4-Methylenedioxolan-2-ones as convenient synthons for the preparation of natural products of the berbine and calycotomine series

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Intramolecular amidoalkylation of nonactivated 3-(2-arylethyl)-4-hydroxyoxazolidin-2-ones in polyphosphoric acid gave oxazolo[4,3-*a*]isoquinolin-3-one whose hydrolysis affords isoquinoline β-amino alcohols, calycotomine analogs. Using the developed procedure, 13,13,13a-trimethylberbine was synthesized.

Key words: β-amino alcohols, 4-hydroxyoxazolidin-2-ones, 1,5,6,10b-tetrahydrooxazolo[4,3-*a*]isoquinolin-3-ones, intramolecular amidoalkylation, calycotomine, 13,13,13a-trimethylberbine, alkaloids, polyphosphoric acid, carbamates.

Berbines are of considerable interest for their versatile biological activities.[1] 4-Hydroxyoxazolidin-2-ones may be convenient starting reagents for the preparation of compounds of this class, as on treatment with acidic reagents they are converted into acyliminium species, which are key intermediates in the intramolecular amidoalkylation. 4-Hydroxyoxazolidin-2-ones are readily formed upon the reaction of 4-methylenedioxolan-2-ones with various amines[2,3] (Scheme 1). The 4-hydroxyoxazolidin-2-ones that have a β-arylethyl substituent in position 3, in which the benzene ring is activated by, for example, two methoxy groups in positions 3 and 4, readily undergo intramolecular amidoalkylation in acidic media, particularly, in anhydrous formic or trifluoroacetic acids. The reaction is carried out at room temperature, the acid (HCO_2H or CF_3CO_2H) serving as both the cyclizing reagent and the solvent.

However, if the 3-substituent in the oxazolidinone molecule contains a nonactivated benzene ring, for example, compound **3a** (see Scheme 1), this oxazolidinone does not undergo intramolecular amidoalkylation under these conditions, being recovered unchanged (in some cases, however, it is partially or completely dehydrated). A temperature rise resulted in virtually complete resinification of the reaction mixture. This set the task of selecting a new cyclizing reagent. We found that polyphosphoric acid (PPA) may be an efficient and simultaneously mild cyclizing reagent; in addition, PPA is a medium in which the reaction temperature can be varied over a broad range without resinification of the reaction mixture. By performing the reactions in PPA at 80—100 °C, we prepared a number of oxazolo[4,3-*a*]isoquinolin-3-ones **4** in high yields (see Scheme 1).

We synthesized a series of oxazolidinones **3a—k**, **5a,b** (Schemes 1 and 2). The ^{1}H NMR spectra exhibit a singlet for the hydroxy group at 5.60—6.20 ppm, and the mass spectra show molecular ion signals. However, in the case of 2-phenylethylamines **1a,b** and 4-methylenedioxolan-2-ones **2a—d**, mixtures of oxazolidinones **3a—d, f—h** and the products of their dehydration, 4-methyleneoxazolidin-2-ones, were formed. This is indicated by TLC and ^{1}H NMR data; the latter contain signals for both the hydroxy groups and the methylene protons as two characteristic doublets at 4.05—4.22 ppm ($J \approx 2$ Hz). In view of the integral intensity ratio between the OH group and one proton of the CH_2 group, about 25% of the 4-hydroxyoxazolidin-2-ones **3a—d,f—h** formed initially are dehydrated. The proton signals of the $—CH_2—CH_2—$ fragment of the β-arylethyl substituent are manifested as two multiplets at 2.50—3.50 ppm, each corresponding to 2H in integral intensity.

Heating of oxazolidinones **3a—i** in PPA gives oxazoloisoquinolines **4a—i** in high yields. Compounds **3a—d, f—h** and the products of their dehydration are protonated to give the same acyliminium species **A** and, therefore, they can be used in the reaction without separation. Oxazolidinones **3f—h** are amidoalkylated much more readily in PPA (even at 50 °C), giving rise to oxazoloisoquinolines we prepared previously.[3]

In the ^{1}H NMR spectra of compounds **4a—i**, the protons of the $—CH_2—CH_2—$ fragment are usually responsible for four multiplets with a total integral intensity equal to four protons and a singlet for the methyl group located in position 10b of the oxazoloisoquinoline system. The benzene ring protons give rise to a four- rather than five-proton multiplet, as contained in the starting oxazol-

