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THE FIRST SYNTHESIS OF MUTAGENIC TRP-P-1 *VIA* THE ELECTROCYCLIC REACTION OF 1-AZAHEXA-1,3,5-TRIENE SYSTEM[1]

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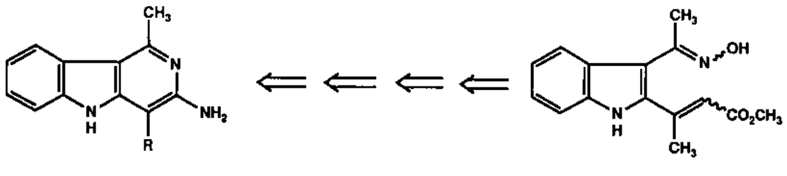
Abstract——The first total synthesis of Trp-P-1 (1) has been completed by the thermal electrocyclic reaction of 1-azahexa-1,3,5-triene system (3).

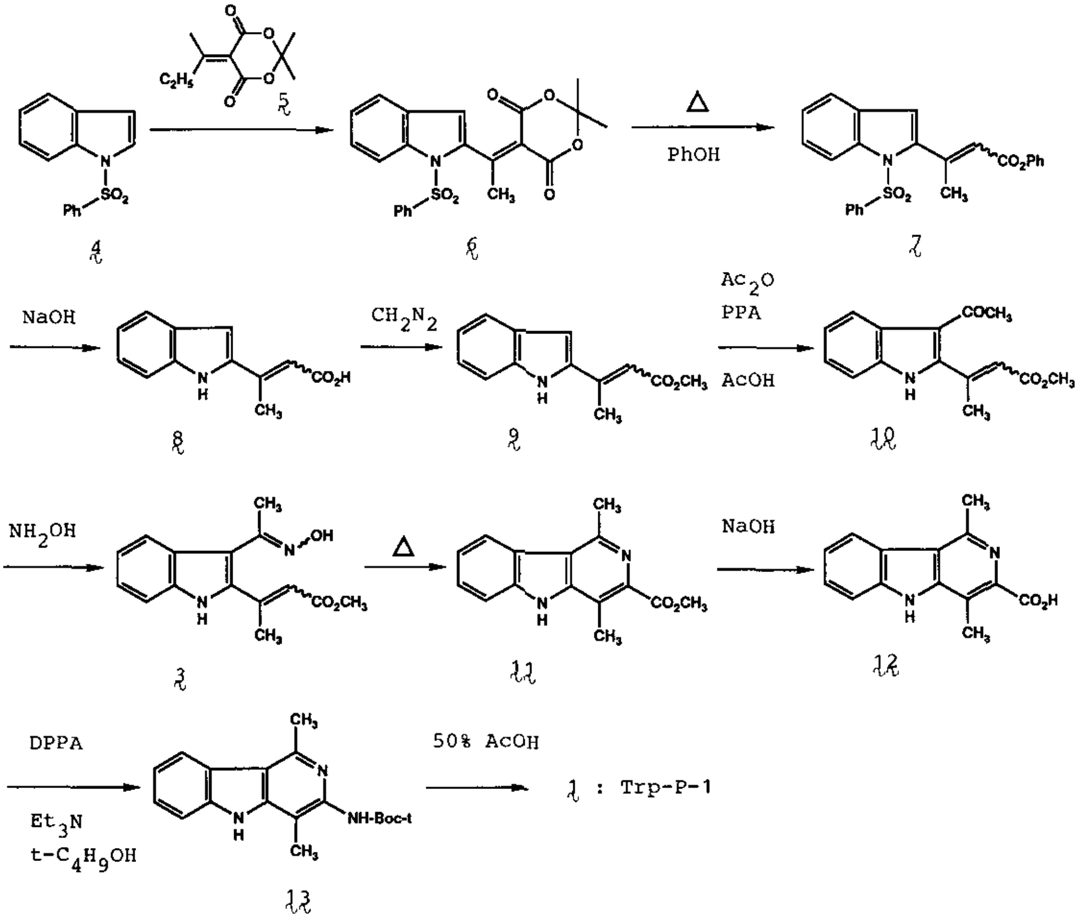
Trp-P-1 (1) and Trp-P-2 (2) isolated from tryptophan pyrolysate in 1977 have potent mutagenic activity.[2] The structure of both compounds was determined by X-ray crystallography and spectroscopic evidences as 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-b]-indole (1) and 3-amino-1-methyl-5*H*-pyrido[4,3-b]indole (2).[3]
In the present communication, we wish to report the first total synthesis of Trp-P-1 (1) using the thermal electrocyclic reaction of the 1-azahexa-1,3,5-triene system[4] (3) for the construction of fused pyridine ring system as depicted below. Initially we aimed to prepare the 1-azahexa-1,3,5-triene system (3) from *N*-benzenesulfonylindole (4). Treatment of *N*-benzenesulfonylindole (4) with lithium diisopropylamide followed by addition of ethoxyethylidene Meldrum's acid (5)[5] gave the addition-elimination product (6) (20.3%).[6] Heating of the compound (6) in phenol



1: Trp-P-1, R=CH_3
2: Trp-P-2, R=H

3

at 180 °C provided the crude phenyl ester (7), which was immediately hydrolysed with sodium hydroxide to give the α,β-unsaturated carboxylic acid (8)[7] (98.3% from 6). Treatment of the compound (8) with diazomethane afforded the methyl ester (9) in 76.2% yield. Acylation to the C-3 position of the indole derivative (9) was carried out by the method of Murakami et al.[8] to give the 2-alkenyl-3-acylindole derivative (10) (93.8%). The reaction of the ketone (10) with hydroxylamine gave the oxime (3) that is 1-azahexa-1,3,5-triene system (86.9%, mp 144-147 °C[6]). Subsequently, the electrocyclic reaction of the key compound (3) was carried out in xylene at reflux temperature to give the γ-carboline (11) (50.4%, mp 101-102 °C[6]). Hydrolysis of the ester (11) with sodium hydroxide followed by Curtius rearrangement[9] afforded the urethane (13) in 59% yield from (11). Finally, the urethane (13) was treated with 50% aqueous acetic acid to give Trp-P-1 (1) as acetate (∿100%, mp 250-260 °C, lit.[3] 252-262 °C). The identification with the authentic sample of Trp-P-1 was performed by the direct comparison (mp, tlc, ^{1}H-nmr, and ms).



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REFERENCES AND NOTES

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6. All new compounds showed satisfactory spectra (ir, ^{1}H-nmr, and ms) and elemental analysis. ^{1}H-Nmr: compound (3); δ 2.27(3H, s), 2.46(3H, s) and compound (11); δ 2.77(3H, s), 3.05(3H, s).
7. The compound (8) was a 1 : 1 mixture of E/Z (by ^{1}H-nmr).
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