# (−)-7-Hydroxy-β-isosparteine, an Alkaloid Accompanying β-Isosparteine in *Lupinus sericeus* Pursh[1a]

MARVIN CARMACK,[1b] STANLEY I. GOLDBERG,[1c] AND ERIC W. MARTIN[2]

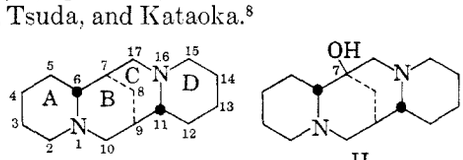
*Department of Chemistry, Indiana University, Bloomington, Indiana 47401, and Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania*

*Received September 30, 1966*

A crystalline alkaloid ($C_{15}H_{26}N_2O$) which accompanies (−)-β-isosparteine[3-5] in specimens of the plant, *Lupinus sericeus* Pursh, grown in southern Utah, has been shown by chemical evidence to be either 7-hydroxy-β-isosparteine or the 8-hydroxy isomer. The 7-hydroxy structure is favored by the chemical evidence and independently confirmed by X-ray crystallographic investigation.[6]

Specimens of dried, above-ground parts of the plant, *Lupinus sericeus* Pursh, collected near Salina, Utah,[5,7] yielded (−)-β-isosparteine as the principal alkaloid. The chemical proof of its structure and stereochemical relationship to (+)-sparteine have been previously described.[3-5]

The absolute configuration of (−)-β-isosparteine (I) follows from our earlier work[4] showing the identity of the configurations of C-7 and C-9 in (−)-β-isosparteine and in (+)-sparteine, and from the interconversions of Okuda, Tsuda, and Kataoka.[8]



I



II

A second crystalline alkaloid (mp 103.5–104.5°) isolated by us from *L. sericeus* Pursh in much smaller yield than (−)-β-isosparteine, was recognized as being one of the possible hydroxy derivatives of (−)-β-isosparteine because of the composition ($C_{15}H_{26}N_2O$), the presence of a strong hydroxyl band in the infrared spectrum, and a general similarity of the infrared spectra of the hydroxy base and of the major alkaloid, β-isosparteine; this similarity was particularly striking in the case of the monoperchlorate salts. In the remainder of this paper, data leading to structure II for this alkaloid are discussed.

The very unreactive character of the hydroxyl group caused us to exclude as improbable the location of the oxygen function at a position in rings A or D, since the many known hydroxysparteine derivatives having the hydroxyl substituents in these rings behave more or less typically as alcohols. A carbinolamine structure with the hydroxyl at any position α to a ring nitrogen (C-2, C-6, C-10, C-11, C-15, C-17) was also quickly ruled out, for the solutions of the hydroxy base in acids showed no tendency toward the very characteristic formation of immonium salts, or any of the other chemical behavior typical of a carbinolamine. Especially, no reduction occurred with lithium aluminum hydride.

The chemical inertness of the hydroxyl function was exemplified by the failure of that group to form a toluenesulfonate ester under any of the usual preparative conditions, complete resistance to oxidation to form a ketonic function, resistance to dehydrating agents, acetylation only under fairly vigorous conditions, and resistance to replacement of the hydroxyl group with halogen except under the special conditions of the Landauer and Rydon reagents, to be described below.

Typical of the inertness of the alcohol to oxidation were the results upon treatment of the hydroxy base with (a) alkaline ferricyanide, a reagent which readily brings about oxidation of β-isosparteine to its 10,17-dioxo derivative, (b) chromic anhydride–pyridine, and (c) chromic anhydride–acetic acid. All of these oxidizing conditions caused the formation from the hydroxy base of the same crystalline hydroxy lactam ($C_{15}H_{24}N_2O_2$), mp 218.5–219° cor.

It was finally possible to effect the replacement of the hydroxyl function with hydrogen by reduction with lithium aluminum hydride of the iodo derivative, which was prepared as a highly reactive compound by vigorous treatment of the hydroxy base with triphenyl phosphite

(1) (a) Contribution No. 1482 from the Department of Chemistry, Indiana University. (b) To whom inquiries should be address: Department of Chemistry, Indiana University, Bloomington, Ind. 47401. (c) A portion of the experimental work is from the Ph.D. Dissertation of S. I. Goldberg, Indiana University Graduate School, 1958; *Chem. Abstr.*, **53**, 3257*f* (1959).

(2) The original isolation of the two principal alkaloids of *L. sericeus* Pursh was described in the Ph.D. Dissertation of E. W. Martin, submitted to the Graduate School, University of Pennsylvania, 1949. Regarding names, *cf.* footnote 3.

(3) We have adopted the name, β-isosparteine, to describe the principal alkaloid of *L. sericeus* Pursh and discontinue the use of the name, spartalupine, used in previous papers,[2,4] as recommended by Leonard.[5] There no longer appears to be likelihood of confusion of this alkaloid with the substance described as β-isosparteine by K. Winterfeld and C. Rauch, *Arch. Pharm.*, **272**, 273 (1934).

