Oxidative Rearrangement of 1-Alkylidene-1,2,3,4-tetrahydro-2-(trichloroacetyl)isoquinolines to 1,5,6,10b-Tetrahydro-10b-(trichloromethyl)-3*H*-oxazolo[4,3-*a*]isoquinolin-3-ones

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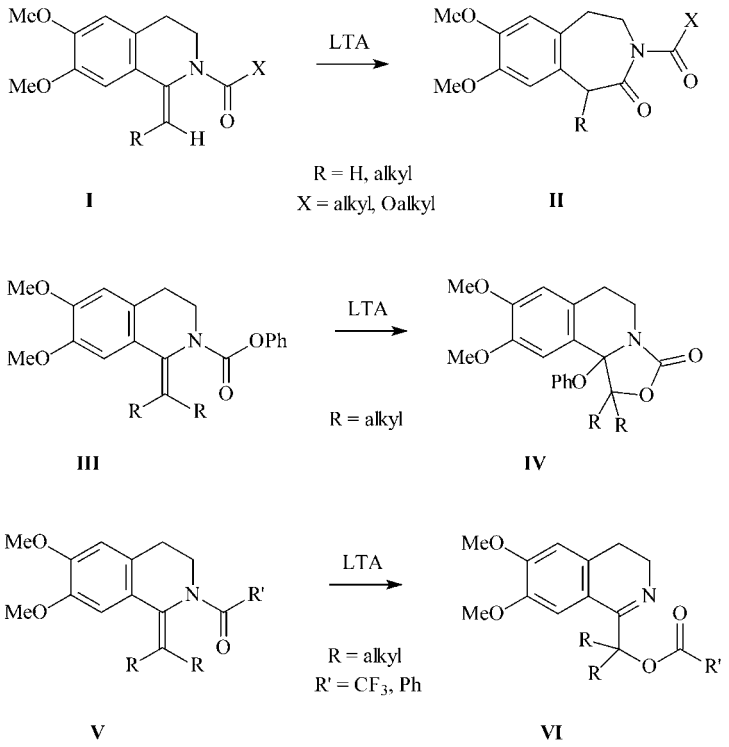
On treatment with lead tetraacetate ($Pb(OAc)_4$), the 1-(alkylidene)-1,2,3,4-tetrahydro-*N*-(trichloroacetyl)-isoquinolines **2a**–**2c** as well as the tribromoacetyl derivative **4** undergo an oxidative cyclization with concomitant migration of the trihalogenomethyl group to afford the 1,5,6,10b-tetrahydro-10b-(trichloromethyl)-3*H*-oxazolo[4,3-*a*]isoquinolin-3-ones **3a**–**3c** or the tribromomethyl derivative **6**, respectively. These tricycles are also accessible *via* esterification of 3,4-dihydro-1-(1-hydroxy-1-methylethyl)isoquinoline **8** with either trichloroacetyl chloride or tribromoacetyl bromide, respectively. A plausible mechanistic description for these reactions involves an – unprecedented – 'intramolecular imino–haloform' rearrangement.

Introduction. – The oxidative ring expansion of 'isoquinoline enamides' to tetrahydro-3-benzazepin-2-ones (*i.e.*, **I** → **II**) occurs readily for different *N*-acyl functionalities when *a*) the isoquinoline ring contains electron-releasing, *e.g.*, MeO substituents and *b*) the exocyclic C=C bond is either unsubstituted or monoalkyl-substituted [1]. For compounds in which the exocyclic C=C bond is dialkyl-substituted, the oxidation with $Pb(OAc)_4$ (LTA) occurs readily, but does not lead to ring expansion. Instead, phenyl tetrahydroisoquinoline-2-carboxylates cyclize to oxazoloisoquinolines (*i.e.*, **III** → **IV**), while *N*-benzoyl or *N*-(trifluoroacetyl) derivatives undergo a formal oxidative rearrangement (*i.e.*, **V** → **VI**) to afford the corresponding carboxylates [2][3] (*Scheme 1*).

In recent studies on effective routes to isoquinoline alkaloids, oxazoloisoquinolines of type **IV** bearing an alkyl group instead of the oxy function at C(10b) have been synthesized by intramolecular amidoalkylation of 4-hydroxyoxazolidin-2-ones [4][5]. Here, we report on the synthesis of such compounds by LTA oxidation of appropriately substituted 'isoquinoline enamides' by interconnecting the latter two reaction types in *Scheme 1* accordingly.

