_1=OH , R_2=Me



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^{1}H (500 MHz) and ^{13}C (50 MHz) nmr data for solidaline (**1**) and its C-13 epimer (**4**), particularly the chemical shifts observed for the methyl group attached to C-13 (δ 1.79 and 22.1 ppm for **1** and δ 1.19 and 26.3 ppm for **4**) are consistent with the structure initially proposed for the alkaloid,[5] with the bridge and the hydroxyl group in a *trans* arrangement. A *cis*-quinolizidine structure was proposed for solidaline based on the observed chemical shift for C-5 and C-6. However, NOESY experiments showed the proximity between H-8 and H-6(eq) on the one hand, and H-6(ax) and H-16 on the other, to strongly suggest a *trans*-quinolizidine conformation for **1**, also supported by the observed coupling constant for ring B protons. HMBC correlation between H-16 and C-14 supported the assumption that the oxygen in the bridge was not connected to C-13, thus excluding the alternative structure **5**, also considered by Shamma and Moniot[19] for solidaline.

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