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A Direct Synthesis of DL-Baikiain

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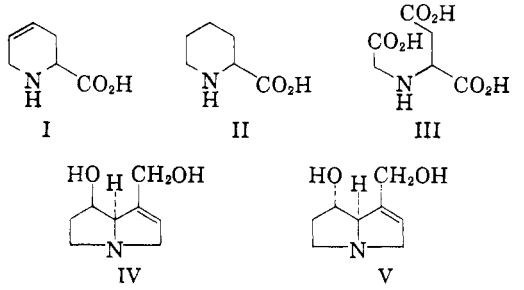
A convenient synthesis of DL-baikiain (DL-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid, I) from *cis*-1,4-dichloro-2-butene and acetamidomalonic ester is described.

The presence of a levorotatory, unsaturated, secondary α-amino acid in the heartwood of Rhodesian teak (*Baikiaea plurijuga*) was first reported in 1950 by King, King, and Warwick.[1] Various experiments by these investigators established the structure of this substance, to which the name "baikiain" was given, as L(−)-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid (I). Thus, on catalytic reduction it took up one mole of hydrogen and furnished L(−)-pipecolic acid (II), while on ozonolysis it afforded *N*-carboxymethyl-L-aspartic acid (III). In addition, there was described a synthetic route to baikiain, which, because of the exceedingly low yield in the last step, was admitted to be only partially successful and certainly of very limited preparative value.

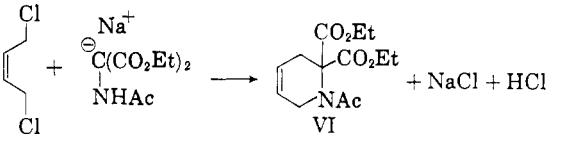


I II III

IV V

Our interest in developing a flexible synthetic approach to the fully oxygenated unsaturated *Senecio* bases[2] retronecine (IV) and heliotridine (V) from the Δ^4-dehydropipecolic acid structure (I) prompted us to seek a more direct route to biakiain than that explored by King and coworkers. In this latter connection, Dobson and Raphael[3] have recently published a synthesis of DL-baikiain somewhat related to our own, but which is much lengthier. These authors, by employing an eight-step sequence starting from 1,4-dichloro-2-butyne, were able to prepare DL-baikiain in an over-all yield of about 8%.

The synthesis now reported utilizes the condensation of *cis*-1,4-dichloro-2-butene with the sodium salt of diethyl acetamidomalonate to furnish an intermediate (VI) capable of being converted to baikiain:



VI

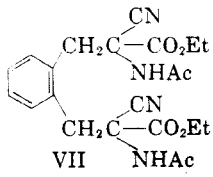
This approach finds analogy in the observation of Burckhalter and Stevens[4] that the reaction of *o*-xylylene dibromide with two molar equivalents of ethyl sodioacetamidocyanoacetate yields not only the diester VII (30%) but also the tetrahydroisoquinoline derivative VIII (43%):

(1) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950); F. E. King and T. J. King, *Chem. & Ind. (London)*, 489 (1953); *cf.* W. R. Carruthers and R. H. Farmer, *Chem. & Ind. (London)*, 641 (1953).

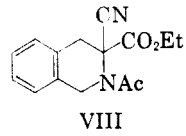
(2) For a recent review of the structure and stereochemistry of the pyrrolizidine alkaloids, see F. L. Warren, *Record Chem. Progr.*, **20**, 13 (1959).

(3) N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, 3642 (1958).

(4) J. H. Burckhalter and V. C. Stevens, *J. Am. Chem. Soc.*, **73**, 56 (1951).

