A Convenient Synthesis of Heterocyclic *N*-Hydroxylactams

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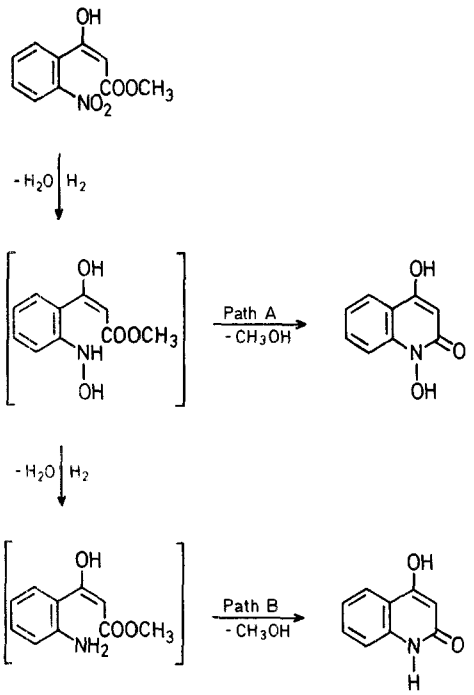
On reductive cyclisation of aromatic nitro compounds containing an alkoxycarbonyl group in the β-position, two types of products may be formed. Six-membered *N*-hydroxylactams will be the products, if the intermediate hydroxylamine arising by partial reduction of the nitro group is cyclised (Path A, Scheme **A**). When, however, the reduction first proceeds to the intermediate amine, six-membered lactams result following the cyclization (Path B, Scheme **A**). Thus, the reductive cyclisation of methyl 2-nitrobenzoylacetate to form 1,4-dihydroxy-1,2-dihydroquinolin-2-one by means of palladium/charcoal/hydrazine was described[1]. Further reducing agents, which are known to provide *N*-hydroxylactams according to Path A are ammonium sulfide[2] and zinc/acetic acid[3].

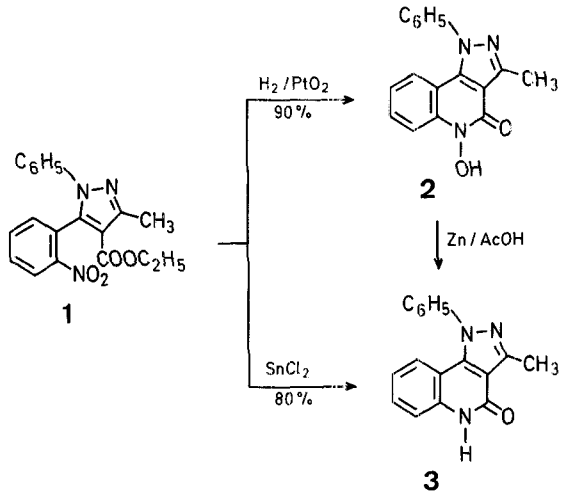


Scheme **A**

When palladium/charcoal/cyclohexene was used, reduction of methyl 2-nitrobenzoylacetate led to 1,2-dihydro-4-hydroxyquinolin-2-one[4] according to Path B. Lactam formation was also observed when tin(II) chloride was the reducing agent. Thus, ethyl 3-methyl-5-(2-nitro-phenyl)-1-phenyl-pyrazole-4-carboxylate (**1**) was cyclised to form 3-methyl-1-phenyl-pyrazolo[4,3-*c*]quinoline-4(5*H*)-one (**3**)[5]. Whether an *N*-hydroxylactam or a lactam is formed depends apparently on the reactivity of the intermediate *N*-hydroxylamine, which can either cyclise itself or undergo further reduction to the amine.

