Synthesis of Substituted Pyrrolo[1,2-a]pyrimidines

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A facile route for the synthesis of pyrrolo[1,2-a]pyrimidine derivatives and data for structural assignment are reported.

Very few examples have been recorded in the literature for the preparation of pyrrolo[1,2-a]pyrimidines (1) (2), although considerable attention has recently been given to the partially saturated derivative, 1,5-diazabicyclo-[4.3.0]nonene-5 (2, DBN) (3). In addition to its use as a reagent for the introduction of double bonds, derivatives of DBN have shown interest as potential fungicidal (4), hypotensive (5) and antiinflammatory (6) agents. No biological activity has been reported for pyrrolo[1,2-a]-pyrimidines, but the isosteric pyrrolo[2,3-d]pyrimidines (7-deazapurine) has been of major medicinal interest in recent years following the discovery of this nucleus in


Tubercidin, Toyocamycin, and Sangivamycin, compounds with antibiotic and antitumor activity (7). In addition some synthetic derivatives of the 7-deazapurine family have shown antibiotic, antitumor and CNS depressant properties (8). From isosteric relationships, one may anticipate that pyrrolo[1,2-a]pyrimidines may possess similar biological properties. The present communication describes a facile method for preparation of substituted pyrrolo[1,2-a]pyrimidines. The ready availability of starting materials should facilitate structure-activity studies.

Alkylation of 2-amino-3-cyano-4,5-dimethylpyrrole (3) (9) with phenacyl bromides in presence of dicyclohexyl-methylamine (DCMA) gave monoalkylated products (4, Scheme I) as characterized by nmr spectra. The hydrogen of the NH at the 2-position is coupled with the methylene protons. The acetyl derivatives (5) gave a singlet for the methylene protons. According to Rae (10), protons attached to very weakly basic nitrogen atoms do couple with those adjacent carbon atoms. Secondary aromatic

amines of pK_a values between 1.0 and 3.5 most often exhibit this effect. The weakly basic nature of the 2-amino group may account for the observation that alkylation by phenacyl bromides could not be achieved in absence of base (DCMA). No attempt has been made to optimize yields at this step, but this observation offers clues for further work.

Upon treating 4 with potassium t-butoxide or potassium hydroxide in absolute ethanol, a facile reaction occurs to yield substituted pyrrolo[1,2-a]pyrimidines (6). Structural assignment was confirmed by elemental analysis, infrared and nmr data. The mass spectrum (11) of 6b gave the parent ion at 419 mass units corresponding to the molecular formula of $C_{23}H_{15}Cl_2N_3O$. A strong peak at 139 amu in conjuction with the isotope peak at 141 amu shows the presence of the $p\text{-ClC}_6H_4CO^+$ group. A doublet at 111 amu and 113 amu shows the $p\text{-ClC}_6H_4^+$ group.

Scheme I

6a. R = CN, X = H
6b. R = CN, X = Cl
6c. R = CN, X = Br
7. R = CONH₂, X = Br
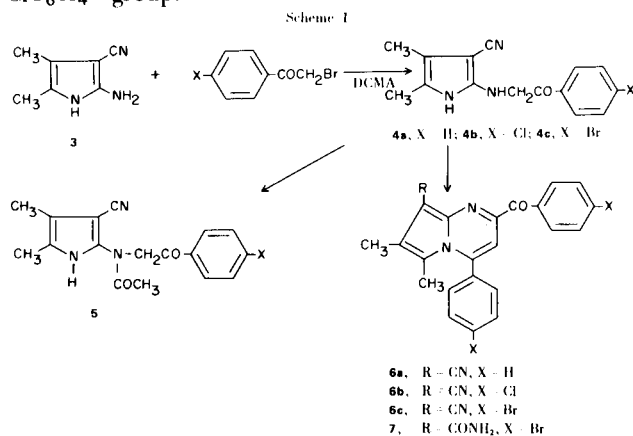
The meta-substitution pattern for the p-chlorophenyl group with reference to the p-chlorobenzoyl group was established by the strong peak at 390 amu. This peak arises from the loss of 29 amu (CHO) from the parent structure. The loss of CHO could only take place if the carbonyl was adjacent to a hydrogen.

A possible mechanism (Scheme II) may involve addition of the pyrrole anion of **4** to the carbonyl group in another molecule of **4** followed by dehydration (12). Addition of the carbanion to the activated olefin (an enamine) followed by elimination of **3a** should give a six-membered ring. Air oxidation of the 1,2-dihydro intermediate results in the pyrrolo[1,2-a]pyrimidine, a 10 π electron system. This oxidation is suggested by the color of the reaction mixture in an opened and sealed reaction vessel. In the absence of air (sealed vessel), the reaction mixture remains yellow, but in presence of air becomes intensely red, indicating increased extent of conjugation and a bathochromic shift.

