Heterocyclic Transformations by Hydrogenolysis. Application to Some Hydrazides of Fused Alicyclic Isoxazoles

M. Ruccia and N. Vivona
Istituto di Chimica Organica, Facoltà di Scienze, Palermo, Italy

and

S. Plescia and V. Sprio
Istituto di Chimica Organica, Facoltà di Farmacia, Palermo, Italy

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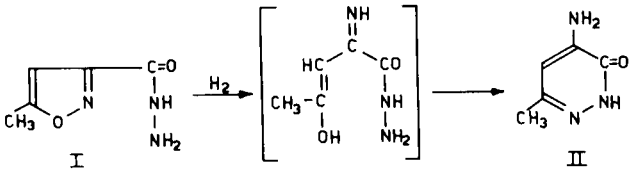
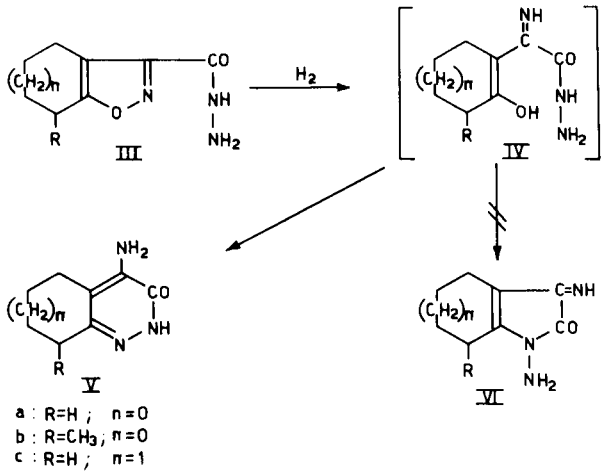
Recently great attention has been directed to the reductive cleavage of isoxazole derivatives containing a suitable side-chain at positions 3, 4 or 5. Catalytic hydrogenation of such derivatives has been successfully used to synthesize a large number of heterocyclic compounds through transformations of the heterocyclic ring. The intermediates resulting from isoxazole ring opening can usually be isolated but sometimes they undergo further reactions leading directly to a different heterocyclic ring. Among many examples on this subject, it has been also reported by one of us (1) that catalytic hydrogenation of the hydrazide of 5-methylisoxazole-3-carboxylic acid (I) on W-2 Raney-nickel (2) in ethanol affords directly 4-amino-6-methylpyridazine-2*H*-3-one (II) whose structure has been confirmed through comparison with a sample synthesized by an independent route (3).



In connection with previous research concerning heterocyclic transformations of the tetrahydroindoxazene derivatives (4), and in order to study the influence of an alicyclic system fused to an isoxazole ring on the course of the above-mentioned reaction, our attention has been directed to the conversion of the hydrazides (IIIa) and (IIIb) into the related aminotetrahydrocinnolinone derivatives (Va) and (Vb).

Hydrogenation of IIIa and IIIb on W-2 Raney-nickel in ethanol yielded high-melting products which were shown to be 4-amino-5,6,7,8-tetrahydrocinnolin-2*H*-3-one (Va) and 4-amino-8-methyl-5,6,7,8-tetrahydrocinnolin-2*H*-3-one (Vb) respectively by elemental analyses and spectroscopic evidence.



Compounds Va and Vb must be considered arising directly from intermediates IVa and IVb resulting from isoxazole ring opening as also reported for aminopyridazinone II. Structures IVa and IVb for the products must be excluded on the basis of elemental analyses and mass spectra (M^+ = 165 and 179 for Va and Vb respectively). On the other hand, the products, which give a positive test with ferric chloride, are recovered unchanged after refluxing 3 hours with hydrochloric acid in ethanol. IR spectra show a set of bands in the NH stretching region and a ν C=O stretching at 1672 cm^{-1}. NMR spectra, besides other signals for alicyclic protons, exhibit a singlet (2H) at *ca.* 5.8 δ ($-NH_2$) and a singlet (1H) at *ca.* 12.2 δ (NH). Furthermore, as conclusive test, UV spectra (λ max = *ca.* 290 nm; log ϵ = *ca.* 4) are similar to that of 4-amino-6-methylpyridazin-2*H*-3-one (II) (1) for the position of maximum absorption and intensity, as expected for structures Va and Vb. Therefore the whole of the reported data allows us to exclude the alternatives cyclic structures VIa and VIb.

