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Muscimol Analogues. Synthesis of Isomuscimol (3-Aminomethyl-5-isoxazolol) and Some Derivatives of Azamuscimol (5-Aminomethyl-3-pyrazolol)

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The syntheses of 3-aminomethyl-5-isoxazolol (isomuscimol) monohydrate (*6*), 5-aminomethyl-1-methyl-3-pyrazolol (1-methylazamuscimol) dihydrochloride (*18*), and 5-aminomethyl-2-methyl-3-pyrazolol (2-methylazamuscimol) monohydrate (*15*), all of which are analogues of muscimol (5-aminomethyl-3-isoxazolol), are described. The preparations proceeded *via* the appropriately protected γ-aminoacetoacetates. Isomuscimol monohydrate (*6*) was synthesized *via* Cbz- (*3a*) or Boc-isomuscimol (*3b*), acid catalyzed deprotection of which gave the β-hydroxyimino-γ-amino acid esters *4a* and *5b*, which upon treatment with triethylamine recyclized to give isomuscimol monohydrate (*6*). Attempts to prepare 1-acetyl-5-aminomethyl-3-pyrazolol (1-acetylazamuscimol) are also described.

Muscimol (5-aminomethyl-3-isoxazolol) is a psychomimetic compound isolated from *Amanita muscaria*.[1] Due to our interest in compounds structurally related to muscimol, thiomuscimol (5-aminomethyl-3-isothiazolol)[2] and certain derivatives of azamuscimol (5-aminomethyl-3-pyrazolol)[3] have previously been synthesized. This paper describes the preparation of isomuscimol (3-aminomethyl-5-isoxazolol) monohydrate (*6*), 1-methylazamuscimol (5-aminomethyl-1-methyl-3-pyrazolol) dihydrochloride (*18*) and 2-methylazamuscimol (5-aminomethyl-2-methyl-azamuscimol) monohydrate (*15*). Attempts to prepare 1-acetylazamuscimol (1-acetyl-5-aminomethyl-3-pyrazolol) dihydrochloride (*9*) are also described.

The initial reaction for the preparation of isomuscimol monohydrate (*6*) was the conversion of *N*-benzyloxycarbonylglycine (Cbz-glycine) (*1a*) into *2a via* reaction of the activated amide with diethoxy[3-ethoxy-3-hydroxyacrylato-(2-)-O^1,O^3]magnesate(2 –). Treatment of *2a* with hydroxylamine in alcoholic potassium hydroxide followed by acidification gave 3-Cbz-aminomethyl-5-isoxazolol (*3a*). Treatment of *3a* with hydrogen bromide in acetic acid and crystallization of the product from methanol – ether gave *4a*, which upon treatment with triethylamine cyclized to give isomuscimol monohydrate (*6*) in a reasonable yield. An analogous reaction based on *tert*-butyloxycarbonylglycine (Boc-glycine) (*1b*) gave a good yield of isomuscimol monohydrate (*6*), *via* *5b*.

A separable mixture of 1- and 2-methylazamuscimol is reported [4] to be formed after treatment of ethyl *N*-phthaloyl-γ-aminoacetoacetate (*2c*) with methylhydrazine and subsequent hydrazinolysis of the intermediates formed. In our hands reaction of *2c* with methylhydrazine gave 2-methyl-5-phthaloylaminomethyl-3-pyrazolol (*13c*) as the only product, from which 2-methylazamuscimol dihydrochloride (*14*) and the corresponding zwitterion as a monohydrate (*15*) were obtained by acid hydrolysis followed by triethylamine treatment.

In order to prepare 1-methylazamuscimol by an unequivocal synthesis ethyl *N*-Cbz-γ-aminoacetoacetate (*2a*) was treated with benzylhydrazine to give *16a*, which upon methylation gave *17a*. Palladium catalyzed hydrogenolysis of an ethanolic solution of *17a* containing two equivalents of hydrochloric acid gave 1-methylazamuscimol dihydrochloride (*18*).

