SYNTHESIS OF HETEROCYCLES *VIA* LACTONES

Synthesis of Some 12-Bromo Berbines

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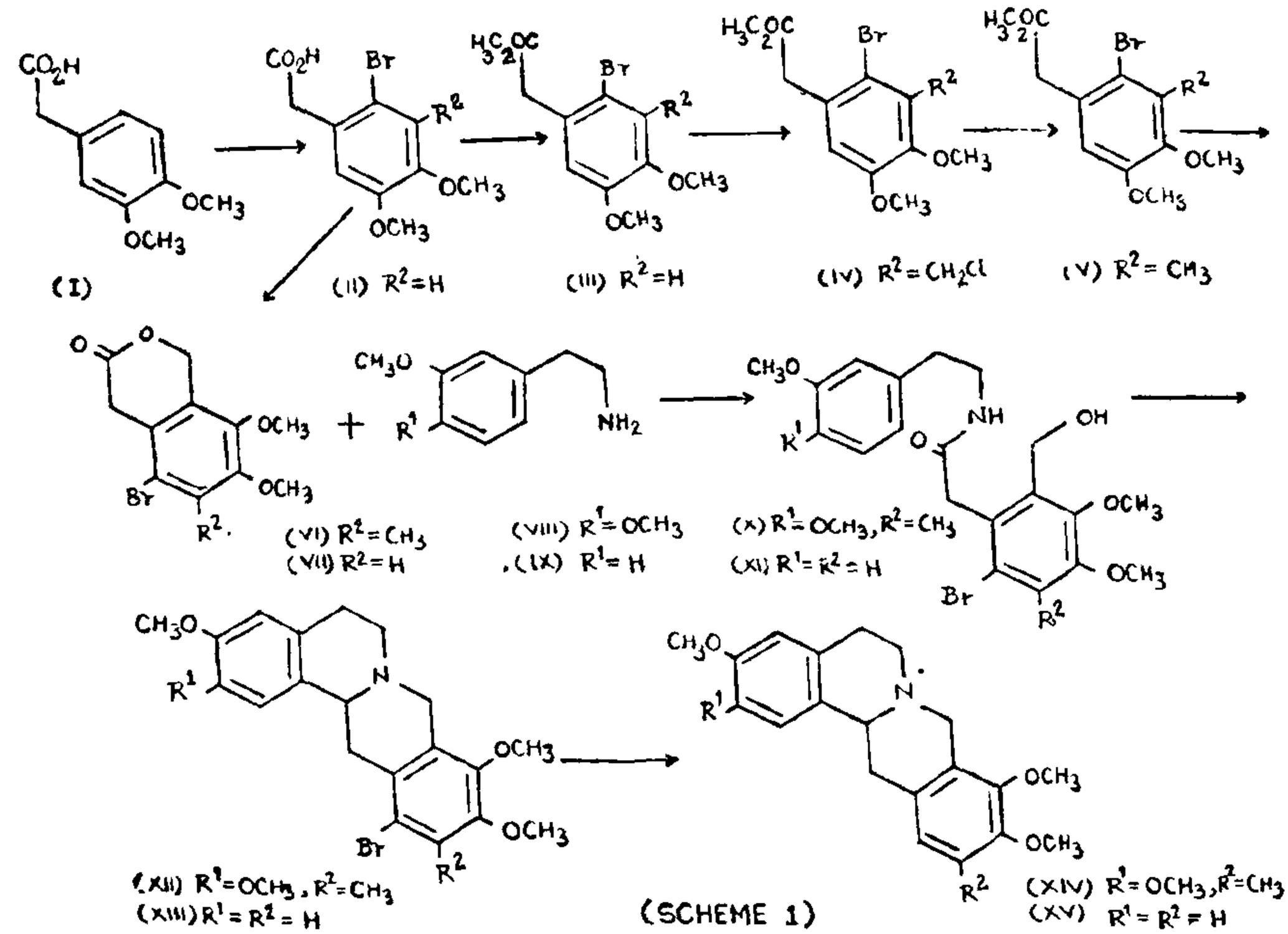
ABSTRACT

Earlier we reported a convenient synthesis of the berbine alkaloids starting from 3-isochromanones. Now, synthesis of some brominated berbines is being described usings lactonic intermediates. A convenient synthesis of brominated 3-isochromanones (VI) and (VII) has been described.

INTRODUCTION

BERBINES[1] comprise a large group of isoquinoline alkaloids of both natural and synthetic origin. Enormous work has been done in the past two decades on various aspects of the berbine chemistry[2], owing chiefly to the great biological activity[3] in this class of compounds. In the recent past our interest in the field of alkaloid synthesis has chiefly been focussed on berbines and some convenient syntheses have been achieved in our laboratory[4-7]. In the present paper we take opportunity to report the synthesis of some brominated berbines by 3-isochromanone[4-7] method (Scheme 1). Two convenient synthesis of the 3-isochromanones have been described (Scheme 1).



