Imidazotriazole and Oxazolotriazole Analogs of Midaflur [4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline]

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Imidazotriazole (**5**) and oxazolotriazole (**10**) analogs of CNS depressant 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (midaflur) were prepared and found to be much less active.

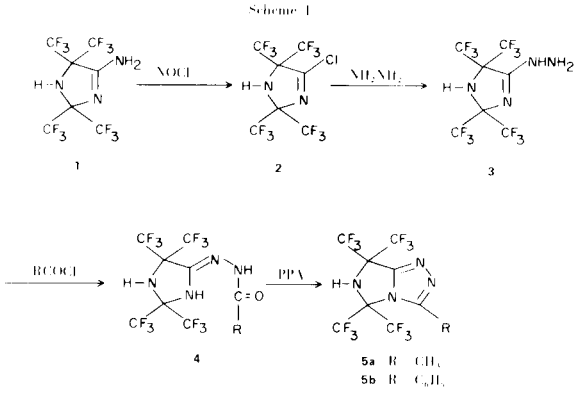
Fusion of a triazole ring to certain benzodiazepine tranquilizers is reported to give compounds of increased potency (1). We have prepared derivatives of midaflur (4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (2,3) each with a similar fused triazole ring in an attempt to modify or improve its muscle relaxant and sedative properties.

Imidazotriazoles (**5**) were prepared from midaflur (**1**) as illustrated in Scheme I. The novel feature of this synthesis is midaflur's conversion to the chloroimidazoline **2** by reaction with nitrosyl chloride in the absence of solvent. The more conventional approach to **2** by treatment of 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (2) with phosphorus pentachloride failed. Reaction of **2** with hydrazine gave **3**. Acylation of **3** and then ring closure of the resulting acyl derivatives (**4**) gave imidazotriazoles (**5**). Two derivatives of this new ring system (4) were prepared in which R = CH_3 and phenyl.

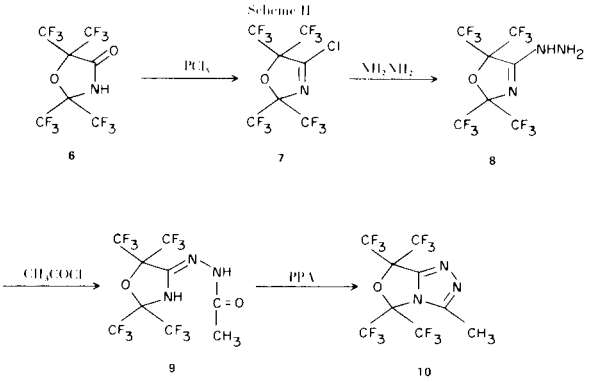
A related compound, the oxazolotriazole **10**, also represents a new ring system. It was prepared as illustrated in Scheme II. In this case, the chloride **7** was easily prepared by treating the lactam **6** (5) with phosphorus pentachloride. Sequential reactions with hydrazine, acetyl chloride, and then polyphosphoric acid gave **10**.

All three of these new triazole analogs of midaflur are appreciably less potent than midaflur as central nervous system depressants (6).

Scheme I



Scheme II



EXPERIMENTAL

Chemical Procedures.

The following are synthetic procedures for the compounds in Scheme I and II. Melting points are uncorrected and were determined with a Mel-Temp capillary melting point apparatus. Where analyses are indicated only by symbols of the elements, results do not deviate more than ±0.4% from calculated. Products were identified by ^{19}F and ^{1}H nmr, and ir spectra. All ^{19}F nmr spectra were run with fluorotrichloromethane internal std; ^{1}H nmr spectra with TMS.

4-Chloro-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**).

A 30 g. (0.45 mole) sample of nitrosyl chloride was added to a Pt-lined bomb charged with 34 g. (0.095 mole) of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**1**) (2) in a sealed glass ampul with a thin-walled fracture bubble. The bomb was shaken and warmed to 60° for 1 hour. After cooling, the excess nitrosyl chloride was vented and the residue sublimed at 25° into a Dry Ice trap (2 mm) to give 26 g. (85%) of very volatile colorless crystals, m.p. 38-39°; ir (potassium bromide): 2.88 μ (NH),

6.13 μ (C=N); ^{1}H nmr (fluorotrichloromethane): δ 3.5 (s); ^{19}F nmr (fluorotrichloromethane): δ -72.0 ppm (m, 6F), δ -76.7 (m, 6F).

