PREPARATION OF HOMOLOGOUS PYRAZOLONEDICARBOXYLATES

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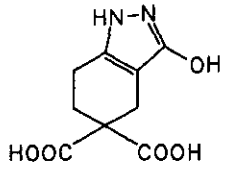
Abstract – Homologous disodium pyrazolonedicarboxylates (**8, 16f** and **16g**) as possible protectors of *cis*-DDP induced nephrotoxicity, have been prepared by the reaction of hydrazine with di-*t*-butyl ethyl β-keto triesters (**5b, 13b** and **13c**) and subsequent hydrolysis of formed di-*t*-butyl pyrazolonedicarboxylates (**6b, 14b** and **14c**).

cis-Diamminedichloroplatinum (*cis*-DDP) is one of the most successful agents in cancer chemotherapy of several solid tumors (ovarian, testicular, bladder, head and neck).[1] A limitation of its usage, however, is its concentration-dependent nephrotoxicity besides a variety of other side effects.[2] A number of sulphur nucleophiles (sodium thiosulphate, thiourea, diethyl dithiocarbamate, WR 2721, glutathione)[3] has been studied as inhibitors of *cis*-DDP-induced nephrotoxicity.

As a part of our continued studies on the syntheses and properties of tetrahydroindazolonecarboxylic acids, we have reported that 4,5,6,7-tetrahydro-3-hydroxy-1*H*-indazole-5,5-dicarboxylic acid (HIDA, **1**),[4,5] as



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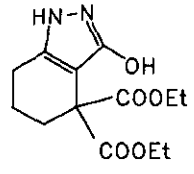

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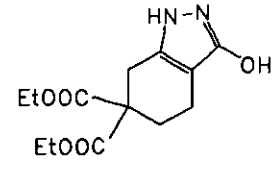

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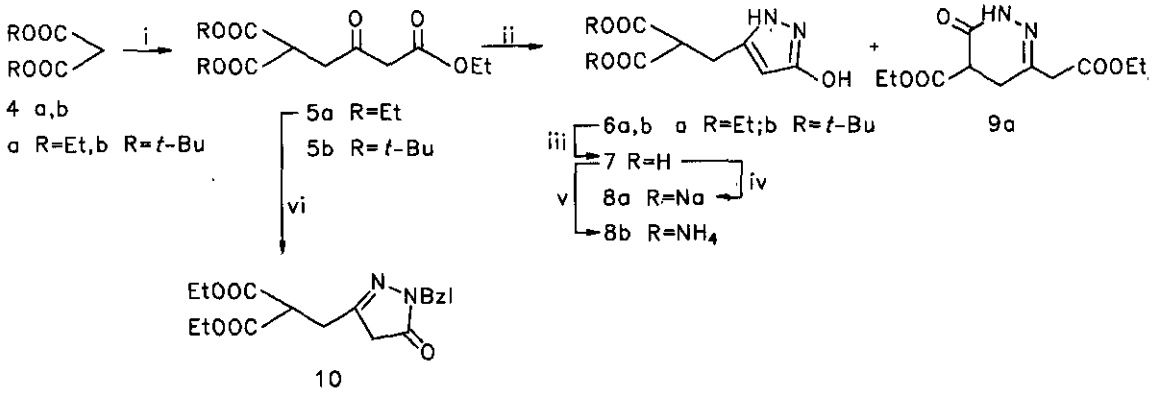
disodium salt, can considerably reduce *cis*-DDP-induced nephrotoxicity.[6] Protective effect of HIDA was studied alone or combined with hyperthermia and radiation treatment.[7] We have also reported its complexation[5] with divalent metal ions and the syntheses[8] of positional isomers of HIDA such as indazolone **(2)** and **(3)**.

Herein, we report the synthesis and properties of pyrazolonedicarboxylic acids being monocyclic, functional analogs of indazolones (**1-3**), in order to test their nephroprotective potential.

Results and Discussion

In order to prepare disodium pyrazolonedicarboxylates (**8**) (*Scheme 1*), and (**16f**, **16g**) (*Scheme 2*) our first approach was based on the synthesis of appropriate triethyl β-keto triesters, which would give the pyrazolones in the subsequent reaction with hydrazine.[9] We found, however, that hydrolysis of the ethyl dicarboxylates (**6a** and **14a**) by refluxing either in 15% HCl or 25% NH_4OH was accompanied by decarboxylation or decomposition. To avoid this problem we investigated the possibility to prepare di-*t*-butyl dicarboxylates (**6b**, **13b** and **13c**) from the corresponding di-*t*-butyl ethyl β-keto triesters, which would allow the trifluoracetic acid (TFA) catalyzed cleavage of *t*-butyl ester instead hydrolysis of ethyl carboxylates, in the last step. In this way the disodium pyrazolonedicarboxylates (**8**, **16f** and **16g**) have been obtained in high yields. In addition, we found that both, the reaction of di-*t*-butyl malonate with ethyl 4-chloroacetoacetate and subsequent reaction of the β-keto ester with hydrazine proceed selectively. In contrast, the same reactions started with diethyl malonate gave considerable amounts of by-products in both steps. We confirmed as previously reported[10] that diethyl malonate (**4a**) and ethyl 4-chloroacetoacetate



Reagents: i,NaH or *t*-BuOK, $ClCH_2COCH_2COOEt$; ii,$NH_2NH_2 \cdot H_2O$; iii,TFA; iv,2N NaOH; v,25% NH_4OH
vi,$BzlNHNH_2 \cdot 2HCl$, $NaHCO_3$

