ALTERNATIVE SYNTHESIS OF PROTOBERBERINE ALKALOID (±)-XYLOPININE

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Treatment of 2-(2-bromo-4,5-dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3) with sodium amide in liquid ammonia afforded the oxoberbine (4) together with the styrene derivative (5) and the hydrolysed product (6). Chlorination of the lactam (4) with phosphoryl chloride gave the chloride, whichwas then reduced with sodium borohydride to afford (±)-xylopinine (8).

Furthermore, a photolysis of the bromo-enamide (3) also gave the oxoberbine (4) in good yield.

In the synthesis of heterocyclic compounds, a benzyne reaction has played an important role.[1] We have reported[2-4] the total synthesis of isoquinoline alkaloids by an application of the benzyne reaction as a key step, such as the synthesis of domesticine.

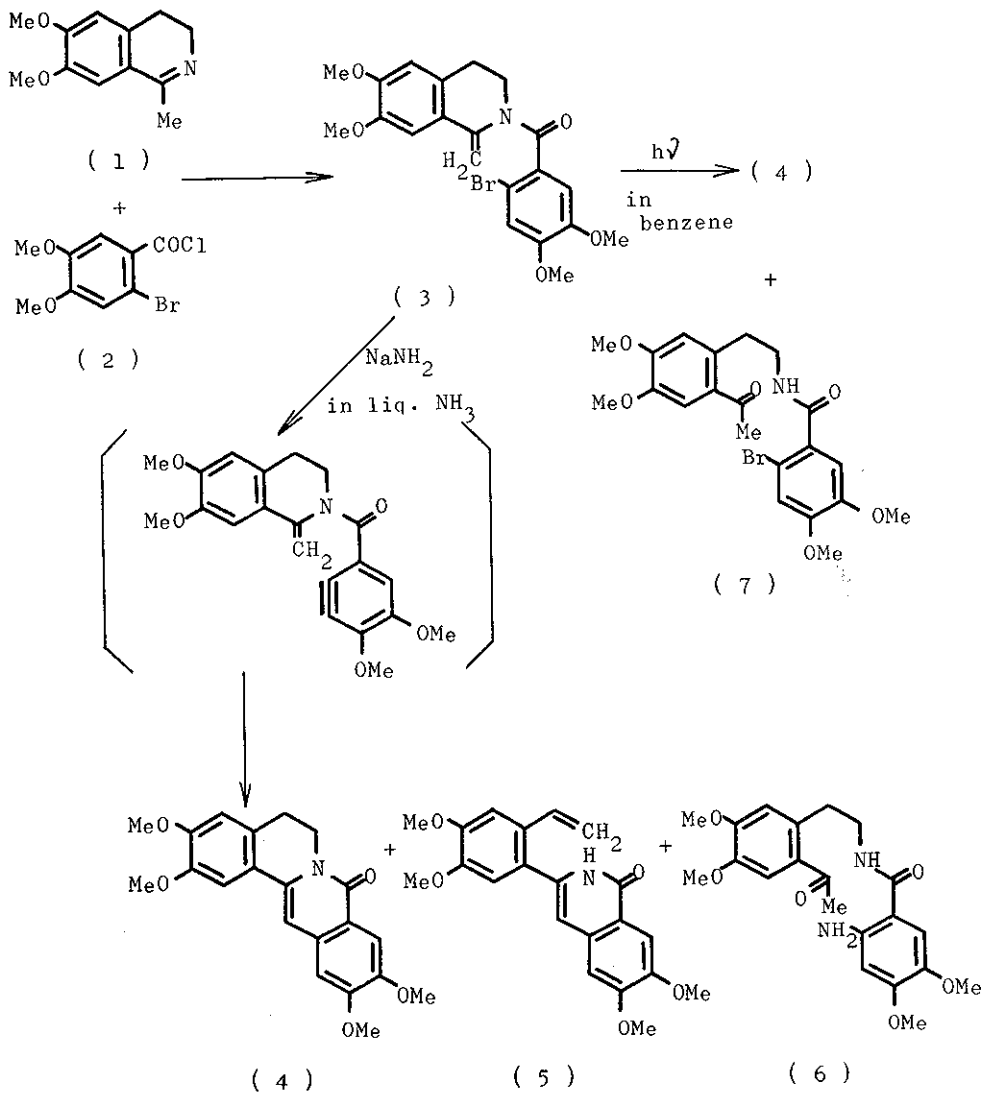
As an extension of this work, we synthesised a protoberberine alkaloid, (±)-xylopinine, from the corresponding bromo-enamide. The bromo-enamide (3) [mp 182 - 184°, ir νmax ($CHCl_3$) 1620 and

1605 cm^{-1}] was prepared in 70 - 80 % yield by treating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) with 2-bromo-4,5-dimethoxybenzoyl chloride (2), in the presence of triethylamine in chloroform. Treatment of the bromo-enamide (3) with sodium amide in liquid ammonia gave three compounds, which were separated by column chromatography on silica gel.

