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Synthesis of Some Pyrazol-5-ols Related to Muscimol

JYTTE LYKKEBERG

Royal Danish School of Pharmacy, Department of Chemistry BC, DK-2100 Copenhagen, Denmark

The syntheses of the zwitterions 3-aminomethylpyrazol-5-ol (*5a*), 3-(2-aminoethyl)pyrazol-5-ol (*5b*), 3-(1-aminoethyl)pyrazol-5-ol (*5c*), and 4,4-dimethyl-4,5,6,7-tetrahydropyrazolo[4,3-*c*]-pyridin-3-ol (*7b*) are described. *5a–c* were prepared from the corresponding dihydrochlorides *4a–c* by treatment with triethylamine. The 3-(2-aminoethyl)- and the 3-(1-aminoethyl)pyrazol-5-ol dihydrochloride (*4b,c*) were obtained by treatment of *N*-phthaloyl *β*- and *α*-alanylmalonic ester (*8b,c*), respectively, with hydrazine hydrate in glacial acetic acid followed by refluxing of the formed 3-(*N*-phthaloylalanyl)-4-ethoxycarbonylpyrazol-5-ols *9b,c* with 7 M hydrochloric acid. The 3-(2-aminoethyl)pyrazol-5-ol dihydrochloride (*4b*) reacted with acetone and triethylamine to give the 4,4-dimethyl-4,5,6,7-tetrahydropyrazolo-[4,3-*c*]pyridin-3-ol (*7b*).

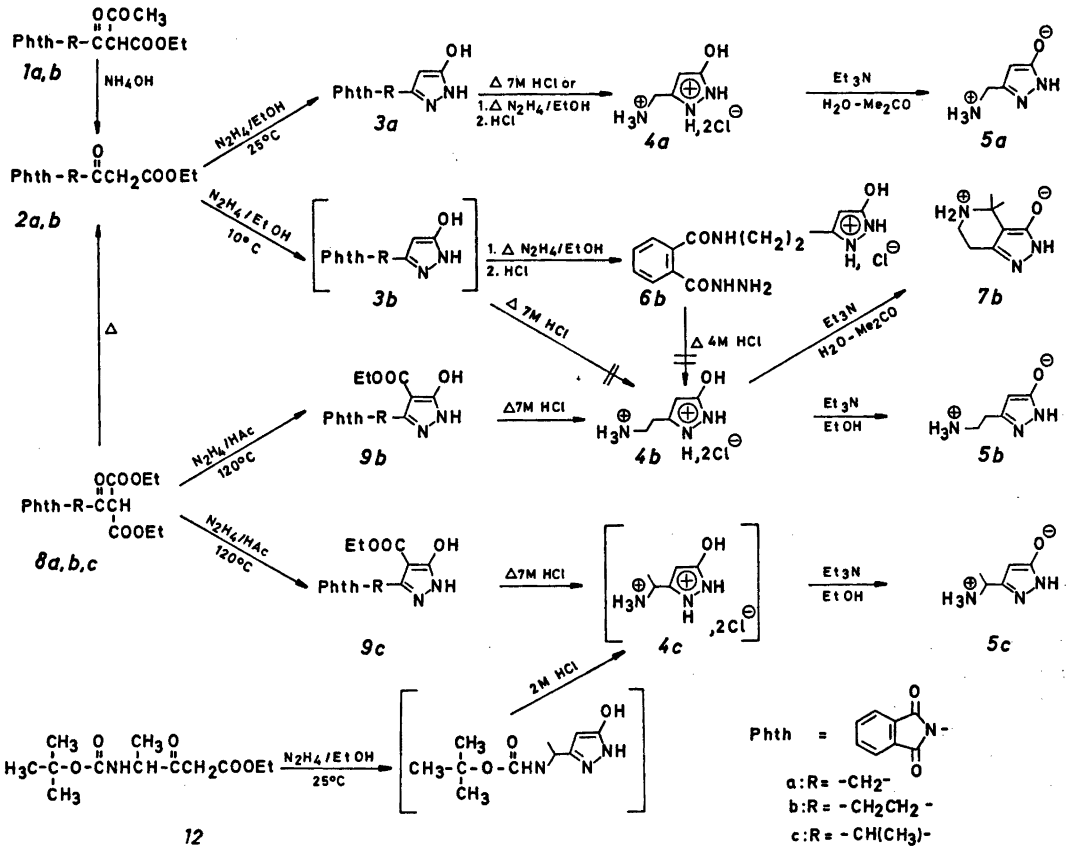
The syntheses of 3-[*N*-(*o*-carbazoylbenzoyl)-2-aminoethyl]pyrazol-5-ol hydrochloride (*6b*), *N*-phthaloyl-*β*-alanine hydrazide (*10b*), and the new tetracyclic ring system 4,5-dihydro-1-hydroxy-7*H*-pyrazolo[4′,3′:3,4]pyrido[2,1-*a*]isoindol-7-one (*11b*) are also described.

