Synthesis of Some 1-Hydroxy Derivatives of 4- and 6-Azaindole Analogues

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Received January 17, 1983

1-Hydroxy-4-azaindole and 1-hydroxy-4-(and 6)-azaindol-2(3*H*)-one derivatives are novel compounds and a facile synthesis by the reductive cyclisation of substituted 3-nitropyridines is described. Problems associated with the catalytic hydrogenation of the parent nitro compounds are also discussed.

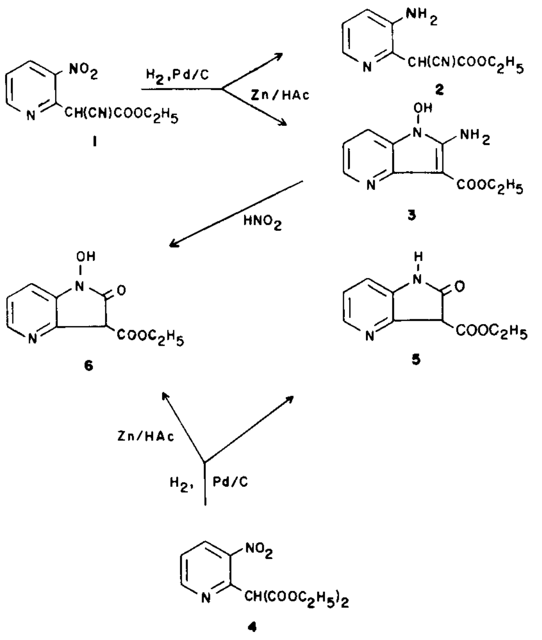
J. Heterocyclic Chem., **20**, 999 (1983).

In the course of our studies on the synthesis of 4- and 6-azaindol-2(3*H*)-one (azaoxindole) derivatives [1,2] we examined the methods of Finch [3] and Clark [4] and found that the final hydrogenation stage in both methods gave a mixture of products.

The cyanoacetate **1** was prepared from 2-chloro-3-nitropyridine as described by Willette [5] who subsequently failed to reduce the compound by hydrogenation using a variety of catalysts and conditions. Finch [3] reported a satisfactory hydrogenation of **1** to **2** using 10% palladised charcoal at 50 psi and room temperature. Clark [4] reported the hydrogenation of **4** to **5** in methanol solution using 10% palladised charcoal.

In our hands (Scheme 1) the catalytic reduction of **1** in ethanol solution using 10% palladised charcoal ceased before the theoretical uptake of hydrogen was achieved. A tlc analysis revealed two major components, the faster running compound was shown to be the expected compound **2**. The slower running compound was assigned structure **3** on the basis of elemental analysis and spectroscopic data, molecular ion at m/e 221 in the mass spectrum and a one proton exchangeable signal at δ 10.8 in the pmr spectrum assigned to the N-OH proton.

