Chemical Synthesis of Phase-I- and Phase-II-Metabolites of Antipyrine

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The chemical synthesis of the hydroxylated phase-I-metabolites **9**, **11**, and **12** is effected by Triton B catalysed saponification of the bromides **7** and **8** and boron tribromide mediated ether cleavage of **6** and **10** to **11** and **12**. The chelated enol **9** was coupled with the bromosugar **13** to afford the glucuronide **14** that was saponified to the phase-II-metabolite **15**.

Chemische Synthese der Phase-I- und Phase-II-Metaboliten des Antipyrins

Die hydroxylierten Phase-I-Metaboliten **9**, **11** und **12** werden durch Triton B-katalysierte Verseifung der Bromide **7** und **8** und Etherspaltung von **6** und **10** mit Bortribromid zu **11** und **12** bereitet. Das chelierte Enol **9** wird mit dem Bromzucker **13** zum Glucuronid **14** gekoppelt und zum Phase-II-Metaboliten **15** verseift.

Antipyrine (1-phenyl-2,3-dimethylpyrazoline-5-one, phenazone, **5**) the classical pyrazolone analgesic, has gained wide acceptance during the last two decades as a model substance in clinical as well as in biochemical pharmacological research[1]. Using this model two different approaches have evolved to test the drug hydroxylation activity in vivo:

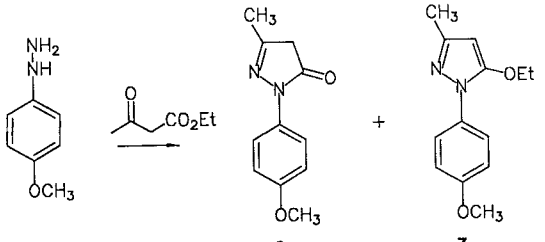
1. direct determination of the elimination kinetics of the unchanged antipyrine (drug) from the blood, plasma or saliva [2-4],
2. assay urinary profiles of antipyrine metabolites either of phase-I [5-8] or phase-II [9].

In fact, determination of the urinary pattern of hydroxylated metabolites has become a promising means for the assessment and the analysis in vivo of the various activities of cytochrome-P450 isoenzymes involved [10-12]. The hydroxylation pattern of antipyrine in humans as well as in animals is sufficiently complex to form a series of primary hydroxylated metabolites (4-hydroxy-antipyrine (**9**), 2-methyl-3-hydroxymethyl-1-phenyl-3-pyrazoline-5-one, ("3-hydroxymethyl-antipyrine"), 4'-hydroxy-antipyrine (**11**) and some secondary hydroxylated metabolites (4,4'-dihydroxy-antipyrine (**12**) the assay of which can now be handled satisfactorily by different analytical approaches[8,13-19].

However, as a consequence of its widespread use in the field of pharmacology, toxicology, and pharmacokinetics etc., there is an actual need for some of these phase-I and phase-II metabolites as standards for use in assays. As 4-hydroxy-antipyrine and norantipyrine are commercially available and a satisfactory synthesis for 3-hydroxymethyl-antipyrine has been described [20] we developed a productive synthesis for 4'-hydroxy-antipyrine (**11**) and 4'-dihydroxy-antipyrine (**12**) as well as the glucuronosylated phase-II-metabolite (4-hydroxy-antipyrine glucuronide (**15**).

Results and Discussion

The direct chemical hydroxylation of antipyrine (**5**) by the method of *Brody* et al.[21] gives a complex mixture in low yield that is difficult to separate (*Bäßmann*[22]). We decided to introduce the hydroxy groups at C-4 and C-4' in a stepwise and clearly defined manner. Our first goal was the preparation of 4'-hydroxy-antipyrine (**11**) via methyl ether cleavage of **6**. An adaptation of the original condensation [23] of acetoacetic ethyl ester with 4-methoxyphenylhydrazine was used to synthesize the starting material **2** [24]. In addition to the desired pyrazolone **2** that was isolated by crystallization in 65% yield the corresponding enol ethyl ether **3** was isolated in 20% yield. Since the cleavage of enol ethers similar to **3** to the pyrazolones **2** is known [25] the overall yield of the condensation reaction amounted to over 80%.



