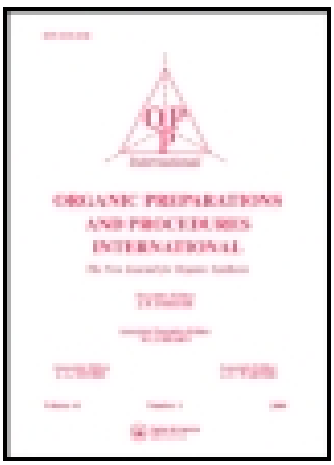

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A SHORT SYNTHESIS OF THE NATURALLY OCCURRING 2,3,3′,4,4′,5,5′-HEPTACHLORO- ("Q1") AND HEPTABROMO-1′-METHYL-1,2′-BIPYRROLES

Liangfeng Fu [a] & Gordon W. Gribble [a]
[a] Department of Chemistry , Dartmouth College , Hanover, New Hampshire, 03755, USA Phone: +001 603 646 3118 E-mail:
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S. C. Turner and H. Rapoport, *J. Org. Chem.*, **66**, 7078 (2001).

7. (a) A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 14844 (2002). (b) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto and K. Tanaka, *J. Am. Chem. Soc.*, **128**, 8404 (2006).

8. M. Conrad and L. Limpach, *Ber.*, **20**, 944 (1887).

9. A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 113 (1946).

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A SHORT SYNTHESIS OF THE NATURALLY OCCURRING 2,3,3',4,4',5,5'-HEPTACHLORO- ("Q1") AND HEPTABROMO-1'-METHYL-1,2'-BIPYRROLES

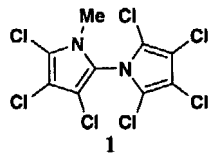
Submitted by Liangfeng Fu and Gordon W. Gribble*
(09/04/08)

Department of Chemistry
Dartmouth College
Hanover, New Hampshire 03755, USA
Tel. +001 603 646 3118; E-mail: ggribble@dartmouth.edu

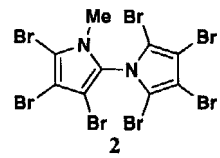
Of the more than 4,500 known naturally occurring organohalogen compounds[1] the halogenated bipyrroles are among the most interesting. For example, hexabromo-1,1'-dimethyl-2,2'-bipyrrole and 3,3',4,4'-tetrabromo-5,5'-dichloro-1,1'-dimethyl-2,2'-bipyrrole are present in the eggs of Pacific and Atlantic Ocean seabirds (albatross, puffin, gull, petrel, auklet) and in bald eagle liver samples,[2,3] and, more recently, 2,3,3',4,4',5,5'-heptachloro-1'-methyl-1,2'-bipyrrole (designated "Q1") (**1**) is found to be a ubiquitous marine natural product, detected in over 100 environmental marine samples from virtually all over the world (sea bird eggs, fish, the blubber of marine mammals, Antarctic air, and, remarkably, human milk from Eskimo women who consume whale blubber).[4] Although we established the structure of Q1 by total synthesis in 2002, the yield was very low due to the difficulty of synthesis and instability of the key intermediate 1,2'-bipyrrolyl **4**.[5] Subsequently, many mixed halogenated 1,2'-bipyrrolyls have been detected in a myriad of marine sources.[6] For example, 2,3,3',4,4',5,5'-heptabromo-1'-methyl-1,2'-bipyrrole (**2**) was tentatively identified in 2006.[6b,c]

To provide a more efficient synthesis of Q1 (**1**) for much needed analytical comparison and biological evaluation in view of its structural similarity to anthropogenic polychlorinated

biphenyls (PCBs), and to corroborate the proposed structure of **2**, we now report both an improved synthesis of **1** and the first synthesis of **2** from the readily available 2-nitropyrrole.[7] Our synthesis makes use of our recently reported tin-mediated reductive-acylation of 1-methyl-2-nitropyrrole (**3**).[7]

