

hydroxide was dissolved in 490 ml. of water and added to 306 ml. of 95% ethyl alcohol contained in a 2-l. beaker. Two hundred and ninety grams (5.0 moles) of acetone was added and the mixture chilled to about 25°. One hundred and forty-nine grams (1.0 mole) of *p*-dimethylaminobenzaldehyde was added and the mixture mechanically stirred. Crystallization began in about thirty minutes and the stirring was continued for an additional two hours. The mixture was kept at 0° overnight and then filtered. The orange crystals were washed with cold water until the wash water was neutral to litmus paper. The washing was completed with about 50 ml. of cold 95% ethyl alcohol. The product was recrystallized from about 4 to 5 times its weight of 95% ethyl alcohol and yielded 149 g. (79%) of product, m. p. of 133–135°. The reported<sup>8</sup> m. p. of 234–235° seems to be a typographical error.

**bis-(*p*-Dimethylaminobenzal)-acetone, III.**—Sixty-three grams (0.3 mole) of *p*-dimethylaminobenzalacetone and 50 g. (0.3 mole) of *p*-dimethylaminobenzaldehyde were dissolved in 500 ml. of hot 95% ethyl alcohol contained in a 1-l. beaker. Twenty-five milliliters of a 10% aqueous solution of sodium hydroxide was added and the solution heated on the steam-bath while being mechanically stirred. After about fifteen minutes dark red crystals began to appear. The stirring and heating was continued for an additional two hours (adding more alcohol as needed to prevent boiling to dryness) after which time crystallization appeared to be complete. The mixture was allowed to cool, then filtered and the product washed with 95% ethyl alcohol. The dark red crystals were then boiled with 250 ml. of alcohol, filtered while hot, and washed with hot alcohol. The yield was 60 g. (55%) of product, m. p. 189.5–191°, reported<sup>8</sup> m. p. 191°.

**2-(2'-Methyl-4'-*p*-dimethylaminophenyl-1,3'-butadiene)-benzothiazole Ethiodide, IV.**—To 1.9 g. of the ketone, II, was added 3.1 g. of the quaternary salt, 2-methylbenzothiazole ethiodide, in a 200 ml. round-

bottom flask fitted with a reflux condenser. Twenty-five milliliters of acetic anhydride was added and the mixture refluxed for fifteen minutes. After cooling, 150 ml. of ether was added and the supernatant liquor decanted. The tarry residue was dissolved in 200 ml. of hot methyl alcohol and 4 g. of potassium iodide added. After cooling, the greenish-black crystalline product was filtered and recrystallized several times from methyl alcohol; m. p. 229–230° (dec.); yield 0.07 g. (1.5%).

*Anal.* Calcd. for  $C_{22}H_{25}N_3SI$ : C, 55.46; H, 5.29; N, 5.88. Found: C, 55.61; H, 5.01; N, 6.02.

**2-(2'-*p*-Dimethylaminostyryl-4'-*p*-dimethylaminophenyl-1,3'-butadiene)-benzothiazole Ethiodide, V.**—To 3.2 g. of the ketone, III, was added 3.1 g. of the quaternary salt, 2-methylbenzothiazole ethiodide, in a 200-ml. round-bottom flask fitted with a reflux condenser. Twenty-five milliliters of acetic anhydride was added and the mixture refluxed for twenty-five minutes. The reaction mixture was treated as above and yielded 0.33 g. (5.4%) of the greenish-black crystalline material; m. p. 242–243° (dec.).

*Anal.* Calcd. for  $C_{31}H_{34}N_3SI$ : C, 61.28; H, 5.64; N, 6.92. Found: C, 61.02; H, 5.76; N, 6.80.

### Summary

Four new derivatives, the oxime, phenylhydrazone, *p*-nitrophenylhydrazone, and 2,4-dinitrophenylhydrazone, of the ketone, *p*-dimethylaminobenzalacetone, were prepared and described.

Two hemicyanines containing substituents on the methylidyne bridge were prepared by the condensation of a ketone with 2-methylbenzothiazole ethiodide in acetic anhydride solution.

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## The Synthesis and Microbiological Properties of $\beta$ -(2-Benzothienyl)- $\alpha$ -aminopropionic Acid<sup>1a</sup>

BY SOUREN AVAKIAN, JACK MOSS AND GUSTAV J. MARTIN

Fildes<sup>1</sup> pioneered the field of tryptophan displacement when he determined the capacity of  $\beta$ -indoleacrylic acid to inhibit the growth of *E. coli* and *B. typhosum*. Subsequently, many other compounds have been synthesized and studied as tryptophan displacers: 1-naphthylacrylic and styrylacetic acids,<sup>2</sup> 5-methyl-DL-tryptophan,<sup>3</sup> 3-acetylpyridine,<sup>4</sup>  $\beta$ -(cumaronyl-(3))-alanine and  $\beta$ -(naphthyl-(1))-alanine,<sup>5</sup> methylated indoles,<sup>6</sup>  $\beta$ -1-naphthylalanine and  $\beta$ -2-naphthylalanine.<sup>7</sup>

Desiring to extend knowledge of this field of displacement, the synthesis and testing of  $\beta$ -(2-benzothienyl)- $\alpha$ -aminopropionic acid was undertaken.

