Heterocyclic Compounds from 2-(Alkoxycarbonylcyanomethylene)-1,3-dioxolanes

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In reverence to and grateful remembrance of David Ginsburg, Haifa, Israel

2-(Alkoxycarbonylcyanomethylene)-1,3-dioxolanes reacted with hydrazines and hydroxylamine to yield 1-substituted 4-alkoxycarbonyl-5-amino-3-(2'-hydroxyethoxy)pyrazoles and 4-alkoxycarbonyl-5-amino-3-(2'-hydroxyethoxy)isoxazoles respectively. With guanidine and benzamidine 2-substituted (R = NH_2, C_6H_5) 5-cyano-6-(2'-hydroxyethoxy)pyrimidin-4-ones were obtained. Reaction of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane with 1,3-diaminopropane afforded 2-(cyanomethoxycarbonylmethylene)-1,3-hexahydropyrimidine whereas treatment of the same compound with 4,5-dimethyl-1,2-phenylenediamine gave 2-(cyanomethoxycarbonylmethylene)-5,6-benzimidazoline. The structures of pyrazoles and pyrimidones were assigned on the basis of ^1H-{^1H} and ^{13}C-{^1H}-nOe experiments.

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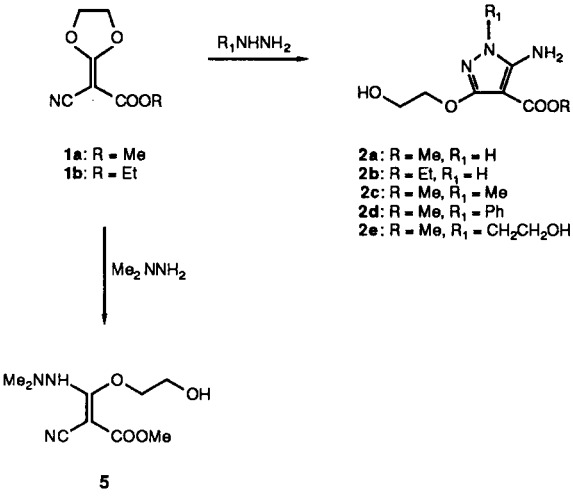
We have recently reported a convenient method for the preparation of hitherto unknown 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes **1** [1]. Since closely related 2-(dicyanomethylene)-1,3-dioxolane [2] and 3,3-bismethylmercapto-2-cyanomethylacrylate [3] have already been utilized in heterocyclic synthesis, it was of interest to investigate reactions of the title compounds with hydrazines, hydroxylamine, guanidine, benzamidine and diamines in order to obtain five- and six-membered heterocyclic compounds.

As shown in Scheme 1, treatment of 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes **1a-b** with hydrazines in refluxing alcohols afforded pyrazoles **2a-e** in good yields. Absence of the infrared absorption of the cyano group and appearance of an exchangeable OH signal in ^1H nmr spectra, which is in most cases split into a triplet provide evidence for the structure of compounds **2a-e**. Because the

Scheme 1



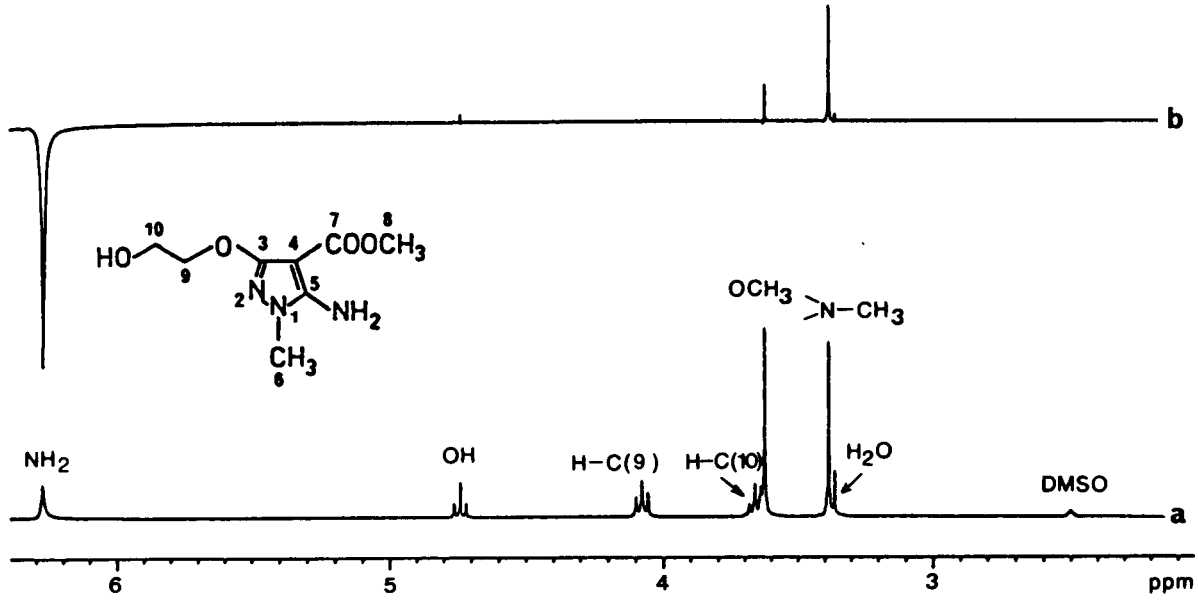


Figure 1. (a) 250 MHz ^1H nmr spectrum of *2c* in DMSO-d_6. (b) NOE difference spectrum resulting from irradiation of NH_2.

structural reasons that favour one or the other isomer in pyrazoles formed by the reaction of monosubstituted hydrazines with appropriate bifunctional compounds are not clearly understood [4], we have decided to study the structure of products **2a-e** with ^1H-{^1H}-nOe difference spectroscopy [5].