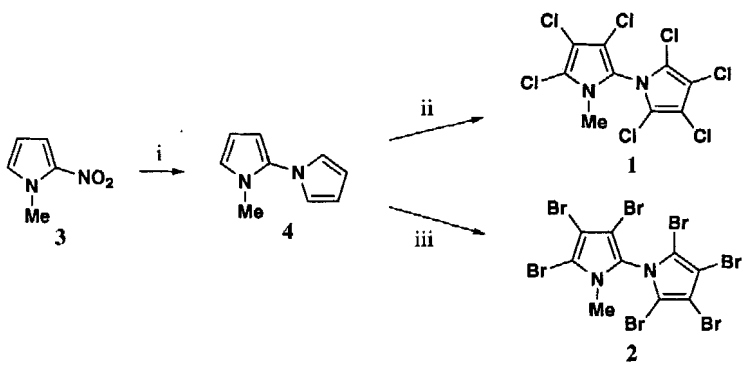


1



2

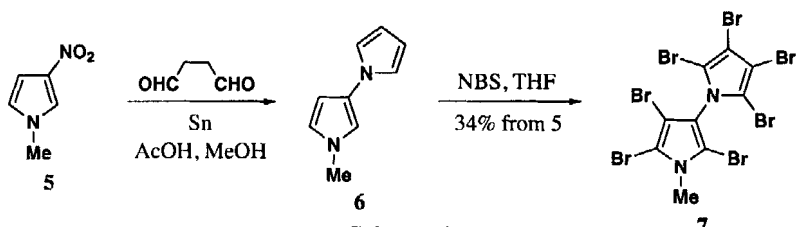
Treatment of nitropyrrole **3** with tin, acetic acid, and succinaldehyde[8] in a 1:1 mixture of methanol and dichloroethane affords bipyrrole **4**, which upon further treatment with *N*-chlorosuccinimide in THF affords Q1 (**1**) in 23% yield from **3** (*Scheme 1*). Likewise, the newly isolated 2,3,3',4,4',5,5'-heptabromo-1'-methyl-1,2'-bipyrrole (**2**) is synthesized for the first time in 31% yield from nitropyrrole **3**, and is identical to the natural product by direct comparison (mass spectral and gas chromatographic data).



i) Sn, AcOH, succinaldehyde, MeOH, $(CH_2Cl)_2$, 60°C; ii) NCS, THF, -78°C to 0°C (23% in 2 steps); iii) NBS, THF, -78°C to 0°C (31% in 2 steps)

Scheme 1

We also synthesized the corresponding unnatural heptahalogenated 1,3-bipyrrolyl **7** from the readily available 1-methyl-3-nitropyrrole (**5**).[7] When **6** was treated with *N*-bromosuccinimide (NBS) in THF, the desired heptabromo-1,3'-bipyrrole **7** was obtained in 34% yield from **5** (*Scheme 2*).



Scheme 2

In conclusion, we have described a simple two-step synthesis of the natural polychlorinated 1,2'-bipyrrolyl Q1 (**1**), and the first syntheses of the related polybrominated 1,2'-bipyrrolyl **2** and the unnatural isomeric polybrominated bipyrrolyl **7** from readily available 2- and 3-nitropyrroles, a sequence that should make these compounds available for comparison with environmental samples.

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen and anhydrous conditions. All solvents were used as received. Flash chromatography was carried out on SiO_2. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvent was accomplished with a rotary evaporator. Melting points were determined with a Mel-Temp Laboratory Device apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or acetone *d*-6 on a Varian 500 MHz Fourier transform NMR spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (*d*) from Me_4Si. Atlantic Microlabs in Norcross, GA, USA, performed elemental analyses. Both low- and high-resolution mass spectra were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign, USA.