Results. – The reaction of appropriate 1-alkylated dihydroisoquinolines **1** with CCl_3COCl affords 1-alkylidene-2-(trichloroacetyl)isoquinolines **2** in good yield. Stirring **2a**–**2c** with LTA in AcOH at room temperature for a short period leads to **3a**–**3c**,

Scheme 1



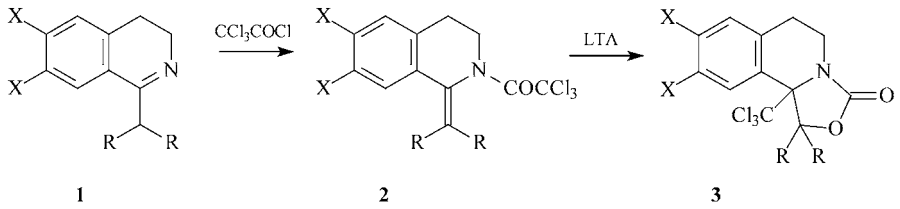
LTA = Lead tetraacetate

respectively, in almost quantitative yield (*Scheme 2*). All new compounds **3a**–**3c** exhibit very similar spectroscopic properties, and a single-crystal X-ray-analysis was performed for **3a**. In contrast, no reaction of **2d** with LTA ocurred, neither as described above, nor by stirring for 48 h at 50°.

This novel reaction was then further extended to enamides **4** and **5**. Oxidation of the tribromoacetyl derivative **4** affords (tribromomethyl)oxazoloisoquinoline **6**, albeit in much lower yield (30%) due to degradation of this compound in AcOH. On the other hand, the dichloroacetyl enamide **5** only undergoes the previously reported oxidative (*i.e.*, **V** → **VI**) rearrangement to form dichloroacetate **7** in 87% yield (*Scheme 3*).

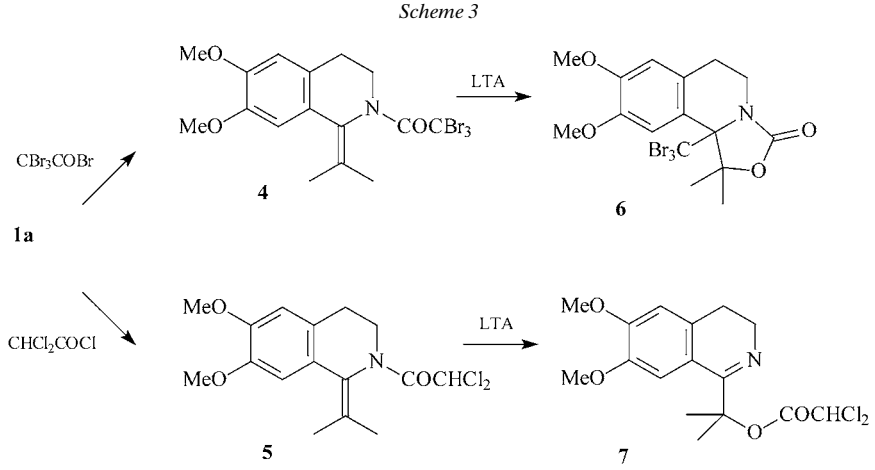
Careful hydrolysis of the ester **7** gives hydroxy imine **8**, which had already been obtained by alkaline hydrolysis of the corresponding trifluoroacetate [3]. Treatment of **8** with either CCl_3COCl or CBr_3COBr in the presence of a base in CH_2Cl_2 leads first to compounds **9** and **10**, both exhibiting very similar ^{13}C-NMR spectra as that of **7**. On standing in solution at room temperature or – even faster – on attempted recrystallization, esters **9** and **10** rearrange quantitatively to oxazoloisoquinolines **3** and **6**, respectively, isolated in yields >70% (*Scheme 4*).