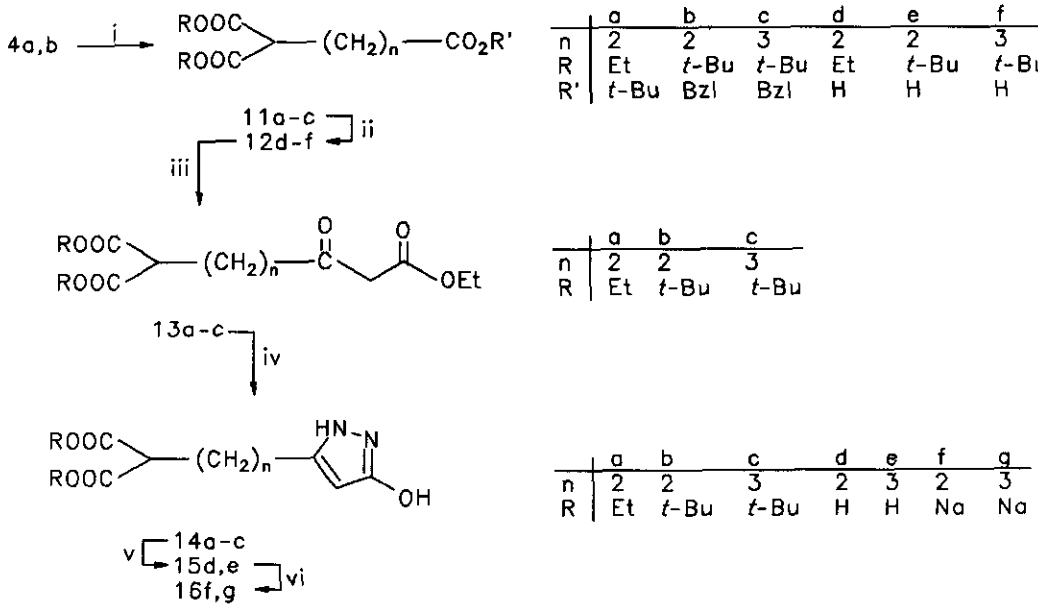
Scheme 1

gave two products, the triethyl β-keto triester (**5a**) in 20% yield and diethyl 2-carboxyl-4-oxohexanedioate in 50% yield, the later resulting from intramolecular cyclization of **5a** into ethyl 5-etoxycarbonylvinyl-2-

oxofuran-3-carboxylate and opening of the five-membered lactone ring by hydrolysis. In contrast, di-*t*-butyl malonate gave exclusively **5b**, due to much lower reactivity of *t*-butyl ester group in possible intramolecular transesterification with 4-enol group.

The triethyl β-keto triester (**5a**) upon treatment with hydrazine gave a mixture of pyrazolone (**6a**) (18% yield) and pyridazinone (**9a**) (30% yield), as the consequence of the concurrent cyclization with 2- and 6-etoxycarbonyl groups. The regioselectivity in the reaction can be affected by using benzylhydrazine which in reaction with **5a** gave the corresponding diethyl 2-(1-benzyl-5-oxo-2-pyrazolin-3-yl)-1,1-ethanedicarboxylate (**10**) in 40% yield. Due to the more reactive 6-etoxycarbonyl group in comparison to 2-*t*-butoxycarbonyl group, the ethyl di-*t*-butyl β-keto triester (**5b**) gave regioselectively the pyrazolone (**6b**) in 91% yield.

Carboxylic acids (**12d, 12e** and **12f**) (*Scheme 2*) were prepared by the reactions of the malonate (**4a**) or (**4b**) with *t*-butyl acrylate (for **11a**) or appropriate benzyl bromoalkanecarboxylate (for **11b** and **11c**) and



Reagents; i,*t*-BuOK or NaH, $Br(CH_2)_nCOOR'$ or CH_2=CHCOOBu-*t*, ii,TFA or H_2, 10% Pd/C
iii,*N*,*N*'-carbonyldiimidazole, $Mg(OOCCH_2COOEt)$; iv,$NH_2NH_2 \cdot H2O$; v,TFA; vi,2N NaOH

Scheme 2

selective deprotection of mixed triesters (**11a, 11b** and **11c**) by TFA-catalyzed cleavage of *t*-butyl esters (**11a**) or hydrogenolysis of benzyl esters (**11c** and **11d**). The β-keto esters (**13a, 13b** and **13c**) were obtained by the use of a slightly modified method,[11] acceptable for the acid sensitive compounds. It

comprises from activation of the appropriate carboxylic acid (**12d, 12e** or **12f**) with *N,N'*-carbonyldiimidazole, followed by the treatment of resulting imidazolide with nucleophilic magnesium enolate of ethyl hydrogen malonate, and spontaneous decarboxylation during workup. The regioselective reactions of **13a**, **13b** and **13c** with hydrazine afforded appropriate pyrazolones (**14a**, **14b** and **14c**). The dicarboxylic acids (**7**, **15d** and **15e**) obtained by TFA deprotection of di-*t*-butyl carboxylates (**6b**, **14b** and **14c**) were treated with 2N NaOH to give disodium salts (**8**, **16f** and **16g**).

The isomeric pyrazolone (**6a**) and pyridazinone (**9a**) have been identified on the bases of their ^{1}H-nmr spectra. In the spectrum of the former, the appearance of the doublet at δ 3.24 ppm coupled to a methine proton (δ 3.76 ppm, t) also present in the spectra of starting β-keto ester (**5a**), together with appearance of one proton singlet at δ 5.08 ppm proves cylisation with hidrazine into five-membered pyrazolone ring. On the other hand, in the spectra of **9a**, a two proton singlet at δ 3.43 ppm assignable to methylene protons α-to etoxycarbonyl group together with two doublet of doublets at δ 2.81 and δ 3.01 ppm and one proton doublet of doublets at δ 3.52 can be observed. The later coupling pattern clearly proved the cylisation into 6-membered pyridazinone ring where 4-methylene protons became diastereotropic.