Although the loss of the anion of **3** is necessary for the proposed mechanism, in no case was this compound isolated. Under the alkaline conditions used for cyclization, it is possible that the pyrrole ring was opened and polymerization occurred. The suggestion that the anion of **3** may serve as a good leaving group and therefore facilitates the reaction sequence is supported by treating (potassium t-butoxide) equimolar quantities of **4** and the appropriate phenacyl bromide, which did not alter the course of the reaction or the yields of **6** (12).

An indication of the stability of the pyrrolo[1,2-a]-pyrimidine may be obtained by the acidic hydrolysis of **6c** to the corresponding amide (**7**) in quantitative yield. Intermediates, **3** or **4**, are not stable under similar conditions.
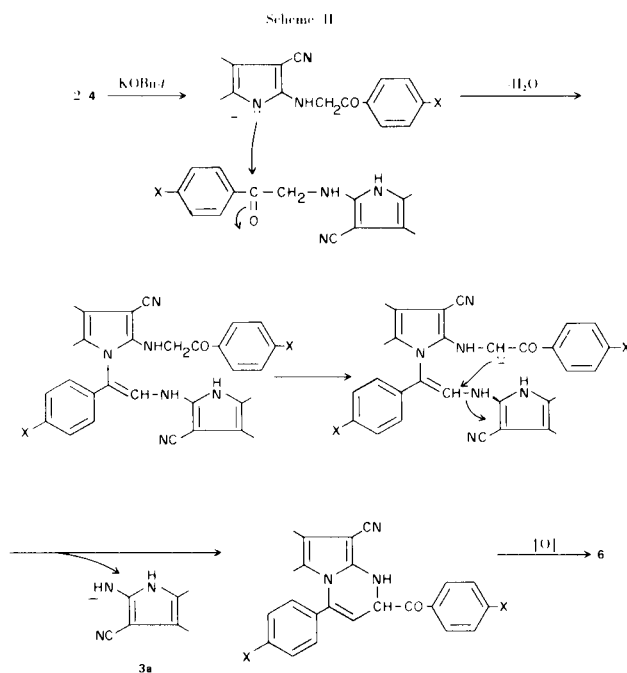
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R 20A High Resolution nmr spectrometer using tetramethylsilane as internal reference. Elemental analysis were by Atlantic Microlab, Inc., Atlanta, Georgia. Infrared spectra were determined on a Perkin-Elmer 237B Grating Spectrophotometer using the potassium bromide technique and ultraviolet spectra were determined in methanol solution with a Perkin-Elmer 202 ultraviolet-visible spectrophotometer. Tlc were performed on Eastman Chromatogram sheets, type 6060 (silica gel).

2-p-Bromophenacylamino-3-cyano-4,5-dimethylpyrrole (4c).

A solution of **3** (9) (20.25 g., 0.15 mole), 2,4'-dibromoacetophenone (47.25 g., 0.17 mole), and dicyclohexylmethylamine (29.25 g., 0.15 mole) in 240 ml. of benzene and 80 ml. of THF was boiled vigorously in an oil bath at 105° for 5 hours. The mixture was chilled in a refrigerator for 5 hours and the insoluble precipitate was collected by filtration, washed in benzene, and allowed to air dry. The crude yellow mixture of amine salt and alkylated pyrrole was stirred with 150 ml. of water and the insoluble fraction collected, washed with 150 ml. of absolute methanol, and air dried. The crude product (24.6 g., 49.4%) was very insoluble in methanol, ethanol, ethyl acetate, THF, and benzene. Five hundred mg. of the crude material was recrystallized from a large volume of methanol to yield a yellow powder (homogeneous on tlc-chloroform, R_f = 0.33; ethyl acetate, R_f = 0.49): m.p. 211-213° dec.; ir (potassium bromide): 3385, 3250, 2180, 1685, 1625, 1600, 1585, 1500, 1335, 1235, 1075, 1000, 830 cm^{-1}; nmr (d$_6$-DMSO): δ 1.84 (s, 3H, CH$_3$ at C$_4$), 1.93 (s, 3H, CH$_3$ at C$_5$), 4.69 (d, 2H, J = 6.0 Hz, NH-CH$_2$-CO), 5.97 (t, 1H, J = 6.0 Hz, NH at C$_2$), 7.82 (q, 4H, aromatic H's), 9.98 (s, 1H, NH of pyrrole).

Anal. Calcd. for $C_{15}H_{14}BrN_3O$: C, 54.23; H, 4.25; Br, 24.05; N, 12.65. Found: C, 54.31; H, 4.30; Br, 24.12; N, 12.64.

