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SYNTHESIS OF HETEROCYCLES VIA LACTONES. PART III[1]. A SYNTHESIS OF BERBINES[2]. – SYNTHESIS OF (±) – SCOULERINE AND PSEUDOEPITETRAHYDROBERBERINE

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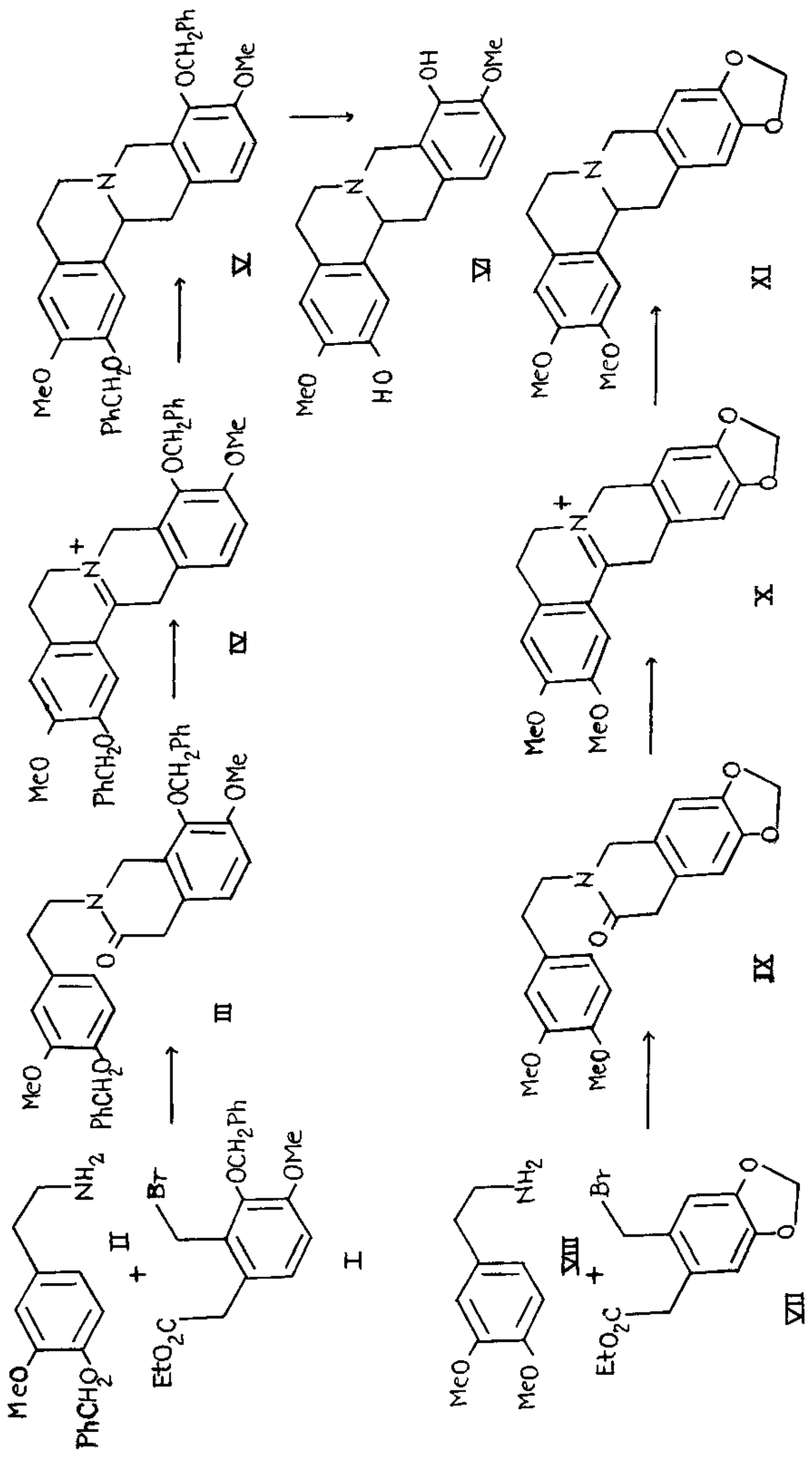
Abstract – The utilization of the bromo esters (I) and (VII) for the functionalization of the ring D can provide an interesting synthetic entry to the berbines.

In the recent past we have been interested in the synthesis of isoquinoline alkaloids[1] and have reported a novel synthesis of the isoquinoline alkaloids by the successful utilization of the bromo ester essentially like (I). As an extension of our approach we took in hand the synthesis of the berbines and wish to report what we believe is the first successful utilization of the bromo esters (I) and (VII) derived from corresponding 3-isochromanones for the functionalization of the ring D of the berbines as examplified by the synthesis of (±)-scoulerine (VI) and pseudoepitetrahydroberberine (XI).