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The methylation of both the norantipyrine (**4**) and the methoxylated derivative **2** was effected with dimethylsulfate (neat.). The reaction proceeded well with a tenfold excess of the reagent that was distilled off and recycled to avoid saponification of larger amounts of dimethyl sulfate. The aryl methyl ether of **6** was cleaved under very mild conditions using BBr_3 in CH_2Cl_2 and the first target of our synthesis, **11**, was isolated in 87%. For the introduction of the second hydroxy group at C-4 a bromination/solvolysis sequence was envisioned. The bromination of **5** and **6** to the bromides **7** and **8** was uneventful but the original saponification procedure [22,25] gave only low yields of the hydroxylated compounds **9** and **10**. This was due to decomposition to polar products under the strongly alkaline conditions. It was probable that the low solubility of the starting bromides **7** and **8** in aqueous medium was the limiting factor of the reaction. Accordingly a number of cosolvents and phase transfer catalysts were tried to improve the solubility. The

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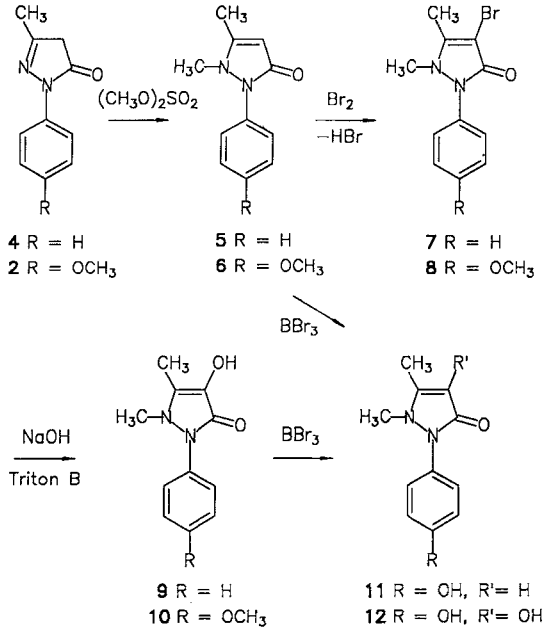
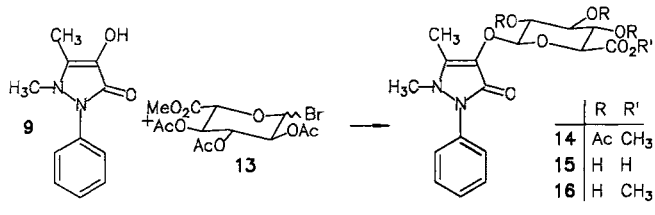
best results were obtained by addition of Triton B (benzyl trimethylammonium hydroxide) and the yield of the enols **9** and **10** could be reproducibly increased to over 60%. Free phenols such as **11** or **12** are known to be very labile in alkaline or even aqueous media [22]. It was thus important to cleave the aryl methyl ether in the final reaction step. Again, BBr_3 was the reagent of choice and the ether cleavage of **10** to the phenol **12** could be realized in 93% yield.



With sufficient amounts of the three phase-I metabolites at hand the synthesis of the glucuronides as important phase-II metabolites was studied next. The major problem was the glycosidation of the less reactive chelated hydroxy group at C-4 in **11** which was studied first. Standard *König-Knorr* conditions gave low yields but the method of *Conrow* and *Bernstein*[26] using cadmium carbonate in boiling toluene was successful and the coupling of **9** with the bromosugar **13** afforded the glucuronide ester **14** in 69% yield. Deprotection with alkaline methanol gave the free glucuronide which was identical to material isolated from the biological transformation of antipyrine (**5**) including the reported data for the mass spectra [27]. For further characterization the acid **15** was transformed to the methyl ester **16** by diazomethane. The ^{1}H-NMR spectrum of the sufficiently soluble ester was in full agreement with the β-glycosidic structure **16**.



