NEW HETEROCYCLIC SKELETONS DERIVED FROM THE APORPHINE ALKALOID BOLDINE

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ABSTRACT

The abundant aporphine alkaloid (*S*)-(+)-boldine (**1**) was selectively nitrosated with sodium nitrite in acetic acid affording 8-nitrosoboldine (**2**) which was hydrogenated catalytically to give 8-aminoboldine (**3**). The latter was used as the starting material for annulations with ethyl *ortho*-formate to afford the corresponding oxazole (''boldine-9,8-oxazole'', **4**), and with methyl benzoylformate giving the phenyl-oxazinone (''boldine-9,8-phenyloxazinone'', **5**). This later product was treated with KOH/EtOH at room temperature and converted quickly

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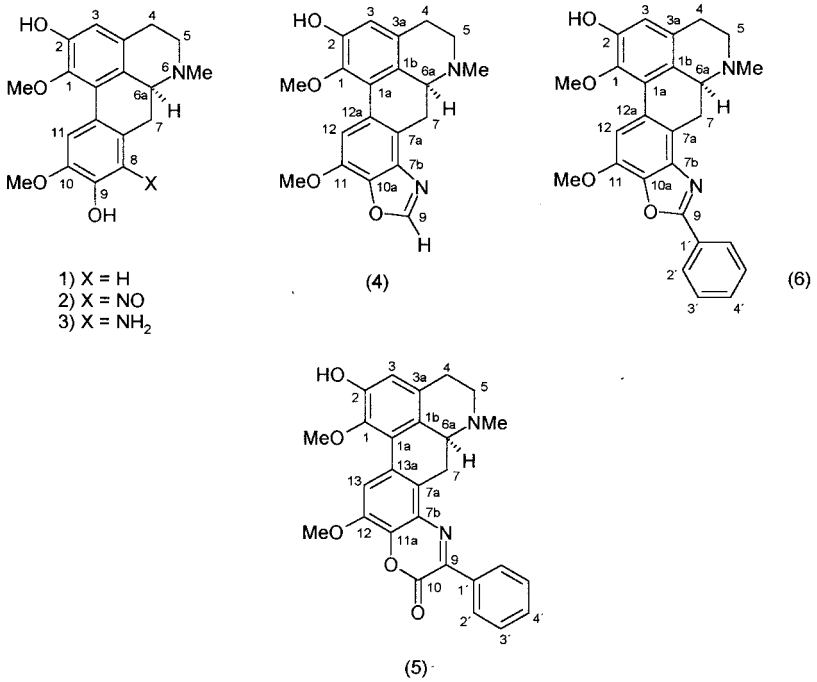
into the ring-contracted phenyloxazole (''boldine-9,8-phenyloxazole'', **6**) in moderate yield.

Boldine (**1**), the major alkaloid present in leaves and bark of the Chilean boldo tree (*Peumus boldus* Mol., Monimiaceae), exhibits a variety of pharmacological activities as an antioxidant and as a catecholamine receptor antagonist.[1] We have previously reported semi-synthetic transformations of boldine to afford products bearing halogen atoms at C-3 or C-3 and C-8 of the aporphine framework, some of which showed greatly increased potency and selectivity at dopamine and adrenergic receptors.[2] As an entry to further elaborated boldine derivatives, we carried out the nitrosation of the alkaloid in acetic acid affording 8-nitrosoboldine (**2**) as only reaction product, which opened up the possibility of synthetizing new heterocyclic systems with benzoxazole or benzoxazinone rings fused to the aporphine skeleton, starting from 8-aminoboldine (**3**) obtained by reduction of the nitroso group.

Benzoxazoles have been prepared by heating *o*-aminophenols with carboxylic acids in the presence of condensation agents such as polyphosphoric acid[3,4] or with ethyl orthoformate in refluxing EtOH.[5] Other options have been based on the Pomeranz-Fritsch reaction on benzalaminoacetals in P_2O_5/H_2SO_4;[6] by cycloaddition of azomethine ylides to 1-nitroso-2-naphthol;[7,8] by treatment of 1-nitroso-2-naphthol and phenacylpyridinium bromide with a NaOH solution at $-30^{\circ}C$;[9] and through the condensation of 1-amino-2-naphthols with aromatic aldehydes in the presence of pyridine in BuOH.[10] Naphth[1,2-d]oxazoles have also been obtained as intermediate products in the preparation of naphthalenesulfonamides as dyes for wool, polyamide fibers and leather.[11] An easy and quick way of obtaining 2-phenylbenzoxazoles is based on the decomposition of naphtho- and benzoxazinones in 10% KOH/MeOH solution.[12] These oxazinones are readily available using a variation of Moffet's method starting from an *o*-aminophenol and methyl benzoylformate in pyridine.[13]