A typical homonuclear nOe experiment is shown in Figure 1. Irradiation at the resonance frequency of NH_2 protons in compound **2c** enhanced OCH_3 and NCH_3 protons.

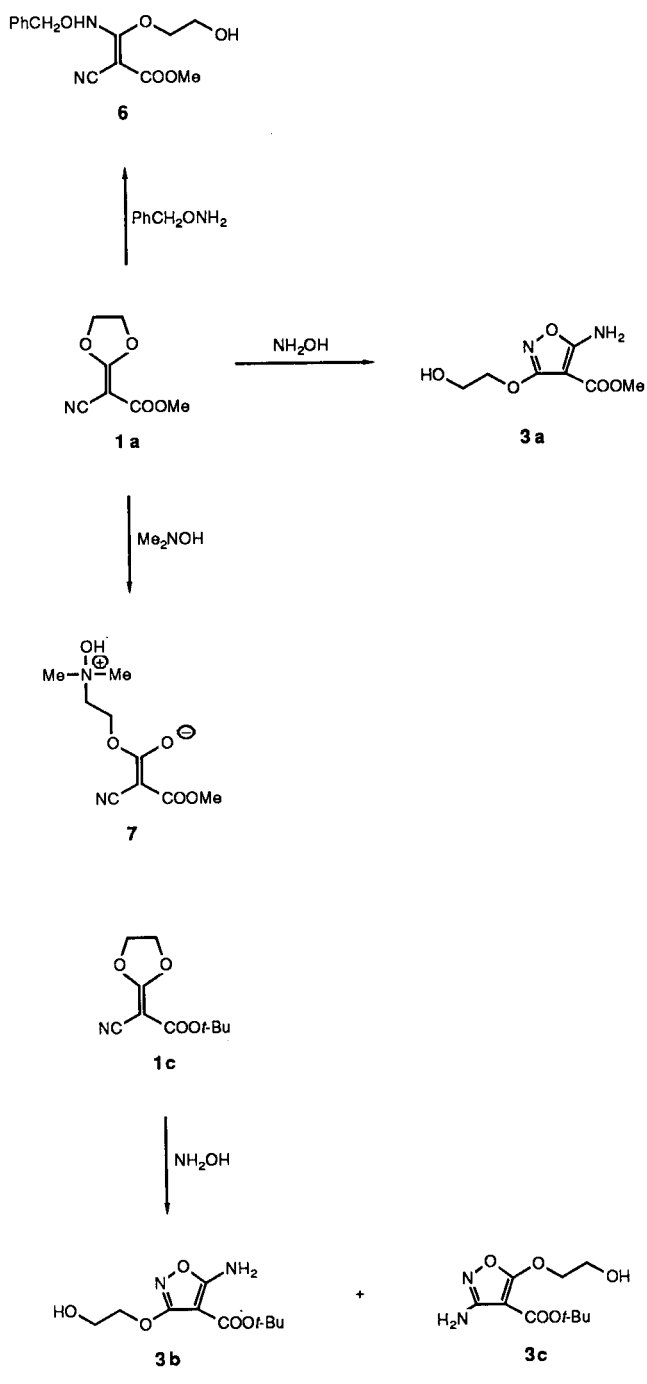
Similar nmr experiments revealed positive nuclear Overhauser effects between NH_2 and NCH_2 protons in compound **2d** as well as between NH_2 protons and *ortho*-protons of the phenyl substituent in **2e**. These studies provide evidence that in pyrazoles **2c-e** the ring nitrogen atom adjacent to the amino group bears a substituent.

In order to elucidate the reaction mechanism of the formation of pyrazoles from 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes, compound **1a** was reacted with *N,N*-dimethylhydrazine. The product **5** which was formed indicates that in the reaction with **1** the primary amino group of hydrazines attacks at C-2 of the dioxolane ring followed by ring opening and subsequent cyclization of the intermediate thus formed with the participation of the cyano group.

Reactions of 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes **1a,c** with hydroxylamine afforded isoxazoles **3a-c** (Scheme 2). Hydroxylamine must be regarded as an ambivalent nucleophile [6]. Therefore, additional experiments were performed to investigate the reaction pathway. Treatment of **1a** with *O*-benzylhydroxylamine gave 3-amino-3-(*O*-benzylhydroxyamino)-2-cyanomethylacrylate **6**, whereas with *N,N*-dimethylhydroxylamine 2-cyano-2-methoxycarbonyl-1-(2-*N,N*-dimethyl-*N*-hydroxyammonio)ethoxy)ethenolate **7** was formed [7]. This indicates that under the actual experimental conditions in the hydroxylamine molecule only the amino group is capable of a nucleophilic attack at C-2 in 1,3-dioxolane ring of **1**. The inertness of 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes **1** towards the attack of the hydroxylamine hydroxyl group is in agreement with the observation that these compounds can be recrystallized unchanged from boiling alcohols. Therefore we believe, that the initial step in the reaction between hydroxylamine and 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolane is the nucleophilic attack of the hydroxylamine amino group at C-2 in 1,3-dioxolane ring. The formation of isomeric product **3c** in addition to isoxazole **3b** in the reaction of 2-(*t*-butoxycarbonylcyanomethylene)-1,3-dioxolane **1c** with hydroxylamine can probably be attributed to the primary attack of NH_2 group of hydroxylamine at cyano group of **1c** and subsequent cyclization of the intermediate formed (Scheme 2).