2,3,3',4,4',5,5'-Heptachloro-1'-methyl-1,2'-bipyrrole (1).- To a mixture of 1-methyl-2-nitropyrrole (**3**) (0.10 g, 0.80 mmol) and granulated tin (0.47 g, 4.0 mmol) was added acetic acid (1 mL), methanol (3 mL), dichloroethane (3 mL) and succinaldehyde (0.80 g, 8.0 mmol). The resulting mixture was heated to 60°C under nitrogen, and the progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction (about 1 h), the reaction mixture was cooled to room temperature and transferred to a beaker. Saturated aqueous $NaHCO_3$ solution was added until the mixture was no longer acidic. The mixture was extracted with EtOAc (5 x 15 mL), washed with brine, and dried over Na_2SO_4. Removal of the solvent gave crude 1'-methyl-1,2'-bipyrrole (**4**) that was used in the next step without further purification. To a solution of **4** in dry THF (25 mL) at –78°C under nitrogen was added *N*-chlorosuccinimide (0.75 g, 5.6 mmol) in portions, and the resulting mixture was stirred and allowed to warm to 0°C over 5 days. The solvent was removed, and the residue was passed through a short silica column using 8:1 hexanes: EtOAc. The solvent was removed and the residue was redissolved in dry THF (25 mL) and cooled to –78°C, and additional *N*-chlorosuccinimide (0.21 g, 1.6 mmol) was added in portions, and the reaction mixture was allowed to warm to 0°C under nitrogen. The progress of the reaction was monitored by GC-MS. After completion of the reaction (1-2 h), the solvent was removed and flash chromatography over hexanes: EtOAc (100:1) gave product **1** as a white solid (0.070 g, 0.18 mmol, 23% from **3**), mp. 160.5-161.5°C (*lit.*[5] mp. 154-155.5°C); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 116.8, 115.9, 115.4, 111.4, 111.3, 108.5, 31.7; MS (EI): *m/z* (%) = 386 ([M^+]), 371, 351 (100), 336, 316, 281, 266, 244, 208, 193, 175, 155, 141, 118, 106, 76; HRMS (EI): *m/z* calcd for $C_9H_3N_2Cl_7$: 383.8116. Found: 383.8115. *Anal.* Calcd for $C_9H_3N_2Cl_7$: C, 27.91; H, 0.78; Cl, 64.08; N, 7.23.

Found: C. 27.89; H, 0.68; Cl, 63.94; N, 7.04

2,3,3',4,4',5,5'-Heptabromo-1'-methyl-1,2'-bipyrrole (2).- To a mixture of 1-methyl-2-nitropyrrole (**3**) (0.10 g, 0.80 mmol), and granulated tin (0.47 g, 4.0 mmol) was added acetic acid (1 mL), methanol (3 mL), dichloroethane (3 mL) and succinaldehyde (0.80 g, 8.0 mmol). The resulting mixture was heated to 60°C under nitrogen and the progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction (0.5-1 h), the reaction mixture was cooled to room temperature and transferred to a beaker. Saturated aqueous $NaHCO_3$ solution was added until the mixture was no longer acidic. The solution was extracted with EtOAc (5 x 15 mL), washed with brine, and dried over Na_2SO_4. Removal of the solvent gave the crude 1'-methyl-1,2'-bipyrrole (**3**) that was used in the next step without further purification. A solution of **3** in dry THF (25 mL) was cooled to –78°C under nitrogen and *N*-bromosuccinimide (1.0 g, 5.6 mmol) was added in portions. The mixture was stirred and allowed to warm to 0°C over 5 days. The solvent was removed, and the residue was passed through a short silica gel column using 8:1 hexanes:EtOAc. The solvent was removed and the residue was redissolved in dry THF (25 mL) and cooled to –78°C, and additional *N*-bromosuccinimide (0.28 g, 1.6 mmol) was added slowly in portions, and the reaction mixture was allowed to warm to 0°C under nitrogen. The progress of the reaction was monitored by GC-MS. After completion of the reaction (2-3 h), the solvent was removed and flash chromatography over hexanes:EtOAc (100:1) gave product **2** as a white solid (0.17 g, 0.25 mmol, 31% from **3**), mp. 198-199°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 123.9, 106.6, 105.4, 104.5, 100.9, 100.5, 34.2; MS (EI): *m/z* (%) = 699 ([M$^+$]), 618 (100), 538, 459, 378, 298, 248, 222, 208, 167, 149, 77; HRMS (EI): *m/z* calcd for $C_9H_3N_2Br_7$: 691.4579. Found: 691.4580. This material was identical by direct comparison with the natural material by gas chromatographic retention time and mass spectroscopy.

Anal. Calcd for $C_9H_3N_2Br_7$: C, 15.48; H, 0.43; Br, 80.08; N, 4.01
Found: C. 16.09; H, 0.39; Br, 79.63; N, 3.98

