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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

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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.

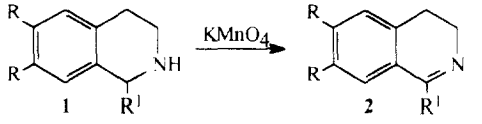
Among the variety of reagents used in oxidation reactions of isoquinoline and quinoline derivatives such as Fremy's salt[1a,b], lead (II) and mercuric acetates[1c-f], chromic acid[1g], peracids[1h], diphenylselenium bis (trifluoroacetate)[1i], etc., potassium permanganate[2a] and active manganese dioxide[2b] 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.[2b] It has been successfully applied to converting 1,2,3,4-tetrahydroquinoline to quinoline and 2,3-dihydroindole into indole, etc.[2c] while $KMnO_4$ has been somehow neglected and has been used only for dehydrogenation of 1-substituted 1,2,3,4-tetrahydro-β-carbolines to 3,4-dihydro-β-carboline derivatives.[2d]

We wish to report the investigations on the synthetic utility of $KMnO_4$ 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.[3a-d] 1(2H)-Isoquinolinone skeleton is also a common building block of a wide variety of benzo[c] phenanthridine

alkaloids.[4] 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.[5a-e]

The oxidation of tetrahydroquinolines, N-alkyl- and N-acyliminium salts of 3,4-dihydroisoquinoline, isoquinoline, tetrahydroquinoline and quinoline with $KMnO_4$ was investigated in acetone, acetonitrile and as phase transfer reaction in chlorinated hydrocarbons (dichloromethane, 1,2-dichloroetane) in the presence of 18-Crown-6.

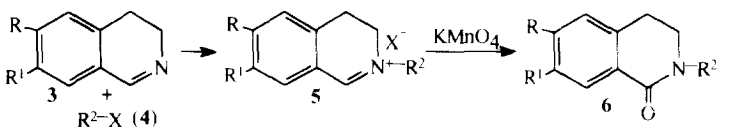
The oxidation of 1,2,3,4-tetrahydroisoquinoline **1** with $KMnO_4$ in acetone at room temperature was a fast exothermic reaction leading to isoquinoline, while at 0°C dehydrogenation occurred for several minutes to 3,4-dihydroisoquinoline in a yield of 80% but it was difficult to control the reaction 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 terahydroisoquinoline 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.



1,2 **a**)R=R^1=H; **b**)R=MeO, R^1=H; **c**)R=CH_2OCH_2, R^1=H; **d**)R=MeO, R^1=C_6H_5; **e**)R=MeO, R^1=3,4(MeO)$_2C_6H_3$; **f**)R=MeO,R^1=4-$NO_2C_6H_4$

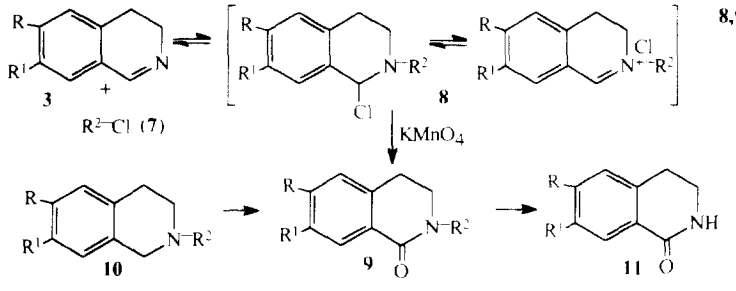
The reaction depended on the amount of $KMnO_4$ and the reaction time, since when the dehydrogenation of tetrahydroisoquinoline (1 mmol) was carried out in dichloromethane in the presence of catalytic amount of 18-Crown-6 and an excess of $KMnO_4$ (4 mmol) for 16 h at room temperature, an aromatization occurred and isoquinoline was obtained in 80% yield. Substituted tetrahydroisoquinolines **1** can be efficiently and conveniently dehydrogenated with $KMnO_4$ 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.[6] The oxidation of N-alkyl-3,4-dihydroisoquinolinium salts **5a-e** obtained from 3,4-dihydroisoquinolines **3** and alkyl halides **4** with $KMnO_4$ 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.[6] 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.



