Synthesis and Oxidant Properties of Phase 1 Benzepine *N*-Oxides of Common Antipsychotic Drugs

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Abstract: There is increasing evidence that cell constituents are oxidized by widely used antipsychotic drugs but until now the underlying chemistry has remained unclear. It is well known that such drugs readily undergo *N*-oxidation as a first key metabolic step. To gain insight into the problem, the tertiary phase 1 *N*-oxides of clozapine, olanzapine, quetiapine, and zotepine were synthesized, together with the *N*,*S*-dioxides of quetiapine and zotepine. These *N*-oxides were then subjected to well-established chemical transformations to test their oxidant properties in group VIII transition-metal-catalyzed reactions. In the osmium tetroxide catalyzed dihydroxylation of styrene or cinnamyl alcohol and in the tetrapropylammonium perruthenate catalyzed oxidation of cinnamyl alcohol, the benzepine *N*-oxides could be used as replacements for the standard oxidant, *N*-methylmorpholine *N*-oxide (NMO) with varying degrees of efficiency. From a chemical point of view, clozapine *N*-oxide displayed a comparable oxidation power to NMO, characterizing the benzepines as oxygen carriers. Moreover, quetiapine was found to be an excellent double oxygen acceptor, undergoing initial N-oxidation and subsequent S-oxidation. It is therefore worthwhile considering whether oxidative damage to the human body might be related to the potential redox properties of common antipsychotic drugs.

Key words: oxidations, catalysis, transition metals, benzepines, dihydroxylations, medicinal chemistry, drugs

Antipsychotic drugs are used to alleviate psychotic symptoms. Despite their metabolic side effects, the benzepines clozapine (**CN**), olanzapine (**ON**), quetiapine (**QN**), and zotepine (**ZN**) represent one of the most beneficial groups of such drugs. For example, **CN** is uniquely effective in treatment-refractory schizophrenia and suicidal ideation. The other drugs, **ON**, **QN**, and **ZN**, were developed as analogues of **CN** with the aim of retaining its pharmacological design and superior efficacy while eliminating its potential to cause adverse reactions (for example, potentially life-threatening agranulocytosis occurs in about 1% of patients). Although these aims were only partly achieved, the **CN** analogues are nevertheless useful as real alternatives or co-medicaments in current psychopharmacotherapeutic practice.[1]

Oxidative damage to DNA, proteins, or lipids are forms of cellular injury that can cause cellular dysfunction without necessarily leading to cell death or tissue degeneration.[2] **CN** and other antipsychotics can induce oxidative stress and injury to mammalian cells by increasing levels of oxidation of lipids and proteins.[3,4]

Recently, a further central role has been found for **CN**, in the form of its second major phase 1 intermediate clozapine N^4-oxide (**CNO**),[5] in the designer receptors exclusively activated by designer drugs (DREADD) technique. In this technique, muscarinic G protein-coupled receptors (GPCRs) are mutated so that their ability to bind to their natural ligands is lost. This induces nanomolar potency for the xenobiotic **CNO**, which otherwise displays weak pharmacological activity. This procedure allows the creation of examinable specific synthetic pathways in vivo with minimal invasiveness. Although GPCR drugs, gene knockouts, and other techniques provided diverse insights, many basic lessons can only be learned by building new GPCR signaling pathways in intact cells or in freely behaving animals.[6] **CNO** is often selected as the synthetic ligand, because: (i) the parent compound **CN** has a high affinity with muscarinic receptors and, hence, relatively few mutations are required to render **CNO** a potent agonist; (ii) **CNO** appears to be highly bioavailable in rodents and humans;[5c,7] and (iii), importantly, **CNO** lacks appreciable affinities (<1 μM) for neuroreceptors.[8] Despite the limited number of studies, contrary findings,[5b,c] and one critical comment by a DREADD pioneer,[6] DREADD researchers continue to treat **CNO** as a compound that is almost biologically and pharmacologically inert.[9]

To examine this presumed inertness in the context of clozapine-associated oxidative modifications of cellular key constituents, we first synthesized the tertiary phase 1 *N*-oxides of **CN** and its congeners **ON**, **QN**, and **ZN**. Next, we compared the *N*-oxides with the established oxidant *N*-methylmorpholine-*N*-oxide (NMO)[10] in terms of their co-oxidative effects in two well-known specific chemical oxidation reactions catalyzed by two transition-metal catalysts: osmium tetroxide[11] and tetrapropylammonium perruthenate (TPAP).[12] The resulting insight into the reactivity/inertness of benzepines and their *N*-oxides might be helpful as a basis for rationalizing the biotransformations of benzepine drugs in the human body.

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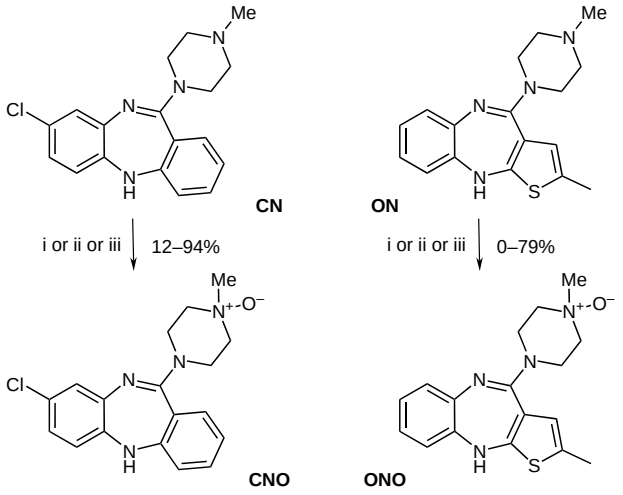
Oxidation of Benzodiazepines and Dibenzothiepines

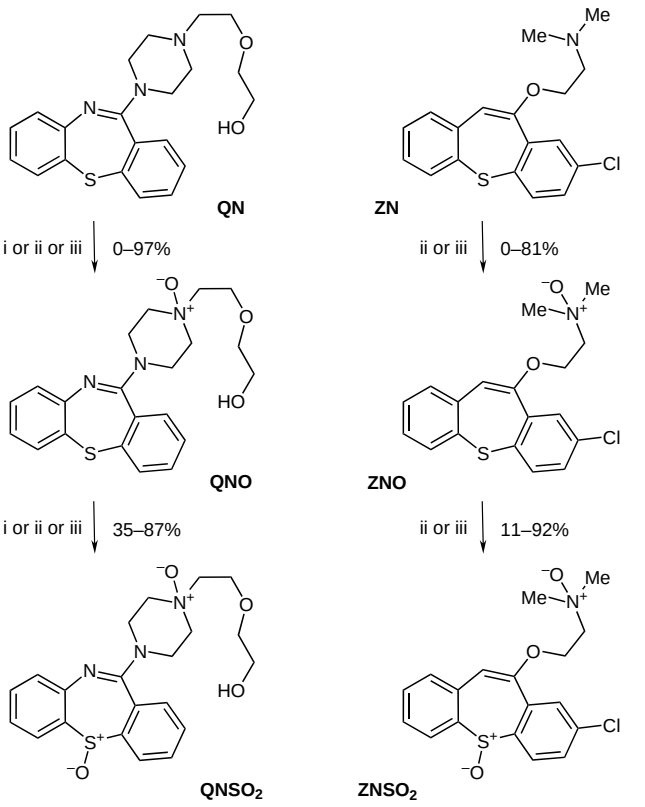
Our first investigations focused on the oxidation of the benzepines under defined conditions (Scheme 1 and Scheme 2).

By using reaction conditions similar to those described by VanRheenen in 1978,[10] the benzepines were treated with an excess of 35% aqueous hydrogen peroxide. Despite the poor solubility of **ON** in water, its oxidation was highly exothermic and the mixture boiled after some minutes. **QN** is moderately soluble in water, and its oxidation was accompanied by modest warming of the solution. In contrast, **CN** dissolved immediately, but its oxidation was not accompanied by a significant change in temperature. Workup of the respective reaction mixtures permitted the isolation of **CNO** and quetiapine N^{19}-oxide (**QNO**), albeit in low yields (12% for **CNO** and trace amounts for **QNO**). Olanzapine *N*-oxide (**ONO**) could not be isolated. In contrast, direct oxidation of **QN** gave quetiapine N^{19},*S*-dioxide (**$QNSO_2$**) in 87% yield, showing that a stable and isolable product is obtained under the oxidation conditions used.



Scheme 1 Oxidation of diazepine neuroleptics: clozapine (**CN**), clozapine N^4-oxide (**CNO**), olanzapine (**ON**), olanzapine N^4-oxide (**ONO**). *Reaction conditions*: i) 35% aq H_2O_2 (~40 equiv), H_2O, 0–23 °C, 18 h; yields: **CNO**, 12%; **ONO**, 0%; ii) 35% aq H_2O_2 (~2–3 equiv), MeOH, 23 °C, 20 h; yields: **CNO**, 79%; **ONO**, 17%; iii) MCPBA (1 equiv), MeOH (**CN**) or $CHCl_3$ (**ON**), 23 °C, 10 min; yields: **CNO**, 94%; **ONO**, 79%.

With the intention of suppressing the formation of multiple products, we performed a second series of experiments by using a slight excess (2–3 equivalents) of aqueous 35% hydrogen peroxide in methanol. Again, **ON**, the most reactive substrate, underwent rapid oxidative degradation and the desired *N*-oxide **ONO** was isolated in only 17% yield.[13] Thiepane-substituted **QN** and **ZN** gave the corresponding *N*-oxides **QNO** and **ZNO** in 61% and 56% yield, respectively.[14,15] Furthermore, S-oxidation



Scheme 2 Oxidation of thiepine neuroleptics: quetiapine (**QN**), quetiapine N^{19}-oxide (**QNO**), quetiapine N^{19},*S*-dioxide (**$QNSO_2$**), zotepine (**ZN**), zotepine N^{20}-oxide (**ZNO**), zotepine *N*,*S*-dioxide (**$ZNSO_2$**). *Reaction conditions*: i) 35% aq H_2O_2 (~40 equiv), H_2O, 0–23 °C, 18 h; yields: **QNO**, 0%; **$QNSO_2$**, 87%; ii) 35% aq H_2O_2 (~2–3 equiv), MeOH, 23 °C, 20 h; yields: **QNO**, 61%; **ZNO**, 56%; **$QNSO_2$**, 35%; **$ZNSO_2$**, 11%; iii) MCPBA (1 equiv), MeOH (**QN**) or $CHCl_3$ (**ZN**), 23 °C, 10 min.; yields: **QNO**, 97%; **ZNO**, 81%; **$QNSO_2$**, 83%; **$ZNSO_2$**, 92%.

also occurred in the case of thiepines, and quetiapine N^{19},*S*-dioxide (**$QNSO_2$**) and zotepine N^{20},*S*-dioxide (**$ZNSO_2$**) were isolated in yields of 35% and 11%, respectively. Finally, **CN**, the least-sensitive substrate, gave the best results, and **CNO** was isolated in 79% yield (Schemes 1 and 2).[16]

Unregulated oxidation of benzepines could be avoided by the use of one equivalent of *m*-chloroperoxybenzoic acid (MCPBA) in an appropriate solvent.[17] The reaction of **ON**, the most sensitive substrate, gave the desired oxide **ONO** in 79% yield. The less reactive dibenzodiazepine **CN** gave the corresponding oxide **CNO** in 94% yield.[18] The oxidations of the thiepane-derived compounds gave the corresponding *N*-oxides as the primary products; **QNO** was isolated in 97% yield and **ZNO** in 81% yield. Furthermore, treatment of these *N*-oxides with a second equivalent of MCPBA gave the corresponding *N*,*S*-dioxides **$QNSO_2$** and **$ZNSO_2$** in 86% and 92% yield, respectively. **CNO** and **ONO** decomposed on treatment with two equivalents of MCPBA. Overall, the oxidation of benzepines with MCPBA gave the best results in terms of selectivity and yield. Detailed information is provided in Table 1.

