Mercuric Acetate Cyclization of 4-(Pyrrolylmethyl)- and 4-(Indolylmethyl)piperidines to Bridged Polycyclic Systems[1]

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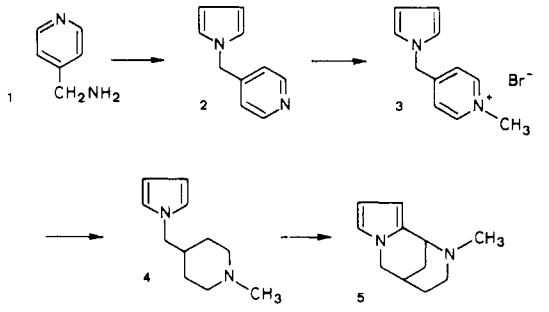
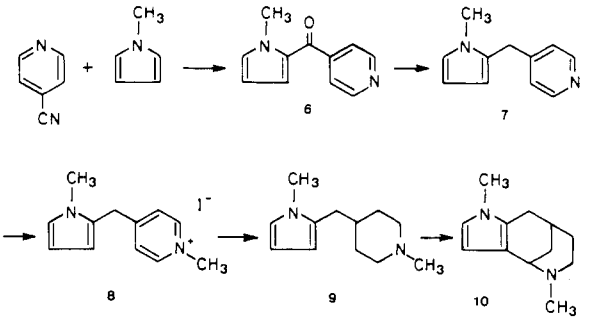
The mercuric acetate cyclization of 4-(pyrrolylmethyl)piperidines **4** and **9** as well as of 4-(indolylmethyl)piperidines **13** and **18** to the corresponding bridged polycyclic systems is studied. When the reaction was carried out in aqueous AcOH solution, mixtures of the starting piperidine and the corresponding cyclized product were obtained. The recovery of piperidine is attributed to the mercuration of the heteroaromatic ring, which prevents the cyclization of the intermediate iminium salt. In the pyrrole series, the use of EDTA in alkaline medium avoids mercuration and gives rise exclusively to the cyclized products **5** and **10** in high yields. However, these alkaline conditions are not appropriate for cyclization of (indolylmethyl)piperidines, because of the formation of the corresponding 2-piperidinones **15** and **20** as the major products. The best yield of methanoazocinoindole **14** was obtained when the oxidative cyclization of **13** was effected in the presence of EDTA at pH 6-7, whereas methanodiazocinoindole **19** was more conveniently prepared in aqueous EDTA solution.

Mercuric acetate[2] is an oxidizing reagent which is able to convert tertiary amines into the corresponding iminium salts[3] through an intermediate amino-mercuric complex which undergoes antiperiplanar elimination of $HgAcO^-$ and an α proton.[4] The iminium salt thus obtained can be attacked by any nucleophilic species present in the reaction medium, and the whole process has been used as a general method for the synthesis of indole alkaloids. Thus, treatment of 3-(2-piperidinoethyl)indoles with mercuric acetate in dilute acetic acid solution usually affords moderate to low yields of the octahydroindolo[2,3-*a*]quinolizine system, via the cyclization of the corresponding iminium salt upon the indole nucleus. This procedure has been successfully applied to the synthesis of the alkaloids flavopereirine,[5] akuammigine,[6] ajmalicine,[6a] hirsutine,[6b] deserpidine,[7] yohimbine,[6b,8] reserpine,[9] and related structures.[10] Similarly, 3-(2-pyrrolidinoethyl)indoles gave indolizino[8,7-*b*]indoles which are intermediates in the synthesis of quebrachamine,[11] vincadine,[11,12] and dihydrocleavamine.[13] Transannular cyclization of iminium salts generated by mercuric acetate oxidation has been also used for the synthesis of iboga (coronaridine, dihydrocatharanthine, catharanthine)[14] and aspidosperma alkaloids (aspidospermidine[14] and related structures[12,14,15]).

Scheme I



Scheme II



To our knowledge, there are no precedents for mercuric acetate oxidative cyclizations upon the pyrrole ring.[16] In the context of our studies on the synthesis of methanopyrroloazocines[17] and methanopyrrolodiazocines,[17b,18] we have investigated the suitability of mercuric acetate oxidation for the synthesis of this kind of bridged polycyclic systems. The substrates we chose were 1-methyl-4-(1-pyrrolylmethyl)piperidine (**4**) and 1-methyl-4-[(1-methyl-2-pyrrolyl)methyl]piperidine (**9**), whose oxidative cyclization should afford methanopyrrolodiazocine **5** and methanopyrroloazocine **10**, respectively.

Pyrrolylmethylpiperidine **4** was prepared from 4-(aminomethyl)pyridine (**1**) by Clauson-Kaas reaction[19,20] with

(1) This work was presented in a preliminary form at the Second European Symposium on Organic Chemistry, Stresa, Italy, 1981.

(2) For a recent review on mercuric acetate as a synthetic reagent, see: Butler, R. N. In "Synthetic Reagents"; Pizey, J. S., Ed.; Ellis Horwood Ltd.: Chichester, 1981; Vol. 4; pp 15-145.

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(8) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109.

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(20) We have described[18] the use of short reaction times (3 min) to enhance yields in the Clauson-Kaas reaction. See also: Nudelman, A.; Braun, F.; Karoly, E. *J. Org. Chem.* **1978**, *43*, 3788.

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Table I. Mercuric Acetate Cyclizations of 4

entry	reaction medium[a]	reaction time	temp, °C	overall yield, %	composition of resulting mixture[b]
1	5% AcOH	15 h	reflux	20	4 + 5 (3:2)
2	5% AcOH	2 h	reflux	20	4 + 5 (1:1)
3	5% AcOH	1 h	reflux	20	4 + 5 (3:4)
4	glacial AcOH	20 h	20	80	4 recovered
5	10% AcOH in MeOH	15 h	20	20	4 + 5 (3:4)
6[c]	H_2O, then 5% AcOH	30 + 30 min	reflux	30	4 + 5 (3:4)
7[c]	H_2O, then 2% AcOH	30 + 30 min	reflux	50	4 + 5 (2:3)
8[c]	H_2O, then 2% AcOH	30 + 1 min	reflux	80	4 + 5 (1:2)

[a] 10 equiv of $Hg(AcO)_2$ in all runs. [b] Determined by NMR. [c] An aqueous solution of 4 and $Hg(AcO)_2$ was refluxed for 30 min, AcOH until the specified concentration was added, and the resulting solution was agin refluxed for the specified time.