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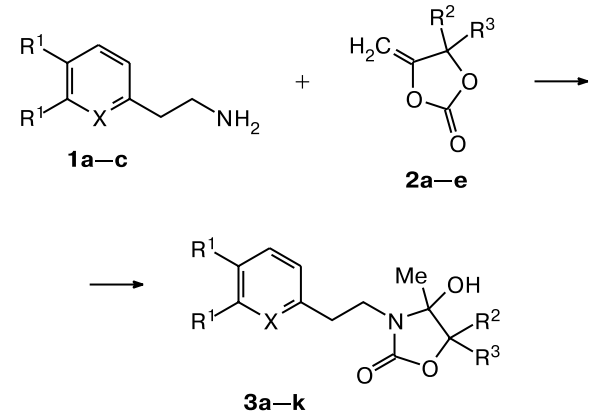
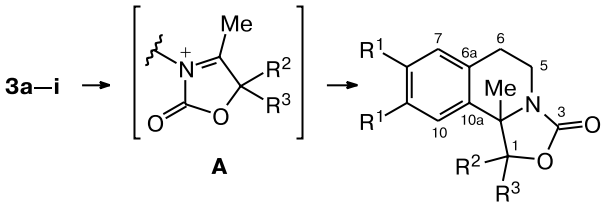
Scheme 1





Compound	R^1	Compound	R^2	R^3
1a	H	**2a**	Me	Me
1b	OMe	**2b**	Me	Et
1c	H	**2c**	$-(CH_2)_5-$	
		2d	$(CH_2C(Me)_2)_2NH$	
		2e	Me	CH_2Ph

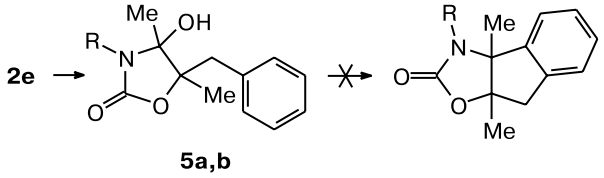
Compound	R^1	R^2	R^3
		$R^2—R^3$	
3a,j, **4a**	H	Me	Me
3b, **4b**	H	Me	Et
3c,k, **4c**	H	$-(CH_2)_5-$	
3d, **4d**	H	$(CH_2C(Me)_2)_2NH$	
3e, **4e**	H	Me	CH_2Ph
3f, **4f**	OMe	Me	Me
3g, **4g**	OMe	Me	Et
3h, **4h**	OMe	$-(CH_2)_5-$	
3i, **4i**	OMe	Me	CH_2Ph

X = CH (**1a,b**, **3a—i**), N (**1c**, **3j,k**)

idinones. This provides evidence for the fact that the acyliminium species attacks an *ortho*-position of the benzene ring. In compound **4a**, the signals for four aromatic protons are resolved into four separate signals. The mass spectra of the compounds contain molecular ion peaks, a typical destruction pathway being elimination of the methyl group yielding the $[M - 15]^+$ ions. The IR spectra of compounds **3** and **4** exhibit an absorption band for the carbamate C=O group.

Oxazolidinones **3j,k** do not undergo intramolecular amidoalkylation, which is apparently due to the pronounced electron-deficiency of the protonated pyridine ring.

Scheme 2



R = H (**a**), Me (**b**)

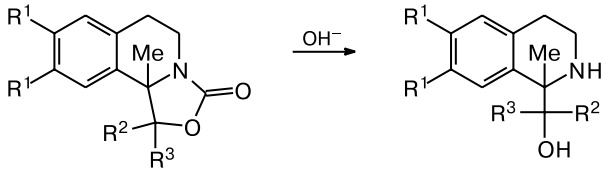
It may be expected that amidoalkylation of the 5-benzyl group of oxazolidinones **5a,b** into the benzene ring will result in a closure of a five-membered ring (see Scheme 2); however, on heating in PPA at 100 °C, **5a,b** are recovered unchanged (NMR).

These data lead to the conclusion that cyclization of oxazolidinones **3e,i** results in the closure of a six-membered ring to give the corresponding oxazoloisoquinolines **4e,i**. As in most cases described in the literature, 6-*exo*-trig- rather than energetically less favorable 5-*exo*-trig-cyclization takes place under these conditions.[4]

Subsequently, we studied hydrolysis of the tricyclic compounds **4**. Hydrolysis of the oxazolidinone moiety of oxazoloisoquinoline could provide a route to β-amino alcohols, which may serve as key intermediates in the synthesis of various analogs of natural products, in particular, berbines.

Numerous methods of hydrolysis of cyclic carbamates are documented; however, the compounds we deal with proved to be stable against both acid[5] and alkaline hydrolysis.[6] First, hydrolysis of compounds **4a—c,f,g** was carried out by heating with a 10-fold molar excess of KOH in a methanol—water mixture (1 : 1) at 120 °C in an autoclave (Scheme 3). Amino alcohols **6** were isolated as oxalates. The results are summarized in Table 1.

