OXIDATION OF CORONARIDINE

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Abstract — A variety of oxidising reagents were used for the oxidation of coronaridine. In this study four new alkaloids 16-hydroxymethylene-3-oxoibogamine (7), 2,3,7-(2H,7H)-trioxo-2,7-(2H,7H)-secocoronaridine (10), bisindole alkaloids 5-(coronaridin-10-yl)-5-hydroxy-6-oxocoronaridine (11) and 5-(6-oxocoronaridin-10-yl)-6-oxocoronaridine (12) were obtained and their structures elucidated. Additionally alkaloids 5-hydroxy-6-oxocoronaridine (3), 5-oxocoronaridine (6) and 6-oxocoronaridine (13) are being reported for the first time semisynthetically.

Various alkaloids isolated from Tabernaemontana divaricata R.Br. ex Roem and Schult[1] were in one way or other oxo derivatives of coronaridine (1) and hence the oxidation study became imperative. Various oxidising reagents were used and results are discussed below.

Potassium permanganate oxidation of coronaridine in acetone furnished six compounds. Reaction proceeded fast to afford compound I which was identified as hydroxyindolenine-coronaridine (2)[2]. The compound II, III and IV were identified as 5-hydroxy-6-oxocoronaridine (3), 5-oxocoronaridine (6), 3-oxocoronaridine (5), respectively.

The compound V, mp 195°C had UV λ_{max} 230, 275 and 290 nm, indicating an indolenine chromophore. The IR bands at 3240, 1740, 1655 and 1645 cm^{-1} were attributed to hydroxyl, methoxycarbonyl, lactam and C=N functions, respectively. The ^1H NMR spectrum (δ) showed multiplets in the region 7-7.5 for an ortho-substituted benzene ring. A sharp singlet at δ 4.7 was assigned to bridgehead

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hydrogen adjacent to nitrogen. A singlet on multiplet at 4.20 was assigned to to NCOCH. A sharp singlet (3H) at 3.52 was due to methoxycarbonyl protons and a triplet at 0.9 (3H) was assigned to methyl protons of ethyl side chain. A clue to the structure of V was obtained by following set of reactions.

When 5 was refluxed with potassium permanganate for 1.5 h, it furnished a compound which was identical (mp, mixed mp, IR & UV) with compound V. Further when V was reduced with sodium borohydride it furnished 16-hydroxymethylene-3-oxoibogamine (7). The reduction of methoxycarbonyl function by sodium borohydride is an unusual phenomenon. The presence of strongly electron withdrawing function C=N activates it and makes it vulnerable for reduction. Additionally when compound V was heated with methanolic hydrochloric acid it afforded 3-oxocoronaridine-pseudoindoxyl (8) which was recognized by its characteristic UV spectrum, thus confirming it to possess 3-oxocoronaridine-hydroxyindolenine structure (9).

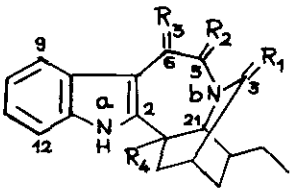
The compound VI, mp 212°C showed UV λ_{max} 220, 240 and 285 nm which showed no bathochromic shift on addition of alkali. This indicated the absence of indole, indolenine, indoline and 3-acylindole chromophore. The IR bands at 3210, 1730, 1685, 1660 and 1650 cm^{-1} were assigned to NH, methoxycarbonyl and carbonyl groups generated at C-7, C-3 and C-2 during the oxidation. The above UV data in conjunction with IR spectrum confirmed the cleavage of C-2 - C-7 bond. This is in accordance with the fact that double bonds are cleaved by potassium permanganate oxidation[3]. The NMR spectrum showed multiplets in the region of 7-7.5 (4H) characteristic of an ortho-substituted benzene ring. A multiplet centred at 4.7(1H) was assigned to CONCH. Sharp singlets at 4.25 (1H) and 3.82 (3H) were assigned to bridgehead hydrogen adjacent to nitrogen and methoxycarbonyl protons respectively. A triplet at 0.9 (3H) was due to methyl protons of ethyl side chain. In the mass spectrum the molecular ion peak at m/e 384 was compatible with the molecular formula $C_{21}H_{24}N_2O_5$. Other characteristic fragments were observed at m/e 355 ($M-CH_2CH_3$), 352 ($M-CH_3OH$), 326 ($M-CO_2Me$), 125 and 124. The presence of four carbonyl groups was also confirmed by ^{13}C NMR spectrum of the compound in $CDCl_3$ (the manuscript for ^{13}C data of compounds is under preparation). All these data could be summarized in structure 2,3,7-(2H,7H)-trioxo-2,7-(2H,7H)-secocoronaridine for VI (10).

