Synthesis of spiroisoxazolines through cycloadditions of nitrile oxides with 3-methylenequinuclidine

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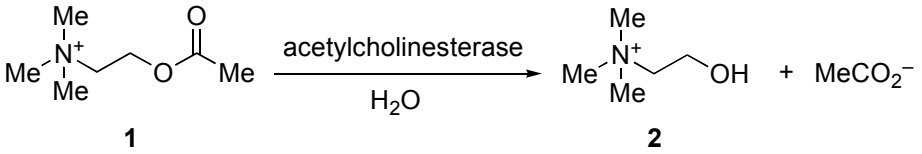
This paper is dedicated to Professor James M. Coxon (Jim) on the occasion of his 65th birthday, and in recognition of his many contributions to chemistry

Abstract
Four spiroisoxazolines have been prepared, by cycloaddition of aceto-, pivalo-, benzo- and mesito-nitrile oxide with 3-methylenequinuclidine. The reactions were completely regioselective, within the limits of detection. None of the isoxazolines showed significant inhibition of acetylcholinesterase.

Keywords: Isoxazolines, nitrile oxides, cycloadditions, quinuclidine, Alzheimer's disease, acetylcholinesterase

Introduction

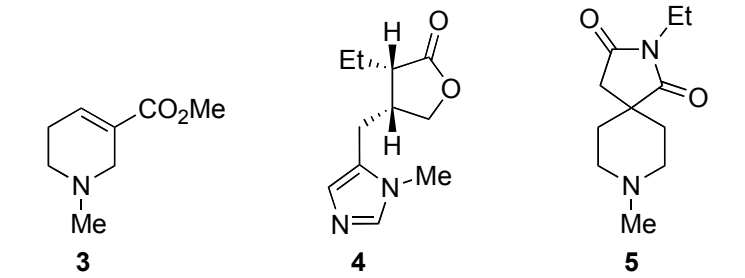
Alzheimer's disease is the most common cause of adult onset dementia.[1] It is an incurable neuropsychiatric condition, where progressive impairment of cognitive functions, as well as affective and behavioral disturbances are observed in sufferers of the disease. Through both human[2] and animal studies,[3] a direct correlation has been established between the severity of memory impairment and a decline in choline acetyltransferase activity. This enzyme is responsible for production of the neurotransmitter acetylcholine (**1**) in the brain. Consistent with this observation, compounds that increase acetylcholine (**1**) concentration are beneficial in alleviating cognitive deficits associated with the disorder[4] and, currently, the only marketed treatments for Alzheimer's disease are inhibitors of acetylcholinesterase,[5] the enzyme responsible for hydrolytic breakdown of acetylcholine (**1**) to choline (**2**) (Scheme 1).



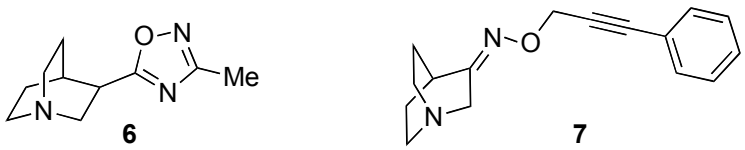
1 **2**

Scheme 1

Acetylcholine (**1**) mediates a diverse range of responses, both excitory and inhibitory, *via* muscarinic receptors in the central nervous system and periphery. An alternative approach to developing pharmaceutical agents for the treatment of Alzheimer's disease involves identifying muscarinic agonists. Clinical trials of some of these, such as arecoline (**3**),[6] pilocarpine (**4**)[7] and RS86 (**5**),[8] have shown modest alleviations of cognitive deficits in patients.[9]



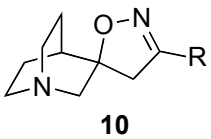
3 **4** **5**



6 **7**

8 **9**

Assays of structures bearing the quinuclidine and 1-azabicyclo[2.2.1]heptane cores tethered to oxadiazole rings and oximes, such as **6** and **7**,[10] and of compounds incorporating the quinuclidine nucleus spiro-annellated to another heterocyclic ring *via* a spirolide bridge, such as the dioxolane *cis*-AF30A (**8**)[11] and its closely related analogue, the oxathiolane *cis*-AF102B (**9**),[12] have also indicated muscarinic activity. Given the activity of these compounds, we set out to prepare the structurally related spiroisoxazolines **10a**–**d**, as potential acetylcholinesterase inhibitors and muscarinic agonists.

