



0040-4020(95)00971-X

## Synthesis of 3,4-Dihydroisoquinolines, 2-Alkyl(Acyl)-1(2H)-3,4-Dihydroisoquinolinones, 2-Alkyl-1(2H)-Isoquinolinones and 1-Alkyl-2(2H)-Quinolinones by oxidation with Potassium Permanganate

Atanas P. Venkov\* and Stela M. Statkova-Abeghe

Department of Chemistry, University of Plovdiv, Plovdiv 4000, Bulgaria

**Abstract:** Synthesis of 3,4-dihydroisoquinolines **2**, 2-alkyl- **6** and 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9**, 2-alkyl-1(2H)-isoquinolinones **14**, N-alkyl-3,4-dihydro-2(2H)-quinolinones **16** and N-alkyl-2(2H)-quinolinones **19** by oxidation of 1,2,3,4-tetrahydroisoquinolines **1**, N-alkyl (acyl)iminium salts of 3,4-dihydroisoquinolines **5,8** and isoquinoline **13** as well as of N-alkyl ammonium salts of tetrahydroquinoline **15** and quinoline **18** with potassium permanganate is described.

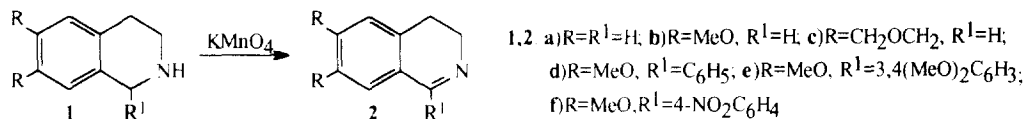
Among the variety of reagents used in oxidation reactions of isoquinoline and quinoline derivatives such as Fremy's salt<sup>1a,b</sup>, lead (II) and mercuric acetates<sup>1c-f</sup>, chromic acid<sup>1g</sup>, peracids<sup>1h</sup>, diphenylselenium bis (trifluoroacetate)<sup>1i</sup>, etc., potassium permanganate<sup>2a</sup> and active manganese dioxide<sup>2b</sup> have acquired a prominent place. Active manganese dioxide has been recommended as a mild and selective reagent for dehydrogenation, aromatization and oxidation of diverse classes of organic compounds and has been particularly useful in elucidation the structure of isoquinoline and quinoline alkaloids.<sup>2b</sup> It has been successfully applied to converting 1,2,3,4-tetrahydroquinoline to quinoline and 2,3-dihydroindole into indole, etc.<sup>2c</sup> while  $\text{KMnO}_4$  has been somehow neglected and has been used only for dehydrogenation of 1-substituted 1,2,3,4-tetrahydro- $\beta$ -carbolines to 3,4-dihydro- $\beta$ -carboline derivatives.<sup>2d</sup>

We wish to report the investigations on the synthetic utility of  $\text{KMnO}_4$  as dehydrogenating reagent on 1,2,3,4-tetrahydroisoquinolines and oxidizing agent on N-alkyl, N-acyl salts of 3,4-dihydroisoquinoline, isoquinoline, 1,2,3,4-tetrahydroquinoline and quinoline for preparation of 3,4-dihydroisoquinolines **2**, 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones (1-oxo-3,4-dihydroisoquinolines) **6**, 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9**, N-alkyl-2(2H)-3,4-dihydroquinolinones **16** and N-alkyl-2(2H)-quinolinones **19**. These derivatives are important intermediates for synthesis of isoquinoline alkaloids and their derivatives, quinoline derivatives and are of increasing interest in the pharmaceutical chemistry because of a large spectrum of biological activity.<sup>3a-d</sup> 1(2H)-Isoquinolinone skeleton is also a common building block of a wide variety of benzo[c] phenanthridine

alkaloids.<sup>4</sup> To date numerous processes for the elaboration of this heterocyclic framework have been reported but few have demonstrated broad synthetic utility. The published preparations of 3,4-dihydroisoquinolines, 1(2H)-isoquinolinones and 3,4-dihydro-1(2H)-isoquinolinones have required drastic reaction conditions, especially of those without electron donating groups in the aromatic ring of heterocycle and yields are generally low.<sup>5a-c</sup>

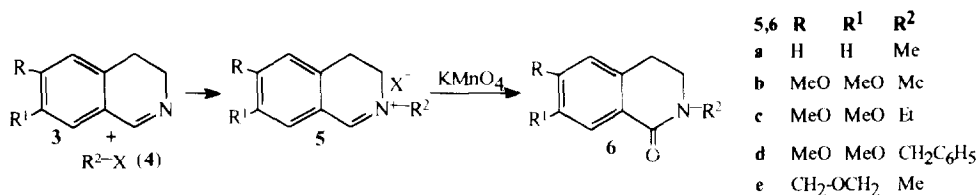
The oxidation of tetrahydroquinolines, N-alkyl- and N-acyliminium salts of 3,4-dihydroisoquinoline, isoquinoline, tetrahydroquinoline and quinoline with  $\text{KMnO}_4$  was investigated in acetone, acetonitrile and as phase transfer reaction in chlorinated hydrocarbons (dichloromethane, 1,2-dichloroethane) in the presence of 18-Crown-6.

