A Modified Curtius Reaction[1]

JOSEPH WEINSTOCK

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The Curtius rearrangement, which involves heating an acid azide to cause loss of nitrogen and formation of an isocyanate, is a valuable method for the conversion of acids to amines.[2] The usual procedure of obtaining acid azides, which consists of treating an acid chloride with sodium azide, suffers from the disadvantage that it is often difficult to obtain pure acid chlorides in good yield from acids which either decompose or undergo isomerization in the presence of mineral acids. The much less convenient alternative sequence of ester to hydrazide to azide has been used to circumvent this difficulty.

Recently the use of mixed carboxylic-carbonic anhydrides in peptide synthesis and in the place of acid chlorides for the preparation of amides and esters of sensitive acids has been developed.[3] We have found that mixed anhydrides react with sodium azide under very mild conditions to form acid azides in excellent yield. These can be rearranged to the isocyanate and hydrolyzed to the amine without isolation of intermediates. For example, *cis*-2-phenylcyclopropylamine[4] was prepared in 77% yield from *cis*-2-phenylcyclopropanecarboxylic acid. In the original preparation of this amine it was found necessary to avoid preparation of the acid chloride to prevent isomerization to the *trans* acid chloride. This new procedure has been applied extensively in our laboratories and elsewhere with excellent results.[5]

EXPERIMENTAL

cis-2-Phenylcyclopropylamine. *cis*-2-Phenylcyclopropanecarboxylic acid (14.0 g., 0.086 mole) was suspended in 15 ml. of water and sufficient acetone was added to complete the solution. The solution was cooled to 0° (ice-salt bath) and 10.2 g. (0.1 mole) of triethylamine in 175 ml. of acetone was added. While maintaining the temperature at 0°, a solution 12.5 g. (0.11 mole) of ethyl chloroformate in 45 ml. of acetone was added slowly. The mixture was stirred for 30 min. at 0° and then a solution of 8.6 g. (0.13 mole) of sodium azide in 30 ml. of water was added dropwise. The mixture was stirred (0°) for 1 hr.; then it was poured into an excess of ice water. The oil which separated was extracted into ether and the combined ether extracts were dried with magnesium sulfate. Solvent was removed *in vacuo* at room temperature to leave a dark red oil (azide), which was dissolved in 50 ml. of anhydrous toluene. The toluene solution was heated on a steam bath until no more nitrogen was evolved. Removal of toluene *in vacuo* afforded a mobile red liquid which was shown to be almost pure isocyanate by its infrared spectra (4.4 μ). The isocyanate was suspended in 90 ml. of 20% aqueous hydrochloric acid and the mixture was heated under reflux for 9 hr. Evaporation of the resulting solution *in vacuo* gave a dark semi-solid residue. This was dissolved in 100 ml. of water and the solution was made strongly alkaline by the addition of a 40% sodium hydroxide solution. The oil which separated was extracted into ether and the combined extracts were dried with anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a clear pale brown oil. This was distilled *in vacuo* (using a bath at a temperature of 70° or below) and gave 8.9 g. (77%) of colorless free base; b.p., (0.3–0.4 mm.) 50–52°.

A hydrochloride was prepared in the usual manner (isopropyl alcohol-ether); it melted at 169–170° and did not depress the melting point of an authentic sample of *cis*-2-phenylcyclopropylamine hydrochloride.

In a variation of the above procedure used in subsequent work the acid azide was extracted directly into toluene rather than into ether. The toluene solution was then dried over magnesium sulfate and added dropwise to a flask equipped with a stirrer which was heated on a steam bath. This helped to control the vigorous evolution of nitrogen which takes place during the rearrangement.

RESEARCH AND DEVELOPMENT DIVISION
SMITH, KLINE AND FRENCH LABORATORIES
PHILADELPHIA 1, PA.

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[1] This work was presented at the Third Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., February 25, 1960.

[2] For a brief review of the Curtius rearrangement see P. A. S. Smith, *Org. Reactions*, **III**, 337 (1946).

