Synthesis of Allonitidine and Related Compounds

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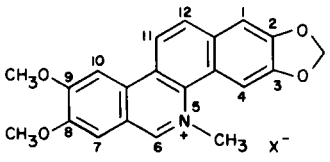
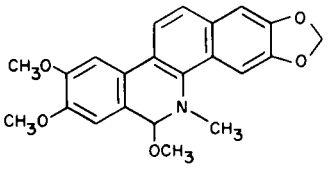
Salts of alkoxybenzophenanthridines have recently aroused much interest since a number of alkaloids bearing this ring system demonstrated antifungal (1), cytotoxic (2), and antileukemic (3-5) activities. In connection with our N-O-O triangular pharmacophore studies (6), nitidine (5) (I), methoxydihydronitidine (5) (II), coralyne (7) (III) and certain related compounds (8) have been synthesized and evaluated. In order to gain additional information on their structure-activity relationship, several specifically designed analogs were prepared. This communication reports the synthesis of hitherto unknown allonitidine (IV) and 5,6-dihydro-6-methoxyallonitidine (V), wherein the positions of dimethoxy and methylenedioxy groups in the nitidine series are interchanged. For comparative purposes, the corresponding tetramethoxy analog (9) (VI) and the pentamethoxy derivative (VII) were also synthesized.

The synthetic route for IV followed essentially the same procedure as that used for the synthesis of nitidine (5): Base-catalyzed condensation of piperonal and 3,4-dimethoxyacetophenone yielded 3′,4′-dimethoxy-3,4-methylenedioxychalcone (VIII). Hydrogen cyanide addition to VIII in 2-ethoxyethanol afforded the cyanoketone IXa. Base hydrolysis of the latter in aqueous ethanol followed by acidification gave γ-(3,4-dimethoxyphenyl)-α-(3,4-methylenedioxyphenyl)-γ-oxobutyric acid IXb, which yielded the butyric acid IXc upon catalytic hydrogenation. Without further purification, IXc was cyclized to 6,7-dimethoxy-2-(3,4-methylenedioxyphenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene (Xa), which was in turn converted, under the Leuckart conditions, to the formamide derivative Xb. This intermediate was cyclized in a mixture of phosphorus oxychloride and toluene to yield the tetrahydrobenzo[*c*]phenanthridine XI. Aroma-



I



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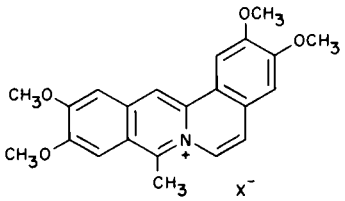

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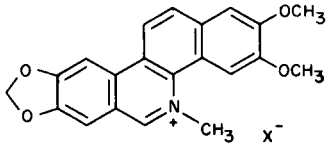
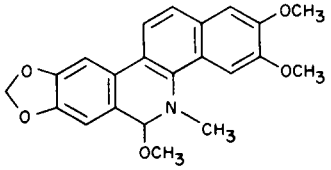
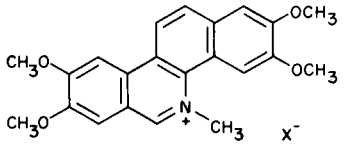


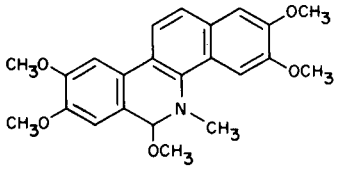
IV



V

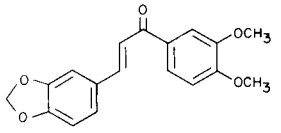


VI

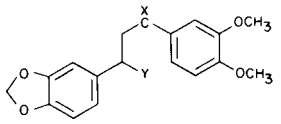


VII

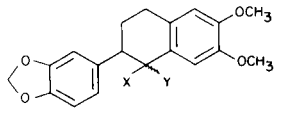
tization of XI to XII was achieved with 30% palladium-on-charcoal. Methylation of XII with dimethyl sulfate at elevated temperature gave the desired product IV. The overall yield of IV from dimethoxyacetophenone was 9%. Treatment of IV with aqueous ammonia followed by heating with methanol afforded the methoxy derivative V. In general, compounds in this series have slightly higher melting points and slightly less solubility in water than the corresponding counterparts in the nitidine series. Compounds VI and VII were obtained in an analogous manner.



