raphy (phenol:collidine–lutidine) is dried, sprayed with ninhydrin and the color is developed in an anaerobic atmosphere (to CO_2), saturated with alcohol at 60°. Thereafter the colored spots are cut out, the ninhydrin color is extracted with 1:1 ethanol–water and the density is determined at 570 $m\mu$ for comparison with a standard curve.

Under these conditions pipecolic acid does not react as strongly as the typical α-amino acids, etc. Pipecolic acid produces a distinctive brilliant purple spot on paper when treated with a solution of ninhydrin in ethanol and when the paper is heated in air. The spot is stable for several days and produces a crimson fluorescence in ultraviolet light. Traces of collidine or lutidine in the paper during the development of the color, however, cause the color to fade rapidly to a yellow-brown. When the pipecolic acid–ninhydrin color is prepared on paper under the anaerobic conditions of Thompson, Zacharius and Steward,[19] which are preferred for most of the amino acids, a reddish rather poorly colored spot results. Some improvement in color production may be obtained by developing it at a higher temperature. Even so, both the aerobically and anaerobically produced spots dissolve only sparingly in 50% ethanol and the undissolved ninhydrin compound immediately turns brown on the paper due to the water content of the solvent. Therefore, the quantitative determination of pipecolic acid by procedures that are suitable for a wide range of amino acids still presents further problems.

Further information on the reaction between pipecolic acid and ninhydrin was obtained from two experiments. When a sample of pure pipecolic acid reacted with ninhydrin according to the method of Van Slyke,[21] it was found that only 0.58 mole of CO_2 was liberated per mole of pipecolic acid added. This is in striking contrast to the usual 1 mole of CO_2 liberated per mole from most α-amino acids and proline. If the method of Moore and Stein[14] was used to determine pipecolic acid, *i.e.*, treating it as a compound analogous to an α-amino acid, it behaved as if only 21% as much color is given by pipecolic acid as by α-amino acids. Under the procedure of Moore and Stein, the reaction mixture had the same reddish color that is produced anaerobically on paper under the conditions described.[19]

Pipecolic acid produces a blue-green compound when treated on paper with a 4% solution of isatin in glacial acetic acid–*n*-butyl alcohol (4:96). Although the isatin compound proved to be extractable in pyridine, collidine, lutidine or glacial acetic acid, it rapidly faded and could not be used as a basis for a quantitative method. Therefore, the most hopeful method of quantitative determination is still the development of the ninhydrin color and its quantitative determination, even though this is not as sensitive a reaction as in the case of α-amino acids.

Grassman and von Arnim[22] have reported that the ninhydrin–pipecolic acid compound is insoluble in water but soluble in glacial acetic acid, pyridine and dioxane. None of these solvents was found to dissolve the purple ninhydrin color produced aerobically on paper to any significant extent. Instead 1:1 ethanol–glacial acetic acid, 1:1:1 ethanol–glacial acetic acid–water, 1:1 methanol–glacial acetic acid or 9:1 glacial acetic acid–water (all by volume) will dissolve both the aerobically and anaerobically produced (red-purple) compound completely from paper. Even so, the pipecolic acid–ninhydrin compound dissolves much more slowly in ethanol–acetic acid than the compounds of the common amino acids do in 50% ethanol. The resulting reddish solution is stable for at least 24 hours at room temperature and has an absorption curve with a pronounced maximum at 560 $m\mu$ as shown in Fig. 1.

Quantities of 20, 40, 60 and 80 μg. of pipecolic acid were chromatographed two-directionally on washed and buffered Whatman No. 1 filter paper with phenol–water and collidine–lutidine–water, and the chromatograms further treated as described by Thompson and Steward.[19,20] The resulting ninhydrin complex was extracted from the paper with 1:1 ethanol–glacial acetic acid and the density of the color measured at 560 $m\mu$ on a Beckman spectrophotometer. The results are represented graphically in Fig. 2. There is a linear relationship between the concentration of pipecolic acid and the resulting color, and therefore an analytical method can conveniently be based on the calibration curve. However, as can be seen from Fig. 2, the method is less sensitive even than for tyrosine.

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[21] D. D. Van Slyke, D. A. MacFayden and P. Hamilton, *J. Biol. Chem.*, **141**, 671 (1941).

