

Structure and Synthesis of a New Bromoindole from a Marine Sponge

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The isolation of methyl (*E*)-3-(6-bromoindol-3-yl)prop-2-enoate (5) from a sponge of the genus *Iotrochota* is described; its structure, (5), was confirmed by synthesis.

BROMOINDOLES are common metabolites of marine organisms¹ and we now report the structural determination and synthesis of a new member of this class, namely methyl (*E*)-3-(6-bromoindol-3-yl)prop-2-enoate (5) which we have isolated from the organic extract of a sponge of the genus *Iotrochota*.

The mass spectrum of the new metabolite exhibited molecular ions of equal intensity at *m/e* 281 and 279 and hence the compound must contain one bromine atom. The i.r. spectrum (Nujol) exhibited an NH stretching frequency at ν 3300 cm^{-1} and bands assigned to an aromatic $\alpha\beta$ -unsaturated ester at ν 1705 (C=O) and 1625 (C=C) cm^{-1} . The ¹H n.m.r. spectrum (90 MHz, CDCl₃) exhibited a 3 H singlet at δ 3.81, assigned to the protons of a methyl ester, and an AB system due to the olefinic protons of an $\alpha\beta$ -unsaturated ester at δ 6.41 and 7.88 with a *trans*-coupling constant of 15.5 Hz. The remaining resonances were reminiscent of those of the indole protons of 6-bromoindole-3-carbaldehyde (4).² The spectrum of the metabolite thus exhibited the 5'-H as a doublet of doublets at δ 7.32 with $J_{4',5'}$ 8.5 and $J_{5',7'}$ 1.5 Hz. The 2'-H resonated as a doublet at δ 7.43 with $J_{2',\text{NH}}$ 3.0 Hz and this signal collapsed to a singlet on irradiation at the frequency of the NH resonance. The 7'-H resonated as a doublet at δ 7.57 with $J_{5',7'}$ 1.5 Hz; the 4'-H resonated as a doublet at δ 7.88 with $J_{4',5'}$ 8.5 Hz; and the NH resonated as a broad signal at δ 8.62. Structure (5) was therefore proposed.

In order to confirm this structure by synthesis (see Scheme) we required an efficient synthesis of 6-bromo-

indole-3-carbaldehyde (4).³ This indole was easily prepared by the condensation⁴ of 4-bromo-2-nitrotoluene (1) with *NN*-dimethylformamide dimethyl acetal and the catalytic reduction of the intermediate β -dimethylamino-2-nitrostyrene (2). Formylation of the resultant 6-bromoindole (3) gave the aldehyde (4) which was allowed to react with monomethyl malonate under the conditions of the Doebner reaction.⁵ The product was identical with the natural indole (5) by the usual criteria, thus confirming the structural assignment.

