VI. INTERMEDIATES FOR CEPHARANTHINE[6]

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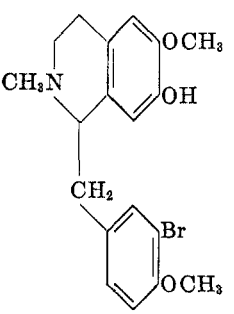
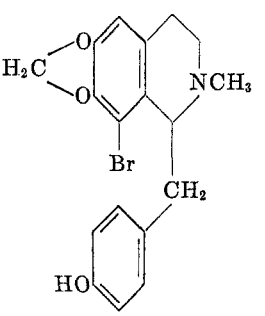
Preliminary experiments have been performed with the intention of synthesizing cepharanthine (III, R + R′ = CH_2, or its isomer XII) by a double Ullmann condensation of compounds XIII and XIV. Only one of the two position isomers (XII) of cepharanthine would be obtained in the synthesis, which would then be unequivocal. However, since isotetrandrine has now been proved (31) to be III (R = R′ = CH_3) it is probable that the structure of cepharanthine is represented by III (R + R′ = CH_2) because alkaloids occurring in the same plant usually have the same structure with reference to the diphenyl ether portion [an exception to this rule has recently been reported (32)]. Moreover, studies on the Ullmann diphenyl ether synthesis reported in previous papers of this series indicate that the double Ullmann condensation would probably not take place because the bromine atoms of both XIII and XIV are hindered. The other route being investigated (through compounds IX, II, and VI for isotetrandrine) is considered more promising.



XIII



XIV

N-(3-Bromo-4-methoxyphenylacetyl)-3-methoxy-4-benzyloxy-β-phenethylamine was prepared from the known O-benzylhomovanillylamine and 3-bromohomoanisoyl chloride. It was also prepared by benzylating N-(3-bromohomoanisoyl)homovanillylamine. The amide was cyclized by the Bischler-Napieralski reaction (29) to 1-(3-bromo-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline. Treatment of the latter with methyl iodide in acetone afforded the corresponding methiodide which was reduced to 1-(3-bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline by sodium borohydride in methanol (33). Compound XIII was obtained by debenzylation with 20% hydrochloric acid.

The methylenedioxy derivative XIV has not been prepared. Various attempts to obtain 5-bromohomopiperonylamine in reasonable yield gave unsatisfactory results. 5-Bromo-3,4-methylenedioxy-β-nitrostyrene could not be obtained from 5-bromopiperonal by the method of Erne and Ramirez (34) or by other standard

[6] This paper had been written before the authors learned that H. Kondo (30) has nearly completed his synthesis of cepharanthine. The kindness of Professor Tomita in sending us reprints is appreciated.

techniques. 5-Bromopiperonal was converted to 5-bromopiperonyl cyanide, but when the latter was reduced with lithium aluminum hydride the bromine atom was removed. The intended reaction may be possible if the amount of lithium aluminum hydride is carefully controlled. In the course of this work 3-bromo-4-methoxy-β-nitrostyrene was prepared.

Hydrohydrastinine prepared by the method of Decker and Becker (35) was brominated in glacial acetic acid, producing a bromo derivative, the structure of which was not proved. It could not be separated into the expected isomers by fractional crystallization.

A quantity of cepharanthine purchased[7] for chemical and clinical evaluation (1) was received as its benzene adduct, m.p. *ca.* 103° (decomp.) (36). After drying *in vacuo* the free base melted at 142–145° [reported as 140–145° (37) and 155° (38)]. When the benzene of crystallization was removed by the method of Kondo (39) the free base melted at 170–172°, or well above any previously reported figure. The melting point of the dimethiodide checked a literature value (39), but analysis of the unsolvated material and its dimethiodide gave very poor results. Specific rotations of samples of the free base prepared in different ways ranged from +318° to +343°, whereas the reported values range from +204° to +296.6° (36, 37). The Labat test for a methylenedioxy group was positive and certain color reactions with acids (37) were verified.

Attempts were made to cleave cepharanthine with sodium and liquid ammonia according to Tomita's directions for isotetrandrine (31), but they failed as did similar attempts by Tomita (40). Attempts were also made to demethylenate cepharanthine with aluminum bromide in nitrobenzene (41) and with phloroglucinol in sulfuric acid (42), followed in each case by methylation with diazomethane or dimethyl sulfate, but no identifiable products were obtained. Complete dealkylation of cepharanthine by hydriodic acid yielded an amorphous product which was not identical with demethylotetrandrine (43).

It is desired to acknowledge the encouragement of Francis L. Schmehl,[8] who first commended this research project to the senior author's attention in 1949.

