−10 to 0°. The oily residue was washed several times by centrifugation with the cold (0°), dry *n*-pentane. The halogen-free product (0.640 g., 50%) was obtained in clusters of colorless needles, m. p. 76.5–77.5°.

Anal.[26] Calcd. for $C_{24}H_{24}O_7NP$: C, 61.40; H, 5.15; P, 6.62. Found: C, 59.43; H, 5.37; P, 6.79.

N-Carbobenzoxyglycine-N-benzyl amide was prepared by adding a few drops of benzylamine to a solution of approximately 10 mg. of N-carbobenzoxyglycyl dibenzyl phosphate in 10 ml. of ether. Colorless rosettes were obtained, m. p. 115.5–116.8°. Recrystallization from ether gave the pure amide, m. p. 115.8–116.8°.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.70; H, 6.37; N, 9.17.

The same amide was prepared from an ethereal solution of the acid chloride and an excess of benzylamine. The product crystallized from ether in fine needles, m. p. 115.8–116.6°. A mixture with the amide obtained from N-carbobenzoxyglycyl dibenzyl phosphate showed no depression in melting point.

(26) The sample was mixed with cupric oxide before combustion. In the absence of cupric oxide the values found were: C, 46.99; H, 5.10.

Summary

Syntheses of two model high-energy phosphorus compounds derived from glycine are described. Both phthalylglycyl dibenzyl phosphate and N-carbobenzoxyglycyl dibenzyl phosphate have the properties of acylating agents. In addition, it has been demonstrated that phthalylglycyl dibenzyl phosphate reacts with glycine and with DL-phenylalanine to form phthalyl peptides under simulated physiological conditions. These reactions represent the first *in vitro* synthesis of peptide bonds employing amino acyl phosphate derivatives.

CAMBRIDGE 39, MASSACHUSETTS
RECEIVED AUGUST 31, 1949

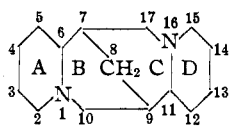
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Total Synthesis of Sparteine and an Isosparteine by Reductive Cyclization[1]

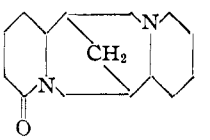
BY NELSON J. LEONARD AND ROGER E. BEYLER[2]

The total synthesis of *dl*-sparteine (I)[3] and the resolution of racemic sparteine[4] have been announced from this Laboratory. It is the purpose of this paper to disclose the details of the synthesis and resolution of sparteine, to report the synthesis of an isosparteine, and to discuss the stereochemistry of these $C_{15}H_{26}N_2$ compounds.

The reduction of *dl*-lupanine (II) (an alkaloid found in the racemic form in *Lupinus albus*,[5a] *Lupinus termis*[5b] *Podalyria buxifolia*,[5c] *Podalyria sericea*[5c] and *Virgilia capensis*[5d]) to "deoxylupanine" (later shown to be *dl*-sparteine (I), an alkaloid occurring in the racemic form in *Cytisus proliferus*,[5e]) was reported in 1928 by Clemo and Leitch.[5b] At that time the structure of both alkaloids was unknown, and because *l*-sparteine,[6] the form of I most abundantly available in nature,[7] could not be racemized and "deoxylupanine" was not resolved, the relation between "deoxylupanine" and *l*-sparteine was unclear. Clemo, Raper and Tenniswood[8] later succeeded in resolving *dl*-lupanine and in reducing *d*- and *l*-lupanine to *l*- and *d*-sparteine, respectively. Their work established the identity of "deoxylupanine" with *dl*-sparteine and also constituted the synthesis of sparteine from an alkaloid source.

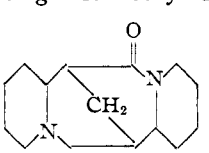


I

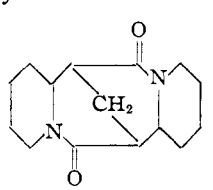


II

In an approach toward the total synthesis of sparteine, Clemo, Morgan and Raper[9] prepared *dl*-oxosparteine (III)[10] by a multi-step procedure starting with ethyl 2-pyridylacetate. Although the carbonyl group in *dl*-oxosparteine (III) is structurally similar to that in *dl*-lupanine (II), reduction of III to I could not be accomplished with reagents available at that time. However, the synthesis of *dl*-oxosparteine served to establish the identity of III with the alkaline ferricyanide oxidation product of I. Since the appearance of our first communication,[3] Clemo, Raper and Short have reported a successful reduction of



III



IV

(1) This investigation was supported in part by a grant from the Research Board of the University of Illinois.

(2) Present address: Merck and Co., Inc., Rahway, New Jersey.

(3) Leonard and Beyler, THIS JOURNAL, **70**, 2298 (1948).

(4) Leonard and Beyler, *ibid.*, **71**, 757 (1949).

(5) (a) Schmidt, *Arch. Pharm.*, **235**, 192 (1897); (b) Clemo and Leitch, *J. Chem. Soc.*, 1811 (1928); (c) White, *New Zealand J. Sci. Tech.*, **25B**, 137 (1944); (d) White, *ibid.*, **27B**, 478 (1946); (e) White, *ibid.*, **25B**, 103 (1943).

(6) The use in this paper of *l* to indicate negative rotation and *d* to indicate positive rotation is consistent with the usage of previous workers in this field.

(7) *l*-Sparteine has been found in *Cytisus scoparius*, *C. ratisbonensis*, *C. proliferus*, *Genista aetnensis*, *Lupinus barbiger*, *L. laxus*, *L. luteus*, *L. niger*, *Retama sphaerocarpa*, *Spartium junceum* and *Chelidonium majus* (Henry, "The Plant Alkaloids," 4th edition J. and A. Churchill, Ltd., London, England, 1949, pp. 116–119).

(8) Clemo, Raper and Tenniswood, *J. Chem. Soc.*, 429 (1931).

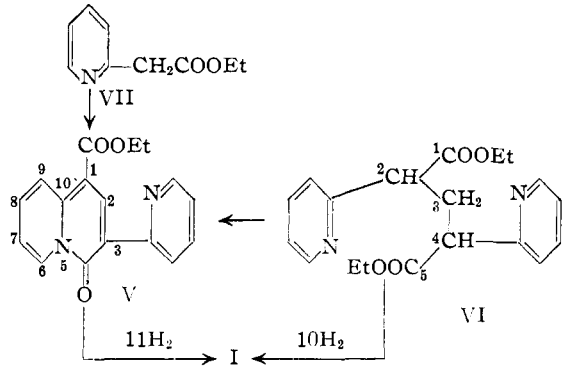
(9) Clemo, Morgan and Raper, *ibid.*, 1025 (1936).

