Activation of Iodosobenzene by Catalytic Tetrabutylammonium Iodide and Its Application in the Oxidation of Some Isoquinoline Alkaloids

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Oxidation of *N*-methyltetrahydroisoquinolines with iodosylbenzene in the presence of a catalytic amount of tetrabutylammonium iodide in various solvents afforded *N*-methyl-2*H*-3,4-dihydroisoquinol-1-ones in almost quantitative yields. The application of this finding to the oxidation of other isoquinolines, including tetrahydroisoquinolines, lycorine diacetate, and benzyltetrahydroisoquinolines, also afforded the corresponding lactams in good yields, however, accompanied by a few minor byproducts. Under similar conditions, tetrahydroberberine gave a rearranged compound, berberal, as the major product, accompanied by 8-oxoberberine and berberine.

Introduction. – During the last two decades, hypervalent iodine (III) reagents have shown their versatility in organic syntheses because of their low toxicity, ready availability, easy handling, and their application to many useful and unique transformations [1]. Among these reagents, iodosylbenzene (ISB) is the least reactive one, probably due to its poor solubility in most organic solvents except MeOH. It has been reported that activation of ISB requires the addition of *Lewis* acids such as BF_3–Et_2O [2], NO_2BF_4 [3], HBF_4–Et_2O [3], TMSOTf [4], *etc.*, however, the number of appropriate solvents from which to choose is limited. Recently, *Kita* and co-workers have reported on the activation of ISB with catalytic amounts of cetyltrimethylammonium bromide (CTAB) in a variety of solvents for the oxidation of sulfides to sulfoxides *via* formation of micellar and reversed-micellar systems [5]. The oxidation of heterocyclic amines by ISB in a two-phase system, CH_2Cl_2/H_2O, yielded the corresponding amides in moderate yield but required longer reaction times (36–96 h), depending on the reactant [6]. Our aim was to modify the above reaction conditions to obtain higher yields and faster reaction rates.

Results and Discussion. – The results of the oxidation of 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**) to 6,7-dimethoxy-*N*-methyl-2*H*-3,4-dihydroisoquinolin-1-one (*N*-methylcorydaldine, **2a**), a naturally occurring cytotoxic alkaloid [7–10], with ISB in the presence or absence of quaternary ammonium salts under different reaction conditions are summarized in *Table 1*. It was found that the reaction with ISB alone and MeCN/H_2O 9:1 as solvent afforded **2a** in only 45% yield, even after 24 h (*Entry 1*). However, the yields were improved (to *ca.* quantitative, *Entries 2–8*) and the reaction time was shortened dramatically after adding catalytic amounts of tetrabutylammonium iodide (TBAI; *Scheme 1*). Addition of H_2O had little effect on the yield, but did increase the reaction rate (*Entries 3–5*). Similar results were

Table 1. *Oxidation of 6,7-Dimethoxy-2-methyltetrahydroisoquinoline* (**1a**) *with Iodosobenzene Under Various Reaction Conditions*

Entry	Quaternary Ammonium		Time [h]	Yield[a]) [%]
	Salts	Solvent		
1	None	MeCN/H_2O 90 : 10	24	45
2	$Bu_4N^+I^-$	MeCN	2	quantitative
3	$Bu_4N^+I^-$	MeCN/H_2O 98 : 02	2	quantitative
4	$Bu_4N^+I^-$	MeCN/H_2O 95 : 05	2	quantitative
5	$Bu_4N^+I^-$	MeCN/H_2O 90 : 10	1	quantitative
6	$Bu_4N^+I^-$	THF/H_2O 90 : 10	2	quantitative
7	$Bu_4N^+I^-$	Toluene/H_2O 90 : 10	2	quantitative
8	$Bu_4N^+I^-$	CH_2Cl_2/H_2O 90 : 10	2	quantitative
9	$[C_{16}H_{33}N^+Me_3]Br^-$	MeCN/H_2O 90 : 10	6	trace
10	$[C_{16}H_{33}N^+Me_3]Br^-$	Toluene/H_2O 90 : 10	6	8
11	$[C_{16}H_{33}N^+Me_3]Br^-$	CH_2Cl_2/H_2O 90 : 10	6	trace
12	$Bu_4N^+Br^-$	MeCN/H_2O 90 : 10	6	trace
13	$Bu_4N^+Cl^-$	MeCN/H_2O 90 : 10	6	trace

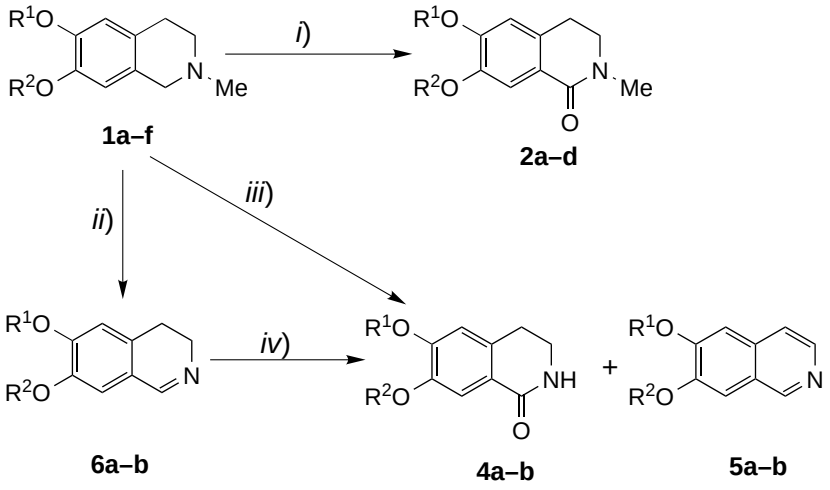
[a]) Yields are based on ^{1}H-NMR analysis of the mixture obtained after workup of the reaction.

