New Synthesis of Condensed Heterocycles from Isoxazole Derivatives VI (1). 2,5-Dimethyl-3-acetyl-7-amino-1*H*-pyrrolo[3,2-*b*]pyridine

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A new synthesis of pyrrolo[3,2-*b*]pyridine starting with pyrrole ring is described. The procedure allows the synthesis of 4-azaindoles bearing a sensitive group at C-7. The nitration of **4b** with nitric acid and acetic anhydride at -15° gave **5**. The hydrogenation of **5** led to simultaneous reduction of *N*-hydroxy and nitro groups and to hydrogenolysis of the isoxazole nucleus, affording an appropriate chain of atoms to building up the pyrrolo[3,2-*b*]pyridine ring.

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The methods employed in the pyrrolo[3,2-*b*]pyridine, 4-azaindoles, syntheses have been predominantly adaptations of standard indole preparations and involve the formation of the pyrrole ring on the pyridine ring.

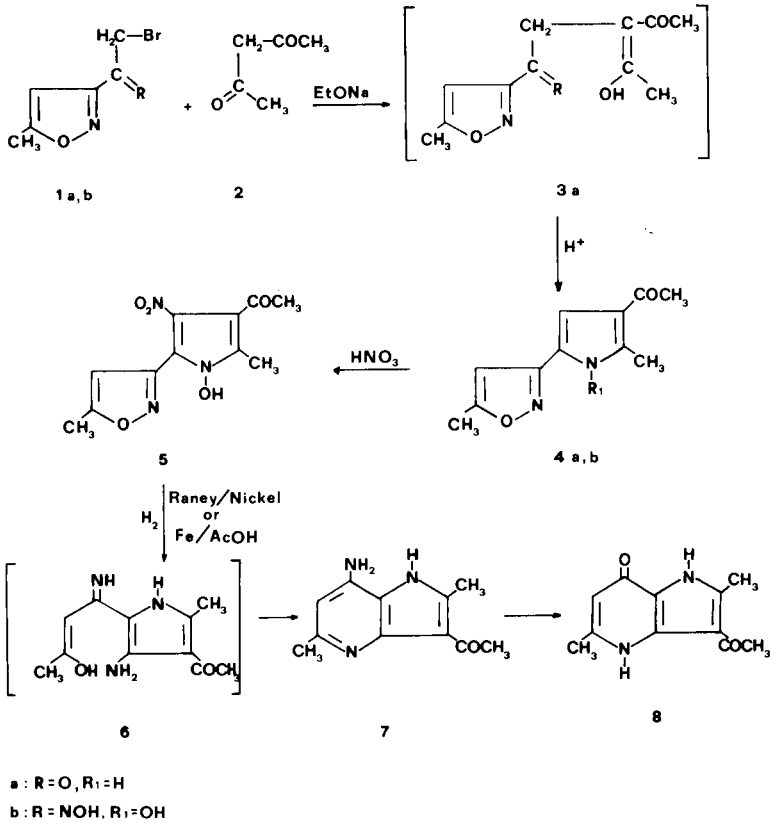
However, the Madelung, Fisher or Reissert type syntheses, or the other synthetic methods already known leading to the 4-azaindoles (2) offer several disadvantages and require harsh reaction conditions which limit the usefulness of methods of synthesis.

Biological interest of azaindoles as possible metabolite antagonists to naturally occurring indoles and purines (3) and the difficulty in obtaining 4-azaindoles with sensitive groups, led us to undertake a new synthesis of 4-azaindole derivatives starting with the pyrrole ring. Other attempts at azaindole synthesis starting with the pyrrole ring have met with only limited success (4).

Results and Discussion.

The reaction of sodium salt of pentane-2,4-dione (**2**) with 3-bromoacethyl-5-methylisoxazole (**1a**) (5) afforded a brown intractable oil **3a** which on reaction with ammonium acetate in acetic acid gave 2-(5-methyl-3-isoxazolyl)4-acetyl-5-methylpyrrole (**4a**) in 8% yield.

The low yield of the reaction was a real handicap to the advancement of our work, but the obstacle was overcome by means of the reaction of the sodium salt of **2** with 3-bromoacethyl-5-methylisoxazole oxime (**1b**) (5) followed by refluxing in ethanolic hydrochloric acid. 1-Hydroxy-2-(5-methyl-3-isoxazolyl)-4-acetyl-5-methylpyrrole (**4b**) was obtained in 70% yield.



This is an interesting alternative pyrrole synthesis (6), in fact the *N*-hydroxypyrroles undergo facile reduction to N-H pyrroles when reduced with zinc and acetic acid in presence of copper sulphate. A sample of **4b** was reduced to **4a** in 90% yield by the previously described procedure (6), but for our purpose, this step was not necessary since nitration of **4b** with nitric acid and acetic anhydride at -15° and subsequent hydrogenolysis of **5** with Raney-nickel produced the desired title compound **7**.