Manganese dioxide[4] oxidation of 1 in chloroform at room temperature proceeded slowly and showed a mixture of four compounds. However with a combination of column chromatography and PLC compounds VII-X were separated and characterized. Compound VII and VIII were shown identical to 3 and 9 respectively (mp, mixed mp, IR & UV). The compound IX showed the molecular ion peak at m/e 704 clearly indicating a bisindole alkaloid. The additional peak at m/e 718 could be explained by the occurrence of trans-methylation[5,6] (intermolecular) in the mass spectrometer which is now known for several compounds in which methoxycarbonyl group lies adjacent to basic nitrogen. In order to interpret mass spectrum of a bisindole alkaloid it is necessary to postulate that the monomers fragment independently. The first structural feature deduced from the upper mass range of the mass spectrum was the presence of methoxycarbonyl function evidenced by substantial M-58 peak at m/e 646. Other important fragments were m/e 674 (M-C=O) and 640. On scanning through lower mass range of the spectrum fragments at m/e 122, 136, 137 and 150 could be encountered indicating the presence of 1 as monomer in the compound IX. On the other hand the absence of indole containing ions m/e 154, 195, 214 and 253 indicated that the linkage from the coronaridine-part must be confined only in the benzene ring. If we substract the spectrum of 1 from the bisindole alkaloid fragments at m/e 122, 230, 280, 308, 336 become clear indicating the presence of 3 as a second part of the molecule. This observation was supported by the fact that UV spectrum of the compound IX had λ_{max} 255, 282 (Sh) and 310 nm, showed bathochromic shift (λ_{max} MeOH-KOH 255, 285 and 340 nm on addition of alkali), exactly similar to our previous observation in the molecule 3 . Of particular importance was the absence of peak produced merely by the loss of hydroxyl group. Secondly the absence of peaks at m/e 256 and 339 (the plausible formulation of which involves C-5 also) clearly indicated that C-5 may be the possible position for linkage of this monomer. On biogenetic ground this position for linkage gets support as hydroxyl group is located on this position in the monomer. Additionally this is the most electrophilic position seeking the attack from the nucleophilic centre. The NMR spectrum of the compound IX showed two sharp singlets at 4.9 (1H) and 3.4 (1H) were assigned to bridgehead hydrogens adjacent to nitrogen of 5-hydroxy-6-oxocoronaridine part and coronaridine part respectively. The presence of two singlets at 3 .6 and 3.65 (3 H each) were due to methoxycarbonyl protons. Triplets at 0.7 and 0.9 (3H each) were assigned to methyl groups of ethyl side

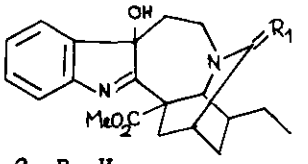
chain. The aromatic protons appeared in the range of 7.2-8 integrating for seven protons. The absence of a peak in the region 5-5.5 corresponding to C_5-H (5-hydroxy-6-oxocoronaridine) confirmed the linkage position of the two monomers and thereby confirming the structure 5-(coronaridin-10-yl)-5-hydroxy-6-oxocoronaridine (11) for the compound IX. Indolic NH appeared at 7.9 and 8.8 as broad singlets.

The substance X showed the molecular ion peak at m/e 702 clearly indicating it to be a bisindole alkaloid. Additional peak at m/e 716 was explained by intermolecular transmethylation. Important fragment ion peaks at m/e 122, 124, 137 and 149 in the lower range and 687 (M-Me), 673 (M-C_2H_5) advocated the presence of iboga skeleton with no rearrangement. The molecular ion peak at m/e 702 was confirmed by chemical ionisation mass spectrum using methane as reagent gas. Other important fragments in CIMS were observed at m/e 645 (M-CO_2Me), 615, 601, 355 and 295. The observation of UV spectrum of compound X clearly indicated the presence of 3-acylindole chromophore which inturn confirmed the presence of 6-oxocoronaridine as monomers. Compound X had UV λ_{max} 230, 240, 280 and 335 nm which showed the enhanced bathochromic shift (λ_{max} MeOH-KOH 230, 282 and 365 nm on addition of alkali). The NMR spectrum showed broad singlet at 8.4 assigned to indolic NH. The low field multiplets at 8.1 and 8.5 (2H each) were assigned to H-9 and H-12 for both the monomers. The doublet at 4.3 (1H, J=0.5) was assigned to bridgehead hydrogen adjacent to nitrogen for one monomer. Absence of other singlet or a partially coupled doublet in this region for another proton indicated its involvement for linkage. Other singlets (3H each) at 3.6 and 3.7 were assigned to methoxycarbonyl protons. Two triplets for methyl groups of the ethyl side chain were seen at 0.6 and 0.9 (3H each). Based on the above observation the structure proposed for compound X is 5-(6-oxocoronaridin-10-yl)-6-oxocoronaridine (12).

