of 9-anthraldehyde (Aldrich, mp 103–105 °C) dissolved in 20 mL of THF was added to the reaction mixture over a period of 30 min, and stirring under N_2 was continued at room temperature for an additional 4 days. During this period (the flask was protected from light) a yellow solid precipitated out. The reaction mixture was poured into 200 mL of ice-cold water. The mixture was acidified with 6 N HCl to pH ~1.0. The product was extracted seven times with ether (total quantity of 100 mL). The ether layer (A) was extracted with 100 mL of 10% NaOH (three times) and washed twice with distilled water. Acidification of the basic extract with 6 N HCl gave a yellow solid. The solid was reextracted with 100 mL of ether (three times), and the solvent was evaporated in a rotary evaporator. This solid **2c** was recrystallized ($HCCl_3$): mp 136–137 °C; 300 mg (32%). For analytical and spectral data, see Tables II and III. From the neutral ether layer (A), 600 mg (97%) of 9-anthaldehyde was recovered.

Preparation of 2d. The procedure was exactly like that used for the preparation of **2c**. From 0.108 g (0.004 mol) of NaH, 1.06 g (0.002 mol) of **1d**, and 0.443 g (0.002 mol) of 9-anthraldehyde (4) after a reaction period of 6 days at room temperature there was obtained 0.580 g (75%) of pure **2c** (recrystallized from ether–petroleum ether), mp 62–62.5 °C. It was possible to recover 9-anthraldehyde (87%) as described earlier.

In another experiment and in the absence of anthraldehyde, 0.108 g (0.004 mol) of NaH and 1.06 g (0.002 mol) of **1d** afforded 0.550 g (71%) of **2d**.

Reaction of 1d with $NaOC_2H_5$ and DMF. In an effort to assess the possible role of a direct participation of Me_2SO in the reaction, the combination of $NaOC_2H_5$/DMF was used instead of NaH/Me_2SO. With 1.06 g (0.002 mol) of **1d** and 0.265 g (0.004 mol) of freshly prepared $NaOC_2H_5$ in 20 mL of DMF and a reaction time of 24 h at room temperature, it was possible to isolate 0.450 g (58%) of **2d**.

Attempted Preparation of the Wittig Reagent of 1d and Reaction with Benzaldehyde. An experiment was also performed with benzaldehyde instead of 9-anthraldehyde (4) using NaH/Me_2SO/THF. With 0.153 g (0.0064 mol) of NaH, 1.59 g (0.003 mol) of **1d**, and 0.32 g (0.003 mol) of freshly distilled benzaldehyde (with 40 mL of Me_2SO and 40 mL of THF) and after a reaction period of 5 days at room temperature (under N_2), 0.500 g (43%) of **2d** was isolated by following the workup procedure described in the preparation of **2d**. Proton NMR analysis of the neutral, ether-soluble portion revealed a large quantity of benzaldehyde.

Preparation of 2e. The oxide **2e** was prepared by a procedure similar to the one described for the preparation of **1d**. From 0.198 g (0.0082 mol) of dry NaH and 2.17 g (0.004 mol) of **1e** (with 30 mL of Me_2SO and 10 mL of THF) and with a reaction time of 4 days at room temperature (under N_2) there was formed a white solid (recrystallized from $HCCl_3$–hexane): mp 120–121 °C; 1.0 g (62%) of **2e**. For analytical and spectral data, see Tables II and III.

Registry No. 1a, 36626-29-6; **1b**, 60633-18-3; **1b** methyl ester, 73367-74-5; **1c**, 50889-29-7; **1d**, 7530-96-3; **1e**, 73367-75-6; **2b**, 73367-76-7; **2c**, 73367-77-8; **2d**, 73367-78-9; **2e**, 73367-79-0; **3a**, 107-94-8; **3b**, 627-00-9; **3c**, 4224-70-8; **3d**, 2834-05-1; **3e**, 73367-80-3; **4**, 642-31-9; **5b**, 73367-81-4; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7.

