soluble inorganic material by gravity filtration, was added 0.4 g. (0.0038 mole) of *o*-phenylenediamine in 20 ml. of ethyl acetate. The pink solution was heated on the steam bath for 30 min., cooled, and on evaporation to dryness under an air stream left an amber residue which recrystallized from benzene as red microcrystalline 1-aminophenazine, 0.41 g. (67.7%) m.p. 183–184°.[4]

This and other phenazines prepared in a similar manner are described in Table I. Lead dioxide could be substituted for silver oxide in each example.

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Acetyl Transfer during Hydrogenation of *p*-Nitrophenyl Acetate[1]

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Received September 1, 1960

In connection with other work, *p*-aminophenyl acetate (II) was needed. Since the literature preparation of II[3] is difficult and attended with low

$$p\text{-}HOC_6H_4NO_2 + Ac_2O \xrightarrow{H^+} \underset{I}{p\text{-}CH_3COOC_6H_4NO_2} \xrightarrow[C_2H_5OH]{Pt,\ H_2} [p\text{-}CH_3COOC_6H_4NH_2] \longrightarrow \underset{III}{p\text{-}HOC_6H_4NHCOCH_3}$$
II

yields, its preparation was attempted by the schematic representation shown above. The acetylation of *p*-nitrophenol went smoothly with acetic anhydride and a catalytic amount of sulfuric acid; however, the reduction of *p*-nitrophenyl acetate (I) at 850 p.s.i. and 120° in the presence of a platinum catalyst, gave not the desired product (II) but rather an isomer, *p*-hydroxyacetanilide (III) in high yield. To our knowledge, this is the first reported example of a *para* acetyl transfer during the reduction of I to yield probably II, then immediately III.

Many investigators,[4] though, have reported *ortho* acetyl and benzoyl transfers. Others[5] have shown that these transfers were, in some instances, intramolecular migrations that occurred because the *ortho* esters of aminophenyl acetate (isomer of II) and aminophenyl benzoate were very unstable. Thus, when formed, they rearranged quickly to the corresponding *N*-acetyl or -benzoyl derivatives; *i.e.*, the acetyl or benzoyl group migrated from the oxygen to the nitrogen atom.

IV V

R = acetyl or benzoyl

A satisfactory explanation for the isolation of *p*-hydroxyacetanilide (III) from *p*-nitrophenyl acetate (I) in high yield is still premature; however, our results indicate that the reaction is a reduction of a nitro group followed by an intermolecular aminolysis of an ester.

EXPERIMENTAL

p-Nitrophenyl acetate (I) was prepared from *p*-nitrophenol (30 g.), acetic anhydride (61 ml.), and 4 drops of concd. sulfuric acid in the usual way; m.p. 79–80°; yield 95%.

p-Hydroxyacetanilide (III) was prepared as follows: *p*-nitrophenyl acetate (290 g.), absolute ethanol (500 ml.), and platinum oxide catalyst (2.5 g.) were kept at 850 p.s.i. of hydrogen and at approximately 120° for 6 hr. The mixture cooled on standing overnight and was filtered. The solvent was removed and crude III crystallized; crude yield was quantitative and the yield after recrystallization from hot water was 77%; m.p. 163–166°; ethyl acetate was later found to be a better solvent than water for the recrystallization of III, so III was then recrystallized from ethyl acetate; m.p. 168–169° (mixed m.p. with known III 168–169°).

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(3) L. Galatis, *Ber.*, **59**, 850 (1926); S. E. Hazlet and C. A. Dornfeld, *J. Am. Chem. Soc.*, **66**, 1781 (1944).

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A Convenient Method for the Preparation of 3-Cyano-6-methyl-2(1H)pyridone

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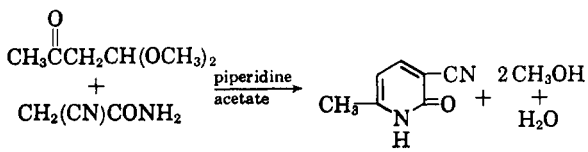
Received October 5, 1960

There has been a continuing interest in this compound since 1944[1] as an intermediate in syn-

(1) T. Matsukawa, and T. Matsuno, *J. Pharm. Soc. Japan* **64**, 145(1944), *Chem. Abstr.*, **45**, 4724f (1951).

