Dehydration of Carbinol-Amide VIIa with Sulfuric Acid.—The carbinol-amide VIIa (1.0 g) dissolved during *ca.* 2 hr in concentrated sulfuric acid (10 ml) at 0° to give a dark brown solution; the reaction was exothermic initially. When the solution was poured into stirred ice and water (100 ml), a cream precipitate was obtained. The latter (0.12 g), when dry, was fawn colored and its infrared spectrum suggested the presence of cinnamic acid. Basification of the filtrate with aqueous ammonia solution (29.5%) furnished a colloidal solution which, overnight, deposited crude unsaturated VIII as a cream solid (0.58 g, 63%). Crystallization from acetonitrile afforded pure VIII (0.40 g, 43%) as colorless acicular plates: mp 177–178°; ν_{max} (Nujol) 3220 (NH), 1680 (C=O), 1635 (C=C), 1545, 1410, 1333, 1267, 1175, 974, 854, 810, 764, 704, and 680 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.81; H, 5.24; N, 12.56.

Unsaturated amide VIII was independently synthesized by adding warm cinnamoyl chloride (1.83 g, 0.011 mol) to a hot solution of 3-aminopyridine (0.94 g, 0.010 mol) and sodium hydroxide (0.44 g, 0.011 mol) in water (15 ml). An exothermic reaction occurred, and a dark yellow tarry precipitate was obtained which solidified when cool. The crude product VIII (0.70 g, 31%) was crytallized from acetonitrile to provide pure VIII (0.34 g, 15%) as colorless acicular plates, mp and mmp 175.5–177°. The infrared spectrum of this compound was identical with that of the dehydration product from VIIa.

Registry No.—*n*-Butyllithium, 109-72-8; IIa, 16054-89-0; IIb, 16054-90-3; IIIa, 16109-47-0; IIIb, 16054-91-4; IV, 16054-92-5; V, 16054-93-6; VIIa, 16054-94-7; VIIb, 16054-95-8; VIII, 16054-96-9.

The N-Hydroxy Protecting Group in Pyridone Syntheses

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We wish to report a new route leading to side chain functionalization of 6-methyl-2-pyridone.[2] This method is illustrated by the synthesis of 2-pyridone-6-alanine (IX), and offers the advantage of producing 6-substituted N-hydroxypyridones as intermediates.

Our attention was first directed toward the N-hydroxy group as a protecting function by reports that the N-hydroxy group could be removed by reduction.[3,4] In practice, it was found that the method of Newbold and Spring,[3] which utilizes stannous chloride, gave excellent yields of the desired 2-pyridone derivatives.

The reaction of ethyl oxalate and 4-methyl-2-benzyloxypyridine-1-oxide[5] was carried out using conditions similar to those described for the condensation of ethyl oxalate with 4-picoline 1-oxide.[6] Only a small amount of material was isolated from the reaction, and, although it gave a positive ferric chloride test and its infrared spectrum was in agreement with that of an α-keto ester, the compound did not analyze correctly. This result appeared to be inconsistent with the report of Adams and Miyano[6] that 6- methyl-2-benzyloxypyridine 1-oxide (II) condensed smoothly with ethyl oxalate.

In order to help explain the discrepancy in the two results, the reaction sequence carried out by Adams and Miyano[6] was repeated. Peracetic acid oxidation of 2-benzyloxy-6-methylpyridine (I) did indeed yield a compound which possessed the characteristics claimed for 2-benzyloxy-6-methylpyridine 1-oxide (II), but the infrared spectrum of this compound showed conclusively that it was, in fact, 1-benzyloxy-6-methyl-2-pyridone (III).[7] The thermal rearrangement of alkoxypyridine 1-oxides to 1-alkoxy-2-pyridones is a well-documented reaction[8] and evidently the higher reaction temperatures used during the oxidation caused rearrangement of the pyridine 1-oxide. In fact, peracetic acid oxidation of 4-methyl-2-benzyloxypyridine yielded only 3-methyl-1-benzyloxy-2-pyridone in contrast to *m*-chloroperbenzoic acid oxidation which gave only 4-methyl-2-benzyloxypyridine 1-oxide.[5] Even *m*-chloroperbenzoic acid oxidation of 2-benzyloxy-6-methylpyridine (II) produced the rearranged product III.

