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OXIDATION OF 1,2-DIHYDROLEPIDINE TO LEPIDINE[1]

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Abstract—Oxidation of 1,2-dihydrolepidine to lepidine using a few oxidizing agents has been studied in ethanolic solution at 65°. 1,2-Dihydrolepidine is easily autoxidized forming lepidine and hydrogen peroxide, while in the presence of HCl, it disproportionates to give lepidine and 1,2,3,4-tetrahydrolepidine. 1,2-Dihydrolepidine is oxidized by benzaldehyde, N-benzylideneaniline or methyl vinyl ketone to give lepidine and the corresponding alcohol, imine or ketone, respectively, but added HCl inhibits the oxidation in preference of the disproportionation. 1,2-Dihydrolepidine is not oxidized by 4-anilinobutan-2-one, β-ethoxyethyl methyl ketone, methyl ethyl ketone and nitrobenzene. Oxidizing agents are effective in the order: $FeCl_3 \gg$ 1,2-dihydrolepidine–HCl (disproportionation) $\gg O_2 >$ PhCHO ~ PhCH=NPh > $CH_3COCH{=}CH_2$.

1,2-DIHYDROQUINOLINES are generally considered to be intermediates in the Doebner–Miller and Skraup syntheses of quinolines,[2,3] although they have not been isolated because of their instability. 1,2-Dihydroquinoline may be oxidized with various oxidants, but little information is available.

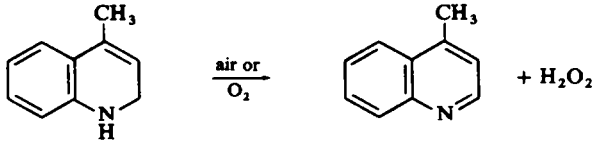
The present study was undertaken to obtain information on the mechanism of the Doebner–Miller synthesis. The supposed intermediate, 1,2-dihydrolepidine, was oxidized by a number of weak oxidizing agents (Eq. 1). In some cases, disproportionation to lepidine and 1,2,3,4-tetrahydrolepidine, i.e. oxidation by itself, was observed.

(1)

Following is a summary of our data concerning the structure of oxidants, acidity of reaction mixture as well as the products formed.

RESULTS AND DISCUSSION

Oxidation in air. An alcoholic solution of 1,2-dihydrolepidine is readily oxidized by air at 65°. The data are shown in Fig. 1. Hydrogen peroxide was detected, which is expected to be formed during autoxidation of 1,2-dihydrolepidine (Eq. 2). Under nitrogen atmosphere, consumption of 1,2-dihydrolepidine was unappreciable at 65°.



(2)

Disproportionation. In ethanolic HCl, 1,2-dihydrolepidine gives a mixture of lepidine and 1,2,3,4-tetrahydrolepidine by disproportionation which was often observed even in the presence of some weak oxidants. No hydrogen gas was evolved. The rates of lepidine formation are shown in Fig. 1. Curve A (0·02M HCl alone) in Fig. 1 differs from the others; i.e. the rate is fast until 40–45% conversion, but then

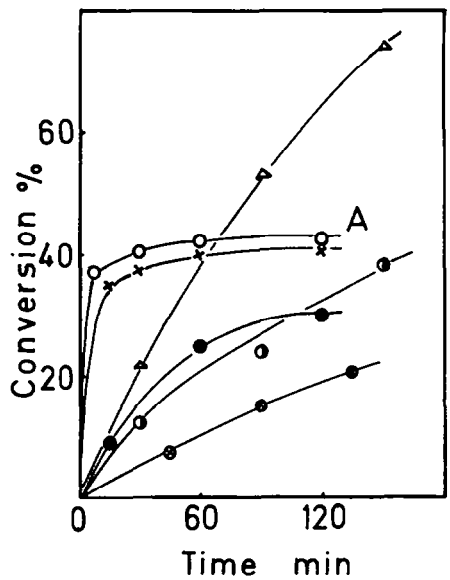
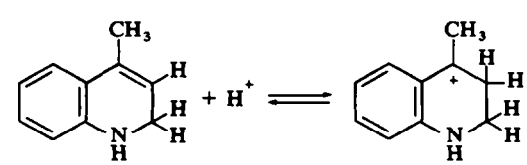
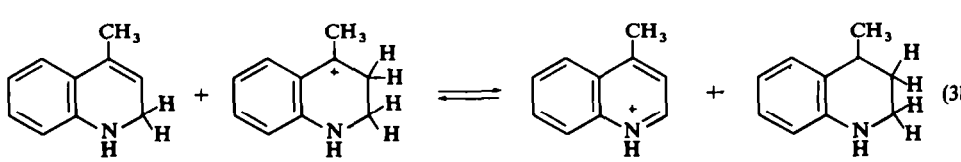