(4) (a) M. Carmack and E. W. Martin, Abstracts of Papers, 124th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1953, 32-O. (b) M. Carmack, B. Douglas, E. W. Martin, and Hanna Suss, *J. Am. Chem. Soc.*, **77**, 4435 (1955).

(5) N. J. Leonard, "The Alkaloids, Chemistry and Physiology," Vol. VII, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 274, 284, 285, 289.

(6) J. M. H. Pinkerton and L. K. Steinrauf, *J. Org. Chem.*, **32**, 1828 (1967).

(7) Collections of plant material were made during the summers of 1943, 1947, and 1954 under the direction of Dr. W. T. Huffman, Veterinarian in Charge, Stock Poisoning by Plants, Salt Lake City Office, Bureau of Animal Industry, U. S. Department of Agriculture Research Administration, U. S. Department of Agriculture. The lupine plants were collected during the flowering season in early summer at the Salina Experiment Station of the U. S. Department of Agriculture, in the Fishlake National Forest, 16 miles from Salina, Utah. Botanical specimens from these collections were examined by several botanists and were found to have characteristics of the species *Lupinus spathulatus*, *L. ornatus*, and *L. sericeus* Pursh. The latter classification, which we have adopted, was made by Charles Piper Smith, Cupertino, Calif., on the basis of specimens from the collection made in 1947 by the Utah group. Smith stated, "The specimen is clearly *L. sericeus* Pursh as represented in the mountains of Utah, at least about Coulter, Soldier Summit, and Park City plus the upper Provo River valley—except that the specimen here concerned has the upper surfaces of the leaflets subsericeus to glabrous for the oldest leaves. This one variation points to relationship with *L. marianus* Rydb., which has the leaves scattered on scattered stems, leaflets green and subsericeus below, glabrate or glabrous above." Although the yields varied slightly, the same alkaloids were found in all three collections made in different years. The study of the alkaloids may prove helpful in the solution of the difficult problems in the taxonomy of the *Lupinus* species; *cf.* C. L. Hitchcock and A. Cronquist, "*Saxifragaceae* to *Ericaceae*, Vascular Plants of the Pacific Northwest," Part 3, University of Washington Press, Seattle, Wash., 1961, p 297 ff, 327 ff. Specimens of the plant material used by us in this investigation are on file in the Indiana University Herbarium under Accession No. 112346-112347.

(8) S. Okuda, K. Tsuda, and H. Kataoka. *Chem. Ind.* (London), 1115 (1961).

methiodide.[9] The chloro derivative was prepared by an analogous procedure. In spite of the difficulty in effecting the replacement of the hydroxyl group, the halogeno derivatives readily hydrolyzed back to the starting hydroxy base. The formation of the halogen substitution products was demonstrated by paper and column chromatography. The reductive elimination of halogen was carried out directly upon the reaction mixture with triphenylphosphite methiodide without separation, and the reduction product, (−)-β-isosparteine, was isolated as its characteristic monoperchlorate salt; unchanged starting material was also recovered together with the deoxygenated base.

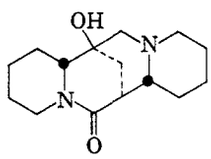
The chemical evidence therefore led us to conclude that the hydroxy base is either (−)-7-hydroxy-β-isosparteine or (−)-8-hydroxy-β-isosparteine. Either of these structures would be uniquely interesting from a biogenetic point of view.[10]

At the time the original chemical studies were carried out,[1c,2] most of the published chemical information on bridgehead hydroxyl groups in small bridged systems such as apocamphanol[11] strongly suggested that a hydroxyl group at the bridgehead positions, C-7 or C-9, of the sparteine nucleus would be extremely difficult or impossible to replace with a halogen substituent, and that such a bridgehead halogenated derivative, if it could be obtained by any means, would be extremely sluggish in its replacement reactions. Thus, the reactivity of the halogeno derivatives obtained by use of the Landauer and Rydon reagents was interpreted by us[1c] and by others[7] as tending to rule out the 7-hydroxy-β-isosparteine structure for our alkaloid from *L. sericeus*.

Efforts to obtain positive nmr spectral evidence supporting or eliminating the 8-hydroxy-β-isosparteine structure were disappointing in that the spectra of β-isosparteine and its natural hydroxy derivative, as well as selected salts, were nearly identical in the region in which a hydrogen atom [≥CCH(OH)C≤] on a methylene group bearing a secondary hydroxyl group normally shows up. This did not unambiguously eliminate, however, the possibility of a secondary alcohol, since some simple model secondary alcohols show the secondary CH in a region in which the nmr spectra of the β-isosparteine and its hydroxy derivative show great complexity.