Scheme 3

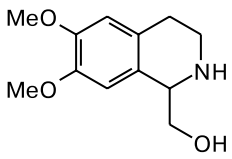


Compound	R^1	R^2	R^3
		$R^2—R^3$	
6a	H	Me	Me
6b	H	Me	Et
6c	H	$-(CH_2)_5-$	
6d	OMe	Me	Me
6e	OMe	Me	Et

Table 1. Hydrolysis of some cyclic oxazoloisoquinolines **4a—c,f,g**

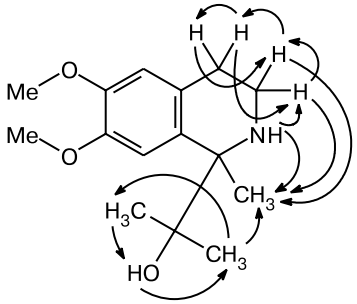
Product	MeOH—H_2O (120 °C)			DMSO—H_2O (80 °C)	
	Yield (%)	τ/h	Conversion (%)	Yield (%)	τ/h
6a	92	64	~100	97	52
6b	74	105	~100	94	80
6c	60	165	~61	93	100
6d	87	80	~100	95	65
6e	Traces	180	<1	79	155

It can be seen that the greater the size of the 1-substituent in structure **4** (see Scheme 1), the longer the reaction; the OMe groups located in positions 8 and 9 also significantly decrease the rate of hydrolysis. Indeed, on attempted hydrolysis of compound **4g**, the starting oxazoloisoquinoline was recovered almost quantitatively, while the final amino alcohol could be detected only by chromatography. Obviously, this method is inapplicable for preparative synthesis of substituted polyfuctionalized amino alcohols. As an alternative, we used hydrolysis with KOH in aqueous DMSO.[7] In this case, the reaction temperature was reduced to 80 °C, the reaction duration decreased, and the yields of β-amino alcohols were higher than in the previous method; in addition, this allowed the preparation of compound **6d**, which could not be obtained by the previous method. The resulting compounds are analogs of the alkaloid calycotomine.



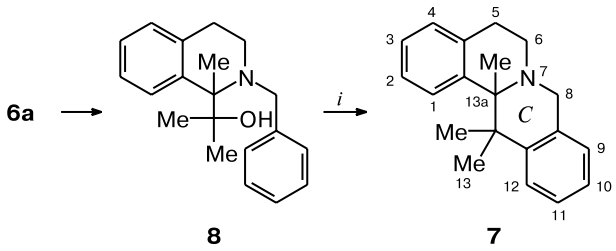
Calycotomine

Since amino alcohols **6** were isolated as oxalates, the signals of the hydroxy and amino groups in their ^{1}H NMR spectra are manifested as broadened singlets with the chemical shift 5.28—5.45 ppm. The IR spectra recorded for amino alcohols exhibit no absorption band for the carbonyl group of the starting compounds; the mass spectra exhibit the molecular ions. The structures of the resulting calycotomine analogs were additionally confirmed by NOESY using compound **6d**, whose spectrum contained all the needed correlation signals.



As noted above, amino alcohols **6** may be intermediates in the synthesis of a series of analogs of various natural products. As an example, one can cite the synthesis of 13,13,13a-trimethylberbine (**7**), which we carried out starting from amino alcohol **6a** (Scheme 4).

Scheme 4



i. PPA, 100 °C, 26 h.

Benzylation of amino alcohol **6a** with benzyl chloride was carried out with phase transfer catalysis in toluene in the presence of triethylbenzylammonium chloride (TEBAC) and potassium iodide. Apparently, due to steric hindrance, the reaction time is rather long (20 h). The alkylation involves exactly the nitrogen atom, as the ^{1}H NMR spectrum of the reaction product exhibits the signal for the hydroxy group with δ 4.17 and integral intensity of 1H. The spectrum also contains signals for three methyl groups with δ 1.04, 1.15, and 1.57, signals for the $-CH_2-CH_2-$ protons of the isoquinoline fragment, two doublets for the benzyl protons (J = 17.8 Hz, δ 3.39 and 4.57), and signals for aromatic protons at 7.00—7.55 ppm with an overall integral intensity corresponding to nine protons. 13,13,13a-Trimethylberbine (**7**) was prepared through the intramolecular Friedel—Crafts reaction by heating benzylated alcohol **8** at 110 °C in a tenfold weight excess of PPA for 18 h. This was accompanied by the formation of a berbine skeleton upon *C* ring closure.