Table 1 Synthesis of *N*-Oxides and *N*,*S*-dioxides

Entry	Reactant	Product	aq H_2O_2 (~40 equiv) Yield (%)	aq H_2O_2 (~2–3 equiv), MeOH Yield (%)	MCPBA (1 equiv) Yield (%)
1	**CN**	**CNO**	12	79	94
2	**ON**	**ONO**	–	17	79[a]
3	**QN**	**QNO**	–	61	97
		$QNSO_2$	87	35	–
4	**QNO**	**$QNSO_2$**	–	–	83
5	**ZN**	**ZNO**	–[b]	56	81[a]
		$ZNSO_2$	–[b]	11	–
6	**ZNO**	**$ZNSO_2$**	–	–	92

[a] Solvent $CHCl_3$.
[b] Zotepine was not available.

The *N*-oxides and the *N*,*S*-dioxides were characterized by means of ^1H, ^{13}C, COSY, HSQC, and HMBC NMR experiments and by high-resolution mass spectrometry.

Oxidation at the 4-position of the piperazine in **CNO** and **ONO** led to significant changes in the ^{13}C NMR shifts at the adjacent carbon centers. Both **CNO** and **ONO** showed a downfield shift of the methyl group by about 14 ppm, and the α-ring CH_2 groups underwent a downfield shift of nearly 10 ppm. In contrast, the β-ring CH_2 groups were shifted upfield by about 4 ppm in **CNO** and 5 ppm in **ONO**. The signals of the other carbon centers of the bicyclic cores showed little, if any, change. The *N*-oxides of the thiepines **QN** and **ZN** showed a related shift pattern. The α-side chain CH_2 group of **QNO** showed a downfield shift of nearly 13 ppm, and the signal of the α-ring CH_2 group moved about 12 ppm downfield. Again, the β-ring CH_2 groups were shifted upfield by about 4 ppm in the side chain and by about 3 to 6.5 ppm in the ring. In contrast, **ZNO** was characterized by α-carbon downfield shifts only (CH_3: 16 ppm, CH_2: 13.5 ppm); the β-CH_2 group attached to the oxygen in **ZNO** remained in almost the original position found in **ZN**. In addition, ^1H NMR spectra of all *N*-oxides showed a downfield shift of the α-CH group by about 1 ppm and of the β-CH group by about 0.3 ppm. Finally, X-ray analyses of **QNO** and **ZNO** unequivocally confirmed their structures and the chemoselectivity of the N-oxidation reactions (Figure 1 and Figure 2).[19]

As expected, the thiepine *N*,*S*-dioxides showed additional characteristic ^{13}C shifts in the tricyclic core fragment. Furthermore, the NMR spectra of **$QNSO_2$** showed a double set of peaks as a result of the presence of two slowly interconverting conformers.[20] In **$QNSO_2$** (both conformers) and **$ZNSO_2$**, the aromatic α-carbon atoms directly bound to the *S*-oxide moiety showed downfield shifts of about 7 ppm. All the β-carbon atoms showed upfield shifts. The

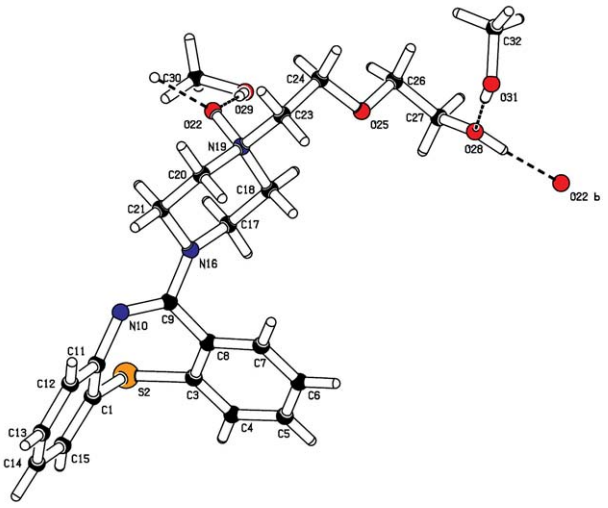


Figure 1 X-ray crystal structure of **QNO** (**2c**)

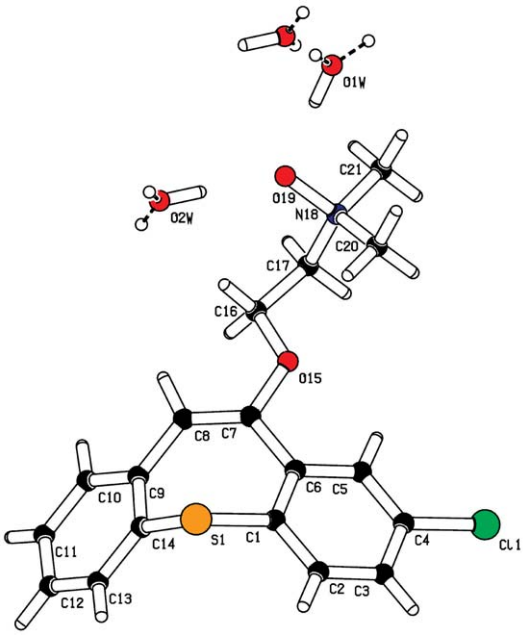


Figure 2 X-ray crystal structure of **ZNO** (**2d**)

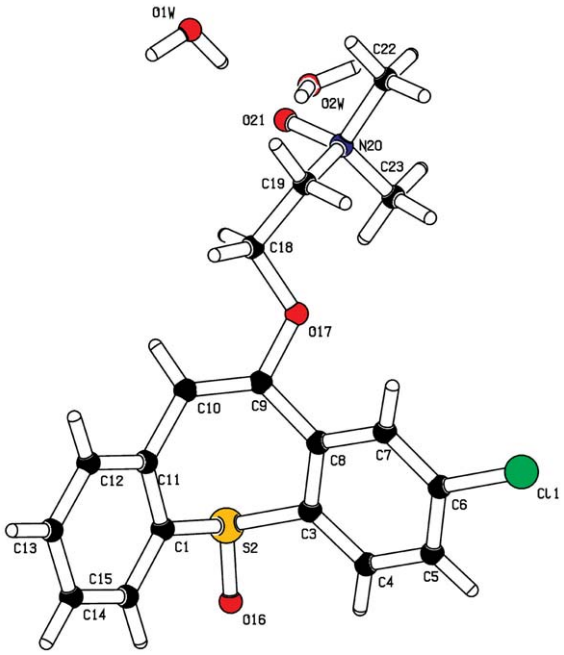


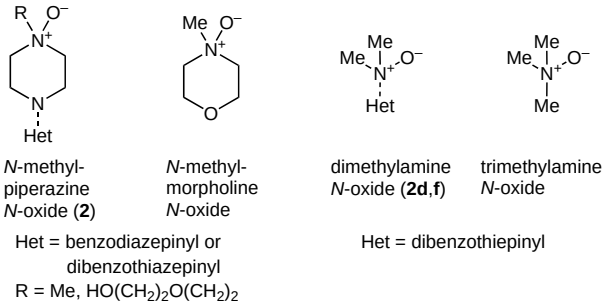
Figure 3 X-ray crystal structure of **ZNSO$_2$** (**2f**)

aromatic CH-groups in **ZNSO$_2$** and **QNSO$_2$** (conformer 1) were shifted upfield by about 11–12 ppm. The corresponding C atoms in **QNSO$_2$** (conformer 2) were shifted only 5 and 8 ppm upfield, respectively. The aromatic C atoms next to the thiepine side chain showed a downfield shift of about 11 to 14 ppm in all the dioxides. Significant differences were observed in the upfield shifts for the aromatic C–N centers in the two conformers of **QNSO$_2$** (conformer 1: 7 ppm, conformer 2: 4 ppm). The aromatic carbon atom adjacent to the enol ether carbon in **ZNSO$_2$** showed an upfield shift of about 9 ppm, whereas the enol ether carbon (γ- position) showed a shift of about 4 ppm. In addition, the ^{1}H NMR spectra showed a downfield shift of the aromatic β-(SO)-CH group by about 0.3 ppm. Finally, the structure of **ZNSO$_2$** was unequivocally confirmed by X-ray crystal structure analysis (Figure 3).[19]

Oxidant Reactivity of Benzepine N-Oxides

We surmised that the benzepine *N*-oxides might be useful as oxidants, as they share features with structurally related well-known chemical reagents such as *N*-methylmorpholine *N*-oxide (NMO) and trimethylamine *N*-oxide (Figure 4). These reagents participate in such oxidation reactions as the osmium tetroxide (OsO_4)-catalyzed dihydroxylation of olefins or allylic alcohols and the TPAP-catalyzed oxidation of primary or secondary alcohols to give aldehydes and ketones, respectively. Consequently, we tested the benzepine *N*-oxides as replacements for the original *N*-oxide oxidants (Figure 4).[11,12]

In most cases, the benzodiazepine *N*-oxide derivatives **CNO** and **ONO** regenerated the corresponding amines **CN** and **ON**, respectively, and therefore displayed a similar reactivity to that of NMO. In contrast, the dibenzothi-



N-methylpiperazine *N*-oxide (**2**)

