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Isolation, structural and synthetic studies on the chemical constituents of medicinal plants of Pakistan

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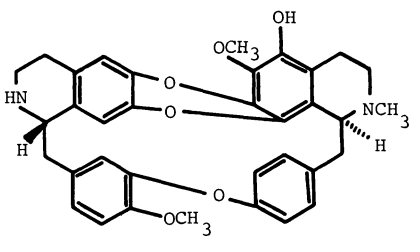
Abstract:A number of new natural products have been isolated from medicinal plants. A novel isomerisation of 19-S-vindolinine to 19-R-vindolinine is described. The two syntheses of the anti-cancer drug vinblastine reported by us were based on a semi-synthetic approach developed on a novel biogenetic hypothesis first proposed by us visualising catharanthine and vindoline as the biosynthetic precursors to these anti-cancer drugs. Continuing studies on the isolation of these precursors as well as vinblastine itself have resulted in 20-50 fold increases in yields of vinblastine from the leaves of Catharanthus roseus.

NEW ALKALOIDS FROM *COCCULUS PENDULUS*

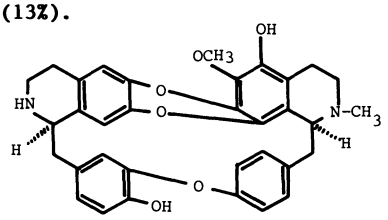
Cocculus pendulus (Forst) Diels (Menispermaceae) is a scandent shrub growing in areas around Karachi. The roots of the plant are used in the indigenous system of medicine for the treatment of intermittent fevers and as a tonic. Hypotensive and anti-cancer activity has been attributed to the alkaloidal fractions from the leaves and stem. Our recent studies on this plant have resulted in the isolation and structure elucidation of the following new alkaloids: 12-O-methylkohatine 1, 5-hydroxyapateline 2, 5'-hydroxytelobine 3, dehydrokohatine 4, 12-O-methyldehydrokohatine 5, 1,2-dehydro-2,-nortelobine 6, siddiquamine 7, siddiquine 8, 1,2-dehydrokohatine-2, N-oxide 9, cocsupendine 10 and O,O-dimethyl-1, 2-dehydronorkohatine 11 (ref.1)

12-O-Methylkohatine 1 (ref.1) $[\alpha]_D$ = 99.4° ($CHCl_3$). I.R. ($CHCl_3$), 3351 (N-H). U.V. (MeOH) λ_{max} 233 nm (log ε 4.35), 235 nm (log ε 4.35), 274 nm (log ε 3.52) and 2.88 nm (log ε 3.51), λ_{min} 234 nm (log ε 4.351), 280 nm (log ε 3.52). ^{1}H-NMR (360 MHz, $CDCl_3$ + 2 drops CD_3OD, δ):2.60 (s, 3H, N-CH_3),3.95 (s, 3H, O-CH_3),3.96 (s, 3H, O-CH_3),4.01 (d, 1H, J = 9.2Hz, H-1),6.62 (s, 1H, H-5),6.25 (s, 1H, H-8),6.60 (d, 1H, J = 2Hz, H-10),6.91 (d, 1H, J = 8.2Hz, H-13),6.83 (dd, 1H, J_1 = 2.1Hz, J_2 = 8.2Hz, H-14),6.77 (dd, 1H, J_1 = 1.89Hz, J_2 = 8.1Hz, H-11),7.01 (dd, 1H, J_1 = 1.8Hz, J_2 = 8.2Hz, H-10),7.20 (dd, 1H, J_1 = 1.89Hz, J_2 = 8.1 Hz, H-13),7.52 (dd, 1H, J_1 = 1.82Hz, J_2 = 8.1Hz, H-14).M.S. m/z 578 (M^+, 47%), 351 (100%), 335 (25%).



(1)

5-Hydroxyapateline 2 (ref.1) $[\alpha]_D$ = 185° (MeOH). I.R. ($CHCl_3$), 3610 cm^{-1} (N-H), 3350 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 210 nm (log ε 4.32), 234 nm (log ε 4.13) and 274 nm (log ε 3.31), λ_{min} 225 nm (log ε 4.20), 255 nm (log ε 3.10). ^{1}H-NMR (200 MHz, $CDCl_3$ + 2 drops CD_3OD, δ):2.58 (s, 3H, N-CH_3),3.96 (s, 3H O-CH_3),4.01 (d, 1H, J = 9.2Hz, H-1),6.61 (s, 1H, H-5),6.30 (s, 1H, H-8),6.33 (d, 1H, J = 1.9Hz, H-10),6.84 (d, 1H, J = 8Hz, H-13),6.70 (br. humps, H-11),6.80 (br. humps, H-10),7.05 (br. humps, H-13),7.73 (br. humps, H-14). M.S. m/z 564 (M^+, 46%), 351 (48%), 335 (13%).



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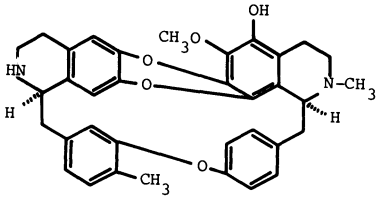
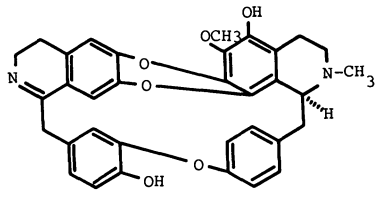


(3)

5-Hydroxytelobine 3 (ref.1) $[\alpha]_D$ = 99.4 ($CHCl_3$). I.R. ($CHCl_3$) 3610 cm^{-1} (N-H), 3351 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 237 nm (log ε 4.30), 267 nm (log ε 3.93), 352 nm (log ε 3.25) and λ_{min} 257 nm (log ε 4.10), 312 nm (log ε 3.43). ^{1}H-NMR (200 MHz, $CDCl_3$, δ):2.60 (s, 3H, N-CH_3),3.86 (s, 3H O-CH_3),3.96 (s, 3H, O-CH_3),4.02 (br. d, 1H, J = 9.1Hz, H-1),6.44 (s, 1H, H-5),6.35 (s, 1H, H-8),6.34 (d, 1H, J = 2Hz, H-10),6.84 (d, 1H, J = 8.1Hz, H-13),6.84 (dd, 1H, J_1=2.2Hz, J_2=8.2Hz, H-14),6.70 (dd, 1H, J_1=2.2Hz, J_2=8.5Hz, H-11),7.03 (dd, 1H, J_1=2Hz, J_2 = 8.3Hz, H-10),7.17 (dd, 1H, J_1 = 2Hz, J_2 = 8.1Hz, H-13),7.36 (dd, 1H, J_1 = 2Hz, J_2 = 8.2Hz, H-14). M.S. m/z 578 (M^+, 8%), 351 (35%), 355 (20%).

