(10 ml.) to the filtrate was evaporated to dryness *in vacuo*. The residue, a mixture of the picrates of III and 1,6-dihydro-1,4-dimethylpyrimidin-6-one, was washed with methanol, and the crude product (1.3 g.) was recrystallized from ethanol to give the analytical sample, m.p. 188–190° dec. with sublimation (lit.[12] m.p. 188–190°).

Anal. Calcd. for $C_{12}H_{11}N_5O_8$: C, 40.80; H, 3.10. Found: C, 41.04; H, 3.35.

The Synthesis of Pyrrolo[1,2-*c*]pyrimidine (6-Azapyrrocoline)[1]

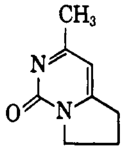
JOHN L. WONG, MELANCTHON S. BROWN,[2] AND HENRY RAPOPORT

Department of Chemistry, University of California, Berkeley, California

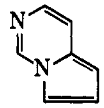
Received February 8, 1965

Pyrrolo[1,2-*c*]pyrimidine, or 6-azapyrrocoline, has been prepared by (a) cyclodehydrogenation of 3-(4-pyrimidyl)-1-propanol and (b) conversion of this propanol to the intermediate 6,7-dihydro-5H-pyrrolo[1,2-*c*]pyrimidinium *p*-toluenesulfonate followed by catalytic dehydrogenation. The intermediate propanol was synthesized from 4-methylpyrimidine *via* sodium borohydride reduction of esters of 3-(4-pyrimidyl)propenoic and 3-(4-pyrimidyl)propanoic acids. Approaches through 3-(4-pyrimidyl)-1,2-propanediol and 4-pyrimidinecarboxaldehyde were unsuccessful. The highly volatile pyrrolo[1,2-*c*]pyrimidine is similar to pyrrocoline in its ultraviolet and infrared absorption. Although its proton resonance is at low field, indicating aromaticity, it darkens rapidly at room temperature and is easily hydrogenated.

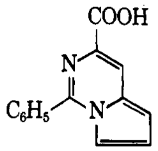
Degradation of saxitoxin, the paralytic shellfish poison, led to the isolation of 3-methyl-6,7-dihydro-5H-pyrrolo[1,2-*c*]pyrimidin-1-one (I), the structure of which was established by synthesis.[3] A literature search revealed that the corresponding parent aromatic system, pyrrolo[1,2-*c*]pyrimidine or 6-azapyrrocoline (II),[4] had never been prepared, and that only two reports of substituted pyrrolo[1,2-*c*]pyrimidines appear in the literature. One is a report[5] suggesting the 3-carboxy-1-phenyl derivative III as the structure of a product resulting from alkali treatment of the azlactone from 2-pyrrolaldehyde and hippuric acid. The second is a recent synthesis of the 3-methyl-6-phenyl derivative IV by a classical Chichibabin procedure using phenacyl bromide and 4,6-dimethylpyrimidine.[6] We now report the synthesis of the parent aromatic nucleus II.



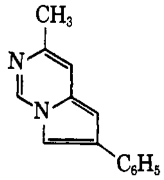
I



II



III



IV

Two general approaches were considered for the synthesis of pyrrolo[1,2-*c*]pyrimidine. One was based on the route which had been successful for the synthesis of the saxitoxin degradation product I[3] and envisaged fusion of a one-carbon unit with 2-pyrrylethylamine. However, the difficulties anticipated in ring closure to the poorly nucleophilic pyrrole nitrogen and subsequent aromatization led us to reject this approach. The other was patterned on methods which had resulted in several syntheses of pyrrocoline and involved suitably substituted 4-pyrimidines as intermediates, analogs of the substituted 2-pyridines previously used.

Our first choice of an intermediate which might be readily cyclized to pyrrolo[1,2-*c*]pyrimidine (II) was 3-(4-pyrimidyl)-1,2-propanediol (VI). This intermediate appeared readily accessible, and its use paralleled the conversion of the corresponding 3-(2-pyridyl)-[7] and 3-(2-quinolyl)-1,2-propanediols[8] to pyrrocolines. Thus 4-methylpyrimidine and diethyl oxalate gave a good yield of the α-keto ester V,[9] isolated as the potassium enolate. Reduction of V with sodium borohydride in methanol gave an oily mixture of products which contained primarily the diol VI plus some of the propanol VII. The propanol presumably arises *via* alkali-catalyzed elimination from the diol followed by reduction of the double bond.[10] Acetylation of the diol VI with acetic anhydride in pyridine gave a mixture of acetates, shown by n.m.r. analysis to be a 2:1 mixture of the diol diacetate VIII and the acetate of the propenol IX, plus a residue from which the propenol IX was obtained. The propenol most probably results from alkali-catalyzed elimination of water or acetic acid followed by hydrolysis of the propenol acetate during isolation. When acetylation was carried out with acetic anhydride–sodium acetate, the only product isolated was the propenol IX. (See Scheme I.)

With these intermediates in hand, various reactions were investigated to convert them to pyrrolo[1,2-*c*]pyrimidine (II). Pyrolysis of the mixture of acetates VIII and X at 450°, as described for the pyridine analog,[7] followed by steam distillation gave a small amount of material with a characteristic ultraviolet spectrum, later identified as that of II and containing

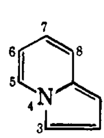
---

[1] Supported in part by the U. S. Army Research Office, Durham, N. C.

