SYNTHESIS OF HETEROCYCLES *VIA* LACTONES—A FACILE SYNTHESIS OF 3-HYDROXY-9, 10-DIMETHOXYBERBINE

Introduction

BERBINES comprise a large group of isoquinoline alkaloids of which over eighty have so far been isolated from plants of many families[1]. A number of efforts has been directed in the past decade towards their synthesis[2], owing to their great biological activity[3]. In continuation of our experiments on isoquinoline alkaloids we recently reported a synthesis of the berbine alkaloid xylopinine from a lactone[4] and later we successfully exploited a bromo ester derived from the lactone (I) for a new synthesis of 1,2,3,4-tetrahydroisoquinoline, N-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids and berbines (Pandey and Tiwari; unpublished results).

The initiation of the present investigation has in its background the degradative experiments of Sawa *et al.*[5] on berbines, who showed that several compounds derived from degradation of the berbine chloride were potent analgetics[5]. These potent analgetics had the skeleton of protopine alkaloids and among these 9,10-dimethoxy-3-hydroxy-7-methyl-5,6,7,8,13,14-hexahydrodibenz (c, g) azecine (VII) was found to be most potent and low in toxicity. That azecine (VII) could be derived by the C_{13}-N bond cleavage in corresponding berbine by specific reagents as reported by Nagata *et al.*[6] prompted us to undertake this work with a two fold aim; firstly, to test the applicability of our own new route (Pandey and Tiwari; unpublished results) for the synthesis of a berbine with a C_3-hydroxyl group and secondly to ascertain whether the final B.N. cyclisation of the lactam (IV) with $POCl_3$ proceeds smoothly to give 9,10-substituted berbine or a mixture of 9,10 and 10,11-berbine. Such isomeric mixtures often arise in the Mannich reaction[2] of the benzyltetrahydroisoquinolines which is a method of choice for the berbine synthesis. Also in this synthesis the presence of C_3-hydroxyl often changes the course of the reaction although the reason for this is still uncertain[2].

The present work thus describes an efficient synthesis of berbine (VI) from the easily available intermediate, which is an important precursor to the potentially analgetic protopine (VII) (Scheme 1).

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi spectrophotometer Model EPI-G$_3$. Mass spectra were recorded on a AEI MS 25 spectrometer at 70 eV.

7,8-Dimethoxy-3-isochromanone (I)

