the hygroscopic betaine (1.2 g, 80%), which decomposes on attempted recrystallization: IR ($CHBr_3$) 1650 (s), 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 7.6–8.4 (m, 10 H), 8.8 (d, 1 H, J = 2 Hz), 8.95 (d, 1 H, J = 2 Hz).

1,4,6-Triphenylpyridinium-2-carboxylate (11). 2-(Ethoxycarbonyl)-1,4,6-triphenylpyridinium tetrafluoroborate (**8a**; 5 g, 10.7 mmol) was stirred at 25 °C as a suspension in aqueous NaOH (0.5 N, 25 mL, 12.5 mmol) for 24 h. The white solid was filtered off and washed with water (500 mL) and ether (50 mL) to give the betaine as microcrystals: 3.2 g (85%); mp 150 °C dec (satisfactory analysis not obtained due to decomposition on attempted recrystallization); IR ($CHBr_3$) 1650 (s), 1618 (s) cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.5–7.9 (m, 15 H), 8.10 (d, 1 H, J = 2 Hz), 8.38 (d, 1 H, J = 2 Hz).

1,2,4-Triphenylpyridinium iodide (13) was obtained by refluxing 1,4,6-triphenylpyridinium-2-carboxylate (11) (2 g, 5.7 mmol) with aqueous HI (65%, 1.20 g, 6.1 mmol) in THF (50 mL) for 4 h to yield yellow crystals (washed with ether). Recrystallization from absolute EtOH gave yellow needles: 2.1 g (85%); mp 273–274 °C; IR ($CHBr_3$) 1630 cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.6–7.9 (m, 15 H), 8.10 (d, 1 H, J^m = 2 Hz), 8.43 and 8.5 (dd, 1 H, J^m = 2 Hz, J^o = 7 Hz), 9.38 (d, 1 H, J^o = 7 Hz). Anal. Calcd for $C_{23}H_{18}NI$: C, 63.5; H, 4.1; N, 3.2; I, 29.2. Found: C, 63.1; H, 4.1; N, 3.2; I, 29.4.

ANRORC Reaction. Method A. The 2-(ethoxycarbonyl)-pyridinium salt (2 mmol) was stirred in CH_2Cl_2 (10 mL) for 12 h with the amine (3–6 mmol) at 25 °C. The yellow solution was concentrated in vacuo (25 mmHg) and triturated with Et_2O.

Deethoxycarbonylation with Amines. Method B. The 2-(ethoxycarbonyl)pyridinium salt (2 mmol) refluxed in EtOH (5 mL) with *tert*-butylamine (6 mmol) for 12 h. The resulting red solution was concentrated in vacuo (25 mmHg) and residue triturated with Et_2O to give a white solid which was recrystallized from ethanol.

Reaction of Maleimides and Ethyl 3-Aminocrotonates. A Reinvestigation Leading to an Improved Synthesis of Pyrrolo[3,4-*c*]pyridines[1]

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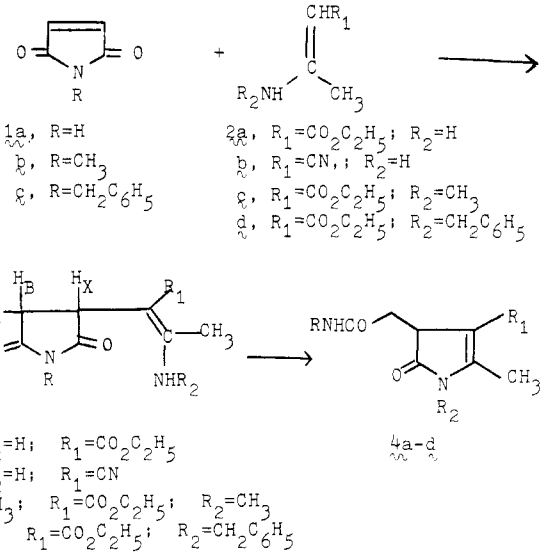
Conditions employed for the reaction between maleimides and ethyl aminocrotonates were shown to yield pyrrolo[3,4-*c*]pyridines rather than the previously reported pyrrolo[2,3-*b*]pyrroles.

The condensation of maleimide (**1a**) and 3-aminocrotonates or 3-aminocrotonitrile in a Nenitzescu-type reaction[2] has been reported[3] to give adducts **3** and **4** (Scheme I). Cyclization under basic conditions was claimed[3] to yield pyrrolo[2,3-*b*]pyrroles, which were converted to various derivatives (e.g., **5–7**).[4] During the preparation of additional derivatives,[5] several observations raised doubts about the structural assignments for compounds **5–7**, and data are presented to account for these observations and the new structural assignment.

Scheme I



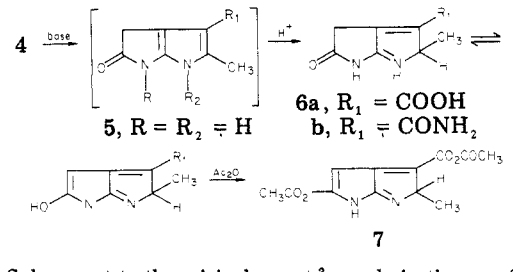
When *N*-methylmaleimide (**1b**, R = CH_3) was treated with ethyl 3-(methylamino)crotonate (**2c**; R_1 = $CO_2C_2H_5$, R_2 = CH_3), an adduct, ethyl 3-(methylamino)-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)crotonate (**3c**; R = R_2 = CH_3, R_1 = $CO_2C_2H_5$) was isolated and characterized. The NMR spectrum of the product obtained upon cyclization[3]

(1) Taken in part from the Ph.D. Dissertation of K.R.S., University of Georgia, Dec 1979.

(2) (a) C. D. Nenitzescu, *Bull. Sci. Chim. Rom.*, 11, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930); (b) M. T. Weiss, G. R. Allen, Jr., G. J. Gibs, C. Pidacks, J. F. Poletto, and W. A. Remers, *Top. Heterocycl. Chem.*, 178 (1969).

(3) C. D. Blanton, Jr., J. F. Whidby, and F. H. Briggs, *J. Org. Chem.*, **25**, 3929 (1971).