2,2',3,4,4',5,5'-Heptabromo-1'-methyl-1,3'-bipyrrole (7).- To a mixture of 1-methyl-3-nitropyrrole (**5**) (0.10 g, 0.80 mmol), and granulated tin (0.47 g, 4.0 mmol) was added acetic acid (1 mL), methanol (5 mL) and succinaldehyde (0.80 g, 8.0 mmol). The resulting mixture was heated to 60°C under nitrogen and the progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction (0.5-1 h), the reaction mixture was cooled to room temperature and transferred to a beaker. Saturated aqueous $NaHCO_3$ solution was added until the mixture was no longer acidic. The solution was extracted with EtOAc (5 x 15 mL), washed with brine, and dried over Na_2SO_4. Removal of the solvent gave crude 1'-methyl-1,3'-bipyrrole (**6**) that was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (dd, *J* = 0.7, 1.3 Hz, 2H), 6.67 (m, 1H), 6.53 (dd, *J* = 0.9, 1.7 Hz, 1H), 6.25 (dd, *J* = 0.7, 1.3 Hz, 2H), 6.20 (dd, *J* = 0.9, 1.4 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 128.0, 121.2, 120.4, 112.1, 108.8, 102.2, 36.9; MS (EI): *m/z* (%) = 146 ([M$^+$], 100), 131, 118, 104, 91, 78; HRMS (EI): *m/z* calcd for $C_9H_{10}N_2$: 146.0844. Found: 146.0844. To a solution of **6** in dry THF (25 mL) at –78°C under nitrogen was added *N*-bromosuccinimide (1.0 g, 5.6 mmol) in portions, and the resulting mixture was stirred and allowed to warm to 0°C over 5 days. The solvent was removed and the residue was passed through a short silica gel column using 8:1 hexanes:EtOAc.

The solvent was removed and the residue was redissolved in dry THF (25 mL) and cooled to –78°C. To the residue was slowly added additional *N*-bromosuccinimide (0.28 g, 1.6 mmol), and the reaction mixture was allowed to warm to 0°C under nitrogen. The progress of the reaction was monitored by GC-MS. After the completion of the reaction (2-3 h), the solvent was removed and flash chromatography over hexanes:EtOAc (100:1) gave **7** as a white solid (0.19 g, 0.28 mmol, 34% from **5**), mp. 228.5-229.5°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 121.7, 106.0, 104.5, 103.7, 103.1, 99.5, 36.7; MS (EI): *m/z* (%) = 697 ([M$^+$]), 618 (100), 577, 538, 497, 459, 382, 362, 309, 275, 229, 208, 149, 111, 71; HRMS (EI) *m/z* calcd for $C_9H_3N_2Br_7$: 691.4579. Found: 691.4579.

Anal. Calcd for $C_9H_3N_2Br_7$: C, 15.48; H, 0.43; Br, 80.08; N, 4.01
Found: C. 15.67; H, 0.33; Br, 80.21; N, 4.00

Acknowledgement.- We thank Dr. Chris Reddy and Kristin Smith (Woods Hole Oceanographic Institution) for comparing synthetic **2** with the natural product isolated from dolphin blubber (*Delphinus delphis*). We also thank the donors of the Petroleum Research Fund administrated by the American Chemical Society, and Wyeth for the support of this work.

REFERENCES

1. (a) G. W. Gribble, Unpublished compilation and *Prog. Chem. Org. Nat. Prod.*, In preparation; (b) G. W. Gribble, *Chemosphere*, **52**, 289 (2003); (c) G. W. Gribble, *Amer. Sci.* **92**, *92*, 342 (2004); (d) G. W. Gribble, *Prog. Chem. Org. Nat. Prod.* **68**, 1 (1996).

2. S. A. Tittlemier, M. Simon, W. M. Jarman, J. E. Elliott and R. J. Norstrom, *Environ. Sci. Technol.* **33**, 26 (1999). For more recent examples of these halogenated bipyrroles, see S. A. Tittlemier, D. H. Blank, G. W. Gribble and R. J. Norstrom, *Chemosphere* **46**, 511 (2002). For the isolation of 3,3',4,4',5,5'-hexabromo-2,2'-bipyrrole from the marine bacterium *Chromobacterium* sp., see R. J. Andersen, M. S. Wolfe and D. J. Faulkner, D. J. *Mar. Biol.* **27**, 281 (1974).

