Oxetanes

DOI: 10.1002/ange.200800450

Spirocyclic Oxetanes: Synthesis and Properties**

Georg Wuitschik, Mark Rogers-Evans, Andreas Buckl, Maurizio Bernasconi, Moritz Märki, Thierry Godel, Holger Fischer, Björn Wagner, Isabelle Parrilla, Franz Schuler, Josef Schneider, André Alker, W. Bernd Schweizer, Klaus Müller,* and Erick M. Carreira**

We were intrigued by the apparent analogy between oxetanes and the van 't Hoff description of $R_2C{=}O$,[1] with the close correspondence of these two structural types in the "bent-bond" model proposed by Pauling.[2] This abstraction sets oxetanes in a context that is broader than merely as surrogates of *gem*-dimethyl groups in drug discovery, as we have previously suggested.[3] Herein we disclose the implementation of this correlation in a study of spirocyclic oxetanes that resemble saturated heterocycles common to medicinal chemistry (Figure 1).

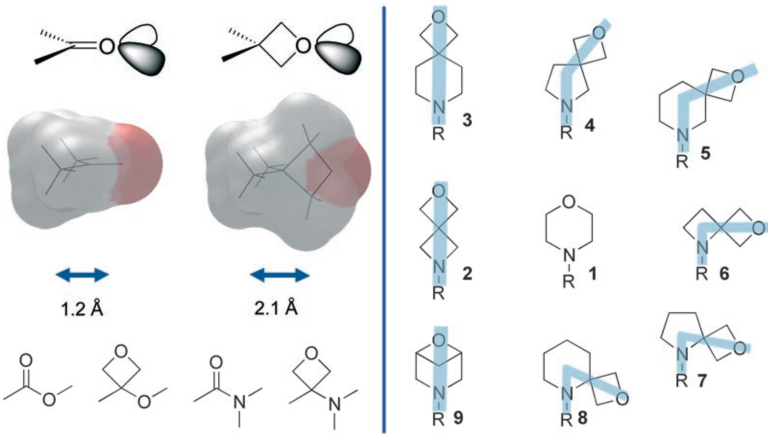


Figure 1. Left: Formal analogy between the C=O and oxetanyl groups. Middle left: Calculated van der Waals surfaces[15] for acetone and 3,3-dimethyloxetane. Bottom left: 3-Alkoxy and 2-amino oxetanes as "van 't Hoff analogues" of esters and amides. Right: Spirocyclic oxetane amines and a methano-bridged morpholine derivative considered in this study.

In druglike structures, there are liabilities associated with carbonyl groups that stem from their susceptibility to enzymatic modification and to the epimerization of adjacent stereogenic centers, as well as their inherent electrophilic reactivity and their potential for covalent binding. Studies suggest that oxetane and aliphatic carbonyl groups have a similarly high H-bonding avidity.[4,5] Consequently, the nominal analogy of an oxetane to C=O may be of interest in molecular design, particularly when a larger volume occupancy and deeper oxygen placement might be advantageous at a receptor pocket.[6]

To establish a point of reference for the oxetane/C=O analogy, we examined the properties of spirooxetane analogues of piperidones, pyrrolidones, and azetidinones. The series is also of practical interest in view of its structural relationship to morpholine (**1**; R = H), an oft encountered heterocycle in medicinal chemistry. We examined a subset of spirooxetanes which position the oxygen atom in the molecular-symmetry plane at an extended distance from the nitrogen atom (**2**, **3**) with similar or decreased lateral bulk (**2**). Others (**4**–**8**) place the oxygen at a reclined angle from the symmetry plane of the parent morpholine, resulting in a reduction of symmetry without introducing chirality. Furthermore, amines **2**–**5** may also be considered to be stable analogues of the corresponding cyclic ketoamines **10**–**13** (Table 1), some of which are chemically or metabolically labile. The aminooxetane derivatives **6**–**8** can be perceived as nonhydrolyzable analogues of the corresponding β-, γ-, and δ-lactams **14**–**16** (Table 1). With a comparable molecular volume, an oxetane moiety may replace a *gem*-dimethyl group;[3] consequently, the *gem*-dimethyl-substituted amines **17**–**23** (Table 1) were included in the study for calibration. The bicyclic oxetane **9** serves as another achiral morpholine analogue. All compounds to be studied were tagged with a piperonyl residue (R in Figure 1) to facilitate analytical measurements.[7]

