

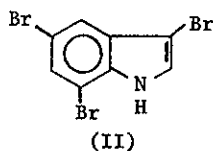
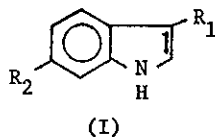
SYNTHESIS AND PROPERTIES OF 6-BROMO-3-CHLORO-
AND OF 3,5,7-TRIBROMOINDOLE[†]

Tatsuo Higa and Paul J. Scheuer^{*}

Department of Chemistry, University of Hawaii
at Manoa, Honolulu, HI 96822

We synthesized 6-bromo-3-chloro- and 3,5,7-tribromoindole,
two marine metabolites first isolated from the invertebrate
Ptychodera flava laysanica (Hemichordata).

Our search for the substance(s) responsible for the reputedly iodoform-
like odor of the marine invertebrate Ptychodera flava laysanica Spengel
(Hemichordata)¹ led to the isolation of four halogenated indoles. 3-Chloro-
indole (Ia), present in the animal in $3 \times 10^{-4}\%$, and the trace constituent



- a $R_1 = \text{Cl}, R_2 = \text{H}$
- b $R_1 = \text{Br}, R_2 = \text{H}$
- c $R_1 = \text{Cl}, R_2 = \text{Br}$

3-bromoindole (Ib) are responsible for the odor of the animals,² while 6-bromo-
3-chloro- (Ic) and 3,5,7-tribromoindole (II) are virtually odorless. We wish
to report the synthesis and properties of (Ic) and (II), which had not pre-
viously been reported as natural or synthetic compounds.

[†] Dedicated to Professor Tsunematsu Takemoto on the occasion of his retirement.

We prepared 6-bromo-3-chloroindole (Ic), mp 54.5-56.5°C, from 6-bromoindole by direct chlorination with N-chlorosuccinimide (MeOH, 3 min, room temperature) in 55% yield. Direct chlorination at C-3 was introduced by Powers³ for the synthesis of 3-chloro-2-methylindole, but he had prepared 3-chloroindole itself by chlorinating 1-benzoylindole, followed by alkaline hydrolysis.⁴ The starting material, 6-bromoindole, mp 91-93°C (lit⁵ mp 93.5-94°C), is unavailable commercially and was made from *p*-toluidine in a six-step conventional sequence [nitration,⁶ Sandmeyer Rx, sidechain oxidation (2 steps),⁷ condensation with nitromethane, and reductive ring closure] in 5% overall yield.

Treatment of (Ic) with acetic anhydride and pyridine furnished an N-acetyl derivative, mp 158-159°C, pmr (CCl₄) δ 2.58 (s, 3H), ms (20 ev): *m/e* 275(15), 273(61), 271(48), 233(25), 231(100), 229(76 rel %).

The parent compound (Ic) was a white crystalline compound, which turned slightly brown on standing. The indole >NH gave rise to a 3490 cm⁻¹ band in the ir (CCl₄) and its pmr spectrum (CCl₄) exhibited the following signals: δ 7.02 (H-2, d, J_{12} = 2.6 Hz), 7.22 (H-5, dd, J_{45} = 8.4, J_{75} = 1.6), 7.40 (H-7, dd, J_{57} = 1.6, J_{47} = 0.6), 7.43 (H-4, dt, J_{14} = 0.6, J_{74} = 0.6, J_{54} = 8.3), 7.89 (>NH; br); its mass spectrum (70 ev) had major peaks at *m/e* 233(26), 231(100), 229(79), 196(8), 194(8), 152(18), 150(46), 125(8), 123(21), 116.6(5), 115.5(12), 114.5(9 rel %).

We synthesized 3,5,7-tribromoindole (II) in 4% overall yield by diazotizing 2,4-dibromoaniline and coupling the diazonium salt with ethyl α -methylacetoacetate. The resulting red oil on treatment with 3N ethanolic HCl furnished the hydrazone which we cyclized (PPA, 120-140°C, 5 min) to ethyl 5,7-dibromoindole-1-carboxylate, which was characterized: pmr (CDCl₃) δ 9.01 (br, >NH), 7.76 (H-4, dd), 7.58 (H-3, d, J = 1.8 Hz), 7.19 (H-6, d, J = 2.5),

4.42 ($=CH_2$, q, $J = 7$), 1.46 ($-Me$, t, $J = 7$); ms, m/e 349(29), 347(58), 345(30 rel %). This intermediate was saponified (aq KOH), decarboxylated (copper chromite, quinoline, 240°C, 5 min) to yield 5,7-dibromoindole, mp 67-68°, which was brominated (pyridinium bromide perbromide, pyridine, 0-2°C) as described by Piers *et al.*⁸ The product (II), after tlc purification (silica gel, $CHCl_3$) had mp 120-122° and an unambiguous nmr spectrum ($CDCl_3$): δ 8.37 ($>NH$, br), 7.60 (H-4, dd, $J_{14} = 0.7$, $J_{46} = 1.6$ Hz), 7.46 (H-6, d, $J_{46} = 1.6$), 7.19 (H-2, d, $J_{12} = 2.6$). Its major ms peaks occurred at m/e 357(21), 355(60), 353(61), 351(22 rel %).

Compounds (Ic) and (II) were identical with the *Ptychodera* metabolites² in all physical and chemical properties.

ACKNOWLEDGEMENT We thank the National Science Foundation for financial support.

REFERENCES

- 1 L. H. Hyman, "The Invertebrates," Vol. 5, McGraw-Hill, New York, 1959, p.143.
- 2 T. Higa and P. J. Scheuer, *Naturwissenschaften*, 1975, 62, 395.
- 3 J. C. Powers, *J. Org. Chem.*, 1966, 31, 2627.
- 4 R. Weissgerber, *Chem. Ber.*, 1913, 46, 651.
- 5 G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, 1958, 88, 1147; *Chem. Abstr.*, 1959, 53, 21876.
- 6 F. Ullmann and P. Dootson, *Chem. Ber.*, 1918, 51, 9.
- 7 N. Rabjohn, Ed., "Organic Syntheses," Coll. Vol. 4, John Wiley and Sons, New York, 1963, p. 713.
- 8 K. Piers, C. Meimaroglou, R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, 1963, 41, 2399.

Received, 17th November, 1975