SYNTHESIS AND REACTIONS OF BIGINELLI-COMPOUNDS, PART II.[1] NITRATION OF 6-METHYL-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATES

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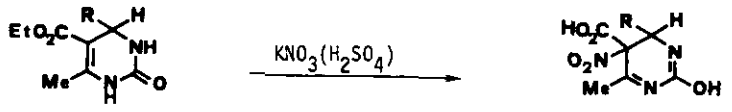
Abstract - The nitration of tetrahydro-5-pyrimidinecarboxylates (Biginelli-Compounds[2]) **1** and **4** does not yield 5-nitro-dihydro-5-pyrimidinecarboxylic acids **2a,b** as assumed earlier, but affords the corresponding 5-nitro-4-nitromethylidene-hexahydro-5-pyrimidinecarboxylates **3**. Single-crystal X-ray studies show that **3a** exists in the intramolecularly H-bondend (Z)-configurated form, whereas nmr spectra indicate that **3a** can exist in both (Z)- and (E)-configurated forms, depending on the solvent used.

The nitration of ethyl 6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate **1a** with potassium nitrate in concentrated sulfuric acid was reported in 1952 by *Khromov-Borisov and Savchenko* [3] and the compound obtained was assigned the structure of a 2-hydroxy-4-methyl-5-nitro-5,6-dihydro-5-pyrimidine-carboxylic acid **2a**. From our point of view the structure proposed by the authors seemed to be rather unlikely, involving a free α-nitrocarboxylic acid and a hydroxy group in 2 position of the pyrimidine ring.

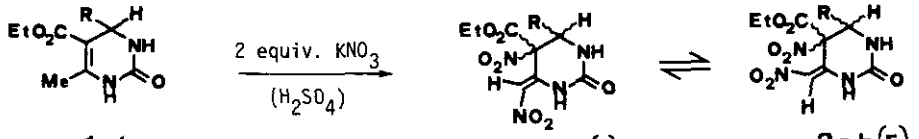


1a, 4
R = H,Ph

2a,b
R = H,p-NO_2Ph

Khromov-Borisov and Savchenko, 1952

Therefore, we repeated the experiments under the same conditions as given by the authors and obtained a compound which was in all respects identicall with the compound obtained by them (see Experimental). The ^{1}H nmr spectrum shows a triplet at δ=1.35 and a quadruplet at δ=4.53 ppm (J=7.2 Hz) representing an ethyl group, which clearly outrules structure **2a** for the nitration product. In addition the mass spectrum shows a peak for M^+ at m/z 274, indicating a dinitrated product (in accordance with the elemental analysis). For that reason we concluded structure **3a** to be the correct one, although the stereochemistry on the exocyclic doublebond remained uncertain.



1a,b R = H,Me

3a,b(Z) **3a,b(E)**

To clarify the situation an X-ray structure determination of **3a** was carried out[4]. Figure 1 shows the solid-state structure of **3a** along with the atom numbering scheme; all atomic parameters, bond lenghts and angles can be depicted from Tables 2 and 3. Most bond lenghts are within the expected regions, the length of the intramolecular hydrogen bridge N(1)-H...O(19) is 1.910A. In the crystal the molecules are associated *via* N(3)-H....O(7') and N(1)-H....O(12')