N-methylmorpholine *N*-oxide

dimethylamine *N*-oxide (**2d**,**f**)

trimethylamine *N*-oxide

Het = benzodiazepinyl or dibenzothiazepinyl
R = Me, $HO(CH_2)_2O(CH_2)_2$

Het = dibenzothiepinyl

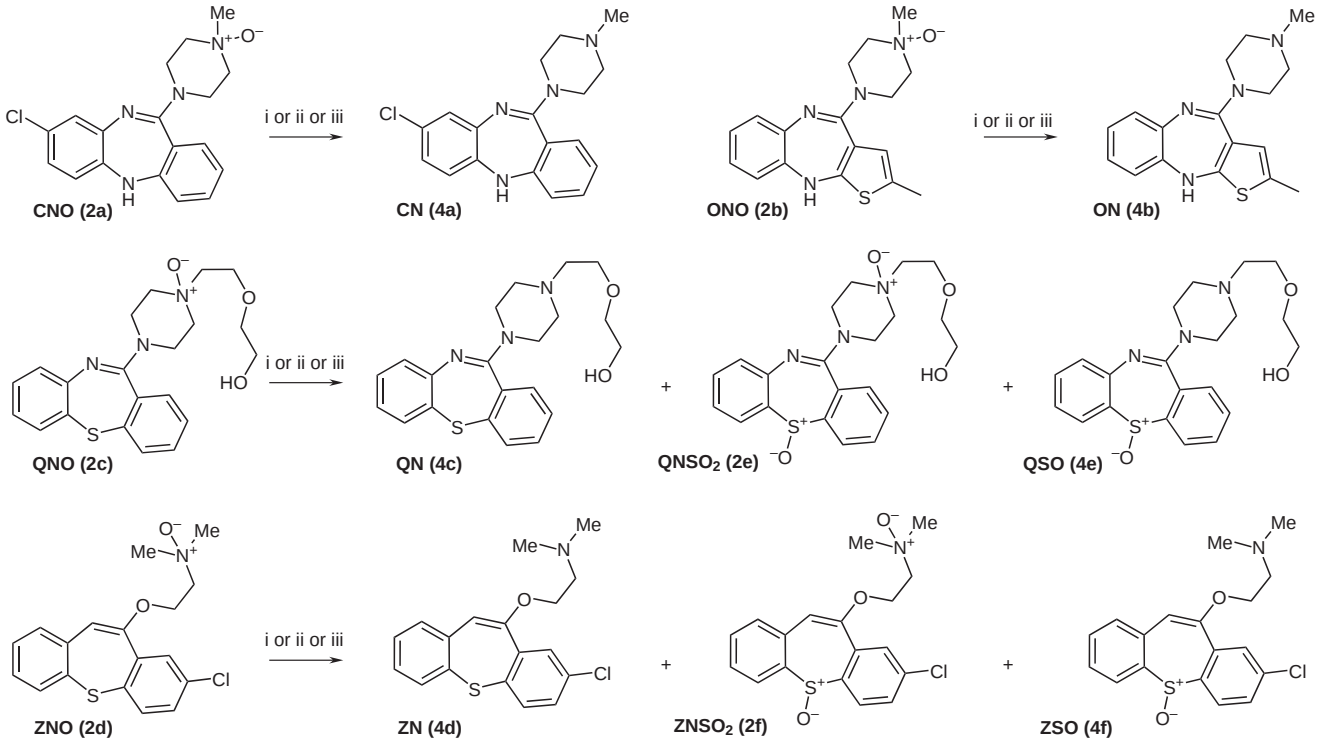
Figure 4 Well-known chemical reagents *N*-methylmorpholine *N*-oxide (NMO) and trimethylamine *N*-oxide and structurally and functionally related benzodiazepine *N*-oxides

epine *N*-oxides **QNO** and **ZNO** underwent a more complex oxygen transfer. In addition to the expected amines **QN** and **ZN**, the corresponding *S*-oxides **QSO**[21] and **ZSO**, as well as smaller amounts of the dioxides **QNSO$_2$** and **ZNSO$_2$**, were produced in the osmium- and ruthenium-catalyzed oxygen-transfer reactions. An overview of these reactions is given in Scheme 3.

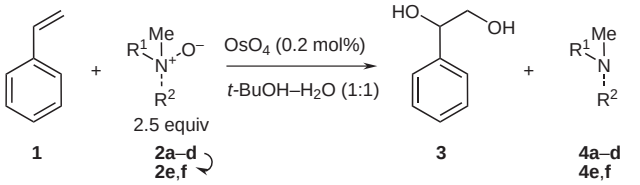
Our first series of experiments focused on the use of benzepine *N*-oxides as a replacement for NMO in the osmium tetroxide catalyzed dihydroxylation of styrene (**1**) (Scheme 3 and Scheme 4).[22]

All reactions were carried out on a 0.2-mmol scale of styrene (**1**) with a 2.5-fold excess of the *N*-oxide **2** to give 1-phenylethane-1,2-diol (**3**) and the corresponding products **4**. In all cases the conversion was terminated after about 20 hours, and the resulting product mixture was analyzed by NMR spectroscopy and by high-performance liquid chromatography. Diol **3** was obtained in all the experiments (Scheme 4; for a HPLC chromatogram, see the Supporting Information), indicating that all the *N*-oxides are active oxidants.[23] The fate and behavior of the *N*-oxides was investigated by analyzing the HPLC chromatograms in a qualitative fashion. The semiquantitative details are presented in Schemes 3 and 4 and in Table 2.

In the dihydroxylation of styrene, **CNO** was the most efficient oxidant in terms of conversion of the olefin and regeneration of the benzepine. In contrast, **ONO** showed slow reaction rates and poor regeneration of **ON**, and it is possible that some unreacted **ONO** remained. The thiepine derivatives **QNO** and **ZNO** behaved as oxidants of medium activity. Despite the consumption of the starting oxidant, **QNO** regenerated no **QN**. Instead, **QSO** (major) and **QNSO$_2$** (minor) were the predominant products, indicating that an efficient *N*–*S* oxygen shift had occurred. The reaction of **ZNO** showed a less distinctive oxygen shift. Here, regenerated **ZN** was the major product, and **ZNSO$_2$** and **ZSO** were detected as minor products. Additionally, **ZNSO$_2$** (as a mixture containing ~13% of **ZNO**) could also be used as the oxidant. The regeneration of **ZSO** showed that the *N*-oxide moiety is the most reactive oxygen donor. However, the minor reactant **ZNO** remained untouched, demonstrating the superior reactivity of the dioxide **ZNSO$_2$** in terms of its oxidation power.



Scheme 3 Product patterns obtained by using benzepine *N*-oxides as oxidants in osmium- and ruthenium-catalyzed oxygen-transfer reactions. *Reaction conditions*: i) styrene (**1**; 1 equiv), OsO_4 (0.2 mol%), *N*-oxide (2.5 equiv), *t*-BuOH–H_2O; ii) cinnamyl alcohol (**5**; 1 equiv), OsO_4 (0.2 mol%), *N*-oxide (2.5 equiv), *t*-BuOH–H_2O; iii) cinnamyl alcohol (**5**; 1 equiv), $(Pr_4N)RuO_4$ (5 mol%), *N*-oxide (1.5 equiv), MS, CH_2Cl_2.



Scheme 4 OsO_4/benzepine *N*-oxide oxidation of styrene (**1**); for products **4**, see Scheme 3. The thiepine *N*-oxides underwent partial S-oxidation to give the *N*,*S*-dioxides **2e** and **2f**; these gave the corresponding *S*-oxides **4e** and **4f** on oxygen transfer.

Having derived a qualitative reactivity chart, we repeated the sequence in a more quantitative manner using cinnamyl alcohol [**5**; (2*E*)-3-phenylprop-2-en-1-ol] as the starting material.[24] All reactions were carried out on a 0.2-mmol scale of alcohol **5** with a 2.5-fold excess of the appropriate *N*-oxide **2** to give 1-phenylpropane-1,2,3-triol (**6**) and the corresponding products **4**. In all cases, the conversion was terminated after about 20 hours and the outcome of the reaction was analyzed by preparative HPLC. In each experiment, triol **6**, benzepine **4**, and unreacted benzepine *N*-oxide **2** were separated from the side products; details are presented in Scheme 3, Scheme 5 and Table 3.

Table 2 Oxidation of Styrene (**1**) by Osmium Tetroxide and an *N*-Oxide

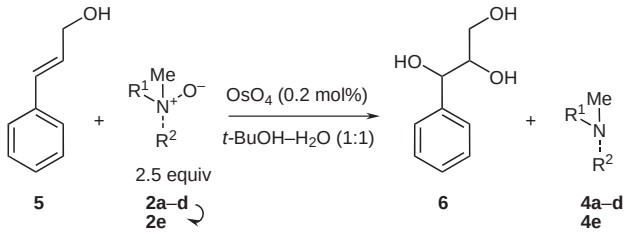
Entry[a]	*N*-Oxide	Yield (%) of **3**	Yield (%) of **2**	Yield (%) of benzepine **4**	Other products
1	**CNO**	8	36	53	
2	**ONO**	4			13% 54% 21%
3	**QNO**	6	21	–	9% **$QNSO_2$** 62% **QSO**
4	**ZNO**	4	50	28	7% **$ZNSO_2$** 5% **ZSO**
5	**$ZNSO_2$**[a]	6	25	38	13% **ZNO**
6[b]	NMO	65	–	–	–

[a] An 87:13 mixture of **$ZNSO_2$** and **ZNO** was used as the starting material. Obviously, the reactant **ZNO** remained unchanged in this experiment.
[b] The NMO-mediated oxidation proved the usefulness of the reaction conditions.

Table 3 Oxidation of Cinnamyl Alcohol (**5**) by Osmium Tetroxide and an *N*-Oxide

Entry	*N*-Oxide	Yield (%) of triol **6**	Yield[a] (%) of *N*-oxide **2**	Yield[a] (%) of benzepine **4**	Other products
1	**CNO**	73	38	84	–
2	**ONO**	0[b]	53	30	–
3	**QNO**	29	0	71	**QSO** (32%)
4	**ZNO**	42	32	71	–
5[c]	NMO	78	–	–	–

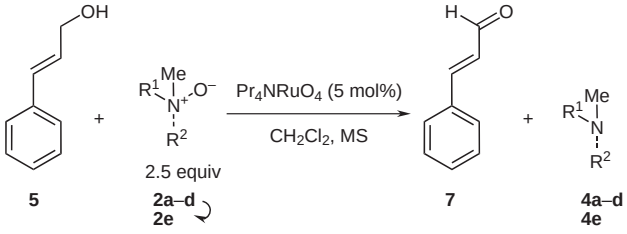
[a] Yields based on recovered starting material.
[b] 60% of cinnamyl alcohol (**5**) was recovered.
[c] The NMO-mediated oxidation proved the usefulness of the reaction conditions.



Scheme 5 OsO_4/*N*-oxide oxidation of cinnamyl alcohol (**5**); for products **4**, see Scheme 3. **QNO** underwent partial S-oxidation to give **2e**, which was converted into *S*-oxide **4e** upon oxygen transfer.