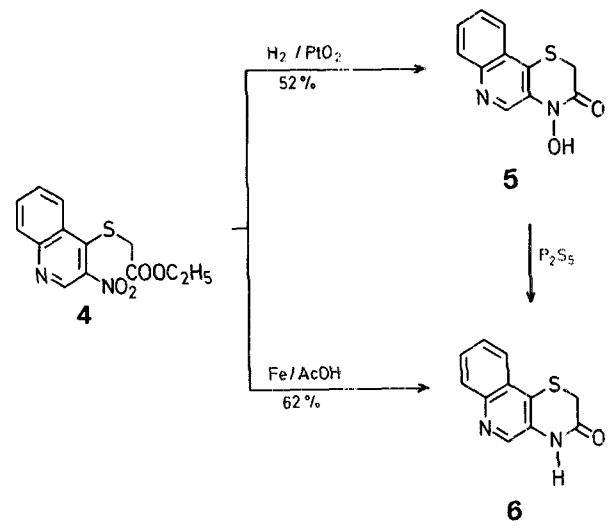
We report here the conversion of heterocyclic substituted nitro compounds to the corresponding heterocyclic *N*-hydroxylactams and lactams by suitable choice of substrates **1**, **4**, **7** and **10**. Thus, in contrast to the tin(II) chloride method, we obtained by catalytic reduction of **1** in acetic acid

with hydrogen/platinum oxide not the lactam **3**, but the corresponding *N*-hydroxylactam, 5-hydroxy-3-methyl-1-phenyl-pyrazolo[4,3-*c*]quinolin-4(5*H*)-one **(2)**, which is converted into **3** by zinc dust in acetic acid (Scheme **B**).

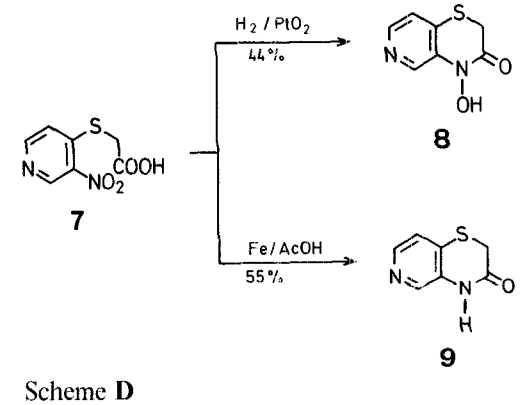


Scheme **B**

In the same way, 4-ethoxycarbonylmethylthio-3-nitroquinoline **(4)** reacts to form 4-hydroxy-2*H*-1,4-thiazino[3,2-*c*]quinolin-3(4*H*)-one **(5)**. However, reaction of **4** with iron powder in acetic acid gives the lactam, 2*H*-1,4-thiazino[3,2-*c*]quinolin-3(4*H*)-one **(6)**. Lactam **6** is also obtained by the reduction of *N*-hydroxylactam **5** with phosphorus pentasulfide in pyridine (Scheme **C**). Under the conditions of catalytic hydrogenation, not only the ethoxycarbonyl compounds are converted to *N*-hydroxylactams, but also suitable substituted carboxylic acids like 4-carboxymethylthio-3-nitropyridine **(7)** react to form 2*H*-4-hydroxypyrido[4,3-*b*]-1,4-thiazine-3(4*H*)-one **(8)**. Again 2*H*-pyrido[4,3-*b*]-1,4-thiazine-3(4*H*)-one **(9)**, as the lactam corresponding to **8**, is formed by conversion of **7** with iron powder/acetic acid (Scheme **D**).

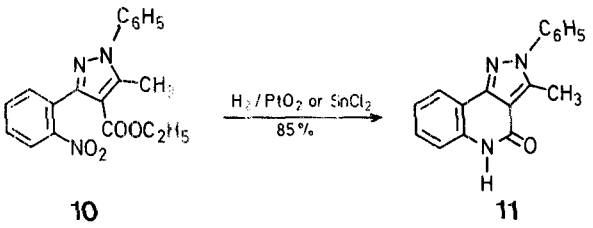


Scheme **C**



Scheme **D**

Only in the case of ethyl 5-methyl-3-(2-nitro-phenyl)-1-phenylpyrazole-4-carboxylate **(10)** the *N*-hydroxylactam is not formed, but the lactam. Thus, catalytic hydrogenation of **10** in boiling acetic acid resulted in the formation of 3-methyl-2-phenyl-pyrazolo[4,3-*c*]-quinoline-4(5*H*)-one **(11)**. This lactam is also formed by treatment of **10** with tin(II) chloride. In the exceptional case of **10**, further reduction of the intermediate *N*-hydroxylamine to the respective amine, followed by cyclisation, is apparently favoured over its direct cyclisation (Scheme **E**).



