Bicyclic [*b*]-Heteroannulated Pyridazine Derivatives. 4 [1]. Cyclization Reactions of 4-Aryltetrahydropyridazine-3,6-dione 3-Hydrazones with Some Keto Esters

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Ethoxycarbonylalkylidene derivatives **2** and **6** of the title hydrazones were obtained in the reaction with ethyl pyruvate or ethyl aroylformate and ethyl acetoacetate, respectively, in methanol. Both compounds were mixtures of geometric isomers with high predominance of one of them. Nmr spectroscopy revealed an unexpected magnetic non-equivalence of the CH_2 protons in the ester ethyl group of the major isomer of **6**. On heating (~200°) in an inert medium or on refluxing in ethanolic sodium ethoxide **2** cyclized to the corresponding pyridazino[6,1-*c*]-triazines **4**, whereas **6** formed pyrazolylpyridazines **7**. The structure of the latter was unambigously established by X-ray analysis. Alkylation of **4a** with benzyl bromide in the presence of tetrabutylammonium bromide occurred selectively on the pyridazine *N* atom.

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Triazolo[4,3-*b*]pyridazines are well known as ligands of the benzodiazepine receptor [2-5]. The most active compound of this type, 3-methyl-6-(3-trifluoromethylphenyl)triazolo[4,3-*b*]pyridazine, often referred to as CL 218,872, was found *in vitro* to be an effective inhibitor of ^{3}H-diazepam and ^{3}H-flunitrazepam binding to the receptor [2,4,6-8]. Although, despite some early expectations, not introduced as a drug, it is still the object of pharmacological interest as a reference ligand with highly selective affinity for the ω_1 subtype of the benzodiazepine receptor [9,10].

Considering the convenient availabilty of the 4-aryl-substituted tetrahydropyridazine-3,6-dione 3-hydrazones [11-13], we report now on the use of these versatile reagents for the preparation of some bicyclic compounds with potential biological activity in the reaction with keto esters.

4-Aryltetrahydropyridazine-3,6-dione 3-hydrazones **1a-d**, obtained in the reaction of ethyl 3-aryl-3-cyanopropionate with hydrazine hydrate [11,12], reacted at room temperature with ethyl pyruvate and ethyl aroylformates to give ethyl 2-[(4-aryl-6-oxo-3-tetrahydropyridazinylidene)hydrazono]propanoates **2a-d** and ethyl α-[(4-phenyl-6-oxo-3-tetrahydropyridazinylidene)hydrazono]-arylacetates **2e-f**, respectively, in the yield of 40-50% (Scheme 1) [13]. In methanol at reflux temperature the conversion was higher (>70%) but purification was required to remove the cyclocondensation by-products.