Overall, the results for the dihydroxylation of cinnamyl alcohol (**5**) confirmed the findings from the oxidation of styrene (**1**). Again, **CNO** showed nearly the same oxidant quality as NMO. **ONO** gave only moderate amounts of **ON**, indicating that its oxidation power is weak. **QNO** underwent complete N-deoxygenation and **QN** (major) and **QSO** (minor) were isolated as product thiazepines. In contrast to the first series, **ZNO** was reduced to **ZN**, and none of the *S*-oxide **ZSO** was detected.

In a third series of experiments, we tested the TPAP/*N*-oxide oxidation of cinnamyl alcohol (**5**) to cinnamaldehyde (**7**) as second type of reaction to ensure that oxidations by benzepine *N*-oxides have a broad scope.[25] All the reactions were carried out on a 0.25-mmol scale of the alcohol **5** with a 1.5-fold excess of the appropriate *N*-oxide **2** to give cinnamaldehyde (**7**) and the corresponding products **4**. In each case, the conversion was terminated after 19 hours and the outcome of the reaction was analyzed by ^1H and ^{13}C NMR spectroscopy. All runs were characterized by smooth conversions, and no side-products were found. The ratio of residual cinnamyl alcohol (**5**), cinnamaldehyde (**7**), and the product benzepine **4** were determined by integrating the characteristic peaks (δ = 4.27 for **5**, δ = 9.67 for **7**, and the characteristic signals for **4**) in the ^1H NMR spectra. Details are given in Scheme 3, Scheme 6 and Table 4.



Scheme 6 Pr_4NRuO_4/*N*-oxide oxidation of cinnamyl alcohol (**5**); for products **4**, see Scheme 3. **QNO** underwent partial S-oxidation to form **2e**; this gave the *S*-oxide **4e** upon oxygen transfer.

Table 4 Oxidation of Cinnamyl Alcohol (**5**) by Tetrapropylammonium Perruthenate and an *N*-Oxide

Entry	*N*-Oxide	Proportion of alcohol **5**[a]	Proportion of aldehyde **7**[a]	Proportion of benzepine **4**[a]	Proportion of other products[a]
1	**CNO**	1	50	90	–
2	**ONO**	1.5	1	2	–
3	**QNO**	1	1.7	1.9	1.4 **QSO**
4	**ZNO**	1	7	14	–
5[b]	NMO	1	35	–	–

[a] Ratios based on recovered starting material.
[b] The NMO-mediated oxidation confirmed the usefulness of the reaction conditions.

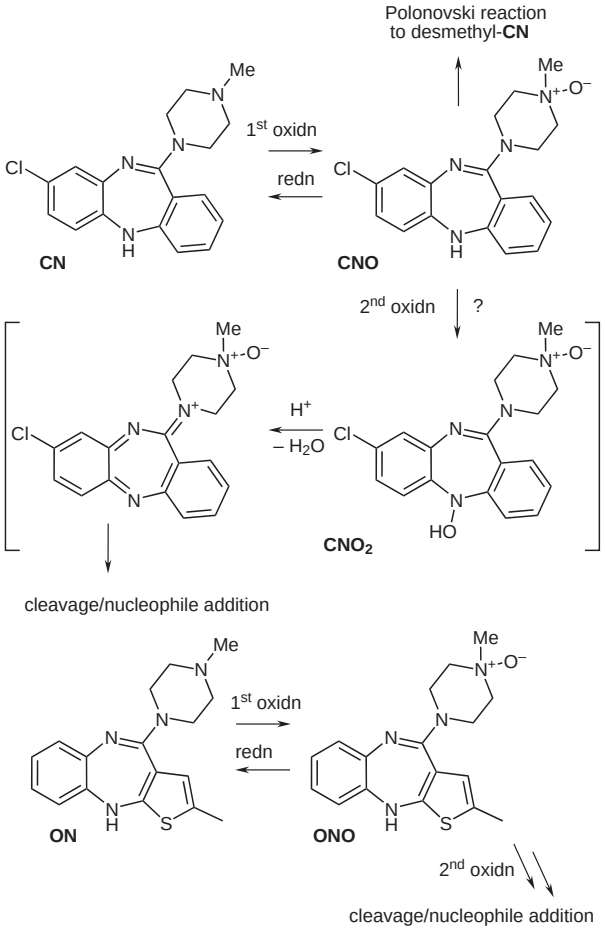
The results for the oxidation of cinnamyl alcohol (**5**) with TPAP to give cinnamaldehyde (**7**) confirmed the trend in reactivity of the benzepine *N*-oxides. **CNO** was the most reactive reagent, giving a nearly quantitative conversion of the alcohol after 19 hours. **ONO** was the least potent oxidant and only 40% of alcohol **5** was converted into the corresponding aldehyde **7** after the standard reaction time. Analogously to the second series, the **ZNO**-supported reaction showed a nearly 90% consumption of the reactant alcohol **5** after 19 hours, and **ZN** was the sole detectable benzepine; no *S*-oxide **ZSO** was formed. **QNO** displayed moderate activity; presumably, the competing oxygen transfer of oxygen from nitrogen to sulfur to form **QSO** reduced the rate of formation of the aldehyde **7**. However, the absence of any $\mathbf{QNSO_2}$ indicated that **QNO** has an excellent oxidation power with respect to the *N*-oxide moiety. Obviously, the formation of $\mathbf{QNSO_2}$ as an intermediate provides much more efficient *N*-deoxygenation in comparison with the reactant **QNO**.

These highly efficient N-deoxygenation reactions permitted the isolation and characterization of the thiepine *S*-oxides. In the ^{13}C NMR spectra of **QSO** and **ZSO**, the carbon shifts for the piperazine moiety were nearly the same as those found in the original **QN**, indicating the presence of a tertiary amine function. For **ZSO**, the chemical shifts of the carbon centers around the dimethylamine moiety were nearly consistent with those of **ZN**, indicating the presence of a nonoxygenated nitrogen center. In contrast, the peak pattern of the thiepine core containing an *S*-oxide moiety showed carbon shifts that were nearly identical with those of $\mathbf{QNSO_2}$ and $\mathbf{ZNSO_2}$, demonstrating conservation of the sulfoxide functions.

Four standard benzepine antipsychotic drugs **CN**, **ON**, **QN**, and **ZN** were subjected to selected oxidizing conditions. The use of excess of hydrogen peroxide caused almost complete degradation of benzepines other than **QN**, which was converted into the almost-stable dioxide $\mathbf{QNSO_2}$. Milder conditions gave the *N*-oxides **CNO**, **QNO**, and **ZNO** as the major products; the thiepines **QN** and **ZN** additionally gave a proportion of the corresponding dioxides $\mathbf{QNSO_2}$ and $\mathbf{ZNSO_2}$. Again, most of the sensitive **ON** was destroyed, and only 17% of the desired **ONO** was obtained. Stepwise selective oxidations with an equimolar ratio of the stronger oxidant, MCPBA, gave the oxides **CNO**, **ONO**, **QNO**, and **ZNO** in 81–97% yield. Furthermore, the thiepines **QNO** and **ZNO** could be subjected to a second oxidation step to give the corresponding dioxides $\mathbf{QNSO_2}$ and $\mathbf{ZNSO_2}$ chemoselectively. In all cases, the exocyclic nitrogen [the alkylated nitrogen in the 4-position of the piperazines in **CN**, **ON**, and **QN** and the (dimethylamino)methyl group in **ZN**] was the best nucleophile; the initial (kinetic) attack of the oxidant occurred on the lone pair of this basic amine center in accordance with the scale of nucleophilicity proposed by Mayr.[26]

In the case of the benzodiazepines, the second oxidation showed a critical difference. **CN** and **ON** underwent rapid cleavage/degradation in the presence of excess oxidant (Scheme 7). Presumably, the NH center of the antiaromatic benzodiazepine core was converted into the hydroxylamine ($\mathbf{CNO_2}$), which underwent subsequent elimination of water. Any resulting amidinium salt might have undergone final hydrolysis with nucleophile addition/rearomatization,[27] ring opening, and irreversible degradation.[28] Comparison of the reaction rates of **CN** and **ON** showed that the latter undergoes more rapid degradation. It seems reasonable, that the 4-chloroaniline moiety in **CN** decreases the nucleophilicity of the NH, leading to a somewhat slower second oxidation. In contrast, the electron-rich **ON** undergoes exothermic multiple oxidation with immediate ring cleavage (Scheme 7).

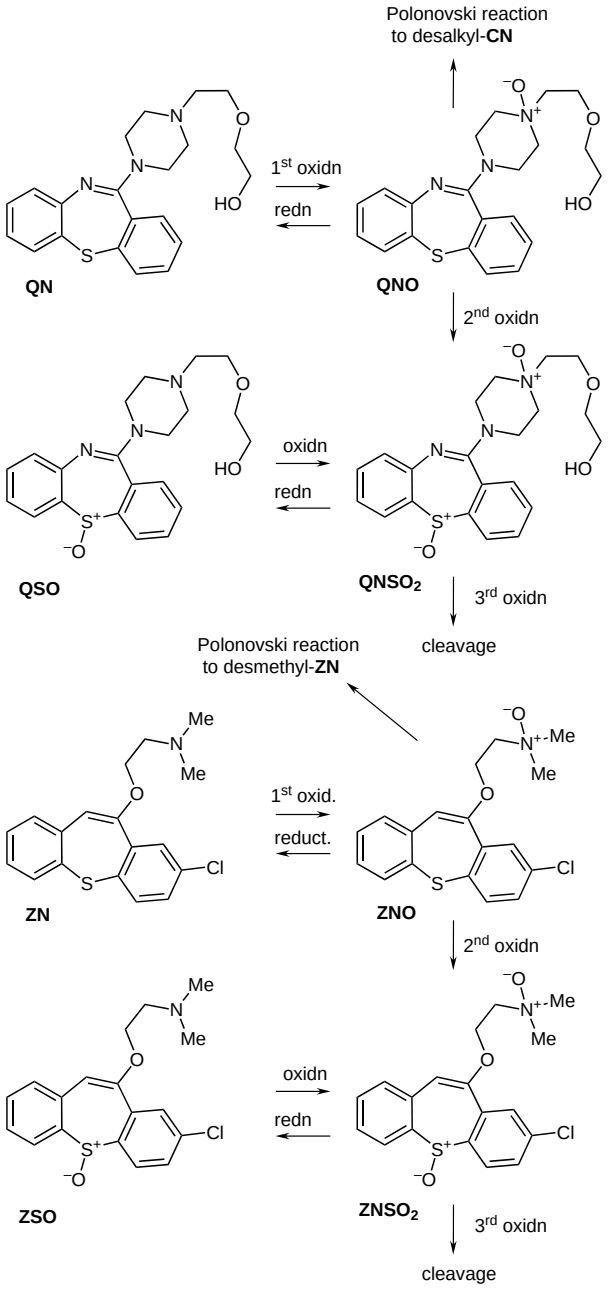
The dibenzothiepine neuroleptics **QNO** and **ZNO** undergo a second oxidation to give stable dioxides. Obviously, the thiepine sulfur atom is converted into the corresponding sulfoxide, delivering the *N*,*S*-dioxides $\mathbf{QNSO_2}$ and $\mathbf{ZNSO_2}$ (Scheme 8). Analogously to the benzodiazepine series, the electron-rich **QNO** undergoes rapid S-oxidation whereas the less electron-rich 4-chlorophenyl-substituted **ZNO** shows slower formation of the *S*-oxide. Because of the bulk of the sulfoxide group, no elimination of water occurs to induce further cleavage. Presumably, a third oxidation is necessary to achieve final cleavage,