(10) The nomenclature used by Clemo and others is "oxysparteine," which the authors consider misleading.

l-oxosparteine to *l*-sparteine by means of lithium aluminum hydride.[11]

Their initial communication[11a] was closely followed by another reported synthesis of sparteine when Sorm and Keil[12] announced the successful electrolytic reduction of two stereoisomerides of dioxosparteine (IV).[13,14] One of the dioxosparteines, m. p. 172°, was reduced to a $C_{15}H_{26}N_2$ base (I) which formed a dipicrate of m. p. 222°. The other dioxosparteine, m. p. 135°, after reduction gave two base dipicrates, m. p. 205 and 190°, which were separated mechanically. The free bases were not isolated. The analyses of the second two picrates did not check as well as might be expected, and on subsequent recrystallizations the melting points decreased to 201 and 178°. The dipicrate of m. p. 205° was thought to be related to that of natural sparteine.

Synthesis of *dl*-Sparteine and *dl*-α-Isosparteine.—We have employed the method of reductive cyclization, which was reported first from this Laboratory,[15] for the synthesis of pyrrolizidines, in order to synthesize sparteine from two different precursors. Our method involves



a one-step cyclization and reduction of either 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline (V) or diethyl 2,4-di(α-pyridyl)-glutarate (VI). Since both V and VI are available directly from ethyl 2-pyridylacetate (VII), the synthesis of sparteine by either route is a simple two-step process.

The preparation of 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline (V) from ethyl 2-pyridylacetate (VII)[16] and ethyl orthoformate in the presence of acetic anhydride was carried out according to the method of Clemo, Morgan and Raper,[9] modified in that the product was not distilled before recrystallization. Hydrogenation of V was effected over copper chromite catalyst in dioxane at 250° and 300–350 atmospheres. Two pure $C_{15}H_{26}N_2$ bases were isolated from the reductive cyclization of V, namely, *dl*-sparteine and an isosparteine which we have chosen to call *dl*-α-isosparteine. The properties of the former product and its derivatives (monopicrate, dipicrate, *dl*-oxosparteine) established its identity with the *dl*-sparteine previously obtained from naturally occurring *dl*-lupanine.[5b] The second product has been fully characterized as a solid isomer of sparteine, m. p. 78–80° (monohydrate, m. p. *ca.* 100°; monopicrate, m. p. 132.5–133.5°; dipicrate, m. p. 222°; monoperchlorate, m. p. 160–162°). It has been shown to be the racemate of the α-isosparteine obtained by Winterfeld and Rauch[17] on hydrogenation of α-didehydrosparteine. The dipicrate of our *dl*-α-isosparteine has the same melting point as Sorm and Keil's highest-melting picrate.[12]

With the comparatively large amount of reduction product which we obtained from V, separation of the isomers by fractional distillation in vacuum was attempted and partially realized. The *dl*-α-isosparteine boiled slightly lower than *dl*-sparteine, and as a result it was more concentrated in the lower boiling fractions. However, a continuous distillation of the two compounds seemed to occur since *dl*-α-isosparteine was found also in the *dl*-sparteine fractions. Chromatographic adsorption on activated alumina is probably the most effective means of obtaining *both* of the racemates in a pure state. It was used satisfactorily on the reduction product obtained by both synthetic routes (from V and VI). If the isolation of pure *dl*-sparteine is the main object, the fractional crystallization of the perchlorate affords a facile method of separation and purification of this racemate. Because of the variety of methods used to work up the reduction product from V and the losses of material thereby incurred, only an estimate of the yields can be made. The yield of crude reduction product before distillation was 85% of the theoretical amount, based on total conversion to $C_{15}H_{26}N_2$. Of this crude material more than one-third, or 30% of the theoretical, was *dl*-sparteine and *dl*-α-isosparteine, isolated in a proportion of approximately five to one.

The preparation of diethyl 2,4-di-(α-pyridyl)-glutarate (VI) was carried out by the condensation of two molecules of ethyl 2-pyridylacetate with one of formaldehyde or methylene iodide. Formaldehyde gave the better yield. Sorm and Keil[13] prepared the corresponding dimethyl ester (homologous with VI), and their methods were followed. Clemo, Raper and Short[11b] have recently reported the preparation of VI using methylene iodide. In our synthesis of the glutarate (VI) by the formaldehyde condensation a by-product was isolated which proved to be

(11) Clemo, Raper and Short, (a) *Nature*, **162**, 296 (1948); (b) *J. Chem. Soc.*, 663 (1949).

(12) Sorm and Keil, *Collection Czechoslov. Chem. Commun.*, **13**, 544 (1948).

(13) Sorm and Keil, *ibid.*, **12**, 655 (1947).

(14) Galinovsky and Kainz, *Monatsh.*, **77**, 137 (1947).

(15) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).

(16) Woodward and Kornfeld, private communication. Their preparation of ethyl 2-pyridylacetate has been submitted for publication in "Organic Syntheses."

(17) Winterfeld and Rauch, *Arch. Pharm.*, **272**, 273 (1934).

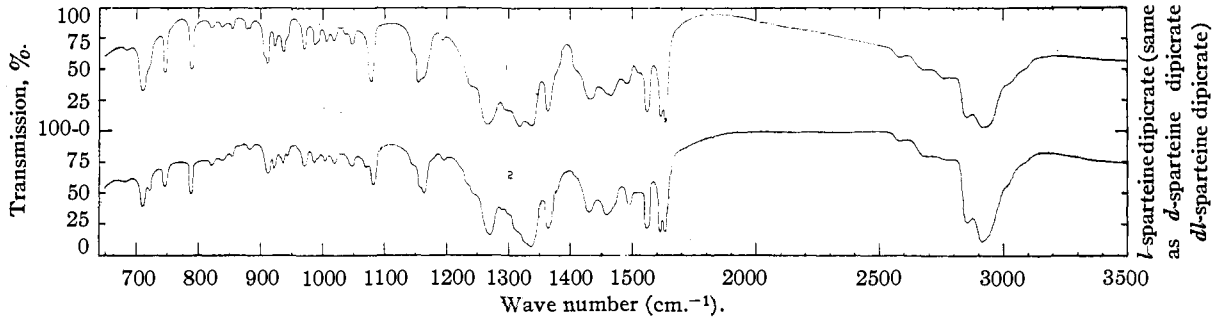


Fig. 1.—1, *l*-Sparteine dipicrate (same as *d*-sparteine dipicrate); 2, *dl*-sparteine dipicrate.