[22] W. Grassman and K. von Arnim, *Ann.*, **509**, 288 (1934).

ITHACA, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Reactions of Succinonitrile. I. Condensation with Cyclohexanone in the Presence of Sodamide[1]

BY PAUL E. FANTA AND SHELBERT SMITH

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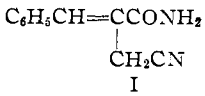
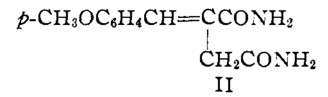
The condensation of succinonitrile with cyclohexanone in the presence of sodamide yields a mixture of 4-cyclohexylidene 5-imino-2-pyrrolidone and 4-(1-cyclohexenyl)-5-imino-2-pyrrolidone. Evidence for these structures was obtained by degradation and measurement of the infrared and ultraviolet absorption spectra. The mechanism of the reaction is believed to be analogous to the well-known Stobbe condensation of succinic esters.

The aldol-type condensation of succinic esters with aldehydes and ketones was discovered by Stobbe in 1893 and recently has been investigated in great detail by Johnson and his co-workers.[2] Although a large number of similar reactions have also been reported for succinic acid and succinic anhydride,[3] only one report of such a condensation involving succinonitrile has been found in the literature.[4] The aldol-type condensations of succinonitrile with benzaldehyde or anisaldehyde in the presence of sodium ethoxide were reported in 1894,[5] but no unambiguous evidence was offered for the structures claimed for the products, I and II.



$$C_6H_5CH{=}\underset{CH_2CN}{\underset{|}{C}}CONH_2$$

I



$$p\text{-}CH_3OC_6H_4CH{=}\underset{CH_2CONH_2}{\underset{|}{C}}CONH_2$$

II

A complication in the use of aldehydes or unsymmetrical ketones in this reaction is the possibility

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[1] (a) Presented in part at the 118th Meeting of the American Chemical Society, Chicago, Illinois, September, 1950. (b) Based on a thesis by Shelbert Smith presented to Illinois Institute of Technology in partial fulfillment of requirements for the M.S. degree, June, 1954.

[2] W. S. Johnson and G. H. Daub in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 1.

[3] D. Billet, *Bull. soc. chim. France*, [5] **16**, 297 (1949).

[4] "Cyanamid New Product Bulletin," Coll. Vol. I, American Cyanamid Co., New York, 1949, pp. 90–100. When the recent work was nearly completed, J. Stanek and V. Jarolim, *Chem. Listy*, **46**, 384 (1952), reported the preparation of cyclohexylidenesuccinic acid in 55% yield by the condensation of cyclohexanone with succinonitrile in the presence of potassium amylate in amyl alcohol followed by hydrolysis. They did not isolate intermediates or propose a mechanism for the reaction.

[5] C. Bechert, *J. prakt. Chem.*, [2] **50**, 1 (1894).

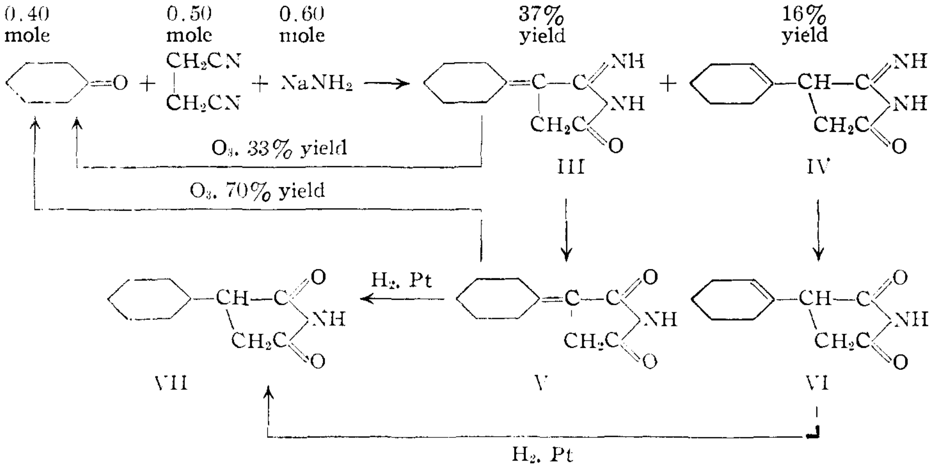

Fig. 1.

of the formation of geometrical isomers of unsaturated products such as I and II. Therefore we began our study with the symmetrical ketone cyclohexanone as summarized in Fig. 1.

