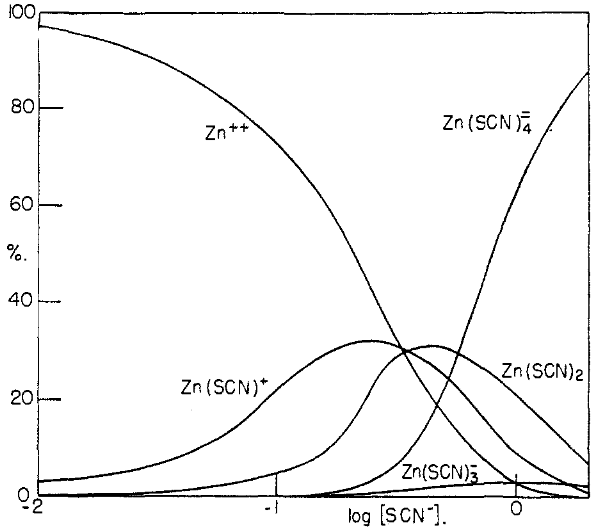

Fig. 3.—Percentage distribution of zinc in various forms as a function of free thiocyanate concentration.

that the relative stabilities of the ions in each series are very similar. The distribution of zinc among the several species as a function of equilibrium thiocyanate ion concentration shown in Fig. 3 is almost identical with the corresponding distribution for cadmium except that the whole family of curves has been displaced toward higher thiocyanate concentrations.

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Synthesis of Isoquinolines by the Use of Acetamidomalonic Ester

BY ALEXANDER GALAT

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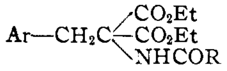
Compounds of the formula



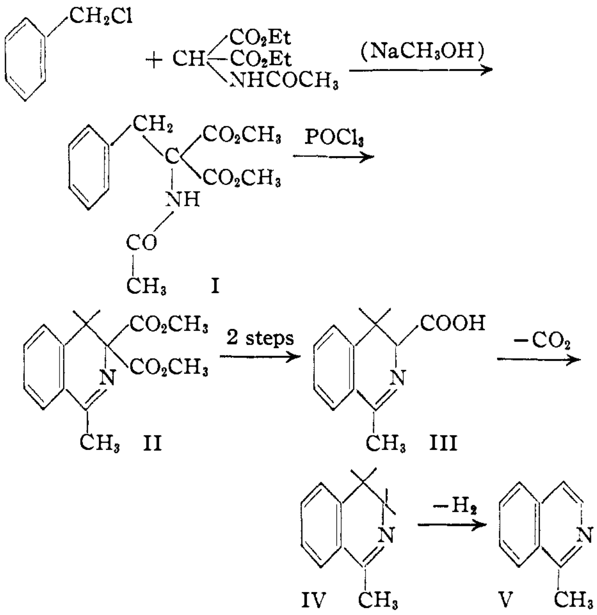
$$\mathrm{Ar{-}CH_2C}\begin{array}{l}\mathrm{CO_2Et}\\ \mathrm{CO_2Et}\\ \mathrm{NHCOR}\end{array}$$

Ar: phenyl, indolyl, naphthyl
R: H, CH_3, phenyl

obtained by the condensation of the appropriate halides or Mannich bases with acylamidomalonic esters, have been used as intermediates in the synthesis of amino acids.[1] Since these compounds are readily accessible, it seemed of interest to investigate their behavior under the conditions of the Bischler–Napieralski reaction.

Methyl 2-acetamido-2-carbomethoxy-3-phenylpropionate (I), obtained by the condensation of benzyl chloride with ethyl acetamidomalonate in methanol, was used as a model substance in this study. It was readily cyclized with phosphorus oxychloride to the dihydroisoquinoline II which was degraded to 1-methylisoquinoline

This synthesis provides a route to a new group of isoquinoline derivatives (compound II) which would be difficult to prepare by any other method, as well as a simple method for the preparation of some of the known compounds. Since substituted benzyl chlorides are readily available, this synthesis should prove of interest for the preparation of a large variety of isoquinolines.