1 - carbethoxy - 4 - keto - 3 - (α - pyridyl) - pyridocoline (V). The identity of the by-product with V was confirmed by mixed melting point with authentic V, mixed melting point of its picrate with V picrate, and infrared spectral comparison. This compound can only be formed by the abstraction of a molecule of ethanol and two hydrogen atoms from VI. The loss of ethanol during distillation of VI was indicated by the collection of a liquid in the Dry Ice-trap which gave positive ceric nitrate and iodoform tests. The ring-closure between the carbethoxyl group and the –NH– group can be rationalized[18] on the basis of the familiar α-methylpyridine-α-pyridone methine equilibrium[19] which in this case is rendered irreversible by lactamization. The simultaneous or subsequent loss of hydrogen was not unexpected since this loss represents the conversion of a dihydroaromatic compound to the completely aromatic type: a 4-ketopyridocoline. Sorm and Keil[12] have isolated the homologous methyl ester of V from the methylene iodide and formaldehyde condensations with methyl 2-pyridylacetate and have proved its identity by mixed melting point and spectral comparison with an authentic sample. Clemo, Raper and Short[11b] reported the isolation of 1-carbethoxy-4-keto-3-(α-pyridyl)-2,3-dihydropyridocoline as a by-product in the synthesis of V by means of methylene idodide. According to their work, the two hydrogen atoms were not abstracted.

Hydrogenation of VI was effected over copper chromite catalyst in dioxane at 250° and 300–350 atmospheres, and both *dl*-sparteine and *dl*-α-isosparteine were again isolated as in the hydrogenation of V. The isomers were separated chromatographically and were apparently present in more nearly equal amounts whereas the total yield of material boiling in the $C_{15}H_{26}N_2$ range was approximately the same as in the hydrogenation of V. The higher boiling fractions were not identified.

Resolution of *dl*-Sparteine.—Synthetic *dl*-sparteine, as prepared by the method of reductive cyclization, was resolved by means of *l*- and *d*-β-camphorsulfonic acid and both optically active forms of sparteine were obtained. The free bases were not isolated but each enantiomorph was identified by means of two known derivatives. The derivatives used to identify *l*-sparteine were the *d*-β-camphorsulfonate and the dipicrate. The former salt was characterized by melting point, mixed melting point with an authentic sample[20] and specific rotation. The latter salt was characterized by melting point, mixed melting point with authentic *l*-sparteine dipicrate and depression of melting point on mixing with *dl*-sparteine dipicrate. *d*-Sparteine *l*-β-camphorsulfonate had a specific rotation equal and opposite to its enantiomorphic *l*-sparteine *d*-β-camphorsulfonate. Characterization of *d*-sparteine[21] was accomplished by conversion of the camphorsulfonate salt to the dipicrate and monoperchlorate, both of which were undepressed in melting point when mixed with the corresponding samples of natural *d*-sparteine dipicrate[22] and natural *d*-sparteine monoperchlorate.[22]

A further confirmation of the resolution was provided by infrared data. The infrared absorption spectra of natural *l*-, resolved *l*-, natural *d*-, and resolved *d*-sparteine dipicrates were determined and were found to be identical for these samples in the crystalline state (as nujol mulls—see Fig. 1, Curve 1) and very slightly different from that of crystalline *dl*-sparteine dipicrate (Fig. 1, Curve 2). In acetone or acetonitrile solution all five compounds exhibited identical spectra. The identity of spectra in solution suggests that the minor spectral differences as measured in the crystalline state are due to differ-

(18) The conversion of VII to V through ethyl orthoformate condensation is understandable on the same basis.

(19) Woodward and Witkop, THIS JOURNAL, **70**, 2409 (1948); Woodward and Kornfeld, *ibid.*, **70**, 2508 (1948).

(20) Authentic *l*-sparteine was obtained as the sulfate from S. B. Penick and Company. Of incidental interest is the fact that we have been able to prepare a *mono*picrate of natural *l*-sparteine, m. p. 96.5–97.5°, a derivative which has not been previously described.

(21) The alkaloid *d*-sparteine (pachycarpine) has been found in *Ammodendron conollyi*, *Ammothamnus lehmanni*, *Anagyris foetida*, *Cytisus caucausicus*, *Sophora pachycarpa*, *Thermopsis lanceolata*, (Henry, "The Plant Alkaloids," 4th edition, J. and A. Churchill, Ltd., London, England, 1949, pp. 116–119), *Baptisia australis* (Marion and Ouellet, THIS JOURNAL, **70**, 691 (1948)), *Baptisia perfoliata* (Marion and Turcotte, *ibid.*, **70**, 3253 (1948)), *Baptisia minor* (Marion and Cockburn, *ibid.*, **70**, 3472 (1948)) and *Lupinus pusillus* (Marion and Fenton, *J. Org. Chem.*, **13**, 780 (1948)).

(22) We wish to acknowledge the kindness of Dr. Léo Marion, National Research Council, Ottawa, Canada, in supplying us with authentic samples of these derivatives.

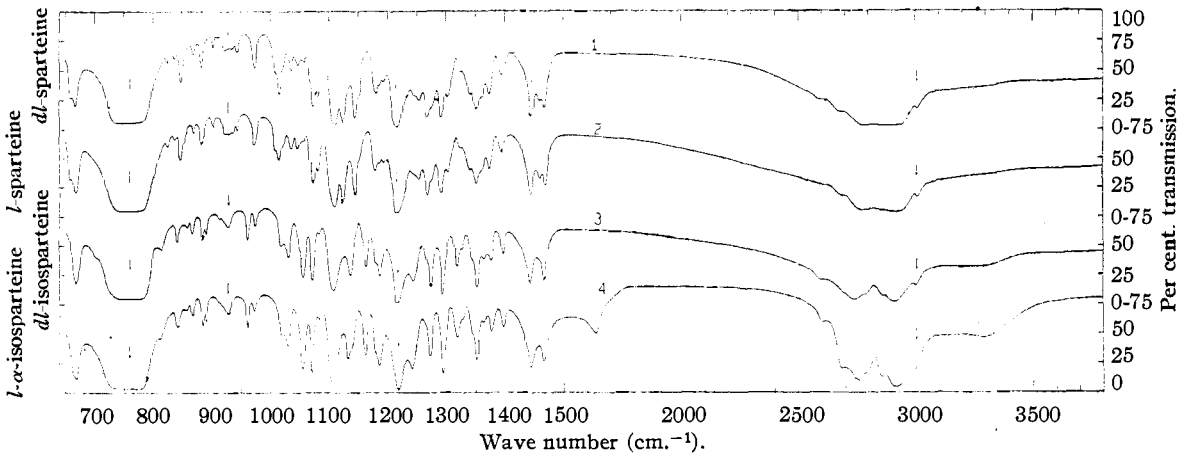


Fig. 2.—1, *dl*-Sparteine; 2, *l*-sparteine; 3, *dl*-isosparteine; 4, *l*-α-isosparteine.

