Studies on the Syntheses of Heterocyclic Compounds. Part DVI (1). Synthesis of Oxynitidine and Nitidine

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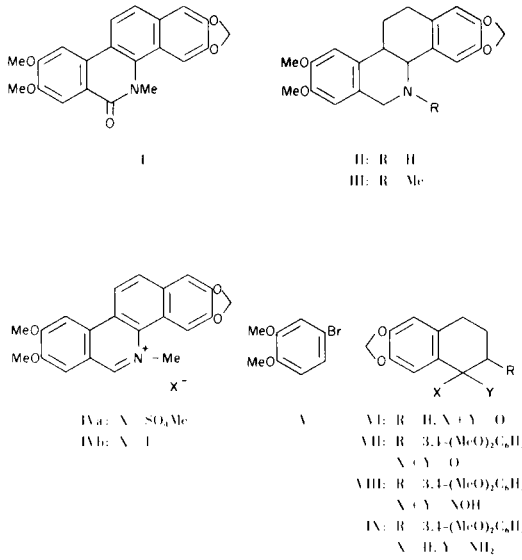
A benzyne type reaction of 1-bromo-3,4-dimethoxybenzene (V) with 3,4-dihydro-6,7-methylenedioxy-1(2*H*)naphthalenone (VI) gave the tetralone derivative VII, which was converted into the amine IX *via* the oxime VIII. A Mannich reaction of IX afforded the benzo[*c*]phenanthridine II which was then transformed into oxynitidine (I) and nitidine (IV).

Oxynitidine and nitidine, two alkaloids isolated from *Zanthoxylum nitidium*, have been assigned the structures I and IV, respectively, by Arthur and his co-workers (3), and their synthesis has been reported by Gopinath and associates (4). We now wish to report an alternative synthesis of nitidine (IV) as well as its transformation into oxynitidine (I). The key intermediate tetralone VII was obtained from 1-bromo-3,4-dimethoxybenzene (V) (5) and 3,4-dihydro-6,7-methylenedioxy-1(2*H*)naphthalenone (VI) by application of the benzyne reaction which had previously been utilized in the synthesis of the benzo[*c*]-phenanthridines from phenylcycloalkanones (6,7).

SCHEME I



I

II: R = H
III: R = Me

IVa: X = SO_4Me
IVb: X = I

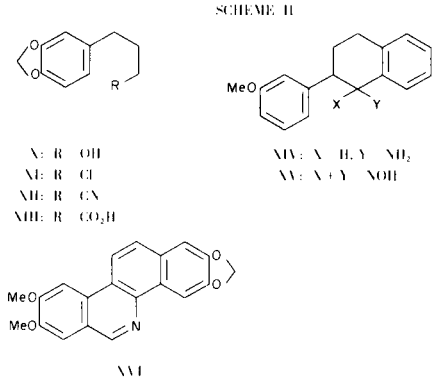
V

VI: R = H, X + Y = O
VII: R = 3,4-$(MeO)_2C_6H_3$-, X + Y = O
VIII: R = 3,4-$(MeO)_2C_6H_3$-, X + Y = NOH
IX: R = 3,4-$(MeO)_2C_6H_3$-, X = H, Y = NH_2

3-(3,4-Methylenedioxyphenyl)propyl alcohol (X), obtained from ethyl 3,4-methylenedioxyphenylpropionate by reduction with lithium aluminum hydride, was treated with thionyl chloride to give the corresponding chloride XI, which was converted into the nitrile XII with sodium cyanide in dimethyl sulfoxide. Saponification of the nitrile XII afforded the carboxylic acid XIII. Friedel-Crafts cyclization of XIII provided the naphthalenone VI which upon benzyne reaction (6) with 1-bromo-3,4-dimethoxybenzene yielded, in the presence of sodium amide in tetrahydrofuran, the tetralone derivative VII. The reduction of the corresponding oxime VIII afforded the amine IX which was assigned the *cis*-configuration based on a coupling constant of J = 4 Hz at δ 4.09 ppm for the 1-methine proton as shown by the nmr spectrum.

In this connection, the substituted amine XIV, previously obtained by catalytic hydrogenation of the corresponding oxime XV and assigned the *trans*-configuration (7), has now been re-examined by nmr (100 M Hz) and found to have the *cis*-configuration.