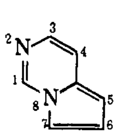
[2] Miller Research Fellow.

[3] W. Schuett and H. Rapoport, *J. Am. Chem. Soc.*, **84**, 2266 (1962).

[4] The accepted numbering systems for pyrrolo[1,2-*c*]pyrimidine and pyrrocoline are shown below. Thus the numbering system used depends on whether the compound is called a pyrrolo[1,2-*c*]pyrimidine or a 6-azapyrrocoline. We have used the former base in naming the two compounds in this series reported in the literature.[5,6]



pyrrocoline



pyrrolo[1,2-*c*]pyrimidine

[5] W. Herz, *J. Am. Chem. Soc.*, **71**, 3982 (1949).

[6] V. Boekelheide and S. S. Kertelj, *J. Org. Chem.*, **28**, 3212 (1963).

[7] V. Boekelheide and R. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959).

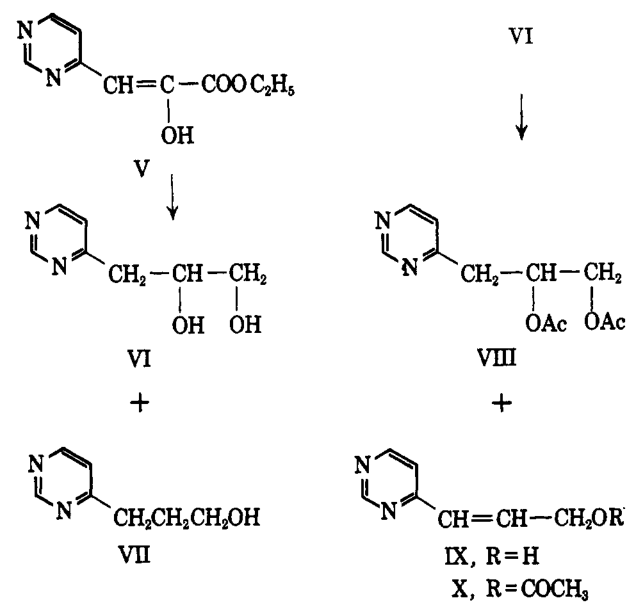
[8] E. Roberts, M. Gates, and V. Boekelheide, *J. Org. Chem.*, **20**, 1443 (1955).

[9] W. Pfleiderer and H. Mosthaf, *Ber.*, **90**, 728 (1957).

[10] Whereas double bonds are usually stable to sodium borohydride, compare the reduction of cinnamyl alcohol to 3-phenylpropanol by lithium aluminum hydride [F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3484 (1948)] and the reduction of several α,β-unsaturated esters to the saturated alcohols by sodium borohydride.[11]

[11] M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

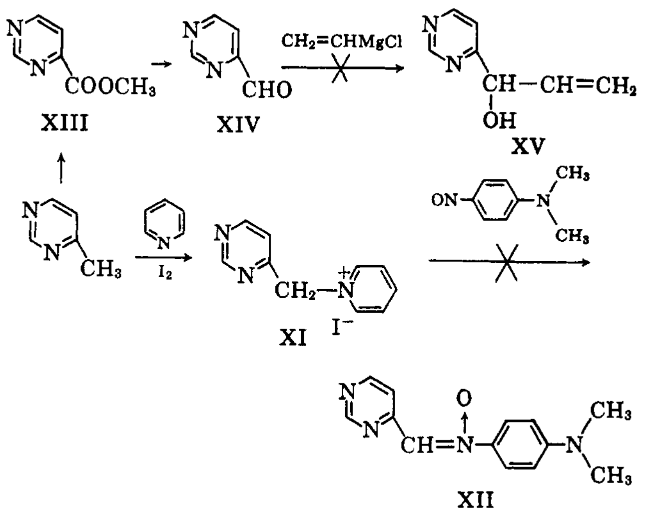
SCHEME I



several substances as judged from thin layer chromatography. Treatment of the diol VI with thionyl chloride in pyridine followed by sodium carbonate solution gave a low yield of material with the same characteristic spectrum. Similarly, a small amount of II, judged from ultraviolet absorption, resulted when the propenol IX was (1) heated with 30% palladium on carbon at 250° or (2) treated with hydrobromic acid followed by alkali[8] and steam distillation. Thus all the reactions did indeed give the desired pyrrolo[1,2-*c*]pyrimidine (II) but the yields were quite low.

These poor yields diverted our attention to another equally interesting intermediate, *viz.*, vinyl-4-pyrimidylcarbinol (XV), since the pyridyl analog has been converted to pyrrocoline in good yield.[7] An obvious preparation of the carbinol would be *via* the vinyl Grignard reagent and 4-pyrimidinecarboxaldehyde. However, the latter compound surprisingly had not been reported.[12] Several approaches were investigated for the conversion of 4-methylpyrimidine to 4-pyrimidinecarboxaldehyde without success. Attempted oxidation of the methyl group with selenium dioxide[13] resulted only in recovery of starting material. Ozonolysis of 4-styrylpyrimidine[14] in a manner analogous to that used for the preparation of 2-pyridinecarboxaldehyde from 2-styrylpyridine[15] gave only a very small amount of unidentified material and no aldehyde. The method of Krohnke[16] was then investigated. Condensation of 4-methylpyrimidine with pyridine and iodine gave the pyridinium salt XI in good yield, but reaction of this salt with *p*-nitrosodimethylaniline under a variety of conditions did not lead to the desired nitrone XII. (See Scheme II.)