Condensation of 6-methyl-1-benzyloxy-2-pyridone (III) with ethyl oxalate proceeded smoothly as reported.[6] All attempts to condense 4-methyl-1-benzyloxy-2-pyridone with ethyl oxalate were, however, unsuccessful. Moreover, no starting material could be recovered from the reaction mixture. The reason for the unusual behavior of the 4-methyl compound is not clear. One explanation might be that there is abstraction of a proton from the benzylic carbon atom leading to benzaldehyde and 4-methyl-2-pyridone (which is water soluble).[9] This process does not appear to be as sterically favorable in the case of the 6-methyl compound III.

The synthesis of the amino acid IX was accomplished as outlined in Scheme I.

Treatment of the α-keto ester IV with hydroxylamine gave the α-oximino ester V already reported by Adams.[5] It seemed advisable to remove the benzyl group from V at this stage in order to prevent possible elimination of benzaldehyde during saponification of the ester. Debenzylation was carried out catalytically[4] and was complete in a few minutes. The product VI gave an intense coloration with aqueous ferric chloride.[3,4] Saponification of VI gave the oximino acid VII which was treated with a solution of stannous chloride in concentrated hydrochloric acid. After the solution had been left standing for several hours at room temperature, the crystalline hydrochloride of the N-hydroxy pyridone amino acid VIII had precipitated. Further treatment of VIII with refluxing stannous chloride–HCl, followed by neutralization, yielded the unsubstituted amino acid IX. Alternatively, treatment of VII with the reduction mixture at reflux gave IX directly. Thus, our original supposition that the N-hydroxy group can be utilized as a protecting group in the syntheses of pyridone derivatives is valid, and appears to offer a method which

(1) Inquiries should be addressed to this author at the Merck Sharpe and Dohme Research Laboratories, Rahway, N. J.

(2) R. L. Gay, S. Boatman, and C. R. Hauser [*Chem. Ind.* (London), 1789 (1965)] have reported a more direct method of obtaining derivatives of 6-methyl-2-pyridone.

(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

(4) E. Shaw, *J. Amer. Chem. Soc.*, **71**, 67 (1949).

(5) W. A. Lott and E. Shaw, *ibid.*, **71**, 70 (1949).

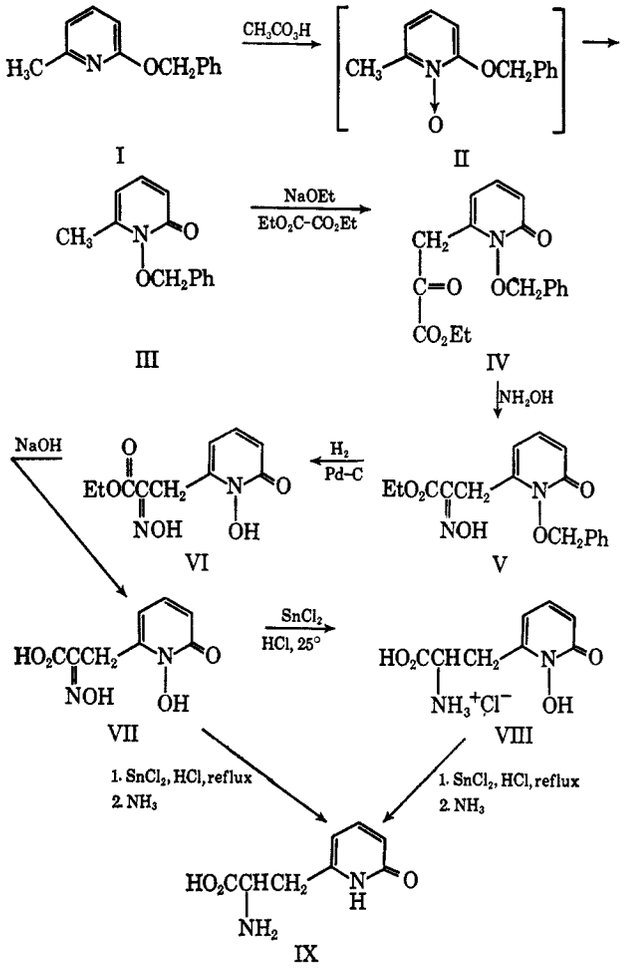
(6) R. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).