More recently, the great proliferation of investigations of bridgehead functional group behavior, particularly in the adamantane system,[12a] have caused us to reevaluate our earlier interpretation of the formation and behavior of the chloro and iodo derivatives formed from the hydroxy-β-isosparteine alkaloid. It was realized that the 1-haloadamantane model is more appropriate to the prediction of the chemical behavior of a 7-halogenosparteine derivative, and that fairly ready hydrolysis or hydrogenolysis could be expected on the basis of this analogy.[12a-c] Further enhancement of the reactivity of such a bridgehead halogen might be expected if participation of electrons on N-1 or N-16 should be possible in a transient aziridinium salt.[12d] Examination of molecular models suggested that such participation might reasonably be postulated even in spite of some strain.

The isolation of a hydroxy lactam from various attempts to oxidize the alkaloid would be easier to explain on the basis of a tertiary bridgehead hydroxyl at C-7 blocking the usually oxidation-sensitive C-17 methylene but allowing for the formation of the 7-hydroxy-10-oxo-β-isosparteine (III). It was expected that, if the hydroxyl were at C-8, oxidation of both C-10 and C-17 methylenes would lead to a hydroxy dilactam or a keto dilactam.




III

Fortunately, the question of the structure of the alkaloid has been settled by a complete X-ray crystallographic determination of the structure of the monoperchlorate.[6,13] Not only has the alkaloid been unambiguously found to be 7-hydroxy-β-isosparteine, but the relative configurations of the parent nucleus have been confirmed as assigned,[4] and the conformations of all four rings in the monoperchlorate salt have been shown to be chairs.

Racemic 7-hydroxy-β-isosparteine (mp 165°) has been synthesized by Bohlmann, *et al.*,[14] in connection with their extensive studies of lupin alkaloids and in particular their recent elucidation of the structure of retamine.[15] It is interesting that Ribas, *et al.*,[16] originally assigned a 7-hydroxy- (or 9-hydroxy-) (+)-sparteine structure;[16] retamine has now been proved to be a 12-hydroxy-(+)-sparteine.[15,17]

Couch[18] was the first to investigate the alkaloids of *L. sericeus* Pursh with specimens collected in Colorado. He described two alkaloids, spathulatine ($C_{33}H_{64}N_4O_5$) and nonalupine ($C_{15}H_{24}N_2O$). In 1951, Marion[19] reexamined Couch's specimens of these two alkaloids and identified spathulatine as the monohydrochloride of an alkaloid, pusilline, which he had first isolated from *L. pusillus*,[20] and had assigned a tricyclic structure.[19] Nonalupine was found to be a hydrate of pusilline. In 1956, Greenhalgh and Marion[21] reported that pusilline is (−)-β-isosparteine, and thus Couch's original report on the alkaloids of Colorado species of *L. sericeus* Pursh finally was interpreted as describing two derivatives of (−)-β-isosparteine.

(9) S. H. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

(10) E. Wenkert, *Experientia*, **15**, 165 (1959).

(11) (a) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); (b) W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, Jr., *ibid.*, **75**, 1008 (1953); (c) D. E. Applequist and J. D. Roberts, *Chem. Rev.*, **54**, 1065 (1954).

(12) (a) R. C. Fort, Jr., and P. von R. Schleyer, *ibid.*, **64**, 277 (1964); (b) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959); (c) J. Savada, J. Krupicka, and J. Sicher, *Collection Czech. Chem. Commun.*, **28**, 1664 (1963); (d) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

(13) *Cf.* ref 6. It is a matter of some general interest to alkaloid chemists that the perchlorate ion proved to be useful as a heavy atom in the X-ray analysis, in view of the general ease of preparation of perchlorates. It is also of considerable interest that the proton was found to be uniquely located on the N-16 atom in monoperchlorate salt.

(14) F. Bohlmann, E. Winterfeldt, D. Schumann, U. Zarnack, and P. Wandrey, *Chem. Ber.*, **95**, 2365 (1962).

(15) F. Bohlmann, H. Overwein, and D. Schumann, *ibid.*, **98**, 659 (1965).

(16) F. Fraga, J. Ma. Gavilán, A. Durán, E. Seoane, and I. Ribas, *Tetrahedron*, **11**, 78 (1960).

(17) I. Ribas, J. L. Castedo, and A. Garcia, *Tetrahedron Letters*, 3181 (1965).

(18) J. F. Couch, *J. Am. Chem. Soc.*, **62**, 554 (1940).

(19) L. Marion, *Can. J. Chem.*, **29**, 959 (1951).

(20) L. Marion and S. W. Fenton, *J. Org. Chem.*, **13**, 780 (1948).

(21) R. Greenhalgh and L. Marion, *Can. J. Chem.*, **34**, 82 (1956).

Couch[22] also studied a related plant, *Lupinus sericeus* var. *flexuosus* C. P. Smith, which he reported to yield octalupine, later shown by Marion and Douglas[23] to be hydroxylupanine. Marion, Leonard, and Moore[24] studied the alkaloids of specimens identified as *L. sericeus* Pursh collected in northern Washington. No pusilline (β-isosparteine) was found, but instead (−)-sparteine, (+)-lupanine, (+)-α-isosparteine, lupilaxine, and lupanoline were found. The latter is 2-hydroxy-17-oxo-β-isosparteine of the (−)-β-isosparteine series.

