Acetylenic Chemistry: Part 15 [1]. Reactions of 1,2,3,4-Tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine with 3-Bromoprop-1-yne

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Reaction of 1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine with 3-bromoprop-1-yne gave 1-prop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4a**), 3-prop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4b**), and 1,3-diprop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4c**). Subsequent boiling of 1,3-diprop-2'-ynylpyrido-[2,3-*d*]pyrimidine-2,4-dione (**4c**) in formic acid afforded 1-methylimidazo[1,2-*a*]pyridyl-*N*-prop-2'-ynylamide (**5**) and 1-acetonyl-3-prop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**6**).

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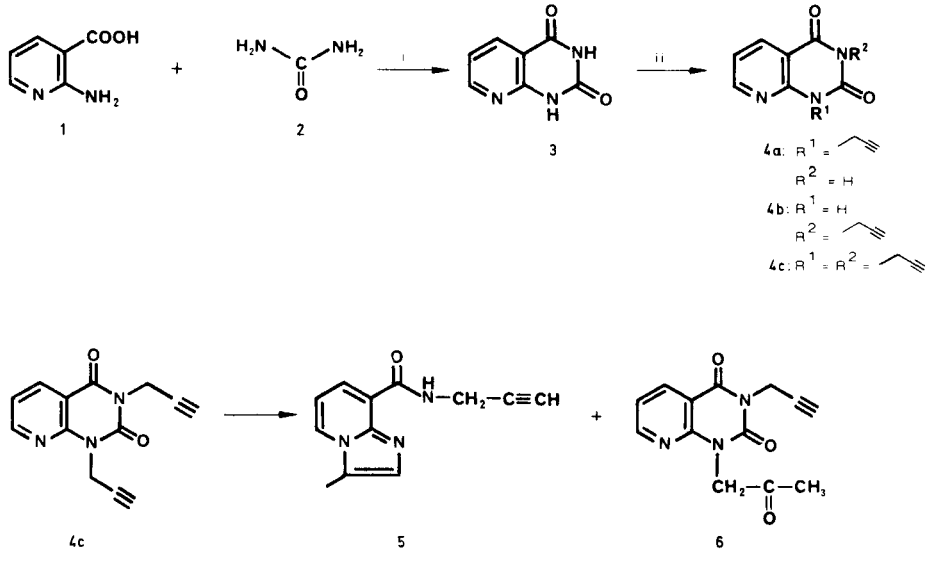
Compounds whose chemical structures are unrelated to any known compound highlighted for future anti-ulcer therapy are of general interest and possess important biological properties [3,4,5,6,7]. Some of these compounds contain the imidazo[1,2-*a*]pyridyl-unit present in 1-methylimidazo[1,2-*a*]pyridyl-*N*-prop-2'-ynylamide (**5**).

Substitution on related ring systems to 1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine (**3**) have been carried out with 3-bromoprop-1-yne in the presence of sodium hydride in dimethylformamide [8]. Using 3-bromoprop-1-yne in 50% methanol in the presence of sodium hydroxide, **3** gave **4a**, **4b** and **4c**. The isolation and purification methods were more convenient and the yields were higher [9].

An increase in the yield of **4c** was observed with a corresponding decrease in the yield of **4a** and **4b** with excess 3-bromoprop-1-yne. It was also observed that the yield of **4a** was higher than that of **4b**. The cyclization of **4c** to **5** in boiling formic acid also afforded **6** which resulted from hydration [10,11].

The structures of the compounds were unequivocally assigned by ir, nmr, ms and elemental analysis. The triple bond of the acetylene appeared at 2100 cm^{-1} while the carbonyl absorptions were centered at 1740-1670 cm^{-1} in the ir spectra. The ^1H nmr spectra showed the presence of long range coupling with a coupling constant of about 2.5 Hz. A distinct triplet for the acetylene proton and a doublet for the methylene protons were evident.



Scheme

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 ir spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in the appropriate solvent at 200 MHz with tetramethylsilane as internal reference on a Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV. Silica gel 60 F_{254} (pre-coated aluminium sheets, 0.2 mm thickness; Merck 5549) were used for analytical tlc. 2-Aminonicotinic acid was obtained from Sprengstoff-Fabrik AG, Switzerland and 3-bromoprop-1-yne from Ega-Chemie, West Germany.

1,2,3,4-Tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine (**3**) [12].

