Studies on the Syntheses of Heterocyclic Compounds. Part CCCXXX (1) Synthesis of a Homocularine Type Compound.

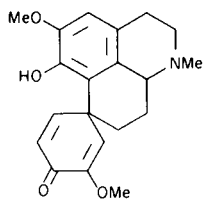
T. Kametani (2) and T. Terui

Pharmaceutical Institute, Tohoku University

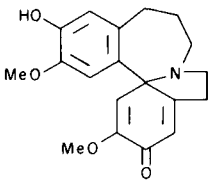
An intramolecular Ullmann reaction of bromophenethylisoquinoline (X) was investigated in order to obtain the homocularine type compound (V), which could be one of the potential alkaloids belonging to 1-phenethylisoquinoline series. Methylation of the phenolic 8-hydroxyisoquinoline (XVIII), one of the position isomers which was separated by silica gel chromatography from a mixture of 6-hydroxy- (XVII) and 8-hydroxyisoquinoline (XVIII) prepared as usual, gave the starting material (X), which was cyclized by the Ullmann reaction in the presence of cupric oxide. The structure of our objective homocularine (V) was assigned from spectral data.

In the previous papers (3,4,5), we reported the syntheses of homoaporphines (I), homoerythrinadienones (II) and homoprotoberberines (III) which were assumed to be potential alkaloids. This assumption was supported partially by the isolation of the naturally-occurring alkaloids, kreysiginone (I) (6) and schelhammerine (IV) (7). In this paper, we report a synthesis of homocularine type compound (V) (8) by an intermolecular Ullmann reaction (9), which would be also one of the potential alkaloids belonging to the 1-phenethylisoquinoline series.

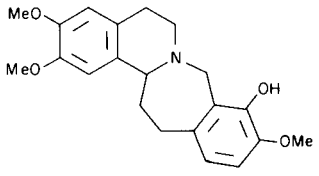
CHART 1



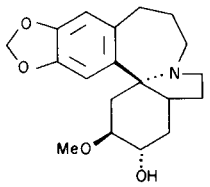
I



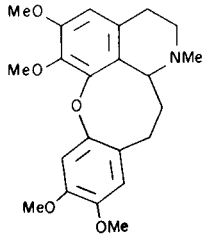
II



III



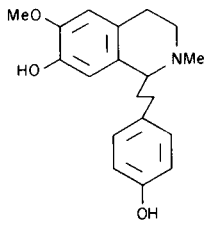
IV



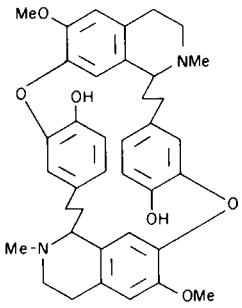
V

Melanthioidine, an alkaloid from *Androcymbium melanthioides*, was assigned to the bisphenethylisoquinoline (VI) by Battersby (10), which would be biosynthesized with intermolecular C–O phenolic oxidation of 1-phenethylisoquinoline (VII). On the other hand, the biogenesis of the cularine (VIII) (11) and curine (IX) (12) belonging to 1-benzylisoquinoline alkaloids has been assumed to be due to intra- or intermolecular C–O phenolic oxidation of reticuline or its biogenetic equivalent. Since the cularine (VIII) in the 1-benzylisoquinoline series has been found in nature, the presence of the homocularine (V) as one of the potential alkaloids in the 1-phenethylisoquinoline series seems to be reasonable and would be found in the plants in the future.

