powder is vigorously stirred under 1 liter of refluxing anhydrous ether. One mole of the alkoxybenzyl halide dissolved in 1 l. of ether is added over a two to five hour interval. The resulting Grignard reagent is then filtered through glass cotton to remove the finely divided magnesium powder, which if not removed usually reacts with objectionable vigor during the ultimate decomposition with water or dilute acid. The yield is estimated by the usual acidimetric titration.

RESEARCH LABORATORIES OF
THE WM. S. MERRELL COMPANY
CINCINNATI, OHIO

RECEIVED MARCH 8, 1948

COMMUNICATIONS TO THE EDITOR

CHEMICAL REACTIONS IN MOVING BOUNDARY SYSTEMS OF WEAK ELECTROLYTES

Sir:

In moving boundary systems containing partially neutralized weak acids or bases there exists the possibility of chemical reactions at the moving boundary which cause the mobility calculated from the boundary velocity and the conductivity of the leading solution to be lower than the ionic mobility.[1] This is illustrated by experiments 2 and 3 in which the indicator electrolyte is a salt of weak acid (cacodylic acid) having a higher pK than the leading weak electrolyte (acetic acid). The following reaction goes to completion

$$\mathrm{Cac^-} + \mathrm{HOAc} \rightleftharpoons \mathrm{HCac} + \mathrm{OAc^-} \quad K_{25^\circ} = 25 \quad (1)$$

to the right at the moving boundary so that none of the acetic acid remains behind that boundary. The concentration of the sodium acetate is 0.05 N (at 0°) in all experiments, and it has been shown that the concentration and pH of the indicator electrolyte (α solution) is unimportant over a wide range.

The moving boundary equation[2] cannot be applied to acetate ion in the presence of acetic acid, but a term may be added for the acetic acid as follows so that the moving boundary equation for acetate constituent becomes

$$T^{\gamma}_{\mathrm{OAc^-}} = V^{\beta\gamma}(C^{\gamma}_{\mathrm{OAc^-}} + C^{\gamma}_{\mathrm{HOAc}}) = \frac{u^{\gamma}_{\mathrm{OAc^-}} C^{\gamma}_{\mathrm{OAc^-}}}{\kappa^{\gamma}\ 1000/F} \quad (2)^3$$

From equation (2) we see that the mobility, u, calculated from the boundary velocity in this case is the "constituent" mobility. The acetate ion mobility, $u^{\gamma}_{\mathrm{OAc^-}}$

$$u = V^{\beta\gamma}\kappa^{\gamma}\frac{1000}{F} = u^{\gamma}_{\mathrm{OAc^-}}\frac{(C^{\gamma}_{\mathrm{OAc^-}})}{(C^{\gamma}_{\mathrm{OAc^-}} + C^{\gamma}_{\mathrm{HOAc}})} \quad (3)$$

calculated from the constituent mobility obtained in experiments 2 and 3 by using equation (3) are -17.62×10^{-5} and -17.55×10^{-5} in agreement with the average value, -17.53×10^{-5}, obtained in experiments 1 and 4.

However, in systems containing weak electrolytes the constituent mobility is not always obtained as illustrated by experiment 5. Whether or not a chemical reaction takes place depends upon the pK and relative mobility of the indicator ion. In this experiment the mobility calculated is slightly lower than the ionic mobility because the acetate ion does not disappear in the $\beta\gamma$ boundary, owing to the slight dissociation of the acetic acid left behind the moving boundary.

Since proteins and buffers used in electrophoresis are weak electrolytes, reactions such as the above occur and must be considered in the quantitative interpretation of electrophoretic patterns.

TABLE I[a]

	Moving Boundary System[b] γ	β	α	$\frac{u \times 10^5}{(0^\circ\mathrm{C.})}$
(1)	NaOAc(0.05) ←	NaCac	:: NaCac	−17.47
(2)	NaOAc(0.05), HOAc(0.05) ←	NaCac, HCac	:: NaCac	− 8.81
(3)	NaOAc(0.05), HOAc(0.01) ←	NaCac, HCac	:: NaCac	− 5.85
(4)	NaOAc(0.05) ←	NaT	:: NaT	−17.59
(5)	NaOAc(0.05), HOAc(0.05) ←	NaT, HOAc	:: NaT	−16.54

[a] OAc, acetate; Cac, cacodylate; T, trichloroacetate. [b] The conventions recommended by Longsworth, THIS JOURNAL, **67**, 1109 (1945), are used.

Since proteins and buffers used in electrophoresis are weak electrolytes, reactions such as the above occur and must be considered in the quantitative interpretation of electrophoretic patterns.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN — ROBERT A. ALBERTY
MADISON, WISCONSIN — J. C. NICHOL

RECEIVED MAY 25, 1948

SYNTHESIS OF DL-THREONINE

Sir:

The structure α-amino-β-hydroxy-n-butyric acid contains two dissimilar asymmetric carbon atoms and hence exists as four optical isomers and

(1) Dr. Harry Svensson, Institutes of Physical and Biological Chemistry, Upsala, Sweden, has independently recognized this fact in work initiated in September, 1946 (*Acta Chem. Scand.*, in press), personal communication.

(2) Weber, *Sitzungsber. Akad. Wissensch. Berlin*, 936 (1897); Svensson, *Ark. Kem. Min. Geol.*, **17A**, No. 14 (1943); Longsworth, THIS JOURNAL, **67**, 1109 (1945).

(3) The symbols have the meanings used by Longsworth ($C_{\mathrm{OAc^-}}$ is taken as negative).

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.

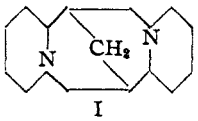
KARL PFISTER, 3rd.
RESEARCH LABORATORIES C. A. ROBINSON
MERCK & CO., INC. A. C. SHABICA
RAHWAY, N. J. MAX TISHLER

RECEIVED MAY 12, 1948

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.