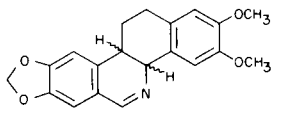
VIII



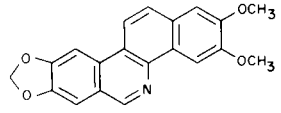
IXa, X = O, Y = CN
b, X = O, Y = CO_2H
c, X = H_2, Y = CO_2H



Xa, X + Y = O
b, X = H, Y = NH-CHO



XI



XII

EXPERIMENTAL

3′,4′-Dimethoxy-3,4-methylenedioxychalcone (VIII).

To a warm (40°) solution of 41.5 g. (0.23 mole) of 3,4-dimethoxyacetophenone and 40.5 g. (0.27 mole) of piperonal in 220 ml. of ethanol was added 60 ml. of 10% aqueous sodium hydroxide. The mixture was warmed for 10 minutes at 40-50° then stirred at room temperature for 2 hours. After standing overnight, the yellow crystalline product was collected by filtration, washed with water (3 x 40 ml.), and dried to give 72 g. (quantitative yield) of VIII, m.p. 127-129°. An analytical sample was prepared by recrystallization of 1.6 g. of the product from 50 ml. of ethanol, giving 1.4 g. of pure chalcone as yellow needles, m.p. 131-133°; λ max (ethanol) 242 (log ε 4.23), 3.60 nm (4.53).

Anal. Calcd. for $C_{18}H_{16}O_5$(312.3): C, 69.22; H, 5.16. Found: C, 68.97; H, 5.26.

γ-(3,4-Dimethoxyphenyl)-α-(3,4-methylenedioxyphenyl)-γ-oxobutyronitrile (IXa).

A solution of 15 g. (0.23 mole) of potassium cyanide in 60 ml. of water was added in 3 minutes, with stirring, to a hot (heated on a steam bath) solution of 36 g. (0.12 mole) of VIII in 200 ml. of 2-ethoxyethanol containing 7.5 ml. (0.12 mole) of acetic acid. The resulting mixture was heated on a steam bath for 10 minutes and stirred at room temperature for 1 hour. To the mixture was added, at 0°, 200 ml. of water. The resulting white solid was collected by filtration, washed with water (3 x 150 ml.), and dried to give 36 g. (92% yield) of IXa, m.p. 159-161°. Recrystallization from ethanol afforded an analytical sample, m.p. 161-162°; λ max (ethanol) 230 (log ε 4.34), 278 nm (4.16) λ sh (ethanol) 306 nm (3.98).

Anal. Calcd. for $C_{19}H_{17}NO_5$ (339.4): C, 67.25; H, 5.05; N, 4.13. Found: C, 67.02; H, 4.96; N, 4.03.

γ-(3,4-Dimethoxyphenyl)-α-(3,4-methylenedioxyphenyl)-γ-oxobutyric Acid (IXb).

A mixture of 20 g. (0.059 mole) of IXa and 22 g. (0.55 mole) of sodium hydroxide in 250 ml. of water and 90 ml. of ethanol was refluxed on a steam bath for 10 hours. It was cooled and acidified with 10% hydrochloric acid to *p*H 1. The resulting mixture was stirred for 2 hours then allowed to stand overnight. The solid was collected by filtration, washed with water and dried, to give 23 g. (quantitative yield) of IXb, m.p. 198-200°. Recrystallization from ethanol yielded an analytically pure sample as white crystals, m.p. 201-203°; λ max (ethanol) 228 (log ε 4.35), 274 nm (4.27); λ sh (ethanol) 294 nm (4.14).

Anal. Calcd. for $C_{19}H_{18}O_7$(358.4): C, 63.68; H, 5.06. Found: C, 63.79; H, 5.02.