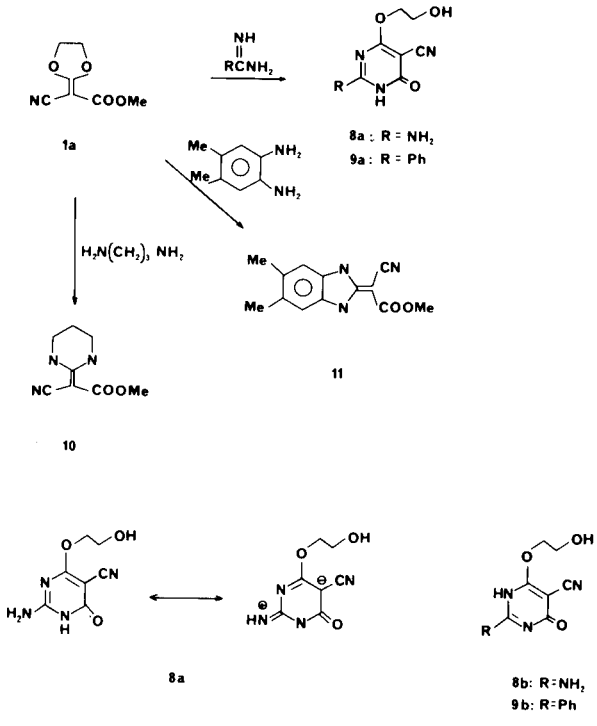
Similarly as in pyrazoles **2a-e**, the absence of CN absorption in infrared and ^{13}C nmr spectra as well as a characteristic triplet of OH proton in ^1H nmr spectra provide evidence for the structure of compounds **3a-c**.

Scheme 2



When 2-(methoxycarbonylcyanomethylene)-1,3-dioxolane **1a** was treated with guanidine and benzamidine respectivley, pyrimidones **8** and **9** were obtained. Unfortunately, in ^1H nmr spectra of **8** and **9** the signal of the side chain OH group was not split into a triplet, what would be a direct confirmation of proposed structures. Nevertheless, the OH signal appears in ^1H nmr spectra as expected

Scheme 3



between 4.80 and 5.00 ppm. Additional evidence for the presence of 2-hydroxyethoxy side chain in products **8** and **9** provide ^{13}C nmr spectra. It has been shown [1] that in ^{13}C nmr spectra of 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes **1** the signals of ring methylene groups appear close together in the region between 68 and 71 ppm. In 2-hydroxyethoxy side chain attached to a heterocyclic nucleus the signal of carbon atom adjacent to OH group is shifted upfield and appears at ca 59 ppm [8]. The ^{13}C chemical shifts of the side chain carbon atoms correlate very well with the described phenomenon and thus prove that in reactions leading to **8** and **9** the 1,3-dioxolane ring of **1a** has been opened.

Using homonuclear and heteronuclear nOe difference spectroscopy [9] we were able to show that in DMSO-d_6 the compounds **8** and **9** exist as pyrimidones and not as tautomeric 4-hydroxypyrimidines. In a heteronuclear experiment, irradiation of a proton signal at 11.21 ppm in compound **8** enhanced the same signal in ^{13}C nmr spectrum as irradiation of either of two broad signals (6.92 and 8.22 ppm) belonging to NH_2 group, namely C-2 (Figure 2). Similarly showed heteronuclear NOE difference spectrum of compound **9** enhancement of C-2 signal when either the proton signal at 13.50 ppm or *ortho* protons at phenyl ring

