Studies on the Syntheses of Heterocyclic Compounds. Part CDXCVII (1). Total Syntheses of (±)-Cryptaustoline and (±)-Thaliporphine by the Benzyne Reaction

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The indisputable benzyne reaction of 1-(5-bromo-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (II) with sodium amide in liquid ammonia afforded the following compounds, (±)-cryptaustoline iodide (VI), (±)-thaliporphine (VIII), 1-(3,4-dimethoxybenzyl)- (III), and 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (IV).

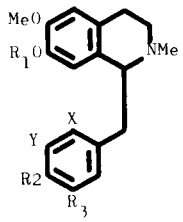
The aporphine system has usually been synthesized from the diazotized aminoisoquinolines by the Pschorr reaction (3), the yield from which is quite low. Some modified methods have been reported by the present authors (4) and Ishiwata (5). The former method (4) was carried out by a photolytic decomposition of the diazonium salt derived from 1-(2-aminobenzyl)isoquinolines and in the latter case (5) the 8-aminoisoquinolines were used as the starting materials. Phenolic oxidation (6) was also applied to the synthesis of this type of compounds (7), but the yield in this method was also very poor. Recently, Kesser (8) and Kametani (9) reported the synthesis of the phenolic aporphine VII by treatment of the phenolic 2′-bromoisoquinoline I with sodium amide and proposed the benzyne mechanism for this type of reaction without direct evidence.

In order to prove the formation of phenolic aporphine by the benzyne reaction, we investigated the reaction of the phenolic 5′-bromoisoquinoline II with sodium amide in liquid ammonia to give thaliporphine as an aporphine alkaloid and cryptaustoline as a dibenzopyrrocoline alkaloid. Hereby we wish to report these results.

The phenolic 5′-bromoisoquinoline II was synthesized as follows. The reaction of the amine IX with the carboxylic acid X afforded the amide XI, the cyclization of which with phosphoryl chloride gave the corresponding 3,4-dihydroisoquinoline XII. Treatment of XII with methyl iodide, followed by the reduction of the methiodide XIII, afforded the tetrahydroisoquinoline XIV, the debenzylation of which gave the phenolic bromoisoquinoline II.

The benzyne reaction of the phenolic bromoisoquinoline II with sodium amide in liquid ammonia was carried out to afford four products together with other