## Experimental Section

**Isolation of (−)-7-Hydroxy-β-isosparteine and (−)-β-Isosparteine from *Lupinus sericeus* Pursh.**—The above-ground parts of mature plants of the species, *Lupinus sericeus* Pursh, were collected near Salina, Utah.[7,25]

The dried and finely ground plant material (3.0 kg) was extracted with 95% alcohol for 3 days, and extraction was repeated several times. The total extract was concentrated to a thick syrup, then diluted with 1 l. of absolute ethanol. From the solution, which had been chilled for several days, approximately 27 g of pinitol separated. It melted at 184–185° (lit.[26] mp 186–188°).

The filtrate was concentrated to 200 ml and diluted with 400 ml of water. The filtered solution was washed with ether, then made strongly basic with sodium hydroxide and exhaustively extracted with chloroform. The chloroform yielded a red-brown, viscous, alkaloidal mass, which was further purified by distribution between ether and aqueous sodium hydroxide. The dried ether yielded 24.5 g (0.8% of dried plant weight) of total alkaloid.

Distillation of the mixture of bases was carried out in a small glass distillation apparatus equipped with an 8 × 25 mm air-jacketed column and a fine capillary for purified nitrogen. The principal fraction of 19.9 g of colorless, viscous oil boiled at 111–112° (0.007 mm) and consisted of (−)-β-isosparteine (or spartalupine[1c,2–4]). A second, smaller fraction of an extremely viscous, pale yellow liquid was collected at bath temperatures of 146–150° (0.007 mm), and this proved to be (−)-7-hydroxy-β-isosparteine. The glassy product of distillation does not readily crystallize, but, after further purification through its salts (as described below), it crystallizes and melts at 103.5–104.5°. It darkens slightly during storage.

**(−)-7-Hydroxy-β-isosparteine Monoperchlorate.**—A solution of the free hydroxy base in absolute methanol was carefully neutralized to an apparent pH of 6.5 with reagent grade concentrated perchloric acid. After the solution had stood for several days in the cold, the crystalline salt was collected and recrystallized several times from water, then dried over phosphorus pentoxide at 0.1 mm. It melted at 207.5–208.5° cor (evacuated capillary). This material was used for the X-ray study.[6]

*Anal.* Calcd for $C_{15}H_{26}N_2O \cdot HClO_4$: C, 51.35; H, 7.76; N, 7.99. Found:[27] C, 51.35; H, 7.82; N, 8.26.

**7-Hydroxy-β-isosparteine Monohydroiodide.**—Some of the free hydroxy base was distilled in a Späth bulb at bath temperatures of 139–146° (0.006 mm). The distillate was titrated in methanol with colorless 57% hydriodic acid reagent to an apparent pH of approximately 6.5. Solid separated rapidly, but the mixture was cooled for several days before the product was collected by filtration. The solid was recrystallized several times from methanol until a constant melting point of 258.5–260° cor (evacuated capillary) was achieved.

*Anal.* Calcd for $C_{15}H_{26}N_2O \cdot HI$: C, 47.62; H, 7.20; N, 7.41. Found:[27] C, 47.64; H, 7.18; N, 7.47.

**(−)-7-Hydroxy-β-isosparteine.**—The free hydroxy alkaloid was recovered from the monohydroiodide salt by treatment with aqueous sodium hydroxide and extraction with ether. The ether extracts were dried over anhydrous magnesium sulfate and after filtration were slowly evaporated under reduced pressure. From the cold, concentrated ether solution, colorless needles of the free base separated; the melting point was 87–94°. Several successive sublimations of the solid at bath temperatures of 97–102° (0.007 mm) yielded a crystalline solid: mp 103.5–104.5°, $[\alpha]^{25.2}D$ −8.0 ± 0.2° (*c* 3.0, ethanol). The apparent $pK_a$ determined in 50% ethanol was 10.7 ± 0.1.

*Anal.* Calcd for $C_{15}H_{26}N_2O$: C, 71.95; H, 10.47; N, 11.19. Found:[27] C, 72.01; H, 10.57; N, 10.99.

The infrared spectra of (−)-7-hydroxy-β-isosparteine and of (−)-β-isosparteine are compared in Figure 1 (A and B). The infrared spectra of the corresponding monoperchlorate salts are compared in Figure 1 (C and D). Similarities will be noted in these pairs of infrared spectra, with the exception of the strong hydroxyl band in the minor alkaloid and its salt.