obtained by replacing MeCN with CH_2Cl_2, toluene, or THF (*Entries 6–8*). Under the conditions (CTAB as catalyst) for the oxidation of sulfides to sulfoxides [5], **1a** afforded **2a** in very poor yield even after 6 h (*Entries 9–11*). In the presence of other phase-transfer reagents, such as tetrabutylammonium bromide (TBAB, *Entry 12*) and tetrabutylammonium chloride (TBAC, *Entry 13*), **2a** was obtained in only trace amounts, even after 6 h. This would suggest that the activation of ISB is not simply attributable to the phase-transfer properties of these quaternary ammonium salts. Based on these observations, we propose that ISB, which exists in polymeric form, upon reaction with TBAI is cleaved *in situ* to form a reactive adduct **3**, shown in *Scheme 2*, as indicated by the immediate formation of a light brown solution upon treating ISB with an equivalent amount of TBAI in MeCN/H_2O 7:3 at room temperature. This suggestion is further supported by the observation that the color of the suspension of ISB persists even after 6 h when TBAI is replaced with TBAC or TBAB.

The generality of the above transformation was verified by treating various *N*-methyl tetrahydroisoquinolines **1b–d** with ISB (2.2 equiv.) in the presence of TBAI (10 mol-%, 0.2 equiv.) in MeCN/H_2O 9:1 at room temperature. The almost quantitative yields (*Table 2*) of the respective dihydroisoquinolones **2b–d** (*Scheme 1*) proved the practicability of this new procedure. The identities of all compounds prepared were confirmed by comparison of their FT-IR, ^{1}H-, ^{13}C-NMR and MS data with those reported in the literature. Yield and m.p. data of **2a–d** are given in *Table 2*. Of these compounds, **2c** was identified as the natural product oxohydrastinine [11][12].

Treatment of tetrahydroisoquinolines **1e–f** under conditions similar to those used for **1a–d** in MeCN afforded 3,4-dihydro-2*H*-isoquinol-1-ones **4a–b** and isoquinolines **5a–b**, respectively. Similar results were obtained with CH_2Cl_2/H_2O 9:1 or MeCN/H_2O 9:1 as the solvent. Compounds **4a**, **4b**, and **5b** are natural products corydaldine [14], noroxyhydrastinine [15][16], and papraline [17], respectively. A plausible mechanism for these transformations is depicted in *Scheme 3*. The first step is the dehydrogenation

Scheme 1



a $R^1 = R^2 = Me$ **b** $R^1 + R^2 = -CH_2-$ **c** $R^1 = Me$, $R^2 = Bn$;
d $R^1 = Me$, $R^2 = Ac$ **e** $R^1 = R^2 = Me$ **f** $R^1 + R^2 = -CH_2-$

i) PhI=O (2.2 equiv.), TBAI (0.2 equiv.), MeCN/H_2O (9:1), r.t. 1–1.5 h. *ii*) PhI=O (1 equiv.), TBAI (0.1 equiv.) MECN, 0°, 15 min. *iii*) PhI=O (2.2 equiv.), TBAI (0.2 equiv.), MeCN/H_2O (9:1), 0°, 15 min and then (r.t.,) 1 h. *iv*) PhI=O (1.1 equiv.), TBAI (0.1 equiv.), MeCN, r.t. 1 h.