Synthesis of Benzothiazoles. α-Amino-(4-hydroxy-6-benzothiazolyl)propionic Acid

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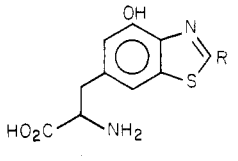
Received February 13, 1980

The tentative structure assigned to the photobiologically important skin pigment pheomelanin is based on degradative studies of the natural chromophore. The title compound was reported to be one of several key amino acids isolated in these studies. The identity of this benzothiazole derivative has now been confirmed via an unambiguous eight-step total synthesis starting from 5-methyl-2-nitrophenol.

We have demonstrated that pheomelanin, the red-brown polymeric pigment found in the skin and hair of fair-skinned humans,[2] is photolabile under physiologically relevant conditions.[3,4] This pigment is composed of a chromophore covalently bonded to a protein fraction. Since the protein is neither involved in nor altered during photolysis,[4b,5] we focused our attentions on the photochemistry of the chromophore. Unfortunately, due to problems with homogeneity and solubility, the chromophore has yet to be properly characterized. However, degradation of the protein-free chromophore by hot concentrated hydriodic acid afforded amino acids **1** and **2** as major products. Isolated as their methyl esters and assigned structures based on spectroscopic data, these two



1, R = H
2, R = CH_3

amino acids, along with degradation products isolated from permanganate oxidation of the chromophore served as the basis for the conclusion that the dominant monomeric unit in the chromophore is a benzothiazole moiety.[2] We report herein a synthesis of amino acid **1** which confirms the identity of one of the amino acids isolated in the aforementioned degradative studies.

At the outset, two synthetic approaches were considered as follows: (1) start with the benzothiazole ring system and build onto it the appropriate functionality, or (2) form the thiazole ring by annelation of a suitably substituted aniline. Benzothiazoles are reported to undergo electrophilic aromatic substitution to give 6-substituted benzothiazoles as the major product,[6] and a second electrophilic substitution

(1) The Johns Hopkins University, Department of Environmental Health Sciences, U.S. Public Health Service Hospital, COEH-Bldg 6, Baltimore, MD 21211.

(2) Prota, G.; Thomson, R. H. *Endeavor* **1976**, *35*, 32–8.

(3) Chedekel, M. R.; Post, P. W.; Deibel, R. M.; Kalus, M. *Photochem. Photobiol.* **1977**, *26*, 651–3.

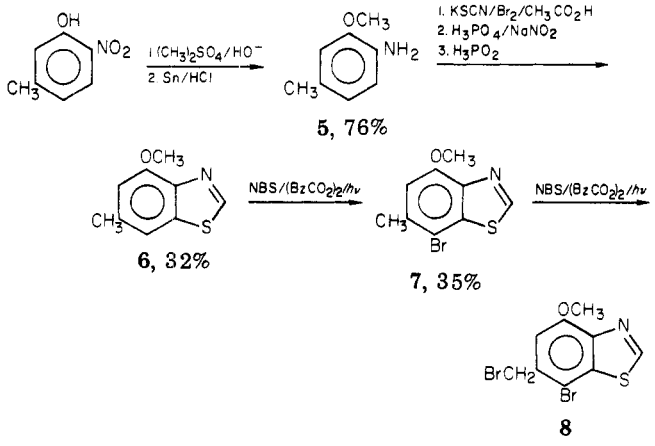
(4) (a) Harsanyi, Z. P.; Post, P. W.; Brinkmann, J.; Chedekel, M. R.; Deibel, R. M. *Experientia* **1980**, *36*, 291–2. (b) Chedekel, M. R.; Smith, S. K.; Post, P. W.; Vessell, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5395–9.

(5) Chedekel, M. R.; Agin, P. P.; Sayre, R. M. *Photochem. Photobiol.*, in press.

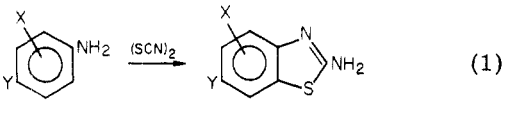
(6) Sprague, J. M.; Land, A. H. *Heterocycl. Compd.* **1957**, *5*, 606–13.

0022-3263/80/1945-2243$01.00/0

Scheme I

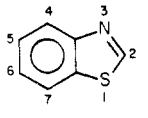


would be expected to yield a 4,6-disubstituted benzothiazole. However, in our hands, benzothiazoles substituted in the 6 position with groups such as nitro, carboxy, chloro, or cyano were unreactive to a variety of common electrophilic aromatic substitution conditions, and thus, this tack was rapidly abandoned in favor of the second approach.