7-Methoxy-8-benzyloxy-3-isochromanone[3] was dissolved in ethanolic hydrobromic acid at 0-5°. After 24 h the solvent and excess reagent was removed at 3-4 mm Hg and 20° to get ethyl-3-benzyloxy-2-bromomethyl-4-methoxyphenylacetate[4](I) in 83% yield, IR ($CHCl_3$) 1710 cm^{-1}, which was condensed with 4-benzyloxy-3-methoxy-β-phenethylamine[5] (II) at 100° for 96 h to get the tricyclic lactam (III), m.p. 121.5° (Et_2O) (lit.[6], 121-122° (Et_2O)) in 78% yield, IR($CHCl_3$) 1638 cm^{-1} (six membered lactam). Cyclization of the lactam (III) in toluene with phosphoryl chloride after usual work


MeO
PhCH2O
NH2
II
+
Br
OCH2Ph
OMe
EtO2C
I
MeO
PhCH2O
N
O
OCH2Ph
OMe
III
MeO
PhCH2O
N+
OCH2Ph
OMe
IV
MeO
PhCH2O
N
OCH2Ph
OMe
V
MeO
HO
N
OH
OMe
VI
MeO
MeO
NH2
VIII
+
Br
EtO2C
VII
MeO
MeO
N
O
IX
MeO
MeO
N+
X
MeO
MeO
N
XI

up gave the salt (IV) as an oil. Sodium borohydride reduction of the salt (IV) in methanol afforded O,O-dibenzylscoulerine (V), m.p. 73° (lit.[6], 73-75°) in 68% yield. Debenzylation of the dibenzyl ether (V) with acetic acid - hydrochloric acid gave (±)-scoulerine (VI) as a yellow powder, m.p. 182.5° (EtOH) (lit.[7], 183-185°, lit.[6], 183-185°) in 64% yield; IR ($CHCl_3$) 2710-2820 cm^{-1} (trans-quinolizidine band) ; m/e (rel.int.) 327 (70), 170 (100), 176 (28), 150(58) and 135 (26). The picrate had m.p. 206° (decomp.) (lit.[7], 205-206° (decomp.)).

Similarly 6,7-methylenedioxy-3-isochromanone[8] was dissolved in ethanolic hydrobromic acid at 0-5°. After 24 h at room temperature the excess solvent and reagent was removed at 3-5 mm Hg and 20° to get ethyl 2-bromomethyl-4,5-methylenedioxyphenylacetate[4] (VII) as a pale brown oil in 76% yield, IR ($CHCl_3$) 1716 cm^{-1}. (VII) was condensed with 3,4-dimethoxy-β-phenethylamine[9] (VIII) at 100° for 80 h to get the tricyclic lactam[4](IX), $C_{20}H_{21}NO_5$, m.p. 115° ($CHCl_3$) in 82% yield, IR ($CHCl_3$) 1640 cm^{-1}; Rf (Silica gel) 0.81 (C_6H_6 : EtOH ; 6 : 4). The lactam (IX) was cyclized with phosphorylchloride to get the imine[4] (X), $C_{20}H_{20}NO_4$, m.p. 102°($CHCl_3$) as a brown powder. Sodium borohydride reduction of the imine (X) in methanol gave pseudoepitetrahydroberberine (XI), $C_{20}H_{21}NO_4$, m.p. 155-156° (Et_2O) (lit.[10] 155-156°, lit.[11] 159-160°) ; Rf (Silica gel) 0.75 (Et_2O) ; IR (KBr) 1620, 1530, 1510 cm^{-1}; NMR ($CDCl_3$)δ: 6.75 (s, 1H), 6.64 (s, 2H), 6.55 (s, 1H), 5.90 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.5-3.75 (m, 9H).

Thus successful utilization of the bromo esters (I) and (VII) has been demonstrated to lead to berbines oxygenated at both 9,10 and 10,11-positions.

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REFERENCES

1. G.D.Pandey and K.P.Tiwari, *Indian J. Chem.*, in press.
2. G.D.Pandey and K.P.Tiwari, *Synthe. Commun.*, in press.
3. W.Nagata, H.Itazaki, K.Okada, T.Wakabayashi, K.Shibata, and N.Tokutake, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2867.
4. This is the first literature record of the compounds (I), (VII), (IX) and (X).
5. J.M.Bobbitt and Tsu-Teh Chai, *J. Org. Chem.*, 1959, **24**, 1106.
6. A.R.Battersby, R.Southgate, J.Staunton, and M.Hirst, *J. Chem. Soc. (C)*, 1966, 1052.
7. T.Kametani and M.Ihara, *J. Chem. Soc. (C)*, 1957, 530.
8. R.J.Spangler, B.G.Beckmann, and Jong Kim-Ho, *J. Org. Chem.*, 1977, **42**, 2989.
9. Obtained from Sisco Chem. Industries, Bombay, India.
10. G.R.Lenz, *J. Org. Chem.*, 1974, **39**, 2846.
11. G.R.Lenz, *J. Org. Chem.*, 1977, **42**, 1117.

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