Scheme 2

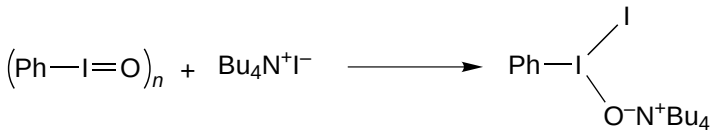


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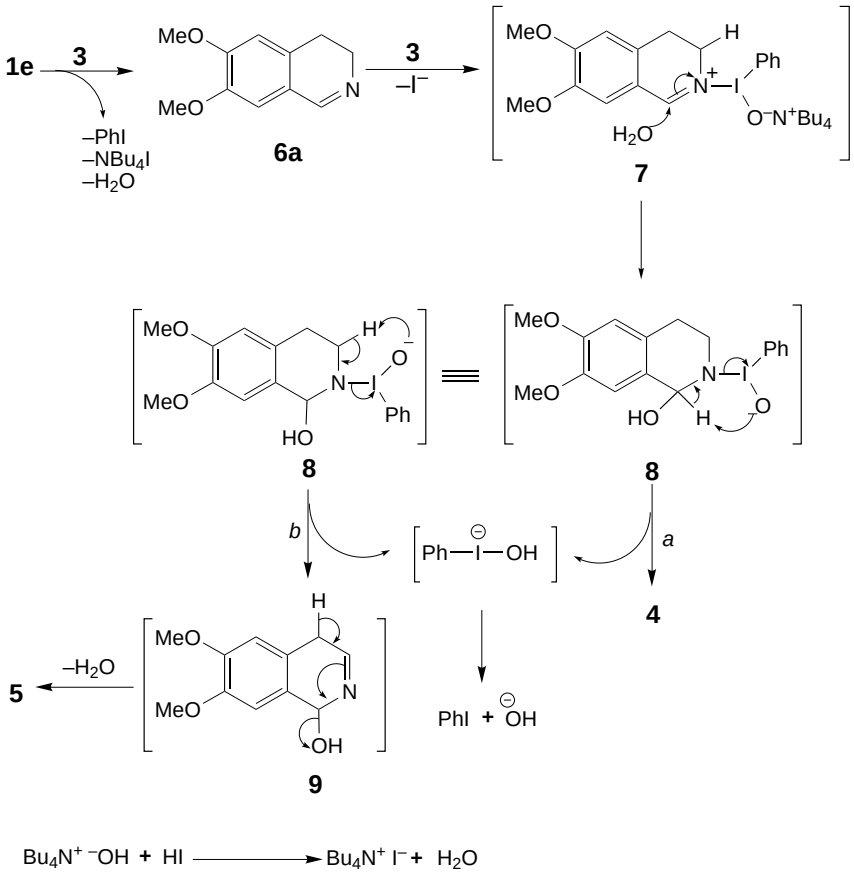
Table 2. *Oxidation of Tetrahydroisoquinolines with ISB in the Presence of TBAI*

Reactant	Product	Time [h]	Yield[a]) [%]	M.p. [lit. m.p.] [°]
1a	**2a**	1	96	123–124 (124–125 [13])
1b	**2b**	1	96	98–99 (98 [13])
1c	**2c**	1	94	110–111
1d	**2d**	1.5	90	131–132
1e	**4a**	1.5	30	173–174 (174–175 [13])
	5a		50	93–94 (92–93 [19])
1f	**4b**	2	35	184–185 (185–186 [20])
	5b		45	120–121 (125–126 [21])

[a]) Yields are based on isolated products.

Scheme 3



of **1e** to form dihydroisoquinoline **6a**, which was confirmed by the following two experiments. First, treating **1e**–**f** with 1 equiv. of ISB in the presence of TBAI at 0° afforded **6a** (dehydroheliamine) [18] and **6b** in almost quantitative yield. Second, dihydroisoquinolines **6a**–**b** on treatment with ISB under the above reaction conditions at room temperature afforded a mixture of **4a**–**b** and **5a**–**b** (*Scheme 1*). Nucleophilic attack of H_2O at the C(1) position of the adduct **7** gave **8** (*Scheme 3*, *Path a*), which, upon elimination of iodobenzene and isomerization, would afford **4**. In a competitive pathway (*Path b*), the elimination of iodobenzene with concomitant loss of a H–C(3) of the adduct **8** would afford **9**, which, upon elimination of H_2O, leads to the isoquinoline **5**. Spontaneous reaction of the hydroiodic acid formed with tetrabutylammonium hydroxide regenerates TBAI to complete the catalytic cycle.

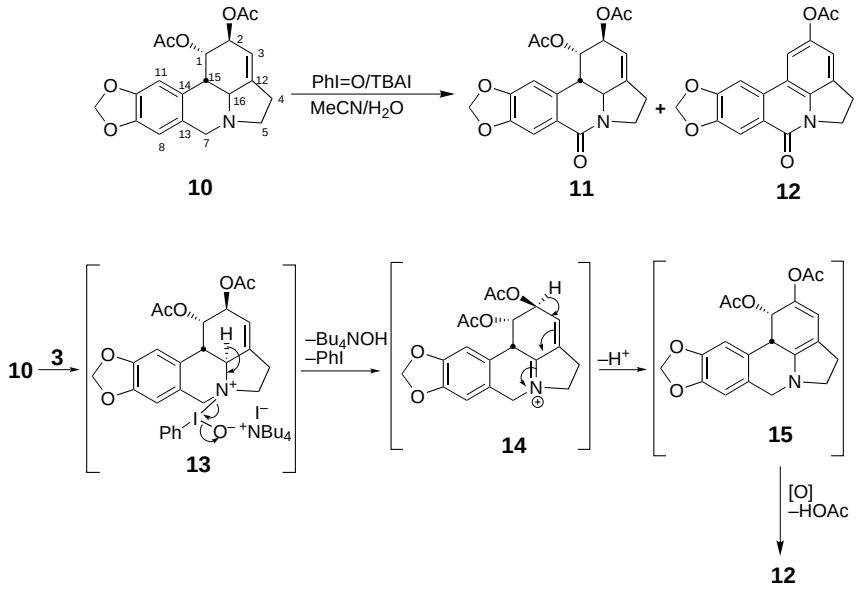
Oxidation of lycorine diacetate (**10**), prepared from *O*-acetylation of lycorine (Ac_2O-py) under similar conditions in MeCN/H_2O 9:1 afforded compound **11** in 80% yield along with a minor compound **12** (5%). Compound **11** was identified as 7-lycorinone diacetate, which has been obtained before by oxidation of **10** with $KMnO_4$,

however, in very low yield (10%) [22]. Compound **12** was identified as 2-acetoxyanhydrolycorine lactam [23], as demonstrated by its ^{1}H-NMR spectrum, which displayed an AX system (δ 7.01, 7.42, $+J = 1.7$ Hz) for H–C(3) and H–C(1) in addition to two *s* (δ 7.42 and 7.89) for H–C(8) and H–C(11), respectively, in the aromatic region, and only one Me(Ac) *s* and four mutually coupled protons in the aliphatic region.

