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Dhanapalan Nagarathnam [a] & Michael E. Johnson [a]

[a] Center for Pharmaceutical, Biotechnology and Department of Medicinal Chemistry & Pharmacognosy, University of Illinois at Chicago, P. O. Box 6998, m/c 781, Chicago, IL 60680, USA

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A NEW SYNTHESIS OF 5-BROMO-DL-TRYPTOPHAN

Dhanapalan Nagarathnam and Michael E. Johnson*
Center for Pharmaceutical Biotechnology and Department of Medicinal Chemistry & Pharmacognosy, University of Illinois at Chicago, P. O. Box 6998, m/c 781, Chicago, IL 60680, USA

ABSTRACT:

A new synthesis of 5-bromotryptophan, a potential antisickling agent, from 5-bromo-3-methylindole is described.

3-Substituted indoles show a wide spectrum of biological activities, and development of facile synthetic routes for such compounds has been the central objective of the synthesis of many alkaloids.[1] Several 5- and 6-bromoindoles have been isolated as marine natural products and some of them possess significant pharmacological properties.[2-4] Recently, computer modeling studies have shown that indole-derived compounds are a good source for potential antisickling agents[5], and 5-bromotryptophan is thus far the most potent compound among the 13 tryptophan derivatives tested.[6,7] Two methods have been reported for the preparation of 5-bromotryptophan from 5-bromoindole[8,9]; the present report describes the synthesis of the same from 5-bromo-3-methylindole.

Though the synthesis of 5-bromo-3-methylindole was reported, these processes involve expensive 5-bromoindole or/and more steps.[10,11] In the present

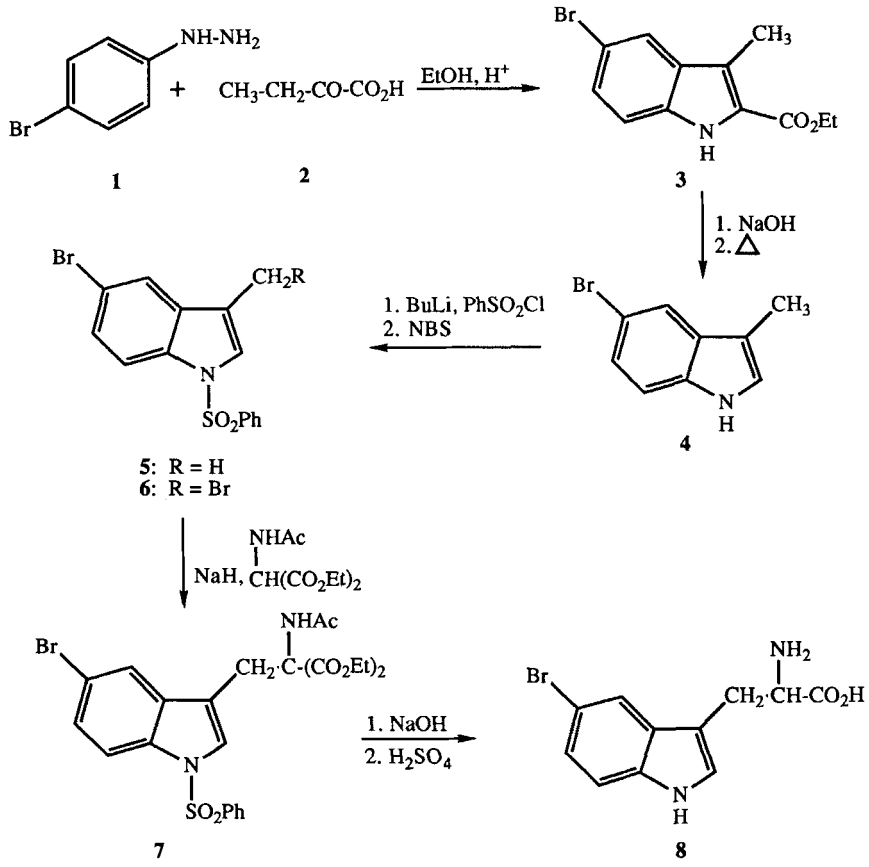
*To whom correspondence should be addressed.