In this communication we describe the formation of the oxazole-annulated ''boldine-9,8-oxazole'' (**4**) and the oxazinone-annulated ''boldine-9,8-phenyloxazinone'' (**5**) starting from an *o*-aminophenol (**3**) derived from boldine, and the instantaneous decomposition of **5** with a 5% ethanolic KOH solution at room temperature to give the corresponding ''boldine-9,8-phenyloxazole'' (**6**) (Sch. 1).

It is noteworthy that 8-aminoboldine (**3**) is formed from the oxazinone (**5**) together with the rapid appearance of the 2-phenyloxazole (**6**). This behavior is quite different from the reactivity found for benzo- and naphthoxazinones, which require many hours at reflux temperature to



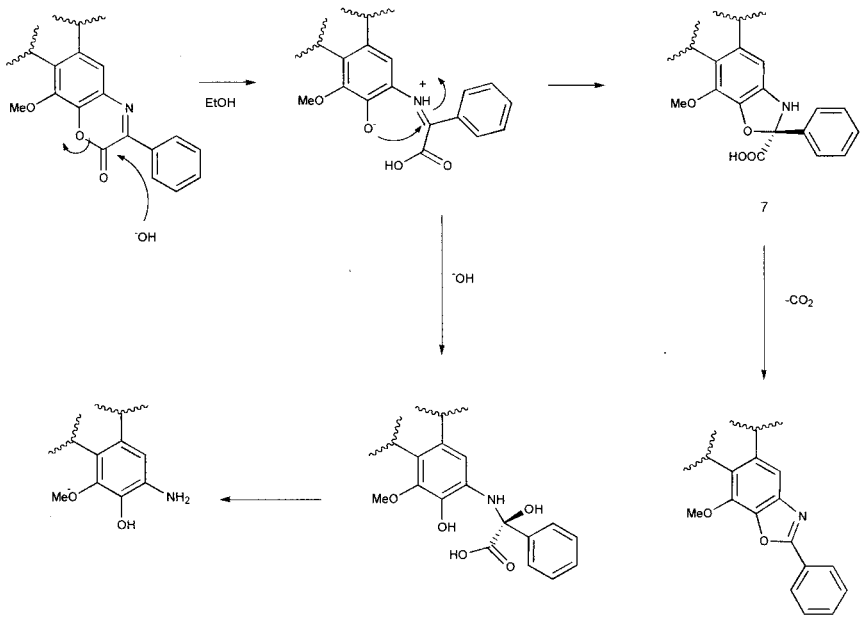
Scheme 1.

afford the oxazole system in good yield. However, the fast reaction of **5** under relatively mild basic conditions resulting in the ring contraction to **6** suggests the existence of a 2,3-dihydrobenzoxazole intermediate (**7**). Decarboxylation of this intermediate and dehydrogenation presumably lead to the formation of **6**, while hydrolysis of **7** or of its ring-opened precursor should give 8-aminoboldine **3** (Sch. 2).

No satisfactory, experimentally based mechanistic rationalization of the base-catalyzed decomposition of benzo- or naphtoxazinones is available yet. In the meantime, it seems prudent to postpone any speculations as to why the annulated oxazinone derived from boldine shows such remarkably enhanced reactivity.