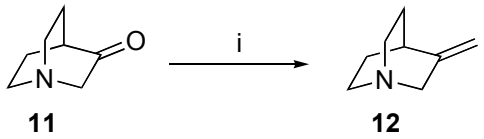


10

a R = Me
b R = *t*-Bu
c R = Ph
d R = 2,4,6-$Me_3C_6H_2$

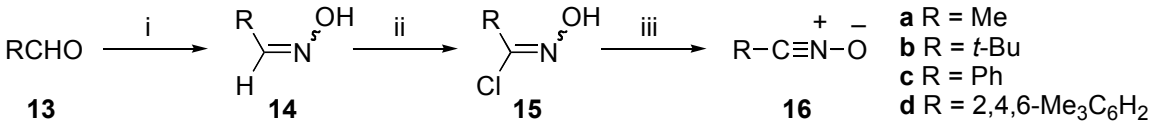
Results and Discussion

The spiroisoxazolines **10a–d** were prepared through cycloadditions of nitrile oxides with 3-methylenequinuclidine (**12**). This was obtained by base neutralization of the commercially available hydrochloride salt of the ketone **11**, followed by Wittig olefination using methyltriphenylphosphonium bromide (Scheme 2). Initially, the alkene **12** was synthesized using sodium amide as the base,[13] but better yields were obtained using *n*-butyllithium.



Scheme 2. *Reagents and conditions*: i. **11** (1.0 equiv.), $MePh_3PBr$ (2.0 equiv.), *n*-BuLi (1.5 equiv.), THF, –40°C for 40 min, reflux for 16 h.

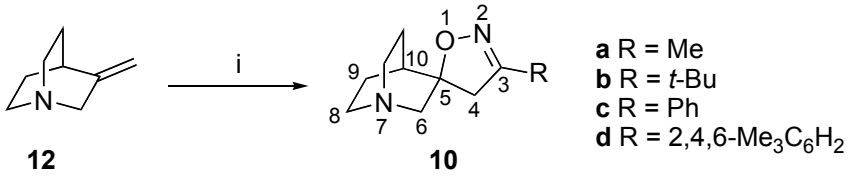
The methods used to access the nitrile oxides **16a–d** and their precursor hydroximinoyl chlorides **15a–d** are summarized in Scheme 3. Acetaldoxime (**14a**) and benzaldoxime (**14c)** were obtained commercially. Pivaldoxime (**14b**) and mesitaldoxime (**14d**) were prepared through oximation of pivaldehyde (**13b**) and mesitaldehyde (**13d**), respectively. The hydroximinoyl chlorides **15a**–**d** were prepared through chlorination of the oximes **14a**–**d** using *N*-chlorosuccinimide. Due to the propensity of the nitrile oxides **16a**–**c** to dimerize,[14] they were generated *in situ* through dehydrohalogenation of the corresponding hydroximinoyl chlorides **15a**–**c** with 3-methylenequinuclidine (**14**), which functioned as an internal base in the cycloaddition reactions. Mesitonitrile oxide (**16d**), which by contrast is inert to dimerization,[14] was pregenerated and used directly in the reaction with the dipolarophile **12**.



Scheme 3. *Reagents and conditions*: for **15a**: ii. **14a** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20–25°C, 3.5 h; for **15b**: i. **13b** (1.0 equiv.), $NH_2OH.HCl$ (1.1 equiv.), 50% w/v aq. NaOH (1.1 equiv.), 30% aq. EtOH, 18°C, 3 h; ii. **14b** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20–25°C, 3.5 h; for **15c**: ii. **14c** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20–25°C, 3.5 h; for **16d**: i. **13d** (1.0 equiv.), $NH_2OH.HCl$ (1.1 equiv.), 50% w/v aq. NaOH (1.1 equiv.), 30% aq. EtOH, 18°C, 3 h; ii. **14d** (1.0 equiv.), NCS (1.0 equiv.), DMF, 20–25°C, 3.5 h; iii. **15d** (1.0 equiv.), NEt_3 (1.2 equiv.), Et_2O, 18°C, 2 h.

