STRUCTURE AND ACTIVITY STUDIES OF GLYCINE RECEPTOR LIGANDS. PART 2. IMIDAZOQUINAZOLINODIONE - DERIVATIVES WITH THE EXPECTED ANTICONVULSANT ACTIVITY

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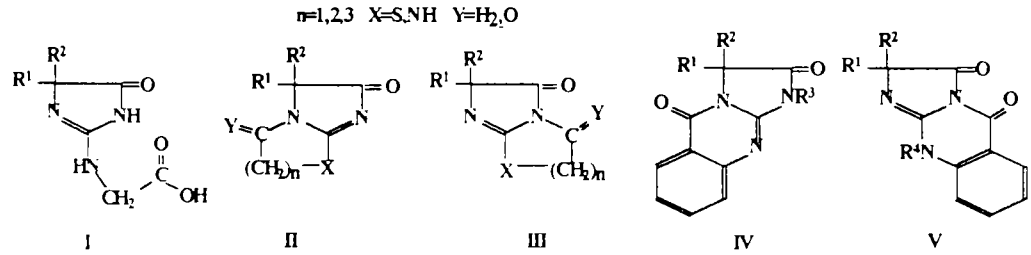
Abstract: The synthesis of several imidazoquinazolinodiones derivatives is reported. Based on NMR, MS and theoretical calculation (MO-AM1) the synthesis problems were rationalized. For selected compounds the preliminary pharmacological tests were provided.

Introduction

In connection with our search for the new glycine receptor ligands we have recently describe some imidazolone derivatives **I** showing an interesting affinity to the receptor [1]. Up to now in our studies concerning the new compounds with anticonvulsant properties we have modified the structure of the well known antiepileptic drug - phenytoin [2-9]. Thus several fused derivatives of 5,5-diphenyl (R^1, R^2 = Ph) and/or 5-arylidene-2-thiohydantoin (R^1, R^2 = (un)substituted ArCH=) were obtained with the general structure of **II** and **III**. In the present study we tried to merge our two scientific problems and as the results we obtained the compounds enriched with the additional benzene ring - the imidazoquinazolinodione **IV** and **V**. In order to investigate the influence of the substituents on their biological properties, we received diphenyl (R^1, R^2 = Ph) and arylidene analogous (R^1, R^2 = (un)substituted ArCH=)