Dehydrokohatine 4 (ref.1) $[\alpha]_D$ = 53° ($CHCl_3$). I.R. ($CHCl_3$) 1679 cm^{-1} (C=N), 3550 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 235 nm (log ε 4.46), 254 nm (log ε 4.29), 287 nm (log ε 3.47) and λ_{min} 242 nm (log ε 4.35), 275 nm (log ε 3.35). ^{1}H-NMR (360 MHz, CD_3OD, δ):2.56 (s, 3H, N-CH_3),3.94 (s, 3H, -OCH_3),4.01 (d, 1H, J = 9.2Hz, H-1),6.53 (s, 1H, H-8),6.59 (s, 1H, H-5),6.56 (d, 1H, J = 1.65Hz, H-10),6.85 (d, 1H, J = 8.2Hz, H-13),6.89 (dd, 1H, J_1 = 1.65, J_2 = 8.2Hz, H-14),6.71 (dd, 1H, J_1 = 2Hz, J_2 = 8.1Hz, H-11),6.94 (dd, 1H, J_1 = 2Hz, J_2 = 8.1Hz, H-10),7.21 (dd, J_1 = 2.1Hz, J_2 = 8.2Hz, H-13),7.4 (dd, 1H, J_1 = 2.1Hz, J_2 = 8.2Hz, H-14). ^{13}C-NMR (100 MHz, CD_3OD, δ):168.84 (C-1),155.9 (C-12),140.36 (C-11),140.36 (C-7),137.26 (C-7),136.10 (C-9), 133.64(C-9),132.57 (C-14),132.04 (C-5),131.38 (C-10),128.9 (C-4a),124.32 (C-4a),124.0 (C-13), 123.71 (C-14),122.25 (C-11),121.8 (C-8a),119.08 (C-8),117.69 (C-5),116.28 (C-10),116.17 (C-13),115.73 (C-8a),61.85 (C-1),59.96 (OCH_3),46.47 (C-3),44.60 (C-3),42.20 (N-CH_3),40.51 (C- α),30.73 (C- α),26.02 (C-4),19.45 (C-4). M.S. m/z 562 (M^+, 75%), 531(30%),333 (45%), 220 (20%).



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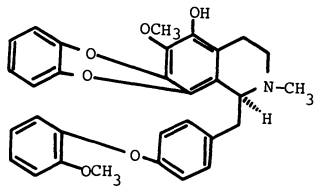
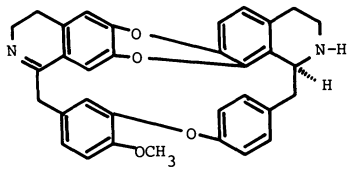


(5)

12-O-methyl-dehydrokohatine 5 (ref.1) $[\alpha]_D$ = + 97° ($CHCl_3$). I.R. ($CHCl_3$) 1600 cm^{-1} (C=N), 3551 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 274 nm (log ε 4.14), 283 nm (log ε 4.12) and 305 nm (log ε 4.08), λ_{min} 280 nm (log ε 4.13), 291 nm (log ε 4.90). ^{1}H-NMR (360 MHz, $CDCl_3$ + CD_3OD, δ):2.52 (s, 3H, N-CH_3),3.90 (s, 3H, OCH_3),3.94 (s, 3H, OCH_3),4.02 (d, 1H, J = 9.3Hz, H-1),6.55 (s, 1H, H-8),6.59 (s, 1H, H-5),6.61 (d, 1H, J = 2Hz, H-10),6.84 (d, 1H, J = 8.2Hz, H-13),6.97 (dd, 1H, J_1 = 2Hz, J_2 = 8.1Hz, H-14),6.74 (dd, 1H, J_1 = 1.8Hz, J_2 = 8.2Hz, H-11),6.92 (dd, 1H, J_1 = 1.8Hz, J_2 = 8.19Hz, H-10),7.20 (dd, 1H, J_1 = 1.8Hz, J_2 = 8.2Hz, H-13),7.38 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.3Hz, H-14). M.S.: m/z 576 (M^+, 85%), 560 (40%), 545 (35%), 333 (70%).

1,2-dehydro-2-nortelobine 6 (ref.1) $[\alpha]_D$ = + 100 ($CHCl_3$) I.R. ($CHCl_3$) 3600 cm^{-1} (-OH), 1590 cm^{-1} (C=N). U.V. (MeOH) λ_{max} 220 nm (log ε 4.45), 265 nm (log ε 4.06), 294 nm (log ε 3.73), 335 nm (log ε 3.57), λ_{min} 230 nm (log ε 4.10), 317 nm (log ε 3.40). ^{1}H-NMR (200 MHz, $CDCl_3$, δ),3.89 (s, 1H, O-CH_3),3.90 (s, 1H, O-CH_3),4.43 (d, 1H, J = 10.1Hz, H-1),6.55 (s, 1H, H-5),6.67 (s, 1H, H-8),6.40 (s, 1H, H-5),6.84 (d, 1H, J = 1.8Hz, H-10),6.58 (d, 1H, J =8Hz, H-13),6.98 (dd, 1H, J_1=1.8Hz, J_2=8Hz, H-14),6.68 (dd, 1H, J_1 = 1.9Hz, J_2 = 8.2Hz, H-11),6.76 (dd, 1H, J_1 = 2Hz, J_2=8.1Hz, H-10),7.19 (dd, 1H, J_1 = 2Hz, J_2 = 8Hz, H-13),7.45 (dd, 1H, J_1 = 2Hz, J_2 = 8Hz, H-14). M.S. m/z = 546 (M^+, 73%), 531 (30%), 333 (70%).



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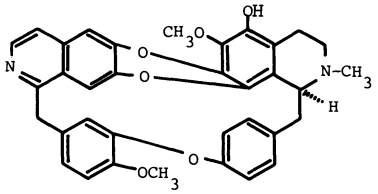
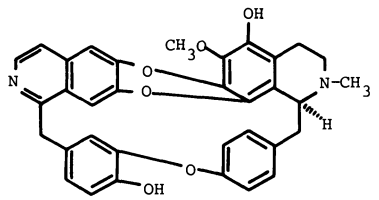


(7)

Siddiquamine 7 (ref.1) $[\alpha]_D$ = + 113° ($CHCl_3$). I.R. ($CHCl_3$) 1679 cm^{-1} (C=N), 1659 cm^{-1} (C=C), 3551 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 232 nm (log ε 4.63), 267 nm (log ε 4.32), 355 nm (log ε 3.63), λ_{min} 251 nm (log ε 4.10), 372 nm (log ε 3.14). ^{1}H-NMR (360 MHz, $CDCl_3$,δ):2.61 (s, 3H, N-CH_3),4.01 (d, 1H, J = 9.3 Hz, H-1),3.88 (s, 3H, -OCH_3),4.03 (s, 3H, OCH_3),7.17 (s, 1H, H-8),7.11 (s, 1H, H-5),7.24 (d, 1H, J = 5.3Hz, H-4),8.24 (d, 1H, J = 5.3Hz, H-3),6.74 (d, 1H, J = 1.89Hz, H-10),6.85 (d, 1H, J = 8.3Hz, H-13),7.12 (dd, 1H, J_1 = 1.89Hz, J_2 = 8.3Hz, H-14),6.68 (dd, 1H, J_1 = 2.4Hz, J_2 = 8.17Hz, H-11),6.97 (dd, 1H, J_1 = 1.91Hz, J_2 = 8.3Hz, H-10),7.26 (dd, 1H, J_1 = 2.1Hz, J_2 = 8.1Hz, H-13),7.46 (dd, 1H, J_1 = 2.0Hz, J_2 = 8.1Hz, H-14). M.S.: m/z = 574 (M^+, 86%), 559 (50%), 544 (30%), 332 (25%).