(7) This finding has also been observed independently by E. C. Taylor, Princeton University, private communication, 1966.

(8) F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, **29**, 1650 (1964).

(9) W. Feely, W. L. Lehn, and V. Boekelheide [*ibid.*, **22**, 1135 (1957)] have prepared benzaldehyde by treating 1-benzyloxypyridinium bromide with alkali.

SCHEME I



could be advantageously applied to other problems of pyridone chemistry.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord. Melting points are uncorrected. We wish to thank Miss M. Carroll of Smith Kline and French Laboratories for performing all the microanalyses.

1-Benzyloxy-6-methyl-2-pyridone (III).—This compound was prepared by oxidation of 2-benzyloxy-6-methylpyridine (I) with peracetic acid.[6] The yield of product was 62%: mp 100–102° (lit.[6] mp 99–100°); λ_{max}^{Nujol} 5.95 μ (C=O).

1-Benzyloxy-4-methyl-2-pyridone.—Oxidation of 2-benzyloxy-4-methylpyridine[5] using peracetic acid, yielded only the pyridone in 52% yield. Purification was accomplished by vacuum sublimation to yield white crystals: mp 78–80°; λ_{max}^{Nujol} 5.95 μ (C=O).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.09; N, 6.67.

Ethyl 1-Benzyloxy-2-pyridone-6-pyruvate (IV).—Sodium (2.3 g, 0.10 g-atom) was dissolved in 75 ml of absolute ethanol and 14.6 g (0.10 mol) of ethyl oxalate was added to the solution. After stirring for several minutes, 21.5 g (0.10 mol) of 1-benzyloxy-6-methyl-2-pyridone was added in several portions. The reaction mixture was stirred for 2 hr and then was allowed to stand for 19 hr at room temperature. The precipitated yellow sodium salt was filtered and was washed with benzene. The filtrate was concentrated to a small volume to yield a large second crop. The total amount of crystalline salt isolated was 32.8 g. This was dissolved in 150 ml of water and was acidified with 10% hydrochloric acid. The keto ester, which precipitated as a light tan solid, was filtered, washed with water, and dried to yield 26.0 g (82.5%): mp 117–120° dec (lit.[6] mp 103–104°); λ_{max}^{Nujol} 2.7, 3.0, 5.78, (CO_2R), and 6.0 μ (amide CO).

Ethyl 1-Benzyloxy-2-pyridone-6-(α-oximino)propionate (V).—A mixture of hydroxylamine hydrochloride (1.4 g, 0.02 mol), 1.64 g (0.02 mol) of sodium acetate, and 6.3 g (0.02 mol) of keto ester IV in 50 ml of absolute alcohol was refluxed for 3 hr. The mixture was filtered through a pad of super-cel while hot; water was then added until the solution turned cloudy. After standing for several hours, a precipitate was collected which yielded 4.8 g (73%) of the oxime V: mp 135–138° (lit.[6] mp 136–137°; λ_{max}^{Nujol} 2.7, 3.0, 5.78 (CO_2R), and 6.0 μ (amide CO).

Ethyl 1-Hydroxy-2-pyridone-6-(α-oximino)propionate (VI).—To a solution of 10.0 g (0.03 mol) of V in 150 ml of methanol was added 0.50 g of 10% palladium on carbon. The mixture was placed in a Paar shaker under an initial hydrogen pressure of 60 psi and was shaken until the theoretical uptake of hydrogen was observed (*ca.* 3 min.). The mixture was filtered and the filtrate was evaporated, leaving the product (5.8 g) as a tan solid, mp 182–185°. After recrystallization from isopropyl alcohol, a yield of 5.1 g (69%) of the hydroxy pyridone as needles was obtained: mp 190–191°; λ_{max}^{Nujol} 2.95 (OH), 5.00 (CO_2R), and 6.02 μ (amide CO).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 49.99; H, 5.04; N, 11.66. Found: C, 50.06; H, 5.11; N, 11.84.