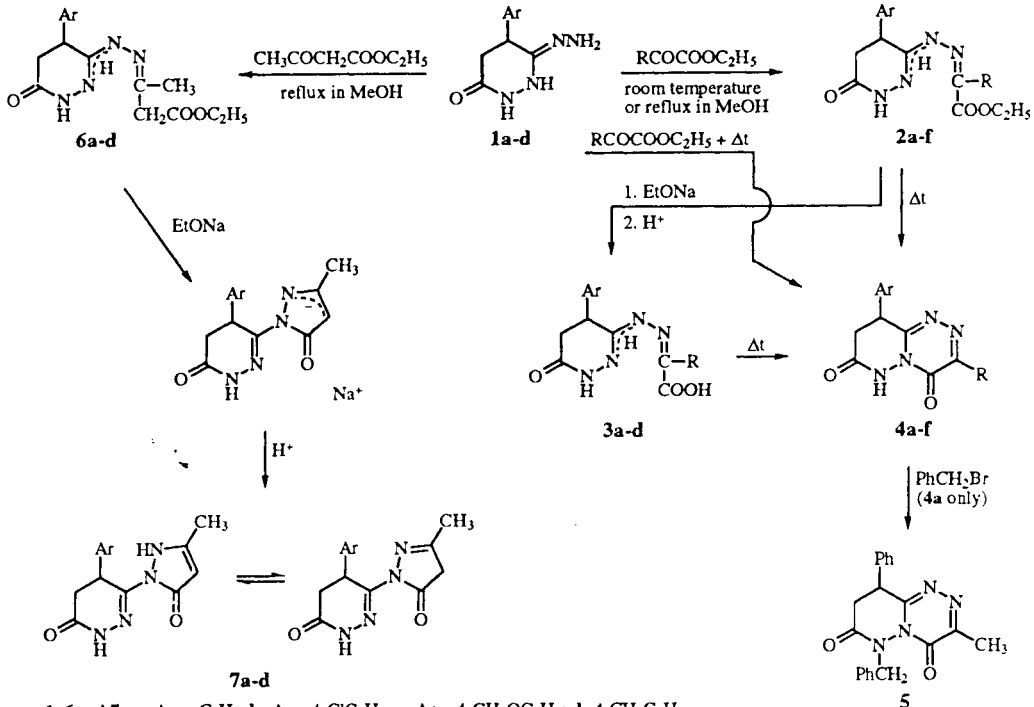
In the ^{1}H-nmr spectra of **2a-d** some signals of the side-chain protons were split thus indicating presence of two geometric isomers involving the C=N bond. This was seen most clearly with the singlet signal of the CH_3 group (2.17 in **2a**) which was accompanied with a low intensity (approximately 15% of the intensity of the former) singlet at δ 2.09. No attempts were made to separate the isomers.

Cyclization of **2** to the pyridazino[6,1-*c*][1,2,4]triazine derivatives **4a-f** was effected most conveniently by heating at approximately 200°, preferably in a high boiling solvent such as 2-(2-ethoxyethoxy)ethanol or ethylene glycol. A similar cyclization of the acids **3a-d**, prepared from **2a-d** by routine sodium ethoxide alcoholysis, gave much lower yields since several recrystallizations were required to remove by-products. The bicyclic compounds **4e-f** were also obtained, although in moderate yields, in a direct condensation of **1a** with the appropriate ethyl aroylformate in refluxing 2-(2-ethoxyethoxy)ethanol or ethylene glycol.

Alkylation of **4a** with benzyl bromide in DMF in the presence of tetrabutylammonium bromide and potassium hydroxide yielded a compound for which the structure of the 6-benzyl derivative **5** was assigned. The assignment was based on the ^{1}H-nmr spectrum in which the benzyl CH_2 protons appeared as a double doublet (AB splitting pattern) owing to chirality of the tetrahedral N6 atom. The formation of the *O*-benzylated compound was not observed [14].

The reaction of **1a-d** with ethyl acetoacetate yielded the corresponding ethyl 3-[(4-aryl-6-oxotetrahydro-3-pyridazinylidene)hydrazono]butanoates **6a-d**. In this case, too, two sets of signals (approximately 6:1 intensity ratio) observed in the ^{1}H-nmr spectra of **6** indicated presence of geometric isomers involving the C=N bond formed in the condensation reaction. Moreover, an unexpected and interesting magnetic non-equivalence of the CH_2 protons in the ester ethyl group (δ 4.08 and 4.10 ppm, a quartet of double-doublet signals of unequal intensities resulting from the combination of the AB- and AX_3-pattern spin couplings) was observed in the spectrum of the major isomer of **6a**. Both protons have practically identical coupling constants

Scheme 1



1, 6 and **7**, **a**: Ar = C_6H_5; **b**: Ar = 4-ClC_6H_4; **c**: Ar = 4-$CH_3OC_6H_4$; **d**: 4-$CH_3C_6H_4$
2, 3 and **4**, **a-d**: Ar as in **1**, R = CH_3; **e**: Ar = R = C_6H_5; **f**: Ar = C_6H_5, R = 3-$O_2NC_6H_4$