When a mixture of cyclohexanone and succinonitrile was added to a suspension of sodamide in ether, the product isolated after addition of water and neutralization was a solid whose analysis corresponded to the empirical formula $C_{10}H_{14}ON_2$. On fractional crystallization from alcohol, this substance was separated into two isomeric compounds of distinctly different crystal form and melting point, which are believed to be 4-cyclohexylidene-5-imino-2-pyrrolidone (III) and 4-(1-cyclohexenyl)-5-imino-2-pyrrolidone (IV). Degradative evidence for these structures was obtained by hydrolysis to the corresponding unsaturated imides, V and VI, which both yielded the same saturated imide, VII, on catalytic hydrogenation. The location of the double bond in III and V was established by ozonolysis.

The degradative evidence does not reveal the location of the carbon–carbon double bonds in IV and VI, nor does it establish that III and IV are not the corresponding 3-cyclohexylidene-(or cyclohexenyl)-5-imino-2-pyrrolidones (VIIIa, b), since the latter pair of iminopyrrolidones would yield the same pair of unsaturated imides on hydrolysis.

Evidence with regard to these points may be obtained by consideration of a logical mechanism for the reaction, Fig. 2, which is analogous to the mechanism accepted for the Stobbe condensation. Reversible aldol-type condensation of succinonitrile anion and cyclohexanone (1) is followed by a reversible cyclization (2), similar to the intermediate cyclization which Johnson regards as an important driving force for the Stobbe condensation.[2] Migration of the α-proton (3) is accompanied by opening of the lactim ring (4, curved arrows) and followed by cyclization of the resulting amide ion to form the iminopyrrolidone anion (5). Since III has been shown by degradation to contain the cyclohexylidene group, IV must possess the alternative 1-cyclohexenyl structure resulting from a similar series of reactions wherein the proton is lost from the γ-position in concerted steps (3) and (4) or, alternatively, from a base-catalyzed 3-carbon tautomerization at some later stage in the reaction.[6] No such logical mechanism can be formulated for the formation of iminopyrrolidones VIIIa, b. The type of reaction represented by (5) has been reported for the base-catalyzed cyclization of 2-cyanobenzamide.[7]

The amphoteric nature of the iminopyrrolidones III and IV is shown by their solubility characteristics. Both compounds are insoluble in water and readily soluble in dilute hydrochloric acid. They both form stable picrates. Compound III is soluble in 10% aqueous sodium hydroxide, while IV is soluble in aqueous trimethylbenzylammonium hydroxide. This behavior becomes understandable in terms of the rather complex resonance and tautomeric possibilities for III or IV, which involve participation of three principal tautomers for the neutral molecule, three principal resonance hybrids for the conjugate base and six principal resonance hybrids and tautomers for the conjugate acid.[1b]

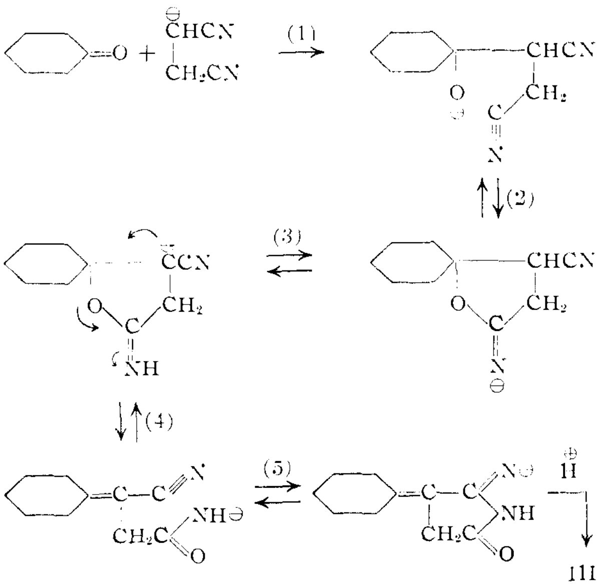

Fig. 2.