Preparation of the spiroisoxazoline **10a** (Scheme 4) was initially hampered due to difficulties associated with the short half-life of acetonitrile oxide (**16a**) and the instability of the

hydroximinoyl chloride **15a**.[15] After extensive experimentation, the optimum procedure was eventually formulated. It involved addition of acetohydroximinoyl chloride (**15a**) to a two-fold excess of the alkene **12** over 48 hours at 20°C and stirring at 20°C for a further 24 hours. This was followed by addition of another equivalent of acetohydroximinoyl chloride (**15a) o**ver 48 hours, and stirring for a further 24 hours. Temperature control was crucial for reaction. To prevent decomposition of the hydroximinoyl chloride **15a**, it was kept at a temperature of 4°C whilst the reaction mixture was maintained at 20°C to promote the cycloaddition. This was accomplished by carrying out the reaction in a 4°C cold room and the reaction vessel containing the dipolarophile **12** was then kept at 20°C using a heated oil bath. This procedure afforded the spiroisoxazoline **10a** in 82% yield.



12 **10**

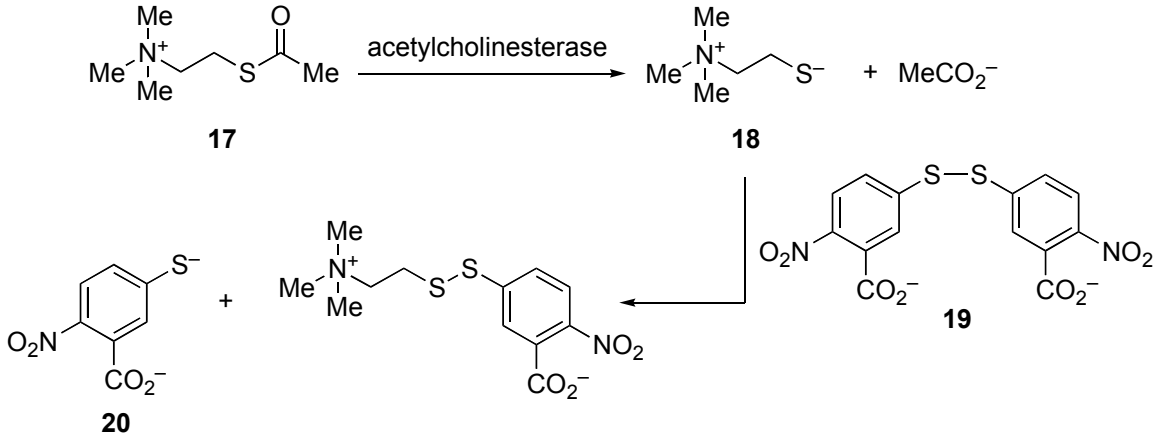
Scheme 4. *Reagents and conditions*: for **10a**: i. **15a** (0.5 equiv.) at 4°C added over 48 h, **12** (1 equiv.), CH_2Cl_2, 20°C, 24 h, **15a** (0.5 equiv.) at 4°C added over 48 h, 20°C, 24 h; for **10b**: i. **15b** (0.5 equiv.) at 4°C added over 48 h, **12** (1 equiv.), CH_2Cl_2, 20°C, 24 h, **15b** (0.5 equiv.) at 4°C added over 48 h, 20°C, 24 h; for **10c**: **15c** (0.5 equiv.) at 4°C added over 48 h, **12** (1 equiv.), CH_2Cl_2, 20°C, 24 h, **15c** (0.5 equiv.) at 4°C added over 48 h, 20°C, 24 h; for **10d**: **15d** (1 equiv.), **12** (1 equiv.), THF, reflux, 3 days.

Similar methods were used to prepare the spiroisoxazolines **10b** and **10c** (Scheme 4), which were obtained in yields of 82 and 90%, respectively. The synthesis of the mesitylspiroisoxazoline **10d** was technically more straightforward, since mesitonitrile oxide (**16d**) is much less prone to dimerization.[14] Reaction of the dipole **16d** with the alkene **12** in refluxing THF gave rise to the isoxazoline **10d** in 85% yield (Scheme 4).