Experimental

Methyl 2-acetamido-2-carbomethoxy-3-phenylpropionate (I) was prepared from benzyl chloride and commercial ethyl acetamidomalonate by the method of Albertson and Archer[1] except that the reaction was run in methanol.[2] The yield was 85%, m.p. 164–165°.

Anal. Calcd. for $C_{14}H_{17}O_5N$: N, 5.02. Found: N, 5.17.

1-Methyl-3,3'-dicarbomethoxy-3,4-dihydroisoquinoline (II).—Ten grams of I was dissolved in 40 ml. of phosphorus oxychloride and heated under reflux until the evolution of hydrogen chloride ceased (1–1.5 hours). The excess phosphorus oxychloride was removed *in vacuo* in a water-bath and the residue was treated with 100 ml. of cold water. The resulting mixture was stirred with charcoal, filtered and made alkaline with sodium carbonate. The product separated as an oil which soon solidified. The water-washed and air-dried product weighed 6.5 g. (70.5%). It was purified by dissolving in dilute hydrochloric acid, treating with charcoal and precipitating with ammonium hydroxide. It was finally recrystallized from methanol to give an analytically pure material, m.p. 94°.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.4; H, 5.75; N, 5.37. Found: C, 64.8; H, 5.65; N, 5.50.

1-Methyl-3-carboxy-3,4-dihydroisoquinoline (III).—One gram of II was suspended in 10 ml. of boiling water and the mixture treated dropwise with 20% sodium hydroxide until the product went into solution and the alkaline reaction persisted. The hot solution was acidified with hydrochloric acid and kept in a bath of boiling water until the evolution of carbon dioxide ceased. The crystalline product which separated on cooling was filtered, washed with water and purified by recrystallization from water. There was obtained 0.65 g. of a product which melted at 160–165° with evolution of carbon dioxide and water. Analytical figures showed it to be a monohydrate.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot H_2O$: C, 63.8; H, 6.29; N, 6.77. Found: C, 64.1; H, 6.20; N, 6.90.

1-Methyl-3,4-dihydroisoquinoline (IV).—One-half gram of III was heated in a flask suspended in an oil-bath at 170–180° in an atmosphere of carbon dioxide. When the evolution of gas ceased, there remained a light-colored oil of floral odor. It was dissolved in methanol and treated with

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(1) C. E. Redeman and M. C. Dunn, *J. Biol. Chem.*, **130**, 341 (1939); N. F. Albertson and S. Archer, THIS JOURNAL, **67**, 308 (1945); E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, *ibid.*, **67**, 38 (1945); A. Galat, *ibid.*, **69**, 965 (1947).

(2) A previous study of similar types of compounds (A. Galat, *ibid.*, **73**, 3654 (1951)) showed that methyl esters give higher yields and purer products on cyclization with phosphorus oxychloride.

picric acid in methanol, giving a precipitate of a crystalline picrate, m.p. 190° (lit.[3] 190°).

1-Methylisoquinoline (V) was obtained by the dehydrogenation of IV in the presence of palladium–charcoal in tetralin or directly from III by a simultaneous decarboxylation and dehydrogenation, following the procedure reported previously[2] for an analogous compound. The crude base was converted to the picrate, m.p. 208–210° (lit.[4] 209–210°) and the sulfate, m.p. 248–250° (lit.[5] 246–247°).

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(3) E. Spath, F. Berger and W. Kuntara, *Ber.*, **63**, 134 (1930).

(4) V. Krauss, *Monatsh.*, **11**, 358 (1889).

(5) C. Pomerantz, *ibid.*, **15**, 299 (1893).