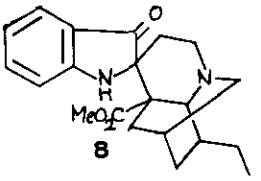
Iodine oxidation of coronaridine furnished three compounds, XI-XIII. XI, mp 250°C had UV λ_{max} 230, 287 and 294 nm characteristic of an indolic chromophore. The IR bands at 3340, 1715 were ascribed to NH and methoxycarbonyl functions respectively. The NMR spectrum showed a singlet at 8.4 (1H) exchangeable with D_2O, assigned to indolic NH. The multiplets in the region of 7-7.5 (4H) were assigned to ortho-substituted benzene ring. A multiplet at 3.38 (1H) was ascribable to α-hydroxylamine proton as the multiplet was simplified by D_2O shake. A sharp singlet at 3.76 was assigned to bridgehead hydrogen adjacent to



1 $R_1=R_2=R_3=H_2$, $R_4 = CO_2Me$
3 $R_1=H_2$, $R_2=OH$, $R_3=O$, $R_4=CO_2Me$
4 $R_1=OH$, $R_2=R_3=H_2$, $R_4=CO_2Me$
5 $R_1=O$, $R_2=R_3=H_2$, $R_4=CO_2Me$
6 $R_1=R_3=H_2$, $R_2=O$, $R_4=CO_2Me$
7 $R_1=O$, $R_2=R_3=H_2$, $R_4=CH_2OH$
13 $R_1=R_2=H_2$, $R_3=O$, $R_4=CO_2Me$
14 $R_1=R_2=R_3=H_2$, $R_4=CO_2Me$, $N_b\rightarrow O$
16 $R_1=R_2=H_2$, $R_3=O$, $R_4=CO_2Me$



2 $R_1=H_2$
9 $R_1=O$
15 $R_1=H_2$ $N_b\rightarrow O$



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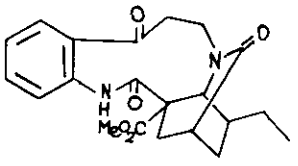

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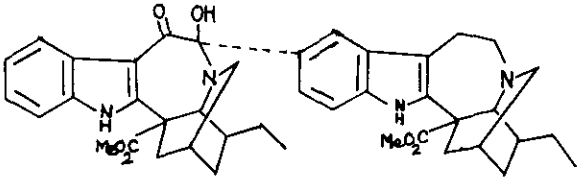

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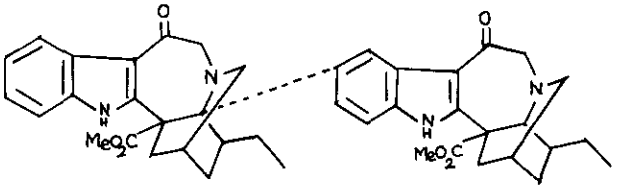

12

nitrogen. The methyl protons of the ethyl group appeared as triplet at 0.9 (3H). A three proton singlet at 3.69 was assigned to methoxycarbonyl protons. The probable position for the placement of hydroxy group was C-3 or C-5 on the basis of above discussion. The oxidation of compound XI with Corey's reagent afforded a compound which was found to be identical to 5 (mp, mixed mp, UV & IR) confirming it to be 3-hydroxycoronaridine (4). This compound has been reported in literature only recently by Schmidt et al[7].

Compound XII and XIII were identified as 6 and 5 respectively.

Selenium dioxide oxidation of 1 in refluxing ethanol furnished solely 6-oxocoronaridine (13) in 50% yield.