ences in crystal form of the racemic and the active compounds. Infrared characterization of *dl*-sparteine (Fig. 2, Curve 1) and natural *l*-sparteine (Fig. 2, Curve 2) as the free bases dissolved in chloroform gave final proof that synthetic *dl*-sparteine was the racemic form of natural *l*-sparteine. The infrared spectrum of *dl*-α-isosparteine (Fig. 2, Curve 3) resembles that of *dl*-sparteine, but exhibits sufficient differences so that the spectrum is useful for characterization and differentiation purposes. The infrared absorption spectra curves for the corresponding picrates were less satisfactory for such purposes. The infrared spectrum of freshly sublimed *l*-α-isosparteine, prepared by the method of Winterfeld and Rauch,[17] was determined in chloroform solution (Fig. 2, Curve 4) and was found to be identical with that of our synthetic *dl*-α-isosparteine (Curve 3) except for the regions of 1110 cm.$^{-1}$, 1140 cm.$^{-1}$ and 1640 cm.$^{-1}$. These small differences in spectra disappeared when the monohydrates of each base were employed. *dl*-α-Isosparteine monohydrate and *l*-α-isosparteine[17] monohydrate both had identical spectra, best represented by Curve 4 in Fig. 2. It appears therefore, that water of hydration accounts for the difference between the absorption curves of *dl*-α-isosparteine and *l*-α-isosparteine, and that these compounds truly bear the relationship of racemate and levorotatory form of the same compound. The ease with which *l*-α-isosparteine took up water was also indicated by the difficulty encountered in attempting to analyze the anhydrous material.

Stereoisomerism of Sparteine.—The question as to the number of stereoisomers of the sparteine molecule is best answered by consideration of representative perspective formulas (Fig. 3). In the sparteine ring system (I) there are four asymmetric carbons, C_6, C_7, C_9 and C_{11}, but the configurations at C_7 and C_9 are interdependent since the C_8 methylene bridge can only span the distance between C_7 and C_9 in a *cis* manner. The most convenient method of designating the configuration of I is by the relation of the hydrogen atoms on C_6 and C_{11} to the C_8 methylene bridge. We find that there are six stereoisomeric forms, or three racemic pairs of I. They are, with respect to the C_8 methylene bridge (in Fig. 3 one enantiomorph of each racemic pair is represented, neglecting rings A and D for clarity): (1) hydrogens on C_6 and C_{11} both *cis*, (2) hydrogens on C_6 and C_{11} both *trans*, (3) hydrogen on C_6 *cis* and hydrogen on C_{11} *trans*.

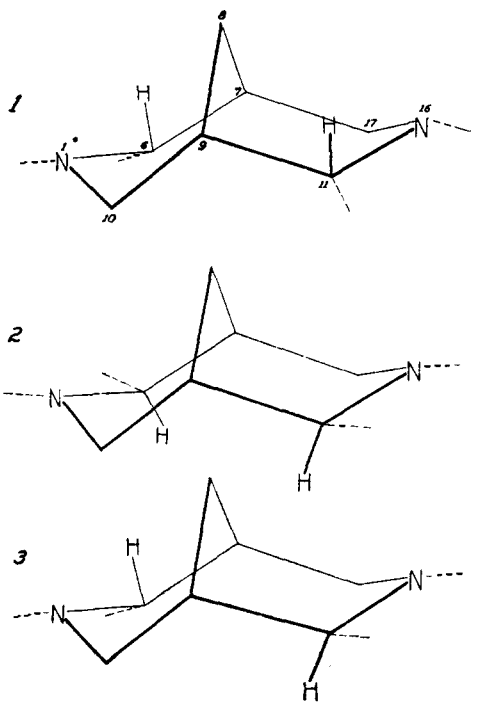


Fig. 3.

In the light of the prediction of the number of isomers of I, it is of interest to survey those $C_{15}H_{26}N_2$ stereoisomers which have been isolated or prepared. In addition to *d*- and *l*-sparteine ($[\alpha]_D = 17°$ in ethanol), which together con-

stitute one of the three racemates, a new isomer appears to have been formed by dehydrogenation of *l*-sparteine followed by rehydrogenation. (The assumption is made that the basic ring structure is unchanged.) Wolffenstein and Reitmann[23a] obtained "pseudosparteine" ($[\alpha]_D$ − 49.8° in chloroform) by dehydrogenation of *l*-sparteine with sodium hypobromite followed by catalytic hydrogenation of the dehydrosparteine ($C_{15}H_{24}N_2$) obtained. The pseudosparteine was not well characterized, but it was perhaps identical with the "α-isosparteine" ($[\alpha]_D$ − 56.2° in methanol) obtained by Winterfeld and Rauch.[17] Their fully characterized solid product, m. p. 118°, was obtained by didehydrogenation of *l*-sparteine by the use of mercuric acetate followed by addition of two molecules of hydrogen to the didehydrosparteine. We have now repeated this preparation and have shown that our synthetic isomer of sparteine is the racemate corresponding to Winterfeld and Rauch's *l*-α-isosparteine. With three of the stereoisomers of $C_{15}H_{26}N_2$ (I) accounted for, the disposition of the two bases of $[\alpha]_D$ − 17° (ethanol) and $[\alpha]_D$ − 1.2° (ethanol), isolated by Winterfeld and Nitzsche[23b] from sparteine sulfate mother liquors, remains in doubt. The missing three isomers of $C_{15}H_{26}N_2$ (I) can reasonably be expected to be a pair of enantiomorphs of as yet unknown specific rotation and a solid isomer of $[\alpha]_D$ *ca.* + 56.2° (methanol).

Sufficient evidence has been accumulated for us to make a provisional assignment of stereochemical structure to sparteine. It is proposed tentatively that the structure of sparteine (*d* or *l*) is represented by formula 3 in Fig. 3. This is the only one of the three structures which exhibits configurational difference between rings B and C. The other two structures have a vertical axis of symmetry through the C_8 methylene group. The assignment is based on the fact that stereochemical difference between rings B and C of sparteine has been observed in three instances: (a) The catalytic reduction of dioxosparteine (IV), which has two structurally equivalent carbonyl groups at C_{10} and C_{17}, produced *dl*-oxosparteine according to Galinovsky and Kainz.[14] Only one of the carbonyl groups could be reduced under their conditions. (b) Aphyllidine (postulated as I with a 5,6-double bond and CO at 10) could be reduced to *d*-sparteine by low pressure hydrogenation, whereas oxosparteine (postulated as I with CO at 17 [III]) could not be reduced.[25] (c) Aphylline (postulated as I with CO at 10) was readily hydrolyzed to the amino acid,[24a] whereas oxosparteine (III) required drastic treatment to effect ring cleavage.[24b] Corroborative evidence for formula 3, Fig. 3, as representing the stereochemical configuration of sparteine is also to be found in an examination of the structures of the related dehydro- and didehydrosparteines.[24c]

Pharmacology.—The pharmacological action of *dl*-sparteine and *dl*-α-isosparteine is being studied by Dr. K. K. Chen, Eli Lily and Company.