2,5-diethoxytetrahydrofuran followed by quaternization of the resulting pyrrolylmethylpyridine **2** and further hydrogenation of the pyridinium bromide **3** (Scheme I). On the other hand, pyrrolylmethylpiperidine **9** was obtained from 4-cyanopyridine in a four-step sequence consisting in the Houben–Hoesch condensation[21] with 1-methylpyrrole to give the ketone **6** (Scheme II), Huang–Minlon reduction to **7**, quaternization, and subsequent catalytic hydrogenation of the resulting pyridinium salt **8**.

The oxidative cyclization of piperidine **4** to methanopyrrolodiazocine **5** was initially attempted under the usual conditions for this kind of reaction. Thus, a solution of **4** and excess $Hg(AcO)_2$ in 5% aqueous AcOH was refluxed, $Hg_2(AcO)_2$ was filtered off, a stream of H_2S was bubbled through the solution until complete precipitation of HgS, and, finally, the possible overoxidation products were reduced with $NaBH_4$. A 2:3 mixture of the cyclized product **5** and the starting piperidine **4** was obtained in 20% yield. This hardly satisfactory result prompted us to modify the conditions, with the results being summarized in Table I.

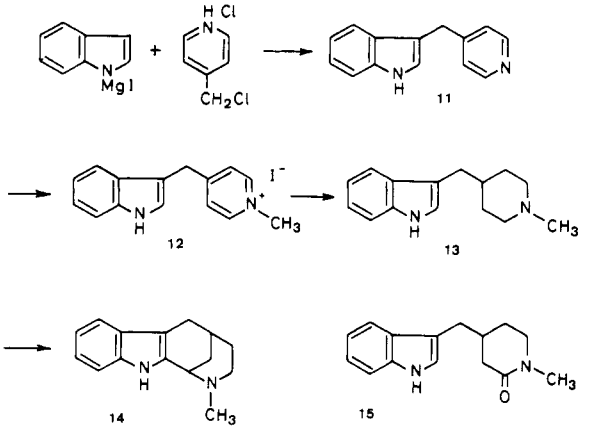
As can be ascertained from Table I, with shorter reaction times (runs 1–3) the overall yield did not increase, although a higher ratio of **5** was obtained. The use of glacial acetic acid[14,15] or methanolic acetic acid[11,13] as a solvent, two sets of conditions described for oxidative cyclization to the indole nucleus, did not improve the yield at all. Finally, when the reaction was carried out in an aqueous phase and the reflux time in AcOH was reduced to 1 min (run 8), a 2:1 mixture of methanopyrrolodiazocine **5** and the starting piperidine **4**, respectively, was obtained in 80% yield. Similar mercuric acetate treatment of pyrrolylmethylpiperidine **9** gave a 3:2 mixture (65% yield) of the methanopyrroloazocine **10** and the starting material **9**.

The cyclized products **5** and **10** were identical with samples previously obtained by alternative procedures.[17b,c]

The recovery of the starting piperidines in the above cyclizations can be explained on the premise that under the reaction conditions the pyrrole ring undergoes a mercuration reaction,[22] which prevents electrophilic attack of the iminium salt. During the H_2S treatment demercuration of the pyrrole ring takes place, and the cyclization occurs. However, during this stage and the subsequent $NaBH_4$ reduction, the metalated intermediate can undergo reduction of the $C{=}N^+$ bond prior to demercuration, leading to the starting pyrrolylmethylpiperidines **4** or **9**.

In good agreement with the above interpretation, when the H_2S treatment was suppressed and the reaction mixture was directly treated with $NaBH_4$, only the starting piperidine (>90% recovery) was isolated (under these conditions, the C—Hg and $C{=}N^+$ bonds of the metalated intermediate iminium salt are reduced). This result demonstrates that cyclization does not occur during the dehydrogenation step, but during the H_2S treatment.

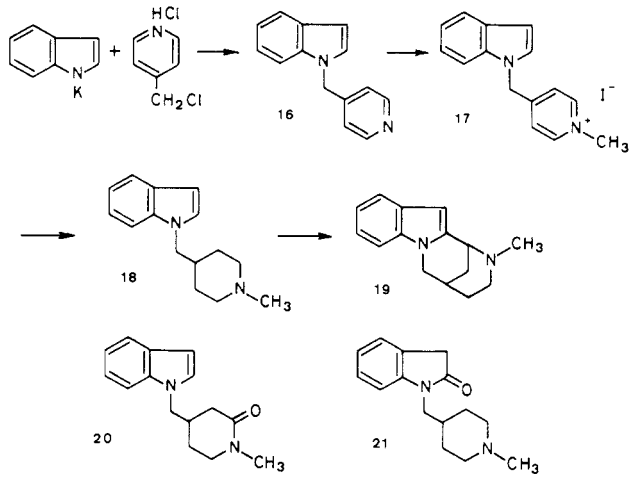
Scheme III



In order to avoid mercuration of the pyrrole ring, we intended to reduce the Hg^{2+} concentration by addition of a complexing agent such as EDTA disodium salt to the reaction medium. This modification of the mercuric acetate oxidation[23] has been used in several instances, especially for the synthesis of indole alkaloids.[6,8,10c] In our case, treatment of piperidine **9** with a 1:1 mixture of $Hg(AcO)_2$ and EDTA, in refluxing either aqueous or 5% AcOH solution, followed by addition of an excess of $NaBH_4$[24] gave results similar to those previously obtained in the absence of complexing agent. However, since these experimental conditions do not include the H_2S treatment, formation of cyclized product **10** in this run made evident that the mercuration reaction had been *partially* prevented by the addition of EDTA, thus allowing some extent of cyclization during the initial $Hg(AcO)_2$–EDTA treatment. In order to increase the stability of the Hg^{2+}–EDTA complex and, consequently, to further reduce the concentration of free Hg^{2+} in the reaction medium, we tried oxidative cyclization under alkaline conditions (pH $\simeq$9)[25] and found that piperidine **9** gave pure methanopyrroloazocine **10** in 92% yield. Similarly, piperidine **4** led to methanopyrrolodiazocine **5** in 91% yield. Therefore, the mercuric acetate cyclization of pyrrolylmethylpiperidines, in the presence of EDTA in alkaline solution, appears to be an excellent procedure for the synthesis of polycyclic structures condensed with the pyrrole ring.