Muscimol (5-aminomethyl-3-isoxazolol), a constituent of *Amanita muscaria*, is a powerful GABA (*γ*-aminobutyric acid) agonist.[1,2] Several muscimol analogues containing various aminoalkyl groups in position 4 or 5 of the 3-isoxazolol nucleus have been synthesized[3–6] and tested biologically.[7] As part of our interest in muscimol analogues in which the heterocyclic ring system has been changed,[8] the zwitterions 3-aminomethylpyrazol-5-ol (azamuscimol) (*5a*), 3-(2-aminoethyl)pyrazol-5-ol (homoazamuscimol) (*5b*), 3-(1-aminoethyl)pyrazol-5-ol (*5c*), and 4,4-dimethyl-4,5,6,7-tetrahydropyrazolo-[4,3-*c*]pyridin-3-ol (*7b*) have now been prepared. Azamuscimol (*5a*) has a relatively weak depressant action on spinal neurons in cats (microelectrophoresis),[7] and it has been shown to be an inhibitor of L-glutamate decarboxylase (GAD).[9] Finally azamuscimol (*5a*) has been tested *in vitro* for antitubercular activity, but no antibacterial activity could be shown. The biological properties of the azamuscimol analogues *5b*, *5c*, and *7b* will be examined in the near future.

Azamuscimol dihydrochloride (*4a*)[10] was converted into the zwitterion *5a* by treatment with triethylamine followed by addition of acetone.

A new improved synthesis of ethyl (*N*-phthaloyl-*β*-alanyl)acetate (*2b*)[11] was based on treatment of ethyl (*N*-phthaloyl-*β*-alanyl)acetoacetate (*1b*) with concentrated aqueous ammonia in ethanol. Attempts to synthesize homoazamuscimol (*5b*) by the reaction sequence used for the preparation of azamuscimol (*5a*) (Scheme 1) failed, as *2b* with hydrazine hydrate in ethanol at room temperature gave *11b* (Scheme 2) as the main product. The tetracyclic ring system of *11b* has not previously been described, but the corresponding tricyclic ring system without the pyrazolo ring is well-known, as *1b* by treatment with base (pyridine) yielded 1-acetyl-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione.[11] Treatment of *2b* with hydrazine hydrate in ethanol at 0–12 °C yielded a mixture of 3-(*N*-phthaloyl-2-aminoethyl)pyrazol-5-ol (*3b*) and unreacted *2b*. Attempts to remove the phthaloyl group of *3b* by treatment with hydrazine hydrate in boiling ethanol led to *6b*, which was stable to boiling with 4 M hydrochloric acid for 3 h. Refluxing of *3b* in 7 M hydrochloric acid for 3 h gave a complex reaction mixture containing unreacted *3b*.

