Synthesis of Pyrido[3,2-*c*]pyridazines

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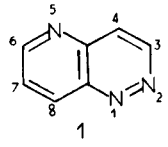
Received December 23, 1981

The synthesis of some 3-methylpyrido[3,2-*c*]pyridazines substituted at positions 6 and 6,7 is described. The first step of the preparation of an aza analog of ellipticine is studied.

J. Heterocyclic Chem., **20**, 101 (1983).

We recently described in this journal (1) the synthesis of the first aminoaldehyde of pyridazine **2**.

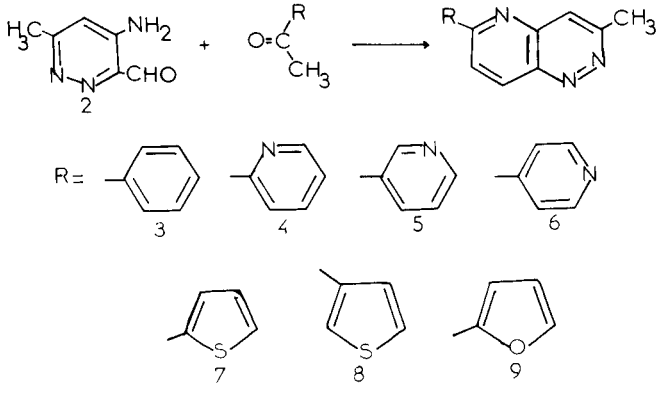


1

Prior to this synthesis of the *o*-amino aldehyde **2**, the pyrido[3,2-*c*]pyridazine system **1** was accessible only by a cycloaddition of azacarboxylates to 2-vinyl pyridine (2,3,4) the availability of **2** now permits the exploitation of this ring system.

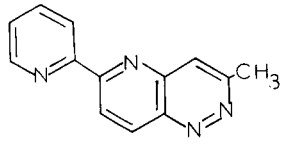
I. Synthesis of 6-Aryl-3-methylpyrido[3,2-*c*]pyridazine.

By action of aromatic ketones upon **1** we could prepare series of 6-aryl substituted 3-methylpyrido[3,2-*c*]pyridazines.



Assignment of H_4, H_7 and H_8 was done with reference to the nmr spectra of **3** first published by Jones and Rafferty (3), moreover, H_7 and H_8 have a coupling constant of 9 Hz in all the compounds **3** to **9**.

The study of the nmr spectra of compounds **3** to **9** shows a particular feature for compound **4**.

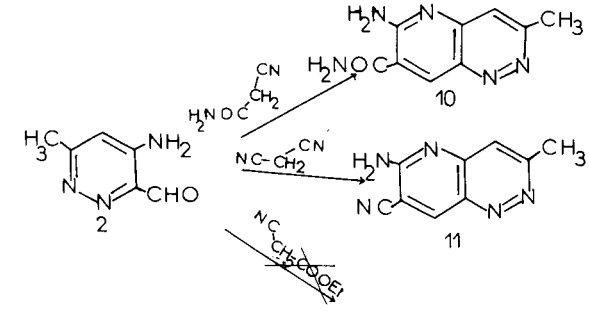


4

The H_7 in **4** is deshielded $\Delta\delta > 0.5$ ppm, this effect is attributed to the proximity of the nitrogen atom in planar formula **4**. The two nitrogen atoms N5 and N2′ repulse each other and 4 is a planar molecule like 2-2′-bipyridines (8). For thienyl and furyl products **7, 8, 9** such an effect was not encountered; the geometry of these ring systems are different and the deshielding effect of the pyridine nucleus is greater than those of thiophene and furan.

II. Synthesis of 3-Methylpyrido[3,2-*c*]pyridazines Possessing Reactive Groups in Positions 6 and 7.

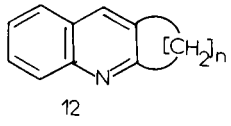
We have used the Friedlander (10) reaction to prepare pyridopyridazines having reactive groups in positions 6 and 7. We attempted the condensation of 6-methyl-4-aminopyridazine-3-carboxaldehyde (**2**) with malonic acid derivatives such as cyanoacetamide; malononitrile and ethyl cyanoacetate.



Cyanoacetamide gave a good yield in 6-amino-7-carbamoyl-3-methylpyrido[3,2-*c*]pyridazine (**10**) which was easily isolated. With malononitrile we obtained a crude product mainly structure **11** which was identified by its nmr spectra, however, purification was not accomplished. The reaction of ethyl cyanoacetate with **2** gave no product.

III. 3-Methyl-6,7-cyclopolymethylenylpyrido[3,2-*c*]pyridazines **12**.

Thummel and Kohli (12) as well as Ruzicka and Goldberry (13) have shown that cyclopolymethylenylnaphthyridines and quinolines **12** had cardiotonic properties. The cardiotonic effect reaches a maximum when n = 6 and disappears when n = 13.



