tered. The filtrate was fractionated to give 1.85 g of the addition product, 3-chlorocyclononene (IX), bp 87–89° (16 mm), $n^{28}D$ 1.5004.

Anal. Calcd for $C_9H_{15}Cl$: C, 68.12; H, 9.53; Cl, 22.35. Found: C, 67.60; H, 9.35; Cl, 23.10.

Oxymercuration of 1,2,6-Cyclononatriene.—1,2,6-Cyclononatriene (V)[12] (6.5 g, 0.054 mole) was added to a solution of 17.65 g (0.065 mole) of mercuric chloride in 85 ml of ethanol and allowed to stand for 12 hr. The resulting green solution was filtered to separate 2.3 g of mercury. The filtrate was dissolved in 300 ml of ether and washed with sodium chloride solution, then water and finally dried over anhydrous magnesium sulfate. The solution was concentrated to 150 ml when it began to deposit fluffy, colorless crystals. These were separated by filtration and the filtrate was concentrated to near dryness at an aspirator without heating. The residue was shaken with a small volume of pentane and filtered. In this way, 1.0 g of white solid, mp 145–155°, was obtained. It was purified by recrystallization from ether, mp 159–160°. The substance was shown by nmr and analytical data to be 1-chloromercury-9-ethoxy-1,5-cyclononadiene (VI).

Anal. Calcd for $C_{11}H_{17}ClHgO$: C, 32.92; H, 4.27; Cl, 8.84. Found: C, 32.77; H, 4.28; Cl, 9.03.

Pentane was removed from the filtrate at an aspirator and the residue was distilled through a short-path system under high vacuum into a receiver cooled to −60°. The distillate (1.90 g) was examined by vapor–liquid chromatography and found to consist of 61% starting material (V) along with six other substances varying from 3 to 17%.

Addition of Hydrogen Chloride to 2,3-Pentadiene.—Dry hydrogen chloride was bubbled through a mixture of 5.0 g of 2,3-pentadiene (VII) and 0.20 g of anhydrous bismuth chloride at −70°. The reaction mixture was kept at −70° for 48 hr and then allowed to warm to 0° to permit the escape of unreacted hydrogen chloride. Only 1.4 g was consumed. The mixture was stirred briefly with anhydrous potassium carbonate and then filtered. Fractionation of the filtrate gave 1.1 g of 4-chloro-2-pentene (X) and 3-chloro-2-pentene (XI), bp 58–59° (197 mm). The proton resonance spectrum suggested the mixture to have a X/XI ratio of 85:15.

Oxymercuration of 2,3-Pentadiene.—A mixture of 1.75 g (0.026 mole) of 2,3-pentadiene (VII), 7.7 g (0.028 mole) of mercuric chloride, and 40 ml of ethanol was stored at 0° for 10 hr. Use of the work-up procedure described for the preparation of II gave 4.15 g of liquid residue. Distillation afforded 3.0 g of 3-chloromercury-4-ethoxy-2-pentene, bp 141° (0.04 mm), $n^{32}D$ 1.5385. The structure assignment is based on nmr and analytical data.

Anal. Calcd for $C_7H_{13}ClHgO$: C, 25.24; H, 3.93; Cl, 10.64. Found: C, 23.85; H, 3.94; Cl, 8.93.

Efforts to obtain better data were unsuccessful.

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Senecio Alkaloids. Synthesis of Sarracinic Acid

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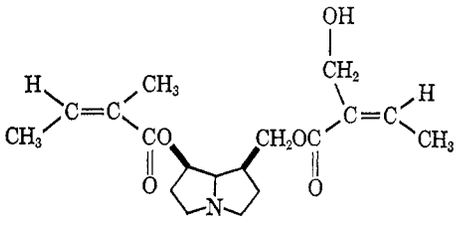
From the studies of Danilova, *et al.*,[2–5] and of Culvenor and Geissman,[6,7] the *Senecio* alkaloid sarracine has been formulated as platynecine esterified by the two pentanecic acids, angelic and sarracinic, as shown in I.



I

The assignment of the *trans* arrangement[8] of the hydrogen and carboxyl groups in sarracinic acid (2-hydroxymethyl-2-butenoic acid) derived from this alkaloid was made by correlation of the chemical shift of the vinyl proton with that published[9] on similar compounds.