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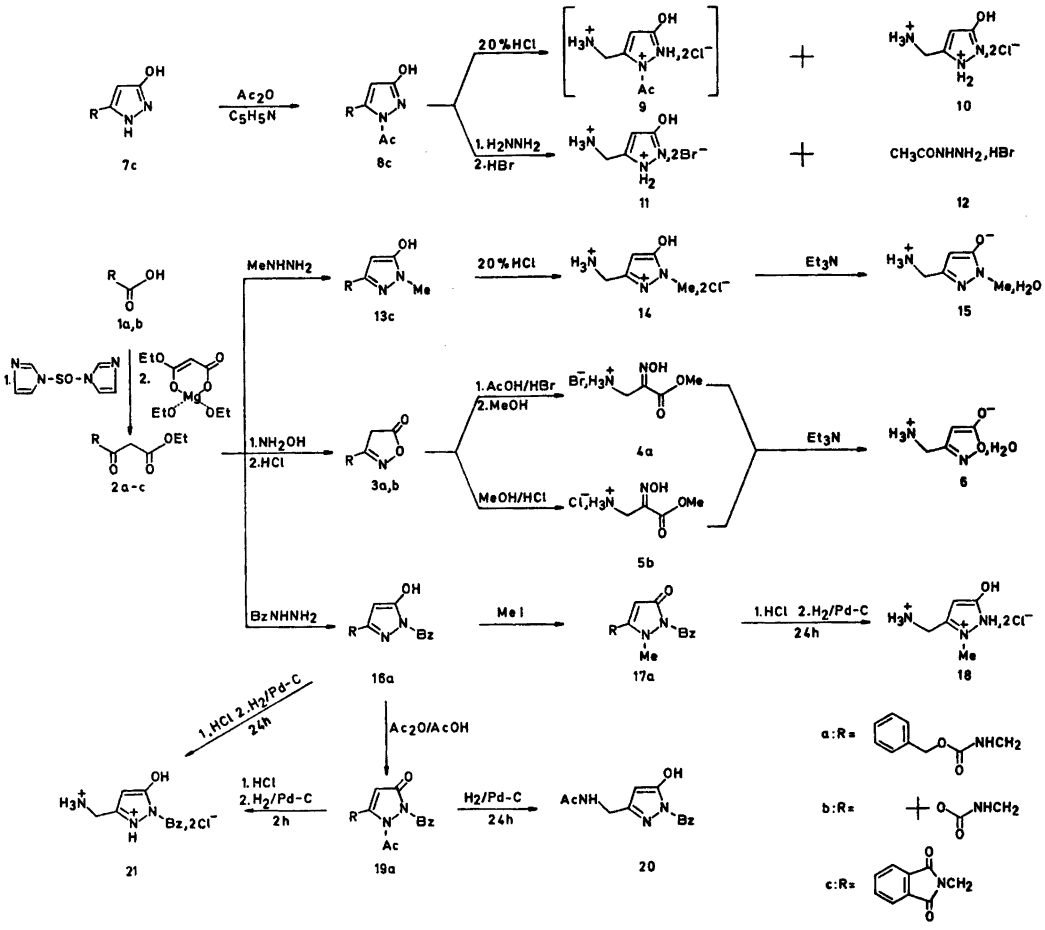

According to the literature [4] 1-acetylazamuscimol dihydrochloride (*9*) could be prepared by treatment of *8c* with 20 % hydrochloric acid. In our hands this procedure gave azamuscimol dihydrochloride (*10*) as the only product. Treatment of *8c* with hydrazine hydrate followed by addition of hydrogen bromide gave azamuscimol dihydrobromide (*11*) and acethydrazide hydrobromide (*12*). Acetylation of *16a* gave *19a*. Hydrogenolysis of *19a* under neutral as well as under acid conditions gave *20* and *21*, respectively. It can be concluded that the acetyl derivatives *8c* and *19a* are very reactive compounds in analogy with other acylpyrazolin-3-ones, which are known to be acylating agents.[6,7]

The structure determination of the compounds *2a*, *3a*, *3b*, *4a*, *5b*, *6*, *13c*, *14*, *15*, *16a*, *17a*, *18*, *19a*, *20* and *21* are based on IR, UV, and ^{1}H NMR spectroscopy, supported by elemental analyses. The structure of isomuscimol monohydrate (*6*) has been unequivocally established by X-ray crystallographic methods.[8]

UV absorption at 251 – 252 nm of *3a,b* and *6* are in agreement with the findings for 3-mono-[9] and 3,4-disubstituted isoxazolin-5-ones.[10]

