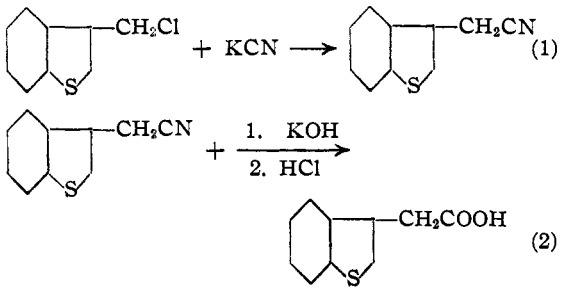
β-(2-Benzothienyl)-α-aminopropionic Acid.—Fourteen grams of ethyl α-carbethoxy-α-formylamido-β-(2-benzothienyl)-propionate was refluxed with 200 cc. of concentrated hydrochloric acid for six hours. The solution was evaporated to dryness under reduced pressure and the residue dissolved in 50% ethyl alcohol. Neutralization with ammonium hydroxide gave 6.5 g. (75% yield) of β-(2-benzothienyl)-α-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.[10]

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 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°.

β-(2-Benzothienyl)-α-aminopropionic acid was tested as a tryptophan displacer employing the technique of Wooley and Sebrell[11] and Snell and Wright.[12] The organism was *Lactobacillus arabinosus* 17–5. All results were read turbidimetrically.

Compound	Concentration μg./10 cc.	Inhibitor–Metabolite ratio
β-(2-Benzothienyl)-α-aminopropionic acid	1 to 10,000	250
5-Methyl-DL-tryptophan	1 to 10,000	2500

Summary

β-(2-Benzothienyl)-α-aminopropionic acid was synthesized and found to be an effective antagonist for tryptophan in microbiological systems.

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

(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).

PHILADELPHIA 44, PA. RECEIVED APRIL 12, 1948

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL AND L'INSTITUT DE CHIMIE, UNIVERSITY OF MONTREAL]

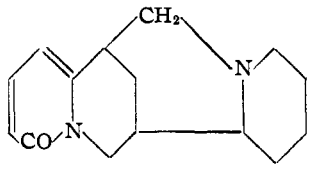
The Papilionaceous Alkaloids. III. Identity of Rhombinine and Monolupine with Anagyrine[1]

BY LÉO MARION AND JACQUES OUELLET

The alkaloid rhombinine, first reported as occurring in *Thermopsis rhombifolia*,[2] has also been found in *Lupinus macounii*[3] 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[2] 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.

As the similarity between the melting points of various salts of rhombinine and those of similar salts of monolupine[4] 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 anagyrine is also represented by $C_{15}H_{20}ON_2$ and is also reducible to *l*-lupanine and *d*-sparteine.[5]



I

Its accepted structure I could differ from that of

(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).