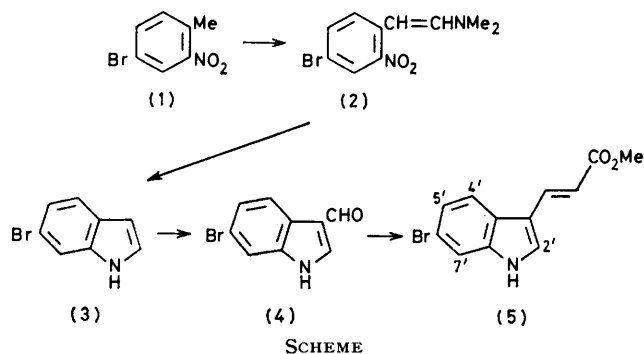
EXPERIMENTAL

Extraction of the *Iotrochota* Sponge.—The sponge (27.4 g, dry weight), collected on the Five Fathom Bank off Fremantle, Western Australia in December 1979, was stored under ethanol (1 l). The ethanol was decanted and evaporated to small volume which was then extracted with ethyl acetate. The sponge was freeze-dried and powdered, and then exhaustively extracted with boiling dichloromethane. The combined extracts (550 mg) were subjected to preparative t.l.c. on Merck Kieselgel GF₂₅₄ plates (20 × 20 × 0.1 cm) using 5% ethyl acetate–light petroleum as the developing solvent. The major u.v. active band gave methyl (*E*)-3-(6-bromoindol-3-yl)prop-2-enoate (5) (53 mg) as clusters of prisms (from ether–hexane), m.p. 186 °C; mass spectrum *m/e* 282 (9%), 281 (60, *M*⁺), 280 (10), 279 (64, *M*⁺), 250 (24), 248 (25), 223 (10), 221 (15), 170 (17), 169 (100), 142 (8), 141 (44), 140 (26), 125 (10), 124 (11), 115 (13), 114 (31), 113 (26), 111 (10), 110 (8), and 100 (20).

6-Bromoindole (3).—4-Bromo-2-nitrotoluene (1) (1 g), prepared from 4-methyl-3-nitroaniline⁶ by the Sandmeyer reaction,⁷ was heated under reflux under dry nitrogen with *NN*-dimethylformamide dimethyl acetal (1.5 g) for 31 h. The excess of acetal was removed under reduced pressure and the residue in ethanol (25 ml) was stirred under hydrogen with W-2 Raney nickel ($\frac{1}{4}$ teaspoon) until the absorption ceased. The catalyst was separated by filtration and the solvent was removed under reduced pressure. The residue, in ethyl acetate, was washed successively with dilute hydrochloric acid, water, and saturated brine, and then dried (MgSO₄). Crystallization of the crude product from dichloromethane–light petroleum gave the indole (3) (340 mg), m.p. 93 °C (lit.,⁸ 93 °C).

6-Bromoindole-3-carbaldehyde (4).—Formylation³ of 6-bromoindole (3) gave the aldehyde (4) (95%), m.p. 198–201 °C (lit.,³ 203–204 °C); δ (90 MHz, CDCl₃, CD₃SOCD₃) 7.32 (1 H, dd, $J_{4,5}$ 8.5 and $J_{5,7}$ 1.5 Hz, 5-H), 7.64 (1 H, d, $J_{5,7}$ 1.5 Hz, 7-H), 7.89 (1 H, s, 2-H), 8.10 (1 H, d, $J_{4,5}$ 8.5 Hz, 4-H), and 9.96 (1 H, s, CHO).

Methyl (*E*)-3-(6-Bromoindol-3-yl)prop-2-enoate (5).—6-Bromoindole-3-carbaldehyde (4) (580 mg), monomethyl malonate (610 mg), dry pyridine (5 ml), and dry piperidine



indole-3-carbaldehyde (4). This compound has usually been prepared by bromination of indole-3-carbaldehyde, but a better method is by the Vilsmeier–Haack formyl-

(3 drops) were heated on a steam-bath for 22 h. The solvents were removed under reduced pressure and the residue was crystallized from chloroform-methanol-light petroleum giving the *indole* (5) (450 mg) as clusters of prisms, m.p. 186 °C, identical (mixed m.p., n.m.r., mass, and i.r. spectra) with the natural product (Found: Br, 28.6; N, 4.9. $C_{12}H_{10}BrNO_2$ requires Br, 28.6; N, 5.0%).

We thank Professor P. Bergquist for identification of the sponge.

[0/1819 Received, 25th November, 1980]

REFERENCES

- ¹ J. T. Baker and V. Murphy, 'Handbook of Marine Science: Compounds from Marine Organisms,' Vol. 1, C.R.C. Press, Cleveland, Ohio, 1976.
- ² P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435.
- ³ A. Da Settimo, M. F. Saettone, E. Nannipieri, and P. Barili, *Gazzetta*, 1967, **97**, 1304.
- ⁴ A. D. Batcho and W. Leimgruber, U.S.P., 3976639, 1976.
- ⁵ F. Piozzi and C. Fuganti, *Ann. Chim. (Italy)*, 1967, **57**, 486 (*Chem. Abs.*, 1967, **67**, 64295).
- ⁶ E. Nölting and A. Collin, *Ber.*, 1884, **17**, 261.
- ⁷ C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 1929, 1229.
- ⁸ H. Plieninger, *Chem. Ber.*, 1955, **88**, 370.