5,6	R	R^1	R^2
a	H	H	Me
b	MeO	MeO	Me
c	MeO	MeO	Et
d	MeO	MeO	$CH_2C_6H_5$
e	CH_2-OCH_2		Me

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 α-amidoalkylation reaction for synthesis of isoquinoline derivatives.[7] 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.



8,9,10	R	R^1	R^2
a	H	H	COOEt
b	H	H	COC_6H_5
c	H	H	COMe
d	H	H	$COCH_2C_6H_5$
e	H	NO_2	COOEt
f	MeO	MeO	COC_6H_5
g	MeO	MeO	COOEt
h	MeO	MeO	CHO

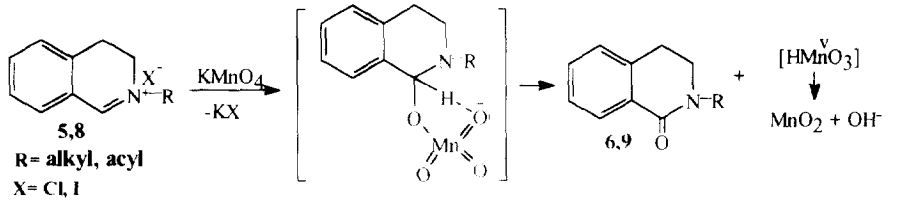
Apparently the phase transfer oxidation of **8** afforded better yields of the corresponding 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9.** The quantity of $KMnO_4$ and the reaction time depended on the nature of the 3,4-dihydroisoquinoline **3** and acyl chloride **7** used for the formation of the 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 $KMnO_4$ 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**. ^{1}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 $KMnO_4$ 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 $KMnO_4$ 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 $KMnO_4$ in phase transfer conditions or in acetonitrile proceeded with the formation of MnO_2 as precipitate. The attempted oxidations of **5** and **8** with activated 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 $KMnO_4$ from the salt formation and the precipitation of MnO_2 in the course of the reaction allowed the following mechanism to be assumed.



5,8
R= alkyl, acyl
X= Cl, I

6,9

An alternative route to 2-acyl-3,4-dihydro-1(2H)-isoquinolinones **9** was worked up by oxidation with $KMnO_4$ of easily available 2-acyltetrahydroisoquinolines **10**[7c] 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[8] after stirring with sodium methoxide in methanol for 3 h at room temperature. The oxidation of **8** with $KMnO_4$ was examined also in acetone but it was found that N-acyliminium salts **8a** reacted with acetone to afford 1-acetonyl-2-ethoxycarbonyltetrahydroisoquinoline.