Scheme 2

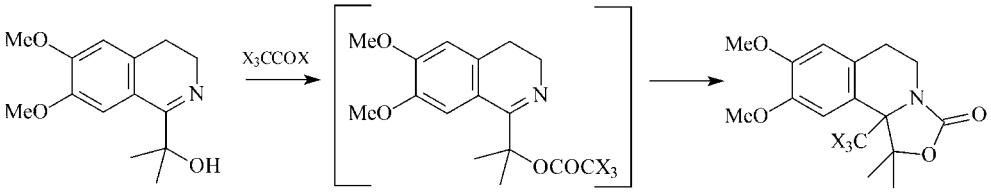


a X = MeO, R = Me
b X = MeO, R = Et
c X = MeO, R,R = $-(CH_2)_5-$
d X = H, R = Me

Scheme 3



Scheme 4



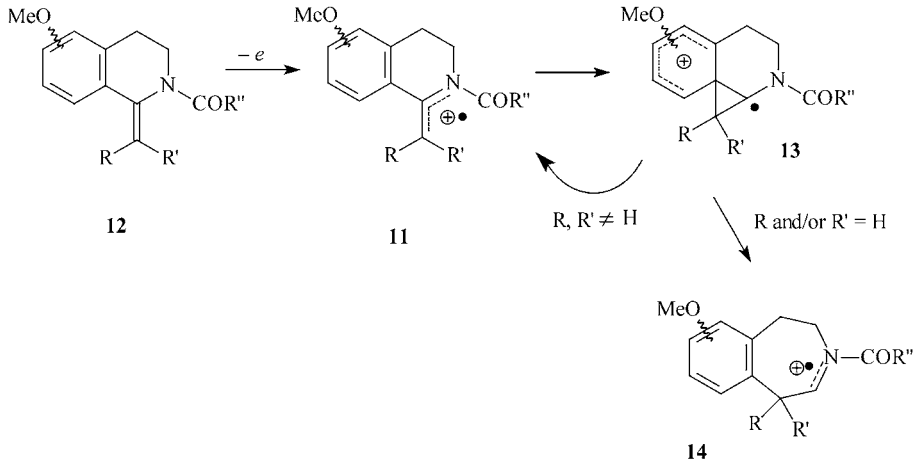
9 X = Cl
10 X = Br

3a X = Cl
4 X = Br

Discussion. – As already expected from previous data, enamides **2**, **4**, and **5** do not undergo an oxidative ring expansion to benzazepinones (*i.e.*, **I** → **II** in *Scheme 1*) but, instead, afford products in which the pyridine moiety remains unaltered (**III** → **IV** or

V → **VI**, resp.). The reason for this different behavior is summarized in *Scheme 5*. The radical cation **11** – formed by one-electron transfer from enamide **12** to LTA – will easily isomerize to the tricyclic radical cation **13** *via* addition of the aromatic ring to the terminal olefinic C-atom. It can now be assumed that, for such an intermediate bearing a dialkyl-substituted C-atom on the three-membered ring, the back reaction will be much more efficient than the cleavage of the central C–C bond, *i.e.*, the path leading to the ring-enlarged radical cation **14**.

