

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation of 2-Pyrrolealdehyde with Hippuric Acid: Isolation of *cis* and *trans* Isomers

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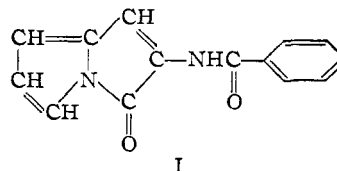
In the course of work which had as its objective the synthesis of β -2-pyrrolealanine,² the condensation of 2-pyrrolealdehyde with several compounds containing active methylene groups was investigated.³ Complications were encountered when attempts were made to repeat earlier work⁴ dealing with the reaction of pyrrolealdehyde and hippuric acid. It has now been found that these difficulties may be attributed to the formation of geometric isomers of the expected azlactone.

Erlenmeyer⁵ first suggested the possibility of *cis-trans* isomerism in the azlactone series when condensing cinnamaldehyde with hippuric acid, although he was unable to isolate the two forms. Carter and co-workers⁶ obtained *cis* and *trans* isomers of α -benzoylaminoacrotic azlactone and of α -benzoylaminoacrotic azlactone on heating the α -benzoylamino- β -methoxy acids with acetic anhydride. It is interesting to note that the condensation of 2-indolealdehyde with hippuric acid⁷ is not reported to result in the formation of a mixture, nor were two products obtained from the few substituted pyrrolealdehydes subjected to the azlactone synthesis.⁸

Asahina and Mitsunaga⁴ reported that 2-pyrrolealdehyde condenses with hippuric acid to give a product which sinters at 155° and melts at 163°. Hydrolysis with 1% sodium hydroxide resulted in two distinct acids, m. p. 173° and m. p. 235°. The only empirical formula given, that of the higher-melting acid, corresponds to the composition of the expected α -benzoylamino- β -(2-pyrrole)-acrylic acid.

The data reported in this article differ markedly from the results reported by these authors. Recrystallization of the crude product from most solvents yielded crystals melting in the range 145–163° which indicated the presence of a mixture. Crystals obtained by recrystallization from benzene melted sharply at 173°; in the following this compound will be referred to as azlactone II. From the mother liquors, fractions with considerably lower melting points were obtained. All fractions gave analyses correct for the predicted azlactone. The existence of *cis* and *trans* isomers

of 2-phenyl-4-pyrrol-5-oxazolone was therefore suspected. Another possibility, the formation of a lactam (I) in a manner similar to the formation of a coumarin from salicylaldehyde and hippuric acid,⁹ was ruled out by the deep color of all fractions and by the fact that the infrared spectra

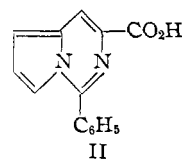


which would be expected to differ widely if the lactam were present showed only minor variations.

Hydrolysis of the low-melting mixture with 0.4 *N* sodium hydroxide yielded two isomeric acids of the composition expected for α -benzoylamino- β -(2-pyrrole)-acrylic acid. Acid I, dec. 192°, precipitated immediately and gave a methyl ester of m. p. 153°. Acid II, dec. 239–240°, separated on standing and was characterized by a methyl ester of m. p. 179°. Undoubtedly it is identical with the high-melting acid of Asahina and Mitsunaga.⁴

Dehydration of acid I with acetic anhydride yielded an azlactone, 2-phenyl-4-pyrrol-5-oxazolone I, different from azlactone II. Acid II on treatment with acetic anhydride regenerated azlactone II. The infrared spectra of the pure azlactones were similar, but not identical. In the double-bond region, azlactone I exhibited two strong bands at 1740 cm.⁻¹ (lactone frequency) and at 1637 cm.⁻¹ (C=N frequency); in azlactone II these bands occur at 1751 and 1649 cm.⁻¹,¹⁰

The alkaline hydrolysis of the azlactones was further complicated by the formation of a third product arising from the reaction of acid II with alkali. This compound, an acid of formula C₁₄H₁₀N₂O₂, could be obtained from acid II or directly from azlactone II by hydrolysis with 1% sodium hydroxide; it frequently contaminated preparations of acids I or II when base was in excess. The absence of NH frequencies from the infrared



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(2) Herz, Dittmer and Cristol, *THIS JOURNAL*, **69**, 1698 (1947); **70**, 504 (1948).

(3) Dittmer and Herz, *ibid.*, **70**, 503 (1948).

(4) Asahina and Mitsunaga, *J. Pharm. Soc. Japan*, 986 (1917).