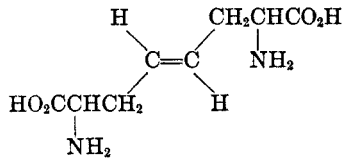


VII



VIII

Initially, the use of *cis*-1,4-dibromo-2-butene in our alkylation studies was contemplated, but the extreme ease with which this substance is known to isomerize, thereby giving rise to *trans* olefinic products,[5] foreshadowed difficulties with this choice. Consequently, it was not surprising that, in the mixture resulting from the hydrolysis and decarboxylation of the material produced by the reaction of this dihalide with diethyl sodioacetamidomalonate at 25–45° in benzene–dimethyl sulfoxide (15:1), merely trace amounts of baikiain could be detected. The major product appeared to be the *dl* or possibly the *meso* form[4] of the *trans* diamino dicarboxylic acid IX, whose structure was confirmed by ozonolysis to DL-aspartic acid. The *trans* configuration of the double bond in IX is assigned on the basis of the strong absorption at 10.3 μ in its infrared spectrum (absent in the spectrum of DL-baikiain).



IX

In sharp contrast to the foregoing results, the alkylation of diethyl acetamidomalonate with *cis*-1,4-dichloro-2-butene under the same conditions proceeded as desired, without detectable isomerization of the double bond. As already indicated, this dihalide served to produce the cyclic diester VI, which was not isolated but was hydrolyzed directly with base. The resulting product was then decarboxylated in hydrochloric acid solution to furnish, after appropriate concentration and extraction, DL-baikiain hydrochloride, in 29% over-all yield from the dichlorobutene. Isolation of the free amino acid was accomplished by the action of silver carbonate on the hydrochloride.

Besides being identical with natural L(−)-baikiain[1] (I) in crystalline appearance, paper chromatographic behavior, and ninhydrin color test, our synthetic product was further characterized by hydrogenation to DL-pipecolic acid (II) and by ozonolysis leading to the trimethyl ester of *N*-carboxymethyl-DL-aspartic acid (III). The identity of these products was confirmed by direct comparisons with authentic preparations. Infrared spectra of the *N*-benzoyl derivative of the synthetic baikiain and of the methyl ester of this derivative were indistinguishable from the respective spectra of the same compounds prepared from the natural material. However, the spectra of the synthetic and the natural amino acid (in Nujol or as potassium bromide pellets) showed considerable differences, as did those of the corresponding hydrochlorides.[6]

Studies to extend this work to the synthesis of the oxygenated pyrrolizidine bases present in the *Senecio* alkaloids are now in progress.

EXPERIMENTAL

Melting points were determined on a microscope hot stage calibrated against standard substances. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

DL-*Baikiain hydrochloride.* To a suspension of 7.2 g. (0.30 mole) of sodium hydride in 250 ml. of dry benzene and 35 ml. of dimethyl sulfoxide (Stepan Chemical Co.), a solution of 34.9 g. (0.16 mole) of diethyl acetamidomalonate (Winthrop Laboratories, 1450 Broadway, New York 18, N. Y.) in 200 ml. of dry benzene was added under nitrogen, with stirring, over a period of 1 hr. The reaction temperature was then raised to 50° and maintained at this temperature for 2 hr. to complete the formation of the sodio derivative (cessation of hydrogen evolution). With stirring continued, the mixture was then cooled to 25°, and 19.2 g. (0.15 mole) of *cis*-1,4-dichloro-2-butene[7] in 25 ml. of dry benzene was added under nitrogen, over a period of 2 hr. After being stirred for 2.5 hr. at 25° and then for an additional 14 hr. at 45°, the reaction mixture was treated with 30 ml. of absolute ethanol to consume unchanged sodium hydride. The resulting suspension was filtered, and the insoluble solids were washed with an additional 100 ml. of alcohol. The solvents were then evaporated under aspirator vacuum on the steam bath, the residue mixed with 180 ml. of water containing 12 ml. of acetic acid, and the resulting mixture extracted with three 100-ml. portions of ether. Removal of the ether at reduced pressure from the combined extracts left an oily, tan-colored product which could not be made to crystallize. This was taken up in 40 ml. of ethanol, 100 ml. of 2.5*N* aqueous sodium hydroxide was added, and the solution heated at reflux for 4 hr. under a nitrogen atmosphere. During this operation two phases slowly separated. The mixture was then cooled in an ice bath, while 50 ml. of conc. hydrochloric acid was added, with shaking (gas evolution). The resulting solution was refluxed for 0.5 hr. (darkening of color) and then evaporated to dryness *in vacuo* on the steam bath. The residual solids, which gave a yellow color with ninhydrin test solution, were then extracted with two 200-ml. portions of refluxing absolute ethanol, each for 0.25 hr., and filtered while hot. Concentration and cooling of the combined, dark-colored ethanolic extracts furnished 7.1 g. (29% over-all yield) of DL-baikiain hydrochloride as glistening, white prisms, m.p. 255–261° (dec.). Purification by crystallization from methanol–ethyl acetate afforded 6.9 g. of colorless product, m.p. 262–264° (dec.) (rapid heating) (lit.[3] 264°, dec.).