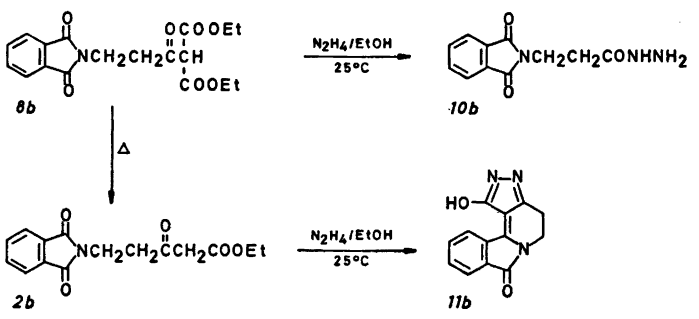
Finally the dihydrochloride *4b* of homoazamuscimol was prepared by treatment of *8b* with hydrazine hydrate in glacial acetic acid followed by refluxing of the pyrazolol *9b*



Scheme 1.

with 7 M hydrochloric acid Treatment of *8b* with hydrazine hydrate in ethanol at ambient temperature yielded *N*-phthaloyl-β-alanine hydrazide (*10b*) (Scheme 2). Homoazamuscimol (*5b*) was prepared by treatment of the dihydrochloride *4b* with triethylamine in ethanol. Attempts to convert *4b* into *5b* by treatment with triethylamine and acetone led to the tetrahydropyrazolo[4,3-*c*]pyridin-3-ol *7b*, instead of the expected zwitterion *5b*.

The 3-(1-aminoethyl)pyrazol-5-ol zwitterion (*5c*) could be prepared by the procedure used for homoazamuscimol (*5b*) using *8c* as the starting material (Scheme 1). In an attempt to elevate the yield of *5c*, *12* was used as starting material but the sequence outlined in



Scheme 2.

Scheme 1 also yielded *5c* in a rather poor yield. Attempts to convert *8c* into ethyl (*N*-phthaloyl-α-alanyl)acetate (*2c*) by refluxing of *8c* with water or pyridine-water failed.

The structure determinations of the new compounds *4b*, *5a–c*, *11b*, *6b*, *9b,c*, *7b* and *10b* were based on IR, UV, and ^{1}H NMR spectroscopy and supported by elemental analyses. The structure of the new ring system of *11b* was further confirmed by mass spectrometry. The described pyrazoles were assigned the pyrazol*ol* structure rather than the pyrazolin*one* structure due to absence of infrared absorption at 1710–1700 cm^{-1} and absence of ultraviolet absorption about 250 nm with an ε value of $1.8-2.5\times10^4$ and about 310 nm with an ε value of 8.0×10^3, all characteristics of pyrazolinones.[12,13] The structure determination of the pyrazolols was supported by ^{1}H NMR spectroscopy and by the finding that the pyrazolols formed coloured complexes with ferric chloride.[12] Broad IR absorptions of *5a–c* and *7b* in the range 3600–1800 cm^{-1} are in agreement with the presence of ammonium groups in these compounds, and consequently these compounds are zwitterions. The zwitterion *5c* crystallized with 1 mol of water, the removal of which by heating was accompanied by destruction of the compound.

EXPERIMENTAL

Melting points are corrected and were determined with a hot stage microscope (Mikroskop-Heiztisch, 350 Ernst Leitz G.m.b.H., Wetzlar). Thin layer chromatography (TCL) was accomplished by using silica gel GF_{254} plates (Merck). The recording of IR (KBr technique), UV (methanol solutions), and ^{1}H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper.[8] The mass spectrum was obtained with an AEI MS 902 mass spectrometer operating at 70 eV. pH values were measured on a Radiometer pH meter 26 and the pK_A values were determined according to the method of Albert and Serjeant.[14]