Experimental

1-Sparteine Monopicrate.—To 300 mg. of natural *l*-sparteine (from *l*-sparteine sulfate, S. B. Penick and Company) in dry ether was added 300 mg. of picric acid in dry ether. An amorphous solid was obtained which gave 85 mg. of *l*-sparteine dipicrate after recrystallization from 90% ethanol. The ethereal and ethanol mother liquors were evaporated to dryness and the residue, recrystallized from ethanol–ether, gave 320 mg. of orange *l*-sparteine monopicrate, m. p. 96–98°. The monopicrate was very soluble in ethanol, methanol, acetone and chloroform and was insoluble in benzene, ether, methylcyclohexane and water. After two recrystallizations from ethanol–ether followed by two recrystallizations from ethanol–water, the tiny elongated prisms melted at 96.5–97.5°.

Anal. Calcd. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.55; H, 6.47; N, 14.94.

1-Carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline (V).—This compound was prepared from ethyl 2-pyridylacetate[16] by the method of Clemo, Morgan and Raper,[9] modified in that the product was not distilled prior to recrystallization. All of the material boiling below 200° at 1 mm. was removed by distillation and the residue containing the desired material was dissolved in benzene. After decolorization with charcoal and filtration a large volume of petroleum ether (b. p. 90–120°) was added and the solution was cooled. The yellow 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline crystallized, and one recrystallization from petroleum ether gave a product, m. p. 130–131°, suitable for hydrogenation.

Diethyl 2,4-Di-(α-pyridyl)-glutarate (VI) Prepared by Formaldehyde Condensation.[13]—A reaction mixture of 25 g. of freshly distilled ethyl 2-pyridylacetate, 2.25 g. of paraformaldehyde and 0.4 g. of piperidine was heated in an oil-bath. The paraformaldehyde dissolved slowly, and the reaction became mildly exothermic when the bath temperature reached 80–90°. After five minutes at 120° the mixture was allowed to cool to 25° and to stand for twenty-four hours. The first fraction contained water and starting material, and the second fraction (b. p. 130–193° at 0.3–0.5 mm.), 14.9 g. (58%), contained the desired **diethyl 2,4-di-(α-pyridyl)-glutarate**. Redistillation gave a red oil, b. p. 175–185° (0.3 mm.), $n^{20}D$ 1.5292. A heart cut of this fraction, b. p. 181° (0.3 mm.), was submitted for analysis.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.82; H, 6.66; N, 8.45.

The picrolonate of diethyl 2,4-di-(α-pyridyl)-glutarate was prepared in ether. Recrystallization from acetone gave light yellow microcrystals, m. p. 146–147°.

Anal. Calcd. for $C_{39}H_{38}N_{10}O_{14}$: C, 53.79; H, 4.40; N, 16.09. Found: C, 54.06; H, 4.59; N, 15.84.

The picrate, m. p. 154–154.5° (dec.),[11b] was prepared in ethanol and recrystallized from acetone.

The third fraction, b. p. 210–215° (0.5–0.8 mm.), from the original distillation crystallized on standing and after recrystallization from benzene–petroleum ether (b. p. 90–120°) gave 1.2 g. of yellow needles, m. p. 130–131°. The same compound was isolated from the residue of the initial distillation. This compound was shown to be **1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline** since it gave no depression in melting point when mixed with an authentic sample of V. The picrate was undepressed in melting point, 221° (cor.), when mixed with 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline picrate. Infrared spectra of the base and the authentic pyridocoline were identical. The liquid which collected in the Dry Ice-trap during the distillation gave a positive ceric nitrate

(23a) Wolffenstein and Reitmann, *Biochem. Z.*, **186**, 269 (1927).

(23b) Winterfeld and Nitzsche, *Arch. Pharm.*, **278**, 393 (1940).

(24) (a) Späth, Galinovsky and Mayer, *Ber.*, **75**, 805 (1942); (b) Orekhov, Kabachnik and Kefeli, *Compt. rend. acad. sci. U. S. S. R.*, **31**, 335 (1941); (c) Beyler, Ph.D. Thesis, University of Illinois, 1949.

test and was converted to iodoform, m. p. 120°, in good yield by the action of sodium hypoiodite. The generation of ethanol in the distillation process was thus indicated.

Diethyl 2,4-Di-(α-pyridyl)-glutarate Prepared by Methylene Iodide Condensation.—To a suspension of 4.4 g. of powdered potassium in 150 ml. of benzene maintained at 25° was added a solution of 18.5 g. of ethyl 2-pyridylacetate in 30 ml. of benzene during one-half hour with stirring. The reaction mixture was heated to boiling for one-half hour and then allowed to stand twelve hours at 25°. Fifteen grams of methylene iodide was added dropwise during fifteen minutes to the well-stirred mixture. The reaction mixture was refluxed for two hours to complete the reaction. To the ice-cold mixture was added a solution of 9 ml. of concentrated hydrochloric acid and 30 ml. of water. The aqueous layer was separated and was made strongly alkaline with saturated aqueous potassium hydroxide. The oil which separated was extracted with ether. The ether was removed and the residual oil was distilled to give 6.0 g. (32%) of diethyl 2,4-di-(α-pyridyl)-glutarate, b. p. 150–175° (0.3–0.5 mm.), $n^{20}D$ 1.5265. A picrate, m. p. 154–154.5°, was prepared which gave no depression in melting point with the picrate of diethyl 2,4-di-(α-pyridyl)-glutarate prepared by the formaldehyde method.

Hydrogenation of 1-Carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline.—A solution of 10 g. of 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline in 96 ml. of purified dioxane was hydrogenated over 5 g. of copper chromite catalyst. Steady absorption of hydrogen at 250–350 atm. pressure was observed at 250° during one and one-half hours. After removal of the dioxane, distillation of the residue yielded 5.39 g. (68%) of yellow oil. Fractionation of 4.50 g. of this product gave 0.31 g., b. p. 90–120° (1.25 mm.); 2.31 g., b. p. 120–126° (1.25 mm.); 1.69 g., b. p. 140–148° (1.25 mm.). ***dl*-Sparteine monopicrate** was prepared from a portion of the second fraction by adding a molar equivalent of picric acid to the base in absolute ethanol. Recrystallization four times from ethanol gave orange-yellow prisms, m. p. 136–137° (reported, 135°).[5b]

Anal. Calcd. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.55; H, 6.49; N, 15.18.

***dl*-Sparteine dipicrate** was obtained by adding excess picric acid in ethanol to a portion of the second fraction dissolved in ethanol. The picrate, which precipitated immediately, was recrystallized twice from ethanol as lemon-yellow crystals, m. p. 208° (cor.) (reported, 206–207°).[5b]

Anal. Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.28. Found: C, 46.76; H, 4.88; N, 16.29.