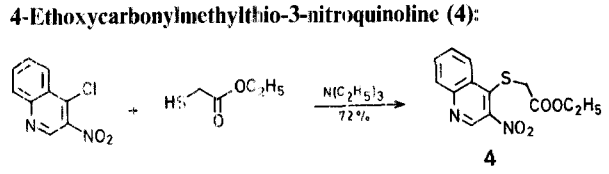
Scheme **E**

In summary, the simplicity of experimental conditions (hydrogen/platinum oxide/acetic acid/room temperature/normal pressure) makes this procedure a desirable method for the preparation of heterocyclic *N*-hydroxylactams.

Melting points were determined on a Boetius micro hotstage apparatus and are corrected. Mass spectra were recorded on a Varian MAT CH6 spectrometer at 70 eV and a source temperature of 200°C. I.R. spectra were obtained on a VEB Carl Zeiss Jena spectrophotometer UR20. ^{1}H-N.M.R. spectra were measured on a TESLA BS 487C spectrometer at 80 MHz.

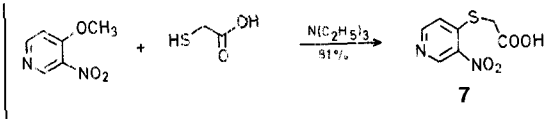
Ethyl 3-Methyl-5-(2-nitrophenyl)-1-phenylpyrazole-4-carboxylate **(1)** is prepared according to Ref.[5].

4-Ethoxycarbonylmethylthio-3-nitroquinoline (4):



To a stirred solution of 4-chloro-3-nitroquinoline (2.1 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in acetone (30 ml) is added dropwise ethyl thioglycolate (1.2 g, 0.01 mol) at room temperature for 1 h. The triethylamine hydrochloride formed is separated by filtration and the acetone is evaporated. The remaining yellow oil crystallises on standing to form yellow plates of **4** (Table).

4-Carboxymethylthio-3-nitropyridine (7):



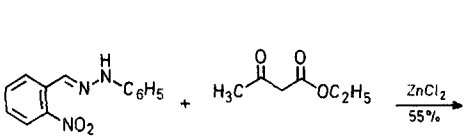
To a stirred solution of 4-methoxy-3-nitropyridine (1.91 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dioxan (30 ml) is added dropwise thioglycolic acid (0.92 g, 0.01 mol), followed by refluxing for 4 h. Cold water (5 ml) is added and the yellow needles of **7** formed are separated by filtration (Table).

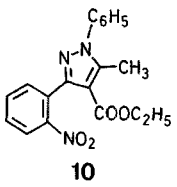
Table. Compounds **1**–**11** prepared

Product No.	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (solvent/HMDS$_{int}$) δ [ppm]	M.S. (M$^+$) *m/e* (rel. inten. %)
1	82	146–147° (ethanol)	146°[5]	1710	Acetone-d_6: 0.92 (t, 3H, J = 7 Hz); 2.44 (s, 3H); 3.91 (q, 2H, J = 7 Hz); 7.10–8.30 (m, 9H)	351(12)
2	90	214° (ethanol)	$C_{17}H_{13}N_3O_2$ (291.2)	1710	CD_3OD: 2.08 (s, 3H); 6.60–7.83 (m, 9H)	291(11)
3	80	273–274[c] (ethanol)	273°[6]	1675	DMSO-d_6: 2.34 (s, 3H); 6.88–8.00 (m, 9H)	275(100)
4	72	42–45° (cyclohexane)	$C_{13}H_{12}N_2O_4S$ (292.3)	1720	Acetone-d_6: 0.93 (t, 3H, J = 7 Hz); 3.80 (s, 2H); 3.87 (q, 2H, J = 7 Hz); 7.66–8.63 (m, 4H); 9.14 (s, 1H)	292(9)
5	52	212–214° (dioxan)	$C_{11}H_8N_2O_2S$ (232.3)	1700	DMSO-d_6: 4.19 (s, 2H); 7.82–8.30 (m, 4H); 9.15 (s, 1H); 11.25 (s, 1H)	232(100)
6	62	254–256° (ethanol)	$C_{11}H_8N_2OS$ (216.3)	1680	DMF-d_7: 3.70 (s, 2H); 7.50–8.00 (m, 4H); 8.56 (s, 1H)	216(100)
7	81	229–230° (dioxan)	$C_7H_6N_2O_4S$ (214.2)	1710	DMF-d_7: 4.13 (s, 2H); 7.63 (d, 1H, J = 6 Hz); 7.94 (s, 1H); 8.61 (d, 1H, J = 6 Hz); 9.23 (s, 1H)	214(100)
8	44	167–169° (xylene)	$C_7H_6N_2O_2S$ (182.2)	1690	$CDCl_3$: 3.24 (s, 2H); 7.17 (d, 1H, J = 6 Hz); 8.08 (q, 1H, J = 6 Hz); 8.54 (s, 1H); 10.81 (s, 1H)	182(87)
9	55	205–206° (chloroform)	$C_7H_6N_2OS$ (166.2)	1685	DMSO-d_6: 3.37 (s, 2H); 7.62 (d, 1H, J = 6 Hz); 8.32 (d, 1H, J = 6 Hz); 8.36 (s, 1H); 11.01 (s, 1H)	166(8)
10	55	122–123° (methanol)	$C_{19}H_{17}N_3O_4$ (351.3)	1695	Acetone-d_6: 0.98 (t, 3H, J = 7 Hz); 2.54 (s, 3H); 3.99 (q, 2H, J = 7 Hz); 7.12–8.19 (m, 9H)	351(4)
11	85	295–296° (acetone/ethanol, 1:1)	$C_{17}H_{17}N_3O$ (275.2)	1675	–[c]	275(85)

