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Semi Synthesis of Open (1,2,9,10) and Closed (1,2 & 9,10) 7-Oxoaporphines and Related Analogues of Boldine

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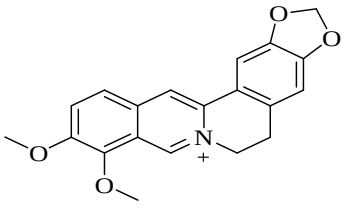
ABSTRACT

Boldine analogues are prepared by modifying the functional groups at 2nd , 7th and 9th positions over the aporphine skeleton. After blocking both the free hydroxyl groups at 2nd and 9thpositions as tetrazolyl derivatives oxidation at 7th position was achieved with manganese(III) acetate. Similarly, oxidation was also attempted over Boldine analogue having the methylene dioxy protection at 1, 2 and 9, 10 catechol fragments after the demethylenation. In both cases yields were considerably good. Selective removal of tzoxy group was also explained enabling the acetylation at 1st and 9th positions. Overall OPEN (1, 2, 9, 10) and CLOSED (1,2 and 9,10) 7-oxoaporphines were synthesized at ease with better yields.

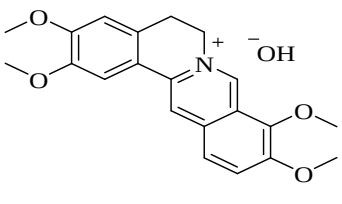
Keywords: Boldine, Aporphine, OPEN (1,2,9,10) 7-OxoAporphine , CLOSED (1,2 and 9,10) 7-OxoAporphines.

INTRODUCTION

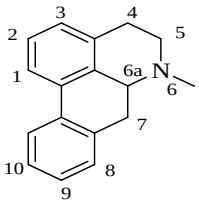
Alkaloids are the nitrogen-containing secondary metabolites biosynthesized in plants eliciting a plethora of medicinal properties. Over the ages without understanding the chemical composition and biological mode of action, these plant products were used for the benefit of human beings and animals. The recent developments in the field of science have helped the scientific community to understand and prepare better analogues in combating various diseases and ailments. Isoquinoline alkaloids are one such a group (ex: Berberine, Palmatine) bestowed with diverse medicinal properties [1].



Berberine



Palmatine

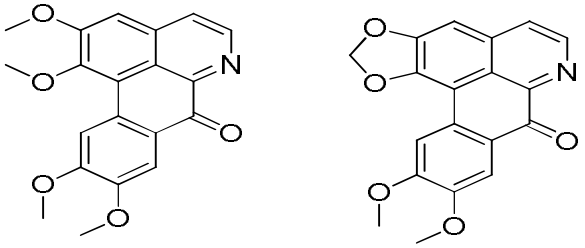


Aporphine

Whereas aporphines, among isoquinoline alkaloids, are a unique class with tetracyclic skeleton (buckled shape) and one stereogenic center at C-6a. Boldine- ((*S*)-2,9-Dihydroxy-1,10-dimethoxy-aporphine) isthe major leaf and bark alkaloid of the Chilean boldo tree (*Peumus boldus* Molina, Monimiaceae). As per the pharmacopoeias and treatises, the extracts of the boldo tree were used for treating nervous weakness, dropsy, dyspepsia, menstrual pain, headache, earache, rheumatism, urinary tract inflammation [2,3]. Boldo leaves reportedly contain 1.2% of tannins and 2-3% of essential oils (up to 45% ascaridole and 30% cineole, and at least 22 other identified constituents, mainly terpenoids [4-7]. It basically absorbs at 280 and 302 nm [8,9] conferring UV light-filtering property relevant to photo-protective action. It produces a reversible concentration-dependent relaxation effect achieved at a concentration 13.5μM (IC_{50}) by directly interfering with the nicotinic cholinergic mechanism associated with the contraction [10,11] in preference over muscarinic receptors.By preventing both the short and long term O2-dependent thermal peroxidation, it acts as a food preservative in protecting PUFA at concentrations markedly lower than those required by other antioxidants. In rendering such property, it was thought that it is similar to quercitin [12] but more recently, it was found to be more efficient than quercetin and BHT in protecting oils against heat-induced oxidation [13].