Scheme 7 Stepwise oxidation of benzodiazepines **CN** and **ON** and reduction of the *N*-oxide moieties in **CNO** and **ONO**

which might take place either through formation of the sulfone or through attack by oxygen at the amidine (**QNSO$_2$**) or the enol ether (**ZNSO$_2$**) group (Scheme 8).[29]

Analysis of the experiments in which the benzepine *N*-oxides were used as oxidants in osmium- and ruthenium-catalyzed reactions gave a reasonable reactivity pattern. In the case of the benzodiazepine *N*-oxides **CNO** and **ONO**, the latter was found to be a very weak oxidant and only low conversion rates were observed in the osmium tetroxide-catalyzed dihydroxylations and the ruthenium-catalyzed formation of aldehyde **7**. In several runs, a dark color formed suggesting some reduction of the metal oxides to the elemental metals. Overall, **ON** underwent easy and rapid oxidation, and the resulting **ONO** showed slow deoxygenation. In contrast, the less easily oxidized clozapine **CN** proved to be a much better oxidant, and **CNO** showed an oxidant behavior similar to that of NMO in an artificial chemical environment. However, simple variation of the conditions permitted the use of **CN** as a reductant (the presence of an oxygen donor) and of **CNO** as an oxidant (in the presence of an oxygen acceptor).[30]



Scheme 8 Stepwise oxidation/cleavage of benzothiepines **QN** and **ZN** and reduction of the *N*-oxide moieties in **QNO**, **ZNO**, **QNSO$_2$**, and **ZNSO$_2$**

ZNO can be regarded as an analogue of **CNO**. As a result of the presence of the chloro substituent on the dibenzothiepine core, the sulfur atom is less electron-rich and therefore less easily oxidized. Consequently, **ZNO** acts as an oxygen donor in the dihydroxylation of cinnamyl alcohol (**5**) to give triol **6** and in the oxidation of **5** to give enal **7**. The oxidation of the less-reactive styrene (**1**) results in the formation of a more complicated product pattern. Obviously, the sulfur atom of **ZNO** is a better oxygen acceptor than is the double bond of styrene. Therefore, some dioxide **ZNSO$_2$** is formed as a result of disproportionation of **ZNO** to form **ZN** and **ZNSO$_2$**. Because **ZNSO$_2$** also displays *N*-oxygen donor properties, the dioxide undergoes N-deoxygenation to give the corresponding *S*-oxide **ZSO**.[31]

In the case of **QNO**, the more electron-rich sulfur tends to act as a much more efficient oxygen acceptor. Consequently, in all the oxidations of styrene (**1**) and cinnamyl alcohol (**5**) using **QNO**, the formation of **QNSO$_2$** is the major competing process, occurring through disproportionation of **QNO** into **QN** and **QNSO$_2$**).[32] Analogously to the zotepine **ZN** series, the *N*-oxide moiety of **QNSO$_2$** also acts as an oxidant, giving the corresponding **QSO** efficiently through *N*-oxygen transfer.[31,33] Because the *S*-oxide **QSO** was obtained as a major product in all the test oxidation reactions, **QNSO$_2$** must have oxidant qualities that are comparable to those of NMO, **CNO**, and **ZNO**. From a chemical point of view, **QN** can behave as an excellent double oxygen acceptor, undergoing a cascade of sequential N-oxidation and S-oxidation reactions. **QNO** is a medium-strength oxygen donor, as the TPAP-catalyzed oxidation of cinnamyl alcohol (**5**) to cinnamaldehyde (**7**) resulted in more efficient N-deoxygenation (the ratio of N-deoxygenation to S-oxidation was 1.9:1.4). In contrast, the corresponding dioxide **QNSO$_2$**, with a less electron-rich dibenzothiazepine *S*-oxide core, is a much more efficient oxidant, undergoing N-deoxygenation in both the osmium- and ruthenium-catalyzed oxidation reactions.

In comparing the chemical reactivity of these benzepine drugs with reported results for their xenobiotic transformations in mammals, some analogies and differences become apparent. Whereas the *N*-oxides **CNO**, **ONO**, and **ZNO** are known to be more-or-less stable metabolites of the parent drugs, only traces of metabolic **QNO** have been reported.[14] In contrast, only **QSO** has been described as a predominant oxidation product of **QN**.[34] Correlation of these findings with the present results suggests that the *S*-oxide might be formed as a result of a rapid N,S-dioxygenation of **QN** and efficient N-deoxygenation of the reactive **QNSO$_2$**.

In accord with the reports of Henning and co-workers,[35] both oxidation of **CN** and deoxygenation of **CNO** can occur: clozapine can be easily oxidized to give one major metabolite, **CNO**, but retroreduction can also be a favored process in the presence of a catalyst and an appropriate oxygen acceptor. In principle, analogous behavior was found for all of the antipsychotic drugs studied, despite some differences in their reactivities. In our hands, none of the *N*-oxides was a stable metabolite under chemical conditions and we can hazard a guess that some related instability of the *N*-oxides might also occur in the human body. Given that (i) clozapine **CN** and (at least) its major metabolites (N^4-desmethylclozapine and **CNO**) can cross biological membranes;[35] (ii) some of the benzepine *N*-oxides represent major catabolites[15] or minor metabolic routes in mammals;[15,17,36] and (iii) transition-metal ions are present in most compartments of the mammalian body, the potential activities of the *N*-oxides **CNO**, **ONO**, **QNO**, and **ZNO** (as well as those of **QNSO$_2$** and **ZNSO$_2$**) as oxygen donors (oxidants) might shed light on the degradation of these compounds and extend the range of sources of oxygen for oxygen-dependent processes in mammalian tissues.[5c,37,38]

Furthermore, a careful reassessment is required of the assumption that *N*-oxides such as **CNO** represent biologically inert synthetic ligands that display reliable and selective receptor-activation properties. Multiple functions, for example, those occurring after **CN** regeneration and oxygen transfer, have to be excluded to maintain the prerequisites of the DREADD technique on a firm basis.

When necessary, reaction solvents were dried by standard procedures before use. All reactions that involved moisture- or air-sensitive reagents were carried out under argon. ^{1}H NMR, ^{13}C NMR, and 2D spectra (COSY, HSQC, HMBC, and NOESY) were recorded at r.t. on a Bruker ARX400 or AV400 spectrometer in $CDCl_3$ with residual $CHCl_3$ as the internal standard or in CD_3OD with residual CH_3OD as the internal standard. IR spectra were recorded with a Jasco FT/IR-400 plus spectrometer with a single-reflection horizontal ATR (ZnSe) window. FD mass spectra were recorded by using a Finnigan MAT 95 spectrometer. High-resolution mass spectra were recorded with a Waters Q Tof Ultima 3 Micromass spectrometer. The progress of reactions was monitored by TLC on Al sheets coated with 60 F254 silica gel (Merck or Macherey & Nagel).

The analytical HPLC systems used to analyze the products were a Knauer HPLC pump 64 connected to a Phenomenex Gemini-NX C18 (110- 4, 6 × 250 mm) column, a Knauer UV/VIS-FILTER photometer (λ = 254 nm), and a Knauer differential refractometer (System A1) or a Knauer Smartline Pump 1000 connected to a Knauer Smartline Autosampler 3950, a Phenomenex Gemini-NX C18 (110-5 4, 6 × 250 mm) column, a Knauer Smartline UV Detector 2550 (λ = 254 nm), and a Knauer Smartline RI-Detector 2300 (System A2). Other conditions for analytical chromatography are noted below.

Various preparative HPLC Systems were used to purify the substances. System P1 consisted of a Knauer MPLC pump connected to a Phenomenex Gemini C18 (110–5 21, 2 × 250 mm) column, a Knauer Variable Wavelength Monitor (λ = 254 nm), and a Bischoff RI-detector 8110. System P2 consisted of a Knauer WellChrom Preparative Pump K-1800 connected to a Phenomenex Gemini-NX C18 (110–5, 30 × 250mm) column, a Knauer Variable Wavelength Monitor (λ = 254 nm), and a Knauer Differential Refractometer. System P3 consisted of two Knauer Smartline 1000 pumps connected to a Knauer Smartline Autosampler 3950, a Phenomenex Gemini C18 (110–5 21, 2 × 250 mm) column, a Knauer Smartline UV Detector 2550 (λ = 254 nm), and a Knauer Smartline RI-Detector 2300. Other conditions for preparative chromatography are noted below.

Oxidation of the Benzepines

General Procedure A (Neat 35% Aqueous H_2O_2): 35% aq H_2O_2 (5 mL) was added to the appropriate benzepine (500 mg, 1.3–1.6 mmol), and the mixture was stirred at r.t. In the case of highly exothermic reactions, the temperature rise was modulated by cooling with ice–water after about 50 min. The mixture was stirred for 18 h, cooled to 0 °C, and treated with Na_2SO_3 (5 g) to destroy excess H_2O_2. After 4 h, H_2O (10 mL) and MeOH (10 mL) were added, and any remaining solid Na_2SO_3 was removed by filtration. The solvents were removed under reduced pressure and the crude product was purified by HPLC. The yields are reported in Table 1. HPLC data are given below.

General Procedure B [35% Aqueous H_2O_2 (2–3 Equivalents) in MeOH]: A soln of the benzepine (0.50 mmol) in MeOH (5 mL) was cooled to 0 °C and 35% aq H_2O_2 (0.1 mL, 1.2 mmol) was added slowly. The mixture was stirred at r.t. for 20 h and then the solvents were removed under reduced pressure. The crude product was purified by HPLC. The yields are reported in Table 1. HPLC data are given below.

General Procedure C (MCPBA in $CHCl_3$ or MeOH): The benzepine or corresponding *N*-oxide (≤8.9 mmol) was dissolved $CHCl_3$ or MeOH (75 mL). A soln of MCPBA (1 equiv) in $CHCl_3$ or MeOH (10 mL) was added dropwise and the mixture was stirred for 10 min at r.t. Et_3N (2 equiv) was added, and the mixture was stirred for a further 10 min. The solvents were then removed under reduced pressure and the crude product was purified by HPLC. The yields are reported in Table 1. HPLC data are given below.