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[5] Unpublished work of Dr. Carl Kaiser, Smith, Kline & French Laboratories and Dr. A. Burger, University of Virginia.

A New Intermolecular Hydrogen-Transfer Reaction[1]

EDWARD C. TAYLOR AND MALCOLM J. THOMPSON

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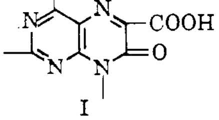
The reactions of mesoxalic acid derivatives with 1,2-diamines which have previously been reported appear to be uncomplicated. Thus, the condensation of sodium mesoxalate with 4,5-diaminopyrimidines yields derivatives of 7(8*H*)-pteridinone-6-carboxylic acid (I)[2,3] and is completely analogous to the condensation of diethyl mesoxalate with 1,2-



I

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[1] This investigation was supported by a grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

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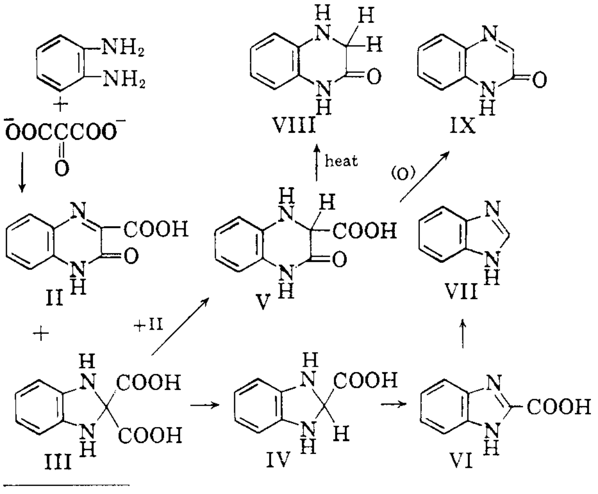
[3] E. C. Taylor and H. M. Loux, *J. Am. Chem. Soc.*, **81**, 2474 (1959).

diamines in the benzene,[4] pyridine,[5] and pyrimidine[3,6] series. Mesoxalic acid itself, liberated in solution from its sodium salt with hydrochloric acid, reacts rapidly with *o*-phenylenediamine hydrochloride at room temperature or on warming to give 2(1*H*)-quinoxalone-3-carboxylic acid (II) in at least 80% yield.[7] The condensation of mesoxalic acid with *o*-methylaminoaniline proceeds similarly to give 1-methyl-2(1*H*)-quinoxalone-3-carboxylic acid.

We have now found that sodium mesoxalate and *o*-phenylenediamine react anomalously in aqueous solution. Heating molar quantities of the two components in water for one and one-half hours, followed by acidification, yielded benzimidazole-2-carboxylic acid (VI) and *3,4-dihydro-2(1H)-quinoxalone-3-carboxylic acid* (V). The considerable stability and insolubility (in acid) of V permitted its ready isolation. This compound was identical with the dihydro derivative prepared from II by reduction either with sodium hydrosulfite[8] or with hydrogen and palladium-on-carbon. Thermal decarboxylation of V yielded 3,4-dihydro-2(1*H*)-quinoxalone (VIII), while oxidation with alkaline ferricyanide gave 2(1*H*)-quinoxalone (IX). When the reaction mixture was acidified before condensation was complete, some 2(1*H*)-quinoxalone-3-carboxylic acid (II) was also isolated. The presence of a small amount of benzimidazole (VII), arising by decarboxylation of benzimidazole-2-carboxylic acid (VI),[9] was detected in the crude acid VI by the presence of its characteristic absorption maxima (272 and 279 mμ) in the spectrum of the acid (280 and 286 mμ).