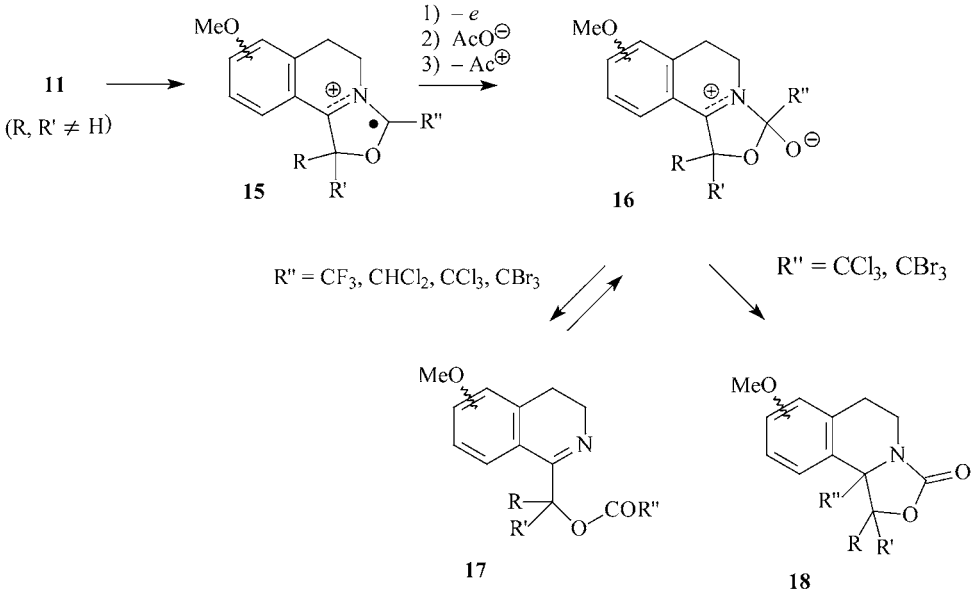
Scheme 5



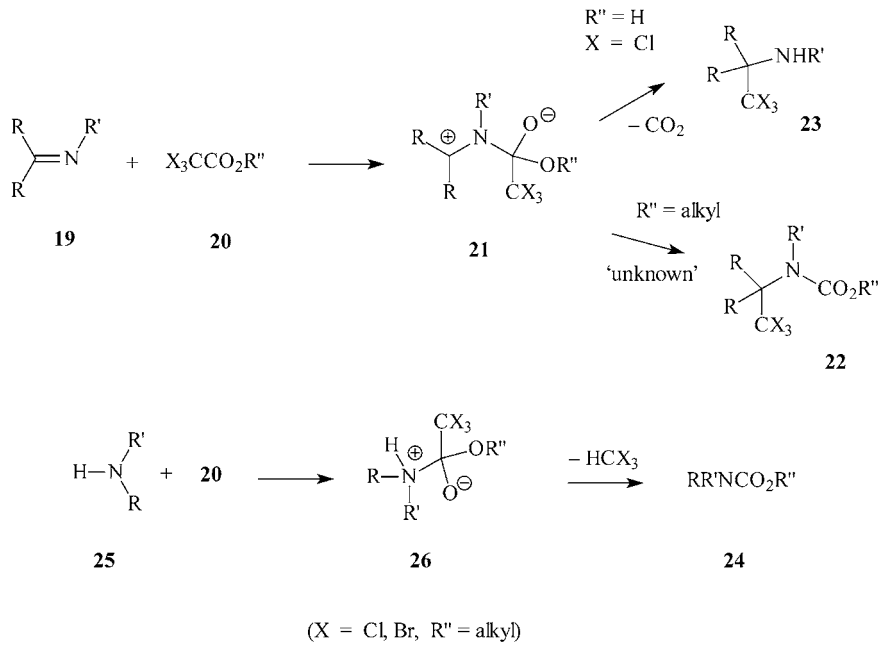
The alternative reaction path for intermediate **11** (with R,R′ ≠ H) , *i.e.*, cyclization to **15**, is depicted in *Scheme 6*. This latter radical cation is then further converted to **16** by a second electron-transfer step (either oxidation to a dication, which is then trapped by acetate, or direct coupling of **15** with an acetoxyl radical), followed by the elimination of an acetyl cation, (equivalent to ketene plus a proton). Intermediate **16** represents the key species for the conversion of dihydroquinoline esters **17** (in equilibrium with **16**) to oxazoloisoquinolines **18**.

The rearrangement of trichloro- and tribromoacetyl esters **17** to tricycles **18** corresponds to an (intramolecular) addition of an imine **19** to an ester **20** of one of these trihalogenoacetic acids (*Scheme 7*). Such a sequence, wherein the imine N-atom adds to the carbonyl C-atom with formation of intermediate **21**, followed by migration of the trihalogenomethyl carbanion to afford carbamate **22**, could be termed an 'imino–haloform' rearrangement. The formation of **18** is insofar unprecedented to the best of our knowledge as no examples of such a (formal) insertion of an imine C=N bond into the $X_3C-C(O)$ bond of a trihalogenoacetate have been reported in the literature. The only related publications found deal with the formation of α-trichloromethyl amines **23** from the addition of either aldimines [6] or ketimines [7] to CCl_3COOH, and the formation of carbamates **24** from secondary amines **25** and esters of either CCl_3COOH or CBr_3COOH [8]. In this latter report on an 'amino–haloform' reaction, it has been pointed out that *no* such reaction occurs for esters of dichloroacetic or trifluoroacetic acid, where, in contrast, the adduct corresponding to **26** undergoes alcohol elimination,

Scheme 6



Scheme 7



i.e., conversion to an amide, exclusively. This result is in excellent agreement with our finding that dichloroacetyl enamide **5** is oxidized selectively to ester **7** without concommitant formation of the corresponding oxazoloisoquinoline.

A final comment deals with the result that, in contrast to **2a**–**2c**, the non-MeO-substituted (parent) compound **2d** is not oxidized by LTA. With the knowledge that the oxidation potential of 3,4-dimethoxystilbene in solution is lower by 0.41 V than that of the parent hydrocarbon [9], it can thus be deduced that LTA is a strong enough oxidant for MeO-substituted 'isoquinoline enamides' but not for the corresponding parent compound.