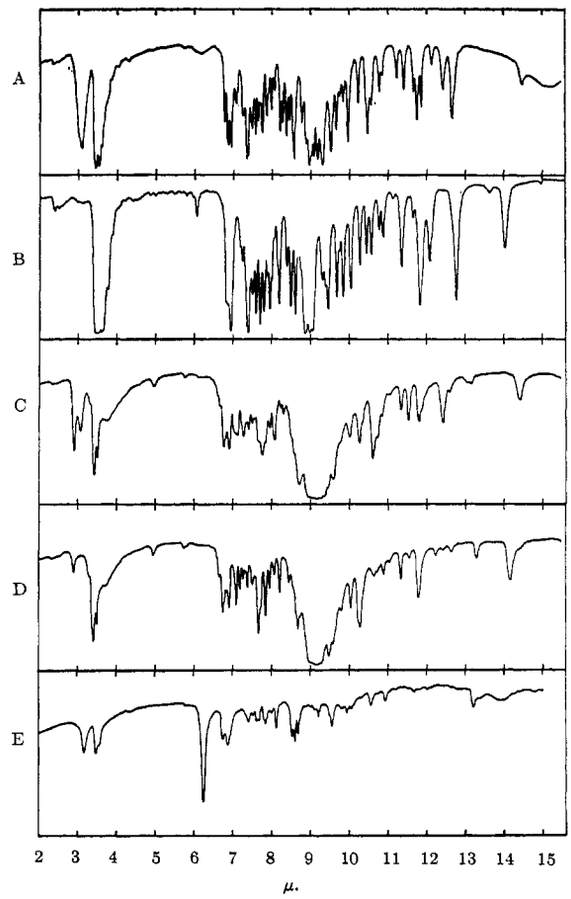



Figure 1.—(A) (−)-7-Hydroxy-β-isosparteine (KBr mull), (B) (−)-β-isosparteine (liquid film), (C) (−)-7-hydroxy-β-isosparteine monoperchlorate (KBr mull), (D) (−)-β-isosparteine monoperchlorate (KBr mull), (E) (−)-7-hydroxy-10(?)-oxo-β-isosparteine (KBr mull).

**7-Acetoxy-β-isosparteine.**—The free hydroxyl group of the minor alkaloid base was acetylated by heating in a sealed Pyrex tube with acetyl chloride at 43–46° for 48 hr. The product was chromatographed as the free base on Woelm nearly neutral alumina (Brockmann, grade II) with *n*-hexane–benzene (1:1) as eluting solvent. The acetoxy derivative was recognized by an $R_f$ value of 0.62 on paper chromatography, compared with 0.54 for the free hydroxy base; recovery of product was in 86% yield. The infrared spectrum lacked the hydroxyl band but showed the acetoxyl carbonyl band; the product could not be induced to crystallize, $[\alpha]^{25.2}D$ +23.5 ± 3.0° (*c* 0.66, ethanol). The apparent $pK_a$ (1) was 9.10 ± 0.1 in 50% ethanol.

**7-Acetoxy-β-isosparteine Diperchlorate.**—The salt was prepared in, and recrystallized from, acetone–ether. It melted at 231–236.5° dec cor, $[\alpha]^{24.2}D$ +4.5 ± 1.6° (*c* 0.32, chloroform).

*Anal.* Calcd for $C_{17}H_{28}N_2O_2 \cdot 2HClO_4$: C, 41.38; H, 6.13; N, 5.68. Found:[28] C, 41.41; H, 6.05; N, 5.55.

(22) J. F. Couch, *J. Am. Chem. Soc.*, **61**, 1523 (1939).

(23) L. Marion and B. Douglas, *Can. J. Chem.*, **29**, 721 (1951).

(24) L. Marion, N. J. Leonard, and B. P. Moore, *ibid.*, **31**, 181 (1953).

(25) *Cf.* C. D. Marsh, U. S. Department of Agriculture, Bulletin No. 1245 Revised, Oct 1929, Washington, D. C.; *cf.* especially pp 22–23.

(26) W. Karrer, "Konstitution und Vorkommen der organischen Pflanzenstoffe (exclusive Alkaloide)," Birkhäuser Verlag, Basel, Switzerland, 1958, p 117.

(27) Microanalysis was by Miss Joanna M. Dickey, Indiana University.

(28) Microanalysis was by Huffman Microanalytical Laboratory, Wheatridge, Colo.

**Attempted Reductive Elimination of the Hydroxyl Group from Hydroxy-β-isosparteine.**—One hundred milligrams of 7-hydroxy-β-isosparteine was heated under reflux in a nitrogen atmosphere with 116 mg of lithium aluminum hydride in 30 ml of ether. The starting material was recovered unchanged; the monoperchlorate prepared from the base showed no alteration in properties or depression of melting point when mixed with the previously described monoperchlorate.

**Attempted Preparation of the O-Toluenesulfonate Ester of 7-Hydroxy-β-isosparteine.**—Six attempts were made to prepare the O-tosylate of the natural hydroxy-β-isosparteine alkaloid. The following summarizes the different procedures used without success: (a) 3 hr of heating with *p*-toluenesulfonyl chloride in ether–pyridine at 5–10°; (b) the same conditions except at room temperature; (c) the same conditions as in (b) except for the omission of pyridine; (d) the same conditions as in (a) except the use of lower temperatures between −10 and −5°; (e) the same conditions as in (d) except that the crude product was directly heated with lithium aluminum hydride in an effort to effect replacement of the functional group with hydrogen before possible hydrolysis could occur during the isolation. In all cases the starting 7-hydroxy-β-isosparteine was the only product recovered.