The oxidation of 1,2,3,4-tetrahydroisoquinoline **1** with  $\text{KMnO}_4$  in acetone at room temperature was a fast exothermic reaction leading to isoquinoline, while at 0°C dehydrogenation occurred for several minutes to 3,4-dihydroisoquinoline in a yield of 80% but it was difficult to control the reaction since aromatization followed to isoquinoline. The dehydrogenation in acetonitrile proceeded slowly (for about 30 min) to 3,4-dihydroisoquinoline (80%) and isoquinoline (20%), which were not easy to separate. Dehydrogenation of tetrahydroisoquinoline to 3,4-dihydroisoquinoline became selective and preparatively useful when the reaction was carried out in dichloromethane or 1,2-dichloroethane at room temperature in the presence of catalytic amount of 18-Crown-6.

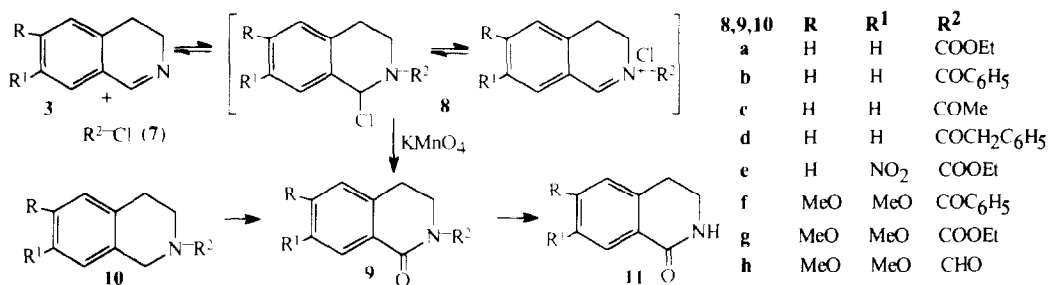


The reaction depended on the amount of  $\text{KMnO}_4$  and the reaction time, since when the dehydrogenation of tetrahydroisoquinoline (1 mmol) was carried out in dichloromethane in the presence of catalytic amount of 18-Crown-6 and an excess of  $\text{KMnO}_4$  (4 mmol) for 16 h at room temperature, an aromatization occurred and isoquinoline was obtained in 80% yield. Substituted tetrahydroisoquinolines **1** can be efficiently and conveniently dehydrogenated with  $\text{KMnO}_4$  to the corresponding 3,4-dihydroisoquinolines **2** in very good yields (Table 1, 2a-f).

The oxidation of some N-alkyl-3,4-dihydroisoquinolinium salts to 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones **6** has been reported by DMSO in concentrated hydrochloric acid.<sup>6</sup> The oxidation of N-alkyl-3,4-dihydroisoquinolinium salts **5a-e** obtained from 3,4-dihydroisoquinolines **3** and alkyl halides **4** with  $\text{KMnO}_4$  in presence of 18-Crown-6 as a phase transfer catalyst in dichloromethane afforded also the corresponding the 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones **6** (Table 1, 6a-e) in yields closed to the reported.<sup>6</sup> The alkaloid N-methylcorydaldine **6b** and its synthetic analogues N-ethylcorydaldine **6c**, N-benzylcorydaldine **6d** and oxyhydrastinine **6e** were obtained by this procedure in good yields.



N-Acyliminium intermediates **8** of 3,4-dihydroisoquinolines **3** and acyl chlorides **7** were successfully used as electrophilic reagents toward aromatics in the inter- and intramolecular  $\alpha$ -amidoalkylation reaction for synthesis of isoquinoline derivatives.<sup>7</sup> The investigations on the oxidation of **8** were carried out in acetone, acetonitrile and as phase transfer reaction in the presence of 18-Crown-6. The oxidation of in situ obtained adduct of 3,4-dihydroisoquinoline with ethyl chloroformate **8a** in acetonitrile proceeded at room temperature for 2 h to 2-ethoxycarbonyl-3,4-dihydro-1(2H)-isoquinolinone **9a** in 42% yield, while its oxidation in the presence of 18-Crown-6 in dichloromethane afforded **9a** in 82% yield.



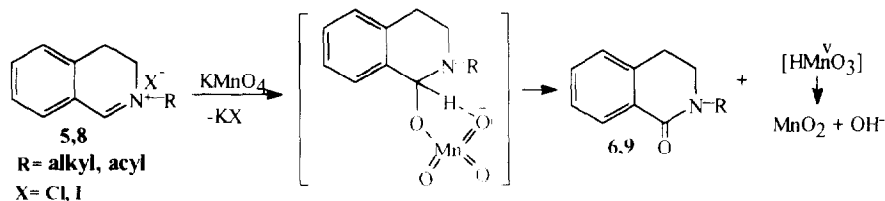
Apparently the phase transfer oxidation of **8** afforded better yields of the corresponding 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9**. The quantity of  $\text{KMnO}_4$  and the reaction time depended on the nature of the 3,4-dihydroisoquinoline **3** and acyl chloride **7** used for the formation of the corresponding N-acyliminium intermediates **8** (Table 1, 9a-e).