Siddiquine 8 (ref.1) $[\alpha]_D$ = 172° ($CHCl_3$). I.R. ($CHCl_3$), 1679 cm^{-1} (C=N), 3550 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 232 nm (log ε 4.70), 267 nm (log ε 4.39), 355 nm (log ε 3.68), λ_{min} 250 nm (log ε 4.58), 310 nm (log ε 3.41). ^{1}H-NMR (360 MHz, $CDCl_3$,δ):2.61 (s, 3H, N-CH_3),4.01 (H, J = 9.3Hz, H-1),4.02 (s, 3H, -OCH_3),7.10 (s, 1H, H-8),7.15 (s, 1H, H-5),7.22 (d, 1H, J = 5.2Hz, H-4),8.23 (d, 1H, J = 5.2Hz, H-3),6.70 (d, 1H, J = 1.89Hz, H-10),6.86 (d, 1H, J = 8.2Hz, H-13),7.05 (dd, 1H, J_1 = 1.89Hz, J_2 = 8.2Hz, H-14),6.65 (dd, 1H, J_1 = 2.4Hz, J_2 = 8.16Hz, H-11),7.00 (dd, 1H J_1 = 1.92Hz, J_2 = 8.3Hz, H-13),7.24 (dd, 1H, J_1 = 2Hz, J_2 = 8.0Hz, H-14). M.S.: m/z = 560 (M^+, 85%), 545 (10%), 530 (18%), 332 (15%).



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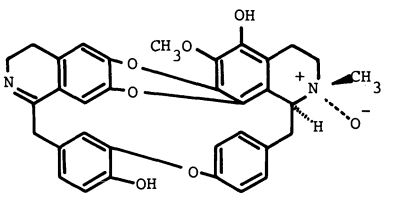
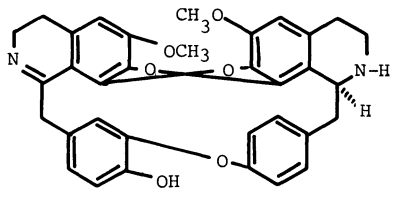


(9)

1,2-Dehydrokohatine-2β-N-oxide 9 (ref.1) $[\alpha]_D$ = 81.2° (methanol). I.R. ($CHCl_3$), 1575 cm^{-1} (C=N), 3620 cm^{-1} (-OH). U.V. (MeOH), λ_{max} 225 nm (log ε 4.54), 278 nm sh (log ε 3.96), 335 nm (log ε 3.52), λ_{min} 260 nm (log ε 3.13), 307 nm (log ε 3.71). ^{1}H-NMR (360 MHz, $CDCl_3$ + 2 drops CD_3OD, δ):2.61 (s, 3H, N-CH_3),3.64 (s, 3H, N-CH_3),3.90 (s, 3H, OCH_3),4.62 (d, 1H, J = 9.1Hz, H-1),6.56 (s, 1H, H-5), 6.53 (s, 1H, H-8),6.45 (d, 1H, J = 1.8Hz, H-10),6.78 (d, 1H, J = 8.2Hz, H-13),6.80 (dd, 1H, J_1 = 1.8Hz, J_2 =7.53Hz, H-14),6.74 (dd, 1H, J_1 = 2Hz, J_2 = 8.3Hz, H-11),6.89 (dd, 1H, J_1 = 2Hz, J_2 = 8.3Hz, H-10),7.21 (dd, 1H, J_1 = 2Hz, J_2 = 8.3Hz, H-13),7.37 (dd, 1H, J_1 = 2Hz, J_2 = 8.3Hz, H-14). M.S. m/z = 578 (M^+, 3%), 562 (87%), 563 (30%), 531 (16%), 333 (12%).

Cocsupendine 10 (ref.1) $[\alpha]_D$ = 116.6° (methanol), I.R. ($CHCl_3$) 1575 cm^{-1} (C=N), 3620 cm^{-1} (-OH), U.V. (MeOH) λ_{max} 208 nm (log ε 4.58), 212 nm (log ε 4.54), 278 nm (log ε 4.35), 337 nm (log ε 3.25), λ_{min} 210 nm (log ε 4.53), 310 nm (log ε 3.25). ^{1}H-NMR (200 MHz, $CDCl_3$ + 2 drops CD_3OD, δ):3.16 (s, 3H, O-CH_3),3.95 (s, 3H, O-CH_3),4.41 (d, 1H, J = 10.80Hz, H-1),6.50 (br, s, 1H, H-10),6.85 (s, 1H, H-13),6.86 (s, 1H, H-14),6.70 (dd, 1H, J_1 = 2Hz, J_2 = 8.2 Hz, H-11),6.88 (dd, 1H, J_1 = 2Hz, J_2 = 8.2 Hz, H-10),7.21 (dd, 1H, J_1 = 2Hz, J_2 = 8.2Hz, H-13), 7.65 (dd, 1H, J_1 = 2Hz, J_2 = 8.2 Hz, H-14). M.S. m/z = 562 (M^+, 92%), 547 (11%), 531 (7%), 333 (11%).



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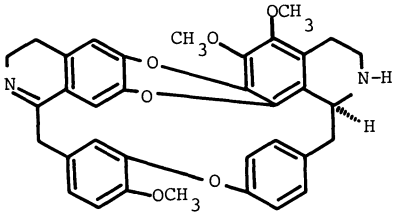
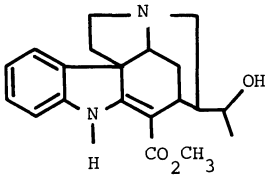


(11)

0,O-dimethyl-1,2-dehydronorkohatine 11 (ref.1) $[\alpha]_D^{25}$ = + 56.6° (MeOH), I.R ($CHCl_3$) 1574 cm^{-1} (C=N), 3575 cm^{-1} (-OH). U.V. (MeOH) λ_{max} 215 nm (log ε 4.64), 226 nm (log ε 4.56), 331 nm (log ε 3.62), λ_{min} 220 nm (log ε 4.22), 312 nm (log ε 3.31). ^{1}H-NMR (200 MHz, $CDCl_3$ + 2 drops CD_3OD, δ):3.81 (s, 3H, O-CH_3),3.84 (s, 3H, O-CH_3),3.83 (s, 3H, OCH_3),4.43 (d, 1H, J = 10.3Hz, H-1),6.56 (s, 1H, H-8),6.58 (s, 1H, H-5),6.43 (d, 1H, J = 1.8Hz, H-10),6.81 (d, 1H, J = 8Hz, H-13),6.84 (dd, 1H, J_1 = 1.8Hz, J_2 = 8Hz, H-14),6.76 (dd, 1H, J_1 =2Hz, J_2 =8.1Hz, H-11).