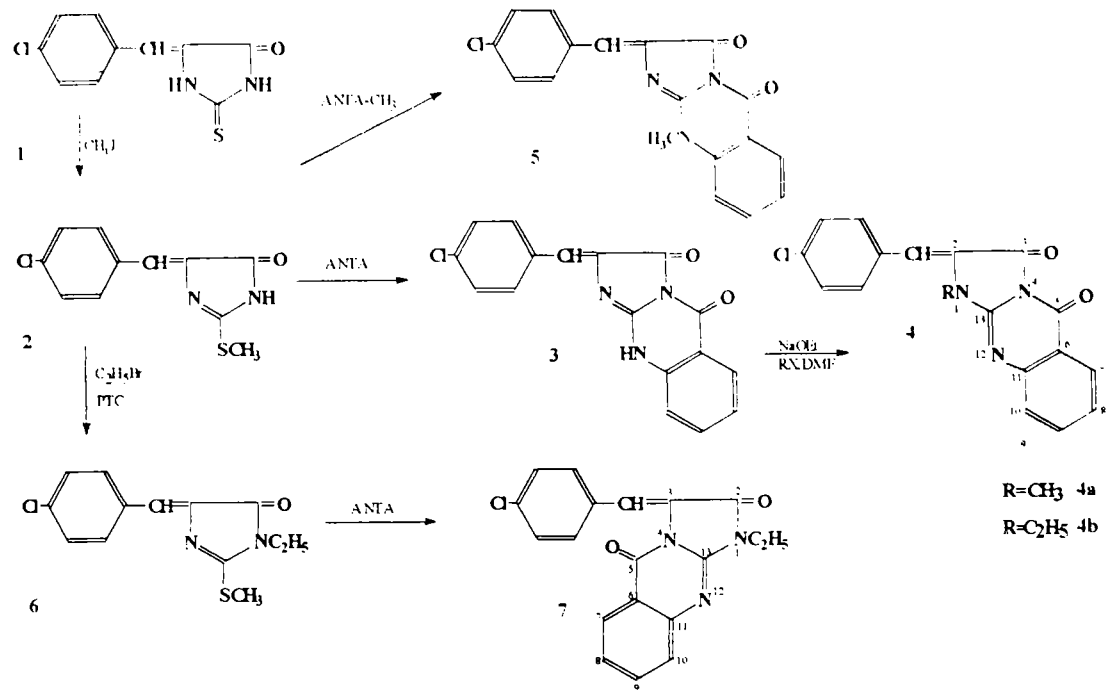


I II III IV V

Results and Discussion

Arylidene derivatives.

Respective methylated derivatives of p-Cl or unsubstituted 5-arylidene-2-thiohydantoin were used in the synthesis of 2-arylidene-imidazoquinazolino-3,5-diones **V** and 2,5-diones **IV**. However, the final products which we obtained during the cyclization of anthranilic acid (ANTA) with p-Cl-derivative **2** or the unsubstituted derivative **8** were different



The compounds of the type **V** are the products of the reactions between monoalkylated derivatives 2 or 8 with ANT Therefore the reaction of 2 with ANTA[10,11] gave fused molecule 3, which via sodium salt could be alkylated to 1-meth 4a or 1-ethyl 4b derivatives. The isomer of 4 alkylated at nitrogen in position 12 (derivative 5) was obtained in separ cyclization of 2 with N-methyl-ANTA. For achieving the molecules of the type **IV** for cyclization with ANTA we us dialkylated p-Cl-derivative 6 producing 3-arylidene-imidazoquinazolino-2,5-dione 7. The structure of this molecule w confirmed by an X-ray determination[12] and undoubtedly indicate its **Z**-configuration (Fig.1). In all cyclizations of parent Cl-derivative 1 only one isomer was always obtained and, by analogy, the molecules of 3, 4, and 5 should also posses configuration.

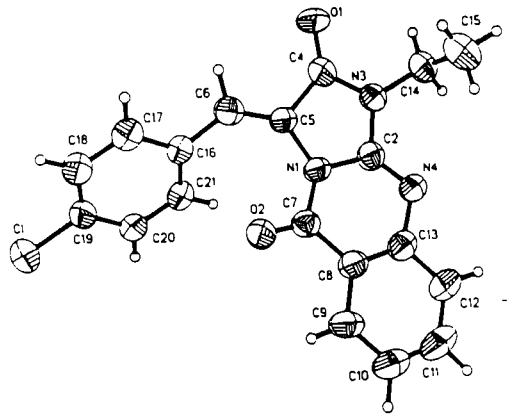
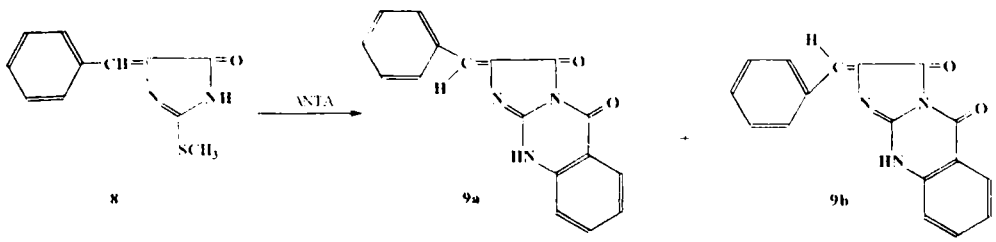


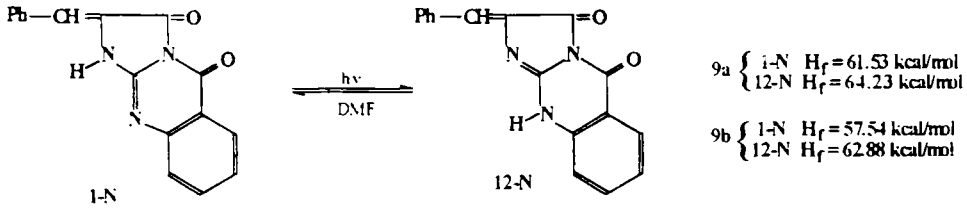
Fig.1. ORTEP drawing of the molecule 7 (**Z**-configuration).