with the methyl group (J = 7.2 Hz) and are coupled with one another with J = 11.0 Hz. Since there are distinct proton-donating and -accepting sites in the molecule, intra- and/or intermolecular hydrogen bonds may be responsible for this non-equivalence. For instance, if one considers the (*Z*)-configuration on the C=N bond formed in the condensation reaction, rotation of the ethoxycarbonylmethyl fragment about the C-C bond can bring the ester alkoxy and carbonyl oxygen atoms quite close (approximately 2.5 Å) to the hydrogen atom attached to N1. The C=N bond linking the chain with the pyridazine core may be involved in a prototropic rearrangement (N2 = C3 or C3 = exocyclic N) [12] so consideration of the (*Z*)-(*E*) isomerism on this bond is hardly possible at present. The assignments of the ^1H- and ^{13}C-nmr signals in the spectrum of both isomers of **6a** are given in detail in the Experimental. The spectra of **6b** and **6d** show a similar non-equivalence but the ester group signals of the major and minor isomers closely overlap each other and therefore they are reported as multiplets. No such non-equivalence was noted in the case of the methoxy derivative **6c**.

When heated with ethanolic sodium ethoxide **6** cyclized with elimination of ethanol. Subsequent acidification of the initially obtained sodium derivatives yielded the corresponding *aci*-forms. Considering the possible tautomerism of **6** [12], the cyclization could have occurred either on N2 with the formation of a 7-membered triazepine ring fused with the pyridazine or on the hydrazine nitrogen atom with the formation of a 5-membered pyrazole ring not fused with the pyridazine. Earlier reports on similar cyclocondensations with various nitrogen heterocycles are rather confusing in that point. Thus, the reaction of ethyl acetoacetate with a derivative of 2-hydrazinothiazole was reported to yield the corresponding thiazolotriazepine [15]. On the other hand, there are several reports on the formation of pyrazolyl heterocycles in related reactions [16-19]. The latter possibility was certainly much more likely but it was not possible to get a definite answer by examination of the ir and nmr spectra of **7**. Since the non-aromatic character of the pyridazine ring distinguished **6** from the objects of those earlier investigations, one of the cyclic compounds, **7d** obtained from **6d**, was subject to an X-ray analysis which confirmed the formation of a pyrazolone. The ORTEP drawing of this structure with atom numbering and selected intermolecular hydrogen bonds is shown as Figure 1 while the non-hydrogen fractional atomic coordinates are collected in Table 1, and bond length and angle data, in Table 2 [20].

In the folded pyridazine ring of **7d**, the sp^3-hybridized C5 atom is located 0.567(6)Å above the plane defined by the two nitrogen atoms and the two sp^2-hybridized carbon atoms C3 and C6 (plane *i*). The dihedral angle between this plane and the phenyl ring was found to be 86.9(2)°. The pyrazolone ring is roughly planar and is twisted by 77.1(2)° with respect to the *i* plane. Standard bond lengths and valence angles characterize the pyridazine and phenyl rings.

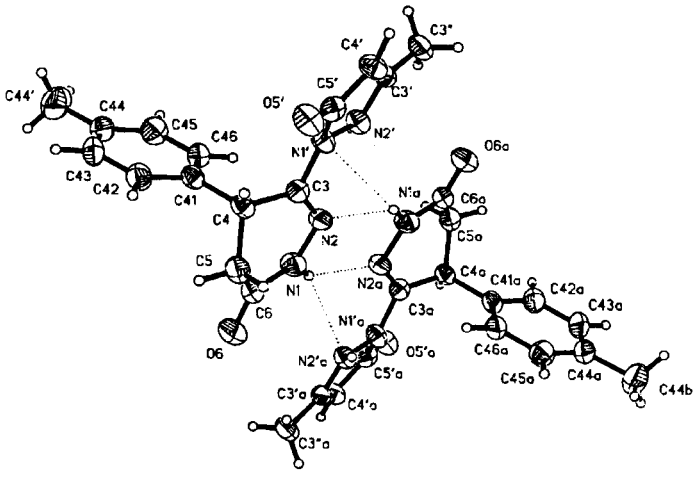


Figure 1. Molecular structure of the **7d** crystal presented as a centrosymmetric hydrogen-bonded dimer. For the sake of drawing clarity, the strong hydrogen bond (N2'-H2'...O5') extending along the x axis is not shown.