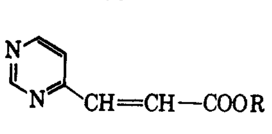
SCHEME II



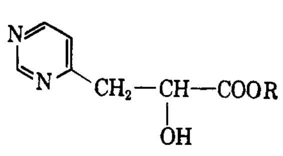
The recent report of the low-temperature lithium aluminum hydride reductions of π-deficient heterocyclic carboxylic esters to aldehydes[17] led us to apply this method to methyl 4-pyrimidinecarboxylate (XIII). When isolated as the 2,4-dinitrophenylhydrazone, a 66% yield of the aldehyde XIV was obtained. However, the free aldehyde was quite unstable and could be isolated directly from the reaction mixture in only 14% yield. Upon reaction with vinyl magnesium chloride,[18] none of the desired vinylcarbinol XV could be isolated.

These results led us to concentrate our efforts on 3-(4-pyrimidyl)-1-propanol (VII) as probably the most useful intermediate for the synthesis of pyrrolo[1,2-*c*]pyrimidine. The obvious route *via* reaction of 4-methylpyrimidine with phenyllithium and then ethylene oxide failed to give the propanol VII owing to competitive addition of phenyllithium to the pyrimidine ring.[19]

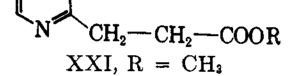
Although condensation with glyoxalates has not been used for such chain-lengthening purposes with active heterocyclic methyl groups, the reaction of 4-methylpyrimidine with excess *n*-butyl glyoxalate in pyridine was attempted and found to yield the unsaturated ester XVIII and the α-hydroxy ester XIX in the ratio of 1:4. On refluxing this mixture with acetic anhydride, it was converted completely to unsaturated ester, in a yield of 14% from 4-methylpyrimidine. Reduction of



XVI, R = H
XVII, R = CH_3
XVIII, R = $n\text{-}C_4H_9$



XIX, R = $n\text{-}C_4H_9$



XXI, R = CH_3
XX, R = H

---

[12] After this work was completed, the synthesis was reported of 4-pyrimidinecarboxaldehyde *via* the condensation of formamidine and (β-dimethylaminovinyl)glyoxal diethyl acetal: H. Brederick, R. Sell, and F. Effenberger, *Ber.*, **97**, 3407 (1964).

[13] R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

[14] S. Gabriel and J. Colman, *Ber.*, **36**, 3379 (1903).

[15] E. P. Hart, *J. Chem. Soc.*, 4540 (1952).

[16] F. Krohnke, *Angew. Chem.*, **65**, 605 (1953); F. Krohnke, H. Leister, and J. Vogt, *Ber.*, **90**, 2792 (1957).

[17] H. Rutner and P. E. Spoerri, *J. Org. Chem.*, **28**, 1891 (1963).

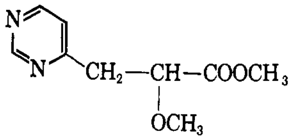
[18] H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, *ibid.*, **22**, 1602 (1957).

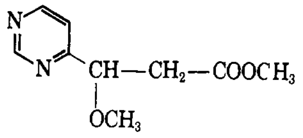
[19] T. D. Hayes and J. C. Roberts, *J. Chem. Soc.*, 328 (1951).

XVIII with sodium borohydride proceeded in good yield to the propanol VII.[11]

As a superior method for the preparation of an ester of the propenoic acid XVI,[20] it was esterified with methanolic hydrogen chloride to give the crystalline unsaturated methyl ester XVII,[11] plus a side product isolated from the mother liquors in 20% yield. As previously described,[11] reduction of the ester XVII gave the propanol VII in excellent yield.

The side product from the esterification was shown by analysis and spectral data to be a methoxy ester of either structure XXII or XXIII. It most likely arose by 1,4 addition, initiated either by protonation of the ester carbonyl followed by attack of methanol to give XXIII, or protonation of the pyrimidine ring leading to XXII. The latter is the most likely, considering the greater basicity of the heterocyclic ring as compared to the ester group.