The preparation of both geometric isomers of 2-hydroxymethyl-2-butenoic acid was undertaken for the following reasons: to establish by synthesis the structure of sarracinic acid; to test the correlation of Nair and Adams[9] which gave characteristic nuclear magnetic resonance (nmr) shifts for β-vinyl protons in stereomers of certain α,β-unsaturated acids; to study the interconversion of the two isomeric forms; and to see if the *cis* form would give mikanecic acid[6] (1-vinyl-3-cyclohexene-1,4-dicarboxylic acid) as does sarracinic acid. For these reasons, a synthesis yielding a reasonable ratio of the geometric isomers of 2-hydroxymethyl-2-butenoic acid was needed. Since House and Rasmusson[10] have shown that the product from reaction of a highly reactive ylid with an α-keto ester contained significant amounts of both geometric isomers, the use of the Wittig reaction was studied. The compound, ethyl acetoxypyruvate, required for this reaction had been prepared by Ratusky and Šorm[11] from the reaction of ethyl diazopyruvate with acetic acid and this α-keto ester on reaction with ethylidenetriphenylphosphorane gave, after the usual work-up, a mixture containing four compounds.

This mixture was separated by column chromatography and the isomeric ethyl 2-acetoxy-2-butenoates (II, III) were present in a 1:1 ratio and in a yield of 10%.

Hydrolysis of II gave a hydroxy acid (IV) identical with sarracinic acid,[12] and from III the isomeric *cis* acid V was formed. The *cis* acid has the higher melting point and is more stable than sarracinic acid. The olefinic proton[13] in sarracinic acid is at τ 3.60 and in V was found at 2.97. This is in line with the shift structure correlation published by Nair and Adams.[9] The substitution of a hydroxyl group for a hydrogen in the allylic position has only a small effect on the chemical shift of the olefinic proton.

(1) Robert A. Welch Foundation Postdoctoral Fellow.

(2) A. V. Danilova, R. Konovalova, P. Massagetov, and M. Garina, *Dokl. Akad. Nauk SSSR*, **89**, 865 (1953).

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(6) C. C. J. Culvenor and T. A. Geissman, *Chem. Ind.* (London), 366 (1959).

(7) C. C. J. Culvenor and T. A. Geissman, *J. Org. Chem.*, **26**, 3045 (1961).

(8) Nomenclature used in this paper.

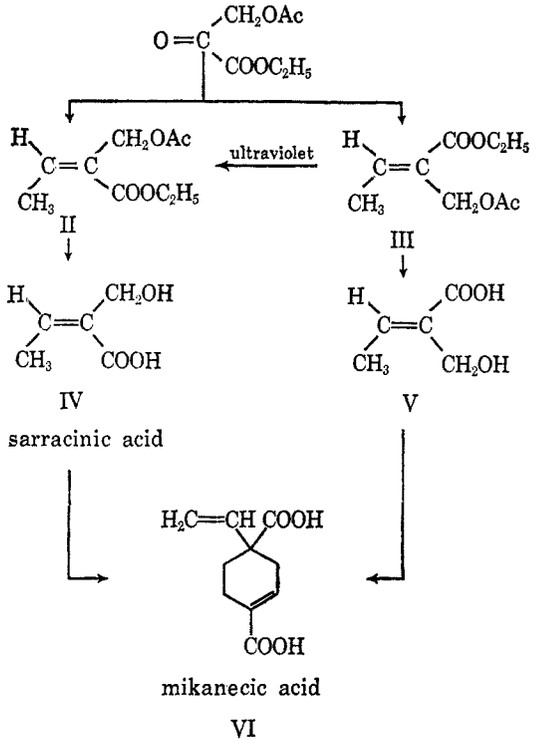
(9) M. D. Nair and R. Adams, *J. Am. Chem. Soc.*, **82**, 3786 (1960).

(10) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

(11) J. Ratusky and F. Šorm, *Chem. Listy*, **51**, 1091 (1957).

(12) The authors are indebted to Dr. C. C. J. Culvenor and Mr. L. W. Smith, CSIRO, Melbourne, Australia, for a sample of sarracine N-oxide.

(13) The authors are indebted to Mr. N. F. Chamberlain, Esso Research and Engineering Co., Baytown, Texas, for the nuclear magnetic resonance results.



The photochemical isomerization of III to II was also studied and this was found to occur in a 38% yield with a 57% recovery of III. The resulting mixture was separated by column chromatography.