NEW ALKALOIDS FROM *ALSTONIA SCHOLARIS*

Alstonia scholaris (Apocynaceae) is a large ornamental tree which is widely cultivated in Pakistan. The bark of the tree is used in China and the Pacific islands as a bitter tonic, febrifuge and as an antimalarial. It is also commonly used in the treatment of diarrhoea, dysentery and snakebite. The alcoholic extracts of the stem bark have shown anti-cancer activity in human sarcoma in the embryonated egg. We have recently isolated a new anilinoacrylate alkaloid, scholaricine 12 (ref. 2), from the leaves of this plant.



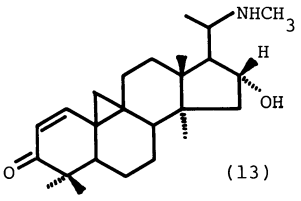
(12)

Scholaricine 12 (ref.2) $[\alpha]_D$ = - 200 ($CHCl_3$), I.R. (KBr) cm^{-1}: 3500 (OH), 3400 (NH), 1600 (α,β unsatd. ester). U.V. λ_{max}(MeOH) nm 210, 235, 285 and 335, λ_{min} 225, 255, 299 nm. ^{1}H-NMR ($CDCl_3$, δ):1.12 (s, 3H, J = 6.0Hz, H-18),3.83 (s, 3H, $COOCH_3$),8.5 (s, 1H, NH),7.12 (m, 3H, aromatic protons). ^{13}C-NMR ($CDCl_3$, δ):169.08 (2),60.17(3),53.88(5),43.37(6),57.96(7),132.15 (8),111.32(9),122.35(10),115.8(11),136.98(12),141.82(13),31.02(14),28.94(15),96.67(16), 172.24(17),19.74(18),68.53(19),45.96(20),48.16(21),51.77($COOCH_3$). M.S. m/z 356, 311, 283, 257 (100%), 196, 149, 122.

NEW ALKALOIDS FROM *BUXUS PAPILOSA*

Buxus papilosa C.K. Schn, Linn (Buxaceae) grows abundantly in the northern regions of Pakistan. The plant extract is used in the indigenous system of medicine as a febrifuge, in rheumatism, malaria, venereal diseases and for the treatment of a number of other ailments. As a result of investigations of its alkaloidal constituents we have isolated eleven new alkaloids: cycloxobuxoviricine 13 (ref.3), cyclobuxoviricine 14 (ref.3), cyclobuxoviricine 14 (ref.4) buximinol-G 15 (ref.5), N-benzoyl-30-acetoxybuxidienine 16 (ref.6), moenjodaramine 17 (ref.7), karachicine 18 (ref.8), papilicine 19 (ref.9), papilinine 20 (ref.10), harappamine 21 (ref.11), buxaquamarine 22 (ref.12) and papilamine 23 (ref.13)

Cycloxobuxoviricine 13 (ref.3) $[\alpha]_D^{26}$ = - 41.2° ($CHCl_3$). I.R. ($CHCl_3$) 3700 cm^{-1} (O-H), 3400 cm^{-1} (N-H), 1661 cm^{-1} (C=C), 1600 cm^{-1} (C=C). U.V. (MeOH) λ_{max} 265 nm (log ε 3.59). ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.76 (d, 1H, J = 4.59Hz, H -19),0.95 (s, 3H, t-CH_3),0.97 (s, 3H t-CH_3),1.10 (s, 3H, t-CH_3),1.13 (s, 3H, t-CH_3),1.20 (dd, 3H, J = 6.09Hz, 21-CH_3),2.11 and 2.15 (dd, 1H, $J_{17,16}$ = 3.9Hz, $J_{17,20}$ =10.63Hz, H-17),2.59 (s, 3H, N-CH_3),2.98 (m, 1H, $J_{20,21}$ = 6.09Hz, $J_{20,17}$ =10.63Hz, H-20),4.28 (m, 1H, H-16),5.94 (d, 1H, J = 10.02Hz, H-2),6.73 (d, 1H, J = 10.02Hz, H-1). M.S. m/z = 385 (M^+, 10%), 370 (18%), 148 (50%), 135 (24%), 115 (20%), 100 (13%), 72 (20%), 58 (100%).



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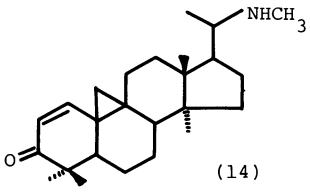

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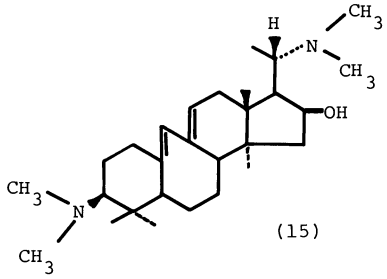
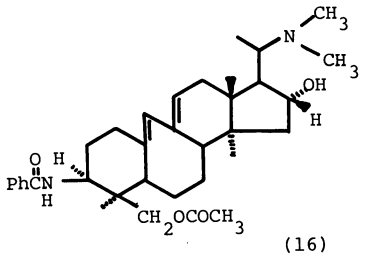


(15)

Cyclobuxoviricine 14 (ref.4) $[\alpha]_D^{10}$ = - 54° ($CHCl_3$). I.R. ($CHCl_3$), 3350 cm^{-1} (N-H), 1647 cm^{-1} (C=C-), 1595 cm^{-1} (C=C). U.V. (MeOH) λ_{max} 203 nm, 268 nm, λ_{min}250 nm. ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.75 and 0.81 (dd, 2H, J = 5.1Hz, 19-CH_2),0.90 (s,3H, t-CH_3),0.95 (s,3H, t- CH_3),1.09 (s, 3H,t-CH_3),1.18 (d, 3H, J = 6.00Hz, 21-CH_3),2.48 (s, 3H, N-CH_3),2.78 (m, 1H, $J_{20,21}$ = 6.00Hz, $J_{20,17}$ = 9.80Hz, H-20),5.94 (d, 1H, J = 10.10Hz, H-2),6.75 (d, 1H, J = 10.10Hz, H-1). ^{13}C-NMR (75MHz, $CDCl_3$, δ):153.18 (C-1),127.08 (C-2),199.20 (C-3),45.53 (C-4),49.20* (C-5),24.42 (C-6),27.59 (C-7),44.61 (C-8),19.14** (C-9),40.17 (C-10),26.98 (C-11),34.57 (C-12),43.45 (C-13),49.34* (C-14),31.94 (C-15),29.02 (C-16),49.99 (C-17),16.50 (C-18),19.50** (C-19),58.57 (C-20),18.60 (C-21),17.15 (C-28),23.40 (C-29),21.50 (C-30),29.90 (N-CH_3). M.S. m/z = 369 (M^+, 10%), 354 (3%), 339 (7%), 312 (10%), 85 (10%), 57 (100%).

