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PREPARATIONS AND REACTIONS OF 1,2,3-TRIALKYL-1,2-DIHYDROQUINOLINES AND ITS RELATED COMPOUNDS

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Abstract—Several 1,2,3-trialkyl-1,2-dihydroquinolines (**4** and **5**) were prepared from the reactions of N-alkylanilinomagnesium bromide (**1** and **2**) with aliphatic aldehydes (**3**). Solutions of these dihydroquinolines in carbon tetrachloride or chloroform gave the corresponding 1,2,3-trialkylquinolinium chlorides (**10** and **11**) in high yields. Alkali treatment of 1,3-dimethyl-2-ethylquinolinium chloride (**10b**) led to 1,3 - dimethyl - 2 - acetyl - 1, 2 - dihydroquinoline (**13**), which was unstable and readily converted to 1,3-dimethyl-2-quinolone (**6**) in the air.

General 1,2,3-trialkyl-1,2-dihydroquinolines have been conventionally prepared from the corresponding quinolinium salts by LAH or $NaBH_4$ reduction, or from reactions of 1,3-dialkylquinolinium salts with alkylmagnesium halides.[1] Nielsen *et al.*[2] isolated 1,2-diethyl-3-methyl-1,2-dihydroquinoline from the reaction of aldol condensation of diethyl ketone with propionaldehyde in the presence of N-ethylanilinomagnesium bromide. We have previously reported that the reaction of N-methylanilinomagnesium bromide with propionaldehyde gave 1,3-dimethyl-2-ethyl-1,2-dihydroquinoline (**4b**) in good yield.[3] In this paper, the direct preparation of new 1,2,3-trialkyl-1,2-dihydroquinolines are described as well as some of the reactions that they undergo.

Ten kinds of 1,2,3-trialkyl-1,2-dihydroquinolines (**4b–f** and **5b–f**) and two kinds of 1,2-dialkyl-1,2-dihydroquinolines (**4a** and **5a**) were synthesized from reactions of two moles of aliphatic aldehydes (**3a–f**) in THF with N-methylanilinomagnesium bromide (**1**) or N-ethylanilinomagnesium bromide (**2**), prepared from N-methylaniline or N-ethylaniline and an equimolar amount of ethylmagnesium bromide. Their structures were confirmed by elemental, IR and ^1H NMR spectral analyses (Table 1).

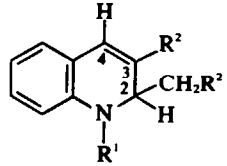
These dihydroquinolines were unstable in the air and readily oxidized to form the corresponding 2- and 4-quinolones. For example, **4b** gave, when heated in the air, 1,3-dimethyl-2-quinolone (**6**, 92%) and 1,3-dimethyl-2-ethyl-4-quinolone (**8**, 5%). And 1 - ethyl - 2 - phenethyl - 3 - benzyl - 1, 2 - dihydroquinoline (**5f**) led to 1 - ethyl - 3 - benzyl - 2 - quinolone (**7**, 64%) and 1 - ethyl - 2 - phenethyl - 3 - benzyl - 4 - quinolone (**9**, 13%) under the same condition.

Solutions of the 1,2-dihydroquinolines (**4** and **5**) in carbon tetrachloride or chloroform were stable under N_2, but in the presence of oxygen crystals of the corresponding 1,2-dialkyl- or 1, 2, 3 - trialkyl - quinolinium chlorides (**10** and **11**) were separated out in high yields (Table 2). Although crystals of the 1,2-dihydroquinoline hydrochlorides were relatively stable in the air, their alcoholic solutions also gave slowly high yields of **10** and **11** at room temperature. Reduction of these quinolinium chlorides (**10** and **11**) with LAH gave **4** and **5** in high yields.

