two racemic modifications. Attempts to synthesize one of these racemic modifications, the essential amino acid DL-threonine, have invariably given poor results, though some of the syntheses have produced the diastereoisomeric DL-allothreonine in good yields. Efforts to convert DL-allothreonine into DL-threonine have met with little success.

It has now been found that esters of N-acyl-DL-allothreonine are converted into DL-threonine in high yield by transformation into the corresponding oxazolines followed by hydrolysis of the latter with mineral acid.

N-Benzoyl-DL-allothreonine was treated with diazomethane and the methyl ester (m. p. 110–111°. *Anal.* Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.36. Found: C, 60.86; H, 5.99.) on reaction with excess thionyl chloride at room temperature gave 2-phenyl-5-methyl-4-carbomethoxyoxazoline hydrochloride, m. p. 118–119°, in quantitative yield. *Anal.* Calcd. for $C_{12}H_{13}O_3N \cdot HCl$: C, 56.36; H, 5.52. Found: C, 56.50; H, 5.71. Hydrolysis with dilute hydrochloric acid followed by isolation and recrystallization gave pure D-threonine in 70% yield. *Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.35; H, 7.70; N, 11.46. By the same sequence of steps N-benzoyl-DL-threonine was converted into pure DL-allothreonine in 77% over-all yield.

A practical synthesis of DL-threonine from acetoacetic ester has been developed by the use of this inversion. Ethyl α-acetamidoacetoacetate, obtained in 88% yield from acetoacetic ester via reductive acetylation of ethyl α-phenylazoacetoacetate, was hydrogenated in aqueous solution with Adams catalyst to give on concentration a mixture of diastereoisomeric ethyl α-acetamido-β-hydroxy-*n*-butyrates containing 80–85% N-acetyl-DL-allothreonine ethyl ester. A purified sample of this product melted at 76–77°. *Anal.* Calcd. for $C_8H_{15}O_4N$: C, 50.78; H, 7.99. Found: C, 50.54; H, 8.04. The crude hydrogenation product was treated with thionyl chloride, and the solution was refluxed with water to decompose the intermediate oxazoline. An isolated sample of this 2,5-dimethyl-4-carbethoxyoxazoline hydrochloride melted at 105–106°. *Anal.* Calcd. for $C_8H_{13}O_3N \cdot HCl$: C, 46.27; H, 6.79; N, 6.75; N. E., 207.7. Found: C, 46.11; H, 6.87; N, 6.97; N. E., 202.2. The aqueous solution was concentrated dry and the amino acid hydrochloride taken up in isopropanol and precipitated with aniline. The crude product (89% yield from ethyl α-acetamidoacetoacetate) was a mixture of DL-threonine and DL-allothreonine containing 83% of the former (microbial assay).

Pure DL-threonine was obtained by separation of the sodium salt from anhydrous alcohol, reconversion into the free acid and recrystallization by precipitation from aqueous solution with alcohol. The over-all yield of DL-threonine from acetoacetic ester was 57%. *Anal.* Found: C, 40.42; H, 7.32; N, 11.82. This product was found 100% pure by microbial assay and better than 99% pure by solubility analysis.

Additional work now in progress indicates that the "oxazoline inversion" described may be a general method for the interconversion in high yield of diastereoisomeric α,β-amino alcohols.

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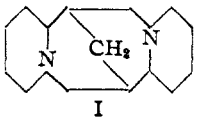
THE TOTAL SYNTHESIS OF SPARTEINE

Sir:

We wish to report a convenient total synthesis of *dl*-sparteine (I). The *Lupin* alkaloid *l*-



I

sparteine was first isolated in 1851 and the correct structure (I) was confirmed by Clemo and Raper[1] in 1933. *l*-Sparteine is used in medicine chiefly as a cardiac stimulant and a diuretic.[2] *d*-Sparteine and the naturally occurring alkaloid pachycarpine[3] have been shown to be identical.[4]

Our synthesis of *dl*-sparteine proceeds in two steps from ethyl 2-pyridylacetate. The first step was the preparation of 1-carbethoxy-4-keto-3-(2′-pyridyl)-pyridocoline by condensation of ethyl orthoformate with ethyl 2-pyridylacetate in the presence of acetic anhydride according to the method of Clemo, Morgan and Raper.[5] The second step was that of reductive cyclization, which was reported first from this Laboratory[6] for the synthesis of pyrrolizidines. 1-Carbethoxy-4-keto-3-(2′-pyridyl)-pyridocoline in dioxane was hydrogenated over copper chromite at 250° and 350 atm. in one and one-half hours. The product was separated into three fractions: b. p. 90–120°, 120–126°, 140–148° (1.25 mm.). The second and largest fraction gave a **monopicrate** (m. p. 136–137°; *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) and a **dipicrate** (m. p. 208°; *Anal.* Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 46.76; H, 4.88; N, 16.28). The analyses and melting points of the derivatives are consistent with the assignment of the *dl*-sparteine structure to the synthetic free base. Clemo and Leitch[7] reported a **monopicrate**

(1) Clemo and Raper, *J. Chem. Soc.*, 644 (1933).

