*Analyses élémentaires des esters orthothioboriques*

Les orthothioborates s'avèrent des substances extrêmement hygroscopiques, la réaction des premiers termes avec l'eau étant quasi explosive. Cette sensibilité a rendu les analyses C—H—S très difficiles et n'ont été effectuées que pour le dérivé éthyle. Les déterminations de bore ont été effectuées en utilisant la méthode spectrométrique à flamme décrite par Yoshizaki (5). Les solutions standards d'acide borique servant à établir une courbe de calibration renfermait de l'éthanethiol dans le rapport molaire $H_3BO_3$/EtSH = 1/3. Des échantillons des esters orthothioboriques (≈1.0 g) ont été pesés exactement dans des ballons jaugés de 100 ml et hydrolysés par simple addition d'eau. Les mesures ont été effectuées à l'aide d'un spectromètre Beckman DU avec une flamme d'hydrogène, à une longueur d'onde de 519 mμ.

Avec l'orthothioborate de méthyle, un échantillon (1.0028 g) de l'ester a été placé dans un dessicateur contenant une solution à 20% de NaOH. Après 48 h sous un léger vide, l'ester est transformé en un solide dont le poids demeure constant; l'acide borique, 0.4162 g, p.f. 178°; soit 7.26% de bore dans l'ester initial.

Anal. Calc. pour $B(SCH_3)_3$: 7.11.

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## THE SYNTHESIS OF 5-MERCAPTOTRYPTAMINE, THE THIOL ANALOG OF SEROTONIN

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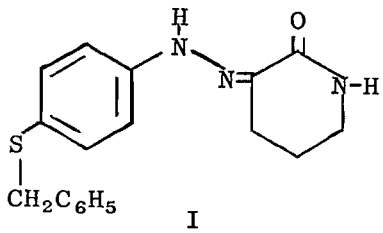
The antimetabolite concept of drug development is, of course, well known and widely utilized. Wooley (1) has discussed the use of antimetabolites of serotonin in the treatment of hypertension and certain other diseases. Serotonin (5-hydroxytryptamine) was first isolated from beef serum and its structure proved in 1948 (2). We report the synthesis of the thiol analog of serotonin, 5-mercaptotryptamine (V).[1]

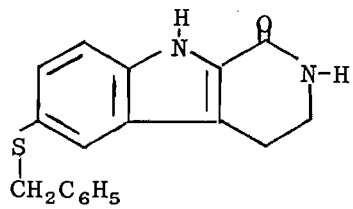
The route to V was via 2,3-piperidione-3-(4′-benzylthio)phenylhydrazone (I). Compound I was prepared in 35% yield by a Japp-Klingemann reaction (3) from 4-benzylthiobenzene diazonium chloride and potassium 2-oxopiperidine-3-carboxylate at 0° by a general, published procedure (4, 5). The hydrazone I was cyclized smoothly with hydrogen chloride in glacial acetic acid (6) to 6-benzylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (II) in 73% yield. Recent experiments in the same field have shown that refluxing hydrazone I in 90% formic acid for 1 h also gave good yields of II. The β-carboline II was cleaved with aqueous-ethanolic potassium hydroxide (4) by refluxing overnight to afford 3-(2′-aminoethyl)-5-benzylthio-2-indole carboxylic acid (III) in quantitative

[1]*C. J. Peake, F. L. Benton, and C. E. Brambel, Abstracts of Papers, 140th A.C.S. Meeting, Chicago, September, 1961, p. 6-O, reported the synthesis of V in 1961. The meeting abstracts give no physical properties nor experimental details and no further reference to this compound is found in the later literature.*