(4) The original pyrrolo[2,3-*b*]pyrrole structural assignment[3] was based on elemental analysis, NMR and IR spectroscopy, and the preparation of several derivatives (e.g., **7**):

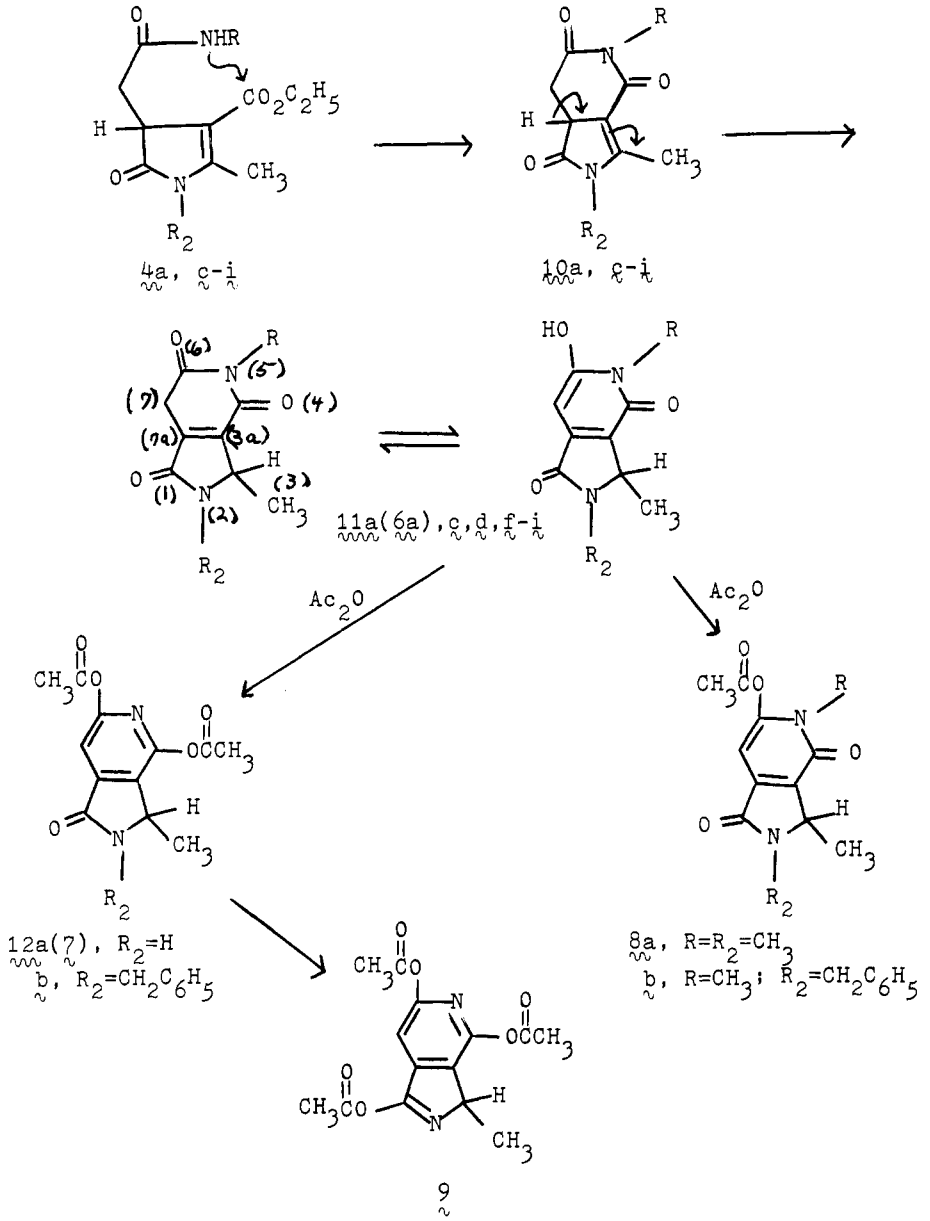


(5) Subsequent to the original report,[3] one derivative was found to possess marginal antineoplastic activity, and further studies were suggested in an effort to exploit this potential lead. Compound **7** (structure reassigned as **12a**) had T/C (test/control) ratios of 133 and 126 at 200 mg/kg in the 3PS31 (P388 lymphocytic leukemia) system and, therefore, met the criterion for activity (T/C = 125). This compound was also active in the 9KB5 (human epidermoid carcinoma of the nasopharynx) cell culture system, but it was inactive against 3B131 (B16 melanocarcinoma), 3CD72 ($CD8F_1$ mammary tumor), 3C872 (colon 38), 3LE21 (L1210 lymphoid leukemia), 3LL39 (Lewis lung carcinoma), 3C2G5 (CX-1 colon xenograft), and 3MBG5 (MX-1 breast xenograft), according to the standard protocol of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.[6]

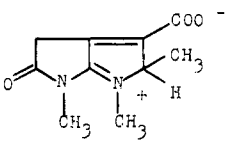
(6) (a) R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3**(2), 1, 1972; (b) "Instruction Booklet 14, Screening Data Summary Interpretation", Drug Research and Development, Chemotherapy, National Cancer Institute: Bethesda, MD, 1972.

0022-3263/82/1947-0502$01.25/0

Scheme II



of adduct **3c** showed a doublet at δ 1.40 (3 H, J = 6.0 Hz) for the 2-methyl protons coupled to the proton at C_2, which appeared as a quartet centered at δ 4.35 (1 H, J = 6.0 Hz). The existence of this NMR pattern in the suspected pyrrolo[2,3-*b*]pyrroles would have required the isolation of the unlikely quaternary species **6c**. This observation



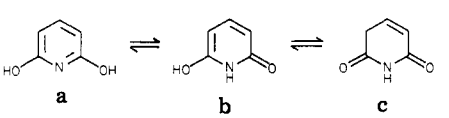
6c

raised a question about the structural assignment for **5** and **6**. Furthermore, treatment of **5c** with acetic anhydride gave a monoacetylated derivative (**8**), whereas **6a** yielded the diacetylated derivative **7**. Subsequently, **6a** was treated with acetic anhydride for longer periods of time, and a product (**9**) was isolated which analyzed as a triacetylated derivative.

A possible alternative structure for **5** and **6**, which could account for these observations, is presented in Scheme II. Formation of a pyrrolo[3,4-*c*]pyridine (**11**) ring system rather than a pyrrolo[2,3-*b*]pyrrole could accommodate the various acetylated products (**8**, **9**, **12**), as well as the NMR spectral data.[7] The NMR and IR data support the predominance of the enol form in polar solvents, while the keto form appears to predominate in nonpolar solvents and in solid-phase IR samples. This is consistent with the tautomerism observed in different pyridones.[8]

(7) Although **8** is designated here as the 6-acetoxy tautomer, it is possible for **8** to exist as the 4-acetoxy tautomer. No attempt was made to distinguish between the two possible isomers. Similar isomers may exist for **12** (**7**).

(8) (a) H. Tieckelmann in "Heterocyclic Compounds", Vol. 14, Supplement, Part 3, R. A. Abramovitch, Ed., Wiley, New York, 1974, p 597. (b) Glutaconimide, for example, has been shown to exist predominately in lactam forms, mainly as 6-hydroxy-2-pyridone (a/b/c ratio of 25:60:15)[9] in polar solvents.