A one proton signal in the ^{1}H NMR spectra of *8c*, *13c*, *14*, *16a*, *17a*, *19a* and *20* in the region δ 5.2 – 6.1 originating from the 4-proton excludes the CH-form of these compounds. No C=O absorption in the 1660 – 1760 cm^{-1} region is found in the IR spectra of *14*, *15*, and *21*, consequently they are ascribed the 3-OH form in the solid state. Based on available spectroscopic data it is not possible to distinguish between the OH/NH forms of

8c, *13c*, *16a*, and *20* in the solid state IR spectra, primarily because exact interpretations of the spectra are made difficult by strong *inter*molecular hydrogen bondings,[11] and secondly because the 1660–1760 cm^{-1} regions have strong C=O absorption bands arising from the exocyclic acyl groups. However, *17a* and *19a* are locked in the NH form by the substituents in the 1- and 2-positions. The remaining compounds are described as the OH forms.

EXPERIMENTAL

Melting points, as determined in capillary tubes, are corrected. Elemental analyses were made by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen. A Perkin-Elmer grating infrared spectrophotometer model 247, a Perkin-Elmer ultraviolet-visible spectrophotometer model 402 and a JEOL JMN-C-60HL (60 MHz) ^1H NMR instrument were used. ^1H NMR spectra were recorded by using TMS as an internal standard and those of compounds dissolved in D_2O by using sodium 3-(trimethylsilyl) propanesulfonate. TLC and CC were accomplished using silica gel GF_{254} plates (Merck) and silica gel 0.05–0.20 mm (Merck), respectively. The pK_A values were determined as earlier described.[12]

Ethyl 4-(N-benzyloxycarbonylamino)-3-oxobutyrate (2a). To a solution of thionyldiimidazole[13] (*ca.* 27 g; *ca.* 0.15 mol) in tetrahydrofurane (THF) (600 ml) was added a solution of *1a* (24.0 g; 0.115 mol) in THF (150 ml) with stirring, which was continued for 15 min. After standing at room temperature for 2 h the solution containing 1-(*N*-benzyloxycarbonylglycin)imidazole (*ca.* 0.115 mol) was added to a suspension of diethoxy[3-ethoxy-3-hydroxyacrylato(2-)-O^1,O^3]magnesate(2-)[14] (0.2 mol) in THF (400 ml) with stirring, which was continued for 2 h. Hydrochloric acid (4 M) was added to pH ~3 and stirring was continued until the CO_2 evolution had ceased.

The THF-phase was separated and the aqueous phase was extracted with three 100 ml portions of ether. The pooled organic phases were washed with three 100 ml portions of saturated aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and evaporated to give 23.2 g of a crude *2a*. 2.5 g of crude *2a* was purified by CC [silica gel: 200 g; eluent: benzene–ethyl acetate–formic acid (60:30:1)] to give 2.0 g of pure *2a* as an oil. Anal. $C_{14}H_{17}NO_5$: C, H, N. IR (neat): 3500–3200 (m), 3040 (w), 2990 (m), 2940 (w), 2900 (w), 1780–1660 (several bands, s), 1560–1490 (several bands, m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.28 (5 H, s), 5.00 (s) and 5.7–4.7 (broad signal) (a total of 3 H), 4.11 (q, J 7.0 Hz) and 4.4–3.5 (m) (a total of 4 H), 3.40 (2 H, s), 1.21 (3 H, t, J 7.0 Hz).

3-(Benzyloxycarbonylaminomethyl)-4-isoxazolin-5-one (3a). To a solution of sodium hydroxide (0.80 g; 20 mmol) and hydroxylamine hydrochloride (0.70 g; 10 mmol) in water (5 ml) was added *2a* (2.78 g; 10 mmol). The mixture was stirred for 2 h at room temperature and after addition of EtOH (10 ml) the mixture was extracted with four 20 ml portions of dichloromethane which were pooled, dried ($MgSO_4$) and evaporated to dryness to give 2.1 g of *3a* as an oil. CC [silica gel: 125 g; eluent: benzene–ethyl acetate–formic acid (90:10:1)] gave 1.30 g of *3a* as crystals. Recrystallization (benzene–cyclohexane) gave *3a* (660 mg; 27 %), m.p. 80–81 °C. Anal. $C_{12}H_{12}N_2O_4$: C, H, N. IR (KBr): 3340 (s), 3100–2850 (several bands, w), 1820 (s), 1800 (s), 1720–1680 (several bands, s), 1620 (w), 1550 (s) cm^{-1}. UV [MeOH (log ε)] 251 (3.77) nm. ^1H NMR ($CDCl_3$): δ 7.30 (5 H, s), 5.75–5.25 (1 H, broad signal), 5.05 (2 H, s), 4.10–3.90 (2 H, d), 3.33 (2 H, broad s).