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

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

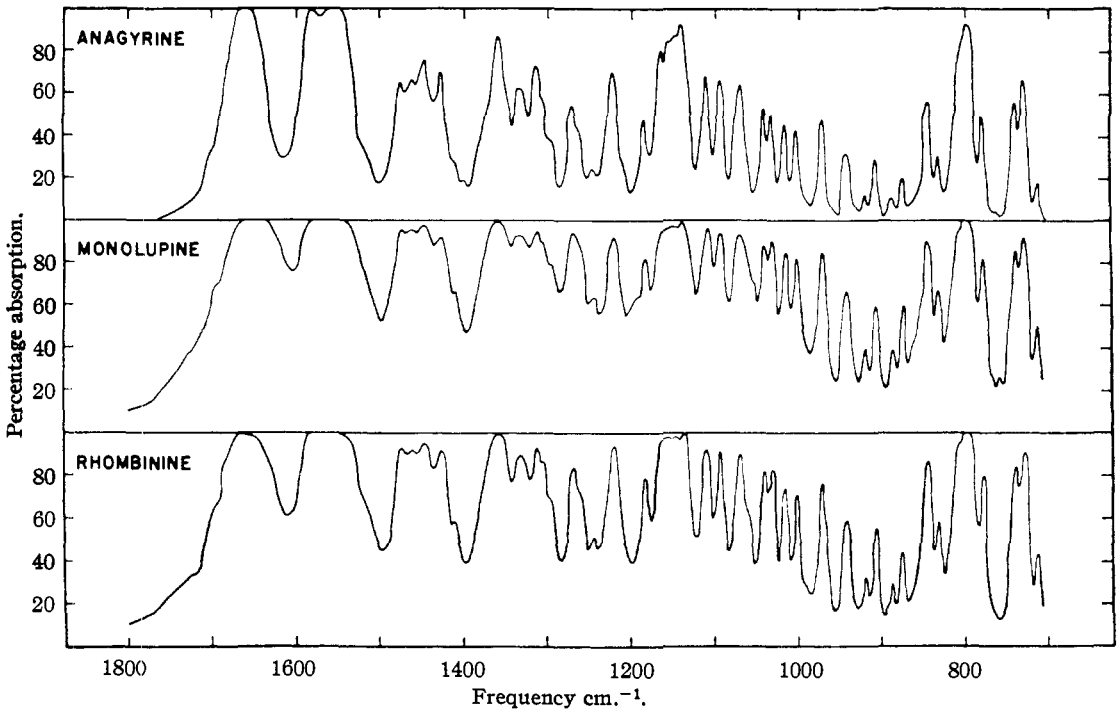


Fig. 1.

rhombinine only in the positions occupied by the double bonds. Although the addition of bromine to rhombinine gives rise to a dibromoderivative having the same melting point as dibromoanagyrine, the reported melting point of anagyrine perchlorate[5,6] differs by 45° and that of anagyrine chloroplatinate[6,7] by 30° from those of the corresponding salts of rhombinine and, therefore, the identity of the two bases seemed precluded. A direct comparison was made possible, however, through the kindness of Prof. G. R. Clemo who sent a sample of anagyrine picrate and of Dr. J. F. Couch who gave a most generous sample of anagyrine dihydrochloride. The results given below leave no doubt as to the identity of rhombinine, monolupine and anagyrine. The statement in the literature[8] that the last two bases are distinct was obviously based on insufficient evidence. The identity has also been confirmed by a comparison of the infrared spectra of thin films of the three alkaloids (Fig. 1). The absorption spectra were taken by Drs. R. N. Jones and D. A. Ramsay, of these laboratories, whose courtesy is gratefully acknowledged.

Experimental

Rhombinine.—Rhombinine perchlorate[2] was dissolved in water, the solution alkalized with ammonia and extracted with chloroform. The base recovered from the extract and distilled, b. p. 165–168° (0.3 mm.), is a very thick oil with a yellowish cast. It has $[\alpha]_D$ −157.0° (*c*, 2.236 in absolute ethanol).

A small quantity of the base was dissolved in methanol and the solution made acid to congo red with 65% perchloric acid. The perchlorate, after several recrystallizations from boiling methanol and from water, consisted of long needles, m. p. 315° (dec.).[9] (Anagyrine perchlorate is reported as melting at 270°, uncor.[5,6])

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot HClO_4$: C, 52.25; H, 6.10; N, 8.13. Found: C, 52.41, 52.31; H, 5.96, 6.03; N, 7.71, 7.90.

Another quantity of rhombinine was converted in methanolic solution to the picrate which separated as an oil. This oil was redissolved in boiling methanol from which it crystallized as fine yellow needles, m. p. 253° (dec.).

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot C_6H_3O_7N_3$: C, 53.27; H, 4.86; N, 14.80. Found: C, 53.66, 53.67; H, 4.87, 4.98; N, 14.73, 15.08.

A further quantity of rhombinine was dissolved in methanol and the solution made acid to congo red by the addition of methanol containing concentrated hydrochloric acid. The solution was evaporated to dryness, the residue redissolved in methanol and again evaporated to dryness. The residual salt was dissolved again in methanol, the solution concentrated to a small volume and diluted with acetone to incipient turbidity. Rhombinine dihydrochloride separated as colorless needles. On heating it liquefied at *ca.* 120° where it lost water of crystallization, solidified again and melted at 265°; it then lost hydrogen chloride, solidified once more and finally melted at 284° (melting point of the monohydrochloride).

