Synthesis of the grass alkaloid perlolidine through a pyridyne cyclisation reaction

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Received 20 February 2001; accepted 4 July 2001

A synthesis of the grass alkaloid perlolidine is described in which the key step involves the pyridyne cyclisation of 2-benzyloxy-5-bromo-3-[(N-phenyl) aminomethyl] pyridine.

Perlolidine 1 and perloline 2 are the two alkaloids present in perennial rye grass (Lolium perenne L) which have been attracting attention of synthetic chemists due to presence of the novel diazaphenanthrene core. Our attempts to build this heterocyclic system through a benzyne cyclisation approach proved to be rewarding.

Results and Discussion

In this paper we report full details of the total synthesis of perlolidine 1 along the lines shown in Scheme I.

A specially noteworthy feature of this synthesis is utilization of the graded reactivity of the three bromines in the intermediate 6. The most reactive benzylic halide was substituted with weakly basic aniline while the aryl bromine in α-position of the pyridine ring was displaced by heating with PhCH 2 ONa in benzyl alcohol. Finally, the least reactive β-bromine was removed to generate the desired pyridyne intermediate 8 by using stronger base in the form of potassium amide. The cyclisation product obtained in this manner was aromatized and debenzylated with refluxing 10% HCl to secure perlolidine 1.

Experimental Section

All m.ps were taken in open capillaries and are uncorrected. UV spectra were taken on Beckman-DB spectrophotometer; NMR spectra on Varian Associates HA-60 and Mass spectra on MS-9 spectrometer. All compounds gave satisfactory microanalytical results.

2-Amino-5-bromo-3-methylpyrididine 4. To a solution of 2-amino-3-methylpyridine (0.05 mole) in ethanol (50 mL) was added bromine (3.10 mL), keeping the temperature below 20°C. After removal of ethanol, the residue was made alkaline with dilute aq. NaOH and extracted with ether. The solvent was distilled off and the resultant solid was crystallized from pet. ether to give the bromo compound 4 (6.9 g., 73.5%), m.p. 90-91°C (Lit. 90-92°C).

2,5-Dibromo-3-methylpyrididine 5. The bromo compound 4 (6.9 g, 0.036 mole) was added at 15°C to hydrobromic acid (25.5 mL, 48%). The mixture was cooled to -5°C and bromine (8 mL) was added dropwise during 1 hr. A solution of sodium nitrite (9 g) in water (13.5 mL) was then added during 1 hr. and the mixture stirred for another 1 hr. It was made alkaline with a solution of NaOH (20 g) in water (21 mL), the temperature being kept below 20°C, and extracted with ether. The ether extract was dried and the solvent was evaporated. The residue on distillation afforded the dibromo compound 5 (6 g, 65%), b.p. 114°/6mm, which became a solid on cooling, m.p. 40-41°C(Lit. 41-42°C).

2,5-Dibromo-3-bromomethylpyridine 6. To a solution of the dibromo compound 5 (5.8 g, 0.023 mole) in carbon tetrachloride (114 mL) was added N-bromosuccinimide (4 g) along with dibenzoyl peroxide (0.1 g). The mixture was irradiated with a 100 W lamp and simultaneously heated to reflux. After 4 hr the separated solid was filtered off. The solvent was evaporated from the filtrate to get an oil (6.8 g), which showed one major, and two minor spots on TLC (hexane). The Rf value of one of the minor spots corresponded to the starting material. This oil was as such used in the next step.

2,5-Dibromo-3-[(N-phenyl) aminomethyl] pyridine 7. To the above oil (6.8 g) in ethanol (20 mL) was added aniline (3.4 g) and the solution allowed to stand overnight. Ethanol was removed under reduced pressure, the residual oil basified with an aq. solution of NaOH and extracted with ether. The ether extract was washed once with water, dried and the solvent removed. The residual oil was chromatographed on a column of alumina (100 g). Elution with pet. ether afforded a solid (1.3 g), m.p. 39-41°C. It was found to be identical with 2,5-dibromo-3-methylpyridine 5 through mixed m.p. and TLC. Further

Note

Dedicated to Prof. U.R. Ghatak on his 70th birthday
elution of the column with ether: pet, ether (1:4) gave the compound 7 as a white solid (2.1 g., 34.5% calculated from 5) which was crystallized from pet. ether, m.p. 108-10°C. Anal. Found: C, 42.12; H, 2.86; N, 8.50. Calcd for C10H10Br2N2: C, 42.10; H, 2.92, N, 8.18%.

2-Benzylloxy-5-bromo-3-[(N-phenyl) aminomethyl] pyridine 8. Sodium metal (0.035 g., 1.5 m mole) and benzyl alcohol (2 mL) were heated on a water bath until a clear solution was formed. The dibromo compound 7 (0.27 g, 0.8 m.mole) was then added and the solution heated on oil bath at 140°C for 1.5 hr. After cooling, ether (50 mL) was added and the solution was washed with water and dried. Ether was distilled off and the residual solution was cooled in an ice bath. The crystallized product was collected by filtration, washed with cold ethanol (0.5 mL) and dried. It was recrystallized from ethanol to give the benzyloxy compound 8 (0.15 g., 52%), m.p. 105-106 °C. Anal. Found: N, 8.21; Calcd for C19H17BrN2O: N, 7.56%.

1-Benzyloxy-9, 10-dihydro-2,9-diazaphenanthrene 10. A solution of 10 (0.13 g, 0.45 mmole) in chloroform (20 mL) was stirred with active manganese dioxide (0.3 g) for 1 hr and filtered. The solvent was removed from the filtrate and the residue was crystallized from benzene to give 11 (0.1 g., 76.5%), m.p. 134-36°C. Anal. Found: N, 10.48. Calcd for C19H14N2O:9.80%.

Perlolidine 1. The benzyloxy compound 11 (0.09 g., 0.3 mmole) was refluxed with hydrochloric acid (5 mL, 10%) for 1 hr. The reaction mixture was cooled and basified with sodium carbonate. The solid that separated was collected by filtration and dried. It was recrystallized from ethanol to give perlolidine (0.05 g, 80.5%), m.p. 338°C (d) (Lit. 7 m.p. 337-341°C (d));
mass spectrum m/z 196 (M+); UV$_{\text{max}}$ (95% ethanol): 239 μm (38,000), 243 (49,700), 252 (36,000), 322 (10,700), 337 (12,250); UV$_{\text{max}}$ (0.01N NaOH): 237 μm (45,100), 284 (13,100), 325 (11,600), 355 (13, 100); UV$_{\text{max}}$ (0.01N HCl): 240 μm (21,850), 249 (26,500), 256 (31,600), 272 (13,600), 283 (11,700), 377 (17,000). Anal. Found : N, 14.73. Calcd for C$_{12}$H$_8$N$_2$O : N, 14.30%.

Acknowledgement
Financial assistance from CSIR, New Delhi is gratefully acknowledged.

References
10 Seide O, Berlt chem Ges, 57, 1924, 1802.