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SYNTHESIS OF QUINOLINE DERIVATIVES INVOLVING HYDRIDE TRANSFER

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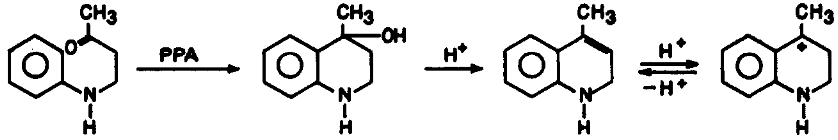
In a recent paper on acid induced disproportionation of thiochromenes[1] we had reported the synthesis of 1,2,3,4-tetrahydrolepidine by cyclodehydration of methyl 2-phenylaminoethyl ketone by treatment with polyphosphoric acid (PPA). We had also indicated that the above synthesis involves hydride transfer from 1,2-dihydrolepidine which is formed as an intermediate. In view of a recent communication by Ardashev and E.Sh. Kagan[2], reporting the synthesis of lepidine and its derivatives from aromatic amines and mannich bases, we wish to report our work on the synthesis of lepidine and quinoline derivatives.

The concomitant synthesis of tetrahydroquinolines and quinolines by the acid catalysed cyclodehydration of β-arylaminoketones reported in the present paper may be generalised as follows:



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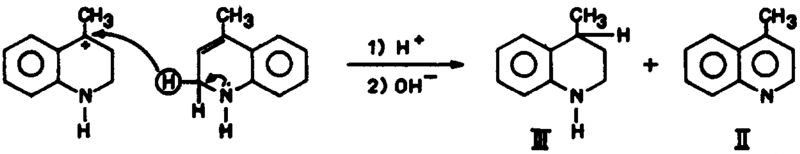


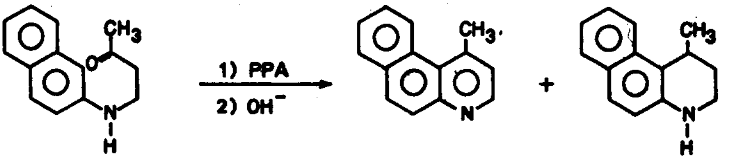
III II

The above synthesis and reaction mechanism involving hydride shift is similar to that reported by us for the disproportionation of thiachromenes[1] and Δ^3-chromenes[1] which will be reported shortly.

Interaction of equimolecular proportion of aniline hydrochloride and 1-diethylamino 3-butanone[4] in aqueous ethanol (50:50) under reflux for one hour gave methyl β-phenylaminoethyl ketone (I)[3] (yield, 80%). Cyclodehydration of (I) (1 g.) by interaction with PPA [from 2.5 ml of H_3PO_4 (d = 1.75) and 4 g. of P_2O_5] gave on workup a liquid (0.91 g.) which on spectrometric analysis showed the presence of lepidine (II) and 1,2,3,4-tetrahydrolepidine (III) in nearly equal proportions (total yield of the two 90%) together with traces of 1,2-dihydrolepidine. The mixture on chromatographic separation on alumina (using petroleum ether and benzene) gave (III) [identified by its spectrum[5] and conversion to known N-benzoyl-1,2,3,4-tetrahydrolepidine, m.p. 131° (lit. m.p. 129°[6])] and (II) [identified by its spectrum[7] and as the picrate, m.p. 210° (lit. m.p. 210-11°[6])].

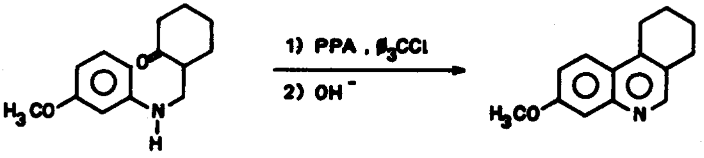
The ketone I was also prepared in poorer yield (40%) by condensation of equimolecular quantities of aniline with methyl vinyl ketone in ethanolic solution in presence of sodium ethoxide. The mixture was left at room temperature (25-27°C) for seven days and then worked up.