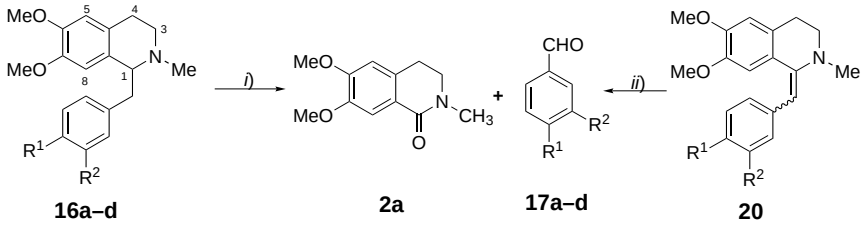
Further study indicated that **12** was not produced from **11** by over oxidation, as confirmed by the absence of a reaction upon treatment of **11** with ISB under similar conditions. Hence, **12** would be formed from **10**, and a probable mechanism is depicted in *Scheme 4*. Elimination of iodobenzene with the loss of an allylic proton H–C(16) of the adduct **13** gives the iminium cation **14**, which, after isomerization, affords **15**. Subsequent oxidation at C(7) and aromatization of ring A with the elimination of an AcOH unit would yield **12**.

Treatment of 1-benzyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**16a**) with 3 equiv. of ISB in presence of a catalytic amount of TBAI at room temperature afforded 6,7-dimethoxy-2-methyl-2*H*-3,4-dihydroisoquinolin-1-one (**2a**) and benzaldehyde (**17a**) in 75% yields *via* the C–C bond cleavage at the dibenzylic position (*Scheme 5*). The C–C bond cleavage is a very rare reaction in hypervalent iodine chemistry except for cleavage of glycols to their respective ketones [24], and only pentafluoroiodobenzene bis(trifluoroacetate), a highly reactive hypervalent iodine reagent, is known to bring about C–C bond cleavage of carbonyl compounds [25]. To the best of our knowledge, this is the first example of C–C bond cleavage by ISB. The generality of this reaction was confirmed by treating benzylisoquinolines **16b–d** under similar reaction conditions, which produced the common product **2a** and the respective substituted aromatic aldehydes **17b–d** in good yields.

Scheme 4



Scheme 5



a $R^1 = R^2 = H$ **b** $R^1 = OMe$, $R^2 = H$ **c** $R^1 = R^2 = OMe$ **d** $R^1 = Br$, $R^2 = H$

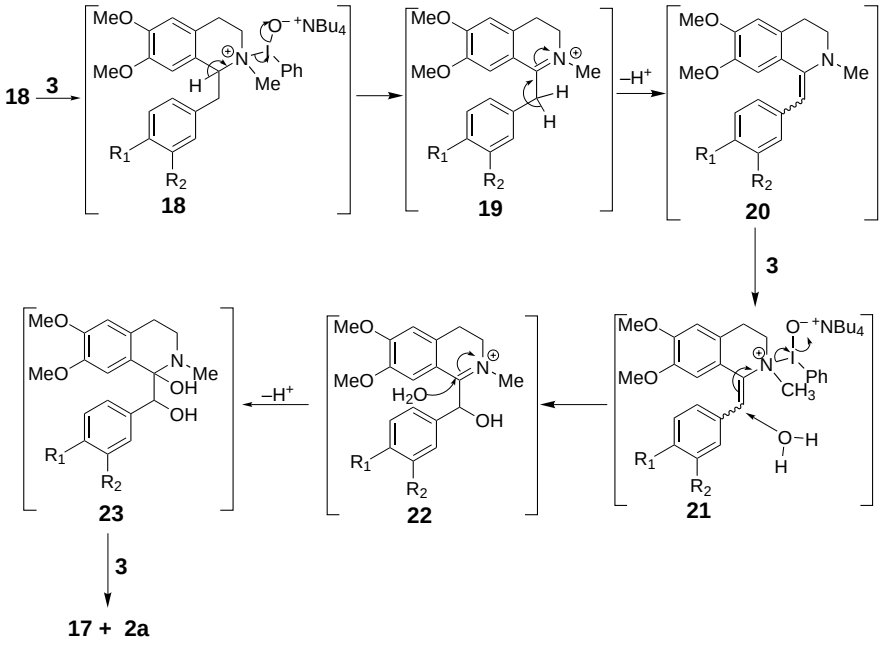
i) PhI=O (3.3 equiv.), TBAI (0.3 equiv.), r.t. 2 h. *ii*) PhI=O (2.2 equiv.), TBAI (0.2 equiv.), r.t., 1.5 h.