EXPERIMENTAL[3]

Starting materials. 3-Methoxy-4-benzyloxy-β-nitrostyrene was prepared in 95% yield according to Tomita (44) and reduced by lithium aluminum hydride in tetrahydrofuran to 3-methoxy-4-benzyloxy-β-phenethylamine (45) in 35% yield. 3-Bromo-4-hydroxyphenylacetic acid (7) was prepared in 98% yield by brominating *p*-hydroxyphenylacetic acid and was methylated with dimethyl sulfate in boiling alkali to form 3-bromohomoanisic acid (7) in 85% yield. Protocatechualdehyde was brominated to afford 5-bromoprotocatechualdehyde (46) in 88% yield. 5-Bromopiperonal was prepared in 20% yield according to Tomita (47) by treating 5-bromoprotocatechualdehyde with methylene sulfate in aqueous potassium hydroxide. Great difficulty was encountered in preparing methylene sulfate (48), yields of only 20% being obtained. Therefore, methylenation with methylene iodide (49) was preferred and it gave the same yield of 5-bromopiperonal. Homopiperonylamine was prepared in 55% yield by reduction of 3,4-methylenedioxy-β-nitrostyrene with lithium aluminum hydride. Hydrohydrastinine hydrochloride was formed in 82% yield by the action of formaldehyde on homopiperonylamine hydrochloride at 130° (35).

[7] Purchased from the Kaken Drug Company, Limited, Tokyo, Japan.

[8] Children's Cancer Research Foundation, Boston 15, Mass.

N-(3-Bromo-4-methoxyphenylacetyl)-3-methoxy-4-benzyloxy-β-phenethylamine. To 10 g. of crude O-benzylhomovanillylamine dissolved in a mixture of 3.3 g. of sodium hydroxide in 50 ml. of water, 100 ml. of ether, and 100 ml. of benzene was slowly added an ethereal solution (100 ml.) of 3-bromohomoanisoyl chloride which was prepared by heating 10 g. of 3-bromohomoanisic acid for 30 minutes with 5 g. of thionyl chloride. The mixture containing the amine was vigorously stirred during the addition of the acid chloride. After standing for 30 minutes, the two layers were separated and the organic layer was evaporated to dryness. The residue, after two decolorizations in acetone, and one recrystallization from ethyl acetate had m.p. 127–128°. There was obtained 4.8 g. of pure amide and evaporation of all the mother liquors yielded 5 g. of crude amide.

Anal. Calc'd for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89.

Found: C, 62.01; H, 5.39; N, 2.99.

N-(3-Bromohomoanisoyl)homovanillylamine. 3-Bromohomoanisoyl chloride prepared from 28 g. of the acid and 24 g. of thionyl chloride was poured into a well-stirred solution of 12 g. of homovanillylamine hydrochloride and 9 g. of sodium hydroxide in 50 ml. of water and 75 ml. of ether. The oil which separated was extracted with chloroform, and the extracts were dried and evaporated to dryness. The residue was decolorized and recrystallized from acetone and water and had m.p. 124–125°. An additional quantity of product (5 g.) could be obtained by allowing the reaction mixture to stand for some time.

Anal. Calc'd for $C_{18}H_{20}BrNO_4$: C, 54.82; H, 5.22; N, 3.51.

Found: C, 54.82; H, 5.11; N, 3.55.

Benzylation of N-(3-bromohomoanisoyl)homovanillylamine with benzyl chloride yielded 97% of N-(3-bromo-4-methoxyphenylacetyl)-3-methoxy-4-benzyloxy-β-phenethylamine.

1-(3-Bromo-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline. To 4.8 g. of N-(3-bromohomoanisoyl)-O-benzylhomovanillylamine dissolved in 70 ml. of chloroform was added 5 g. of phosphorus pentachloride, and the reaction mixture was allowed to stand for 2 days, then an additional 5 g. of phosphorus pentachloride was added. After standing for 2 more days, the reaction mixture was poured into 1 l. of ether, and the precipitate was removed and triturated with 100 ml. of ethanol. After standing for 1 hour, this was filtered, and the solid was washed with ether and dried to yield 2 g. (40%) of the dihydroisoquinoline hydrochloride. When recrystallized from water, the hydrochloride crystallized in fine, white needles as the sesquihydrate, m.p. 194–196°.

Anal. Calc'd for $C_{25}H_{25}BrClNO_3 \cdot 1.5\ H_2O$: C, 56.66; H, 5.33; N, 2.64.

Found: C, 56.44; H, 5.29; N, 2.43.

1-(3-Bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline hydrochloride. 1-(3-Bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinolinium iodide (0.5 g.), which was prepared in acetone from the dihydro base and methyl iodide, was reduced by sodium borohydride as previously described (33). There was obtained 0.35 g. (82%) of the tetrahydroisoquinoline hydrochloride. Recrystallization from 2-propanol yielded white needles which melted first at 104–105°, resolidified at 127–130°, and remelted at 202–204°.