***dl*-Oxosparteine.**[9]—To a solution of 0.7 g. of the second fraction in 1 ml. of 6 *N* sulfuric acid was added 6 g. of potassium ferricyanide and 1.05 g. of sodium hydroxide in 15 ml. of water. The reaction mixture was shaken for thirty minutes and was then extracted with ether. The ethereal solution was dried and the ether was removed. The residue was sublimed and the sublimate was triturated with petroleum ether (b. p. 40–60°) to give colorless crystals, m. p. 110–111° (reported, 110–111°,[9] 112–113°,[25] 113°).[5b]

Separation of *dl*-Sparteine and *dl*-α-Isosparteine

A. By Distillation.—The combined reduction product from the hydrogenation of 125.2 g. of 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline in eight runs amounted to 85 g. (85% based on total conversion to $C_{15}H_{26}N_2$). This yellow oil was distilled through a six-inch helix-packed column at a reflux ratio of 5–10 to 1. The following fractions were obtained: (1) b. p. 70–85° (0.05 mm.); $n^{21}D$ 1.4790; 2.6 g. colorless oil; (2) b. p. 95–117° (0.03–0.5 mm.); 11.8 g. colorless solid; (3) b. p. 117–137° (0.5 mm.); $n^{21}D$ 1.5020–1.5175; 28.9 g. colorless oil; (4) b. p. 137–150° (0.6 mm.); $n^{21}D$ 0.4913–1.4940; 32.8 g. light yellow oil; (5) b. p. 150–208° (0.6 mm.); $n^{21}D$ 1.4988–1.5082; 4.0 g. yellow oil. Storage of all fractions at −70° prevented their slow darkening, which can be observed at 5°. Fraction 2 was found to contain the major amount of *dl*-α-isosparteine, but contaminated with *dl*-sparteine. Recrystallization of this fraction from aqueous ethanol gave 2.3 g. of ***dl*-α-isosparteine monohydrate** as elongated prisms. The melting point of *dl*-α-isosparteine monohydrate varied considerably with the rate of heating employed. The melting point was 98–105° (softening at 87°) when the bath temperature was elevated at a rate of 2° per minute.

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10; H_2O, 7.14. Found: C, 71.62; H, 11.23; N, 11.07; H_2O, 8.10 (by loss of weight on drying to constant weight *in vacuo*).

Anhydrous *dl*-α-isosparteine, m. p. 78–80°, was obtained most conveniently by sublimation of the hydrate at 55–75° (0.1 mm.).

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.96. Found: C, 76.93; H, 11.41; N, 12.05.

dl-α-Isosparteine was soluble in non-polar and polar solvents with the exception of water. Solutions in ethanol, acetone, chloroform and dioxane turned pink on standing or on warming slightly. ***dl*-α-Isosparteine monopicrate**, m. p. 132.5–133.5°, was formed when equimolar amounts of *dl*-α-isosparteine and picric acid were mixed in ether and was obtained pure by recrystallization from absolute ethanol. It depressed the melting point of *dl*-sparteine monopicrate to 114–120°.

Anal. Calcd. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.65; H, 6.41; N, 14.85.

***dl*-α-Isosparteine dipicrate** was readily prepared by mixing the base with picric acid (1:2 molar proportion) in absolute ethanol. Two recrystallizations from aqueous ethanol gave lemon-yellow plates, m. p. 222–223° (cor.).

Anal. Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.28. Found: C, 47.08; H, 4.53; N, 15.93.

***dl*-α-Isosparteine monoperchlorate** was prepared by dissolving 40 mg. of base in 0.5 ml. of methanol and adding 65% perchloric acid to *p*H 2. After the addition of 3 ml. of water the methanol was evaporated on the steam-bath. The aqueous solution was basified by adding concentrated ammonium hydroxide to cloudiness (*p*H 10). Solid separated on cooling and after recrystallization from ethanol–ether, colorless elongated prisms, m. p. 160–162°, were obtained.

Anal. Calcd. for $C_{15}H_{27}ClN_2O_4$: C, 53.80; H, 8.13; N, 8.37. Found: C, 53.78; H, 8.30; N, 8.25.

From the ethanolic mother liquor of fraction 2 (see above), 7.3 g. of non-crystallizable base was recovered. This was combined with fraction 3 and the whole was redistilled through an eleven-inch helix-packed column at a reflux ratio of 10 to 1. The following fractions were collected: (1′) b. p. 114–119° (1.1 mm.); $n^{20}D$ 1.5211 to 1.5227; 5.02 g.; (2′) b. p. 119–121° (1.0 mm.); $n^{20}D$ 1.5221 to 1.5224; 10.32 g.; (3′) b. p. 121–146° (1.0 mm.); $n^{20}D$ 1.4927 to 1.5210; 13.83 g. From fraction 1′ there was obtained 1.7 g. additional of *dl*-α-isosparteine. Fraction 2′ consisted primarily of *dl*-sparteine, as shown by the preparation of *dl*-sparteine dipicrate. In addition, ***dl*-sparteine monoperchlorate** was prepared from 2′ in good yield by the method employed for the isomeric perchlorate. Recrystallization from ethanol–ether gave plates, m. p. 130–132°.

Anal. Calcd. for $C_{15}H_{27}ClN_2O_4$: C, 53,80; H, 8.13; N, 8.37. Found: C, 53.87; H, 8.27; N, 8.14.

B. By Chromatography.—A portion of fraction 2′ (see above) (1.23 g.) was dissolved in 200 ml. of hexane and the solution was passed through a 7-in. column (12 mm. i. d.) of 20 g. of freshly activated alumina. The column was washed with 200-ml. portions, in order, of hexane (212),[26] hexane–benzene (278), benzene (35), benzene–ether (85), ether (59), ether–acetone (38), acetone (21),

(25) Galinovsky and Stern, *Ber.*, **77**, 132 (1944).

(26) The figures in parentheses represent mg. of base obtained upon evaporation of each percolate portion.

acetone–ethanol (90), ethanol (4 portions) (102). The total amount of base represented a 75% recovery. Each percolate portion was converted to perchlorate salt. The portions through acetone–ethanol gave *dl*-sparteine monoperchlorate and the last two ethanol percolates gave solid *dl*-α-isosparteine, also identified as the monoperchlorate. Thus distillation fraction 2′ still retained a small amount of *dl*-α-isosparteine.

C. By Fractional Crystallization of the Perchlorate.—A major portion of distillation fraction 2′ (7.7 g.) was converted to monoperchlorate by the addition of 12 g. of 65% perchloric acid. Sufficient water was added to dissolve the resulting thick liquid and the aqueous solution was made strongly basic with concentrated ammonium hydroxide. The colorless solid which precipitated was recrystallized five times from methanol–ether to constant melting point, 130–132°; yield 3.25 g. of pure *dl*-sparteine monoperchlorate. The salt was warmed with 50 ml. of 5% sodium hydroxide to liberate the free base, which was extracted with five 15-ml. portions of ether. The ethereal extract was dried and the ether was removed. The residual oil was distilled at 0.2 mm. to give 1.51 g. of colorless oil, $n^{20}D$ 1.5272.[27] The hydrochloride of *dl*-sparteine proved to be hygroscopic. ***dl*-Sparteine bisulfate** was obtained by adding excess dilute sulfuric acid to the base. The solid, recrystallized from methanol, melted at 254° with decomposition and frothing.