(1a) Presented in part before Organic Section, American Chemical Society Meeting in Miniature, Philadelphia Section, Jan. 22, 1948.

(1) P. Fildes, *Biochem. J.*, **32**, 1600 (1948).

(2) H. Bloch and H. Erlenmeyer, *Helv. Chim. Acta.*, **25**, 694 (1942).

(3) T. F. Anderson, *Science*, **101**, 565 (1945).

(4) D. W. Woolley, *J. Biol. Chem.*, **162**, 179 (1946).

(5) H. Erlenmeyer and W. Grubenmann, *Helv. Chim. Acta*, **30**, 297 (1947).

(6) P. Fildes and H. N. Rydon, *Brit. J. Exp. Path.*, **28**, 211 (1947).

(7) K. Dittmer, W. Herz and S. J. Cristol, *J. Biol. Chem.*, **173**, 323 (1948).

### Experimental

**2-Chloromethylbenzothiophene.**—A rapid current of hydrogen chloride was passed through a vigorously stirred mixture of 20.1 g. (0.15 mole) of benzothiophene<sup>8</sup> and 20 cc. of 40% formaldehyde cooled in an ice-bath. The reaction temperature was kept at 20–25° for five minutes and then at 10–15°. After half an hour the mixture was diluted with ice water and extracted with ether. The ether layer was washed with aqueous sodium bicarbonate solution, and dried over sodium sulfate. Distillation gave 15.5 g. (56.3% yield) of product boiling at 129–131° (5.0 mm.). Crystallization from petroleum ether gave a white crystalline product melting at 44–45°.

*Anal.* Calcd. for  $C_9H_7ClS$ : Cl, 19.44. Found: Cl, 19.38.

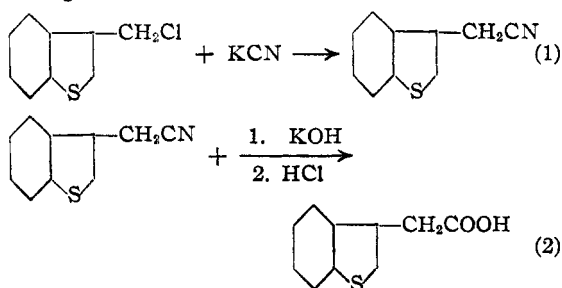
**Ethyl- $\alpha$ -carbethoxy- $\alpha$ -formylamido- $\beta$ -(2-benzothienyl)-propionate.**—To a solution of 1.2 g. of sodium in 100 cc. of absolute alcohol, was added 10.2 g. of ethyl formylaminomalonate<sup>9</sup> followed by 9.2 g. of 2-chloromethylbenzothiophene. The mixture was refluxed for three hours, poured into ice water, and the precipitate filtered; yield of the crude product, melting at 103–105° was 29 g. (83%). An analytical sample crystallized from benzene-petroleum ether melted at 106–107°. *Anal.* Calcd. for  $C_{17}H_{19}O_6NS$ : S, 9.15. Found: S, 8.91.

(8) C. Hansch and H. G. Lindwall, *J. Org. Chem.*, **10**, 381 (1945).

(9) A. Galat, *THIS JOURNAL*, **69**, 965 (1947).

**$\beta$ -(2-Benzothiényl)- $\alpha$ -aminopropionic Acid.**—Fourteen grams of ethyl  $\alpha$ -carbethoxy- $\alpha$ -formylamido- $\beta$ -(2-benzothiényl)-propionate was refluxed with 200 cc. of concentrated hydrochloric acid for six hours. The solution was evaporated to dryness under reduced pressure and the residue dissolved in 50% ethyl alcohol. Neutralization with ammonium hydroxide gave 6.5 g. (75% yield) of  $\beta$ -(2-benzothiényl)- $\alpha$ -aminopropionic acid, m. p. 279–280°. *Anal.* Calcd. for  $C_{11}H_{11}O_2NS$ : S, 14.48. Found: S, 14.28.