Scheme I



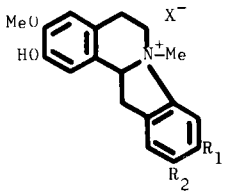
I : R_1=Y=H, R_2R_3=OCH_2O, X=Br

II : R_1=X=H, R_2=R_3=OMe, Y=Br

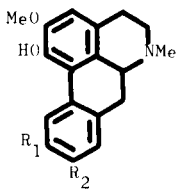
III : R_1=X=Y=H, R_2=R_3=OMe

IV : R_1=Y=H, R_2=R_3=OMe, X=NH_2

V : R_1=Ac, R_2=R_3=OMe, X=NHAc, Y=H



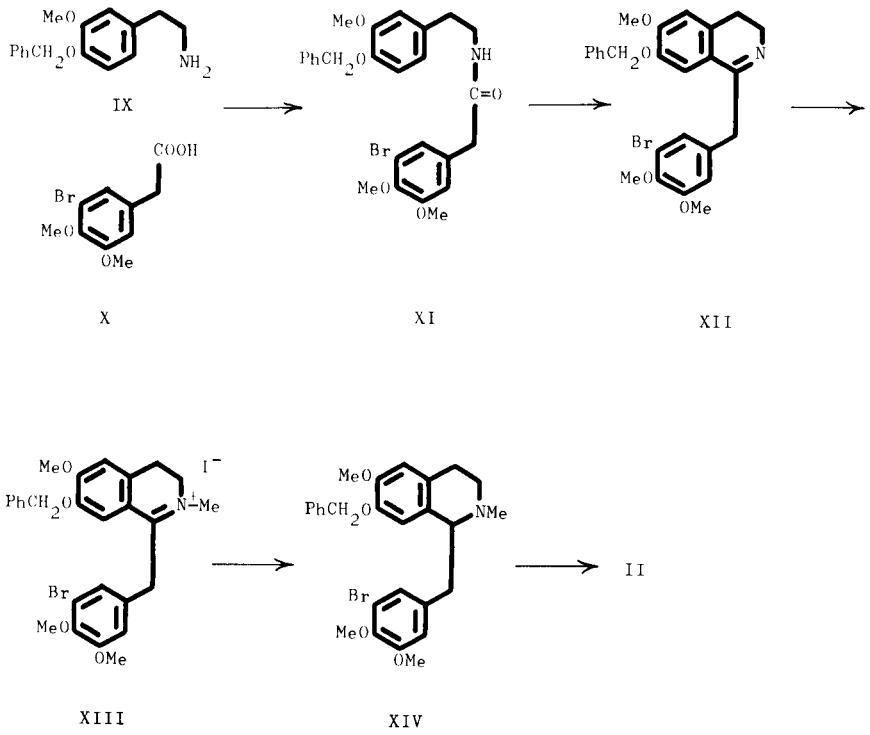
VI : R_1=R_2=OMe, X=I



VII : R_1R_2=OCH_2O

VIII : R_1=R_2=OMe

Scheme 2



unidentified materials which were separated by column chromatography.

The first compound obtained on silica gel column chromatography revealed the molecular formula $C_{20}H_{23}NO_4$ by microanalysis and mass spectrum (M^+, m/e 341), which showed the uv spectrum [λ max (ethanol) 305, 280, and 220 nm (log ε 4.12, 4.12, and 4.52)], characteristic of a 1,2,9,10-tetrasubstituted aporphine (10). The mass spectrum showed a typical aporphine type fragmentation pattern (11) at m/e $M^+ - 1$, $M^+ - 2$, $M^+ - 15$, $M^+ - 31$, and $M^+ - 43$. The nmr spectrum (deuteriochloroform) (τ) revealed an aromatic proton at 1.98 (C-11) (12) in addition to two aromatic protons (3.26 and 3.50) and four methyl resonances. These data were superimposable on those of (±)-thaliporphine (VIII) reported by Shamma (12,13).

The second compound III on column chromatography was obtained as a pale yellow viscous oil, which was characterized as its methiodide, $C_{21}H_{28}INO_4$. The nmr spectrum (τ) of the second compound III revealed four methyl resonances at 7.53, 6.26, 6.20 (6H) and five aromatic protons at 3.62, 3.50, 3.43 (d, J = 2.5 Hz), and 3.32 (2H). This material III was identical with the compound obtained by the debromination of II in ir and nmr spectra.

The third compound on chromatography was proved to be the 1-(2-aminobenzyl)isoquinoline derivative IV, microanalysis of which showed the molecular formula $C_{20}H_{26}N_2O_4$. The nmr spectrum (τ) revealed four methyl resonances at 7.48, 6.37, 6.25, and 6.23 and four aromatic protons at 3.76, 3.73, 3.60, and 3.54, and three protons of the hydroxy and amino groups were shown at 4.74. The acetylation of IV gave the corresponding amide V.

After extraction of the above compounds with chloroform, evaporation of the resulting aqueous solution, followed by treatment with potassium iodide, gave the (±)-cryptaustoline iodide (VI) as the fourth compound, the structure of which was proved as follows. The nmr spectrum (τ) revealed four methyl resonances at 6.50 (NMe), 6.22 (2 x OMe), and 6.16 (OMe) and four aromatic protons at 3.27, 3.19, 2.93, and 2.45. Furthermore, a methine proton was observed as a triplet with a center at 4.70. This fact indicated the fourth compound to be a quaternary ammonium salt of a dibenzopyrrocoline type compound. The mass spectrum of the above iodide

showed the same fragmentation pattern (15) as (±)-cryptaustoline iodide (VI) at m/e 327 [M^+ - 142 (Mel)] and 325 (M^+ - Mel - 2). Moreover, the above iodide VI was proved to be identical with an authentic sample (16) by mixed melting point and comparisons of their ir spectra.