Interaction of β-naphthylamine and hydrochloride of 1-diethylamine-3-butanone as above gave methyl 2-(β-naphthylamino-)ethyl ketone (IV)[3], m.p. 72-74°. Cyclodehydration of (IV) by 1% ethanolic hydrogen chloride at reflux for one hour gave a product which on chromatographic separation on alumina (using benzene and petroleum ether) gave 5,6-benzo-4-methyl-1,2,3,4-tetrahydroquinoline (identified by comparison with the spectrum of 5,6-benzo-1,2,3,4-tetrahydroquinoline[8]) and 5,6-benzo-4-methylquinoline[8], m.p. 100-1°[6]. The two products were obtained in near equal amounts and total yield of the two together was nearly quantitative.



2-Dimethylaminomethylcyclohexanone[9] was converted into its hydrochloride by interaction with ethanolic hydrogen chloride. After removal of ethanol and excess hydrogen chloride, the dry mannich base hydrochloride (0.02 moles) was dissolved in water (15 ml.) and the aqueous solution was slowly added to a boiling suspension of m-anisidine (0.04 moles) in water containing sodium carbonate (0.028 moles). After heating the mixture under reflux for 10 minutes, it was basified (pH 7-8) and then extracted with ether. Removal of excess ether and excess m-anisidine (at 0.05 mm) gave the hitherto unknown 2-(m-methoxyphenylamino)-methyl cyclohexanone (V) m.p. 65.5-65.5° (methanol) (structure confirmed by analysis and I. R.).

A mixture of PPA (10 g) and triphenylmethyl chloride (1.5 g.) was stirred for ½ hour and to this mixture was added compound V (1.17 g.). The mixture was then heated at 100° for 3 hours and then worked up by dilution in ice, basification and extraction with chloroform. The product was chromatographed over alumina (benzene, petroleum ether) when it gave triphenylmethane and the hitherto unreported 6-aza-8-methoxy-1,2,3,4-tetrahydrophenanthridine (VI), m.p. 56-58° (colourless flakes from ethanol) in quantitative yield, picrate (pale yellow needles from benzenechloroform), m.p. 223-224°.

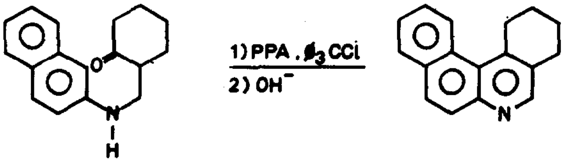


V VI

It is interesting to note that in the above synthesis where triphenylmethyl chloride was used as an external hydride abstractor quantitative yield of (VI) was obtained with little or no disproportionation of the intermediate 1,2-dihydroquinoline.

Condensation of 1-diethylamino 3-butanone with m-anisidine and N-methylaniline gave the corresponding β-arylaminoethyl methyl ketone, which on cyclodehydration with PPA gave the corresponding 4-methyl-7-methoxyquinoline (identified as a picrate, m.p. 224°[10]) and lepidine methophosphate (identified by comparison with the U. V. spectrum of quinoline methiodide).

Condensation of 2-dimethylaminomethylcyclohexanone hydrochloride with β-naphthylamine in 1:1 aqueous ethanol at reflux for 1 hour in presence of equivalent quantities of sodium carbonate gave 2-(β-naphthylamino) methylcyclohexanone (VII) m.p. 130° (needles from ethanol), which on cyclisation with PPA and trityl chloride as above at 100° for 1 hour gave 1,2,3,4-tetrahydro-9,10-benzophenanthridine (VIII) m.p. 117° (cubes from petroleum ether) (literature[11], m.p. 115°).



VII VIII

The U. V., I. R. and analytical data for compounds described in the paper are in conformity with the structures assigned and compare well with the spectral data for the corresponding compounds reported by the other workers. It is hoped that a full account of the work will be published shortly in Tetrahedron.

Acknowledgement

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