The ^{1}H NMR spectrum of compound **7** contains a eight-proton multiplet in the field of aromatic protons. No signals are present for the hydroxy group of the initial compound or for the methylene protons of the hypothetical dehydration product of compound **8**, and the chemical shift (3.82 and 4.06 ppm) and coupling constant (J = 12.4 Hz) of the benzyl protons have changed (with respect to the starting compound **8**).

The use of 4-methylenedioxolan-2-ones as synthons allows rather easy introduction of C_5-isoprenoid fragments, which is often difficult to attain by other methods.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX500 instrument operating at 500.13 MHz. DMSO-d_6 was used as the solvent. Mass spectra were run on a Kratos MS-30 instrument (direct sample injection into the ion source, energy 70 eV, ioniz-

ing chamber temperature 250 °C). IR spectra were measured on a Perkin—Elmer 577 instrument (KBr pellets). The reactions were monitored by TLC on Silufol UV_{254} plates in benzene—ethyl acetate, 1 : 1 (*A*), 2 : 1 (*B*), and 9 : 1 (*C*) and propan-2-ol—ethyl acetate—25% aq. NH_3, 7 : 9 : 4 (*D*) solvent systems.

The characteristics and yields of the reaction products are summarized in Table 2, elemental analysis data are in Table 3, and the ^{1}H NMR spectra are in Tables 4—6.

Synthesis of compounds 4a—d (general procedure). A solution of the specified dioxolanone **2** (0.025 mol) in CH_2Cl_2 (15 mL) was added to a solution of **1a** (3.025 g, 0.025 mol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 24 h, the solvent was removed *in vacuo*, and a tenfold (by weight) amount of cold PPA was added to the residue. The mixture was stirred, kept for 4 h at 120 °C (TLC monitoring), and cooled. Cold water (250 mL) was added, and the precipitate was filtered off and washed with water to neutral pH. In the synthesis of compound **4d**, the reaction mixture after the addition of water was neutralized with aqueous ammonia and worked-up as described above.

The following new compounds were obtained: 1,1,10b-trimethyl-1,5,6,10b-tetrahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (**4a**), 1,10b-dimethyl-1-ethyl-1,5,6,10b-tetrahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (**4b**), 10b-trimethyl-1,1-cyclopentamethylene-1,5,6,10b-tetrahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (**4c**), and 2′,2′,6′,6′,10b-pentamethyl-1,5,6,10b-tetrahydrospiroo[1,3-oxazolo[4,3-*a*]isoquinoline-1,4′-piperidine]-3-one (**4d**).

Synethesis of compounds 3j,k (general procedure). A solution of the specified dioxolanone **2** in acetonitrile (10 mL) was added to a solution of 2-(2-aminoethyl)pyridine (**1b**) (0.02 mol) in acetonitrile (10 mL), and the reaction mixture was stirred for 20 h. Then the solvent was evaporated, and the product crystallized.

The following new compounds were obtained: 4-hydroxy-4,5,5-trimethyl-3-(2-pyridin-2-ylethyl)-1,3-oxazolidin-2-one (**3j**), 4-hydroxy-4-methyl-3-(2-pyridin-2-ylethyl)-1-oxa-3-azaspiro[4.5]decan-2-one (**3k**).

Synthesis of compounds 3e—i, 5a,b (general procedure). The specified amine (0.01 mol) was added to a solution of dioxolanone **2e** (0.01 mol) in acetonitrile (10 mL). The solution was left for 24 h at 40 °C, the solvent was evaporated, and the resulting oil was crystallized from a *tert*-butyl methyl ether—petroleum ether mixture (1 : 1).

The following new compounds were obtained: 5-benzyl-4-hydroxy-4,5-dimethyl-3-(2-phenylethyl)-1,3-oxazolidin-2-one (**3e**), 4-hydroxy-3-[2-(3,4-dimethoxyphenyl)ethyl]-4,5,5-trimethyl-1,3-oxazolidin-2-one (**3f**), 5-ethyl-4-hydroxy-3-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethyl-1,3-oxazolidin-2-one (**3g**), 4-hydroxy-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-methyl-1-oxa-3-azaspiro[4.5]decan-2-one (**3h**), 5-benzyl-4-hydroxy-3-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethyl-1,3-

Table 2. Physicochemical characteristics and yields of synthesized compounds[a]