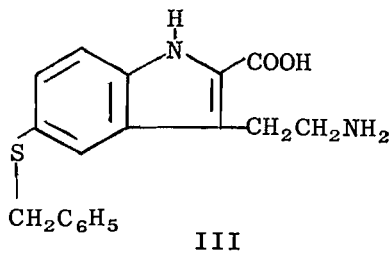
yield. The decarboxylation of III was achieved with a mixture of 2 *N* hydrochloric acid and acetic acid (3:2, v/v) giving 5-benzylthiotryptamine (IV) in 70% yield. This facile decarboxylation during overnight refluxing was somewhat unexpected because of the published report (4) that 3-(2′-aminoethyl)-5-benzyloxy-2-indole carboxylic acid could not be decarboxylated under a variety of conditions. The thio ether IV was debenzylated with sodium in liquid ammonia under a nitrogen atmosphere and 5-mercaptotryptamine (V) was isolated as the picrate in 67% yield. The thiol V in dilute ammonia gave the characteristic aromatic thiol test with nitroprusside. Quantitative determination of the SH function of thiol V hydrochloride by ultraviolet spectrophotometry according to the method of Ellman (7) showed the absence of appreciable disulfide.



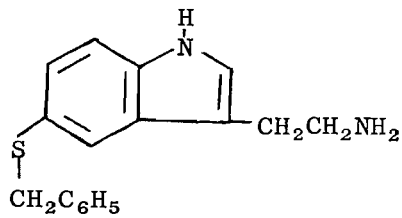

I



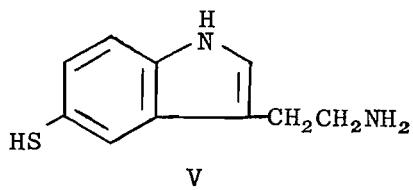

II




III




IV




V

## EXPERIMENTAL[2]

*2,3-Piperidione-3-(4′-benzylthio)phenylhydrazone (I)*

Ethyl 2-oxopiperidine-3-carboxylate (23.3 g, 0.136 mole) was dissolved in 60 ml of warm ethyl alcohol, cooled to 0° and diluted with a solution of 9.29 g (0.139 mole) of potassium hydroxide in 50 ml of water. This clear solution was cooled overnight, diluted with 500 g of ice water, and stirred while adding a suspension of 4-benzylthiobenzene diazonium chloride (prepared from 0.13 mole of 4-benzylthioaniline and 0.13 mole of sodium nitrite in 100 ml of 4 *N* hydrochloric acid). Immediately after the addition was complete, 20 g of sodium acetate was added. The tan mixture was stirred at 0° for 5 h then left at 25° overnight. The solid product was collected, washed with water, and recrystallized from dilute ethyl alcohol or methyl ethyl ketone to give 14.8 g deep-yellow rosettas, m.p. 203–205°. The analytical sample prepared by further recrystallizations from the same solvents melted at 207–208°. $\lambda_{max(\mu)}^{Nujol}$ 3.10, 3.15 (NH); 6.00 (amide C=O); 6.23 (aryl); 6.44 (amide II); 12.1 (1,4-disubstituted benzene).

Anal. Calcd. for $C_{18}H_{19}N_3OS$: C, 66.4; H, 5.89; N, 12.9. Found: C, 66.2; H, 5.99; N, 13.0.

[2]*All melting points are uncorrected and were taken with a Fisher–Johns melting block.*

*6-Benzylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (II)*

Dry hydrogen chloride was passed into a solution of 6.2 g (0.019 mole) of 2,3-piperidione-3-(4′-benzylthio)phenyl hydrazone (I) in 120 ml of warm acetic acid for 15 min. The resulting suspension was refluxed 15 min, reduced to half volume *in vacuo*, and poured over cracked ice. The resulting grey solid was collected and recrystallized from isopropyl alcohol to give 4.3 g of β-carboline II, m.p. 194–195°. Additional purification by recrystallization gave m.p. 197–198° $\lambda_{max(\mu)}^{CHCl_3}$ 2.89, 3.07 (NH); 5.97 (amide C=O); absence of 1,4-disubstituted benzene band at 12.1.

Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.1; H, 5.23; N, 9.09. Found: C, 70.3; H, 5.45; N, 9.26.

*3-(2′-Aminoethyl)-5-benzylthio-2-indole Carboxylic Acid (III)*

6–Benzylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (II) (4.0 g, 0.013 mole) was refluxed overnight with a solution of 8.6 g (0.13 mole) of potassium hydroxide, 48 ml of ethyl alcohol, and 32 ml of water. The red solution was concentrated to half volume and adjusted to pH 5 with acetic acid. The white solid was collected, washed with water, and dried to give a quantitative yield of product III, m.p. 224–227°. The analytical sample (dilute ethyl alcohol) decomposed at 237°. $\lambda_{max(\mu)}^{Nujol}$ 2.94 (NH); 3.10 (NH, OH); 5.90 (acid C=O); 6.20 (aryl); 13.0, 14.3 (monosubstituted benzene).

Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.2; H, 5.56; N, 8.58. Found: C, 66.0; H, 5.57; N, 8.70.

*5-Benzylthiotryptamine (IV)*

A solution of 3.0 g (0.009 mole) of 3-(2′-aminoethyl)-5-benzylthio-2-indole carboxylic acid (III) in 45 ml of 2 *N* hydrochloric acid and 30 ml of acetic acid was refluxed overnight. The clear, red solution was concentrated to half volume and cooled to yield 2.0 g of 5-benzylthiotryptamine hydrochloride, m.p. 207–210°. Recrystallization from isopropyl alcohol – ether produced the analytical sample, m.p. 213–214°. $\lambda_{max(\mu)}^{Nujol}$ 3.00 (indole NH); absence of acid C=O at 5.90; 6.20, 6.25 ($NH_2$, aryl); 12.9, 14.2 (monosubstituted benzene).

Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 64.0; H, 6.01; N, 8.79. Found: C, 63.9; H, 6.02; N, 8.90.

*5-Mercaptotryptamine (V)*

Dry 5-benzylthiotryptamine hydrochloride (0.5 g, 1.58 mmoles) in a dried 50 ml flask was finely powdered and covered with 15 ml of anhydrous ammonia. The reaction was immersed in a dry ice – acetone bath and protected from moisture with a drying tube packed with dried cotton. The mixture was stirred magnetically and 0.2 g of sodium in small pieces was added in one portion. The blue reaction mixture was stirred for 0.5 h. Then 0.002 mole of ammonium iodide was added and the ammonia removed at 25° under a dense stream of dry nitrogen. A prepared solution of 0.002 mole of hydroquinone, 0.002 mole of acetic acid, and 0.002 mole of picric acid in 33 ml water and 2 ml ethyl alcohol was quickly added. The solution was adjusted to pH 5 with 5 ml of acetic acid and the orange precipitate was stirred under nitrogen for 0.5 h, then left at 25° overnight. The picrate was collected and washed with water and dried to give 0.45 g, m.p. 220° (decomp.). The picrate (150 mg) was recrystallized from ethyl alcohol – water.

Anal. Calcd. for $C_{10}H_{12}N_2S \cdot C_6H_3N_3O_7$: C, 45.6; H, 3.59; N, 16.6. Found: C, 45.7; H, 3.55; N, 16.7.

5-Mercaptotryptamine picrate (0.4 g) was suspended in 50 ml of boiled ethyl alcohol and stirred under nitrogen overnight with 5 g of Dowex chloride resin. The mixture was filtered and the filtrate concentrated to give 5-mercaptotryptamine hydrochloride as an oil which was stored in a cold, dark place under nitrogen. $\lambda_{max(\mu)}^{film}$ 2.95, 3.05 (NH); 6.18 (aryl); absence of benzene monosubstitution bands at 12.9, 14.2. A solution of mercuric chloride was added to 0.043 mmoles of the thiol V hydrochloride in water to give 21.6 mg of the salt; theoretical weight for RSHgCl·HCl is 21.4 mg.

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