Anal. Calcd. for $C_6H_9O_2N\cdot HCl$ (163.61): C, 44.05; H, 6.16; N, 8.56; Cl, 21.67. Found: C, 44.31; H, 6.32; N, 8.69; Cl, 21.44.

An ascending paper chromatogram of this product with phenol-water as the mobile phase gave a yellow-brown

(5) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 844 (1957); see also ref. 10.

(6) In private correspondence with us Professor Raphael has indicated that the identity of the potassium bromide infrared spectra mentioned in ref. 3 actually referred only to the *N*-benzoyl derivatives.

(7) L. H. Amundsen, R. H. Mayer, L. S. Pitts, and L. A. Malentacchi, *J. Am. Chem. Soc.*, **73**, 2118 (1951).

ninhydrin spot with an R_f value of 0.85, identical in position, shape, and color with that produced by L(−)-baikiain.[1,8] The infrared spectrum of the synthetic product in Nujol or as a potassium bromide pellet differed significantly from the published spectrum[8] of the optically active compound.

DL-*Baikiain* (I). Treatment of 300 mg. of the above hydrochloride with 350 mg. of silver carbonate in 5 ml. of water, with stirring, for 10 min., followed by filtration of the mixture, evaporation of the solvent, and recrystallization of the residue from methanol-acetone, provided 210 mg. (90% yield) of DL-baikiain as small, elongated prisms, m.p. 251–254° (dec.) (lit.[3] 273–274° dec.).

Anal. Calcd. for $C_6H_9O_2N$ (127.14): C, 56.68; H, 7.14; N, 11.02. Found: C, 56.54; H, 7.33; N, 10.77.

A mixed melting point of this substance with natural L(−)-baikiain,[1] m.p. 270–273° (dec.), was 255–261° (dec.). The paper chromatographic behavior was identical with that of L(−)-baikiain. Nujol and potassium bromide pellet infrared spectra showed a number of similarities but were quite different from those of the natural material.[6]

*N-Benzoyl-*DL-*baikiain.* The procedure described by King, *et al.*,[1] for the preparation of the *N*-benzoyl derivative of L(−)-baikiain was followed. The crude product, obtained in 80% yield, recrystallized from water to form irregular, flattened needles, m.p. 172–173° (lit.[3] 179–180°).

Anal. Calcd. for $C_{13}H_{13}O_3N$ (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.63; H, 5.89; N, 5.85.

The infrared spectrum of this substance in chloroform solution or as a potassium bromide pellet[3] was identical with that of *N*-benzoyl-L(−)-baikiain. The spectra of the respective methyl esters (diazomethane) in carbon disulfide or chloroform solution were likewise indistinguishable.

DL-*Baikiain hydrochloride methyl ester.* This derivative was obtained in 85% yield from DL-baikiain hydrochloride by the procedure of King, *et al.*,[1] for the preparation of L(−)-baikiain hydrochloride methyl ester. It crystallized from ethanol-acetone as fine prisms, m.p. 183–184°.

Anal. Calcd. for $C_7H_{11}O_2N\cdot HCl$ (177.58): C, 47.34; H, 6.76; N, 7.89; Cl, 19.97. Found: C, 47.13; H, 6.82; N, 7.75; Cl, 19.69.