work, the required amount of 5-bromo-3-methylindole was obtained in 68% yield from 4-bromophenylhydrazine and 2-ketobutyric acid. 4-Bromophenylhydrazine reacted with 2-ketobutyric acid[12] in absolute ethanol in the presence of concentrated sulfuric acid to provide ethyl 5-bromo-3-methyl-2-indolecarboxylate (**3**) in 74% yield, which on alkaline hydrolysis followed by decarboxylation in boiling quinoline gave the required 5-bromo-3-methylindole (**4**) in 92% yield as a single product. Reaction of **4** with *n*-butyl lithium, followed by treatment with benzenesulfonyl chloride gave 1-benzenesulfonyl-5-bromo-3-methylindole (**5**) in 92% yield, which on treatment with *N*-bromosuccinimide in boiling tetrachloromethane in the presence of catalytic amount of benzoyl peroxide provided 1-benzenesulfonyl-5-bromo-3-bromomethylindole (**6**) in an excellent yield. Alkylation of diethyl acetamidomalonate with the bromomethylindole **6** in THF gave the intermediate **7**, which on alkaline hydrolysis followed by treatment with dil. H_2SO_4 gave 5-bromo-DL-tryptophan in 63% yield from **6**.

The process described above could be used to synthesize a variety of substituted tryptophan derivatives and the bromomethylindole **6** could also be used as potential starting materials for a variety of marine natural products and biologically important indole derivative. Efforts are currently underway to synthesize several congeners of 5-bromotryptophan to obtain clinically useful antisickling agents.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Spectra were obtained as follows: ci mass spectra on a Finnegan MAT-90 double focussing spectrometer; pmr spectra on a Varian



XL-300S spectrometer with TMS as an internal standard; ir spectra were obtained on a Midac 101280-1 spectrophotometer. All organic solvents were appropriately dried and/or purified prior to use.

Ethyl 5-Bromo-3-methyl-2-indolecarboxylate (3). A solution of conc. H_2SO_4 (6 g) in absolute ethanol (100 mL) was added to a suspension of 4-bromophenylhydrazine hydrochloride (22.3 g, 0.1 mol) and 2-ketobutyric acid (10.21 g, 0.1 mol) in ethanol (60 mL) and the mixture was refluxed for 8 h and kept at 5 °C for 24 h. The pale yellow colored product formed was filtered,

washed with 15 mL of ice-cold ethanol, followed by water (200 mL) and dried; yield: 20.85 g (74%); mp 164-165 °C.

$C_{12}H_{12}BrNO_2$ (282.2): calc. C, 51.06 H, 4.29

found C, 51.31 H, 4.36

^{1}H-NMR ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3 H), 2.55 (s, 2 H), 4.20 (q, J = 7 Hz, 2 H), 7.25 (d, J = 8.9 Hz, 1 H), 7.38 (d, J = 8.9 Hz, 1 H), 7.77 (s, 1 H), 8.86 (bs, 1 H, N-H).

^{13}C-NMR ($CDCl_3$) δ 9.82, 14.43, 60.93, 105.33, 113.13, 119.33, 123.33, 124.55, 128.44, 130.26, 134.37, 162.36.

5-Bromo-3-methylindole (4). Ethyl 5-bromo-3-methyl-2-indolecarboxylate (**3**) (14.1 g, 50 mmol) was added to a solution of potassium hydroxide (10 g) in water (20 mL) and ethanol (20 mL) and the mixture was refluxed for 12 h. Most of the ethanol was evaporated at reduced pressure and the residue was poured into 6 N HCl. The white crystalline precipitate formed was filtered, washed with water and dried. It was mixed with quinoline (10 mL) and heated at reflux under nitrogen for 2 h and cooled. The mixture was poured onto a mixture of ice (400 g) and conc. HCl (50 mL), and the product was extracted with chloroform (3 x 50 mL). Evaporation of solvents from the dried extract gave the product as an oil, which solidified on standing. The tlc analysis showed that it was pure and was used as such in subsequent reaction. An analytical sample was prepared by recrystallization from 2-propanol; yield: 9.65 g (92%); mp 79 °C (lit.[12] mp 79.5-80.5 °C).