The ^{1}H-nmr spectrum of *N*-benzylpyrazolone derivative (**10**) taken in $CDCl_3$ differ considerably from the spectra of **6a, 6b** and **14b** recorded in the same solvent. While in the spectra of **6a, 6b** and **14b** only one proton singlet assignable to pyrazolone C4'-H at δ 5.46-5.48 ppm can be observed, in the spectrum of **10** a two proton singlet at δ 3.24 ppm assignable pyrazolone C4' methylene appeared.

The observed differences in ^{1}H-nmr spectra of **10** and **6a,b** and **14b**, indicated the prevalence of tautomer (**A**) for **10** and tautomer (**B**) for **6a, 6b** and **14b,** that is in agreement with well known tautomer

A B

equilibrium of *N*-1-substituted pyrazol-5-ones and *N*-unsubstituted pyrazolones.[12] In support for that, the C3' pyrazolone resonance in ^{13}C-nmr spectra of **10** appears for about 5 ppm downfield (δ 168.4 ppm) in comparison to the corresponding signals in **6a, 6b** and **14b** (δ 162.8, 162.5 and 163.8 ppm, respectively). The evaluation of prepared disodium pyrazolonedicarboxylates (**8, 16f** and **16g**) as possible protectors of *cis*-DDP induced nephrotoxicity is in progress.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Kofler hot-stage apparatus. ^{1}H- and ^{13}C-nmr spectra were recorded on either a JOEL FX 90Q (90/22.5 MHz) or a Varian Gemini 300 (300/75 MHz) with TMS as an internal standard; ir spectra were recorded in KBr pallets on a Perkin-Elmer 297 spectrometer and uv (in EtOH) on a Philips PUB700 UV/visible spectrophotometer. Mass spectra were recorded on Shimadzu GCMS-QP 1000.

1-*t*-Butyl 6-ethyl 2-*t*-butyloxycarbonyl-4-oxohexanedioate (5b). A solution of **4b** (6 ml, 26.798 mmol) in dry THF (20 ml) was treated with *t*-BuOK/*t*-BuOH freshly prepared from 1.047 g (26.780 mmol) K and 25 ml *t*-BuOH, and the mixture was stirred at room temperature for 2 h. Ethyl 4-chloroacetoacetate (1.80 ml, 13.320 mmol) was added dropwise and the stirring was continued for 18 h. The most of the solvent was evaporated and the residue was partitioned between 20% NH_4Cl and EtOAc. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The purification of the residue on silica gel column (light petroleum-Et_2O, 100:0 → 10:1) gave 3.275 g (71.39%), oil, R_f 0.49 (Et_2O/ light petroleum, 1:1). ^{1}H-Nmr($CDCl_3$): 4.20 (2H, q, J=7.1, H_2(OEt)), 3.70 (1H, t, J=7.2, H(C-2)), 3.50 (2H, s, H_2(C-5)), 3.06 (2H, d, J=7.2, H_2(C-3)), 1.46 (18H, s, 6H_3(OBu-*t*)), 1.28 (3H, t, J=7.1, H_3(OEt)). ^{13}C-Nmr($CDCl_3$): 199.5 (C-4), 167.6, 166.5 (CO_{esters}), 81.7 (C_{OBu-t}), 61.2 ($CH_{2(OEt)}$), 49.0 (C-5), 48.8 (C-2), 41.2 (C-3), 27.6 ($CH_{3(OBu-t)}$), 13.8 ($CH_{3(OEt)}$). Ir: 1740, 1725 cm^{-1}. Uv: λ_{max}(log ε): 238.4(2.824). *Anal.* Calcd for $C_{17}H_{28}O_7$: C,59.28; H,8.19. Found: C,59.15; H,8.13.

Diethyl 2-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-ethanedicarboxylate (6a) and **ethyl 3-ethoxycarbonylmethyl-6-oxo-1,4,5,6-tetrahydropyridazine-5-carboxylate (9a)**. A solution of **5a** (3.532 g, 12.252 mmol) in 96% EtOH (353 ml) was heated to reflux, and a solution of hydrazine monohydrate (0.595 ml, 12.266 mmol) in 96% EtOH (35 ml) was added during 25 min. The heating was continued through 2.5 h and the solvent was evaporated. The residue was chromatographed on a silica gel column (20% EtOAc/ light petroleum → EtOAc) to give starting material (0.489 g, 13.84%), and two products, R_f 0.34 and R_f 0.14 (Et_2O).

The oily fraction, R_f 0.34 (0.939 g, 29.91%), was identified as **9a**. The analytical sample was obtained by distillation at 135°C / 7.1·10^{-2} Tor. ^{1}H-Nmr($CDCl_3$): 9.37 (1H, s, H(N-1)), 4.24, 4.20 (4H, 2q, J=7.0, 2H_2(OEt)), 3.52 (1H, dd, $J_{5,4a}$=8.9, $J_{5,4b}$=7.3, H(C-5)), 3.43 (2H, s, CH_2(COOR)), 3.01 (1H, dd, $J_{4a,5}$=8.9, $J_{4a,4b}$=17.1, H_a(C-4)), 2.81 (1H, dd, $J_{4b,5}$=7.3, $J_{4a,4b}$=17.1, H_b(C-4)), 1.29 (6H, t, J=7.0, 2H_3(OEt)).
^{13}C-Nmr($CDCl_3$): 169.0, 168.1 (CO_{esters}), 163.7 (C-6), 149.3 (C-3), 62.1, 61.4 ($CH_{2(OEt)}$), 43.1 (C-5), 42.1

(CH_2), 28.0 (C-4), 14.1 ($CH_{3(OEt)}$). Ir: 3300, 2990, 1740, 1690, 1650 cm^{-1}. Uv, λ_{max}(log ε): 245.8(3.815). Ms: m/z 257 (M^++1). *Anal.* Calcd for $C_{11}H_{16}N_2O_5$; C,51.55; H,6.29; N,10.93. Found: C,51.53; H,6.15; N,10.79.

