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

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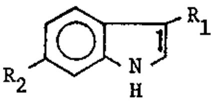
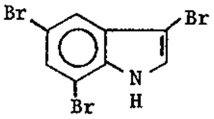
We synthesized 6-bromo-3-chloro- and 3,5,7-tribromoindole, two marine metabolites first isolated from the invertebrate *Ptychodera flava laysanica* (Hemichordata).

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-Chloroindole (Ia), present in the animal in 3 x 10^{-4}%, and the trace constituent 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 previously been reported as natural or synthetic compounds.



(I)



(II)

a R_1 = Cl, R_2 = H
b R_1 = Br, R_2 = H
c R_1 = Cl, R_2 = Br

[†] 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 Powers[3] 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 (lit[5] 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 (CCl_4) 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 (CCl_4) and its pmr spectrum (CCl_4) 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 ($CDCl_3$) 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 metabolites[2] in all physical and chemical properties.

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