**Attempts to Generate an Olefin by Dehydration of 7-Hydroxy-β-isosparteine.**—Several attempts were made to prepare methyl xanthate derivatives at the hydroxyl function, and to utilize the Chugaev elimination to generate an olefin, but all of these failed. Under relatively mild conditions the starting material was recovered. Under vigorous conditions a hydroxy lactam was isolated from the pyrolysis mixture, but in no case was a simple olefinic derivative formed.

Heating of the hydroxy-β-isosparteine with phosphorus pentoxide under nitrogen for 4 hr at 120–140° gave a product which, after distillation under high vacuum, still consisted largely of starting hydroxy base, together with some hydroxylactam (see below for the description of this product). The mixture was heated under reflux in ether, and the product was shown by its infrared spectrum to be the hydroxy-β-isosparteine. The lactam which had been formed during the attempts at vigorous dehydration probably resulted from partial oxidation at one or more methylene groups attached to basic nitrogen.

**Attempts to Replace the Hydroxyl Function with Halogen.**—Several unsuccessful attempts were made to prepare a chloro-β-isosparteine by treatment of the hydroxy base with thionyl chloride. An ethereal solution of the hydroxy base was treated with thionyl chloride in a dry atmosphere at 0–5°, then was subsequently allowed to warm to room temperature and to stand for more than 12 hr. A precipitate had separated but no solid could be crystallized. When the products were taken up in water, made basic, extracted with ether, and distilled under reduced pressure, hydroxy-β-isosparteine was recovered unchanged; identification was by means of infrared spectrum of the free base and comparison of the melting point and mixture melting point of the monoperchlorate.

**Preparation of 7-Iodo-β-isosparteine and Its Reduction to (−)-β-Isosparteine.**—Success in the replacement of the hydroxyl group was finally achieved by use of the special Landauer and Rydon[9] procedures. Very reactive iodo and chloro derivatives were prepared by the use, respectively, of triphenyl phosphite methiodide and triphenyl phosphite–benzyl chloride.

Triphenyl phosphite methiodide, prepared as described[9] and preserved crystalline under dry ether, was allowed to react with the natural alkaloid, hydroxy-β-isosparteine, in dry acetone solution at room temperature for 48 hr; the reaction mixture was treated with aqueous acid in the cold, extracted with ether, basified, and extracted with chloroform to remove the basic products. A paper chromatogram on Whatman No. 2 paper, developed with butanol–acetic acid–water, then treated with the Munier–Dragendorff color-forming reagent, showed that a new product had been formed which was somewhat faster running than the hydroxy compound but which readily hydrolyzed back to the starting hydroxy base. All efforts to obtain the iodo compound in pure form failed because it so easily reverted to the starting base.

In order to remove the iodo group before hydrolysis, an immediate reductive treatment was used: 3 mmoles of triphenyl phosphite methiodide and 1.3 mmoles of hydroxy-β-isosparteine were heated at reflux temperature in pure, dry acetone (protected from moisture) for 7 hr. The reaction mixture was cooled, the acetone was slowly evaporated *in vacuo*, and the reaction product was extracted slowly with ether from a paper extraction thimble directly into a refluxing ethereal solution of lithium aluminum hydride. After a suitable processing of the basic products, distillation under 0.2 mm yielded two fractions similar to those isolated directly from the original plant extract. The lower boiling fraction (26% yield) consisted of (−)-β-isosparteine, which was identified as its monoperchlorate salt, mp 218.5–220.5° cor (evacuated capillary); it showed no depression of melting point when mixed with authentic (−)-β-isosparteine monoperchlorate. The infrared absorption spectra of the perchlorate prepared by the replacement–reduction procedure from the hydroxy base and that prepared directly from the principal alkaloid of the plant were likewise the same (see Figure 1D for the infrared spectra).

*Anal.* Calcd for (−)-β-isosparteine monoperchlorate ($C_{15}H_{26}N_2 \cdot HClO_4$): C, 53.81; H, 8.12; N, 8.37. Found:[27] C, 53.87; H, 8.69; N, 8.48.

When the monoperchlorate of 7-hydroxy-β-isosparteine (mp 207.5–208.5° cor) was mixed with the salt isolated from the two-stage replacement–reduction procedure just described, the mixture showed a strong depression of melting point to 202–207°. When it was mixed with the monoperchlorate of synthetic racemic β-isosparteine[5] (mp 188–189°), the mixture melted at 182–203°.