Scheme I

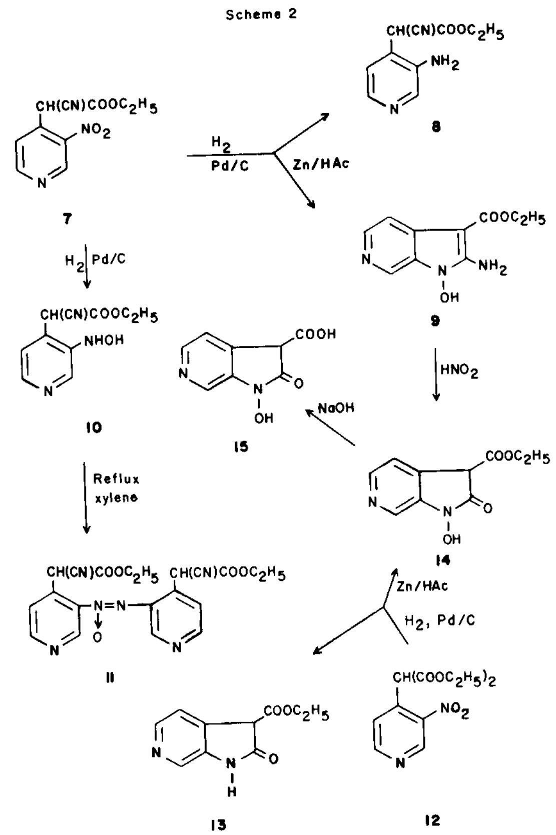


Hydrogenation of the pure diester **4** [4] in ethanol solution as described by Clark [4] gave **5** as the expected product. However, when a sample of the crude ester was hydrogenated under the same conditions, hydrogen uptake ceased at 0.66 of the theoretical amount and the product isolated was assigned the structure 3-ethoxycarbonyl-1-hydroxy-4-azaindol-2(3*H*)-one (**6**) on the basis of elemental analysis and spectroscopic data, molecular ion at m/e 222 in the mass spectrum and a one proton exchangeable signal at δ 11.1 in the pmr spectrum assigned to the N-OH proton.

The cyanoacetate **7** was also found to resist hydrogenation by Willette [5], however, Clark [4] reported the formation of a mixture of **8** and **9** on hydrogenation in methanol solution using 10% palladised charcoal as catalyst. He did not isolate **8** but converted it directly to 3-cyano-4-azaindol-2(3*H*)-one. We also (Scheme 2) usually observed the formation of a mixture of **8** and **9**, but in one case using a different batch of catalyst hydrogen uptake ceased at 0.67 of theory. The product exhibited nitrile, ester carbonyl and hydroxyl absorptions in the ir, a hydroxyl proton which disappeared on deuteration in the pmr. It also reduced Fehlings solution and gave a red colour with iron salts which indicated the hydroxylamino derivative **10**. Refluxing **10** in xylene in an attempt to produce 3-cyano-1-hydroxy-6-azaindol-2(3*H*)-one failed, instead the corresponding azoxy compound **11** was produced due to aerial oxidation.

The diester **12** was prepared from 4-chloro-3-nitropyridine as described for the corresponding dibenzyl ester [2] in 85% yield, the properties were identical to those reported earlier [6]. Reduction of **12** as described for **4** instead of giving **13** as previously reported [4] again gave a mixture of **13** (62-70%) and the 1-hydroxy analogue **14** (26-32%), the latter having identical spectroscopic properties to **6**. Attempts to hydrolyse and decarboxylate **6** and **14** to the corresponding 1-hydroxyazaindol-2(3*H*)-one failed, the

Scheme 2



products appeared extremely unstable, however, when **14** was boiled under reflux with sodium hydroxide solution (50% w/v) for 30 minutes, the resultant product was identified as the corresponding carboxylic acid **15**. All attempts to decarboxylate **15** failed. Compounds **3**, **6**, **9**, and **14** were probably formed by the partial reduction of the nitro group to the hydroxylamino group, followed by a relatively rapid nucleophilic intramolecular attack on the cyano or ethoxycarbonyl group. The isolation of **10** helps to substantiate this.

Other authors have found that catalytic reduction of nitropyridines often leads to a variety of products.

Additional support for the structure of the *N*-hydroxy compounds was that they all reduced Tollen's reagent and gave purple-red colours with triphenyltetrazolium chloride, the latter having been claimed to be specific for hydroxylamine derivatives [8,9]. Assignment of the D-exchangeable signal to the N-OH group is also consistent with the conclusions reached by other workers [10-12]. However, confirmation of this structure was obtained from the mass spectra of these derivatives in that they all contained an abundant molecular ion and diagnostic $(M-1)^+$, $(M-16)^+$ and $(M-17)^+$ ions. The last two fragments corresponding to the loss of an oxygen atom and a hydroxyl radical from the molecular ion. A strong metastable ion of appropriate m/e value in the spectra indicated that the transition $M^+ \rightarrow (M-17)^+$ was direct. These findings are consistent with previous studies on hydroxylamines [13,14].

- Conversion of **3** and **9** to **6** and **14** respectively in order to confirm our structural assignments was achieved by treating **3** and **9** in dilute sulphuric acid (10% w/v) at 0° with sodium nitrite solution, although, not unexpectedly [15] the yields were very low.