Since it is known that sarracinic acid is slowly converted[6] to VI by heating in aqueous alkali, the isomer V of sarracinic acid was heated under reflux in dilute sodium hydroxide for 24 hr. The product was shown to be identical with VI prepared from sarracinic acid. As with sarracinic acid this reaction probably proceeds by the formation of 1,3-butadiene-2-carboxylic acid which dimerizes to mikanecic acid.[6]

For the sarracinic acid synthesis, the phosphonate modification of the Wittig reaction also was attempted but, not unexpectedly,[14] the Arbusov reaction of triethyl phosphite with methyl 3-acetoxy-2-bromopropionate gave a complex mixture containing at least five components as shown by gas chromatography. The methyl 3-acetoxy-2-bromopropionate was prepared from 2-bromo-3-hydroxypropanoic acid[15] by esterification with diazomethane and subsequent acetylation with acetyl chloride–pyridine.

Experimental Section[16]

Ethyl Acetoxypyruvate.—The best yield of this compound from ethyl diazopyruvate was 51%. After the initial very vigorous reaction,[11] the mixture was heated on a steam bath for 4 hr, filtered, and distilled. Attempts to acetoxylate ethyl pyruvate with lead tetraacetate,[18] lead tetraacetate–boron trifluoride etherate,[19] or mercuric acetate[20] were unsuccessful as were the reactions between ethyl bromopyruvate[21] and potassium, sodium, or silver acetate in different solvents.

Wittig Reaction.—Under dry nitrogen and with good stirring there was added dropwise 0.096 mole of a benzene–ether solution of phenyllithium to a suspension of 36 g (0.097 mole) of ethyltriphenylphosphonium bromide in 200 ml of anhydrous ether. After stirring for 1 hr the ylid solution was decanted under nitrogen and added dropwise with good stirring during 1.5 hr to a solution of 14 g (0.08 mole) of ethyl acetoxypyruvate in 30 ml of ether at a temperature of 23–25°. After the resulting mixture was refluxed under nitrogen for 26 hr, the bulk of the ether was distilled, 400 ml of anhydrous tetrahydrofuran was added, and the mixture was refluxed for 42 hr. The tetrahydrofuran was distilled to a volume of 150 ml, 300 ml of ether was added, and the mixture was filtered. After concentration to 20 ml, the mixture was again filtered and solvents were removed and distilled to give 2.6 g, bp 57–74° (0.15 mm). Gas chromatography, 3% XE-60 column 5 ft × 1/8 in., indicated at least four components.

Chromatography of Wittig Reaction Product.—A 4 × 32 cm column was prepared from 200 g of silica gel (E. Merck AG, 0.08 mm) suspended in purified chloroform.[22] To this was added 2.1 g of the Wittig reaction product and elution with chloroform containing 3% dry ether was carried out at a flow rate of 120 ml/hr maintained by air pressure. Fractions 1–3 (755 ml) gave 472 mg of colorless crystals. The infrared spectrum showed aromatic but no carbonyl or hydroxyl absorption. Fractions 4–11 (175 ml) gave 652 mg of crude II and fractions 12–24 (325 ml) gave 679 mg of crude III.

Sarracinic Acid.—The oil obtained from fractions 4–11 was rechromatographed as described above on 150 g of silica gel. Fractions 1–2 (610 ml) gave 36 mg which was discarded. Fractions 3–10 (195 ml) gave 572 mg (oil) of pure II. Fractions 11–13(370 ml) gave 37 mg of a II–III mixture. A solution of 0.535 g of II in 10 ml of ethanol was added to 2 g of barium hydroxide octahydrate in 20 ml of water and refluxed for 1.5 hr. After cooling, 5% hydrochloric acid was added dropwise until acid to congo red paper followed by extraction with ether six times. The combined ether extracts were washed with water, dried, and after removal of the ether the residue was dried under high vacuum to give 163 mg of solid. Later the aqueous phase from the hydrolysis was continuously extracted for 8 hr with ether and after the same work-up gave 139 mg of solid. Recrystallization from ether–petroleum ether (30–60°) gave colorless crystals, mp 52–54° (lit.[7] mp 57–58°). A mixture melting point with sarracinic acid (mp 51–53°) was 51–53°. The infrared spectra of natural and synthetic sarracinic acid were identical.

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94; equiv wt, 116. Found: C, 51.53; H, 6.75; equiv wt, 117.

Hydrolysis of III.—The crude III obtained from fractions 12–24 (679 mg) on the chromatography of the Wittig reaction product was rechromatographed on 150 g of silica gel. Fractions 1–2 (650 ml) gave 60 mg of II. Fractions 3–13 (265 ml) gave 610 mg (oil) of pure III. Hydrolysis of III (560 mg) was carried out as described for II to give 345 mg of a solid. Recrystallization from ether–petroleum ether (30–60°) several times gave colorless crystals of V, mp 74–75°. A prepared mixture of these crystals and sarracinic acid was a liquid.