**Preparation of 7-Chloro-β-isosparteine.**—Triphenyl phosphite–benzyl chloride adduct (0.1 mole) was prepared as described.[9] The product was allowed to react with 1 mmole of 7-hydroxy-β-isosparteine monoperchlorate at 70–75° for 36 hr, during which the salt gradually melted into solution in the reagent. The product was cooled, treated with cold, dilute hydrochloric acid, extracted with ether, then frozen and lyophilized to a fluffy, yellow powder which could not be induced to crystallize as the hydrochloride salt. Paper chromatography of the freshly liberated base from butanol–acetic acid–water showed a spot ($R_f$ 0.68) which moved more rapidly than the parent hydroxy base ($R_f$ 0.59). Column chromatography on Woelm nearly neutral alumina (grade II) gave a small fraction having only a weak hydroxyl band in the infrared and giving a positive halogen test; during efforts to crystallize this fraction it reverted to the starting hydroxy-β-isosparteine base.

**Attempts to Oxidize the Hydroxyl Group of Hydroxy-β-isosparteine. A. Oppenauer Procedure.**—The natural hydroxy alkaloid was treated in the usual way with aluminum *t*-butoxide in toluene, then heated under reflux with an excess of cyclohexanone in dry nitrogen for 18 hr. Careful processing revealed only the unchanged starting hydroxy alkaloid and no carbonyl-containing product. Two unsuccessful attempts were made and the products were examined by several techniques in an effort to detect ketone formation.

**B. Alkaline Ferricyanide.**—The 7-hydroxy-β-isosparteine (0.4 mmole) was treated in 10 ml of water with 4.7 mmoles of potassium ferricyanide for 12 hr at room temperature. Extraction with chloroform yielded a product which crystallized from ethyl acetate. Chromatography of the solid on Woelm nearly neutral alumina (grade II), with ethyl acetate as eluent, followed by sublimation at 180° (0.4 mm) yielded a hydroxy lactam, probably 7-hydroxy-10-oxo-β-isosparteine (III), mp 218.5–219° cor (evacuated capillary). Figure 1E shows the infrared absorption spectrum of this product, whose intense carbonyl band at 6.1 μ indicates oxidative attack at a methylene adjacent to nitrogen.

*Anal.* Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15. Found:[28] C, 68.35; H, 9.23.

**C. Chromic Anhydride–Pyridine Complex.**—To chromic anhydride (3.0 mmoles) in 3.0 g of ice-cold pyridine was added 150 mg (0.6 mmole) of natural 7-hydroxy-β-isosparteine in 15 ml of pure, dry pyridine. After 30 hr at room temperature, the mixture was diluted with 25 ml of water, treated with some sulfurous acid, and extracted with chloroform. The product was chromatographed twice, first from Woelm nearly neutral alumina (grade III) washed with chloroform, then on grade II alumina with ethyl acetate as eluent. Crystals thus obtained were identical with hydroxy lactam obtained with alkaline ferricyanide and described in the foregoing paragraphs.

**D. Potassium Chromate in 50% Aqueous Acetic Acid.**—The natural 7-hydroxy-β-isosparteine (0.1 mmole) in 5 ml of glacial acetic acid was treated with 0.28 mmole of potassium chromate in 5 ml of water at room temperature for 14 hr. Basification and extraction with chloroform yielded unchanged hydroxy-β-isosparteine, identified by its infrared spectrum and by paper chromatography.

**E. Chromic Anhydride in Acetic Acid.**—The natural 7-hydroxy-β-isosparteine (0.48 mmole) in 5 ml of glacial acetic acid was treated with 200 mg (2 mmoles) of chromic anhydride at 55–65° for 16 hr. The mixture was cooled in an ice bath, made strongly basic, and extracted with chloroform. The same hydroxy lactam was isolated which was formed under the conditions of B and C above.

**Registry No.**—I, 10146-70-0; II, 10146-71-1; III, 10146-72-2; (−)-7-hydroxy-β-isosparteine monoperchlorate, 10182-05-5; 7-hydroxy-β-isosparteine monohydroiodide, 10146-73-3; 7-acetoxy-β-isosparteine, 3279-73-0; 7-acetoxy-β-isosparteine diperchlorate, 10146-75-5; (−)-β-isosparteine monoperchlorate, 10146-76-6.

**Acknowledgments.**—We wish to express appreciation to Dr. W. T. Huffman and Mr. Moran for the collections of plant material; to Drs. Charles Piper Smith and John M. Fogg, Jr., for the classification of the botanical specimens; to Drs. J. M. H. Pinkerton and L. K. Steinrauf for thier interest in this problem and for making available to us the results of their X-ray crystallographic analysis in advance of publication; and to Edward F. Szymanski for nmr studies of the alkaloid salts. We thank also the Rohm and Haas Co., the Sharp and Dohme Laboratories, Smith, Kline and French Laboratories, and the National Institutes of Health for financial assistance.