The cycloadditions of the nitrile oxides **16a–d** with the alkene **12** were completely regioselective, to the extent that no other cycloadducts were detected in NMR spectra of the crude product mixtures. This may be attributed to steric effects controlling the reactions,[14] such that the oxygen of the dipoles **16a–d** becomes bonded to the most substituted olefinic carbon of the dipolarophile **12**. Good yields of the isoxazolines **10a–d** were obtained, which is particularly noteworthy for nitrile oxide cycloadditions to a 1,1-disubstituted alkene that is not activated by conjugating substituents.[14]

The spiroisoxazolines **10a–d** were evaluated as acetylcholinesterase inhibitors, using a combination of the methods developed by Ellman *et al*.,[16] and Devonshire and Moores.[17] In this assay, the iodide of acetylthiocholine (**17**) is used as the enzyme substrate. In this regard it has been shown to be a satisfactory substitute for acetylcholine (**1**) and inhibition of the enzyme is then indicated by a reduction in the rate of production of thiocholine (**18**), as detected through its

reaction with the disulfide **19** to give the yellow thionitrobenzoate anion **20** (Scheme 5). Prior to screening the activity of the spiroisoxazolines **10a**–**d**, the validity of the assay was evaluated using the known acetylcholinesterase inhibitor, Paraoxon®, which showed 89% inhibition of the enzyme when used at a concentration of 1 mg/mL. However, none of the spiroisoxazolines **10a**–**d** displayed any significant enzyme inhibition when used at this concentration. To date it has not been practical for us to investigate the activity of these compounds as muscarinic agonists.



Scheme 5

Experimental Section

General Procedures. Acetaldoxime (**14a**), pivaldehyde (**13b**), benzaldoxime (**14c**), mesitaldehyde (**13d**), the iodide of acetylthiocholine (**17**), the disulfide **19**, eserine sulfate and bovine erythrocyte acetylcholinesterase were purchased from Sigma–Aldrich Chemical Co. 3-Quinuclidinone (**11**) was prepared from the hydrochloride salt that had also been purchased from Sigma–Aldrich Chemical Co. The oximes **14b** and **14d**, the hydroximinoyl chlorides **15a–d** and the nitrile oxide **16d** were prepared using literature procedures.[18]

3-Methylenequinuclidine (12). To a stirred suspension of methyltriphenylphosphonium bromide (15.6 g, 43.5 mmol) in dry THF (150 mL) at –78°C (dry ice–acetone bath), *n*-BuLi (13.1 mL of a 2.5 M solution in hexanes, 32.7 mmol) was added dropwise. The mixture was allowed to warm to –40°C and stirred for 40 min, then it was re-cooled to –78°C (dry ice–acetone bath) and a solution of 3-quinuclidinone (**11**) (2.70 g, 21.6 mmol) in dry THF (50 mL) was added dropwise over 15 min. The mixture was then heated at reflux for 16 h, before it was cooled to 18°C and neutralized through the dropwise addition of aq. NH_4Cl (10 mL). After the solvent was removed under reduced pressure, Et_2O (500 mL) was added to the residue. The resultant suspension was filtered through a pad of celite and the filter cake was washed with Et_2O

(5 x 100 mL). The combined filtrates were concentrated to *ca.* 100 mL and that solution was extracted with 1M HCl (3 x 50 mL). The extracts were combined and washed with CH_2Cl_2 (5 x 50 mL), then adjusted to pH 12 with 1M NaOH and extracted with Et_2O (5 x 100 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried (anhydrous Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to afford the *title compound* **12**[13] (2.23 g, 84%) as a pale yellow liquid. ^{1}H NMR (300 MHz) δ 1.70 (m, 4H), 2.70 (m, 1H), 2.88 (m, 4H), 3.49 (s, 2H), 4.66 (m, 1H), 4.78 (m, 1H).