However the reaction of the unsubstituted benzylidene derivative 8 with ANTA presumably give the mixture of **E** anc isomers 9a and 9b. Both isomers were isolated in pure form. The effort to examine their structures by X-ray analysis v fruitless because of crystals decomposition during the diffractometric experiment. Therefore the structures were assigned basis of their physicochemical properties, elemental and spectral analysis (MS, ^{1}H-NMR). These molecules show the sa molecular ions and fragmentation patterns in MS. According to the literature data on the properties of **E** and **Z** isom [13,14], **E**-9a isomer has higher melting point and is less soluble in comparatione with **Z**-9b isomer. The identity of isomers was also confirmed by ^{1}H-NMR singlet of vinyl protons lying for **Z**-9b in higher field than for **E**-9a - 6.96p and



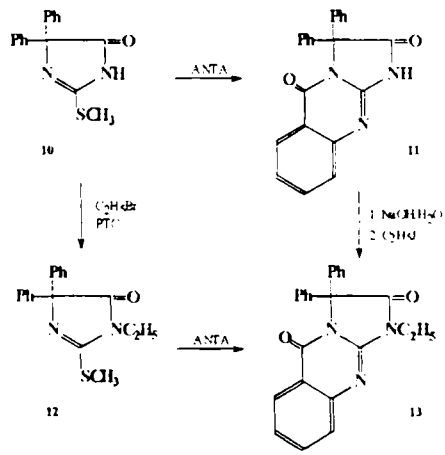
6.74ppm respectively. Semiempirical quantum-chemistry calculations (AM1 method) confirm the comparable thermodynamic stability of both isomers. The heat of formation H_f for slightly more stable Z-isomer 9b (62.88 kcal/mol) is only 2.65 kcal/mol lower than for E-form 9a (65.53 kcal/mol). The calculated barrier of transformation Z ⇒ E (via biradical state) equals about 30 kcal/mol and is too high for the isomerization during cyclization.

Two tautomeric forms, 1-N and 12-N, can be proposed for each isomer. It should be emphasised that the classification of 9a and 9b as two tautomers of one isomer (supposed Z) is groundless based on our results. On the other hand, from the energetic point of view (for the values of calculated H_f see below), the existence of each isomer in both tautomers is acceptable but 1-N form is in both cases thermodynamically beneficial. We suppose that tautomers transformation may cause decomposition of 9a and 9b in solid. It is quite possible that lower energetically tautomers 1-N exists in the crystal for both 9a and 9b. After exciting by X-ray wave (hν) this tautomer undergoes the relocation of the proton to 12-N (probably via H-bond). This process is reversible during dissolving and recrystallization when 12-N is again converted to 1-N in DMF solution.



Unfortunately till now it is not clear why the p-Cl-arylidene derivative 2 during cyclization generates only one Z-product when unsubstituted molecule 8 yields two isomers - Z and E. Both parent- molecules are energetically lower in Z-form (ΔH_f ~ 2.65 kcal/mol). Moreover barriers of Z ⇒ E transformation for 2 and 8 are similar equalling about 11 kcal/mol. We can only intuitively suppose that the p-Cl-substituent in 1 rigidities whole molecule and therefor the lack of generation of E-isomer from initial Z-material is able to form only one isomer while in unsubstituted 8 spatial interactions are probably significantly weaker. In this last case both isomers were isolated, however with yield in favour of 9b (Z-isomer).

Diphenyl derivatives



In the reaction of 5,5-diphenyl-2-thiohydantoin 10 with ANTA 3,3-diphenylimidazoquinazolino-2,5-diones (IV and 13 were obtained. The compound 11 was synthesised as the result of cyclization methyl-thio-derivative 10. Th alkylated derivative of imidazoquinazolino-2,5-dione 13 was formed as a result of dialkylated structure 12 cyclization ANTA or as a results of 11 alkylation with ethyl iodide. Two ways of compound 12 synthesis prove clearly that for structure 11 is imidazoquinazolino-2,5-dione (IV) and not imidazoquinazolino-3,5-dione (V)