3-Aminomethylpyrazol-5-ol zwitterion (5a). A solution of 1.86 g (10 mmol) of *4a*[10] in 3 ml of water was chilled in an ice bath and treated with 2.23 g (22 mmol) of triethylamine. The reaction mixture was diluted with 10 ml of acetone, stirred thoroughly, and filtered. Recrystallization (ethanol–water) gave 870 mg (66 %) of *5a*.H_2O, m.p. 220 °C (decomp.). Anal. $C_4H_7N_3O.H_2O$: C, H, N. The water of crystallization could be removed upon heating *in vacuo* at 110 °C for 3 h: Anal. $C_4H_7N_3O$: C, H, N. λ_{max} 240 nm ($\varepsilon=4.00\times10^3$). IR data: 3600–2000 (s) (with submaxima at 3350, 3200, 3050, 2900, 2800, 2700, 2600, 2450, 2100), 1660 (m), 1620 (s), 1580 (s), 1550 (s), 1470 (s) cm^{-1}. ^{1}H NMR data (DMSO-d_6): δ 5.24 (s, 1 H, C=CH); 4.2 (broad signal from H_2O and NH protons); 3.52 (s, 2 H, N-CH_2). pK_A values (H_2O, 21 °C): 1.85 ± 0.09, 6.15 ± 0.02, and 9.78 ± 0.02.

Ethyl (N-phthaloyl-β-alanyl)acetate (2b). A solution of 13 g (40 mmol) of *1b*[11] in 60 ml of ethanol was treated with 4 ml of aqueous ammonia (ϱ 0.88) during 10 min at 80 °C. After cooling to room temperature the precipitate was collected and washed with two 5 ml portions of ethanol. After drying 6.1 g (53 %) of *2b* was obtained, m.p. 90–91 °C (Ref. 11, m.p. 90 °C). λ_{max} 290 nm ($\varepsilon=1.80\times10^3$), 241 nm ($\varepsilon=9.79\times10^3$), 232 nm ($\varepsilon=1.36\times10^4$), and 220 nm ($\varepsilon=3.63\times10^4$). IR data: 3450 (m), 1770 (m), 1740 (s), 1710 (s), 1440 (m) cm^{-1}. ^{1}H NMR data (DMSO-d_6): δ 7.87 (s, 4 aromatic protons); 4.10 (q, $J\sim7$ Hz, 2 H, C–CH_2–OCO); 3.82 (t, $J\sim7$ Hz, 2 H, N–CH_2–C); 3.63 (s, 2 H, CO–CH_2–COO); 2.98 (t, $J\sim7$ Hz, 2 H, C–CH_2–CO); 1.17 (t, $J\sim7$ Hz, 3 H, CH_3).

4,5-Dihydro-1-hydroxy-7H-pyrazolo[4',3':3,4]-pyrido[2,1-a]isoindol-7-one (11b). To a suspension of 5.2 g (18 mmol) of *2b*[11] in 75 ml of ethanol was added 900 mg (18 mmol) of hydrazine hydrate. After stirring overnight at room temperature, the precipitate was collected and dried to give 1.2 g (28 %) of *11b*. An analytical sample was recrystallized in ethanol to give *11b* as red needles, m.p. 284–285 °C. Anal. $C_{13}H_9O_2N_3$: C, H, N. λ_{max} 306 nm ($\varepsilon=1.61\times10^4$) and 232 nm ($\varepsilon=2.18\times10^4$). IR data: 3250 (m), 1710 (s), 1680 (s), 1620 (s), 1570 (m), 1470 (m), 1410 (m) cm^{-1}. ^{1}H NMR data (CF_3COOD): δ 9.1 (broad signal, 1 H, NH); 8.0 (s, 4 aromatic protons); 4.40 (t, 2 H, CH_2); 3.53 (t, 2 H, CH_2). MS [*m/e* (% rel. int.)]: 237 (100, M), 210 (32 [M–N_2H]),[15] 182 (71, [M–CON_2H]).[15]

