Aminopyrazoles. Part 3 (1). Synthesis of the Novel Ring Systems Pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzoxazepine and [1,5]benzothiazepine

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Two-step synthesis of the novel fused heterocycles pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzoxazepine (**8**) and pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzothiazepine (**9**) from the pyrazolo[3,4-*b*]pyridine derivative **1** is described.

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Elsewhere (1) we reported on the Vilsmeier-Haack reaction of 5-acetylaminopyrazoles (2) as well as the separation and structure elucidation of the pyrazolo[3,4-*b*]pyridine derivatives obtained.

In the present paper a simplified preparation and some displacement reactions of the 1-phenyl-3-methyl-6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**1**) resulting in the synthesis of the previously unknown title ring systems are reported.

Reacting **1** with anionic nucleophiles *e.g.*, ethoxide, phenoxide or phenylthio anions the nucleophilic substitution products **2** were obtained.

Unlike in 4-chloro analogs (3,4), however, substitution of the 6-chlorine of **1** could not be achieved by aliphatic or aromatic primary amines, *e.g.*, *n*-butylamine, 2-[3,4-dimethoxyphenyl]ethylamine or aniline. With these reagents azomethine derivatives **3** were formed which on reduction with sodium borohydride gave compounds **4**.

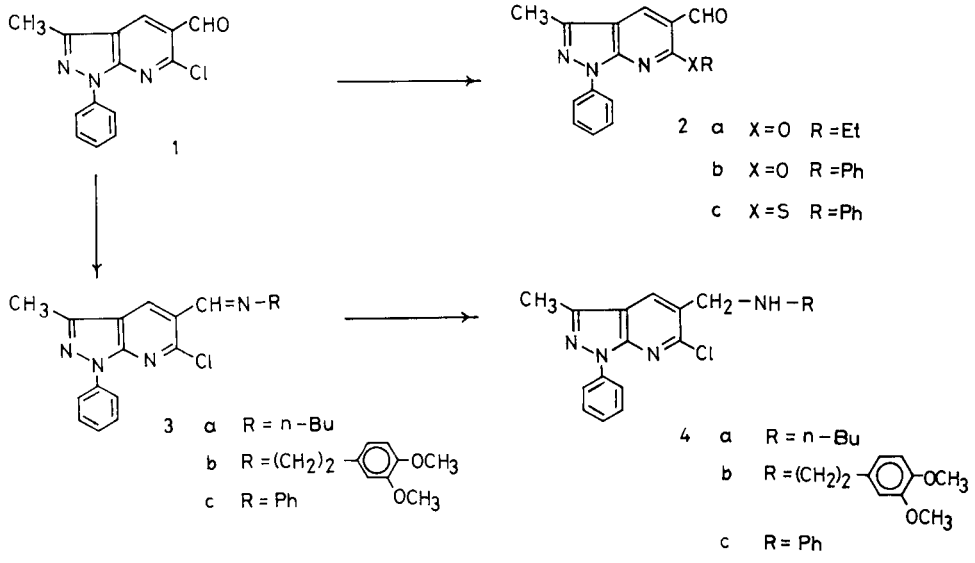
Intramolecular combination of nucleophilic substitution and aldehyde condensation reactions leading to compounds **2** and **3**, respectively, gave rise to the title ring systems. Thus, treating **1** with 2-aminophenol the azomethine derivative **3d** was obtained. In the reaction of **1** and 2-aminothiophenol, however, exclusively the benzothiazoline derivative **5** was isolated, in accordance with literature data (5-7). Structure **5** is supported by spectroscopic evidences listed in the Experimental.

Reaction of compounds **3d** and **5** with ethanolic sodium ethoxide resulted in the formation of **8** and **9**, derivatives of the novel ring systems pyrazolo[4',3':5,6]pyrido[2,3-*b*]-[1,5]benzoxazepine and pyrazolo[4',3':5,6]pyrido[2,3-*b*]-[1,5]benzothiazepine, respectively. Both the cyclization of **3d** to **8** and the ring-transformation of **5** to **9** proceeds probably *via* the non-isolated anionic intermediates **6** and **7** (6), respectively.