# Flavins. XIII. Rearrangement Reactions of 1,3,10-Trialkylflavinium Salts[1]

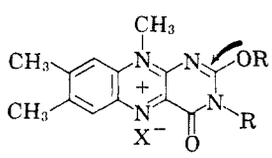
KENNETH H. DUDLEY[2,3] AND PETER HEMMERICH

*Institut für anorganische Chemie an der Universität Basel, 4000 Basel, Switzerland*

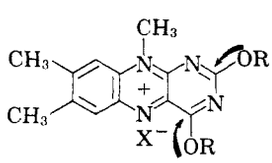
*Received April 21, 1967*

Spirohydantoins have been found to result from reactions of several nucleophiles with 1,3,10-trimethylflavinium perchlorate (**3**). Observations regarding an incorrectly formulated "alloxan-anil" have been reinvestigated and interpreted in the light of Clark-Lewis' findings and the results presented herein.

Mager and Berends' recent inference[4] on operative intermediates in the leucoflavin autoxidation scheme has prompted us to report chemical studies related to the proposed scheme. In previous publications,[5,6] we noted that the 2(O),3(N)-dialkyl- and 2(O),4(O)-dialkylflavinium salts (*e.g.*, **1** and **2**, respectively) reacted



**1**



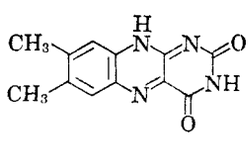
**2**

with hydroxyl ion and/or ammonia at positions denoted by arrows (by simple nucleophilic addition–elimination processes). The present article deals with the reactions of the 1(N),3(N)-dialkylflavinium salt **3** with several nucleophiles, namely hydroxyl ion, ammonia, and borohydride ion. The 1,3,10-trimethylflavinium salt **3** reacted with these agents (the latter under a specific set of conditions) to undergo a skeletal rearrangement reaction leading to the spirohydantoins **4**, **5**, and **6**, respectively (Scheme I). The experimental conditions for the preparation of **6** require special mention, for an isomeric tetrahydroflavin **7** was produced when a suspension of **3** in absolute methanol was treated with an excessive quantity of borohydride. The spirohydantoin **6** was obtained by intermittently treating a stirred aqueous suspension of **3** with *very small amounts* of sodium borohydride. After each addition, a quantity of **3** gradually dissolved, imparting a transient orange color to the solution. The white spirohydantoin **6** crystallized during the course of the reaction, but the difference in the crystalline forms (and colors thereof) allowed one to easily determine by microscopic examination the point of complete solution of **3**.

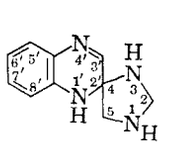
The infrared spectrum of each of the spirohydantoins **4**, **5**, and **6** contained a sharp band in the 3279–3311-$cm^{-1}$ region ($\nu_{NH}$) and two bands in the 1761–1770- and 1709–1715-$cm^{-1}$ regions. The latter two absorption bands are attributable to the 4-oxo and 2-oxo groups, respectively, of the hydantoin ring.[7] The nmr spectrum (60 Mc, benzene-$d_6$, 65° for solubility requirement) of the spirohydantoin **6** contained an AB quartet ($J$ = 11.5 cps) with resonances centered at 2.48 and 3.05 ppm. This AB spin system is assignable to a nonequivalent methylene group.[8]

The identity of the spirohydantoin system was further substantiated by comparing, and finding identical, the product obtained by rearranging the alloxazinium salt **11** with the known **12**, which was obtained from the ureide **13** by the procedure of Clark-Lewis[9a] (eq 1).

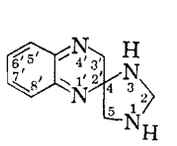
(1) In common usage, the term "flavin" represents derivatives of 7,8-dimethylisoalloxazine (*e.g.*, 7,8-dimethylbenzo[*g*]pteridine-2,4(3H,10H)-dione). For simplicity of terminology in the text, we have employed "spirohydantoin" for derivatives of the spiro[imidazolidine-4,2′(1′H)-quinoxaline] and spiro[imidazolidine-4,2′(3′H)-quinoxaline] systems.



7,8-dimethylbenzo[*g*]-pteridine-2,4(3H,10H)-dione



spiro[imidazolidine-4,2′(1′H)-quinoxaline]



spiro[imidazolidine-4,2′(3′H)-quinoxaline]

(2) National Science Foundation Postdoctoral Fellow, 1963–1964.

(3) Center for Research in Pharmacology and Toxicology, University of North Carolina, Chapel Hill, N. C. 27514.

(4) H. I. X. Mager and W. Berends, *Biochim. Biophys. Acta*, **118**, 440 (1966).

(5) P. Hemmerich, C. Veeger, and H. C. S. Wood, *Angew. Chem.*, **77**, 699 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 671 (1965).

(6) K. H. Dudley and P. Hemmerich, *Helv. Chim. Acta*, **50**, 355 (1967).

(7) A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 228.

(8) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, **7**, 355 (1966).

(9) (a) J. W. Clark-Lewis, *J. Chem. Soc.*, 422 (1957); (b) J. W. Clark-Lewis and M. J. Thompson, *ibid.*, 430 (1957); (c) F. E. King and J. W. Clark-Lewis, *ibid.*, 3379 (1951).