Compound	R_f (system)	m.p./°C	Yield (%)	IR, ν(C=O)/cm^{-1}	MS, m/z (I_{rel} (%))
3e	0.70 (*B*)	130—131[b]	63	1736	325 $[M]^+$ (0.5), 307 (21.5), 216 (60.4), 128 (14.9), 105 (100)
3i	0.30 (*B*)	126—127[b]	92	1740	385 $[M]^+$ (12.9), 367 (6.8), 276 (2.7), 208 (3.6), 164 (100)
3j	0.37 (*A*)	172—174[c]	96	1744	250 $[M]^+$ (3.8), 232 (0.6), 206 (14.7), 178 (54.3), 105 (100)
3k	0.41 (*A*)	158—160[c]	91	1750	290 $[M]^+$ (4.7), 272 (1.1), 246 (12.7), 208 (43.8), 105 (100)
4a	0.62 (*A*)	147—149[c]	98	1743	231 $[M]^+$ (4.7), 216 (17.9), 172 (67.9). 145 (100)
4b	0.57 (*A*)	124—126[c]	97.5	1737	245 $[M]^+$ (2.1), 230 (19.3), 186 (32.4), 173 (12.8), 145 (100)
4c	0.67 (*A*)	158—160[c]	95	1754	271 $[M]^+$ (0.7), 256 (17.7), 212 (19.3), 173 (11.9), 145 (100)
4d	0.82 (*D*)	121—125[c]	96	1746	328 $[M]^+$ (0.9), 313 (100), 269 (1.4), 212 (3.4), 197 (2.8)
4e	0.77 (*B*)	114—115[c]	91	1744	307 $[M]^+$ (24.7), 234 (8.6), 216 (53.0), 172 (100)
4i	0.49 (*B*)	175—176[c]	92	1728	368 $[M]^+$ (0.8), 352 (15.3), 205 (58.2), 190 (9.5), 91 (100)
5a	0.10 (*B*)	174—175[b]	52	1684	221 $[M]^+$ (0.9), 203 (13.3), 135 (15.5), 91 (90.8), 87 (52.5), 43 (100)
5b	0.27 (*B*)	130—131[b]	96	1748	235 $[M]^+$ (0.5), 217 (72.7), 144 (26.7), 135 (16.6), 126 (100)
6a	0.52 (*D*)	89—93[d]	92/97	—	No $[M]^+$, 190 (1.6), 172 (2.1), 146 (100.0), 130 (10.6), 115 (8.5)
6b	0.54 (*D*)	112—115[d]	74/94	—	219 $[M]^+$ (1.1), 201 (0.5), 172 (1.4), 146 (100), 130 (3.3)
6c	0.62 (*D*)	129—131[d]	61/93	—	No $[M]^+$, 231 (0.9), 195 (4.1), 184 (2.7), 146 (100)
6d	0.59 (*D*)	103—106[d]	87/95	—	265 $[M]^+$ (4.3), 232 (40.5), 205 (100.0), 164 (82.8)
6e	0.64 (*D*)	162—165[d]	0/79	—	279 $[M]^+$ (2.1), 261 (2.7), 207 (12.2), 203 (37.4), 164 (100)
7	0.65 (*C*, 3 times)	57—59[e]	67	—	277 $[M]^+$ (40.0), 210 (82.5), 132 (100.0), 117 (57.5), 91 (57.6)
8	0.43 (*C*)	34—36[b]	68	—	No $[M]^+$, 236 (81.9), 144 (13.8), 91 (100.0), 65 (7.4), 43 (7.4)

[a] Compounds **3f—h** and **4f—h** were described in our previous publication.[3]
[b] From *tert*-butyl methyl ether (TBME).
[c] From a TBME—hexane mixture.
[d] From a TBME—ethyl acetate mixture .
[e] From *n*-hexane.

Table 3. Elemental analysis data for compounds **3—5**, **7**, and **8**

Compound	Found / Calculated (%)			Molecular formula
	C	H	N	
3e	73.85 / 73.82	7.10 / 7.13	4.31 / 4.30	$C_{20}H_{23}NO_3$
3i	68.52 / 68.55	7.07 / 7.06	3.66 / 3.63	$C_{22}H_{27}NO_5$
3j	62.49 / 62.38	7.21 / 7.25	11.12 / 11.19	$C_{13}H_{18}N_2O_3$
3k	66.08 / 66.18	7.65 / 7.64	9.74 / 9.65	$C_{16}H_{22}N_2O_3$
4a	72.73 / 72.70	7.38 / 7.41	6.05 / 6.06	$C_{14}H_{17}NO_2$
4b	73.51 / 73.44	7.78 / 7.81	5.67 / 5.71	$C_{15}H_{19}NO_2$
4c	75.22 / 75.24	7.80 / 7.80	5.19 / 5.16	$C_{17}H_{21}NO_2$
4d	73.08 / 73.13	8.61 / 8.59	8.57 / 8.53	$C_{20}H_{28}N_2O_2$
4e	78.13 / 78.15	6.91 / 6.89	4.55 / 4.56	$C_{20}H_{21}NO_2$
4i	71.87 / 71.91	6.88 / 6.86	3.83 / 3.81	$C_{22}H_{25}NO_4$
5a	65.16 / 65.14	6.83 / 6.83	6.31 / 6.33	$C_{12}H_{15}NO_3$
5b	66.35 / 66.36	7.29 / 7.28	5.96 / 5.95	$C_{13}H_{17}NO_3$
7	86.58 / 86.59	8.38 / 8.36	5.04 / 5.05	$C_{20}H_{23}N$
8	81.29 / 81.31	8.55 / 8.53	4.75 / 4.74	$C_{20}H_{25}NO$

