Synthesis, Properties and Structure of 1-Acetyl-6-(4-chlorobenzylidene)-2,3,5,6-tetrahydroimidazo[2,1-*b*]imidazole-3,5-dione

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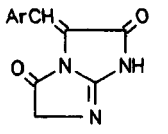
Cyclization of *N*-[5-(4-chlorobenzylidene]-4-oxo-2-imidazolidinyl]glycine (**4**) in acetic acid anhydride yielded 1-acetyl-6-(4-chlorobenzylidene)-2,3,5,6-tetrahydroimidazo[2,1-*b*]imidazole-3,5-dione (**5**). The structure of **5** was ascribed on basis of its MS, ^{1}H- and ^{13}C-NMR properties. The crystal structure of **5** was solved by X-ray analysis. On the basis of semiempirical quantum chemistry calculations (PM3 method) the thermodynamic stability of theoretically possible cyclization products was determined. These data allow to predict the direction of cyclization. The stability and the reactivity of **5** toward nucleophilic attack were examined.

Synthese, Eigenschaften und Kristallstruktur von 1-Acetyl-6-(4-chlorbenzyliden)-2,3,5,6-tetrahydroimidazo[2,1-*b*]imidazol-3,5-dion
Cyclisierung von *N*-[5-(4-chlorbenzyliden)-4-oxo-2-imidazolidinyl]glycin (**4**) mit Acetanhydrid lieferte 1-Acetyl-6-(4-chlorbenzyliden)-2,3,5,6-tetrahydroimidazo-[2,1-*b*]imidazol-3,5-dion (**5**). Zur Charakterisierung von **5** wurden ^{1}H-, ^{13}C-NMR und Massenspektren herangezogen. Die Struktur **5** wurde durch Röntgenstrukturanalyse bestätigt. Mittels semiempirischen Quantenchemieberechnungen wurde die thermodynamische Stabilität der theoretisch möglichen Produkte der Cyclisierung ermittelt. Diese Daten lassen den Verlauf der Cyclisierung voraussehen. Die Stabilität und Reaktivität von **5** wurde untersucht.

In a search for new compounds with an influence on the central nervous system (CNS), we have examined annelated derivatives of 5,5-diphenyl-2-thiohydantoin (thio-analog of the antiepileptic drug phenytoin-5,5-diphenylhydantoin). Thus, imidazothiazole, -thiazine and -thiazepine derivatives were obtained[1-5]. In continuation of our studies on structure-activity relationships, we have obtained fused 5-arylidene-2-thiohydantoin derivatives[6]. The preliminary pharmacological tests stated that while the annelated 5,5-diphenyl-2-thiohydantoin derivatives show sedative properties, the appropriate 5-arylidene-2-thiohydantoin derivatives possess analgetic, anxiolytic, antidepressant, and anticonvulsive properties[7].

In the present work our efforts were focused on the synthesis of new annelated 5-arylidene-2-thiohydantoin derivatives with an annelated imidazolone ring, *i.e.* with the heterocyclic ring where the S-atom was isosterically substituted by N. The synthesis of such compounds (Scheme 1,**1**) was described[8] and we have repeated that procedure. So the starting 5-(4-chlorobenzylidene)-2-thiohydantoin (**2**) reacted with methyl iodide to give the 2-methylthio-derivative **3** which in reaction with glycine gave the glycine-amidine **4**. This reacts with acetic acid anhydride contrary to the lit. data to the bicyclic product **5** (mp. 263-264°C; mp.[8]: 240°C) (Scheme 2).