Hydrogenation experiments. A. The reduction of 100 mg. (0.61 mmole) of DL-baikiain hydrochloride over Adams' catalyst according to the procedure of King, *et al.*,[1] for the hydrogenation of L(−)-baikiain hydrochloride, resulted in the uptake of 14.7 ml. of hydrogen in 10 min. at 25° and 745 mm. (theory 15.3 ml.). Separation of the catalyst, evaporation of the solvent, and recrystallization of the residue from ethanol-benzene gave DL-pipecolic acid hydrochloride, m.p. 257–260°, undepressed on admixture with an authentic sample, m.p. 259–261°, prepared by hydrogenation of picolinic acid hydrochloride.[9] Ascending paper strip chromatograms (phenol-water) of both samples gave identical deep violet ninhydrin spots with an R_f value of 0.87 (lit.[8] 0.895).

B. A solution of 0.2312 g. (1.0 mmole) of *N*-benzoyl-DL-baikiain in 15 ml. of ethanol was mixed with 0.1 g. of 10% palladium-charcoal (Adams' platinum catalyst[1] led to over-reduction) and shaken under hydrogen at 25° and 747 mm. The reduction was complete in 25 min., with an uptake of 22.8 ml. of hydrogen (theory 24.9 ml.). After filtration and concentration of the solution, colorless prisms, crystallizing as a solvate from benzene–petroleum ether (b.p. 40–60°), were obtained. After being dried at 100° these melted at 125.5–127°, undepressed on admixture with an authentic sample of *N*-benzoyl-DL-pipecolic acid, m.p. 126–127° (lit.[9] 126–127°), prepared by benzoylation[9] of DL-pipecolic acid.

*Trimethyl N-carboxymethyl-*DL-*aspartate.* The procedure and scale recorded by King, *et al.*,[1] for the preparation of the L form of this substance were employed. From 1.8 g. of methyl bromoacetate and 3.8 g. of dimethyl DL-aspartate, a colorless crude product was obtained which, after work-up, afforded 2.1 g. (76% yield from the bromoacetate) of the trimethyl ester of *N*-carboxymethyl-DL-aspartic acid (III) as an oily liquid, b.p. 124° (0.06 mm.), n_D^{23} 1.4498 [L-ester[1] b.p. 120° (bath) (0.1 mm.)].

Anal. Calcd. for $C_9H_{15}O_6N$ (233.22): C, 46.35; H, 6.48; N, 6.01. Found: C, 46.56; H, 6.45; N, 6.31.

The *picrate* was prepared in ethanol and recrystallized from ethanol-ether to give clusters of light yellow needles, m.p. 137–138° (L-picrate[1] m.p. 137°).

Anal. Calcd. for $C_9H_{15}O_6N\cdot C_6H_3O_7N_3$ (462.33): C, 38.97; H, 3.92; N, 12.12. Found: C, 39.02; H, 4.15; N, 12.32.

The picrolonate crystallized from ether containing a small amount of ethanol as deep yellow hexagonal prisms, m.p. 126–127° (L-picrolonate[1] m.p. 182°).

Anal. Calcd. for $C_9H_{15}O_6N_4\cdot C_{10}H_8O_5N_4$ (497.42): C, 45.87; H, 4.66; N, 14.08. Found: C, 45.92; H, 4.94; N, 14.36.

Ozonolysis of DL-*baikiain hydrochloride.* The procedure described by King, *et al.*,[1] for the ozonolysis of L(−)-baikiain hydrochloride was employed on one-half scale, esentially without change. After esterification of the ozonization product with methanol there was obtained 270 mg. of a redistilled, pale yellow oil, b.p. 120–125° (0.1 mm.). Its infrared spectrum was practically identical with that of authentic trimethyl *N*-carboxymethyl-DL-aspartate described above. The picrate deposited from ethanol-ether as light yellow needles, m.p. 137–138°, undepressed on admixture with the foregoing authentic preparation. The picrolonate crystallized from the same solvent pair as deep yellow hexagonal prisms, m.p. 126–127°, likewise undepressed on admixture with the authentic sample noted above.