SCHEME II



X: R = OH
XI: R = Cl
XII: R = CN
XIII: R = CO_2H

XIV: X = H, Y = NH_2
XV: X + Y = NOH

XVI

A Mannich reaction of the amine IX with formalin and hydrochloric acid gave the 4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine II, which was dehydrogenated with 30% palladium-charcoal to afford the benzo[*c*]phenanthridine XVI, followed by conversion into the quaternary nitidines IVa and IVb by successive treatments with dimethyl sulphate and potassium iodide. Oxidation (8) of the methosulfate IVa with potassium ferricyanide in the presence of potassium hydroxide then yielded oxynitidine (I) [ν 1640 cm^{-1} (amide carbonyl); nmr δ 3.80 (*N*-methyl), λ max 276, 288, and 335 nm].

On the other hand, an Eschweiler-Clarke reaction of the benzo[*c*]phenanthridine II with formalin and formic acid gave 4b,5,6,10b,11,12-hexahydro-8,9-dimethoxy-5-methylenedioxybenzo[*c*]phenanthridine (III).

EXPERIMENTAL

Melting points are uncorrected. The ir and nmr spectra were measured with Hitachi-215 and JNM-MH-60 spectrometers with tetramethylsilane as internal standard, respectively.

3-(3,4-Methylenedioxyphenyl)propanol (X).

To a stirred suspension of 32 g. of lithium aluminum hydride in 500 ml. of dry tetrahydrofuran was added dropwise a solution of 110 g. of ethyl 3,4-methylenedioxyphenylpropionate in 100 ml. of dry tetrahydrofuran, and the stirring was continued under reflux for 4 hours. To the reaction mixture, a 40% sodium hydroxide solution was then added in order to decompose the excess of lithium aluminum hydride. The organic layer was separated, washed with water, dried over magnesium sulfate and evaporated to give an oil, which was distilled under reduced pressure to give 80 g. of the alcohol (X) as a colorless oil, b.p. 120-122° (0.6 mm Hg); ir ν max (neat) cm^{-1}: 3450 (OH); nmr δ (carbon tetrachloride): 1.70 (2H, m, $ArCH_2CH_2$), 2.51 (2H, t, J = 7 Hz, $ArCH_2CH_2$), 3.51 (2H, t, J = 7 Hz, CH_2CH_2OH), 3.60 (1H, broad s, OH), 5.80 (2H, s, OCH_2O).

3-(3,4-Methylenedioxyphenyl)propyl Chloride (XI).

To a stirred solution of 10 g. of the alcohol X in 100 ml. of benzene, 10 g. of thionyl chloride was added dropwise at room temperature and the stirring was continued for 2 hours. After removal of the solvent and the excess of thionyl chloride, water was added to the remaining residue and the resulting mixture was extracted with benzene. The extract was washed with water, saturated sodium bicarbonate solution and water, dried over calcium chloride and evaporated to give a solid, which was recrystallized to give 9.2 g. of the chloride XI as colorless needles, m.p. 60-61° (from benzene-*n*-hexane).

Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58. Found: C, 60.06; H, 5.72.

4-(3,4-Methylenedioxyphenyl)butyronitrile (XII).

A mixture of 87 g. of the chloride XI, 32 g. of sodium cyanide and 100 ml. of dimethyl sulfoxide was stirred at 60° for 6 hours. Water was added to the above reaction mixture, which was extracted with benzene. The extract was washed with water, dried over magnesium sulfate, and evaporated to give a residue, which was distilled under reduced pressure to give 60 g. of the nitrile XII as a colorless oil, b.p. 125-127° (0.8 mm. Hg); ir νmax (neat) cm^{-1}: 2250 (C≡N).

4-(3,4-Methylenedioxyphenyl)butyric Acid (XIII).

A mixture of 60 g. of the nitrile XII and 300 ml. of 40% potassium hydroxide aqueous solution was heated at 140° for 7 hours. After the reaction mixture had been diluted with water, the aqueous layer was washed with benzene, acidified with concentrated hydrochloric acid, and extracted with benzene. The benzene layer was washed with water, dried over magnesium sulfate, and evaporated to give a residue, which was recrystallized to give 51 g. of the acid XIII as colorless needles, m.p. 75-76° (from benzene-*n*-hexane); ir ν max (potassium bromide) cm^{-1}: 1705 (C=O); nmr δ (deuteriochloroform): 5.83 (2H, s, OCH_2O), 12.37 (1H, broad s, COOH).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.79.

3,4-Dihydro-6,7-methylenedioxy-1(2*H*)naphthalenone (VI).