Although the nomenclature and structural evidence are more conveniently discussed in terms of the unconjugated structure of III, it is evident that the cross conjugated and linearly conjugated tautomers may be the principal contributors to the true structure of the neutral molecule as well as its conjugate acid and base. A similar set of

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[6] The latter explanation for the formation of IV was suggested by the referee; *cf.* R. P. Linstead, *J. Chem. Soc.*, 2498 (1929), and preceding papers.

[7] A. Braun and J. Tscherniac, *Ber.*, **40**, 2709 (1907).

tautomers and resonance hybrids is possible for the isomeric iminopyrrolidone IV, except that no linear or cross conjugation with the carbon–carbon double bond can occur.

Further evidence with regard to the proposed structures was obtained from the infrared and ultraviolet absorption spectra. In the infrared double-bond region compounds IV and III have broad unresolved bands at 1650–1680 and 1630–1670 cm.$^{-1}$, respectively. The lower value of the latter is suggestive of conjugation. Similarly the imide VI has sharp bands at 1670, 1700 and 1760 cm.$^{-1}$, while V shows absorption in this region at longer wave lengths, namely, 1640, 1690 and 1730 cm.$^{-1}$.

In the ultraviolet absorption spectra, measured in water solution, the conjugated iminopyrrolidone III has a maximum at a much higher wave length (λ_{max} 262 mμ, log ϵ 4.29) than the unconjugated isomer IV (λ_{max} 226 mμ, log ϵ 4.30). Similarly, the conjugated imide V has a principal maximum at higher wave length and greater extinction coefficient (λ_{max} 250 mμ, 208 mμ; log ϵ 4.20, 3.91) than the unconjugated isomer VI (λ_{max} 244 mμ, log ϵ 3.43).

Experimental[8]

Reaction of Succinonitrile with Cyclohexanone in the Presence of Sodamide.—Sodamide[9] prepared from 13.8 g. (0.60 mole) of sodium was stirred in 200 ml. of anhydrous ether. The flask was first cooled with Dry Ice, then a solution of 40.0 g. (0.50 mole) of succinonitrile[10] in 39.3 g. (0.40 mole) of cyclohexanone was added dropwise in the course of 20 minutes while the temperature was permitted to rise, from −20 to 0°. The reaction product separated as a dark, heavy oil which soon set to a tan solid. It was allowed to stand for 30 minutes, then dissolved by the addition of several hundred grams of crushed ice, with stirring. When the solid had completely dissolved to form a dark brown solution, about 60 ml. of concentrated hydrochloric acid was added with rapid stirring to bring the *p*H to 7.0. The product separated as a fine, tan, crystalline solid which was collected on a büchner funnel, washed with ice-cold water and dried in the air. The yield was 65 g. (91%). Crystallization from alcohol without fractionation gave a colorless product which sintered at 223–226° and melted with decomposition at 226–226.5°.

Anal. Calcd. for $C_{10}H_{14}ON_2$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.65; H, 7.43; N, 15.77.

Isolation of 4-Cyclohexylidene-5-imino-2-pyrrolidone (III) and 4-(1-cyclohexenyl)-5-imino-2-pyrrolidone (IV).—The crude product described above was dissolved in 1 l. of hot 95% ethanol and fractionally recrystallized. The head fraction (compound III) consisted of 26.2 g. (37%) of thick, short, colorless needles which turned brown at 210° and melted with decomposition at 235–236°.

Anal. Calcd. for $C_{10}H_{14}ON_2$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.59; H, 8.14; N, 15.84.

Systematic working-up of the liquors gave 11.5 g. (16%) of a second fraction (compound IV) of fine, white needles which melted with decomposition at 245–245.5°.

Anal. Calcd. for $C_{10}H_{14}ON_2$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.25; H, 8.04; N, 15.25.

Picrates of the iminopyrrolidones were prepared by mixing a solution of the iminopyrrolidone in 95% alcohol with a solution of an equimolar quantity of picric acid in the same solvent. The precipitate was collected, washed with cold alcohol and dried for analysis. The picrate of III melted at 214–215.5°.

Anal. Calcd. for $C_{16}H_{17}O_8N_5$: C, 47.17; H, 4.21; N, 17.20. Found: C, 47.40; H, 4.41; N, 17.25.

The picrate of IV melted at 215–216°.