Experimental Part

1. *General*. IR Spectra: KBr pellets. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$; 400 and 100.6 MHz, resp.; chemical shifts δ in ppm rel. to Me_4Si (=0 ppm). MS: at 70 eV; in *m*/*z* (rel. intensity in %). X-Ray crystal-structure analysis: *Rigaku AFC5S* diffractometer at 293 K with CuK_α radiation ($\lambda = 1.54178$ Å).

2. *Starting Materials.* 3,4-Dihydroisoquinolines **1a** [10], **1b** [10], **1c** [11], **1d** [12], and **8** [3] were prepared according to the references indicated. CCl_3COCl, $Cl_2CHCOCl$, and $Pb(OAc)_4$ (=LTA) were commercially available. CBr_3COBr was prepared according to [13].

3. *Preparation of 2-(Trichloroacetyl)isoquinolines* **2**. To a soln. of **1** (50 mmol) and Et_3N (7.6 ml, 50 mmol) in 100 ml of CH_2Cl_2 was added dropwise a soln. of CCl_3COCl (5.6 ml, 50 mmol) in 50 ml of CH_2Cl_2, and the mixture was stirred for 18 h at 25°. After filtration of the precipitated ammonium salt, the filtrate was washed twice with 5% aq. HCl, H_2O, and then with 5% aq. Na_2CO_3. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the residue was purified by CC (SiO_2; AcOEt/hexane 1:1).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(1-methylethylidene)-2-(trichloroacetyl)isoquinoline (**2a**). Yield: 13.8 g (73%). M.p. 127–130°. IR: 1677. ^{1}H-NMR: 6.93 (*s*); 6.65 (*s*); 4.78 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.85 (*s*, 3 H); 3.83 (*s*, 3 H); 3.72 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.50 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.84 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.10 (*s*, 3 H); 1.75 (*s*, 3 H). MS: 379 (3, $M^{+\cdot}$), 342.

1-(1-Ethylpropylidene)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-(trichloroacetyl)isoquinoline (**2b**). Yield: 18.4 g (92%). M.p. 134–135°. IR: 1675. ^{1}H-NMR: 6.95 (*s*); 6.65 (*s*); 4.80 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.90 (*s*, 3 H); 3.89 (*s*, 3 H); 3.88 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.25 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.89 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.45–2.15 (*m*, 4 H); 1.25 (*t*, 3 H); 1.15 (*t*, 3 H). MS: 405 (5, $M^{+\cdot}$), 341.

1-Cyclohexylidene-1,2,3,4-tetrahydro-6,7-dimethoxy-2-(trichloroacetyl)isoquinoline (**2c**). Yield: 17.2 g (86%). M.p. 139–142°. IR: 1680. ^{1}H-NMR: 6.89 (*s*); 6.62 (*s*); 4.81 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.86 (*s*, 3 H); 3.85 (*s*, 3 H); 3.84 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.23 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.87 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.57–1.35 (*m*, 10 H). MS: 417 (2, $M^{+\cdot}$), 382.

1,2,3,4-Tetrahydro-1-(1-methylethylidene)-2-(trichloroacetyl)isoquinoline (**2d**). Yield: 12.4 g (82%). M.p. 126–127°. IR: 1675. ^{1}H-NMR: 7.42–7.15 (*m*, 4 H); 4.80 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.84 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.30 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.92 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.05 (*s*, 3 H); 1.80 (*s*, 3 H). ^{13}C-NMR: 158.3 (*s*); 134.5 (*s*); 134.4 (*s*); 131.6 (s); 130.2 (s); 128.8 (*d*); 128.7 (*d*); 127.8 (*d*); 125.9 (*d*); 115.9 (*s*); 48.2 (*t*); 28.9 (*t*); 21.7 (*q*); 20.9 (*q*). MS: 317 (2, $M^{+\cdot}$), 282.

4. *LTA Oxidation of* N-*(Trichloroacetyl)isoquinolines* **2**. A soln. of **2** (5 mmol) and LTA (4.43 g, 10 mmol) in 50 ml of AcOH was stirred for 1 h at r.t., and then three drops of glycerol were added to quench excess LTA. After stirring for an additional 10 min, the mixture was diluted with 200 ml of CH_2Cl_2, and washed with H_2O and then with aq. Na_2CO_3. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the residue was purified by crystallization from AcOEt/hexane.