The possible mechanism for the formation of **2a** and **17a**–**d** from **16a**–**d** is depicted in *Scheme 6*. Elimination of iodobenzene with concomitant loss of H–C(1) of the adduct **18** afforded the iminium cation (**19**), which, upon isomerization, yielded **20**. Hydration of the adduct **21** together with the elimination of iodobenzene and H_2O would give **22**. Subsequent hydration yields the 1,2-diol **23**, and cleavage of the glycol, which was shown to be effected by a similar reagent, iodobenzene diacetate [24], gives rise to the lactam **2a** and the respective aldehydes **17a**–**d**. That **20** is a key intermediate during this transformation was evidenced indirectly by the reaction of **20** with 2.2 equiv. of ISB and a catalytic amount of TBAI, affording **2a** and **17a** in 80% yields (*Scheme 5*).

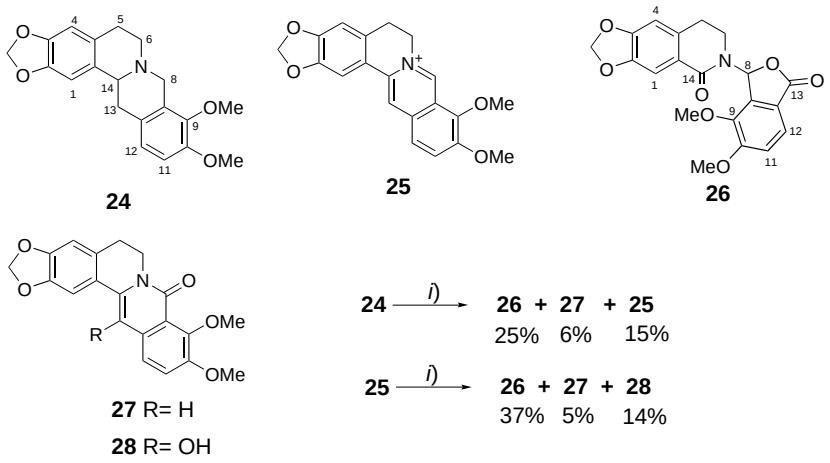
To study the applicability of this C–C-bond-cleavage reaction, tetrahydroberberine (**24**), a benzylisoquinoline derivative prepared by $NaBH_4$ reduction of berberine (**25**), was treated under similar reaction conditions for 5 h at room temperature, yielding **25** as the major product together with compounds **26** and **27** (*Scheme 7*). Compound **26** was identified as berberal through comparison of its physical and spectral data with those reported [26]. This structure was also confirmed by 2D NMR analysis including HMQC, NOESY, and HMBC. The key evidence included the shift correlation of H–C(1) (δ 7.58) and H–C(8) (δ 7.96) to C(14) (δ 164.4), and H–C(8) and H–C(12) (δ 7.64) to C(13) (δ 168.3), confirming the location of the lactam and lactone moieties. Based on these analyses, complete assignments of the ^{1}H- and ^{13}C-NMR data of **26** were made for the first time and the results are listed in the *Exper. Part*. Compound **27** was identified as 8-oxoberberine based on comparison of its spectral data with those reported [27]. Raising the reaction temperature of 50° and prolonging the reaction time to 18 h **24** gave **25**, **26**, and **27** in 15%, 25%, and 6% yields, respectively. The increased yield of **26** and decreased yield of **25** due to the change of reaction conditions might indicate that **26** is derived from **25**. Indeed, in support of this proposal, treatment of **25** under such reaction conditions (3.3 equiv. ISB, MeCN/H_2O 9:1, 50°, 18 h) yielded **26** as the major product (37%) along with **27** (5%) and **28** (14%) as byproducts. Compound **28** was recognized as 13-hydroxy-8-oxoberberine, as evidenced by its ^{1}H-NMR spectrum, which revealed only four aromatic proton signals, two *s* and one AX system in the aromatic region, and by comparison of its physical data with those reported [28].

This study provides a quick and high yielding method involving much less-toxic reagents for the conversion of tetrahydroisoquinolines to the corresponding dihydro-

Scheme 6



Scheme 7



i) PhI=O (3.3 equiv.), TBAI (10 mol-%), MeCN/H_2O 9 :1, 50°, 18 h.

isoquinolones, one that could be used in place of reported methods involving toxic reagents such as mercuric acetate [29]. Its application in the oxidation of lycorine diacetate to lycorinone diacetate, which is useful for preparing bioactive lycorine analogues, solved the low-yield problem. This study also provides an alternative

method for the preparation of berberal, which had been synthesized from **26** in 32% yield by photo-oxygenation [26].

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Experimental Part

General. Iodosylbenzene (ISB) was prepared before use by hydrolysis of iodobenzene diacetate and stored at r.t. in the dark for a maximum of 15 d. 1-Benzyl-2-methyl-1,2,3,4-tetrahydroquinolines (**16a**–**d**) and 1-benzylidene-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**20**) were synthesized according to the literature [30]. Lycorine and berberine were obtained from our collection. TLC (silica gel) plates were developed with $CHCl_3$/MeOH and visualized under UV at 254 nm and with *Dragendorff*'s spray reagent. M.p.: in open capillaries, *Fisher-Johns* melting-point apparatus, uncorrected. $[\alpha]_D$: *JASCO DIP-181* digital polarimeter. UV/Spectra: *Hitachi 150-20* spectrophotometer; MeOH soln. FT-IR Spectra: *JASCO IR Report-100* spectrophotometer; KBr pellets ν in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Bruker DPX-200* and *AMX-400* δ in ppm, J in Hz. EI-MS: *JEOL JMS-SX-102* spectrometer; 70 eV; m/z (%).