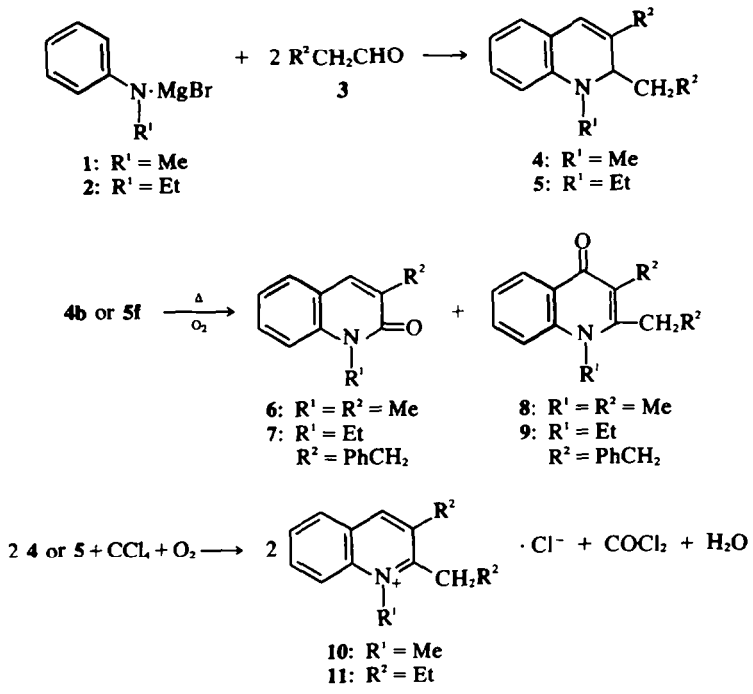
The addition of a dilute potassium hydroxide solution to an aqueous solution of **10b** liberated an unstable yellow oil. Purification of this oil by column chromatography under N_2 gave 80% of **6** and 10% of 1, 3 - dimethyl - 2 - acetyl - 1, 2 - dihydroquinoline (**13**) which was rapidly oxidized to **6** in the air. When the alkali treatment of **10b** and extraction of the reactant were carried out using all deuterated reagents (D_2O, NaOD and $CDCl_3$) in a stream of N_2, NMR spectrum of the chloroform-D_1 extract suggested the presence of 1,3 - dimethyl - 2 - ethyliden - 1,2 - dihydroquinoline (**12**)† by signals at δ 1·90 (d, $J = 8$ Hz, 3H, $=CH-CH_3$), 2·00 (d, $J = 0{\cdot}5$ Hz, 3H, $\doteq CH_3$), 3·43 (s, 3H, $N-CH_3$), 4·62 (q, $J = 8$ Hz, 1H, $=CH-CH_3$), 6·37 (s, 1H, $\doteq H$), and 6·7–7·4 (m, 4H, aromatic protons). Nevertheless an attempt of isolation of pure **12** was unsuccessful because of high reactivity of **12** with oxygen. A mixture of **13** and 2,4-dinitrophenylhydrazine in ethanol was allowed to stand under an atmosphere to obtain **6** and acetaldehyde 2,4-dinitrophenylhydrazone. These experi-

†Rosenhauer *et al.*[4] have been reported that alkali treatment of 1,2-dimethylquinolinium salts gave 1 - methyl - 2 - methylene - 1,2 - dihydroquinoline, which was only stable for a limited period in the air (turning red and resinifying).

Table 1. 1,2-Dialkyl-1,2-dihydroquinolines and 1,2,3-trialkyl-1,2-dihydroquinolines