(5) Erlenmeyer and Matter, *Ann.*, **337**, 271 (1904).

(6) Carter and Stevens, *J. Biol. Chem.*, **133**, 117 (1940); Carter and Risser, *ibid.*, **139**, 255 (1941).

(7) Restelli, *Atas asoc. quim. argentina*, **23**, 58 (1935).

(8) Fischer and Hofmann, *Z. physiol. Chem.*, **245**, 139 (1936–1937); Fischer and Wasenegg, *Ann.*, **461**, 277 (1928).

(9) Erlenmeyer and Stadlin, *Ann.*, **337**, 283 (1904).

(10) These frequencies are in the range given for the lactone and C=N bands of azlactones containing a 4-exocyclic double bond.¹¹

(11) Thompson, Brattain, Randall and Rasmussen, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 387.

spectrum of the acid and its methyl ester as well as the solubility of both compounds in dilute acid suggests the formula of 4-phenyl-pyrrolo[1,2-C]-pyrimidine-2-carboxylic acid (II), the product of an intramolecular condensation between the benzoyl radical and the pyrrole nitrogen. If this interpretation is correct, configurations may be assigned to azlactones I and II and the acids resulting from their hydrolysis. Because the pyrrolopyrimidine could not be obtained from acid I or azlactone I, the pyrrole nitrogen and the benzoyl group in these compounds must be *trans* to each other, whereas the *cis* configuration of acid II permits ring closure to occur. It is intended to investigate the applicability of this reaction to other compounds of this type.

Experimental

2-Phenyl-4-pyrrol-5-oxazolone, II.—An intimate mixture of 9 g. of 2-pyrrolealdehyde,¹² 18 g. of hippuric acid and 18 g. of anhydrous sodium acetate was heated on the steam-bath with 45 ml. of acetic anhydride. After one hour, the mixture was cooled, broken up with a stirring rod, triturated with water, filtered, washed with water and dried. The yield of dark-brown material was 16.5 g. Eleven grams of the crude product was extracted with 200 ml. of boiling benzene. The benzene solution was treated with charcoal and deposited 1.5 g. of orange plates, m. p. 173°. The melting point was not raised by further recrystallizations from benzene. This fraction had the analysis given below. On evaporation of the benzene mother liquor to 125 ml. and cooling, 1.1 g. of material, m. p. 172°, precipitated. Further evaporation and cooling yielded 3.5 g. of material melting in the range 135–145°.

*Anal.*¹³ Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 71.10; H, 4.49; N, 11.76.

Five grams of the crude condensation product was extracted with two 50-ml. portions of boiling ethanol. The combined extracts were treated with charcoal and on cooling deposited 1.5 g. of yellow crystals, m. p. 148–163°. On evaporation of the filtrate to smaller volume, 0.6 g. of material melting in the same range was obtained. Dilution of the mother liquor with water yielded 1.6 g. of lower-melting material. Hydrolysis experiments showed that the first two fractions consisted almost exclusively of azlactone II in spite of the melting point range. Reprecipitation from pyridine solution with water raised the m. p. to 173°.

α -Benzoylamino- β -(2-pyrrole)-acrylic Acids I and II.—The crude product resulting from the condensation of 9 g. of 2-pyrrolealdehyde and 18 g. of hippuric acid was stirred with one portion of 50 ml. and one portion of 25 ml. of cold ethanol. This removed a considerable portion of azlactone II. The undissolved material was recrystallized from acetone–water and weighed 4.5 g., m. p. 155–160°. Four grams was heated on the steam-bath with 200 ml. of 0.4 *N* sodium hydroxide. After three hours, the solution was acidified with concd. hydrochloric acid. A light-yellow precipitate which appeared to decompose rapidly was filtered immediately and washed with water. The filtrate deposited 1.4 g. of grey-blue needles on standing. Five recrystallizations of the first precipitate from dilute ethanol, accompanied each time by treatment with charcoal, gave 0.23 g. of slightly-colored crystals (acid I) which decomposed at 192° when the capillary was immersed at a bath temperature of 185°.

(12) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 152.

(13) Analyses by Miss Emily Davis, Miss Rachel Kopel and Mr. Maurice Dare. Infrared measurements were carried out by Miss Elizabeth Peterson.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.94. Found: C, 65.74; H, 4.94; N, 10.80.