*1,5,6,10b-Tetrahydro-8,9-dimethoxy-1,1-dimethyl-10b-(trichloromethyl)-3*H-*oxazolo[4,3-*a*]isoquinolin-3-one* (**3a**). Yield: 1.95 g (97%). M.p. 188–189°. IR: 1750. ^{1}H-NMR: 7.30 (*s*, 1 H); 7.00 (*s*, 1 H); 4.25 (*m*, 1 H); 4.01 (*m*, 1 H); 3.91 (*s*, 3 H); 3.89 (*s*, 3 H); 2.95 (*m*, 2 H); 2.05 (*s*, 3 H); 1.06 (*s*, 3 H). ^{13}C-NMR: 155.9 (*s*); 150.1 (*s*); 147.1 (*s*); 128.9 (*s*); 121.1 (*s*); 112.5 (*d*); 112.1 (*d*); 105.8 (*s*); 87.1 (*s*); 76.8 (*s*); 56.5 (*q*); 55.9 (*q*); 37.6 (*t*); 29.6 (*t*); 25.3 (*q*); 24.5 (*q*). MS: 395 (2, $M^{+\cdot}$), 277. X-Ray crystal-structure analysis: clear colorless parallelepiped (0.38 × 0.13 × 0.43 mm) from AcOEt/hexane, $C_{16}H_{18}NO_4Cl_3$, M_r 394.68, triclinic, space group *P*1, *Z* = 4, *a* = 13.606(2), *b* = 15.346(2), *c* = 8.820(3) Å, $\alpha = 102.35(2)°$, $\beta = 103.91(2)°$, $\gamma = 84.06°$, *V* = 1743.6(7) Å^3, $D_x = 1.50\ g \cdot cm^{-3}$.

*1,1-Diethyl-1,5,6,10b-tetrahydro-8,9-dimethoxy-10b-(trichloromethyl)-3*H-*oxazolo[4,3-*a*]isoquinolin-3-one* (**3b**). Yield: 1.97 g (93%). M.p. 165–167°. IR: 1755. ^{1}H-NMR: 7.30 (*s*, 1 H); 6.55 (*s*, 1 H); 4.20 (*m*, 1 H); 3.94 (*m*, 1 H); 3.88 (*s*, 3 H); 3.85 (*s*, 3 H); 2.95 (*m*, 2 H); 2.56 (*dq*, *J* = 13.5, 7.4); 2.42 (*dq*, *J* = 13.5, 7.4); 1.47 (*dq*, *J* = 13.5, 7.4); 1.27 (*dq*, *J* = 13.5, 7.4); 1.27 (*t*, *J* = 7.4, 3 H); 1.22 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR: 156.2 (*s*); 149.6 (*s*); 146.5 (*s*); 129.1 (*s*); 120.3 (*s*); 112.6 (*d*); 111.6 (*d*); 106.0 (*s*); 92.5 (*s*); 78.6 (*s*); 56.1 (*q*); 55.9 (*q*); 37.7 (*t*); 29.6 (*t*); 27.6 (*t*); 25.7 (*t*); 9.9 (*q*); 7.6 (*q*). MS: 423 (1, M^+), 304.

*1′,5′,6′,10′b-Tetrahydro-8′,9′-dimethoxy-10b-(trichloromethyl)spiro[cyclohexane-1,1′-[3*H*]oxazolo[4,3-*a*]isoquinolin]-3′-one* (**3c**). Yield: 1.82 g (84%). M.p. 204–206°. IR: 1750. ^{1}H-NMR: 7.33 (*s*, 1 H); 6.64 (*s*, 1 H); 4.21 (*m*, 1 H); 3.99 (*m*, 1 H); 3.96 (*s*, 3 H); 3.87 (*s*, 3 H); 3.02–2.75 (*m*, 3 H); 2.02 (*m*, 1 H); 1.82–1.61 (*m*, 4 H); 1.42 (*m*, 1 H); 1.25–0.97 (*m*, 3 H). ^{13}C-NMR: 156.0 (*s*); 149.5 (*s*); 146.6 (*s*); 128.8 (*s*); 120.5 (*s*); 111.6 (*d*); 111.4 (*d*); 105.6 (*s*); 88.9 (*s*); 77.2 (*s*); 56.1 (*q*); 55.7 (*q*); 37.5 (*t*); 35.6 (*t*); 33.1 (*t*); 27.6 (*t*); 24.6 (t); 22.6 (*t*); 21.5 (*t*). MS: 435 (2, $M^{+\bullet}$), 316.