It appears that sodium mesoxalate and *o*-phenylenediamine react initially to give 2(1*H*)-quinoxalone-3-carboxylic acid (II) and 1,2-dihydrobenzimidazole-2,2-dicarboxylic acid (III) as the major product. In an extremely efficient noncatalyzed intermolecular hydrogen-transfer reaction, III then reduces II to V, being itself oxidized and decarboxylated to VI. The presence of an excess of reducing agent in the reaction mixture was readily demonstrated by addition (at any stage of the reaction) of excess 2(1*H*)-quinoxalone-3-carboxylic acid (II), which was promptly reduced to V. Astonishingly, the formation of the dihydro acid V was not affected by bubbling a vigorous stream of oxygen through the mixture during the entire time of reaction. The product composition was not altered when the reaction was carried out at lower temperatures (50° for six hours).

We suggest 1,2-dihydrobenzimidazole-2,2-dicarboxylic acid (III) rather than its decarboxylated product, 1,2-dihydrobenzimidazole-2-carboxylic acid (IV) as the reducing agent, since the latter compound would not be expected to be (and is apparently not) stable to oxygen. Thus, isolation of III was not possible, since in the acidification of the reaction mixture during the work-up immediate decarboxylation of III to IV, followed by air oxidation to VI, apparently takes place.

The hydrogen transfer reaction appears to be specific, since the reaction mixture failed to reduce added *o*-nitroaniline or 2-ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid.[2]

EXPERIMENTAL

3,4-Dihydro-2(1H)quinoxalone-3-carboxylic acid (V). A solution of 8.1 g. (0.05 mole) of sodium mesoxalate and 5.3 g. (0.05 mole) of freshly crystallized *o*-phenylenediamine in 100 ml. of water was boiled for 1.5 hr., cooled to 60°, acidified with concentrated hydrochloric acid and then cooled to 45° with stirring and scratching. The white crystalline solid which separated was collected by filtration and recrystallized from water to give 1.6 g. (15%) of long white needles, m.p. 154–155° dec. ($\lambda_{\max}^{C_2H_5OH}$ 224, 305 mμ; ϵ = 29,100, 4040).

Anal. Calcd. for $C_9H_8N_2O_3.H_2O$: C, 51.4; H, 4.8; N, 13.3. Found: C, 51.1; H, 4.9; N, 13.2.

This compound was identical in all respects with an authentic sample of 3,4-dihydro-2(1*H*)-quinoxalone-3-carboxylic acid monohydrate, reported m.p. 152° dec., prepared either by the method of Habib and Rees[8] or by catalytic reduction of 2(1*H*)-quinoxalone-3-carboxylic acid in potassium carbonate solution with hydrogen and palladium-on-carbon catalyst at atmospheric pressure. When 1 g. of 2-(1*H*)-quinoxalone-3-carboxylic acid, dissolved in an equivalent of dilute potassium hydroxide, was added to the above reaction mixture at any stage of the reaction, the yield of the dihydro acid V was raised to 2.6 g.

Refrigeration of the acidic filtrate above yielded 3–4 g. of a colorless solid which was shown to be predominately benzimidazole-2-carboxylic acid (contaminated by benzimidazole) by comparison of its ultraviolet absorption spectrum with an authentic sample[9] and by decarboxylation to benzimidazole, m.p. 172–173°.

3,4-Dihydro-2(1H)-quinoxalone (VIII). Sublimation of 0.5 g. of 3,4-dihydro-2(1*H*)-quinoxalone-3-carboxylic acid at 170°/0.1 mm. gave 0.34 g. (96%) of a white sublimate which

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[6] G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **75**, 4311 (1953).

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was recrystallized from water to give long, white needles. They turned yellow on standing and melted indefinitely commencing at 136°, with a complete melt appearing only at 195° ($\lambda_{max}^{C_2H_5OH}$ 226, 306 mμ; ϵ = 24,600, 3010).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.4: N, 18.9. Found: C, 64.7; H, 5.2; N, 18.8.

2(1H)-Quinoxalone (IX). To a solution of 1 g. of 3,4-dihydro-2(1*H*)-quinoxalone-3-carboxylic acid, 1.5 g. of potassium carbonate, and 20 ml. of water was added a strong solution of potassium ferricyanide until a persistent green color developed. Gas was strongly evolved and a white precipitate separated from the reaction mixture. Filtration gave 0.63 g. (90%) of fine white needles, m.p. 270–271°, which were shown to be 2(1*H*)-quinoxalone by comparison with an authentic sample.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, N. J.