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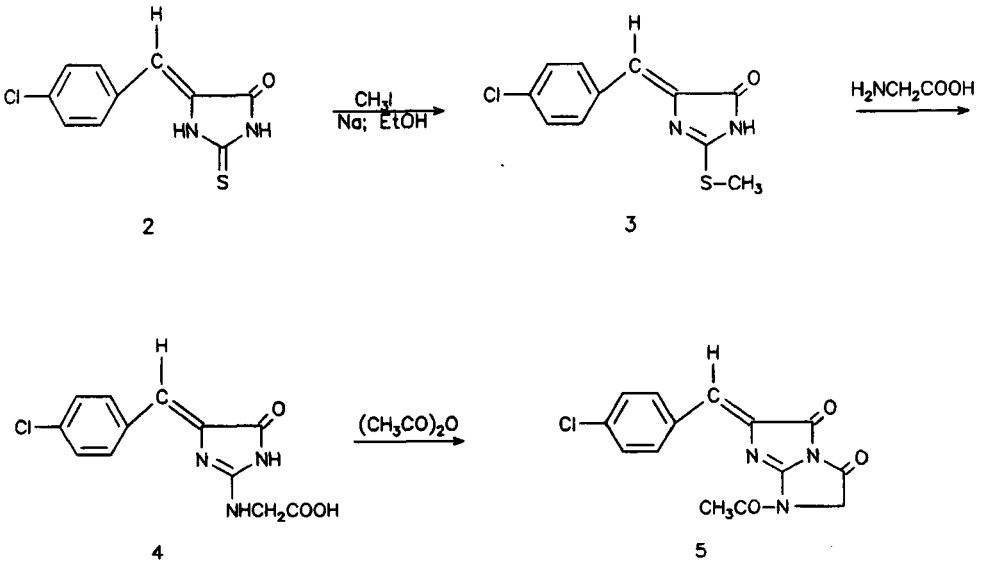
Scheme 1



2 **3** **4** **5**

Scheme 2

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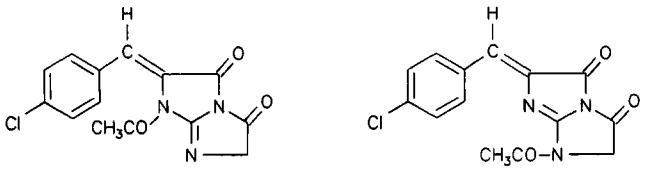
The MS of **5** shows $M^{+\cdot}$ at m/z = 303, equivalent to structure **5**; peaks at m/z = 285 and 261 correspond to the loss of H_2O and $H_2C{=}C{=}O$, respectively. Corresponding to our experiences[6] with 5-arylidene-2-thiohydantoin derivatives, cyclization should mainly proceed to 2,3-annelated products, *e.g.* **5** or **6** (Scheme 3). In the ^{13}C-NMR spectra chemical shifts of the C=N groups of 1,2-annelated compounds were observed at lower fields: 185-188 ppm, in comparison with the 2,3-disubstituted compounds (*e.g.* like **5**): 165-173 ppm. The chemical shift of the C=N group of the obtained compound at 167.3 ppm could indicate the structure **5** (Scheme 3).



Scheme 3

In order to get unquestionable evidence for the suggested structure **5** the crystals were subjected to X-ray analysis. This analysis confirmed the assumed structure **5**.

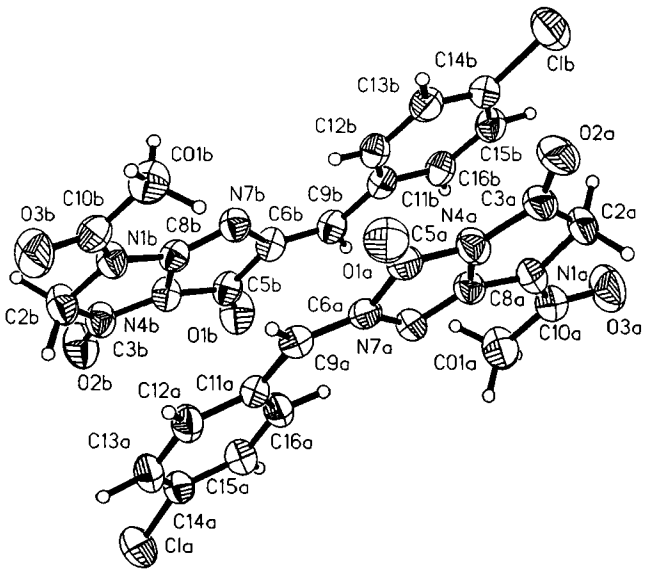


Figure: 1. Molecular structure of 1-acetyl-6-(4-chlorobenzylidene)-2,3,5,6-tetrahydroimidazo-[2,1-*b*]-imidazole-3,5-dione **5**. Selected bond lengths [Å]: molecule **I**: N1a-C8a 1.367 (3); N1a-C10a 1.389 (3); C8a-N7a 1.281 (3); C5a-O1a 1.201 (3); C3a-O2a 1.207 (2); C6a-C9a 1.336 (3); molecule **II**: N1b-C8b 1.375 (3); N1b-C10b 1.393 (3); C8b-N7b 1.283 (3); C5b-O1b 1.195 (3); C3b-O2b 1.193 (2); C6b-C9b 1.341 (3); selected bond angles [°]: molecule **I**: C8a-N1a-C2a 109.8 (2); C8a-N1a-C10a 129.5 (2); C2a-N1a-C10a 120.7 (2); molecule **II**: C8b-N1b-C2b 109.8 (2); C8b-N1b-C10b 129.5 (2); C2b-N1b-C10b 120.3 (2).