Oxidation of **2d**. Neither the above procedure nor using 4 equiv. of LTA and stirring the soln. at 45° for 24 h led to any conversion of **2d**.

5. *Preparation of 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(1-methylethylidene)-2-(tribromoacetyl)isoquinoline* (**4**). To a soln. of **1a** (5.93 g, 25 mmol) and Et_3N (5.8 ml) in 25 ml of CH_2Cl_2 cooled to 0–5° was added dropwise a freshly prepared soln. of CBr_3COBr (10.6 g, 29 mmol) in 15 ml of CH_2Cl_2 during 5 min, and the mixture was then stirred at 25° for an additional 2 h. After filtration of the precipitated ammonium salt, the filtrate was washed twice with 5% aq. HCl, H_2O, and then with 5% aq. Na_2CO_3. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the residue was purified by recrystallization from MeOH. Yield: 15.5 g (78%). M.p. 140–142°. IR: 1668, 1645. ^{1}H-NMR: 6.96 (*s*); 6.68 (*s*); 4.95 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.86 (*s*, 3 H); 3.84 (*s*, 3 H); 3.82 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.43 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.92 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.10 (*s*, 3 H); 1.81 (*s*, 3 H). MS: 513/511 (1, $M^{+\bullet}$), 353/351.

6. *LTA Oxidation of* **4**. A mixture of **4** (2.6 g, 5 mmol) and LTA (2.6 g, 5.9 mmol) in 25 ml of AcOH was stirred for 18 h at 25°. The reaction mixture was then quenched with three drops of glycerol, and the mixture was stirred for additional 20 min. After removal of most of the solvent at reduced pressure, the residue was diluted with 60 ml of CH_2Cl_2, and then washed with H_2O and aq. Na_2CO_3 soln. After drying ($MgSO_4$) and evaporation of the solvent, the residue was dissolved in 25 ml of MeCN, and the soln. was warmed to 50° for 20 min. After removal of the solvent, the residue was purified by CC (MeOH/CH_2Cl_2 3:97) to afford 0.79 g (30%) of *1,5,6,10b-tetrahydro-8,9-dimethoxy-1,1-dimethyl-10b-(tribromomethyl)-3*H-*oxazolo[4,3-*a*]isoquinolin-3-one* (**6**). M.p. 192–194°. IR: 1747. ^{1}H-NMR: 7.49 (*s*, 1 H); 6.62 (*s*, 1 H); 4.30–4.20 (*m*, 2 H); 3.85 (*s*, 6 H); 3.00–2.90 (*m*, 2 H); 2.15 (*s*, 3 H); 1.08 (*s*, 3 H). ^{13}C-NMR: 155.9 (*s*); 149.6 (*s*); 146.5 (*s*); 128.3 (*s*); 121.4 (*s*); 111.7 (*d*); 111.3 (*d*); 87.8 (*s*); 75.4 (*s*); 56.1 (*q*); 55.7 (*q*); 50.8 (s); 37.7 (*t*); 30.2 (*t*); 27.4 (*q*); 24.5 (*q*). MS: 529/527 (1, $M^{+\bullet}$), 234.

7. *Preparation of 2-(Dichloroacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(1-methylethylidene)isoquinoline* (**5**). To a soln. of **1a** (5.93 g, 25 mmol) and pyridine (2.5 ml) in 25 ml of CH_2Cl_2 cooled to −70° was added dropwise a soln. of $CHCl_2COCl$ (3.8 g, 26 mmol) in 15 ml of CH_2Cl_2 during 5 min, the mixture was then stirred for 30 min. at −70° and then allowed to warm to 25°. The mixture was washed twice with 5% aq. HCl, H_2O, and then aq. $NaHCO_3$ soln. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, the residue was purified by CC (AcOEt/hexane 1:3). Yield: 5.5 g (64%). M.p. 135–137°. IR: 1664. ^{1}H-NMR: 6.84 (*s*); 6.66 (*s*); 6.40 (*s*); 4.22 (*ddd*, *J* = 2.6, 7.6, 13.5); 3.86 (*s*, 6 H); 3.43 (*ddd*, *J* = 6.7, 9.6, 13.5); 3.05 (*ddd*, *J* = 7.6, 9.6, 17.0); 2.76 (*ddd*, *J* = 2.6, 6.7, 17.0); 2.06 (*s*, 3 H); 1.91 (*s*, 3 H). MS: 343 (5, $M^{+\bullet}$), 308.