a b c

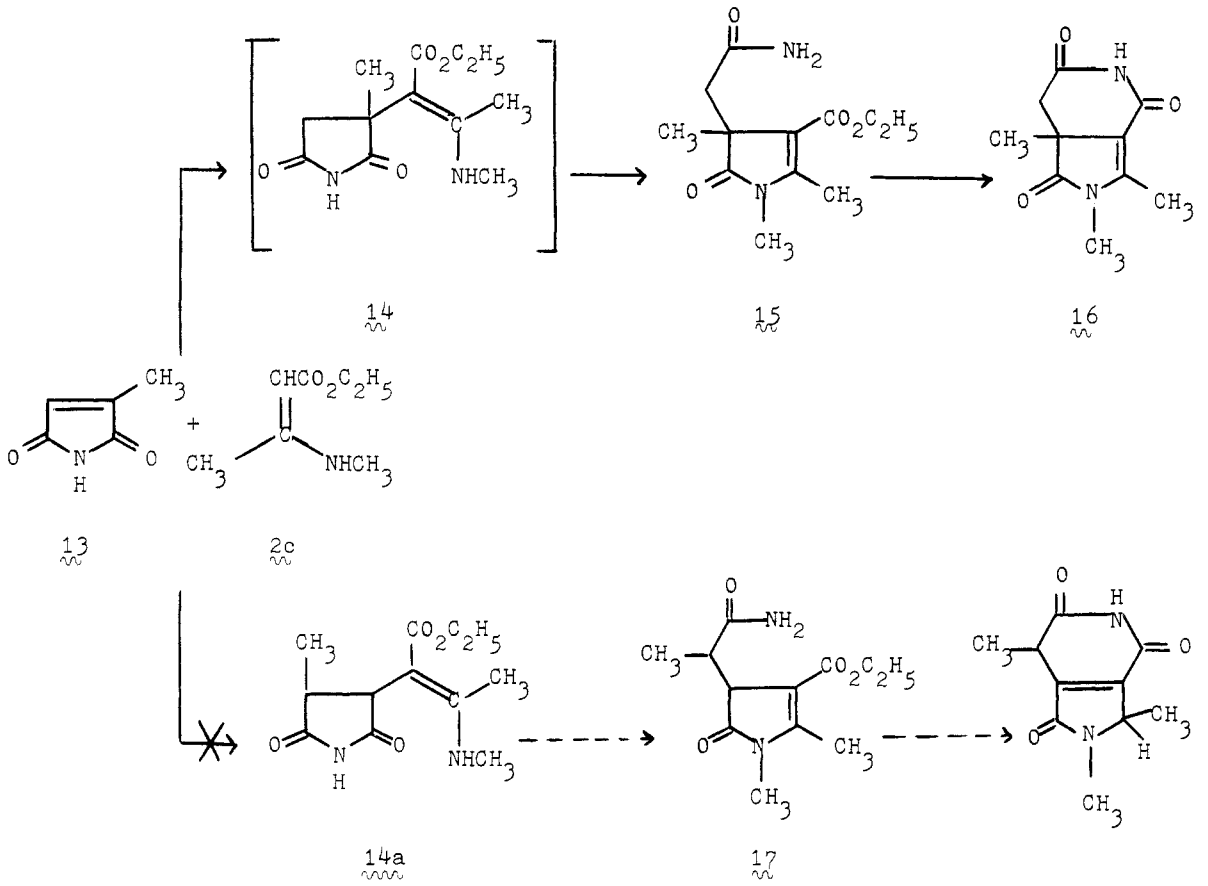
(9) E. Spinner and J. C. B. White, *J. Chem. Soc. B*, 991 (1966).

Table I. Condensation Products from Maleimides and 3-Aminocrotonates

	R	R_1	R_2	% yield (solvent)	mp, °C	formula [b]
3d	H	$CO_2C_2H_5$	$CH_2C_6H_5$	48 (EtOH)	140-142	$C_{17}H_{20}N_2O_4$
3e	$CH_2C_6H_5$	$CO_2C_2H_5$	H	58 (benzene)	133-137	$C_{17}H_{20}N_2O_4$
3f	CH_3	$CO_2C_2H_5$	$CH_2C_6H_5$	58 (EtOH)	89-90	$C_{18}H_{22}N_2O_4$
3g	$CH_2C_6H_5$	$CO_2C_2H_5$	$CH_2C_6H_5$	25 (EtOH)	100-107	$C_{24}H_{26}N_2O_4$
4h [a]	$CH_2C_6H_5$	$CO_2C_2H_5$	CH_3	54 (benzene	119-123	$C_{18}H_{22}N_2O_4$
4i [a]	H	$CO_2C_2H_5$	CH_3	43 (benzene)	119-123	$C_{11}H_{16}N_2O_4$
3j	CH_3	$CO_2C_2H_5$	H	56 (EtOH)	130-133	$C_{11}H_{16}N_2O_4$
4d [a]	H	$CO_2C_2H_5$	$CH_2C_6H_5$	74 (EtOH)	122-125	$C_{17}H_{20}N_2O_4 \cdot H_2O$

[a] Products 4d,h,i were obtained directly without the isolation of intermediates 3d,h,i. [b] Satisfactory analytical data (±0.3 % for C, H, and N) were reported for all compounds in this table.

Scheme III



Synthesis of an additional derivative, in which only one of the nitrogen atoms was substituted, was undertaken to further substantiate the trend seen for acetylation of 2,5-unsubstituted pyrrolo[3,4-*c*]pyridines (**11a**) and 2,5-disubstituted pyrrolo[3,4-*c*]pyridines (**11c**). Ethyl 3-(benzylamino)crotonate (**2d**) was obtained from ethyl acetoacetate and benzylamine.[10] Condensation of **2d** with maleimide **1a** gave an adduct **3d** which was cyclized by the standard procedure[3] to yield **11d** ($R_2 = CH_2C_6H_5$, R = H). When **11d** was subjected to acetylation, the product analyzed correctly for the expected diacetylated derivative (**12b**, $R_2 = CH_2C_6H_5$).

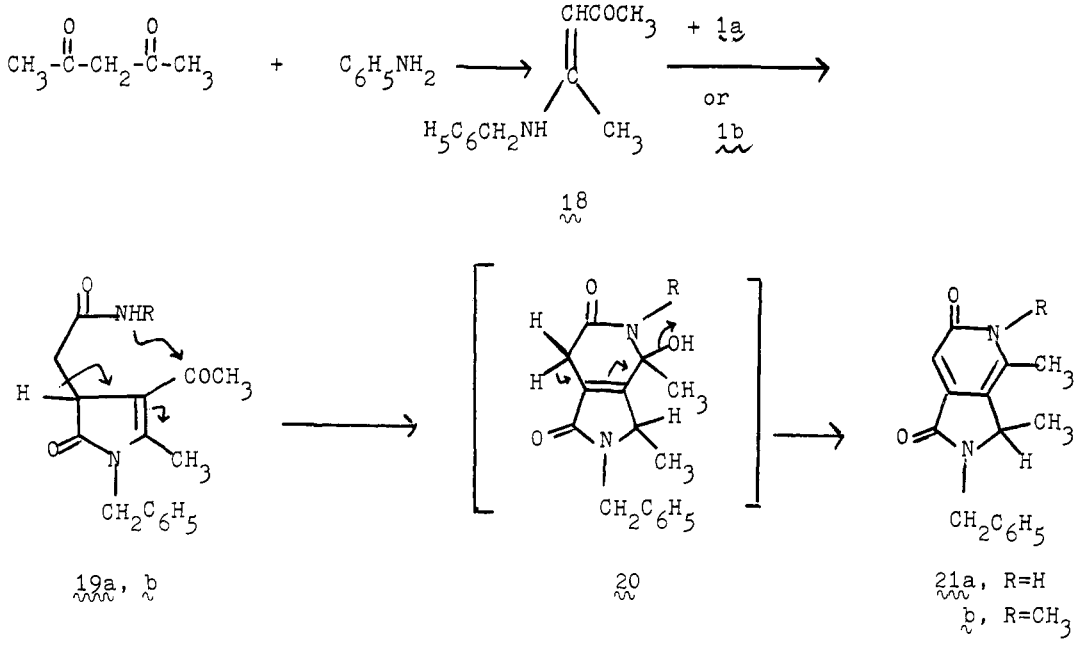
As previously noted,[3] intermediates **3** and **4** were readily isolated and characterized. However, since cyclization to the pyrrolopyridines could be achieved by utilizing either **3** or **4**, many of the intermediates related to **4** were not characterized (see Table I). Intermediates relates to **10** (Scheme II) were not readily isolated, but in one experiment this proposed cyclized intermediate (**10e**; R_2 = H, $R = CH_2C_6H_5$) was isolated and characterized, albeit in low yield (ca. 15%). In this case, *N*-benzylmaleimide (**1c**) was condensed with ethyl 3-aminocrotonate (**2a**) to yield ethyl 3-amino-2-(1-benzyl-2,5-dioxopyrrolidin-2-yl)crotonate (**3e**). When **3e** was treated with potassium *tert*-butoxide in *tert*-butyl alcohol,[3] 5-benzyl-3-methyl-1,4,6-trioxo-2,4,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-*c*]pyridine (**10e**) was obtained. The important NMR characteristics for **10e** are the doublet at δ 2.39 (3 H, J = 2.0 Hz) for protons of the 3-methyl group and the multiplets at δ 2.75 (2 H) and 3.6 (1 H) for the C_7 and C_{7a} protons, respectively. The long-range coupling of the C_3 methyl and the C_{7a} proton is similar to that seen in some cases for compounds with structure **4**.[3]