The crystalline fraction, R_f 0.13 (0.571 g, 18.19%), was identified as **6a**, mp 113-114°C (CH_2Cl_2-Et_2O-light petroleum). ^{1}H-Nmr($CDCl_3$): 9.66 (2H, s, H(N-1') and OH(C-3')), 5.68 (1H, s, H(C-4')), 4.35 (4H, q, J=7.0, $2H_2$(OEt)), 3.76 (1H, t, J=7.0, H(C-1)), 3.24 (2H, d, J=7.0, H_2(C-2)), 1.29 (6H, t, J=7.0, $2H_3$(OEt)). ^{13}C-Nmr($CDCl_3$): 168.7 (CO_{esters}), 162.8 (C-3'), 141.7 (C-5'), 90.7 (C-4'), 62.0 ($CH_{2(OEt)}$), 51.6 (C-1), 25.3 (C-2), 13.9 ($CH_{3(OEt)}$). Ir: 3390, 2664, 1735, 1589, 1518 cm^{-1}. Uv, λ_{max}(log ε): 218.8(4.585); 247.2(3.100). Ms: m/z 256 (M^+). *Anal.* Calcd for $C_{11}H_{16}N_2O_5$: C,51.55; H,6.29; N,10.93. Found: C,51.60; H,6.03; N,10.87.

Di-*t*-butyl 2-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-ethanedicarboxylate (6b). To a solution of **5b** (3.228 g, 9.373 mmol), in *t*-BuOH (22 ml), hydrazine monohydrate (0.47 ml, 9.689 mmol) was added. The mixture was refluxed for 3 h, the solvent was evaporated and the residue crystallized from Et_2O-light petroleum to give **6b**; 2.697 g (92.12%), mp 155.5-157°C (EtOAc-Et_2O-light petroleum), R_f 0.43 (Et_2O/light petroleum, 1:1). ^{1}H-Nmr($CDCl_3$): 7.40 (2H, br s, NH and OH), 5.49 (1H, s, H(C-4')), 3.44 (1H, t, J=6.8, H(C-1)), 3.04 (2H, d, J=6.8, H_2(C-2)), 1.44 (18H, s, $6H_3$(OBu-*t*)). ^{13}C-Nmr(acetone-d_6): 167.7 (CO_{esters}), 162.9 (C-3'), 142.0 (C-5'), 89.7 (C-4'), 81.4 (C_{OBu-t}), 53.5 (C-1), 27.4 ($CH_{3(OBu-t)}$, 25.4 (C-2). Ir: 3.405, 2710 br, 1724, 1609, 1568, 1518, 1468 cm^{-1}. Uv, λ_{max}(log ε): 219.1(3.597), 245.2(3.181). *Anal.* Calcd for $C_{15}H_{24}N_2O_5$; C,57.67; H,7.74; N,8.97. Found: C,57.91; H,7.56; N,9.08.

2-(3-Hydroxy-1*H*-pyrazol-5-yl)-1,1-ethanedicarboxylic acid (7). Purification as reported for HIDA.[5] A solution of **6b** (0.947 g, 3.032 mmol) in trifluoroacetic acid (5 ml) was stirred at 4°C overnight and the solvent was evaporated. The residue was dissolved in EtOH and treated with concentrated NH_4OH to a slightly alkaline reaction. Crystalline product (**8b**), was separated and washed with EtOH and Et_2O, and used directly for further reaction. Yield; 0.665 g (93.65%), mp 227-230°C. ^{1}H-Nmr(DMSO-d_6): 5.16 (1H, s, H(C-4')), 3.00 (2H, d, J=5.2, H_2(C-2)), 2.91 (1H, t, J=5.2, H(C-1)). ^{13}C-Nmr(D_2O): 177.2($COONH_4$), 164.7 (C-3'), 149.3 (C-5'), 91.2 (C-4'), 56.7 (C-1), 27.4 (C-2). A solution of **8b** (0.262 g, 1.119 mmol) in water (150 ml) was proposed through a column of Amberlite ir-120 (10 ml) and eluted by water (600 ml). Water was removed under reduced pressure to give **7** as a monohydrate; 0.130 g (53.27%), mp 214-219°C (water). ^{1}H-Nmr(DMSO-d_6): 5.25 (1H, s, H(C-4')), 3.55 (1H, t, J=7.6, H(C-1)), 2.92 (2H, d, J=7.6, H_2(C-2)). ^{13}C-Nmr(D_2O); 170.2 (COOH), 160.5 (C-3'), 141.5 (C-5'), 88.4 (C-4'), 51.5 (C-1), 29.6 (C-2).

Ir: 3300 br, 3130 br, 1965 br, 1687, 1636, 1530 cm^{-1}. Uv(D_2O), λ_{max}(log ε); 220.7(3.598), 246.8(3.103). *Anal.* Calcd for $C_7H_8N_2O_5 \cdot H_2O$; C,38.53; H,4.62; N,12.84. Found: C,38.78; H,4.87; N,12.63.