6,7-Dimethoxy-2-(3,4-methylenedioxyphenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene (Xa).

A mixture of 22 g. (0.062 mole) of IXb and 3 g. of 10% Pd/C in 200 ml. of acetic acid in the presence of 1.5 ml. of 70% perchloric acid was hydrogenated at 55-60° under 4 kg./cm^2 for 2 hours. The catalyst was filtered from the warm reaction mixture and washed with acetic acid (3 x 40 ml.). The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was extracted with benzene (4 x 300 ml.). The benzene extract was washed with water (3 x 150 ml.) and dried (sodium sulfate). Evaporation of solvent gave 20 g. (95% yield) of the butyric acid IXc; λ max (ethanol) 230, 280 nm.

To a stirred suspension of 25.5 g. (0.12 mole) of phosphorus pentachloride in 100 ml. of dry chloroform was added a solution of 40 g. (0.115 mole, a combination of two runs) of IXc in 300 ml. of chloroform at 0°. The resulting mixture was stirred in an ice bath for 2 hours and then at room temperature for 16 hours. To this was added dropwise at 0° a solution of 15 ml. (0.12 mole) of anhydrous stannic chloride in 40 ml. of dry chloroform in 15 minutes. The mixture was stirred at 0° for 3 hours and poured into a mixture of 450 ml. of 10% hydrochloric acid and 200 g. of ice. The complex, which gradually decomposed, was extracted with chloroform (5 x 300 ml.). The chloroform solution was washed successively with water (3 x 350 ml.), 3% sodium hydroxide (3 x 350 ml.) and water (3 x 350 ml.). The washings were back-extracted with chloroform. The combined chloroform solution was dried (sodium sulfate) and treated with Celite. The solvent was removed *in vacuo* and the residue triturated with 40 ml. of methanol. The resulting solid was collected by filtration, washed with cold methanol, and dried to give 29.4 g. (77% yield) of Xa, m.p. 168-170°. Recrystallization from ethanol yielded an analytical sample as white needles, m.p. 173-175°; λ max (ethanol) 233 (log ε 4.31), 277 (4.13), 313 nm (3.91), m/e: 326 (M^+).

Anal. Calcd. for $C_{19}H_{18}O_5$(326.4): C, 69.93; H, 5.56. Found: C, 70.16; H, 5.50.

α,γ-Bis(3,4-dimethoxyphenyl)butyric Acid.

This intermediate (for the preparation of the pentamethoxy analog VII) was prepared in a manner similar to the foregoing and

isolated from the acetic acid solution in 86% yield, m.p. 127-129° (lit. (10), m.p. 118-120°); λ max (ethanol) 230 (log ε 4.42), 279 nm (3.92).

6,7-Dimethoxy-1-formamido-2-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene (Xb).

A stirred mixture of 24 g. (0.074 mole) of Xa, 3.5 g. of ammonium sulfate, 60 ml. of formamide and 3.5 ml. of formic acid was heated in an oil bath at 185° for 6 hours. Addition of a 3.5 ml. portion of formic acid to the reaction mixture was made three times at hourly intervals. The reaction mixture was cooled and to it was added 150 ml. of water followed by 250 ml. of chloroform. The mixture was stirred for 15 minutes and transferred into a separatory funnel. The chloroform layer was separated and the aqueous layer extracted three times with chloroform. The combined chloroform solution was washed with water and dried (sodium sulfate). The solvent was evaporated *in vacuo* and the residue triturated with 50 ml. of methanol. After it had stood overnight, the resulting white solid was collected by filtration to give 20.8 g. of crude Xb, m.p. 150-190° (it contained 40-45% of the desired formamide Xb by tlc estimation), which was used in the following step since the impurity could readily be removed after the cyclization step. For analytical purposes, the crude product was purified through a neutral alumina column using chloroform as the eluent. Evaporation of the chloroform solution followed by recrystallization of the residue from methanol gave a pure product, m.p. 201-203°; λ max (ethanol) 233 (log ε 4.19), 285 nm (3.98), m/e: 355 (M^+).