The structure, consisting of two molecules in the independent unit, is shown in Fig. 1, the legend lists some selected bond lengths and angles. Both molecules, not differing significantly in the geometric details, possess *Z*-configuration. For selected geometrical data see Table 1. Table 1 shows respective values obtained from semi-empirical quantum chemical PM3 and AM1 (from MOPAC.6 programme[9,10]) calculations (with option PRECISE). When we compare these data, the PM3 method seems to be better than AM1 for the investigated compound: the geometry of molecule **5** from PM3 is closer to the crystallographic one than that from AM1.

Interestingly, **5** is the main product. Scheme 4 shows some tautomers of **4**; all of them have the atoms arrangement necessary for cyclization to 1,2- or 2,3-annelated compounds (**4a**-1 and **4a**-2 are rotational isomers of the same tautomeric form).

For the molecules of Scheme 4 we first constructed 3-D models (PCMODEL programme[11,12]) then we established the lowest energy conformations using the PM3 programme[9,10]. Corresponding heat of formation values (H_f in kcal/mol) are given in Scheme 4: **4b** is the lowest energy form. By cyclization of **4b** only **7b** (and **7a**) can be obtained and subsequent acetylation is leading to product **5**. Comparing the final heat formation H_f for both possible isomers (**5** and **6**, Scheme 3) it can be concluded that molecule **5** is by 2.2 kcal/mol more stable than **6**. Similar calculations for **7a** and **7b** (Scheme 4) indicate that **7a** should be by 3.2 kcal/mol more stable than **7b**, but acetylation of tautomer **7b** may give[13] product **5**.

Compound **5**, when stored in an ethanolic solution of ammonia at room temp., underwent destruction with formation of ester **9** (Scheme 5).

9 was also obtained by acetylation of **8**. Additionally amide **10** was separated from the reaction mixture. Amide **10** may also be obtained by refluxing **5** with ammonia in THF. Refluxing **5** with two equivalents of benzylamine in toluene gave the amide **11**.

We are grateful to Professor *G. Blaschke* (University in Münster) for the financial support of the spectral analysis, and Dr. *D. Bergenthal* for recording ^{1}H- and ^{13}C-NMR spectra. - The financial support of the crystallographic computational parts of research (J.K-W) carried out under the Polish State Committee for Scientific Research project No. 3.0302/91/01, and synthetic part of work project No. 2185/419, are also gratefully acknowledged.

