Preparation of some Substituted Imidazo[1,2-*a*]pyridine Derivatives

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2-Bromopyridine derivatives **2a-2c** were prepared. Compounds **2b** and **2c** and ammonia yielded aminopyridines **3b** and **3c** which were converted to imidazo[1,2-*a*]pyridine derivatives **4b** and **4c**. Compound **4b** was nitrated giving the analogue **5b** of metronidazole **1**.

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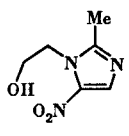
We have recently been interested in the synthesis of imidazo[1,2-*a*]pyridine derivatives **5a** and **5b** as analogues of the anti-bacterial agent metronidazole **1** [1-6]. The 2-aminopyridine derivatives **2b** and **2c** would be potential intermediates in any synthesis as the transformation of 2-aminopyridines into imidazo[1,2-*a*]pyridines is well established [7]. Derivative **2b** would be a direct precursor of analogue **5b** and an indirect precursor of analogue **5a** after demethylation at a suitable stage in the synthesis. Additionally, the methoxyethoxymethyl (MEM) ether substituent [8,9] of derivative **2c** could be removed at an appropriate stage in an alternative synthesis of analogue **5a**. The required 2-aminopyridines would be available from the corresponding 2-bromopyridine derivatives and ammonia [10]. Compounds **2b** and **2c** were both readily synthesised from alcohol **2a** which was prepared by sodium borohydride reduction of either 2-bromopyridine-6-carboxaldehyde [11] or methyl 2-bromopyridine-6-carboxylate [12]. Compounds **2b** and **2c** reacted with aqueous ammonia (180-200°) and gave the required products **3b** (71% yield) and **3c** (93% yield). Compounds **3b** and **3c** were both coverted into their corresponding imidazo[1,2-*a*]pyridine derivatives **4b** and **4c** (89% and 76% yields respectively) when treated with chloroacetaldehyde under basic conditions. Nitration of compound **4b** occurred as expected [7] at the 3-position and yielded the methyl-analogue **5b** (52% yield) of metronidazole **1**. Attempted demethylation of compound **5b** under a variety of conditions to yield analogue **5a** was unsuccessful [8,13]. It was anticipated that compound **5a** might be available from compound **4c** by replacing the MEM group with an alternative protecting group such as acetate prior to the nitration step. However, attempted removal of the MEM group failed to yield any characterisable product, possibly due to the sensitive nature of compound **4c**.



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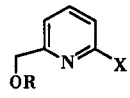
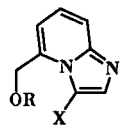


2, X = Br
3, X = NH_2



4, X = H
5, X = NO_2

a, R = H, **b**, R = Me, **c**, R = $CH_2OCH_2CH_2OMe$(MEM)

EXPERIMENTAL

Proton-nmr were determined in deuteriochloroform solution at 90 MHz using tetramethylsilane as an internal standard. Infrared spectra were recorded as liquid films.

2-Bromo-6-hydroxymethylpyridine **2a**.

Method One.

Sodium borohydride (6.8 g) was added slowly to a stirred solution of 2-bromopyridine-6-carboxaldehyde (22.3 g) [11] in methanol (200 ml) at 0°. The mixture was stirred (0.25 hour), heated at reflux (1 hour), allowed to cool to room temperature and then poured into salt water. The mixture was extracted several times with ether, dried (magnesium sulfate) and evaporated giving compound **2a** [14] as a pale yellow liquid, 20 g (89%); ir: ν 3350, 1590, 1560, 1410 and 1125 cm^{-1}; ^1H nmr: δ 7.80-7.10 (3H, m, ArH), 4.70 (2H, s, $>CH_2$) and 3.25 (1H, s, -OH) ppm.

Anal. Calcd. for C_6H_6BrNO: C, 38.3; H, 3.2; N, 7.5; Br, 42.5. Found: C, 38.1; H, 3.2; N, 7.6; Br, 42.9.

Method Two.

A mixture of methyl 2-bromopyridine-6-carboxylate (2.5 g) [12] and sodium borohydride (0.5 g) in ethanol (20 ml) was heated at reflux (2 hours). The mixture was allowed to cool to room temperature, poured into salt water and extracted several times with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated giving compound **2a**, 1.52 g (70%), identical with an authentic sample.