EXPERIMENTAL

Boldine (**1**), isolated from *P. boldus* bark was crystallized from $CHCl_3$ as the 1 : 1 complex (**1**-$CHCl_3$) and used as such. Melting points were



Scheme 2.

determined on a Reichert-Jung Galen III Kofler hot stage. Optical rotations were determined with a Schmidt-Haensch Polartronic electronic polarimeter. Column chromatography was performed on Merck silica gel 60, 230–400 mesh, and TLC on Merck silica gel G. Microanalyses were obtained using a Fisons EA 1108 analyzer and were carried out by the CEPEDEQ, Faculty of Chemical and Pharmaceutical Sciences, University of Chile. NMR spectra were recorded in DMSO-d_6 using a Bruker AMX 300 instrument, operating at 300.13 MHz (^{1}H) or 75.48 MHz (^{13}C). Compounds **4** to **6** were fully characterized by concerted use of one- and two dimensional NMR techniques as described in our previous paper.[14]

2,9-Dihydroxy-1,10-dimethoxy-6-methyl-8-nitrosodibenzo[*de*,*g*]quinoline (2): A solution of **1**-$CHCl_3$ (2.4 g, 7.33 mmol) dissolved in HOAc (60 mL) was treated with solid $NaNO_2$ (0.64 g, 9.28 mmol) at room temperature. After 1 h stirring, the mixture was poured into 100 mL cold H_2O, and the aqueous solution was adjusted to pH 8–9 with concentrated NH_3, extracted with EtOAc (4 × 50 mL), worked up, and separated from unreacted **1** by Si gel flash chromatography (EtOAc) to give **2** as the only reaction product (1.66 g, 64%), R_f (EtOAc) 0.4, ($CHCl_3$-MeOH 4 : 1) 0.8. **2** crystallized in $CHCl_3$ as reddish rhombi, m.p. 128–130°C; $[\alpha]_D^{24}$ +231° (*c* 0.11, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.20 (1H, dd, $J = J' = 14.0$ Hz), 2.36 (3H, s), 2.39 (1H, s),

2.6 (1H, m), 2.74 (1H, dd, $J = 14.4$ Hz, $J' = 3.8$ Hz), 2.9 (3H, m), 3.6 (3H, m), 3.90 (3H, s), 6.61 (1H, s), 8.03 (1H, s); ^{13}C NMR (DMSO-d_6) δ 28.99, 29.03, 44.08, 53.35, 57.19, 60.39, 62.11, 113.7, 116.2, 120.9, 124.1, 125.5, 129.7, 138.7, 141.0, 144.0, 147.7, 150.3. Anal. calcd for $C_{19}H_{20}N_2O_5$. 0.7 $CHCl_3$: C, 54.60; H, 4.81; N, 6.37%. Found: C, 54.41; H, 4.90; N, 7.30%.

2,9-Dihydroxy-1,10-dimethoxy-6-methyl-8-aminodibenzo[*de*,*g*]quinoline (3): A solution of **2** (0.316 g, 0.88 mmol) dissolved in EtOH (120 mL) was catalytically hydrogenated over 10% Pd/C (60 mg) at 50 psi and room temperature. After 2.5 h, the mixture was filtered over Celite and concentrated to give a brown residue. After work up as before, **3** (0.312 g, 100%) crystallized from C_6H_6 as gray needles, m.p. 177–179°C; $[\alpha]_D^{24}$ +189° (*c* 0.094, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.85 (1H, dd, $J = J' = 13.8$ Hz), 2.33 (1H, m), 2.46 (3H, s), 2.5 (1H, m), 2.7 (1H, m), 2.9 (2H, m), 3.16 (1H, dd, $J = 14.3$ Hz, $J' = 4.0$ Hz), 3.50 (3H, s), 3.77 (3H, s), 6.48 (1H, s), 7.36 (1H, s); ^{13}C NMR (DMSO-d_6) δ 27.75, 28.81, 44.12, 53.21, 56.05, 59.51, 62.69, 101.7, 114.2, 115.0, 122.9, 125.9, 127.4, 128.7, 132.7, 133.8, 143.2, 145.8, 149.4. Anal. calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18%. Found: C, 66.24; H, 6.46; N, 8.27%.