Pharmacological screening

The compounds 3, 7, 9b and 11 were tested in vivo for their ability to prevent electrically and pentatra induced seizures according to the Antiepileptic Drug Development Program in the National Institute of Health in Beth [16]. In the doses up to 300 mg/kg (mice) they were inactive. However in our previous unpublished pharmacological tests higher doses (400 mg/kg) it was possible to discriminate the activities of isomeric compounds 9a and 9b. Compound 9a isomer protect against death 50% of animals after s.c. administration of pentetrazole (100 mg/kg) (control-death in 7 In electrically induced seizures after 9b (Z-isomer) administration death of mice occurred in 8% (control 33%; 9a 50% the dose of 400 mg/kg compound 9b in contrary to 9a preserved in 75% mice against tonic seizures.

These insignificant activities without practical value become worth for comparing the biological properties of isome and Z.

Experimental

Chemistry

Melting points: Boetius apparatus, uncorrected. IR spectra: Specord 80 IR (VEB Carl Zeiss, Jena); KBr discs. ^{1}H-N spectra and ^{13}C-NMR spectra: Bruker VM 300 or Varian Gemini 200, δ [ppm] relative to TMS. Mass spectra: LKB- (EI/70eV); m/z(%); direct inlet. TLC: Al sheets 0.2 mm layer silica gel (60F_{254} Merck); solvent systems: I: $CHCl_3$:Ac (1:1); II: benzene:aceton (20:1.5); III: $CHCl_3$:MeOH (8:2).

Z-2-(4-chlorobenzylidene)-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-3,5-dione (3)

The mixture of 5-(4-chlorobenzylideno)-2-methylthioimidazolidine-4-one 2 (2.52 g ; 0.01 mole) and anthranilic acid (1 0.01 mole) in 20 ml of acetic acid was refluxed for 4 hrs. On the next day the solid was filtered of and recrystallized DMF to yield garish yellow crystalls of 3 m.p. 322-324°C (lit.[11] 270°C), R_f(I)=0.73 R_f(II)=0.20 R_f(III)=0.48. Yield (40%), $C_{17}H_{10}N_3O_2Cl$ (323.74), Calc. C 63.1 H 3.11 N 13.0 Found C 63.0 H 3.27 N 12.7.

^{1}H-NMR ([D_6] DMSO): 6.76 (s, 1H, CH=); 7.25 (d, 2H, $J_{9,8}$=7.3Hz, H-9, H-8); 7.52 (d, 2H, J=8.3Hz, H-17, H-19), (dt, 1H, $J_{10,9}$=8.0Hz, $J_{10,8}$=1.6Hz, H-10); 8.00 (dd, 1H, $J_{7,8}$=8.1Hz, $J_{7,9}$=1.4Hz, H-7), 8.15 (d, 2H, J=8.3Hz, H-16, H 12.30 (b.s., 1H, NH).

^{13}C-NMR ([D_6] DMSO): 115.98 (C-6), 123.42 (C-14), 128.27 (C-17,C-19), 128.47 (C-18), 128.89 (C-8,C-9), 132.4 16,C-20), 133.40 (C-10), 133.84 (C-15), 133.90 (C-11), 136.17 (C-7), 147.65 (C-2), 157.34 (C-3,C-5), 173.73 (C-1

IR: 3400, 3228 (NH), 1752 and 1698 (C=O), 1650 (ArCH=), 1610, 1568 (C=N), 1480, 1300, 784, 754.

MS (m/z): 323 (15,M^+); 162(2), 150(3), 145(100), 117(16).

1-ethyl-Z-2-(4-chlorobenzylidene)-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-3,5-dione (4b)

To the solution of 0.30 g (0.013 mole) sodium in 40 ml of ethanol 3.23 g (0.01 mole) of p- chlorobenzylidenequinaz 3,5-dione 3 was added. The dark brown suspension was refluxed for 3 hrs. The precipitate containing the sodium salt (m.p. 350°C) was filtered off and dissolved in 30 ml of DMF. Then 3.2 g (0.02 mole) of ethyl iodide was added. Th obtained mixture was warmed on boiling water bath for 3 hrs and left overnight at r.temp. On the next day the solid filtered off and recrystallized from acetic acid to yield 3.0 g (85%) yellow crystalls of 4b m.p. 240-242°C (lit.[11] 26 R_f(I)=0.91 R_f(II)=0.81, $C_{19}H_{14}N_3O_2Cl$ (351.79), Calc. C 64.9 H 4.01 N 11.9 Found C 65.1 H 4.05 N 11.6,