The second product was dissolved in dilute sodium hydroxide and filtered from insoluble material. The precipitate obtained on acidification was recrystallized three times from dilute ethanol, each recrystallization being accompanied by treatment with charcoal. The almost white needles weighed 0.25 g. and decomposed at 239–240° when the capillary was immersed at 230° and the bath was heated up rapidly.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.94. Found: C, 65.86; H, 4.90; N, 10.96.

Hydrolysis of 2 g. of the low-melting material obtained from the benzene mother liquors of azlactone II, using 80 ml. of 0.5 *N* sodium hydroxide, yielded 0.85 g. of crude acid I, contaminated by acid II.

Methyl Ester of Acid I.—A solution of 95 mg. of acid I in 5 ml. of methanol was treated with an ethereal solution of diazomethane. After removal of the ether, the solution was diluted with water and deposited 79 mg. of ester. Recrystallization from dilute methanol gave needles melting at 153°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.85; H, 5.44; N, 10.46.

Methyl Ester of Acid II.—In the same way, 93 mg. of acid II gave 87 mg. of light-yellow crystals melting at 179°. The ester was also obtained in 70% yield when azlactone II was treated with sodium methoxide in methanol, following the procedure of Fischer and Hofmann.⁸

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.88; H, 5.41; N, 10.11.

2-Phenyl-4-pyrrol-5-oxazolone I.—A mixture of 27 mg. of pure acid I and 1 ml. of acetic anhydride was warmed on the steam-bath for ten minutes. Dilution with water caused the separation of a light-brown precipitate weighing 24 mg. Repeated slow crystallization from ethanol yielded golden needles, m. p. 186°, mixed m. p. with azlactone II 145–155°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.41; H, 4.16; N, 11.63.

Treatment of 38 mg. of acid II with acetic anhydride gave 33 mg. of orange crystals, m. p. 173°, showing no depression on admixture of azlactone II.

Hydrolysis of Azlactone II with 1% Sodium Hydroxide.—A mixture of 300 mg. of azlactone II and 15 ml. of 1% sodium hydroxide solution was warmed on the steam-bath for one hour until the azlactone was dissolved completely. The red solution was cooled and made barely acid to congo-red paper. A light-green precipitate separated. It was filtered and washed rapidly to prevent decomposition. The mother liquor on chilling deposited a small amount of acid II. The precipitate was recrystallized three times from 10 ml. of ethanol, using charcoal. The light-green needles were soluble in dilute base and acid, insoluble in water, m. p. 182–183° with decomposition. The infrared spectrum showed the complete absence of any —NH and C=O frequencies other than those ascribed to conjugated carboxyl at 1680 cm^{-1} and acid —OH. In ethanol solution the compound gave a carmine-red color with ferric chloride.

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.25; N, 11.71.

This acid was also obtained by warming acid II with 1% sodium hydroxide solution on the steam-bath.

The methyl ester was prepared by dissolving 150 mg. of the acid in methanol and adding an ether solution of diazomethane. Removal of the ether followed by dilution with water yielded a yellow oil which solidified on standing. Three recrystallizations from methanol–water gave yellow needles, m. p. 107°, soluble in dilute acid, insoluble in base. The infrared spectrum contained a strong band at 1718 cm^{-1} which can be ascribed to a conjugated ester group.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.44; H, 4.84; N, 11.11. Found: C, 71.35; H, 5.06; N, 11.13.

Summary

The condensation of 2-pyrrolealdehyde with hippuric acid and acetic anhydride gives rise to two isomeric azlactones. Configurations have

been tentatively assigned to these isomers on the basis of an intramolecular condensation which only one of them appears to undergo.

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Comparative Properties of Some Methyl Substituted 8-Quinolinols

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As part of an investigation in this Laboratory of some new analytical reagents of the 8-quinolinol series, the 2- and 4-methyl derivatives were studied.^{2,3} Because these derivatives showed some rather interesting differences from each other and from 8-quinolinol, the properties here described were determined and the results compared.

Experimental

Purification of Materials.—The substituted 8-quinolinols were prepared and purified as previously described.^{3,4} A further check on the purity of the 8-quinolinol and 2-methyl-8-quinolinol used was obtained through their quantitative bromination⁵ with standard potassium bromate, both analyzing better than 99.7%.

Infrared Spectra.—All spectra were obtained with a Beckman IR-2 instrument with automatic recording. The intensity curves for solvent and solution were recorded on the same graph and the ratios of the two curves calculated at corresponding wave lengths in order to get per cent. transmission. The assignment of wave lengths was calculated from the known absorption bands of carbon tetrachloride, carbon dioxide and water vapor with an estimated accuracy of $\pm 0.05\mu$ over most of the range studied.