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94; equiv wt, 116. Found: C, 51.84; H, 6.78; equiv wt, 114.

Proton Magnetic Resonance and Infrared Spectra.[16]—Results from the nmr spectra[18] of the isomeric acids are given in Table I.

TABLE I

τ VALUES

IV	H type	Multiplicity	V
3.16	OH	Singlet	2.82
3.60	HC=	Quartet	2.97
	|		
5.78	CH_2	Singlet	5.66
7.95	CH_3	Doublet	8.12

(14) P. C. Crofts, *Quart. Rev.* (London), **12**, 347 (1958).

(15) C. F. Koelsch, *J. Am. Chem. Soc.*, **52**, 3364 (1930).

(16) All elemental analyses were done by Huffman Analytical Laboratories, Wheatridge, Colo. Temperatures reported are uncorrected and the melting points were made on a Fisher-Johns block. The nmr spectra were determined on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as internal standard. Infrared spectra were made on a Beckman IR-V with 0.1-mm matched cells in 3% chloroform solution. The authors gratefully acknowledge the assistance of the undergraduate research participants Mr. John C. Price, Mr. Richard T. McDill,[17] and Mr. Robert W. Preston.

(17) Robert A. Welch Foundation Scholar.

(18) R. Criegee, "Newer Methods of Preparative Organic Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1941, p 8.

(19) J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).

(20) A. K. Macbeth and W. G. P. Robertson, *ibid.*, 3515 (1953).

(21) S. Archer and M. G. Pratt, *J. Am. Chem. Soc.*, **66**, 1656 (1944).

(22) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p 283.

Infrared studies on II and III showed C=C absorption at 1650 cm^{-1}, stronger in III. In the 1700–1735-cm^{-1} range, III has a doublet. Bands characteristic of II are at 1180 cm^{-1} and of III, at 1465, 1287, 1147, and 1075 cm^{-1}. For the acids IV and V, the C=C band was at 1647 cm^{-1}, stronger in V. Bands characteristic of IV are at 1082 and 858 cm^{-1} and for V, at 1145 and 1025 cm^{-1}.

Ultraviolet Irradiation of III.—A solution of III (100 mg) in 3 ml of ethanol in a stoppered quartz spectrophotometer cell was irradiated 6 in. from an unscreened Hanovia ultraviolet 325-w lamp for 4 hr in a hood. The alcohol was removed under vacuum and the residue was resolved by chromatography on silica gel (30 g) as described above. In this way there was obtained 38 mg of II and 57 mg of III. The identity of II was established by infrared spectra and hydrolysis to sarracinic acid.

Mikanecic Acid.—Compound V, the isomer of sarracinic acid, was heated with aqueous sodium hydroxide as described[7] for the conversion of sarracinic acid to mikanecic acid. After acidification, the aqueous solution was continuously extracted with ether for 6 hr. After drying and evaporation of the ether, the residue was recrystallized from aqueous acetone to give colorless crystals, mp 239–241° (lit.[7] mp 240°). A mixture melting point with VI prepared from sarracinic acid showed no depression.

Methyl 3-Hydroxy-2-bromopropanoate.—To a solution of 31 g (0.183 mole) of 2-bromo-3-hydroxypropanoic acid[15] in 150 ml of anhydrous ether, there was added dropwise with stirring at 5°, an ethereal solution of diazomethane (0.144 mole). After concentration by distillation to a volume of 200 ml, the ether solution was extracted with 10 ml of a saturated sodium bicarbonate solution, dried, and on evaporation of ether gave a 26-g residue which distilled at 58–60° (0.3 mm).

Anal. Calcd for $C_4H_7BrO_3$: C, 26.25; H, 3.86. Found: C, 25.69; H, 3.62.

Methyl 3-Acetoxy-2-bromopropanoate.—At 0° there was added dropwise with stirring 12.3 ml (0.17 mole) of freshly distilled acetyl chloride to 26.6 g (0.144 mole) of methyl 2-bromo-3-hydroxypropanoate in 25 ml of dry ether followed by 13.9 ml (0.17 mole) of anhydrous pyridine. After standing at room temperature for 30 hr, the mixture was poured into 500 ml of ice water and extracted with ether. The ether solution was dried and after removing the ether, the product was distilled at 74–75° (1.3 mm) in a 80% yield.