Regarding the formation of the dibenzopyrrocoline alkaloid by the benzyne reaction, Gibson (17) presumed the presence of the indolizinium ion as possible intermediate, the result of which, however, was not confirmed completely. Thus, we have succeeded in accomplishing simple syntheses of (±)-cryptaustoline iodide and (±)-thaliporphine *via* the benzyne reaction.

EXPERIMENTAL

Ir spectra were measured with a Hitachi EPI-3 recording spectrophotometer, uv spectra with a Hitachi recording spectrophotometer, and nmr spectra with a Hitachi H-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were taken with a Hitachi RMU-7 mass spectrophotometer at 80 eV.

N-(4-Benzyloxy-3-methoxyphenethyl)-5-bromo-3,4-dimethoxyphenylacetamide (XI).

A mixture of 27.3 g. of 4-benzyloxy-3-methoxyphenethylamine (IX) and 31.5 g. of 5-bromo-3,4-dimethoxyphenylacetic acid (X) was heated at 190° for 1.5 hours. After cooling, the mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to afford 32.5 g. of the amide XI as colorless needles, m.p. 131.5-132.5° (from ethanol); ir ν max (chloroform) cm^{-1}: 3380 (NH), 1660 (C=O); nmr (deuteriochloroform) τ: 7.30 (2H, t, J = 7.5 Hz, CH_2CH_2NH) 6.60 (2H, t, J = 7.5 Hz, CH_2CH_2NHCO), 6.60 (2H, s, CH_2CONH), 6.20 (3H, s, OCH_3), 6.16 (6H, s, 2 x OCH_3), 4.78 (2H, s, $C_6H_5CH_2O$), 4.35 br (1H, NH), 3.53 (1H, d, d, J = 2.5 Hz, J = 7.5 Hz, ArH), 3.35 (1H, d, J = 2.5 Hz, ArH), 3.20 (1H, d, J = 7.5 Hz, ArH), 3.04 (1H, d, J = 2.5 Hz, ArH), 2.73 (1H, d, J = 2.5 Hz, ArH), 2.60 br (5H, $C_6H_5CH_2O$).

Anal. Calcd. for $C_{26}H_{28}BrNO_5$: C, 60.73; H, 5.49; N, 2.75. Found : C, 60.54; H, 5.52; N, 2.68.

7-Benzyloxy-1-(5-bromo-3,4-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (XII).

A mixture of 30 g. of the amide XI, 30 ml. of phosphoryl chloride, and 450 ml. of dry benzene was refluxed for 1 hour. After removal of the solvent, the resulting residue was washed with *n*-hexane to afford a brown viscous oil, which was recrystallized from methanol to give 25.2 g. of the hydrochloride of the benzylisoquinoline XII as colorless needles, m.p. 206-208°; ir ν max (chloroform) cm^{-1}: 1645 ($\overset{+}{>}C=N-$).

Anal. Calcd. for $C_{26}H_{26}BrNO_4 \cdot HCl$: C, 58.61; H, 5.11; N, 2.63. Found : C, 58.58; H, 5.08; N, 2.52.

7-Benzyloxy-1-(5-bromo-3,4-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (XIII).

A mixture of the 3,4-dihydroisoquinoline XII (prepared from 20 g. of the above hydrochloride), 100 ml. of methyl iodide and 100 ml. of methanol was refluxed for 2 hours, and then the mixture was set aside overnight at room temperature. The solvent was evaporated to a volume of about 40 ml. After cooling, the precipitate was collected to afford 21 g. of the methiodide XIII as yellow needles (from methanol), m.p. 216-218°; ir ν max (potassium bromide) cm^{-1}: 1625 ($\overset{+}{>}C=N-$).

Anal. Calcd. for $C_{26}H_{26}BrNO_4 \cdot CH_3I$: C, 50.80; H, 4.58; N, 2.19. Found: C, 50.54; H, 4.49; N, 2.08.

7-Benzyloxy-1-(5-bromo-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XIV).