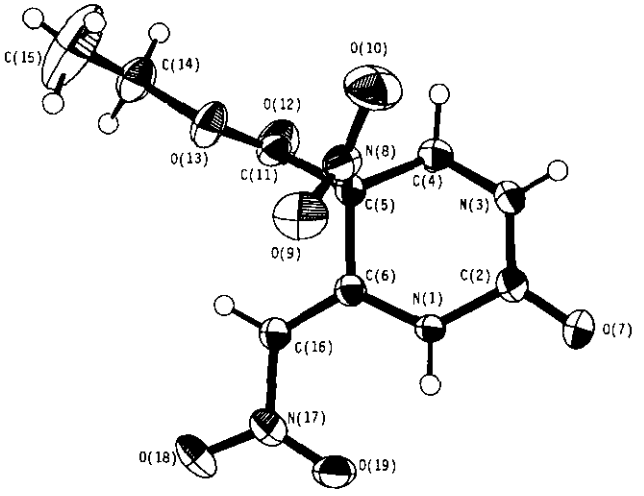


Figure 1: ORTEP drawing of the solid-state structure of **3a**

hydrogen bridge bindings (1.867 and 2.270A). As we expected the X-ray data show (Z)-configuration for the solid-state of **3a**. The (E)-configurated form **3a(E)** would be expected to be sterically unfavourable. However, the ^{1}H and ^{13}C nmr spectra of **3a** indicated a mixture of two species depending on the solvents used. In acetone-d_6, **3a** exists as a single species, the (Z)-isomer with intramolecular H-bonding. In DMSO-d_6 the (Z)- and (E)-isomers were observed simultaneously in a ratio of about Z:E ≈ 9:1. To our knowledge the effect of solvent-dependent (Z)/(E) isomerisation in 2-(nitromethylidene)heterocycles has been observed only in the case of 2-(nitromethylidene)thiazolidine and was recently studied in detail by *von Philipsborn et al.*[5] The most distinct signal in the ^{1}H nmr spectrum of **3a** is due to the olefinic proton, observed at δ= 6.92 for the (Z)- and δ≈ 7.37 ppm for the (E)-isomer (in DMSO-d_6). These values are in good agreement with the chemical shifts given by *von Philipsborn et al.* for similar nitroenamines [5]. Table 1 shows the ^{1}H and ^{13}C chemical shifts for **3a** in acetone-d_6 and DMSO-d_6. The chemical shifts of the ethyl group are also changed significantly during the (Z)/(E)-isomerisation, due to the effect of the nitro group, which is directed towards the ester group in **3a(E)**. In the ^{13}C nmr the changes effect almost all carbon atoms. The data show that in **3a(E)** the olefinic carbon atoms are deshielded and the C5-atom is shielded compared to the situation in **3a(Z)**. The assignement of signals was made on the basis of chemical shift values and long range coupling constants. One must consider that the higher polarity (higher dielectric constant) of DMSO favours the (E)-isomer because of an disruption of the intramolecular H-bonding in the (Z)-isomer in favour of intermolecular bonding. In solvents with lower dielectric constants

Table 1: ^{1}H and ^{13}C Chemical Shifts (δ, [ppm]) of **3a**

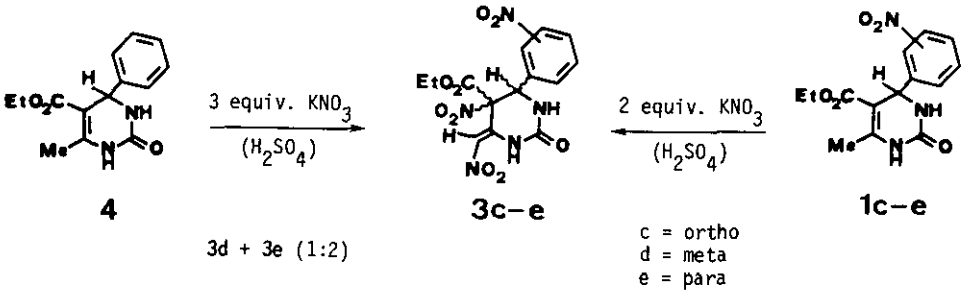
		protons					
solvent		ethyl CH_3	C6-H	ethyl CH_2	=CH-NO_2	N1-H	N3-H
acetone-d_6	Z	1.36	4.46	4.53	6.86	7.44	10.07
DMSO-d_6	Z	1.26	4.39	4.43	6.92	8.45	-
	E	1.16	4.39	4.19	7.37	8.45	-

		carbons							
solvent		CH_2CH_3	C6	CH_2CH_3	C5	=CH-	C4	C2	$CO_2C_2H_5$
acetone-d_6	Z	19.8	51.7	72.2	97.5	124.1	146.6	155.5	167.9
DMSO-d_6	Z	13.3	44.2	65.3	90.6	117.0	139.4	148.7	160.6
	E	13.3	46.4	63.7	88.4	120.1	143.7	151.2	159.9

(acetone) the (Z)-isomer is the only one observed. However, due to the energy gained by steric release of the interaction between the olefinic nitro group and the ester- and nitro-groups on C5 in the (E)-configuration, **3a** exists predominantly in the (Z)-configurated form (≈90%) even in solvents with high dielectric constants.