Note. Compounds **6** are hydrated oxalates of variable composition. No elemental analysis data for these compounds are available, but their structures were proved by ^{1}H NMR and mass spectra.

Table 4. ^{1}H NMR spectra (DMSO-d_6) of compounds **3e,i,j,k** and **5a,b**

Compound	δ (*J*/Hz)				
	Me	$NC\underline{H}_2C\underline{H}_2Ar$	$PhC\underline{H}_2$	Ar	Other signals
3e	0.97, 1.04, 1.13, 1.19 (all s, 6 H, Me)	2.85—2.95 (m, 2 H); 3.20—3.30, 3.35—3.45 (both m, 1 H each)	2.78, 2.93, 3.01, 3.21 (all d, 2 H, *J* = 12.6)	7.12—7.30 (m, 10 H)	5.83, 6.00 (both s, 1 H, OH)
3i	0.92, 1.09, 1.13, 1.23 (all s, 6 H, Me)	2.75—2.85 (m, 2 H); 3.20—3.30, 3.30—3.40 (both m, 1 H each)	2.55, 2.86, 3.04, 3.16 (all d, 2 H, *J* = 12.3)	6.70—6.80 (m, 3 H); 7.18—7.38 (m, 5 H)	3.83, 3.85 (both s, 3 H each, OMe); 5.99, 6.16 (both s, 1 H, OH)
3j	1.08, 1.15, 1.27 (all s, 3 H each)	2.88—3.05, 3.37—3.49 (both m, 2 H each)	—	7.22 (t, 1 H, *J* = 7.2); 7.26 (d, 1 H, *J* = 7.2); 7.69 (t, 1 H, *J* = 8.4); 8.49 (d, 1 H, *J* = 8.4)	5.97 (s, 1 H, OH)
3k	1.52 (s, 3 H)	2.82, 3.37 (both distorted t, 2 H each, *J* = 8.7, *J* = 10.1, *J* = 9.1; *J* = 9.4, *J* = 11.3, *J* = 9.0)	—	7.31 (t, 1 H, *J* = 7.7); 7.48—7.53 (m, 2 H); 8.15 (d, 1 H, *J* = 8.9)	5.97 (s, 1 H, OH)
5a*	1.04, 1.27 (both s, 3 H each)	—	2.83, 3.14 (both d, 1 H each, *J* = 12.4)	7.18 (t, 1 H, *J* = 7.8); 7.25 (t, 2 H, *J* = 7.8); 7.29 (d, 2 H, *J* = 7.8)	5.84 (s, 1 H, OH); 7.83 (s, 1 H, NH)
5b	1.05, 1.15, 1.27, 1.43 (all s, 6 H, Me)	—	2.64, 3.14 (both d, 1 H each, *J* = 12.4)	7.16—7.22, 7.23—7.28 (both distorted t, 2 H each, *J* = 5.8, *J* = 7.9; *J* = 6.2, *J* = 7.1); 7.28—7.31 (d, 2 H, *J* = 5.8)	2.72, 2.75 (both s, 3 H each, OMe); 5.79, 5.95 (both s, 1 H each, OH)

* This compound was isolated as one diastereomer pair; therefore, its spectrum contains no doubled signals.

oxazolidin-2-one (**3i**), 5-benzyl-4-hydroxy-4,5-dimethyl-1,3-oxazolidin-2-one (**5a**), 5-benzyl-4-hydroxy-3,4,5-trimethyl-1,3-oxazolidin-2-one (**5b**).

Synthesis of compounds 4e—i (general procedure). A tenfold weight of PPA was added to a mixture of oxazolidinones **3e—i**, and the mixture was stirred for 6 h at 80 °C (TLC monitoring) and cooled. Cold water (150 mL) was added, and the precipitate was filtered off and washed with water to neutral pH.