To a stirred suspension of 20 g. of the methiodide XIII in methanol was added in small portions 20 g. of sodium borohydride during 1.5 hours at 0-5°. After the stirring had been continued overnight at room temperature, the solvent was evaporated and the resulting residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to afford 17.6 g. of the tetrahydroisoquinoline XIV as a pale orange viscous oil, nmr (deuteriochloroform) τ : 7.52 (3H, s, NCH_3), 6.30 (3H, s, OCH_3), 6.22 (3H, s, OCH_3), 6.18 (3H, s, OCH_3), 5.13 (2H, s, $C_6H_5CH_2O$), 3.80 (1H, s, ArH), 3.54 (1H, d, J = 2.5 Hz, 2′ - H), 3.45 (1H, s, ArH), 3.16 (1H, d, J = 2.5 Hz, 6′ - H), 2.71 (5H, s, $C_6H_5CH_2O$).

1-(5-Bromo-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (II).

A mixture of 10.2 g. of the preceding isoquinoline XIV, 100 ml. of concentrated hydrochloric acid and 100 ml. of ethanol was refluxed for 1 hour. The solvent was evaporated, and the remaining residue was made basic with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 6.7 g. of the phenolic 1,2,3,4-tetrahydroisoquinoline II as a pale yellow solid, which was crystallized as the methiodide, m.p. 195-197° (from ethanol); ir ν max (chloroform) cm^{-1}: 3455 (OH); nmr (deuteriochloroform) τ (free base): 7.53 (3H, s, NCH_3), 6.27 (3H, s, OCH_3), 6.19 (3H, s, OCH_3), 6.18 (3H, s, OCH_3), 3.56 (1H, s, ArH), 3.50 (1H, s, ArH), 3.48 (1H, d, J = 2.5 Hz, 2′ - H), 3.07 (1H, d, J = 2.5 Hz, 6′ - H).

Anal. Calcd. for $C_{20}H_{24}BrNO_4 \cdot CH_3I$: C, 44.70; H, 4.82; N, 2.48. Found: C, 44.31; H, 5.10; N, 2.18.

To a stirred solution of sodium amide (prepared from 1.75 g. of sodium metal in 300 ml. of liquid ammonia) was added a suspension of 3 g. of the phenolic bromoisoquinoline II in 30 ml. of dry tetrahydrofuran. Stirring was continued for 2 hours and the excess of sodium amide was then decomposed with 6 g. of crystalline ammonium chloride. The reaction mixture was diluted with 300 ml. of water. The precipitate, separated from the aqueous solution (A) by filtration, was extracted with chloroform (B). The above aqueous solution (A) was washed with 50 ml. of chloroform, which was combined with the above extract (B). The above solution (A) was acidified with concentrated hydrochloric acid and evaporated *in vacuo*. The resulting residue was extracted with ethanol. The ethanolic extract was evaporated to leave a residue, which was again extracted with ethanol. The brown solid (200 mg.) which was obtained by the evaporation of the solvent was treated with potassium iodide in water at room temperature to yield a precipitate. Recrystallization from ethanol afforded 100 mg. of (±)-cryptaustoline iodide (VI) as pale yellow prisms, m.p. 259-260° [lit. (15), m.p. 260° dec.], which was identified by the mixed m.p. and ir spectral comparison; nmr (deuteriodimethylsulfoxide) τ : 6.50 (3H, s, NCH_3), 6.22 (6H, s, 2 x OCH_3), 6.16 (3H, s, OCH_3), 4.70 (1H, t, J = 9 Hz, 12a - H), 3.27 (1H, s, ArH), 3.19 (1H, s, ArH), 2.93 (1H, s, ArH), 2.45 (1H, s, 8 - H). Mass m/e (16) : 327 [M^+ - 142 (CH_3I) = M^*], 326 (M^* - 1), 325 (M^* - 2), 310 (M^* - 17), 296 (M^* - 31), 294 (M^* - 33), 282 (M^* - 45) and 266 (M^* - 61).

Anal. Calcd. for $C_{20}H_{24}INO_4 \cdot 0.5H_2O$: C, 50.22; H, 5.27; N, 2.93. Found :C, 49.90; H, 5.04; N, 2.88.