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot 2HCl \cdot 2.5H_2O$: C, 49.73; H, 7.46; Cl, 19.62. Found: C, 49.97, 50.03; H, 7.44, 7.42; Cl, 20.05, 20.44.

On standing, the mother liquor from the dihydrochloride deposited a crop of small, colorless prisms, m. p. 286°.

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot HCl \cdot H_2O$: C, 60.32; H, 7.60; Cl, 11.90. Found: C, 60.00, 59.84; H, 7.65, 7.68; Cl, 12.24, 12.48.

(6) A. Orechoff, S. Norkina and H. Gurewitsch, *Ber.*, **67**, 1394 (1934).

(7) G. R. Clemo and R. Raper, *J. Chem. Soc.*, 10 (1935).

(8) J. F. Couch, THIS JOURNAL, **61**, 3327 (1939).

(9) All melting points are corrected.

A small quantity of rhombinine dihydrochloride was dissolved in dilute hydrochloric acid and added to a 5% solution of platinic chloride. A chloroplatinate separated which after recrystallization from 20% hydrochloric acid, consisted of orange prisms which darkened at 275° and melted at 278° (dec.). (The m. p. 250–251° is recorded in the literature for anagyrine chloroplatinate[6,7].)

Rhombinine (0.12 g.) was dissolved in ethyl acetate and an excess of methyl iodide added. After a few hours at room temperature, the methiodide had separated as small prisms. Recrystallized from methanol-ethyl acetate, it melted at 257°.

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot CH_3I$: C, 49.74; H, 5.96; N, 7.25. Found: C, 49.91, 49.73; H, 5.75, 5.83; N, 7.39, 7.22.

Dibromorhombinine hydrobromide was prepared by the method described for the preparation of dibromoanagyrine.[10] The base was liberated from its salt and recrystallized from ethanol from which it separated as colorless flakes, m. p. 202.5–203°.

Anal. Calcd. for $C_{15}H_{20}ON_2Br_2$: Br, 39.60. Found: Br, 43.28, 42.76.

Hydrogenation of Rhombinine.—Rhombinine in aqueous solution was hydrogenated in the presence of Raney nickel at 105° and 400 lb. pressure as previously described.[3] The hydrogenated base, b. p. 120–130° (0.08 mm.), is a colorless oil which was converted in methanol to the perchlorate which, after recrystallization from boiling methanol, consisted of colorless, stout prisms, m. p. 213°, $[\alpha]_D$ −40.3° (*c*, 1.06 in water). When a quantity of this perchlorate was mixed with an equal weight of *d*-lupanine perchlorate (m. p. 209°) the mixture melted at 249° and this was not altered by further admixture with *dl*-lupanine perchlorate. The base recovered from the perchlorate consisted of a colorless oil.

Anal. Calcd. for $C_{15}H_{24}ON_2$: C, 72.57; H, 9.68. Found: C, 72.50, 72.35; H, 9.53, 9.73.

A solution of a small quantity of the free base in methanol was made just acid to congo red with concentrated hydrochloric acid and evaporated to dryness. The residue was dissolved in a little methanol and diluted with acetone. On standing, the dihydrochloride separated as colorless needles shrinking at 215° and melting at 216°.

Anal. Calcd. for $C_{15}H_{24}ON_2 \cdot 2HCl \cdot H_2O$: C, 53.10; H, 8.26; Cl, 20.94. Found: C, 52.79, 52.84; H, 8.07, 8.21; Cl, 20.09, 20.06.

When heated *in vacuo* the dihydrochloride lost hydrogen chloride and the monohydrochloride sublimed at 145–150° (0.05 mm.). Recrystallized from methanol-ether, it consisted of colorless prisms, m. p. 263°.

Anal. Calcd. for $C_{15}H_{24}ON_2 \cdot HCl \cdot 0.5H_2O$: C, 60.92; H, 8.80; Cl, 12.01. Found: C, 61.40, 61.57; H, 8.47, 8.60; Cl, 11.53, 11.68.