Buximinol-G 15 (ref.5) $[\alpha]_D$ = + 83.33° ($CHCl_3$). I.R. ($CHCl_3$) 3550 cm^{-1} (O-H), 1550 cm^{-1} (C=C), 1380 cm^{-1} (C-N). U.V. (MeOH) λ_{max} 237 nm (ε 6040), 245 nm (ε 5866), 253 nm (ε 4151). ^{1}H-NMR (100 MHz, $CDCl_3$,δ):0.72 (d, 3H, J = 5Hz, 21-CH_3),0.74 (s, 3H, t - CH_3),0.87 (s, 3H, t - CH_3),0.90 (s, 3H, t - CH_3),2.30 (s, 3H, N-CH_3),2.33 (s, 3H, N-CH_3),3.52 (d, 1H, J = 10Hz H 30),3.84 (d, 1H, J = 10Hz, H-30),4.21 (m, 1H, H-16),5.15 (s, 1H, 19-H),5.45 (1H, 11-H). M.S. m/z = 444 (M^+ G 1.28%), 84 (13%), 72 (100%), 71 (27%), 58 (11%).

Benzoyl-30-acetoxybuxidienine 16 (ref.6) $[\alpha]_D^{20}$ = - 4.08° ($CHCl_3$). I.R. ($CHCl_3$), 3400 cm^{-1} (O-H), 3350 cm^{-1} (N-H), 1761 cm^{-1} (ester C=O), 1662 cm^{-1} (C=C-C-N), 1610 cm^{-1} (C=C). U.V. (MeOH) λ_{max} 238 nm, 245 nm, 253 nm, 268 nm, 279 nm, 290 nm, λ_{min} 241 nm, 252 nm, 263 nm, 273n, 287 nm. ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.76 (s, 3H, t - CH_3),0.77 (s, 3H, t - CH_3),0.94 (s, 3H, t - CH_3),1.19 (α,3H, J = 6.39Hz, 21-CH_3),2.12 (s, 3H, ester CH_3),2.61 (s, 6H, N_b -CH_3), 3.82 (d, 1H, J = 10.98Hz, H-30),4.02 (d, 1H, J = 10.98Hz, H-30),3.94 (m, 1H, 16-CH_2),5.52 (m, 1H, H-11),6.07 (s, 1H, H-19),7.43 - 7.71 (m, 5H, aromatic H). ^{13}C-NMR (75 MHz, $CDCl_3$,



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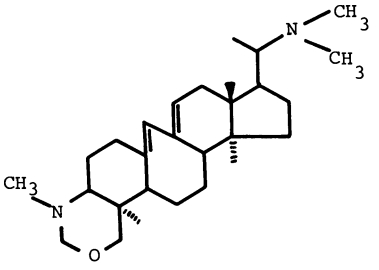

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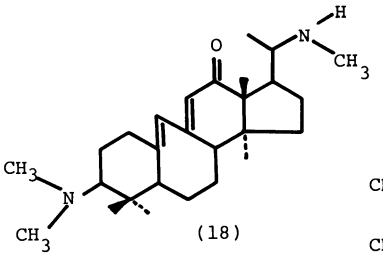

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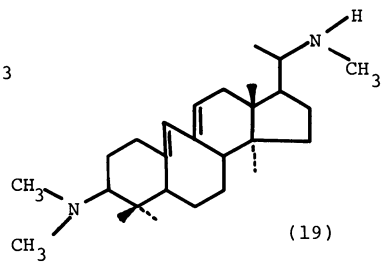

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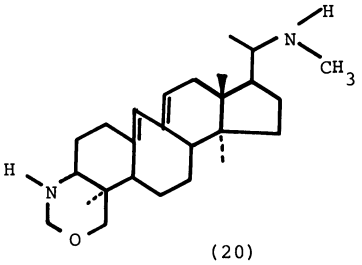

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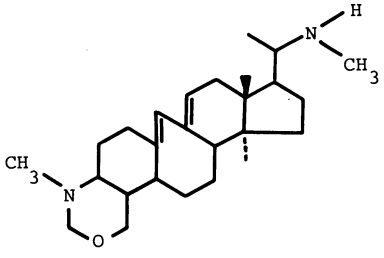

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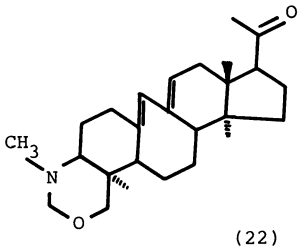

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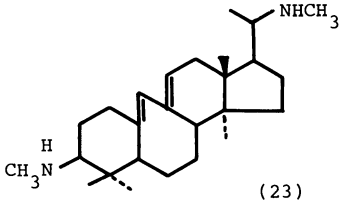
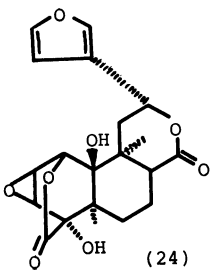


(23)

δ):36.00 (C-1),30.22 (C-2),47.28 (C-3),43.90 (C-4),50.76 (C-5),25.70 (C-6),29.50 (C-7),49.89 (C-8),138.70* (C-9),138.30* (C-10),125.92 (C-11),32.00 (C-12),45.37 (C-13),48.60 (C-14),42.90 (C-15),77.80 (C-16),63.30 (C-17),16.61 (C-18),126.92 (C-19),60.30 (C-20),10.29 (C-21),39.77 (N_b-$\underline{C}H_3$),42.11 (N_b -$\underline{C}H_3$),18.40 (C-28),11.37 (C-29),65.36 (C-30),136.90 (C-1),128.67 (C-2), 129.00** (C-3),131.10*** (C-4),130.00*** (C-5),129.20 (C-6),167.25 (-$\underline{C}$-N),21.00 (C-$\underline{C}H_3$),171.34 (-$\underline{C}$-CH_3). M.S. m/z 562 (M^+, 10%), 547 (5%), 503 (5%), 457 (6%), 115 (10%), 105 (35%), 85 (8%), 72 (100%), 71 (10%), 58 (4%).

NEW CHEMICAL CONSTITUENTS OF *TINOSOPORA MALABARICA*

Tinospora malabarica (Menispermaceae) is cultivated throughout Pakistan. It contains berberine, and its watery extract "Sat Giloe" is used as a febrifuge, for intermittent fever and dyspepsia. As a result of our studies on its chemical constituents, we have isolated a new high oxygenated diterpene tinosporicide 24 (ref.14).