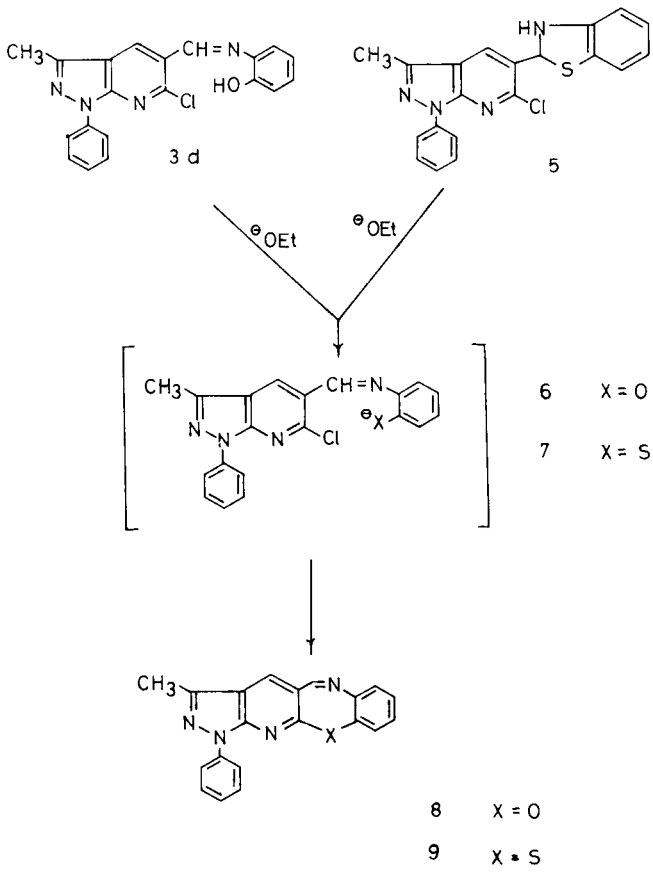
EXPERIMENTAL

Melting points are uncorrected. Ultraviolet spectra were recorded on a Unicam SP-800A spectrometer in 96% ethanol, infrared spectra on a Zeiss UR-20 instrument in potassium bromide, nmr spectra on a Bruker

Scheme 1



Scheme 2



WP-80 (80 MHz) spectrometer in deuteriochloroform. Spectral data are given as λ max (log ε) in nm, ν max in cm^{-1} and δ in ppm, respectively.

1-Phenyl-3-methyl-6-chloropyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**1**).

1-Phenyl-3-methyl-5-acetylaminopyrazole (21.5 g, 0.1 mole) and phosphoryl chloride (46.0 ml, 0.5 mole) were warmed for 3 hours at 90-95°. Dimethyl formamide (24.5 ml, 0.3 mole) was added dropwise while stirring and warming was continued for 2 hours. After pouring into ice-water the solid product was filtered, washed with water and dried. Two-fold recrystallization from glacial acetic acid gave 11.2 g (41%) of compound **1**, mp 184-186°; uv: 264 (4.35), 270 (4.26), 317 (3.76); ir: 1693 ms (C=O); nmr: 2.65 (s, 3H, CH_3), 7.3-8.3 (m, 5H, aromatic), 8.62 (s, 1H, C_4-H), 10.50 (s, 1H, aldehyde).

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.88; H, 3.71; Cl, 13.05; N, 15.47. Found: C, 61.74; H, 3.43; Cl, 12.65; N, 15.30.

1-Phenyl-3-methyl-6-ethoxypyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**2a**).