(21) Gabel, N. W. *J. Heterocycl. Chem.* **1967**, *4*, 627.
(22) The tetramercuration of pyrrole by aqueous $Hg(AcO)_2$ treatment has been described: O'Connor, G. N.; Crawford, J. V.; Wang, C.-H. *J. Org. Chem.* **1965**, *30*, 4090.
(23) Knabe, J. *Arch. Pharm.* **1959**, *292*, 416.
(24) In order to reduce the possible overoxidized products and to destroy the excess of $Hg(AcO)_2$.
(25) It is well-known that the stability of metal–EDTA complexes is pH dependent, log $K_{formation}$ for the Hg^{2+}–EDTA complex being approximately 11.2 at pH 3 and 20.5 at pH 9: Schwarzenbach, G.; Flaschka, H. "Complexometric Titrations"; Methuen and Co.: London, 1969; pp 10–15.

Scheme IV



The above results prompted us to study similar alkaline $Hg(AcO)_2$–EDTA oxidative cyclizations from (piperidylmethyl)indoles **13** and **18**, since there are no precedents for the use of these reaction conditions in cyclizations upon the indole nucleus. The cyclization of **13** would lead to the methanoazocinoindole **14**[26] (Scheme III), which bears four of the five rings of the indole alkaloids strictamine[27] and akuammiline,[28] and (piperidylmethyl)indole **18** would cyclize to the tetracyclic system **19**[29] (Scheme IV), the fundamental framework of the indole alkaloid vinoxine.[30]

3-(Piperidylmethyl)indole **13** was obtained from 3-(4-pyridylmethyl)indole (**11**) by reaction with methyl iodide followed by catalytic hydrogenation over PtO_2 of the resulting pyridinium salt **12**. Similarly, 1-(piperidylmethyl)indole **18** was prepared from 4-(chloromethyl)-pyridine hydrochloride in a three-step sequence by condensation with indolyl potassium,[31] quaternization of the resulting 1-(4-pyridylmethyl)indole (**16**), and catalytic hydrogenation of the pyridinium methiodide **17**.[29]

The oxidative cyclization of **18** with $Hg(AcO)_2$–EDTA in alkaline medium (pH 9–10), followed by the usual workup treatment, was found to lead to a single product, which was identified as 4-(1-indolylmethyl)-1-methyl-2-piperidinone (**20**). Thus, the IR spectrum of **20** showed a carbonyl absorption at 1630 cm^{-1}, whereas the most characteristic signals in the NMR spectrum were two doublets (J = 4 Hz) at δ 6.97 and 6.45 due to the 2- and 3-indole protons, respectively, and a downfield singlet (δ 2.82 as compared with δ 2.12 in **18**) corresponding to the N-methyl group.

Similarly, the oxidative cyclization of (piperidylmethyl)indole **13** under the above alkaline conditions afforded piperidinone **15** as the major product, together with the expected cyclization product **14**. In the IR spectrum of lactam **15** a carbonyl absorption at 1620 cm^{-1} was observed, and in the NMR spectrum a singlet at δ 2.84, due to the N-methyl group, and signals for six aromatic protons were found. On the other hand, the NMR spectrum of **14** showed five indole protons, a singlet at δ 2.21 due to the N-methyl group, and a triplet at δ 3.76 corresponding to the hydrogen atom at the C-1 bridgehead position.

The formation of piperidinones **15** and **20** can be interpreted by considering a nucleophilic attack of the hydroxyl anion upon the intermediate iminium salt to give a carbinol amine which undergoes further oxidation by $Hg(AcO)_2$. Oxidation of cyclic tertiary amines to lactams by $Hg(AcO)_2$ treatment is a well-established procedure[32] which in some instances may be of synthetic value.[33] Due to the lesser nucleophilic character of indole as compared to pyrrole, the cyclization of the iminium salts resulting from piperidines **13** and **18** is slower than that of the pyrrole analogues. The attack of the hydroxyl anion, undetected in the pyrrole series, becomes here the major pathway.[34]

As could be expected, when the $Hg(AcO)_2$–EDTA oxidative cyclizations were carried out at lower pH values (several runs at pH 3 to 7), the attack of the hydroxyl anion was slower, and the cyclized products **14** and **19** were the major products in all runs. However, under these conditions the starting piperidines were recovered to some extent, thus indicating that mercuration of the indole nucleus[36] had partially occurred. From a preparative standpoint, the best yields (59%) of pure methanoazocinoindole **14** were obtained at pH 6–7 (attained by addition of 1 N NaOH solution to an aqueous solution of the reagents) due to the negligible amount of piperidine recovered under these conditions and to the easy separation of the lactam **15** by acid–base treatment. Lower pH values resulted in an increased ratio of recovered piperidine. In turn, pure methanodiazocinoindole **19** was more conveniently obtained (40% yield) at pH 3–4 (hydrolysis of $Hg(AcO)_2$–EDTA·Na_2 in water as the solvent).

The above interpretations are consistent with the results obtained when oxidative cyclizations of **13** and **18** were carried out in 5% aqueous AcOH solution in the absence of EDTA, usual conditions for this kind of reactions. Thus, the piperidylmethylindole **13** gave a mixture of the cyclized product **14** (40% yield) and the starting material **13** (10% recovery). In turn, piperidine **18** led (55% yield) to a more complex mixture containing the expected tetracyclic system **19**, the starting compound **18**, and 1-[(1-methyl-4-piperidyl)methyl]oxindole (**21**; which had never been detected when cyclizations were carried out in the presence of EDTA) in an approximate 3:2:3 ratio, respectively. As in the pyrrole series, the recovery of starting (piperidylmethyl)indoles **13** and **18**, as well as the formation of oxindole **21**,[37] can be attributed to the mercuration of the

(26) The preparation of the N-demethyl analogue of **14** has been described by two alternative procedures: Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882.

(27) Schnoes, H. K.; Biemann, K.; Mokrý, J.; Kompiš, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966** *31*, 1641.