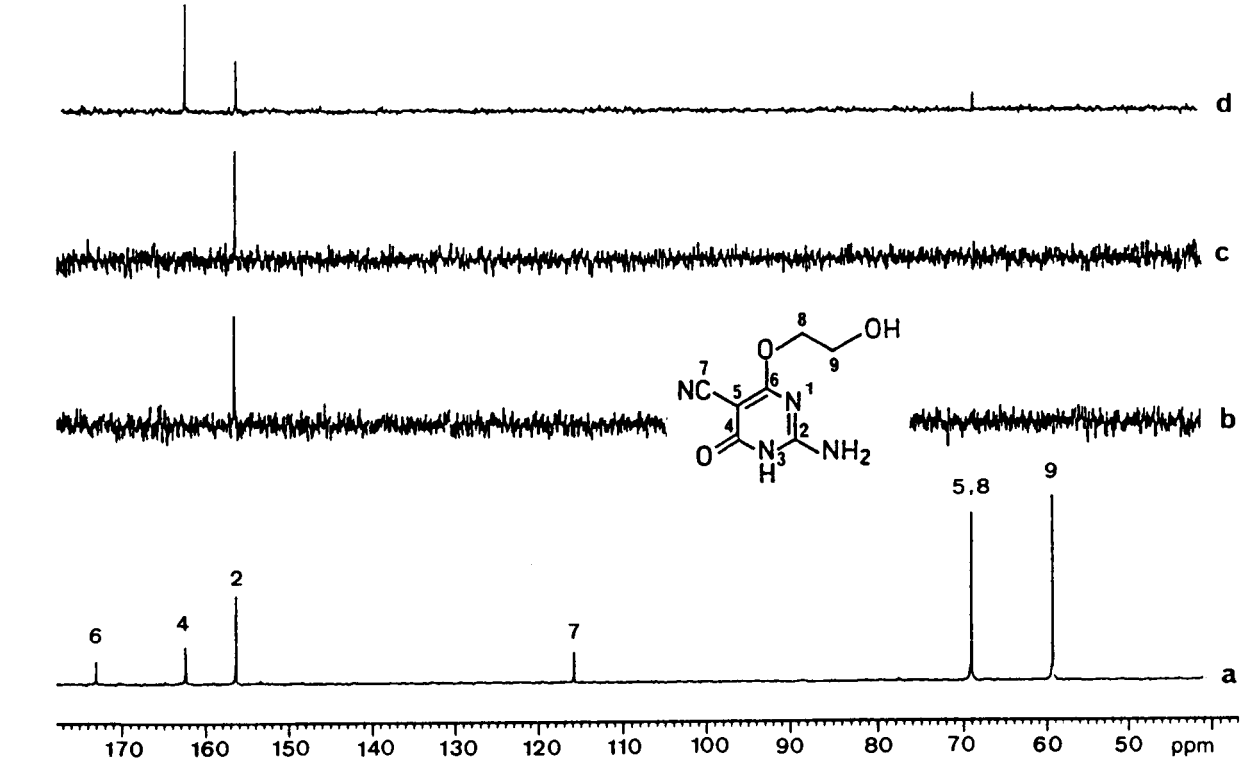


Figure 2. (a) 62.13 MHz ^{13}C nmr spectrum of **8** in DFSO-d_6. (b) NOE difference spectrum resulting from irradiation of a proton signal at 8.22 ppm. (c) NOE difference spectrum resulting from irradiation of a proton signal at 6.29 ppm. (d) NOE difference spectrum resulting from irradiation of a proton signal at 11.21 ppm [10].

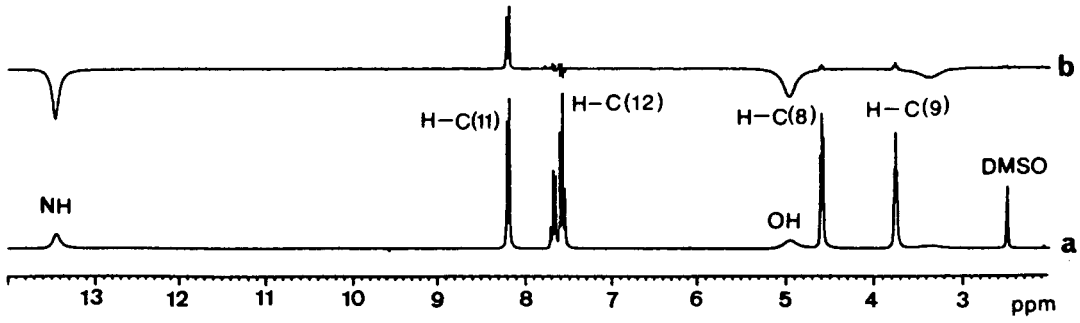


Figure 3. (a) 250.13 MHz ^{1}H nmr spectrum of **9** in DMSO-d_6. (b) NOE difference spectrum resulting from irradiation of a proton signal at 13.50 ppm.

were irradiated. Thus, it is clear that the broad signals at 11.21 ppm in compound **8** and at 13.50 ppm in compound **9** belong in each case to a proton bound to N-3 and not to the OH proton at C-4 because in the latter case, the distance of this proton to C-2 would be too long to make the observation of a heteronuclear NOE possible.

In compound **9** the pyrimidone structure was additionally proved by a homonuclear ^{1}H-^{1}H NOE experiment (Figure 3). Irradiation of the signal at 13.50 ppm in ^{1}H nmr spectrum enhanced *ortho* protons at phenyl ring. If the irradiated proton was bound to oxygen at C-4, NOE would not be observed because of too long distance.

Between both alternative structures **8a** and **8b** as well as **9a** and **9b** it can be distinguished on the basis of different chemical shifts of carbon atom C-5 in compounds **8** and **9** respectively. A high field shift of the C-5 signal in compound **8** (68.7 ppm) in comparison to the compound **9** (78.2 ppm) can be explained with a +M effect of the amino group. However, this effect can be active only in structure **8a** but not in structure **8b**. Therefore, we believe that formulas **8a** and **9a** represent the actual structures of compounds **8** and **9** in DMSO-d_6.