Spirooxetanes **3**, **4**, and **6**–**8** were prepared by conjugate addition to acceptors **24** or **25**,[3] followed by a short sequence of steps (Scheme 1). For the preparation of **2**, **5**, and **9**, new approaches were developed (Scheme 2). Tribromopentaerythritol (**26**) provides ready access to 2-oxa-6-azaspiro[3.3]heptane, which can be stored conveniently as its stable

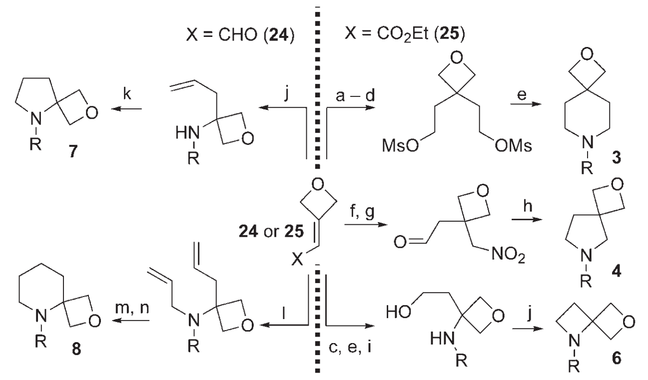
[*] Dr. M. Rogers-Evans, Dr. T. Godel, Dr. H. Fischer, B. Wagner, I. Parrilla, Dr. F. Schuler, Dr. J. Schneider, A. Alker, Prof. Dr. K. Müller
F. Hoffmann-La Roche AG
Pharmaceuticals Division
4070 Basel (Switzerland)
Fax: (+41) 61-688-6965
E-mail: mark.rogers-evans@roche.com
klaus.mueller@roche.com

G. Wuitschik, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie
ETH Hönggerberg, HCI H335
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1328
E-mail: carreira@org.chem.ethz.ch

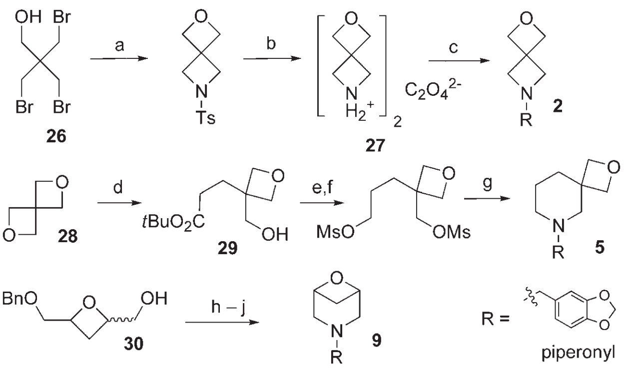
A. Buckl, M. Bernasconi, M. Märki, W. B. Schweizer
Laboratorium für Organische Chemie
ETH Zürich (Switzerland)

[**] We thank F. Hoffmann-La Roche AG for support of this research. We are indebted to Frank Senner and Pia Warga for their great dedication in measuring the physicochemical data described herein.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. R = piperonyl. Reagents and conditions: a) $H_2C(CO_2Me)_2$, NaH; b) NaCl, DMSO, 160°C, 82% (2 steps); c) $LiAlH_4$; d) MsCl, NEt_3; e) RNH_2, 38% (3 steps); f) $MeNO_2$, cat. DBU, 92%; g) DIBAL-H, 73%; h) H_2, Pd/C, then piperonal, $NaBH(OAc)_3$, 53%; i) PPh_3, CBr_4, 71%; j) RNH_2, then CH_2PPh_3, 29%; k) $Hg(O_2CCF_3)_2$, then $NaBH_4$, 38%; l) RN(H)allyl, then CH_2PPh_3, 53%; m) *p*-TsOH, Grubbs II (2.5 mol%), 88%; n) H_2, Rh/C, 79%. DBU = 1,8-diazabicyclo[5.4.0]-7-undecene, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl.