Oxidation of N*-Methyl-1,2,3,4-tetrahydroisoquinolines with ISB in the Presence of TBAI: General Procedure.* TBAI (74 mg, 0.2 mmol) was added to a suspension of ISB (484 mg, 2.2 mmol) in MeCN/H_2O 9:1 (20 ml) and stirred at r.t. for 5 min. To this suspension, *N*-methyltetrahydroisoquinoline (**1a**–**d**, 1 mmol) was added and the resultant mixture was stirred for additional 1–1.5 h until a clear soln. was obtained. The reaction was monitored by TLC, and, after completion, the mixture was concentrated under reduced pressure to give a residue that was then dissolved in $CHCl_3$ (100 ml). The $CHCl_3$ soln. was washed with 5% aq. $Na_2S_2O_3$, H_2O, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography (CC; silica gel) to afford the respective *N*-methyl-2*H*-3,4-dihydroisoquinolin-1-ones (**2a**–**d**) (*Table 2*).

*7-Benzyloxy-3,4-dihydro-6-methoxy-2-methyl-2*H*-isoquinolin-1-one* (**2c**). FT-IR: 1654 (C=O, amide). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.86 (*t*-like, J = 6.8, 2 H, H–C(4)); 3.06 (*s*, MeN); 3.47 (*t*-like, J = 6.8, 2 H, H–C(3)); 3.85 (*s*, MeO–C(6)); 5.13 (*s*, OCH_2); 6.59 (*s*, H–C(5)); 7.23–7.27 (*m*, H–C(4′)); 7.30–7.34 (*m*, H–C(2′), H–C(6′)); 7.42–7.44 (*m*, H–C(3′), H–C(5′)); 7.63 (*s*, H–C(8)). EI-MS: 297 (100).

*7-Acetoxy-3,4-dihydro-6-methoxy-2-methyl-2*H*-isoquinolin-1-one* (**2d**). FT-IR: 1760 (C=O, ester), 1652 (C=O, amide). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.28 (*s*, Me(Ac)); 2.95 (*t*-like, J = 6.8, 2 H, H–C(4)); 3.09 (*s*, MeN); 3.52 (*t*-like J = 6.6, 2 H, H–C(3)); 3.83 (*s*, MeO); 6.68 (*s*, H–C(5)); 7.72 (*s*, H–C(8)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 20.5 (*q*, Me(Ac)); 27.9 (*t*, C(4)); 35.1 (*q*, MeN); 48.1 (*t*, C(3)); 56.0 (*q*, MeO); 110.3 (*d*, C(5)); 122.4 (*s*, C(8a)); 122.8 (*d*, C(8)); 137.5 (*s*, C(7)); 138.6 (*s*, C(4a)); 153.7 (*s*, C(6)); 164.0 (*s*, C(1)); 168.9 (*s*, CO(Ac)). FAB-HR-MS: 250.1074 ($[M+1]^+$, $C_{13}H_{16}O_4N$; calc. 250.1079).

Oxidation of 1,2,3,4-Tetrahydroisoquinolines (**1e, f**): *General Procedure.* TBAI (74 mg, 0.2 mmol) was added to a suspension of ISB (484 mg, 2.2 mmol) in MeCN (20 ml) and stirred at r.t. for 5 min. The mixture was cooled in an ice bath and **1e** or **1f** (1 mmol) was added in one portion. After stirring for 10 min, the mixture was brought to r.t. and stirred for additional 2 h. The soln. was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, (100 ml) washed with 5% aq. $Na_2S_2O_3$ and H_2O, and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by CC (neutral alumina, MeOH (0–5%) in $CHCl_3$) to afford the corresponding isoquinoline (**5a** or **5b**) and 3,4-dihydroisoquinol-1-one (**4a** or **4b**). See *Table 2* for yield and m.p. data.

Oxidation of 1,2,3,4-Tetrahydroisoquinolines (**12e, f**) *with ISB* (1 equiv.), *in the Presence of TBAI: General Procedure.* To a suspension of ISB (220 mg, 1 mmol) in MeCN (10 ml) was added TBAI (37 mg, 0.1 mmol) and the mixture was stirred at r.t. for 5 min. The reagent mixture was cooled to 0° and the tetrahydroisoquinoline (**1e** or **1f**, 1 mmol) was added in one portion. The reaction mixture was stirred for further 15 min and a clear brown soln. was obtained. Under work-up and separation similar to that described above, the product 3,4-dihydroisoquinoline (**6a** or **6b**, resp.) was obtained.

*6,7-Dimethoxy-3,4-dihydro-2*H*-isoquinoline* (**6a**). Yield 176 mg (92%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.68 (*t*-like, J = 8.0, 2 H, H–C(4)); 3.72 (*m*, 2 H, H–C(3)); 3.89 (*s*, MeO); 3.90 (*s*, MeO); 6.66 (*s*, H–C(5)); 6.81 (*s*, H–C(8)); 8.14 (br. *s*, H–C(1)).