Treatment of 2-(methoxycarbonylcyanomethylene)-1,3-dioxolane **1a** with 1,3-diaminopropane gave 2-(cyanomethoxycarbonylmethylene)hexahydropyrimidine **10**, whereas with 4,5-dimethyl-1,2-phenylenediamine 2-(cyanomethoxycarbonylmethylene)-5,6-dimethylbenzimidazoline **11** was obtained.

In summary we have shown with few examples that new 2-(alkoxycarbonylcyanomethylene)-1,3-dioxolanes are versatile starting materials for the synthesis of a variety of heterocyclic compounds.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus automatic C,H,N analyzer. Electron impact mass spectra were measured at 100 eV on a Varian MAT 311 A mass spectrometer. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker WM-250 spectrometer operating at 250.13 MHz for protons and at 62.89 MHz for ^{13}C. Tetramethylsilane was used as internal standard. The ir spectra were recorded on a Perkin-Elmer model 325 instrument as potassium bromide pellets. The uv spectra were obtained by a Carl Zeiss DMR 4 spectrophotometer.

5-Amino-3-(2'-hydroxyethoxy)-4-methoxycarbonylpyrazole (**2a**).

A mixture of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) and hydrazine hydrate (1.20 g, 24 mmoles) in methanol (50 ml) was heated under reflux for 2 hours. After removal of the solvent under reduced pressure the residue was purified by chromatography over silica gel using chloroform/methanol (9/1) as eluent. Recrystallization from acetonitrile furnished 1.61 g (40%) of pure **2a**, mp 157°; ir (potassium bromide): 3520, 3470, 3390, 3320, 1705, 1675, 1635, 1620, 1590, 1570 cm^{-1}; uv (acetonitrile): λ max (log ε) 225 (3.97), 250 sh (3.75) nm; ms: (220°) m/e 201 (M$^+$, 16), 125 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.64 (s, 3H, CH_3), 3.68 (t, 2H, CH_2OH, J = 5.8 Hz), 4.12 (t, 2H, OCH_2, J = 5.8 Hz), 5.20 (s br, 3H, OH + NH_2), 10.74 (s br, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 49.90 (CH_3), 59.30 (CH_2OH), 69.30 (OCH_2), 80.50 (C-4), 152.30 (C-5), 159.70 (C-3), 163.60 (C=O).

Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.75; H, 5.61; N, 20.95.

5-Amino-3-(2'-hydroxyethoxy)-4-ethoxycarbonylpyrazole (**2b**).

A mixture of 2-(cyanoethoxycarbonylmethylene)-1,3-dioxolane (**1b**) (3.66 g, 20 mmoles) and hydrazine hydrate (1.20 g, 24 mmoles) in ethanol (50 ml) was refluxed for 2 hours. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel with chloroform/methanol (9/1). Recrystallization from acetonitrile gave 1.08 g (25%) of white **2b**, mp 127°; ir (potassium bromide): 3490, 3405, 3360, 3340, 1710, 1680, 1630, 1565 cm^{-1}; uv (acetonitrile): λ max (log ε) 225 (3.94), 250 sh (3.72) nm; ms: (150°) m/e 215 (M$^+$, 17), 125 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 1.22 (t, 3H, CH_3), 3.68 (t, 2H, CH_2OH, J = 5.8 Hz), 4.12 (q, 2H, OCH_2), 4.13 (t, 2H, OCH_2, J = 5.8 Hz), 4.76 (s, br, 1H, OH), 6.01 (s, br, 2H, NH_2), 10.90 (s, br, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 14.43 (CH_3), 58.08 (CH_2-ester), 59.40 (CH_2OH), 69.05 (OCH_2), 80.70 (C-4), 152.13 (C-5), 159.96 (C-3), 163.19 (C=O).

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.52. Found: C, 44.93; H, 6.18; N, 19.69.

5-Amino-3-(2'-hydroxyethoxy)-4-methoxycarbonyl-1-methylpyrazole (**2c**).

A mixture of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (16.9 g, 100 mmoles) and methylhydrazine (5.52 g, 120 mmoles) in methanol (150 ml) was refluxed for 2 hours. The clear solution was concentrated to 50 ml and a precipitate which formed upon cooling was filtered off to give 15.92 g (74%) of white **2c**, mp 146° (from methanol); ir (potassium bromide): 3430, 3340, 3250, 1670, 1640, 1570 cm^{-1}; uv (acetonitrile): λ max (log ε) 232 (4.06) nm; ms: (120°) m/e 215 (M$^+$, 31), 139 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.41 (s, 3H, NCH_3), 3.64 (s, 3H, OCH_3), 3.66 (dt, 2H, CH_2OH, $J_{CH_2CH_2}$ = 5.5 Hz, J_{CH_2OH} = 5.4 Hz), 4.08 (t, 2H, OCH_2, J = 5.5 Hz), 4.76 (t, 1H, OH), 6.28 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 33.61 (NCH_3), 49.87 (OCH_3), 59.28 (CH_2OH), 69.11 (OCH_2), 80.61 (C-4), 150.96 (C-5), 158.81 (C-3), 163.46 (C=O).

Anal. Calcd. for $C_6H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.76; H, 6.13; N, 19.40.

5-Amino-3-(2'-hydroxyethoxy)-4-methoxycarbonyl-1-phenylpyrazole (**2d**).

