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RESEARCH NOTE

PHOTOSENSITIZED CONVERSION OF TRYPTOPHAN TO β-CARBOLINE DERIVATIVES

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WHEN *L-tryptophan* was irradiated by visible light, in acetic acid solution and in the presence of methylene blue or rose bengal as sensitizers, a photocyclodehydrogenation reaction, leading to 1-methyl-3-carboxy-β-carboline (I), did occur. In addition, partial photolytic decarboxylation was observed (see Fig. 1).

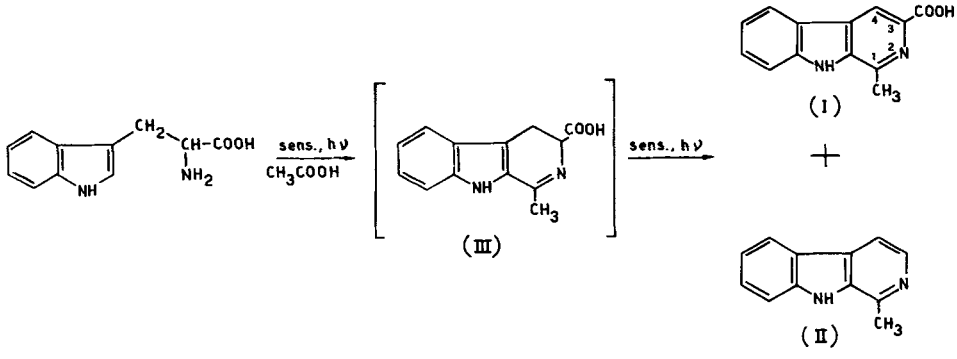

Fig. 1. Proposed scheme for the photooxidation of tryptophan on irradiation by visible light in 99–100 per cent acetic acid and in the presence of rose bengal or methylene blue as sensitizers.

In a typical experiment, 4 ml of a 1 mM tryptophan solution in 99–100 per cent acetic acid, added with an equimolar amount of sensitizer, were irradiated by four 150-w tungsten lamps, using the same experimental arrangement as described previously[1]. The reaction vessel (Pyrex test tube) was kept at 37 ± 0·1°C by a thermojacket which was connected to a thermostat. During irradiation, a stream of purified oxygen was slowly fluxed through the solution. The progress of the reaction was followed by descending paper chromatography on Whatman No. 1, using 5 per cent ammonia (solvent 1) or the Partridge mixture[2] (solvent 2) as eluents.

The disappearance of tryptophan was attended by the formation of two products, blue fluorescent under 254 nm u.v. light, which were named product *A* ($R_{f_1} = 0{\cdot}23$, $R_{f_2} = 0{\cdot}57$) and product *B* ($R_{f_1} = 0{\cdot}11$, $R_{f_2} = 0{\cdot}32$). The two photoproducts gave negative colour tests both with ninhydrin (0·4 per cent butanolic solution) and with the Ehrlich's reagent[3]: this suggested that, after photooxidation, both the α-amino group of tryptophan and the 2-position of the indole ring, respectively, were hindered.

The two spots were eluted from the paper with absolute methanol, and the solutions were spectrally analyzed from 200 to 400 nm. The chromatographic and spectrophotometric features of the two photoproducts, as well as the fluorescence under 254 nm u.v. light, were similar to the ones of some β-carboline derivatives, as described by Tschesche, Jenssen and Rangachari[4]. Moreover, if the reaction rate was lowered by running the photooxidation in the presence of smaller dye concentrations, a third photoproduct was isolated by paper chromatography at intermediate irradiation times. This product ($R_{f_1} = 0{\cdot}44$, $R_{f_2} = 0{\cdot}83$) was indistinguishable as to chromatographic R_f values, fluorescence under 254 nm u.v. light, and u.v. absorption spectra, from a sample of authentic 1-methyl-3-carboxy-3,4-dihydro-β-carboline (III), prepared according to Tschesche and Jenssen[5]. The photooxidation of (III), sensitized by methylene blue or rose bengal, in acetic acid solution yielded the same photoproducts as those obtained by photooxidation of tryptophan.