3. G. W. Gribble, D. H. Blank and J. P. Jasinski, *Chem. Commun.*, 2195 (**1999**).

4. (a) W. Vetter, *Organohalogen Compd.* **43**, 433 (1999); (b) W. Vetter, E. Scholz, C. Gaus, J. F. Muller and D. Haynes, *Arch. Environ. Contam. Toxicol.* **41**, 221 (2001); (c) W. Vetter, *Chemosphere* **46**, 1477 (2002); (d) W. Vetter, *Organohalogen Compd.* **59**, 271 (2002); (e) W. Vetter and E. Stoll, *Eur. Food Res. Technol.* **215**, 523 (2002); (f) W. Vetter and J. Wu, *Anal. Chem.* **74**, *74*, 4287 (2002); (g) W. Vetter, J. Wu and A. Gerhard, *Chemosphere* **52**, 415 (2003); (h) W. Vetter and J. Wu, *Chemosphere* **52**, 423 (2003); (i) W. Kurt and G. Helmut, *Chemosphere* **53**, 667 (2003); (j) W. Vetter, M. E. Hahn, G. Tomy, S. Ruppe, S. Vatter, N. Chahbane, D. Lenoir, K.-W. Schramm and G. Scherer, *Arch. Environ. Contam. Toxicol.* **48**, 1 (2005); (k) W. Vetter, *Rev. Environ. Contam. Toxicol.* **188**, 1 (2006); (l) W. Vetter and G. Gleixner, *Rapid Commun. Mass Spectrom.* **20**, 3018 (2006); (m) S. Gaul and W. Vetter, *Chemosphere* **70**, 1721 (2008).

5. J. Wu, W. Vetter, G. W. Gribble, J. S. Schneekloth, Jr., D. H. Blank and H. Gorls, *Angew. Chem. Int. Ed.* **41**, 1740 (2002).

6. (a) W. Vetter and J. Wu, *Chemosphere* **52**, 423 (2003); (b) E. L. Teuten, B. E. Pedler, A. N. Hangsterfer and C. M. Reddy, *Environ. Pollut.* **144**, 336 (2006); (c) E. L. Teuten, R. Saint-Louis, B. E. Pedler, L. Xu, E. Pelletier and C. M. Reddy, *Mar. Pollut. Bull.* **52**, 572 (2006); (d) W. Vetter, S. Gaul, D. Olbrich and C. Gaus, *Chemosphere* **66**, 2011 (2007); (e) E. L. Teuten and C. M. Reddy, *Environ. Pollut.* **145**, 668 (2007); (f) K. Pangallo, R. K. Nelson, E. L. Teuten, B. E. Pedler and C. M. Reddy, *Chemosphere* **71**, 1557 (2008).

7. (a) L. Fu and G. W. Gribble, *Synthesis*, 788 (**2008**); (b) L. Fu and G. W. Gribble, *Tetrahedron Lett.* **48**, 9155 (2007); (c) L. Fu and G. W. Gribble, *Tetrahedron Lett.* **49**, 3545 (2008).

8. (a) H. O. House and T. H. Cronin, *J. Org. Chem.* **30**, 1061 (1965); (b) R. Mueller, J. Yang, C. Duan, E. Pop, L. H. Zhang, T. Huang, A. Denisenko, O. V. Denisko, D. C. Oniciu, C. L. Bisgaier, M. E. Pape, C. D. Freiman, B. Goetz, C. T. Cramer, K. L. Hopson and J. H. Dasseux, *J. Med. Chem.* **47**, 5183 (2004).

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SYNTHESIS OF SUBSTANCES RELATED TO FLUTICASONE PROPIONATE

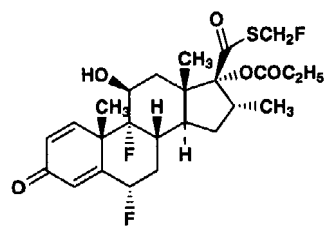
Submitted by (03/27/08) Jin Zheng,† Qinglin Lai,† Yiru Dai,‡ Qingjie Zhao† and Jingshan Shen*†

† Shanghai Institute of Materia Medica, Chinese Academy of Sciences Shanghai 201203, P. R. CHINA

‡ Topharman Shanghai Co., Ltd., Shanghai 201209, P. R. CHINA

E-mail: jsshen@mail.shcnc.ac.cn

Related substances or impurities of active pharmaceutical ingredients (API) are important issues in process development, manufacturing and quality control of pharmaceutical compounds. In addition to drug efficacy, there is a strong emphasis on the purity of final drug substances and it is necessary to do full characterization and identification of any impurities to ensure the drug safety in clinical trials.[1] Fluticasone propionate is widely used for the treatment of allergy and inflammatory disorders,[2-4] and analysis and control of impurities are important to clinical safety. Gram-scale amounts of such impurities were required by quality control (QC) department as markers to locate the known related substances in fluticasone. The preparation of



Fluticasone Propionate