A derivative was also designed (Scheme III) such that the proton at position 7a in **10** could not be lost for rearrangement of the 3,3a double bond and subsequent formation of type-**11** compounds. For the synthesis of citraconimide **13**, the procedure of Tawney and co-workers[11]

(10) E. A. Steck, R. Pauline, and L. T. Fletcher, *J. Org. Chem.*, **24**, 1750 (1959).

(11) P. O. Tawney, R. H. Snyder, C. E. Bryan, R. P. Conger, F. S. Dovell, R. J. Kelly, and C. H. Stitler, *J. Org. Chem.*, **25**, 56 (1960).

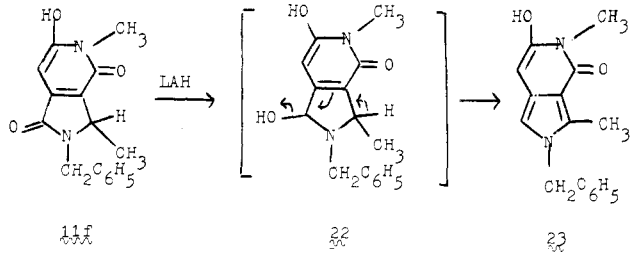
Scheme IV



was utilized. When **13** was refluxed with **2c** in acetone for 21 h, only the acetamide intermediate **15** could be isolated and characterized. Intermediate **14** and the possible isomeric acetamide derivative **17** were not detected. That compound **15** was the only product isolated by this procedure, and not the alternative isomer **17**, was supported by the NMR spectra. The methyl peaks for N_1, C_2, and C_4 were observed as singlets at δ 3.09, 2.45, 1.3, respectively. Compound **17** would be expected to exhibit splitting patterns for the α-methyl group in the 4-acetamido moiety, as well as long-range coupling between the C_2-methyl and the C_4-hydrogen. These latter splitting patterns were not observed, and hence it was concluded that isomeric compound **17**, although possible, was not isolated in this procedure. Treating **15** with potassium *tert*-butoxide led to the expected cyclized product **16**. The isolation and characterization of **16**, along with the spectral data, further confirms the structural assignment and the proposed reaction pathway.

As an extension of this route for synthesis of pyrrolopyridines, two additional derivatives were synthesized, **21a,b** (Scheme IV). In this sequence ethyl 3-(alkylamino)crotonates were replaced by 2-(benzylamino)prop-1-enyl methyl ketone (**18**).[12] The structural assignments for **21** were substantiated by IR, NMR, and elemental analyses.

As a final note, one of the analogues, 2-benzyl-6-hydroxyl-3,5-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (**11f**), upon reduction with lithium



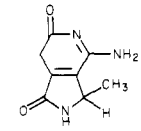
aluminum hydride, gave 2-benzyl-6-hydroxyl-3,5-dimethyl-4-oxo-4,5-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine (**23**). This is consistent with the assigned structure and the observed reduction pattern in related lactams.[13]

The condensation of ethyl 3-aminocrotonates (**2**) or 2-aminoprop-1-enyl methyl ketones (e.g., **18**) with maleimides followed by base-catalyzed cyclization affords a convenient method for the synthesis of a variety of pyrrolo[3,4-*c*]pyridines[14] by a route involving fewer steps and generally less vigorous conditions than those reported by other investigators.[15,16]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 467 grating spectrophotometer. The NMR spectra were obtained on a 60-MHz Hitachi Perkin-Elmer R20A high-resolution spectrometer using Me_4Si as an internal standard. Mass spectra were determined on a Du Pont 21-490 low-resolution mass spectrometer. Microanalyses were performed by Atlantic Microlab, Inc. TLC was performed on Eastman chromatogram sheets, Type 6060, coated with silica gel.

Ethyl 3-(Methylamino)-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)crotonate (3c). A mixture of 2.22 g (0.02 mol) of *N*-methylmaleimide (**1b**) and 2.85 g (0.02 mol) of ethyl 3-(methylamino)crotonate (**2c**) in 15 mL of acetone was refluxed for 24 h. The solution was cooled and concentrated to dryness in vacuo, and the viscous residue was washed with petroleum ether. Recrystallization from absolute ethanol afforded 2.3 g (45%) of the desired product as a white solid: mp 127–130 °C; IR(KBr) 3260,



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(12) L. Rugheimer and G. Ritter, *Ber.*, **45**, 1332 (1912).

(13) P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, 71, 3206 (1949).

(14) By analogy, when 3-aminocrotonitrile (**2b**) is reacted with maleimide, **6b**[3,4] becomes the 4-amino-substituted pyrrolo[3,4-*c*]pyridine **24** rather than the pyrrolo[2,3-*b*]pyrrole **6b**.

(15) S. M. Gadekar, J. L. Frederick, J. Semb, and J. R. Vaughan, Jr., *J. Org. Chem.*, **26**, 468 (1961).

(16) W. B. Wrights, Jr., J. S. Webb, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **79**, 2199 (1957).

1770, 1685, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.0 Hz, CH_3 of ethyl), 2.0 (s, 3 H, vinyl CH_3), 2.65 (m, 1 H, pyrrolidine C_4 H_A), 2.92 (m, 1 H, pyrrolidine C_4 H_B), 3.00 (d, 6 H, NCH_3's), 3.6 (m, 1 H, pyrrolidine C_3 H_x), 4.0 (q, 2 H, J = 7.0 Hz, CH_2 of ethyl), 9.5 (br s, 1 H, NH, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.42; H, 7.08; N, 10.95.