(28) Olivier, L.; Levy, J.; LeMen, J.; Janot, M.-M.; Budzikiewicz, H.; Djerassi, C. *Bull. Soc. Chim. Fr.* **1965**, 868.

(29) For a preliminary report on this part of the work, see: Bosch, J.; Feliz, M.; Bennasar, M. L. *Heterocycles* **1982**, *19*, 853.

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(31) It has been established that reactions of indole potassium salts with alkyl halides give rise to 1-substituted indoles whereas indolylmagnesium halides lead preferentially to 3-substituted derivatives: (a) Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771. (b) Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1970; pp 19–31.

(32) (a) Leonard, N. J.; Conrow, K.; Sauers, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 5185. (b) Möhrle, H. *Arch. Pharm.* **1966**, *299*, 122. (c) Sanders, E. B.; DeBardeleben, J. F.; Osdene, T. S. *J. Org. Chem.* **1975**, *40*, 2848 and references cited therein.

(33) (a) Ruenitz, P. C.; Smissman, E. E. *J. Org. Chem.* **1977**, *42*, 937. (b) Honma, Y.; Ban, Y. *Heterocycles* **1977**, *6*, 285. (c) Yoshifuji, S.; Tanaka, K.; Arata, Y. *Tetrahedron Lett.* **1979**, 809. (d) Fujii, T.; Hiraga, T.; Ohba, M. *Chem. Pharm. Bull.* **1981**, *29*, 2691 and references cited therein.

(34) Cyclization of the iminium salt resulting from **13** can occur through a spiroindolenine intermediate and, therefore, can be expected to be faster[35] than cyclization of the isomeric iminium salt derived from **18**. This fact would explain the formation of the cyclized product only in the first case.

(35) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089 and references cited therein.

(36) (a) Ramachandran, L. K.; Witkop, B. *Biochem. J.* **1964**, *3*, 1603. (b) Kirby, G. W.; Shah, S. W. *J. Chem. Soc., Chem. Commun.* **1965**, 381. (c) Remers, W. A. In "Indoles", Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Part I, p 126. (d) Powers, J. C. *Ibid.* 1972, Part II, p 152.

indole nucleus,[36] which prevents cyclization of the intermediate iminium salt during the dehydrogenation step of the process.[38]

In conclusion, the mercuric acetate oxidation in the presence of EDTA in alkaline medium is a high-yield procedure for the cyclization of (pyrrolylmethyl)piperidines to bridged polycyclic systems. These alkaline conditions are not appropriate for similar reactions upon (piperidylmethyl)indoles because of the formation of lactams as the major products. However, oxidative cyclizations upon the indole nucleus worked better when they were carried out in an aqueous EDTA solution than when carried out in the absence of complexing agent in an aqueous AcOH solution.

Experimental Section

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. NMR spectra were measured on a Perkin-Elmer R-24B (60 MHz) instrument with internal Me_4Si (δ 0) as a reference and $CDCl_3$ as a solvent, unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63–200 μm), and the spots were located with UV light or iodoplatinate reagent. All microdistillations were made on a Büchi GKR-50 Kugelrohr apparatus. Microanalyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

4-(1-Pyrrolylmethyl)pyridine (2). A solution of 2.59 g (24 mmol) of 4-(aminomethyl)pyridine (**1**)[39] and 4.02 g (25 mmol) of 2,5-diethoxytetrahydrofuran in 20 mL of glacial AcOH was refluxed for 3 min, cooled, and poured into 100 mL of ice–H_2O. The mixture was basified with 2 N NaOH solution and extracted with Et_2O. The organic layers were extracted with 0.5 N HCl solution, and the acidic aqueous phase was basified with NaOH solution and extracted with Et_2O. Evaporation of the dried ethereal extracts gave an oil which was purified by distillation to yield **2**: 1.88 g (49%); bp 150 °C (0.1 mmHg; oven temperature); NMR (CCl_4) δ 4.90 (s, 2 H, CH_2), 6.01 (t, J = 2.4 Hz, 2 H, pyrrole H_β), 6.42 (t, J = 2.4 Hz, 2 H, pyrrole H_α), 6.70 (m, 2 H, pyridine H_β), 8.28 (m, 2 H, pyridine H_α). For the picrate: mp 164–166 °C (EtOH). Anal. Calcd for $C_{16}H_{13}N_5O_7$: C, 49.62; H, 3.38; N, 18.08. Found: C, 49.33; H, 3.25; N, 18.03.

1-Methyl-4-(1-pyrrolylmethyl)pyridinium Bromide (3). To a cooled (−20 °C) solution of 5.6 g (35.5 mmol) of **2** in 45 mL of anhydrous acetone and 9 mL of anhydrous benzene was added 9 mL (15 g, 158 mmol) of CH_3Br. The mixture was stirred at room temperature (under an acetone–CO_2 condenser) for 8 h and allowed to stand at 5 °C for 24 h. The hygroscopic bromide **3** (8.0 g, 89%) was collected by filtration and dried: mp 176–178 °C (Me_2CO–EtOH); NMR ($CDCl_3$–Me_2SO-d_6) δ 4.38 (s, 3 H, NCH_3), 5.51 (s, 2 H, CH_2), 6.09 (t, J = 2 Hz, 2 H, pyrrole H_β), 6.81 (t, J = 2 Hz, 2 H, pyrrole H_α), 7.61 (d, J = 7.5 Hz, 2 H, pyridine H_β), 9.00 (d, J = 7.5 Hz, 2 H, pyridine H_α).

1-Methyl-4-(1-pyrrolylmethyl)piperidine (4). A mixture of 108 mg of PtO_2 (Adams catalyst), 2 g (7.9 mmol) of **3**, and 70 mL of absolute EtOH was shaken under H_2 at atmospheric pressure and room temperature for 20 h. The catalyst was filtered off, and the clear solution was evaporated. The residue was dissolved in H_2O, basified with 2 N NaOH solution, and extracted with Et_2O. Evaporation of the dried ethereal extracts gave **4**: 1.15 g (82%); NMR (CCl_4) δ 0.8–2.9 (complex signal, 9 H, piperidine), 2.10 (s, 3 H, NCH_3), 3.61 (d, J = 6 Hz, 2 H, CH_2), 5.90 (t, J = 2.4 Hz, 2 H, pyrrole H_β), 6.39 (t, J = 2.4 Hz, 2 H, pyrrole H_α). For the picrate: mp 170–172 °C (EtOH). Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 50.40; H, 5.18; N, 17.19.