(2) Wood and Osol, "United States Dispensatory," J. B. Lippincott Company, Philadelphia, Pa., twenty-third edition, 1943, p. 1012; "The Merck Index," Merck and Company, Rahway, N. J., fifth edition, 1940, p. 524.

(3) Orechov, Rabinowitch and Konovalova, *Ber.*, **66**, 621 (1933).

(4) Galinovsky and Stern, *ibid.*, **77**, 132 (1944).

(5) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1025 (1936).

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

(7) Clemo and Leitch, *J. Chem. Soc.*, 1811 (1928).

(m. p. 135°) and a **dipicrate** (m. p. 206–207°) of *dl*-sparteine, which they obtained from naturally occurring *dl*-lupanine. As a further proof of identity, our *dl*-sparteine was converted to *dl*-oxysparteine, m. p. 110–111°, by treatment with alkaline potassium ferricyanide. The melting point of *dl*-oxysparteine has been reported as 110–111°,[5] 112–113°,[4] 113°.[7] Finally, the infrared absorption spectra of our synthetic *dl*-sparteine dipicrate and an authentic sample of *l*-sparteine dipicrate (m. p. 208°) were found to be identical in solution.[8]

We are aware of the desirability of resolving *dl*-sparteine and of isolating the other two racemates of I. We also foresee the applicability of our method to the synthesis of other bases related to sparteine.

(8) The authors are indebted to Mrs. James L. Johnson for determination of the infrared absorption spectra.

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A CRYSTALLINE FACTOR FUNCTIONALLY RELATED TO FOLIC ACID

Sir:

In a systematic study of factors functionally related to *p*-aminobenzoic acid and folic acid and occurring in liver extracts used for the treatment of pernicious anemia, a factor was discovered which prevented the toxic action of methylfolic acid[1] upon the growth of *Leuconostoc mesenteroides* 8293. In a medium previously described[2] but supplemented with 300 γ of thymine per 10 cc., the ratio of methylfolic acid to folic acid just necessary for maximum inhibition was 3,000. The addition of this factor in adequate amounts (equivalent to 0.01–0.03 γ of crystalline material per 10 cc.) increases the antibacterial index about tenfold.

A medium suitable for quantitative assay was obtained by the addition of 0.03 γ of folic acid and 200 γ of methylfolic acid per 10 cc. to the above medium. Under these conditions increasing concentrations of the factor resulted in increasing growth levels.

Employing this assay, a principle has been isolated from hog liver in crystalline form. Recrystallized from isopropyl alcohol, this principle appears as fine, colorless prisms, m. p. 189–190°. Under the testing conditions, the factor is several times as active as folic acid in promoting a half-maximum growth response.

Extracts prepared from either liver, hog duodenal mucosa, or grass are highly active, but milk, muscle tissue and yeast extract are relatively poor sources of active material. Liver extracts used in treatment of pernicious anemia are relatively potent, and some experimental extracts of high potency (determined clinically) assayed by the above method appear to contain as much as 1% of this factor.

Preliminary investigation of the structure of the compound indicated that it was thymidine[3] or a structurally related compound.

We acknowledge our indebtedness to Eli Lilly and Company for their coöperation. Particular thanks are due Drs. Ewald Rohrmann and Edward D. Campbell for their coöperation in furnishing experimental extracts and analytical facilities.

(1) Crude mixture from the condensation of α,β-dibromobutyraldehyde, 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid obtained from Dr. E. L. R. Stokstad [Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947)].

(2) Snell, *et al.*, *ibid.*, **148**, 519 (1942).

(3) Since this paper was submitted, we have obtained a sample of thymidine originally isolated from desoxyribonucleic acid by Levene and London (*J. Biol. Chem.*, **83**, 793 (1929)). The X-ray diffraction pattern and the biological properties of this sample are identical with those of the isolated factor.

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THE KINETICS OF THE POLYMERIZATION OF CARBONIC ANHYDRIDES

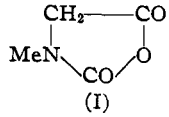
Sir:

Carothers (*Chem. Rev.*, **8**, 353 (1931)) has divided polymerizations into two types, "addition" and "condensation." In the former type, initiation, propagation, transfer and termination reactions are involved (*cf.* Bamford and Dewar, *Proc. Roy. Soc.* (*London*), **192**, 309 (1948)), but in condensation polymerizations only chain-growth occurs, and in this reaction every species reacts with every other. There is, however, a third type of polymerization in which there are only two reactions, initiation, and a propagation reaction where the polymers do not react with each other, but only with the monomer. The polymerizations of carbonic anhydrides (*e. g.*, I) appear to belong to this third type, and are also important since they can be used to synthesize polypeptides of some complexity. The reactions involved are

$$M + A \longrightarrow X + CO_2 \quad (k_1) \qquad (1)$$

$$M + X \longrightarrow X + CO_2 \quad (k_2) \qquad (2)$$

where M denotes the carbonic anhydride, X any polymer species, and A the initiator which may be a hydroxylic or amino compound.



(I)

$$MeNHCH_2CO(NMeCH_2CO)_nNMeCH_2CONMe_2$$

(II)

Although a complete formal solution of the kinetic equations is impossible, the following methods are available for the absolute determina-