3-Methyl-1-oxa-2,7-diaza-7,10-ethanospiro[4.5]dec-2-ene (10a). In a 4°C cold room, a solution of acetohydroximinoyl chloride (**15a**) (302 mg, 3.25 mmol) in CH_2Cl_2 (10 mL) in a gas-tight syringe was added *via* a syringe pump over 48 h to a solution 3-methylenequinuclidine (**12**) (800 mg, 6.50 mmol) in dry CH_2Cl_2 (60 mL) heated to 20°C with an oil bath. After stirring at 20°C for 24 h, another solution of **15a** (302 mg, 3.25 mmol) in CH_2Cl_2 (10 mL) at 4°C was added over 48 h to the mixture and stirring was continued for a further 24 h at 20°C. The solution was then extracted with 1M HCl (3 x 75 mL). The combined extracts were washed with Et_2O (2 x 75 mL) then adjusted to pH 12 with 1M NaOH and extracted with EtOAc (5 x 75 mL). The organic extracts were combined, washed with brine (1 x 75 mL), dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the residue on silica, eluting with CH_2Cl_2:MeOH:10% aq. NH_4OH (63:21:1) afforded the *title compound* **10a** (960 mg, 82%) as a colorless oil. ^{1}H NMR (300 MHz) δ 1.38–2.10 (m, 4H), 1.97 (s, 3H), 2.40 (m, 1H), 2.68 (d, J = 17.2 Hz, 1H), 2.68–3.00 (m, 4H), 2.92 (d, J = 14.4 Hz, 1H), 3.05 (d, J = 17.2 Hz, 1H), 3.24 (d, J = 14.4 Hz, 1H). ^{13}C NMR (75.4 MHz) δ 13.4, 21.2, 23.6, 30.8, 46.3, 46.6, 48.4, 63.1, 85.3, 154.4. IR (thin film) υ_{max} 2948, 2874, 1630, 1457, 1434, 1388, 1332, 1219, 1072, 1050, 1038, 982, 897, 800, 688, 630 cm^{-1}. LRMS (EI) *m/z* (%) 180 ($M^{+\bullet}$, 0.8), 167 (6), 149 (21), 139 (63), 124 (7), 111 (3), 96 (100), 82 (43), 69 (49), 55 (44). HRMS (EI) Found *m/z* 180.1264 ($M^{+\bullet}$). $C_{10}H_{16}N_2O$ requires *m/z* 180.1263.

3-*tert*-Butyl-1-oxa-2,7-diaza-7,10-ethanospiro[4.5]dec-2-ene (10b). Using the procedure described above for the synthesis of the spiroisoxazoline **10a**, reaction of 3-methylenequinuclidine (**12**) (790 mg, 6.42 mmol) and pivalohydroximinoyl chloride (**15b**) (867 mg, 6.42 mmol) afforded the *title compound* **10b** (1.17 g, 82%) as a colorless oil, after flash column chromatography on silica, eluting with CH_2Cl_2:MeOH:10% aq. NH_4OH (63:21:1). ^{1}H NMR (300 MHz) δ 1.19 (s, 9H), 1.10–2.05 (m, 4H), 2.10–2.23 (m, 1H), 2.72 (d, J = 16.8 Hz, 1H), 2.77–3.01 (m, 4H), 2.94 (d, J = 14.5 Hz, 1H), 3.08 (d, J = 16.8 Hz, 1H), 3.26 (d, J = 14.5 Hz, 1H). ^{13}C NMR (75.4 MHz) δ 18.6, 20.3, 27.8, 29.8, 33.1, 43.8, 45.4, 45.0, 58.9, 82.4, 166.3. IR (thin film) υ_{max} 3436, 2960, 2870, 1609, 1596, 1458, 1365, 1336, 1253, 1125, 1071, 1051, 979, 894, 802, 699, 602, 502 cm^{-1}. LRMS (EI) *m/z* (%) 222 ($M^{+\bullet}$, 4), 165 (100), 149 (2), 139 (57), 122 (16), 111 (6), 96 (62), 82 (37), 69 (26), 55 (20). HRMS (EI) Found *m/z* 222.1730 ($M^{+\bullet}$). $C_{13}H_{22}N_2O$ requires *m/z* 222.1732.

3-Phenyl-1-oxa-2,7-diaza-7,10-ethanospiro[4.5]dec-2-ene (10c). Using the procedure described above for the synthesis of the spiroisoxazoline **10a**, reaction of 3-methylenequinuclidine (**12**) (300 mg, 2.44 mmol) and benzohydroximinoyl chloride (**15c**) (379