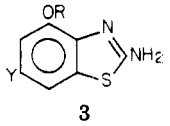


(1)

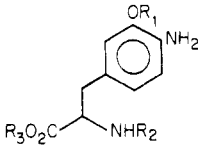
Several methods are available for converting anilines to benzothiazoles,[7] and after examining a number of examples we settled on reaction 1 as being the most general and



applicable to our needs. At this juncture, two strategies looked promising; the first involved constructing a 2-aminobenzothiazole such as 3 in which Y is a group easily



3



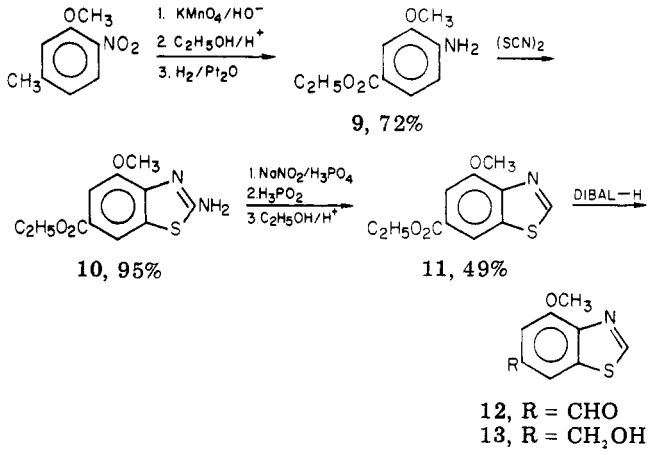
4

transformable to an alanyl side chain, and the second required thiocyanation of an aniline, e.g. 4, already possessing the requisite side chain.

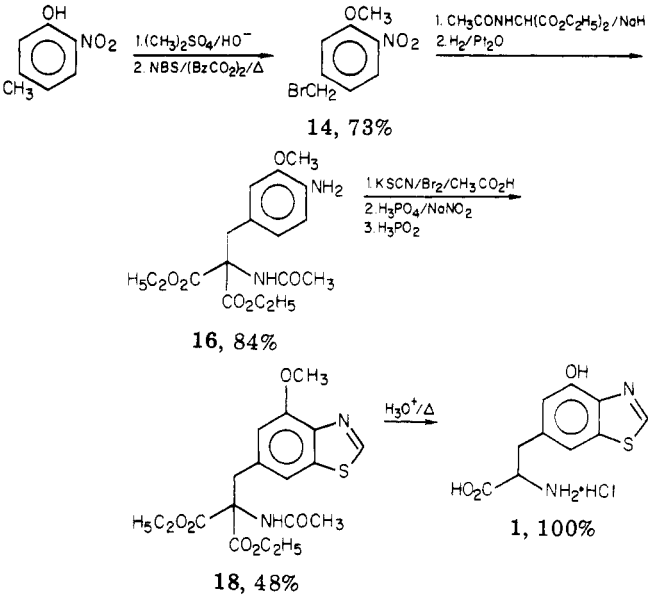
Preparation of a suitably substituted benzothiazole, e.g. 6, using reaction 1 and subsequent replacement of the 2-amino functionality with hydrogen was straightforward (see Scheme I). However, selective functionalization of the 6-methyl group proved to be problematic. Free-radical brominating reagents such as *N*-bromosuccinimide (NBS) or *N,N*-dibromohydantoin gave ring bromination at the 7 position prior to benzylic substitution. Attempts to oxidize this methyl group with harsher reagents, e.g. $KMnO_4$, resulted in destruction of the benzothiazole chromophore. Functionalization of this methyl group prior to removal of the 2-amino functionality proved to be equally frustrating, and thus it became evident that the incipient 6-methyl group must be functionalized prior to formation of the benzothiazole moiety.

(7) Sprague, J. M.; Land, A. H. *Heterocycl. Compd.* **1957**, *5*, 506–13.