1-Methyl-2-pyrrolyl 4-Pyridyl Ketone (6). A stream of dry HCl was bubbled for 1 h through an ice-cooled solution of 2.0 g (19.2 mmol) of 4-cyanopyridine and 1.8 g (22.2 mmol) of 1-methylpyrrole in 30 mL of BF_3–Et_2O and 70 mL of anhydrous $CHCl_3$. The resulting mixture was poured into ice–H_2O, basified with concentrated NaOH solution, and extracted with $CHCl_3$. The organic layers were evaporated, and the residue was taken up in 150 mL of 4 N HCl solution. The mixture was refluxed for 5 min, cooled, basified with 5 N NaOH solution, and extracted with $CHCl_3$. The organic extracts were dried and evaporated to give 2.5 g of a dark brown solid which was purified by column chromatography. On elution with 7:3 benzene–$CHCl_3$, 1.06 g (30%) of **6** was obtained: mp 113–114 °C (hexane); IR (KBr) 1620 cm^{-1} (CO); NMR δ 3.95 (s, 3 H, NCH_3), 6.08 (m, 1 H, pyrrole C^4H), 6.62 (m, 1 H, pyrrole C^3H), 6.89 (m, 1 H, pyrrole C^5H), 7.48 (m, 2 H, pyridine H_β), 8.63 (m, 2 H, pyridine H_α). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.91; H, 5.45; N, 14.96.

4-[(1-Methyl-2-pyrrolyl)methyl]pyridine (7). Ketone **6** (12.2 g, 65.5 mmol) and 80% hydrazine hydrate (13.5 g, 216 mmol) were added to a solution of 13.5 g (237 mmol) of KOH in 184 mL of ethylene glycol. The resulting mixture was refluxed for 1 h, distilled to raise the temperature to 190 °C, and then refluxed again for 3 h. The cooled reaction mixture was poured into ice–H_2O and extracted with Et_2O. The ethereal extracts were washed with H_2O, dried, and evaporated to give **7**: 9.7 g (86%); mp 64–66 °C (hexane); NMR (CCl_4) δ 3.28 (s, 3 H, NCH_3), 3.79 (s, 2 H, CH_2), 5.7–5.9 (m, 2 H, pyrrole H_β), 6.35 (m, 1 H, pyrrole H_α), 6.85 (d, J = 6 Hz, 2 H, pyridine H_β), 8.26 (d, J = 6 Hz, 2 H, pyridine H_α). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.90; H, 7.11; N, 16.29.

1-Methyl-4-[(1-methyl-2-pyrrolyl)methyl]pyridinium Iodide (8). A solution of 3.35 g (19.5 mmol) of **7** and 11.4 g (80 mmol) of CH_3I in 30 mL of anhydrous acetone and 5 mL of anhydrous benzene was stirred at 0–5 °C for 1 h and at room temperature for 2 h. After the mixture was cooled at 5 °C for 24 h, the methiodide **8** (5.90 g, 96%) was collected by filtration: mp 167–169 °C (Me_2CO–EtOH); NMR (Me_2SO-d_6) δ 3.40 (s, 3 H, pyrrole NCH_3), 4.30 (s, 5 H, NCH_3 and CH_2), 5.82 (d, 2 H, pyrrole H_β), 6.61 (m, 1 H, pyrrole H_α), 7.80 (d, J = 6.5 Hz, 2 H, pyridine H_β), 8.85 (d, J = 6.5 Hz, 2 H, pyridine H_α). Anal. Calcd for $C_{12}H_{15}N_2I$: C, 45.87; H, 4.81; N, 8.91; I, 40.41. Found: C, 46.01; H, 4.81; N, 8.87; I, 40.57.

1-Methyl-4-[(1-methyl-2-pyrrolyl)methyl]piperidine (9). A suspension of 85 mg of PtO_2 and 1.50 g (4.7 mmol) of **8** in 60 mL of absolute MeOH was hydrogenated as the above pyridinium bromide **3**. After the usual workup, **9** was obtained: 0.79 g (87%); NMR (CCl_4) δ 1.15–2.9 (complex signal, 11 H, piperidine and interannular CH_2), 2.12 (s, 3 H, piperidine NCH_3), 3.44 (s, 3 H, pyrrole NCH_3), 5.6–5.9 (m, 2 H, pyrrole H_β), 6.28 (m, 1 H, pyrrole H_α). For the picrate: mp 167–169 °C (EtOH). Anal. Calcd for $C_{18}H_{23}N_5O_7$: C, 51.30; H, 5.50; N, 16.62. Found: C, 51.08; H, 5.43; N, 16.30.

2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrrolo[1,2-*a*][1,4]diazocine (5). A solution of 7.4 g (23.2 mmol) of $Hg(AcO)_2$ and 10.4 g (28 mmol) of EDTA·Na_2·$2H_2O$ in 80 mL of H_2O was stirred under a N_2 stream for 30 min. The mixture was basified (pH 9) with aqueous 40% NaOH solution and heated until it boiled. Then, 0.40 g (2.24 mmol) of **4** was added, and the resulting mixture was refluxed for 10 min. The solution was cooled and poured into a solution of $NaBH_4$ (1.5 g) in MeOH (40 mL). The precipitate of Hg was filtered off and washed with MeOH. The combined filtrate and washings were concentrated to 70 mL and extracted with CH_2Cl_2. The extracts were dried and evaporated to give **5**: 0.36 g (91%); NMR (CCl_4) δ 1.2–2.4 (complex signal, 7 H, alicyclic), 2.02 (s, 3 H, NCH_3), 3.3–4.2 (complex signal, 3 H, C^6H_2 and C^1H), 5.64 (m, 1 H, $C^{10}H$), 5.90 (m, 1 H, C^9H), 6.38 (m, 1 H, C^8H). For the picrate: mp 188–190 °C (EtOH). Anal. Calcd for $C_{17}H_{19}N_5O_7$: C, 50.37; H, 4.72; N, 17.28. Found: C, 50.16; H, 4.62; N, 17.11.