mg, 2.44 mmol) afforded the *title compound* **10c** (531 mg, 90%) as a viscous oil, after flash column chromatography on silica, eluting with CH_2Cl_2:MeOH:10% aq. NH_4OH (75:8:1). ^1H NMR (300 MHz) δ 1.42–1.55 (m, 1H), 1.56–1.98 (m, 2H), 1.99–2.03 (m, 1H), 2.21–2.30 (m, 1H), 2.76–2.98 (m, 4H), 3.03 (d, *J* = 14.5 Hz, 1H), 3.12 (d, *J* = 16.7 Hz, 1H), 3.36 (d, *J* = 14.5 Hz, 1H), 3.49 (d, *J* = 16.7 Hz, 1H), 7.38–7.48 (m, 2H), 7.60–7.68 (m, 3H). ^{13}C NMR (75.4 MHz) δ 21.9, 24.2, 31.6, 45.3, 47.0, 47.3, 63.7, 86.3, 127.0, 129.2, 130.4, 130.5, 156.2. IR (thin film) υ_{max} 3430, 2922, 2871, 1596, 1445, 1356, 1318, 1072, 1050, 1013, 980, 923, 801, 759, 692, 645, 545 cm^{-1}. LRMS (EI) *m/z* (%) 242 ($M^{+\bullet}$, 2), 165 (5), 149 (10), 139 (100), 124 (12), 117 (3), 110 (5), 103 (8), 96 (92), 82 (47), 69 (33), 55 (20). HRMS (EI) Found *m/z* 242.1418 ($M^{+\bullet}$). $C_{15}H_{18}N_2O$ requires *m/z* 242.1419.

3-(2,4,6-Trimethylphenyl)-1-oxa-2,7-diaza-7,10-ethanospiro[4.5]dec-2-ene (10d). A mixture of 3-methylenequinuclidine (**12**) (482 mg, 3.92 mmol) and mesitonitrile oxide (**16d**) (632 mg, 3.92 mmol) in dry THF (20 mL) was heated at reflux for 3 days, then it was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and the solution was extracted with 1M HCl (5 x 50 mL). The combined extracts were washed with Et_2O (2 x 50 mL), then adjusted to pH 12 with 1M NaOH and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), then they were dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the residue on silica, eluting with $CHCl_3$:MeOH:10% aq. NH_4OH (33:8:1) afforded the *title compound* **10d** (946 mg, 85%), mp 215–217°C. ^1H NMR (300 MHz) δ 1.62–1.80 (m, 2H), 1.82–1.94 (m, 1H), 2.22 (s, 6H), 2.28 (s, 3H), 2.32–2.44 (m, 1H), 2.94–3.28 (m, 5H), 3.00 (d, *J* = 17.5 Hz, 1H), 3.22 (d, *J* = 14.5 Hz, 1H), 3.30 (d, *J* = 17.5 Hz, 1H), 3.54 (d, *J* = 14.5 Hz, 1H), 6.90 (s, 2H). ^{13}C NMR (75.4 MHz) δ 18.7, 19.7, 20.3, 21.0, 30.3, 45.4, 46.0, 48.3, 59.3, 82.7, 125.1, 128.5, 136.2, 139.2, 157.6. IR (thin film) υ_{max} 3435, 2946, 2920, 2654, 2584, 1610, 1486, 1462, 1332, 1248, 1037, 1002, 890, 855, 835, 733, 667, 583 cm^{-1}. LRMS (EI) *m/z* (%) 284 ($M^{+\bullet}$, 0.7), 214 (0.4), 181 (0.3), 172 (0.5), 149 (5), 139 (100), 124 (10), 111 (7), 96 (100), 82 (49), 69 (31). HRMS (EI) Found *m/z* 284.1888 ($M^{+\bullet}$). $C_{18}H_{24}N_2O$ requires *m/z* 284.1889.

Assay for inhibition of bovine acetylcholinesterase. A solution of acetylcholinesterase in water (1 mg/mL, 1 mL) was mixed with a solution of the disulfide **19** in 0.1 M phosphate buffer at pH 7.0 (1 mg/10 mL, 5 mL). Aliquots (200 μL) of the solution, along with a 50 μL aliquot of a solution of the iodide of acetylthiocholine (**17**) in 0.1 M phosphate buffer at pH 7.0 (75 mg/mL) and a 25 μL aliquot of a solution containing either Paraoxon® or one of the spiroisoxazolines **10a–d** in DMSO (1 mg/mL) were incubated at 37°C for 10 minutes, then 25 μL of a 0.1% aqueous eserine sulfate solution was added to terminate the reaction. The extent of reaction was then determined by measuring the absorbance due to the thiolate **20** at 405 nm.

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