The oxidation of adducts **8** from 6,7-dimethoxy-3,4-dihydroisoquinoline and acyl chlorides with  $\text{KMnO}_4$  in acetonitrile or as phase transfer reaction led to low yields of **9** (30-40%). These results can be explained by the equilibrium of the covalent and salt structures of **8** in solution, depending on the substituents of 3,4-dihydroisoquinoline and the nature of acyl chloride. The presence of electron donating groups in **8f-h** probably led to domination of the covalent structure that can not be oxidized. We isolated by column chromatography the less polar of the two compounds for adduct **8a**. <sup>1</sup>H-NMR spectrum of the isolated compound showed a singlet at 6.55 ppm for the covalent structure of **8a**, since the signal for the C-1 proton in 3,4-dihydroisoquinoline is at 8.10 ppm. The attempts for oxidation of the compound with  $\text{KMnO}_4$  in a phase transfer condition or in acetonitrile even after 10 h led to unchanged material, which led us to the conclusion that N-acyliminium salts are capable to oxidation.

The synthesis of 2-acyl-1(2H)-isoquinolinones **9** can be carried out also as one pot reaction starting from the corresponding tetrahydroisoquinolines **1**. For example, dehydrogenation of 1,2,3,4-tetrahydroisoquinoline

with  $\text{KMnO}_4$  in the presence of 18-Crown-6 in dichloromethane for 30 min at room temperature to 3,4-dihydroisoquinoline, then treatment with acetyl chloride for the formation of the N-acyliminium intermediate **8c** and following oxidation with potassium permanganate afforded **9c** in 58% yield.

Oxidations of N-alkyl- **5** and N-acyliminium salts **8** of 3,4-dihydroisoquinolines with  $\text{KMnO}_4$  in phase transfer conditions or in acetonitrile proceeded with the formation of  $\text{MnO}_2$  as precipitate. The attempted oxidations of **5** and **8** with activated  $\text{MnO}_2$  in acetonitrile or in phase transfer conditions led to unchanged starting salts. For example, **8a** did not change after 24 h at room temperature. The dependence to oxidation of **5** and **8** with  $\text{KMnO}_4$  from the salt formation and the precipitation of  $\text{MnO}_2$  in the course of the reaction allowed the following mechanism to be assumed.



An alternative route to 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9** was worked up by oxidation with  $\text{KMnO}_4$  of easily available 2-acyltetrahydroisoquinolines **10**<sup>7</sup> at phase transfer conditions (Table 1, 9a-h). The procedure was especially suitable for synthesis of **9** when the adducts **8** existed predominantly in the covalent structure as those with electron donating groups in the aromatic ring and their oxidation led to poor yields of 2-acyl-3,4-dihydro-1(2H)-isoquinolinones (Table 1, 9f-h).

The oxidation of 2-acyltetrahydroisoquinolines **10** in acetone afforded also **9** but a partial hydrolysis was observed to 3,4-dihydro-1(2H)-isoquinolinone **11**. For example, the oxidation of **10c** and **10d** in acetone led to **9c** and **9d** that were accompanied by 3,4-dihydro-1(2H)-isoquinolinone **11** in a yield of 45% and 35% respectively. 2-Acyl-3,4-dihydro-1(2H)-isoquinolinones **9** as cyclic imides hydrolyzed to the corresponding 3,4-dihydro-1(2H)-isoquinolinones **11** depending upon the nature of N-acyl group. Thus, **9c** and **9d** hydrolyzed to **11** even at stirring with neutral aluminum oxide in diethyl ether solution for 3 h at room temperature, while **9f** was converted to the alkaloid corydaldine<sup>8</sup> after stirring with sodium methoxide in methanol for 3 h at room temperature. The oxidation of **8** with  $\text{KMnO}_4$  was examined also in acetone but it was found that N-acyliminium salts **8a** reacted with acetone to afford 1-acetyl-2-ethoxycarbonyltetrahydroisoquinoline.

The usefulness of the phase transfer oxidation with  $\text{KMnO}_4$  in the presence of 18-Crown-6 of tetrahydroisoquinolines **1**, N-alkyl-**5** and N-acyliminium salts of 3,4-dihydroisoquinoline **8** prompted us to investigate the oxidation of in situ obtained N-alkyl- and N-acyliminium salts **13** of isoquinoline. The oxidation of N-methylisoquinolinium iodide **13a** with  $\text{KMnO}_4$  in dichloroethane in the presence of catalytic amount of 18-Crown-6 for 3 h at room temperature led to 2-methyl-1(2H)-isoquinolinone **14a** in 50% yield. However, the same oxidation in acetonitrile, without phase transfer catalyst for 45 min, afforded **14a** in 82% yield. This

**Table 1:** 3,4-Dihydroisoquinolines **2a-f**, 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones **6a-e**, 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9a-h**, 2-alkyl-1(2H)-isoquinolinones **14a-c**, 2-alkyl-3,4-dihydro-2(2H)-quinolinones **16b,c** and 2-alkyl-2(2H)-quinolinones **19a-c** Prepared

