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STUDIES ON THE FISCHER INDOLE SYNTHESIS: BEHAVIOUR OF CYCLIC HYDRAZONES OF TETRAHYDROPYRIDAZINE AND PYRAZOLINE SERIES IN POLYPHOSPHORIC ACID.

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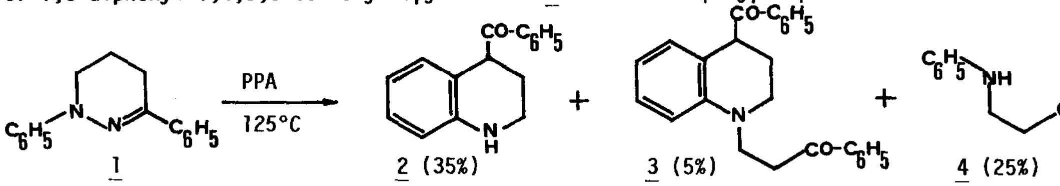
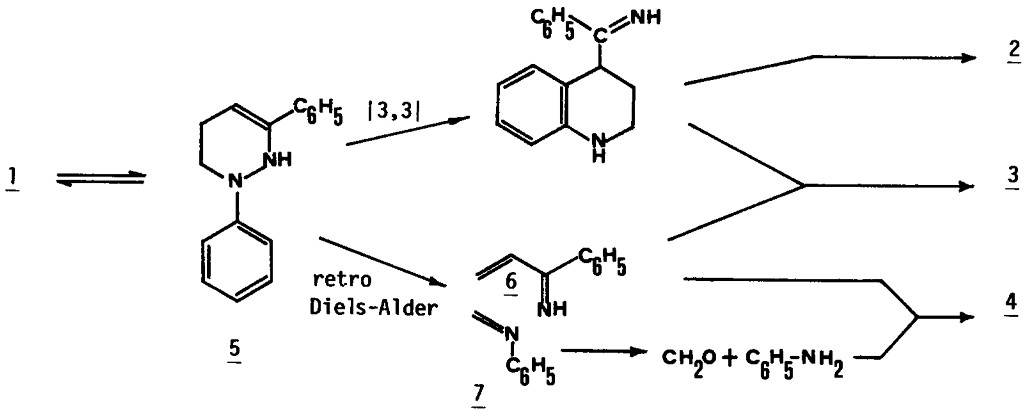
Abstract: Heating 1,3-diphenyl-1,4,5,6-tetrahydropyridazine in PPA affords mainly 4-benzoyl-1,2,3,4-tetrahydroquinoline and 2-anilinopropiophenone.In analogous conditions 1,5-diphenyl-3-methyl-2-pyrazoline gives 2-styrylindole, benzidine and benzylideneacetone.

This note reports the preliminary results of a research intended to investigate the reactivity under the Fischer indole synthesis conditions of 1-phenyl-1,4,5,6-tetrahydropyridazine and 1-phenyl-2-pyrazoline systems, which incorporate a hydrazonic function in a six and five membered ring respectively. Fischer rearrangement of these substrates would require a fusion of an ortho position of the phenyl group with carbon 4 of the ring simultaneous with the N-N bond cleavage. I felt it attractive to verify whether the transition state required for this process was compatible with the rather severe steric strain. The following scheme reports the results of the reaction of 1,3-diphenyl-1,4,5,6-tetrahydropyridazine 1 [2] with hot polyphosphoric acid (PPA).



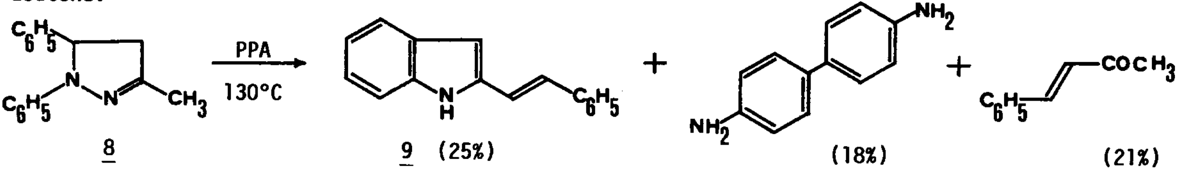
The structure assigned to the hitherto unknown 4-benzoyl-1,2,3,4-tetrahydroquinoline 2 [1] [mp 125°C (isoPrOH)] was confirmed through its aromatization (Pd/C in refluxing xylene) to 4-benzoylquinoline and comparison of the latter with an authentical sample.[3] The Mannich base 3, isolated as a viscous oil [1] by chromatography, was independently synthetized by the addition of the base 2 to phenylvinylketone in refluxing CH_3CN solution. Compound 4 was found to be identical [1] to an authentical sample prepared according to the literature.[4]

As for the mechanism of formation of 2,3 and 4, the enehydrazine 5 would be the common intermediate, which could evolve along two different paths; the preferred one, which ends in 2, would be a |3,3| sigmatropic rearrangement typical of the Fischer indole synthesis.[5] In the present case the closure of the indole ring was prevented by the unacceptable strain that the resulting structure would suffer. The second pathway, a retro Diles-Alder reaction, produces the phenylvinylketoneimine 6 and methyleneaniline 7, which is easily hydrolized under reaction conditions giving formaldehyde and aniline; the latter would compete against base 2 in adding to 7 to afford 3 and 4 respectively.



The formation of 4-benzoyltetrahydroquinoline 2 from 1 confirms the outstanding tendency of arylhydrazones to undergo Fischer rearrangement and joins the few known cases in which this reaction overcomes similar strong steric limitations.[6]

The 1,5-diphenyl-3-methyl-2-pyrazoline 8 showed a completely different behaviour. Its reaction with PPA gave 2-styrylindole 9 as the main product [mp 202°C, MW (mass spectrometry) 219; ^{1}H N.M.R. δ (CDCl$_3$):8.20 (1H,broad s,NH); 7.0-7.7(10H,m,aromatic and -CH=); 6.88 (1H,d,=CH-C$_6$H$_5$, J=18Hz); 6.61 (1H,d,aromatic in position 3, J=3Hz)] together with benzidine and benzylidene acetone.



This reaction picture describes an unexpected equilibration of pyrazoline 8 with its synthetic precursor, the phenylhydrazone of benzylideneacetone, which can in turn either undergo indolization to 9 or further decay to benzylideneacetone and benzidine according to an already observed path.[7]

Efforts are being made to extend these observations to other related substrates.

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