During the hydrogenolysis, a small amount of methanol-isoluble material was produced. This solid was also insoluble in most organic solvents and could not be separated from the catalyst. However, dissolution took place in 10% sodium hydroxide solution. After removal of catalyst and acidification, the aqueous solution deposited 2.1 g of the oximino acid VII (see below). After similar treatment, the oximino ester VI, which dissolved in dilute sodium hydroxide solution, was recovered unchanged.[10,11]

1-Hydroxy-2-pyridone-6-(α-oximino)propionic Acid (VII).—Ethyl 1-hydroxy-2-pyridone-6-(α-oximino)-6-pyruvate (4.5 g, 0.0188 mol was refluxed for 3 hr with 100 ml of 10% sodium hydroxide solution. The hot solution was acidified with concentrated hydrochloric acid to a pH of *ca.* 3. On standing, the solution slowly deposited the acid VII. In order to obtain the maximum yield of VII, the acid solution was kept overnight at 4°. Recrystallization from water yielded 3.1 g (78.5%) of white crystals: mp 178° dec; λ_{max}^{Nujol} 2.90 (OH), 5.90 (CO_2H), and 6.05 μ (amide CO).

Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.21. Found: C, 45.29; H, 3.91; N, 13.25.

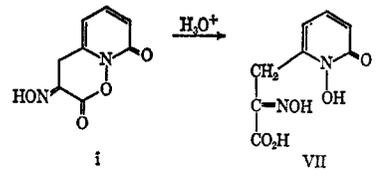
1-Hydroxy-2-pyridone-6-alanine Hydrochloride (VIII).—To a solution of 11.6 g (0.048 mol) of stannous chloride dihydrate in 75 ml of concentrated hydrochloric acid was added 5.1 g (0.024 mol) of the oximino acid VII. The reaction mixture was stirred at room temperature for 18 hr; the crystalline precipitate was filtered and was washed well with acetone to yield 3.1 g (55%) of product: mp 208–210° dec; λ_{max}^{Nujol} 5.80 (CO_2H), and 6.05 μ (amide CO). Recrystallization from methanol–ether yielded the analytical sample.

Anal. Calcd for $C_8H_{11}ClN_2O_4$: 40.95; H, 4.73; N, 11.94. Found: C, 41.15; H, 5.03; N, 11.63.

2-Pyridone-6-alanine (IX).—A solution of 7.0 g (30.0 mmol) of stannous chloride and 2.0 g (9.45 mmol) of oximino acid VII in 30 ml of concentrated hydrochloric acid was refluxed for 19 hr. The clear solution was evaporated *in vacuo* and the residue was dissolved in 100 ml of water. Hydrogen sulfide was passed into the solution until no further precipitation occurred. The mixture was filtered through super-cel and the filtrate was evaporated to dryness. The residue of amino acid hydrochloride (mp 235–240°) was contaminated with about 1% of inorganic matter (ash on combustion). The hydrochloride was dissolved in the minimum amount of water and was made slightly basic with concentrated ammonia. Acidification with acetic acid at

(10) Formation of VII under mild hydrolytic conditions could be visualized as occurring from a compound such as i, which is a 1-acyloxypyridone.[11]

(11) L. A. Paquette, *J. Amer. Chem. Soc.*, 87, 5186 (1965).



i VII

If the unknown is indeed i, its formation would be difficult to account for since the ester VI, on prolonged reflux in ethanol with a catalytic amount of sodium ethoxide, is unchanged. It is conceivable that i could arise from VI during the hydrogenolysis of V by loss of toluene and ethanol, concomitant with cyclization on the catalyst surface.

5° yielded colorless needles of 2-pyridone-6-alanine which were recrystallized from water to yield 1.07 g (58.6%). The analytical sample had mp 278–280° dec, λ_{max}^{Nujol} 6.15 μ. A ferric chloride test of this compound was negative, showing that the N–OH group had been removed.

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.76; H, 5.69; N, 15.50.

Registry No.—1-Benzyloxy-4-methyl-2-pyridone, 16753-75-6; VI, 16753-76-7; VII, 16753-77-8; VIII, 16753-78-9; IX, 16753-79-0.