Hydrogen peroxide and m-chloroperbenzoic acid oxidation of coronaridine yielded XIV-XVI. XIV was identified as 2. XV had UV λ_{max} 235, 284 and 291 nm characteristic of indolic chromophore. The molecular ion peak was observed at m/e 354 which showed loss of 16 mass unit to give peak at m/e 338. Other fragmentation peaks were as usual as in case of 1. The presence of intense band at 1230 cm^{-1} in IR spectrum and loss of 16 mass unit in mass spectrum confirmed it to be coronaridine N_b-oxide (14). Compound XVI, mp 225°C had UV λ_{max} 235, 262 and 286 nm indicating an indolenine chromophore. The mass spectrum showed the molecular ion peak at m/e 370 which showed the characteristic loss of 16 mass unit from the molecular ion peak. The IR band at 1230 cm^{-1} in combination with mass spectrum showed it to be coronaridine-hydroxyindolenine N_b- oxide (15).

EXPERIMENTAL

Melting points were taken in sulphuric acid bath and are uncorrected. The UV spectra were recorded on Perkin-Elmer 202 automatic recording spectrometer. The IR spectra were taken either on Perkin-Elmer infracord 157 or 177 instrument. The NMR spectra (chemical shifts value in δ) were recorded on Varian A-60 and R-32 spectrometers in $CDCl_3$ (unless otherwise stated) with TMS as internal standard. The mass spectra were taken on JEOL JMSD-300 instrument. Homogenity of compounds was routinely checked on silica gel GF-254. The spots were visualized by spraying either with 1% potassium permanaganate or Dragendorff's reagent.

Oxidation of coronaridine (1) with Potassium permanganate - A suspension of potassium permanganate (2.76 g) in acetone (400 ml) was added gradually to a boiling

solution of 1 (1.36 g) in acetone (72 ml). The refluxing was continued for another 2.5 h. It was cooled, filtered and the residue was washed with acetone (100 ml). The combined acetone solution was concentrated under reduced pressure and the residue (1.4 g) which showed six spots on TLC, was chromatographed over a column of silica gel (30 g). Elution with benzene yielded 1 (40 mg). Further elution with benzene-ethyl acetate (90:10) afforded hydroxyindolenine-coronaridine 2 (67 mg). Elution with increasing percentage of ethyl acetate afforded a mixture of compounds. They were separated by PLC in benzene-ethyl acetate (70:30) to give 5-hydroxy-6-oxocoronaridine (3) (60 mg), 5-oxocoronaridine (6) (10 mg), 3-oxocoronaridine (5) (240 mg); 3-oxocoronaridine-hydroxyindolenine (9) (250 mg) and 2,3,7-(2H,7H)trioxo-2,7-(2H,7H)-secocoronaridine (10) (200mg).

Oxidation of coronaridine with manganese dioxide - To a stirred solution of 1 (500 mg) in chloroform (250 ml) manganese dioxide (5 g) was added and stirring was continued for 24 h. The reaction mixture was filtered and washed with chloroform (3x20 ml). The organic layer was concentrated under vacuo to afford a residue (520 mg). This was chromatographed over a column of silica gel (25g) and elution with benzene yielded the unreacted coronaridine (60 mg). The increasing percentage of ethyl acetate did not afford any pure substance. These fractions were mixed, concentrated and separated by PLC in benzene-ethyl acetate (70:30) into 3 (100 mg), 3-oxocoronaridine-hydroxyindolenine (9) (50 mg) and 5-(coronaridin-10-yl)-5-hydroxy-6-oxocoronaridine (11) (10 mg) and 5-(6-oxocoronaridine-10-yl)-6-oxocoronaridine (12) (10 mg).

3-Oxocoronaridine-hydroxyindolenine - A solution of 3-oxocoronaridine (100 mg) in acetone (100 ml) was refluxed with potassium permanganate (500 mg) for 2 h. It was filtered, concentrated and the residue after purification yielded 9 (80 mg), $[\alpha]_D^{25^\circ}$ -7° (methanol); IR (KBr) $^{cm-1}$ 3240, 1740 (CO_2Me), 1652 (NC=O), 1560, 1480, 1460, 1425, 1230, 1150, 980, 770 and 660.

Reduction of 3-oxocoronaridine-hydroxyindolenine with sodium borohydride - To a stirred solution of 9 (25 mg) in methanol (2 ml) was added sodium borohydride (50 mg) in 15 min. The stirring was continued for 10 h. The methanol was distilled of under reduced pressure, water added (2 ml) and the solution was extracted with methylene chloride (3x10 ml). The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to afford 16-hydroxymethylene-3-

oxoibogamine (7) (18 mg), UV λ_{max}^{MeOH} 230, 288 and 292; IR (KBr)$^{cm-1}$ 3400 (NH and/or OH), 2990, 2900, 1650 (NC=O), 1480, 955 and 750; MS (rel.int) m/e 324 (100%), 293 (12), 236 (5), 223 (10, 183 (35), 182 (50, 143 (20) and 122 (10); NMR 8.0 (br s,1H,NH), 7-7.5 (m,4Ar-H), 3.8 (s,2H,CH_2OH), 3.44 (s,1H,NCH) and 0.85 (t,3H, CH_2CH_3).