The formation of **7** is explained by intramolecular cyclization of the intermediate **6** resulting from isoxazole ring opening by hydrogenolysis and simultaneous reduction of the *N*-hydroxy and nitro groups. The structure of **7** was confirmed by elemental analysis and spectroscopic determinations. In fact the ir spectrum showed absorption bands at 3140, 3270 and 3330 cm^{-1} attributable to the pyrrole NH and NH_2 groups and at 1675 cm^{-1} due to the CO group of the acetyl group. The nmr spectrum exhibited, in addition to other signals for the remaining protons, a NH_2 signal at δ 5.86 exchangeable with deuterium oxide.

An attempt was made to prepare **7** by reduction of **5** in glacial acetic acid with iron powder (method B), by analogy with the data recently reported by us (1a). A product identical with **7** was obtained. Moreover, **7** was readily converted into the 7-one derivative **8** by action of nitrous acid as described in the experimental.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mulls with a Perkin-Elmer 137 spectrophotometer; nmr spectra (DMSO-d_6) were obtained with a Jeol C-60 spectrometer (TMS as the internal reference). Low resolution mass spectra were run on a Jeol JMS-01SG-2 double focusing mass spectrometer.

2-(5-Methyl-3-isoxazolyl)-4-acetyl-5-methylpyrrole (**4a**).

To a mixture of 1.36 g. (20 mmoles) of **2** in absolute ethanol (10 ml.) was added dropwise with stirring and cooling in an ice bath, 4.1 g. (20 mmoles) of **1a** in 10 ml. of absolute ethanol. After standing 12 hours at room temperature the mixture was poured into ice-water and extracted with ether (4 x 60 ml.). The organic extracts were dried (sodium sulphate) and the solvent removed by rotatory evaporation (steam bath). The brown oil residue **3a**, which could not be purified was refluxed with ammonium acetate (5 g.) in acetic acid (30 ml.). After 2 hours, the dark solution was poured in ice-water and extracted with ether (4 x 60 ml.). The extracts were dried (sodium sulphate) and solvent removed by rotatory evaporation (steam bath). The dark residue which resulted was then dissolved in 10 ml. of ethyl acetate and the solution placed on a column (50 x 2 cm) packed with 40 g. of silica gel. Elution with benzene-ethyl acetate (95:9) afforded **4a** which was recrystallized from ethanol (8% yield), m.p. 209°; ir: cm^{-1} 3260 (NH) 1670 (CO); nmr: δ 11.92 (broad, 1H, NH) 7.00 (d, 1H, pyrrole CH, J = 1.5 Hz) 6.50 (q, 1H, isoxazole CH, J = 0.75 Hz) 2.45 (s, 3H, CH_3) 2.38 (s, 3H, isoxazole CH_3, J = 0.75 Hz) 2.30 (s, 3H, CH_3); ms m/e (relative intensities): 204 (70, M^+) 190 (13) 189 (100) 162 (7) 161 (9) 148 (10) 147 (26) 135 (15) 134 (30) 120 (6) 119 (5) 118 (4) 105 (6) 102 (4) 92 (5) 79 (4) 78 (10) 77 (6) 65 (5) 64 (4) 63 (4) 53 (8) 52 (10) 51 (10) 43 (37).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.71; H, 5.87; N, 13.86.

1-Hydroxy-2-(5-methyl-3-isoxazolyl)-4-acetyl-5-methylpyrrole (**4b**).

To a mixture of 1.36 g. (20 mmoles) of sodium ethylate in absolute ethanol (30 ml.) and 2 g. (20 mmoles) of **2** was added dropwise with stirring and cooling in an ice bath 4.4 g. (20 mmoles) of **1b**.

After 20 minutes the mixture was acidified with ethanolic hydrochloric acid and refluxed for 30 minutes. After cooling the resultant solution was poured on crushed ice. The solid precipitate was filtered off, air dried and recrystallized from benzene (yield 70%), m.p. 204°; ir: cm^{-1} 2640 (OH) 1660 (CO); nmr: δ 11.60 (s, 1H, OH) 6.90 (s, 1H, CH) 6.54 (q, 1H, isoxazole CH, J = 0.70 Hz) 2.47 (s, 3H, CH_3) 2.42 (d, 3H, CH_3, J = 0.70 Hz) 2.32 (s, 3H, CH_3); ms m/e (relative intensities): 220 (100 M^+) 206 (9) 205 (65) 204 (8) 203 (48) 188 (4) 161 (15) 160 (5) 149 (4) 148 (5) 147 (7) 133 (10) 132 (48) 121 (4) 119 (5) 118 (6) 110 (5) 109 (4) 107 (4) 106 (5) 104 (5) 94 (11) 85 (14) 80 (4) 79 (4) 78 (9) 77 (7) 69 (4) 68 (5) 67 (5) 66 (6) 65 (6) 64 (5) 63 (7) 62 (4) 53 (7) 52 (10) 51 (13) 50 (6) 44 (5) 43 (53).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.18; H, 5.55; N, 12.91.