Anal. Calcd. for $C_7HN_2ClF_6$: C, 22.32; H, 0.27; N, 7.44. Found: C, 22.54; H, 0.57; N, 7.24.

4-Hydrazino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**3**).

A solution of 5.6 g. (0.17 mole) of hydrazine, 2.8 g. (0.076 mole) of 4-chloro-2,2,5,5-tetrakis(trifluoromethyl)imidazoline (**2**) and 100 ml. of ether were refluxed for 3 hours. The cooled solution was washed (water), dried (magnesium sulfate), and evaporated to give 26.37 g. (95%) of the hydrazine **3**, m.p. 145-149°; ir (potassium bromide): 6.02 μ (C=N); ^{1}H nmr (DMSO-d_6): δ 7.06 (s), δ 6.45 (s) ratio 1 to 2; ^{19}F nmr (DMSO-d_6): δ -71.8 ppm (m, 6F), δ -76.6 ppm (m, 6F).

Anal. Calcd. for $C_7H_4F_{12}N_4$: C, 22.59; H, 1.08; N, 15.06; F, 61.27. Found: C, 22.76; H, 1.10; N, 15.23; F, 61.06.

4-Acetylhydrazono-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (**4a**).

Acetyl chloride (2.18 g., 0.022 mole) was added dropwise to 6.37 g. (0.017 mole) of 4-hydrazino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline in 50 ml. of ether. The temperature was kept at 30° by ice bath cooling. The slurry was stirred for 12 hours and filtered. The precipitate after an ether wash weighed 6.88 g. (98%), m.p. 209-210°; ir (potassium bromide) 2.87, 3.06 μ (NH's), 5.82, 5.97 μ (C=O, C=N); 8 μ (C-F); 7.31 μ (C-CH_3); ^{1}H nmr (DMSO-d_6): δ 1.9 (2s, 3H), δ 7.29, 7.54 (2s, 1H), δ 10.1, 9.8 (2s, 1H); ^{19}F nmr (DMSO-d_6): δ -78 ppm (m).

Anal. Calcd. for $C_9H_6F_{12}N_4O$: C, 26.10; H, 1.5; N, 13.5. Found: C, 25.6; H, 1.3; N, 13.2.

4-Benzoylhydrazono-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (**4b**).

This compound was prepared by the same method as **4a**, 6 g. (75%), m.p. 250°.

Anal. Calcd. for $C_{14}H_8N_4F_{12}O$: C, 35.31; H, 1.69; N, 11.76. Found: C, 35.55; H, 1.62; N, 11.33.

5,5,7,7-Tetrakis(trifluoromethyl)-3-methyl-6,7-dihydro-5*H*-imidazo-[5,1-*c*]-*s*-triazole (**5a**).

A slurry of 2.8 g. (0.007 mole) of 4-acetylhydrazono-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (**4a**) and 100 ml. of polyphosphoric acid was stirred vigorously at 130° for 6 hours. The light-brown solution was poured into water and filtered. Sublimation of the gray solid yielded 2.0 g. (75%) of colorless crystals, m.p. 208-209°; ir (potassium bromide) 3.17 μ (NH); 3.38 μ (sat. CH); 6.31, 6.57 μ (C=C and C=N); 8 μ (C-F); ^{1}H nmr (deuteriochloroform): δ 1.58 (s, 3H), δ 7.29 (s, 1H).

Anal. Calcd. for $C_9H_4F_{12}N_4$: C, 27.29; H, 1.02; N, 14.14. Found: C, 27.05; H, 0.93; N, 14.01.

5,5,7,7-Tetrakis(trifluoromethyl)-3-phenyl-6,7-dihydro-5*H*-imidazo-[5,1-*c*]-*s*-triazole (**5b**).

A slurry of 3 g. of 4-benzoylhydrazono-2,2,5,5-tetrakis(trifluoromethyl)imidazoline and 100 ml. of polyphosphoric acid was stirred vigorously at 130° for 4 hours. The slurry was poured into water, extracted with ether, and evaporated. Sublimation of the residue yielded 2.66 g. (93%) of white crystals, m.p. 72-80°; ir (potassium bromide): 2.72, 2.87, 3.10, 3.37 μ (NH, salt. CH), 6.10, 6.42, 6.54, 6.72 μ (conjugated C=C, C=N); ^{1}H nmr (DMSO-d_6): δ 7.6 (m, 3H), δ 8.25 (m, 2H), δ 9.15 (s, 1H); ^{19}F nmr (DMSO-d_6): δ -75 ppm (septet, 6F), δ -73 ppm (septet, 6F).

