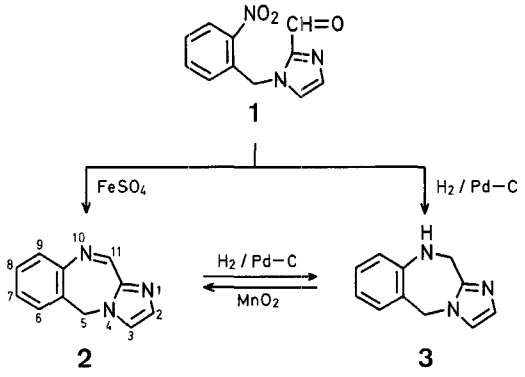
Research on Nitrogen Heterocyclic Compounds; XIII. Synthesis of 5*H*-Imidazo[2,1-*c*][1,4]benzodiazepine, a Novel Tricyclic Ring System

Giorgio STEFANCICH, Marino ARTICO*, Silvio MASSA, Federico CORELLI

Istituto di Chimica Farmaceutica e Tossicologica, 2ª e 4ª Cattedra, Piazzale Aldo Moro, I-00100 Roma, Italy

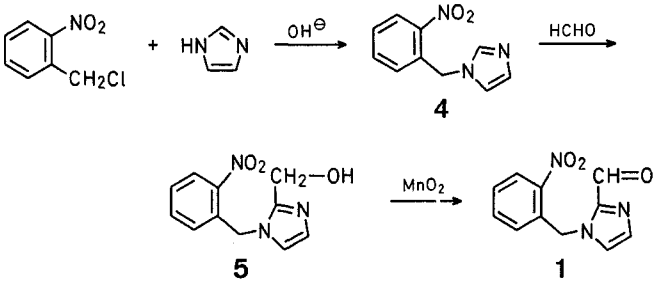
In a search for synthetic tumor inhibitors, we have developed new convenient approaches to 6,7,5-membered tricyclic heteroaromatic ring systems with a bridgehead nitrogen atom. In fact, the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine ring is the fundamental structure of various anti-tumoral antibiotics, namely anthramycin, sibiromycin, tomaymycin and neothramycin[1]. Furthermore, harringtonine and the related anti-leukemic alkaloids are esters of cephalotaxine, a natural substance built on 1*H*-pyrrolo[2,1-*b*][3]benzazepine skeleton[2].

Previously, we described[3] the synthesis of 5*H*-pyrrolo[1,2-*b*][2]benzazepine, an isosteric analog of the above-mentioned rings. Now we report the synthesis of a new tricyclic nitrogen system, 5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2**) by a simple, one-step procedure starting from 1-(*o*-nitrobenzyl)-imidazo-2-carboxyaldehyde (**1**).



Reduction of **1** with iron(II) sulfate, in fact, gave directly the title tricyclic ring by intramolecular condensation of the supposed intermediate 1-(*o*-aminobenzyl)-imidazo-2-carboxyaldehyde. When compound **1** was reduced with hydrogen in the presence of palladium on carbon as catalyst, 10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3**) was formed instead of **2**. Then conversion of **2** to **3** and vice versa was achieved respectively by hydrogenation of **2** using palladium on carbon as catalyst and by oxidation of **3** with manganese dioxide.

The nitro-aldehyde **1** was obtained by oxidizing, with activated manganese dioxide[4], 1-(*o*-nitrobenzyl)-2-hydroxymethylimidazole (**5**). This compound was formed when 1-(*o*-nitrobenzyl)-imidazole (**4**) and 40% aqueous formaldehyde were heated in a sealed tube. Derivative **4** was prepared in good yield by treating imidazole with *o*-nitrobenzyl chloride in the presence of anhydrous sodium carbonate in dimethylformamide.



All the compounds were characterized by I.R. spectra and microanalysis. N.M.R. spectral data of **2** and **3** were consistent with their tricyclic structures.