In order to further characterize the products *A* and *B*, 150 mg of tryptophan (0·74 mmoles) and 240 mg of methylene blue (0·74 mmoles) were dissolved in 250 ml of 99–100 per cent acetic acid, and irradiated at 37°C within a Pyrex vessel, in the presence of oxygen. After 5 hr, the irradiation was stopped, the solvent was removed by lyophilization, and the residue was taken up with water and loaded on a column of a carboxylic acid resin (Amberlite CG-50, 200 to 400 mesh).

Elution with water allowed us to isolate one fraction, which appeared by chromatographic and spectrophotometric analysis to be identical with product *A*. Crystallization from 80 per cent methanol yielded pale green needles (103 mg, 63%), m.p. 302–304°. The assignment of structure (I) for product *A* was possible on the basis of the elemental analysis (Found%: C 67·88*, N 11·91, H 4·76; $C_{13}H_{10}N_2O_2$ requires: C 68·80, N 12·32, H 4·81) and spectroscopy. The u.v. spectrum [λ_{max} (methanol) 236·5 nm ($\log \epsilon = 4{\cdot}623$), 269 nm ($\log \epsilon = 4{\cdot}975$), 295 nm ($\log \epsilon = 4{\cdot}434$), 332 nm ($\log \epsilon = 3{\cdot}596$), 347 nm ($\log \epsilon = 3{\cdot}605$)] was in agreement with a β-carboline structure[4]. The i.r. spectrum [ν_{max} (KB_r) 2·93 μ (indole NH), 3·46 μ (broadened band due to the bridged NH and OH groups, overlapping the CH stretching bands), 5·95 μ (aryl–C=O), 6·68 μ (C=C and C=N), 13·6 μ (indole CH)] suggested the presence of a carboxyl group conjugated with an aromatic system. Since the same product was obtained by photooxidation of (III), it appeared reasonable to place the carboxyl group in the 3-position of the β-carboline molecule. The n.m.r. spectrum (trifluoroacetic acid, tetramethylsilane as internal standard) showed signals at $\tau = 6{\cdot}70$ (singlet, three protons of the 1-methyl group), 2·14 (center of multiplet, four protons of the phenyl ring), and 0·77 (singlet, proton in the 4-position of the pyridine ring; this shift is expected for a proton which is meta to a protonated nitrogen atom and ortho to a carboxyl group). These data unambiguously confirmed the structure (I).

Subsequent elution from the column with 3 per cent ammonia yielded a second fraction, which appeared to be identical with product B. Crystallization from 80 per cent methanol gave white needles (40 mg, 16%), m.p. 233–235°. It was identified as 1-methyl-β-carboline (II) by elemental analysis (Found %: C 79·08, N 15·68, H 5·48; $C_{12}H_{10}N_2$ requires: C 79·12, N 15·39, H 5·50) and by mixed melting point and u.v. and i.r. comparison with a sample of (II) chemically prepared[4].

*The experimental value for carbon is low and was not raised by recrystallization or by drying in vacuo for several hours. A low analytical figure for carbon in product A is reported by other authors[6], and is attributed to the retainment of some water of crystallization.

Many preparative routes leading from indoles to β-carboline derivatives have been described[4–9]. However, the experimental procedure was often arduous and low yields were generally obtained, the main difficulty consisting in the aromatization of the intermediate dihydro[4, 5, 8] or tetrahydro[6, 7] compounds. In particular, the methyl ester of (I), but not the free acid, was isolated[4]. On the contrary, the described photoreaction appears to provide a simple method for the preparation of β-carbolines from indoles in fairly good yields.

Presently, we are studying the scope and the limitations of this novel photocyclization, by varying the nature of the solvent, the character of the indole moiety of the molecule, and the length and the type of 3-substituting side chain. Apart from mechanistic insights, these investigations may open the way for interesting preparative approaches to new heterocyclic compounds. Moreover, the photoactivation of the 2-position of tryptophan has theoretical and practical correlations with the synthesis and the biosynthesis of the indole alkaloids[10].

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