XXII

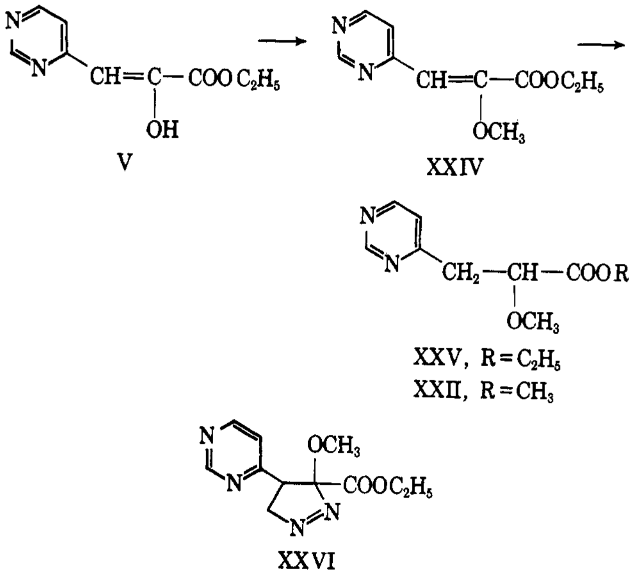

XXIII

To confirm this structural assignment, XXII was prepared by first treating the enol V with diazomethane, affording the enol ether XXIV. In one case, when treatment with diazomethane was extended for an overnight period, reaction proceeded beyond etherification to give the product of diazomethane addition to the double bond, ethyl 3-methoxy-4-(4-pyrimidyl)-Δ^1-pyrazoline-3-carboxylate (XXVI). The enol ether XXIV was hydrogenated to yield the α-methoxy ester XXV. Transesterification with methanol and a trace of acid afforded the methyl ester which was identical in infrared and ultraviolet absorption with the side product. Since the unsaturated ester XVII is unchanged by these transesterification conditions, elimination followed by readdition to form the β-methoxy ester XXIII could not have occurred, and the structure of the transesterified product, and hence of the side product, is established as XXII. (See Scheme III.)

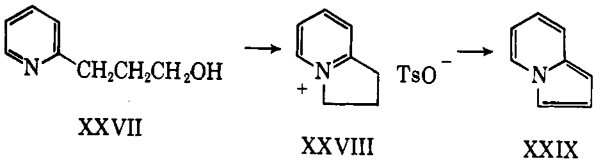
From the above reactions, the advantage of avoiding esterification of the unsaturated acid became clear. The best procedure for preparing propanol VII is to reduce the propenoic acid XVI to the propanoic acid XX, esterify to the methyl ester XXI, and reduce the latter with sodium borohydride.[11] This affords pure propanol VII in excellent yield.

Since the best method described to date for preparing pyrrocoline (XXIX)[7,21] is to heat 3-(2-pyridyl)-1-propanol with 30% palladium on carbon, this method was applied to 3-(4-pyrimidyl)-1-propanol (VII). When the propanol VII was heated with this catalyst at 250° for 4 hr., two products were obtained and separated by alumina chromatography. One was pyrrolo[1,2-*c*]pyrimidine (II), obtained in 5% yield, and the other was 4-ethylpyrimidine in 12% yield.[22] The yield of II is approximately one-seventh that obtained in the corresponding synthesis of pyrrocoline and is rationalized as due to the lower basicity of the pyrimidine compound as compared to the pyridine (a factor of 10^3). Attack at the nitrogen to give ring closure would thus be slower, and competing side reactions, not dependent on basicity, would predominate.

SCHEME III



To overcome this disadvantage, an alternative procedure was sought which would assure initial ring closure. As a model, 3-(2-pyridyl)-1-propanol (XXVII) was treated with tosyl chloride in pyridine to give a water-soluble product identified as 1,2-dihydro-3H-pyrrocolinium *p*-toluenesulfonate (XXVIII). Treatment of this salt with rhodium on alumina at 200° gave pyrrocoline (XXIX) in 60% yield. This two-step conversion of the propanol XXVII to pyrrocoline is thus comparable to the best previously reported synthesis of pyrrocoline.[7,21] A parallel procedure was then applied to the pyrimidylpropanol VII, the intermediate tosylate XXX being heated at 250° with rhodium on alumina. Although the yield was less than in the pyrrocoline case, a 9% yield of pure pyrrolo[1,2-*c*]pyrimidine (II) was isolated.



Pyrrolo[1,2-*c*]pyrimidine (II), m.p. 36–39°, has an odor reminiscent of naphthalene and pyrrocoline and an unusually high volatility which contributes to the difficulty in its isolation. Its infrared and ultraviolet spectra are very similar to those of pyrrocoline,[23] with the complex peaks between 260 and 300 mμ shifted approximately 10 mμ hypsochromically. However, its n.m.r. spectrum is less complex. A singlet at δ 8.84 is unambiguously assigned to the C-1 H, a triplet at δ 6.94 and a doublet at 6.5 are tentatively assigned to C-6 H and C-5 H, respectively, and an unsymmetrical doublet at δ 7.37 which integrates for three protons accounts for the C-3, 4, and 7 H. The low-field positions of these protons attest to the aromaticity of pyrrolo[1,2-*c*]pyrimidine, but it is easily perhydro-

---

[20] R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950).

[21] A. Galbriath, T. Small, R. A. Barnes, and V. Boekelheide, *ibid.*, **83**, 453 (1961).

[22] *Cf.* 2-ethylpyridine isolated from the cyclodehydrogenation of 3-(2′-pyridyl)-1-propanol.[21]

[23] V. Boekelheide and W. Feely, *J. Org. Chem.*, **22**, 589 (1957).

genated at room temperature in acidic ethanol over a platinum catalyst (as is pyrrocoline) and darkens rapidly on standing.

Experimental[24]

3-(4-Pyrimidyl)-1,2-propanediol (VI).—The potassium enolate of ethyl 4′-pyrimidylpyruvate (V),[9] 36 g. in 250 ml. of methanol, and a solution of 24 g. of sodium borohydride in 200 ml. of methanol were mixed, boiled for 4 hr., and stirred overnight. Most of the methanol was evaporated, 200 ml. of 25% aqueous sodium hydroxide was added, and the solution was extracted continuously with chloroform for 40 hr. giving 15 g. of an oil. Chromatography on silica gel and elution with methanol–chloroform (1:3) separated this oil into two components. The first compound eluted (3 g., 14% yield) was 3-(4-pyrimidyl)-1-propanol (VII). The second fraction was the diol (8 g., 33% yield), and short-path distillation at 100° (30 μ) gave the analytical sample as a clear, viscous oil: ultraviolet absorption, λ_{max} 245 mμ (ε 3500), 270 (450); n.m.r. absorption (D_2O), C-2′ H, δ 9.40 (s); C-6′ H, 9.00 (d); C-5′ H, 7.83; C-2 H, 4.50 (m); C-1 H_2, 3.97 (t); C-3 H_2, 3.25 (t).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.5; H, 6.4; N, 18.2.