Anal. Calcd. for $C_{20}H_{21}NO_5$(355.4): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.44; H, 5.68; N, 3.99.

2,3-Dimethoxy-8,9-methylenedioxy-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (XI).

To a stirred suspension of 3 g. (0.0085 mole) of the formamide Xb in 30 ml. of toluene was added 7.5 ml. of redistilled phosphorus oxychloride. The mixture was heated at 100-110° for 30 minutes, during which time a brown solution formed followed by precipitation of a yellow solid. The reaction mixture was cooled to 45°, the solid was collected by filtration, washed with hot toluene and ether, and dried to give 2.4 g. of the hydrochloride salt of XI, m.p. 234-235° dec. The salt was suspended in 30 ml. of methanol, basified with methanolic ammonia, and chilled. The resulting white solid was collected by filtration, washed with methanol, and dried to give 1.2 g. (42% yield) of XI, m.p. 208-210°. Recrystallization from methanol and pyridine yielded white crystals, m.p. 210-212°; λ max (ethanol) 232 (log ε 4.61), 280 (4.02), 316 nm (3.72), m/e: 337 (M^+).

Anal. Calcd. for $C_{20}H_{19}NO_4$ (337.4): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.16; H, 5.88; N, 4.15.

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

A mixture of 0.5 g. (0.0015 mole) of XI, 0.2 g. of 30% palladium-on-charcoal and 7 ml. of Dow Corning 550 fluid was heated under nitrogen at 255-260° for 2 hours with stirring. The mixture was cooled, diluted with 30 ml. of chloroform, and filtered. The catalyst was extracted continuously with chloroform. The combined filtrate and extract was evaporated *in vacuo* to a syrup which, upon trituration with 10 ml. of ethanol, yield a light yellow solid. This was collected by filtration, washed with ethanol and petroleum ether (b.p. 35-60°), and dried to give 0.4 g. (80% yield) of XII, m.p. 275-277° (recrystallized from pyridine-methanol); λ max (chloroform) 273 (log ε 4.83), 283 (4.08), 305 (4.38), 333 (3.98), 351 (3.76), 368 nm (3.48); m/e: 333 (M^+).

Anal. Calcd. for $C_{20}H_{15}NO_4$(333.4): C, 72.06; H, 4.54; N, 4.20. Found: C, 72.22; H, 4.79; N, 4.42.

Allonitidine Methyl Sulfate (2,3-Dimethoxy-8,9-methylenedioxy-5-methylbenzo[*c*]phenanthridinium Methyl Sulfate, or 2,3-Dimethoxy-5-methylbenzo[*c*][1,3]dioxolo[4,5-*j*]phenanthridinium Methyl Sulfate) (IV, X = CH_3SO_4).

To a hot solution of 11 g. (0.33 mole) of XII in 110 ml. of xylene and 250 ml. of nitrobenzene was added 30 ml. of dimethyl sulfate. The mixture was heated at 175-180° for 20 minutes with stirring whereupon a yellow solid gradually separated from the reaction mixture. The mixture was cooled and diluted with 250 ml. of ether. The yellow solid was collected by filtration on a fritted glass funnel, washed with ether and petroleum ether (b.p. 35-60°), and dried to give 13.9 g. (91% yield) of product, m.p. 322-324° dec. An analytical sample was prepared by recrystallization from methanol, m.p. 328-330° dec.; λ max (methanol) 231 (log ε 4.43), 272 (4.80), 302 (4.59), 328 (4.51) and 390 nm (3.98); m/e: 333 (M^+-$(CH_3)_2SO_4$).

Anal. Calcd. for $C_{22}H_{21}NO_8S$ (459.5): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.71; H, 4.41; N, 2.94.

2,3,8,9-Tetramethoxy-5-methylbenzo[*c*]phenanthridinium Methyl Sulfate (VI, X = CH_3SO_4).

This compound was obtained in 90% yield in a manner similar to that used in the foregoing experiment; m.p. 311-312° (lit. (9), m.p. 305-308°).