Approximately saturated solutions in carbon tetrachloride in 0.1 mm. thick salt cells were used throughout.

Ultraviolet Spectra.—Curves were recorded with a Beckman Model DU Quartz Spectrophotometer using 1.00 cm. cells and slit widths from 0.1–2.0 mm. as required. Readings were made every one millimicron in the vicinity of an absorption maximum and at somewhat wider intervals elsewhere. All compounds obeyed Beer's law satisfactorily in the concentration range studied. Molecular extinctions are considered accurate to two significant figures.

Powder Diffraction Lines.—The finely powdered samples, mounted on a rotating hard glass fiber coated with vaseline, were exposed for five hours to filtered copper X-ray radiation. The " d " values, calculated in the usual way, are the average values from two or more photographs for each compound. Relative intensities were estimated visually.

Quantitative Precipitations of Metals.—The procedure was the same as previously described² except that, owing to coprecipitation of the excess substituted quinolinol, it was usually necessary to ignite the precipitates to the oxides for weighing.

The standard solutions of Cu^{++} , Zn^{++} , Mg^{++} , Co^{++} , Mn^{++} , Fe^{+++} and Al^{+++} were prepared by standard methods from weighed quantities of reagent grade chemi-

cals and further analyzed by precipitation with 8-quinolinol. Determinations were made at 0.2 pH unit intervals to obtain the pH values at which precipitation begins and is complete.

Reactions with Diazomethane.—A 100–200% excess of an ether solution of diazomethane was added to an ether solution of the substituted 8-quinolinol. Red precipitates formed with 8-quinolinol, 4-methyl-8-quinolinol and 5,7-dibromo-8-quinolinol but did not form with 2-methyl- or 2,4-dimethyl-8-quinolinol. The red products were filtered and recrystallized from benzene; they had indefinite decomposition points and were, therefore, characterized by their ultraviolet and visible absorption spectra. Nitrogen analyses on the product from 8-quinolinol (7.20%) do not conform to that calculated (8.80%) from the structure proposed by Schenkel-Rudin.⁶

Results and Discussion

The infrared absorption spectra (Figs. 1–4) from 2–11 μ of these four quinolinols in approximately saturated solutions show several bands that can be correlated with known structural features of all the compounds, but few characteristics capable of distinguishing the compounds from each other. (It is evident from the graphs that 4-methyl-8-quinolinol has a low solubility in carbon tetrachloride compared to its 2-methyl isomer.)

The absorption band at 2.8 μ is evidently the O–H stretching band; it is completely absent in the 8-methoxy derivatives of these compounds.⁷ The bands at approximately 3.2–3.3 μ are due to C–H stretching and vary somewhat in wave length and structure probably because of the different kinds of C–H linkages in the different compounds. (The absence of these bands in 4-methyl-8-quinolinol can be attributed to the low concentration of the solution.) The strong absorption maxima at about 6.35, 6.65 and 6.8 μ are fundamental frequencies of the aromatic ring system. The bands at 7.1, 7.3 and 7.5 μ are probably due to C–H bending, the one at 7.5 μ perhaps being caused by the C–H bond in the active 2-methyl group since it is lacking in 8-quinolinol and 4-methyl-8-quinolinol. Maxima at 7.9–8.1 μ are perhaps associated with C–O or C–N stretching vibrations.

No maxima identifiable with a C=O linkage could be found in any of these compounds, although the existence of a considerable proportion of the keto tautomer of 8-quinolinol in non-

(1) Abstracted from a thesis by John P. Phillips in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, 1949. Du Pont Fellow for 1948–1949.

(2) L. L. Merritt and J. Walker, *Ind. Eng. Chem., Anal. Ed.*, **16**, 387 (1944).

(3) J. P. Phillips and L. L. Merritt, *THIS JOURNAL*, **70**, 410 (1948).

(4) J. P. Phillips, R. L. Elbinger and L. L. Merritt, *THIS JOURNAL*, **71**, 3986 (1949).

(5) M. V. Tsympkin, *Farmatsiya i Farmakol.*, 1937, No. 2, 43.

(6) Schenkel-Rudin, *Helv. Chim. Acta*, **27**, 1456 (1944).

(7) Unpublished observations in this Laboratory.