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Concentration Effect on Sedimentation Rate and its Use in Estimating Molecular Weights[1]

By Richard H. Golder

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Concentration Effect on Sedimentation Rate.—Many studies have been made relating sedimentation rate to the concentration of the sedimenting substance. The results have been found in almost all cases to follow the equation

$$S_0/S = 1 + Ac \qquad (1)$$

where S is the rate at concentration c, S_0 is the rate extrapolated to zero concentration, and A is an experimentally determined constant which may be called the specific sedimentation slope. This relation is in agreement with theoretical considerations of Burgers[2] as demonstrated by Schachman and Kauzmann,[3] and of Powell and Eyring.[4]

The common practice has been to plot the sedimentation rate against the concentration of the solution which prevails at the start of the centrifugation. During the course of the centrifugation, however, the concentration decreases continuously. This decrease, due to the sector shape of the cell and the increase in centrifugal force with increasing distance from the axis of rotation, was shown by Svedberg and Rinde[5] to follow the equation

$$c = c_1 x_1^2/x^2 \qquad (2)$$

where c and c_1 are the colloid concentrations at the boundary distances, x and x_1, respectively, from the axis of rotation. The combined effects expressed by equations (1) and (2) result in a continuous increase in the sedimentation rate during each run. This increase was assumed by Sanigar, Krejci and Kraemer,[6] and was demonstrated experimentally by Lauffer.[7] The rate measured in the usual way is, therefore, a composite value, equaling the instantaneous rate at some time *after* the start of the centrifugation. The concentration at *that* particular time should be used for obtaining the correct relation between sedimentation rate and concentration; or, the rate at *any* given time, and the concentration which prevails at the same time, may be used. Kegeles and Gutter[8] related the concentrations at the mid-points between the first and last photographs of the runs to the over-all sedimentation rates. As will be shown, this is a very close approximation to the correct relation.

The correct relation between sedimentation rate and concentration may be found by substituting equations (1) and (2) into Svedberg's equation[9] defining sedimentation rate

$$S = k(\mathrm{d}x/\mathrm{d}t)/\omega^2 x \qquad (3)$$

where $\mathrm{d}x/\mathrm{d}t$ is the velocity of the sedimenting boundary at the distance x from the axis of rotation, ω is the angular velocity of the rotor and k represents a constant which comprises the different corrections for reducing the observed rate to its value at the standard conditions of sedimentation in water at 20°. The combined equations may be written

$$S_0\mathrm{d}t = (k/\omega^2 x)(1 + Ac_1x_1^2/x^2)\mathrm{d}x \qquad (4)$$

Taking $t = 0$ at x_1, and $t = t$ at x_2, and integrating, one obtains

$$S_0 = (k/\omega^2 t)[\ln(x_2/x_1) + (Ac_1/2)(1 - x_1^2/x_2^2)] \qquad (5)$$

S_0 and A may be evaluated by the usual methods of solving simultaneous equations. Measurements from two runs at different initial concentrations would generally be best, but measurements from two intervals within a single run may be used if they are precise enough. The values of c_1 may be found in each case with the aid of equation (2). The greater the difference between the two values of c_1 used in equation (5), the more accurate will be the determination of A.

The specific sedimentation slope of rabbit myosin,[10] determined in the above manner, is about 1% lower than that determined by the method of Kegeles and Gutter. Since myosin has an unusually high change of sedimentation rate with concentration, most other substances should show even better agreement. The use of the method of Kegeles and Gutter is, therefore, fully justified for most work; further, because it is simpler, it is generally preferable to the more complicated procedure described above. When sedimentations are carried out over the full range of the cell, it is found that the concentrations at the mid-points are about 85% of the starting concentration.[11] This approximation may be used in calculating A by Kegeles and Gutter's method from ultracentrifuge studies in which more detailed information is not given. Of course, the value of S_0 obtained by either of these methods should be the same as that found by simply plotting $1/S$ against c.

Relation between Specific Sedimentation Slope and Intrinsic Viscosity.—Both theoretical[2,3,4,12] and

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(1) This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, Public Health Service; and in part by an institutional grant from the American Cancer Society.

(2) J. M. Burgers, *Proc. Acad. Sci. Amsterdam*, **44**, 1045, 1177 (1941); **45**, 9, 126 (1942).

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(7) M. A. Lauffer, *ibid.*, **66**, 1195 (1944).

(8) G. Kegeles and F. J. Gutter, *ibid.*, **73**, 3770 (1951).

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(11) G. L. Miller and R. H. Golder, *Arch. Biochem.*, **36**, 249 (1952).

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