1-Hydroxy-2-(5-methyl-3-isoxazolyl)-3-nitro-4-acetyl-5-methylpyrrole (**5**).

A mixture of 0.4 ml. of nitric acid (10 mmoles) (d = 1.52) and 0.51 g. of acetic anhydride (10 mmoles) was added dropwise with stirring to a suspension of 2.2 g. of **4b** (10 mmoles) in nitromethane (40 ml.) at -15°. The resultant solution was allowed to warm to room temperature. The solid precipitate was filtered off, washed with ether, air dried, and recrystallized from benzene-ethanol (yield 80%), m.p. 207°; ir: cm^{-1} 2700-2800 (broad OH) 1675 (CO); nmr: δ 12.50 (broad, 1H, OH) 6.54 (q, 1H, CH, J = 0.70 Hz) 2.48 (s, 3H, CH_3) 2.37 (s, 3H, CH_3) 2.30 (d, 3H, CH_3, J = 0.70 Hz); ms m/e (relative intensities): 265 (54, M^+) 250 (10) 249 (11) 248 (61) 164 (12) 146 (19) 109 (5) 85 (5) 77 (4) 76 (4) 67 (7) 66 (6) 52 (4) 51 (6) 44 (11) 43 (100).

Anal. Calcd. for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 50.07; H, 4.10; N, 16.10.

1-*H*-2,5-Dimethyl-3-acetyl-7-aminopyrrolo[3,2-*b*]pyridine (**7**).

Method A.

A mixture of 1.35 g. of **5** (5 mmoles), 50 ml. of ethanol and *ca.* 1 g. of W-2 Raney nickel was hydrogenated in a Parr apparatus at 45 psi for 8 hours at room temperature. Removal of the catalyst and evaporation of ethanol left a residue, which was recrystallized from ethanol (yield 40%), m.p. 272°; ir: cm^{-1} 3140, 3270, 3330 (NH and NH_2) 1675 (CO); nmr: δ (pyrrole NH unobserved), 6.25 (s, 1H, CH) 5.86 (s, 2H, NH_2) 2.77 (s, 3H, CH_3) 2.65 (s, 3H, CH_3) 2.40 (s, 3H, CH_3); ms m/e (relative intensities): 203 (34, M^+) 189 (13) 188 (100) 174 (5) 161 (5) 160 (12) 158 (6) 123 (15) 122 (6) 121 (5) 93 (5) 92 (4) 78 (5) 77 (5) 76 (4) 68 (4) 67 (10) 66 (18) 65 (8) 64 (4) 63 (4) 53 (5) 52 (8) 51 (6) 43 (14) 42 (13) 41 (9) 39 (19).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.15; H, 6.25; N, 21.00.

Method B.

To a solution of 1.35 g. of **5** (5 mmoles) in acetic acid (50 ml.)

iron powder (1.5 g.) was added at room temperature by three portions over a period of two days. After standing for a week, the mixture was poured into crushed ice and alkalynized with aqueous sodium hydrate (10%) and extracted with ethylacetate (6 x 100 ml.). The organic layer was dried (sodium sulphate) and evaporated to give a product (yield 10%) which was identical (mixed m.p., ir and nmr) with the 1-*H*-2,5-dimethyl-3-acetyl-7-aminopyrrolo[3,2-*b*]pyridine (**7**) obtained by the method A.

1-*H*-2,5-Dimethyl-3-acetylpyrrolo[3,2-*b*]pyridin-7-one (**8**).

Sodium nitrite (0.27 g., 4 mmoles) was added to a solution of 0.4 g. of **7** (2 mmoles) in 20 ml. of acetic acid; the mixture was heated on a water bath for 30 minutes, concentrated by rotatory evaporation (steam bath) to dryness and washed with water; the residue was dissolved in sodium hydroxide (10%), filtered, and acidified with hydrochloric acid. The precipitate was recrystallized from ethanol, (yield 70%), m.p. $> 325°$; ir: cm^{-1} 2440 (NH) 3080 (NH) 1660 (CO) 1630 (CO); nmr: δ 11.10 (broad, 1H, NH) 9.95 (broad, 1H, NH) 5.87 (s, 1H, CH) 2.63 (s, 3H, CH_3) 2.45 (s, 3H, CH_3) 2.34 (s, 3H, CH_3); ms m/e (relative intensities): 204 (60, M^+) 190 (13) 189 (100) 161 (5) 134 (6) 133 (4) 88 (4) 80 (4) 66 (5) 44 (7) 43 (5).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.90; H, 6.00; N, 13.53.

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