The above chloroform extract (B) was washed with water, dried over potassium carbonate and evaporated to give 1.5 g. of a brown solid, which was chromatographed on 60 g. of silica gel using chloroform [fractions (each 50 ml.) 1-30, monitored by ir and uv spectra], chloroform-methanol (99:1 v/v) [fractions (each 50 ml.) 31-105], chloroform-methanol (97:3 v/v) [fractions (each 50 ml.) 106-129], and chloroform-methanol (95:5 v/v) [fractions (each 50 ml.) 130-178] as eluants.

Fractions 50-58 were combined and evaporated to leave 40 mg. of a brown solid, which was recrystallized from ethanol to give 20 mg. of the phenolic aporphine VIII, (±)-thaliporphine, as colorless prisms, m.p. 189-191° [lit. (13) m.p. 190-192°], uv λ max (ethanol) nm: 305, 280, and 220 (log ε 4.12, 4.12, and 4.52) (11,12); nmr (deuteriochloroform) τ: 7.46 (3H, s, NCH_3), 6.16 (3H, s, OCH_3), 6.13 (6H, s, 2 x OCH_3), 3.50 (1H, s, ArH), 3.26 (1H, s, ArH), 1.98 (1H, s, 11 - H). Mass m/e: 341 (M^+), 340 (M - 2), 326 (M - 15), 310 (M - 31) and 298 (M - 43) (11). The nmr and uv spectra were superimposable upon those of the authentic sample (12,13).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.03; H, 7.95; N, 4.07.

Fractions 66-119 gave 310 mg. of 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-1-(3,4-dimethoxybenzyl)-2-methylisoquinoline (III) as a brown oil, the methiodide of which formed colorless prisms, m.p. 229-231° (from ethanol) (14); nmr (deuteriochloroform) τ (free base): 7.53 (3H, s, NCH_3), 6.26 (3H, s, OCH_3), 6.20 (6H, s, 2 x OCH_3), 5.0 br (1H, OH), 3.62 (1H, s, ArH), 3.50 (1H, s, ArH), 3.43 (1H, d, J = 2.5 Hz, ArH), 3.32 (2H, s, ArH).

Anal. Calcd. for $C_{20}H_{25}NO_4 \cdot CH_3I \cdot 0.5H_2O$: C, 51.01; H, 5.91; N, 2.83. Found: C, 51.40; H, 5.83; N, 2.64.

The structure of this product was also confirmed as follows. The above free base III was superimposable on that of the debromination product, which was obtained by catalytic hydrogenation of II in the presence of 30% palladium-charcoal, by mixed m.p. and ir spectral comparison.

Fractions 132-178 gave 230 mg. of 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (IV) as a dark red solid, which was recrystallized from benzene to give colorless prisms, m.p. 146-148°; nmr (deuteriochloroform) τ: 7.48 (3H, s, NCH_3), 6.37 (3H, s, OCH_3), 6.25 (3H, s, OCH_3), 6.23 (3H, s, OCH_3), 4.7 br (3H, NH_2 and OH), 3.76 (1H, s, ArH), 3.73 (1H, s, ArH), 3.60 (1H, s, ArH), 3.54 (1H, s, ArH).

Anal. Calcd. for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.88. Found: C, 66.89; H, 7.38; N, 7.77.

Moreover, the above compound IV was acetylated with acetic anhydride in the presence of pyridine to afford the corresponding acetylated product V quantitatively, which was recrystallized from ethanol to give colorless needles, m.p. 199-201°; ir ν max (chloroform) cm^{-1}: 1755 ($OCOCH_3$), 1660 ($NHCOCH_3$); nmr (deuteriochloroform) τ: 7.90 (3H, s, $COCH_3$), 7.72 (3H, s, $COCH_3$), 7.43 (3H, s, NCH_3), 6.32 (3H, s, OCH_3), 6.26 (3H, s, OCH_3), 6.18 (3H, s, OCH_3), 3.74 (1H, s, ArH), 3.48 (1H, s, ArH), 3.23 (1H, s, ArH), 2.47 (1H, s, ArH).

Anal. Calcd. for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.09; H, 6.85; N, 6.29.

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