Diethyl 2-(1-benzyl-5-oxo-2-pyrazolin-3-yl)-1,1-ethanedicarboxylate (10). To a solution of **5a** (0.316 g, 1.096 mmol) and benzylhydrazine dihydrochloride (0.224 g, 1.148 mmol) in 96% EtOH (4 ml) a solution of $NaHCO_3$ (0.212 g, 2.524 mmol) in H_2O (0.8 ml) was added dropwise. The reaction mixture was refluxed for 2.5 h, and the solvent was evaporated. Purification by the preparative tlc (Et_2O) afforded crystalline product, 0.150 g (39.51%), mp 93-94°C (CH_2Cl_2-Et_2O-light petroleum), R_f 0.50 (Et_2O). ^{1}H-Nmr($CDCl_3$): 7.28 (5H, s, $5H_{arom}$), 4.76 (2H, s, CH_2(Bzl)), 4.14 (4H, q, J=7.1, $2H_2$(OEt)), 3.82 (1H, t, J=7.0, H(C-1)), 3.24 (2H, s, H_2(C-4')), 2.95 (2H, d, J=7.0, H_2C(-2)), 1.22 (6H, t, J=7.1, $2H_3$(OEt)). ^{13}C-Nmr($CDCl_3$): 171.7 (CO_{estrs}), 168.4 (C-5'), 155.6 (C-3'), 136.4, 128.5, 128.1, 127.6 (C_{arom}), 61.8 ($CH_{2(OEt)}$), 48.5 (C-1), 47.8 ($CH_{2(Bzl)}$), 40.7 (C-4), 29.9 (C-2), 14.0 ($CH_{3(OEt)}$). Ir: 3450 br, 2400 br, 1737, 1552 cm^{-1} Uv, λ_{max}(log ε): 206.5(3.985), 252.6(3.311) . *Anal.* Calcd for $C_{18}H_{22}N_2O_5$; C,62.41; H,6.40; N,8.09. Found: C,62.53; H,6.15; N,8.01.

5-*t*-Butyl 1-ethyl 2-ethoxycarbonylpentanedioate (11a). To a solution of **4a** (1.79 ml, 11.790 mmol) in *t*-BuOK/*t*-BuOH freshly prepared from 0.460 g (11.766 mmol) K and 7 ml *t*-BuOH, *t*-butyl acrylate (1.0 ml, 6.975 mmol) was added and the mixture was heated under reflux for 2 h, and stirred at room temperature for 17 h. The most of the solvent was evaporated, the residue was partitioned between EtOAc and 20% NH_4Cl; the organic layer was washed with water, dried over Na_2SO_4 and evaporated. Purification of the residue on a silica gel column (light petroleum → 5% Et_2O/ light petroleum) afforded **11a**; 1.70 g (84.53%), R_f 0.58 (Et_2O/ light petroleum, 1:1). ^{1}H-Nmr($CDCl_3$): 4.24 (4H, q, J=7.0, $2H_2$(OEt)), 3.42 (1H, t, J=7.3, H(C-2)), 2.38-2.10 (4H, m, H_2(C-3) and H_2(C-4)), 1.45 (9H, s, $3H_3$(OBu-*t*)), 1.27 (6H, t, J=7.0, $2H_3$(OEt)). ^{13}C-Nmr($CDCl_3$): 170.9, 168.3 (CO_{esters}), 79.7 (C_{OBu-t}), 60.6 ($CH_{2(OEt)}$, 50.1 (C-2), 31.9 (C-4), 23.3 (C-3), 27.4 ($CH_{3(OBu-t)}$), 13.4 ($CH_{3(OEt)}$). Ir: 1750, 1724 cm^{-1}. *Anal.* Calcd for $C_{14}H_{24}O_6$; C,58.31; H,8.39. Found: C,58.54; H,8.28.

5-Benzyl 1-*t*-butyl 2-*t*-butyloxycarbonylpentanedioate (11b). To a solution of **4b** (1.51 g, 6.982 mmol) in dry dioxane (15 ml), 50% NaH (0.336 g, 6.700 mmol) was added and the mixture was stirred at a room temperature for 30 min. Benzyl 3-bromopropionate (1.69 g, 6.999 mmol) was added dropwise and the stirring was continued for 2 days. The workup was run as described for **11a**. Yield; 1.607 g (61.08%), R_f 0.44 (Et_2O/ light petroleum, 1:3). ^{1}H-Nmr($CDCl_3$): 7.34 (5H, s, H_{arom}), 5.12 (2H, s, H_2(Bzl)), 3.22 (1H,

t, J=7.4, H(C-2)), 2.44 (2H, t, J=7.4, H_2(C-4)), 2.15 (2H, q, J=7.4, H_2(C-3)), 1.45 (18H, s, $6H_3$(OBu-*t*)). ^{13}C-Nmr($CDCl_3$): 171.5, 167.6 (CO_{esters}), 135.4, 127.9, 127.5 (C_{arom}), 80.7 (C_{OBu-t}), 65.5 ($CH_{2(Bzl)}$), 57.0 (C-2), 30.8 (C-4), 27.2 ($CH_{3(OBu-t)}$), 23.0 (C-3). Ir: 1740, 1725, 1599, 1583 cm^{-1}. Uv, λ_{max}(log ε); 212.8 (3.622). *Anal.* Calcd for $C_{21}H_{30}O_6$; C,66.64; H,7.99. Found: C,66.71; H,7.81.