Pro- duct	Sub- strate	React. Conditions		Yield (%)	mp (°C)	Mol. Formula <sup>a</sup> or Lit. mp (°C)
		KMnO <sub>4</sub> (mol)	Time (min)			
<b>2a</b>	<b>1a</b>	1.0	60	95	176-178 <sup>b</sup>	174-176 <sup>11a</sup>
<b>2b</b>	<b>1b</b>	1.0	180	78	204-206 <sup>b</sup>	201-203 <sup>11b</sup>
<b>2c</b>	<b>1c</b>	1.0	60	80	95-96	91 <sup>11a</sup>
<b>2d</b>	<b>1d</b>	1.0	20	75	121-122	121-123 <sup>11c</sup>
<b>2e</b>	<b>1e</b>	1.0	30	82	167-168	171 <sup>11d</sup>
<b>2f</b>	<b>1f</b>	2.0	120	89	153	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> (312.3)
<b>6a</b>	<b>5a</b>	2.0	360	66	oil	C <sub>10</sub> H <sub>11</sub> NO (161.1)
<b>6b</b>	<b>5b</b>	1.0	180	63	130	126-127 <sup>12a</sup>
<b>6c</b>	<b>5c</b>	1.0	180	70	98	95 <sup>12a</sup>
<b>6d</b>	<b>5d</b>	1.0	120	62	102-103	101-102 <sup>12b</sup>
<b>6e</b>	<b>5e</b>	1.0	120	56	98-99	97-98 <sup>12c</sup>
<b>9a</b>	<b>8a</b>	2.0	120	92	oil	C <sub>12</sub> H <sub>13</sub> NO <sub>3</sub> (219.2)
	<b>10a</b>	2.0	120	86		
<b>9b</b>	<b>8b</b>	2.0	360	68	132	132 <sup>12d</sup>
	<b>10b</b>	2.0	180	73		
<b>9c</b>	<b>8c</b>	2.0	120	76	99-100	100 <sup>12d</sup>
	<b>10c</b>	2.0	180	65		
<b>9d</b>	<b>8d</b>	2.0	180	57	73-74	C <sub>17</sub> H <sub>15</sub> NO <sub>2</sub> (265.3)
	<b>10d</b>	2.0	180	90		
<b>9e</b>	<b>8e</b>	3.0	360	65	138-140	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>5</sub> (264.2)
<b>9f</b>	<b>10f</b>	3.0	300	62	195-6	194-195 <sup>12e</sup>
<b>9g</b>	<b>10g</b>	3.0	240	79	129-131	C <sub>14</sub> H <sub>17</sub> NO <sub>5</sub> (279.3)
<b>9h</b>	<b>10h</b>	3.0	120	89	188-190	C <sub>12</sub> H <sub>13</sub> NO <sub>4</sub> (235.2)
<b>14a</b>	<b>7a</b>	2.0	45	82	55-56	56-57 <sup>13a</sup>
<b>14b</b>	<b>7b</b>	2.0	60	86	oil	oil <sup>13b</sup>
<b>14c</b>	<b>7c</b>	3.0	60	85	73-5	C <sub>16</sub> H <sub>13</sub> NO (235.3)
<b>16b</b>	<b>15b</b>	3.0	120	43	oil	oil <sup>14</sup>
<b>16c</b>	<b>15c</b>	3.0	120	30	60-63	C <sub>16</sub> H <sub>15</sub> NO (237.3)
<b>19a</b>	<b>18a</b>	2.0	20	50	70-71	73-74 <sup>14</sup>
<b>19b</b>	<b>18b</b>	2.0	20	60	52-53	53-55 <sup>15a</sup>
<b>19c</b>	<b>18c</b>	1.0	30	35	48-49	50-51 <sup>15b</sup>