(2) L. A. Perez-Medina, R. P. Mariella, and S. M. McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).

thetic programs centered around the B vitamins and other physiologically active pyridines. The starting materials employed in its preparation[1-4] have been difficult to handle. Recently, since we required kilogram quantities of 3-cyano-6-methyl-2(1H)pyridone, we evaluated the various synthetic methods. In the method of Matsukawa and Matsuno,[1] and, subsequently, that of Perez-Medina, Mariella and McElvain,[2] a condensation of sodium formyl acetone and cyanoacetamide was utilized. However, we found that the yield and quality varied widely when this method was employed. More recently, Kochetkov[3] reported an attractive method, wherein 3-ketobutyraldehyde-1-dimethyl acetal is condensed with cyanoacetamide under aqueous conditions with piperidine acetate as a catalyst. Furthermore, 3-ketobutyraldehyde-1-dimethylacetal[5] had recently become commercially available.[6]



Our experimental work has demonstrated that the desired pyridone is quickly obtained in good yield and high purity. A typical preparation is outlined below.

EXPERIMENTAL

A mixture of 650 g. (5.0 moles) of 3-ketobutyraldehyde-1-dimethylacetal (Henley & Co., n_D^{25} 1.4160), 462 g. (5.5 moles) cyanoacetamide (Eastman), 1 l. of water, and piperidine acetate solution[7] was prepared in a 3-l., three-necked, round bottom flask equipped with a mechanical stirrer and reflux condenser.

On gentle heating (about 80°), a clear solution was obtained. This was heated under reflux for 24 hr. in a Glas-Col mantle. The product began to precipitate after 1 hr. at reflux. After the reaction was complete, the reddish-tan slurry was cooled to 20°, filtered, and washed well with cold water. The light tan product was dried overnight in a steam oven at 50–60°; yield, 545 g. (81%), m.p. 285° dec.

This procedure has been extremely satisfactory on a 1- to 17-mole scale and has presented few operational problems. It obviates the need for organic solvents and difficultly handled starting materials. The product thus prepared was satisfactory for use in subsequent steps without further purification.

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(3) N. K. Kochetkov, *Doklady Akad. Nauk U.S.S.R.*, **84**, 289(1952), *Chem. Abstr.*, **47**, 3309a (1953).
(4) R. P. Mariella, *Org. Syntheses*, **32**, 32 (1952).
(5) A. C. Cope, *J. Am. Chem. Soc.* **59**, 2327 (1937).
(6) Henley & Co., New York, N. Y.
(7) The piperidine acetate was prepared by adding piperidine (about 25 ml.) to 100 ml. of 20% acetic acid solution until a *p*H of 9–10 was reached.

Synthesis of L-Valyl-L-tyrosyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine Methyl Ester Dihydrochloride

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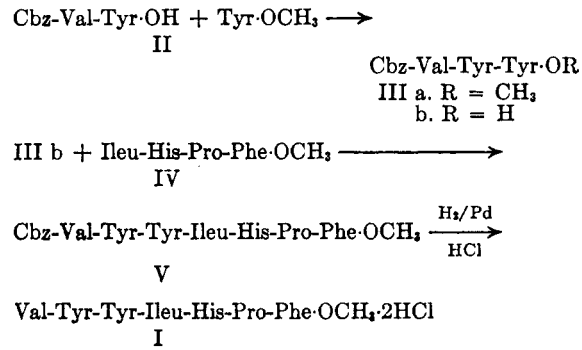
Received October 10, 1960

During the course of work related to the angiotensin peptides, the heptapeptide ester, L-valyl-L-tyrosyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester dihydrochloride (I), was synthesized. This paper reports the methods of synthesis and purification which were used. The scheme shown below indicates the order in which the amino acids were coupled together forming the final sequence I. *N*-Carbobenzyloxy-



L-valyl-L-tyrosyl-L-tyrosine methyl ester (III a) was obtained by coupling *N*-carbobenzyloxy-L-valyl-L-tyrosine[1] with L-tyrosine methyl ester[2] using dicyclohexylcarbodiimide[3] in dimethylformamide. Alkaline hydrolysis of the crystalline ester IIIa formed the acid IIIb which after adsorption on alumina and elution with methanol–formic acid was obtained crystalline. This acid was coupled with L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester[4] (IV) using dicyclohexylcarbodiimide, and chromatography of the crude product on alumina gave the crystalline *N*-carbobenzyloxy-heptapeptide ester V. Hydrogenation of V over a palladium catalyst followed by addition of hydrogen chloride yielded the heptapeptide ester I.

EXPERIMENTAL

Melting points were taken on a Kofler Micro Hot Stage. Radial paper chromatograms[5] were done on 32-cm. Whatman No. 1 circles. The developing solvent mixtures are desig-

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