*6,7-Methylenedioxy-3,4-dihydro-2*H*-isoquinoline* (**6b**). Yield 164 mg (94%). M.p. 96–97° (96–97° [31]). ^{1}H-NMR (200 MHz, $CDCl_3$): 2.63 (*t*-like, J = 7.3, 2 H, H–C(4)); 3.66 (*dt*, J = 2.1, 2 H, 7.5, H–C(3)); 5.95 (*s*, OCH_2O); 6.61 (*s*, H–C(5)); 6.73 (*s*, H–C(8)); 8.14 (br. *s*, H–C(1)).

Oxidation of 3,4-Dihydroisoquinolines (**6a**,**b**) *with ISB and TBAI: General Procedure.* TBAI (18 mg, 0.05 mmol) was added to a suspension of ISB (121 mg, 0.55 mmol) in MeCN (10 ml) and stirred at r.t. for 5 min.

To this mixture was added the respective 3,4-dihydroisoquinoline (**6a** or **6b**, 0.5 mmol) in one portion, and, after stirring for 1 h at r.t., the reaction was worked up as described above to afford the respective isoquinoline (**5a** or **5b**) and 3,4-dihydro-isoquinol-1-one (**4a** or **4b**). The yield and m.p. data of products **4a**,**b** and **5a**,**b** are given in *Table 2*.

Oxidation of Lycorine Diacetate (**10**) *with ISB and TBAI*. To the suspension of TBAI (37 mg, 0.1 mmol) and ISB (308 mg, 1.4 mmol) in MeCN/H_2O 9:1 (10 ml) was added lycorine diacetate (185 mg, 0.5 mmol). The resultant mixture was stirred at r.t. for 2 h. At the end of reaction, a clear brown soln. formed and was concentrated under reduced pressure. After work-up similar to that described above, except with Me_2CO/toluene (5–10%) as eluent, two products, 2-acetoxyanhydrolycorine lactam (**12**) and (+)-lycorinone diacetate (**11**), were obtained.

Data of **11**. Yield 153 mg (80%). M.p. 114–115° (114° [22]). $[\alpha]_D^{25}+60$ (*c* 1, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.98 (*s*, Me(Ac)); 2.04 (*s*, Me(Ac)); 2.73–2.80 (*m*, 2 H, H–C(4)); 2.94–3.03 (*m*, H–C(15)); 3.71–3.80 (*m*, H–C(5)); 4.19 (*d*, *J* = 12.5, H–C(16)); 5.24 (br. *d*, *J* = 1.5, H–C(1)); 5.57 (br. *s*, H–C(2)); 5.69 (br. *s*, H–C(3)); 5.95 (*s*, OCH_2O); 6.62 (*s*, H–C(11)); 7.48 (*s*, H–C(8)).

Data of **12**. Yield 8 mg (5%). M.p. 248–250° (248–50° [23]). ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.33 (*s*, Me(Ac)); 3.41 (*t*, *J* = 7.8, 2 H, H–C(4)); 4.48 (*t*, *J* = 7.9, 2 H, H–C(5)); 6.12 (*s*, OCH_2O); 7.01 (*d*, *J* = 1.7, H–C(3)); 7.42 (*m*, H–C(1), H–C(8)); 7.89 (*s*, H–C(11)). ^{13}C-NMR ($CDCl_3$, 50 MHz): 21.1 (*q*, Me(Ac)); 29.7 (*t*, C(4)); 47.0 (*t*, C(5)); 101.0 (*s*); 102.2 (*t*, OCH_2O); 106.8 (*d*); 112.3 (*d*); 116.8 (*s*); 118.2 (*d*); 130.0 (*s*); 132.9 (*s*); 137.1 (*s*); 146.9 (*s*, C(9)); 148.8 (*s*, C(10)); 151.9 (*s*, C(2)); 160.5 (*s*, C(7)); 170.2 (*s*, Ac*C*O). EI-HR-MS: 323.0801 (M^+, $C_{18}H_{13}NO_5$; calc. 323.0794).

Oxidation of 1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**16a–d**): *General Procedure*. TABI (37 mg, 0.1 mmol) was added to a suspension of ISB (242 mg, 1.1 mmol) in MeCN/H_2O 9:1 (20 ml) and the mixture was stirred at r.t. for 5 min. To this suspension was added the respective reactant (**16a–d**, each 0.33 mmol, corresponding to 99, 109, 125 and 119 mg, respectively), and the resultant mixture was stirred for additional 1.5 h until a clear soln. was obtained. After work-up similar to that described above, the residue was separated by column chromatography over silica gel (10 g, 70–230 mesh), eluted by hexane-$CHCl_3$ (1:3) and $CHCl_3$ to afford the aldehydes (**17a**, 21 mg, 60%; **17b**, 27 mg, 60%; **17c**, 37 mg, 70%; **17d**, 41 mg, 75%) and 2-methyl-2*H*-3,4-dihydroisoquinol-1-one (**2a**: 58 mg, 80%; 62 mg, 85%; 60 mg, 82%; 62 mg, 85%) from the respective reactant (**16a–16d**).