Scheme II



Scheme III



Preparation of 6-carboethoxy-4-methoxybenzothiazole (11) was easily accomplished by slightly modifying Scheme I (see Scheme II). Although it has been reported that 6-(carbomethoxy)-2-methylbenzothiazole is cleanly reduced to the 6-hydroxymethyl derivative with lithium aluminum hydride (LAH) at low temperatures,[8] treatment of 11 with LAH at −78 °C resulted in production of a multitude of products (as determined by thin-layer chromatography). Milder reducing reagents such as diisobutylaluminum hydride (DIBAL-H) are only slightly more successful; treatment of 11 with DIBAL-H at low temperatures gave the corresponding aldehyde 12 and hydroxymethyl derivative 13 in yields too low to be of synthetic utility. Apparently, the thiazole ring, when unsubstituted at the 2 position, is readily attacked by hydride donors with subsequent cleavage occurring during workup.[9]

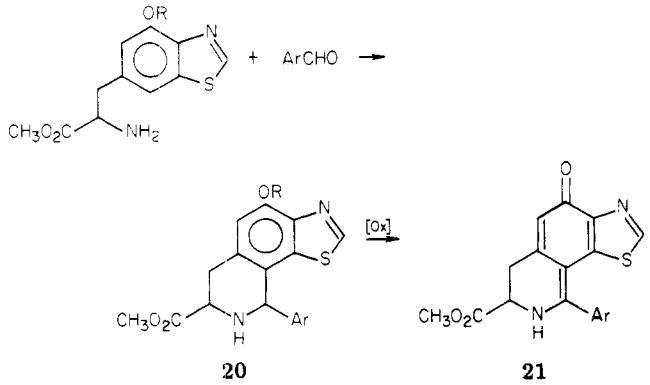
In light of the problems associated with elaborating the 4,6-disubstituted benzothiazoles, we decided to pursue our second pathway, i.e., thiocyanation of an aniline such as 4. Preparation of the appropriate substrate was accomplished by NBS bromination of 5-methyl-2-nitroanisole (see Scheme III). We could not drive the reaction to completion and had to settle for 60–80% conversion.

(8) Zuborovskii, V. M.; Khodot, G. P. *Zh. Obshch. Khim.* **1964**, *34*, 3801–6.

(9) Knapp, K. K.; Keller, P. C.; Rund, J. V. *J. Chem. Soc., Chem. Commun.* **1978**, 971.

However, since the starting material could be recycled and the product purified by simple recrystallization, this step is acceptable for large-scale preparations. Displacement of the benzylic bromine by sodio diethyl acetamidomalonate proceeds smoothly affording **15** in 94% yield when the reaction is run in DMF. Reduction of the aromatic nitro group can be accomplished either by catalytic hydrogenation or the action of stannous chloride in HCl-saturated methanol; for large-scale preparations we prefer the latter. Thiocyanation of aniline **16** was accomplished via the method of Kaufmann;[10] i.e., bromine was added to a cooled acetic acid solution of **16** and potassium thiocyanate. Subsequent workup of this reaction afforded 2-aminobenzothiazole **17** in 71% yield. The next reaction, replacement of the 2-amino functionality with hydrogen, was perplexing; previous attempts to replace the 2-amino group of benzothiazoles with hydrogen gave yields much too low to be of synthetic utility.[11] The problem, apparently, is that these amines are much less basic than normal aryl amines and thus conditions used to effect diazotization had to be harsher than normally encountered. We have now worked out conditions which give yields for this transformation that are low but acceptable for our purposes.[12] In practice, **17** is not normally purified; the crude product from thiocyanation of **16** is diazotized and treated with hypophosphorous acid to give **18** in 48% overall yield. Quantitative yields of **1** are obtained by heating **18** in an evacuated sealed tube with 6 N HCl at 150 °C for 24 h.

In summary, both the spectral data (NMR, IR, and mass spectra) and physical properties (melting point and solubility) of **1**, its methyl ester, and the bis(2,4-dinitrophenyl) derivative **19** agree in all respects with those reported[13,14] for one of the amino acids isolated from the acid hydrolysis of pheomelanin. Our synthesis has been scaled up to a 200-g level to produce 91 g (29% yield) of **1** which will be used to prepare pheomelanin model compounds such as **20** and **21** for spectroscopic and photochemical comparison with the natural pigment.