Anal. Calcd. for $C_{14}H_6F_{12}N_4$: C, 36.70; H, 1.32; N, 12.23. Found: C, 36.54; H, 0.96; N, 12.26.

4-Chloro-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**7**).

A 700 ml. Hastelloy bomb was charged with 90 g. (0.25 mole) of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone (**5**) and 55 g. (0.26 mole) of phosphorus trichloride. The evacuated bomb was heated at 200° for 16 hours. The crude product was stirred with water and the organic layer separated, washed (water), dried (magnesium sulfate), and distilled to give 52 g. (55%), b.p. 104-106° (ambient pressure); n_D^{25} = 1.3168; ir (neat); 6.12 μ (C=N); ^{19}F nmr (neat): δ -72.0 ppm (m, 6F), δ -76.5 ppm (m, 6F).

Anal. Calcd. for $C_7ClF_{12}NO$: C, 22.27; Cl, 9.39; F, 60.39; N, 3.71. Found: C, 22.10; Cl, 9.21; F, 60.58; N, 3.75.

4-Hydrazino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**8**).

This was prepared as **3** yielding 13.6 g. (73%) of a white solid, m.p. 96-100°; ir (potassium bromide): 6.00 μ (C=N), 6.55 μ (NH_2), ^{1}H nmr (DMSO-d_6): δ 8.67 ppm (s); ^{19}F nmr (DMSO-d_6): δ -77.0 ppm (m, 6F), δ -72.1 ppm (m, 6F).

Anal. Calcd. for $C_7H_3F_{12}N_3O$: C, 22.54; H, 0.81; N, 11.26; F, 61.10. Found: C, 22.53; H, 0.88; N, 11.14; F, 61.27.

4-Acetylhydrazono-2,2,5,5-tetrakis(trifluoromethyl)oxazolidine (**9**).

This was prepared as **4** yielding 12.38 g. (90%), m.p. 160-165°; ir (potassium bromide): 3.14 μ, 3.30 μ (NH's), 5.80 and 6.04 μ (C=O, C=N), 6.51 μ Amide II band, 7.26 μ (C-CH_3); ^{1}H nmr (DMSO-d_6): δ 10.05 (s, 1H-exchanges), δ 8 (s, 1H-exchanges), δ 1.92 (s, 3H); ^{19}F nmr (DMSO-d_6): δ -72.5 ppm (6F), δ -77.5 ppm (6F).

Anal. Calcd. for $C_9H_5F_{12}N_3O_2$: C, 26.05; H, 1.21; N, 10.12. Found: C, 25.92; H, 1.18; N, 9.83.

5,5,7,7-Tetrakis(trifluoromethyl)-3-methyl-6,7-dihydro-5*H*-oxazolo[4,3-*c*]-*s*-triazole (**10**).

This was prepared in the manner of **5b** yielding 1.8 g. (25%) very volatile colorless solid, m.p. 30°; ir (nujol): 6.45, 6.62 μ (C=C and C=N); ^{1}H nmr (deuteriochloroform): δ 2.7 (septet, J = 0.8 cps); ^{19}F nmr (deuteriochloroform): δ -75.3 ppm (septet, 3F), δ -76.7 ppm (septet, 3F).

Anal. Calcd. for $C_9H_3F_{12}N_3O$: C, 27.22; H, 0.76; N, 10.58. Found: C, 27.18; H, 1.15; N, 10.44.

REFERENCES

(1) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, 14, 1078 (1971).

(2) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, 35, 1480 (1970).

(3) R. Clark, T. E. Lynes, W. A. Price, D. H. Smith, J. K. Woodward, J. P. Marvel, and V. G. Vernier, *Toxicol. Appl. Pharmacol.*, 18, 917 (1971).

(4) H. W. Heine, A. B. Smith, H, and J. D. Bower, *J. Org. Chem.*, 33, 1097 (1968) reports the preparation of diethyl 5,7a-dihydro-5,5-dimethyl-3-(*p*-nitrophenyl)-7-phenyl-1*H*-imidazo[5,1-*c*]-*s*-triazole-1,2(3*H*)dicarboxylate. This compound has a ring system containing atoms in the same arrangement but in a different state of oxidation than **5**.

(5) W. J. Middleton, D. Metzger, and K. B. Cunningham, *J. Fluorine Chem.*, 1, 69 (1971/1972).

(6) V. G. Vernier, Private Communication.