A mixture of 8-hydroxy-7-methoxy-3-isochromanone, (2·0 g), K_2CO_3 (1·0 g) and dimethyl sulphate (1·1 ml)
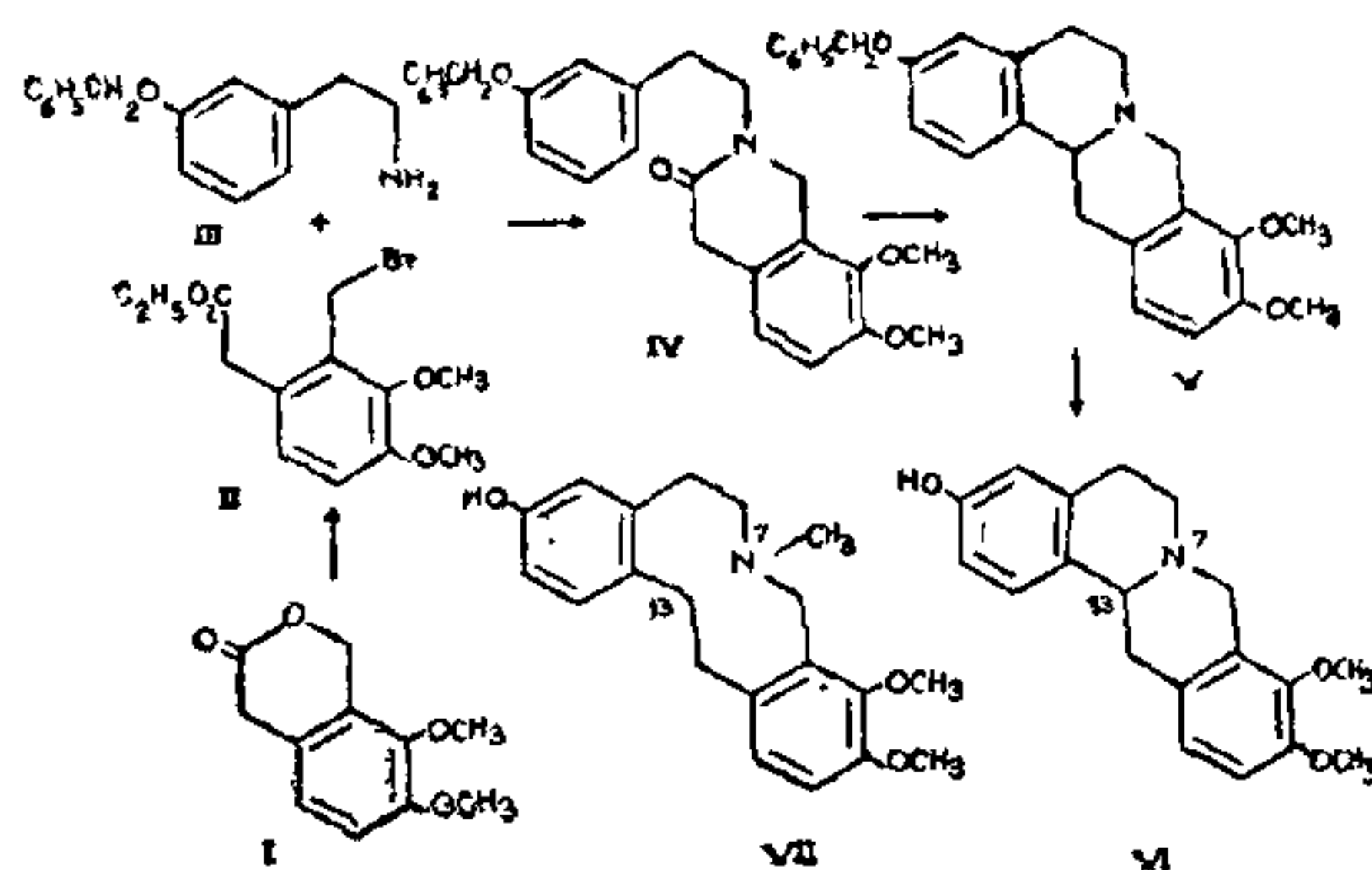
SCHEME 1

was refluxed for 3 hrs. After cooling the reaction mixture, water was added and the mixture extracted with CH_2Cl_2. The extract was washed well with water, dried (Na_2SO_4) and solvent removed *in vacuo* to get a crystalline residue, yield, 1·5 g (71·4%), m.p. 99° (lit.[6], 98–100°).

Ethyl 2-bromomethyl-3,4-dimethoxyphenyl acetate (II)

To a well stirred and cooled (0–2°) mixture of hydrobromic acid (0·68 ml) in ethanol (17·0 ml) under stirring was added the preceding isochromanone (I) (1·5 g) in portions. After the addition was complete, the mixture was removed from ice bath and allowed to reach room temperature and set aside for 24 hours. Solvent and excess hydrobromic acid were removed under vacuum at 20° C to afford the ester (II) as an oil. Yield, 2·0 g (90%); IR (CHCl$_3$) : 1720 cm^{-1}. It was used without further purification.

2-(3-Benzyloxy-β-phenethyl)-7,8-dimethoxy-3-isoquinolone (IV)

The bromo ester (II) (3·10 g) dissolved in DMF (12 ml) was added to 3-benzyloxy-β-phenethylamine (III) (2·20 g) in DMF (10 ml) containing Et$_3$ N (4·0 ml). The mixture was refluxed for 72 hrs. on a water bath. The cooled mixture was diluted with water, extracted with CHCl$_3$, washed with 20% HCl then with water and finally dried (Na$_2$SO$_4$). Removal of the solvent *in vacuo* left a syrupy residue, which could not be induced to crystallize in our hands, yield, 3·20 g (76%), IR (CHCl$_3$) : 1655 (6 membered lactam), 1600, 1460 cm^{-1}.