20 21

Experimental Section

All melting points were recorded on a Fisher-Johns melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman model 4250 spectrophotometer. Proton NMR spectra were recorded on a Varian EM-360 spectrometer with $(CH_3)_4Si$ as an internal standard. Mass spectra were recorded on an AEI MS-9 spectrometer at 70 eV and in all cases there were no peaks higher than those of the molecular ion. Preparation of compounds **5–8** has been previously described.[15]

3-Methoxy-4-nitrotoluene. A 5-L three-necked flask fitted with a mechanical stirrer was charged with 300 mL of 6 N NaOH. The solution was warmed to 40–50 °C and 60.0 g of 5-methyl-2-nitrophenol (Aldrich) was added in one portion. The solution was heated to 80 °C and dimethyl sulfate was rapidly added until the color changed from red to yellow. More base was added until the color changed back to red. The alternate addition of dimethyl sulfate and base was continued until no more red color was observed on addition of base. When the solution was allowed to cool, a yellow precipitate formed which was collected and recrystallized from 95% ethanol to give 58.9 g (90.0% yield) of yellow needles, mp 58–60 °C (lit.[16] mp 62 °C).

Ethyl 4-Amino-3-methoxybenzoate (9). To a solution of 51.3 g of 3-methoxy-4-nitrotoluene in 3.5 L of boiling water containing 25.0 g of Na_2CO_3 was added 200 g of powdered $KMnO_4$. The solution was refluxed for 1.5 h, filtered through diatomaceous earth, cooled to 0 °C, and acidified with dilute H_2SO_4. The mixture was heated to dissolve the product, decolorized with charcoal, filtered, and allowed to cool and crystallize. The product was recrystallized from 95% ethanol, affording 60.5 g (100% yield) of 3-methoxy-4-nitrobenzoic acid as colorless crystals, mp 230–233 °C (lit.[17] mp 233 °C).

A solution containing 27.0 g of 3-methoxy-4-nitrobenzoic acid, 200 mL of absolute ethanol, 150 mL of benzene (dried over sodium), and 5 mL of concentrated H_2SO_4 was heated to reflux for 24 h. A Dean–Stark trap was used to remove the water of reaction. The solution was allowed to cool and then extracted with 100 mL of 10% aqueous Na_2CO_3. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed in vacuo, affording 29.6 g (95.9% yield) of ethyl 3-methoxy-4-nitrobenzoate as a light tan residue. This residue was sufficiently pure for the next step; however, it could be recrystallized from benzene/petroleum ether to give yellow needles, mp 93–94 °C (lit.[18] mp 93 °C).

Ethyl 3-methoxy-4-nitrobenzoate (25.4 g) dissolved in 300 mL of 95% ethanol with 0.3 g of Pt_2O catalyst added was placed in a Paar hydrogenation bottle and shaken at room temperature under 65 psi of H_2 for 3 days. The catalyst was filtered off and the solvent removed in vacuo, affording 16.8 g (74.6% yield) of **9** as a colorless solid: mp 81–83 °C; ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H), 3.7 (s, 3 H), 4.1 (s, 2 H), 4.2 (q, 2 H), 6.5 (m, 2 H), 7.4 (d, 1 H).

2-Amino-6-carboethoxy-4-methoxybenzothiazole (10). **9** (10 g) was dissolved in 135 mL of anhydrous methanol to which an intimate mixture of 50.0 g of KSCN and 40.0 g of $CuSO_4$[10] was added and the resultant mixture heated to reflux until the black precipitate turned gray (ca. 2 h). The suspension was filtered and the filtrate diluted with water and heated to boiling. Ethanol (95%) was added to the boiling filtrate until a clear slightly yellow solution resulted. Cooling of this solution resulted in crystallization of **10** (11.6 g, 94.6% yield): mp 265–267 °C; IR (KBr) 3400, 3280, 3120, 3000, 1680, 1660, 1560 cm^{-1}; ^1H NMR (CF_3CO_2H) δ 1.3 (t, 3 H), 3.9 (s, 3 H), 3.4 (q, 2 H), 7.6 (d, 1 H), 7.9 (d, 1 H), 8.3 (s, 2 H); mass spectrum, $C_{11}H_{12}N_2O_3S$ (calcd m/e 252.0569, found m/e 252.0575).