1-Benzenesulfonyl-5-bromo-3-methylindole (5). *n*-BuLi in THF (1 *M*, 28 mL, 28 mmol) was added to a well-stirred solution of **4** (5.25 g, 25 mmol) in THF (50 mL) at -78 °C under nitrogen in 15 minutes and the mixture was

allowed to warm to room temperature. After 2 h, it was cooled again to -78 °C and benzenesulfonyl chloride (4.95 g, 28 mmol) was added in 5 minutes. The cooling bath was removed after 30 minutes and the stirring was continued for 4 h. The mixture was poured onto ice (250 g) and extracted with chloroform (3 x 50 mL). Evaporation of solvents from the dried extracts (Na_2SO_4) and trituration of the residue with 2-propanol gave the product as a white crystalline solid. An analytical sample was prepared by recrystallization from 2-propanol; yield: 8.05 g (92%); mp 130-131 °C.

$C_{15}H_{12}BrNO_2S$ (350.2): calc. C, 51.43 H, 3.45

found C, 51.62 H, 3.60

IR (KBr): 1446, 1369, 1176, 1149, 1122, 812, 799, 721 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ 2.20 (s, 3 H), 7.31 (s, 1 H), 7.39-7.45 (m, 3 H), 7.53 (d, 7.2 Hz, 1 H), 7.57 (s, 1 H), 7.82-7.88 (m, 3 H).

^{13}C-NMR ($CDCl_3$) δ 9.51, 115.01, 116.60, 118.12, 122.29, 124.14, 126.56, 127.42, 129.21, 133.48, 133.80, 133.84, 137.87.

1-Benzenesulfonyl-5-bromo-3-bromomethylindole (6).

Compound **5** (3.5 g, 10 mmol) was mixed with powdered *N*-bromosuccinimide (1.87 g, 10.5 mmol) and benzoyl peroxide (10 mg) in tetrachloromethane (50 mL) and the mixture was refluxed for 3 h. Succinimide was removed by filtration and the solvent was evaporated from the filtrate to give **6** as a viscous oil, which solidified on trituration with hexane; yield: 4.13 g (96%); mp 149-150 °C.

$C_{15}H_{11}Br_2NO_2S$ (429.1): calc. C, 41.98 H, 2.58

found C, 41.93 H, 2.71

^{1}H-NMR ($CDCl_3$) δ 4.56 (s, 2 H), 7.42-7.55 (m, 4 H), 7.65 (s, 1 H), 7.77 (d, J = 1.9 Hz, 1 H), 7.83-7.88 (m, 3 H).

Preparation of Product 7. 1-Benzenesulfonyl-5-bromo-3-bromomethylindole (**6**) (2.15 g, 5 mmol) in THF (25 mL) was added to a suspension of the sodium salt obtained by the reaction of NaH (0.12 g, 5 mmol) with diethyl acetamidomalonate (1.09 g, 5 mmol) in THF (25 mL) at 0 °C under nitrogen, and the mixture was allowed to warm to room temperature in 1 h. It was further heated at 55-60 °C for 5 h and the solvents were evaporated. The residue was mixed with ice (50 g) and HCl (2 mL) and extracted with chloroform (3 x 25 mL). Solvents were evaporated from the dried (Na_2SO_4) extracts and the residue was chromatographed on a column of silica gel. Elution with ethyl acetate-chloroform (1:1) gave the product as a viscous oil, which solidified on trituration with hexane; yield: 2.35 g (83%); mp 153-154 °C.

$C_{24}H_{25}BrN_2O_7S$ (565.4): calc. C, 50.97 H, 4.45

found C, 50.88 H, 4.62

^{1}H-NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, 6 H), 2.03 (s, 3 H), 3.76 (s, 2 H), 4.22-4.27 (m, 4 H), 6.74 (s, 1 H), 7.30 (s, 1 H), 7.37-7.40 (dd, 1 H), 7.44-7.60 (m, 4 H), 7.81-7.85 (m, 3 H).

5-Bromo-DL-tryptophan (8). Compound **7** (1.13 g, 2 mmol) was mixed with NaOH (1.5 g), ethanol (3 mL), and water (7 mL) and the mixture was heated under reflux for 8 h. Solvents were completely evaporated from the mixture, and the residue was mixed with sulfuric acid (2 *N*, 10 mL). The mixture was heated under reflux for 4 h, cooled and the pH was adjusted to about 7 by careful addition of 5% NaOH. Water was evaporated completely and the residue was extracted with boiling ethanol (3 x 10 mL). The combined extracts on concentration and cooling gave **8**, as white crystals; yield 0.43 g (76%); mp 262-263 °C (lit.[8] 264 °C).

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