

An unusual 3,4-dihydroisoquinoline ring enlargement with the annulation of pyrazole

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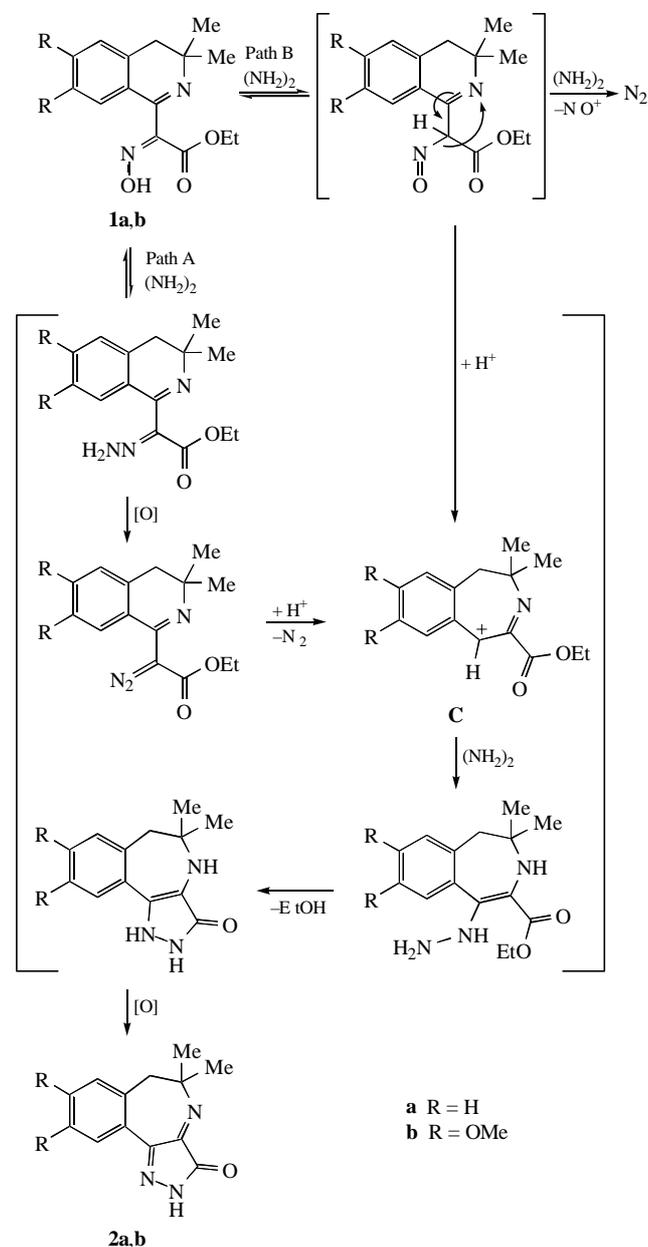
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The treatment of substituted ethyl 1-(3',4'-dihydro-3',3'-dimethylisoquinolyl)-1-oximinoacetates with hydrazine hydrate leads to a 3,4-dihydroisoquinoline ring enlargement with the annulation of a pyrazole ring to form substituted 5,5-dimethyl-2,3,5,6-tetrahydro-3-oxopyrazolo[3,4-*b*]benzo-3-azepines.

Alkyl 1-(3',4'-dihydroisoquinolyl)-1-oximinoacetates exhibit biological activity.¹ Studying chemical properties of ethyl 1-(3',3'-dimethyl-3',4'-dihydroisoquinolyl)-1-oximinoacetates **1a,b**,² we found an unusual transformation of these compounds by the

reaction with hydrazine hydrate. The treatment of compounds **1a,b** with 3–6 equiv of hydrazine in propan-2-ol leads to the slow evolution of N₂ from the reaction mixture. The subsequent refluxing (3–5 min) and exposure to air for 1–3 days resulted in the formation of substituted 5,5-dimethyl-2,3,5,6-tetrahydro-3-oxopyrazolo[3,4-*b*]benzo-3-azepines **2a,b** in good yields (47–74 %).[†]

The mechanism of this reaction is not clear. Possible reaction paths for the conversion of **1a,b** into **2a,b**, are depicted in Scheme 1. Path A involves oxidation of the initially formed hydrazone to a diazo compound, decomposition of this latter with a ring enlargement to form benzo-3-azepine, addition of hydrazine to electrophilic intermediate **C**, intramolecular cyclization and oxidation with air to form substituted 5,5-dimethyl-2,3,5,6-tetrahydro-3-oxopyrazolo[3,4-*b*]benzo-3-azepines **2a,b**. Path B involves the base-induced tautomeric conversion of the oxime into a nitroso form (pH of the reaction mixture was ~8), the elimination of NO⁺ and the insertion into the C=N bond to form electrophilic intermediate **C**; the subsequent transformations are similar to path A.



Scheme 1

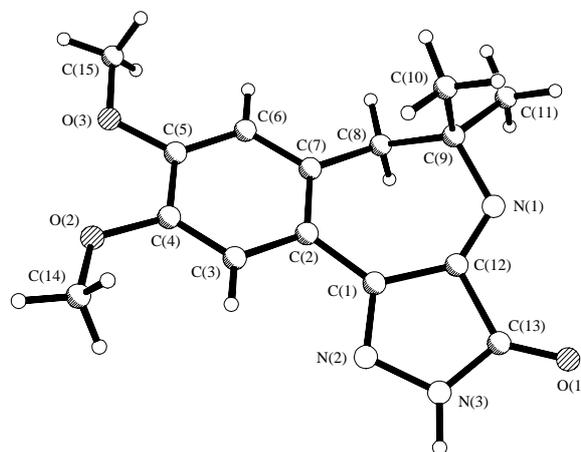


Figure 1 The structure of compound **2b**. Selected bond lengths (Å): N(1)–C(12) 1.252(5), N(1)–C(9) 1.475(5), N(2)–C(1) 1.304(4), N(2)–N(3) 1.386(4), N(3)–C(13) 1.348(5), O(1)–C(13) 1.205(5).