Scheme 2. a) $TsNH_2$, KOH, 58%; b) Mg, MeOH, ultrasound, then $H_2C_2O_4$, 81%; c) $NaBH(OAc)_3$, piperonal, 73%; d) LiO(*t*BuO)C=CH_2, BF_3OEt_2, 75%; e) $LiAlH_4$, 0°C; f) MsCl, NEt_3; g) RNH_2, 80°C, 49% (3 steps); h) H_2, $Pd(OH)_2$/C; i) MsCl, pyridine; j) RNH_2, 20% (3 steps). Bn = benzyl.

Table 1: Physicochemical and biochemical properties.[a]

Compound		log D[b] (log P)[c]	Sol.[d]	Cl_{int} (h/m)[e]	pK_a[f]
gem-Me_2	17	0.8 (3.1)	290	0/16	9.6
oxetane	2	0.5 (1.2)	24000	3/7	8.0
carbonyl	10	n.d.[g]	n.d.[g]	n.d.[g]	n.d.[g]
gem-Me_2	18	2.3 (4.4)	220	23/31	9.5
oxetane	3	1.0 (2.0)	1400	6/22	8.3
carbonyl	11	1.2 (1.6)	4000	120/88	7.5
gem-Me_2	19	1.4 (3.7)	40	10/39	9.7
oxetane	4	0.7 (1.5)	730	2/27	8.1
carbonyl	12	−0.1 (−0.1)	4100	100/580	6.1
gem-Me_2	20	2.3 (4.3)	13	31/89	9.4
oxetane	5	1.7 (2.3)	2000	16/55	7.9
carbonyl	13	0.1 (0.5)	2100	120/120	7.6
gem-Me_2	21	0.1 (2.8)	380	7/14	10.1
oxetane	6	1.3 (1.3)	1400	21/26	6.2
carbonyl	14	1.1 (1.1)	2100	5/190	–
gem-Me_2	22	0.9 (3.5)	41	0/13	10.0
oxetane	7	1.9 (1.9)	2100	31/74	6.3
carbonyl	15	1.2 (1.2)	1500	5/16	–
gem-Me_2	23	1.1 (3.9)	30	0/18	10.2
oxetane	8	2.2 (2.4)	750	19/230	7.0
carbonyl	16	1.6 (1.6)	6200	8/39	–
	9	1.6 (1.8)	> 2600	15/41	7.1
x = 3	31	0.9 (3.1)	450	8/18	9.6
x = 2	32	0.2 (2.5)	580	6/18	9.7
x = 1	33	−0.1 (2.1)	2500	0/11	9.5
	1	1.5 (1.6)	8000	9/8	7.0

[a] R = piperonyl. [b] Logarithmic *n*-octanol/water distribution coefficient at pH 7.4. [c] Intrinsic lipophilicity of the neutral base according to the equation $\log P = \log D + \log_{10}(1+10^{(pK_a-pH)})$. [d] Intrinsic solubility of the neutral base. The values were obtained from the experimental thermodynamic solubility [µg mL^{-1}] in phosphate buffer (50 mM) at pH 9.9 and 22.5 ± 1 °C, and corrected for the pK_a value. [e] Intrinsic clearance rates [min^{-1} mg^{-1} µL] measured in human (h) and mouse (m) liver microsomes. [f] Amine basicity in H_2O measured spectrophotometrically at 24 °C; for details, see the Supporting Information. [g] Data not determined as a result of the insufficient stability of compound **10**.

oxalate salt **27**. Reductive alkylation of **27** provides *N*-substituted variants of **2**. Dibromopentaerythritol can be transformed in one step into 2,6-dioxaspiro[3.3]heptane (**28**).[10] We observed that one of the oxetane rings in **28** undergoes opening by an ester enolate with ease to furnish the hydroxymethyl derivative **29**. Compound **9** was synthesized from alcohol **30** through a short three-step sequence. Collectively, these access routes offer convenient pathways to diverse compound libraries.[11]

All oxetanes were found to be chemically stable at pH 1–10 (37°C/2 h). This stability is noteworthy for the strained azetidines **2** and **6**. The introduction of the oxetane moiety into cyclic amines markedly reduces their basicity (Table 1). The shifts in the pK_a values of **3**, **5**, and **8** relative to the value for the parent piperidine **31** are $\Delta pK_a = -1.3$, -1.7, and -2.6, respectively, for γ, β, and α substitution. Similar effects are observed for the pyrrolidine **4** and the azetidine **2**. In contrast to piperidine **8**, α-oxetanes **6** and **7** are considerably less basic ($\Delta pK_a = -3.3$). X-ray crystal data and NMR spectroscopic data suggest that the attenuated basicity reduction in **8** can be attributed to its conformational preferences.[12,13]