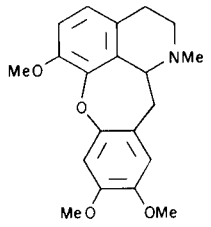
CHART 2



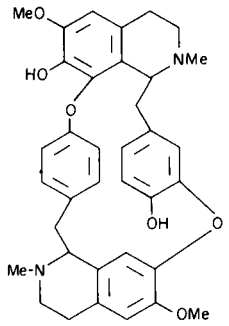
VII



VI

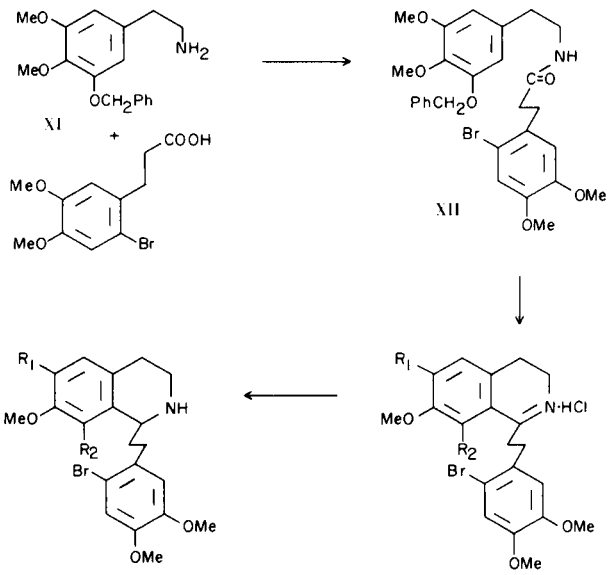


VIII



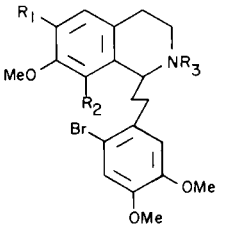
IX

CHART 3



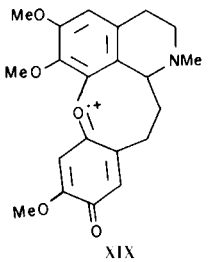
XV: R_1 = OCH_2Ph, R_2 = OMe
XVI: R_1 = OMe, R_2 = OCH_2Ph

XIII: R_1 = OCH_2Ph, R_2 = OMe
XIV: R_1 = OMe, R_2 = OCH_2Ph

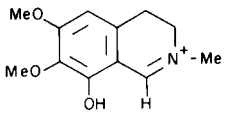


XVII: R_1 = OH, R_2 = OMe, R_3 = H
XVIII: R_1 = OMe, R_2 = OH, R_3 = H
X: R_1 = OMe, R_2 = OH, R_3 = Me

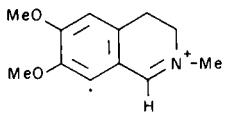
CHART 4



XIX
m/e 370 (M^+-15)



XX
m/e 222 (M^+-163)



XXI
m/e 205 (M^+-180)

The starting phenolic bromophenethylisoquinoline (X) was synthesized by the usual method. Fusion of 3-benzyloxy-4,5-dimethoxyphenethylamine (XI) with 2-bromo-4,5-dimethoxyphenylpropionic acid afforded the corresponding amide (XII), which was subjected to Bischler-Napieralski reaction. A mixture of the resulting 3,4-dihydroisoquinoline hydrochlorides (XIII and XIV) was, without separation and purification, reduced with sodium borohydride to give a mixture of 1,2,3,4-tetrahydroisoquinolines (XV and XVI). Debenzylation of these products with concentrated hydrochloric acid in ethanol afforded a mixture of phenolic isoquinolines (XVII and XVIII), which were separated by silica gel chromatography using chloroform as an eluant; one of them was characterized as its hydrochloride, m.p. 212-213°, and its nmr spectrum (ppm in deuteriochloroform) showed the following important signals at 3.82 (2 x OCH_3), 3.83 (2 x OCH_3), 6.22 (C_5–H), 6.85 (C_6'–H) and 7.01 (C_3'–H) as singlets. The other compound was obtained as a viscous syrup, whose nmr spectrum showed the following resonances at 3.72, 3.76, 3.80 (4 x OCH_3) as singlest, 6.32 (C_5–H), 6.78 (C_6'–H) and 6.90 (C_3'–H) as singlets.

In general, the chemical shift of the C_5-proton of 1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxyisoquinoline is known to resonate at a higher field than that of the 6-hydroxy-7,8-dimethoxy isomer (9,13). Therefore, the former compound was assigned to 1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxyisoquinoline (XVIII) and the latter to 6-hydroxy-7,8-dimethoxy isomer (XVII). Methylation of the isoquinoline (XVIII) with the modified Eschweiler-Clarke reaction gave the starting phenolic bromophenethylisoquinoline (X).

The Ullmann reaction of the above isoquinoline (X) by using cupric oxide in the presence of dry pyridine and anhydrous potassium carbonate at 160-170° for 10 hours with stirring in a current of nitrogen gave the nonphenolic isoquinoline showing a negative Beilstein test, in low yield, after purification by silica gel chromatography. This compound was assigned to the homocularine type compound (V) by the following spectral data; the mass spectrum

showed the typical pattern of cularine type compound (14) at m/e 370 (M^+ -15, XIX), 222 (M^+ -163, XX) and 205 (M^+ -180, XXI) in addition to the molecular ion (M^+ 385), and the nmr spectrum (ppm in deuteriochloroform) showed the following resonances 2.63 ($N-CH_3$), 3.87 (2 x OCH_3) and 3.90 (2 x OCH_3) as singlets, 6.57 (two aromatic protons) and 7.18 (aromatic proton) as singlets.