Boldine blocks Ca2+ channels in rat uterus [14], aorta [15] and cerebral cortex [16] possibly through the benzothiazepine receptor site.It has been extensively reported as a potent natural antioxidant and possesses several health-promoting properties like anti-inflammatory, antitumor, antidiabetic, and cytoprotective and diuretic [17].At sub-micromolar concentrations, it protects the red blood cells against free radical–induced hemolytic damage, lysozyme inactivation against 2,2-azo-bis(2-amidinopropane) dihydrochloride–derived peroxyl radical damage and inhibits spontaneous autoxidation of brain membrane lipids, peroxidation of lipids in human liver microsomes [18-22]. One of the serious draw backs of boldine is its poor plasma half-life lasting for few minutes due its rapid glucuronidation in the liver. These relatively weak and short-lived systemic actions restrict its clinical utility. Hence it stands as a challenge to the medicinal chemists in preparing, the better analogues having the longer systemic activity by retaining or enhancing favorable pharmacokinetic and pharmacological activities. In order to improve the lipophilicity, alkyl groups not very large are introduced in the phenyl rings without greatly affecting the key phenolic and amine functional groups [23].

Oxoaporphines are most probably derived in the plants by the oxidation of corresponding aporphinesand widely distributed in plant families: annonaceae, araceae, hernandiaceae, lauraceae, papaveraceae, rannunculaceae, menispermaceae, etc., although in minor amounts [24]. These are bright yellow or orange in colour, turn pink or red with the addition of mineral acids [24] and possess a broad range of biological activities such as antimicrobial [25], antiviral [26], cytotoxic [27] and platelet aggregation inhibition [28].



Oxoglaucine Liriodenine

Oxoglaucine had immunomodulatory activity [29] while liriodenine displayed topoisomerase II inhibitory activity [30] as well as anti-arrhythmic activity [31]. The non-degradative oxidation of aporphines to oxoaporphines is accomplished with several reagents namely chromium trioxide (CrO3) in pyridine [32], manganese dioxide [33], lead(IV) acetate (LTA) [34], ceric ammonium nitrate (CAN) [35] and periodic acid [36] and still remains the subject of publications. In the present work, we have synthesized semisynthetic analogues of boldine to utilize them in the future studies.

MATERIALS AND METHODS

General Methods. All commercial solvents were purified according to reported procedures (*Vogel 6th Edition*), and the commercially available reagents were used as received. Separation by column chromatography was performed using 60-120 mesh. Petroleum refers to the fraction with distillation range 40-65 °C. ^{1}H NMR spectra were recorded on Bruker spectrometer at 400 MHz spectrometer, ^{13}C NMR spectra were acquired on 100.6 MHz with tetramethylsilane as an internal standard, chemical shift (d) are reported in ppm (d) Shift (multiplicity, coupling constant, proton count). Mass spectral analysiswas accomplished using electro spray ionization (ESI) techniques.

2,9-0-bis(1-phenyltetrazol-5-yl)-boldine (2): Boldine (**1**) (5g; 15.29 mmol) was dissolved in dry acetonitrile (180 mL) to which anhydrous potassium carbonate (3.2 g) and N-phenyltetrazol-5- chloride (6.06 g; 33.64 mmol) were added. The reaction mixture was refluxed for 24 h. After the completion of the reaction, inorganic salts were filtered off, washed with acetonitrile (25 ml) and the combined solution was concentrated under reduced pressure. The residue was dissolved in chloroform (200 ml) and washed with water (2 x 100 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and the solvent was distilled off under reduced pressure. The residue was chromatographed over silica gel using $CHCI_3$: MeOH (99:1) as eluent to afford the product **2** (9.056 g; 14.678 mmol). ^{1}H NMR (400 MHz; $CDC1_3$): 2.50 (s, 3H), 2.58 - 2.74 (m, 3H), 3.01 - 3. 18 (m, 4H), 3.51 (s, 3H), 3.77 (s, 3H), 7.19 (s, 1H), 7.31 (s, 1H), 7.49 - 7.58 (m, 6H), 7.84 - 7.88 (m, 4H), 8.09 (s, 1H); ^{13}C NMR (100 MHz; $CDC1_3$): 28.3, 32.9, 43.4, 52.3, 55.9, 60.7, 61.8, 112.9, 120.4, 120.4, 121.7, 121.7, 127, 128.9, 129.1, 129.1, 129.2, 129.3, 129.4, 129.9, 130.2, 132.6, 132.7, 134.3, 141.2, 145.7, 145.9, 148.7, 159.4, 159.6;ESI MS: m/z 615 $[M]^+$