6-(Carboethoxy)-4-methoxybenzothiazole (11). **10** (27.8 g) was dissolved in 80 mL of hot 85% H_3PO_4. The resulting solution was cooled to −8 °C and a concentrated aqueous solution of 18.5 g of $NaNO_2$ was added slowly below the surface with stirring at such a rate as to maintain the temperature below −4 °C. The resultant red solution was added dropwise to 60 mL of prechilled (0 °C) 50% H_3PO_2 (Fisher) with vigorous stirring. The reaction was allowed to warm to room temperature with continued stirring until all gas evolution ceased, whereupon the solution was extracted with diethyl ether (3 × 100 mL). After the solvent was removed from the combined ether extracts, the residue was re-

(10) Wood, J. L. *Org. React.* **1946**, *3*, 253 and 256.
(11) Erlenmeyer, H.; Ueverwasser, H. *Helv. Chim. Acta* **1942**, *25*, 515–20.
(12) Chedekel, M. R.; Sharp, D. E.; Jeffery, G. A. *Synth. Commun.* **1980**, *10*, 167–73.
(13) The Italians make no mention of the chiroptical properties of **1** or any derivatives of **1**. Since we have prepared the racemic modification, it may only be fortuitous that the melting point and solubility of the synthetic sample match those of the natural product.
(14) Minale, L.; Fattorusso, E.; Cimino, G.; DeStefano, S.; Nicolaus, R. A. *Gazz. Chim. Ital.* **1967**, *97*, 1636–63.
(15) Ismail, I. A. Masters Thesis, The Ohio State University, 1978.
(16) *Beilstein*, 13^2, 326.
(17) "Dictionary of Organic Compounds", 4th revision; Pollock, J. R. A.; Stevens, R. A., Eds.; Eyre and Spottiswood Ltd.: London, 1965; Vol. 3, 1756.
(18) Iskander, Y.; Tewfik, R.; Wasif, S. *J. Chem. Soc. B* **1966**, 424–6.

fluxed for 24 h together with a solution of 100 mL of absolute ethanol, 150 mL of benzene, and 5 mL of concentrated H_2SO_4 (a Dean–Stark trap was employed for water removal). After being cooled, the solution was washed with 100 mL of a saturated Na_2CO_3 solution and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The resultant residue was recrystallized from hexane, giving 12.8 g (49.1% yield) of pale yellow needles: mp 86–87 °C; IR (KBr) 3100, 2950, 2890, 1725, 1575, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 4.1 (s, 3 H), 4.4 (q, 2 H), 7.6 (d, 1 H), 8.4 (d, 1 H), 9.1 (s, 1 H); mass spectrum, $C_{11}H_{11}NO_3S$ (calcd m/e 237.0460, found m/e 237.0465).

4-(Bromomethyl)-2-nitroanisole (14). 3-Methoxy-4-nitrotoluene (101.6 g), 116.0 g of NBS, and 2 g of dibenzoyl peroxide were added to 3000 mL of CCl_4 and heated to reflux for 3 days. Suspended succinimide was filtered from the hot solution with subsequent removal of the solvent in vacuo. The resultant brown oil was triturated with petroleum ether and then recrystallized from CCl_4, affording 99.1 g of 14 as light yellow needles, mp 100–101 °C (lit.[19] mp 97–98 °C). Starting material (18.9 g) could be recovered from the mother liquor, giving an effective yield of 81.3%.

Diethyl 1-Acetamido-2-(3-methoxy-4-nitrophenyl)-1,1-ethanedicarboxylate (15). Diethyl acetamidomalonate (43.2 g) in 100 mL of DMF (freshly distilled from CaH_2) was added dropwise to a stirred suspension of 4.6 g of NaH (50% in mineral oil; previously washed several times with pentane) in 200 mL of DMF. After the addition, the mixture was stirred for an additional 2 h and filtered into a stirred solution of 20.0 g of **14** in 100 mL of DMF. Stirring was continued for an additional 2 h whereupon 2000 mL of water was added. The white precipitate which formed was collected by suction filtration and recrystallized from ethyl acetate to give 29.2 g of **15** (94% yield) as colorless crystals: mp 163–164 °C; IR (KBr) 3480, 3340, 2960, 1700, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.3 (t, 6 H), 2.1 (s, 3 H), 3.6 (s, 2 H), 3.9 (s, 3 H), 4.3 (q, 4 H), 6.6 (d, 1 H), 6.8 (dd, 1 H), 7.8 (d, 1 H), 8.3 (s, 1 H); mass spectrum, $C_{17}H_{22}N_2O_8$ (calcd m/e 382.1376, found m/e 382.1382). Anal. ($C_{17}H_{22}N_2O_8$) C, H, N.