EXPERIMENTAL

Melting points were not corrected. Infrared spectra were measured in chloroform solution.

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-β-(2-bromo-4,5-dimethoxyphenyl)propionamide (XII).

A mixture of 8.0 g. of 5-benzyloxy-3,4-dimethoxyphenethylamine (XI) and 8.4 g. of 2-bromo-4,5-dimethoxyphenylpropionic acid was heated at 180° for 3 hours in a current of nitrogen. After cooling at room temperature, the reaction mixture was recrystallized from benzene-hexane to give 10 g. of the amide (XII) as colorless needles, m.p. 93-95°. The amide showed NH absorption at 3375 cm^{-1} and CO absorption at 1660 cm^{-1} in the infrared.

Anal. Calcd. for $C_{28}H_{32}BrNO_6$: C, 60.21; H, 5.78; N, 2.51. Found: C, 60.23; H, 5.86; N, 2.98.

A Mixture of 6-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-7,8-dimethoxyisoquinoline (XIII) and 8-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (XIV).

A mixture of 10 g. of the amide (XII), 12 g. of phosphoryl chloride and 200 ml. of dry benzene was refluxed for 2.5 hours and the reaction mixture was poured into 500 ml. of cold *n*-hexane. After being allowed to stand overnight, the upper layer was removed by decantation. The resulting residue was washed repeatedly with *n*-hexane and dissolved in chloroform. This solution was washed with water, dried over sodium sulfate and evaporated to give 12.8 g. of a mixture of 3,4-dihydroisoquinoline hydrochlorides (XIII and XIV) as a pale yellow viscous syrup, whose separation was so difficult that it was used in the following reaction without purification.

One part of the above pale yellow viscous syrup was treated with 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give a syrup, whose picrolonate was recrystallized from acetone-ethanol to give yellow needles, m.p. 157-158°. It showed C=N absorption at 1640 cm^{-1} in the infrared region.

Anal. Calcd. for $C_{38}H_{38}BrN_5O_{10}\cdot H_2O$: C, 55.48; H, 4.9. Found: C, 55.67; H, 4.43.

A Mixture of 6-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline (XV) and 8-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline (XVI).

To a stirred mixture of 12 g. of the above 3,4-dihydroisoquinoline (XV and XVI) and 400 ml. of methanol was added portionwise 12 g. of sodium borohydride under cooling within 30 minutes, and the reaction mixture was heated under reflux for 1 hour. After the solvent had been distilled off, the residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 8.0 g. of a mixture of 1,2,3,4-tetrahydroisoquinolines (XV and XVI) as a brown viscous syrup, which could not be purified and therefore was used in the following reaction without purification.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxyisoquinoline (XVIII).

A mixture of 8.0 g. of the above 1,2,3,4-tetrahydroisoquinolines (XV and XVI), 80 ml. of ethanol and 80 ml. of concentrated hydrochloric acid was refluxed for 4 hours. After removal of ethanol and hydrochloric acid by distillation, the residue was washed with *n*-hexane. This residue was made basic by ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give 5.8 g. of a mixture of 1,2,3,4-tetrahydroisoquinolines as a brown viscous syrup, which was separated by chromatography on 160 g. of silica gel using chloroform as an eluant. The residue of the appropriate fraction was converted into its hydrochloride, which was recrystallized from methanol-ether to give 1.6 g. of 1-phenethylisoquinoline (XVIII) hydrochloride as colorless needles, m.p. 212-213°. The nmr spectrum (ppm in deuteriochloroform) showed an 8 proton multiplet at 1.95-3.5 corresponding to the methylene protons, (12H) at 3.82, 3.83 attributable to the 4 methoxy groups, a 1 proton singlet at 6.22 for the C_5, a 1 proton singlet at 6.85 for the $C_{6'}$ and a 1 proton singlet at 7.01 for the $C_{3'}$.

Anal. Calcd. for $C_{21}H_{27}ClBrNO_5\cdot\frac{1}{4}H_2O$: C, 51.13; H, 5.62; N, 2.84. Found: C, 51.07; H, 5.66; N, 2.61.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxy-2-methylisoquinoline (X).