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Experimental Part

Melting points: a Büchi 510 m. p. apparatus, uncorrected. – IR spectra: Perkin-Elmer spectral photometer 1420 (KBr, cm^{-1}). – ^{1}H-NMR spectra: Bruker AM 300 (300 MHz), WM-400 (400 MHz) and AC-200 (200 MHz) spectrometers. Chemical shifts in ppm (δ), TMS as standard (in $CDCl_3$ if not otherwise stated). – UV/VIS spectra: Beckman UV 5230 spectral photometer in methanol [λ max (lg ε)] nm. – Mass spectra: Finnigan MAT 8430 mass spectrometer (70 eV, % rel. int. in brackets). – Analytical TLC: silica gel plates (0.25 mm, Merck). – Elemental analyses: Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, FRG.

1-(4-Methoxyphenyl)-3-methyl-3-pyrazoline-5-one (**2**) *and 5-Ethoxy-3-methyl-1-(4-methoxyphenyl)-pyrazole* (**3**)

A solution of 20.00 g (115 mmol) of 4-methoxyphenylhydrazin hydrochloride in 30 ml of ethanol was treated with 14.90 g (114.62 mmol) of freshly distilled ethyl acetoacetic ester. The mixture was stirred 1/2 h at 20 °C, 2 h at 50 °C and 5 h at 80 °C. The solvent was removed under reduced pressure and the residue triturated with ether. The crystals were filtered off and recrystallized from ethanol to afford 15.30 g (65%) of 4'-methoxynorantipyrin (**2**). The ethereal mother liquor was concentrated and the residue crystallized from ethanol to yield 5.32 g (20%) of 5-ethoxy-3-methyl-1-(4-methoxyphenyl)-pyrazole (**3**).

Data of **2**: M. p.: 139 °C (ref. [25]: 138 °C. – IR: μ = 3010 (olefin); 2950; 2930; 2840 (OCH_3); 1635 (C=O); 1600; 1570; 1530 cm^{-1} (Ar). – UV: λmax (lg ε) = 207 (4.08), 245 nm (4.16). – ^{1}H-NMR (400 MHz): δ (ppm) = 2.18 (s, 3 H, CH_3), 3.40 (s, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 6.90 - 6.94 (m, 2 H, Ar-H), 7.70 - 7.74 (m, 2 H, Ar-H). - MS (40 °C): m/z (%) = 204 (100, M^+), 189 (15, M-CH_3)$^+$, 147 (10), 135 (28), 121 (22), 107 (29), 77 (11). – $C_{11}H_{12}N_2O_2$ (204.2) calc. C 64.7 H 5.93 N 13.7 found C 64.7 H 5.94 N 13.6.

Data of **3**: M. p.: 58 °C. – IR: μ = 2980; 2940 (olefin); 2840 (OCH_3); 1590; 1565; 1520 cm^{-1} (Ar). – UV: λmax (lg ε) = 207 (4.07), 247 nm (4.16). – ^{1}H-NMR (200 MHz): δ (ppm) = 1.41 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.26 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.11 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.45 (s, 1 H, = CH), 6.91-6.93 (m, 2 H, Ar-H), 7.55 - 7.57 (m, 2 H, Ar-H). – MS: m/z (%) = 232 (100, M^+), 204 (45), 203 (60, M-C_2H_5), 135 (58).