The previously described[3] compounds **4f—h** were prepared here in higher yields: **4f**, 96%; **4g**, 95%; **4h**, 93%. The following

Table 5. ^{1}H NMR spectra (DMSO-d_6) of compounds **4a—e,i**

Compound	δ (*J*/Hz)			
	10b-Me (s, 3 H)	CH_2CH_2	Ar	Other signals
4a	0.82	2.67—2.72 (m, 1 H); 2.82—2.89 (m, 2 H); 12.4 (q, 1 H, *J* = 11.2)	7.14, 7.18 (both d, 1 H each, *J* = 7.2, *J* = 7.5); 7.29—7.33, 7.62—7.69 (both m, 1 H each)	1.22, 1.27 (both s, 3 H each, Me)
4b	0.80	2.77—2.84, 2.86—2.96, 3.10—3.17 (all m, 1 H each)	7.16—7.26 (m, 4 H)	0.77 (distorted t, *J* = 8.4, *J* = 9.2, *J* = 8.7); 0.93—0.96, 1.05—1.09, 1.20—1.24, 2.16—2.21 (all m, 1 H each, Et); 1.48, 1.51 (both s, 3 H each, Me)
4c	1.38	2.75—2.78, 2.83—2.92, 3.09—3.12, 3.86—3.89 (all m, 1 H each)	7.17—7.28 (m, 4 H)	0.75—0.78, 1.06—1.70 (both m, 1 H each); 1.25 (d, 1 H, *J* = 11.9); 1.38—1.51, 1.54—1.68 (both m, 1 H each); 2.25 (d, 1 H, *cyclo*-Hex, *J* = 12.1)
4d	0.83	2.79—2.84, 2.90—2.95, 3.11—3.23 (all m, 1 H each); 3.91 (q, 1 H, *J* = 11.7)	7.18—7.31 (m, 4 H)	0.71, 1.22, 1.70, 2.15 (all d, 4 H, *J* = 14.2, CH_2^{pyp}); 1.20, 1.25, 1.36, 1.46 (all s, 3 H each, Me^{pyp}); 3.21 (s, 1 H, NH)
4e*	1.26	2.65—2.72, 2.81—2.90, 3.39—3.46, 3.50—3.58 (all m, 1 H each)	7.54 (d, 1 H, *J* = 7.4); 7.24—7.33 (m, 5 H); 7.16—7.23 (m, 3 H)	1.37 (s, 3 H, Me); 3.13, 3.22 (both d, 1 H each, *J* = 13.2, $PhC\underline{H}_2$)
4i	1.51, 1.63	**	6.78 (d, 2 H, *J* = 7.8); 7.21 (t, 1 H, *J* = 7.2); 7.30—7.37 (m, 4 H)	0.62, 1.47 (both s, 3 H Me); 3.72, 3.74, 3.78, 3.81 (all s, 6 H, OMe)
4i***	1.57, 1.69	2.62—2.73, 2.73—2.83, 2.87—2.96, 3.20—3.28 4.06—4.13 (all m, 1 H each)	**	0.74, 1.48 (both s, 3 H, Me); 2.23, 3.59 (both d, 1 H, *J* = 13.8, 13.2), 2.96 (d, 1 H, $PhC\underline{H}_2$, *J* = 13.2); 3.83, 3.90, 3.88, 3.92 (all s, 6 H, OMe

* This compound was isolated as one diastereomer pair; therefore, its spectrum contains no doubled signals.
** The signals cannot be described due to overlap.
*** The spectrum was recorded in $CDCl_3$.

Table 6. ^{1}H NMR spectra (DMSO-d_6) of compounds **6**

Compound	δ (*J*/Hz)				
	1-Me	CH_2CH_2	Ar	NH_2^+ + OH (br.s, 3 H)	Other signals
6a	0.85	2.79—2.83, 2.88—2.92, 3.10—3.14, 3.80—3.86 (all m, 1 H each)	7.15—7.30 (m, 4 H)	5.45	1.50, 1.65 (both s, 3 H each, Me)
6b	0.94	2.72—2.85 (m, 1 H); 2.94—3.08 (m, 2 H); 3.39—3.47 (m, 1 H)	7.11—7.23 (m, 4 H)	5.61	0.89—1.08, 1.62—1.83, 1.25—1.43, 2.21—2.35 (all m, 2 H, $C\underline{H}_2Me$); 0.80—0.91 (m, 3 H, $CH_2\underline{Me}$); 3.82, 3.86 (both s, 3 H each, OMe)
6c	0.88	3.76—3.84 (m, 1 H); 2.92—3.09 (m, 2 H); 3.34—3.43 (m, 1 H)	7.15—7.29 (m, 4 H)	5.31	0.89—1.52, 1.38—1.72 (both m, 10 H, *cyclo*-Hex)
6d	0.89	2.83—2.87, 2.88—2.94, 3.10—3.15, 3.81—3.85 (all m, 1 H each)	6.72, 7.05 (both s, 1 H each)	5.43	3.86, 3.89 (both s, 3 H each, OMe)
6e	0.91	2.64—2.72, 3.11—3.20 (both m, 2 H each)	6.92, 7.12 (both s, 1 H each)	5.42	0.83—0.95, 1.71—1.84, 1.98—2.02 (all m, 2 H); $C\underline{H}_2Me$); 0.79—0.84 (m, 3 H, $CH_2\underline{Me}$); 3.84, 3.87 (both s, 3 H each, OMe)