2-Aminonicotinic acid (**1**), 5 g (0.036 mole) and urea (**2**), 9 g (0.15 mole) were finely ground and gradually heated together in a porcelain boat until 185°. After 15 minutes the temperature was raised to 200° until the clear melt became mushy. Heating was stopped after raising it to 210°. It was then cooled, dissolved in 100 ml of 2*N* sodium hydroxide by warming. Subsequent precipitation and recrystallisation from glacial acetic acid gave 1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine (**3**) as colorless crystals [12] 3.3 g (66%), mp >350°; ir (potassium bromide): 3150, 3080, (NH), 1730, 1680 (C=O) cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 7.80 (t, J = 6.2 Hz, 1H, H-6), 8.90 (dd, J = 1.4, 6.1 Hz, 1H, H-7), 9.28 (dd, J = 1.3, 7.8 Hz, 1H, H-5); ^{13}C nmr (deuteriotrifluoroacetic acid): δ 115.9 (C-4a), 122.8 (C-6), 147.8 (C-7), 148.9 (C-5), 150.2 (C-8a), 151.8 (C-2), 162.4 (C-4); ms: (m/e) 163 (M^+, 100), 120 (56), 93 (68), 65 (28).

Alkylation of 1,2,3,4-Tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine (**3**) with 3-Bromoprop-1-yne.

To 1.0 g (0.006 mole) 1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]-pyrimidine (**3**) in 25 ml 50% methanol was added 0.24 g (0.006 mole) sodium hydroxide and stirred at room temperature for 30 minutes. 3-Bromoprop-1-yne 0.83 g (0.007 mole) was added and the reaction mixture gradually heated to reflux and maintained at reflux for 4 hours, cooled, treated with 0.7 *N* sodium hydroxide to dissolve the monoalkylated products **4a** and **4b**. The green insoluble dialkylated product **4c** was filtered off and dried. The monoalkylated products **4a** and **4b** were precipitated at *p*H 5 with 5% hydrochloric acid to give a brown solid which was filtered and dried.

Column chromatography was used to purify the compounds and then recrystallised from appropriate solvents.

1-Prop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4a**).

Purification on silica gel of the brown solid (chloroform-ethyl acetate 3:1) afforded as first eluate 1-prop-2′-ynylpyrido[2,3-*d*]-pyrimidine-2,4-dione (**4a**) which were colorless crystals from ethyl acetate 0.15 g (15%) mp 232-233°; ir (potassium bromide): 3280 (≡CH), 3080 (NH), 2100 (C≡C), 1725, 1690 (C=O) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 3.17 (t, J = 2.4 Hz, 1H, H-3′), 4.94 (d, J = 2.4 Hz, 2H, H-2′), 7.34-7.44 (dd, J = 4.8, 7.7 Hz, 1H, H-6), 8.38 (dd, J = 1.9, 7.8 Hz, 1H, H-7), 8.77 (dd, J = 1.9, 4.8 Hz, 1H, H-5), 11.95 (s, 1H, NH); ^{13}C nmr (deuteriodimethyl sulphoxide): δ 30.5 (C-1′), 73.2 (C-3′), 79.5 (C-2′), 111.4 (C-4a), 119.5 (C-6), 137.2 (C-5), 150.0 (C-8a), 150.9 (C-2), 154.3 (C-7), 161.3 (C-4); ms: (m/e) 201 (M^+, 46), 172 (2), 158 (96), 147 (10), 130 (100), 103 (42), 91 (12), 76 (30), 58 (32), 51 (20).

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.89; H, 3.42; N, 21.19.

3-Prop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4b**).

The second eluate from the column (chloroform-ethyl acetate 3:1) of the brown solid gave as colorless needles from ethyl acetate 3-prop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4b**), 0.08 g (8%) mp 240-242°; ir (potassium bromide): 3280 (≡CH), 3020 (NH), 2100 (C≡C), 1720, 1670 (C=O) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 3.17 (t, J = 2.5 Hz, 1H, H-3′), 4.63 (d, J = 2.4 Hz, 2H, H-2′), 7.28-7.35 (dd, J = 4.8, 7.8 Hz, 1H, H-6), 8.35 (dd, J = 1.8, 7.8 Hz, 1H, H-7), 8.66 (dd, J = 1.9, 4.8 Hz, 1H, H-5), 12.15 (s, 1H, NH); ^{13}C nmr (deuteriodimethyl sulphoxide): δ 29.7 (C-1′), 73.2 (C-3′), 79.2 (C-2′), 109.4 (C-4a), 119.5 (C-6), 137.3 (C-5), 149.9 (C-8a), 151.3 (C-2), 155.4 (C-7), 161.3 (C-4); ms: (m/e) 201 (M^+, 58), 172 (20), 159 (14), 147 (16), 130 (14), 119 (12), 103 (8), 93 (12), 84 (100), 72 (18), 65 (14), 58 (64).

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.43; H, 3.37; N, 20.78.