(SCHEME 1)

EXPERIMENTAL

General

All melting points are uncorrected and were recorded in open capillaries on a Toshniwal m.p. apparatus. IR spectra were recorded on a JASCO model IR S. Mass spectra were recorded on an Atlas AEI MS 902

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spectrometer at 70 eV. TLC was carried out on silica gel G (Merck). All the solutions were dried over anhydrous sodium sulphate.

2-Bromo-4,5-dimethoxyphenylacetic acid (II)

3,4-Dimethoxyphenylacetic acid (I) (1·96 g) was dissolved in glacial AcOH and mixture cooled to 0° in an ice bath. The solution was stirred and Br_2 (0·7 ml) added dropwise over a period of 15 minutes. After 30 minutes, water (10 ml) was added and mixture further stirred for 1·5 hrs. The precipiate was filtered washed with water and dried at 70° for 6 hrs. to afford the bromo acid (II) as fine threads, 2·54 g (92·3%); m.p. 105–106°; IR (KBr) 1700 cm^{-1}. (Found C, 43·52; H, 3·93; Br, 29·0, $C_{10}H_{11}O_4Br$ requires C, 43·63; H, 4·00; Br, 29·04%).

Methyl 2-bromo-4,5-dimethoxyphenylacetate (III)

The bromo acid (II) (2·0 g) was dissolved in MeOH (8·0 ml) and conc. HCl (1·0 ml) added. The solution was refluxed at 100° for 30 minutes. The solvent was removed *in vacuo* to give a syrup which was taken in $CHCl_3$ and washed well with water. Removal of solvent *in vacuo* afforded the methyl ester (III) which recrystallized from pet. ether to give (III), 1·65 g (78%); m.p. 66°; IR (Nujol) 1715 cm^{-1} (>C=O).

(Found C, 45·50; H, 4·4; O, 22·34; Br, 26·99, $C_{11}H_{13}O_4Br$ requires C, 45·67; H, 4·49; O, 22·14; Br, 27·68%).

Methyl 2-bromo-3-chloromethyl-4,5-dimethoxyphenylacetate (IV)

The bromo ester (III) (3·00 g) was dissolved in CH_2Cl_2 (12 ml) and 3·0 ml of the solvent distilled out. The solution was cooled and powdered $ZnCl_2$ (1·5 g) and chlorodimethyl ether (2·0 ml) added. The mixture was stirred at room temperature for 3 days, then filtered and solvent and excess reagent removed *in vacuo* to yield crude (IV). Recrystallization from methanol gave (IV), 2·10 g (60%); m.p. 65°.

(Found C, 42·50; H, 4·04; O, 18·5; Br, 23·35, $C_{12}H_{14}O_4BrCl$ requires C, 42·66; H, 4·14; O, 18·96; Br, 23·70%).

Methyl 2-bromo-3-methyl-4, 5-dimethoxyphenylaceatate (V)

The preceding ester (IV) (3·50 g) was taken in AcOH (15 ml) warmed to 80° and zinc powder (1·5 g) added in it over a period of one hr., the temperature being maintained at 80°. The solution was filtered and the filtrate diluted with an excess of water. The solution was extracted with $CHCl_3$, washed well with water, dried and solvent removed *in vacuo* to yield (V), 2·35 g (72%); m.p. 70°.

(Found C, 47·10; H, 9·80; O, 21·32; Br, 26·00; $C_{12}H_{15}O_4Br$ requires C, 47·52; H, 4·95; O, 21·12; Br, 26·40%).

5-Bromo-6-methyl-7, 8-dimethoxyisochroman-3-one (VI)

The ester (V) (2·50 g) was taken in CH_2Cl_2 (15 ml) and fused $ZnCl_2$ (1·2 g) and $ClCH_2 \cdot OCH_3$ (2·0 ml) added. The mixture was stirred for 96 hrs., poured into a mixture of water and CH_2Cl_2, washed alternately with water and aqueous NaOH (5%) to neutrality. To this solution, isopropyl alcohol (10 ml) and aqueous NaOH (10%) were added and mixture refluxed at 100° for 2 hrs. The solvent was then removed, HCl (2·0 ml) added and after one hr. excess water was added. Extraction with $CHCl_3$, washing with water, followed by drying and distillation gave the lactone (VI), 1·75 g (70·5%); m.p. 135–136° ($CHCl_3$); IR (KBr) 1740 (lactone), 1680, 1410, 730 cm^{-1}, mass spectrum m/e (rel. int.) 301 (M^+), 302 $(M+1)^+$, 256, 221 (M^+–Br).

(Found C, 47·80; H, 4·12; Br, 26·4, $C_{11}H_{11}O_4Br$ requires C, 47·84; H, 4·31; Br, 26·57%).