FIG. 1 Conversion curve for the oxidation of 1,2-dihydrolepidine (0·05 M) in ethanol at 65°. Oxidant: ○ HCl (0·02M); × Methyl vinyl ketone (0·05M)–HCl (0·02M); △ Under air; ● Benzaldehyde (0·05M); ◑ Benzylideneaniline (0·05M); ⊗ Methyl vinyl ketone (0·05M).

drops sharply. GLC analysis of the products shows that substantially equimolar amounts of 1,2,3,4-tetrahydrolepidine (47%) and lepidine (54%) are formed during this conversion. These facts suggest that one molecule of 1,2-dihydrolepidine abstracts hydrogen from a second molecule. The disproportionation may involve an acid-catalysed intermolecular hydride shift, since the reaction is inhibited in the absence of acid.



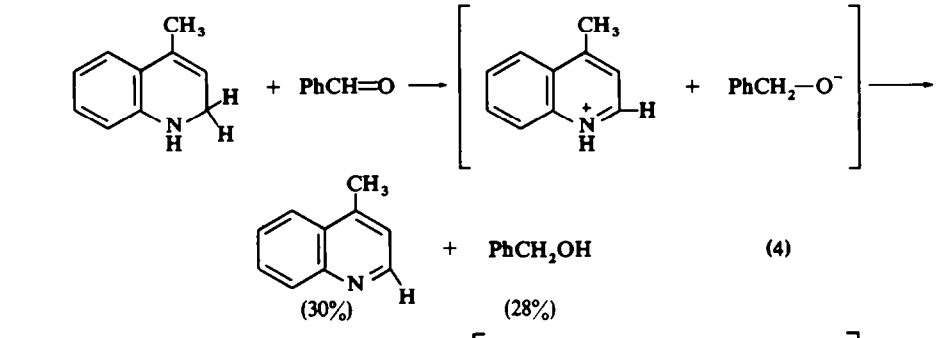
(3a)

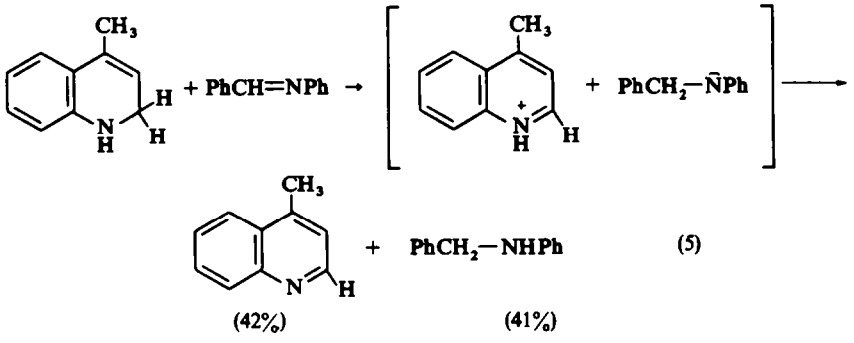


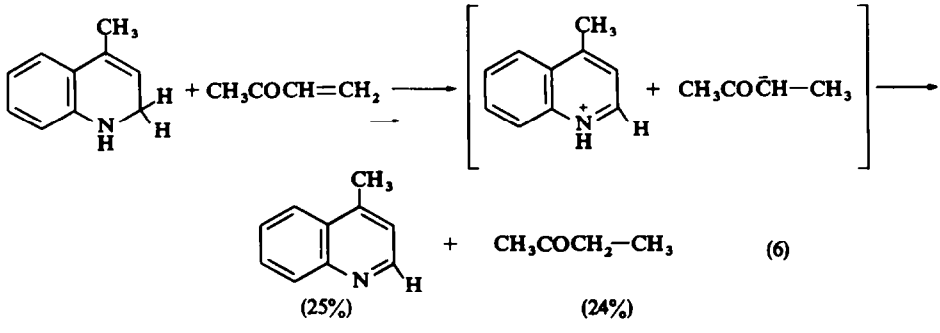
(3b)

The protonation on a β-carbon atom of 1,2-dihydrolepidine produces a tertiary carbonium ion (Eq. 3a), which may be stabilized by resonance with benzene ring and *o*-amino group. The carbonium ion may abstract a hydride ion from another 1,2-dihydrolepidine rather easily, since it gives stable protonated lepidine and 1,2,3,4-tetrahydrolepidine. In other words, 1,2-dihydrolepidine is an effective hydride donor or a reducing agent. Addition of acid to the reaction system results in not only the protonation at the β-carbon atom (Eq. 3a), but also the protonation at the nitrogen atom of 1,2-dihydrolepidine which inhibits the hydride donation in Eq. 3b. In fact, the rate of oxidation is reduced with increasing concentration of HCl.