(37) The formation of oxindole **21** could be accounted for on the basis of a *gem*-dimercuration on the free 3-position of the indole ring followed by a nucleophilic attack of the hydroxyl anion upon the resulting 3,3-bis(acetoxymercuri)indoleninium salt. The carbinol amine thus formed would then be oxidized to an amide, and the final H_2S and $NaBH_4$ treatments would break the C–Hg bonds and reduce the 2,3,4,5-tetrahydropyridinium salt formed by dehydrogenation of the piperidine ring.

(38) When the H_2S treatment was omitted and the reaction mixture from **18** was reduced with $NaBH_4$, a mixture of compounds **18**, **19**, and **21** was again obtained, the cyclized product **19** being the minor product. The formation of **19** under these conditions indicates that indole was only partially mercurated.

(39) Bullock, M. W.; Hand, J. J.; Stokstad, E. L. R. *J. Am. Chem. Soc.* **1956**, *78*, 3693.

1,5-Dimethyl-4,5,6,7,8,9-hexahydro-4,8-methanopyrrolo[3,2-*c*]azocine (10). By use of the above procedure, from 0.40 g (2.08 mmol) of **9** was obtained **10**: 0.363 g (92%); NMR (CCl_4) δ 1.3–2.9 (complex signal, 9 H alicyclic), 1.99 (s, 3 H, N^5CH_3), 3.40 (s, 3 H, N^1CH_3), 3.40 (m, 1 H, C^4H), 5.58 (d, J = 3 Hz, 1 H, C^3H), 6.19 (d, J = 3 Hz, 1 H, C^2H). For the picrate: mp 173–174 °C (EtOH). Anal. Calcd for $C_{18}H_{21}N_5O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.61; H, 5.05; N, 16.51.

4-(3-Indolylmethyl)-1-methylpyridinium Iodide (12). A solution of 6 g (42 mmol) of CH_3I in 5 mL of anhydrous benzene was added dropwise to a solution of 3.4 g (16.3 mmol) of 3-(4-pyridylmethyl)indole (**11**)[40] in 24 mL of anhydrous acetone. The resulting mixture was stirred at room temperature for 10 h, cooled, and filtered to give **12**: 4.8 g (85%); mp 217–218 °C (Me_2CO); NMR (Me_2SO-d_6) δ 4.21 (s, 3 H, NCH_3), 4.34 (s, 2 H, CH_2), 6.8–7.6 (m, 5 H, indole), 7.95 (d, J = 7 Hz, 2 H, pyridine H_β), 8.77 (d, J = 7 Hz, 2 H, pyridine H_α). Anal. Calcd for $C_{15}H_{15}N_2I$: C, 51.44; H, 4.32; N, 8.00; I, 36.24. Found: C, 51.46; H, 4.07; N, 8.05; I, 36.22.

3-[(1-Methyl-4-piperidyl)methyl]indole (13). A suspension of 0.25 g of PtO_2 and 6 g (17 mmol) of **12** in 200 mL of EtOH was hydrogenated at 40 °C and atmospheric pressure. When hydrogen absorption ceased, the catalyst was filtered off, and the solution was evaporated. The residue was distributed between 10% KOH solution and Et_2O. The organic layer was separated, the aqueous one was extracted with Et_2O, and the combined ethereal extracts were dried and evaporated to give **13**: 3.3 g (85%); mp 162–164 °C (Me_2CO); NMR δ 1.3–2.2 (complex signal, 7 H), 2.28 (s, 3 H, NCH_3), 2.6–3.1 (complex signal, 4 H), 6.8–7.7 (m, 5 H, indole), 8.30 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{20}N_2 \cdot 0.5H_2O$: C, 75.91; H, 8.92; N, 11.80. Found: C, 75.99; H, 8.79; N, 11.86.

1-(4-Pyridylmethyl)indole (16). Indole (20 g, 170 mmol) was added under N_2 to a solution of 34 g (0.6 mol) of ground KOH in 200 mL of anhydrous Me_2SO. The resulting mixture was stirred at room temperature for 90 min, and then 10 g (61 mmol) of 4-chloromethylpyridine hydrochloride[41] was added portionwise. The suspension was stirred at room temperature for 4 h, poured into ice–H_2O, and extracted with Et_2O. The ethereal layers were extracted with 10% HCl solution, and the acidic aqueous phase was basified with concentrated NH_4OH and extracted with Et_2O. The organic extracts were dried and evaporated to give **16**: 12 g (94%); mp 67–68 °C (Me_2CO–Et_2O); NMR δ 5.20 (s, 2 H, CH_2), 6.56 (d, J = 4 Hz, 1 H, indole C^3H), 6.83 (d, J = 7 Hz, 2 H, pyridine H_β), 7.0–7.3 (m, 5 H, indole), 7.5–7.8 (m, 1 H, indole C^7H), 8.47 (d, J = 7 Hz, 2 H, pyridine H_α). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 81.01; H, 5.78; N, 13.54.

4-(1-Indolylmethyl)-1-methylpyridinium Iodide (17). A solution of 31.2 g (220 mmol) of CH_3I in 15 mL of anhydrous benzene was added dropwise to a solution of 12 g (58 mmol) of **16** in 75 mL of anhydrous acetone. The resulting mixture was stirred at room temperature for 10 h, and the precipitate of **17** (18.3 g, 90%) was collected by filtration: mp 177–178 °C (EtOH); NMR (Me_2SO-d_6) δ 4.29 (s, 3 H, NCH_3), 5.88 (s, 2 H, CH_2), 6.62 (d, J = 4 Hz, 1 H, indole C^3H), 7.0–7.9 (m, 7 H, indole and pyridine H_β), 8.90 (d, J = 7 Hz, 2 H, pyridine H_α). Anal. Calcd for $C_{15}H_{15}N_2I$: C, 51.44; H, 4.32; N, 8.00; I, 36.24. Found: C, 51.69; H, 4.21; N, 7.89; I, 36.12.

