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

Yurii V. Shklyaev,*[a] Vladimir A. Glushkov,[a] Viktor V. Davidov,[b] Valentina I. Sokol[c] and Vladimir S. Sergienko[c]

[a] *Institute of Technical Chemistry, Urals Branch of the Russian Academy of Sciences, 614600 Perm, Russian Federation. Fax +7 3422 124 375; e-mail:cheminst@mpm.ru*
[b] *Peoples' Friendship University of Russia, 117198 Moscow, Russian Federation. Fax: +7 095 952 1186; e-mail: vdavidov@mx.pfu.edu.ru*
[c] *N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 117907 Moscow, Russian Federation. Fax: +7 095 954 1279; e-mail: sokol@ionchran.msk.ru*

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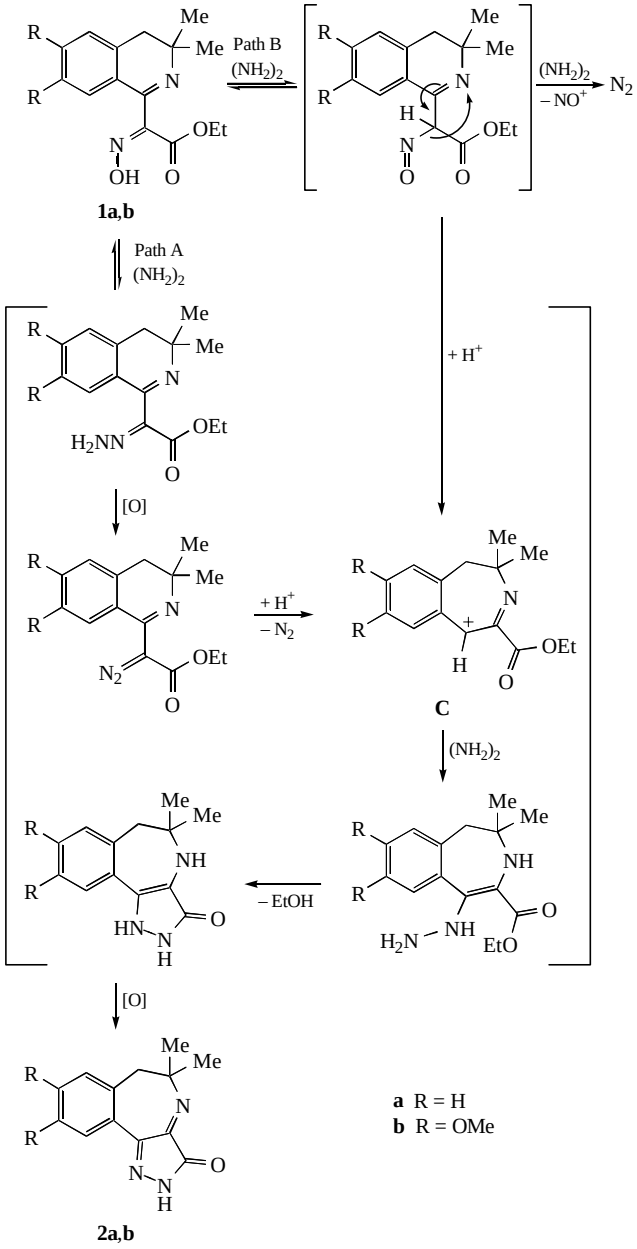
The treatment of substituted ethyl 1-(3′,4′-dihydro-3′,3′-dimethylisoquinolyl)-1-oximinoacetates with hydrazine hydrate leads to a 3,4-dihydroisoquinoline ring enlargement with the annulation of a pyrazole ring to form substituted 5,5-dimethyl-2,3,5,6-tetrahydro-3-oxopyrazolo[3,4-*b*]benzo-3-azepines.

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 equivalents of hydrazine in propan-2-ol leads to the slow evolution of N_2 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%).†



Scheme 1

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 nitrozo 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.

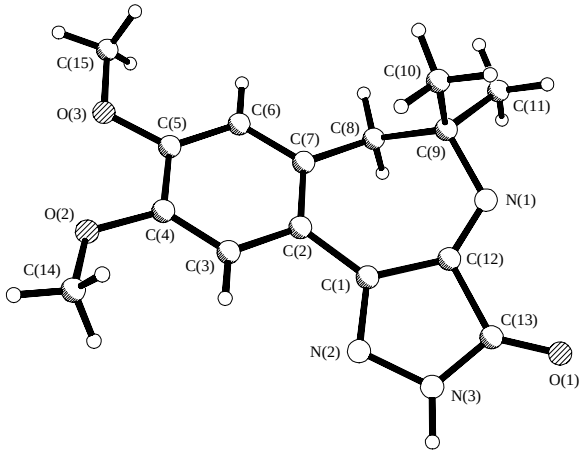


Figure 1 The structure of compound **2b**. Selected bond lengths (Å): N(1)–C(12) 1.252(5), N(1)–C(9) 1.475(5), N(2)–C(1) 1.304(4), N(2)–N(3) 1.386(4), N(3)–C(13) 1.348(5), O(1)–C(13) 1.205(5).

† Oxime **1b** was synthesised from ethyl 1-(3′,3′-dimethyl-3′,4′-dihydroisoquinolyl)acetate[10] 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–$CHCl_3$, 5:1).

The role of the tautomeric nitrozo 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 homodeoxyharringtonine[9] of *Cephalotaxus* from *Cephalotaxus harringtonia* var. *drupacea*.

The structure of compounds **2a**,**b** was confirmed by elemental analysis, ^{1}H NMR and IR spectroscopy,‡ and compound **2b** was additionally examined by ^{13}C 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). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.17 (t, 3H, CH_2*Me*), 1.23 (s, 6H, 3-Me), 2.68 (s, 2H, 4-CH_2), 3.75 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.19 (q, 2H, OCH_2), 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). ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.32 (s, 6H, 5-Me), 3.10 (s, 2H, 6-CH_2), 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). ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.31 (s, 6H, 5-Me), 3.02 (s, 2H, 6-CH_2), 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). ^{13}C NMR ([$^2H_6$]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-Me_2 are overlapped by [$^2H_6$]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**: $C_{15}H_{17}N_3O_3$, monoclinic, space group $P2_1/n$, a = 8.733(2), b = 10.646(2), c = 16.093(3) Å, β = 104.40(3)°, V = = 1449.2(5) Å^3, Z = 4, d_c = 1.317 g cm^{-3}, λ(MoKα) = 0.7107 Å, μ(MoKα) = = 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 ($2\theta_{max}$ = = 56.9°). The structure was solved by the direct method (SHELXS-88[11]) and refined by a full-matrix least-squares procedure (SHELXL-93[12]) in an anisotropic approximation for all non-hydrogen atoms. The coordinates and thermal parameters of the hydrogen atoms were fixed (U_H 0.08 Å^2, C–H 0.096 Å). Final R_1 = 0.054, wR_2 = 0.120 and S = 1.115 for 1384 observed reflections with $I > 2\sigma(I)$. 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.