Effect of the Alkali Cation Upon the Rate of the Benzilic Acid Rearrangement

W. H. PUTERBAUGH AND W. S. GAUGH

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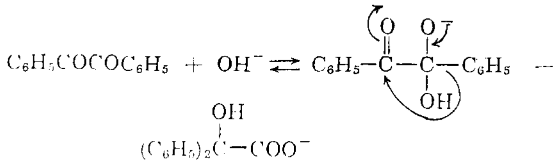
As part of a continuing investigation on the influence of the metallic cation in organic reactions, we initiated a study of the effect of varying the alkali hydroxide on the rate of the benzilic acid rearrangement. After our work had been in progress for some time, we came upon the excellent work of E. Pfeil and co-workers[1] bearing on this same field. However, as our work was concerned primarily with the alkali cation, and was done under conditions which brought out a greater magnitude of difference between lithium and the other alkali cations than was done in the former study, we felt it worthwhile to continue the project and submit the completed results.

The mechanism of the benzilic acid rearrangement has been the subject of much recent study which has shed light on a number of disputed points, but has not yet led to an undisputed mechanism. The work of Roberts and Urey[2] showing that benzil undergoes rapid exchange of carbonyl oxygen with H_2O^{18} under alkaline conditions provides the main evidence for the generally accepted mechanism[3] involving preliminary reversible addition of hydroxide ion to benzil followed by irreversible migration of a phenyl group and proton exchange (Equation 1).



$$C_6H_5COCOC_6H_5 + OH^- \rightleftarrows C_6H_5-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{\displaystyle O^-}{\overset{|}{\underset{\underset{\displaystyle OH}{|}}{C}}}-C_6H_5 \longrightarrow (C_6H_5)_2\overset{\displaystyle OH}{\overset{|}{C}}-COO^- \qquad (1)$$

More recently, Doering and Urban[4] showed that the rearrangement is subject not only to specific hydroxide ion catalysis, as was long believed, but may be brought about more generally by means of certain alkoxides to yield benzilic esters as well. Hine and Haworth[5] have demonstrated that the rearrangement can not have as its rate-controlling step a mechanism involving proton transfer, since the reaction was about 85% faster with sodium deuteroxide in deuterium oxide than with sodium hydroxide in water under the same conditions. Clark, Hendley, and Neville[6] showed that in the rearrangement of unsymmetrically substituted benzils, rings containing electron-withdrawing substituents migrated preferentially to phenyl, while the reverse was true with rings containing electron-donating substituents. These workers suggested that the mechanism involving preliminary reversible addition of hydroxide ion may be incorrect, and that hydroxide ion may participate in the rate-controlling step, preferentially attacking the more reactive carbonyl group, and thus accounting for the preferred migration tendencies observed.

In view of the fact that the nature of the metallic cation has been found to play an important role in aldol condensations of esters with ketones,[7] and in certain displacement reactions[8] among others, we felt it worthwhile to study the effect of varying the alkali (and the tetramethylammonium) cation upon the rate of the benzilic acid rearrangement. The kinetic results obtained with these hydroxides

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF BENZIL[a] WITH ALKALI HYDROXIDES[b] IN 67% DIOXANE–33% WATER[c] AT 49.5°

Hydroxide Used	10^5k_2, l./mole^{-1}/sec.$^{-1}$
Lithium[d]	29.96 ± 0.49
Sodium[d]	9.40 ± 0.28
Potassium[d]	8.29 ± 0.38
Cesium[e]	8.76 ± 0.41
Tetramethylammonium[e]	7.98 ± 0.15
Lithium[e]	29.79 ± 0.83

[a] Initial concentrations 0.05931–0.06174*M*. [b] Initial concentrations 0.04749–0.04878*M*. [c] By volume. [d,e] These runs were carried out simultaneously in the same thermostated bath using the same reagents except for the hydroxide.

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