Anal. Calcd. for $C_{15}H_{30}N_2O_8S_2$: C, 41.84; H, 7.02; N, 6.51. Found: C, 41.97; H, 7.24; H, 6.24.

Hydrogenation of 2,4-Di-(α-pyridyl)-glutarate.—A solution of 10 g. of 2,4-di-(α-pyridyl)-glutarate in 100 ml. of purified dioxane was hydrogenated over 15 g. of copper chromite catalyst at 200–310 atm. and 265° during three hours. The catalyst and solvent were removed and the residue was fractionated *in vacuo* to give 1.17 g. of b. p. 98–105° (0.1 mm.), 1.18 g. of b. p. 105–115° (0.1 mm.) and 2.06 g. of b. p. 115–125° (0.1 mm.). The first two fractions represented a 31% yield based on total conversion to $C_{15}H_{26}N_2$. Chromatography of the combined fractions on alumina followed by percolation with solvents of increasing polarity gave two major fractions, identified through their dipicrates, m. p. 206–207° (cor.) and 222–223° (cor.), as *dl*-sparteine and *dl*-α-isosparteine, respectively.

Resolution of *dl*-Sparteine.—To 1.37 g. of racemic base in 10 ml. of absolute ethanol was added 2.74 g. of *d*-β-camphorsulfonic acid. The solution was concentrated and cooled. The solid which separated was recrystallized from acetone as 230 mg. of colorless needles, m. p. 240–241°, $[\alpha]^{29}D$ 24.4 ± 0.5° (*c*, 2.04 in chloroform). There was no depression in melting point when this solid was mixed with authentic *l*-sparteine *d*-β-camphorsulfonate, $[\alpha]^{29}D$ 24.4 ± 0.5° (*c*, 2.30 in chloroform). Further recrystallization of the salt from acetone did not change the specific rotation. Three further crops of crystals were collected from the original ethanolic mother liquor. The total yield of *l*-sparteine *d*-β-camphorsulfonate after one recrystallization from acetone was 565 mg. (28% of the theoretical amount). The *l*-sparteine *d*-β-camphorsulfonate was converted directly to ***l*-sparteine dipicrate**, yellow needles, m. p. 207–208° (cor.), by the addition of ethanolic picric acid.

Anal. Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 47.13; H, 4.54; N, 15.94.

The melting point of this resolved *l*-sparteine dipicrate was depressed to 200–202.5° (cor.) when mixed with *dl*-sparteine dipicrate and was undepressed when mixed with natural *l*-sparteine dipicrate, m. p. 208°.[28,5b]

The ethanol mother liquor which remained after the removal of *l*-sparteine *d*-β-camphorsulfonate was evaporated to dryness and the residue was warmed in 10 ml. of 10% sodium hydroxide. The liberated base was extracted with ether, the ethereal solution was dried, and the ether was removed. To the 0.5 g. of residual oil was added 1.1 g. of *l*-β-camphorsulfonic acid[29] in 2 ml. of absolute ethanol. The solution was allowed to stand in the ice-box for ten days. The crystals which separated were recrystallized twice from acetone to give 119 mg. of *d*-sparteine *l*-β-camphorsulfonate, m. p. 239–241°, $[\alpha]^{29}D$ −24.0 ± 0.5° (*c*, 2.04 in chloroform). *d*-Sparteine dipicrate, yellow needles, m. p. 208–209° (cor.), was prepared directly from the *l*-β-camphorsulfonate. There was no depression in melting point when it was mixed with an authentic sample[22] of *d*-sparteine dipicrate, m. p. 208°.[30] For direct conversion of *d*-sparteine *l*-β-camphorsulfonate to *d*-sparteine perchlorate, 50 mg. of the former was dissolved in water and to this solution was added 10 drops of 65% perchloric acid followed by 12 drops of concentrated ammonium hydroxide. The solid which separated on cooling was recrystallized from ethanol–ether and was obtained as colorless needles, m. p. 174°. This melting point was undepressed when the salt was mixed with an authentic sample[22] of *d*-sparteine monoperchlorate, m. p. 173°.[30]

α-Didehydrosparteine.—The method of Winterfeld and Rauch was employed with some modifications. The free base was obtained from 100 g. of *l*-sparteine sulfate (S. B. Penick and Company) by treatment with excess 15% potassium hydroxide solution and ether extraction. The ether solution containing theoretically 55.4 g. (0.236 mole) of *l*-sparteine was extracted with five 150-ml. portions of 4% acetic acid in water. To the combined aqueous solution of *l*-sparteine acetate was added 603 g. (1.888 mole) of mercuric acetate, and the resulting solution was heated under reflux in a nitrogen atmosphere for seven hours. The cooled reaction mixture was filtered from insoluble mercurous acetate, and the mercuric salts were precipitated by excess hydrogen sulfide. After removal of mercuric sulfide, 46.3 g. of concentrated sulfuric acid (sp. gr. 1.84) was added to the filtrate, and the solution was evaporated *in vacuo* with nitrogen bubbling gently through the solution. To the oily, partially crystalline residue was added 200 ml. of methanol. The solvent was again evaporated. Methanol was again added, and the methanol-insoluble α-didehydrosparteine bisulfate was collected on a filter. After washing with methanol and drying overnight in a vacuum desiccator there was obtained 39.9 g. of nearly colorless α-didehydrosparteine bisulfate. The methanol filtrate containing β-didehydrosparteine bisulfate was retained. The α-didehydrosparteine was obtained from the salt by alkalization, ether extraction and evaporation. Twenty grams of bisulfate furnished 9.8 g. of amber crystals. Sublimation at 95–100° (0.1 mm.) gave 7.06 g. of colorless crystalline α-didehydrosparteine, m. p. 105–107° (dec.). The infrared spectrum of α-didehydrosparteine showed a strong C=C band (1645 $cm.^{-1}$) and indicated that the two double bonds are probably not conjugated. The ultraviolet spectrum of α-didehydrosparteine in 95% ethanol exhibited no maximum, which confirmed this hypothesis.

***l*-α-Isosparteine.**—Winterfeld and Rauch[17] called this compound α-isosparteine, but because of our synthesis of the racemic material, it seems advisable to indicate that the product obtained from sparteine by dehydrogenation and rehydrogenation is the levorotatory form. Five grams (0.022 mole) of freshly sublimed α-didehydrosparteine in 100 ml. of methanol was hydrogenated over 1 g. of 2% palladium-on-calcium carbonate catalyst at 25° and 3 atm. The catalyst and methanol were removed and the residue was twice sublimed at 70–80° (0.1 mm.) to give colorless crystals of *l*-α-isosparteine, m. p. 98–117° (partially hydrated). Considerable effort was made to obtain analytical data on the anhydrous base, but all of the

(27) Moureu and Valeur (*Compt. rend.*, **137**, 194 (1903)) gave $n^{19}D$ 1.5293 for *l*-sparteine; Couch (THIS JOURNAL, **58**, 1296 (1936)) reported $n^{27}D$ 1.5256 for *l*-sparteine.