Color and Conformation in Pyrazolone Azomethine Dyes

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Pyrazolone azomethine dyes related to I and II are well known in color photography as image formers,[1] and are generated from pyrazolones and the *p*-phenylenediamines used as color developers through the action of silver ion as the oxidizing agent. The *p*-phenylenediamines usually employed are based upon 4-amino-N,N-diethylaniline and 4-amino-3-methyl-N,N-diethylaniline, and with these the dyes are magenta in hue, showing peak absorption near 520 nm in ethyl acetate. When, however, 4-amino-3,5-dimethyl-N,N-diethylaniline is used, the resulting dyes are cyan and absorb near 640 nm. The bathochromic shift of the absorption maximum is consistent with the twisting of a double bond in the conjugated system[2] and evidence has now been obtained from an nmr study that the developer-derived aromatic ring and the pyrazolone ring are not coplanar in these compounds.

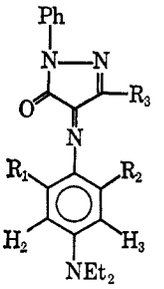
Results

The nmr spectra of dyes I–IV have been determined at 100 MHz in deuteriochloroform solution and Table I gives the chemical shifts of the relevant aromatic protons and methyl substituents. From this it will be seen that in dyes II and III the aryl methyl group resonates at approximately 2.53 ppm whether the dye exists with the aromatic ring *syn* or *anti* with respect to the pyrazolone carbonyl group.[3] It may thus be assumed that the chemical shift of the methyl protons is determined largely by the electron density on the aromatic ring, rather than by any long-range shielding effects.

On introduction of the second methyl group (IV), the methyl resonance shifts to 2.19 ppm, corresponding to a shielding of 0.34 ppm; this is approximately twice the magnitude of the shifts undergone at the same time by the aromatic proton resonances, and is thus unlikely to be accounted for by electronic considerations alone. It should be noted that the introduction of the second methyl group produces the same effect on the aromatic proton resonances as the introduction of the first methyl group. It is thought that the observed shielding of the methyl groups is a consequence of their situation within the shielding cone of the pyrazolone carbonyl group.[4] If this assessment is correct, these observations constitute direct evidence for the nonplanarity of such dyes since, if they were planar, a large deshielding of the methyl groups by the carbonyl group would be expected. Such deshieldings have been observed[3] for the aromatic protons of planar members of this series of dyes, and are shown by R_2 in dyes I–III (*syn*). Examination of Courtauld models supports these findings, since it is revealed that, whereas coplanarity of the aromatic and pyrazolone rings can be achieved in dyes I–III, it is impossible for dye IV.

TABLE I

CHEMICAL SHIFTS OF *p*-PHENYLENEDIAMINE AROMATIC PROTONS AND METHYL SUBSTITUENTS[a]



I, $R_1 = H_1$; $R_2 = H_4$; $R_3 = CH_3$
II, $R_1 = CH_3$; $R_2 = H_4$; $R_3 = CH_3$
III, $R_1 = CH_3$; $R_2 = H_4$; $R_3 = H$
IV, $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = CH_3$

Dye	Chemical shift, ppm: Ar–CH_3	H_1	H_4	H_2	H_3
I		8.29	8.29	6.67	6.67
II	2.53		8.92	6.57	6.50
III *syn*	2.50		8.92	*b*	*b*
III *anti*	2.53		7.65	6.60	6.54
IV	2.19			6.42	6.42

[a] Chemical shifts are expressed in parts per million (ppm) downfield from TMS as an internal reference. [b] Chemical shifts for these protons could not be obtained in the original analysis,[3] since the relevant signals were hidden under aromatic resonances from the other stereoisomer.

Discussion

The visible absorption spectra of pyrazolone azomethine dyes exhibit two maxima,[5] a low-intensity y band near 440 nm and an x band of higher intensity near 520 nm. It is known that the x bands of these dyes are solvent sensitive, shifting to longer wavelengths and becoming more intense with increasing solvent polarity.[5] This normally indicates that the resonance of the chromophoric system of the dyes is energetically asymmetric, the energy of the classical structure Va being lower than that of the dipolar extreme structure Vb.

(1) C. E. K. Mees and T. H. James, Ed., "The Theory of the Photographic Process," 3rd ed, The Macmillan Co., New York, N. Y., 1966, Chapter 17.

(2) L. L. Ingraham in "Steric Effects in Organic Chemitry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 493.

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(4) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 122.

(5) G. H. Brown, B. Graham, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **73**, 919 (1951); W. F. Smith, Jr., *J. Phys. Chem.*, **68**, 1501 (1964).