2,9-O-bis(l-phenyItetrazoI-5-yl)-l,10-dimethoxy-N-methyl-7-oxoaporphine(3): 2,9-O-bis(l-phenyltetra zol-5-yl)-l,10-dimethoxy-N-methylaporphine 2 (470 mg; 0.763 mmol) was dissolved in acetic acid (5 mL) and added manganese (III) acetate dihydrate (818 mg; 3.05 mmol). The reaction mixture was stirred for 4 h at 70 °C. At the end, the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with saturated sodiumbicarbonate solution (60 mL) followed by water (3 X 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and the solvent was distilled off under reduced pressure. The residue was chromatographed over silica gel using $CHCl_3$:MeOH (99.5 : 0.5) as eluent to afford the compound**3** as yellow crystalline solid (34 mg; 7.2% yield).
Note: The above reaction was also carried out with Thallium (III) acetate as oxidizing agent but the product obtained in very low yield.
IR: 3067, 2924, 2852, 1661, 1597, 1538, 1500, 1453, 1295 cm^{-1};^{1}HNMR (400 MHz; $CDC1_3$): 5 3.89 (s, 3H), 3.97 (s, 3H), 7.61 (m, 6H), 7.76 (m, 4H), 8.02 (d, J = 5.1 Hz, 1H), 8.35 (s, 1H), 8.47 (s, 1H), 8.76 (s, 1H), 9.02 (d, *J*= 5.1 Hz, 1H); ^{13}C NMR (100 MHz; $CDC1_3$): 56.23, 56.5, 113.2, 114.4, 117.4, 120.7, 122.7, 124.9, 125.5, 127.5, 128.6, 129.7, 130.3, 132.1, 141.4, 149.3, 152.6, 155.7, 171.6, 181.2; ESI MS: m/z 611 $[M]^+$

1,2,9,10-tetrahydroxy-N-methylaporphine(4): Boldine (**1**) (1.00 g; 3.06 mmol) was slowly dissolved in 12 ml of 48% HBr-H2O and heated for 1 h at 110 °C. Cool the reaction mixture to room temperature and the separated solid was filtered and washed with acetone to obtain colourless solid 9 (982 mg; 84% yield). IR: 3391, 3084, 2719, 2516, 2311(7), 1607, 1466, 1421, 1283 cm^{-1}; ^{1}H NMR (400 MHz; MeOD): 2.89 (m, 2H), 3.24 (m, 5H including N-CH_3), 3.49 (m, 1H), 3.77 (m,lH), 4.16 (dd, J = 28, 6.7 Hz, 1H), 6.61 (s, 1H), 6.79 (s, IH), 8.03 (s,lH); ^{13}C NMR (100 MHz; MeOD): 25.4, 31.3, 40.6, 52.8, 63.3, 114.6, 116.1, 119.2, 126.0, 127.4, 130.8, 131.9, 141.2, 144.9, 146.4, 147.1; ESI MS:m/z 299 $[M]^+$