3-(tert-Butyloxycarbonylaminomethyl)-4-isoxazolin-5-one (3b). To a solution of sodium hydroxide (1.60 g; 40 mmol) in water (16 ml) was added hydroxylamine hydrochloride (1.39 g; 20 mmol) with stirring which was continued for 5 min. The solution was cooled to 0 °C and *2b*[15] (4.90 g; 20 mmol) was added with stirring which was continued for 2 h at 0 °C and the mixture was left overnight at 5 °C to complete the crystallization. Yield of crude *3b* (2.50 g; 58 %). *3b* (500 mg) was recrystallized (EtOH–light petrol) to give 189 mg (44 %), m.p. 116–116.5 °C. Anal. $C_9H_{14}N_2O_4$: C, H, N. IR (KBr): 3380 (s), 2975 (m), 2930 (m), 1810 (s), 1785 (s), 1700–1680 (several bands, s), 1620 (w), 1530–1500 (several bands, s). UV [MeOH (log ε)]: 2.52 (3.58) nm. ^1H NMR ($CDCl_3$): δ 5.2–4.7 (1 H, broad signal), 4.10–3.80 (2 H, d), 3.40 (2 H, broad s), 1.42 (9 H, s).

Methyl 3-hydroxyimino-4-aminobutyrate hydrobromide (4a). A mixture of *3a* (2.0 g; 8 mmol) and acetic acid containing 43 % of hydrogen bromide (4 ml) was left at room temperature for 1 h and at 5 °C overnight. To the reaction mixture was added MeOH (25 ml) and after standing at room temperature for 1 h the mixture was evaporated *in vacuo* to give an oil. Crystallization (MeOH–ether) gave *4a* (1.42 g; 78 %), m.p. 153–154 °C. Anal. $C_6H_{11}BrN_2O_3$: C, H, N, Br. IR (KBr): 3700–2750 (several bands, s), 3300 (s), 3050 (s), 2690 (w), 1900 (w), 1740 (s) cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.5 (0.5 H, s), 8.4–7.8 (1.8 H, broad signal), 3.75–3.20 (m), 3.58 (s), 3.40 (s) (a total of 7 H).

Methyl 3-hydroxyimino-4-aminobutyrate hydrochloride (5b). To a solution of hydrogen chloride in MeOH (4 ml; 6 %) was added *3b* (428 mg; 2 mmol) and the clear solution was left at room temperature overnight. Obtained was *5b* (198 mg; 54 %), m.p. 166–167 °C (decomp.). Anal. $C_5H_{11}ClN_2O_3$: C, H, N, Cl. IR (KBr): 3700–2750 (several bands, s), 3250 (s), 3040 (s), 2700 (w), 2600 (w), 2000 (w), 1740 (s).

^{1}H NMR (DMSO-d_6): δ 11.6 (0.6 H, s), 8.8–8.0 (2.5 H, broad signal), 3.8–3.0 (m), 3.57 (s), 3.43 (s) (a total of 7 H).

3-Aminomethyl-5-isoxazolol monohydrate (6). To a solution of *5* (107 mg; 0.5 mmol) in a mixture of water (100 μl) and EtOH (1 ml) was added a solution of triethylamine (60 mg; 0.6 mmol) in EtOH (0.5 ml) and the solution was left at 5 °C overnight. Yield of *6* (41 mg; 62 %), m.p. 183.5–184.5 °C (decomp.). The compound loses one mol of water of crystallization upon standing at room temperature. Anal. $C_4H_6N_2O_2$: C, H, N [after drying of *6* over P_2O_5 (3 h, 24 °C, 13 Pa)]. IR (KBr): 3700–3100 (s), 3100–2300 (several bands, s), 2150 (w), 1680–1550 (several bands, s), 1520–1450 (several bands, s). UV [MeOH (log ε)]: 251 (3.89) nm. ^{1}H NMR (D_2O): δ 4.77 (6 H, s), 3.97 (2 H, s). pK_A values (H_2O, 25 °C): 2.62±0.04; 8.96±0.04.