6-Benzyl 1-*t*-butyl 2-*t*-butyloxycarbonylhexanedioate (11c). To a solution of **4b** (3.246 g, 15.008 mmol) in DMF (30 ml), 50% NaH (0.726 g, 15.122 mmol) was added and the mixture was stirred at room temperature for 30 min. Benzyl 4-bromobutanoate (3.246 g, 12.624 mmol) was added and the stirring was continued for 18 h, and worked up as described for **11a**. Yield; 3.354 g (67.69%), R_f 0.62 (Et_2O/ light petroleum, 1:1). ^{1}H-Nmr($CDCl_3$): 7.34 (5H, s, H_{arom}), 5.11 (2H, s, H_2(Bzl)), 3.13 (1H, t, J=7.3, H(C-2)), 2.39 (2H, t, J=7.3, H_2(C-5)), 1.88-1.79, 1.74-1.62 (4H, 2m, H_2(C-3) and H_2(C-4)), 1.45 (18H, s, $6H_3$(OBu-*t*)). ^{13}C-Nmr($CDCl_3$): 172.2, 168.1 (CO_{esters}), 135.6, 128.0, 127.7 (C_{arom}), 80.8 (C_{OBu-t}), 65.6 ($CH_{2(Bzl)}$), 53.1 (C-2), 33.35 (C-5), 27.5 ($CH_{3(OBu-t)}$), 27.5, 22.20 (C-3 and C-4). Ir: 1740, 1728 cm^{-1}. Uv, λ_{max}(log ε); 209.9(3.863). *Anal.* Calcd for $C_{22}H_{32}O_6$; C,67.32; H,8.22. Found: C,67.54; H,7.99.

4,4-Diethoxycarbonylbutanoic acid (12d). A solution of **11a** (0.682 g, 2.365 mmol) in tifluoroacetic acid (3 ml) was stirred at 4°C for 18 h. The solvent was evaporated. Purification by the preparative tlc (Et_2O) gave **12d**; 0.472 g (85.93%), R_f 0.45 (Et_2O). ^{1}H-Nmr($CDCl_3$): 9.05 (1H, br s, COOH), 4,21 (4H, q, J=7.1, $2H_2$(OEt)), 3.47 (1H, t, J=7.4, H(C-4)), 2.47 (2H, t, J=7.4, H_2(C-2)), 2.21 (2H, q, J=7.4, H_2(C-3)), 1.28 (6H, t, J=7.1, $2H_3$(OEt)). ^{13}C-Nmr($CDCl_3$): 177.2 (C-1), 168.4 (CO_{esters}), 60.9 ($CH_{2(OEt)}$), 50.2 (C-4), 30.5 (C-2), 27.9 (C-3), 13.3 ($CH_{3(OEt)}$). Ir: 3250 br, 1730 br cm^{-1}. *Anal.* Calcd for $C_{10}H_{16}O_2$; C,51.72; H,6.94. Found: C,51.92; N,6.99.

General Procedure for the Preparation of β-keto esters (**13a**, **13b** and **13c**). To a solution of carboxylic acid (**12d-f**) (1 mmol) in dry THF (5 ml), cooled to 0°C, *N,N'*-carbonyldiimidazole (0.195 g, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 17 h. A solution of ethyl hydrogen malonate (0.199 g, 1.5 mmol) in dry THF (3 ml), under argon, was cooled to 0°C, and 2N *i*-PrMgCl (1.5 ml, 3 mmol) was added. The reaction mixture was stirred at 0°C for 30 min, at room temperature for 1.5 h and at 40°C for 30 min. This solution was added to the cooled (0°C) imidazolide solution and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ice cooled solution of 20% NH_4Cl and EtOAc, the organic layer washed with brine and dried over $NaSO_4$. The solvent was removed under reduced pressure, and the product was purified by preparative tlc

(Et_2O/light petroleum, 4:5 for **13a** or 1:4 for **13b** and **13c**).

Triethyl 4-oxo-1,1,5-pentanetricarboxylate (13a).[13] From **12d**; oil, 54.47%, R_f 0.15 (Et_2O/ light petroleum, 4:5). ^{1}H-Nmr ($CDCl_3$): 4.19 (6H, q, J=7.1, $3H_2$(OEt)), 3.43 (2H, s, H_2(C-5)), 3.40 (1H, t, J=7.3, H(C-1)), 2.68 (2H, t, J=7.3, H_2(C-3)), 2.18 (2H, q, J=7.3, H_2(C-2)), 1.28, 1.27 (9H, each t, J=7.1, $3H_3$(OEt)). ^{13}C-Nmr($CDCl_3$): 200.3 (C-4), 168.3, 166.4 (CO_{esters}), 60.7, 60.6 ($CH_{2(OEt)}$), 59.9 (C-1), 48.5 (C-5), 39.2 (C-3), 21.7 (C-2), 13.4 ($CH_{3(OEt)}$). Ir: 1730 br, 1640 br cm^{-1}. Uv, λ_{max}(log ε); 244.0(3.017). *Anal.* Calcd for $C_{14}H_{22}O_7$; C,55.62; H,7.34. Found: C,55.86; N,7.21.