Compounds **3d–g,j** (Table I) were prepared similarly.

***N*-Methyl(3-carbethoxy-1,2-dimethyl-5-oxo-2-pyrrolin-4-yl)acetamide (4c).** *N*-Methylmaleimide (**1b**; 4.44 g, 0.04 mol) was treated with 5.4 g (0.04 mol) of ethyl 3-(methylamino)crotonate (**2c**) in 20 mL of dioxane, and the mixture was refluxed for 12 h. Evaporation of the solvent in vacuo and recrystallization of the residue from ethanol afforded 6.9 g (67%) of **4c** as a light green solid: mp 120–124 °C; IR (KBr) 3300, 1725, 1695, 1635, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.45 (d, 3 H, J = 2.0 Hz, 2-CH_3 of pyrroline), 2.7 (d, 3 H, J = 5.0 Hz, NCH_3), 2.86 (d, 2 H, J = 5.5 Hz, CH_2 of acetamide), 3.1 (s, 3 H, NCH_3 of pyrroline), 3.39 (m, 1 H, C_4 H of pyrroline), 4.18 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl), 6.45 (q, 1 H, J = 5.0 Hz, NH, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68, H, 7.13; N, 11.02. Found: C, 56.48; H, 7.17; N, 10.99.

Compounds **4d,h,i** (Table I) were prepared similarly.

6-Hydroxyl-2,3,5-trimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11c). To a suspension of **3c** (1.27 g, 0.005 mol) in 15 mL of *tert*-butyl alcohol was added 0.6 g (0.005 mol) of potassium *tert*-butoxide, and the mixture was refluxed for 5 h. The reddish brown solution was concentrated in vacuo and then treated with 5 mL of cold 2 N H_2SO_4. After the mixture was allowed to stand overnight and cool, the crystallized material was collected and washed with water. The product was recrystallized from water: 0.32 g, (31%); mp 195–198 °C; IR (KBr) 2860–2560 (br), 1690, 1640 cm^{-1}; NMR (Me_2SO-d_6) δ 1.40 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.95 (s, 3 H, 2-CH_3), 3.40 (s, 3 H, 5-CH_3), 4.35 (q, 1 H, J = 6.0 Hz, C_3 H), 5.8 (s, 1 H, C_7 H, exchangeable with D_2O).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.40. Found: C. 57.52; H, 5.83; N, 13.40.

6-Acetoxy-2,3,5-trimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (8a). The pyrrolopyridine **11c** (1 g, 0.005 mol) was suspended in 30 mL of acetic anhydride and the mixture heated at 120 °C. The suspension dissolved, and a red solution occurred. After 10 min, the temperature was lowered to 90–100 °C and maintained there for 1 h. The excess acetic anhydride was removed in vacuo, and the syrupy residue was repeatedly extracted with petroleum ether. Evaporation of the solvent and recrystallization from petroleum ether gave 0.4 g (32%) of the desired product: mp 102–105 °C; IR (KBr) 1685, 1635, 1585 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.67 (s, 3 H, acetoxy CH_3), 3.18 (s, 3 H, 2-CH_3), 3.32 (s, 3 H, 5-CH_3), 4.5 (q, 1 H, J = 6.0 Hz, C_3 H), 6.3 (s, 1 H, C_7 H).

Anal. Calcd for $C_{12}N_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.67; H, 5.72; N, 11.27.

Ethyl 3-(Benzylamino)crotonate (2d). Benzylamine (80.3 g, 81.9 mL, 0.75 mol) was added gradually to ethyl acetoacetate (98.5 g, 96.6 mL, 0.85 mol) with the temperature maintained at 40–45 °C. The mixture was stirred at this temperature for 2 h and then overnight at room temperature. A small portion of ether was added to facilitate the separation of the two layers. The organic phase was separated, dried over $MgSO_4$, and distilled under reduced pressure. The yield was 131 g (80%) of **2d**, bp 161–163 °C (1.1 mm) [lit.[10] bp 129–130 °C (0.4 mm)].

2-Benzyl-6-hydroxyl-3-methyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11d). The adduct **3d** (6.4 g, 0.02 mol) was suspended in 70 mL of *tert*-butyl alcohol, and 2.4 g (0.02 mol) of potassium *tert*-butoxide was added, under an atmosphere of nitrogen. The mixture was refluxed for 6 h. After evaporation of the solvent in vacuo, the bright yellow solid was dissolved in cold water, and the solution was made acidic with 2 N H_2SO_4 (approximately 10 mL). The precipitated product was recrystallized from 95% ethanol to give **11d** as a pale yellow solid: 4 g (74%); mp 231–235 °C; IR (KBr) 3300–2600 (br), 1690–1530 (br) cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 3 H, J = 6.0 Hz, 3-CH_3), 4.3 (q, 1 H, J = 6.0 Hz, C_3 H), 4.4 (d,[17] 1 H, J = 15.0 Hz, CH_A of benzyl), 4.98 (d,[17] 1 H, J = 15.0 Hz, CH_B of benzyl), 5.8 (s, 1 H, C_7 H, exchangeable with D_2O), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.41; H, 5.27; N, 10.33.

5-Benzyl-3-methyl-1,4,6-trioxo-2,4,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-*c*]pyridine (10e). The title compound was prepared as above in 15% yield (benzene): mp 178–181 °C; IR (KBr) 3220–3110 (br), 1750, 1665 cm^{-1}; NMR (Me_2SO-d_6) δ 2.39 (d, 3 H, J = 2.0 Hz, 3-CH_3), 2.75 (m, 2 H, C_7 H's), 3.6 (m, 1 H, C_{7a} H), 4.7 (s, 2 H, CH_2 of benzyl), 7.34 (s, 5 H, aromatic), 8.65 (br s, 1 H, NH, exchangeable with D_2O).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.55; H, 5.23; N, 10.31.

2-Benzyl-6-hydroxyl-3,5-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11f). The title compound was prepared as above in 35% yield (methanol): mp 162–165 °C; IR (KBr) 3100–2800 (br), 1690, 1650, 1595 cm^{-1}; NMR (Me_2SO-d_6) δ 1.36 (d, 3 H, J = 6.0 Hz, 3-CH_3), 3.38 (s, 3 H, 5-CH_3), 4.25 (q, 1 H, J = 6.0 Hz, C_3 H), 4.4 (d,[17] 1 H, J = 15.0 Hz, CH_A of benzyl), 4.98 (d,[17] 1 H, J = 15.0 Hz, CH_B of benzyl), 5.9 (s, 1 H, C_7 H, exchangeable with D_2O), 7.31 (s, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.68; N, 9.68. Found: C, 67.65; H, 5.71; N, 9.87.

2,5-Dibenzyl-6-hydroxyl-3-methyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine Hemihydrate (11g). The title compound was prepared as above in 68% yield [$CHCl_3$–petroleum ether (30–60 °C)]: mp 67–75 °C; IR (KBr) 2920, 1690–1650, 1545 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 3 H, J = 6.0 Hz, 3-CH_3), 4.25 (q, 1 H, J = 6.0 Hz, C_3 H), 4.3 (d,[17] 1 H, J = 17.0 Hz, CH_A of 2-benzyl), 5.0 (d,[17] 1 H, J = 17.0 Hz, CH_B of 2-benzyl), 5.15 (s, 2 H, CH_2 of 5-benzyl), 5.29 (s, 1 H, C_7 H), 7.3 (s, 10 H, aromatic).