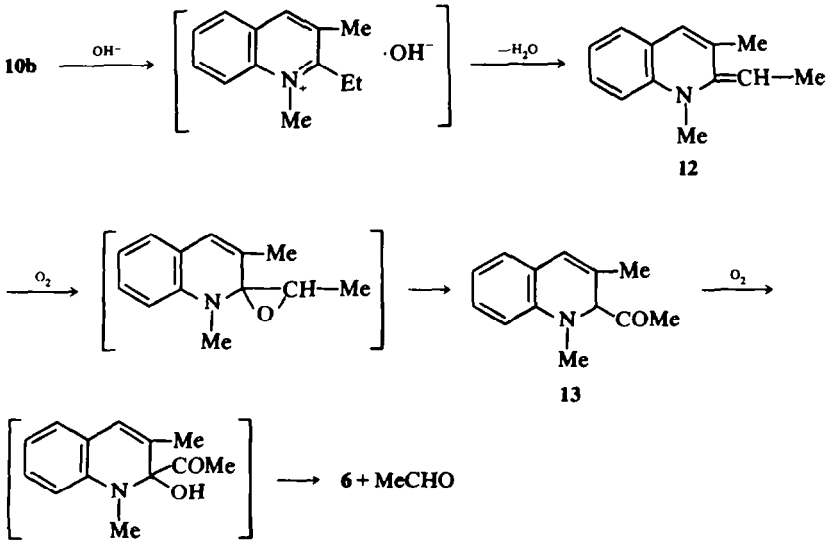


Compound	R^1	R^2	Reaction Condition °C(h)	Yield %	B.p. °C (mmHg)	NMR H-2 δ	NMR H-4	HCl salt m.p. °C	HCl salt Formula	Analysis Found (Calcd.), % C	H	N
4a	Me	H	−10–0 (1)	2·1	40–45 (0·1)	4·10, quintet J = 5·0, 6·0 Hz	6·40, d J = 10·0 Hz	110–112	$C_{11}H_{13}N$·HCl	67·51 (67·64)	7·18 (7·23)	7·32 (7·17)
4b	Me	Me	10(0·5), then 50–60(1)	61·9	75–78 (0·07)	3·82, t J = 3·5 Hz	6·14, s	121–123	$C_{13}H_{17}N$·HCl	69·68 (69·79)	8·01 (8·11)	6·66 (6·26)
4c	Me	Et	10 (0·5), then 50–60(1)	49·2	95–99 (0·05)	3·95, t J = 3·5 Hz	6·26, s	108–109	$C_{15}H_{21}N$·HCl	71·43 (71·55)	8·72 (8·81)	5·63 (5·56)
4d	Me	i-Pr	10(0·5), then 50–60 (1)	44·7	100–105 (0·25)	3·94, t J = 5·0 Hz	6·27, s	115–116	$C_{17}H_{25}N$·HCl	72·83 (72·97)	9·38 (9·37)	5·21 (5·01)
4e	Me	n-Am	10(0·5), then 50–60 (1)	28·6	140–145 (0·07)	3·84, t J = 4·0	6·07, s	136–137	$C_{21}H_{33}N$·HCl	75·11 (75·08)	10·13 (10·20)	4·23 (4·17)
4f	Me	$PhCH_2$	10(0·5), then 50–60 (1)	14·5	190–194 (0·03)	4·02, t J = 5·0 Hz	6·28, s	91–92	$C_{25}H_{25}N$·HCl	79·52 (79·88)	6·99 (6·97)	3·68 (3·73)
5a	Et	H	−10–0(1)	0·3	54–57 (0·04)	4·26, quintet J = 5·0, 6·0 Hz	6·41, d J = 10·2 Hz	110–113	$C_{12}H_{15}N$·HCl	69·03 (68·73)	7·66 (7·68)	6·84 (6·68)
5b	Et	Me	10(0·5), then 50–60 (1)	55·5	78–82 (0·12)	3·95, t J = 4·5 Hz	6·10, s	124–125	$C_{14}H_{19}N$·HCl	70·45 (70·72)	8·51 (8·48)	5·76 (5·89)
5c	Et	Et	10(0·5), then 50–60 (1)	46·5	85–91 (0·06)	3·94, t J = 5·0 Hz	6·04, s	110–112	$C_{16}H_{23}N$·HCl	72·35 (72·27)	8·92 (9·10)	5·01 (5·27)
5d	Et	i-Pr	10(0·5), then 50–60 (1)	18·5	93–96 (0·07)	3·94, t J = 5·0 Hz	6·27, s	115–116	$C_{18}H_{27}N$·HCl	73·46 (73·55)	9·45 (9·60)	4·96 (4·77)
5e	Et	n-Am	10(0·5), then 50–60 (1)	46·2	110–113 (0·03)	3·38, t J = 5·0 Hz	6·03, s	144–145	$C_{22}H_{35}N$·HCl	75·48 (75·50)	10·24 (10·37)	4·18 (4·00)
5f	Et	$PhCH_2$	10(0·5), then 50–60(1)	35·6	m.p. 88	4·06, t J = 5·2 Hz	6·30, s	78–79	$C_{26}H_{27}N$·HCl	79·69 (80·08)	7·27 (7·24)	3·89 (3·56)



a: $R^2 = H$
b: $R^2 = Me$
c: $R^2 = Et$
d: $R^2 = n\text{-}Pr$
e: $R^2 = n\text{-}Am$
f: $R^2 = PhCH_2$

SCHEME 1.



SCHEME 2.