The position of the chloromethyl group was established through the reactions



The benzothiophene-2-acetic acid had the same melting point as that prepared from 2-bromobenzothiophene by Crook and Davies.<sup>10</sup>

**2-Benzothiopheneacetonitrile.**—A solution of 9.2 g. (0.05 mole) of 2-chloromethylbenzothiophene in 50 cc. of alcohol was added dropwise and with stirring to a hot solution of 2.8 g. of potassium cyanide in 10 cc. of water. The mixture was heated and stirred for four hours, the

(10) E. M. Crook and W. Davies, *J. Chem. Soc.*, 1697 (1937).

alcohol replaced with water, and then extracted with ether. Distillation of the dried solution yielded 4.5 g. (50.5%) of product boiling at 124–126° (0.2 mm.). Crystallization from benzene-petroleum ether gave the pure product melting at 66–67°. *Anal.* Calcd. for  $C_{10}H_7NS$ : S, 18.47. Found: S, 18.36.

**Benzothiophene-2-acetic Acid.**—A solution of 3 g. of 2-benzothiophene acetonitrile and 5 g. of potassium hydroxide in 40 cc. of 50% ethyl alcohol was refluxed for eighteen hours. The alcohol was evaporated and the solution acidified with hydrochloric acid. The crude product was filtered off and on crystallization from dilute alcohol gave the pure product melting at 108–109°.

$\beta$ -(2-Benzothiényl)- $\alpha$ -aminopropionic acid was tested as a tryptophan displacer employing the technique of Wooley and Sebrell<sup>11</sup> and Snell and Wright.<sup>12</sup> The organism was *Lactobacillus arabinosus* 17-5. All results were read turbidimetrically.

Compound	Concentration μg./10 cc.	Inhibitor- Metabolite ratio
$\beta$ -(2-Benzothiényl)- $\alpha$ -aminopropionic acid	1 to 10,000	250
5-Methyl-DL-tryptophan	1 to 10,000	2500

### Summary

$\beta$ -(2-Benzothiényl)- $\alpha$ -aminopropionic acid was synthesized and found to be an effective antagonist for tryptophan in microbiological systems.

(11) J. G. Wooley and W. H. Sebrell, *J. Biol. Chem.*, **157**, 141 (1945).

(12) E. E. Snell and L. D. Wright, *ibid.*, **139**, 675 (1941).

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## The Papilionaceous Alkaloids. III. Identity of Rhombinine and Monolupine with Anagryne<sup>1</sup>

BY LÉO MARION AND JACQUES OUELLET

The alkaloid rhombinine, first reported as occurring in *Thermopsis rhombifolia*,<sup>2</sup> has also been found in *Lupinus macounii*<sup>3</sup> in which it is accompanied by its saturated derivative, hydrorhombinine. This last alkaloid has now been found to be identical with *l*-lupanine. Whereas the catalytic hydrogenation of rhombinine at 400 lb. pressure produces *l*-lupanine, hydrogenation at higher pressures gives rise to *d*-sparteine, thus establishing the structural relationship between the base and the sparteine molecule. On the basis of the analysis of its perchlorate, the empirical formula of rhombinine had been assumed<sup>2</sup> to be  $C_{16}H_{22}O_2N_2$ . However, the results of the catalytic hydrogenation of the base together with the preparation of several more salts and derivatives make it evident that the formula is more correctly represented by  $C_{15}H_{20}ON_2$  and, therefore, the base must contain two double bonds.

(1) (a) Published as National Research Council Bull. No. 1730;

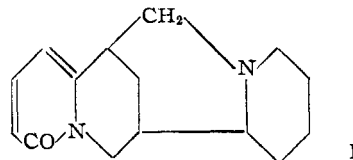
(b) Previous paper in this series: *THIS JOURNAL*, **70**, 691 (1948).

(2) R. H. F. Manske and L. Marion, *Can. J. Research*, **B21**, 144 (1943).

(3) L. Marion, *THIS JOURNAL*, **68**, 759 (1946).

As the similarity between the melting points of various salts of rhombinine and those of similar salts of monolupine<sup>4</sup> is striking, a comparison of the two bases was made. A sample of monolupine hydrochloride, which had kindly been sent by Dr. J. F. Couch to Dr. R. H. F. Manske, was made available and from it several salts were prepared. These salts had the same melting points as the corresponding salts of rhombinine and admixture failed to cause any depression. Hence, the two bases are identical.

The alkaloid anagryne is also represented by  $C_{15}H_{20}ON_2$  and is also reducible to *l*-lupanine and *d*-sparteine.<sup>5</sup>



Its accepted structure I could differ from that of

(4) J. F. Couch, *ibid.*, **58**, 686 (1936).

(5) H. R. Ing, *J. Chem. Soc.*, 504 (1933).