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SYNTHESES OF POTENT MUTAGENS IN TRYPTOPHAN PYROLYSATES

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The mutagenic γ-carbolines, 3-amino-1-methyl-5H-pyrido[4,3-b]indole (IV) and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (XIII) have been synthesized by condensation of 3-acetylindole-2-acetonitrile (III) with ammonia and by thermal decomposition of 2-amino-3,6-dimethyl-4-(1-benzotriazolyl)pyridine (XII), respectively. Synthesis of IV has been achieved by an alternative route involving acid catalyzed cyclization of α-acetamido-β-(2-indole)propionic acid (V), followed by dehydrogenation and Curtius rearrangement.

Special attention has been paid to the mutagenic activities of smoked condensates, charred surfaces of broiled fish and meat[1,2] and, to the high correlation between mutagenicity and carcinogenicity[3]. Quite recently, several mutagenic principles were found out on pyrolysis of amino acids[4] and proteins[1]. Furthermore, highly active principles showing mutagenicity in a bacterial system were isolated from tryptophan pyrolysates and their chemical structures were determined to be the 3-amino-1-methyl-5H-pyrido[4,3-b]-indole, IV, and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole, XIII[4]. These mutagens showed the ability to induce morphological transformation of cultured mammalian embryo cells[5], and are strongly suspected to be carcinogenic.

For studies on the carcinogenicity in animals, syntheses of these compounds in large scale by facile methods are urgently required. This communication outlines new routes by which two γ-carbolines, IV and XIII, have been synthesized.

The synthetic methods for IV are shown in Chart 1.

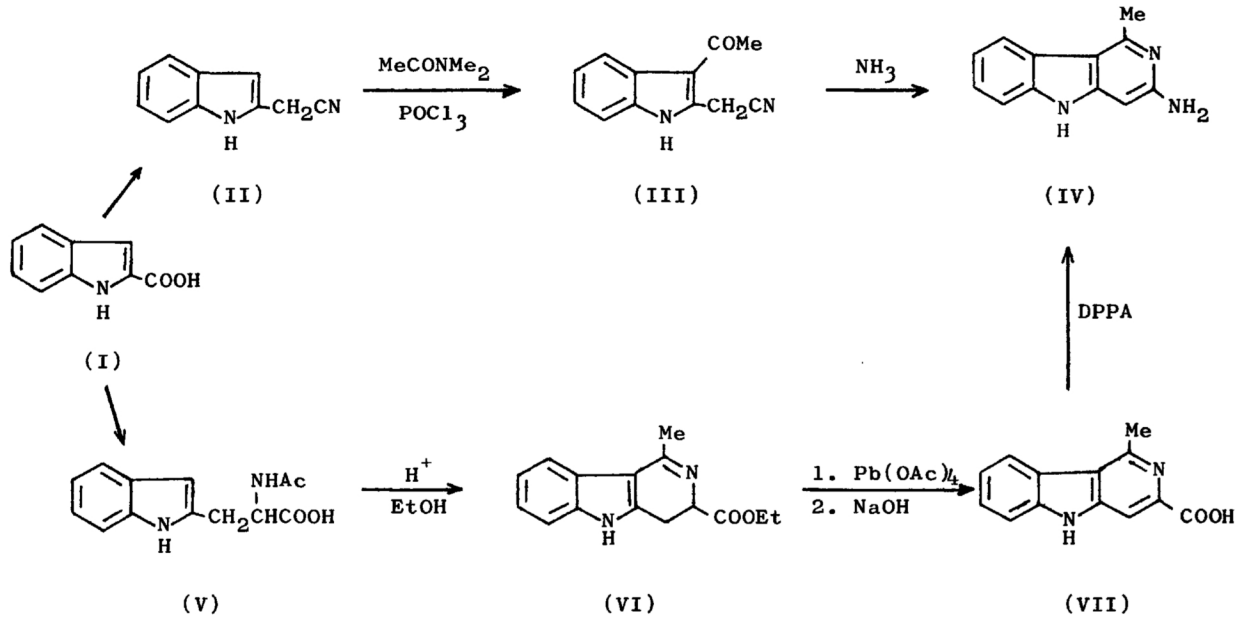

Chart 1

Indole-2-acetonitrile (II)[6], prepared from commercially available indole-2-carboxylic acid, was chosen as an intermediate for the synthesis of IV. Vilsmeier reaction[7] of II, with dimethylacetamide and $POCl_3$, yielded 3-acetylindole-2-acetonitrile (III), mp 223-225°. Cyclization of III on treatment with methanolic ammonia and aromatization involving a hydrogen transfer of the α-methylene group gave the desired 3-amino-1-methyl-5H-pyrido-[4,3-b]indole (IV), mp 223-224° (acetate); m/e 197 (M^+); ν_{max}(KBr): 1635, 1605 cm^{-1}; δ (CD_3OD): 2.30 (3H, s), 5.92 (1H, s), 6.53-7.00 (3H, m), 7.35 (1H, d). This method includes a new cyclization reaction to a γ-carboline system and therefore the synthesis by an alternative route was undertaken in order to confirm the validity of the structure of the product, IV.