Anal. Calc'd for $C_{26}H_{29}BrClNO_3$: C, 60.17; H, 5.63; N, 2.70.

Found: C, 60.01; H, 5.74; N, 2.83.

1-(3-Bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (XIII). Debenzylation was accomplished by warming the benzyloxy compound for 1 hour on the steam-cone with 20% hydrochloric acid. The gelatinous precipitate (70% yield) which separated on cooling was collected and dried. Both the free base and the hydrochloride were amorphous and difficult to purify. The picrate had m.p. 200–201° after recrystallization from ethanol.

Anal. Calc'd for $C_{25}H_{25}BrN_4O_{10}$: C, 48.32; H, 4.06; N, 9.02.

Found: C, 48.89; H, 4.01; N, 9.14.

5-Bromopiperonyl alcohol. Reduction of 15 g. (0.066 mole) of 5-bromopiperonal was accomplished by refluxing with 2.4 g. (0.011 mole) of freshly-distilled aluminum isopropoxide in 150 ml. of dry 2-propanol for 5 hours. Most of the 2-propanol was removed by distillation and the cooled residue was hydrolyzed with cold, dilute hydrochloric acid (20 ml. of conc'd

acid in 150 ml. of water). The yellow solid was collected and recrystallized (charcoal) from ethanol, affording 12 g. (80%) of white needles melting at 133–134°.

Anal. Calc'd for $C_8H_7BrO_3$: C, 41.59; H, 3.05.
Found: C, 41.69; H, 3.04.

5-Bromopiperonyl bromide. 5-Bromopiperonyl alcohol (12 g.) was shaken for 2.5 hours with 90 g. of 48% hydrobromic acid, then another 90 g. of 48% hydrobromic acid was added to the solid mass and it was shaken a further 2.5 hours. The solid was collected in approximately theoretical yield. Recrystallization from methanol yielded a product melting at 120–122°.

Anal. Calc'd for $C_8H_6Br_2O_2$: C, 32.68; H, 2.20.
Found: C, 32.55; H, 1.84.

5-Bromopiperonyl cyanide. Conversion of 5-bromopiperonyl bromide to the corresponding cyanide was accomplished by shaking 3 g. of the bromide with 3 g. of potassium cyanide in 100 ml. of ethanol for 29 hours. The solution was diluted with water and extracted with ether. Evaporation of the ether yielded a yellow oil which solidified. It was recrystallized from dilute ethanol, then from 95% ethanol, and finally melted at 92–93°.

Anal. Calc'd for $C_9H_8BrNO_2$: C, 45.00; H, 2.50.
Found: C, 45.10; H, 2.63.

Reduction of the cyanide with an equimolar quantity of lithium aluminum hydride in ether yielded only homopiperonylamine, the nuclear halogen having been lost in the reaction.

x-Bromohydrohydrastinine. Hydrohydrastinine hydrochloride (5 g., 0.022 mole) was dissolved by warming in 50 ml. of glacial acetic acid, and 3.5 g. (0.022 mole) of bromine was added to the cooled solution. After 12 hours, 2.5 g. of bromohydrohydrastinine hydrobromide had precipitated. It was recrystallized from water and dilute methanol, and then it melted at 303–305°. The original acetic acid filtrate was diluted with ether, which precipitated 3.5 g. of the hydrochloride, m.p. 262–264° after recrystallization from ethanol. The compounds appeared to be homogeneous as they were not altered by crystallization from various solvents. However, no attempt was made to prove the position of the bromine atom.

Anal. Calc'd for $C_{11}H_{13}Br_2NO_2$: C, 37.64; H, 3.73; N, 3.99.
Found: C, 37.99; H, 3.71; N, 4.17.

3-Bromo-4-methoxy-β-nitrostyrene. A mixture of 54 g. of 3-bromoanisaldehyde, 16 g. of nitromethane, 1.4 g. of methylamine hydrochloride, 0.5 g. of sodium carbonate, and 50 ml. of ethanol was stored in the dark for 4 days. Addition of hot ethanol caused crystals to appear. After recrystallization from dilute ethanol the fine, yellow needles melted at 108–109°.

Anal. Calc'd for $C_9H_8BrNO_3$: C, 41.85; H, 3.10; N, 5.43.
Found: C, 41.99; H, 3.20; N, 5.47.

SUMMARY

The synthesis of 1-(3-bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline is recorded. The compound is an intermediate for a cepharanthine synthesis which has now been discarded. No successful synthetic route to 5-bromohomopiperonylamine was achieved. Data obtained on commercial cepharanthine were not in complete agreement with literature values.

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