1-[(1-Methyl-4-piperidyl)methyl]indole (18). A mixture of 0.5 g of PtO_2 and 11 g (31.4 mmol) of **17** in 200 mL of EtOH and 20 mL of H_2O was hydrogenated as the above pyridinium salt **12**. After the usual workup, **18** was obtained: 6.3 g (88%); NMR δ 1.1–1.9 (complex signal, 7 H), 2.12 (s, 3 H, NCH_3), 2.4–2.9 (complex signal, 2 H), 3.75 (d, J = 6 Hz, 2 H, $ArCH_2$), 6.40 (d, J = 4 Hz, 1 H, indole C^3H), 6.83 (d, J = 4 Hz, 1 H, indole C^2H), 6.9–7.3 (m, 3 H, indole), 7.4–7.7 (m, 1 H, indole C^7H). For the picrate: mp 226–227 °C (EtOH). Anal. Calcd for $C_{21}H_{23}N_5O_7$: C, 55.14; H, 5.07; N, 15.31. Found: C, 55.40; H, 4.86; N, 15.32.

2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole (14). A solution of 0.29 g (1.27 mmol) of **13** in 5 mL of CH_2Cl_2 was added to a solution of 2.04 g (6.4 mmol) of $Hg(AcO)_2$ and 2.45 g (6.6 mmol) of EDTA·Na_2·$2H_2O$ in 50 mL of H_2O. The CH_2Cl_2 was evaporated by heating the mixture at 40 °C under a stream of N_2, and the resulting mixture was brought to pH 6–7 by the addition of aqueous 1 N NaOH solution. The mixture was refluxed for 35 min, cooled, and basified with 1 N NaOH solution. After addition of 100 mL of EtOH and 2 g of $NaBH_4$, the mixture was stirred at room temperature for 20 min and filtered. The filtrate was concentrated under reduced pressure and extracted with CH_2Cl_2. The evaporation of the dried organic extracts gave an oil (0.26 g) which by NMR was found to be an approximately 4:1 mixture of the cyclized product **14** and lactam **15**, respectively. This oil was dissolved in Et_2O and extracted with 1 N HCl solution. The aqueous phase was basified with 2 N NaOH solution and extracted with Et_2O. Evaporation of the latter ethereal extracts gave azocinoindole **14**: 0.17 g (59%); mp 198–199 °C (Me_2CO); NMR δ 2.21 (s, 3 H, NCH_3), 3.76 (t, 1 H, NCH), 7.0–7.7 (m, 4 H, indole), 7.90 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.88; H, 7.92; N, 12.36.

When the reaction was carried out as above, but the pH of the reaction medium was adjusted to 9–10 and the period of reflux was shortened to 15 min, a 3:2 mixture of piperidinone **15** and cyclized product **14** was obtained. The mixture was dissolved in Et_2O and extracted several times with 1 N HCl solution. The ethereal phase was dried and evaporated to give **4-(3-indolylmethyl)-1-methyl-2-piperidinone (15)** in 47% yield. An analytical sample was obtained by column chromatography (elution with $CHCl_3$ and 94:6 $CHCl_3$–EtOH): mp 177–178 °C (Et_2O–EtOH); IR (KBr) 1620 cm^{-1} (CO); NMR δ 1.1–2.5 (complex signal, 5 H), 2.70 (d, 2 H, $ArCH_2$), 2.84 (s, 3 H, CH_3), 3.18 (m, 2 H, NCH_2), 6.75 (s, 1 H, indole C^2H), 6.8–7.5 (m, 4 H, indole), 8.96 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.46; H, 7.46; N, 11.24.

5-Methyl-1,2,3,4,5,6-hexahydro-2,6-methano-1,4-diazocino[1,2-*a*]indole (19). Following the above procedure, a solution of **18** (0.28 g, 1.23 mmol), $Hg(AcO)_2$ (2.0 g, 6.3 mmol), and EDTA·Na_2·$2H_2O$ (2.4 g, 6.5 mmol) in 50 mL of H_2O (without added NaOH) was refluxed for 1 h. The usual workup gave 0.2 g of an oil (an approximately 6:1:1 mixture of the cyclized product **19**, piperidine **18**, and lactam **20**, respectively). This oil was dissolved in Et_2O and extracted with 1 N HCl solution. The aqueous phase was basified with 2 N NaOH solution and extracted with Et_2O. Evaporation of the dried extracts followed by column chromatography of the residue (elution with 3:2 benzene–$CHCl_3$ and $CHCl_3$) left pure **19**: 0.11 g (40% yield); mp 80–82 °C (Et_2O); NMR δ 2.30 (s, 3 H, NCH_3), 3.90 (t, 1 H, NCH), 4.10 (d, J = 4 Hz, 2 H, $ArCH_2$), 6.22 (s, 1 H, indole C^3H), 7.0–7.4 (m, 3 H, indole), 7.5–7.8 (m, 1 H, indole C^7H). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.79; H, 7.72; N, 12.28.

4-(1-Indolylmethyl)-1-methyl-2-piperidinone (20). By use of the above procedure, a solution of **18** (0.5 g, 2.19 mmol), $Hg(AcO)_2$ (3.5 g, 11 mmol), and EDTA·Na_2·$2H_2O$ (4.8 g, 13 mmol) in 100 mL of H_2O was adjusted to pH 9–10 and then refluxed for 20 min. After the usual workup, the resulting oily residue (0.45 g) was chromatographed. On elution with 7:3 benzene–$CHCl_3$ and $CHCl_3$, pure piperidinone **20** was obtained: 0.38 g (71%); IR ($CHCl_3$) 1630 cm^{-1} (CO); NMR δ 1.2–2.7 (complex signal, 5 H), 2.82 (s, 3 H, NCH_3), 3.11 (dd, 2 H, NCH_2), 3.92 (d, J = 6 Hz, 2 H, $ArCH_2$), 6.45 (d, J = 4 Hz, 1 H, indole C^3H), 6.97 (d, J = 4 Hz, 1 H, indole C^2H), 7.0–7.4 (m, 3 H, indole), 7.5–7.8 (m, 1 H, indole C^7H). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.67; H, 7.60; N, 11.21.