It was possible to locate the proton bonded to N2' in the pyrazolone moiety using X-ray techniques. The C3'-C4' distance (1.356(8) Å) indicates the presence of a double bond between these atoms. Other endocyclic bonds are relatively short, whereas the exocyclic C5'-O5' bond is slightly longer than expected (1.260(7) Å). The hybridization of the N2' atom is close to sp^2 (the sum of valence angles around this atom is 353.9). Crystals of **7d** show therefore a possible tautomerism of this compound (Scheme 2).

Table 1

Fractional Atomic Coordinates (x 10^{-4}) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for the Non-hydrogen Atoms of **7d**. U_{eq} defined as 1/3 of the trace of the orthogonalized U_{ij} tensor

Atom	x/a	y/b	z/c	U_{eq}
C3	4144(10)	-1266(6)	-854(5)	30(1)
N2	2357(9)	-585(5)	-524(4)	36(1)
N1	1502(9)	565(5)	-1241(4)	40(1)
C6	2759(11)	1215(6)	-2120(5)	37(1)
O6	1857(8)	2221(5)	-2694(4)	58(1)
C5	5200(10)	660(6)	-2256(5)	38(2)
C4	5501(10)	-878(6)	-1931(4)	32(1)
N1'	4729(8)	-2520(5)	-182(4)	34(1)
N2'	2976(8)	-3038(5)	573(4)	34(1)
C3'	4044(11)	-4115(5)	1248(4)	33(1)
C3"	2557(11)	-4940(6)	2080(5)	43(2)
C4'	6382(10)	-4203(6)	1015(5)	38(2)
C5'	6879(10)	-3177(6)	113(5)	33(1)
O5'	8774(7)	-2829(4)	-371(3)	44(1)
C41	4758(10)	-1600(6)	-2819(4)	33(1)
C42	6104(11)	-1581(6)	-3790(5)	44(2)
C43	5520(12)	-2222(6)	-4628(5)	48(2)
C44	3480(12)	-2855(6)	-4518(5)	44(1)
C45	2121(12)	-2863(7)	-3553(5)	48(2)
C46	2682(11)	-2208(6)	-2722(5)	38(1)
C44'	2825(14)	-3550(8)	-5422(6)	71(2)