<sup>a</sup> Satisfactory microanalysis obtained: C±0.22, H±0.18, N±0.20

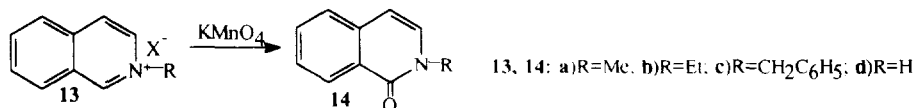
<sup>b</sup> Picrate salts

**Table 2**  $^1\text{H-NMR}$  ( $\text{CDCl}_3/\text{TMS}$ ),  $\delta$ , J (Hz)

<b>6a</b>	2.94(t,2H,J=6), 3.10(s,3H), 3.50(t,2H,J=6), 6.98-7.36(m,3H), 7.89-8.04(m,1H)
<b>6b</b>	2.89(t,2H,J=6), 3.09(s,3H), 3.51(t,2H,J=6), 3.50(t,2H,J=6), 3.90(s,6H), 6.57(s,1H), 7.50 (s,1H)
<b>6c</b>	1.20(t,3H,J=6), 2.90(t,2H,J=6), 3.53(t,2H,J=6), 3.60(q,2H,J=6), 3.86,(s,6H), 6.57(s,1H), 7.54(s,1H)
<b>6d</b>	2.85(t,2H,J=6), 3.30(t,2H,J=6), 3.86(s,3H), 3.90(s,3H), 4.74(s,2H), 6.57(s,1H), 7.25(s,5H), 7.60(s,1H)
<b>6e</b>	2.93(t,2H,J=6), 3.15(s,3H), 3.57(t,2H,J=6), 6.02(s,2H), 6.67(s,1H), 7.60(s,1H)
<b>9a</b>	1.38(t,3H,J=7), 2.95(t,2H,J=6), 4.00(t,2H,J=6), 4.28(q,2H,J=7), 7.02(d,1H,J=8), 7.25(t,2H,J=7), 8.00(d,1H,J=8) <sup>a</sup>
<b>9b</b>	3.10(t,2H,J=6), 4.05(t,2H,J=6), 7.10-7.52(m,3H), 7.28(s,5H), 7.93(d,1H,J=8)
<b>9c</b>	2.58(s,3H), 2.93(t,2H,J=6), 4.03(t,2H,J=6), 7.08(d,1H,J=8), 7.28(t,2H,J=7), 7.97(d,1H,J=8) <sup>a</sup>
<b>9d</b>	2.88(t,2H,J=6), 4.0(t,2H,J=6), 4.31(s,2H), 7.13(s,5H), 7.00-7.45(m,3H), 7.85-8.08(d,1H,J=8) <sup>a</sup>
<b>9e</b>	1.41(t,3H,J=6), 3.16(t,2H,J=6), 4.13(t,2H,J=6), 4.36(q,2H,J=6), 7.42(d,1H,J=8), 8.15, (d,1H,J=8), 8.93(s,1H) <sup>a</sup>
<b>9f</b>	3.05(t,2H,J=6), 3.78(s,3H), 3.90(s,3H), 4.05(t,2H,J=6), 6.60(s,1H), 7.12(s,1H), 7.20-7.58(m,5H)
<b>9g</b>	1.38(t,3H,J=7), 2.91(t,2H,J=6), 3.85(s,3H), 3.88(s,3H), 4.00(t,2H,J=6), 4.30(q,2H,J=7), 6.52 (s,1H), 7.51(s,1H)
<b>9h</b>	2.96(t,2H,J=6), 3.94(s,6H), 4.08(t,2H,J=5), 6.69(s,1H), 7.56(s,1H), 9.42(s,1H)
<b>14a</b>	3.50(s,3H), 6.45(d,1H,J=7), 7.00(d,1H,J=8), 7.25-7.62(m,3H), 8.36(d,1H,J=8) <sup>a</sup>
<b>14b</b>	1.37(t,3H,J=7), 4.00(q,2H,J=7), 6.45(d,1H,J=8), 7.00(d,1H,J=8), 7.25-7.62(m,3H), 8.36(d,1H,J=8)
<b>14c</b>	5.12(s,2H), 6.40(d,1H,J=7), 6.97(d,1H,J=8), 7.12-7.45(m,3H), 7.20(s,5H),8.42(d,,1H,J=8) <sup>a</sup>
<b>14d</b>	6.55(d,1H,J=5), 7.13(d,1H,J=6), 7.25-7.60(m,3H), 8.32(d,1H,J=8) <sup>a</sup>
<b>16b</b>	2.67-2.77(m,2H), 2.85-2.97(m,2H), 3.32(s,3H), 6.92-7.20(m,4H) <sup>d</sup>
<b>16c</b>	2.67-2.77(m,2H), 2.85-2.98(m,2H), 5.10(s,2H), 6.72-7.25(m,4H), 7.17(s,5H) <sup>a</sup>
<b>19a</b>	3.70(s,3H), 6.65(d,1H,J=8), 7.40(d,1H,J=8), 7.05-7.60(m,4H)
<b>19b</b>	1.40(t,3H,J=7), 4.30(q,2H,J=7), 6.67(d,1H,J=10), 7.00-7.45(m,4H), 8.00(d,1H,J=10) <sup>a</sup>
<b>19c</b>	5.50(s,2H), 6.75(d,1H,J=10), 6.92-7.45(m,4H), 7.12(s,5H), 7.62 (d,1H,J=10)

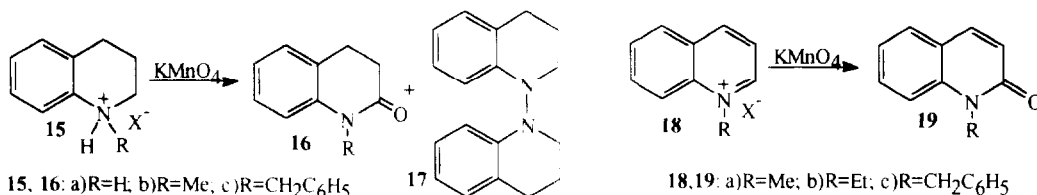
<sup>a</sup>Some of signals for aromatic protons are doubled because of stereoisomers.

procedure was applied for oxidation of salts of isoquinoline with ethyl iodide and benzyl chloride to the corresponding **14b,c** in very good yields.



The attempted oxidation of N-acyliminium salts **13** of isoquinoline with acetyl chloride or ethyl chloroformate with KMnO<sub>4</sub> in acetonitrile or at phase transfer conditions led to 2-acyl-1(2H)-isoquinolinones that at working up of the reaction mixtures easily hydrolyzed to **14d**.<sup>9</sup>

The oxidation of tetrahydroquinoline with KMnO<sub>4</sub> in refluxed acetone was reported to lead to the dimer **17** as a main product of the reaction.<sup>10</sup> We investigated the oxidation with KMnO<sub>4</sub> of tetrahydroquinoline and N-alkyl salts of tetrahydroquinoline **15b,c** and quinoline **18a-c**. The oxidation of tetrahydroquinoline in acetone at room temperature afforded two products, identified as 3,4-dihydro-2(2H)-quinolinone **16a** and dimer **17** in yields of 10% and 50 % respectively. The oxidation of in situ obtained N-methyl- **15b** and N-benzyl- **15c** ammonium salts of tetrahydroquinoline was carried out in acetonitrile and afforded 1-alkyl-2(2H)-3,4-dihydroquinolinones **16b,c** in moderated yields. The oxidation of N-alkyliminium salts of quinoline **18a-c** was carried out also in acetonitrile and afforded 1-alkyl-2(2H)-quinolinones **19a-c**.