To an ethanolic sodium ethoxide solution prepared from 0.23 g, (10 mmoles) of sodium and 40 ml of ethanol, compound **1** (2.72 g, 10 mmoles) was added. This mixture was refluxed for 4 hours. On cooling overnight, there was obtained 1.72 g (61%) of crystalline **2a**, mp 139-142° (ethanol); uv: 252 (4.12), 271 (4.38), 336 (4.02); ir: 1690 s (C=O), 1212 ms, 1045 ms, (C-O-C); nmr: 1.50 (t, J = 7 Hz, 3H, CH_3), 2.56 (s, 3H, C_3-CH_3), 4.58 (q, J = 7 Hz, 2H, CH_2), 7.05-8.3 (m, 5H, aromatic), 8.44 (s, 1H, C_4-H), 10.35 (s, 1H, aldehyde).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.36; N, 14.94. Found: C, 68.23; H, 5.37; N, 14.89.

1-Phenyl-3-methyl-6-phenoxypyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**2b**).

To an ethanolic sodium ethoxide solution prepared from 0.20 g (8.7 mmoles) of sodium and 20 ml of ethanol, 0.85 g of phenol (9 mmoles) was added. To this solution, 2.0 g (7.4 mmoles) of compound **1** was added and the mixture was refluxed for 4 hours. After cooling overnight, the solid was separated, filtered and recrystallized from ethyl acetate to give 1.12 g (46%) of **2b**, mp 182-185°; uv 274 (4.18), 332 (3.74); ir: 1690 m (C=O); nmr: 2.62 (s, 3H, CH_3), 7.05-8.1 (m, 10H, aromatic), 8.62 (s, 1H, C_4-H), 10.58 (s, 1H, aldehyde).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.93; H, 4.60; N, 12.76. Found: C, 72.76; H, 4.52; N, 12.78.

1-Phenyl-3-methyl-6-phenylthiopyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**2c**).

This compound was prepared in 65% yield as described for **2b** using thiophenol instead of phenol, mp 178-180° (1-butanol); uv: 292 (4.26); ir: 1694 m (C=O); nmr: 2.59 (s, 3H, CH_3), 7.0-8.0 (m, 10H, aromatic), 8.38 (s, 1H, C_4-H), 10.29 (s, 1H, aldehyde).

Anal. Calcd. for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.37; N, 12.16; S, 9.28. Found: C, 70.04; H, 4.58; N, 12.25; S, 9.23.

1-Phenyl-3-methyl-5-(*N*-substituted)iminomethylene-6-chloropyrazolo[3,4-*b*]pyridines (**3**). General Procedure.

To 2.7 g (10 mmoles) of compound **1** in 120 ml of ethanol, 10 mmoles of the appropriate amine was added and the mixture was refluxed for 2 hours. After evaporation to a small volume (in the case of **3a** and **b**) and/or cooling, the crystalline product was filtered, dried and recrystallized.

According to the above general method the following compounds were prepared:

1-Phenyl-3-methyl-5-(1-butyl)iminomethylene-6-chloropyrazolo[3,4-*b*]-pyridine (**3a**).

This compound was obtained in 79% yield, mp 92-94° (isopropyl alcohol); uv: 274 (4.50), 335 sh (3.71); ir: 1639 m (C=N); nmr: 0.97 (t, J = 6.5 Hz, 3H, C-CH_3), 1.15-2.05 (m, 4H, CH_2-CH_2), 2.63 (s, 3H, C_3-CH_3), 3.72 (t, J = 6.5 Hz, 2H, N-CH_2), 7.1-8.3 (m, 5H, aromatic), 8.67, 8.72 (2 × s, 2H, C_4-H and azomethine).

Anal. Calcd. for $C_{18}H_{19}ClN_4$: C, 66.15; H, 5.86; Cl, 10.85; N, 17.14. Found: C, 66.64; H, 5.68; Cl, 10.48; N, 17.10.

1-Phenyl-3-methyl-5-[2-(3,4-dimethoxyphenyl)ethyl]iminomethylene-6-chloropyrazolo[3,4-*b*]pyridine (**3b**).