Diethyl 1-Acetamido-2-(3-methoxy-4-aminophenyl)-1,1-ethanedicarboxylate (16). Stannous chloride dihydrate (3.0 g) was dissolved in 25 mL of saturated methanolic HCl. This solution was added dropwise with stirring to 1.0 g of **15**. The homogeneous solution was allowed to stir for 2.5 h at room temperature, at which time the solvent was removed in vacuo, the residue made basic with saturated $NaHCO_3$, and the resultant suspension extracted with 10% ethyl acetate in $CHCl_3$ (5 × 40 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo, affording a brown oil, which when triturated with ether/petroleum ether gave 0.81 g (88% yield) of **16** as a colorless solid. An analytical sample was prepared by recrystallization from ether/petroleum ether: mp 93–94 °C; IR (KBr) 3460, 3340, 2980, 2920, 1740, 1700, 1660, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 6 H), 2.0 (s, 3 H), 3.6 (s, 2 H), 3.8 (s, 5 H), 4.3 (q, 4 H), 6.5 (m, 4 H). Anal. ($C_{17}H_{24}N_2O_6$) C, H, N.

Pt_2O (0.1 g) was added to a solution of 5.0 g of **15** in 300 mL of ethyl acetate. The suspension was shaken in a Paar hydrogenator under 65 psi of H_2 for 3 days, at the end of which the catalyst was removed by filtration and the solvent was removed in vacuo, affording 4.1 g of **16** as a viscous brown oil. This oil was sufficiently pure for the next step; however, it could be purified (vide supra).

Diethyl 1-Acetamido-2-(2-amino-4-methoxy-6-benzothiazolyl)-1,1-ethanedicarboxylate (17). A solution of 5.0 g of **16** and 2.8 g of KSCN in 30 mL of acetic acid was cooled to 10–12 °C whereupon a solution of 4.5 g of Br_2 in 20 mL of acetic acid was added dropwise with stirring. The reaction mixture was stirred for an additional 0.5 h at 12 °C and then concentrated in vacuo. The resultant yellow precipitate was digested in hot aqueous Na_2CO_3 solution to give yellow crystals which were recrystallized from 50% aqueous ethanol, affording 4.1 g (70.6% yield) of **17** as colorless needles: mp 251–253 °C; IR (KBr) 3410, 3390, 2980, 2940, 1740, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.3 (t, 6 H), 2.1 (s, 3 H), 3.6 (s, 2 H), 3.8 (s, 3 H), 4.2 (q, 4 H), 6.4 (s, 1 H), 6.9 (s, 1 H), 7.4 (s, 1 H), 8.2 (s, 2 H); mass spectrum, $C_{18}H_{23}N_3O_6S$ (calcd m/e 409.1307, found m/e 409.1312). Anal. ($C_{18}H_{23}N_3O_6S$) C, H, N, S.

Diethyl 1-Acetamido-2-(4-methoxy-6-benzothiazolyl)-1,1-ethanedicarboxylate (18). **16** (18.0 g) and 9.72 g of KSCN were placed in a 500-mL round-bottom flask and dissolved in 200 mL of glacial acetic acid. The solution was cooled to just above its freezing point whereupon 16 g of Br_2 dissolved in 25 mL of acetic acid was added with rapid stirring. After the addition of Br_2, the reaction mixture was filtered to remove KBr. The filtrate was then evaporated to dryness in vacuo to give a quantitative yield of the crude hydrobromide salt of **17**, mp 210–216 °C.