1-(or 2-)-Acetyl-5-phthaloylaminomethyl-3-pyrazolol (8c). A mixture of *7c* [5] (7.29 g; 30 mmol), acetic anhydride (4.02 g; 30 mmol) and pyridine (40 ml) was stirred at room temperature for 30 min to give a clear solution which was poured into ice-cooled water (500 ml). The crystals were filtered and recrystallized (DMA–H_2O) to give *8c* (4.24 g; 50 %), m.p. 146.5–147.5 °C. Anal. $C_{14}H_{11}N_3O_4$: C, H, N. IR (KBr): 3380 (s), 1765 (s), 1730–1680 (several bands, s), 1575 (s). UV [MeOH (log ε)]: 216 (4.67) nm; shoulder at 236 nm; 271 (4.12) nm. ^{1}H NMR (DMSO-d_6): δ 12.9–12.5 (1 H, broad signal), 7.85 (4 H, s), 5.95 (1 H, s), 4.73 (2 H, s), 2.20 (3 H, s).

5-Aminomethyl-3-pyrazolol dihydrochloride (10). A suspension of *8c* (1.0 g; 3.5 mmol) in hydrochloric acid (20 ml; 20 %) was refluxed for 3 h. After cooling the precipitate of phthalic acid was filtered and discarded. The filtrate was evaporated to dryness. Crystallization (MeOH–ether) gave *10*, m.p. 239–240 °C (Ref. 5: 240–241 °C). IR (KBr) was identical with that of an authentic sample.

5-Aminomethyl-3-pyrazolol dihydrobromide (11). A solution of *8c* in MeOH was treated with excess of hydrazine hydrate at room temperature or at reflux for 3 h. After cooling, excess of hydrogen bromide was added and the reaction mixture was evaporated to dryness. The only compounds which could be isolated were azamuscimol dihydrobromide (*11*) and acethydrazide hydrobromide (*12*) according to TLC and IR which were identical with those of authentic samples.

2-Methyl-5-phthaloylaminomethyl-3-pyrazolol (13c). To a solution (60 °C) of *2c* (25.5 g; 0.1 mol) in EtOH (500 ml) was added methylhydrazine (5.3 g; 0.11 mol). After standing at room temperature for 2 h the mixture was filtered to give crude *13c* (8.2 g). Recrystallization (DMA–EtOH) gave *13c* (5.8 g; 23 %), m.p. 239–240 °C. Anal. $C_{13}H_{11}N_3O_3$: C, H, N. IR (KBr): 3600–3300 (m), 1760 (m), 1705 (s), 1610 (w), 1580–1520 (several bands, s) 1465 (m). UV [MeOH (log ε)]: 220 (4.74) nm; shoulder at *ca.* 140 nm. ^{1}H NMR (DMSO-d_6): δ 10.84 (1 H, broad s), 7.86 (4 H, s), 5.23 (1 H, s), 4.53 (2 H, s), 3.40 (3 H, s).

5-Aminomethyl-2-methyl-3-pyrazolol dihydrochloride (14). A mixture of *13c* (5.14 g; 20 mmol) and hydrochloric acid (100 ml; 20 %) was heated under reflux for 4 h. After standing at 5 °C overnight the separated phthalic acid was filtered off and discarded. The filtrate was evaporated to dryness and the residue was crystallized (MeOH–ether) to give *14* (3.0 g; 75 %), m.p. 211–212 °C (decomp.). Anal. $C_5H_{11}Cl_2N_3O$: C, H, N, Cl. IR (KBr): 3600–2200 (several peaks, s), 3425 (m), 2040 (w), 1620 (s), 2545 (s), 1500–1440 (several peaks, m), 1405 (m). UV [MeOH (log ε)]: 222 (3.66) nm. ^{1}H NMR (DMSO-d_6): δ 11.80 (2 H, s), 8.77 (3 H, broad s), 5.93 (1 H, s), 4.2–3.6 (2 H, d), 3.57 (3 H, s). pK_A values (H_2O, 26 °C): 5.50±0.3; 9.77±0.05.