Anal. Calcd for $C_6H_9BrO_4$: C, 32.02; H, 4.03. Found: C, 32.29; H, 4.11.

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A Synthesis of L-Cystathionine and D-Allocystathionine[1]

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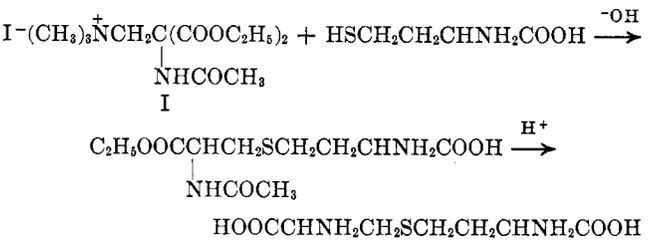
For metabolic studies with experimental animals, we needed convenient source of L-cystathionine. Diethyl α-acetamido-α-dimethylaminomethylmalonate methiodide (I) was an intermediate available in the laboratory known to be useful for synthesizing a variety of β-substituted alanines. It had recently been employed in a condensation with $KC^{14}N$ to prepare 4-C^{14}-β-cyanoalanine, 4-C^{14}-aspartic acid, and 4-C^{14}-asparagine.[2-5] Its reaction with diethyl acetamidomalonate leads to 2,4-diaminoglutaric acid[6] and with sulfide ion and sodium benzylmercaptide, to lanthionine and S-benzylcysteine, respectively.[7,8] Condensation of I with the nucleophilic sulfur of homocysteine was therefore expected to be potentially capable of yielding cystathionine. The present Note reports a synthesis of a mixture of L-cystathionine and D-allocystathionine through this route, as shown in the diagram below.[9]



Also described are the separation of the formed diastereomeric mixture into L-cystathionine and D-allocystathionine in high yield, and a convenient method for analyzing such mixtures of diastereomers. This route is suitable for large-scale preparations of cystathionine. By substituting D-homocysteine, it should serve equally well to prepare D-cystathionine and L-allocystathionine. By employing I prepared from either labeled formaldehyde or labeled diethyl acetamidomalonate, the synthesis should yield L-cystathionine labeled with C^{14} in the cysteine moiety.

Compound I was prepared, in 50-g batches, by the method of Atkinson, *et al.*[7] Although its melting point differed significantly from that reported,[4] it had the expected elementary composition. Commercial L-methionine served as the other starting material. Other syntheses of cystathionine that use an L-homocysteinyl unit have frequently started from DL-methionine, which is converted to S-benzyl-DL-homocysteine and then resolved.[9b] For this, conversion of the S-benzylhomocysteine to an appropriate N-acyl derivative, followed by formation of diastereomeric salts,[10] or by stereospecific enzymatic anilide synthesis[9b,11] or hydrolysis,[12] has been required. In the present synthesis, S-benzyl-L-homocysteine was prepared directly from L-methionine[13] by refluxing with benzyl chloride and HCl, as described by Armstrong[14] for the preparation of S-benzyl-DL-homocysteine from DL-methionine. The crude S-benzyl-L-homocysteine was obtained on a 2-mole scale in 50% yield. After one reprecipitation, its optical rotation agreed with that of material prepared through the enzymatic synthesis of N-acetyl-S-benzyl-L-homocysteine anilide.[9b,11] The rotation, which

(1) This work was aided by U. S. Public Health Service grant NB 04316 and by Muscular Dystrophy Associations of America.

(2) C. Ressler, Y.-H. Giza, and S. N. Nigam, *J. Am. Chem. Soc.*, **85**, 2874 (1963), footnote 8.

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(8) For reactions of I with other nucleophiles, see H. Hellmann and E. Folz, *Chem. Ber.*, **89**, 2000 (1956).

(9) For a review of other syntheses of cystathionine, see (a) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, pp 2683–2687; (b) A. Schöberl and G. Täuber, *Ann. Chem.*, **599**, 23 (1956); (c) A. Schöberl and J. Borchers, *Angew. Chem.*, **77**, 591 (1965).

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(12) S. M. Birnbaum and J. P. Greenstein, *Arch. Biochem. Biophys.*, **42**, 212 (1953).

(13) This route to S-benzyl-L-homocysteine has been noted briefly before but without detail and yield [W. Sakami, *Biochem. Prepn.*, **8**, 8 (1961)].

(14) M. D. Armstrong, *ibid.*, **5**, 91 (1957).