Synthesis and identification of two halogenated bipyrroles present in seabird eggs

Gordon W. Gribble,*[a] and David H. Blank[a] and Jerry P. Jasinski[b]

[a] *Department of Chemistry, Dartmouth College, Hanover, NH 03755-3564, USA. E-mail: grib@dartmouth.edu*
[b] *Department of Chemistry, Keene State College, Keene, NH 03435-2001, USA*

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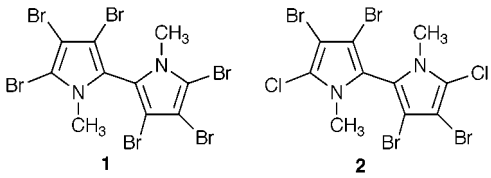
Two of the four halogenated bipyrroles recently discovered in seabird eggs and eagle liver samples have been identified by synthesis as 1,1′-dimethyl-3,3′,4,4′,5,5′-hexabromo-2,2′-bipyrrole 1 and 5,5′-dichloro-1,1′-dimethyl-3,3′,4,4′-tetrabromo-2,2′-bipyrrole 2, and the structure of the latter compound, which is the major component in the mixture, is further confirmed by X-ray crystallography.

Although more than 3200 naturally occurring organohalogen compounds are now known to exist,[1] most of these are produced by marine organisms, bacteria, fungi and terrestrial plants. Very few have been found in higher animals. The recent report[2] of the presence of several novel halogenated bipyrroles in the eggs of Pacific and Atlantic Ocean seabirds (albatross, puffin, gull, petrel, auklet) and in bald eagle liver samples dramatically reveals that natural organohalogen compounds are more pervasive in the environment than previously believed.

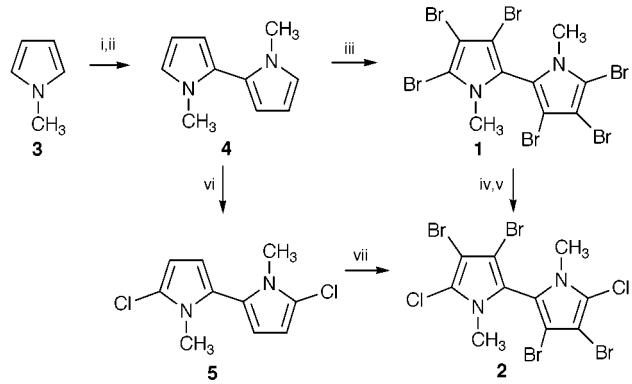
Although sufficient material was not available for full characterization of these compounds, low- and high-resolution mass spectrometry tentatively identified the four major groups of compounds, $C_{10}H_6N_2Br_4Cl_2$, $C_{10}H_6N_2Br_6$, $C_{10}H_6N_2Br_5Cl$ and $C_{10}H_6N_2Br_3Cl_3$, as hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles.[2] We now describe the synthesis and identification of two congeners in this mixture as 1,1′-dimethyl-3,3′,4,4′,5,5′-hexabromo-2,2′-bipyrrole **1** and 5,5′-dichloro-1,1′-dimethyl-3,3′,4,4′-tetrabromo-2,2′-bipyrrole **2**, and establish their probable identity with the two major compounds found in seabird eggs. Bipyrrole **2** appears to be the major seabird compound and is present, for example, in bald eagle liver at a concentration up to 140 ppb.



We began with the premise that the compound with molecular formula $C_{10}H_6N_2Br_6$ would have structure **1** and that, given the propensity of pyrroles to undergo electrophilic substitution at C-2, compound $C_{10}H_6N_2Br_4Cl_2$ most likely would have structure **2**. This proved to be correct. Our syntheses of **1** and **2** are shown in Scheme 1.