5-Aminomethyl-2-methyl-3-pyrazolol monohydrate (15). To a solution (30 °C) of *14* (1.00 g; 0.5 mmol) in a mixture of water (2 ml) and ethanol (20 ml) was added triethylamine (1.11 g; 1.10 mmol) and the mixture was left at room temperature overnight to complete crystallization. Yield of *15* (0.60 g; 80 %), m.p. 201–202 °C (decomp.). Anal. $C_5H_9N_3O,H_2O$: C, H, N. IR (KBr): 3600–3150 (s), 3150–2300 (s), 2200 (w), 1650–1620 (doublet, m) 1580–1500 (several bands, s), 1500–1420 (several bands, s), 1425 (w), 1380 (m). UV [MeOH (log ε)]: 245 (3.69) nm. ^{1}H NMR (D_2O): δ 3.85 (2 H, s), 3.38 (3 H, s).

2-Benzyl-5-benzyloxycarbonylaminomethyl-3-pyrazolol (16a). A mixture of *2a* (8.38 g; 30 mmol), benzylhydrazine oxalate (6.37 g; 50 mmol), sodium acetate trihydrate (4.08 g; 30 mmol) and EtOH (100 ml) was heated under reflux for 2 h. After cooling the mixture was poured into 500 ml of ice-cooled water. The crystals were filtered and recrystallized from ethyl acetate to give *16a* (4.0 g; 40 %), m.p. 154–155 °C. Anal. $C_{19}H_{19}N_3O_3$: C, H, N. IR (KBr): 3600–3100 (broad band, m), 3250 (s), 3050 (w), 3030 (w), 2830 (w), 2800–2000 (broad band, m), 1700 (s), 1670 (s), 1580–1520 (several bands, s). ^{1}H NMR (DMSO-d_6): δ 7.8–6.8 (broal signal), 7.32 (s), 7.20 (s), (a total of 12 H), 5.27 (1 H, s), 4.98 (s), 4.94 (s) (a total of 4 H), 3.95 (2 H, d, *J* 9 Hz).

2-Benzyl-5-benzyloxycarbonylaminomethyl-1-methylpyrazolin-3-one (17a). A mixture of *16a* (1.26 g; 3.75 mmol), methyl iodide (1.07 g; 7.5 mmol), and MeOH (50 ml) was heated in an autoclave to 60 °C for 12 h with stirring. After cooling the mixture was concentrated to an oil, which was taken up in methylene chloride (30 ml). The organic phase was treated with aqueous sodium dithionite (30 ml, 2 %), sodium hydroxide (30 ml, 0.2 M) and water (30 ml). After drying ($MgSO_4$) and evaporation the residue was crystallized (benzene) to give *17a* (248 mg; 19 %), m.p. 129.5–130.5 °C. Anal. $C_{20}H_{21}N_3O_3$: C, H, N. IR (KBr): 3600–2700 (broad absorption with several bands, m),

1685 (s) with shoulder at 1690 and 1700, 1620–1580 (several bands, s) 1560–1500 (several bands, m). UV [MeOH (log ε)]: 248 (3.95) nm. ^{1}H NMR ($CDCl_3$): δ 7.3–6.8 (10 H, m), 6.6–5.6 (1 H, broad signal), 5.20 (1 H, s), 4.95 (2 H, s), 4.82 (2 H, s) 4.01 (2 H, d, *J* 9 Hz), 3.03 (3 H, s).