3-(4-Pyrimidyl)-1-propenol (IX).—A mixture of 26.7 g. (0.17 mole) of the diol VI, 270 ml. of acetic anhydride, and 18 g. of sodium acetate was heated on the steam bath for 2 hr. Addition of 450 ml. of water and sufficient 10 *N* sodium hydroxide to make the solution strongly alkaline was followed by continuous extraction with ether. Evaporation of the ether and sublimation of the residue at 75° (20 μ) gave 4.6 g. (19% yield) of IX: m.p. 67–68° after crystallization from ether; λ_{max} 242 mμ (ε 10,900), 272 (11,300).

Anal. Calcd. for $C_7H_8N_2O$: C, 61.7; H, 5.9; N, 20.6. Found: C, 61.7; H, 6.0; N, 20.6.

Pyrimidine-4-methylenepyridinium Iodide (XI).—A mixture of 4.7 g. (50 mmoles) of 4-methylpyrimidine[25] plus 9.5 g. (75 mmoles) of iodine in 150 ml. of dry pyridine was refluxed for 3 hr. with stirring. Benzene (200 ml.) was added after cooling, and the mixture was stirred for 15 min. and filtered. The precipitate was extracted with six 50-ml. portions of boiling 2-propanol, and the combined extracts were decolorized with charcoal, concentrated, and cooled to yield 8.65 g. (58%) of the pyridinium salt XI, m.p. 175–176° dec.

Anal. Calcd. for $C_{10}H_{10}IN_3$: C, 40.2; H, 3.4; I, 42.4; N, 14.0. *Found*: C, 40.1; H, 3.3; I, 42.6; N, 13.8.

Methyl 4-Pyrimidinecarboxylate (XIII).—A solution of 20 g. (0.16 mole) of pyrimidine-4-carboxylic acid[26] [m.p. 234–235° dec., lit.[26] m.p. 236–237° dec., $\lambda_{max}^{H_2O\ pH\ 13}$ 253 mμ (ε 3850)] and 6 ml. of concentrated hydrochloric acid in 660 ml. of methanol was boiled for 8 hr. The resulting solution was neutralized with sodium bicarbonate, concentrated, and extracted with five 100-ml. portions of ether. The combined ether extracts were dried, concentrated, and cooled at −60° to give 19 g. (86%) of the ester XIII: m.p. 69–70°; λ_{max} 257 mμ (ε 6229), 300 sh (384); $\lambda_{max}^{CHCl_3}$ 5.75 (ester), 6.34 μ (pyrimidine).

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.2; H, 4.4; N, 20.3. Found: C, 52.1; H, 4.6; N, 20.2.

4-Pyrimidinecarboxaldehyde (XIV).—Methyl pyrimidine-4-carboxylate (XIII, 16 g., 0.12 mole) in 430 ml. of tetrahydrofuran was cooled to −67° under nitrogen and 170 ml. of 0.34 *M* lithium aluminum hydride in tetrahydrofuran was added with stirring over 30 min. Stirring was continued for another 15 min., 7 ml. of acetic acid was slowly added, and the resulting mixture was evaporated to dryness at 0° with the exclusion of light. Water (200 ml.) was added, the pH was adjusted to 4 with concentrated hydrochloric acid, and the solution was extracted with ten 50-ml. portions of chloroform. Washing the combined chloroform extracts with aqueous bicarbonate, drying, and evaporating at 0° gave 4.5 g. of viscous oil, from which fractional distillation afforded 1.82 g. (15%) of the aldehyde: b.p. 42–44° (0.7 mm.) (the extreme instability of the aldehyde resulted in significant polymerization during distillation); λ_{max} 245 mμ (ε 3431), 273 sh (377); λ_{max} 5.78 (aldehyde), 6.34 μ (pyrimidine); n.m.r. absorption, C-2 H, δ 9.35 (s); C-6 H, 8.93 (d); C-5 H, 7.58 (d); CHO, 9.95 (s).[12]

Anal. Calcd. for $C_5H_4N_2O$: C, 55.6; H, 3.7. Found: C, 55.7; H, 4.2.

The **2,4-dinitrophenylhydrazone** was prepared from the reduction product from 138 mg. (1 mmole) of ester by pouring the reaction mixture, after addition of acetic acid, into 55 ml. (1.1 mmoles) of saturated 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid, causing immediate precipitation. After 36 hr., the precipitate was removed, washed with 5% hydrochloric acid and water, and dried at 57° (2 mm.) for 15 hr. to give 0.19 g. (66%) of the 2,4-dinitrophenylhydrazone, m.p. 278–279° after recrystallization from chloroform.

Anal. Calcd. for $C_{11}H_8N_6O_4$: C, 45.8; H, 2.8; N, 29.2. Found: C, 45.6; H, 2.9; N, 29.1.