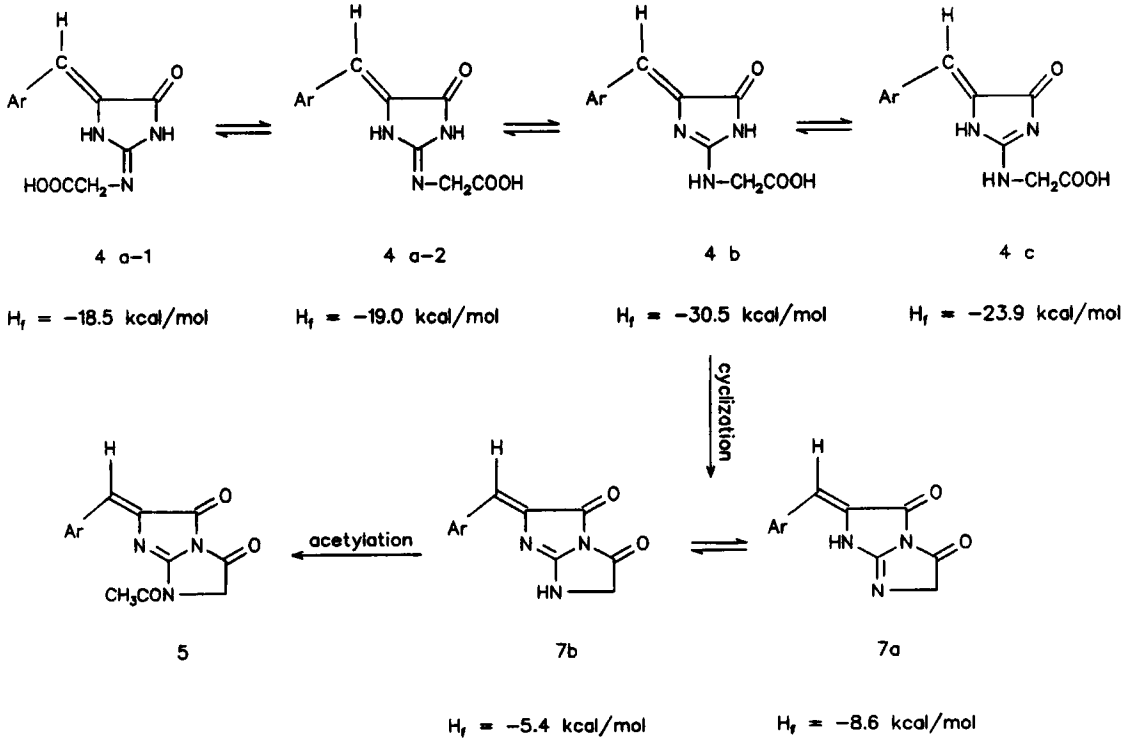
Experimental Part

Melting points: Kofler hot stage microscope, uncorrected.- IR spectra: Specord 80 IR (VEB Carl Zeiss, Jena); KBr.- ^{1}H-NMR spectra and ^{13}C-NMR spectra: Bruker VM 300 or Varian Gemini 200, δ [ppm] relative to TMS.- Mass spectra: LKB-2091 (EI/70 eV): m/z (%); direct inlet.- TLC: Al sheets, 0.2 mm layer of silica gel (60 F_{254} Merck); solvent systems: I: $CHCl_3$:2-propanol:NH_3aq (9:11:2); II: $CHCl_3$:MeOH (8:2); III: $CHCl_3$:AcOEt (1:1).

The starting compounds **2**, **3**, **4** were prepared as described[8,14].

Table 1: Selected geometrical data of **5** from X-ray in comparison with respective values after optimization by PM3 and AM1 methods.

	X-ray (two molecules)	PM3	AM1
C12-C11-C9-C6 [°]	1.1(4), 0.7(4)	-0.3	-0.8
C11-C9-C6-N7 [°]	7.2(4), 6.1(4)	-0.1	-32.8
angles Σ at N1[°]	360.0(2),359.6(2)	359.6	355.0
N7-C8 [Å]	1.281(3),1.283(3)	1.317	1.334
C8-N1 [Å]	1.367(3),1.375(3)	1.421	1.404
C8-N4 [Å]	1.393(2),1.390(2)	1.440	1.465
C5-C6 [Å]	1.497(2),1.498(2)	1.503	1.530



Scheme 4

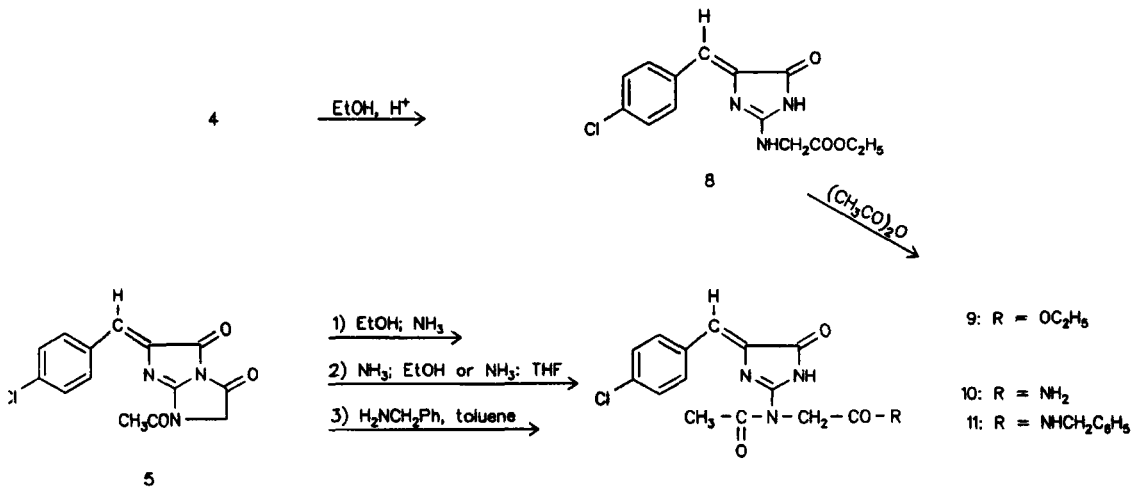
N-[5-(4-Chlorobenzylidene)-4-oxo-2-imidazolidinyl]glycine (**4**)