A mixture of 34 g. of the phenylbutyric acid (XIII) and 26 g. of thionyl chloride was heated at 60° for 30 minutes, and evaporation of the excess of thionyl chloride gave 4-(3,4-methylenedioxyphenyl)butyric acid chloride as a colorless syrup, to a solution of which 150 ml. of carbon disulfide was added 25 g. of aluminum chloride at 0°. The resulting mixture was kept aside at room temperature for 1 hour, and then heated under reflux for 1.5 hours. The excess of aluminum chloride was then decomposed with water. The resulting mixture was extracted with benzene. The extract was washed with water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and evaporated to give crystals, which were recrystallized to give 21.5 g. of VI as colorless prisms, m.p. 71-72° (from benzene-*n*-hexane); ir ν max (potassium bromide) cm^{-1}: 1660 (C=O); nmr δ (deuteriochloroform): 2.04 (2H, m, C_3-H_2), 2.50 (2H, t, J = 6 Hz, C_4-H_2), 2.80 (2H, t, J = 6 Hz, C_2-H_2), 5.95 (2H, s, OCH_2O), 6.60 (1H, s, C_5-*H*), 7.38 (1H, s, C_8-*H*).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.85; H, 5.59.

3,4-Dihydro-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-1(2*H*)-naphthalenone (VII).

To a stirred suspension of 15 g. of sodium amide in dry tetrahydrofuran was added dropwise under reflux a solution of 15.3 g. of 1-bromo-3,4-dimethoxybenzene (V) and 20 g. of 3,4-dihydro-6,7-methylenedioxy-1(2*H*)naphthalenone (VI) in dry tetrahydrofuran and the stirring was continued for 8 hours under reflux. An aqueous ammonium chloride solution was then added to the above reaction mixture in order to decompose the excess of sodium amide. After extraction with benzene, the extract was washed with water, 10% hydrochloric acid and water, dried over magnesium sulfate and evaporated to give an oil, which was purified by chromatography on 200 g. of alumina to give a solid. This was recrystallized to give 3 g. of VII as colorless prisms, m.p. 169-170° (from benzene-*n*-hexane); ir max (potassium bromide) cm^{-1}: 1660 (C=O); nmr δ (deuteriochloroform): 3.79 (1H, t, J = 6 Hz, C_2-H), 3.90 (6H, s, 2 x OCH_3), 6.11 (2H, s, $-OCH_2O-$).

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 70.16; H, 5.84.

3,4-Dihydro-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-1(2*H*)-naphthalenone Oxime (VIII).

A solution of 3.5 g. of the naphthalenone VII, 5 g. of hydroxylamine hydrochloride, 5 ml. of pyridine and 20 ml. of ethanol was heated under reflux for 3.5 hours, and the solvent was evaporated to give a residue, which was extracted with benzene. The extract was washed with water, 5% hydrochloric acid, 10% sodium bisulfite and water, dried over magnesium sulfate, and evaporated

to give a solid, which was recrystallized to give 2.8 g. of the oxime VIII as colorless prisms, m.p. 170-171° (from ethanol); ir ν max (potassium bromide) cm^{-1}: 3440 (OH), 1609 (C=N); nmr δ (deuteriochloroform): 3.86 (6H, s, 2 x OCH_3), 4.80 (1H, broad s, OH), 6.02 (2H, s, OCH_2O).

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.66; H, 5.72; N, 4.07.

1-Amino-1,2,3,4-tetrahydro-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxynaphthalene (IX).

A solution of 1.5 g. of the oxime VIII in 50 ml. of ethanol was hydrogenated over 4 ml. of Raney Nickel at room temperature under an atmosphere of hydrogen. After the inorganic material had been removed from the reaction mixture, ethanol was distilled off and the residue was extracted with ether. The extract was washed with water, dried over potassium carbonate and evaporated to give a solid, which was recrystallized to give 1.2 g. of IX as colorless prisms, m.p. 137° (from ethanol); ir ν max (potassium bromide) cm^{-1}: 3470 (NH); nmr δ (deuteriochloroform): 1.40 (2H, broad s, NH_2), 3.96 (6H, s, 2 x OCH_3), 4.09 (1H, d, J 4 Hz, C_1-H), 6.06 (2H, s, OCH_2).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.21; H, 6.60; N, 4.46.

4b,5,6,10b,11,12-Hexahydro-8,9-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (II).