2,3-Dimethyl-1-phenyl-3-pyrazoline-5-one (**5**)

A mixture of 2.30 (13.22 mmol) of norantipyrine (**4**) and 8.33 g (66.11 mmol) of freshly distilled dimethyl sulfate was heated for 5 h at 160 °C. Excess dimethyl sulfate was distilled off under reduced pressure. The residue was adjusted to pH 14 with aqueous NaOH and the solvent was evaporated under reduced pressure and carefully extracted with 300 ml of CH_2Cl_2. The residue crystallized from ether and was recrystallized from toluene to afford 1.76 g (71%) of **5**. M. p.: 112 °C. – IR: μ = 3085 (olefin); 1665 (C=O); 1590; 1575; 1485 cm^{-1} (Ar). – UV: λmax (lg ε) = 207 (5.03), 221 (3.93), 243 (3.99), 267 nm (3.98). – ^{1}H-NMR (200 MHz): δ (ppm) = 2.24 (s, 3 H, CH_3), 3.07 (s, 3 H, NCH_3), 5.41 (s, 1 H, = CH), 7.24 - 7.51 (m, 5 H, Ar-H). - MS: m/z (%) = 188 (10, M^+), 173 (7, M-CH_3), 159 (7), 105 (21), 96 (55), 77 (33), 57 (19).

2,3-Dimethyl-1-(4-methoxyphenyl)-3-pyrazoline-5-one (**6**)

The methylation of 10.00 g (49.02 mmol) of 4'-methoxynorantipyrin (**2**) with 14.70 g (196.03 mmol) of dimethyl sulfate was effected as described for **5** to yield 7.90 g (74%) of **6**. M. p.: 83 °C; (ref. [25]: 82 °C. - IR: μ = 3100 (olefin); 2840 (OCH_3); 1650 (C=O); 1615; 1590; 1515 (Ar); 1250; 1035; 835; 800; 610 cm^{-1}. – UV: λmax (lg ε) = 207 (3.95), 231 (4.02), 243 (3.99), 259 nm (3.96). – ^{1}H-NMR (200 MHz): δ (ppm) = 2.23 (d, J = 0.8 Hz, 3 H, CH_3), 3.07 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 5.42 (d, J = 0.8

Hz, 1 H, = CH), 6.94 - 6.29 (m, 4 H, Ar-H). – MS (50 °C): m/z (%) = 218 (100, M^+), 203 (15, M- CH_3), 189 (31), 135 (22), 123 (13), 56 (24). – $C_{12}H_{14}N_2O_2$ (218.3) calc. C 66.0 H 6.46 N 12.8 found C 65.4 H 6.58 N 12.4.

4-Bromo-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one (**7**)

A solution of 15.00 g (79.79 mmol) of antipyrine (**5**) in 50 ml of $CHCl_3$ was treated with 12.75 g (79.69 mmol) of Br_2. The solvent was removed under reduced pressure and the residue was treated with 50 g of ice water. An oily product separated that crystallized slowly and was recrystallized from hot water to yield 16.28 g (76%) of 4-bromoantipyrine (**7**). M. p. 113 °C; (ref. [28]: 117 °C). – IR: μ = 3060 (olefin); 1670 (C=O); 1595; 1575; 1500 cm^{-1} (Ar). – UV: λ max (lg ε) = 206 (4.02), 222 (3.87), 237 (3.86), 248 (3.88), 276 nm (3.97). – ^{1}H-NMR (400 MHz): δ (ppm) = 2.30 (s, 3 H, CH_3), 3.09 (s, 3 H, NCH_3), 7.27 - 7.49 (m, 5 H, Ar- H). – MS: m/z (%) = 266/268 (100, M^+), 251/253 (8, M-CH_3), 187 (13, M-Br), 174/176 (29), 105 (43), 77 (54), 56 (69).