M.p. 279-281°C (Ref.[8]: 269°C), lightly yellow crystals.- ^{1}H-NMR ([D$_6$]DMSO): 4.07 (s, 2H, NCH_2), 6.32 (s, 1H, CH=), 7.41 (d, 2H, J = 8.55 Hz, Ar-H_m), 7.72* (br. s, 1H, NH), 8.04 (br. s, 2H, Ar-H_o), 10.87* (br. s, 1H, NHCO), 12.7* (br. s, 1H, COOH).- (*: H/D exchange by D_2O).- MS: 279 (20, $M^{+\cdot}$), 261 (20, M - $H_2O)^+$, 234 (10, M - COOH)$^+$, 55 (100).

1-Acetyl-6-(4-chlorobenzylidene)-2,3,5,6-tetrahydroimidazo-[2,1-b]imidazole-3,5-dione (**5**)

a. The suspension of 2.0 g acid **4** in 20 ml of acetic acid anhydride was refluxed for 4 h. Precipitated **5** was filtered off on the next day and was purified by recrystallization from DMF or acetic acid. M.p. 263-264°C, yield 40%, yellow crystals.

b. The suspension of 2.0 g acid **4** in acetic acid anhydride (2 ml) and pyridine (3 ml) was stored at room temp. for two days. The precipitate was filtered off and purified as in method **a.** R_f(I) 0.21, R_f(II) 0.21, yield 46%.- $C_{14}H_{10}ClN_3O_3$ (303.7) Calcd. C 55.4 H 3.32 N 13.8 Found C 55.2 H 3.25 N 13.7.- IR: 1810 (CH_3CO), 1722 and 1710 (C=O), 1650 (ArCH=), 1595 (C=N).- ^{1}H-NMR ([D$_6$]DMSO): 2.66 (s, 3H, CH_3CO), 4.61 (s, 2H, CH_2CO), 7.05 (s, 1H, CH=), 7.55 (d, 2H, J = 8.25 Hz, Ar-H_m), 8.17 (d, 2H,J = 8.25 Hz, Ar-H_o).- ^{13}C-NMR ([D$_6$]DMSO): 23.90 (CH_3), 54.04 (CH_2), 122.19 (CH=), 128.84 (C-3'), 132.35 (C-4'), 132.92 (C-2'), 134.55 (C-1'), 141.94 (C-6), 156.24 ($CH_3\underline{C}O$), 160.58 (C-3), 160.76 (C-5), 167.26 (C-8).- MS: 303 (32, $M^{+\cdot}$), 285 (10, M - $H_2O)^{+\cdot}$, 261 (100, M - $COCH_3)^+$.



Scheme 5

Ethyl N-acetyl-N-[5-(4-chlorobenzylidene)-4-oxo-2-imidazolidinyl]glycinate (**8**)

a. The suspension of acid **4** (2.8 g, 0.01 mol) in 100 ml of ethanol was refluxed for 5 h with 1.5 ml of conc. H_2SO_4. After cooling the precipitate was filtered off and recrystallized from ethanol: m.p. 269-271°C, yield 65%, light yellow crystals.