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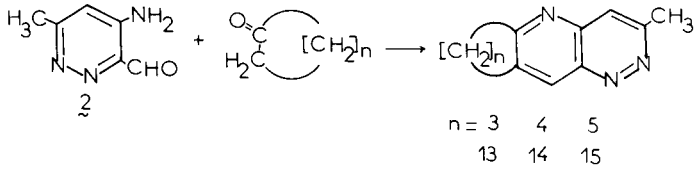
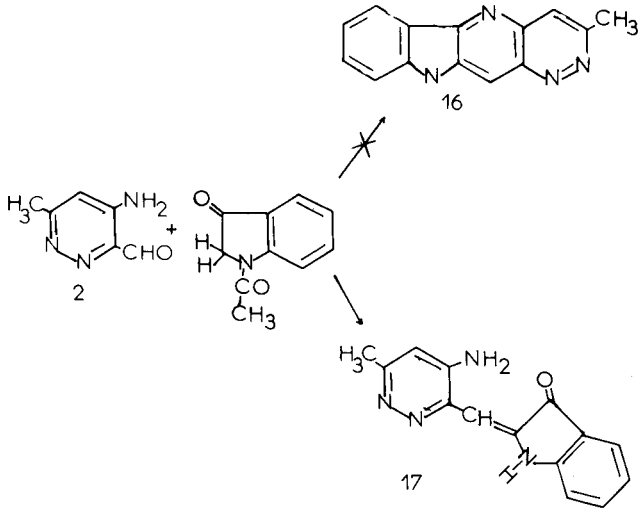
By condensation of **2** with C_5, C_6, C_7 cyclanones we obtained the following similar compounds.



n = 3 4 5
13 14 15

IV. Condensation With Acetylindolinone.

We attempted to condense acetylindolin-3-one with **2** to prepare the 3-methylindolo[2,3-*b*]pyrido[3,2-*c*]pyridazine **16** which is an azaanalogue of a well known antitumor agent, ellipticine (6,7).



We obtained a metallic red compound which was not the expected azaellipticine product, but rather compound **17** was obtained. The spectral characteristics of this product are given as follows: the mass spectra shows a molecular ion [M⁺] = 252 with the characteristic fragmentation of pyridazine (-HCN) 225. In the nmr spectra the signal at 10.18 ppm (CHO aldehyde) is absent and there are two complex signals between 7.66-7.17 (3H) and 6.91-6.43 (4H). The methyl group of pyridazine is still present at 2.33 ppm. The infrared spectra shows signals at 3360, 3320, 3120 cm^{-1} corresponding to NH and OH vibration and a ν C=O at 1670 cm^{-1}; for *N*-acetylindolin-3-one, ν C=O = 1680 cm^{-1}.

All of these observations lead to the conclusion that only one condensation has occurred between the aldehyde group of pyridazine and the methylene group of *N*-acetylindolin-3-one leading to compound **17**. In the literature, Majewich (13) has observed such a type of condensation while allowing 2-amino-3-formylpryidine to react with cyclohexane-1,4-dione.

EXPERIMENTAL

Preparation of 6-Aryl-3-methylpyrido[3,2-*c*]pyridazines. Model Procedure.

To 200 mg (1.46 mmoles) of 4-amino-6-methylpyridazine-3-carboxaldehyde (**2**) in ethanol, 1.46 mmoles of the ketone and three drops of a 10% alcoholic solution of potassium hydroxide was added. The solution was refluxed and the solvent evaporated under vacuum. The compound was purified by continuous extraction with ligroin and recrystallised from the same solvent.

Compound **3**, **4**, **5**, **6**, **7**, **8** and **9** were prepared by the above procedure.

3-Methyl-6-[2'-pyridyl]pyrido[3,2-*c*]pyridazine (**4**).

2-Acetylpyridine was refluxed for 2 hours and 167 mg (52%) of compound **4** was obtained, mp 197°; ir (potassium bromide): ν cm^{-1} 3050 (CH), 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3), 2.97 (s), H_4 7.85 (s), H'_4 8.0-7.67 (m); H_7, H_8, H'_3, H'_6 8.78-8.5 (m), $J_{7,8}$ = 9 Hz, H'_5 7.48-7.18 (m).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.35; H, 4.67; N, 25.19.

3-Methyl-6-[3'-pyridyl]pyrido[3,2-*c*]pyridazine (**5**).