Anal. Calcd. for $C_{16}H_{17}O_8N_5$: C, 47.17; H, 4.21; N, 17.20. Found: C, 47.16; H, 4.36; N, 17.15.

Cyclohexylidenesuccinimide (V).—A solution of one gram of III in a mixture of 1 ml. of sulfuric acid and 9 ml. of water was heated on the steam-bath for one hour. The deposit of shiny, white plates was collected and washed with cold water; yield 80%, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.72; H, 7.10; N, 8.08.

(1-Cyclohexenyl)-succinimide (VI).—A solution of one gram of IV in a mixture of 1 ml. of sulfuric acid and 9 ml. of water was heated on the steam-bath for one hour. An oily precipitate was formed which solidified on cooling. Recrystallization from benzene–petroleum ether gave a 90% yield of flat, colorless needles which melted at 89–89.5°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.34; H, 7.20; N, 8.04.

Ozonolysis of V.—An excess of ozone was passed into a solution of 1.00 g. of V in 25 ml. of acetic acid. One gram of 1% palladium-on-barium sulfate catalyst was added and the solution was shaken with hydrogen at three atmospheres pressure for five hours. An aliquot portion of the resulting solution was added to a solution of an excess of 2,4-dinitrophenylhydrazine.[11] The addition of 10 ml. of water to the mixture produced a yellow precipitate of crude cyclohexanone 2,4-dinitrophenylhydrazone, yield 70%, m.p. 155–156°. After recrystallization from 95% alcohol the m.p. was 159–160.5°, undepressed by mixture with an authentic sample.

Ozonolysis of III.—When III was treated according to the procedure described above, a 33% yield of crude cyclohexanone 2,4-dinitrophenylhydrazone was obtained.

Cyclohexylsuccinimide (VII) was obtained in about 70% yield by the catalytic hydrogenation of either V or VI for 30 minutes in acetic acid at 1500 lb. pressure using Adams platinum oxide catalyst. After recrystallization from ligroin it melted at 117–117.5°.[12]

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.50; H, 8.20; N, 7.40.

Alternative Synthesis of VII.—One gram of a mixture of cyclohexylidenesuccinic acid and cyclohexenylsuccinic acid[14] in 8 ml. of acetic acid was hydrogenated for 30 minutes at 120° and 1000 lb. pressure with 10 mg. of Adams platinum oxide catalyst. The yield of cyclohexylsuccinic acid, IX, melting at 145–146.5°[13] was 72%. A 0.10-g. portion of IX was dissolved in 2 ml. of aqueous ammonium hydroxide, evaporated to a sirupy residue and heated in an oil-bath at 180–185° for one hour. Recrystallization from ligroin gave 0.07 g. (70% yield) of a crude product which melted at 109–112°. When the product was purified by precipitation from aqueous sodium hydroxide solution with carbon dioxide and recrystallization from ligroin it melted at 116.5–117.5° and the melting point was not depressed on mixing with the analytical sample of VII.

Spectra.—Utlraviolet spectra were measured with the Beckman Model DU spectrophotometer. Infrared spectra were obtained on Nujol mulls in the Perkin-Elmer Model 21 spectrophotometer.

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[8] All melting points corrected. Analyses by Micro-Tech Laboratories of Skokie, Illinois.

[9] Sodamide was prepared according to the procedure of M. T. Leffler in R. Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 99. Sodamide obtained from the Farchan Research Laboratories, Cleveland, Ohio, was equally satisfactory.

[10] The succinonitrile was a gift of the American Cyanamid Company.

[11] Prepared according to the procedure of R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

[12] It has been claimed[13d] that this compound melts at 164°. However there is some doubt about the structure assigned, since the analytical values reported by the Indian workers are C, 63.2; H, 8.9.

[13] Melting points previously reported are (a) S. K. Ranganathan, *Current Sci. (India)*, **6**, 277 (1937), 143°; (b) S. K. Ranganathan, *J. Indian Chem. Soc.*, **16**, 107 (1939), 145°; (c) M. Naps and I. B. Johns, THIS JOURNAL, **62**, 2450 (1940), 146°; (d) R. D. Desai and G. S. Sahariya, *J. Univ. Bombay*, **9**, Pt. 3, 107 (1940), 150°.

[14] W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, THIS JOURNAL, **70**, 3022 (1948).