Anal. Calcd for $C_{22}H_{20}N_2O_3 \cdot 0.5H_2O$: C, 71.53; H, 5.73; N, 7.59. Found: C, 71.87; H, 5.93; N, 7.31.

5-Benzyl-6-hydroxyl-2,3-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11h). The title compound was prepared as above in 47% yield (absolute methanol): mp 184–189 °C; IR (KBr) 3100–2300 (br), 1700, 1655 cm^{-1}; NMR (Me_2SO-d_6) δ 1.4 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.97 (s, 3 H, 2-CH_3), 4.31 (q, 1 H, J = 6.0 Hz, C_3 H), 5.25 (s, 2 H, CH_2 of benzyl), 5.85 (s, 1 H, C_7 H), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.68; N, 9.86. Found: C, 67.57; H, 5.71; N, 9.84.

6-Hydroxyl-2,3-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11i). The title compound was prepared as above in 59% yield (hot water): mp 245–255 °C (sealed tube); IR (KBr) 2870 (br), 1690, 1600, 1540 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 3 H, J = 5.0 Hz, 3-CH_3), 2.9 (s, 3 H, 2-CH_3), 4.3 (q, 1 H, J = 5.0 Hz, C_3 H), 5.7 (s, 1 H, C_7 H, exchangeable with D_2O); mass spectrum, m/e 194 (M), calcd 194.19.

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.60; H, 5.22; N, 14.47.

6-Hydroxyl-3,4-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (11j). The title compound was prepared as above in 26% yield (hot water): mp 200–207 °C; IR (KBr) 3200 (br), 1700–1610 (br), 1600, 1500 cm^{-1}; NMR (Me_2SO-d_6) δ 1.3 (d, 3 H, J = 6.0 Hz, 3-CH_3), 3.31 (s, 3 H, 5-CH_3), 4.35 (q, 1 H, J = 6.0 Hz, C_3 H), 5.79 (s, 1 H, C_7 H, exchangeable with D_2O), 8.8 (s, 1 H, NH, exchangeable with D_2O).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.46; H, 5.19; N, 14.46.

6-Acetoxy-2-benzyl-3,5-dimethyl-1,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (8b). The compound **11f** (2.85 g, 0.01 mol) was suspended in 50 mL of acetic anhydride and heated to 95–105 °C. The solid dissolved, and a red solution occurred. After 2 h, the solution was cooled to room temperature, and the excess acetic anhydride was evaporated in vacuo. The gummy residue was then extracted repeatedly with petroleum ether. The solid obtained from the extract was recrystallized from absolute ethanol to give **8b** (1 g, 30%) as a white crystalline substance: mp 149–153 °C (sealed tube); IR (KBr) 1700–1480 (br), 1425, 1240, 990, 845, 735, 685 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.68 (s, 3 H, acetoxy CH_3), 3.32 (s, 3 H,

(17) (a) W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975); (b) R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2015 (1965).

5-CH_3), 4.3 (d,[17] 1 H, J = 15.0 Hz, CH_A of benzyl), 4.45 (q, 1 H, J = 6.0 Hz, C_3 H), 5.25 (d,[17] 1 H, J = 15.0 Hz, CH_B of benzyl), 6.5 (s, 1 H, C_7 H), 7.31 (s, 5 H, aromatic).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.59. Found: C, 66.17; H, 5.56; N, 8.60.

4,6-Diacetoxy-2-benzyl-3-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (12b). A suspension of **11d** (5.0 g, 0.0185 mol) in 150 mL of acetic anhydride was heated at 110–125 °C for 2 h. The suspension dissolved at 100–105 °C, and a red solution occurred. After 2 h, the heating was discontinued, and the mixture was stirred overnight at room temperature. The excess acetic anhydride was removed in vacuo, and the gummy residue was washed with 300 mL of cold water and 50 mL of ethanol. The residue was dried, dissolved in chloroform, and reprecipitated with petroleum ether as a yellow gum. This was further purified on a silica gel column with chloroform as eluent. The product, obtained as a yellow gum (3.3 g, 50%), was homogenous by TLC ($CHCl_3$) examination: IR (neat) 1780, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (d, 3 H, J = 6.0 Hz, 3-CH_3) 2.33 (s, 3 H, CH_3 of acetoxy), 2.37 (s, 3 H, CH_3 of acetoxy), 4.28 (d,[17] 1 H, J = 15.0 Hz, CH_A of benzyl), 4.5 (q, 1 H, J = 6.0 Hz, C_3 H), 5.33 (d,[17] 1 H, J = 15.0 Hz, CH_B of benzyl), 7.31 (s, 5 H, aromatic), 7.52 (s, 1 H, C_7 H).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40% H, 5.12; N, 7.91. Found: C, 64.14; H, 5.18; N, 7.80.

1,4,6-Triacetoxy-3-methyl-1*H*-pyrrolo[3,4-*c*]pyridine (9). The title compound was prepared from **11a**:[3] 35% yield ($CHCl_3$–ligroine); mp 114–115 °C; IR (KBr) 1780, 1750, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 6.5 Hz, 3-CH_3), 2.35 (s, 3 H, acetoxy CH_3), 2.39 (s, 3 H, acetoxy CH_3), 2.62 (s, 3 H, acetoxy CH_3), 5.22 (q, 1 H, J = 6.5 Hz, C_3 H), 7.50 (s, 1 H, C_7 H).

Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.92; H, 4.62; N, 9.13.

Citraconimide (13). A stoppered flask containing 54 g of glacial acetic acid, 12 g (0.2 mol) of urea, and 22.4 g (0.2 mol) of citraconic anhydride was heated at 75 °C for 1 h and at 50 °C for 12 h. After being allowed to stand overnight at room temperature, the mixture was chilled to achieve precipitation of a white mass. This was collected on a filter, washed with 10 mL of glacial acetic acid, and dried under reduced pressure. The crude product (38%), consisting of 2-methyl-*N*-carbamylmaleamic acid and 3-methyl-*N*-carbamylmaleamic acid, melted at 113–120 °C and was used for cyclization without further purification. The mixture of methyl-*N*-carbamylmaleamic acids was slowly added to 100 g of acetic anhydride which was preheated to 95–100 °C. The solid dissolved in 5 min, and a pale yellow solution occurred. The temperature was maintained at 85–95 °C for 0.5 h. After being allowed to stand overnight, the solution was concentrated in vacuo, and the precipitated solid was collected and dried. Recrystallization from acetic anhydride afforded the desired product, *N*-carbamylcitraconimide, in 42% yield as light yellow plates: mp 142–150 °C; NMR (Me_2SO-d_6) δ 2.0 (d, 3 H, J = 1.5 Hz, 3-CH_3), 6.7 (d, 1 H, J = 1.5 Hz, C_4 H), 7.5 (br s, 2 H, NH_2, exchangeable with D_2O).