[a] Yield of pure isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.19, N ± 0.16.
[c] Insoluble in common organic solvents used to measure ^{1}H-N.M.R.

Ethyl 5-Methyl-3-(2-nitrophenyl)-1-phenyl-pyrazole-4-carboxylate 10:





10

2-Nitrobenzaldehydephenylhydrazone (9.64 g, 0.04 mol), ethyl acetoacetate (31.2 g, 0.24 mol) and dry zinc chloride (5.0 g) are heated to reflux. After part of the ethyl acetoacetate has been distilled off the temperature is raised to 170 °C and kept for 5 min. The excess ethyl acetoacetate is removed in vacuo. The remaining brown oil yields on crystallisation from methanol pale-yellow crystals of **10** (Table).

Reductive Cyclisation in the Presence of Platinum Oxide to form Quinolinones 2, 5, 11 and Thiazinone 8; General Procedure:
The respective nitro compounds **1**, **4**, **10** and **7** (0.01 mol) in acetic acid (50 ml) [ethanol (150 ml), in the case of **1**] are hydrogenated over platinum oxide (50 g) under normal pressure at room temperature (for **1**, **4** and **7**) or under reflux (for **10**) until no more hydrogen is consumed. After filtration, the solvent is removed in vacuo and the residue recrystallised (Table).

Reductive Cyclisation by means of Iron/Acetic Acid to form Thiazinones 6 and 9; General Procedure:
To a stirred solution of **4** or **7**, (0.01 mol), respectively, in acetic acid (50 ml), iron powder (10.0 g) is added. After a few minutes the mixture becomes warm and clear. It is kept at 90 °C for 2 h, and then the solvent is removed in vacuo. The solid residue is extracted with xylene (2 × 30 ml) and the solvent evaporated. The product crystallises as white needles and is recrystallised (Table).

3-Methyl-1-phenylpyrazolo[4,3-*c*]quinolin-4(5*H*)-one (3):
N-Hydroxylactam **2** (0.582 g, 2 mmol) in acetic acid (30 ml) is refluxed with zinc dust (1.0 g) for 30 min. Water (200 ml) is added and the precipitate collected by filtration. The precipitate is extracted with ether (4 × 25 ml). On evaporation of the ether, **3** crystallizes in colorless needles (Table).

2*H*-1,4-Thiazino[3,2-*c*]quinolin-3(4*H*)-one (6):
To a stirred solution of **5** (2.32 g, 0.01 mol) in pyridine (30 ml) phosphorus pentasulfide (1.11 g, 5 mmol) is added in portions. The mixture is then refluxed for 1 h. After cooling, the orange-red coloured solution is poured into water (40 ml). The precipitate formed is collected by filtration and recrystallised to yield yellow needles of **6** (Table).

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