^{1}H-NMR ($CDCl_3$): 1.45 (t, 3H, J=7.0Hz, CH_3); 4.35 (q, 2H, J=7.0Hz, CH_2); 7.06 (s, 1H, CH=); 7.38 (d, 1H, $J_{9,10}$=7 H-9); 7.40 (d, 2H, J=8.6Hz, H-17, H-19); 7.73 (dt, 1H, $J_{8,9}$=8.6Hz, $J_{8,10}$=1.3Hz, H-8); 8.08 (d, 2H, J=8.6Hz, H-16, H 8.23 (def d, 1H, $J_{10,9}$=7.3Hz, H-10); 8.73 (d, 1H, $J_{7,8}$=8.4Hz, H-7),

^{13}C-NMR ($CDCl_3$): 12.83 (CH_3), 37.85 (CH_2), 115.54 (C-14), 123.55 (C-8, C-9), 125.95 (C-7), 129.20 (C-17, C 133.20 (C-16, C-20), 135.57 (C-10) - because of the low solubility of the investigated compound in $CDCl_3$ only ca linked with at least one proton were observed.

IR: 1732, 1686 (C=O), 1642 (ArCH=), 1590 (C=N), 1564, 1548, 1484, 1444, 1354, 1264, 1156, 1090, 1076, 996, 760, 750, 668.

MS (m/z) 351 (100, M^+); 323 (39, M-CO), 295 (6, M-Et-CO), 228 (2), 174 (6), 173 (50), 145 (22), 117 (6), 90 ((2).

4a - obtained in the similar manner as 4b, m.p. 296-298°C, yield 80%, R_f(I)=0.87 R_f(II)=0.81, $C_{18}H_{12}N_3O_2Cl$ (337.77) Calc. C 64.0 H 3.58 N 12.4 Found C 64.1 H 3.68 N 12.3.
^{1}H-NMR (300MHz, [D_6] DMSO): 3.55 (s, 3H, CH_3), 7.06 (s, 1H, CH=), 7.48 (t, 1H, H-8), 7.50 (d, 2H, H_m), 7.94 (d, 1H, H-10), 8.09 (d, 1H, H-9), 8.25 (d, 2H, H_o), 8.60 (d, 1H, H-7)
MS (m/z) 337(35, M^+), 311(4), 168(7), 159(100), 131(8), 90(7)

12-methyl-Z-2-(4-chlorobenzylidene)-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-3,5-dione (5)
The mixture of 2 (2.52 g ; 0.01 mole) and N-methyl anthranilic acid (1.66 g ; 0.011 mole) in 20 ml of acetic acid was warmed at temp 120°C for 3 hrs. The solid was dissolved and the new one appeared. The precipitate was filtered off and recrystallized from acetic acid to yield 1.85 g (55%) yellow crystalls of 5 m.p. 315-316°C, R_f(I)=0.77 R_f(II)=0.39, $C_{18}H_{12}N_3O_2Cl$ (337.77) Calc. C 64.0 H 3.58 N 12.4 Found C 64.1 H 3.62 N 12.2
^{1}H-NMR (300MHz, [D_6] DMSO): 3.75 (s, 3H, CH_3), 6.83 (s, 1H, CH=), 7.33 (t, 1H, H-8), 7.50 (d, 3H, J=8.0Hz, $2H_m$, H-7), 7.83 (t, 1H, H-9), 8.08 (d, 1H, J=8.2Hz, H-10), 8.23 (d, 2H, J=8.0Hz, $2H_o$), MS (m/z) 337(48,M^+), 168(2), 159(100), 104(6), 77(26).