4-Bromo-2,3-dimethyl-1-(4-methoxy-phenyl)-3-pyrazoline-5-one (**8**)

A solution of 5.01 g (22.98 mmol) of 4'-methoxyantipyrine (**6**) in 15 ml of $CHCl_3$ was brominated as described for **7** with 3.67 g (22.94 mmol) of Br_2 to afford 5.17 g (76%) of 4-bromo-4'-methoxy-antipyrine (**8**). M. p.: 175 °C. – IR: ν = 3000 (olefin); 2835 (OCH_3); 1650 (C=O); 1610; 1515 cm^{-1} (Ar). – UV: λmax (lg ε) = 208 (4.29), 231 (4.21), 248 (4.12), 270 (4.13), 320 nm (3.05). – ^{1}H-NMR (200 MHz): δ = 2.38 (s, 3 H, CH_3), 3.29 (s, 3 H, NCH_3), 3.85 (s, 3 H, OCH_3), 6.97 - 7.33 (m, 4 H, Ar-H). - MS: m/z (%) = 296/298 (100, M^+), 281 (4, M-CH_3), 217 (7, M-Br), 189 (2), 148 (37), 135 (20), 82 (36), 80 (39), 57 (53). – $C_{12}H_{13}BrN_2O_2$ (97.2) calc. C 48.5 H 4.41 N 9.4 found C 48.7 H 4.40 N 9.3.

2,3-Dimethyl-4-hydroxy-1-phenyl-3-pyrazoline-5-one (**9**)

A mixture of 15.00 g (56.17 mmol) of 4-bromoantipyrine (**7**), 360 ml of an aqueous 3 M KOH solution and 10 ml of a 40% aqueous solution of benzyltrimethylammonium hydroxide (Triton B) was refluxed for 3 h. The solution was neutralized with 25% HCl and carefully extracted with CH_2Cl_2. The extract was dried with Na_2SO_4, evaporated to dryness and the residue was crystallized from ether to yield 6.25 g (54%) of **9**. M. p.: 184 °C; (ref. [29]: 182 °C). – IR: μ = 3200- 2900 (OH chelated); 1665 (C = O); 1630; 1595; 1500 cm^{-1} (Ar). – UV: λ max (lg ε) = 207 (4.06), 251 (4.07), 275 nm (3.99). – ^{1}H-NMR (400 MHz): δ (ppm) = 2.18 (s, 3 H, CH_3), 2.85 (s, 3 H, NCH_3), 7.22-7.45 (m, 5 H, Ar-H), 8.72 (s, 1 H, OH). – MS: m/z (%) = 204 (9, M^+). 176 (2, M-CO), 119 (3), 77 (10), 57 (24), 56 (100), 42 (23).

2,3-Dimethyl-4-hydroxy-1-(4-methoxy-phenyl)-3-pyrazoline-5-one (**10**)

A solution of 5.01 g (16.87 mmol) of 4-bromo-4'-methoxy-antipyrine (**8**) in 100 ml 3 M KOH and 15 ml of Triton B was saponified as described for **9** to afford 2.15 g (54%) of **10**. M. p.: 207 °C. – IR: μ = 3100 (OH, broad); 2840 (OCH_3); 1650 (C=O); 1610; 1585; 1515 cm^{-1} (Ar); 1320 (OH). – UV: λ max (lg ε) = 206 (4.03), 233 (4.02), 267 nm (4.11). – ^{1}H-NMR (200 MHz): δ = 2.19 (s, 3 H, CH_3), 3.00 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 6.94 - 6.98 (m, 2 H, Ar-H), 7.27 - 7.34 (m, 2 H, Ar-H). – MS (130 °C): m/z (%) = 234 (100, M^+), 206 (12, M-CO), 178 (30), 105 (10), 58 (28), 57 (38). – $C_{12}H_{14}N_2O_3$ (234.3) calc. C 61.5 H 6.02 N 12.0 found C 62.1 H 6.51 N 12.1.