1,2, 9,10-Dimethylenedioxy-N-methyl aporphine (Methylene dioxy derivative of O-demethylated boldine) (5): *O*-Demethylated boldine (**4**) (860 mg; 2.257 mmol), 10.1 g of dry potassium carbonate and potassium iodide (150 mg) were dissolved in dry DMF (30 mL) and added 40 mL of dichloromethane. The

reaction mixture was heated at 110 °C for 6 h. During this period, dichloromethane (4 mL) was added at every one hour. The reaction mixture was cooled to rt, filtered and concentrated under reduced pressure. The residue was chromatographed over silica gel using ethyl acetate and hexane (8:2) as eluent to yield colourless solid **5**(348 mg; 48% yield), IR: 2987, 2909, 2872, 2785, 1607, 1503, 1485, 1458, 1241, 1041 cm^{-1}; ^{1}H NMR (400 MHz; $CDC1_3$): 5 2.53 (m, 5H includes N-CH_3), 2.63 (s, IH), 3.02 (m, 4H), 5.88 (d, J= 2.6 Hz, IH), 5.92 (dd, .7 = 8.3, 2.5 Hz, 2H), 6.02 (d, *J*= 2.6 Hz, IH), 6.48 (s, IH), 6.71 (s, IH), 7.58 (s, IH); ^{13}C NMR (100 MHz; $CDC1_3$): 529.1, 34.5, 43.8, 53.4, 62.1, 100.5, 100.8, 106.7, 107,3, 108.5, 116.5, 124.4, 126.3, 129.6, 141.7, 146.5; ESI MS:m/z 323 $[M]^+$

1, 2; 9, l0-dimethylenedioxy-7-oxoaporphine (6): 1,2, 9,10-Dimethylenedioxy-N-methyl aporphine (5) was dissolved in acetic acid (5 mL) and added manganese (III) acetate dihydrate (818 mg; 3.05 mmol). The reaction mixture was stirred for 4 h at 70 °C, then cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with saturated sodiumbicarbonate solution (60 mL) followed by water (3 X 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and the solvent was distilled off under reduced pressure. The residue was chromatographed over silica gel using $CHCl_3$:MeOH (99.5 : 0.5) as eluent to afford the compound **3** as yellow crystalline solid (34 mg; 7.2% yield) and the starting material 2 (240 mg; 51% yield). IR: 2987, 2909, 2872, 2785, 1607, 1503, 1485, 1458, 1241, 1041 cm^{-1}; ^{1}H NMR (400 MHz; $CDC1_3$): 5 2.53 (m, 5H includes N-CH_3), 2.63 (s, IH), 3.02 (m, 4H), 5.88 (d, J= 2.6 Hz, IH), 5.92 (dd, .7 = 8.3, 2.5 Hz, 2H), 6.02 (d, *J*= 2.6 Hz, IH), 6.48 (s, IH), 6.71 (s, IH), 7.58 (s, IH); ^{13}C NMR (100 MHz; $CDC1_3$): 529.1, 34.5, 43.8, 53.4, 62.1, 100.5, 100.8, 106.7, 107,3, 108.5, 116.5, 124.4, 126.3, 129.6, 141.7, 146.5. ESI MS:m/z 319 $[M]^+$