5,6-Dihydro-6-methoxyallonitidine (5,6-Dihydro-5-methyl-8,9-methylenedioxy-2,3,6-trimethoxybenzo[*c*]phenanthridine or 5,6-Dihydro-5-methyl-2,3,6-trimethoxybenzo[*c*][1,3]dioxolo[4,5-*j*]-phenanthridine) (V).

A mixture of 1.4 g. (3 mmoles) of finely ground allonitidine methyl sulfate (IV) and 200 ml. of 28% aqueous ammonia was stirred in an ice bath for 30 minutes. The mixture was extracted with chloroform (5 x 200 ml.), the extract washed with water (50 ml.) and dried (sodium sulfate). To the dried solution was added 50 ml. of methanol. The resulting mixture was evaporated below 30° *in vacuo*. The pasty residue was extracted with 150 ml. of hot methanol. The methanol extract was concentrated to 50 ml. and cooled. White crystals, which gradually separated from the solution, were collected by filtration, washed with ether and petroleum ether (b.p. 35-60°), and dried to give 0.6 g. (52% yield) of V, m.p. 211-213° dec.; λ max (chloroform) 281 (log ε 4.63), 311 nm (4.38); m/e: 379 (M^+), 348 (M^+-OCH_3), 333 (M^+-OCH_3-CH_3); nmr (trifluoroacetic acid): 0.63 τ (*s*, 1P, 6-H), 1.43 τ (*d*, 1P, J = 9 Hz, 11-H), 1.73 τ (*d*, 1P, J = 9Hz, 12-H), 1.79 τ (*s*, 2P, 4-H and 10-H), 2.30 τ (*s*, 1P, 7-H), 2.35 τ (*s*, 1P, 1-H), 3.58 τ (*s*, 2P, -OCH_2O-), 4.91 τ (*s*, 3P, N-CH_3), 5.74 τ (*s*, 3P, 2-OCH_3), 5.75 τ (*s*, 3P, 3-OCH_3), 5.90 τ (*s*, 3P, 6-OCH_3). The nmr pattern is similar and in accord with that reported and assigned by other investigators for isomeric alkaloids (11,12).

Anal. Calcd. for $C_{22}H_{21}NO_5$(379.4): C, 69.64; H, 5.58; N, 3.69. Found: C, 69.40; H, 5.49; N, 3.62.

5,6-Dihydro-5-methyl-2,3,6,8,9-pentamethoxybenzo[*c*]phenanthridine (VII).

This compound was prepared, in 63% yield, from VI in a manner similar to that of the previous experiments, m.p. 212-214°; λ max (chloroform) 281 (log ε 4.62) 310 nm (4.36); m/e: 395 (M^+), 364 (M^+-OCH_3), 349 (M^+-OCH_3-CH_3); nmr (trifluoroacetic acid): 0.49 τ (*s*, 1P, 6-H), 1.29 τ (*d*, 1P, J = 9 Hz, 11-H), 1.63 τ (*d*, 1P, J = 9 Hz, 12-H), 1.65 τ (*s* 1P, 10-H), 1.73 τ (*s*, 1P, 4-H), 2.17 τ (*s*, 1P, 7-H), 2.23 τ (*s*, 1P, 1-H), 4.84 τ

(*s*, 1P, N-CH_3), 5.57 τ and 5.70 τ (*s*, 6P, 8,9-$(OCH_3)_2$), 5.70 τ and 5.71 τ (*s*, 6P, 2,3-$(OCH_3)_2$), 5.88 τ (*s*, 3P, 6-OCH_3). The nmr spectrum of this compound in deuteriochloroform is rather different from that in trifluoroacetic acid, particularly that the proton signal of 6-H was shifted from 0.49 τ to 4.90 τ. This is also in accord with that reported for analogous compounds (12).

Anal. Calcd. for $C_{23}H_{25}NO_5$ (395.5): C, 69.86; H, 6.37; N, 3.54. Found: C, 70.08; H, 6.14; N, 3.58.

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