We also used ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate **1b** as starting material, and obtained the expected 6-methyl analog **3b** as product.

Khromov-Borisov and Savchenko [3] also stated in their paper that ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate **4** would yield the corresponding p-nitrophenyl derivative **2b**. Our investigations showed that this compound, obtained upon nitration of **4** with three equivalents of potassium nitrate, is a mixture of **3d** and **3e**.



The ratio of m-nitrophenyl- (**3d**) to p-nitrophenyl- (**3e**) derivative (≈1:2) was determined by nmr studies, based upon the relative intensity of proton signals in the aromatic and olefinic regions (see Experimental). Any attempt to seperate the two isomers by recrystallization or chromatographic techniques failed. However, the three possible mononitrophenyl regioisomers **3c-e** can be obtained independently upon nitration of the three corresponding ethyl 6-methyl-4-nitrophenyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylates **1c-e** (prepared by classical Biginelli condensation[6,7]), using two equivalents of potassium nitrate. The effect of (Z)/(E)-isomerisation in solvents with high polarity is also observed in compounds **3b-e**, which have to be considered as diastereoisomeric mixtures, since the starting materials **1b-e** are applied as racemic mixtures.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus Mod.MFB-595 and are uncorrrected. CHN - elemental analyses were performed on a Carlo Erba Elemental Analyzer Model 1106, Ir spectra were recorded on a Perkin-Elmer 298 spectrophotometer using samples in potassium bromide disks. ^{1}H and ^{13}C nmr spectra were obtained either on a Varian XL-200 or XL-300 spectrometer in the solvents indicated. Chemical shifts (δ) are expressed in ppm downfield from TMS used as internal standard. The letters b, s, d, t, q and m are used to indicate broad, singlet, doublet, triplet, quadruplet and multiplet, respectively. Mass spectra were obtained on a Finnigan mass spectrometer 4500 at 70eV (EI) using a direct inlet system. Uv spectra were recorded in aqueus solution (c= $1.00x10^{-4}$M, pH=2.9) on a Perkin-Elmer UV/VIS spectrophotometer Model lamda 5.

Compounds **1a-e** and **4** were prepared according to Ref. 6, except for **1c**[7].

Synthesis of 6-(Un)substituted 5-nitro-4-(Z)-nitromethylidene-2-oxo-hexahydro-5-pyrimidinecarboxylates 3a-e.

General procedure:

To a solution of 20 mmol of starting material **1a-e** in 25 ml of concentrated sulfuric acid a solution of 4.15 g of potassium nitrate (41 mmol) in 22 ml of concentrated sulfuric acid was added portionwise keeping the temperature below 5°C, while stirring in an ice-bath. After one hour of stirring at room temperature the mixture was poured into 500 ml of ice-water. The precipitated solids were filtered and recrystallized from ethanol to give the corresponding nitromethylidenepyrimidines **3a-e**.

3a: 4.24 g (78%), mp 142-143°C(lit.[3] mp142.5-143.5°C).- Ir: ν 3300, 3240, 3130, 1765, 1755, 1705, 1645, 1585, 1370, 1260 cm^{-1}. Ms: m/z (relative intensity) M^{+} 274 (12), 227 (14), 181 (21), 155 (23), 139 (100), 123 (15), 110 (18), 95 (58). ^{1}H Nmr (acetone-d_6): δ 1.36 (t, 3H, J=7.2Hz, ethyl CH_3), 4.46 (m, 2H, C6-H), 4.53 (q, 2H, J=7.2Hz, ethyl CH_2), 6.86 (s, 1H, =CH), 7.44 (b, 1H, N1-H), 10.07 ppm (b, 1H, N3-H). ^{13}C Nmr (acetone-d_6): δ 19.8 (q, J=127Hz, $CH_2\underline{C}H_3$), 51.7 (t,J=148Hz, C6), 72.2 (t, J=148Hz, $\underline{C}H_2CH_3$), 97.5 (s, C5), 124.1 (d, J=196Hz,