In order to circumvent the variability of the catalytic hydrogenation process we examined other reducing systems for the conversion of **1**, **4**, **7** and **12** to **3**, **6**, **9** and **14** respectively and found that the use of zinc and acetic acid at 20° gave reproducible quantitative yields of the 1-hydroxy derivatives.

EXPERIMENTAL

Perkin Elmer 554, 157G and R32 spectrophotometers were used to record uv, ir and pmr spectra (TMS 1%, internal standard), respectively. Microanalyses are by Dr. J. A. Baker, Department of Pharmacy, Brighton Polytechnic. Melting points are corrected.

Catalytic Reduction of Ethyl 2-Cyano-2(3-nitropyrid-2-yl)acetate (1).

A solution of **1** (2.35 g, 0.01 mole) in ethanol (200 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladised charcoal (100 mg). When the uptake of hydrogen ceased (two hours, 90% of theory) the mixture was filtered. A tlc examination of the filtrate revealed two main components (Silica Gel HF_{254}, ethanol) at R_f 0.29 and 0.96 (major spot). The filtrate was evaporated carefully to dryness under reduced pressure and the residue chromatographed on silica gel using ethanol as the eluant. The first fraction corresponding to the major spot at R_f 0.96, yielded the expected ethyl 2-cyano-2(3-aminopyrid-2-yl)acetate (**2**) on evaporation to dryness. Recrystallisation from methanol yielded **2** as pale yellow needles, 1.49 g (64%), mp 115-117°, (lit [3] mp 115-117°). Attempted recrystallisation of **2** from 1-butanol caused cyclisation to yield 3-cyano-4-azaindol-2(3*H*)-one, identical with that reported by Finch [3].

The second fraction corresponded to the minor spot at R_f 0.29 and yielded a cream coloured solid on evaporation to dryness. Recrystallisation from isopropanol yielded cream plates of ethyl 2-amino-1-hydroxy-4-azaindole-3-carboxylate (**3**), 0.33 g (15%), mp 194-196° dec; ir (potassium bromide): 3300, 3250, 3000, 2750, 1680, 1654, 1600 cm^{-1}; pmr (DMSO-d_6): δ 1.27 (t, 3H, J = 6 Hz, ester CH_3), 4.17 (q, 2H, J = 6 Hz, ester CH_2), 6.72 (t, 1H, J = 6 Hz, ring 6H), 7.1 (s, 2H, exch, NH_2), 7.20 (d, 1H, J = 6 Hz, ring 7H), 7.56 (d, 1H, J = 6 Hz, ring 5H), 10.80 (br s, 1H, exch, N-OH); ms: 221 (M^+, 60), 220 (15), 205 (45), 204 (21).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.28; H, 5.01; N, 19.00. Found: C, 54.16; H, 5.00; N, 18.88.

Catalytic Reduction of 2-Bis(ethoxycarbonyl)methyl-3-nitropyridine (4).

A solution of pure ester **4** (2.82 g, 0.01 mole) in ethanol (100 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladised charcoal (100 mg). When the theoretical uptake of hydrogen was achieved the mixture was filtered and the filtrate evaporated to dryness. The resulting yellow viscous oil solidified on addition of ethanol (15 ml) and was recrystallised from methanol to yield pale green prisms of 3-ethoxycarbonyl-4-azaindol-2(3*H*)-one (**5**), 1.73 g (84%), mp 283° dec, (lit [4] mp 282° dec).

However, when a solution of the crude ester **4** (2.82 g, 0.01 mole) was hydrogenated as described for the pure ester, uptake of hydrogen ceased at 0.66 of theory. The catalyst was removed by filtration and the resulting yellow filtrate slowly deposited a tan solid. Recrystallisation from methanol yielded white plates of 3-ethoxycarbonyl-1-hydroxy-4-azaindol-2(3*H*)-one (**6**), 1.78 g (80%), mp 230° dec; ir (potassium bromide): 3280, 3100, 1720, 1700, 1580, 1530, 1440 cm^{-1}; pmr (DMSO-d_6): δ 1.29 (t, 3H, J = 6 Hz, ester CH_3), 3.16 (s, 1H, CH), 4.27 (q, 2H, J = 6 Hz, ester CH_2), 6.84 (t, 1H, J = 6 Hz, ring 6H), 7.20 (d, 1H, J = 6 Hz, ring 7H), 7.62 (d, 1H, J = 6 Hz, ring 5H), 11.1 (br s, 1H, exch, N-OH); ms: 222 (M^+, 55), 221 (12), 206 (50), 205 (26).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.10; H, 4.52; N, 12.60.