Butyl 3-(4-Pyrimidyl)propenoate (XVIII).—A mixture of 8.27 g. (88 mmoles) of 4-methylpyrimidine and 18.2 g. (0.14 mole) of butyl glyoxalate[27] in 24 ml. of pyridine was heated at 100° for 70 hr. The pyridine was evaporated, 30 ml. of acetic anhydride was added, and the solution was refluxed for 15 hr. Cooling and evaporating left a residue which was fractionally distilled to give 2.56 g. (14.1%) of the butyl ester XVIII: b.p 100–120° (50 μ); λ_{max} 277 (ε 13,660), 240 (12,970); λ_{max} 5.82 (ester), 6.08 (C═C), 6.35 μ (pyrimidine); n.m.r. absorption, C-2 H, δ 9.9 (s); C-6′ H, 9.46 (d); C-5′ H, 8.07 (d); C-2 and C-3 H, 8.00 (q); *n*-C_4H_9, 4.90 (t), 2.3 (m), 1.63 (t).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.9; H, 7.0; N, 13.9.

Esterification of 3-(4-Pyrimidyl)propenoic Acid (XVI).—To 100 ml. of 3% methanolic hydrogen chloride solution was added 5.01 g. (3.3 mmoles) of 3-(4-pyrimidyl)propenoic acid[20] and the mixture was refluxed for 2 hr. The resulting solution was poured into 100 ml. of water, neutralized with sodium bicarbonate, concentrated, and extracted with five 100-ml. portions of chloroform. The combined extracts were dried and evaporated to a residue which was crystallized from cyclohexane to give 3.66 g. (67%) of **methyl 3-(4-pyrimidyl)propenoate (XVII)**: m.p. 86–88°, lit.[11] m.p. 86–88; λ_{max} 277 mμ (ε 13,760), 242 (13,020).

Concentration of the mother liquor and cooling gave additional material which yielded, by chromatography on silicic acid with ether or fractional crystallization from cyclohexane, 1.0 g. (15.4%) of **methyl 2-methoxy-3-(4-pyrimidyl)propionate (XXII)**: m.p. 49–50°; λ_{max} 245 mμ (ε 3859), 270 sh (510); $\lambda_{max}^{CHCl_3}$ 5.78 (ester), 6.34 (pyrimidine), 8.95 μ (C–O–C); n.m.r. absorption, C-2′ H, δ 9.23 (s); C-6′ H, 8.75 (d); C-5′ H, 7.34 (d); C-2 H, 4.45 (t); C-3 H_2, 3.27 (d); C-2 OCH_3, 3.85 (s); $COOCH_3$, 3.46 (s); mass spectrum, *m/e* peaks 137 (1.00), 122 (0.2), 121 (0.27), 94 (0.13).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.2; N, 14.3. Found: C, 55.3; H, 6.0; N, 14.3.

Ethyl 2-Methoxy-3-(4-pyrimidyl)propenoate (XXIV).—The potassium enolate of ethyl 4-pyrimidylpyruvate[9] (25 g.) was dissolved in 150 ml. of water, 7 ml. of glacial acetic acid was added, and the precipitate was removed and recrystallized from ethanol to give 14.4 g. (70%) of **ethyl 2-hydroxy-3-(4-pyrimidyl)propenoate (V)**: m.p. 130–131°, lit.[9] m.p. 135–136°; λ_{max} 313 mμ (ε 13,960), 380 (6600); n.m.r. absorption, C-2′ H, δ 9.12 (s); C-6′ H, 8.75 (d); C-5′ H, 7.24 (d); C-3 H, 6.52 (s); $COOCH_2CH_3$, 4.46 (q), 1.52 (t).

This enol ester (340 mg., 175 mmoles) in 40 ml. of dry ether was stirred with 100 ml. of ethereal diazomethane solution (12 mmoles) at room temperature for 15 hr. Evaporation of the solvent and crystallization of the residue from cyclohexane followed by sublimation at 60° (20 μ) yielded yellow crystals of **ethyl 3-methoxy-4-(4-pyrimidyl)-Δ^1-pyrazoline-3-carboxylate (XXVI)**: m.p. 76–77°; λ_{max} 245 mμ; $\lambda_{max}^{CHCl_3}$ 5.72 (ester), 6.3 μ (pyrimidine); n.m.r. absorption, C-2′ H, δ 9.12 (s); C-6′ H, 8.75 (d); C-5′ H, 7.24 (d); C-3 OCH_3 and C-4 H, 3.7 (s); C-5 H_{cis}, 5.35 (d), J = 5 c.p.s.; C-5 H_{trans}, 5.08 (d), J = 9 c.p.s.; $COOCH_2CH_3$, 4.46 (q), 1.52 (t).

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.8; H, 5.6; N, 22.4. Found C, 52.8; H, 5.7; N, 22.7.

---

[24] All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley; all evaporations were made *in vacuo* using a rotary evaporator. Ultraviolet spectra were taken in ethanol, infrared neat, and n.m.r. in deuteriochloroform (reported as δ values referred to internal tetramethylsilane, δ 0) unless otherwise specified.

[25] V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955); H. Brederick, *Org. Syn.*, **43**, 77 (1963).

[26] J. F. W. McOmie and I. M. White, *J. Chem. Soc.*, 3129 (1953).