b. The stirred suspension of acetyl derivative **9** (0.349 g, 0.001 mol) in 30 ml ethanol was refluxed with 10 drops of 25% NH_3 for 3 h. The precipitate was purified as in method **a.** R_f(III) 0.20, yield 88%.- $C_{14}H_{14}ClN_3O_3$ (307.73) Calcd. C 54.6 H 4.59 N 13.6 Found C 54.4 H 4.52 N 13.4.- IR: 3336 (NH), 1734 (C=O), 1688 (COOEt), 1656 (ArCH=), 1594 (C=N).- ^{1}H-NMR ([D$_6$]DMSO): 1.23 (t, 3H, J = 7.00 Hz, CH_3), 4.11-4.22 (m, 4H, CH_2), 6.34 (s, 1H, CH=), 7.39 (d, 2H, J = 8.60 Hz, Ar-H$_m$), 7.88 (br. s, 1H, N<u>H</u>CH$_2$), 8.07 (d, 2H, J = 8.60 Hz, Ar-H$_o$), 10.95 (br. s, 1H, CONH).- ^{13}C-NMR ([D$_6$]DMSO): 14.12 (CH_3), 43.88 (<u>C</u>H$_2$CH$_3$), 60.74 (<u>C</u>H$_2$CO), 110.95 (CH=), 128.21 (C-4'), 128.52 (C-3'), 131.93 (C-2'), 135.16 (C-1'), 142.00 (C-5), 159.30 (<u>C</u>OOEt), 170.06 (C=O), 171.45 (C=N).- MS: 307 (40, M$^{+\cdot}$), 234 (25, M - $COOC_2H_5$)$^+$, 55 (100).

Ethyl N-acetyl-N-[5-(4-chlorobenzylidene)-4-oxo-2-imidazolidinyl]glycinate (**9**)

a. A suspension of ester **8** (3.07 g, 0.01 mol) in 40 ml acetic acid anhydride was refluxed for 1 h. The solid was dissolved. After cooling the precipitate was filtered off and recrystallized from acetic acid: m.p. 252-254°C, yield 62%, pale yellow crystals.

b. The mixture of acetyl derivative **5** (0.303 g, 0.001 mol) in 20 ml of ethanol and 5 drops of 25% NH_3 was stirred at room temp. for 12 h. Then the precipitate of **9** was filtered off and purified as in method **a.**, yield 57%. To the ethanolic filtrate water was added. The separated solid **10** was filtered off and recrystallized from DMF/H_2O. R_f(I) 0.84, R_f(III) 0.67, yield 31%.- $C_{16}H_{16}ClN_3O_4$ (349.8) Calcd. C 54.9 H 4.61 N 12.0 Found C 55.0 H 4.72 N 12.0.- IR: 3420, 3276 (NH), 1738 and 1714 (C=O), 1684 (COOEt), 1636 (ArCH=), 1580, 1560, 1540 (C=N).- ^{1}H-NMR ([D$_6$]DMSO): 1.23 (t, 3H, J = 7.10 Hz, CH_3), 2.44 (s, 3H, CH_3CO), 4.19 (q, 2H, J = 7.10 Hz, C<u>H</u>$_2$CH$_3$), 4.71 (s, 2H, CH_2COO), 6.86 (s, 1H, CH=), 7.47 (d, 2H, J = 8.50 Hz, Ar-H$_m$), 8.10 (d, 2H, J = 8.50 Hz, Ar-H$_o$), 11.50 (s, 1H, NH).- ^{13}C-NMR ([D$_6$]DMSO): 13.98 (<u>C</u>H$_3$CH$_2$), 24.24 (<u>C</u>H$_3$CO), 47.59 (<u>C</u>H$_2$CH$_3$), 61.04 (<u>C</u>H$_2$CO), 119.77 (CH=), 128.52 (C-3'), 132.69 (C-2'), 133.17 (C-4'), 133.73 (C-1'), 137.86 (C-5), 156.57 (<u>C</u>OOEt), 168.26 (CH_3<u>C</u>O), 170.06 (C=O), 171.59 (C=N).- MS: 349 (36, M$^{+\cdot}$), 309 (34), 307 (100, M - CH_3CO)$^+$, 261 (29), 234 (62).

N-[5-(4-chlorobenzylidene)-4-oxo-2-imidazolidinyl]glycinamide (**10**)

a. To the stirred suspension of acetyl derivative **5** (0.303 g, 0.001 mol) in 6 ml ethanol 5 drops of 25% NH_3 were added. Stirring was continued in room temp. for 15 min. The precipitate was filtered off and crystallized from DMF/H_2O: m.p. 248-250°C, yield 59%, pale yellow crystals.

b. The mixture of **5** (0.303 g, 0.001 mol) in 10 ml THF and 5 drops of 25% NH_3 was refluxed for 1 h. R_f(I) 0.25, R_f(III) 0.05, yield 75%.- $C_{14}H_{13}ClN_4O_3$ (320.7) Calcd. C 52.4 H 4.08 N 17.5 Found C 52.4 H 3.94 N 17.3.- IR: 3420 (NH), 1802 (CH_3CO), 1708 and 1690 (C=O), 1664 (ArCH=), 1638, 1598 (C=N).- MS: 320 (8, M$^{+\cdot}$), 278 (37), 261 (37), 234 (70), 43 (100, CH_3CO)$^+$.