A 250-mL flask, fitted with a stirrer and thermometer, was charged with 53 mL of dimethylformamide and heated to 90–95 °C in an oil bath. *N*-Carbamylcitraconimide (28 g, 0.18 mol) was then added with stirring. Heating was discontinued momentarily so that the reaction temperature did not exceed 100 °C. At the end of the exothermic period, heating was resumed to maintain the temperature at 95–100 °C for 1 h. The mixture was cooled to room temperature and chilled to achieve precipitation of cyanuric acid. This was filtered off, and dimethylformamide was removed from the filtrate under vacuum. The product was then distilled rapidly under reduced pressure to yield 5 g (25%) of citraconimide (**13**), mp 101–104 °C (lit.[18] mp 109–110 °C).

(3-Carbethoxy-1,2,4-trimethyl-5-oxo-2-pyrrolin-4-yl)acetamide Hydrate (15). A mixture of 1.11 g (0.01 mol) of citraconimide (**13**) and 2.86 g (0.02 mol) of ethyl 3-(methylamino)-crotonate (**2c**) in 10 mL of acetone was heated at 110–115 °C for 21 h. The solvent was evaporated in vacuo and the residue washed with petroleum ether. After purification by being passed through a silica gel column, the product was obtained as a pale yellow syrup: 0.6 g (22%); IR (neat) 3440, 3360, 3220, 1730–1625 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (s, 3 H, 4-CH_3), 1.31 (t, 3 H, J = 6.5 Hz, CH_3 of ethyl), 2.45 (s, 3 H, 2-CH_3), 2.85 (s, 2 H, CH_2 of acetamide), 3.09 (s, 3 H, 1-CH_3), 4.21 (q, 2 H, J = 6.5 Hz, CH_2 of ethyl), 6.25 (br d, 2 H, NH_2, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{18}N_2O_4 \cdot H_2O$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.18; H, 6.83; N, 10.40.

2,3,7a-Trimethyl-1,4,6-trioxo-2,4,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-*c*]pyridine (16). A mixture of 1.27 g (0.005 mol) of **15** and 0.6 g (0.005 mol) of potassium *tert*-butoxide in 80–100 mL of *tert*-butyl alcohol was refluxed for 12 h. After cooling to room temperature, the solution was filtered to remove the insoluble material and evaporated to dryness in vacuo. The yellow residue was dissolved in water, and the solution was made acidic with 2 N H_2SO_4 (pH 5–6). The precipitated product was filtered and recrystallized from ethanol to yield 0.5 g (48%) of **16** as a yellow crystalline solid: mp 212–214 °C; IR (KBr) 3470, 3180, 3065, 1690, 1645 cm^{-1}; NMR (Me_2SO-d_6) δ 1.19 (s, 3 H, 7a-CH_3), 2.39 (s, 3 H, 3-CH_3), 3.0 (s, 3 H, 2-CH_3), 3.3 (s, 2 H, C_7 H's), 10.4 (br s, 1 H, NH exchangeable with D_2O); mass spectrum, m/e 208 (M), calcd 208.12.

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.73; H, 5.85; N, 13.46.

2-(Benzylamino)prop-1-enyl Methyl Ketone (18). Benzylamine (42.8 g, 0.4 mol) was gradually added to 2,4-pentanedione (40 g, 0.4 mol) with continuous stirring. After the mixture had been allowed to stand overnight, distillation under reduced pressure gave the product **18**: 60 g (79%); mp 24–25 °C (lit.[12] mp 24 °C).

(3-Acetyl-1-benzyl-2-methyl-5-oxo-2-pyrrolin-4-yl)acetamide (19a). Compound **18** (22.7 g, 0.12 mol) was treated with 11.6 g (0.12 mol) of maleimide in 80 mL of acetone, and the mixture was refluxed for 17 h. Evaporation of acetone in vacuo afforded a syrup which crystallized upon treatment with a chloroform–petroleum ether mixture. Recrystallization from ethanol afforded 21 g (61%) of the desired product as a light, pale yellow solid: mp 155–158 °C; IR (KBr) 3400–3200 (br), 1650 (br), 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.31 (s, 6 H, CH_3 of acetyl and 2-CH_3), 2.97 (m, 2 H, CH_2 of acetamide), 3.6 (m, 1 H, C_4 H of pyrroline), 4.85 (s, 2 H, CH_2 of benzyl), 5.9 (br s, 2 H, NH_2), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.79. Found: C, 67.16; H, 6.35; N, 9.79.

***N*-Methyl(3-acetyl-1-benzyl-2-methyl-5-oxo-2-pyrrolin-4-yl)acetamide (19b).** The title compound was prepared as above in 42% yield (benzene): mp 119–123 °C; IR (KBr) 3380, 1720, 1670, 1630, 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.3 (s, 6 H, 2-CH_3 and acetyl CH_3), 2.73 (d, 3 H, J = 4.5 Hz, NCH_3, reappears as a singlet when exchanged with D_2O), 2.94 (d, 2 H, J = 5.5 Hz, CH_2 of acetamide), 3.57 (m, 1 H, C_4 H of pyrroline), 4.82 (s, 2 H, CH_2 of benzyl), 6.2 (br s, 1 H, NH, exchangeable with D_2O), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.01; H, 6.74; N, 9.34.

2-Benzyl-3,4-dimethyl-1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (21a). A suspension of **19a** (9.6 g, 0.034 mol) in 100 mL of *tert*-butyl alcohol was treated with 4.5 g (0.04 mol) of potassium *tert*-butoxide, and the mixture was refluxed for 21 h. The solid dissolved gradually as the temperature was increased, and a yellow solution occurred. After evaporation of the solvent in vacuo, the residue was dissolved in cold water and the solution made acidic with dilute acetic acid. The product which precipitated as a pale yellow solid was filtered, washed with benzene, and recrystallized from ethanol: 5.5 g (60%); mp 195–197 °C; IR (KBr) 3400 (br), 1690, 1665, 1620, 1575 cm^{-1}; NMR (Me_2SO-d_6) δ 1.44 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.4 (s, 3 H, 4-CH_3), 4.2 (d, 1 H, J = 15.0 Hz, CH_A of benzyl), 4.34 (m, 1 H, C_3 H), 5.3 (d, 1 H, J = 15.0 Hz, CH_B of benzyl), 6.81 (s, 1 H, C_7 H), 7.3 (s, 5 H, aromatic); mass spectrum, m/e 268 (M), calcd 268.3.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.45. Found: C, 71.51; H, 6.05; N, 10.44.

2-Benzyl-3,4,5-trimethyl-1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine (21b). The title compound was prepared as above in 35% yield [benzene–petroleum ether (30–60 °C)]: mp 143–147 °C; IR (KBr) 1698–1675, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 6.0 Hz, 3-CH_3), 2.37 (s, 3 H, 4-CH_3), 3.51 (s, 3 H, 5-CH_3), 4.25 (d, 1 H, J = 15.0 Hz, CH_A of benzyl), 4.35 (q, 1 H,

(18) G. Trummilitz and J. G. Moffatt, *J. Org. Chem.*, **38**, 1841 (1972).

J = 6.0 Hz, C_3 H), 5.25 (d, 1 H, J = 15.0 Hz, CH_B of benzyl), 6.81 (s, 1 H, C_7 H), 7.31 (s, 5 H, aromatic).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.93. Found: C, 72.28; H, 6.43; N, 9.92.