3-Benzyloxy-9,10-dimethoxyberbine (V)

Freshly distilled POCl$_3$ (0·7 ml) was added to a solution of the foregoing anhydrous lactam (2·0 g) in dry xylene (15·0 ml). The solution was then heated on a water bath for 1·5 hours. The residue left after evaporation of the reagent and solvent was treated with an excess of ice. The organic materials were extracted with CHCl$_3$ (40 ml) and the solvent removed *in vacuo* to yield a residue which was dissolved in MeOH (20 ml) and treated with NaBH$_4$ (100 mg)

in portions over a period of 20 minutes. The mixture was then refluxed for 1 hour. Evaporation of the solvent dilution with water and extraction with ether gave a gum which recrystallised from acetone-ether to give (V), yield 900 mg (64·0%), m.p. 150–152° (lit.[6], m.p. 150–155°). The compound (V) was identical in all respects with an authentic sample (m.m.p. IR, NMR).

3-*Hydroxy*-9,10-*dimethoxyberbine* (*VI*)

The foregoing benzyl ether (V) (620 mg) was mixed with ethanolic-HCl (7·0 ml) and the mixture was refluxed for 8 hours. Ice pieces (5 g) were added to the cooled mixture and it was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated to give the crystals of (VI), m.p. 172° (acetone), yield 310 mg (63%). (VI) was identical in all respecss with an authentic sample (m.m.p. IR).

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LEWIS ACID CHARACTER OF TETRAPHOSPHORUS TRISELENIDE (P_4Se_3)

THE ease of preparation of tetraphosphorus triselnide[1] has created some interest in its chemistry. As compared to tetraphosphorus tisulphide, very little is known about the nature of tetraphosphorus triselenide though it has a similar cage-like structure[2]. Penney and his coworkers[3] have reported a compound of iodine of composition $P_4Se_3I_2$ with it. No addition compound of bases with this molecule has been reported in literature. We report the isolation and characterisation of the adducts of organic tertiary bases with P_4Se_3.

Organic tertiary bases (B) such as pyridine, quinoline, α-picoline, piperidine, pyridine N-oxide give rise to P_4Se_3 . 2B while 1, 10-phenanthroline, N, N′-dioxide and 2, 2′-bipyridyl N, N′-dioxide form addition compounds of the composition P_4Se_3.B. Stoichiometric composition of these compounds has been established by elemental analysis which agrees with the calculated values within the limits of experimental errors. All these compounds are hygroscopic in nature. They change their colours and become liquids but are quite stable in dry air. They are insoluble in most of the polar organic solvents; therefore molecular weight and molar conductance values could not be determined.

Infrared spectra of these compounds especially in the low wave number region is very informative. The shift of electrons from nitrogen or oxygen of the base to the acceptor molecule results in the perturbation of their bands, identical to those observed in the complexes of these bases with metal halides[4] and acid halides[5,6] which are typical of the base coordination. The four principal bands between 1600–1430 cm^{-1} due to C=C and C=N stretching vibrations are shifted to higher frequencies in the complexes, P_4Se_3 . $2C_5H_5N$ and P_4Se_3 . $2C_6H_7N$. Absorption frequency in the region 1230–1430 cm^{-1} is considerably enhanced at 1388, 1328 and 1245 cm^{-1}. The strong band at 705 cm^{-1} (the out of plane C–H deformation) and the band at 748 cm^{-1} (the out of plane ring deformation), which are observed in the spectrum of pyridine, are shifted to 678 and 742 cm^{-1} respectively in these complexes. The ring vibrations at 405 and 605 cm^{-1} are shifted to 420 and 615 cm^{-1}. These shifts are characteristic of the coordination of pyridine through the nitrogen[4,7,8] which is supported by the formation of a new band at 500 cm^{-1} assigned to Se–N stretching mode[9].

In the case of the compound P_4Se_3 . BipyO$_2$, the NO bending vibrations at 840 and 852 cm^{-1} undergo a small negative shift due to the coordination on the NO group and the decrease in the double bond character[10]. The two NO stretching vibration in BipyO$_2$ shifts to lower frequency on coordination.