Oxidation of 1-benzylidene-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**20**). TABI (26 mg, 0.07 mmol) was added to a suspension of ISB (160 mg, 0.73 mmol) in MeCN/H_2O 9:1 (20 ml) and the mixture was stirred at r.t. for 5 min. To this suspension was added **20** (0.33 mmol, 98 mg), and the resultant mixture was stirred for an additional 1.5 h until a clear soln. was obtained. The reaction was worked up as described above to afford benzaldehyde (**17a**, 24 mg, 70%) and 2-methyl-2*H*-3,4-dihydroisoquinol-1-one (**2a**: 59 mg, 80%).

Oxidation of Tetrahydroberberine (**24**) *with ISB*. To the suspension of ISB (145 mg, 0.66 mmol) and **24** (68 mg, 0.20 mmol) in MeCN/H_2O 9:1 (20 ml) was added TBAI (22 mg, 0.06 mmol). The mixture was stirred at 50° for 18 h, and, after a work-up procedure similar to that described above, the residue was separated by CC (silica gel, 5 g, 70–230 mesh, 5–15% acetone in toluene, sat. with aq. NH_4OH (28%), as eluent to afford berberal (**26**, 19 mg, 25%), 8-oxoberberine (**27**, 4 mg, 6%), and berberine (**25**, 11 mg, 15%).

Data of **26**. M.p. 151–152° (150–151° [26]). FT-IR: 1768 (C=O, lactone), 1656 (C=O, amide). ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.73 (*t*-like, *J* = 6.5 Hz, 2 H, H–C(5)); 2.99 (*m*, H–C(6)); 3.15 (*m*, H–C(6)); 3.85 (*s*, MeO); 3.95 (*s*, MeO); 6.00 (*s*, OCH_2O); 6.58 (*s*, H–C(4)); 7.12 (*d*, *J* = 8.3, H–C(11)); 7.58 (*s*, H–C(1)); 7.64 (*d*, *J* = 8.3, H–C(12)); 7.96 (br. *s*, H–C(8)). ^{13}C-NMR ($CDCl_3$, 50 MHz): 27.8 (*t*, C(5)); 40.1 (*t*, C(6)); 56.5 (*q*, MeO–C(10)); 60.7 (*q*, MeO–C(9)); 82.1 (*d*, C(8)); 101.6 (*t*, OCH_2O); 107.0 (*d*, C(4)); 108.5 (*d*, C(1)); 115.0 (*d*, C(11)); 120.6 (*s*, C(12a)); 121.8 (*d*, C(12)); 122.3 (*s*, C(14a)); 134.5 (*s*, C(4a)); 135.7 (*s*, C(8a)); 143.9 (*s*, C(9)); 147.0 (*s*, C(2)); 151.3 (*s*, C(3)); 157.2 (*s*, C(10)); 164.4 (*s*, C(14)); 168.33 (*s*, C(13)). HMBC ($CDCl_3$): H–C(1) to C(2), C(3), C(4a), C(14), and C(14a); H–C(4′) to C(2), C(3), C(5), and C(14a); H–C(5′) to C(4), C(4a), C(6), and C(14a); H–C(6′) to C(5), H–C(11′) to C(9) and C(12a); H–C(12′) to C(8a), C(10), and C(13); MeO–C(9) to C(9); MeO–C(10) to C(10); OCH_2O to C(2) and C(3). NOESY ($CDCl_3$): H–C(1) ↔ H–C(6) ↔ H–C(5); H–C(5) ↔ H–C(8) MeO–C(9); H–C(12) ↔ H–C(11) ↔ MeO–C(10); EI-HR-MS: 383.0991 (M^+, $C_{20}H_{17}NO_7$; calc. 383.1005).

Data of **27**. M.p. 200–201° (200° [27]). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.86 (*t*-like, *J* = 6.0, H–C(5)); 3.92 (*s*, MeO); 3.98 (*s*, MeO); 4.26 (*t*, *J* = 6.0, H–C(6)); 5.98 (*s*, OCH_2O); 6.67 (*s*, H–C(3)); 6.69 (*s*, H–C(14)); 7.19 (*s*, H–C(1)); 7.24 (*d*, *J* = 8.6, H–C(11)); 7.29 (*d*, *J* = 8.6, H–C(12)).

Oxidation of Berberine (**25**) *with ISB*. To a suspension of ISB (145 mg, 0.66 mmol) and **25** (80 mg, 0.20 mmol) in MeCN/H_2O 9:1 (20 ml) was added TBAI (22 mg, 0.06 mmol). The mixture was stirred at 50° for

18 h. After work up similar to that described above, the residue was separated by CC (silica gel, 5 g, 70–230 mesh, eluted stepwise with 5–15% acetone in toluene, saturated with aq. NH_4OH (28%)) to afford **26** (30 mg, 37%). **27** (4 mg, 5%), and 13-hydroxy-8-oxoberberine (**28**, 11 mg, 14%).

Data of **28**. M.p. 216–217° (216–217° [28]). ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.80 (*t*, *J* = 5.9, 2 H, H–C(5)); 3.96 (*s*, MeO); 3.98 (*s*, MeO); 4.18 (*t*, *J* = 5.7, 2 H, H–C(6)); 6.01 (*s*, OCH_2O); 6.72 (*s*, H–C(3)); 7.39 (*d*, *J* = 9.1, H–C(11)); 7.72 (*s*, H–C(1)); 7.86 (*d*, *J* = 9.1, H–C(12)).

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