=CH-NO_2), 146.6 (s, C4), 155.5 (s, C2), 167.9 ppm (s, -CO_2Et). Uv: λ 205 (ε = 7550), 330 (ε = 9480) nm. Anal. Calcd for $C_8H_{10}N_4O_7$: C, 35.05; H, 3.68; N, 20.43; Found: C, 35.00; H, 3.54; N, 20.60. Anal. Calcd for $C_6H_7N_3O_5$ **2a**[9]: C, 35.82; H, 3.48; N, 20.89; Found: C, 35.83, 35.70; H, 3.67, 3.66; N, 20.74, 20.79.

3b: 4.95 g (86%), mp 144-145°C. Ir: ν 3320, 3240, 3130, 1765, 1730, 1640, 1580, 1360, 1275 cm^{-1}. Ms: m/z (relative intensity) M^+ 288 (31), 242 (28), 228 (33), 212 (30), 196 (30), 182 (43), 170 (70), 153 (100). ^1H Nmr (acetone-d_6): δ 1.33 (t, 3H, J=7.2Hz, ethyl CH_3), 1.58 (d, 3H, J=7.2Hz, C6 CH_3), 4.50 (q, 2H, J=7.2Hz, ethyl CH_2), 4.76 (dq, 1H, J=7.2 and 2.4Hz, C6-H), 7.01 (s, 1H, =CH), 7.55 (b, 1H, N1-H), 10.08 ppm (b, 1H, N3-H). Anal. Calcd for $C_9H_{12}N_4O_7$: C, 37.51; H, 4.20; N, 19.44; Found: C, 37.41; H, 4.18; N, 19.05.

3c: 6.06 g (77%), mp > 144°C (decomp.). Ir: ν 3370, 3310, 3150, 1760, 1735, 1625, 1575, 1525, 1450, 1430, 1340 cm^{-1}. ^1H Nmr (acetone-d_6): δ 1.02 (t, 3H, J=7.2Hz, ethyl CH_3), 4.08-4.34 (m, 2H, ethyl CH_2), 6.84 (m, 1H, C6-H), 6.90 (s, 1H, =CH), 7.71 (b, 1H, N3-H), 7.70-7.98 (m, 3H, ArH), 8.16 (d, 1H, J=8.8Hz, ArH), 10.30 ppm (b, 1H, N1-H). Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.54; H, 3.32; N, 17.72; Found: C, 42.55; H, 3.41; N, 17.50.

3d: 5.69 g (72%), mp > 139°C (decomp.). Ir: ν 3305, 3220, 3130, 1740, 1720, 1630, 1570, 1525, 1420, 1345 cm^{-1}. ^1H Nmr (acetone-d_6): δ 1.09 (t, 3H, J=7.2Hz, ethyl CH_3), 4.17-4.36 (m, 2H, ethyl CH_2), 6.17 (m, 1H, C6-H), 7.16 (s, 1H, =CH), 7.79 (t, 1H, J=8.0Hz, ArH), 8.02 (d, 1H, J=8.0Hz, ArH), 8.16 (b, 1H, N1-H), 8.33 (dq, 1H, J=8.0 and 2.1Hz, ArH), 8.40 (t, 1H, J=2.1Hz, ArH), 10.31 (b, 1H, N3-H). Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.54; H, 3.32; N, 17.72; Found: C, 42.58; H, 3.46; N, 17.50.