5-Aminomethyl-1-methyl-3-pyrazolol dihydrochloride (18). A mixture of *17a* (1.00 g; 2.8 mmol), hydrochloric acid (5.6 mmol, 0.1 M), EtOH (100 ml), and 10 % Pd-C (250 mg) was hydrogenated at 300 kPa H_2-pressure in a PARR low-pressure hydrogenation apparatus for 18 h. After filtration the mixture was concentrated to give crystals. Recrystallization (MeOH–ether) gave *18* (456 mg; 80 %) as hygroscopic crystals, m.p. 213–214 °C. Anal. $C_5H_{11}Cl_2N_3O$: C, H, N, Cl. IR (KBr): 3600–3250 (s), 3250–2200 (s), 2020 (w), 1620 (s), 1565 (w), 1530 (w), 1485 (s). UV [MeOH (log ε)]: 233 (3.60) nm. ^{1}H NMR (DMSO-d_6): δ 8.9–8.1 (1 H, broad signal), 7.65 (4 H, broad s), 5.90 (1 H, s), 4.2–3.7 (2 H, m), 3.70 (3 H, s). ^{1}H NMR (DMSO-d_6–D_2O) (the solution was heated to 70 °C for 5 min): δ 4.60 (6 H, s), 4.05 (2 H, s), 3.65 (3 H, s). pK_A values (H_2O, 25 °C): 7.97± 0.05; 10.0± 0.1.

1-Acetyl-2-benzyl-5-benzyloxycarbonylaminomethylpyrazolin-3-one (19a). A solution of *16a* (1685 mg; 5 mmol) and acetic anhydride (1.0 g; 10 mmol) in acetic acid (10 ml) was refluxed for 30 min. After cooling the mixture was poured into 200 ml of iced water, which was extracted with four 50 ml portions of methylene chloride. The pooled organic phases were dried and evaporated *in vacuo* to give an oil, which was crystallized (ether–light petroleum to give *19a* (1.05 g; 55 %), m.p. 85–86.5 °C. Anal. $C_{21}H_{21}N_3O_4$: C, H, N. IR (KBr): 3600–3200 (m), 3320 (s), 3100–2700 (several bands, w), 1770 (s) with shoulder at 1790, 1690 (s), 1550 (s). ^{1}H NMR ($CDCl_3$): δ 7.5–6.8 (10 H, m), 6.03 (1 H, s), 5.6–4.8 (1 H, broad signal), 5.07 (4 H, s), 4.28 (2 H, d, *J* 9 Hz), 2.15 (3 H, s).

5-Acetaminomethyl-2-benzyl-3-pyrazolol (20). To a solution of *19a* (800 mg; 2.1 mmol) in EtOH (50 ml) was added a suspension of 10 % Pd-C (100 mg) in water (25 ml). The mixture was hydrogenated at 300 kPa H_2-pressure in a PARR low-pressure hydrogenation apparatus for 24 h at room temperature. After filtration and concentration *in vacuo* the residue was crystallized (EtOH–ether) to give *20* (127 mg; 24 %), m.p. 190–191 °C (decomp.). Anal. $C_{13}H_{15}N_3O_2$: C, H, N. IR (KBr): 3600–2000 (several bands, m), 1660–1600 (several bands, s), 1580–1520 (several bands, s). UV [MeOH (log ε)]: 252 (3.36) nm. ^{1}H NMR (DMSO-d_6): δ 8.3–7.7 (1 H, broad signal), 7.22 (5 H, s), 5.21 (1 H, s), 4.92 (2 H, s), 3.95 (2 H, d, *J* 9 Hz), 1.80 (3 H, s).

5-Aminomethyl-2-benzyl-3-pyrazolol dihydrochloride (21). To a solution of *16a* (298 mg; 1.0 mmol) in EtOH (50 ml) was added hydrochloric acid (1.1 mmol; 0.1 M) and 10 % Pd-C (100 mg) suspended in water (10 ml). The reaction mixture was hydrogenated at 300 kPa H_2-pressure in a PARR low-pressure hydrogenation apparatus for 2 h at room temperature. After filtration and evaporation *in vacuo* the residue was crystallized (MeOH–ether) to give *21* (51 mg; 21 %), m.p. 224–225 °C (decomp.). Anal. $C_{11}H_{15}Cl_2N_3O$: C, H, Cl, N. IR (KBr): 3600–3300 (m), 3250–2100 (s), 1950 (w), 1565 (s), 1490 (w), 1400 (m). UV [MeOH (log ε)]: 211 (4.16) nm; 248 (3.73) nm. ^{1}H NMR (DMSO-d_6): δ 11–8 (4 H, broad signal), 7.30 (5 H, s), 5.70 (1 H, s), 5.07 (2 H, s), 3.80 (2 H, s), 4.2–2.8 (1 H, broad signal).

Compound *21* was also prepared in a 29 % yield by hydrogenation for 24 h of *19a* using the same conditions as mentioned above.

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