2-Bromo-6-methoxymethylpyridine **2b**.

Sodium hydride (5.09 g) was added slowly over 0.25 hour to a cooled (ice-bath) mixture of compound **2a** (20 g) and methyl iodide (33.2 ml) in anhydrous tetrahydrofuran (THF) (50 ml). The mixture was stirred at 5° (0.5 hour) and then at room temperature (2 hours) before methanol was added cautiously to destroy excess hydride. The mixture was poured into salt water, extracted several times with ether and the organic extracts were dried (magnesium sulfate) and evaporated giving compound **2b**, 19.1 g (89%) [15] as a pale liquid; ir: ν 1590, 1560, 1410 and 1125 cm^{-1}; ^1H nmr: δ 7.50-7.10 (3H, m, ArH), 4.40 (2H, s, $>CH_2$), and 3.40 (3H, s, -OMe) ppm.

Anal. Calcd. for C_7H_8BrNO: C, 41.6; H, 4.0; N, 7.0; Br, 39.6. Found: C, 41.7; H, 4.1; N, 7.2; Br, 39.5.

2-Bromo-6-[(2-methoxyethoxymethoxy)methyl]pyridine **2c**.

To a solution of compound **2a** (18.0 g) in anhydrous THF (75 ml) at 0° was added sodium hydride (5.35 g). After the evolution of hydrogen had ceased, a solution of 2-methoxyethoxymethylchloride (13.83 g) in anhydrous THF (30 ml) was added dropwise.

The mixture was stirred at room temperature (0.5 hour) and a methanol-water solution was then added cautiously to destroy excess hydride. The mixture was evaporated and the residue extracted several times with ether. The organic extracts were washed with salt solution, dried (magnesium sulfate) and evaporated giving compound **2c**, 25.95 g (98%) as a yellow liquid; ir: ν 1580, 1560, 1410, 1125 and 1055 cm^{-1}; ^1H nmr: δ 7.70-7.30 (3H, m, ArH), 4.85 (2H, s, $>CH_2$), 4.70 (2H, s, $>CH_2$), 3.75 (2H, m, $-OCH_2CH_2O-$), 3.55 (2H, m, $-OCH_2CH_2O-$) and 3.55 (3H, s, -OMe) ppm.

Anal. Calcd. for $C_{10}H_{14}BrNO_3$: C, 43.5; H, 5.1; N, 5.1; Br, 28.9. Found: C, 43.4; H, 5.2; N, 5.1; Br, 29.2.

2-Amino-6-methoxymethylpyridine **3b** and 5-Methoxymethylimidazo[1,2-*a*]pyridine **4b**.

Compound **3b**.

A mixture of compound **2b** (15 g) and aqueous ammonia solution (d = 0.880) (75 ml) were heated at 200° for 10 hours. The mixture was allowed to cool to room temperature and extracted several times with dichloromethane. The organic extracts were washed with salt solution, dried (magnesium sulfate) and evaporated giving compound **3b**, 7.32 g (71%) as a yellow oil; ir: ν 3300, 1610, 1470 and 1100 cm^{-1}; ^1H nmr: δ 7.40 (1H, t, J = 9 Hz, ArH), 6.70 (1H, d, J = 9 Hz, ArH), 6.40 (1H, d, J = 9 Hz, ArH), 4.65 (2H, broad s, $-NH_2$), 4.40 (2H, s, $>CH_2$) and 3.45 (3H, s, -OMe) ppm. Compound **3b** was used directly in the preparation of compound **4b**.

Compound **4b**.

A stirred mixture of compound **3b** (4.0 g), sodium bicarbonate (5 g), chloroacetaldehyde (5.5 ml, 45% w/v in water) and methanol (40 ml) was heated at reflux for 3 hours. The mixture was evaporated and the residue was added to salt solution. The mixture was extracted several times with ether, the organic extracts were dried (magnesium sulfate) and evaporated. The resulting dark oil was purified by column chromatography (silica gel, eluent dichloromethane:methanol 95:5) giving compound **4b**, 4.2 g (89%) as a pale liquid which rapidly darkened in air; ir: ν 2930, 1515, 1300 and 1090 cm^{-1}; ^1H nmr: δ 7.65 (3H, m, ArH), 7.15 (1H, t, J = 8 Hz, ArH), 6.80 (1H, d, J = 8 Hz, ArH), 4.65 (2H, s, $>CH_2$) and 3.40 (3H, s, -OMe) ppm. Compound **4b** was converted into its picrate, mp 162-163° (from ethanol) for microanalysis.