trans-2,7-Diamino-4-octenedioic acid (IX). The already-presented description of the preparation of DL-baikiain hydrochloride was duplicated on the same scale, save that *cis*-1,4-dibromo-2-butene[10] was used in place of the dichloro derivative. The crude hydrolysis-decarboxylation product gave a strong blue-violet ninhydrin color test and had an R_f value of 0.35 when chromatographed on paper with phenol-water. Baikiain (yellow spot with an R_f of 0.85) was also detected on the chromatogram. Purification by extraction with hot alcohol from the inorganic contaminants was only partially successful. Ion exchange chromatography, however, did facilitate the isolation. Absorption of 2.0 g. of the crude hydrochloride (total yield 4.5 g.) on a well washed column of Dowex-50 (20 × 300 mm.), followed by washing with water until sodium chloride was no longer eluted, and then elution with 1.2 l. of 3*N* hydrochloric acid, afforded, after concentration of the amino acid fraction (last 850 ml.), 1.2 g. of the colorless *bis* (?) hydrochloride of the *dl* or *meso* form of *trans*-2,7-diamino-4-octenedioic acid (IX), which crystallized from methanol-water as small, flattened needles, m.p. *ca.* 235–240° (dec.). Attempted purification by repeated recrystallization from hot methanol-acetone resulted in extensive loss of hydrogen chloride, leading finally to the *free* amino acid, which deposited as fine, difficultly-soluble granules, m.p. 355–360° (dec.) (darkening at 320°). The analysis appeared to indicate that partial dehydration had also occurred.

Anal. Calcd. for $C_8H_{14}O_4N_2$ (202.21): C, 47.52; H, 6.98; N, 13.86. Found: C, 48.35; H, 7.32; N, 14.35; Cl, nil.

The infrared spectrum (Nujol) of this product indicated the presence of a *trans*-1,2-disubstituted olefinic linkage (strong band at 10.3 μ). Ozonolysis of a 2.0-g. sample of a partially purified sample of the hydrochloride, followed by esterification of the ozonization product with methanol, as in the degradation of baikiain,[1] furnished 0.8 g. of a colorless liquid, b.p. 85–90° (0.1 mm.), n_D^{23} 1.4425. The infrared spectrum of this material indicated it to be substantially identical with dimethyl DL-aspartate, an authentic sample of which

(8) R. M. Zacharius, J. F. Thompson, and F. C. Steward, *J. Am. Chem. Soc.*, **76**, 2908 (1954).

(9) C. M. Stevens and P. B. Ellman, *J. Biol. Chem.*, **182**, 75 (1950).

(10) A. Vallette, *Ann. chim.*, (12) **3**, 644 (1948).

was found to have b.p. 85–90° (0.1 mm.) and n_D^{23} 1.4420. Passage of anhydrous hydrogen chloride into an ether solution of this ester deposited the *hydrochloride* of *dimethyl* DL-*aspartate*, which crystallized from ethanol–ethyl acetate as slightly hygroscopic, colorless, hard prism clusters, m.p. 115–116.5°, undepressed on admixture with an authentic specimen prepared from DL-aspartic acid.

Anal. Calcd. for $C_6H_{11}O_4N \cdot HCl$ (197.63): C, 36.46; H, 6.12; N, 7.09. Found: C, 36.67; H, 6.17; N, 7.10.

Acknowledgment. We are deeply grateful to Dr. F. E. King, F.R.S., British Celanese Ltd., for supplying a generous comparison sample of *L*(−)-baikiain and to Professor Joseph H. Burckhalter for giving much helpful advice and encouragement during the course of this work. We also wish to thank the University of Kansas for providing a grant from the General Research Fund and the General Aniline and Film Corp. for furnishing *cis*-2-butene-1,4-diol.

