SOME REACTIONS OF PYRIDO[4,3-b]INDOLE (γ-CARBOLINE)

Ching-Shing LEE, Toshihary OHTA, Koichi SHUDO, and Toshihiko OKAMOTO

Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo, Japan

Abstract — Nitration, N-oxidation and N-amination of pyrido[4,3-b]indole (γ-carboline) and reactions of the 2-oxide with phosphorus oxychloride, acetic anhydride, phenyl isocyanate and cyanogen bromide were described.

Recently 3-amino-1-methyl- (1a) and 3-amino-1,4-dimethylpyrido[4,3-b]indole (1b) were isolated as very potent mutagens in a pyrolysate of L-tryptophan1 and proved to be carcinogenic.2 These compounds were synthesized3 and biological studies are in progress.4,5 On the other hand, chemical study on pyrido[4,3-b]indole (2; γ-carboline) is very poor compared to that on pyrido-[3,4-b]indole (3; β-carboline). Only the synthesis of the skeletal compound has been reported.6 This paper reports on some reactions of γ-carboline (2) and synthesis of amino-γ-carbolines in relation to the potent mutagens.

![Chemical structures](image)

**NITRATION** As the most fundamental electrophilic substitution, nitration of γ-carboline (2) was undertaken. Nitration with fuming nitric acid in acetic acid at 90-95°C proceeded smoothly to give a mixture of mono-nitro-γ-carbolines. The major product was proved to be 8-nitro-γ-carboline (4; 58%) [mp >300°C] by NMR analysis and finally by an independent synthesis from 3-formyl-5-nitroindole and 2,2-diethoxyethylamine. The minor isomer was deduced to be 6-nitro-γ-carboline (5) [mp 290°C] because its NMR spectrum showed the presence of three adjacent hydrogens, one of which is a characteristic hydrogen at the 9-position appearing at a very low magnetic field (δ 9.60 ppm).
According to the Lindemann's procedure which was reported for the nitration of carbazole, \(^7\) was first treated with sodium nitrite in acetic acid, and the resultant 5-nitroso-\(\gamma\)-carboline was nitrated by fuming nitric acid in acetic acid at 90-95°C followed by hydrolysis by potassium hydroxide. Nitro-\(\gamma\)-carbolines obtained in this way consisted of 4 (58%) and 5 (26%).

The nitro-\(\gamma\)-carbolines, 4 and 5, were reduced to amines, 8-amino-[mp 230-231°C] and 6-amino-\(\gamma\)-carboline [mp 240-241°C], respectively, with zinc or iron powder in CF\(_3\)COOH-CH\(_3\)COOH. These amines were isolated as crystals but unstable. Carbamoylation by ethyl chloroformate gave 8- [mp 218-220°C] and 6-carbamoylethyl ester [mp 245°C].

**N-OXIDATION** \(\gamma\)-Carboline can be oxidized with m-chloroperbenzoic acid in refluxing ethanol-chloroform, and 2-oxide (6) [mp 300°C] was isolated in good yield, but could not be prepared with 30% hydrogen peroxide-acetic acid at 80°C.

**REACTION OF 2-OXIDE WITH ELECTROPHILES** Nitration of the 2-oxide (6) was performed according to the Lindemann's procedure. The major product was 8-nitro-\(\gamma\)-carboline 2-oxide [mp 283°C] in 75% yield. Deoxygenation by phosphorus trichloride gave 8-nitro-\(\gamma\)-carboline (4).

Heating the 2-oxide (6) in phosphorus oxichloride at 80-90°C for 60 h yielded 1-chloro-\(\gamma\)-carboline (7) [mp 269-270°C] in 73% yield. 7 could be substituted by ammonia at 200-230°C to give 1-amino-\(\gamma\)-carboline (8) [mp 231-232°C]. The following 1-amino-\(\gamma\)-carbolines were also prepared by the same way; 1-(N,N-dimethylamino)- [mp 58-60°C], 1-benzylamino- [mp 176-178°C], 1-isopentenylamino-[mp 164-165°C] and 1-anilino-\(\gamma\)-carbolines [mp 239-240°C].

When 6 was refluxed in acetic anhydride, 1-acetoxy-\(\gamma\)-carboline (9) [mp 264-266°C] was obtained in 60% yield. Hydrolysis of 9 gave 1-hydroxy-\(\gamma\)-carboline (10) [mp 300°C] which was also obtained by hydroxydediazoniation of 1-amino-\(\gamma\)-carboline (8).

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When the 2-oxide (6) was treated with phenyl isocyanate in N,N-dimethylformamide at 40°C, 1-anilino-γ-carboline (11) [mp 239-240°C] was isolated as the sole product in 28% yield. Though the identification of other products or intermediates failed, the formation of 11 is interpreted by 1,3-addition of phenyl isocyanate to 6.

\[ \text{PhNCO} \quad \text{DMF} \quad \text{6} \quad \text{11} \]

The reaction of 6 with cyanogen bromide was very complex. When an ethanol solution of 6 and cyanogen bromide (1.6 equiv) was refluxed for 8 h, the products isolated were γ-carboline (15%), 6 (15%), and 2-(ethoxycarbonylamino)-2-carbolinium bromide (12; 3%) [mp 236-237°C]. 12 was identical with the sample prepared from 2-amino-γ-carboline (14) (vide infra). If the reaction was carried out in the presence of additional potassium isocyanate, another product, 2-γ-carbolinium-2-(cyanoamine) (13) [mp 276-277°C], was isolated in 10% yield. UV spectrum of 13 is very close to that of 6.

\[ \text{12} \quad \text{13} \]

N-AMINATION

Amination of γ-carboline with 0-mesitylenesulfonylhydroxylamine (MSH) in methylene chloride gave 2-amino-γ-carbolinium mesitylenesulfonate (14) [mp 193°C] in 94% yield. The amino group could be easily carbamoylated, and treatment of the product with hydrogen bromide gave 12.

γ-Carboline was treated with sodium hydride in tetrahydrofuran, and then a solution of MSH in N,N-dimethylformamide was added at 0°C followed by warming up to room temperature to give 5-amino-γ-carboline (15) [mp 167-168°C] in 28% yield, whose UV spectrum was similar to that of γ-carboline. Reaction of 15 with ethyl chloroformate gave the 5-carbamoyl ethyl ester [mp 213°C].

\[ \text{14} \quad \text{15} \]
REACTION OF 2-METHOXY SALT Treatment of the γ-carboline 2-oxide (6) with dimethyl sulfate in toluene at 80°C gave the 2-methoxy methyl sulfate (16) [mp 151-152°C]. UV spectrum of 16 is similar to that of 12. Reaction of 16 with potassium cyanide in dimethyl sulfoxide gave 1-cyano-γ-carboline (17) [mp 260°C] in 68% yield. When the reaction was performed in dioxane, the isolated products were γ-carboline (30%) and 17 (32%).

\[
\begin{align*}
6 & \xrightarrow{(CH_3)_2SO_4} \text{toluene} \rightarrow 16 \\
 & \xrightarrow{KCN, DMSO} \rightarrow 17
\end{align*}
\]

The 2-methoxy salt (16) was treated with excess ammonia in the presence of potassium hydroxide at 100-120°C to give 1-amino-γ-carboline (8; 15%), but even a trace of 3-amino-γ-carboline was not detected. Direct introduction of an amino group to N-alkoxy salt is exceptional, only the example being found in the reaction of α-carboline N-alkoxyl salt. 10

References
2. T. Sugimura and co-workers, unpublished results.

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