A small quantity of the base (0.0572 g.) was dissolved in a little water and added to a solution of ammonium thiocyanate (0.0175 g.) in a little water. The resulting solution was concentrated on the steam-bath and allowed to stand. The thiocyanate separated as colorless prisms which, after recrystallization from methanol-ether, melted at 143°, resolidified when cooled and melted again at 184.5°; wt. 0.0288 g., $[\alpha]_D$ −55.7° (*c*, 1.44 in water). The literature[11] gives $[\alpha]_D$ −55.3° for the *l*-lupanine thiocyanate.

The methiodide of the base crystallizes from methanol-ethyl acetate as stout colorless prisms, m. p. 274°.

Anal. Calcd. for $C_{15}H_{24}ON_2 \cdot CH_3I$: C, 49.22; H, 6.92; N, 7.18. Found: C, 49.43, 49.21; H, 6.88, 6.86; N, 7.25.

Conversion of Rhombinine to Sparteine.—Rhombinine (0.4 g.) was dissolved in water and hydrogenated over Raney nickel at 100° and 750 lb. pressure. After filtration of the catalyst the base was extracted from the aqueous solution with chloroform, the extract evaporated and the residual oil distilled *in vacuo*. It yielded the following fractions: I, b. p. 70–90° (0.05 mm.); II, b. p. 95–115° (0.05 mm.); III, b. p. 130–140° (0.05 mm.). The first fraction had $[\alpha]_D$ +17.1° (*c*, 1.39 in absolute ethanol). Fractions I and II were combined and converted in methanolic solution to a picrate which, after several recrystallizations from boiling methanol, consisted of yellow needles, m. p. 208°, either alone or after admixture with an authentic sample of *d*-sparteine dipicrate. Fraction III yielded a perchlorate, the melting point (213°) of which was not depressed by admixture with *l*-lupanine perchlorate.

Monolupine.—The sample of monolupine dihydrochloride obtained from Dr. Couch was recrystallized from methanol-acetone; it became liquid at *ca.* 115–116°, solidified and melted again at 256°, lost hydrogen chloride, solidified once more and finally melted at 285°. From this salt, the monohydrochloride, the picrate and the perchlorate were prepared as already described for rhombinine (Table I). Admixture of the salts with the corresponding salts of rhombinine failed to alter any of the melting points.

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot HClO_4$: C, 52.25; H, 6.10; N, 8.13. Found: C, 52.21, 52.12; H, 5.96, 6.03; N, 7.90.

TABLE I

MELTING POINTS, °C.

	Rhombinine	Monolupine	Anagyrine
$[\alpha]_D$	−157.0		−165.3
B·$HClO_4$	315	315	315
B·$C_6H_3O_7N_3$	253	252	253
B·HCl·H_2O	286	285	285
B·2HCl·2.5H_2O	120 265 284	116 256 285	120 260 284
B·H_2PtCl_6·2H_2O	278		280
$C_{14}H_{20}ON_2Br_2$	203		199

Anagyrine.—The sample of anagyrine dihydrochloride[3] received from Dr. Couch, after one recrystallization, became liquid at *ca.* 120°, solidified, melted again at 260°, lost hydrogen chloride, solidified once more and finally melted at 284°. From this salt the monohydrochloride, the picrate, the perchlorate, the chloroplatinate and the dibromo derivative were prepared as above (Table I). On mixing these salts and the derivative with the corresponding salts and derivative of rhombinine, none of the melting points was depressed. It may be noted that anagyrine is best purified by recrystallization of the picrate. The anagyrine picrate received from Prof. Clemo melted at 253°, either alone or after admixture with rhombinine picrate.

Summary

The alkaloid rhombinine has been shown to be identical with anagyrine. Anagyrine perchlorate and chloroplatinate have melting points higher than those hitherto on record. The alkaloid monolupine has also been shown to be identical with anagyrine. The identity of the three alkaloids is confirmed by a comparison of their infrared spectra.

OTTAWA, CANADA RECEIVED MAY 11, 1948

(10) M. Klostermann, *Arch. Pharm.*, **238**, 227 (1900).

(11) G. R. Clemo, R. Raper and C. R. S. Tenniswood, *J. Chem. Soc.*, 429 (1931).