2-methylthio-3-ethyl-Z-5-(4-chlorobenzylidene)-imidazoline-4-one (6)
Compound 6 was obtained as a result of 2 alkylation with stoichiometric amount of ethylbromide in acetone, K_2CO_3, using TEBA as phase transfer catalyzator m.p. 116-119°C (EtOH), (lit.[11] 204°C), yield 75% R_f(I)=0.97 R_f(II)=0.81, $C_{13}H_{13}N_2OSCl$ (280.77) Calc. C 55.6 H 4.66 N 10.0 Found C 55.9 H 4.78 N 10.1
^{1}H-NMR (60MHz, $CDCl_3$) 1.42 (t, 3H, J=6.6Hz, CH_3), 2.89 (s, 3H, SCH_3), 3.82 (q, 2H, J=6.6Hz, CH_2), 7.00 (s, 1H, ArCH=), 7.52 (d, 2H, J=8.2Hz, ArH_m), 8.25 (d, 2H, J=8.2Hz, ArH_o). IR: 1706(C=O), 1632(ArCH=), 1484(C=N), 1368, 1240, 1154, 1080, 828, 668.

1-ethyl-Z-3-(4-chlorobenzylidene)-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-2,5-dione (7)
Compound 7 was obtained according to the literature data[11] as a result of 6 melting with anthranilic acid for 2 hrs, yield 63%, m.p. 236-238°C (lit.[11] 220°C), R_f(I)=0.89 R_f(II)=0.70
$C_{19}H_{14}N_3O_2Cl$ (351.79), Calc. C 64.9 H 4.01 N 11.9 Found C 64.7 H 3.89 N 11.8
^{1}H-NMR (300MHz, $CDCl_3$) 1.39 (t, 3H, J=7.2Hz, CH_3), 3.99 (q, 2H, J=7.2Hz, CH_2), 7.39 (d, 2H, J=8.6Hz, H-17, H-19), 7.36-7.44 (m, 1H, H-8), 7.60 (dd, 1H, $J_{9,8}$=8.2Hz, $J_{9,7}$=1.0Hz, H-9), 7.68-7.73 (dt, 1H, $J_{10,9}$=7.7Hz, $J_{10,8}$=1.6Hz, $J_{10,7}$=1.3Hz, H-10), 7.95 (def.d, 2H, J=8.5Hz, H-16, H-20), 8.29 (dd, 1H, $J_{7,8}$=7.9Hz, H-7), 8.99 (s, 1H, H-14)
^{13}C-NMR ($CDCl_3$): 12.96(CH_3), 34.88(CH_2), 119.94(C-6), 125.12(C-15), 125.33(C-8), 126.53(C-9), 127.24(C-7), 128.50(C-17, C-19), 129.00(C-14), 130.60(C-18), 132.84(C-16, C-20), 134.83(C-10), 136.37(C-3), 145.20(C-5), 146.98(C-11), 159.06(C-2), 159.08(C-13).
IR: 1720, 1680(C=O), 1640(ArCH=), 1600, 1468(C=N), 1442, 1416, 1372, 1320, 1188, 1012, 774, 712, 688.
MS (m/z) 351(89, M^+), 322(100, M-Et), 295 (6M-Et-CO), 288(5), 212(7), 173(11), 150(12), 145(52), 117(15), 102(9), 90(31), 76(10), 73(10).

E-2-benzylidene-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-3,5-dione (9a)
Z-2-benzylidene-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-3,5-dione (9b)
The both compounds were obtained from methylthioderivative[11] 8 with the method as described for compound 3. The raw material was fractionally crystallized from acetic acid. The part of solid which was dissolved in refluxing acetic acid, recrystallized from DMF was compound 9b m.p. 287-289°C (lit.[11] 263°C) yield 36%. The part of solid which was not soluble in hot acetic acid recrystallized from DMF gave 9a m.p. 305-307°C yield 30%.
9a - lemon-yellow thin needles, R_f(I)=0.78 R_f(III)=0.49 , $C_{17}H_{11}N_3O_2$ (289.31) Calc. C 70.6 H 3.84 N 14.5 Found C 70.8 H 3.64 N 14.8
^{1}H-NMR (300MHz, [D_6] DMSO): 6.74 (s, 1H, ArCH=), 7.19-7.27 (m, 2H, H-8, H-9), 7.30-7.45 (m, 3H, H-17, H-18, H-19), 7.68 (dd, 1H, H-10), 7.98 (dd, 1H, H-7), 8.05 (def.dd, 2H, H-16, H-20), 12.2 (br.s., 1H, NH).
IR: 3402, 3204(NH), 1750, 1698(C=O), 1650(ArCH=), 1614, 1574(C=N), 1486, 1444, 1366, 1296, 1140, 764, 684, 668.
MS (m/z) 289(63, M^+), 261(8), 145(100), 117(23), 90(55), 76(10), 69(7), 63(15)
9b - lemon-yellow thick crystalls, R_f(I)=0.73, R_f(III)=0.43, $C_{17}H_{11}N_3O_2$ (289.31) Calc. C 70.6 H 3.84 N 14.5 Found C 70.8 H 3.60 N 14.4
^{1}H-NMR (300MHz, [D_6] DMSO): 6.96 (s, 1H, ArCH=), 7.33-7.48 (m, 4H, H-8, H-17, H-18, H-19), 7.82 (dd, 1H, $J_{9,10}$=8.0Hz, $J_{9,7}$=2.0Hz, H-9), 8.06 (dd, $J_{10,9}$=8.0Hz, $J_{10,8}$=1.5Hz, H-10), 8.17 (dd, 2H, $J_{16,17}$=8.0Hz, $J_{16,18}$=1.8Hz, H-16, H-20), 8.59 (dd, 1H, $J_{7,8}$=8.5Hz, $J_{7,9}$=2.0Hz, H-7), 12.55 (br.s., 1H, NH).