new compounds were obtained: 1-benzyl-1,10b-dimethyl-1,5,6,10b-tetrahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (**4e**), 1-benzyl-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (**4i**).

Synthesis of compounds 6 (general procedure). *Method 1.* Compound **4** (0.02 mmol), MeOH (20 mL), water (20 mL), and KOH (11.2 g, 0.2 mmol) were placed in a 100 mL-autoclave and kept for 64—180 h at 120 °C (see Table 1), methanol was evapo-

rated *in vacuo*, the residue was extracted with CH_2Cl_2 (5×35 mL), and the extracts were combined and washed with water to neutral pH. The organic phase was dried and the solvent was evaporated *in vacuo*. The residue was dissolved in ether (200 mL) and added to a solution of oxalic acid (2.52 g, 0.02 mol) in ether. The precipitate was filtered off, washed with ether 2×5 mL, and dried.

Method 2. Dimethyl sulfoxide (20 mL), water (20 mL), and KOH (11.2 g, 0.2 mmol) were added to **4** (0.02 mmol), and the mixture was kept for 52—155 h at 80 °C (see Table 1). Water (150 mL) and ether (300 mL) were added, and the organic phase was washed to neutral pH, dried, and then worked-up as in method *1*.

The following new compounds were obtained: 2-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (6a), 2-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-ol (**6b**), 1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanol (**6c**), 2-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-ил)propan-2-ol (**6d**), 2-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-ol (**6e**).

2-Benzyl-1-(1-hydroxy-1-methyl)ethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (8). Benzyl chloride (2.86 g, 0.023 mol) in toluene (10 mL) was added over a period of 10 h to a mixture of amino alcohol **6a** (3.08 g, 0.015 mol) (as a free base), KI (0.1 g), TEBAC (0.2 g), and K_2CO_3 (3.1 g) in anhydrous toluene (15 mL), and the reaction mixture was refluxed for 20 h. The solvent was removed *in vacuo*, the residue was treated with water (30 mL), the product was extracted with CH_2Cl_2 (3×15 mL), and the extracts were combined, washed with water to neutral reaction, and dried by filtration through cotton wool. The solvent was evaporated. The residue was triturated in hexane with ether (4 : 1) to give 3.00 g (68%) of product **8** as a light-yellow powder. ^{1}H NMR, δ: 1.09, 1.23, 1.63 (all s, 3 H each, Me); 2.74—2.82 (m, 1 H, CH_2CH_2); 2.95—3.05 (m, 2 H, CH_2CH_2); 3.33—3.40 (m, 1 H, CH_2CH_2); 3.76, 3.80 (both s, 3 H each, OMe); 5.28 (br.s, 3 H, OH, NH_2^+); 7.05, 7.23 (both d, 1 H each, H_{Ar}, J = 8.7 Hz).

13,13,13a-Trimethylberbine (7). Compound **8** (1.45 g, 0.005 mol) and PPA (30 g) were heated for 18 h at 110 °C. The reaction mixture was cooled, water (50 mL) was added, the mixture was alkalized by aqueous ammonia, the product was extracted with CH_2Cl_2 (3×15 mL), and the extracts were combined and washed with water to neutral reaction. The solution was dried with Na_2SO_4 and the solvent was evaporated. The residue was purified by flash chromatography (benzene) to give 0.93 (67%) of compound **7** as a light powder. ^{1}H NMR, δ: 0.86, 1.32, 1.52 (all s, 3 H each, Me); 2.56, 2.72 (both t, 1 H each, CH_2CH_2, J = 12.1 Hz); 2.82 (dd, 1 H, CH_2CH_2, J = 9.3 Hz); 3.07 (m, 1 H, CH_2CH_2); 3.82, 4.06 (both d, 1 H each, $PhCH_2$, J = 14.1 Hz); 7.03 (d, 1 H, H_{Ar}, J = 8.9 Hz); 7.06—7.21 (m, 5 H, H_{Ar}); 7.43, 7.54 (both d, 1 H each, H_{Ar}, J = 8.6 Hz).

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