The lipophilicity (log *D*, Table 1) of spirocycles **2**–**8** increases markedly as the oxetane unit is positioned closer to the nitrogen atom. This trend follows from the reduction in basicity, which leads to a higher proportion of the neutral species at pH 7.4. However, the intrinsic lipophilicities (log *P*) of the oxetanes are all significantly below those of the corresponding *gem*-dimethyl derivatives and those of the parent amines **31**–**33**. The pronounced polarity of the oxetane unit is a feature that is also manifested in a generally higher intrinsic solubility.

Oxetanes **2**–**8** have a higher intrinsic lipophilicity ($\Delta \log P$: 0.2–1.8) than the carbonyl derivatives **10**–**16** and, accordingly, in most cases a lower intrinsic solubility (difference in intrinsic solubility: 100–5000 μg mL^{-1}; Table 1). In general, the polarity of an oxetane unit falls between that of a *gem*-dimethyl unit and that of a carbonyl group. Although this trend also applies to amine basicity in these compounds, it does not apply to oxidative metabolic degradation, as measured by intrinsic clearance rates in human or mouse microsomal preparations (Table 1). Except for the unstrained γ- and δ-lactams **15** and **16**, which exhibit reasonably good resistance to degradation, all ketoamines (**10**–**13**) are degraded rapidly. By contrast, the oxetane derivatives display better stability, except in those cases (**6**–**8**) in which the oxetane is at the α position to the basic amine functionality, as noted previously.[3] Of particular interest are the azetidines, in which both the *gem*-dimethyl and oxetane derivatives in either position are remarkably resistant to oxidative degradation.[14]

The comparison of spirooxetane **2**, morpholine **1**, and 4-piperidone **11** reveals another interesting feature. Spirooxetane **2** is more slender than morpholine, and it displays its polar ether approximately 1.3 Å further out. Consequently, it may be regarded as a prolate morpholine, and **4**–**8** as oblate counterparts. Whereas the lone pairs of electrons on the oxygen atom in oxetane **2** and ketone **11** have the same spatial orientation, in **1** and **2** they are orthogonal (Figure 2). Furthermore, in 4-piperidone and **2** the O and N atoms are colocated. Although the two compounds exhibit comparable basicity, **2** is considerably less lipophilic, more soluble, and less sensitive to oxidative metabolic degradation than 4-piperidone. Owing to these features and its ready synthetic availability, **2**, or "homospiromorpholine", is particularly promising for further applications.

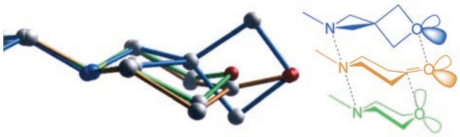


Figure 2. Superposition of three structures: the X-ray crystal structures of the *N*-benzhydryl derivative of **2** (blue; the benzhydryl group is omitted)[13] and *N*-methylmorpholine[15] (green), and a model of *N*-methyl-4-piperidone (ochre).[16] The positions of the N and O atoms in matched 4-piperidone and **2** (R = *N*-benzhydryl) differ by 0.12 and 0.16 Å, respectively.

One conclusion from this study is that the oxetane unit can be employed to access novel analogues of and expand the chemical space around morpholine. As this heterocycle is common in medicinal chemistry, we anticipate that its oxetanyl analogues will find wide use. These analogues are particularly promising in terms of both their physicochemical properties and the ease with which the oxetane functionality can be grafted onto structures. More broadly, we also suggest a novel interpretation of the oxetane functionality that draws on the structural resemblance of this unit to a carbonyl group. The data indeed highlight the position of an oxetane ring between a *gem*-dimethyl unit and a carbonyl group in terms of lipophilicity, solubility, and influence on basicity. These useful features provide new prospects for the implementation of oxetanes in molecular design, drug discovery, materials, and beyond.