On treatment with thionyl chloride in ethanol, α-acetamido-β-(2-indole)propionic acid (V)[8] underwent an acid-catalyzed cyclization, which was accompanied by esterification to give the dihydro-γ-carboline ester (VI), mp 181-183°. This compound, on treatment with lead tetraacetate followed by hydrolysis with ethanolic sodium hydroxide, yielded 1-methyl-5H-pyrido[4,3-b]indole-3-carboxylic acid (VII), mp 275-277°. The carboxylic acid (VII) was submitted to Curtius rearrangement by DPPA method[9] to yield the desired 3-amino derivative (IV), which was confirmed to be exactly identical with the product obtained by the first method described above.

The second mutagenic principle, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (XIII) was synthesized according to the following route (Chart 2).

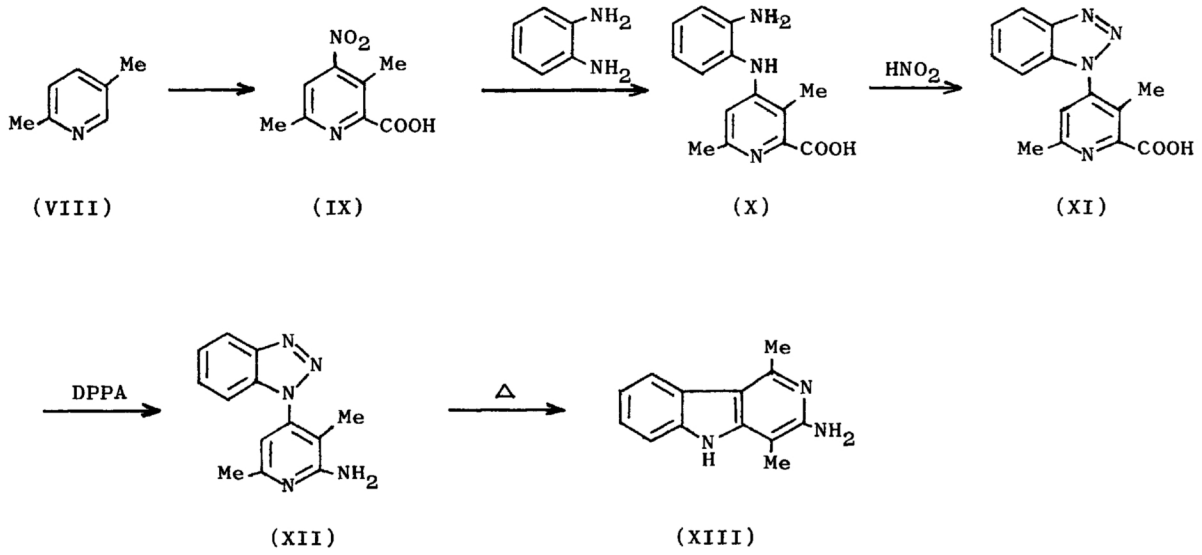

Chart 2

2,5-Dimethyl-4-nitropicolinic acid (IX), mp 144.5-145°, was prepared from commercially available 2,5-lutidine (VIII) according to the method described in the report[10] which relates to the synthesis of 2-ethyl-5-methyl-4-nitropicolinic acid. The reactive nitro group of the picolinic acid (IX) was smoothly substituted with o-phenylenediamine to give an amino-picolinic acid (X), mp 249-250°, which on treatment with nitrous acid resulted in a benzotriazolylpicolinic acid (XI) in quantitative yield, mp 147-148°. The carboxylic acid group on XI was easily converted to an amino group via Curtius rearrangement by DPPA method[9], forming the compound XII, mp 138-139°. Finally, the resulting compound XII was submitted to thermal decomposition in the usual way[11] yielding the desired compound XIII, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole, mp 219-220° (acetate); m/e 211 (M^+); ν_{max}(KBr): 1620, 1600 cm^{-1}; δ (CD_3OD): 3.32 (3H, s), 2.73 (3H, s), 7.13-7.33 (3H, m), 7.86 (1H, m). Spectral and analytical data on all compounds shown in Chart 1 and 2 are in agreement with the assigned structures.

The two mutagenic γ-carbolines (IV and XIII), thus obtained, showed essentially the same mutagenic activities as to the compounds obtained from tryptophan pyrolysis. The chemical and biological data in detail will be published elsewhere.

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