[†] Oxime **1b** was synthesised from ethyl 1-(3',3'-dimethyl-3',4'-dihydroisoquinolyl)acetate¹⁰ by the known method.²

Oxime **1b** (0.31 g, 0.93 mmol) was dissolved in 30 ml of propan-2-ol (50 °C); next 0.3 g (6 mmol) of hydrazine hydrate was added; the mixture was refluxed for 3 min and allowed to stand in air for 1–3 days. Next, a small amount of a polymeric substance was filtered off, and the red solution was evaporated. The residue was twice treated with cool water (2×3 ml) for removing hydrazine, dried and recrystallised to result in **2b**. Compound **2a** was purified by chromatography on a silica gel column (eluent: benzene–CHCl₃, 5:1).

The role of the tautomeric nitroso form was supported by the fact that corresponding O-methylated ethyl 1-(3',3'-dimethyl-3',4'-dihydroisoquinolyl)-1-oximinoacetates treated by hydrazine in the same manner did not form compounds **2a,b**.

Note that the ring enlargement of 3,4-dihydroisoquinolines to benzo-3-azepines is well known,³⁻⁷ but these reactions frequently give a variety of products.⁸ Moreover, the simultaneous annulation of a pyrazole ring to benzoazepine is of synthetic importance. Compounds **2a,b** are the diaza analogues of the recently discovered alkaloids nordeoxyharringtonine and homodeoxyharringtonine⁹ of *Cephalotaxus* from *Cephalotaxus harringtonia* var. *drupacea*.

The structure of compounds **2a,b** was confirmed by elemental analysis, ¹H NMR and IR spectroscopy,[‡] and compound **2b** was additionally examined by ¹³C NMR spectroscopy, mass spectrometry[‡] and X-ray diffraction analysis.[§] The general view of molecule **2b** is given in Figure 1.

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‡ **1b**: mp 196–197 °C (ethanol). ¹H NMR (80 MHz, CDCl₃) δ: 1.17 (t, 3H, CH₂Me), 1.23 (s, 6H, 3-Me), 2.68 (s, 2H, 4-CH₂), 3.75 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.19 (q, 2H, OCH₂), 6.60 (s, 2H, 5,8-H), 9.56 (br. s, 1H, N–OH). IR (Nujol, ν/cm⁻¹): 3100 (br.), 1720 (O=C=O), 1600, 1565, 1520, 1270, 1240, 1215, 1170, 1160 (sh.), 1100, 1035, 960, 920, 900, 865, 845, 825.

2a: mp 199–202 °C (decomp.) (benzene-hexane). ¹H NMR (250 MHz, [²H₆]DMSO) δ: 1.32 (s, 6H, 5-Me), 3.10 (s, 2H, 6-CH₂), 7.15–7.40 (m, 3H, 7,8,9-H), 7.90 (d, 1H, 10-H), 11.95 (s, 1H, NH). IR (Nujol, ν/cm⁻¹): 3245 (NH), 1730 (C=O), 1620 (C=N), 1325, 1260, 1240, 1173, 1105, 1040, 965, 925, 895, 770.

2b: mp 206–210 °C (decomp.) (ethanol). ¹H NMR (250 MHz, [²H₆]DMSO) δ: 1.31 (s, 6H, 5-Me), 3.02 (s, 2H, 6-CH₂), 3.83 (s, 6H, 8,9-OMe), 6.74 (s, 1H, 7-H), 7.36 (s, 1H, 10-H), 11.80 (br. s, 1H, NH). ¹³C NMR ([²H₆]DMSO) δ: 161.38 (C=O), 151.54 [C(3a)], 150.61 [C(10b)], 147.52 [C(8)], 140.18 [C(9)], 130.27 [C(6a)], 121.70 [C(10a)], 114.08 [C(10)], 107.62 [C(7)], 60.63 [C(5)], 55.51 and 55.38 [8,9-(MeO)₂], 45.25 [C(6)]; signals of 5,5-Me₂ are overlapped by [²H₆]DMSO. IR (Nujol, ν/cm⁻¹): 3290 (NH), 1720 (C=O), 1680 (sh.), 1600 (C=N), 1530, 1500, 1260, 1215, 1165, 1100, 1050, 1030, 1000, 860. MS, m/z (%): M⁺ 287 (100), 272 (28), 256 (9), 243 (27), 229 (32), 203 (99), 188 (19), 176 (20), 160 (12), 144 (11), 129 (20), 115 (20).

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§ *Crystallographic data for 2b*: C₁₅H₁₇N₃O₃, monoclinic, space group *P2₁/n*, *a* = 8.733(2), *b* = 10.646(2), *c* = 16.093(3) Å, β = 104.40(3)°, *V* = 1449.2(5) Å³, *Z* = 4, *d_c* = 1.317 g cm⁻³, λ(MoK_α) = 0.7107 Å, μ(MoK_α) = 0.90 cm⁻¹, *F*(000) = 608, *T* = 294 K. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using the ω scan method (2θ_{max} = 56.9°). The structure was solved by the direct method (SHELXS-88¹¹) and refined by a full-matrix least-squares procedure (SHELXL-93¹²) in an anisotropic approximation for all non-hydrogen atoms. The coordinates and thermal parameters of the hydrogen atoms were fixed (*U_H* 0.08 Å², C–H 0.096 Å). Final *R*₁ = 0.054, *wR*₂ = 0.120 and *S* = 1.115 for 1384 observed reflections with *I* > 2σ(*I*). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/57.