Oxidation by the other organic oxidants. 1,2-Dihydrolepidine in ethanol is also oxidized by aldehyde, imine and α,β-unsaturated ketone to lepidine. These oxidizing agents were converted to alcohol, amine and saturated ketone, respectively. The reaction also seems to involve the intermolecular hydride abstraction from 1,2-dihydrolepidine by carbonyl, imine and α,β-unsaturated carbonyl group (Eqs. 4, 5 and 6, respectively).







Analogous reactions which involve the hydride shift are known, e.g. Cannizzaro reaction,[4] Meerwein–Ponndorf reduction[5] and Sommelet reaction.[6] However, 4-anilinobutan-2-one, β-ethoxyethyl methyl ketone, methyl ethyl ketone, and nitrobenzene cannot oxidize 1,2-dihydrolepidine at all in ethanol at 65°. Wahrin has shown by means of an isotopic labelling that nitrobenzene does not act as an oxidizing agent but as a moderator in the Doebner–Miller synthesis.[7]

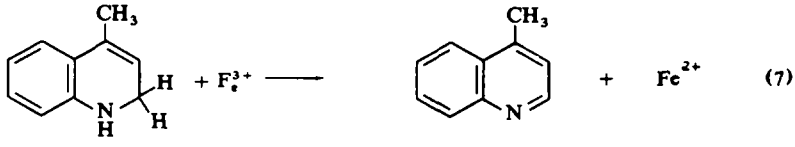
Oxidation in the presence of HCl. In the presence of HCl, organic oxidants such as benzaldehyde, β-ethoxyethyl methyl ketone and methyl vinyl ketone do not oxidize 1,2-dihydrolepidine, instead, disproportionation occurs under these conditions, since equimolar amounts of lepidine and tetrahydrolepidine are formed. Therefore, the rate of disproportionation of 1,2-dihydrolepidine, i.e. oxidation by β-protonated dihydrolepidine, is much higher than the rate of oxidation by the other organic oxidants in the presence of acid. The disproportionation under similar conditions has been postulated for the formation of quinoline derivatives.[8–10]

TABLE 1. HCl-CATALYSED DISPROPORTIONATION OF 1,2-DIHYDROLEPIDINE (0·05M) TO LEPIDINE AND 1,2,3,4-TETRAHYDROLEPIDINE IN THE PRESENCE OF CARBONYL COMPOUNDS IN ETHANOL AT 65° FOR 3 HR

Additive	Yield (%)		
	Lepidine	THL[a]	
PhCHO (0·05M)–HCl (0·10M)	21·0	21·0	No $PhCH_2OH$
CH_2=$CHCOCH_3$ (0·05M)–HCl (0·10M)	26·0	25·0	No $CH_3CH_2COCH_3$
$EtOCH_2CH_2COCH_3$ (0·05M)–HCl (0·02M)	42·1	41·5	No $EtOCH_2CH_2CHOHCH_3$
HCl (0·02M)	53·5	46·5	

[a] 1,2,3,4-tetrahydrolepidine.

Oxidation by ferric ion. The oxidation rate of 1,2-dihydrolepidine with $FeCl_3$ to give lepidine and $FeCl_2$ is too rapid to measure. Even in very dilute solutions such as a mixture of 5×10^{-5}M $FeCl_3$ and 5×10^{-5}M 1,2-dihydrolepidine in ethanol, i.e. the concentration of both reactants are 1/1000 of those under ordinary conditions, lepidine is formed instantaneously. The α,α′-dipyridyl test indicates that this reaction proceeds via ferric-ferrous redox mechanism. 1,2,3,4-Tetrahydrolepidine cannot be oxidized even with $FeCl_3$.



(7)

In conclusion, the relative reactivities of these oxidants are as follows: Fe(III) ≫ 1,2-dihydrolepidine–HCl (disproportionation) ≫ O_2 > PhCHO ~ PhCH=NPh > CH_3COCH=CH_2.

Therefore, exclusive disproportionation should occur in the presence of HCl except for the case of $FeCl_3$ as an oxidant.

EXPERIMENTAL

Materials. $FeCl_3 \cdot 6H_2O$ used was of guaranteed reagent grade. Benzaldehyde, b.p. 90° (44 mm), and N-ethylaniline, b.p. 107·5° (30 mm), were distilled under reduced N_2 atm. Benzylidenaniline was prepared from benzaldehyde and aniline and recrystallized from MeOH, m.p. 52° (lit.[11] 51°). β-Ethoxyethyl methyl ketone, b.p. 64·5° (30 mm) [lit.[11] 57–58° (20 mm)] was prepared from methyl vinyl ketone and EtOH.[12] Methyl vinyl ketone, b.p. 82° (lit.[13] 82°) and 4-anilinobutan-2-one, m.p. 34·5° (lit.[13] 34·5°), were prepared according to our previous report.[13] Lepidine was prepared from 4-anilinobutan-2-one by Murata's procedure,[14] b.p. 102° (5 mm) [lit.[14]; 95° (3 mm)], n_D^{21} 1·6175 (lit.[14] 1·6185); picrate m.p. 213° (lit.[14] 212–213°). The IR spectrum of lepidine was identical with that reported.[15] 1,2-Dihydrolepidine was prepared by LAH reduction of lepidine,[16] purified by distillation under N_2, b.p. 86° (1 mm), and stored in a sealed tube under N_2 in a refrigerator. 1,2,3,4-Tetrahydrolepidine was prepared by reduction of lepidine[17] or by treatment of 4-anilinobutan-2-ol with conc H_2SO_4.[18] The IR spectra of these products obtained by different procedures were identical. The IR spectra were measured by a Perkin–Elmer grating IR spectrophotometer Model 337.