IR: 3450(NH), 1720, 1705(C=O), 1660(ArCH=), 1605, 1595(C=N), 1575, 1478, 1320, 1105, 1075, 765, 690.
MS (m/z) 289(30,M^+), 261(15), 145(100), 117(27), 90(83), 76(18), 63(14)

3,3-diphenyl-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-2,5-dione (11)
The mixture of 2.82 g (0.01 mole) of 5,5-diphenyl-2-methylthioimidazoline-4-one (10)[17] and 1.37 g (0.01 mole) o anthranilic acid in 20 ml of acetic acid was refluxed for 5 hrs. In that time the solid appeared. The obtained crystalls wer filtered off and recrystallized from acetic acid to give 2.5 g of 11 m.p. 338-340°C yield 71%, R_f(I)=0.50, $C_{22}H_{15}N_3O$ (353.39) Calc. C 74.8 H 4.27 N 11.9 Found C 74.6 H 4.07 N 11.9
IR: 3416(NH), 1760, 1712(C=O), 1660, 1650(C=N), 1604, 1472, 1440, 1402, 766, 700, 668
MS (m/z) 353 (100, M^+), 324(13, M-HCO), 276(3), 205(2), 192(56), 167(28), 145(32), 104(12), 90(20), 77(13)

2-methylthio-3-ethyl-5,5-diphenylimidazoline-4-one (12)
Compound 11 was obtained in the similar way as 6 m.p. 121-122°C yield 91% R_f(II)=0.80 $C_{18}H_{18}N_2OS$ (310.41) Calc C 69.7 H 5.83 N 9.02 Found C 69.7 H 5.73 N 8.84
IR: 1726(C=O), 1560(C=N), 1444, 1364, 1344, 1324, 1236, 1118, 776, 768, 706, 668.

1-ethyl-3,3-diphenyl-2,3,4,5-tetrahydroimidazo-[2,1-b]-quinazoline-2,5-dione (13)
a. The suspension of 1.4 g (4 mmole) of imidazoqinazolinedione 11 in 50 ml of 5% NaOH was refluxed for 0.5h. Th solid was dissolved. After cooling the obtained precipitate of sodium salt of 11 was filtered off and dried. The alkylatio with ethyl iodide was performed as for product 3. Precipitation with water afforded crude product which wa recrystallized from ethanol to give white crystalls of 13 m.p. 191-193°C yield 66% R_f(II)=0.74, $C_{24}H_{19}N_3O_2$ (381.4- Calc. C 75.6 H 5.03 N 11.0 Found C 75.6 H 4.98 N 11.0
^{1}H-NMR (200MHz, $CDCl_3$): 1.45 (t, 3H, J=7.1Hz, CH_3), 4.01 (q, 2H, J=7.1Hz, CH_2), 7.40 (s, 11H, Ph-H, H-10), 7.6 7.73 (m, 2H, H-8, H-9), 8.16 (dd, 1H, $J_{7,8}$=7.9Hz, $J_{7,9}$=1.6Hz, H-7).
^{13}C-NMR ($CDCl_3$): 13.22(CH_3), 35.74(CH_2), 77.36(C-3), 120.90(C-6), 125.56(C-9), 126.57(C-8), 127.55(C-7 128.58(C-15), 128.86(C-16), 129.21(C-17), 134.95(C-10), 135.04(C-14), 148.14(C-11), 148.60(C-5), 158.76(C-2 171.79(C-13).
IR: 1748, 1690(C=O), 1636(C=N), 1604, 1472, 1440, 1416, 1328, 1112, 776, 736, 692, 668.
MS (m/z) 381 (100, M^+), 353 (57, M-CO), 324 (15, M-CO-Et), 192(11), 173(32), 171(42), 165(94), 145(41), 117(18 103(29), 90(45), 77(41), 63(15).
b. Compound 13 was obtained as a result of melting the mixture of 12 with stoichiometric ammount of anthranilic ac during 2 hrs at temp. 240-250°C yield 65%