Table 2. 1-Ethyl-2-methylquinolinium chloride and 1,2,3-trialkylquinolinium chlorides

Compounds	R¹	R²	Reaction time day	Yield %	M.p. °C	Formula	Analysis Found (Calcd.), % C	H	N
10b	Me	Me	1	98·2	230–232 dec	$C_{13}H_{16}NCl$	70·52 (70·42)	7·52 (7·27)	6·31 (6·32)
10c	Me	Et	2	92·7	164–166 dec	$C_{15}H_{20}NCl$	72·03 (72·16)	8·16 (8·48)	5·53 (5·61)
10d	Me	i-Pr	7	73·5	226–227 dec	$C_{17}H_{24}NCl$	73·34 (73·48)	8·48 (8·70)	5·11 (5·04)
10e	Me	n-Am	7	61·8	163–164 dec	$C_{21}H_{32}NCl$	75·47 (75·53)	9·73 (9·66)	4·20 (4·19)
11a	Et	H	1	97·7	255–258 dec	$C_{12}H_{14}NCl$	69·28 (69·39)	6·52 (6·79)	6·73 (6·73)
11b	Et	Me	1	96·4	225–227 dec	$C_{14}H_{18}NCl$	71·24 (71·34)	7·78 (7·69)	5·61 (5·94)
11c	Et	Et	2	90·1	189–190 dec	$C_{16}H_{22}NCl$	72·69 (72·84)	8·14 (8·41)	5·30 (5·31)
11f	Et	$PhCH_2$	5	95·5	194–195 dec	$C_{26}H_{26}NCl$	80·34 (80·50)	7·01 (6·75)	3·24 (3·61)

mental results could be regarded as the reactions proceed by way of the route shown in Scheme 2.

EXPERIMENTAL

NMR spectra were recorded using a JNM-MH-60 (JEOL) spectrometer employing TMS as an internal standard. IR spectra were measured on a IRA-2 (JASCO) spectrometer. Gas-liquid chromatographic analyses were performed on JGC-1100FP (JEOL). All m.ps were determined on a Yanagimoto Micro Melting Point Apparatus, and are uncorrected.

1,2-Dialkyl-1,2-dihydroquinolines (**4a** *and* **5a**) *and* 1, 2, 3 - *trialkyl* - 1, 2 - *dihydroquinolines* (**4b-f** *and* **5b-f**). A solution of *aliphatic aldehyde* (120 mmol) in 30 ml of dry THF was added slowly to a chilled (0–10°) solution of N-methyl (or ethyl)-anilinomagnesium bromide (**1** or **2**) prepared by the addition of N-methyl (or ethyl) aniline (60 mmol) to a soln of EtMgBr (60 mmol) in 90 ml of THF. The mixture was stirred at room temp for 30 min, and then heated at 50–60° for 1 h. After the addition of 50 ml of a sat NH_4Claq, the THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated. Distillation of the residue gave 1,2-dihydroquinoline derivative. Their data are listed in Table 1.

Autoxidation of 1,3 - *dimethyl* - 2 - *ethyl* - 1,2 - *dihydroquinoline* (**4b**). Compound **4b** (3·74 g, 20 mmol) was heated at 110° with stirring for 30 h in the air, then chromatographed on a silica gel column. The first fraction of benzene gave 3·18 g (92%) of **6**: m.p. 64–65°; NMR ($CDCl_3$) δ 2·28 (s, 3H, =CH_3), 3·75 (s, 3H, N-CH_3), 7·6–6·9 (m, 5H, =H and aromatic H); IR (KBr) 1630 cm^{-1}. (Found: C, 76·29; H, 6·49; N, 7·95. $C_{11}H_{11}ON$ requires: C, 76·27; H, 6·40; N, 8·09%).

The second fraction of benzene gave 20 mg (5%) of **7**: m.p. 109–110°; NMR ($CDCl_3$) δ 1·26 (t, 7·5 Hz, 3H, $-CH_2CH_3$), 2·73 (s, 3H, =CH_3), 2·98 (q, 7·5 Hz, 2H, $-CH_2CH_3$), 3·61 (s, 3H, N-CH_3), 7·2–7·9 (m, 4H, aromatic H); IR (KBr) 1643 cm^{-1}. (Found: C, 77·25; H, 7·54; N, 6·88. $C_{13}H_{15}ON$ requires: C, 77·58; H, 7·51; N, 6·96%).