A mixture of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) and phenylhydrazine (2.16 g, 20 mmoles) in methanol (40 ml) was heated under reflux for 3 hours. After removal of the solvent under reduced pressure the crude product was purified by column chromatography on silica gel using chloroform/methanol (9/1) as eluent. Recrystallization from acetonitrile afforded 3.60 g (65%) of white **2d**, mp 108°; ir (potassium bromide): 3450, 3360, 1675, 1610, 1570 cm^{-1}; uv (acetonitrile): λ max (log ε) 242 (4.33) nm; ms: (120°) m/e 277 (M^+, 45), 201 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.72 (s, 3H, CH_3), 3.73 (dt, 2H, CH_2OH, $J_{CH_2CH_2}$ = 5.5 Hz, J_{CH_2OH} = 5.4 Hz), 4.19 (t, 2H, OCH_2, J = 5.5 Hz), 4.82 (t, 1H, OH, J = 5.4 Hz), 6.48 (s br, 2H, NH_2), 7.80 (m, 1H, ArH-para), 7.52 (m, 4H, ArH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 50.28 (CH_3), 59.18 (CH_2OH), 69.39 (OCH_2), 81.84 (C-4), 123.19, 126.75, 129.30, 137.75 (phenyl), 150.66 (C-5), 160.11 (C-3), 163.80 (C=O).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.23; H, 5.43; N, 15.00.

5-Amino-3-(2'-hydroxyethoxy)-1-(2"-hydroxyethyl)-4-methoxycarbonylpyrazole (**2e**).

A solution of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) and 2-hydrazinoethanol (1.83 g, 24 mmoles) in methanol (50 ml) was refluxed for 3 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using chloroform/methanol (9/1) as eluent to give 2.94 g (60%) of white crystals, mp 117°; ir (potassium bromide): 3450, 3360, 3250, 1685, 1640, 1575, 1555 cm^{-1}; uv (acetonitrile): λ max (log ε) 232 (4.04) nm; ms: (160°) m/e 245 (M^+, 47), 125 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.64 (m, 7H, CH_3 + 2CH_2OH), 3.82 (t, 2H, NCH_2, J = 5.5 Hz), 4.10 (t, 2H, OCH_2, J = 5.5 Hz), 4.76 (t, 1H, OH, J = 5.4 Hz), 4.89 (t, 1H, OH, J = 5.4 Hz), 6.22 (s br, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 48.58 (NCH_2), 49.93 (CH_3), 59.05 (CH_2OH), 59.26 (CH_2OH), 69.10 (OCH_2), 80.68 (C-4), 151.29 (C-5), 158.92 (C-3), 163.54 (C^{3}O).

Anal. Calcd. for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 44.03; H, 6.08; N, 16.93.

5-Amino-3-(2'-hydroxyethoxy)-4-methoxycarbonylisoxazole (**3a**).

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.46 g, 2 mmoles) in methanol (30 ml) hydroxylamine hydrochloride (1.39 g, 20 mmoles) and five minutes later 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) were added. The suspension was heated under reflux for 2 hours and filtered when still warm. A white precipitate which separated upon cooling was recrystallized from methanol to give 2.55 g (63%) **3a**, mp 152°; ir (potassium bromide): 3470, 3430, 3340, 3180, 1700, 1660, 1580, 1550 cm^{-1}; uv (acetonitrile): λ max (log ε) 215 (3.82), 240 (4.00) nm; ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.68 (s, 3H, CH_3), 3.69 (dt, 2H, CH_2OH, $J_{CH_2CH_2}$ = 5.5 Hz, J_{CH_2OH} = 5.4 Hz), 4.15 (t, 2H, OCH_2, J = 5.5 Hz), 4.88 (s, 1H, OH), 7.81 (s br, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 50.38 (CH_3), 58.94 (CH_2OH), 70.58 (OCH_2), 75.93 (C-4), 161.86 (C=O), 168.46 (C-3), 171.90 (C-5).

Anal. Calcd. for $C_7H_{10}N_2O_5$: C, 41.59; H, 4.99; N, 13.86. Found: C, 41.42; H, 4.92; N, 13.89.

5-Amino-3-(2'-hydroxyethoxy)-4-*t*-butoxycarbonylisoxazole (**3b**) and 3-Amino-5-(2'-hydroxyethoxy)-4-*t*-butoxycarbonylisoxazole (**3c**).

To a solution of sodium hydroxide (0.2 g, 5 mmoles) in a mixture of ethanol (5 ml) and water (5 ml) hydroxylamine hydrochloride (0.42 g, 6 mmoles) and 2-(cyano-*t*-butoxycarbonylmethylene)-1,3-dioxolane (**1c**) (1.06 g, 5 mmoles) were added. The mixture was refluxed for 3 hours, whereupon the solvent was removed under reduced pressure. Separation of the residue by column chromatography (silica gel, chloroform/methanol = 9/1) afforded 0.40 g (33%) **3b** and 0.16 g (13%) **3c**.