The known[3] 1,1′-dimethyl-2,2′-bipyrrole **4**, which is readily available from 1-methylpyrrole **3**, was treated with excess NBS to give **1**† in 79% yield. Regioselective halogen–lithium exchange to give the presumed more stable 5,5′-dilithio intermediate followed by chlorination with 2 equiv. of hexachloroethane[4] gave **2**† in 80% yield. The structures of **1** and **2** are fully established by spectral and analytical data, and the X-ray crystallographic molecular structure of **2**‡ is shown in Fig. 1. Compound **2** was also prepared by treating **4** with NCS to give **5**‡ (97% yield). Reaction of **5** with excess NBS afforded **2** in 76% yield, identical with the material prepared from **1**. A one pot reaction of **4** first with NCS and then NBS was less successful and led to a mixture.[5] Interestingly, this mixture closely matched by GC-MS the natural product mixture from the seabirds that contains several other halogenated bipyrroles of formulas $C_{10}H_6N_2Br_4Cl_2$, $C_{10}H_6N_2Br_5Cl$ and $C_{10}H_6N_2Br_3Cl_3$, perhaps implicating a somewhat random biological halogenation sequence involving first chlorination with chloroperoxidase and then bromination with bromoperoxidase.[1] In any event, based on a data set of retention times derived from a series of chromatograms, compounds **1** and **2** are the probable compounds found in the seabirds.[6]

The presumed dietary origin of these halogenated bipyrroles is unknown, although it is relevant that 3,3',4,4',5,5'-hexabromo-2,2'-bipyrrole has been isolated from the marine bacterium *Chromobacterium* sp. along with 2,3,4,5-tetrabromopyrrole.[7] Furthermore, several polybrominated 1-methylpyrroles and polychlorinated pyrroles are produced naturally.[1] Compound **2** and the other as yet unidentified mixed



Scheme 1 *Reagents and conditions*: i, BuLi; ii, $NiCl_2$ (55% for 2 steps); iii, NBS (7 equiv.), −78 °C to room temp. (79%); iv, BuLi; v, Cl_3CCCl_3, −78 °C to room temp. (80% for 2 steps); vi, NCS (2 equiv.), −78 °C to room temp. (97%); vii, NBS (5 equiv.), −78 °C to room temp. (76%).

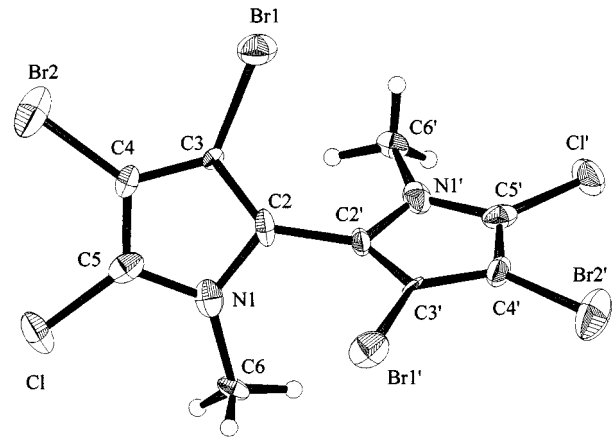
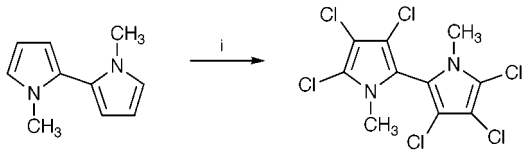


Fig. 1 ORTEP view of the molecular structure of **2.** Thermal ellipsoids are drawn at the 30% probability level. The dihedral angles between the pyrrole ring planes are 67 and 106°.



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Scheme 2 *Reagents and conditions*: i, NCS (7 equiv.), −78 °C to room temp. (91%).

bromochlorobipyrroles represent the first examples of naturally occurring pyrroles containing both chlorine and bromine.[8]

We have also synthesized the hexachloro analogue **6**† by treating **4** with excess NCS (Scheme 2). The use of sulfuryl chloride in chlorinations of **4** to give either **5** or **6** was less successful.