Clozapine N^4-Oxide (CNO)

Pale yellow slowly crystallizing oil; mp 199–206 °C with decomposition (colour changed to red).

Prepared from **CN** (508 mg, 1.55 mmol) by following General Procedure A; yield: 62 mg (0.18 mmol, 12%).

Prepared from **CN** (164 mg, 0.5 mmol) by following General Procedure B; yield: 126 mg (0.4 mmol, 79%).

Prepared from **CN** (2.00 g, 6.1 mmol) by following General Procedure C; yield: 1.97 g (5.8 mmol, 94%).

Analytical HPLC: System A1; flow rate: 1 mL/min; mobile phase: MeOH–H_2O– 25% aq NH_4OH (60:40:0.35); t_R = 10.08 min; System A1; flow rate: 2 mL/min; mobile phase MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 2.47 min.

Preparative HPLC: System P1; flow rate: 15 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 5.6 min.

IR (ATR): 3262 (br w), 2944 (w), 2819 (w), 1604 (m), 1566 (m), 1461 (m), 1430 (w), 1401 (w), 11378 (w), 1303 (w), 1282 (w), 1260 (w), 1232 (m), 1215 (w), 1159 (w), 1120 (w), 1099 (w), 1083 (w), 1031 (m), 970 (m), 930 (w), 879 (w), 845 (w), 816 (m), 749 (s), 695 (w), 669 (w) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 3.08–3.15 (m, 2 H, H-2), 3.18 (s, 3 H, H-1), 3.48–3.59 (m, 2 H, H-2), 3.65–3.77 (m, 2 H, H-3), 3.71–3.93 (m, 2 H, H-3), 6.81 (d, *J* = 8.4 Hz, 1 H, H-12), 6.86 (dd, *J* = 8.4, 2.3 Hz, 1 H, H-13), 6.98 (d, *J* = 2.3 Hz, 1 H, H-15), 7.00 (dd, *J* = 7.9, 1.0 Hz, 1 H, H-9), 7.02 (dt, *J* = 7.5, 7.5, 1.0 Hz, 1 H, H-7), 7.27 (dd, *J* = 7.7, 1.3 Hz, 1 H, H-6), 7.34 (dt, *J* = 7.8, 7.7, 1.5 Hz, 1 H, H-8).

^{13}C NMR (100 MHz, CD_3OD): δ = 43.2 (br, C-3), 60.1 (C-1), 65.8 (C-2), 121.4 (C-9), 121.6 (C-12), 123.8 (C-5), 124.2 (C-7), 124.9 (C-13), 127.4 (C-15), 129.5 (C-14), 131.1 (C-6), 133.7 (C-8), 142.8 (C-16), 143.2 (C-11), 155.4 (C-10), 164.0 (C-4).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{20}ClN_4O$: 343.1326; found: 343.1333.

Olanzapine *N*^{4}-Oxide (ONO)
Orange solid; mp 183–187 °C with decomposition (colour changed to violet).

Prepared from **ON** (501 mg, 1.6 mmol) by following General Procedure A: no **ONO** found.

Prepared from **ON** (156 mg (0.5 mmol) by following General Procedure B; yield: 28 mg (0.09 mmol, 17%).

Prepared from **ON** (1.0 g, 3.2 mmol) by following General Procedure C; yield: 759 mg (2.3 mmol, 72%). In the absence of Et_3N, the corresponding 3-chlorobenzoic acid salt (**ONO·HOBz′**) was isolated; yield: 124 mg (0.26 mmol, 78%). For details of the purification and analytical data for **ONO-HOBz′**, see the Supporting Information.

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 2.10 min.

Preparative HPLC: System P1; flow rate: 12 mL/min; mobile phase: MeOH–H_2O– 25% aq NH_4OH (60:40:0.35); t_R = 10.0 min; System P1; flow rate: 21 mL/min; mobile phase: MeOH–H_2O (70:30); t_R = 4.0 min.

IR (ATR): 3223 (br m), 2920 (w), 2818 (w), 1590 (s), 1509 (w), 1467 (m), 1396 (m), 1285 (w), 1263 (m), 1219 (m), 1175 (w), 1137 (m), 1119 (w), 1032 (s), 981 (w), 950 (m), 927 (m), 837 (w), 817 (w), 757 (s), 674 (w) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.30 (d, *J* = 1.1 Hz, 3 H, H-15), 3.14 (br d, *J* = 11.4 Hz, 2 H, H-2eq), 3.19 (s, 3 H, H-1), 3.51 (dt, *J* = 11.7, 11.7, 3.1 Hz, 2 H, H-2ax), 3.65–3.74 (m, 2 H, H-3), 3.91 (br d, *J* = 13.9 Hz, 2 H, H-3), 6.38 (d, *J* = 1.2 Hz, 1 H, H-6), 6.67–6.72 (m, 1 H), 6.87–6.94 (m, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 15.3 (C-15), 42.9 (C-3), 60.1 (C-1), 66.0 (C-2), 119.0 (C-5), 120.1 (C-10), 123.6 (C-6), 125.3 (C-12), 125.8 (C-11), 128.9 (C-13), 130.7 (C-7), 141.6 (C-14), 145.6 (C-9), 156.4 (C-8), 159.3 (C-4).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{21}N_4OS$: 329.1436; found: 329.1432.

Quetiapine *N*^{19}-Oxide (QNO)
Colourless foam; mp 106–110 °C.

Prepared from **QN** (506 mg, 1.32 mmol) by following General Procedure A: no **QNO** found.

Prepared from **QN** (235 mg, 0.61 mmol) by following General Procedure B; yield: 149 mg (0.37 mmol, 61%).

Prepared from **QN** (3.40 g, 8.9 mmol) by following General Procedure C; yield: 3.45 g (8.6 mmol, 97%).

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 2.56 min.

Preparative HPLC: System P1; flow rate: 15 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 6.0 min.

Recrystallization from toluene–H_2O–MeOH (~40:1:1) gave **QNO**·2MeOH as a colorless block; mp 114 °C. The structure of **QNO**·2MeOH was confirmed by X-ray crystallography.[19]

IR (ATR): 3056 (w), 3000 (w), 2952 (w), 2869 (w), 1597 (m), 1577 (m), 1557 (m), 1473 (w), 1454 (w), 1397 (m, br), 1303 (m), 1261 (m), 1245 (m), 1216 (w), 1166 (w), 1123 (m, br), 1079 (m, br), 1038 (m), 947 (w), 922 (w), 832 (w), 741 (s), 687 (w), 664 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10–3.30 (m, 3 H, H-5), 3.28–3.35 (m, 2 H, H-4), 3.45–3.58 (m, 3 H, H-2, H-5), 3.61–3.67 (m, 2 H, H-1), 3.84–3.96 (m, 1 H, H-6), 3.96–4.14 (m, 3 H, H-3, H-6), 4.39–4.85 (m, 2 H, H6), 6.88 (dt, *J* = 7.6, 7.6, 1.2 Hz, 1 H, H-16), 7.03 (dd, *J* = 7.9, 1.1 Hz, 1 H, H-18), 7.15 (dt, *J* = 7.6, 7.6, 1.2 Hz, 1 H, H-17), 7.23–7.34 (m, 3 H, H-9, H-10,H-11), 7.37 (dd, *J* = 7.7, 1.1 Hz, 1 H, H-15), 7.47 (d, *J* = 7.1 Hz, 1 H, H-12).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (br, C-6″), 43.2 (br, C-6′), 60.4 (C-1), 63.6 (C-3), 64.1 (br, C-5″), 65.0 (C-5′), 70.7 (C-4), 72.4 (C-2), 123.2 (C-16), 125.0 (C-18), 127.6 (C-14), 128.5 (C-9 or C-10), 128.7 (C-9 or C-10), 129.1 (C-17), 131.1 (C-11), 132.0 (C-12 or C-15), 132.1 (C-12 or C-15), 133.3 (C-8), 139.6 (C-13), 148.2 (C-19), 159.8 (C-7).

Quetiapine *N*^{19},*S*-Dioxide (QNSO$_2$)
Colourless sticky foam (no defined melting point).

Prepared from **QN** (506 mg, 1.32 mmol) by following General Procedure A; yield: 475 mg (1.14 mmol, 87%).

Prepared from **QN** (235 mg, 0.61 mmol) by following General Procedure B; yield: 90 mg (0.22 mmol, 35%).

Prepared from **QN** (461 mg, 1.15 mmol) by following General Procedure C; yield: 399 mg (0.96 mmol, 83%).

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 1.63 min.

Preparative HPLC: System P3; flow rate: 16 mL/min; mobile phase: MeOH–H_2O– 25% aq NH_4OH (60:40:0.35); t_R = 5.55 min (major conformer), 6.05 min (minor conformer); System P1; flow rate: 16 mL/min, mobile phase: MeOH–H_2O–25% aq NH_4OH (50:50:0.35); t_R = 11.3 min (major conformer), 12.8 min (minor conformer).

IR (ATR): 3356 (br w), 2935 (w), 2820 (w), 1592 (m), 1577 (s), 1556 (s), 1451 (m), 1420 (m), 1303 (m), 1284 (w), 1265 (m), 1244 (w), 1166 (w), 1113 (m), 1079 (s), 1028 (s), 949 (w), 922 (w), 829 (w), 767 (s), 741 (m), 713 (w), 685 (m), 668 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major conformer) = 2.95–3.41 (m, 2 H, H-5), 3.26–3.50 (m, 2 H, H-5′), 3.30–3.42 (m, 2 H, H-4), 3.50–3.57 (m, 2 H, H-2), 3.63–3.70 (m, 2 H, H-1), 3.99–4.13 (m, 2 H, H-3), 6.96 (dd, *J* = 1.0, 7.8 Hz, 1 H, H-18), 7.14 (dt, *J* = 1.0, 7.6, 7.6 Hz, 1 H, H-16), 7.22 (dt, *J* = 1.4, 7.7, 7.7 Hz, 1 H, H-17), 7.33 (dd, *J* = 0.8, 7.6 Hz, 1 H, H-10), 7.41 (dt, *J* = 0.8, 7.4, 7.4 Hz, 1 H, H-9), 7.56 (dd, *J* = 1.2, 7.6 Hz, 1 H, H-15), 7.60 (t, *J* = 7.6, 7.6 Hz, 1 H, H-11), 7.80 (d, *J* = 7.7 Hz, 1 H, H-12); δ (minor conformer) = 2.93–3.01 (m, H-5), 3.12–3.21 (m, H-5′), 3.26–3.30 (m, H-4), 3.27–3.38 (m, H-6), 3.42–3.52 (m, H-5), 3.45–3.50 (m, H-2), 3.54–3.64 (m, H-5′), 3.57–3.63 (m, H-1), 3.92–3.97 (m, H-3), 3.95–4.07 (m, H-6′), 4.14–4.25 (m, H-6), 4.69–4.79 (m, H-6′), 6.92–7.00 (m, 1 H, H-16), 7.09 (dd, *J* = 0.8, 8.0 Hz, 1 H, H-18), 7.30 (dt, *J* = 1.5, 7.8, 7.8 Hz, 1 H, H-17), 7.41–7.51 (m, 2 H, H-9, H-15), 7.51–7.54 (m, 2 H, H-10, H-11), 7.62 (d, *J* = 8.5 Hz, 1 H, H-12); H6 (major conformer) occurred as a very broad 4 H integral between 3.4 and 5.0 ppm. Because of extensive overlaps with the major conformer, the integrations of the minor conformer peaks are omitted.