Computational Procedures

All molecules were created and roughly optimised by using PCMODEL.4 [18] programme. MO calculations were carri out with AM1 method [19] using MOPAC programme (version 6.0) [20].

Acknowledgement

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References and Notes.

1. K. Kieć-Kononowicz, P. Leeson, S. Grimwood, J. Karolak-Wojciechowska and J. Handzlik, *Pharmazie* (19 submitted
2. K.Kieć-Kononowicz, A.Zejc, M.Mikołajczyk, A.Zatorski, M.W.Wieczorek and J.Karolak-Wojciechowska *Tetrahedron* 36, 1079 (1980)
3. K.Kieć-Kononowicz, A.Zejc, M.Mikołajczyk, A.Zatorski, M.W.Wieczorek and J.Karolak-Wojciechowska *Tetrahedron* 37, 409 (1981)
4. J.Karolak-Wojciechowska, M.Mikołajczyk, A.Zatorski, A.Zejc and K.Kieć-Kononowicz, *Tetrahedron* 41, 459 (1985)
5. J.Karolak-Wojciechowska, K.Kieć-Kononowicz and W.Kwiatkowski, *J.Crystallogr.Spectrosc.Res.* 18, 563 (1988)

6. K.Kieć-Kononowicz, A.Zatorski and J.Karolak-Wojciechowska, *Phosphorus, Sulfur and Silicon* **42**, 191 (1989)
7. K.Kieć-Kononowicz and J.Karolak-Wojciechowska, *Phosphorus, Sulfur and Silicon* **73**, 235 (1992)
8. K.Kieć-Kononowicz and J.Karolak-Wojciechowska, *Arch.Pharm (Weinheim)* **328**, 119 (1995)
9. K.Kieć-Kononowicz and J.Karolak-Wojciechowska, *Arch.Pharm (Weinheim)* **328**, 517 (1995)
10. H.Daboun, A.M.Abd-Elfattah, M.M.Hussein and A.F.A Shalaby, *Z.Naturforsch* **36b**, 366 (1981)
11. S.M.Hussain, M.A.Abdel-Aziz, N.A.Abdel-Reheim, *Egypt.J.Pharm.Sci* **30**, 309 (1989)
12. J.Karolak-Wojciechowska and K.Kieć-Kononowicz, *Acta Cryst.* **C51**, 1833 (1995)
13. G.Süss-Fink, G.F.Schmidt and G.Herrmann, *Chem.Ber.* **120**, 1451 (1987)
14. S.F.Tan, K.P.Ang and Y.F.Fong, *J.Chem.Soc.Perkin Trans.II* 1941 (1986)
15. Z.Kleinrok - *unpublished results*
16. H.Kupferberg, *Epilepsia* **30** (Suppl. 1) S51-S56 (1989)
17. H.C.Carrington and W.S.Waring, *J.Chem.Soc.* 354 (1950)
18. PCMODEL.4 Molecular Modeling Software for the IBM PC, Serena Software, Bloomington, (1990)
19. Stewart, J.J. *J.Comput.Chem.* **10**, 209 (1989)
20. MOPAC programme version 6, QCPE No. 455, (1990) Department of Chemistry, Indiana University, Bloomington, IN 47405

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