3-[N-(o-Carbazoylbenzoyl)-2-aminoethyl]-pyrazol-5-ol hydrochloride (6b). To a suspension of 2.6 g (9 mmol) of *2b*[11] in 60 ml of ethanol was added 450 mg (9 mmol) of hydrazine hydrate. After stirring at 12 °C for 3 h the precipitate was collected and dried to give 1.4 g of a mixture of *3b* and *2b* (rendered probable by TLC). The crude mixture (1.4 g) and 300 mg (6 mmol) of hydrazine hydrate in 15 ml of ethanol was heated at reflux for 1 h. After cooling to room temperature the precipitate was collected and dissolved in 4 N hydrochloric acid. The solution was concentrated *in vacuo* and the crystalline residue recrystallized from methanol-ether to give 580 mg of *6b* (20 %), m.p. 285 °C (decomp.). Anal. $C_{13}H_{16}N_5O_3Cl$: C, H, N, Cl. λ_{max} 299 nm ($\varepsilon=6.73\times10^3$), 249 nm ($\varepsilon=1.02\times10^4$), and 219 nm ($\varepsilon=2.69\times10^4$). IR data: 3700–1900 (s), 1660–1560 (s) (with

submaxima at 1655, 1645, 1635, 1630, 1620, 1610), 1545 (m), 1530 (s), 1480 (m), 1465 (s) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 12.7 (s, 1 H, NH); 8.2 (m, 2 H, NH); 7.8 (m, 4 aromatic protons); 5.8 (broad, 5 H, NH, OH, and C=CH); 2.9 (s, 4 H, $2 \times CH_2$).

3-(N-Phthaloyl-2-aminoethyl)-4-ethoxycarbonylpyrazol-5-ol (9b). A mixture of 1.8 g (5 mmol) of *8b*[11] and 250 µl (5 mmol) of hydrazine hydrate in 8 ml of glacial acetic acid was refluxed for 1 h. The solution was evaporated *in vacuo* and upon recrystallization (ethanol) of the residue 0.9 g (55 %) of *9b* was obtained; m.p. 175–177 °C. Anal. $C_{16}H_{15}N_3O_5$: C, H, N. λ_{max} 263 nm ($\varepsilon = 6.12 \times 10^3$), 240 nm ($\varepsilon = 1.31 \times 10^4$), and 220 nm ($\varepsilon = 4.67 \times 10^4$). IR data: 3250 (m), 1770 (s), 1710 (s), 1590 (s), 1530 (m), 1470 (m), 1440 (m) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 9–12 (broadened signal, 2 H, NH and OH); 7.83 (s, 4 aromatic protons); 4.05 (q, $J \sim 7$ Hz, 2 H, $C-CH_2-OCO$); 3.85 (t, $J \sim 6$ Hz, 2 H, $N-CH_2-C$); 3.03 (t, $J \sim 6$ Hz, 2 H, $C-CH_2-C=N$); 1.22 (t, $J \sim 7$ Hz, 3 H, CH_3).

3-(2-Aminoethyl)pyrazol-5-ol dihydrochloride (4b). A mixture of 3.7 g (11 mmol) of *9b* and 90 ml of 7 M hydrochloric acid was refluxed for 2 h. After cooling to room temperature the precipitate was removed and the solution was concentrated *in vacuo*. The crystalline residue was recrystallized from methanol-ether to give 1.2 g (55 %) of *4b*, m.p. 185–188 °C (decomp.). Anal. $C_5H_{11}N_3OCl_2$: C, H, N, Cl. λ_{max} 246 nm ($\varepsilon = 1.73 \times 10^3$), and 218 nm ($\varepsilon = 5.49 \times 10^3$). IR data: 3600–2100 (s) (with submaxima at 3350 and 3150), 1625 (s), 1570 (m), 1540 (m), 1470 (s) cm^{-1}. ^1H NMR (DMSO-d_6): δ 13.37 (s, 3 H, NH and OH, exchangeable with D_2O); 8.40 (s, 3 H, NH); 5.87 (s, 1 H, C=CH); 3.07 (s, 4 H, $2 \times CH_2$).