Compound **3b** was obtained as white needles, mp 121° (from diethyl ether); ir (potassium bromide): 3560, 3400, 3300, 1680, 1660, 1575, 1520 cm^{-1}; uv (acetonitrile): λ max (log ε) 215 (3.82), 240 (4.01) nm; ms: (100°) m/e 244 (M^+, 5), 127 (100): ^{1}H-nmr (DMSO-d_6): δ (ppm) 1.47 (s, 9H, $C(CH_3)_3$), 3.68 (dt, 2H, CH_2OH, $J_{CH_2CH_2}$ = 5.5 Hz, J_{CH_2OH} = 5.4 Hz), 4.11 (t, 2H, OCH_2, J = 5.5 Hz), 4.82 (t, 1H, OH, J = 5.4 Hz), 7.58 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 28.01 (3 CH_3), 59.18 (CH_2OH), 70.31 (OCH_2), 77.13 (C-4), 79.42 (*C*Me_3), 161.29 (C=O), 168.49 (C-3), 171.73 (C-5).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47. Found: C, 49.21; H, 6.62; N, 11.36.

Compound **3c** was obtained as white needles, mp 181° (from ethanol); ir (potassium bromide): 3370, 3330, 3150, 1715, 1680, 1635, 1620, 1570; uv (acetonitrile): λ max (log ε) 207 (4.22), 235 (4.20); ms: (150°) m/e 244 (M^+, 2), 157 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 1.47 (s, 9H, $C(CH_3)_3$), 3.56 (m, 4H, 2 CH_2), 4.82 (t, 1H, OH, J = 5.4 Hz), 8.27 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 28.07 (3 CH_3), 51.37 (OCH_2), 57.43 (CH_2OH), 77.81 (C-4), 79.28 (*C*Me_3), 162.74 (C=O), 169.68 (C-5), 171.86 (C-3).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47. Found: C, 49.25; H, 6.60; N, 11.44.

3-(*O*-Benzylhydroxyamino)-3-(2'-hydroxyethoxy)methylacrylate (**6**).

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.46 g, 20 mmoles) in methanol (30 ml) *O*-benzylhydroxylamine hydrochloride (3.18 g, 20 mmoles) and 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) were added. After heating the mixture for 3 hours under reflux, sodium chloride was remained by filtration. Evaporation of the solvent under reduced pressure and recrystallization of the residue from methanol afforded white crystals of **6**, mp 145°; ir (potassium bromide): 3450, 2200, 1700, 1630 cm^{-1}; uv (acetonitrile): λ max (log ε) 240 (3.64) nm; ms: (145°) m/e 292 (M^+, 0.4), 91 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.41 (t, 2H, CH_2OH, J = 5.5 Hz), 3.48 (s, 3H, CH_3), 3.40-4.00 (s br, 2H, NH + OH), 4.21 (t, 2H, OCH_2, J = 5.5 Hz), 5.10 (s, 2H, CH_2-benzyl), 7.42 (m, 5H, ArH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 48.26 (CH_2-benzyl), 49.32 (CH_3), 55.12 (C-2), 56.30 (CH_2OH), 74.51 (OCH_2), 122.51 (CN), 128.40, 128.61, 128.93, 134.53 (C-arom.), 167.89 (C-3), 168.58 (C=O).

For C,H,N analysis the product was converted into a sulfate by trituration with 20% sulfuric acid.

Anal. Calcd. for $C_{14}H_{16}N_2O_5 \cdot H_2SO_4$: C, 43.08; H, 4.65; N, 7.18. Found: C, 43.30; H, 5.00; N, 7.39.

2-Cyano-2-methoxycarbonyl-1-(2-(*N,N*-dimethyl-*N*-hydroxyammonio)-ethoxy)ethenolate (**7**).

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.46 g, 20 mmoles) in methanol (40 ml) *N,N*-dimethylhydroxylamine hydrochloride (1.95 g, 20 mmoles) and 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) were added. The mixture was refluxed for 1 hour whereupon sodium chloride was removed by filtration and filtrate was concentrated *in vacuo*. Recrystallization of the residue from methanol afforded white crystals of **7**, mp 185°; ir (potassium bromide): 3420, 3200-2700, 2180, 1710, 1610 cm^{-1}; uv (acetonitrile): λ max (log ε) 212 (4.11), 245 (4.26) nm; ms: (110°) m/e 105 (6), 58 (41), 43 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.42 (s, 3H, OCH_3), 3.52 (s, 6H, $N(CH_3)_2$), 3.88 (t, 2H, NCH_2), 4.33 (t, 2H, OCH_2, J = 5.5 Hz), 12.18 (s, 1H, OH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 48.99 (OCH_3), 54.62 (NCH_2), 54.89 (C-2), 56.49 (2 CH_3), 67.72 (OCH_2), 123.43 (CN), 166.11 (C-1), 167.36 (C=O).

Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.67; H, 6.06; N, 12.11.

2-Amino-5-cyano-6-(2'-hydroxyethoxy)pyrimidin-4-one (**8**).

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.46 g, 20 mmoles) in methanol (40 ml) guanidine hydrochloride (2.10 g, 22 mmoles) and 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) were added. After heating under reflux for 2 hours the mixture was cooled to room temperature and the precipitate which formed was separated and suspended in water (20 ml). The suspension was acidified with 1*N* sulfuric acid to *p*H 1-2. The precipitate was filtered off and recrystallized from water to give 1.69 g (43%) of white crystalline **8**, mp 278°; ir (potassium bromide): 3370, 3140, 2210, 1665, 1635, 1600, 1550 cm^{-1}; uv (acetonitrile): λ max (log ε) 225 (3.10), 275 (3.28), 445 (2.40) nm; ms: (255° m/e 196 (M^+, 27), 43 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.67 (t, 2H, CH_2OH, J = 5.5 Hz), 4.34 (t, 2H,

OCH_2, J = 5.5 Hz), 4.90 (s, 1H, OH), 6.92 (s, 1H, NH), 8.22 (s, 1H, NH), 11.21 (s, 1H, CONH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 58.99 (CH_2OH), 68.79 (OCH_2), 68.73 (C-5), 115.54 (CN), 156.14 (C-2), 162.19 (C-4), 172.78 (C-6).

Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.67; H, 4.08; N, 28.47.

5-Cyano-6-(2'-hydroxyethoxy)-2-phenylpyrimidin-4-one (**9**).

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.46 g, 20 mmoles) in methanol (40 ml) benzamidine hydrochloride hydrate (3.84 g, 20 mmoles) and 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (3.38 g, 20 mmoles) were added. The mixture was refluxed for 2 hours. Then the solvent was evaporated under reduced pressure and water (80 ml) was added. The mixture was acidified with 1*N* sulfuric acid to *p*H 1-2 and a precipitate which formed was filtered off. Recrystallization from methanol afforded 3.55 g (69%) of white crystalline **9**, mp 259°; ir (potassium bromide): 3300, 3170, 3100, 2230, 1670, 1610, 1595, 1550 cm^{-1}; uv (acetonitrile): λ max (log ε) 210 sh (4.40), 250 (4.04), 318 (4.04) nm; ms: (200°) m/e 257 (M^+, 1), 104 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 3.78 (t, 2H, CH_2OH, J = 5.5 Hz), 4.64 (t, 2H, OCH_2, J = 5.5 Hz), 5.00 (s br, 1H, OH), 7.62 (dd, 2H, ArH), 7.71 (dd, 1H, ArH), 8.22 (d, 2H, ArH), 13.50 (s br, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 59.06 (CH_2OH), 69.91 (OCH_2), 78.15 (C-5), 113.97 (CN), 128.72, 128.81, 130.63, 133.40 (phenyl), 159.87 (C-2), 162.66 (C-4), 171.78 (C-6).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.65; H, 4.39; N, 16.22.

2-(Cyanomethoxycarbonylmethylene)hexahydropyrimidine (**10**).

To a stirred solution of 2-(cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (1.69 g, 10 mmoles) in tetrahydrofurane (50 ml) 1,3-diaminopropane (0.89 g, 12 mmoles) was added. Stirring was continued for 30 minutes whereupon the solvent was removed under reduced pressure and the residue recrystallized from methanol to give 1.36 g (75%) of white **8**, mp 159°; ir (potassium bromide): 3400, 3300, 2220, 1660, 1605, 1590 cm^{-1}; uv (acetonitrile): λ max (log ε) 208 (4.07), 260 (4.37) nm; ms: (145°) m/e 181 (M^+, 87), 150 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 1.80 (quint, 2H, H-C (5)), 2.28 (m, 4H, H-C (4, 6)), 3.55 (s, 3H, CH_3), 8.10 (s, 2H, 2NH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 19.45 (C-5), 30.24 (C-4, 6), 59.99 (CH_3), 52.40 (= *C*-CN), 119.60 (CN), 158.60 (C-2), 168.82 (CO).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.02; H, 6.12; N, 23.19. Found: C, 52.73; H, 6.20; N, 22.90.

2-Cyanomethoxycarbonylmethylene)-5,6-dimethylbenzimidazoline (**11**).

2-(Cyanomethoxycarbonylmethylene)-1,3-dioxolane (**1a**) (1.69 g, 10 mmoles) and 4.5-dimethyl-1,2-phenylenediamine (1.36 g, 10 mmoles) in methanol (50 ml) were refluxed for 1 hour. The precipitate which separated upon cooling was purified by column chromatography on silica gel using chloroform/methanol (9/1) as eluent to give 1.09 g (45%) of **11**, gray crystals, mp 309°; ir (potassium bromide): 3250, 2200, 1650, 1625, 1585 cm^{-1}; uv (acetonitrile): λ max (log ε) 218 (4.08), 258 (3.84), 310 sh (4.28), 320 (4.39) nm; ms: (240°) m/e 243 (M^+, 64), 211 (100); ^{1}H-nmr (DMSO-d_6): δ (ppm) 2.21 (s, 6H $2CH_3$), 3.72 (s, 3H, OCH_3), 7.22 (s, 2H, 2CH), 12.22 (s, 2H, 2NH); ^{13}C-nmr (DMSO-d_6): δ (ppm) 19.63 (CH_3), 50.32 (OCH_3), 50.64 (= *C*-CN), 111.76 (CH), 119.42 (CN), 129.10, 131.01 (C-1a, 3a, 5, 6), 151.72 (C-2), 167.20 (CO).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.07; H, 5.50; N, 17.11.

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[10] The signal at 68.73 ppm was also enhanced. This signal belongs to C-5 which has the same chemical shift as C-8. The observed nOe can be explained by a dipole-dipole interaction between C-5 and OH proton (which exchanges in a ^{1}H nOe experiment with the proton at 11.21 ppm) with the assumption that the side chain is folded over the heterocyclic ring.