A mixture of 1.6 g. of the above isoquinoline derivative (XVIII) 16 ml. of 37% formalin and 240 ml. of methanol was refluxed for 40 minutes. After cooling at room temperature, 26 g. of sodium borohydride was added in small portions to the reaction mixture under cooling within 1 hour, and the resulting mixture was heated under reflux for 30 minutes. After removal of the solvent, the residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 1.2 g. of a brown viscous syrup, which was purified by chromatography on 30 g. of silica gel using chloroform-methanol (99.5-0.5) as an eluant. Evaporation of the appropriate fraction gave a syrup, which was converted into its hydrochloride. Recrystallization from methanol-ether afforded 690 mg. of colorless needles, m.p. 214-215°. The nmr spectrum of the free base (X) (ppm in deuteriochloroform) showed a 3 proton singlet at 2.45 due to the *N*-methyl group, two singlets (12H) at 3.79, 3.80 corresponding to the 4 methoxy groups, a 1 proton singlet at 6.17 for the C_5 proton, a 1 proton singlet at 6.77 for the $C_{6'}$ proton and a 1 proton singlet at 6.93 for the $C_{3'}$ proton.

Anal. Calcd. for $C_{22}H_{29}BrClNO_5$: C, 52.55; H, 5.84; N, 2.80. Found: C, 52.61; H, 6.00; N, 2.69.

2,3,12,13,13*b*-Pentahydro-5,6,9,10-tetramethoxy-1-methyl-4*H*-[1]-benzoxocino[2,3,4-*i,j*]isoquinoline (V).

A mixture of 600 mg. of the above 1,2,3,4-tetrahydroisoquinoline derivative (X), 20 mg. of dry pyridine, 1 g. of anhydrous potassium carbonate and 300 mg. of cupric oxide was heated at 160-170° with stirring for 10 hours in a current of nitrogen. After the reaction mixture had been filtered, the filtrate was concentrated to dryness and the resulting residue was subjected to silica gel (25 g.) chromatography. Evaporation of the chloroform-methanol (96:4) belonging to fraction F_{10}–F_{13} (25 ml. each) gave 25 mg. of a brown syrup, which was again chromatographed on 25 g. of silica gel. Evaporation of the chloroform-methanol

(97.5:2.5) from the fractions F_{52}–F_{57} (25 ml. each) afforded 10 mg. of a homocularine type compound (V) as a yellow viscous syrup, whose Beilstein test was negative. Its tlc showed one spot [chloroform-methanol = 8.5:1.5; silica gel] which was detected by iodine. The OH absorption disappeared in the infrared (chloroform). The mass spectrum showed the typical patterns characteristic to the cularine derivatives at m/e 370 (M^+ -15, XIX) 222 (M^+ -163, XX) and 203 (M^+ -180, XXI) in addition to the molecular ion (M^+ 385), and the nmr spectrum (ppm in deuteriochloroform) showed the following resonances, a 3 proton singlet at 2.63 attributable to the *N*-methyl group, two singlets (12H) at 3.87, 3.90 due to 4 methoxy groups, and 3 aromatic protons at 6.57 (2H) and 7.18 (1H) as singlets.

Acknowledgment.

We thank Dr. Keiichiro Fukumoto, Pharmaceutical Institute, Tohoku University for his assistance. We also thank Misses T. Yoshida, K. Shima, R. Kato, R. Hasebe, A. Kawakami, and Y. Tadano for the spectral measurements and microanalyses.

REFERENCES

(1) Part CCCXXIX: *J. Heterocyclic Chem.*, 7, 51 (1970).

(2) Communications concerning this paper should be directed to Professor Tetsuji Kametani.

(3) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *Chem. Commun.*, 878 (1967); *J. Org. Chem.*, 33, 690 (1968).

(4) T. Kametani and K. Fukumoto, *Chem. Commun.*, 26 (1968); *J. Chem. Soc. (C)*, 2156 (1968).

(5) T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *ibid.*, 874 (1969).

(6) A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 934 (1967).

(7) S. R. Gohns, C. Kowala, J. A. Lamberton, A. A. Sioumis, and G. A. Wunderlich, *ibid.*, 1102 (1968).

(8) T. Kametani, T. Sugahara, and K. Fukumoto, *Yakugaku Zasshi*, 89, 610 (1969).

(9) T. Kametani, H. Iida, T. Kikuchi, M. Mizushima, and K. Fukumoto, *Chem. Pharm. Bull. (Tokyo)*, 17, 709 (1969).

(10) A. R. Battersby, R. B. Herbert, E. Mo, and F. Santavy, *J. Chem. Soc. (C)*, 1739 (1967).

(11) R. H. F. Manske, *J. Am. Chem. Soc.*, 72, 55 (1950).

(12) G. W. Milne and G. R. Plimmer, *J. Chem. Soc. (C)*, 1966 (1966).

(13) T. Kametani and T. Kikuchi, *Chem. Pharm. Bull. (Tokyo)*, 15, 879 (1967).

(14) T. Kametani, S. Shibuya, and S. Sasaki, *Tetrahedron Letters*, 3215 (1966).

Received September 15, 1969 Aobayama, Sendai, Japan