This compound was obtained in 83% yield, mp 121-123° (methanol); uv: 275 (4.29), 338 sh (3.48); ir: 1635 m (C=N), 1240 m, 1040 m (CH_3-O-C); nmr: 2.64 (s, 3H, C_3-CH_3), 2.85 (t, J = 7.5 Hz, 2H, C-CH_2), 3.84 (s, 6H, OCH_3),3.94 (t, J = 7.5 Hz, 2H, N-CH_2), 6.77 (s, 3H, dimethoxyphenyl), 7.2-8.3 (m, 5H, N_1-phenyl), 8.63, 8.70 (2 × s, 2 × 1H, C_4-H and azomethane).

Anal. Calcd. for $C_{24}H_{23}ClN_4O_2$: C, 66.28; H, 5.33; Cl, 8.15; N, 12.88. Found: C, 65.99; H, 4.92; Cl, 8.59; N, 12.38.

1-Phenyl-3-methyl-5-phenyliminomethylene-6-chloropyrazolo[3,4-*b*]-pyridine (**3c**).

This compound was obtained in 87% yield, mp 164-166° (ethyl acetate); uv: 280 (4.12), 314 (3.86); ir: 1645 sh (C=N); nmr: 2.66 (s, 3H, CH_3), 7.1-8.3 (m, 10H, aromatic), 8.89, 8.92 (2 × s, 2H, C_4-H and azomethine).

Anal. Calcd. for $C_{20}H_{15}ClN_4$: C, 69.26; H, 4.36; Cl, 10.22; N, 16.16. Found: C, 69.27; H, 4.26; Cl, 10.20; N, 16.05.

1-Phenyl-3-methyl-5-(2-hydroxyphenyl)iminomethylene-6-chloropyrazolo-[3,4-*b*]pyridine (**3d**).

This compound was obtained in 86% yield; mp 232-233° (chloroform); uv: 266 sh, 277, 320 (due to insufficient solubility log ε cannot be given); ir: 3410 m, br (OH), 1615 sh (C=N); nmr: 2.69 (s, 3H, CH_3), 6.75-8.3 (m, 9H, aromatic), 8.78, 9.13 (2 × s, 2 × 1H, C_4-H and azomethine).

Anal. Calcd. for $C_{20}H_{15}ClN_4O$: C, 66.20; H, 4.17; Cl, 9.77; N, 15.44. Found: C, 65.75; H, 4.13; Cl, 10.03; N, 15.40.

1-Phenyl-3-methyl-5-(2,3-dihydro-2-benzothiazolyl)-6-chloropyrazolo[3,4-*b*]pyridine (**5**).

This compound was prepared from **1** and 2-aminothiophenol according to the general procedure given for compounds **3**. The yield obtained was 92%, mp 188-190° (benzene); uv: 261, 314 (due to insufficient solubility log ϵ cannot be given); ir: 3368 s (NH); nmr: 2.58 (s, 3H, CH_3), 4.5 (broad d, J = 4.5 Hz, 1H, NH), 6.68 (d, J = 4.5 Hz, 1H, C_5-CH), 6.7-8.3 (m, 9H, aromatic), 8.47 (s, 1H, C_4-H).

Anal. Calcd. for $C_{20}H_{15}ClN_4S$: C, 63.40; H, 3.99; Cl, 9.36; N, 14.79; S, 8.46. Found: C, 63.05; H, 3.54; Cl, 9.16; N, 14.45; S, 8.31.

1-Phenyl-3-methyl-5-(1-butyl)aminomethyl-6-chloropyrazolo[3,4-*b*]pyridine (**4a**).

To 0.98 g (3 mmoles) of compound **3a** dissolved in 50 ml of methanol, 0.12 g (3 mmoles) of sodium borohydride was added in small portions. After standing overnight at room temperature the reaction mixture was evaporated to a small volume and diluted with water to precipitate 0.84 g (85%) of **4a**, mp 90-93° (ethanol); uv: 260 (4.23), 322 (3.40); ir: 3300 w (NH); nmr: 0.95 (t, J = 6.5 Hz, 3H, C-CH_3), 1.1-1.8 (m, 5H, CH_2-CH_2 and NH), 2.61 (s, 3H, C_3-CH_3), 2.70 (t, J = 6.5 Hz, 2H, N-CH_2), 3.97 (s, 2H, C_5-CH_2), 7.1-8.3 (m, 5H, aromatic), 8.08 (s, 1H, C_4-H).