The usefulness of the phase transfer oxidation with $KMnO_4$ 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 $KMnO_4$ 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 $KMnO_4$ (mol)	Time (min)	Yield (%)	mp (°C)	Mol. Formula[a] or Lit. mp (°C)
2a	**1a**	1.0	60	95	176-178[b]	174-176[11a]
2b	**1b**	1.0	180	78	204-206[b]	201-203[11b]
2c	**1c**	1.0	60	80	95-96	91[11a]
2d	**1d**	1.0	20	75	121-122	121-123[11c]
2e	**1e**	1.0	30	82	167-168	171[11d]
2f	**1f**	2.0	120	89	153	$C_{17}H_{16}N_2O_4$ (312.3)
6a	**5a**	2.0	360	66	oil	$C_{10}H_{11}NO$ (161.1)
6b	**5b**	1.0	180	63	130	126-127[12a]
6c	**5c**	1.0	180	70	98	95[12a]
6d	**5d**	1.0	120	62	102-103	101-102[12b]
6e	**5e**	1.0	120	56	98-99	97-98[12c]
9a	**8a**	2.0	120	92	oil	$C_{12}H_{13}NO_3$ (219.2)
	10a	2.0	120	86		
9b	**8b**	2.0	360	68	132	132[12d]
	10b	2.0	180	73		
9c	**8c**	2.0	120	76	99-100	100[12d]
	10c	2.0	180	65		
9d	**8d**	2.0	180	57	73-74	$C_{17}H_{15}NO_2$ (265.3)
	10d	2.0	180	90		
9e	**8e**	3.0	360	65	138-140	$C_{12}H_{12}N_2O_5$ (264.2)
9f	**10f**	3.0	300	62	195-6	194-195[12e]
9g	**10g**	3.0	240	79	129-131	$C_{14}H_{17}NO_5$ (279.3)
9h	**10h**	3.0	120	89	188-190	$C_{12}H_{13}NO_4$ (235.2)
14a	**7a**	2.0	45	82	55-56	56-57[13a]
14b	**7b**	2.0	60	86	oil	oil[13b]
14c	**7c**	3.0	60	85	73-5	$C_{16}H_{13}NO$ (235.3)
16b	**15b**	3.0	120	43	oil	oil[14]
16c	**15c**	3.0	120	30	60-63	$C_{16}H_{15}NO$ (237.3)
19a	**18a**	2.0	20	50	70-71	73-74[14]
19b	**18b**	2.0	20	60	52-53	53-55[15a]
19c	**18c**	1.0	30	35	48-49	50-51[15b]

[a] Satisfactory microanalysis obtained: C±0.22, H±0.18, N±0.20

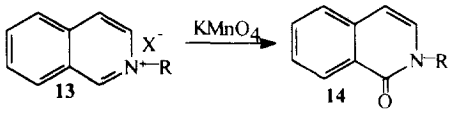
[b] Picrate salts

Table 2 ^{1}H-NMR ($CDCl_3$/TMS), δ , J (Hz)

6a	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)
6b	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)
6c	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)
6d	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)
6e	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)
9a	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)[a]
9b	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)
9c	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)[a]
9d	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)[a]
9e	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)[a]
9f	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)
9g	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)
9h	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)
14a	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)[a]
14b	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)
14c	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)[a]
14d	6.55(d,1H,J=5), 7.13(d,1H,J=6), 7.25-7.60(m,3H), 8.32(d,1H,J=8)[a]
16b	2.67-2.77(m,2H), 2.85-2.97(m,2H), 3.32(s,3H), 6.92-7.20(m,4H)[a]
16c	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)[a]
19a	3.70(s,3H), 6.65(d,1H,J=8), 7.40(d,1H,J=8), 7.05-7.60(m,4H)
19b	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)[a]
19c	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)

[a]Some of signals for aromatic protons are doubled because of stereoisomers.

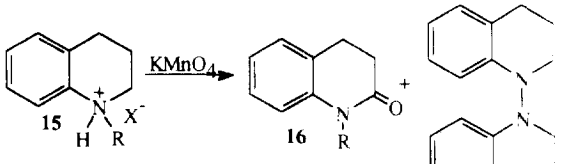
procedure was applied for oxidation of salts of isoquinoline with ethyl iodide and benzyl chloride to the corresponding **14b,c** in very good yields.



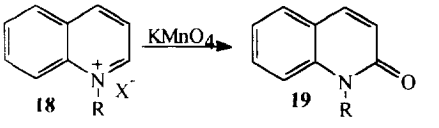
13, 14: a)R=Me, b)R=Et, c)R=$CH_2C_6H_5$; d)R=H

The attempted oxidation of N-acyliminium salts **13** of isoquinoline with acetyl chloride or ethyl chloroformate with $KMnO_4$ 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**.[9]

The oxidation of tetrahydroquinoline with $KMnO_4$ in refluxed acetone was reported to lead to the dimer **17** as a main product of the reaction.[10] We investigated the oxidation with $KMnO_4$ 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-dihydro-quinolinones **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**.