[27] F. J. Wolf and J. Weijlard, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 124.

Treatment of the enol ester (0.592 g., 3.33 mmoles) in 50 ml. of dry ether with 200 ml. of ethereal diazomethane (24 mmoles) for 4 hr. at room temperature, evaporation of the solvent, and distillation of the residue at 50–60° (20 μ) gave 0.52 g. (82%) of **ethyl 2-methoxy-3-(4-pyrimidyl)propenoate (XXIV)**: λ_{max} 290 mμ (ϵ 33,040); λ_{max} 5.79 (ester), 6.1 (C=C), 6.34 (pyrimidine), 9.04 (C–O–C), 10.1 μ (=CH); n.m.r. absorption, C-2′ H, δ 9.36 (s); C-6′ H, 8.84 (d); C-5′ H, 8.1 (d); C-3 H, 6.95 (s); C-2 OCH_3, 4.04 (s); $COOCH_2CH_3$, 4.45 (q), 1.47 (t).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5. Found:. C, 57.4; H, 5.7; N, 14.2.

Methyl 2-Methoxy-3-(4-pyrimidyl)propionate (XXII).—Ethyl 2-methoxy-3-(4-pyrimidyl)propenoate (XXIV, 0.303 g., 1.46 mmoles) in 10 ml. of absolute ethanol was hydrogenated over 50 mg. of 10% palladium on charcoal at an initial pressure of 3 atm. for 6 hr. Hydrogen pick-up ceased, and the resulting mixture was filtered, the filtrate was evaporated, and the residual oil was distilled at 70° (20 μ) to give 0.19 g. (62%) of **ethyl 2-methoxy-3-(4-pyrimidyl)propionate (XXV)**: λ_{max} 244 mμ (ϵ 3442), 273 sh (405); n.m.r. absorption, C-2′ H, δ 9.23 (s); C-6′ H, 8.75 (d); C-5′ H, 7.34 (d); $COOCH_2$ and C-2 H, 4.38 (q); C-2 OCH_3, 3.47 (s); C-3 H_2, 3.28 (d); $COOCH_2CH_3$, 1.43 (t).

A mixture of 51 mg. (0.24 mmole) of the saturated ester in 10 ml. of dry methanol plus 10 μl. of concentrated sulfuric acid was refluxed for 5 hr. The solution was cooled, neutralized with sodium bicarbonate, dried, and filtered. Evaporation of the filtrate and sublimation of the residue at 40–50° (10 μ) afforded 28 mg. (59%) of **methyl 2-methoxy-3-(4-pyrimidyl)propionate (XXII)**, m.p. 48–49°, identical in all respects with material isolated from the direct esterification of 3-(4-pyrimidyl)propenoic acid, above.

Methyl 3-(4-Pyrimidyl)propionate (XXI).—To a solution of 6 ml. of concentrated sulfuric acid in 60 ml. of methanol was added 7.45 g. (49 mmoles) of **3-(4-pyrimidyl)propionic acid (XX)**.[20] The solution was refluxed for 17 hr., cooled, added to 100 ml. of ice–water, neutralized with concentrated aqueous ammonia, concentrated, and continuously extracted with ether for 24 hr. The ether extracts were dried and evaporated and the residue was distilled at 60–70° (40 μ), giving 6.6 g. (81.1%) of **methyl 3-(4-pyrimidyl)propionate**: λ_{max} 245 mμ (ϵ 3450), 270 (320); λ_{max} 5.8 (ester), 6.31 μ (pyrimidine); n.m.r. absorption, C-2′ H, δ 9.14 (s); C-6′ H, 8.62 (d); C-5′ H, 7.35 (d); $COOCH_3$, 3.54 (s); C-2 H_2 and C-3 H_2, 2.9 (m).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.7; H, 6.1; N, 17.1.

Reduction of butyl 3-(4-pyrimidyl)propenoate (XVIII) and methyl 3-(4-pyrimidyl)propionate (XXI) to 3-(4-pyrimidyl)propanol (VII) by sodium borohydride was carried out in the manner reported.[11]

1,2-Dihydro-3H-pyrrocolinium *p*-Toluenesulfonate (XXVIII).—To a mixture of 5 g. (36.5 mmoles) of 3-(2-pyridyl)-1-propanol (XXVII) and 50 ml. of pyridine at −15° was added 7.65 g. (40.2 mmoles) of *p*-toluenesulfonyl chloride. The suspension was stirred for 2 hr. at −10°, 5 ml. of ice–water was added, the resulting solution was diluted with 50 ml. of water, the pH was adjusted to 9 with 6 *N* sodium hydroxide, and the solution was continuously extracted with ether for 3 hr. The aqueous phase was then adjusted to pH 1 with concentrated hydrochloric acid and evaporated to dryness, and the residue was digested with six 20-ml. portions of absolute ethanol. Evaporation of the combined extracts with crystallization of the residue from ethanol–ether gave 7 g. (66%) of the tosylate salt XXVIII: m.p. 120–121°, lit.[28] m.p. 120–122°; ultraviolet absorption, λ_{max} 220 mμ (ϵ 12,660), 264 (5210), 271 sh (3900); λ_{max}^{Nujol} 6.12 (pyridine), 9.72, 9.92 μ (tosylate ion); n.m.r. absorption (D_2O), C-4, -5, -6, and -7 H and toluene C-2′, -3′, -5′ and -6′ H, δ 7.10–8.77 (m); C-3 H_2, 4.81 (t); C-1 H_2, 3.52 (t); C-2 H_2, 2.47 (m); C-1′ CH_3, 2.35 (s).

