TOTAL SYNTHESIS OF CAERULOMYCIN+

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Abstract - Caerulomycin, a metabolite of Streptomyces caeruleus, is (E)-4-methoxy-2, 2'-bipyridyl-6-aldoxime. Its synthesis and that of its (Z)-isomer is described starting from methyl picolinate and 3,5-dimethylisoxazole.

A bipyridine antibiotic known as Caerulomycin (1) was isolated from Streptomyces caeruleus in 1959[1]. A synthesis of caerulomycin from a known bipyridine precursor[2] reported in 1969[3], confirms its structure as the E-aldoxime. The marked activity of caerulomycin against Entamoeba histolytica found in our laboratories[4] prompted us to explore possibilities of a facile total synthesis of the antibiotic, which we could adapt to our ongoing programmes to develop compounds for antiamoebic screening.

Although many disubstituted 2,2'-bipyridines have been reported, there are few examples of the synthesis of 4,6-disubstituted 2,2'-bipyridines[5]. We report here a total synthesis of 1, and the characterization of its Z-isomer 2. The starting point of our approach is a pyridine derivative such as 3 and a synthon such as 3,5-dimethylisoxazole (6).

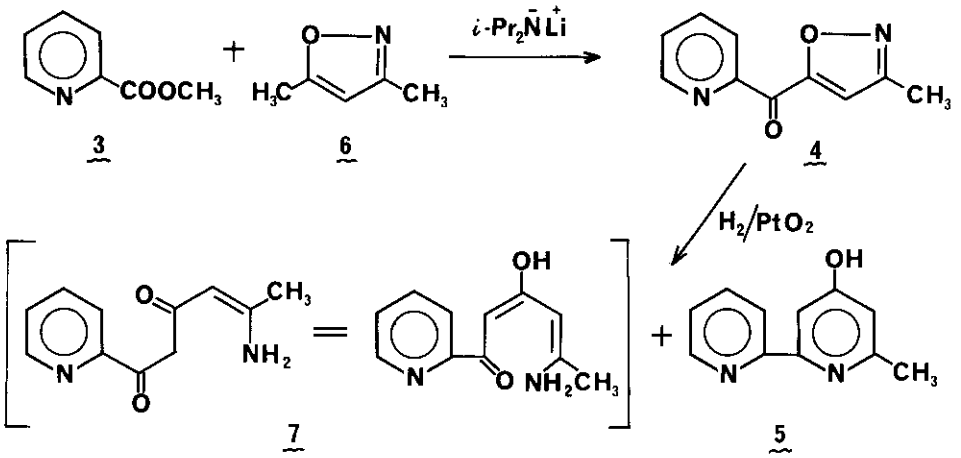
3,5-Dimethylisoxazole (6) undergoes electrophilic substitution selectively at the 5-methyl group[6]. Treatment of 6 with one equivalent lithium diisopropylamide (LDA) generates 3-methyl-5-isoxazolyl methyl carbanion. The carbanion is quenched with an excess of methyl-picolinate (3) to afford 3-methyl-5-(2-pyridoylmethyl)isoxazole (4) in essentially quantitative yield (Scheme I). Catalytic hydrogenation of 4 cleaves the isoxazole. The hydrogenation product over PtO_2 is an approximately 1:1 mixture of two compounds.

On attempting to purify this product by chromatography over alumina, it was found to convert to a structure that was determined to be 4-hydroxy-6-methyl-2,2'-bipyridine (5) by ^1H NMR. The composition of the hydrogenation product mixture was inferred to be the cyclized product 5 and the uncyclized ß-amino-enone 7 based on literature evidence for the formation of ß-aminoenones during catalytic opening of isoxazoles[6]. The isolation of pure 7 is problematic due to its facile quantitative cyclisation during chromatography or under mild conditions such as treatment with dilute acetic acid.