3e: 5.90 g (75%), mp > 145°C (decomp.). Ir: ν 3295, 3120, 1730, 1635, 1580, 1520, 1345 cm^{-1}. ^1H Nmr (acetone-d_6): δ 1.09 (t, 3H, J=7.2Hz, ethyl CH_3), 4.17-4.36 (m, 2H, ethyl CH_2), 6.10 (m, 1H, C6-H), 7.17 (s, 1H, =CH), 7.85 (dd, 2H, J=9.0 and 2.1Hz, ArH), 8.01 (b, 1H, N1-H), 8.31 (dd, 2H, J=9.0 and 2.1Hz, ArH), 10.31 ppm (b, 1H, N3-H). Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.54; H, 3.32; N, 17.72; Found: C, 42.44; H, 3.45; N, 17.43.

Nitration of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate 4 [3].

To a solution of 5.2 g of **4** (20mmol) in 30 ml of concentrated sulfuric acid a solution of 6.60g (65mmol) of potassium nitrate in 30 ml of concentrated sulfuric acid was added portionwise, keeping the temperature below 5°C while stirring in an ice-bath. After one hour of stirring at room temperature the mixture was poured into 1000 ml of ice-water and the precipitated solid was collected by filtration to give 7.62 g (96%) of crude product, mp > 135°C (decomp.) (lit.[3], 133.5-134.5°C). This product was shown to be a mixture of the p-nitrophenyl- and m-nitrophenyl-pyrimidines **3e** and **3d** by ^{1}H nmr studies (p/m ≈ 2:1). However, any attempt to seperate the two isomers by recrystallization or chromatographic techniqes failed. ^{1}H Nmr (acetone-d_6): δ 1.09 (t, 3H, J=7.2Hz, ethyl CH_3), 4.17-4.36 (m, 2H, ethyl CH_2), 6.10, 6.17 (2m, 1H, C6-H), 7.16, 7.17 (2s, 1H, =CH), 7.79-8.40 (m, 5H, ArH, N1-H), 10.31 (b, 1H, N3-H). Anal. Calcd for $C_{14}H_{13}N_3O_6$: C, 42.54; H, 3.32; N, 17.72; Found: C, 42.60, 42.49; H, 3.15, 3.24; N, 17.34, 17.61.

X-Ray Analysis Data for 3a. The crystallographic analysis of a colorless crystal (0.3x0.3x0.3 mm) obtained by slow crystallization from methanol was performed on a locally modified Stoe four-circle diffractometer with graphite monochromatized MoK$_\alpha$ radiation (λ=0.71069 A) in the ω-scan mode. Cell constants were determined by a least-squares fit to the diffractometer setting angles of 33 reflections with 7≤ 2θ ≤ 16°. Crystal Data: $C_8H_{10}N_4O_7$ (274.19), space group P1, a = 6.477(4), b = 7.230(5), c = 13.219(13) A, α = 98.05(6), β = 97.39(5), γ = 105.72(5)°, V = 581.1(0.5) A^3, Z = 2. The measured intensities were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved on the basis of 1741 significant reflections (I≥3σ(I), 2θ range = 3-60°) using direct methods. All non-hydrogen atoms were refined with anisotropic, hydrogen atoms with isotropic temperature coefficients. All hydrogen atoms were located from a difference Fourier synthesis. Bonded C-H and N-H distances were constrained in the terminal refinement cycles (C-H 1.08A, N-H 1.05A). The refinement converged at a residual of R = 0.074 (214 parameters, 1751 observations). A final difference map showed no significant residual electron density. The computer programs used (some in locally modified versions) are summerized in Ref. 8.

Table 2: Bond lenghts [Å] and bond angles [°] involving nonhydrogen atoms of **3a**.