Anal. Calcd. for $C_{15}H_{13}N_5O_8$: C, 46.0; H, 3.3; N, 17.9. Found: C, 46.0; H, 3.3; N, 17.8.

2-Amino-6-[(2-methoxyethoxymethoxy)methyl]pyridine **3c** and 5-[(2-Methoxyethoxymethoxy)methyl]imidazo[1,2-*a*]pyridine **4c**.

Compound **3c**.

Compound **2c** (20 g) and aqueous ammonia solution (d = 0.880) (100 ml) were heated at 180° for 11 hours. Compound **3c** was isolated as a brown oil, 14.2 g (93%) using the procedure described above for compound **3b** and was sufficiently pure for further use. Compound **3c** had; ir: ν 3350, 2920 and 1465 cm^{-1}; ^1H nmr: δ 7.40 (1H, t, J = 8 Hz, ArH), 6.70 (1H, d, J = 8 Hz, ArH), 6.40 (1H, d, J = 8 Hz, ArH), 4.85 (4H, broad s, $>CH_2$ and $-NH_2$), 4.55 (2H, s, $>CH_2$), 3.80 (2H, m, $-OCH_2CH_2O-$), 3.55 (2H, m, $-OCH_2CH_2O-$) and 3.40 (3H, s, -OMe) ppm. A sample of compound **3c** was converted into its picrate, mp 110-111° (from ethanol) for microanalysis.

Anal. Calcd. for $C_{16}H_{19}N_5O_{10}$: C, 43.5; H, 4.4; N, 15.9. Found: C, 43.7; H, 4.3; N, 16.2.

Compound **4c**.

Using a similar method to that described for compound **4b**, compound **3c** (4 g) sodium bicarbonate (3.3 g) and aqueous chloroacetaldehyde (3.5 ml) gave, after chromatography with dichloromethane as eluent, compound **4c**, 3.38 g (76%) as a light sensitive oil; ir: ν 2900, 1300, 1100 and 1050 cm^{-1}; ^1H nmr: δ 7.70 (3H, m, ArH), 7.20 (1H, t, J = 7 Hz, ArH), 6.85 (1H, d, J = 5 Hz, ArH), 4.85 (2H, s, $>CH_2$), 4.80 (2H, s, $>CH_2$), 3.75 (2H, m, $-OCH_2CH_2O-$), 3.55 (2H, m, $-OCH_2CH_2O-$) and 3.35 (3H, s, -OMe) ppm; ms: Calcd. for $C_{12}H_{16}N_2O_3$: 236.1157. Found: 236.1164. A sample of compound **4c** was converted to its picrate, mp 113-115° for microanalysis.

Anal. Calcd. for $C_{18}H_{19}N_5O_{10}$: C, 46.5; H, 4.1; N, 15.05. Found: C, 46.3; H, 4.0; N, 14.9.

5-Methoxymethyl-3-nitroimidazo[1,2-*a*]pyridine **5b**.

To a solution of compound **4b** (2.5 g) in concentrated sulfuric acid (30 ml) was added fuming nitric acid (1.33 ml) dropwise. The mixture was kept overnight, poured into iced water and sufficient 2*M* sodium hydroxide solution was added to bring the *p*H to 5. The mixture was then extracted with dichloromethane, the organic extracts were washed with salt solution, dried (magnesium sulfate) and evaporated. The resulting oil was purified by column chromatography (silica gel, eluent petroleum ether:ethyl acetate 3:2) giving compound **5b**, 1.66 g, (52%) as a yellow oil which crystallised upon standing, mp 83-84.5°; ir: ν 1510, 1465, 1380 and 1165 cm^{-1}; ^1H nmr: δ 8.45 (1H, s, ArH), 7.84-7.50 (2H, m, ArH), 7.25 (1H, d, J = 8 Hz, ArH), 4.88 (2H, s, $>CH_2$), and 3.28 (3H, s, -OMe) ppm.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.2; H, 4.4; N, 20.3. Found: C, 52.2; H, 4.3; N, 20.3.

Acknowledgements.

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