In conclusion, the investigations described here provide a convenient, simple and versatile access to isoquinoline and quinoline derivatives such as 3,4-dihydroisoquinolines, N-alkyl- and N-acyl-3,4-dihydro-1(2H)-isoquinolinones, N-alkyl-1(2H)-isoquinolinones, N-alkyl-3,4-dihydro-2(2H)-quinolinones, and N-alkyl-2(2H)-quinolinones.

<sup>1</sup>H-NMR data of the obtained 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones **6a-e**, 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9a-h**, 2-alkyl-1(2H)-isoquinolinones **14a-c**, 2-alkyl-3,4-dihydro-2(2H)-quinolinones **16b,c** and N-alkyl-2(2H)-quinolinones **19a-c** are given in Table 2.

### Experimental

**3,4-Dihydroisoquinolines (Table 1, 2a-f); Typical Procedure:** A stirred at room temperature solution of tetrahydroisoquinoline **1** (10 mmol) and 18-Crown-6 (50mg) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was treated portionwise with KMnO<sub>4</sub> (1.58g, 10 mmol). The precipitation of brown MnO<sub>2</sub> was observed in the course of the reaction. The mixture was stirred for 1 h, then cooled and saturated aqueous sodium metabisulfite solution (50mL) was added carefully to a clear solution (pH 7-8). Occasionally during this operation rapid gas evolution occurred. The

organic layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and distilled to afford products purified by recrystallization or filtration through a short column of neutral  $\text{Al}_2\text{O}_3$  using  $\text{Et}_2\text{O}$  as eluent.

**2-Alkyl-3,4-dihydro-1(2H)-isoquinolinones 6 (Table 1, 6a-e): Typical Procedure:** Mixture of 3,4-dihydroisoquinoline **3** (3 mmol) and alkyl halides **4** (3 mmol) was stirred for 1 h at room temperature or at  $60^\circ\text{C}$ , then cooled, dissolved in 1,2-dichloroethane (5 mL) and 18-Crown-6 (50mg) was added.  $\text{KMnO}_4$  was added portionwise to the solution and the mixture was stirred for the time given (Table 1). The colour of the reaction mixture turned from violet to brown from the formed  $\text{MnO}_2$ . Saturated aqueous sodium metabisulfite solution (50mL) was then carefully added. The resulting mixture was treated with aq. 10% HCl (20 mL) and the solution was extracted with  $\text{CHCl}_3$  (3x20mL). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), the solvent evaporated under vacuum and the products purified by recrystallization or column chromatography on silica gel, using p.ether,  $\text{Et}_2\text{O}$  as eluents.

**2-Acyl-3,4-dihydro-1(2H)-isoquinolinones (Table 1, 9a-h): Typical Procedures:**

**Oxidation of N-acyliminium salts 8 (Table 1, 9a-e):** Acyl chloride **7** (3 mmol) was added to a solution of 3,4-dihydroisoquinoline **3** (3 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and the mixture was stirred for 30 min at room temperature. 18-Crown-6 (30-50 mg) and then the corresponding amounts of  $\text{KMnO}_4$  (Table 1) were added and the reaction mixture was stirred at a room temperature (the time of oxidation was followed by TLC and is given in Table 1).. The colour of the reaction mixture turned from violet to brown from the formed  $\text{MnO}_2$ . The reaction mixture was worked up as above and the crude products were purified by column chromatography on silica gel using p.ether,  $\text{Et}_2\text{O}$  as eluents.

**Oxidation of 2-Acyltetrahydroisoquinolines 10 (Table 1, 9a-h):**  $\text{KMnO}_4$  (Table 1) was added to a solution of 2-acyltetrahydroisoquinoline **10** (2 mmol) and 18-Crown-6 (30-50mg) in  $\text{CH}_2\text{Cl}_2$  (5mL) and the mixture was stirred at room temperature for the time given (Table 1). The reaction mixture was worked up as above and the products were purified by recrystallization or column chromatography on a silica gel, using p.ether,  $\text{Et}_2\text{O}$  as eluents.

**1-Chloro-2-ethoxycarbonyltetrahydroisoquinoline 8:** Adduct **8a** was obtained from 3,4-dihydroisoquinoline (1 mmol) and ethyl chloroformate (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) by stirring for 1 h at room temperature. The less polar of two compounds on TLC plates (silica gel, Merck) was isolated by column chromatography on a neutral aluminum oxide (eluent p.ether / ether) as a white crystalline product (mp  $169\text{-}170^\circ\text{C}$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{CO}}$   $1697\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.32(t, 3H, J=6), 2.62-2.87(m, 2H), 3.30-3.57(m, 2H), 4.17(q, 2H, J=6), 6.55(s, 1H), 6.95(s, 3H), 7.00 (s, 1H); MS, m/e (M+): 239 (Calc. for  $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{Cl}$ , 239.1).