15, 16: a)R=H; b)R=Me, c)R=$CH_2C_6H_5$



18,19: a)R=Me; b)R=Et; c)R=$CH_2C_6H_5$

In conclusion, the investigations described here provide a convenient, simple and versatile access to isoquinoline and quinoline derivatives such as 3,4-dihydroisoquinolnes, 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.

^{1}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_2Cl_2 (50 mL) was treated portionwise with $KMnO_4$ (1.58g, 10 mmol). The precipitation of brown MnO_2 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 (Na_2SO_4) and distilled to afford products purified by recrystallization or filtration through a short column of neutral Al_2O_3 using Et_2O 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°C, then cooled, dissolved in 1,2-dichloroethane (5 mL) and 18-Crown-6 (50mg) was added. $KMnO_4$ 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 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 $CHCl_3$ (3x20mL). The combined extracts were dried (Na_2SO_4), the solvent evaporated under vacuum and the products purified by recrystallization or column chromatography on silica gel, using p.ether, Et_2O 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 CH_2Cl_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 $KMnO_4$ (**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 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, Et_2O as eluents.

Oxidation of 2-Acyltetrahydroisoquinolines 10 (Table 1, 9a-h): $KMnO_4$ (**Table 1**) was added to a solution of 2-acyltetrahydroisoquinoline **10** (2 mmol) and 18-Crown-6 (30-50mg) in CH_2Cl_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, Et_2O as eluents.

1-Chloro-2-ethoxycarbonyltetrahydroisoquinoline 8: Adduct **8a** was obtained from 3,4-dihydroisoquinoline (1 mmol) and ethyl chloroformate (1 mmol) in CH_2Cl_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 169-170°C); IR ($CHCl_3$): ν_{CO} 1697cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ,: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 $C_{12}H_{14}NO_2Cl$, 239.1).

One-pot synthesis of 9c: $KMnO_4$ (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 CH_2Cl_2 (10 mL) at room temperature. Acetyl chloride was added (0.158g, 2 mmol) and the mixture was stirred for 15 min. $KMnO_4$ (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 recryztallization from MeOH.

Corydaldine: 2-Benzoyl-6,7-dimethoxy-1(2H)-isoquinolinone **9f** (0.311g, 1 mmol) in MeOH (5 mL) was treated with CH_3ONa (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 Et_2O (0.205g, 98%); mp 170-171°C (lit.[8] 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 $KMnO_4$ (**Table 1**) was added portion-wise. The colour of the reaction mixture turned from violet to brown from the formed 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, Et_2O as eluents.

Oxidation of tetrahydroquinoline: $KMnO_4$ (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 $CHCl_3$ (3x20mL). The combined extracts were dried (Na_2SO_4), the solvents evaporated under vacuum and the products were separated by column chromatography on a neutral Al_2O_3.The dimer **17** was isolated using p. ether as eluent in 50% yield (0.2 g): Mp 139-140°C (lit.[10] 141-142°C): ^{1}H-NMR ($CDCl_3$/TMS), δ, 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 $C_{18}H_{20}N_2$ 266.3). 3,4-Dihydro-2(2H)quinolinone **16a** was isolated at eluent Et_2O in 10% yield (45mg); Mp 167-168°C; IR ($CHCl_3$): ν_{NH} 3407cm^{-1}, ν_{CO} 1679cm^{-1}. ^{1}H-NMR ($CDCl_3$/TMS), δ, 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 $KMnO_4$ (**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 MnO_2. The reaction mixture was worked up as for **6** and the crude products were purified by column chromatography on neutral Al_2O_3 using p.ether, Et_2O 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 $KMnO_4$ (**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 MnO_2. The reaction mixture was worked up as for **6** and the crude products were purified by column chromatography on neutral Al_2O_3 using p.ether, Et_2O 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,I., *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., Manscuso,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. Ruchirawart,S., Chuankamnerdkarn,M., Thiampatanagul,S., *Tetrahedron Let.* **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.

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