2-Benzyl-6-hydroxyl-3,5-dimethyl-4-oxo-4,5-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine (23). To a stirred suspension of 1 g (0.026 mol) of LAH in 40 mL of dry THF under a nitrogen atmosphere was added 2 g (0.007 mol) of **11f** gradually over the period of 20 min. The mixture was refluxed for 12 h. After being allowed to stand overnight, the mixture was cautiously treated with 5 mL of H_2O, 5 mL of 15% NaOH, and 10–20 mL of H_2O. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. This was chromatographed on a silica gel column with chloroform as an eluent. Fractions with similar R_f values were combined and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to yield 0.3 g (16%) of **23** as yellow needles: mp 148–152 °C; IR (KBr) 1700, 1660, 1590, 1538 cm^{-1}; NMR ($CDCl_3$) δ 2.52 (s, 3 H, 3-CH_3), 3.25 (s, 3 H, 5-CH_3), 3.78 (s, 2 H, C_7 H's), 5.03 (s, 2 H, CH_2 of benzyl), 6.4 (s, 1 H, C_1 H), 6.9–7.5 (m, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.68; H, 6.02; N, 10.46.

Registry No. 1a, 541-59-3; **1b**, 930-88-1; **1c**, 1631-26-1; **2a**, 7318-00-5; **2c**, 870-85-9; **2d**, 1020-67-3; **3c**, 78753-77-2; **3d**, 66668-10-8; **3e**, 78753-79-4; **3f**, 78753-78-3; **3g**, 78753-81-8; **3j**, 78753-76-1; **4c**, 80049-15-6; **4d**, 80049-16-7; **4h**, 80049-17-8; **4i**, 80049-18-9; **8a**, 80049-19-0; **8b**, 80049-20-3; **9**, 80049-21-4; **10e**, 80049-22-5; **11c**, 80049-23-6; **11d**, 80049-24-7; **11f**, 80049-25-8; **11g**, 80049-26-9; **11h**, 80049-27-0; **11i**, 80049-28-1; **11j**, 80049-29-2; **12b**, 80049-30-5; **13**, 1072-87-3; **15**, 80049-31-6; **16**, 80049-32-7; **18**, 21396-42-9; **19a**, 66668-08-4; **19b**, 80049-33-8; **21a**, 80049-34-9; **21b**, 80049-35-0; **23**, 80049-36-1; benzylamine, 100-46-9; ethyl acetoacetate,, 141-97-9; urea, 57-13-6; citraconic anhydride, 616-02-4; 2-methyl-*N*-carbamylmaleamic acid, 80049-37-2; 3-methyl-*N*-carbamylmaleamic acid, 80049-38-3; *N*-carbamylcitraconimide, 7564-40-1; 2,4-pentanedione, 123-54-6.

New Hydantoin Synthesis via a Reactive 5-Oxo-6-methylenepyrimidine Intermediate[1]

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Treatment of the 1-substituted 5-acetoxy-6-(acetoxymethyl)uracils **4a** and **4b** with very dilute sodium hydroxide solution and then with acid affords the 5-methylhydantoins **7a** and **7b**, respectively, in 75% yield. UV, NMR, and chemical evidence shows that this new type of hydantoin synthesis proceeds via the exocyclic methylene intermediates **5a** and **5b**. The N-unsubstituted diacetate **4c** similarly affords 5-methylhydantoin (**7c**, 58% yield), although the intermediate in this case exists as the methyl tautomer **13**. A mechanism that explains the formation of **5a,b** and **13** in terms of the generation and ring contractions of the pyrimidine exocyclic enones **3** is discussed. The 1,3-dimethyl intermediate **5a** is stable at pH 13–14, but the 1-methyl analogue **5b** rearranges under these conditions to give 2,3-dihydro-6-(hydroxymethyl)-2-oxo-1*H*-imidazole-4-carboxylic acid (**16**). This reaction also affords small amounts of the 5,5′-methylenebis[imidazole] compound **18**.

5-Hydroxyuracil and its N-substituted derivatives (**1**, Scheme I) are phenolic substances that undergo a variety of electrophilic substitution reactions at the C-6 position.[2] For example, we showed some years ago[2f] that the sodium salt of 1-methyl-5-hydroxyuracil (**1b**) reacts with formaldehyde to give the 6-hydroxymethyl derivative **2b** in good yield, and we have since extended this observation to include the 1,3-dimethyl- and 1,3-unsubstituted compounds **2a** and **2c**. During our studies of the chemistry of the diols **2** and the corresponding diacetates **4**, we have found that some of their reactions involve the intermediacy of the pyrimidine enone **3**, a highly reactive species that is of interest in view of the alkylating properties and possible antitumor activities expected for such structures.[3] As far as we are aware, reactions involving **3** have not been described before, although an unsuccessful attempt to generate **3c** via a retro-Diels–Alder reaction of a pyrimidine-[4,5-*e*]-1,3-oxazine-6,8-dione was recorded recently.[4] In the present paper, we describe the conversion of the diacetates **4** into a variety of imidazole derivatives by a series of in situ reactions that involve the generation and ring contraction of enones **3a–c**.[5]

As illustrated in Figure 1, treatment of dilute aqueous solutions of **4a** with sodium hydroxide results in the rapid loss of the original absorption at 277 nm and the appearance of a new peak at 242 nm. The process is complete within 15 min, and, judging from the sharp isosbestic points at 223 and 255 nm, it proceeds in an essentially quantitative manner. Several lines of evidence establish that the 242-nm-absorbing intermediate in Figure 1 is the ring-contracted, exocyclic olefin **5a**. The UV spectrum is in accord with this structure,[6] as is the ^1H NMR spectrum

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(2) For example, 5-hydroxyuracils undergo the following reactions. (a) Nitrosation: D. Davidson and M. T. Bogert, *Proc. Natl. Acad. Sci. U.S.A.*, 18, 490 (1932). (b) Diazocoupling; M. T. Bogert and D. Davidson, *Ibid.*, 18, 215 (1932). (c) Mannich reactions: D. E. O'Brien, R. H. Springer, and C. C. Cheng, *J. Heterocycl. Chem.*, 3, 115 (1966); D. E. O'Brien, L. T. Weinstock, R. H. Springer, and C. C. Cheng, *ibid.*, 4, 49 (1967). (d) Deuteration: B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, 34, 2636 (1969). (e) Intramolecular hydroxylation: J. Rabi and J. J. Fox, *ibid.*, 37, 3898 (1972); B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 41, 3133 (1976). (f) Hydroxymethylation: B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 36, 1251 (1971).

(3) (a) A. J. Lin, B. J. Lillis, and A. C. Sartorelli, *J. Med. Chem.*, 18, 917 (1975), and references therein; (b) H. W. Moore, *Science* 197, 527 (1977).

(4) J. L. Asherson, O. Bilgic, and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 522 (1980).

(5) The enones **3** resemble quinone methides, and, consequently, they share some common properties. For example, enones **3** form spiro dimers in concentrated solutions. This aspect of their chemistry will be described in a later paper.

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