1-*t*-Butyl 7-ethyl 2-*t*-butyloxycarbonyl-5-oxoheptanedioate (13b). A solution of **11b** (2.81 g, 7.425 mmol) in EtOAc (60 ml) was hydrogenated over 10% Pd/C (0.140 g) at room temperature and 2.1 kTor for 18 h. The catalyst was filtered off and the filtrate evaporated to give 4,4-di-*t*-butyloxycarbonylbutanoic acid(**12e**)(2.033 g) which was used directly for further reaction. From **12e** (general procedure); 66.70%, R_f 0.30 (Et_2O/ light petroleum, 1:4), oil. ^{1}H-Nmr($CDCl_3$): 4.19 (2H, q, J=7.1, H_2(OEt)), 3.44 (2H, s, H_2(C-6)), 3.18 (1H, t, J=7.2, H(C-2)), 2.65 (2H, t, J=7.2, H_2(C-4)), 2.09 (2H, q, J=7.2, H_2(C-3)), 1.46 (18H, s, $6H_3$(OBu-*t*)), 1.28 (3H, t, J=7.1, H_3(OEt)). ^{13}C-Nmr($CDCl_3$): 201.4 (C-5), 168.1, 166.8 (CO_{esters}), 81.4 ($C_{(OBu\text{-}t)}$), 61.1 ($CH_{2(OEt)}$), 52.3 (C-2), 49.1 (C-6), 39.7 (C-4), 27.7 ($CH_{3(OBu\text{-}t)}$), 22.0 (C-3), 13.8 ($CH_{3(OEt)}$). Ir: 1720 br, 1630 br cm^{-1}. Uv, λ_{max}(log ε); 244.0(3.100). *Anal.* Calcd for $C_{18}H_{30}O_7$; C,60.31; H,8.44. Found: C,60.41; H,8.37.

1-*t*-Butyl 8-ethyl 2-*t*-butyloxycarbonyl-6-oxooctanedioate (13c). A solution of **11c** (1.417 g, 3.610 mmol) in EtOAc (35 ml) was hydrogenated as described for **11b** to give 5,5-di-*t*-butyloxycarbonylpentanoic acid (**12f**) which was used directly for further reaction. From **12f** (general procedure): 89.46%, oil, R_f 0.45 (Et_2O/ light petroleum, 1:4). ^{1}H-Nmr($CDCl_3$): 4.20 (2H, q, J=7.1, H_2(OEt)), 3.43 (2H, s, H_2(C-7)), 3.12 (1H, t, J=7.2, H(C-2)), 2.58 (2H, t, J=7.2, H_2(C-5)), 1.84-158, 1.68-158 (4H, 2m, H_2(C-3) and H_2(C-4)), 1.46 (18H, s, $6H_3$(OBu-*t*)), 1.28 (3H, t, J=7.1, H_3(OEt)). ^{13}C-Nmr($CDCl_3$): 201.5 (C-6), 168.1, 166.7 (CO_{esters}), 80.8 ($C_{(OBu\text{-}t)}$), 60.8 ($CH_{2(OEt)}$), 53.2 (C-2), 48.8 (C-7), 41.9 (C-5), 27.4 ($CH_{3(OBu\text{-}t)}$, 27.4, 20.5 (C-3, C-4), 13.6 ($CH_{3(OEt)}$). Ir: 1730 br, 1640 br cm^{-1}. Uv, λ_{max}(logε); 244.5(3.143). *Anal.* Calcd for $C_{19}H_{32}O_7$; C,61.27; H,8.66. Found: C,61.26; H,8.42.

General procedure for the preparation of pyrazolone (**14a, 14b** and **14c**). To a solution of **3a-c** (1 mmol) in 96% EtOH (2 ml) for **14a** or *t*-BuOH (3 ml) for **14b** and **14c**, hydrazine monohydrate (0.056 g, 1.1

mmol) was added. The mixture was stirred at room temperature for 17 h. The crystalline product was separated by filtration and washed with EtOH and Et_2O (for **14a**), or the solvent was evaporated and the residue crystallized from Et_2O-light petroleum (for **14b** and **14c**).

Diethyl 3-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-propanedicarboxylate (14a). From **13a**; 73.64%, mp 139-140°C (EtOH-Et_2O), R_f 0.14 (Et_2O). ^{1}H-Nmr(py-d_5): 5.80 (1H, s, H(C-4')), 4.16, 4.15 (4H, each q, J=7.1, $2H_2$(OEt)), 3.80 (1H, t, J=7.4, H(C-1)), 2.92 (2H, t, J=7.4, H_2(C-3)), 2.55 (2H, q, J=7.4,, H_2(C-2)), 1.10 (6H, t, J=7.1, $2H_3$(OEt)). ^{13}C-Nmr(*DMSO*-d_6): 168.7 (CO_{esters}), 160.6 (C-3), 143.2 (C-5'), 88.1 (C-4'), 61.0 ($CH_{2(OEt)}$), 50.6 (C-1), 27.7, 23.4 (C-2 and C-3), 13.9 ($CH_{3(OEt)}$). Ir: 3340, 3130, 2605 br, 1744, 1723, 1585, 1524 cm^{-1}. Uv, λ_{max}(log ε); 217.9(3.597), 245.2(3.295). *Anal.* Calcd for $C_{12}H_{18}N_2O_5$; C,53.32; H,6.71; N,10.37. Found: C,53.59; H,6.70; N,10.20.