N-[5-(4-chlorobenzylidene)-4-oxo-2-imidazolidinyl]glycinbenzamide (**11**)

The suspension of acetyl derivative **5** (1.51 g, 0.005 mol) and benzylamine (1.02 g, 0.01 mol) in 50 ml of toluene was warmed to 80°C. The precipitate changed. The mixture was left at room temp. for 2 h. The precipitate was filtered off and recrystallized from DMF: m.p. 268-269°C, yield 73%, pale yellow crystals.- $C_{21}H_{13}ClN_4O_3$ (410.8) Calcd. 61.4 H 4.66 N 13.6 Found C 61.2 H 4.55 N 13.6.- IR: 3328, 3296 (NH), 1724, 1688 (C=O), 1644 (C=O and ArCH=), 1544 (C=N).- MS: 410 (8, M$^{+\cdot}$), 368 (50), 234 (100).

Crystallographic Measurement was performed on a KM-4 diffractometer with Cuk α radiation (λ = 1.54178 Å) using crystal of 0.2 x 0.2 x 0.3 mm. The ω-2θ scan technique was applied for 2θ < 150°. Two reflections were used as standards and remeasured during the data collection; crystal decomposition was not observed: 5260 reflections measured (h < 27; k < 21; l < 19) and 4186 were classified as observed with F > 4σ (F). Only *Lorentz*-polarization corrections were applied. The cell dimensions were obtained and refined by the least-square method on the basis of the diffractometric measurement for 25 reflections (10 < θ < 42°).

The structure was solved by direct methods (from SHELXTL-PC program) with R(E) used as a figure of merit equaling 0.21 for all non-H atoms. The structure was refined on F's by the full-matrix least-squares method (SHELXTL-PC[15]) first isotropically. The positions of all H-atoms were found from Δρ map at the end of the anisotropic refinement. The H-atoms were refined with fixed isotropic factors (1.5 of the respective factor for the carbon atom). The R factors at the end of the refinement were R = 0.0415 and R_w = 0.0399 with w = $1/\rho^2$ (F) and the extinction correction factor g = 0.0009; s = 3.71. During the refinement 9 reflections per parameter were used. The maximum changes [Δ/ρ_{max}] in the parameter were 0.01. The maximum and minimum residual electron density equal 0.206 and -0.248 eÅ^{-3}.

Crystal data for **5**[16]: $C_{14}H_{10}N_3O_3Cl$; mol.mass: 303.7; orthorhombic, Pbca space group; a = 21.469 (4), b = 16.508 (3), c = 14.988 (3) Å; V = 5311.9 (2) $Å^3$, d_x = 1.528 g/cm^3; z = 16; F(000) = 2496; μ(Cuk α) = 2.71 mm^{-1}. Final R = 0.0415 for 4186 reflections with F > 4ρ (F) (5260 of unique data).

List of Deposited Tables:

1. Non-hydrogen fractional atomic coordinates (x 10^4) and equivalent isotropic displacement parameters [$Å^2$ x 10^3] of **5**; U_{eq} defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

2. Bond lengths (Å) and bond angles (°) with e.s.d.'s in parentheses.

3. Non-H-atoms anisotropic temperature factors (x 10^3) ($Å^2$) with e.s.d.'s in parentheses.

4. H-atoms fractional coordinates (x 10^3) and isotopic temperature factors ($Å^2$) (x 10^2) with e.s.d.'s in parentheses.

5. The structure factors for 1-acetyl-6-(4-chlorobenzylidene)-2,3,5,6-tetrahydroimidazo[2,1-*b*]imidazole-3,5-dione **5**.

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16 Further details of the crystal structure investigations are available on request from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information GmbH, D-76344 Eggenstein-Leopoldshafen 2, on quotation the depository number, the names of the authors, and the journal citation. [Ph253]