3-Acetylpyridine was refluxed for 2 hours and 207 mg (64%) of **5** was obtained, mp 188°; ir (potassium bromide): ν cm^{-1} 3050 (CH), 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3) 3.03 (s), H_4 7.93 (s), H_7 8.13 (d) $J_{7,8}$ = 9 Hz, H_8 8.87 (d), $J_{8,7}$ = 9 Hz, H'_2 9.4 (s), H'_2 8.53 (m), H'_5 7.57-7.27 (q), H'_6 8.8 (s).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.46; H, 4.81; N, 24.97.

3-Methyl-6-[4'-pyridyl]pyrido[3,2-*c*]pyridazine (**6**).

4-Acetylpyridine was refluxed for 2 hours and 136 mg (42%) of **6** was obtained after recrystallisation in ethanol, mp 181°; ir ν cm^{-1} 3075, 3025 (CH), 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3) 3.07 (s), H_4, H_7, H'_3, H'_5 8.27-7.97 (m); $J_{7,8}$ = 9 Hz, H_8, H'_2, H'_6 9-8.83 (m); $J_{8,7}$ = 9 Hz.

3-Methyl-6-[2'-thienyl]pyrido[3,2-*c*]pyridazine (**7**).

2-Acetylthiophene was refluxed for 1 hour and 175 mg (53%) of **7** was obtained, mp 156°; ir (potassium bromide): ν cm^{-1} 3050 (CH, 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3) 2.95 (s), H_7 7.95 (d), $J_{7,8}$ = 9 Hz, H_8 8.6 (d), $J_{8,7}$ = 9 Hz, H_4, H'_3 7.72 (s), H'_4 7.27-7.06 (m), H'_5 7.55 (d), $J_{4',5'}$ = 5 Hz.

Anal. Calcd. for $C_{12}H_9N_3S$: C, 63.41; H, 3.99; N, 18.48. Found: C, 62.95; H, 4.39; N, 18.48.

3-Methyl-6-[3'-thienyl]pyrido[3,2-*c*]pyridazine (**8**).

3-Acetylthiophene was refluxed for 1 hour and 170 mg (51%) of **8** was obtained, mp 158°; ir (potassium bromide): ν cm^{-1} 3080 (CH), 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3) 2.96 (s), H'_4 7.37-7.5 (m), H_7 8.0 (d), $J_{7,8}$ = 9 Hz, H_8 8.7 (d), $J_{8,7}$ = 9 Hz, H_4 7.8 (s), H'_4, H'_5 7.37-7.5 (m), H'_2 8.1.

Anal. Calcd. for $C_{12}H_9N_3S$: C, 63.41; H, 3.99; N, 18.48. Found: C, 63.12; H, 4.28; N, 18.35.

3-Methyl-6-[2'-furyl]pyrido[3,2-*c*]pyridazine (**9**).

2-Acetyl furan was refluxed for 1 hour and 168 mg (55%) of **9** was obtained, mp 170°; ir (potassium bromide ν cm^{-1} 3090 (CH) 1600 (C=C, C=N); nmr (deuteriochloroform): δ ppm H(CH_3) 2.96 (s), H_4 7.84 (s), H_7 8.03 (d), $J_{7,8}$ = 9 Hz, H_8 8.7 (d), $J_{8,7}$ = 9 Hz, H'_3 7.7 (s), H'_4 6.60-6.5 (m),

H'$_5$ 7.37 (d), J = 3 Hz.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.07; H, 4.50; N, 20.09.

3-Methyl-6-phenylpyrido[3,2-*c*]pyridazine (**3**).

Acetophenone was refluxed for 2 hours and 170 mg (53%) of **3** was obtained, mp 169°; ir (potassium bromide): ν cm^{-1} 3050, 3030, 3010 (CH), 1600 (C=C, C=N); nmr (deuteriochloroform): δ H(CH_3) 3.0 (s), H_4 7.90 (s), $J_{7,8}$ = 9 Hz, H'$_3$, H'$_4$, H'$_5$ 7.63-7.46 (m), H'$_2$, H'$_6$, H_7 8.3-8.07 (m), H_8 8.80 (d), $J_{8,7}$ = 9 Hz.

3-Methyl-6-amino-6-carbamoylpyrido[3,2-*c*]pyridazine (**10**).

To 200 mg (1.46 mmoles) of aminoaldehyde **2** in 10 ml of absolute ethanol was added 122 mg (1.46 mmoles) of 2-cyanoacetamide and three drops of a 10% alcoholic solution of potassium hydroxide. We then refluxed it for 2 hours and cooled it in ice. The product **10** precipitated and was recrystallised from absolute ethanol to give 197 mg (66%) of a white solid, mp >250° sublimes; ir (potassium bromide): ν cm^{-1} 3360, 3300 (NH_2), 3140 (CH), 1690 (C=O), 1645 (C=C, C=N); nmr (dimethylsulfoxide): δ ppm/HMDS, H(CH_3) 2.75 (s), H_8 8.8 (s), 7.4 (s), H(NH_2) 7.9, 8.5, 8.05.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.20; H, 4.46; N, 37.46. Found: C, 52.95; H, 4.81; N, 37.09.