Received: January 28, 2008
Published online: May 9, 2008

Keywords: carbonyl compounds · heterocycles · morpholine · oxetanes · spiro compounds

[1] J. H. van 't Hoff, *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 445.
[2] L. Pauling, *J. Am. Chem. Soc.* **1931**, *53*, 1367.
[3] G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem.* **2006**, *118*, 7900; *Angew. Chem. Int. Ed.* **2006**, *45*, 7736.
[4] M. Berthelot, F. Besseau, C. Laurence, *Eur. J. Org. Chem.* **1998**, 925.
[5] F. Besseau, M. Luçon, C. Laurence, M. Berthelot, *J. Chem. Soc. Perkin Trans. 2* **1998**, 101.
[6] The conformational aspects of a carbonyl with its attendant substituents and an oxetane have to be cautiously examined. This is particularly evident in the case of esters, lactones, amides, or lactams, where the replacement of the carbonyl group by an oxetane unit eliminates the π conjugation in the former and may result in substantially nonplanar arrangements in the latter.
[7] The parent spirocyclic piperidine derivative corresponding to **3** has been described in the patent literature,[8] and some *N*-alkyl and *N*-sulfonyl derivatives of the spirocyclic azetidine **27** have been reported.[9]
[8] a) J. L. Castro Pineiro, K. Dinnell, J. M. Elliott, G. J. Hollingworth, D. E. Shaw, C. J. Swain (Merck Sharp & Dohme, UK), WO2001087838, **2001**, p. 199; b) N. Watanabe, N. Karibe, K. Miyazaki, F. Ozaki, A. Kamada, S. Miyazawa, Y. Naoe, T. Kaneko, I. Tsukada, T. Nagakura, H. Ishihara, K. Kodama, H. Adachi (Eisai Co., Japan), WO 9942452, **1999**, p. 148.
[9] a) J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 157; b) R. K. Khazipov, N. L. Izbitskaya, T. K. Kiladze, O. B. Chalova, E. S. Kurmaeva, E. A. Kantor, *Izv. Vyssh. Uchebn. Zaved. Neft Gaz* **1984**, *27*, 86; c) F. S. Zarudii, D. N. Lazareva, E. S. Kurmaeva, O. B. Chalova, T. K. Kiladze, E. A. Kantor, D. L. Rakhmankulov, *Pharm. Chem. J.* **1985**, *19*, 108; d) C. G. Krespan, *J. Org. Chem.* **1975**, *40*, 1205.
[10] A.-R. Abdun-Nur, C. S. Issidorides, *J. Org. Chem.* **1962**, *27*, 67.
[11] For varied interpretations and the implementation of diversity in synthesis, see: a) G. Zinzalla, L.-G. Milroy, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 1977; b) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; c) R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2006**, *71*, 8329.
[12] We speculated that the *N*-piperonyl substituent in protonated **8** might adopt an axial position in aqueous solution, thus stabilizing the protonated base by juxtaposition of the *N*-proton and the oxetane O atom. Indeed, detailed $^{1}H,^{1}H$ NOE NMR spectroscopic analysis in D_2O at a low pH value confirmed the exclusive existence of the N-axial configuration of the *N*-piperonyl group. Remarkably, a similar axial configuration was also found by X-ray crystal-structure analysis for the crystalline neutral base **8**. By contrast, in the crystal structures of the neutral bases **7** and **3**, the *N*-piperonyl group occupies an equatorial position. The preference for the axial orientation of the N substituent in **8** demonstrates a strong *gauche* driving effect for the C–C-(oxetane)–N–C backbone owing to the steric requirements of the bulky oxetane unit. This steric congestion is alleviated partially in the five- and four-membered rings as a result of the increased spatial separation between vicinal groups.

[13] CCDC 675323 (**2**), CCDC 675330 (**8**), CCDC 675331 (**7**), and CCDC 675332 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[14] Metabolic liability is dependent upon the molecular environment and can thus not be quantitatively transferred to other structural contexts. This is particularly relevant when considering an incorporation into drug candidates by *N*-acylation or -sulfonylation.
[15] Q. L. Chu, Z. M. Wang, Q. C. Huang, C. H. Yan, S. Z. Zhu *New. J. Chem.* **2003**, *27*, 1522.
[16] P. R. Gerber, K. Mueller, *J. Comput.-Aided Mol. Des.* **1995**, *9*, 251; for further information, see www.moloc.ch.