Anal. Calcd. for $C_{18}H_{21}ClN_4$: C, 65.74; H, 6.44; Cl, 10.78; N, 17.04. Found: C, 65.43; H, 6.44; Cl, 11.09; N, 17.43.

1-Phenyl-3-methyl-5-[2-(3,4-dimethoxyphenyl)ethyl]aminomethyl-6-chloropyrazolo[3,4-*b*]pyridine (**4b**).

This compound was prepared in 75% yield from **3b** as described for **4a**, mp 120° (acetonitrile); uv: 261 (4.24), 323 (3.40); ir: 3295 w (NH), 1262 s, 1040 m (CH_3-O-C); nmr: 2.0 (broad s, 1H, NH), 2.58 (s, 3H, C_3-CH_3), 2.86, 2.89 (2 × t, J = 5 Hz, 4H, CH_2-CH_2), 3.83 (s, 6H, OCH_3), 4.00 (s, 2H, C_5-CH_2), 6.77 (broad s, 3H, trimethoxyphenyl), 7.05-8.3 (m, 5H, N_1-phenyl), 8.02 (s, 1H, C_4-H).

Anal. Calcd. for $C_{24}H_{25}ClN_4O_2$: C, 65.96; H, 5.76; Cl, 8.12; N, 12.83. Found: C, 65.51; H, 5.58; Cl, 8.15; N, 12.74.

1-Phenyl-3-methyl-5-phenylaminomethyl-6-chloropyrazolo[3,4-*b*]pyridine (**4c**).

This compound was prepared in 44% yield from **3c** as described for **4a**, mp 170-173° (toluene); uv: 260, 325 (due to insufficient solubility log ϵ cannot be given); ir: 3280 m, br (NH); nmr: 2.56 (s, 3H, CH_3), 4.2 (broad s, 1H, NH), 4.52 (s, 2H, C_5-CH_2), 6.5-8.4 (m, 10H, aromatic), 8.03 (s, 1H, C_4-H).

Anal. Calcd. for $C_{20}H_{17}ClN_4$: C, 68.85; H, 4.91; Cl, 10.16; N, 16.06. Found: C, 68.96; H, 4.78; Cl, 9.88; N, 16.15.

1-Phenyl-3-methyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzoxazepine (**8**).

To an ethanolic sodium ethoxyde solution prepared from 0.12 g (5 mmoles) of sodium and 60 ml of ethanol 1.8 g (5 mmoles) of compound **3d** was added. The mixture was refluxed for 2 hours, then evaporated to a small volume and diluted with water to give 0.88 g (54%) of compound **8**, mp 188-190° (methanol); uv: 243 (4.15), 277 (4.01), 336 (3.79); nmr: 2.62 (s, 3H, CH_3), 7.1-8.3 (m, 9H, aromatic), 8.09, 8.53 (2 × s, 2 × 1H, C_4-H and C_5-H).

Anal. Calcd. for $C_{20}H_{14}N_4O$: C, 73.60; H, 4.32; N, 17.16. Found: C, 73.13; H, 4.26; N, 17.09.

1-Phenyl-3-methyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzothiazepine (**9**).

This compound was prepared in 70% yield from **5** as described for compound **8**, mp 218-220° (methanol); uv: 254, 290, 340 sh (due to insufficient solubility log ϵ cannot be given); nmr: 2.59 (s, 3H, CH_3), 7.05-8.35 (m, 9H, aromatic), 7.98, 8.80 (2 × s, 2 × 1H, C_4-H and C_5-H).

Anal. Calcd. for $C_{20}H_{14}N_4S$: C, 70.15; H, 4.12; N, 16.36; S, 9.37. Found: C, 70.30; H, 4.22; N, 16.44; S, 9.54.

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