1,3-Diprop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4c**).

Purification by column chromatography of the green solid (chloroform) gave as colorless plates 1,3-diprop-2′-ynylpyrido-[2,3-*d*]pyrimidine-2,4-dione 0.4 g (40%) mp 160-162°; ir (potassium bromide): 3250 (≡CH), 2100 (C≡C), 1728, 1670 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.23 (t, J = 2.5 Hz, 2H, H-3′, 3″), 4.88 (d, J = 2.5 Hz, 2H, H-2″), 5.18 (d, J = 2.5 Hz, 2H, H-2′), 7.26-7.33 (dd, J = 4.8, 7.8 Hz, 1H, H-6), 8.52 (dd, J = 1.9, 7.8 Hz, 1H, H-7), 8.75 (dd, J = 1.9, 4.8 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 31.3 (C-1″), 32.1 (C-1′), 71.4 (C-3′, C-3″), 78.0 (C-2″), 78.6 (C-2′), 111.3 (C-4a), 119.9 (C-6), 138.5 (C-5), 150.2 (C-8a), 150.3 (C-2), 155.0 (C-7), 160.7 (C-4); ms: (m/e) 239 (M^+, 18), 200 (M^+-C_3H_3, 6), 171 (12), 158 (48), 130 (36), 103 (14), 86 (100), 77 (8), 58 (32).

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.39; H, 3.88; N, 17.84.

1,3-Diprop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4c**) in Boiling Formic Acid.

1,3-Diprop-2′-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**4c**) 1 g (0.004 mole) was gradually heated to reflux in 15 ml of formic acid (96%) and maintained at reflux for 3 hours; 100 ml water was added after cooling and extracted into chloroform/2-propanol (3:1) at *p*H 9. The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo*. A column chromatography of the yellowish-green solid on silica gel (ether) afforded **6** as the first eluate and subsequently **5** as the second eluate.

1-Methylimidazo[1,2-*a*]pyridyl-*N*-prop-2′-ynylamide (**5**).

This compound was isolated as colorless plates from methanol to give 1-methylimidazo[1,2-*a*]pyridyl-*N*-prop-2′-ynylamide, 0.15 g (15%), mp 181-182°; ir (potassium bromide): 3500 (NH), 1660 (C=O), 1550, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.23 (t, J = 2.6 Hz, 1H, H-3′), 2.53 (s, 3H, H-2), 4.36 (dd, J = 2.6, 2.6 Hz, 2H, H-1′), 7.00 (t, J = 7.1 Hz, 1H, H-6), 7.44 (s, 1H, H-3), 8.03 (dd, J = 1.2, 6.8 Hz, 1H, H-7), 8.21 (dd, J = 1.2, 7.0 Hz, 1H, H-5), 10.58 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 8.9 (CH_3), 29.2 (C-1′), 71.1 (C-3′), 80.1 (C-2′), 112.0 (C-6), 120.7 (C-1), 121.0] (C-4),

125.8 (C-5), 127.0 (C-7), 130.9 (C-2), 143.4 (C-2a), 163.7 (C = O); ms: (m/e) 213 (M^+, 12), 160 (8), 132 (100), 104 (10), 92 (8), 71 (10), 57 (12).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.47; H, 5.22; N, 19.72.

1-Acetonyl-3-prop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione (**6**).

Isolated as colorless plates from methanol to give 1-acetonyl-3-prop-2'-ynylpyrido[2,3-*d*]pyrimidine-2,4-dione, 0.06 g (6%), mp 138-140°; ir (potassium bromide): 1740, 1720, 1670 (C = O), 1605 (aromat), 1500 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.24 (t, J = 2.6 Hz, 1H, H-3''), 2.50 (s, 3H, C-3'), 4.85 (d, J = 2.5 Hz, 2H, H-1''), 5.21 (s, 2H, C-1'), 7.28 (dd, J = 4.8, 7.8 Hz, 1H, H-6), 8.48 (dd, J = 1.9, 7.8 Hz, 1H, H-7), 8.58 (dd, J = 1.9, 4.8 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 27.2 (C-1''), 31.2 (C-3'), 51.3 (C-1'), 71.4 (C-3''), 78.0 (C-2''), 111.0 (C-4a), 119.8 (C-6), 138.4 (C-5), 150.7 (C-8a), 150.8 (C-2), 154.6 (C-7), 160.7 (C-4), 201.2 (C-2'); ms: (m/e) 257 (M^+, 10), 242 (2), 214 (20), 149 (8), 133 (100), 106 (28), 78 (32), 57 (28).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 60.69; H, 4.31; N, 16.38. Found: C, 60.76; H, 4.21; N, 16.37.

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