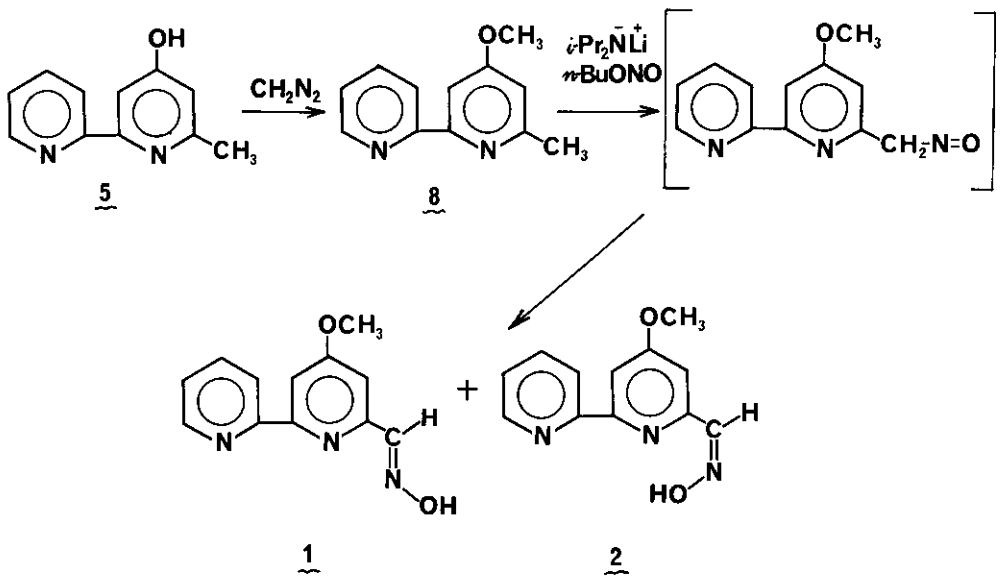
+ Dedicated to the memory of the late Dr. Balbir S. Bajwa, who was responsible for the project in its early stages.

Compound 5 is smoothly converted to its methyl ether (8) by diazomethane treatment (Scheme II). Attempts to oxidise the 6-methyl group in 8 to an aldehyde function with iodine-dimethyl sulfoxide[7] or selenium dioxide[8] were not successful. Whereas nitrosation of anions formed from picolines by sodium amide in liquid ammonia has been reported[9], the carbanion at the 6-methyl of bipyridine 8 was generated with lithium diisopropylamide in THF. Treatment of the carbanion with butyl nitrite results in the formation of 1 and its Z-isomer 2 in approximately equimolar quantities. Isomers 1 and 2 are separable by chromatography and crystallisation.

Scheme I



Scheme II



Configurational assignments for 1 and 2 are evidenced by their ^{1}H NMR spectral data. The formyl proton syn to the oxime hydroxyl in 1 resonates at 8.3 ppm (in $CDCl_3$ solution), whereas the

corresponding formyl proton is observed at 7.67 ppm in 2, consistent with E and Z assignments respectively[1]. Further, the exchangeable hydroxyl proton in E-oxime 1 appears at 8.19 ppm, whereas the oxime hydroxyl proton in 2 is far downfield at 16.2 ppm.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. 60 MHz and 270 MHz ^{1}H-NMR spectra were run on Varian T-60 and Brucker-270 spectrometers respectively. IR spectra were recorded on a Perkin Elmer 157 spectrophotometer. Elemental analyses were performed on a Heraeus Mikro U/D.

2-(3'-Methyl-5'-isoxazolyl)acetylpyridine (4) :

A solution of 3,5-dimethylisoxazole (32 g) in anhydrous THF (100 ml) was added dropwise to a freshly prepared solution of lithium diisopropylamide [diisopropylamine (35.7 g), n-butyllithium in hexane (234 ml of 1.55 M solution)] cooled to -70°C with stirring under nitrogen. After the addition, stirring was continued at -70°C for 1 h followed by addition of methyl picolinate (50 g) in THF (300 ml) maintaining the temperature at -70°C. The reaction mixture was stirred for 1 h and treated with ammonium chloride solution (100 ml). The organic layer was separated and the aqueous solution extracted with ethyl acetate (3 X 300 ml). The extract was combined with the organic layer and washed with water, dried over anhydrous Na_2SO_4 and concentrated to obtain a residue which was purified by chromatography over silica gel. Compound 4 was obtained in petroleum ether-ethyl acetate (4:1) as a solid which was crystallised from diisopropyl ether (58 g, 79%), mp 250-254°C (dec.); ^{1}H NMR (60 MHz, $CDCl_3$) : δ 2.30 (3H, s, CH_3), 4.70 (2H, s, $COCH_2$), 6.1 (1H, s, 4'H), 7.26-8.10 (3H, m, aryl) and 8.80 (1H, d, J=5Hz, aryl); IR (KBr) νmax 1720 cm^{-1}; Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. Found: C, 64.97; H, 4.81; N, 14.30%.