8. *LTA Oxidation of* **5**. A mixture of **5** (1.8 g, 5 mmol) and LTA (2.6 g, 5.9 mmol) in 25 ml of AcOH was stirred for 18 h at 25°. The reaction was then quenched with three drops of glycerol, and the mixture was stirred for additional 20 min. After removal of most of the solvent at reduced pressure, the residue was diluted with 60 ml of CH_2Cl_2, and then washed with H_2O and aq. Na_2CO_3 soln. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by CC (MeOH/CH_2Cl_2 3:97) to afford 1.62 g (87%) of *1-[1-(dichloroacetoxy)-1-methylethyl]-3,4-dihydro-6,7-dimethoxyisoquinoline* (**7**). M.p. 96–97°. IR: 1761, 1746. ^{1}H-NMR: 7.26 (*s*, 1 H); 6.71 (*s*, 1 H); 5.78 (*s*); 3.91 (*s*, 3 H); 3.89 (*s*, 3 H); 3.67 (*AA′XX′*, 2 H); 2.62 (*AA′XX′*, 2 H); 1.96 (*s*, 6 H). ^{13}C-NMR: 172.1 (*s*); 165.7 (*s*); 149.5 (*s*); 146.6 (*s*); 138.3 (*s*); 130.4 (*s*); 116.7 (*d*); 114.6 (*d*); 76.9 (*s*); 74.1 (*d*); 56.0 (*q*); 55.8 (*q*); 46.7 (*t*); 31.7 (*t*); 22.5 (*q*, 2 Me). MS: 359 (4, $M^{+\bullet}$), 232.

9. *Reaction of 3,4-Dihydro-1-(1-hydroxy-1-methylethyl)-6,7-dimethoxyisoquinoline* (**8**) *with Trihalogenoacetyl Halides.* To a soln. of **8** (1.25 g, 5 mmol) and 4-(dimethylamino)pyridine (0.72 g, 6 mmol) in 15 ml of CH_2Cl_2 cooled to 0–5° in an ice-water bath was added dropwise a soln. of either CCl_3COCl or CBr_3COBr (6 mmol) in 5 ml of CH_2Cl_2, and the mixture was stirred at r.t. for 2 h (Cl) or 18 h (Br), resp. The mixture was then washed with 10% aq. HCl, then with H_2O, and finally with aq. Na_2CO_3 soln. After drying ($MgSO_4$) and

evaporation of the solvent, the residue was recrystallized from acetone/hexane (Cl) or CH_2Cl_2/hexane (Br) to afford **3a** (1.38 g, 71%) or **6** (2.0 g, 77%), resp.

REFERENCES

[1] G. R. Lenz, R. A. Lessor, *Org. Synth.* **1991**, *70*, 139.
[2] G. R. Lenz, *J. Chem. Soc., Perkin Trans. 1* **1990**, 33.
[3] G. R. Lenz, R. A. Lessor, P. W. Rafalko, Z. Kosarych, *J. Chem. Soc., Perkin Trans. 1* **1993**, 745.
[4] M. I. Collado, I. Manteca, N. Sotomayor, M. J. Villa, E. Lete, *J. Org. Chem.* **1997**, *62*, 2080.
[5] N. B. Chernysheva, A. A. Bogolyubov, V. V. Muravev, V. V. Elkin, V. V. Semenov, *Khim. Geterots. Soedin.* **2000**, *36*, 1219.
[6] A. Lukasiewicz, *Tetrahedron* **1964**, *20*, 1.
[7] A. Lukasiewicz, J. Lesinska, *Tetrahedron* **1965**, *21*, 3247.
[8] M. M. Joullie, *J. Am. Chem. Soc.* **1955**, *77*, 6662.
[9] T. Majima, *J. Phys. Chem.* **1996**, *100*, 13615.
[10] P. N. Kraig, F. P. Nabenhauer, P. M. Williams, E. Macko, J. Toner, *J. Am. Chem. Soc.* **1952**, *74*, 1316.
[11] V. S. Georgiev, R. P. Carlson, R. G. van Inwegen, A. Khandwala, *J. Med. Chem.* **1979**, *22*, 348.
[12] N. M. Gray, B. K. Cheng, S. J. Mick, C. M. Lair, P. C. Contreras, *J. Med. Chem*. **1989**, *32*, 1242.
[13] W. T. Brady, *J. Org. Chem.* **1966**, *32*, 2676.

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