1.10-Dimethoxy-N-methylaporphine(7):(Reductivecleavageof2,9-0-bis(l-phenyltetrazol-5-yl)-boldine): A mixture of 2,9-O-bis(l-phenyltetrazol-5-yl)-l,10-dimethoxy-N-methylaporphine (**3**) (8.2 g; 13.33 mmol) and 10% palladium-carbon (1.5 g) in acetic acid (65 mL) was hydrogenated at 70 °C with a pressure of 120 psi in hydrogen bomb for 3 days. TLC showed that the reaction was not completed and added additional 10%Pd-C (1.5 g) and continued for 2 days with a pressure of 250 psi at 70 °C. The reaction mixture was filtered through celite, washed thoroughly with chloroform and combined filtrates were concentrated under reduced pressure. The residue was dissolved in chloroform, washed with 10% sodiumbicarbonate solution (60 mL) followed by water (3 X 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and the solvent were removed under reduced pressure. The residue was chromatographed over silica gel using $CHC1_3$:MeOH (98: 2) eluent to afford the desired product **7** (1915 mg; yield 48.7%), unidentified compound (229 mg). IR: 2935, 1663, 1607, 1585, 1469, 1266, 1090, 1043 cm^{-1}; ^{1}HNMR (200 MHz; $CDC1_3$): 52.57-2.61 (m, 4H), 2.63-2.66 (m, 1H), 2.94-3.14 (m, 5H), 3.84 (s, 3H), 3.89 (s, 3H), 6.80 (dd, *J*= 8.3, 2.7 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J*= 8.5 Hz, 1H), 7.16 (d, *J*= 8.3 Hz, 1H), 7.89 (d, *J*= 2.7 Hz, 1H); ^{13}C NMR (50 MHz; $CDC1_3$): 28.3, 33.6, 43.7, 53.1, 55.3, 55.7, 63.1, 110.9, 112.1, 114.7, 121.9, 125.2, 128.1, 128.3, 128.6, 133, 136.2, 155.0, 158.1; ESI MS:m/z 295 $[M]^+$.

1,10-Dihydroxy-N-methylaporphine hydrobromide (8): 1,10-Dimethoxy-N-methylaporphine (**7**) (500 mg; 1.69 mmol) was dissolved in 48% HBr-H_2O (7 ml) and the solution was heated for 3 hrs at 110 °C. Cool the reaction mixture to room temperature and the separated solid was filtered and washed with acetone to yield colorless salt (332 mg; yield 56.3%). IR: 3290, 2940, 2721, 1606, 1485, 1420, 1302, 1209 cm^{-1}; ^{1}HNMR (400 MHz; MeOD): 8 2.83 (t, *J*= 13.4 Hz, 1H), 3.07 (dd, *J*= 17.2, 3.8 Hz, 1H), 3.24 (s, 3H), 3.42 (dd, ,7 = 13.2, 4.0 Hz, 1H), 3.53 (ddd, *J*= 4.6 Hz, 1H), 3.84 (dddd, *J*= 4.8, 1.1 Hz, 1H), 4.29 (dd, *J*= 14.1, 3.4 Hz, 1H), 6.73 (dd, *J*= 8.1, 2.6 Hz, 1H), 6.98 (d, *J*= 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J*= *7.9* Hz, 1H), 8.01 (d, *J*= 2.6 Hz, 1H); ^{13}C NMR (100 MHz; $CDC1_3$): 5 26.9, 32.3, 42.5, 54.4, 65.2, 115.6, 117.3, 118.9, 121.5, 121.8, 124.4, 129.9, 130.2, 131.3, 134.4, 155.5, 157.9; ESI MS:m/z 267 $[M]^+$