1-[(1-Methyl-4-piperidyl)methyl]oxindole (21). A solution of 30 g (94 mmol) of $Hg(AcO)_2$ and 2 g (8.8 mmol) of piperidine **18** in 120 mL of aqueous 5% AcOH was refluxed for 4 h, and then the precipitate was filtered off and washed with 5% AcOH. The solution was treated with H_2S for 1 h at 90 °C. After filtration of the mixture and careful washing of the filter cake with aqueous AcOH, the combined filters were concentrated to half of their volume, diluted with 100 mL of EtOH, basified with solid K_2CO_3, and treated with $NaBH_4$ (0.2 g). The resulting mixture was stirred at room temperature for 1 h, concentrated to a small volume, diluted with H_2O, and extracted with Et_2O. Evaporation of the dried extracts gave 1.1 g (55% recovery) of an oil which was identified by NMR as a mixture of compounds **18**, **19**, and **21** in a 2:3:3 ratio. Column chromatography (9:1 $CHCl_3$–EtOH as eluent) afforded oxindole **21**: 0.32 g (15%); IR ($CHCl_3$) 1690 cm^{-1}

(40) We have obtained improved yields (55%) of **11** by a previously described reaction between indolylmagnesium iodide and 4-(chloromethyl)pyridine hydrochloride: DeGraw, J. I.; Kennedy, J. G.; Skinner, W. A. *J. Heterocycl. Chem.* **1966**, *3*, 67.

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(CO); NMR δ 1.2–2.1 (complex signal, 7 H), 2.20 (s, 3 H, NCH_3), 2.6–3.1 (complex signal, 2 H), 3.46 (s, 2 H, $NCOCH_2$), 3.54 (d, 2 H, $CONCH_2$), 6.6–7.4 (m, 4 H, Ar). For the hydrochloride: mp 244–246 °C (EtOH). Anal. Calcd for $C_{15}H_{21}ClN_2O$: C, 64.16; H, 7.54; N, 9.98; Cl, 12.62. Found: C, 64.23; H, 7.60; N, 9.82; C, 12.60.

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Registry No. 1, 3731-53-1; 2, 87451-35-2; 3, 87451-36-3; 4, 87451-37-4; 5, 80077-92-5; 6, 87451-38-5; 7, 87451-39-6; 8, 87451-40-9; 9, 87451-41-0; 10, 83348-32-7; 11, 5275-07-0; 12, 87451-42-1; 13, 87451-43-2; 16, 82485-24-3; 17, 82485-29-8; 18, 82485-25-4; 19, 87451-44-3; 20, 87451-45-4; 21, 87451-46-5; 2,5-diethoxytetrahydrofuran, 3320-90-9; 4-cyanopyridine, 100-48-1; 1-methylpyrrole, 96-54-8; indole, 120-72-9; mercuric acetate, 1600-27-7; 4-chloromethylpyridine hydrochloride, 1822-51-1.

Synthesis of 2,4-Disubstituted Pyrimidines, Polypyrimidinediyls, and Annulated Pyrimidines[1]

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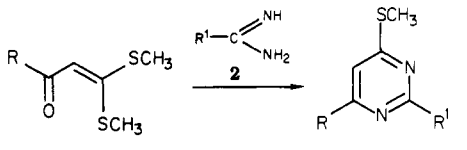
Carboxamidines reacted with α-oxoketene dithioacetals in benzene/DMF solution in the presence of sodium hydride, giving 2,4-disubstituted-6-(methylthio)pyrimidines containing a variety of alkyl, aryl, and heteryl substituents in the 2 and 4 positions. Bis(α-oxoketene dithioacetals) and 2 equiv of carboxamidine allowed the introduction of several pyrimidine nuclei into the polyheteryl system. Thiourea also reacted with bis(α-oxoketene dithioacetals), giving the corresponding bis(pyrimidinethione).

α-Oxoketene dithioacetals have been shown[2] to be versatile synthons for 1,5-enediones, intermediates in the synthesis of 2,6-disubstituted pyridines, polypyridindiyls, and annulated pyridines. In this publication we describe the application of these α-oxoketene dithioacetals to the synthesis of a variety of 2,4-disubstituted pyrimidines and related derivatives. Numerous syntheses of pyrimidines have been described[3] in the literature. Ketene acetals and amidines readily form pyrimidines,[4] and *S*-methylisothiourea and guanidine derivatives also react readily with α-oxoketene dithioacetals to form the appropriately substituted pyrimidines.[5] This present procedure is characterized by the variety of substituents (alkyl, aryl, and heteryl) which may be introduced into the 2,4-positions and by the 6-methylthio substituent which may be converted into other groups. It is particularly suited to the synthesis of heterocyclic systems with considerable potential for behaving as ligands.

Reaction of the α-oxoketene dithioacetal **1** with a carboxamidine **2** in benzene–DMF solution in the presence of sodium hydride resulted in the formation of the 2,4-disubstituted-6-(methylthio)pyrimidine **3** in moderate yields (Table I). The carboxamidine was usually used as its salt, an additional quantity of sodium hydride being added to generate the free amidine.



1 **3**

Spectral and analytical data for the products described in Table I were consistent with the assigned structures. Thus 2,4-di-2-thienyl-6-(methylthio)pyrimidine (**3**, R = R^1 = 2-C_4H_3S) was prepared from 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (**1**, R = C_4H_3S) and 2-thiophenecarboxamidine[6] (**2**, R^1 = C_4H_3S). Its seven aromatic protons were distinguishable as a singlet for the new pyrimidine proton and multiplets for the six thiophene protons, together with the SCH_3 protons at δ 2.66. The 13 line ^{13}C NMR spectrum was also consistent with this structure.

The pyridinecarboxamidines, prepared conveniently from their nitriles, sodium methoxide, and ammonium chloride,[7] underwent ready pyrimidine formation with the 3- and 4-substituted pyridines. 2-Pyridinecarboxamidine, however, resulted in a poor yield of the corresponding pyrimidine. Solvent variation or the use of potassium hydride had little influence on the reaction, and we tentatively attribute this poor yield to an intramolecular stabilization of the amidine anion with the pyridine nitrogen and the counter ion.

Use of heterocyclic bis(ketene dithioacetals) provides an opportunity of appreciably extending the number of heterocyclic units in a particular system. Thus reacton of 2,6-bis[3,3-bis(*n*-propylthio)-1-oxo-2-propen-1-yl]pyridine (**4**) with 2 equiv of 2-thiophenecarboxamidine (**2**, R = 2-C_4H_3S) in benzene/sodium hydride resulted in **5** (R =

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