1,1-Di-*t*-butyl 3-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-propanedicarboxylate (14b). From **13b**; 97.35%, mp 154-155°C (CH_2Cl_2-light petroleum), R_f 0.23 (Et_2O). ^{1}H-Nmr($CDCl_3$): 9.22 (2H, br s, NH and OH), 5.46 (1H, s, H(C-4')), 3.18 (1H, t, J=7.4, H(C-1)), 2.61 (2H, t, J=7.4, H_2(C-3)), 2.11 (2H, q, J=7.4, H_2(C-2)), 1.46 (18H, s, $6H_3$(OBu-*t*)). ^{13}C-Nmr(DMSO-d_6): 167.9 (CO_{esters}), 160.6 (C-3'), 143.3 (C-5'), 88.0 (C-4'), 80.81 (C_{OBu-t}), 52.4 (C-1), 27.5 ($CH_{3(OBu-t)}$, 27.5, 23.3 (C-2 and C-3). Ir: 3420 br, 2710 br, 1743, 1720, 1622, 1545 br, 1500 br, 1450 br cm^{-1}. Uv, λ_{max}(log ε); 219.3(3.591), 242.6(3.249). *Anal.* Calcd for $C_{16}H_{26}N_2O_5$; C,58.88; H,8.03; N,8.58. Found: C,59.05; H,7.86; N,8.36.

1,1-Di-*t*-butyl 4-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-butanedicarboxylate (14c). From **13c**; 88.76%, mp 141-143°C (CH_2Cl_2-light petroleum), R_f 0.22 (Et_2O). ^{1}H-Nmr(DMSO-d_6): 5.33 (1H, s, H(C-4')), 3.30 (1H, t, J=7.4, H(C-1)), 2.56 (2H, t, J=7.2, H_2(C-4)), 1.82-1.72, 1.66-1.56 (4H, 2m, H_2(C-2) and H_2(C-3)), 1.51 (18H, s, $6H_3$(OBu-*t*)). ^{13}C-Nmr(DMSO-d_6): 168.2 (CO_{esters}), 160.8 (C-3'), 143.8 (C-5'), 87.8 (C-4'), 80.7 (C_{OBu-t}), 52.8 (C-1), 27.5 ($CH_{3(OBu-t)}$), 27.5 , 26.1, 25.3 (C-2, C-3 and C-4). Ir: 3390, 2660 br, 1742, 1725, 1581, 1510, 1457 cm^{-1}. Uv, λ_{max}(log ε); 218.9(3.632), 243.7(3.421). *Anal.* Calcd for $C_{17}H_{28}N_2O_5$; C,59.98; H,8.29; N,8.23. Found: C,60.26; H,8.10; N,8.43.

Generale procedure for the preparation of disodium pyrazolonedicarboxylates (**8a**, **16f**, and **16g**). A solution of **6b**, **14b,c** (1 mmol) in trofluoroacetic acid (3 ml) was stirred at 4°C for 17 h, and the solvent was evaporated. The residue was dissolved in EtOH (8 ml) and treated with 2N NaOH to the slightly alkaline reaction, stirred 30 min and allowed to cool (4°C). The solid was filtered off and washed with

EtOH and Et_2O to give **8a**, **16f** and **16g**.

Disodium 2-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-ethanedicarboxylate (8a). From **6b**; 84.88%; ^{1}H-nmr(DMSO-d_6): 5.18 (1H, s, H(C-4')), 3.02 (2H, d, J=4.9, H_2(C-2)), 2.95 (1H, t, J=4.9, H(C-1)). ^{13}C-Nmr(D_2O): 178.3 (COONa), 164.3 (C-3'), 148.7 (C-5'), 91.2 (C-4'), 54.2 (C-1), 27.0(C-2'). Ir: 3400 br, 2925 br, 2740 br, 2580 br, 1720, 1628, 1595, 1542, 1520 cm^{-1}. Uv(H_2O), λ_{max}(log ε); 240.8(3.902). *Anal.* Calcd for $C_7H_6N_2O_5Na_2 \cdot H_2O$; C,32.07; H,3.08; N,10.69. Found: C,31.93; H,3.26; N,10.62.

Disodium 3-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-propanedicarboxylate (16f). From **14b**; 67.37%; ^{1}H-nmr(DMSO-d_6): 5.24 (1H, s, H(C-4')), 2.95 (1H, t, J=6.1, H(C-1)), 2.45 (2H, t, J=8.1, H_2(C-3)), 2.04-1.95 (2H, m, H_2(C-2)). ^{13}C-Nmr(D_2O): 176.1 (COONa), 163.2 (C-3'), 150.7 (C-5'), 91.1 (C-4'), 53.0 (C-1), 28.4 (C-3), 24.4 (C-2). Ir: 3430 br, 2900 br, 2600 br, 1720, 1712, 1610, 1540, 1498 cm^{-1}. Uv(H_2O), λ_{max}(log ε); 237.7(3.889). *Anal.* Calcd for $C_8H_8N_2O_5Na_2 \cdot 2H_2O$; C,32.66; H,4.11; N,9.52. Found: C,32.62; H,4.35; N,9.56.

Disodium 4-(3-hydroxy-1*H*-pyrazol-5-yl)-1,1-butanedicarboxylate (16g). From **14c**; 81.01%; ^{1}H-nmr(DMSO-d_6): 5.19 (1H, s, H(C-4')), 2.69 (1H, t, J=5.6, H(C-1)), 2.39 (2H, t, J=7.69, H_2(C-4)),1.80-1.74, 1.53-1.45 (4H, 2m, H_2(C-2) and H_2(C-3)). ^{13}C-Nmr(D_2O): 174.5 (COONa), 164.6 (C-3'), 151.8 (C-5'), 91.2 (C-4'), 53.7 (C-1), 29.6, 26.3, 26.2 (C-2, C-3 and C-4). Ir: 3430 br, 2730 br, 2590 br, 1710, 1625, 1591, 1545, 1500 cm^{-1}. Uv(H_2O), λ_{max}(log ε); 238.8(3.896). *Anal.* Calcd for $C_9H_{10}N_2O_5Na_2$; C,39.71; H,3.70; N,10.29. Found: C,39.59; H,3.92; N,10.22.

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