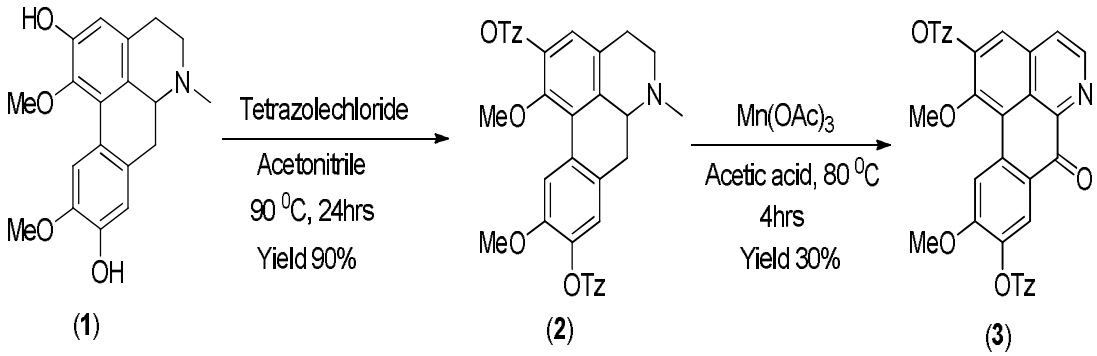
1,10-Diacetoxy-N-methylaporphine (9): 1,10-Dihydroxy-N-methylaporphine hydrobromide (**8**) (80 mg; 0.23 mmol) was dissolved in acetic anhydride (3 ml) and pyridine (0.6 ml). The reaction mixture was stirred for 6 hrs. Then absolute ethyl alcohol (4 ml) was added and stirred for 2 hours more. The solvent was removed under reduced pressure. Toluene (3 ml) was added and removed as azeotropic mixture with pyridine two times under reduced pressure. The residue was chromatographed over silica gel using $CHC1_3$: MeOH (99 : 01) as eluent to yield the product**9**(67 mg; 8.1%) IR: 2921, 2850, 2790, 1760, 1607, 1578, 1467, 1370, 1211, 1016cm^{-1}; ^{1}H NMR (400 MHz; $CDC1_3$): S 2.27 *(s*, 3H), 2.29 (s, 3H), 2.54 (m, 4H includes N-CH_3), 2.60 - 2.75 (m, 3H), 3.07 (in, 3H); 6.92 (dd, J= 8.2, 2.3 Hz, 1H), 6.95 (d, *J= 8.3* Hz, 1H), 7.08 (d, *J*= 8.3 Hz, IH), 7.24 (dd, *J*= 8.3, 2.4 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H); $^{!3}$C NMR (100 MHz; $CDC1_3$): 521.1, 21.2, 283, 33.6, 43.4, 52.7, 62.3, 120.4, 120.5, 121.9, 125.4, 128.8, 128.9, 130.9, 132.2, 133.9, 135.9, 145.6, 149.4, 169.3, 169.4;ESI MS: m/z 374 (M^++Na).

RESULTS AND DISCUSSION

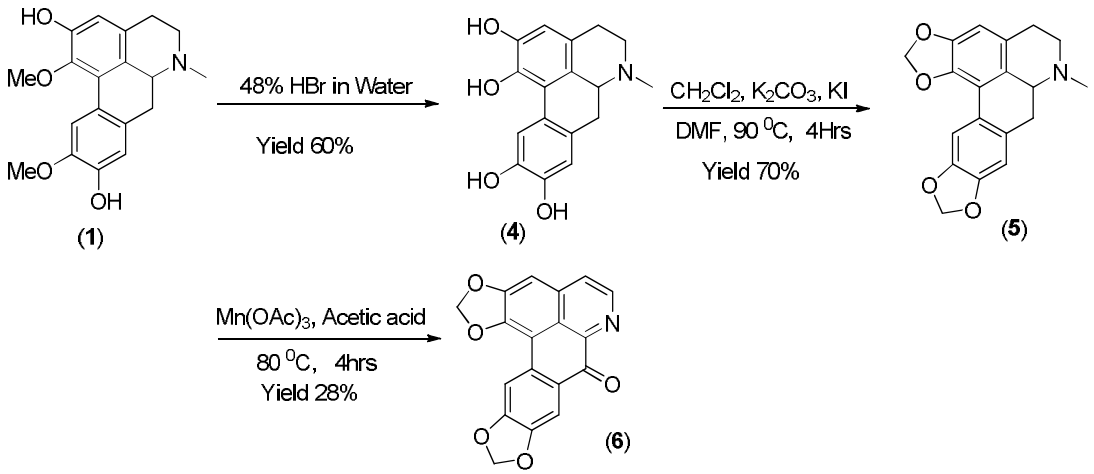
In this study Boldine (**1**) was modified at 2, 7 and 9 positions [37] to get the analogues with an intention to understand the pharmacokinetic and pharmacological issues in future. As of now 3 schemes are describedhere. Boldane(**1**) on heating with 5-chloro-l-phenyl-l-tetrazoIe in acetonitrile at 90^{0}C for 24 h gave 2,9-0-bis(l-phenyltetrazol-5-yl)-boldine (**2**) in an overall yield of 96%. This in the next step subjected to $Mn(OAc)_3$ oxidation [38] in acetic acid to give 2,9-0-bis(l-phenyltetrazol-5-yl)-l,10-dimethoxy-7-oxoaporphine (**3**) (Scheme-1).