Catalytic Reduction of Ethyl 2-Cyano-2(3-nitropyrid-4-yl)acetate (**7**).

A solution of **7** (2.35 g, 0.01 mole) in ethanol (200 ml) was hydrogenated as described for **1**. Hydrogen uptake ceased at 82% of theory (two hours) and tlc revealed two main components (Silica Gel HF_{254}, ethanol) at R_f 0.34 (major spot) and 0.95. Chromatographic separation after filtration and careful evaporation of the hydrogenation mixture on silica gel using ethanol as the solvent yielded **8** as the first fraction (R_f 0.95), 0.47 g (23%) which was characterised as the picrate salt. Recrystallisation from ethanol gave the picrate salt of **8** as yellow needles, mp 270° dec.

Anal. Calcd. for $C_{16}H_{14}N_6O_9$: C, 44.24; H, 3.25; N, 19.35. Found: C, 44.23; H, 3.18; N, 19.32.

The second fraction corresponded to the major spot at R_f 0.34 and yielded a tan coloured solid on evaporation to dryness. Recrystallisation from ethanol-ether yielded **9** as cream needles 1.30 g (59%) mp 219-221° dec, (lit [4] mp 234-235° dec). This product had identical spectroscopic properties to those previously reported [4] but was extremely electrostatic and difficult to handle and was converted to the hydrochloride salt for further study. Recrystallisation from ethanol gave the hydrochloride of **9** as cream plates, mp 234-236°.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_3$: C, 46.61; H, 4.69; N, 16.31. Found: C, 46.62; H, 4.71; N, 16.26.

During one attempt at this hydrogenation a different batch of catalyst was used and hydrogen uptake ceased at 0.66 of theory. The residue after filtration and evaporation of the ethanol was recrystallised from methanol to yield ethyl 2-cyano-2(3-hydroxylaminopyrid-4-yl)acetate (**10**) as pink plates, 1.44 g (65%), mp 185° dec; ir (potassium bromide): 3450, 3320, 3100, 3000, 2200, 1700, 1675, 1645, 1600, 1520, 1480, 1380, 1350, 1310 cm^{-1}; pmr (DMSO-d_6): δ 1.28 (t, 3H, J = 7 Hz, ester CH_3), 4.09 (q, 2H, J = 7 Hz, ester CH_2), 6.65-7.40 (v br s, 2H, exch, NHOH), 7.62 (d, 1H, J = 6 Hz, ring 5H), 8.14 (d, 1H, J = 6 Hz, ring 6H), 8.44 (s, 1H, ring 2H); ms: 221 (M^+).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.30; H, 4.96; N, 19.00.

Attempted cyclisation of **10**.

A solution of **10** (2.21 g, 0.01 mole) in xylene (120 ml) was boiled under reflux for twenty hours. The xylene was evaporated under reduced pressure and the residue recrystallised twice from ethanol to yield white plates, 1.05 g, mp >330°. Microanalytical and spectroscopic data showed this to be diethyl 3,3'-azoxy-4,4'-pyridyl cyanoacetate (**11**); ir (potassium bromide): 3180, 2200, 1700, 1600, 1540, 1500, 1455, 1405, 1330 cm^{-1}; pmr (DMSO-d_6): δ 1.36 (t, 6H, J = 6 Hz, ester 2 × CH_3), 4.30 (q, 4H, J = 6 Hz, ester 2 × CH_2), 7.23 (s, 1H, ring 2H), 7.52 (d, 2H, J = 3 Hz, ring 5 and 6H), 8.09 (d, 2H, J = 3 Hz, ring 5' and 6'H), 8.39 (s, 1H, ring 2'H); ms: 422 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_6O_5$: C, 56.86; H, 4.29; N, 19.90. Found: C, 56.90; H, 4.32; N, 19.86.