4-Hydroxy-6-methyl-2,2'-bipyridyl (5)

A solution of 4 (16 g) in methanol (300 ml) was subjected to hydrogenation at room temperature and atmospheric pressure using platinum oxide (1.0 g) for 1.5 h. The reaction mixture was then filtered and the filtrate concentrated under vacuum to 100 ml. Acetic acid (1 ml) was added and the mixture stirred for 2 h at 60-70°C. Evaporation of the reaction mixture to dryness and recrystallization of the residue from methanol-diisopropyl ether gave the 4-hydroxy-6-methyl-2,2'-bipyridyl (13.55 g, 92%) as colourless needles, mp 170-172°C; ^{1}H NMR (60 MHz, CD_3OD) : δ 2.41 (3H, s, CH_3), 6.23, 6.83 (2H, 2d, J=3Hz, 3- and 5-H), 7.43, 7.86 (3H, 2m, 3', 4', 5'-H), 9.0 (1H, d, J=5Hz, 6'-H); Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38; N, 15.05. Found: C, 70.64; H, 5.43; N, 15.31%.

4-Methoxy-6-methyl-2,2'-bipyridyl (8)

A solution of diazomethane (6.7 g) in ether (200 ml) was added to a well-stirred solution of 5 (12 g) in methanol and cooled to 0°C. After 3 h at 0°C, the mixture was concentrated under nitrogen to a residue which was purified by chromatography over neutral alumina column. The eluent of petroleum ether-ethyl acetate (95:5) gave 8 (5.75 g, 45%) as colourless needles, mp 59-60°C; ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.56 (3H, s, 6-CH_3), 3.88 (3H, s, OCH_3), 6.65 (d, J=3Hz, 5-H), 7.2 (1H, m, 5'-H), 7.73 (2H, m, 3- and 4'-H), 8.33 (1H, dd, J=8Hz, 2Hz, 3'-H), 8.6 (1H, dd, J=4Hz, 2Hz, 6'-H); Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.00; N, 14.00. Found : C, 72.24; H, 6.11; N, 14.34%.

(Z)-4-Methoxy-2,2'-bipyridyl-6-aldoxime (2)

A solution of 8 (20 g) in anhydrous tetrahydrofuran (200 ml) was added to a freshly prepared solution of lithium diisopropylamide (0.2 moles) in hexane (150 ml) and cooled to -70°C under stirring. The reaction mixture was stirred for 45 min followed by addition of butyl nitrite (23.2 g) at -70°C, and stirred for an additional h. Aqueous ammonium sulfate solution (100 ml) was added to the reaction mixture and it was warmed to room temperature. The organic layer was separated from the reaction mixture and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The residue obtained was semipurified by chromatography over alumina. Final purification was done using a silica gel column and eluting with $CHCl_3$ and $CHCl_3$-NH_4OH (99:1). Recrystallization from ethyl acetate-petroleum ether gave (Z)-4-methoxy-2,2'-bipyridyl-6-aldoxime (6.66 g, 29%) as colourless needles, mp 172-174°C; ^1H NMR (270 MHz, $CDCl_3$): δ 4.02 (3H, s, OCH_3), 6.89 (1H, d, J=4Hz, 3-H), 7.4 (1H, dd, J=8Hz, 4Hz, 5'-H), 7.67 (1H, s, CH=N), 7.86 (1H, m, 4'-H), 8.1 (1H, d, J=4Hz, 5-H), 8.14 (1H, d, J=8Hz, 3'-H), 8.7 (1H, d, J=4Hz, 6'-H and 16.26 (1H, s, OH); Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.91; H, 4.62; N, 18.74%.

(E)-4-Methoxy-2,2'-bipyridyl-6-aldoxime (1)

Further elution of the residue remaining after recrystallisation of 2 with chloroform containing 1% ammonium hydroxide solution gave pure 1 (3.75 g, 16%) recrystallised from methanol to give colourless needles, mp 172-174°C: ^1H NMR (270 MHz, $CDCl_3$) : δ 3.97 (3H, s, OCH_3), 7.35 (2H, m, 3-, 5'-H), 7.83 (1H, dd, J=8Hz, 2Hz, 4'-H), 7.97 (1H, m, 5-H), 8.19 (1H, s, OH), 8.3 (1H, s, CH=N), 8.44 (1H, d, J=8Hz, 3'-H), and 8.68 (1H, d, J=4Hz, 6'-H); Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.68; H, 4.63; N, 18.15%.

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