4-Anilinobutan-2-ol was prepared by a new method. Na metal (3 g) was added to a soln of 4-anilinobutan-2-one (3·2 g) in EtOH (20 ml) and the soln was refluxed for 5 hr. The soln was poured into water and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and distilled. 4-Anilinobutan-2-ol, 2·8 g (87%), m.p. 58° (lit.[18] 61). The IR spectrum was identical with that by Bringi,[18] ν_{NH} (3400 cm^{-1}) and ν_{CH_2} (2900 cm^{-1}).

Analysis. Identification of 1,2-dihydrolepidine was done as follows. On addition of one drop of 1,2-dihydrolepidine to an ethanolic soln of 2,6-dichlorophenol-indophenol, the pink colour of the soln immediately disappeared, whereas lepidine and tetrahydrolepidine were unreactive with this reagent. This phenomenon indicates the much more reactive nature of the H atoms of 1,2-dihydrolepidine as compared with those of 1,2,3,4-tetrahydrolepidine.

Lepidine, 1,2-dihydrolepidine and 1,2,3,4-tetrahydrolepidine were estimated by GLC employing a Yanagimoto gas chromatograph Model GCG-550 with a 0·75 m × 4 mm column packed with PEG 20M (30 wt%) on celite 545 of 80–100 mesh, using N_2 as carrier gas. Specific retention times were 1·00 for 1,2,3,4-tetrahydrolepidine, 1·05 for 1,2-dihydrolepidine and 1·10 for lepidine. The concentration of lepidine was also measured by the absorption at 233 mμ (λ_{max}) in 0·1N HClaq, where 1,2-dihydrolepidine and 1,2,3,4-tetrahydrolepidine have no appreciable absorption. UV spectra were measured by a Shimadzu automatic spectrophotometer Model SV 50A.

H_2O_2, which is supposed to be an autoxidation product of 1,2-dihydrolepidine, was identified by lead sulfide test,[19] i.e. an ethanolic soln of 1,2-dihydrolepidine kept for 5 min at room temp can effect a colour change of brown PbS into white $PbSO_4$, which indicates the presence of H_2O_2. It was confirmed that the colour change occurred immediately in the presence of over $1{\cdot}1 \times 10^{-3}$M H_2O_2. Under the stream of N_2, no change in colour was observed.

The ferrous ion formed in the reaction of 1,2-dihydrolepidine with $FeCl_3$ was detected as follows: A mixture of $FeCl_3$ (5×10^{-4}M) and 1,2-dihydrolepidine (5×10^{-4}M) (10 ml) in EtOH were mixed in a flask under N_2 atm. When one drop of 2% ethanolic α,α'-dipyridyl soln was added to the soln, the colourless soln was immediately changed to pink, which shows the presence of ferrous ion. A blank test with ethanolic 1,2-dihydrolepidine alone or ethanolic $FeCl_3$ alone showed no change in colour. Ferrous ion was also detectable by a mixture of 1% dimethylglyoxime and NH_3 in EtOH which gave a ppt of ferrous complex.

The oxidation of 1,2-dihydrolepidine. Except for the case of autoxidation, the reaction was carried out under N_2 atm. A typical experiment was as follows: An ethanolic soln of 0·05M 1,2-dihydrolepidine (10 ml), and an ethanolic soln of 0·05M benzaldehyde (10 ml), which had reached thermal equilibrium, were mixed in a glass-stoppered flask under N_2 atm. Aliquots (1 ml) were pipetted out at regular intervals and diluted 1000 fold with 0·1N HClaq to stop the reaction. The concentration of resulting lepidine was estimated by the measurement of absorbance at 233 mμ.

Attempted oxidation of 1,2,3,4-tetrahydrolepidine. A soln of 1,2,3,4-tetrahydrolepidine (0·14 g) and $FeCl_3$ (0·27 g) in EtOH (20 ml) was heated for 3 hr at 65° under N_2 atm. The reaction mixture was analysed by GLC. Neither 1,2-dihydrolepidine nor lepidine was detected.

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