2-p-Chlorophenacylamine-3-cyano-4,5-dimethylpyrrole (4b).

The procedure described for the preparation of **4c** was employed. The crude yellow alkylated pyrrole (2.80 g., 24.4%) was washed with absolute methanol and was suitable for further reactions, m.p. 245-246°; ir (potassium bromide): 3385, 3250, 2180, 1680, 1615, 1600, 1585, 1490, 1330, 1230, 1090, 990, 830 cm^{-1}.

2-Phenacylamino-3-cyano-4,5-dimethylpyrrole (4a).

The general alkylation procedure for **4c** was employed. The crude product (7.0 g., 34.6%) was recrystallized twice from absolute ethanol to yield yellow needles (homogenous on tlc-ethyl acetate, R_f = 0.51), m.p. 212-214° dec.; ir (potassium bromide): 3385, 3260, 2180, 1680, 1620, 1590, 1580, 1485, 1450, 1340, 1235, 1190, 1155, 1000, 980, 755, 690 cm^{-1}; nmr (d$_6$-DMSO): δ 1.87 (s, 3H, CH$_3$ at C$_4$), 1.97 (s, 3H, CH$_3$ at C$_5$), 4.75 (d, 2H, J = 6.0 Hz, -CH$_2$-CO), 5.95 (t, 1H, J = 6.0 Hz, NH at C$_2$), 7.50-8.05 (complex m, 5H, aromatic H's), 10.03 (s, 1H, NH of pyrrole).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.05; H, 6.04; N, 16.50.

2-(N-Acetyl-N-p-bromophenacyl)amino-3-cyano-4,5-dimethylpyrrole (5).

A suspension of **4c** (15.0 g., 0.0452 mole) in 300 ml. of acetic

Scheme II

anhydride was heated with continuous stirring in an oil bath at 140-145° until a solution was obtained. This required 20 to 30 minutes. Once solution was obtained, the mixture was heated for an additional 5 minutes. The acetic anhydride solution was allowed to cool to 70°, then poured into 700 to 800 ml. of water. Precipitate was deposited within 5 minutes from the rapidly stirred mixture. After stirring for 10 minutes, 500 g. of ice was added. After the ice had melted, the precipitate was collected by filtration, washed with water, and air dried. The crude product (15.8 g., 93.7%) was recrystallized from benzene-cyclohexane to yield white needles (homogenous on tlc--chloroform, R_f = 0.44: ethyl acetate, R_f = 0.58; benzene, R_f = 0.05), m.p. 199.5-200°; ir (potassium bromide): 3240, 2210, 1700, 1670, 1600, 1590, 1380, 1230, 1080, 1000, 975, 830, 820 cm^{-1}; nmr (deuteriochloroform): δ 2.08 (s, 6H, CH₃ at C₄ and CH₃ of acetyl), 2.16 (s, 3H, CH₃ at C₅), 5.03 (s, 2H, methylene), 7.71 (q, 4H, aromatic H's) of 9.00-9.40 (broad s, 1H, NH of pyrrole).

Anal. Calcd. for $C_{17}H_{16}BrN_3O_2$: C, 54.56; H, 4.31; Br, 21.35; N, 11.23. Found: C, 54.65; H, 4.38; Br, 21.26; N, 11.24.

2-p-Bromobenzoyl-4-p-bromophenyl-8-cyano-6,7-dimethylpyrrolo[1,2-a]pyrimidine (6c).

A suspension of **4c** (12.7 g., 0.038 mole) in 200 ml. of absolute ethanol was treated with potassium t-butoxide (4.75 g., 0.042 mole). Immediately, a blood red color was observed. The suspension was stirred at room temperature for 12 hours, and the orange precipitate collected, washed with ethanol and air dried. The crude product (8.9 g., 91.5%) was recrystallized three times from benzene-cyclohexane to yield fine pale orange needles (homogenous on tlc--chloroform, R_f = 0.64; THF, R_f = 0.66; ethyl acetate, R_f = 0.60; compound fluorescence under uv light), m.p. 256-258°; ir (potassium bromide): 2220, 1640, 1580, 1545, 1485, 1410, 1365, 1250, 1140, 1075, 1020, 830, 775, 750 cm^{-1}; nmr (deuteriochloroform): δ 1.89 (s, 3H, CH₃ at C₇), 2.41 (s, 3H, CH₃ at C₆) (13), 7.28-8.35 (complex m, 9H, aromatic H's of pyrimidine and phenyl ring).

Anal. Calcd. for $C_{23}H_{15}Br_2N_3O$: C, 54.25; H, 2.97; Br, 31.38; N, 8.25. Found: C, 54.28; H, 3.19; Br, 31.17; N, 8.17.