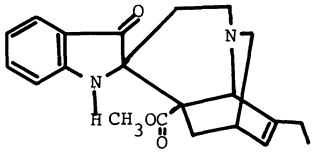
(24)

Tinosporicide 24 (ref.14) $[\alpha]_D^{23}$ = ± 0. I.R. (KBr), 3470, 3450 cm^{-1} (-OH), 1758, 1717 cm^{-1} (C=O), 1210, 1115 cm^{-1} (C-O-C), 1510, 880 cm^{-1} (furan ring). U.V. λ_{max} (CH_3OH) 212 nm. ^{1}H-NMR (δ):5.68 (dd, 1H, J=12.0, 5.5Hz),2.25 (dd, 1H, J=14.4, 12.0Hz),2.05 (dd, 1H, J=14.4, 5.5Hz),1.08 (s, 3H), 1.03 (s, 3H),3.61 (d, 1H, J=4.4Hz),3.95 (dd, 1H, J=4.4, 3.0Hz),5.05

(d, 1H, J=3.0Hz),2.83 (m, 1H),1.63 (m, 1H),1.23 (m, 1H),1.53 (m, 1H),1.33 (m, 1H),6.53 (dd, 1H),7.68 (dd, 1H),7.71 (dd, 1H),6.10 (s, 1H, OH),6.30 (s, 1H, OH). ^{13}C-NMR: (δ):70.03 (C-1),51.10 (C-2),49.22 (C-3),80.42 (C-4),40.60 (C-5),26.23 (C-6),26.66 (C-7),45.80 (C-8), 38.79 (C-9),71.85 (C-10),34.91 (C-11),70.50 (C-12),125.68 (C-13),108.99 (C-14),139.92 (C-15), 143.84 (C-16),172.98 (C-17),22.76(C-18),20.12 (C-19),171.40 (C-20). M.S. m/z = 390(2%), 345(3%), 291(2%), 252(30%), 124(100%), 95(21%), 94(16%), 81(15%).

ISOLATION AND STRUCTURAL STUDIES ON ALKALOIDS OF *CATHARANTHUS ROSEUS*

Catharanthus roseus (L.) G.Don. (Apocynaceae) is one of the most thoroughly investigated plants. Previous investigations have resulted in the isolation of over 120 alkaloids of different type. It has been found that some of them such as vinblastine and vincristine are highly promising chemotherapeutic agents against malignant tumours and for treating maladies due to high blood pressure. Our continuing studies on this plant have previously resulted in the isolation of a number of alkaloids. More recently we have investigated and elucidated the structures of rosamine 25 (ref.15), gomaline 26 (ref.16), rosicine 27 (ref.17) and bannucine 28 (ref.18).



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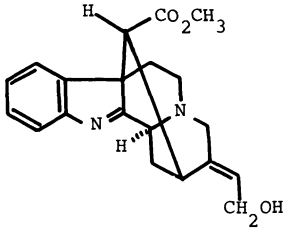

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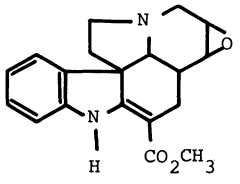
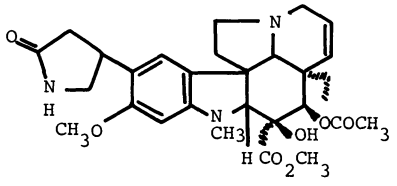


(27)



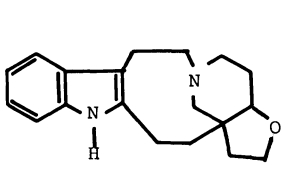
(28)

Bannucine 28 (ref.18) $[\alpha]_D$ = 33° ($CHCl_3$). I.R. ($CHCl_3$), 3511 cm^{-1} (NH), 3400 cm^{-1} (OH), 1710 cm^{-1} (ester C=O) and 1690 cm^{-1} (amide C=O). U.V. (MeOH) λ_{max} 236 nm, 380 nm. ^{1}H-NMR (300 MHz, $CDCl_3$,δ):3.83 (3H, s, $CO_2\underline{CH}_3$),2.07 (3H, s, $OCO\underline{CH}_3$),3.79 (3H, s, $O\underline{CH}_3$),2.65 (3H, s, $N\underline{CH}_3$),1.22 (1H, m, $\underline{CH}_2CH_3$, C-19 H),1.59 (1H, m, $\underline{CH}_2CH_3$, C-19 H),0.44 (3H, t, $\underline{CH}_2\underline{CH}_3$, C-18 H, $J_{19,18} = J_{19,18}$ = 7.3Hz),5.20 (1H, d, C-15H, $J_{15,14H}$=10.31Hz),5.82 (1H, ddd, C-14H, $J_{14,3}$ =3.50Hz, $J_{14,3}$ =3.51Hz, $J_{14,15}$ = 10.31Hz),2.27 (1H, m, C-3 H),2.91 (1H, m, C-3 H),2.84 (1H, m, C-5 H),1.81 (1H, m, C-5 H),2.33 (1H, m, C-6 H),2.55 (1H, m, C-6 H),6.08 (1H, s, C-9),6.90 (1H, s, C-12H),81.78 (1H, m, C-4 H),2.56 (1H, m, C-4 H),2.24 (1H, m, C-3 H),2.77 (1H, m, C-3 H). ^{13}C-NMR ($CDCl_3$,δ),75 MHz):83.60 (C-2),51.60 (C-3),51.62 (C-5),44.00 (C-6),53.24 (C-7), 124.01 (C-8),119.01 (C-9),121.20 (C-10),158.10 (C-11),93.60 (C-12),153.21 (C-13),124.40 (C-14),130.40 (C-15),79.70 (C-16),76.68 (C-17),7.63 (C-18),30.88 (C-19),42.80 (C-20),66.96 (C-21),170.60 ($CH_3\text{-}\underline{C}O_2$-),52.05 ($\underline{CH}_3\text{-}CO_2$-),176.00 (-$O\underline{C}OCH_3$),52.00 (-$OCO\underline{CH}_3$),178.50 (-$\underline{C}ONH$), 29.82 (C-3),20.93 (C-4),55.20 (C-5),38.50 (N-$\underline{CH}_3$). M.S. m/z = 539 (M^+, 20%), 480 (68), 420(4%), 392 (4%), 379(18%), 350(5), 282(16%), 271(30%), 257(10%), 135(100%), 122 (33%), 121(36%) and 107(17%).

NEW ALKALOIDS OF *ERVATAMIA CORONARIA*

Ervatamia coronaria (Apocynaceae) is a glabrous evergreen tree (commonly grown in the gardens of West Pakistan. Various parts of the plant are used in the indigenous system of medicine for the treatment of opthalamia, for application on wounds and inflammed parts of the body,

as anthelmintic, etc. Anti-cancer activity has also been reported from the crude extracts of the plant. As a result of our studies we have isolated six new alkaloids, named hyderabadine 29 (ref.19), mehranine 30 (ref.20), lahoricine 31 (ref.21), ervatinine 32 (ref.22), stapfinine 33 (ref.23) and ervaticine 34 (ref.24).



