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.

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

(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).

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

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

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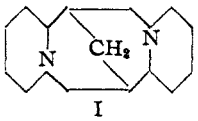
THE TOTAL SYNTHESIS OF SPARTEINE

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).