3-(2-Aminoethyl)pyrazol-5-ol zwitterion (5b). A solution of 400 mg (2 mmol) of *4b* in 10 ml of ethanol was chilled in an ice bath and treated with 600 µl (4.4 mmol) of triethylamine. The precipitate was collected and dried to give 195 mg of crude *5b*. Recrystallization (water-ethanol-ether) gave 95 mg (37 %) of *5b*, m.p. 200 °C (decomp.). Anal. $C_5H_9N_3O$: C, H, N. λ_{max} 240 nm ($\varepsilon = 3.30 \times 10^3$), and 226 nm ($\varepsilon = 3.77 \times 10^3$). IR data: 3500–1800 (s) (with submaxima at 3250, 2950, 2750, 2650, 2400), 1660–1490 (s) (with submaxima at 1580, 1570, 1560, 1550), 1490–1390 (s) (with submaxima at 1470, 1460, 1450, 1420) cm^{-1}. pK_A values (H_2O, 21 °C): 2.08 ± 0.06, 6.98 ± 0.01, 10.31 ± 0.05.

4,4-Dimethyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-3-ol zwitterion (7b). *7b* was synthesized as described above for *5a* using 600 mg (3 mmol) of *4b* and 920 µl (6.6 mmol) of triethylamine to give 500 mg of crude product. Recrystallization (methanol-ether) gave 380 mg (68 %) of $7b.H_2O$; m.p. 200 °C (decomp.). Anal. $C_8H_{13}N_3O.H_2O$: C, H, N. The water of crystallization could be removed upon heating *in vacuo* at 120 °C for 18 h. Anal. $C_8H_{13}N_3O$: C, H, N. λ_{max} 243 nm ($\varepsilon = 4.82 \times 10^3$). IR data: 3600–2000 (s) (with submaxima at 3200, 3100, 2980, 2700, 2600, 2480, 2250), 1630 (s), 1580 (s), 1530 (s), 1490 (s), 1430 (s) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 5.5 (broad s, 5 H, H_2O and 3 NH, exchangeable with D_2O); 2.85 (t, $J \sim 5$ Hz, 2 H, CH_2); 2.32 (t, $J \sim 5$ Hz, 2 H, CH_2); 1.22 (s, 6 H, $2 \times CH_3$).

N-Phthaloyl-β-alanine hydrazide (10b). *10b* was synthesized as described above for *11b* using 1.8 g (5 mmol) of *8b*[11] and 250 µl (5 mmol) of hydrazine hydrate. After stirring for 5 min 0.9 g (77 %) of *10b* was obtained. An analytical sample was recrystallized (ethanol) to give *10b*; m.p. 174–176 °C. Anal. $C_{11}H_{11}N_3O_3$: C, H, N. λ_{max} 293 nm ($\varepsilon = 1.67 \times 10^3$), 241 nm ($\varepsilon = 1.06 \times 10^4$), 232 nm ($\varepsilon = 1.59 \times 10^4$), and 220 nm ($\varepsilon = 4.01 \times 10^4$), IR data: 3300 (m), 1770 (m), 1710 (s), 1640 (s), 1610 (m), 1530 (m), 1440 (m) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 7.85 (s, 4 aromatic protons); 5.1 (broad signal, 3 H, NH, exchangeable with D_2O); 3.75 (t, $J \sim 7$ Hz, 2 H, $N-CH_2-C$); 2.37 (t, $J \sim 7$ Hz, 2 H, $C-CH_2-CO$).