3-Methyl-6-amino-7-cyanopyrido[3,2-*c*]pyridazine (**11**).

To 200 mg (1.46 mmoles) of aminoaldehyde **2** in 10 ml of absolute ethanol was added 95 mg (1.46 mmoles) of malononitrile and three drops of a 10% alcoholic solution of potassium hydroxide. The mixture was refluxed for 2 hours and cooled in ice. A black oil, mainly insoluble in the usual solvents except DMSO, was obtained. The analysis of nmr spectra indicates the main product of the crude oil is 3-methyl-6-amino-6-cyanopyrido[3,2-*c*]pyridazine (**11**) which could not be further purified; nmr (dimethylsulfoxide): δ ppm/HMDS, H(CH_3) 2.70 (s), H_4 7.38 (s), H_8 9.0 (s), H(NH_2) 7.78 (s).

3-Methyl-6,7-cyclopolymethylenylpyrido[3,2-*c*]pyridazine.

To 200 mg (1.5 mmoles) of 6-methyl-4-aminopyridazine-3-carboxaldehyde in 10 ml of aboslute ethanol was added 1.5 mmoles of the cyclic ketone and 5 drops of a 10% alcoholic solution of potassium hydroxide. The mixture refluxed and the solvent was evaporated in vacuum. The product was extracted in a Soxhlet extractor with ligroin and was further purified by recrystallization from hexane or by thin layer chromatography.

3-Methyl-6,7-dihydrocyclopentapyrido[3,2-*c*]pyridazine (**13**).

Cyclopentanone was refluxed for ½ hour and purification was accomplished by thin layer chromatography with silica gel and chloroform with 2% ethanol as the eluent. We obtained 129 mg (48%) of **13**, mp 188°; ir (potassium bromide): ν cm^{-1} 3030, 2990, 2950, 2900 (CH), 1605, 1580 (C=C, C=N); nmr (deuteriochloroform): δ ppm/TMS, (CH_2) 2.96-3.36 (m) 4H, (CH_2) 2.1-2.56 (q) 2H, CH_3 2.98 (s), H_4 7.77, H_8 8.42.

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.38; H, 6.20; N, 22.57.

3-Methyl-6,7-dihydrocyclohexapyrido[3,2-*c*]pyridazine (**14**).

Cyclohexanone was refluxed for ½ hour and purification was accomplished as for compound **13**. We obtained 117 mg (54%) of **15**, mp 98°; ir (potassium bromide): ν cm^{-1} 3020, 2930, 2860 (CH), 1600 1580 (C=C, C=N); nmr (deuteriochloroform): δ ppm (CH_2), 1.87-2.13 (m) 2H, (CH_2) 3-3.2 (m) 4H, CH_3 2.96 (s), H_8 8.38 (s), H_4 7.73 (s).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.09. Found: C, 72.20; H, 6.76; N, 20.95.

3-Methyl-6,7-dihydrocycloheptapyrido[3,2-*c*]pyridazine (**15**).

Cycloheptanone was refluxed for 12 hours and purification was accomplished by recrystallisation from hexane. We obtained 167 mg (72%) of **5** mp 108°; ir (potassium bromide): ν cm^{-1} 3030, 2970, 2950, 2920, 2840 (CH), 1610, 1580 (C=C, C=N); nmr (deuteriochloroform): δ ppm CH_2 1.88 (s) 6H, CH_2 3.0-3.3 (m) 4H, CH_3 2.95 (s), H_4 7.73 (s), H_8 8.33 (s).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.57; H, 7.10; N, 19.39.

2-(4-Amino-6-methyl-3-pyridazinylmethylenylindolin-3-one (**17**).

To 200 mg (1.46 mmoles) of 4-amino-6-methylpyridazine-4-carboxaldehyde (**2**) in 100 ml of ethanol was added 260 mg (1.46 mmoles) of *N*-acetylindolin-3-one under an atmosphere of argon. After 1 hour of contact with a slight stream of argon we added five drops of a 10% solution of alcoholic potassium hydroxide. The reaction was continued during 24 hours after which the product began to crystallize. The product cooled in an ice bath, filtered and washed with ethanol. We obtained 155 mg of the strongly coloured red product **1**, mp >250° dec; ir (potassium bromide): ν cm^{-1} 3360, 3320 (NH), 3120 (OH), 1670 (CO), 1620, 1570 (C=C, C=N); nmr (dimethylsulfoxide): δ ppm H(CH_3) 2.33 (s), H 6.91-6.43 (m) 3H, H 7.66-7.17 (m) 5H; ms: (75 eV) m/e M^+, 252, (-HCN), 225.

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