Anal Calcd. for $C_{15}H_{17}NO_3S$: C. 61.9; H, 5.9; N, 4.8; S, 11.0. Found: C, 61.8; H, 5.9; N, 4.9; S, 11.0.

Pyrrocoline (XXIX).—The above tosylate (1 g.) was heated with 0.4 g. of 5% rhodium on alumina at 200° for 2.5 hr. under a slow nitrogen sweep and 0.24 g. (60%) of pyrrocoline, m.p. 73–74°, was collected on the cold finger. All physical properties were identical with those reported.[23]

6,7-Dihydro-5H-pyrrolo[1,2-*c*]pyrimidinium *p*-Toluenesulfonate (XXX).—To a mixture of 1 g. (7.24 mmoles) of 3-(4-pyrimidyl)propanol (VII) and 10 ml. of pyridine at −15° was added 3.07 g. (16.1 mmoles) of *p*-toluenesulfonyl chloride which dissolved to give a yellow solution on stirring for 10 min. Precipitation occurred after 0.5 hr., and the solution was stirred for another 0.5 hr. before it was acidified to pH 3.5 with cold 3 *N* sulfuric acid (34 ml.). The resulting solution was extracted with five 60-ml. portions of cold ether, and the combined ether extracts were washed with 30 ml. of cold aqueous sodium bicarbonate and 50 ml. of ice–water. Drying and evaporating left a residue which was crystallized from ethanol–ether to give 1.35 g. (63.6%) of the pyrimidine tosylate: m.p. 131–133°; λ_{max} 297 mμ (ϵ 2620), 249 (3580), 220 (12,360); λ_{max}^{Nujol} 6.3 (pyrimidine), 9.7, 9.9 μ (tosylate ion); n.m.r. absorption (D_2O), C-1 H, δ 9.54 (s); C-3 H, 9.12 (d); C-4 H, 8.04 (d); C-7 H_2, 4.85 (t); C-5 H_2, 3.54 (t); C-6 H_2, 2.46 (m); C-2′, -3′, -5′, and -6′ H, 7.41 (q); C-1′ CH_3, 2.33 (s).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.5; H, 5.5; N, 9.6. Found: C, 57.1; H, 5.5; N, 9.3.

Pyrrolo[1,2-*c*]pyrimidine (II). A. *Via* the Pyrimidine Tosylate XXX.—The above pyrimidine salt (83 mg.) was heated with 160 mg. of 5% rhodium on alumina at 260° for 2.5 hr. under a steady nitrogen sweep which was led through an ether solution at −60°. The resulting ether solution was dried and evaporated, and the yellow residue was sublimed at 35° (1 mm.) giving 3 mg. (9%) of pyrrolo[1,2-*c*]pyrimidine, homogeneous on thin layer chromatography with ether on silicic acid: m.p. 36–39°; λ_{max} 229 mμ (ϵ 27,400), 272 (5450), 283 (5900), 345 (1080); $\lambda_{max}^{CHCl_3}$ 3.52 6.92, 7.24, 7.41, 8.71, 9.1, 9.31, 11.85 μ; n.m.r. absorption, C-1 H, δ 8.84 (s); C-3, -4, and -7 H, 7.37 (unsym. d); C-6 H, 6.94 (t); C-5 H, 6.5 (d).

Anal. Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.2; H, 5.1; N, 23.9.

The **picrate** was prepared with ethanolic picric acid and was crystallized from ethanol; m.p. 162–165°.

Anal. Calcd. for $C_{13}H_9N_5O_7$: C, 45.0; H, 2.6; N, 20.2. Found: C, 45.0; H, 2.8; N, 20.1.

B. Directly from 3-(4-Pyrimidyl)propanol (VII).—A mixture of 2.2 g. (15.9 mmoles) of 3-(4-pyrimidyl)propanol and 0.2 g. of 30% palladium on charcoal was heated at 180° for 4 hr. and 260° for 4 hr. under a slow nitrogen sweep connected to two cold traps at −60°. The reaction mixture was cooled and extracted with five 50-ml. portions of ether, and the combined ether extracts were dried, concentrated, and chromatographed on alumina (neutral, activity III) with pentane as eluent. Fractions containing pyrrolo[1,2-*c*]pyrimidine (II) (as shown by ultraviolet absorption and thin layer chromatography) were combined, evaporated, and sublimed at 35° (1 mm.), giving 94 mg. (5%) of white crystalline product, m.p. 36–39°, identical with material prepared above *via* the tosylate. Another major component (0.2 g., 12%) from the chromatogram was 4-ethylpyrimidine, with ultraviolet and infrared absorption similar to 4-methylpyrimidine: n.m.r. absorption, C-2 H, δ 8.95 (s); C-6 H, 8.41 (d); C-5 H, 7.05 (d); C-4 CH_2CH_3, 2.63 (q), 1.12 (t).

---

[28] O. G. Lowe and L. C. King, *J. Org. Chem.*, **24**, 1200 (1959). The pyrrocolinium salt was prepared by selective hydrogenation of pyrrocoline in hydrobromic acid, removal of bromide ion with silver oxide, and neutralization with *p*-toluenesulfonic acid.