The first compound obtained in 15 % yield was identified as the known tetramethoxy-8-oxoberbine (4) [mp 192 - 194° (lit.,[5,6] mp 196.5 - 198°, 187 - 188°); ir νmax ($CHCl_3$) 1640, 1605 and 1585 cm^{-1}; uv λmax (MeOH) 228, 262, 333, 346, and 364 nm; nmr ($CDCl_3$) δ 2.90 (2H, t, J 5 Hz, C_5 - H_2), 3.88 (3H, s, OCH_3), 3.96 (9H, s, 3 x OCH_3), 4.35 (2H, t, J 5 Hz, C_6 - H_2), 6.70, 6.87, 6.92, 7.18, and 9.65 (each 1H, eash s, ArH and C_{13}- H)], which was also synthesised by photolysis of the bromo-enamide (3) in 75 % yield. Thus irradiation of a benzene solution of the bromo-enamide (3) with a high-pressure mercury lamp equipped with pyrex filter at room temperature for 3 hr afforded the oxoberbine (4) together with the hydrolysed product (7) [mp 178 - 181°, ir νmax ($CHCl_3$) 1665, 1640 and 1600 cm^{-1}; nmr ($CDCl_3$) δ 2.57 (3H, s, $COCH_3$), 3.13 (2H, t, J 6 Hz, $ArCH_2CH_2N$), 3.68 (2H, t, J 6 Hz, $ArCH_2CH_2N$), 3.86 (6H, s, 2 x OCH_3), 3.89 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.84, 6.93, 7.07 and 7.20 (each 1H, each s, ArH); m/e 465 (M^+) and 467 (M^+ + 2, isotope peak)].

Treatment of the lactam (4) with phosphoryl chloride afforded the quaternary chloride, which was then reduced with sodium borohydride in methanol to give (±)-xylopinine, identical with an authentic sample.[7]

The second product [mp 197 - 200°, 35 % yield] has formula


MeO
MeO
N
Me
(1)
+
COCl
Br
(2)
(3)
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in benzene
(4)
+
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in liq. NH3
NH
Me
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OMe
(7)
CH2
(4)
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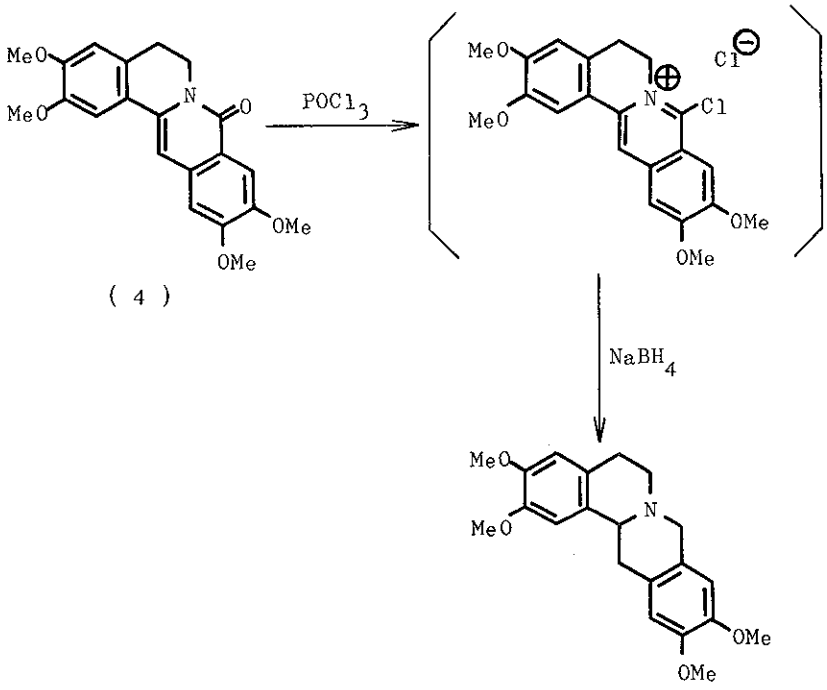
(6)
NH2



(4)

Xylopinine (8)

$C_{21}H_{21}NO_5$ [microanalysis and mass spectrum, m/e 367 (M^+)]. Its nmr spectrum showed a characteristic ABX type of signals for the styrenic protons at δ5.28 (1H, q, J 2 and 11 Hz), 5.66 (1H, q, J 2 and 17 Hz) and 6.76 (1H, q, J 11 and 17 Hz) in addition to four methoxy signals as each singlet at δ3.89, 3.94, 3.98 and 4.03, while its ir spectrum revealed the presence of a secondary amide group at 3400, 1630 and 1605 cm^{-1}. Based on the above spectral data, the structure of the second product was characterised as a styrene derivative (5), which would be formed by Hofmann-like elimination of 4[8].

The third compound obtained [mp 148 - 150°, 40 % yield] has a formula $C_{21}H_{26}N_2O_6$ [microanalysis and mass spectrum, m/e 402 (M^+)]. Its ir spectrum showed the presence of an acetophenone type carbonyl group at 1660 cm^{-1} and a secondary amide group at 3350 and 1635 cm^{-1}, while nmr spectrum showed an acetophenone methyl signal at δ 2.56 in addition to four aromatic protons as each singlet at δ6.10, 6.76, 6.86 and 7.12, respectively. These data indicate that the third product is the hydrolysed compound (6).

We proposed that the formation of the oxoberbine would proceed *via* a benzyne intermediate and the reaction mechanism is under investigation.

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