The crude hydrobromide salt was dissolved in 500 mL of 85% H_3PO_4 with gentle heating. The solution was then cooled to −15 °C and with vigorous mechanical stirring, 19 g of $NaNO_2$ dissolved in the minimal amount of water was added dropwise such that the temperature remained below −8 °C. The resultant purple syrup was added to 200 mL of chilled 50% H_3PO_2 with vigorous stirring and then allowed to stand overnight. The mixture was then extracted with CH_2Cl_2 and the solvent was removed in vacuo to afford 22.8 g of crude product. This residue was purified by chromatography over silica gel (8 × 20 cm column, eluting with increasing ethyl acetate/chloroform mixtures) to give 9.7 g (48% yield) of **18**. An analytical sample was prepared by crystallization from CH_2Cl_2/hexane/ether: mp 121–123 °C; IR (KBr) 3255, 1745, 1639, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 6 H), 2.1 (s, 3 H), 3.8 (s, 2 H), 4.0 (s, 3 H), 4.3 (q, 4 H), 6.7 (s, 1 H), 6.9 (s, 1 H), 7.3 (s, 1 H), 9.0 (s, 1 H). Anal. (($C_{18}H_{22}N_2O_6S)_2 \cdot H_2O$) C, H, N, S.

α-Amino-(4-hydroxy-6-benzothiazolyl)propionic Acid (1). **18** (68.7 mg) was heated at ca. 144 °C together with 2 mL of 6 N HCl in an evacuated sealed tube for 24 h. Pure amino acid hydrochloride **1** (47.8 mg, 100% yield) was obtained by removal of the solvent in vacuo followed by crystallization from absolute ethanol/ethyl acetate; mp 205 dec. We were not able to prepare suitable analytical samples due to the compound's sensitivity to air: IR (KBr) 2920, 1750, 1600, 1500, 1450 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.2 (m, 2 H), 4.1 (m, 1 H), 6.9 (s, 1 H), 7.5 (s, 1 H), 8.3, 8.6 (D_2O exchangeable signals), 9.2 (s, 1 H).

Methyl α-Amino-(4-hydroxyl-6-benzothiazolyl)propionate. **1** (200 mg) was dissolved in HCl-saturated methanol and the resultant solution heated to reflux for 3 h. After being cooled, the solvent was removed in vacuo and the residue crystallized from acetone to afford 160 mg (80.0% yield) of the hydrochloride salt of methyl α-amino-(4-hydroxy-6-benzothiazolyl)propionate as colorless crystals, mp 198–202 °C. Anal. ($C_{11}H_{12}N_2O_3S \cdot HCl$) C, H, N, S, Cl.

***N,N*-Bis(2,4-dinitrophenyl) Derivative of Methyl α-Amino-(4-hydroxy-6-benzothiazolyl)propionate (19).** 2,4-Dinitrofluorobenzene (148 mg) in 1 mL of ethanol was added to a solution of 100 mg of methyl α-amino-(6-benzothiazole-4-hydroxy)propionate hydrochloride and 200 mg of Na_2CO_3 in 2 mL of water. The mixture was shaken vigorously for several minutes and stirred at room temperature for 1 h. The mixture was then decanted and 1 mL of saturated NaCl solution added to the aqueous phase prior to extraction with ether (1 × 25 mL). The aqueous layer was acidified with dilute HCl and the resultant precipitate collected and recrystallized from 95% ethanol to yield 72 mg (31% yield) of light yellow crystals, mp 168–171 °C (lit.[14] mp 174–176 °C).

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Registry No. (±)-**1**·HCl, 73368-39-5; (±)-**2**·HCl, 73368-40-8; **9**, 73368-41-9; **10**, 73368-42-0; **11**, 73368-43-1; **14**, 23145-65-5; **15**, 73384-27-7; **16**, 73368-44-2; **17**, 73384-28-8; **17**·HBr, 73384-29-9; **18**, 73384-30-2; (±)-**19**, 73368-45-3; 5-methyl-2-nitrophenol, 700-38-9; 3-methoxy-4-nitrobenzoic acid, 5081-36-7; ethyl 3-methoxy-4-nitrobenzoate, 10259-23-1; diethyl acetamidomalonate, 1068-90-2; 2,4-dinitrofluorobenzene, 70-34-8; 3-methoxy-4-nitrotoluene, 38512-82-2.

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