3-(N-Phthaloyl-1-aminoethyl)-4-ethoxycarbonylpyrazol-5-ol (9c). A mixture of 1.8 g (5 mmol) of *8c*[16] and 250 µl (5 mmol) of hydrazine hydrate in 8 ml of glacial acetic acid was refluxed for 10 min. The solution was evaporated *in vacuo* to give a yellow gum. The residue was taken up in a saturated sodium carbonate solution. The basic solution was extracted with ether and adjusted to pH 1–2 with 4 M hydrochloric acid. The precipitate was collected and recrystallized from ethanol-water to give 0.8 g (49 %) of *9c*; m.p. 150–152 °C. Anal $C_{16}H_{15}N_3O_5$: C, H, N. λ_{max} 260 nm ($\varepsilon = 3.80 \times 10^3$), 240 nm ($\varepsilon = 1.13 \times 10^4$), and 220 nm ($\varepsilon = 3.75 \times 10^4$). IR data: 3500 (m), 3400 (m), 3200 (m), 1780 (m), 1710 (s), 1540 (m), 1515 (m), 1505 (m), 1470 (m) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 11.4 (broad signal, 2 H, NH and OH); 7.82 (s, 4 aromatic protons); 5.60 (q, $J \sim 7$ Hz, 1 H, $N-CH-C$); 4.03 (q, $J \sim 7$ Hz, 2 H, $C-CH_2-OCO$); 1.75 (d, $J \sim 7$ Hz, 3 H, CH_3-C-N); 1.08 (t, $J \sim 7$ Hz, 3 H, $CH_3-C-OCO$).

3-(1-Aminoethyl)pyrazol-5-ol zwitterion (5c). (a) A mixture of 500 mg (1.5 mmol) of *9c* and 12 ml of 7 M hydrochloric acid was refluxed for 2 h. After cooling to room temperature the precipitate was removed and the solution was concentrated *in vacuo* to give 200 mg (1 mmol) of *4c* as an oil. The oily product was dissolved in 5 ml of ethanol and treated with 280 µl (2 mmol) of triethylamine and 100 µl of ether. The precipitate was collected, dried and upon recrystallization (water-ethanol-ether) 45 mg (21 %) of $5c.H_2O$ was obtained; m.p. 207–210 °C. Found: C 41.05; H 7.10; N 28.50. Calc. for $C_5H_9N_3O.H_2O$: C 41.37; H 7.64; N 28.95. λ_{max} 240 nm ($\varepsilon = 3.12 \times 10^3$), and 221 nm ($\varepsilon = 4.85 \times 10^3$). IR data: 3600–2000 (s) (with submaxima at 3250, 3050, 2875, 2675,

2500, 2100), 1660–1490 (s) (with submaxima at 1640, 1565, 1550, 1540), 1490–1420 (s) (with submaxima at 1460, 1450, 1440) cm^{-1}. ^1H NMR data (DMSO-d_6): δ 7.9 (broad signal, 6 H, 4 NH and H_2O); 5.3 (s, 1 H, C=CH); 4.0 (broad signal, 1 H, CH); 1.4 (broad signal, 3 H, CH_3).

(b) A solution of 1.3 g (5 mmol) of *12*[18] in 20 ml of ethanol was treated with 250 µl (5 mmol) of hydrazine hydrate for 10 min. The solution was concentrated *in vacuo* and the oily residue was dissolved in 20 ml of 2 M hydrochloric acid. The acid solution was evaporated *in vacuo* to give 450 mg (2.3 mmol) of *4c* as an oil. The oily product was dissolved in 10 ml of ethanol and treated with 550 µl (4 mmol) of triethylamine. The precipitate was collected, dried and upon recrystallization (water-ethanol) 70 mg (10 %) of *5c*.H_2O was obtained.

Biological test. Azamuscimol (*5a*) was tested *in vitro* on Löwenstein-Jensen medium against strains of *M. tuberculosis* (No. E 10883/45 and 1921/41) as described by Engbæk *et al.*[17] Azamuscimol (*5a*) had no influence on the bacteria growth at concentrations where isoniazid caused complete inhibition.

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