Autoxidation of 1 - *ethyl* - 2 - *phenethyl* - 3 - *benzyl* - 1, 2 - *dihydroquinoline* (**5f**). In the same manner as described above, **5f** (3·53 g, 10 mmol) gave 1·68 g (66%) of **7** and 482 mg (13%) of **9**.

Compound **7**: B.p. 200–205° (0·03 mm); NMR ($CDCl_3$) δ 1·40 (t, 7·0 Hz, 3H, $-CH_3$), 4·04 (s, 2H, =CH_2Ph), 4·43 (q, 7·0 Hz, 2H, N-CH_2–), 6·9–7·4 (m, 10H, =H and aromatic H); IR (film) 1642 cm^{-1}. (Found: C, 82·21; H, 6·43; N, 5·28. $C_{18}H_{17}ON$ requires: C, 82·10; H, 6·51; N, 5·32%). **9**: b.p. 210–215° (0·03 mm); NMR ($CDCl_3$) δ 1·42 (t, 7·0 Hz, 3H, $-CH_3$), 2·46 (m, 2H, CH_2CH_2Ph), 3·45 (m, 2H, CH_2CH_2Ph), 4·50 (q, 7·0 Hz, 2H, N-CH_2–), 4·53 (s, 2H, =CH_2Ph), 7·1–7·6 (m, 14H, aromatic H); IR (film) 1653 cm^{-1}. (Found: C, 84·92; H, 6·74; N, 3·95. $C_{26}H_{25}ON$ requires: C, 84·98; H, 6·86; N, 3·81%).

1-Ethyl-2-methylquinolinium chloride (**11a**) *and* 1, 2, 3 - *trialkylquinolinium chlorides* (**10b-e** *and* **11b, c, f**). A soln of **4b–e** or **5a–c, f** (10 mmol) in CCl_4 (10 ml) was stirred at room temp for 1–7 days. The ppt was filtered and recrystallized to give the corresponding quinolinium chloide. The results are summarized in Table 2.

Lithium aluminum hydride reduction of 1,3-*dimethyl*-2-*ethylquinolinium chloride* (**10b**). A soln of **10b** (250 mg, 1·13 mmol) and LAH (40 mg, 1·05 mmol) in 60 ml of ether was stirred for 20 min and then hydrolyzed with a sat NH_4Claq. The mixture was extracted with ether. The extract was dried and concentrated. Silica gel column chromatography of the residue gave 180 mg (92·2%) of **4b**.

In a similar manner, **11f** 388 mg, 1·00 mmol) gave 353 mg (100%) of **5f**.

Alkali treatment of 1,3-*dimethyl*-2-*ethylquinolinium chloride* (**10b**). To a soln of **10b** (2·21 g, 10 mmol) in 10 ml of H_2O was added 10 ml of 15% KOH at 0–5°. Yellow oil was liberated immediately. The oil was extracted with ether and chromatographed on a silica gel column under N_2. The first fraction of benzene gave 200 mg (10%) of **13**: NMR ($CDCl_3$) δ 1·82 (d, 0·5 Hz, 3H, =CH_3), 2·21 (s, 3H, $COCH_3$), 2·85 (s, 3H, N-CH_3), 4·33 (s, 1H, >CH-Ac), 6·23 (d, 0·5 Hz, 1H, =H), 6·4–7·2 (m, 4H, aromatic H); IR (film) 1703 cm^{-1}; mass spectrum *m/e* 201 (M^+, 9), 173 (30), 158 (100), 143 (21), and 115 (25). The second benzene fraction gave 1·40 g (80%) of **6**.

Autoxidation of **13**. (a) Compound **13** (50 mg, 0·25 mmol) was allowed to stand for 24 h in the air and then purified on a silica gel column (benzene) to give 36 mg (86%) of **6**.

(b) A mixture of **13** (130 mg, 0·647 mmol), 2,4-dinitrophenylhydrazine (128 mg, 0·647 mmol) and 35% HCl (1 ml) in 50 ml of EtOH was allowed to stand for 24 h at room temp. The mixture was neutralized with KOH and extracted with $CHCl_3$. The extract was dried and chromatographed on a silica gel column. The first fraction of benzene gave 145 mg (64·7%) of acetaldehyde 2, 4 - dinitrophenylhydrazone, which was identified with an authentic sample by comparison of their IR. The second benzene fraction gave 79 mg (70·6%) of **6**.

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