^{13}C NMR (100 MHz, $CDCl_3$): δ (major conformer) = 39.2 (br, C-6′), 43.3 (br, C-6), 60.4 (C-1), 63.6 (C-3), 64.2 (C-5′), 64.9 (C-5), 70.5 (C-4), 72.5 (C-2), 119.8 (C-12), 120.1 (C-15), 121.9 (C-8), 124.3 (C-16), 124.6 (C-18), 128.0 (C-10), 130.3 (C-9), 130.3 (C-17), 132.1 (C-11), 135.1 (C-14), 141.7 (C-19), 147.5 (C-13), 156.6 (C-7); δ (minor conformer) = 39.3 (C-6′), 44.5 (C-6), 60.6 (C-1), 63.5 (C-5′), 63.8 (C-3), 65.9 (C-5), 71.0 (C-4), 72.4 (C-2), 122.4 (C-16), 124.3 (C-8), 124.4 (C-12), 126.9 (C-18), 127.2 (C-15), 129.5 (C-10), 130.9 (C-9), 132.1 (C-11), 132.6 (C-17), 133.0 (C-14), 144.3 (C-19), 146.9 (C-13), 157.7 (C-7).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}N_3NaO_4S$: 438.1436; found: 438.1464.

Zotepine *N*^{20}-Oxide (ZNO)
Colourless solid; mp 110–115 °C.

Prepared from **ZN·*x*HCl** (1.7 g, 4.6 mmol) by following General Procedure B; yield: 898 mg (2.6 mmol, 56%).

Prepared from **ZN** (1.97 g, 6.0 mmol) by following General Procedure C; yield: 1.69 g (4.9 mmol, 81%).

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 4.29 min.

Preparative HPLC: System P1; flow rate: 20 mL/min; mobile phase MeOH–H_2O (70:30); t_R = 12.8 min.

Recrystallization from toluene–H_2O (~40:1) gave **ZNO**·$2H_2O$ as colorless plates; mp 117.5 °C. The structure of **ZNO**·$2H_2O$ was confirmed by X-ray crystallography.[19]

IR (ATR): (**ZNO**·$2H_2O$): 3311 (br m), 2940 (w), 2826 (w), 1622 (m), 1577 (w), 1550 (w), 1463 (m), 1432 (w), 1396 (w), 1357 (w), 1277 (w), 1256 (w), 1226 (m), 1199 (s), 1140 (m), 1116 (s), 1099 (s), 1059 (w), 1028 (s), 956 (w), 917 (w), 889 (w), 816 (s), 754 (s), 735 (w), 715 (w), 689 (w), 658 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 6 H, H-1), 3.78–3.81 (m, 2 H, H-2), 4.68–4.72 (m, 2 H, H-3), 6.48 (s, 1 H, H-17), 7.20 (ddd, *J* = 2.6, 6.3, 7.5 Hz, 1 H, H-13), 7.22–7.27 (m, 2 H, H-14, H-15), 7.29 (dd, *J* = 2.4, 8.3 Hz, 1 H, H-8), 7.44 (s, 1 H, H-6), 7.46 (d, *J* = 6.6 Hz, 1 H, H-9), 7.47 (dd, *J* = 1.2, 7.6 Hz, 1 H, H-12).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.0 (C-1), 62.4 (C-3), 69.7 (C-2), 108.7 (C-17), 127.4 (C-6), 127.9 (C-13), 128.5 (C-14), 129.4 (C-15), 130.1 (C-8), 132.2 (C-12), 133.3 (C-11), 133.7 (C-9), 134.3 (C-7 or C-10), 134.5 (C-7 or C-10), 138.1 (C-16), 139.3 (C-5), 155.2 (C-4).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}ClNO_2S$: 348.0825; found: 348.0818.

Zotepine *N*[20],S-Dioxide (ZNSO$_2$)
Pale brownish solid; mp 105–110 °C.

Prepared from **ZN·*x*HCl** (1.7 g, 4.6 mmol) by following General Procedure B; yield: 188 mg (0.5 mmol, 11%).

Prepared from **ZNO** (515 mg, 1.4 mmol) by following General Procedure C; yield: 471 mg (1.3 mmol, 93%).

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 1.97 min.

Preparative HPLC: System P1; flow rate: 12 mL/min; mobile phase: MeOH–H_2O (60:40); t_R = 12.1 min; System P1; flow rate: 20 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 5.2 min.

Recrystallization from toluene–H_2O (~40:1) gave **ZNSO$_2$**·$2H_2O$ as colorless plates; mp 111 °C. The structure of **ZNSO$_2$**·$2H_2O$ was confirmed by X-ray crystallography.[19]

IR (ATR): 3223 (br m), 3052 (w), 2953 (w), 1615 (m), 1583 (w), 1552 (m), 1471 (m), 1458 (m), 1434 (w), 1395 (w), 1355 (m), 1260 (m), 1226 (m), 1202 (s), 1119 (s), 1095 (s), 1077 (s), 1038 (s), 955 (m), 889 (m), 825 (s), 757 (s), 734 (s), 710 (s), 657 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.28 (s, 3 H, H-1), 3.36 (s, 3 H, H-1), 3.73 (t, *J* = 4.5, 4.5 Hz, 2 H, H-2), 4.60–4.66 (m, 1 H, H-3), 4.72–4.78 (m, 1 H, H-3), 6.51 (s, 1 H, H-17), 7.26 (dd, *J* = 1.4, 7.7 Hz, 1 H, H-15), 7.30 (dt, *J* = 1.3, 7.4, 7.4 Hz, 1 H, H-14), 7.44 (dt, *J* = 1.4, 7.5, 7.5 Hz, 1 H, H-13), 7.49 (d, *J* = 2.0 Hz, 1 H, H-6), 7.53 (dd, *J* = 2.1, 8.5 Hz, 1 H, H-8), 7.72 (dd, *J* = 1.1, 7.9 Hz, 1 H, H-12), 7.76 (d, *J* = 8.4 Hz, 1 H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.9 (C-1), 62.5 (C-3), 69.2 (C-2), 105.2 (C-17), 120.8 (C-12), 122.2 (C-9), 126.6 (C-6), 128.5 (C-13), 128.6 (C-16), 128.8 (C-15), 129.2 (C-5), 129.5 (C-14), 131.0 (C-8), 135.7 (C-7), 140.1 (C-11), 141.4 (C-10), 152.4 (C-4).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}ClNO_3S$: 364.0774; found: 364.0768.

Osmium Tetroxide-Catalyzed Dihydroxylations With *N*-Oxides as Co-oxidants: General Procedure D
Styrene (**1**) or (*E*)-cinnamyl alcohol (**5**) (0.2 mmol) and *N*-oxide **2** (0.5 mmol) were dissolved or suspended in *t*-BuOH–H_2O (1:1; 5 mL), and the mixture was stirred for 15 min at r.t. A 4% aq soln of OsO_4 (5 μL) was injected into the mixture, which was then stirred for 19 h at r.t. 10% aq Na_2SO_3 (1 mL) was added and stirring was continued for 1–2 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure.

The yields of 1-phenylethane-1,2-diol (**3**) obtained by using the various *N*-oxides **2** were compared by means of analytical HPLC. Aliquots were injected and the resulting peak areas were integrated to provide qualitative information.

Analytical HPLC (qualitative): System A2; flow rate; 1 mL/min; mobile phase: MeOH–H_2O (50:50); System A2; flow rate: 1 mL/min; mobile phase: MeOH–H_2O (70:30).

The products of the styrene reactions were determined by means of analytical HPLC with co-injection of reference substances, and by ^1H and ^{13}C NMR of the crude product; yields were determined integrating peak areas obtained from the RI detector.

Analytic HPLC (quantitative): System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (70:30:0.35).

The yields from (*E*)-cinnamyl alcohol (**5**) were measured after preparative HPLC.

Preparative HPLC: System P2; flow rate: 20 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (70:30:0.35).

For details of the use of the benzepine *N*-oxides as oxidants, see the Supporting Information.

Tetrapropylammonium Perruthenate-Catalyzed Oxidation of (*E*)-Cinnamyl Alcohol (5) by Using *N*-Oxides 2 as Co-oxidants: General Procedure E
(*E*)-Cinnamyl alcohol (**5**; 34 mg, 0.25mmol) was added to a soln of *N*-oxide **2** (375 μmol) in CH_2Cl_2 (2 mL) containing 4-Å MS (100 mg) under argon, and the mixture was stirred for 30 min. 1 mL of a soln of $Pr_4N(RuO_4)$ (105 mg) in anhyd CH_2Cl_2 (10 mL) containing 4-Å MS (750 mg) was added and the mixture was stirred for 19 h at r.t. 10% aq Na_2SO_3 (2 mL) was added, and the mixture was stirred for a further 1–2 h. The aqueous layer was then extracted with CH_2Cl_2 (3 × 3 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The yield was determined by analyzing the ^1H NMR spectra by integration of the characteristic peaks for cinnamyl alcohol (**5**) (δ = 4.3 ppm, 2 H, CH_2OH) and cinnamaldehyde (**7**) (δ = 9.7 ppm, 1 H, CH=O) and one signal for the corresponding amine **4**. If necessary, signals for the residual *N*-oxide **2** and any *S*-oxide were also integrated.

Quetiapine *S*-Oxide (QSO)
Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 2.03 min; System A1; flow rate: 2 mL/min, mobile phase: MeOH–H_2O–25% aq NH_4OH (60:40:0.35); t_R = 4.11 min; System A1; flow rate: 2 mL/min; mobile phase MeOH–H_2O–25% aq NH_4OH (50:50:0.35); t_R = 9.90 min.

Preparative HPLC: System P1; flow rate: 18 mL/min; mobile phase MeOH–H_2O (50:50); t_R = 28.0 min.

Pale green viscous oil.