In the scheme-2, demethylation of boldine (**1**) was achieved with 48% HBr in water solution to afford 1,2,9,10-tetrahydroxyaporphine (**4**). The catechol OH groups are converted to the methylene ethers by treating compound **4** with dichloromethane in the presence of K_2CO_3 and a catalytical amount of KI in dryDMF at 90 ^{0}C to give 1,2, 9,10-dimethylenedioxyaporphine(**5**) with 70% yield. In the final step oxidation was achieved with $Mn(OAc)_3$ in acetic acid at 80 ^{0}C for 4 h to give 1,2, 9, l0-dimethylenedioxy-7-oxoaporphine (**6**).

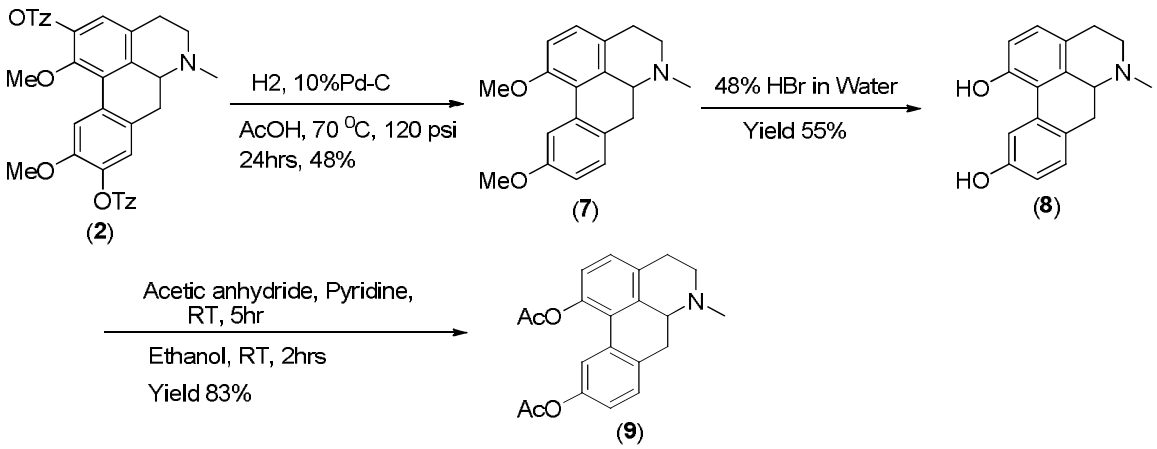
In scheme-3, compound-**2** subjected to the catalytic hydrogenolysis at 2ndand 9th positions [39] at 70 ^{0}C under120psi pressure in acetic acid for 24 h to give the 1,10-dimethoxyaporphine (**7**) with 48% yield. This after demethylation followed by acetylation with acetic anhydride in pyridine gave 1,10-diacetoxyaporphine (**9**) via 1,10-dihydroxyaporphine (**8**) in 80% yield.All the compounds were column chromatographed to get in 99% purity before generating the analytical data.



Scheme-1: Synthesis of 2,9-0-bis(l-phenyltetrazol-5-yl)-l,10-dimethoxy-7-oxoaporphine (3)



Scheme-2: Synthesis of 1,2, 9, l0-dimethyienedioxy-7-oxoaporhhine (6)



Scheme-3: Synthesis of 1,10-diacetoxyaporphine (9)

CONCLUSIONS

OPEN (1,2,9,10) and CLOSED (1,2 and 9,10) 7-oxoaporphine derivatives of boldine were synthesized successfully using the derivatisation of aporphine skeleton of boldine with tetrazolylations, methylene dioxylations and complete removal of hydroxyl groups at 2nd, 9th positions followed by acetylation gave the corresponding analogues for future pharmacological and pharmacokinetic studies.

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