(28) Moureu and Valeur, *Bull. soc. chim.*, [3] **29**, 1135 (1903).

(29) Obtained by resolution of *dl*-β-camphorsulfonic acid according to the method of Burgess and Gibson, *J. Soc. Chem. Ind.*, **44**, 496T (1925).

(30) Marion and Ouellet, THIS JOURNAL, **70**, 691 (1948); Marion and Turcotte, *ibid.*, **70**, 3253 (1948); Marion and Cockburn, *ibid.*, **70**, 3472 (1948).

carbon analyses lay between the theoretical values for the monohydrate and the anhydrous base. The chief difficulty in drying was caused by the fact that the base sublimed at temperatures as low as 35° (0.1 mm.). The best analysis was obtained on a sample which had been twice sublimed, twice recrystallized from aqueous ethanol, and sublimed three more times.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.96. Found: C, 75.81; H, 11.22; N, 11.60.

***l*-α-Isosparteine Monohydrate.**—The monohydrate was prepared by recrystallizing *l*-α-isosparteine from aqueous ethanol; m. p. 98–115°, $[\alpha]^{30}D$ − 55.8 ± 0.8° (*c* = 7.216, methanol). Since this would correspond to a rotation of −60.1° in terms of the anhydrous base, it seems likely that Winterfeld and Rauch,[17] who reported $[\alpha]$ −56.2° in methanol, probably experienced partial hydration of their α-isosparteine.

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10. Found: C, 71.57; H, 11.37; N, 10.95.

***l*-α-Isosparteine Dipicrate.**—Prepared in ethanol and recrystallized from aqueous ethanol, the dipicrate formed tiny diamond-shaped plates, m. p. 221° (dec.).

Anal. Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 47.06; H, 4.68; N, 16.15.

The melting point of a mixture of *l*- and *dl*-α-isosparteine dipicrates melted at 213–218° with decomposition. In this behavior, they are similar to the corresponding *l*- and *dl*-sparteine dipicrates.

***l*-α-Isosparteine Bisulfate.**—Prepared by addition of methanolic sulfuric acid to an ethanolic solution of the base, the bisulfate formed tiny rhombic crystals, m. p. 267° (dec.) (reported, 244–245°[17]).

Infrared Spectra.[31]—The crystalline dipicrates of natural *l*-, resolved *l*-, natural *d*- and resolved *d*-sparteine gave identical infrared spectra (as nujol mulls). The spectrum of crystalline synthetic *dl*-sparteine dipicrate (as a nujol mull) was slightly different from the active forms (Fig. 1). In a solvent these minor spectral differences between racemic and active forms disappeared. A suitable solvent for determination of the infrared spectra in solution was difficult to find, but in acetonitrile and in acetone the curves of *d*-, *l*- and *dl*-sparteine dipicrates appeared to be identical. There was considerable absorption due to the solvent and to the picric acid portion of the molecule.

A comparison of synthetic *dl*-sparteine, obtained by purification through the perchlorate, with natural *l*-sparteine, each in chloroform solution, showed the infrared absorption spectra to be identical (Fig. 2, Curves 1 and 2).

The infrared spectra of *dl*-sparteine dipicrate and *dl*-α-isosparteine dipicrate showed minor differences in the absorption curves when the compounds were measured in acetone solution or in the crystalline state. The curves of the free bases, *dl*-sparteine and *dl*-α-isosparteine, in chloroform solution were more satisfactory for differentiation between these compounds (Fig. 2, Curves 1 and 3). The infrared spectrum of freshly sublimed *l*-α-isosparteine in chloroform (Fig. 2, Curve 4) was identical with that of synthetic *dl*-α-isosparteine (Curve 3) except for small differences in the regions of 1110, 1140 and 1640 $cm.^{-1}$. The spectra of the hydrates of these two bases were completely identical and were best represented by Curve 4 of Fig. 2.

(31) The authors are indebted to Mrs. James L. Johnson and Miss Elizabeth M. Petersen for determination of the infrared absorption spectra.

Summary

1. *dl*-Sparteine and *dl*-α-isosparteine have been synthesized by the reductive cyclization of both 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline and diethyl 2,4-di-(α-pyridyl)-glutarate.

2. Methods of separation of *dl*-sparteine and *dl*-α-isosparteine have been described.

3. *dl*-Sparteine has been resolved into its optical antipodes and the identity of the resolved bases with natural *d*- and *l*-sparteine has been established.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Epimerization, Dehydrogenation, and Ring Cleavage of Some Steroids and Related Compounds by Palladium. Stereochemistry of the Estrogens

BY W. E. BACHMANN AND ANDRE S. DREIDING[1]

An investigation of the action of 5% palladium-on-charcoal on equilenin, estrone and some related compounds at 250° and at 350° has shown that epimerization at C_{14}, dehydrogenation and even cleavage of the D ring can occur depending on (1) the configuration of the C–D ring juncture, (2) the state of reduction of rings A and B, and (3) the temperature of the reaction. The epimerization can occur without concomitant dehydrogenation. The cleavage reaction takes place only at the higher temperature.

Reactions with 5% Palladium-on-Charcoal at 250°.—When *d*-equilenin (I) or its methyl ether (III) was heated briefly with an equal weight of 5% palladium-on-charcoal at 250° *d*-isoequilenin (II) or its methyl ether (IV), respectively, was obtained in good yield. This represents a convenient method of preparing the diastereoisomer from the natural hormone. The change in the reverse direction could not be brought about. Since the product was a pure diastereoisomer and not a racemic mixture, an inversion of the configuration must have taken place at only one carbon atom and the change may be called an epimerization. The epimerization occurs at C_{14} since *d*-equilenin and *d*-isoequilenin differ in configuration only at that carbon atom.[2]

(1) Alfred H. Lloyd Postdoctoral Fellow in the Horace H. Rackham School of Graduate Studies, 1947–1948.

(2) (a) Hirschmann and Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938); (b) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940). This evidence is based on the conclusion that an isomerization at the C–D ring juncture took place during Hirschmann and Wintersteiner's acid-catalyzed conversion of equilin to isoequilin A. The conditions of this experiment could produce an epimerization only at C_{14}. Recently some doubt has been expressed on the configuration of isoequilin A by Heer and Miescher, *Helv. Chim. Acta*, **31**, 1289 (1948). They consider the possibility that the epimerization may have occurred during the dehydrogenation of isoequilin A to *d*-isoequilenin with six times the weight of palladium at 80° for sixteen hours. If this were so then the epimerization could not be located with certainty at C_{14}. This possibility had been excluded