Catalytic Reduction of 4-Bis(ethoxycarbonyl)methyl-3-nitropyridine (**12**).

A solution of ester **12** (2.82 g, 0.01 mole) in ethanol (150 ml) was hydrogenated as described for **4**. Hydrogen uptake ceased at 76% of theory (two hours).The product which had precipitated during hydrogenation and the catalyst were removed by filtration and the filtrate evaporated to approximately 15 ml. On standing overnight the filtrate deposited cream needles of 3-ethoxycarbonyl-6-azaindol-2(3*H*)-one (**13**), 1.27 g (62%), mp >340°, (lit [4] mp >340°).

The precipitate filtered with the catalyst was recrystallised twice from toluene to yield 1-hydroxy-3-ethoxycarbonyl-6-azaindol-2(3*H*)-one (**14**) as light brown needles 0.57 g (26%), mp >340°; ir (potassium bromide): 3280, 3090, 3000, 1720, 1650, 1600, 1500, 1440, 1340 cm^{-1}; pmr (TFA-D): δ 1.59 (t, 3H, J = 6 Hz, ester CH_3), 4.66 (q, 2H, J = 6 Hz, ester CH_2), 8.32 (m, 2H, ring 4 and 7H), 8.80 (m, 1H, ring 5H); ms: 222 (M^+, 66), 221 (20), 206 (63), 205 (28).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.06; H, 4.52; N, 12.57.

1-Hydroxy-6-azaindol-2(3*H*)-one-3-carboxylic Acid (**15**).

A solution of **14** (0.55 g, 0.0025 mole) in sodium hydroxide solution (50% w/v, 10 ml) was boiled under reflux for half an hour and filtered hot. When cold, the filtrate was diluted with water (40 ml) and made acidic with acetic acid. On standing overnight light tan crystals of **15** appeared, 0.22 g (45%), mp >320°; ir (potassium bromide): 3240, 3110, 1700, 1690, 1680, 1650, 1620, 1570, 1500, 1430, 1370, 1330 cm^{-1}; ms: 194 (M^+).

Anal. Calcd. for $C_8H_6N_2O_4$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.46; H, 3.16; N, 14.39.

Conversion of **3** and **9** to **6** and **14**.

A solution of sodium nitrite (0.69 g, 0.01 mole) in water (5 ml) was added dropwise to a cold (0°) stirred solution of **3** (1.11 g, 0.005 mole) in sulphuric acid (10% w/v, 20 ml). The resulting solution was maintained at 0° for one hour and then left at room temperature overnight. The *p*H was adjusted to 4 and the precipitated solid collected by filtration and dried. Three recrystallisations from methanol yielded **6** as cream plates, 78 mg (7%), mp 230° dec.

Similar treatment of **9** gave **14** as tan needles from toluene 56 mg (5%), mp >340°.

Ethyl 2-Amino-1-hydroxy-4(and 6)-azaindole-3-carboxylate (**3** and **9**).

A solution of **1** (2.35 g, 0.01 mole) in glacial acetic acid (40 ml) was cooled to 15° and zinc dust (6 g) added slowly over thirty minutes. When the addition was complete stirring was continued for a further one hour at this temperature and then at room temperature for six hours. The resulting mixture was filtered and the filtrate diluted with ice cold water to precipitate a brownish solid. Recrystallisation from isopropanol gave cream plates whose physicochemical and spectroscopic properties were identical with **3** prepared previously, 1.90 g (86%), mp 194-196° dec.

Similar treatment of **7** gave **9**, which was isolated as the hydrochloride, 1.85 g (72%), mp 234-236°, identical with that prepared previously.

3-Ethoxycarbonyl-1-hydroxy-4(and 6)-azaindol-2(3*H*)-one (**6** and **14**).

Treatment of **4** (2.82 g, 0.01 mole) as described for the preparation of **3** using zinc dust and acetic acid yielded **6** as white plates from methanol, 1.95 g (88%), mp 230° dec, identical with that prepared earlier.

Similar treatment of **12** gave **14** as light brown needles from toluene, 1.66 g (75%), mp >340°, identical with that prepared earlier.

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