2,3-Dimethyl-1-(4-hydroxyphenyl)-3-pyrazoline-5-one (**11**)

A solution of 5.11 g (23.44 mmol) of 4'-methoxyantipyrine (**8**) in 100 ml of CH_2Cl_2 was treated at -78 °C under N_2 with 117 ml (117.02 mmol) of a 1 M solution of BBr_3 in CH_2Cl_2. The solution was stirred for 1 h at this temp. and was then slowly allowed to warm to 20 °C. After 4 h the mixture was hydrolysed with cold water and extracted with 10 ml of CH_2Cl_2 to remove traces of starting material. The aqueous phase was concentrated to 1/4 of the volume at reduced pressure and carefully extracted three times with 100 ml of CH_2Cl_2 to yield 4.16 g (87%). M. p.: 204 °C; (ref. [30]: 205 - 207 °C). – IR: μ = 3040 (OH); 3000 (olefin); 2920; 2770; 1625 (C=O); 1605; 1580; 1510 (Ar); 1265 cm^{-1} (OH). – UV: λmax (lg ε) = 207 (4.15), 243 nm (4.21). – ^{1}H-NMR (200 MHz) (d_6-DMSO): δ = 2.24 (d, J = 0.7 Hz, 3 H, CH_3), 3.11 (s, 3 H, NCH_3), 5.37 (d, J = 0.7, 1 H, = CH), 6.62 - 6.60 (m, 2 H, Ar-H), 6.90 - 6.95 (m, 2 H, Ar-H). – MS (120 °C): m/z (%) = 204 (100, M^+), 175 (18), 149 (10), 134 (9), 121 (20), 109 (12), 96 (24), 57 (32). – $C_{11}H_{12}N_2O_2$ (204.2) calc. C 64.7 H 5.92 N 13.7 found C 64.7 H 5.89 N 13.6.

2,3-Dimethyl-4-hydroxy-1-(4-hydroxy-phenyl)-3-pyrazoline-5-one (**12**)

A solution of 0.50 g (21.37 mmol) of methyl ether **10** in 5 ml of dry CH_2Cl_2 was treated with 6.5 ml (6.50 mmol) of a 1 M solution of BBr_3 as described for **11** to yield 0.44 g (93%) of phenol **12**. M. p.: 215 °C; (ref. [31]: 202 - 206 °C). – IR: μ = 3200 (OH); 1615 (C = O); 1600; 1580; 1520 (Ar); 1280 cm^{-1} (OH). – UV: λ max (lg ε) = 207 (3.88), 233 (3.81), 270 nm (3.90). – ^{1}H-NMR (400 MHz) (d_6-DMSO): δ = 2.06 (s, 3 H, CH_3), 273 (s, 3 H, NCH_3), 6.81 - 6.85 (m, 2 H, Ar-H), 7.11 - 7.15 (m, 2 H, Ar-H), 8.50 (s, 1 H, C=COH), 9.62 (s, 1 H, Ar-OH). – MS (150 °C): m/z (%) = 220 (100, M^+), 192 (29, M-CO), 164 (55), 135 (18), 82 (39), 80 (40), 57 (39), 56 (43). – $C_{11}H_{12}N_2O_3$ (220.3) calc. C 60.0 H 5.49 N 12.7 found C 59.2 H 5.42 N 12.4.

Methyl 1'-[4-Hydroxy-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one]-2',3',4'-tri-O-acetyl-β-D-glucopyranuronate (**14**)