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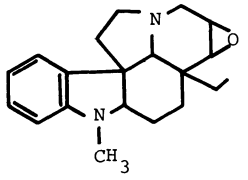

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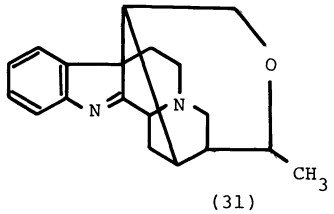

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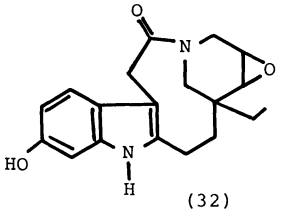

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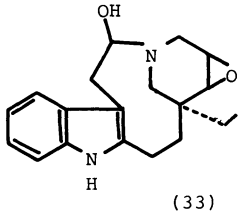

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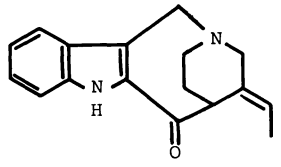


(34)

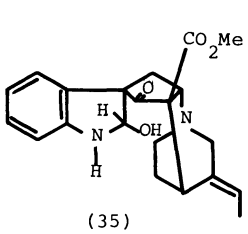
Stapfinine 33 (ref.23) $[\alpha]_D$ = + 25° ($CHCl_3$). I.R. ($CHCl_3$) 3450 (OH), 3300 (N-H) cm^{-1}. U.V. (MeOH): λ_{max} 222 nm (log ε 4.58), 275 nm (log ε 3.84), 292 nm (log ε 3.83). ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.74 (t, 3H, J = 7.4Hz, H-18),1.22 (q, 2H, J = 7.4Hz, H-19),2.90 (m, 1H, H-14),3.25 (d, 1H, J = 3.0Hz, H-15),5.2 (ddd, 1H, J_1 = 2.4Hz, J_2 = 5.0Hz, J_3 = 11.4Hz, H-5),2.49 (dd, 1H, J_1 = 2.4Hz, J_2 = 14.0Hz, H-6),1.95 (dd, 1H, J_1 = 5.0Hz,, J_2 = 14.0Hz, H-6),7.08 (t, 1H, J = 6Hz, H-10),7.13 (t, 1H, J = 6.0Hz, H-11),7.29 (d, 1H, J = 6.0Hz, H-12),7.47 (d, 1H, J = 6.0Hz, H-9),7.73 (bs 1H, N-H). ^{13}C-NMR (75 MHz, $CDCl_3$,δ):139.0 (C-2),137.0 (C-13),129.0 (C-8),121.4 (C-11),119.1(C-10),117.9 (C-9),110.3 (C-12),103.0(C-7),68.9 (C-5),58.6 (C-15),54.9 (C-3),53.1 (C-14),52.8(C-21),42.4 (C-6),32.6 (C-18),29.7(C-17),29.3(C-20)24.4(C-16),7.5 (C-19). M.S. m/z = 312 (18.3%), 294 (2.4%), 265(98%), 243(2.15), 158(4.3%), 156(13.1%), 144(9.4%), 138(3.4%), 130(7.2%), 124(3.0%), 110(2.7%), 108(4.2%), 96(3%).

Ervaticine 34 (ref.24) $[\alpha]_D$ = + 120° ($CHCl_3$) I.R. (KBr) 3400 (NH), 1640 (C=O) and 1580 (C=C) cm^{-1}. U.V. (MeOH) λ_{max} 235 nm (log ε 4.15) and 312 nm (log ε 4.20); λ_{min} 265 nm (log ε 3.05) ^{1}H-NMR (300 MHz, $CDCl_3$, δ):1.52 (d, 3H, J = 6.9Hz, H-18),2.08 (m, 1H, H-14),2.30(m, 1H, H-14),3.10 (m, 1H, H-3),3.33 (d, 1H, J = 15.9Hz, H-21),3.40 (m, 1H, H-3),3.87 (d, 1H, J = 15.9Hz, H-21),3.98 (d, 1H, J = 6Hz, H-15),4.28 (d, 1H, J = 18.6Hz, H-6),4.79 (d, 1H, J = 18.6Hz, H-6),5.49 (q, 1H, J = 6.9Hz, H-19),7.10 (ddd, 1H, J_1 = 5.4Hz, J_2 = 5.1Hz, J_3 = 2.4Hz, H-11),7.11 (ddd, 1H, J_1 = 7.5Hz, J_2 = 5.4Hz, J_3 = 2.4Hz, H-10),7.33 (d, 1H, J = 5.1Hz, H-12),7.57 (d, 1H, J = 7.5Hz, H-9). ^{13}C-NMR (75 MHz, $CDCl_3$, δ):12.75 (C-18),29.7 (C-14),44.2(C-15),48.0 (C-3),53.2 (C-6),54.9 (C-21),126.7 (C-19),120.3(C-9),120.9(C-10), 126.6(C-11),111.6(C-12). M.S. m/z = 266(51%), 251(13%), 237(61%), 223(23%), 185(26%), 158(19%), 156(41%0, 130(100%) and 109 (77%).

NEW ALKALOIDS FROM *RHAZYA STRICTA*

Rhazya stricta Decaisne (Apocynaceae) is a small, glabrous, erect shrub, widely distributed in Western Asia and abudantly found in Pakistan. It has along been used in the indigenous system of medicine as a bitter tonic, for soure throat, in fever, in general debility and as a curative for chronic rheumatism.

As a result of our investigation on the chemical constituents of Rhazya stricta, we have isolated several new alkaloids namely rhazicine 35 (ref.25), strictamine N-oxide 36 (ref.26), rhazimine 37 (ref.27), 2-methoxy 1,2-dihydrorhazimine 38 (ref.28), strictimine 39 (ref.29), postsecamidine 40 (ref.30) and 1,2-dehydroaspidospermidine N-oxide 41 (ref.31).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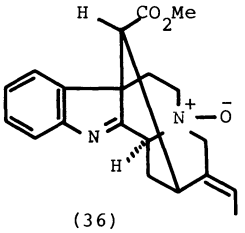
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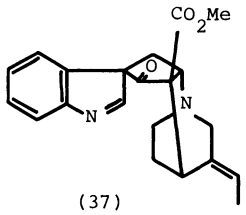
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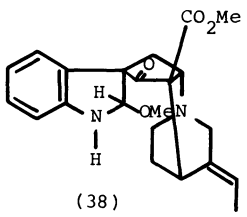
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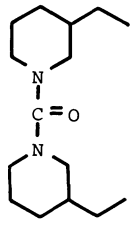
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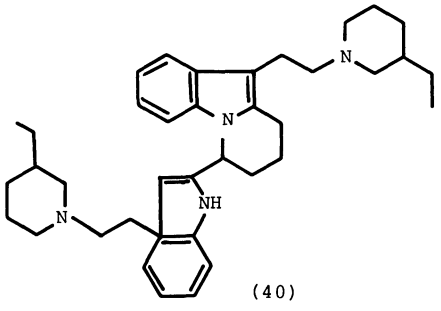
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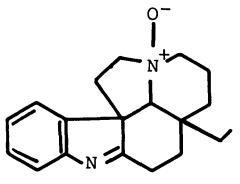
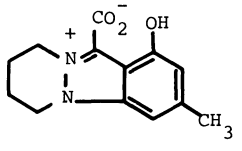

(41)

Postsecamidine 40 (ref.30) $[\alpha]_D$ = + 30° ($CHCl_3$). I.R.($CHCl_3$) 3500(NH), 2880 (C-H) cm^{-1}. U.V. (MeOH) λ_{max} 224 nm (log ε 2.16), 284 (log ε 1.45), 290 nm (sh, log ε 1.38), λ_{min} 255 nm(log ε 1.32). ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.69 (t, 3H, J = 7.3Hz, H-18),1.16 (m, 2H, H-19),4.04 (t, 1H, J = 6.7Hz, H-16),7.07-7.6 (m, 8H, Ar-H). M.S. m/z = 564 (0.43%), 451(0.54%), 438(0.33%), 295 (3.65%), 283(1.12%), 126(100%), 112(0.87%).