THE NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
NELSON J. LEONARD
ROGER E. BEYLER

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.

THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH, AUSTIN, TEXAS
WILLIAM SHIVE
ROBERT E. EAKIN
W. M. HARDING
JOANNE M. RAVEL
JUDITH E. SUTHERLAND

RECEIVED APRIL 16, 1948

THE KINETICS OF THE POLYMERIZATION OF CARBONIC ANHYDRIDES

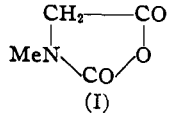
Sir:

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-

tion of the velocity constants k_1 and k_2. If (M) = M_0 and (A) = A_0 when $t = 0$, and (A) = A_∞ when (M) = 0, it can be shown that

$$k_2/k_1 = (M_0 - A_0 + A_\infty)/(A_0 \log (A_0/A_\infty) - A_0 + A_\infty) \quad (3)$$

Since end-group estimation gives $A_0 - A_\infty$, this equation enables k_2/k_1 to be evaluated.

The experimental conditions can be adjusted so that the concentration of initiator (A) is approximately constant, when it can be shown that there is a maximum rate given by

$$[\mathrm{d(M)/dt}]^2_{\mathrm{max.}} = \frac{1}{27} k_1 k_2 A_0 (2M_0 + k_1 A_0/k_2)^3 \quad (4)$$

A simpler procedure, however, is to use the preformed polymer to initiate the polymerization, so that the second step (equation (2)) is isolated. The molar concentration of polymer (X_0), is thus constant, and the rate of disappearance of carbonic anhydride is given by

$$-\mathrm{d(M)/dt} = k_2 X_0 (\mathrm{M}) \quad (5)$$

The kinetics of the polymerization of sarcosine carbonic anhydride (I) is being investigated. The polymer (II) used for initiating is obtained as a colorless, hygroscopic solid by the action of dimethylamine on the anhydride (I) in dioxane.

The polymerization in nitrobenzene is followed manometrically by the evolution of carbon dioxide. In accordance with equation (10) the reaction shows first-order dependence on (M); this confirms the assumption that k_2 is independent of the molecular weight of the polymer, for molecular weights between about 500 and 5000. Preliminary measurements indicate that the velocity constant, k_2, can be expressed by the equation

$$k_2 = 1600e^{-5,800/RT} \text{ liters mole}^{-1} \text{ sec.}^{-1}$$

The low value of the frequency factor is noteworthy.

We hope to extend this investigation to other carbonic anhydrides and to co-polymerizations.

COURTAULDS, LIMITED
MAIDENHEAD, BERKS.
ENGLAND
S. G. WALEY
J. WATSON

RECEIVED APRIL 20, 1948

NEW BOOKS

Chemical Insect Attractants and Repellents. By VINCENT G. DETHIER, A.M., Ph.D., Professor of Zoology and Entomology, The Ohio State University; formerly Entomologist, Inter-Allied Malaria Control Commission, Gold Coast, B. W. A. The Blakiston Company, Philadelphia, Pennsylvania, 1947. xv + 298 pp. Illustrated. 15.5 × 23.5 cm. $5.00.

The manner in which various chemicals attract or repel insects is of considerable interest to both chemists and entomologists working in economic entomology, to students of insect ecology and to others. The subject has also intrigued biologists not so well acquainted with the peculiarly specialized behavior of the insect world. Although the literature on attractants and repellents is extensive, most of the effort has been expended on research by the trial-and-error method, with not enough consideration of the chemical, physical, physiological and botanical factors involved. In an effort to remedy the situation and to impart a greater impetus to research in this field, Dr. Dethier has undertaken the difficult task of assembling and correlating the widely scattered literature. In this respect he has done a commendable piece of work.

The text is not a compilation of formulas of attractant and repellent substances. Rather it represents a theoretical approach to the study of the subject. The book is divided into ten chapters. An introductory chapter is followed by six that deal specificially with attractants, one with repellents, and two that are devoted to a more general discussion. There are approximately 750 literature citations.

Although the importance of research on insect repellents, especially for those insects that transmit disease, such as malaria-carrying mosquitoes, is pointed out, no mention is made of the extensive studies carried on during the recent war by the Bureau of Entomology and Plant Quarantine, United States Department of Agriculture; neither are the excellent fundamental studies on repellents by DeLong at the Ohio State University, nor is adequate treatment given the work of Granett at Rutgers University. The important subject of mothproofing warrants more than a brief paragraph. The book contains numerous errors in chemical nomenclature and in the structural formulas of compounds. These errors might have been avoided if the manuscript had been submitted to an organic chemist for review. Nevertheless the book is a valuable one and meets a definite need for both the chemist and the entomologist.

H. L. HALLER

Fundamentals of Photographic Theory. By T. H. JAMES, Ph.D., and GEORGE C. HIGGINS, Ph.D., Research Laboratories of Eastman Kodak Company. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1948. vii + 286 pp. 14 × 22 cm. Price, $3.50.

The recognized standing of the authors, not to mention coöperation by members of the Eastman staff, arouses in the reader expectations which are not disappointed. By concentrating upon black and white photography, exclusive of cameras or accessories, a coverage of the central theme admirable from physical, chemical and psychophysical standpoints is achieved. Consistent use of the sensitivity-speck basis for the latent image, together with the Gurney–Mott hypotheses, resolves in plausible fashion a great variety of complicated or at first sight contradictory phenomena. The chemistry of essential dark-room procedures is set forth in detail, but some will regret the omission of intensification, reduction and toning. Conflicting theories are critically examined in the light of data and of physico-chemical generalizations. Objective and subjective evaluations of photographic images are