N(1) - C(2)	1.414(6)	C(2) - N(3)	1.332(5)	N(3) - C(4)	1.453(6)
C(4) - C(5)	1.533(7)	C(5) - C(6)	1.525(5)	N(1) - C(6)	1.372(5)
C(2) - O(7)	1.222(5)	C(5) - N(8)	1.540(5)	N(8) - O(9)	1.220(6)
N(8) - O(10)	1.210(5)	C(5) - C(11)	1.551(6)	C(11) - O(13)	1.309(5)
O(13) - C(14)	1.474(7)	C(14) - C(15)	1.462(10)	C(6) - C(16)	1.346(6)
C(16) - N(17)	1.435(5)	N(17) - O(18)	1.231(6)	N(17) - O(19)	1.235(5)
C(11) - O(12)	1.192(6)				

C(2) - N(1) - C(6)	126.6(3)	N(1) - C(2) - N(3)	115.8(4)
N(1) - C(2) - O(7)	118.2(3)	N(3) - C(2) - O(7)	126.0(4)
C(2) - N(3) - C(4)	122.2(4)	N(3) - C(4) - C(5)	109.6(4)
C(4) - C(5) - C(6)	109.5(3)	C(4) - C(5) - N(8)	109.6(3)
C(4) - C(5) - C(11)	109.4(4)	C(6) - C(5) - N(8)	107.5(3)
C(6) - C(5) - C(11)	112.1(3)	N(1) - C(6) - C(16)	125.8(3)
C(5) - C(6) - C(16)	119.6(4)	C(5) - N(8) - O(9)	118.2(3)
C(5) - N(8) - O(10)	117.5(4)	O(9) - N(8) - O(10)	124.3(4)
C(5) - C(11) - O(12)	120.9(4)	C(5) - C(11) - O(13)	111.5(4)
O(12) - C(11) - O(13)	127.6(4)	C(11) - O(13) - C(14)	116.9(4)
O(13) - C(14) - C(15)	106.6(7)	C(6) - C(16) - N(17)	123.6(4)
C(16) - N(17) - O(19)	119.0(4)	O(18) - N(17) - O(19)	124.1(4)
C(16) - N(17) - O(18)	117.0(4)		

Table 3: Atomic coordinates and thermal parameters [Å²] for nonhydrogen atoms (x 10^4) and hydrogen atoms (x 10^3) of **3a**.

Atom	X/a	Y/b	Z/c	U_{eq}	Atom	X/a	Y/b	Z/c	U_{iso}
N(1)	679(5)	4764(4)	6283(3)	270(19)	H -N(1)	-35(5)	355(2)	626(3)	21(10)
C(2)	2481(6)	4942(6)	5762(3)	288(22)	H -N(3)	503(6)	692(8)	539(4)	62(16)
N(3)	3717(6)	6759(5)	5795(3)	353(22)	H1-C(4)	186(6)	872(6)	552(3)	39(13)
C(4)	3001(7)	8456(6)	6114(4)	337(25)	H2-C(4)	441(5)	973(4)	629(4)	52(15)
C(5)	1950(6)	8215(5)	7081(3)	259(20)	H1-C(14)	-94(1)	1196(8)	864(5)	77(20)
C(6)	199(6)	6247(5)	6884(3)	257(21)	H2-C(14)	146(10)	1352(7)	832(5)	93(24)
O(7)	2769(5)	3447(4)	5329(3)	388(19)	H1-C(15)	83(13)	1170(8)	1014(7)	109(36)
N(8)	3678(5)	8221(5)	7998(3)	318(20)	H2-C(15)	336(8)	1289(16)	1007(8)	137(46)
O(9)	3097(6)	7244(5)	8648(3)	506(23)	H3-C(15)	146(13)	1429(6)	1021(6)	117(29)
O(10)	5512(5)	9261(6)	8046(3)	604(25)	H -C(16)	-189(6)	727(4)	781(3)	27(11)
C(11)	1023(7)	9948(6)	7367(3)	309(23)					
O(12)	80(6)	10545(5)	6713(3)	482(23)					
O(13)	1457(5)	10610(4)	8368(3)	408(20)					
C(14)	821(9)	12363(7)	8734(4)	458(32)					
C(15)	1697(25)	12947(15)	9844(6)	965(86)					
C(16)	-1585(7)	6072(6)	7329(3)	298(23)					
N(17)	-3279(6)	4267(5)	7219(3)	346(21)					
O(18)	-4791(6)	4295(6)	7693(3)	576(25)					
O(19)	-3154(5)	2799(4)	6657(3)	447(21)					

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