1,2-Dehydroaspidospermidine N-oxide 41 (ref.31) $[\alpha]_D$ = + 120° ($CHCl_3$). I.R. ($CHCl_3$) 1710 (C=N) cm^{-1}. U.V. (MeOH) λ_{max} 206 nm, 222 nm and 260 nm; λ_{min} 217 nm and 245 nm. ^{1}H-NMR (300 MHz, $CDCl_3$,δ):0.49 (t, 3H, J = 7.5Hz, H-21),1.71 (q, 2H, J = 6.0Hz, H-20),3.74 (s, 1H, H-19),7.13-7.52 (m, 4H, Ar-H). M.S. m/z 296, 280, 251, 210, 194, 169, 168, 149, 125, 97, 83, 56.

ISOLATION, STRUCTURAL AND SYNTHETIC STUDIES ON ALKALOIDS FROM *NIGELLA SATIVA*

Nigella sativa Linn. (Ranunculaceae) is an indigenous herbaceous plant. It grows in the Mediterranean countries and is also found in Pakistan. It is used as a spice as an well as attenuant, as diuretic, for the treatment of dyspepsia and for skin eruptions. As a result of our investigations on the chemical constituents of Nigella sativa, we have isolated three new alkaloids, nigellicine 42 (ref.32), nigellimine, and nigellimine N-oxide 43 (ref.33). The structures of nigellimine and nigellimine N-oxide have been confirmed by synthesis (ref.34).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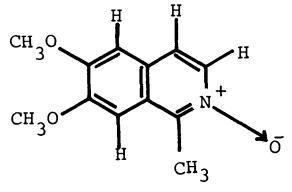
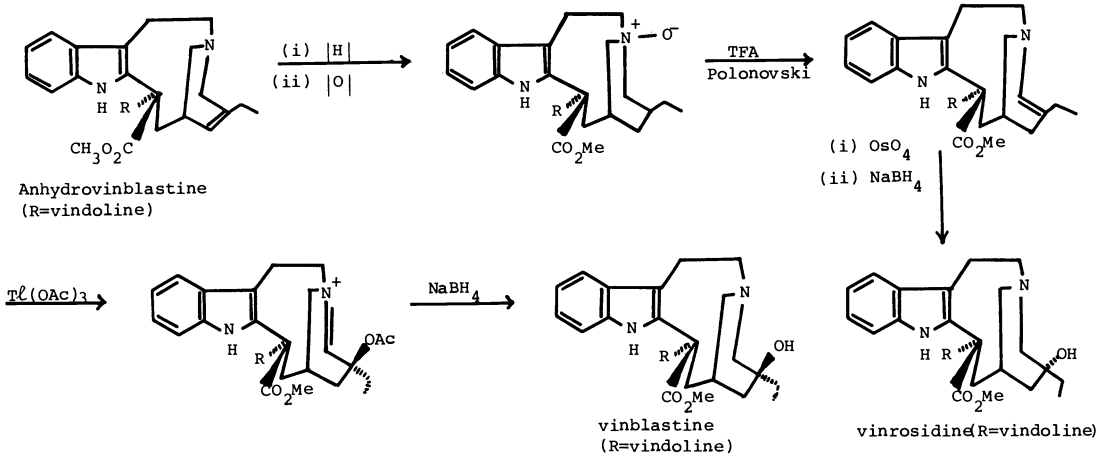

(43)

SYNTHETIC STUDIES ON ALKALOIDS OF *CATHARANTHUS ROSEUS*

We have previously reported the first two syntheses of vinblastine. The first approach was based on the functionalisation of catharanthine by a modified Prevost reaction prior to its combination with vindoline. This functionalisation reaction was found to have a low reproducibility on account of the known tendency of catharanthine to be transformed into a number of other by-products in hot acetic acid, the medium in which the modified Prevost reaction was carried out. An improved partial synthesis of vinblastine patented by us in 1978 (ref.35)

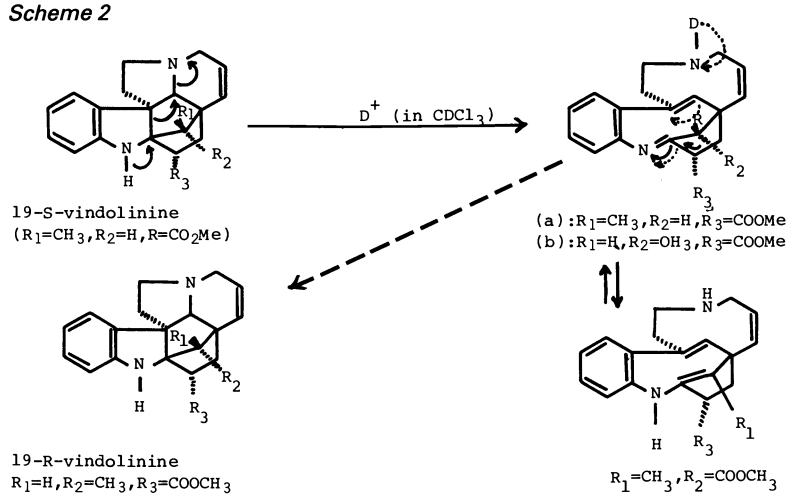
(Scheme 1) involved a coupling of catharanthine N-oxide with vindoline by a modified Polonovski reaction followed by reduction. The resulting anhydrovinblastine was converted to vinblastine by reduction, formation of N-oxide, elimination and functionalisation of the resulting enamine with Tl $(OAc)_3$ followed by reduction/hydrolysis (ref.35) (Note a). An identical route was reported by the French group a year later (ref.36). As a result of subsequent studies we have succeeded in developing a new superior procedure for the isolation of vinblastine from the leaves of C.roseus which affords the pure drug in quantities 20-50 times higher than has been internationally achievable previously. Our procedure is based on selective extraction of vinblastine with a judicious combination of solvents after pH fractionation without the need of any elaborate chromatographic separations (ref.37)

Scheme 1



19-S-vindolinine has been found to undergo a remarkable isomerisation in solution to 19-R-vindolinine at room temperature. NOEDS measurements have been carried out on both isomers and a ^{13}C-solid state CP-MAS spectrum recorded for 19-S-vindolinine (ref.38). A plausible mechanism for the transformation is presented in Scheme 2.

Scheme 2



Note a : Copy of patent obtainable from Patent Office, Government of Pakistan, Karachi or from author.

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