All reaction vessels and reagents have to be carefully dried prior to use. A mixture of 690 mg (3.38 mmol) of 4-hydroxyantipyrine (**9**), 1.65 g (6.77 mmol) of $CdCO_3$ as catalyst and 40 ml of dry toluene was heated to reflux. A solution of 2.68 g (6.76 mmol) of bromide **13** in 40 ml dry toluene was added at the same rate as toluene was distilled off. After 3 h the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed with water, dried with Na_2SO_4, evaporated and triturated with ether to give colourless crystals that were purified by cc on silica gel (CH_2Cl_2) to afford 962 mg (69%) of glycoside **14**. M. p.: 215 °C; (ref. [32]: 232 - 236 °C). – IR: μ = 2950 (olefin); 1760; 1685; 1650 (C=O); 1595; 1490 cm^{-1} (Ar). – UV: λ (lg ε) = 206 (4.01), 246 (3.93), 272 nm (3.95). – ^{1}H-NMR (400 MHz): δ = 2.02 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO), 2.21 (s, 3 H, CH_3), 2.97 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3), 4.05 (d, J = 9.9 Hz, 1 H, 5'-H), 5.23 (dd, 1 H, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.4 Hz, 2'-H), 5.25 ("t", 1 H, 3'-H), 5.32 ("t", 1 H, 4'-H), 5.37 (d, 1 H, $J_{1,2}$ = 7.9 Hz, 1'-H), 7.27 - 7.47 (m, 5 H, Ar-H). – MS (150 °C): m/z (%) = 520 (2, M^+), 489 (1, M-OCH_3), 461 (1, M-CH_3OCO), 317 (4, M- aglycone), 204 (44), 155 (58), 127 (37), 56 (100). – $C_{24}H_{28}O_{11}N_2$ (520.5) calc. C 55.4 H 5.42 N 5.4 found C 55.5 H 5.47 N 5.1.

1'-[4-Hydroxy-2,3-dimethyl-3-pyrazoline-5-one]-β-D-glucopyranuronic acid (**15**)

A solution of 0.60 g (1.15 mmol) of glucuronide **14** in 20 ml of MeOH was treated with 2.0 ml (12.00 mmol) of 6 M NaOH for 2 h at 20 °C and 6 h at 45 °C. The solution was then carefully neutralized with equivalent amounts of HCl in methanol and the precipitated NaCl was filtered off. The solvent was removed under reduced pressure and the residue was purified by tlc (CH_2Cl_2/MeOH = 10:1) to afford 312 mg (71%) of the glucuronide **15**. M. p.: 280 °C. – IR: μ = 3380 (OH, broad); 2910; 1635 (C=O); 1610;

1595; 1495 (Ar); 1300 cm^{-1} (OH). - UV: λ max (lg ε) = 207 (4.03), 246 (3.93), 268 nm (3.92). – MS: m/z (%) = FAB pos. 425 (100, $[MNa + Na]^+$), 403 (42, $[M + Na]^+$), 227 (71), 204 (33, aglycone), 115 (24), 57 (33). FAB neg. 379 (100, $[M-H]^-$), 325 (27), 277 (26), 205 (32), 203 (77, aglycone), 110 (25), 92 (21), 71 (18). – $C_{17}H_{20}N_2O_8$ (420.4) calc. C 48.6 H 4.56 N 6.7 found C 48.3 H 4.59 N 6.5.

Methyl 1'-[4-Hydroxy-2,3-dimethyl-3-pyrazoline-5-one]-β-D-glucopyranuronate (**16**)

A solution of 20 mg (0.053 mmol) of 4-hydroxyantipyrine glucuronide (**15**) in 5 ml of MeOH was treated with 1 ml of a 1 M solution of diazomethane in ether. The solvent was removed under reduced pressure and the residue was purified by tlc (CH_2Cl_2/MeOH = 9:1) to yield 17 mg (81%) of oily methyl ester **16**. - ^{1}H-NMR (400 MHz) (d_6-DMSO): (ppm) δ = 2.18 (s, 3 H, CH_3), 2.97 (s, 3 H, NCH_3), 3.14 ("t", 1 H, 2'-H), 3.27 ("t", 1 H, 3'-H), 3.33 ("t", 1 H, 4'- H), 3.67 (s, 3 H, OCH_3), 3.82 (d, J = 9.5 Hz, 1 H, 5'-H), 4.92 (d, J = 7.9 Hz, 1 H, 1'-H), 7.31-7.37 (m, 3 H, Ar-H), 7.48- 7.52 (m, 2 H, Ar-H).

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