3-Oxocoronaridine-pseudoindoxyl (8) hydrochloride - A solution of 9 (25 mg) in methanolic HCl (1 ml) was heated on a water bath for 1 h. It was concentrated and the residue was crystallized with methanol-acetone to give 8 (20 mg), mp 251-253°C (dec). UV λ_{max}^{MeOH} 230, 255, 265(Sh) 285, 292(Sh) and 412 nm.

Oxidation of 1 with iodine - To a stirred solution of 1 (310 mg) in benzene (30 ml) and water (30 ml) was slowly added a solution of iodine (250 mg in 350 ml of benzene). The stirring was continued for another 24 h. Finally the benzene layer was separated and washed with sodium bicarbonate (5 ml) and sodium thiosulphate (5 ml, 5%) and extracted with methylene chloride (3x30 ml). The combined organic layer was washed with water, dried (Na_2SO_4) and evaporated to give 360 mg which was separated by PLC in benzene-ethyl acetate (80:20) to give 3-hydroxycoronaridine (4) (100 mg), mp 255°C, (6) (50 mg) and 5 (60 mg).

Oxidation of 1 with selenium dioxide - 1 (100 mg) dissolved in ethanol (25 ml) was refluxed with selenium dioxide (200 mg) for 1 h. Reaction mixture was filtered and the solvent evaporated and the residue (120 mg) was chromatographed over silica gel and elution with benzene, benzene-ethyl acetate (80:20) yielded coronaridine (20 mg) and 6-oxocoronaridine (16) (40 mg), mp 264-267°C; $[\alpha]_D^{25}$-35° (MeOH), UV λ_{max} nm 218, 255, 260 (Sh), 268 (Sh) and 335 $\lambda_{max}^{MeOH-KOH}$ nm: 218, 260, 280 and 3 65; IR (KBr)$^{cm-1}$ 3240, 2850, 1730, 1645, 1470, 1398, 1250, 880, 755 and 745; ^{1}H-NMR (py-d_5) 14 (br s, 1H, NH), 8.61 (d, 1H, C-9 J=6Hz), 7.5 (d, 1H, C-12 J=6Hz), 7.34 (m, 2H, C-10 and C-11H), 4.64 (d, 1H, NCH, J=1.5Hz), 3.88 and 3.09 (q, 2H, C-3 CH_2) and 3.54 (t, 3H, CO_2CH_3), 3.24 and 1.8 (q, 2H, C-5 CH_2) and 0.68 (t, 3H, CH_2CH_3), MS m/e (rel.int): 352 (100%), 322 (25), 279 (25), 228 (24), 141 (38) and 121 (5); Found: m/e 352. 1809. $C_{21}H_{24}N_2O_3$ requires M^+ 352.1789.

Oxidation of 1 with hydrogen peroxide - To a stirred solution of 1 (100 mg) in methanol (1 ml) hydrogen peroxide (30%, 5 ml) was added at room temperature.

The stirring was continued for another 24 h and diluted with water (10 ml). The aqueous solution was extracted with ethyl acetate (3x20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. It was chromatographed over silica gel and elution with benzene-ethyl acetate (95:5) afforded coronaridine-hydroxyindolenine (2) (50 mg). Other fractions were mixture and separated by PLC in chloroform-methanol (90:10) into coronaridine N_b-oxide (14) (20 mg) and coronaridine-hydroxyindolenine N_b-oxide (15) (15 mg).

Oxidation of 1 with m-chloroperbenzoic acid - To a stirred solution of 1 (150 mg) in methylene chloride (7 ml) was added m-chloroperbenzoic acid (230 mg) in methylene chloride (150 ml) slowly at 0-10°C. The reaction mixture was stirred for another 30 min, neutralized with sodium carbonate solution (5%, 15 ml) and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and concentrated at reduced pressure to afford a residue (130 mg) which afforded coronaridine-hydroxyindolenine (40mg) by column chromatography, 14 (30 mg) and 15 (20 mg) by PLC in chloroform-methanol (90:10).

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