All melting points were measured with a Fisher-Johns apparatus and are uncorrected. I.R. spectra (nujol mulls) were recorded on a Perkin-Elmer model 157 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Varian EM-390 instrument (TMS internal standard). The mass spectrum was recorded on a Hewlett-Packard 5908-A mass spectrometer with an electron beam energy of 70 eV. Merck alumina (activity according to Brockmann) was used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

1-(*o*-Nitrobenzyl)-imidazole-2-carboxaldehyde (1):

Manganese dioxide[4] (6.0 g) is added to a solution of **5** (1.17 g, 5 mmol) in acetone (250 ml). The mixture is stirred at room temperature overnight and then filtered. The filtrate is evaporated on a steam bath under reduced pressure to afford 1-(*o*-nitrobenzyl)-imidazo-2-carboxyaldehyde; yield: 1.0 g (87%); m.p. 130–133 °C (after crystallization from benzene/petroleum ether).

$C_{11}H_9N_3O_3$	calc.	C 57.14	H 3.92	N 18.18
(231.2)	found	57.40	4.03	18.07

I.R.: $\nu_{C=O} = 1680\ cm^{-1}$.

5*H*-Imidazo[2,1-*c*][1,4]benzodiazepine (2):

Method A: From compound **1**: A solution of **1** (1.5 g, 6.5 mmol) in hot ethanol (100 ml) is added to a suspension of iron(II) sulfate heptahydrate (18.2 g, 0.065 mol) in water (85 ml) and 20% ammonia (5 ml). The mixture is heated at 120 °C for 1 h with stirring while 20% ammonia (20 ml) is added dropwise. After filtration, the residue is washed with ethanol and discarded. The solution is partially evaporated, then extracted with ethyl acetate, and dried with anhydrous sodium sulfate. After concentration to a small volume, the solution is purified by passing through an alumina column, eluting with ethyl acetate. The eluates are collected and evaporated to give 5*H*-imidazo[2,1-*c*][1,4]benzodiazepine; yield: 1.0 g (84%); m.p. 110–111 °C (after crystallization from benzene/petroleum ether).

$C_{11}H_9N_3$	calc.	C 72.11	H 4.95	N 22.94
(183.2)	found	72.30	4.87	22.90

^{1}H-N.M.R. ($CDCl_3$): $\delta = 4.93$ (s, 2H, CH_2), 6.8–7.5 (m, 6H, benzene and imidazole protons), 8.6 ppm (s, 1H, H—C-11).

M.S.: $m/e = 183$ (M^+).

Method B: From compound **3**: Manganese dioxide[4] (4.0 g) is added to a solution of 10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3**; 1.48 g, 80 mmol) in dry benzene (100 ml). The mixture is stirred, heated under reflux overnight, and then filtered. The filtrate after evaporation furnishes a crude residue (1.2 g), which is dissolved in chloroform (20 ml) and passed through an alumina column eluting with the same solvent. The first eluates are discarded, then the central fractions are collected and evaporated under reduced pressure to afford the title compound; yield: 1.0 g (69%); identical (mixture m.p., superimposable I.R. and N.M.R. spectra) with the sample prepared as described in Method A.

0039-7881/81/0432-0321 $ 03.00

10,11-Dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (3):

Method A: From Compound **1**: A suspension of **1** (2.31 g, 10 mmol) and 10% palladium on carbon (400 mg) in ethyl acetate (250 ml) is hydrogenated at 50 °C under 4 atmospheres of hydrogen for 6 h. Removal of the catalyst by filtration and evaporation of the solvent in vacuo gives 10,11-dihydro-5*H*-imidazo[2.1-*c*][1,4]benzodiazepine; yield: 1.7 g (92%); m.p. 186–188 °C (after crystallization from ethyl acetate).