**One-pot synthesis of 9c:**  $\text{KMnO}_4$  (0.316g, 2 mmol) was added portionwise for 30 min to a stirred solution of tetrahydroisoquinoline (0.262g, 2 mmol) and 18-Crown-6 (30mg) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature. Acetyl chloride was added (0.158g, 2 mmol) and the mixture was stirred for 15 min.  $\text{KMnO}_4$  (0.632g, 4 mmol) was added again and the stirring continued for 6 h at room temperature. The mixture was



worked up as above to afford **7c** (0.255g, 58%), purified by recrystallization from MeOH.

**Corydaldine**: 2-Benzoyl-6,7-dimethoxy-1(2H)-isoquinolinone **9f** (0.311g, 1 mmol) in MeOH (5 mL) was treated with  $\text{CH}_3\text{ONa}$  (0.08g, 1.5 mmol) and the solution was stirred for 3 h at rt. Worked up of the mixture afforded a crystalline product from  $\text{Et}_2\text{O}$  (0.205g, 98%); mp 170-171°C (lit.<sup>8</sup> mp 172°C).

**Typical procedure for the preparation of 2-alkyl-1(2H)-isoquinolinones 14 a-c**: Isoquinoline (3 mmol) and alkyl halide (3 mmol) were stirred in MeCN (15 mL) at room temperature for 1 h or at reflux (3 h for benzyl chloride). The mixture was cooled to room temperature and  $\text{KMnO}_4$  (**Table 1**) was added portionwise. The colour of the reaction mixture turned from violet to brown from the formed  $\text{MnO}_2$ . The reaction mixture was worked up as for **6** and the products purified by recrystallization or column chromatography on a silica gel, using p.ether,  $\text{Et}_2\text{O}$  as eluents.

**Oxidation of tetrahydroquinoline**:  $\text{KMnO}_4$  (0.95 g, 6 mmol) was added portionwise to a stirred solution of tetrahydroquinoline (0.4 g, 3 mmol) in acetone (20 ml) at room temperature for 20 min. Saturated aq. sodium metabisulfite solution (20mL) was added to clear solution, followed by extraction with  $\text{CHCl}_3$  (3x20mL). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), the solvents evaporated under vacuum and the products were separated by column chromatography on a neutral  $\text{Al}_2\text{O}_3$ . The dimer **17** was isolated using p. ether as eluent in 50% yield (0.2 g): Mp 139-140°C (lit.<sup>10</sup> 141-142°C);  $^1\text{H-NMR}$  ( $\text{CDCl}_3/\text{TMS}$ ),  $\delta$ , ppm: 1.95-2.20 (m,4H), 2.65-2.90(m,4H), 3.24-3.45(m,4H), 6.41-7.00 (m,8H); MS, m/e (M+): 266 (Calc. for  $\text{C}_{18}\text{H}_{20}\text{N}_2$  266.3). 3,4-Dihydro-2(2H)quinolinone **16a** was isolated at eluent  $\text{Et}_2\text{O}$  in 10% yield (45mg); Mp 167-168°C; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{NH}}$  3407 $\text{cm}^{-1}$ ,  $\nu_{\text{CO}}$  1679 $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3/\text{TMS}$ ),  $\delta$ , ppm: 2.40-2.70(m,2H), 2.77-3.07(m,2H), 6.67-7.15(m,4H), 9.20 (s, br., 1H).

**Typical procedure for the preparation of 1-alkyl-3,4-dihydro-2(2H)-quinolinones 16 b,c:**

Tetrahydroquinoline (3 mmol) and MeI or BzCl (3 mmol) were mixed without solvent and the mixture was kept for 3 h at rt. or 80°C (with BzCl). Solidified mixture was dissolved in MeCN (10 mL) and  $\text{KMnO}_4$  (**Table 1**) was added portionwise to a stirred at room temperature solution. The colour of the reaction mixture turned from violet to brown from the formed  $\text{MnO}_2$ . The reaction mixture was worked up as for **6** and the crude products were purified by column chromatography on neutral  $\text{Al}_2\text{O}_3$  using p.ether,  $\text{Et}_2\text{O}$  as eluents.

**Typical procedure for the preparation of 1-alkyl-2(2H)-quinolinones 19 a-c**: Quinoline (3 mmol) and haloalkane (3 mmol) were mixed without solvent and the mixture was kept for 3 h at room temperature or 80°C (with BzCl). Solidified mixture was dissolved in MeCN (10 mL) and  $\text{KMnO}_4$  (**Table 1**) was added portionwise to a stirred at room temperature solution. The colour of the reaction mixture turned from violet to brown from the formed  $\text{MnO}_2$ . The reaction mixture was worked up as for **6** and the crude products were purified by column chromatography on neutral  $\text{Al}_2\text{O}_3$  using p.ether,  $\text{Et}_2\text{O}$  as eluents.

