1, 2, 5-TRIMETHYL-4-PHENYLETHynyLPipErIDol-4 AND ITS ReACTIONS

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1, 2, 5-Trimethyl-4-phenylethynylpiperidol-4 and 1, 2, 5-trimethyl-4-β-phenylethynylpiperidol-4 are prepared by various methods. Their interconversion is studied, and individual stereoisomeric forms of these piperidols isolated. 1, 2, 5-Trimethyl-4-phenylethynylpiperidol-4 is hydrated, and the resultant ω-(1', 2', 5'-trimethyldehydroperidyl-4') acetophenone used to effect synthesis of a number of secondary and tertiary carbinols. 2, 5-Dimethyl-4-β-phenylethylpyridine is prepared from 1, 2, 5-trimethyl-4-β-phenylethynylpiperidol-4.

Many tertiary amino alcohols containing aromatic and aliphatic groups, are highly active physiologically. In particular, they include effective spasmolytics, and compounds with a tranquilizing action on the central nervous system. Continuing work on preparing various piperidine and pyridine derivatives, the authors turned to synthesizing some tertiary amino alcohols containing these ring systems.

The starting compound used was 1, 2, 5-trimethylpiperidone-4 (I) [1]. Condensation of that ketone with phenylacetylene in the presence of potassium hydroxide gave a mixture of isomeric 1, 2, 5-trimethyl-4-phenylethynylpiperidols-4 (II) [2], from which two isomers of the piperidol II, having melting points 186-189.5° and 101-108°, were isolated by chromatography on alumina. The mixed isomeric piperidols II were also prepared by reacting the piperidone I with phenylacetylene magnesium bromide. Complete hydrogenation of the triple bond of these stereoisomeric piperidols led to the isolation of two isomeric 1, 2, 5-trimethyl-4-β-phenylethylpiperidols-4 (III), melting points 122-123° and 88-91°. The last of these isomeric piperidols III was obtained in low yield (3.5%) by reacting 1, 2, 5-trimethylpiperidone-4 (I) with β-phenylethylmagnesium bromide. The piperidol II and propionyl chloride gave 1, 2, 5-trimethyl-4-phenylethynyl-4-propionoxypiperidine (IV), which is a structural analog of the known analgesic promedol [3]:

Further 1, 2, 5-trimethyl-4-phenylethynylpiperidol-4 (II) has been hydrated with 47% sulfuric acid and the sulfate of mercuric oxide. Under these conditions triple bond hydration was accompanied by dehydration to give ω-(1', 2', 5'-
trimethyldidehydropiperidyl-4') acetophenone (V). From spectrum characteristics it can be assumed that the carbonyl group in that compound is conjugated with the phenyl group. It would also be expected that under the hydration reaction conditions for compound II, an acetylene-allene rearrangement will occur, leading to formation of \( \omega-(1', 2', 5'-\text{trimethylpiperidylidene}-4') \) acetophenone. To test this hypothesis, on the one hand 1, 2, 5-trimethyl-4-phenylethynyl-piperidol-4 was treated with mixed glacial acetic acid - sulfuric acid (50-60°), and on the other with 5% sulfuric acid plus mercuric sulfate (80-85°), i.e., conditions suitable for the acetylene-allene transformation were brought about. However, in both cases the piperidol II was recovered unchanged. Reduction of ketone V with sodium borohydride, i.e., under conditions preserving the double bond, led to isolation of 1-phenyl-2-(1', 2', 5'-trimethyldidehydropiperidyl-4') ethanol-1 (VI), while catalytic hydrogenation gave 1-phenyl-2-(1', 2', 5'-trimethylpiperidyl-4') ethanol-1 (VII).

Treatment of ketone V with phenyllithium led to isolation of 1, 1-diphenyl-2-(1', 2', 5-trimethyldidehydro-piperidyl-4') ethanol-1 (VIII), hydrogenation of the double bond of which gave 1, 1-diphenyl-2-(1', 2', 5'-trimethyl-piperidyl-4') ethanol-1 (IX).

The piperidol III was used to synthesize 2, 5-dimethyl-4-\( \beta \)-phenylethylpyridine (XI). Dehyration of the piperidol III with hydrochloric acid led to isolation of 1, 2, 5-trimethyl-4-\( \beta \)-phenylethylididehydropiperidine (X). The latter was converted to the pyridine base XI by catalytic N-demethylation and dehydrogenation over Mark K-12 catalyst.