IR (ATR): 3437 (br w), 3054 (w), 2928 (w), 2858 (w), 2821 (w), 1591 (m), 1577 (s), 1554 (s), 1452 (m), 1422 (m), 1367 (w), 1352 (w), 1306 (m), 1286 (w), 1259 (m), 1243 (m), 1122 (m), 1085 (m), 1038 (m), 1014 (s), 909 (w), 831 (w), 767 (m), 739 (m), 687 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.55 (br s, 1 H, H-5), 2.64 (br s, 1 H, H-5), 2.64 (t, *J* = 5.3, 5.3 Hz, 2 H, H-4), 3.61 (m, 2 H, H-2), 3.66 (t, *J* = 5.3, 5.3 Hz, 2 H, H-3), 3.70 (m, 2 H, H-1), 7.00 (dd, *J* = 0.8, 7.8 Hz, 1 H, H-18), 7.16 (dt, *J* = 1.0, 7.5, 7.5 Hz, 1 H, H-16), 7.26 (dt, *J* = 1.5, 7.7, 7.7 Hz, 1 H, H-17), 7.34 (dd, *J* = 0.8, 7.6 Hz, 1 H, H-9), 7.44 (dt, *J* = 0.9, 7.5, 7.5 Hz, 1 H, H-10), 7.58 (dd, *J* = 1.4, 7.8 Hz, 1 H, H-15), 7.62 (dt, *J* = 0.9, 7.6, 7.6 Hz, 1 H, H-11), 7.84 (dd, *J* = 0.7, 7.9 Hz, 1 H, H-12); remaining H5 and H6 occurred as a very broad 6 H integral between 2.8 and 4.0 ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.8 (br, C-6), 52.9 (br, C-5), 57.8 (C-4), 61.8 (C-1), 67.4 (C-3), 72.4 (C-2), 119.7 (C-12), 120.2 (C-15), 122.6 (C-8), 123.8 (C-16), 124.8 (C-18), 128.0 (C-9), 130.0 (C-10), 130.3 (C-17), 131.8 (C-11), 135.5 (C-14), 142.4 (C-19), 147.7 (C-13), 157.3 (C-7).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_3S$: 400.1695; found: 400.1690.

Zotepine *S*-Oxide (ZSO)

Analytical HPLC: System A1; flow rate: 2 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 4.68 min.

Preparative HPLC: System P1; flow rate: 21 mL/min; mobile phase: MeOH–H_2O–25% aq NH_4OH (75:25:0.35); t_R = 10.22 min.

Colourless solid; mp 128–130 °C (very slow decomposition, colour changed to brown).

IR (ATR): 3054 (w), 2976 (w), 2946 (w), 2821 (m), 2771 (m), 1613 (m), 1583 (w), 1552 (m), 1470 (m), 1400 (w), 1353 (m), 1261 (m), 1227 (m), 1202 (m), 1141 (m), 1119 (s), 1096 (m), 1078 (s), 1039 (s), 992 (w), 963 (w), 914 (w), 875 (w), 827 (s), 756 (m), 735 (m), 710 (m), 688 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.5 Hz, 1 H, H-9), 7.78 (dd, *J* = 1.0, 8.0 Hz, 1 H, H-12), 7.66 (d, *J* = 2.1 Hz, 1 H, H-6), 7.58 (dd, *J* = 2.1, 8.5 Hz, 1 H, H-8), 7.49 (dt, *J* = 1.1, 7.6, 7.6 Hz, 1 H, H-13), 7.35 (dt, *J* = 1.3, 7.4, 7.5 Hz, 1 H, H-14), 7.27 (d, *J* = 7.4 Hz, 1 H, H-15), 6.41 (s, 1 H, H-17), 4.18 (t, *J* = 5.7, *J* = 5.7 Hz, 2 H, H-3), 2.93–2.78 (m, 2 H, H-2), 2.40 (s, 6 H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7 (C-4), 141.3 (C-10), 140.4 (C-11), 135.8 (C-7), 131.0 (C-8), 129.8 (C-5), 129.4 (C-14), 129.2 (C-16), 128.6 (C-15), 128.3 (C-13), 127.3 (C-6), 122.1 (C-9), 121.0 (C-12), 104.4 (C-17), 66.7 (C-3), 57.9 (C-2), 45.9 (C-1).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}ClNO_2S$: 348.0825; found: 348.0836.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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double bond (amidine mesomerism), the *N*-oxide-derived piperazine–thiazepine moiety can form a chiral axis (racemate). In combination with the chiral *S*-oxide (racemate), this led to the presence of two slowly interconverting diastereomeric conformers that appeared as a double set of peaks in the spectra. The two conformers were successfully separated by preparative HPLC. On standing, the separated conformers underwent slow equilibration to regenerate the original conformer mixture.

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(22) (a) Moreno-Dorado, F. J.; Guerra, F. M.; Ortega, M. J.; Zubía, E.; Massanet, G. M. *Tetrahedron: Asymmetry* **2003**, *14*, 503. (b) Branco, L. C.; Afonso, C. A. M. *J. Org. Chem.* **2004**, *69*, 4381. (c) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229. For data on diol **3**, see, for example: (d) Huang, K.; Wang, H.; Stepanenko, V.; De Jesús, M.; Torruellas, C.; Correa, W.; Ortiz-Marciales, M. *J. Org. Chem.* **2011**, *76*, 1883.

(23) HPLC analyses showed that diol **3** was obtained in low yields. This might have been a consequence of the presence of residual styrene (**1**) (not analyzed), the long reaction time, or the presence of excess oxidant permitting subsequent transformations of **3**, such as glycol cleavage. Our investigation focused on the fate and behavior of the *N*-oxides.

(24) (a) By analogy to: Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716. For data on triol **6**, see, for example: (b) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270.

(25) (a) By analogy to: Ley, S. V.; Ramarao, C.; Smith, M. D. *J. Chem. Soc. Chem. Commun.* **2001**, 2278. For data on cinnamaldehyde (**7**), see, for example: (b) Koenning, D.; Hiller, W.; Christmann, M. *Org. Lett.* **2012**, *14*, 5258.

(26) For the nucleophilicity of piperazine, morpholine, piperidine, and anilines, see: (a) Botzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679. For the nucleophilicity of *N*-methylmorpholine and *N*-methylpiperidine, see: (b) Phan, T. B.; Brugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3869; *Angew. Chem.* **2006**, *118*, 3954 . (c) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379. (d) Ammer, J.; Baidya, M.; Kobayashi, S.; Mayr, H. *J. Phys. Org. Chem.* **2010**, *23*, 1029. In the presence of additional protons, the most nucleophilic and most basic position can be blocked (protonated). Oxidation might then be directed towards the N^5 (diazepine) and S^5 (thiepine) sites, inducing alternative reaction cascades.

(27) Dragovic, S.; Gunness, P.; Ingelman-Sundberg, M.; Vermeulen, N. P. E.; Commandeur, J. N. M. *Drug Metab. Dispos.* **2013**, *41*, 651.

(28) For oxidative metabolism of drugs, see: Poraj-Kobielska, M.; Kinne, M.; Ullrich, R.; Scheibner, K.; Kayser, G.; Hammel, K. E.; Hofrichter, M. *Biochem. Pharmacol.* **2011**, *82*, 789.

(29) The third nucleophilic position in QN might be the dibenzothiepine ring nitrogen center, by analogy to N-alkylation; see: Noskov, V. G.; Kalinina, L. N.; Noskova, M. N.; Kruglyak, Y. L.; Strukov, O. G.; Kurochkin, V. K. *Pharm. Chem. J. (Engl. Trans.)* **1998**, *32*, 210.

(30) Generally, deoxygenation might proceed by demethylation, following a competing pathway. In the presence of a metal oxide (especially Fe^{2+}), a Polonovski-type elimination delivers an iminium salt, the final hydrolysis leads to the well-known desmethylclozapine through elimination of formaldehyde. For related demethylations, see: (a) Schildan, A.; Schirrmacher, R.; Samochocki, M.; Christner, C.; Maelicke, A.; Rösch, F. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 247. (b) Rosenau, T.; Potthast, A.; Kosma, P. *Tetrahedron* **2002**, *58*, 9809. (c) Herlem, D.; Martin, M.-T.; Thal, C.; Guillou, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2389. (d) Mary, A.; Renko, D. Z.; Guillou, C.; Thal, C. *Tetrahedron Lett.* **1997**, *38*, 5151.

(31) Because of their less electron-rich dibenzothiepine *S*-oxide tricyclic cores, **$ZNSO_2$** and **$QNSO_2$** could be rated as more powerful oxidants in relation to *N*-oxide deoxygenation than the less-oxidized **ZNO** and **QNO**.

(32) Furthermore, **$QNSO_2$**, as the better oxygen donor, tends to convert **QN** into **QNO** as follows: **$QNSO_2$** + **QN** → **QSO** + **QNO**. The analogous process is possible within the **ZN** series: **$ZNSO_2$** + **ZN** → **ZSO** + **ZNO**.

(33) Two S-oxides have been described; see: DeVane, C. L.; Nemeroff, C. B. *Clin. Pharmacokinet.* **2001**, *40*, 509.

(34) We succeeded in oxidizing QN directly to QSO in the presence of a hemifumarate buffer. The N4-nitrogen underwent protonation–deactivation, and the oxidation was directed towards the still-nucleophilic sulfur atom; see: Mittapelli, V.; Vadali, L.; Sivalakshmi, D. A.; Suryanarayana, M. V. *Rasayan J. Chem.* **2010**, *3*, 677.

(35) (a) Henning, U.; Krieger, K.; Loeffler, S.; Klimke, A. *Pharmacopsychiatry* **2003**, *36*, 233; abstract 116. (b) Henning, U.; Krieger, K.; Klimke, A. *Pharmacopsychiatry* **2003**, *36*, 233; abstract 115.

(36) Dain, J. G.; Nicoletti, J.; Ballard, F. *Drug Metab. Dispos.* **1997**, *25*, 603.

(37) (a) Meier, J. *Br. J. Pharmacol.* **1975**, *53*, 440. (b) Jann, M. W.; Lam, Y. W. F.; Chang, W.-H. *Arch. Int. Pharmacodyn. Ther.* **1994**, *328*, 243. (c) Pirmohamed, M.; Williams, D.; Madden, S.; Templeton, E.; Park, B. K. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 984.

(38) **CNO** and the other *N*-oxides can act as powerful oxidants and, hence, the parent drugs can be regarded as vehicles of varying efficiency for atomic oxygen. In this way, the current study might contribute to a basic understanding of oxidative effects of the antioxidant clozapine **CN**, see also: (a) Dalla Libera, A.; Scutari, G.; Boscolo, R.; Rigobello, M. P.; Bindoli, A. *Free Radical Res.* **1998**, *29*, 151. For some examples of reductions, see: (b) Kitamura, S.; Sugihara, K.; Tatsumi, K. *Drug Metab. Dispos.* **1998**, *27*, 92. (c) Parte, P.; Kupfer, D. *Drug Metab. Dispos.* **2005**, *33*, 1446.