A mixture of 1 g. of the amine IX, 5 ml. of 37% formalin, 2 ml. of concentrated hydrochloric acid, 10 ml. of water and 10 ml. of ethanol was heated under reflux for 2.5 hours. After removal of the solvent, the residue was made basic with 10% sodium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over potassium carbonate, and evaporated to give a solid, which was recrystallized to give 710 mg. of II as colorless needles, m.p. 194-196° (from benzene); ir ν max (potassium bromide) cm^{-1}: 3400 (NH); nmr δ (deuteriochloroform): 1.70 (1H, broad s, NH), 3.90 (2H, s, C_6-H_2), 3.95 (6H, s, 2 x OCH_3), 4.10 (1H, d, J = 4 Hz, C_{4b}-H), 6.0 (2H, s, OCH_2O), λ max (ethanol): 287 nm (log ϵ 3.66).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.78; H, 6.14; N, 3.79.

4b,5,6,10b,11,12-Hexahydro-8,9-dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridine (III).

A mixture of 560 mg. of the phenanthridine II, 5 ml. of 37% formalin and 5 ml. of formic acid was heated for 5 hours on a water-bath. After evaporation of the solvent, the residue was made basic with 10% sodium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give a solid, which was recrystallized to give 540 mg. of III as colorless prisms, m.p. 160-161° (from ethanol); ir ν max (potassium bromide) cm^{-1}: 2840 (N-Me); nmr δ (deuteriochloroform): 2.24 (3H, s, N-CH_3), 3.92 (2H, s, C_6-H_2), 3.99 (6H, s, 2 x OCH_3), 4.39 (1H, d, J 4 Hz, C_{4b}-H), 6.06 (2H, s, OCH_2O).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.51; N, 3.96. Found: C, 70.98; H, 6.24; N, 4.13.

8,9-Dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (XVI).

A mixture of 250 mg. of the phenanthridine II and 300 mg. of 30% palladium-charcoal was heated at 240° for 0.5 hour under an atmosphere of nitrogen and the reaction mixture was extracted with chloroform. The solution was evaporated to afford a solid, which was recrystallized to give 100 mg. of XVI as colorless needles, m.p. 281-282° (from acetic acid); ν max (potassium bromide) cm^{-1}: 1620 (C=N); nmr δ (trifluoroacetic acid): 4.10, 4.29 (each 3H, s, OCH_3), 6.50 (2H, s, OCH_2O).

Anal. Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.63; H, 4.56; N, 4.13.

Oxynitidine (I).

To a mixture of 700 mg. of the benzo[*c*]phenanthridine XVI, 5 ml. of nitrobenzene, and 20 ml. of xylene was added under reflux one drop of dimethyl sulfate and the mixture was heated for 10 minutes. After cooling, the precipitate was collected, washed with ether, and crystallized from water-ethanol to give 700 mg. of IVa as pale yellowish needles, m.p. 300°.

Anal. Calcd. for $C_{22}H_{21}NO_8S$: N, 3.05. Found: N, 2.73.

To a stirred solution of 50 mg. of the above methosulfate in 30 ml. of water was added a mixture of 200 mg. of potassium hydroxide and 400 mg. of potassium ferricyanide in 20 ml. of water, and the mixture was heated at 80° for 40 minutes. The reaction mixture was extracted with benzene and the extract was washed with water, 10% hydrochloric acid and water, dried over magnesium sulfate and evaporated to give the crystals, which were recrystallized to afford 10 mg. of oxynitidine as colorless needles, m.p. 284-285° (from ethanol) [lit. (3) 284-285°]; ν max (potassium bromide): 1640 cm^{-1} (amide C=O); nmr δ (deuteriochloroform): 3.80 (3H, s, NCH_3), 3.99, 4.02 (each 3H, s, 2 x CH_3), 6.05 (2H, s, OCH_2O); uv λ max (ethanol): 335, 288 and 276 nm (log ϵ = 4.13, 4.65, and 4.59).

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.42; H, 4.72; N, 3.86. Found: C, 69.69; H, 4.64; N, 3.80.

Nitidine Iodide (IVb).

To a solution of 5 mg. of 7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine methosulfate (IVa) in 2 ml. of water was added 1 ml. of saturated potassium iodide solution, and the resulting mixture was heated on a water-bath for 3 hours. The separated crystals were collected by filtration and crystallized to give 2 mg. of nitidine iodide as pale yellow needles, m.p. 284-285° (from ethanol) [lit. (3) 284-285°].

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

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