It seems that the size of the alicyclic system fused to the isoxazole ring does not affect the observed reaction. In fact, we have prepared 5,6,7,8-tetrahydro-4*H*-cyclo-

hepta[*d*]isoxazol-3-carboxylic acid (see experimental) and we have found that the corresponding hydrazide IIIc, analogously with IIIa and IIIb, undergoes catalytic hydrogenation to afford 4-amino-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*c*]pyridazin-2*H*-3-one (Vc), whose structure has been confirmed by analytical and spectroscopic data (MS, IR, UV, NMR).

Refluxing Va with acetic anhydride for 10 minutes yielded a diacetyl derivative as confirmed by analytical data, mass spectra (M^+ = 249) and NMR spectra which exhibit, besides other signals, a singlet (6H) at 2.36 δ (2 x $COCH_3$) and a singlet (1H) at 13.05 δ (NH). Analogously, Vb and Vc yielded diacetyl derivatives.

EXPERIMENTAL

All melting points (Kofler) are uncorrected. IR (nujol mull): Perkin-Elmer Infracord 137 spectrophotometer. UV (Ethanol solution): Beckmann DB (with recorder) spectrophotometer. NMR: Jeol C-60H spectrometer (TMS as internal reference). Mass spectra were recorded on a Hitachi-Perkin Elmer RMU-6D spectrometer (courtesy of Dr. A. Selva, Institute of Chemistry, Politechnic School, Milano).

The Hydrazide of 4,5,6,7-Tetrahydroindoxazen-3-carboxylic Acid (IIIa).

To a solution of 5 mmoles of the methyl ester of 4,5,6,7-tetrahydroindoxazen-3-carboxylic acid [m.p. 64° (ethanol-water) (5)] in 20 ml. of ethanol a slight excess of 85% hydrazine hydrate was added. After some hours standing at room temperature, removal of the solvent left IIIa in quantitative yield, m.p. 100° (benzene/ligroin) [lit. (6) m.p. 105°]; ir 1684 (C=O) and 3247, 3205 cm^{-1} (NH-NH_2).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.38; H, 6.45; N, 23.39.

The Hydrazide of 7-Methyl-4,5,6,7-tetrahydroindoxazen-3-carboxylic Acid (IIIb).

Compound IIIb was prepared from the methyl ester of 7-methyl-4,5,6,7-tetrahydroindoxazen-3-carboxylic acid [m.p. 62° (ethanol-water) (5)] as above. M.p. 98° (benzene/ligroin); ir 1672 (C=O) and 3257, 3205 cm^{-1} (NH-NH_2).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.20; H, 6.77; N, 21.77.

5,6,7,8-Tetrahydro-4*H*-cyclohepta[*d*]isoxazol-3-carboxylic Acid.

This compound was prepared by the method reported in (4). Thus equimolar amounts of 1-*N*-morpholinyl-1-cycloheptene (0.1 mole) and ethyl chlorooximinoacetate in anhydrous chloroform (300 ml.) were refluxed for 2 hours. After removing the solvent, the residue was taken up many times with ether. The organic layers, evaporated, gave a oily residue which was refluxed for 30 minutes with 10% aqueous sodium hydroxide (80 ml.). After cooling, acidification with 2*N* hydrochloric acid gave the title compound, yield, 30%, m.p. 100-101° (water).

Anal. Calcd. for $C_9H_{11}NO_3 \cdot H_2O$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.25; H, 6.39; N, 7.22.

The Hydrazide of 5,6,7,8-Tetrahydro-4*H*-cyclohepta[*d*]isoxazol-3-carboxylic Acid (IIIc).

The acid was converted into the methyl ester by treatment with ethereal diazomethane. The crude methyl ester was transformed into the hydrazide as previously reported, m.p. 76° (benzene/ligroin); ir 1667 (C=O) and 3247, 3145 cm^{-1} (NH-NH_2).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.72; H, 6.52; N, 21.55.

Hydrogenation of the Hydrazides.

General Procedure.

A mixture of 5 mmoles of the hydrazide, 200 ml. of ethanol and *ca.* 2 g. of W-2 Raney-nickel (2) was hydrogenated in a Parr apparatus at 45-50 psi for 6 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the reduced products, yield, *ca.* 70%.