## REFERENCES

1. a) Wehrli, P.A., Schaer, B., *Synthesis* **1974**, 288; b) Castedo, L., Puga, A., Saa, J.M., Suau, R., *T. Lett.* **1981**, 2283. c) Butler, R.N., *Chemical Rev.* **1984**, **84**, 249.; d) Boyers, J.T., Glover, E.E., *J. Chem. Soc. Perkin I* **1977**, 1960; e) Ohba, M., Shinbo, Y., Ohashi, T., Toda, M., Fujii, T., *Heterocycles* **1992**, **34**, 1857; f) Venkov, A., Vodenicharov, D., Ivanov, J., *Synthesis* **1991**, 476; g) Urbanski, J., Vrobel, L., *Pol. J. Chem.* **1984**, 58; *Chem. Abstr.* **1986**, **104**, 88372; h) Hanquet, G., Lusinchi, X., Millet, P., *Tetrahedron* **1993**, **49**, 423; i) Marino, J.P., Larsen Jr., R.D., *J. Am. Chem. Soc.* **1981**, **103**, 4642.
2. a) Fatiadi, A.J., *Synthesis*, **1987**, 85; b) *ibid.*, **1976**, 133; c) Pratt, E.F., McGovern, T.P., *J. Org. Chem.* **1964**, **29**, 1540; d) Misztal, S., Segla, M., *Synthesis* **1985**, 1134.
3. a) Shamma, M. *The Isoquinoline Alkaloids. Chemistry and Pharmacology*; Acad. Press, New York and London, **1972**; b) Suto, M.S., Turner, W.R., *Anti-Cancer Drug Des.* **1991**, 6(2), 107; *Chem. Abstr.* **1991**, **115**, 92038; c) Reiffen, M., Eberlein, W., Muller, P., Psiorz, M., Noll, K., Heider, J., Lillie, Koibinger, W., Luger, P., *J. Med. Chem.* **1990**, **33**, 1496; d) Sharma, S.D., Mehra, U., Gupta, P.K., *Tetrahedron* **1980**, **26**, 3427.
4. Ninomiya, I., Kigushi, T. *The Alkaloids*, Brossi, A. Ed.: Academic Press, New York, **1990**, vol. **38**, p.1.
5. a) Wiley, W.M., Govendachari, T.R., *Org. Reactions* **1951**, 6, 74; b) Fodor, G., Nagubandi, S., *Tetrahedron* **1980**, **36**, 1279; c) Lansbury, P.T., Colson, J.G., Mancuso, N.R., *J. Am. Chem. Soc.* **1964**, **86**, 5225; d) Kawase, M., *J. Chem. Soc., Chem. Commun.* **1990**, 1328; e) Poindexter, G.S., *J. Org. Chem.* **1982**, **47**, 3787.
6. Ruchirawat, S., Chuankamnerdkarn, M., Thiampatanagul, S., *Tetrahedron Lett.* **1984**, 3479.
7. a) Venkov, A., Statkova, S., *Synth. Commun.* **1991**, **21**, 1511; b) Venkov, A., Statkova, S., Ivanov, I., *Synth. Commun.* **1992**, **22**, 125; c) Venkov, A.P., Lukanov, L.K., *Synth. Commun.* **1992**, **22**, 3235.
8. Brossi, A., Besendorf, H., Pellmont, B., Walter, M., Schnider, O., *Helvetica Chim. Acta* **1960**, 1459.
9. Brown, R., White, P., *Soc.* **1957**, 1589, 1591.
10. Rosenkranz, H.J., Winker-Lardelli, B., Hansen, H.J., Schmid, H., *Helv. Chim. Acta* **1974**, **57**, 887.
11. a) Decker, H. *Lieb. Ann. Chem.* **1913**, **395**, 282; b) Spath, E., Polgar, N., *Monatsh. Chem.* **1929**, 51, 196; c) Yamada, S., Omar, A.M.E., *Chem. Pharm. Bull. (Tokyo)* **1964**, **12**(6), 738; *Chem. Abstr.* **1964**, **61**, 9462; d) Slotta, K.H., Haberland, G., *Angew. Chem* **1933**, **46**, 766; *Chem. Abstr.* **1934**, **28**, 1103
12. a) Pyman, F.L. *J. Chem. Soc.* **1909**, **95**, 1746, 1772; b) Battersby, A.R., Davidson, G.C., Turner, J., *J. Chem. Soc.* **1961**, **9**, 3839; c) Perkin, W.H., *J. Chem. Soc.* **1890**, **57**, 1037; d) Bamberger, E., Dieckmann, W., *Berichte* **1893**, **26**, 1205; e) Mayer, M.I., McEwen, W.E., *J. Chem. Am. Soc.* **1951**, **93**, 3075.
13. a) Spath, E., Galinovsky, F., *Berichte* **1936**, **69**, 2059; b) Fischer, Hamer, F.M., *J. Chem. Soc.* **1934**, 1905.
14. Mayer, F., Van Zutphen, L., Philipps, H., *Berichte* **1927**, **60**, 858.
15. a) Mills, W.H., Hamer, F.M., *J. Chem. Soc.* **1920**, **117**, p.2, 1550; b) Arbusow, A.E., Bastanowa, M., *Izv. Akad. Nauk USSR* **1952**, 831; *Chem. Abstr.* **1953**, **47**, 11195.