The obvious relationship of these polyhalogenated bipyrroles to polychlorinated biphenyls (PCBs) leads one to wonder if the former natural compounds will have similar toxicity profiles to the anthropogenic PCBs. One further wonders if some of the earlier reports of anthropogenic chlorinated compounds in seabirds, fish, and marine mammals were in reality describing, at least in part, naturally occurring organohalogen compounds.

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Notes and references

† *Selected data* for **1**: mp 247–248 °C; δ_H(300 MHz, $CDCl_3$) 3.50 (s, 6 H); δ_C($CDCl_3$) 122.5, 107.0, 103.6, 101.5 and 35.7; *m*/*z* (M^+) 628, 630, 632, 634, 636, 638, 640 (1:6:15:20:15:6:1); (M^+ − Br) 550, 552, 554, 556, 558, 560 (1:5:10:10:5:1); (M^+ − $Br)_2$ 472, 474, 476, 478, 480 (1:4:6:4:1) (Calc. for $C_{10}H_6N_2Br_6$: C, 18.96; H, 0.95; N, 4.42; Br, 75.67. Found: C, 19.19; H, 0.93; N, 4.42; Br, 75.44%). For **2**: mp 221 °C (decomp.); δ_H(500 MHz, $CDCl_3$) 3.46 (s, 6 H); δ_C($CDCl_3$) 121.0, 119.6, 103.6, 98.1 and 34.3; *m*/*z* (M^+) 544, 424, 384, 192, 139 (Calc. for $C_{10}H_6N_2Br_4Cl_2$: C, 22.05; H, 1.11; N, 5.14; Cl, 13.02; Br, 58.68. Found: C, 23.06; H, 1.18; N, 5.21; Cl, 12.80; Br, 57.72%). For **4**: oil; δ_H(300 MHz, $CDCl_3$) 3.60 (s, 3 H), 6.27 (m, 4 H) and 6.80 (m, 2 H); δ_C($CDCl_3$) 125.4, 122.9, 110.8, 107.6 and 34.7; *m*/*z* (M^+) 160, 159, 145, 132, 118. 117. For **5**: oil which solidified slowly; δ_H(500 MHz, DMSO-d_6) 3.36 (s, 6 H), 6.18 (m, 4 H); δ_C(DMSO-d_6) 125.2, 117.3, 111.6, 107.1 and 32.6; *m*/*z* (M^+) 228, 213, 193, 178, 152; (M^+) 228, 230, 232 (5:3:1); (M^+ − CH_3 213, 215, 217 (5:3:1); (M^+ − Cl) 193, 195 (3:1); (M^+ − CH_3 − Cl) 178, 180 (3:1); (M^+ − CH_3 − N − CCl) 152, 154 (3:1). For **6**: mp 209 °C (decomp.); δ_H(300 MHz, $CDCl_3$) 3.46 (s, 6 H); δ_C($CDCl_3$) 116.8, 116.7, 113.8, 108.7 and 33.1; *m*/*z* (M^+) 364, 366, 368, 370, 372 (3:5:4:2:1) (Calc. for $C_{10}H_6N_2Cl_6$: C, 32.74; H, 1.65; N, 7.64; Cl, 57.98. Found: C, 32.85, H, 1.67; N, 7.61; Cl, 57.83%).

‡ *Crystal data* for **2**: The compound crystallized from acetone as cloudy white prismatic crystals in the orthorhombic system *Pbcn* (#60). Unit cell dimensions are as follows: a = 12.438(6), b = 8.753(6), c = 13.696(3) Å, V = 1491(1) $Å^3$, Z = 4. The crystal data were collected on an AFC6S diffractometer, Mo-Kα radiation, at 296 K. Total data collected = 1460 and 310 with $I > 4\sigma(I)$. Full-matrix least-squares refinement based on F^2 of 82 parameters has an agreement value, $R1$, of 0.047 and a weighted R ($wR2$) of 0.248. The error of fit is 0.92 and the maximum residual density is 0.73 e $Å^3$. CCDC 182/1425.

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