N-[β-(3,4-dimethoxyphenyl)] ethyl-2-(bromo-3-methyl-4, 5-dimethoxy-6-hydroxymethyl) phenylacetamide (X)

A solution of lactone (VI) (3·00 g) and 3,4-dimethoxy-β-phenethylamine (VII) (1·81 g) in abs. EtOH (20 ml) was refluxed with stirring for 24 hrs. The reaction was monitored by TLC (silica gel/CH_2Cl_2 : 97 : 3). After the EtOH has been removed *in vacuo* the resulting residue was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried. Evaporation of the solvent left a syrup which recrystallized from aqueous EtOH to give (X), 3·75 g (65·3%); m.p. 119°; IR (Nujol) 3420, 3330, 1660, 1600, 1580 cm^{-1}.

(Found C, 54·60; H, 5·60; N, 3·00; Br, 17·01, $C_{22}H_{28}NO_6Br$ requires C, 54·77; H, 5·80; N, 2·90 Br, 16·59%).

2, 3, 9, 10-Tetramethoxy-11-methyl-12-bromoberbine (XII)

The phenylacetamide (X) (3·00 g) in $POCl_3$ (5·0 ml) was refluxed at 100° for one hr. Removal of excess reagent left a dry residue which was diluted with ice cold water. The mixture was extracted with $CHCl_3$ and solvent removed. The residue obtained was taken in MeOH and reduced with $NaBH_4$ over a period of 30 minutes with stirring. Usual work up gave the berbine (XII), 2·20 g (75%).

(Found: C, 59·0; H, 5·71; N, 3·00; Br, 17·10, $C_{22}H_{26}NO_4Br$ requires C, 58·92; H, 5·80; N, 3·12 Br, 17·85%).

2, 3, 9, 10, 11-Tetramethoxy-11-methylberbine (XIV)

The above berbine (XII) (250 mg) was taken in THF (10·0 ml) at 0° in an ice bath and LAH (600 mg) added in portions. The mixture was refluxed at 100° for 10 hrs., cooled and excess reagent destroyed by addition of moist EtOAc. The gel which formed was separated and mixture extracted with EtOAc. The

organic layer was washed (water), dried and distilled to afford the berbine (XIV), 220 mg (73%), m.p. 141°.

(Found C, 70·9; H, 7·00; N, 3·56, $C_{22}H_{27}NO_4$ requires C, 71·54; H, 7·31; N, 3·79%).

5-Bromo-7, 8-dimethoxyisochroman-3-one (VII)

A mixture of the bromo acid (II) (2·75 g), dissolved in glacial AcOH (10·0 ml) mixed with 37% formaldehyde (2·0 ml) and concd. HCl (1·0 ml) was refluxed on a water bath for 4 hrs. After cooling the reaction mixture was diluted with an excess of water and exhaustively extracted with $CHCl_3$. The organic layer was washed with 10% $NaHCO_3$ till neutrality, H_2O dried and distilled to leave a syrup which was kept in refrigerator at 10° for 15 minutes and then in air to yield the desired 3-isochromanone (VII), 2·15 g (75%); m.p. 185–90°; IR (Nujol) 1740 (lactone) cm^{-1}.

(Found C, 46·0; H, 3·72; Br, 27·61, $C_{11}H_{11}O_4$ Br requires C, 45·99; H, 3·83; Br, 27·87%).

The lactone (VII) dissolves in NaOH solution and is reprecipitated on acidification.

N-[β-(3-methoxyphenyl)] ethyl-2-(bromo-4,5-dimethoxy-6-hydroxymethyl) phenylacetamide (XI)

A solution of the lactone (VII) (280 mg) and the 3-methoxy-β-phenethylamine (IX) (150 mg) in EtOH was refluxed at 100° for 70 hrs. work up as for the compound (X) afforded the phenylacetamide (XI), 370 mg (85%); m.p. 135–137° (Iso-PrOH–EtOAc); IR (KBr) 3435, 3327, 1670, 1595, 1540 cm^{-1}).

(Found: C, 54·3; H, 5·4; N, 3·08; Br, 18·1, $C_{20}O_{24}O_5N$ Br requires C, 54·79; H, 5·47; N, 3·19; Br, 18·26%).

3, 9, 10-Trimethoxy-12-bromo berbine (XIII)

The foregoing phenylacetamide (XI) (200 mg) was dissolved in dry benzene and $POCl_3$ (2·0 ml) added. The solution was refluxed for 3 hrs. at 100°. Work up as for the compound (XIV) gave the bromo berbine (XIII), 140 mg (76%); m.p. 142° (aqueous EtOH).

(Found C, 60·0; H, 5·39; N, 3·40; Br, 19·11, $C_{20}H_{22}NO_3$ Br requires C, 59·40; H, 5·44; N, 3·46; Br, 19·80%).

3, 9, 10-Trimethoxyberbine (XV)

The bromo berbine (XIII) (170 mg) was dissolved in THF (5 ml) and LAH (230 mg) added with stirring. The mixture was refluxed for 8 hrs. usual work up as for the compound (XIV) gave (XV), 110 mg (79%); m.p. 127·5–129·5°.

(Found C, 73·5; H, 7·00; N, 4·22, $C_{20}H_{23}NO_3$ requires C, 73·84; N, 7·07; N, 4·30%).

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