LAWRENCE, KAN.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

α-Oximinoketones. V. The Synthesis of 5-Cyano-2-oximinovaleric Acid and DL-Lysine from 2,6-Dioximinocyclohexanone[1]

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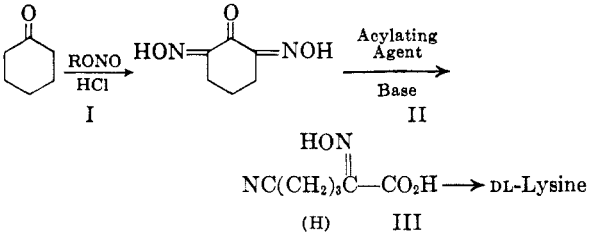
A new three-step synthesis which gives DL-lysine monohydrochloride in 20% overall yield from cyclohexanone has been developed. The reaction sequence is: (1) conversion of cyclohexanone to 2,6-dioximinocyclohexanone by the action of methyl nitrite, (2) partial cleavage of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid by the action of acylating agent and aqueous base, and (3) reduction of 5-cyano-2-oximinovaleric acid to DL-lysine by catalytic hydrogenation.

The importance of L-lysine as an essential amino acid in the diet of man and some higher animals and its relative scarcity in most of the common cereal proteins have led to many attempts to prepare this amino acid synthetically. Perhaps the largest number of published syntheses have proceeded from ε-caprolactam (most commonly prepared by Beckmann rearrangement of cyclohexanone oxime).[3] Other favorite starting materials have been malonic ester[4–6] or its derivative, acetamidomalonic ester.[7,8] Several elegant syntheses have been based on oxygen-containing heterocyclic materials such as acrolein dimer (3,4-dihydro-2H-pyran-2-carboxaldehyde)[9] or furfural.[10–12]

The need for a better method of preparing DL-lysine than any of those described has led to an extended effort in this laboratory to realize the deceptively simple three-step synthesis shown in equation form below:



This research is described in this and the next two papers of this series.

The preparation of 2,6-dioximinocyclohexanone (Step I) was described first by Borsche[13] and has been studied more recently by Treibs and coworkers.[14] The reduction of the ethyl ester of 5-cyano-2-oximinovaleric acid has been carried out successfully,[4–6] so that it seemed logical to believe that step III could be made to succeed. The critical step thus appeared to be II, which may be described as a partial "second order" Beckmann rearrangement, wherein it was desired to bring about rearrangement at one oxime group but not at the

(1) A preliminary account of this and the next two papers in this series was published in *Chem. & Ind. (London)*, 996 (1959).

(2) Present address: General Aniline and Film Co., Linden, N. J.

(3) R. J. Wineman, E. T. Hsu, and C. E. Anagnostopoulos, *J. Am. Chem. Soc.*, **80**, 6233 (1958); W. C. Francis, J. R. Thornton, J. C. Werner, and T. R. Hopkins, *J. Am. Chem. Soc.*, **80**, 6238 (1958). Previous work is summarized in these papers.

(4) E. Fischer and F. Weigert, *Ber.*, **35**, 3772 (1902).

(5) H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley, and P. H. Lowy, *J. Biol. Chem.*, **176**, 1383 (1948).

(6) P. Olynyk, D. B. Camp, A. M. Griffith, S. Woislowski, and R. W. Helmkamp, *J. Org. Chem.*, **13**, 465 (1948).

(7) M. Servigne and E. Szarvasi, *Compt. rend.*, **238**, 1595 (1954).

(8) D. T. Warner and O. A. Moe, *J. Am. Chem. Soc.*, **70**, 2763, 3918 (1940).

(9) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

(10) A. O. Rogers, R. D. Emmick, L. W. Tyran, L. B. Phillips, A. A. Levine, and N. D. Scott, *J. Am. Chem. Soc.*, **71**, 1837 (1949).

(11) R. Gaudry, *Can. J. Research*, **26B**, 387 (1948).

(12) H. Conroy, U. S. Patents **2,786,848** and **2,786,850**, March 26, 1957; H. Conroy and W. J. Paleveda, U. S. Patent **2,786,849**, March 26, 1957.

(13) W. Borsche, *Wallach Fest.*, 301 (1909); *Chem. Abstr.*, **5**, 883 (1911).

(14) A. Treibs and D. Dinelli, *Ann.*, **517**, 152 (1935); A. Treibs and A. Kuhn, *Chem. Ber.*, **90**, 1691 (1957).