The use of potassium hydroxide gave a 65.3% yield after stirring at room temperature for 55 hours.

2-p-Bromobenzoyl-4-p-bromophenyl-8-carbamyl-6,7-dimethylpyrrolo[1,2-a]pyrimidine (7).

A solution of **6c** (1.0 g., 0.00196 mole) in 15 ml. of concentrated sulfuric acid was stirred in a stoppered flask at room temperature for 35 minutes, 1 g. of ice was added, and the solution stirred for an additional 25 minutes. The purple-maroon solution was diluted with 50 g. of ice, then 50 ml. of water was added, to yield an orange precipitate. After the ice had melted, the precipitate was collected, washed with water, absolute methanol, and air dried. The crude product (1.05 g., 100%) was recrystallized from benzene-cyclohexane to yield fine bright orange crystals (homogenous on tlc--ethyl acetate, R_f = 0.41; chloroform, R_f = 0.36), m.p. 293-294°; ir (potassium bromide): 3450 (weak), 3360, 1660, 1640, 1575, 1500, 1480, 1410, 1390, 1350, 1250, 1105, 1010, 830, 770 cm^{-1}.

Anal. Calcd. for $C_{23}H_{17}Br_2N_3O_2$: C, 52.40; H, 3.25; Br, 30.31; N, 7.97. Found: C, 52.50; H, 3.32; Br, 30.29; N, 8.03.

2-p-Chlorobenzoyl-4-p-chlorophenyl-8-cyano-6,7-dimethylpyrrolo[1,2-a]pyrimidine (6b).

By the procedure utilized for **6c**, **4b** gave an 82.9% yield after stirring at room temperature for 20 hours. Recrystallization

from benzene-cyclohexane yielded pale orange needles (homogenous on tlc-ethyl acetate, R_f = 0.55; chloroform, R_f = 0.58; THF, R_f = 0.58), m.p. 246.0-246.5°; ir (potassium bromide): 2215, 1640, 1580, 1485, 1410, 1365, 1250, 1175, 1135, 1095, 1045, 1020, 955, 850, 830, 775, 750 cm^{-1}; nmr (deuteriochloroform): δ 1.86 (s, 3H, CH₃ at C₇), 2.40 (s, 3H, CH₃ at C₆), 7.25-8.40 (complex m, 9H, aromatic H's of pyrimidine and phenyl rings), Mol. wt. (MS) Calcd. 419. Found 419.

Anal. Calcd. for $C_{23}H_{15}Cl_2N_3O$: C, 65.73; H, 3.60; Cl, 16.87; N, 10.00. Found: C, 65.71; H, 3.64; Cl, 17.05; N, 9.97.

2-Benzoyl-8-cyano-6,7-dimethyl-4-phenylpyrrolo[1,2-a]pyrimidine (6a).

Utilizing the procedure for **6c**, this compound was prepared from **4a** in 65.6% yield. After recrystallization twice from benzene-cyclohexane and finally from absolute ethanol, fine pale orange needles were obtained (homogenous on tlc--ethyl acetate, R_f = 0.64; chloroform, R_f = 0.64; THF, R_f = 0.61), m.p. 219.5-220.5°; ir (potassium bromide): 2215, 1645, 1600, 1580, 1540, 1480, 1440, 1385, 1360, 1250, 1175, 1135, 1025, 955, 825, 775, 725, 710, 700 cm^{-1}; nmr (deuteriochloroform): δ 1.80 (s, 3H, CH₃ at C₇), 2.38 (s, 3H, CH₃ at C₆), 7.38-8.45 (complex m, 11H, aromatic H's of pyrimidine and phenyl rings); uv max (MeOH) 213 nm (ε, 28,750), 238 (25,875), and 303 (19,170); vis. max (MeOH) 430 nm (ε, 8,950).

Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.57; H, 4.86; N, 11.84.

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(12) We thank the referee for helpful comments on the proposed mechanism. One may also envision S_N2 attach of the carbanion on another molecule of 4 with elimination of 3a, followed by addition of the pyrrole anion to the carbonyl group and dehydra-

tion, yielding the dihydro intermediate. Use of a weakly basic nucleophile (sodium azide) gave quantitative recovery of starting material (4) and suggest the first step involves addition of the pyrrole anion to the carbonyl group (Scheme II).

(13) In the starting material (4c), the methyl at the 5-position corresponding to the 6-position in the product, 6c, appeared as a singlet at δ 1.93. The shift to δ 2.41 may be explained in terms of the deshielding effect that the phenyl ring at the 4-position has on the protons of the methyl group at the 6-position.