(a) Hydrogenation of IIIa: 4-Amino-5,6,7,8-tetrahydrocinnolin-2*H*-3-one (Va).

The product melted at 320° dec., (ethanol); uv λ max 292 nm (log ε = 4.03); ir 1672 (C=O) and 3356, 3311, 3185 cm^{-1} (NH, NH_2); NMR (DMSO-d_6) 1.65 δ (m, 4H, -C_6H_2-C_7H_2-), 2.45 δ (m, 4H, -C_5H_2- and -C_8H_2-), 5.85 δ (s, 2H, NH_2), 12.20 δ (s, 1H, NH); Mass: 165 (M^+), 150, 136, 121, 109, 94 m/e.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.48; H, 6.88; N, 25.70.

The Diacetyl Derivative of Va.

A mixture of Va (0.5 g.) and acetic anhydride (4 ml.) was refluxed for 10 minutes. After the addition of water and solid sodium bicarbonate, the diacetyl derivative was obtained, m.p. 168° (water); ir 1724, 1706, 1661 (C=O) and 3106 cm^{-1} (NH); NMR ($CDCl_3$) 1.82 δ (m, 4H, -C_6H_2-C_7H_2-), 2.36 δ (s, 6H, 2 x $COCH_3$), 2.70 δ (m, 4H, -C_5H_2- and -C_8H_2-), 13.05 δ (s, 1H, NH); Mass: 249 (M^+), 207 (M-42), 189, 165 (M-84), 150, 137, 121 m/e.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.60; H, 6.15; N, 17.00.

(b) Hydrogenation of IIIb: 4-Amino-8-methyl-5,6,7,8-tetrahydrocinnolin-2*H*-3-one (Vb).

The product melted at 280° (ethanol); uv λ max 290 nm (log ε = 4.05); ir 1672 (C=O) and 3356, 3289, 3185 cm^{-1} (NH, NH_2); NMR (DMSO-d_6) 1.18 δ (d, 3H, CH_3), 1.73 δ (m, 4H, -C_6H_2-C_7H_2-), 2.30 δ (m, 3H, -C_5H_2- and -C_8H-), 5.80 δ (s, 2H, NH_2), 12.28 δ (s, 1H, NH); Mass: 179 (M^+), 164, 150, 135, 121, 109, 94 m/e.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.09; H, 7.18; N, 23.64.

The Diacetyl Derivative of Vb.

This compound was prepared as for the previous sample, m.p. 164° (water); ir 1724, 1704, 1661 (C=O) and 3096 cm^{-1} (NH); NMR (deuteriochloroform) 1.38 δ (d, 3H, CH_3), 1.82 δ (m, 4H, -C_6H_2-C_7H_2-), 2.38 δ (s, 6H, 2 x $COCH_3$), 2.60 δ (m, 3H, -C_5H_2- and C_8H-), 12.64 δ (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.53; H, 6.47; N, 16.33.

(c) Hydrogenation of IIIc: 4-Amino-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridazin-2*H*-3-one (Vc).

This compound melted at 330° dec. (ethanol); uv λ max 287 nm (log ε = 4.04); ir 1667 (C=O) and 3344, 3289, 3165 cm^{-1} (NH, NH_2); NMR (DMSO-d_6) 1.62 δ (m, 6H, -C_6H_2-C_7H_2-C_8H_2-), 2.50 δ (m, 4H, -C_5H_2- and -C_9H_2-), 5.88 δ (s, 2H, NH_2), 12.16 δ (s, 1H, NH); Mass: 179 (M^+), 164, 150, 135, 122, 107, 94 m/e.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.49; H, 7.08; N, 23.29.

The Diacetyl Derivative of Vc.

This compound was prepared as described for the previous samples, m.p. 175° (water); ir 1718, 1701, 1640 (C=O) and 3086 cm^{-1} (NH); NMR (deuteriochloroform) 1.76 δ (m, 6H, $-C_6H_2-C_7H_2-C_8H_2-$), 2.38 δ (s, 6H, 2 x $COCH_3$), 2.74 δ (m, 4H, $-C_5H_2-$ and $-C_9H_2-$), 12.68 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.55; H, 6.40; N, 16.10.

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