$C_{11}H_{11}N_3$	calc.	C 71.33	H 5.99	N 22.69
(185.2)	found	71.23	5.94	22.76

I.R.: $\nu_{NH} = 3280$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 4.25$ (broad, NH, exchangeable with D_2O), 4.54 (s, 2H, CH_2—N=), 5.10 (s, 2H, CH_2—N), 6.6–7.2 ppm (m, 6H, aromatic protons).

M.S.: $m/e = 185$ (M^+).

Method B: From compound **2**: A suspension of **2** (1.83 g, 10 mmol) and 10% palladium on carbon (300 mg) in ethyl acetate (200 ml) is hydrogenated at 50 °C under 4 atmospheres of hydrogen for 4 h. Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure on a steam-bath affords 10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3**); yield: 1.76 g (95%); identical (mixture m.p., superimposable I.R. and N.M.R. spectra) with the sample prepared as described in Method A.

1-(*o*-Nitrobenzyl)-imidazole (4):

A mixture of imidazole (6.8 g, 0.1 mol), *o*-nitrobenzyl chloride (17.16 g, 0.1 mol) and anhydrous sodium carbonate (11.0 g, 0.103 mol) in dimethylformamide (50 ml) is heated at 125 °C under stirring for 3 h. The solvent is then evaporated to give a residue, which is extracted with chloroform. The extract is filtered, then passed through a column of alumina eluting with chloroform. The first eluates are discarded, then the central fractions are collected and evaporated under reduced pressure to afford 1-(*o*-nitrobenzyl)-imidazole; yield: 11.0 g (54%); m.p. 82–83 °C (after crystallization from benzene/petroleum ether).

$C_{10}H_9N_3O_2$	calc.	C 59.10	H 4.46	N 20.68
(203.3)	found	59.30	4.63	20.95

I.R.: $\nu_{NO_2} = 1530$; 1345 cm^{-1}.

1-(*o*-Nitrobenzyl)-2-hydroxymethylimidazole (5):

A mixture of **4** (10.16 g, 0.05 mol) and 40% formalin (35.0 g) is heated at 115 °C in a sealed tube overnight. Trituration of the residue many times with methanol and evaporation of the collected fractions affords 1-(*o*-nitrobenzyl)-2-hydroxymethylimidazole; yield: 6.3 g (54%); m.p. 165–166 °C (after crystallization from ethyl acetate).

$C_{11}H_{11}N_3O_3$	calc.	C 56.65	H 4.75	N 18.02
(233.2)	found	56.92	4.68	18.27

I.R.: $\nu_{OH} = 3145$ cm^{-1}.

This work was supported by the financial aid of Italian C.N.R. (Roma).

Received: November 14, 1980

* Address for correspondence.

[1] M. Artico, G. De Martino, R. Giuliano, S. Massa, G. C. Porretta, *J. Chem. Soc. Chem. Commun.* **1969**, 671.
M. Artico, G. De Martino, R. Giuliano, S. Massa, G. C. Porretta, *Il Farmaco, Ed. Sc.* **24**, 980 (1969).
L. H. Hurley, *J. Antibiotics* **30**, 349 (1977).
W. Leimgruber, A. D. Batcho, F. Schenker, *J. Am. Chem. Soc.* **87**, 5793 (1965).

[2] K. L. Mikolajczak, R. G. Powell, C. R. Smith, Jr., *Tetrahedron* **28**, 1995 (1972).
L. J. Dolby, S. J. Nelson, D. Senkovich, *J. Org. Chem.* **37**, 3691 (1972).
K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, *J. Med. Chem.* **20**, 328 (1977).
I. Tse, V. Snieckus, *J. Chem. Soc. Chem. Commun.* **1976**, 505.

[3] G. Stefancich, M. Artico, S. Massa, S. Vomero, *J. Heterocyclic Chem.* **16**, 1443 (1979).

[4] M. Harfenist, A. Bavley, W. A. Lazier, *J. Org. Chem.* **15**, 1608 (1954).