1,11-Dimethoxy-2-hydroxy-6-methyloxazolo[4,5-*k*]5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (4): A solution of **3** (0.150 g, 0.44 mmol) dissolved in EtOH (20 mL) was treated with ethyl *ortho*-formate (1.5 mL, 9 mmol) and refluxed with stirring for 48 h under N_2. After concentrating the solution under reduced pressure, the residue was chromatographed on Si gel (4 : 1 $CHCl_3$–MeOH) affording **4** (0.138 g, 89%), R_f 0.65, which crystallized from C_6H_6 as brownish white needles, m.p. 189–191°C; $[\alpha]_D^{18}$ +227° (*c* 0.069, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.3 (2H, m), 2.44 (3H, s), 2.5 (1H, m), 2.84 (1H, dd, $J = 14.1$ Hz, $J' = 4.0$ Hz), 2.9 (2H, m), 3.58 (3H, s), 3.66 (1H, dd, $J = 14.0$ Hz, $J' = 4.0$ Hz), 3.99 (3H, s), 6.61 (1H, s), 8.01 (1H, s), 8.71 (1H, s), 9.18 (1H, s); ^{13}C NMR (DMSO-d_6) δ 27.13, 27.98, 43.13, 52.11, 55.50, 59.02, 61.23, 107.5, 114.8, 120.0, 125.3, 128.3, 128.7, 136.9, 138.7, 142.1, 142.6, 148.8, 153.3. Anal. calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 67.93; H, 5.82; N, 8.02%.

1,12-Dimethoxy-2-hydroxy-6-methyl-9-phenyl-10*H*-oxazin[5,6-*k*]5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10-one (5): A solution of **4** (0.166 g, 0.49 mmol) in EtOH (30 mL) was treated with methyl benzoylformate (0.6 mL, 4 mmol) and refluxed with stirring for 48 h under N_2. After concentrating under reduced pressure, the residue was chromatographed on Si gel (4 : 1 $CHCl_3$–MeOH) to give **5** (0.131 g, 60%), R_f 0.77, which crystallized from C_6H_6 as yellowish needles, m.p. 202–203°C; $[\alpha]_D^{17}$ +242° (*c* 0.091, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.20 (dd, $J = 14.0$ Hz, $J' = 3.8$ Hz, 1H), 2.3 (1H, m), 2.46 (3H, s), 2.6 (1H, m), 2.9 (3H, m), 3.62 (3H, s), 3.96 (3H, s), 4.17 (1H, dd, $J = 14.0$ Hz, $J' = 3.8$ Hz), 6.65 (1H, s), 7.6 (3H, m), 8.18 (1H, s),

8.26 (2H, s), 9.27 (1H, s); ^{13}C NMR (DMSO-d_6) δ 26.70, 28.32, 43.69, 52.67, 56.18, 59.68, 61.66, 113.1, 115.8, 125.1, 126.0, 127.3, 128.3, 128.6, 128.8, 129.1, 129.3, 131.1, 134.6, 135.2, 143.4, 144.0, 149.4, 150.0, 151.5. Anal. calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14%. Found: C, 70.59; H, 5.46; N, 6.26%.

1,11-Dimethoxy-2-hydroxy-6-methyl-9-phenyloxazolo[4,5-*k*]5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (6): A solution of **5** (0.101 g, 0.22 mmol) in EtOH (100 mL) was treated with a 5% KOH-EtOH solution (0.45 mL) at room temperature. Immediately the yellowish solution changed to a clear orange color. Stirring was stopped within 30 s and the solution was immediately concentrated under reduced pressure. The residue was taken up in 100 mL H_2O, and the aqueous solution was adjusted with concentrated NH_3 to pH 8–9 and extracted with $CHCl_3$. After purifying the mixture by Si gel flash chromatography (4 : 1 $CHCl_3$–MeOH), **3** (40 mg, 53%), R_f 0.10 and **6** (32 mg, 34%), R_f 0.74 were obtained, the latter crystallizing in cyclohexane–benzene as beige needles, m.p. 179–181°C; $[\alpha]_D^{16}$ +225° (*c* 0.24, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.4 (2H, m), 2.48 (3H, s), 2.5 (1H, m), 2.9 (3H, m), 3.60 (3H, s), 3.73 (1H, dd, $J = 14.0$ Hz, $J' = 3.6$ Hz), 4.03 (3H, s), 6.62 (1H, s), 7.6 (3H, m), 8.01 (1H, s), 8.2 (2H, m), 9.19 (1H, s); ^{13}C NMR (DMSO-d_6) δ 27.17, 27.97, 43.18, 52.12, 55.49, 59.03, 61.19, 107.7, 114.8, 119.7, 125.2, 125.3, 125.9, 126.8, 128.4, 128.7, 128.8, 131.3, 137.6, 140.4, 141.8, 142.7, 148.8, 161.5. Anal. calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54%. Found: C, 72.54; H, 5.48; N, 6.52%.

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