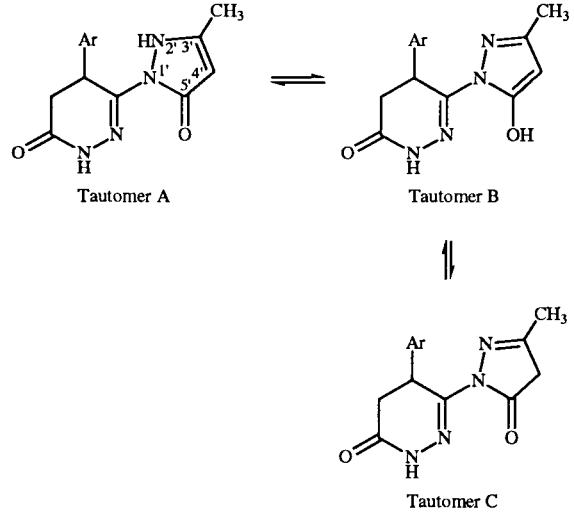
Table 2

Bond Lengths (Å) and Bond Angles (deg) in **7d**

C(3)-N(2)	1.266(8)	N(2)-C(3)-C(4)	124.5(5)
C(3)-C(4)	1.503(8)	N(2)-C(3)-N(1')	115.7(5)
C(3)-N(1')	1.412(7)	C(4)-C(3)-N(1')	119.6(5)
N(2)-N(1)	1.400(6)	C(3)-N(2)-N(1)	117.7(5)
N(1)-C(6)	1.365(8)	N(2)-N(1)-C(6)	124.5(5)
C(6)-O(6)	1.224(7)	N(1)-C(6)-O(6)	119.5(6)
C(6)-C(5)	1.472(8)	N(1)-C(6)-C(5)	115.3(5)
C(5)-C(4)	1.536(8)	O(6)-C(6)-C(5)	125.1(6)
C(4)-C(41)	1.531(9)	C(6)-C(5)-C(4)	112.6(5)
N(1')-N(2')	1.402(6)	C(3)-C(4)-C(5)	108.2(5)
N(1')-C(5')	1.387(7)	C(3)-C(4)-C(41)	111.2(5)
N(2')-C(3')	1.369(7)	C(5)-C(4)-C(41)	113.0(5)
C(3')-C(3")	1.484(8)	C(3)-N(1')-N(2')	116.5(5)
C(3')-C(4')	1.356(8)	C(3)-N(1')-C(5')	131.0(5)
C(4')-C(5')	1.415(8)	N(2')-N(1')-C(5')	109.6(5)
C(5')-O(5')	1.260(7)	N(1')-N(2')-C(3')	105.9(4)
C(41)-C(42)	1.379(8)	N(2')-C(3')-C(3")	117.9(5)
C(41)-C(46)	1.391(9)	N(2')-C(3')-C(4')	110.3(5)
C(42)-C(43)	1.394(10)	C(3")-C(3')-C(4')	131.8(5)
C(43)-C(44)	1.385(10)	C(3')-C(4')-C(5')	108.4(5)
C(44)-C(45)	1.377(9)	N(1')-C(5')-C(4')	105.4(5)
C(44)-C(44')	1.511(11)	N(1')-C(5')-O(5')	122.7(5)
C(45)-C(46)	1.392(10)	C(4')-C(5')-O(5')	131.9(6)
		C(4)-C(41)-C(42)	119.4(5)
		C(4)-C(41)-C(46)	122.6(5)
		C(42)-C(41)-C(46)	117.8(5)
		C(41)-C(42)-C(43)	122.1(6)
		C(42)-C(43)-C(44)	119.9(6)
		C(43)-C(44)-C(45)	118.0(6)
		C(43)-C(44)-C(44')	120.4(6)
		C(45)-C(44)-C(44')	121.5(6)
		C(44)-C(45)-C(46)	122.1(6)
		C(41)-C(46)-C(45)	119.8(6)

From the thermodynamic point of view the form C, shown in Scheme 2, appears to be the most stable. The heat of its formation, calculated by the PM3-MNDO method, is 8.09 kcal/mole as compared with 12.13 and 18.84 kcal/mole for tautomers **A** and **B**, respectively [21]. In the crystalline state, however, presumably because of the presence of the

Scheme 2



NH group which favors the formation of intermolecular hydrogen bonds, tautomer **A** predominates. Two bifurcate hydrogen bonds (N1-H1....N2 and N1-H1....N2') join two molecules of **7d** together which forms a dimer with the molecules related by a center of symmetry (Figure 1). Another strong hydrogen bond (N2'-H2'....O5'), which for the sake of clarity is not shown in Figure 1, links one dimer to another dimer separated by a cell translation along the *x* axis (Table 3). It is worth noting that the latter hydrogen bond may be regarded as a kind of a bridge through which the H2' proton can pass from N2' to O5' and *vice versa* in the interconversion of the **A** and **B** tautomers.

Table 3

Hydrogen Bonding Contacts (Å) and Angles (deg)

X-H...Y	X-H	H...Y	X...Y	X-H...Y	Symmetry translation of Y
N1-H1....N2	0.95(7)	2.217(6)	3.002(7)	139.7(4)	-x, -y, -z
N1-H1....N2'	0.95(7)	2.754(6)	3.576(7)	145.5(4)	-x, -y, -z
N2'-H2'....O5'	1.05(7)	1.739(6)	2.736(6)	156.3(4)	-1+x, y, z

Analysis of the molecular electrostatic potential distribution [21-23] in **4a-f** revealed two distinct minima associated with the =N-N= fragment of the triazine ring and with the carbonyl oxygen in the pyridazine ring, *i.e.*, with atoms capable of acting as proton acceptors in the hydrogen-bond binding of the ligand with the receptor protein. Since the distance between them (approximately 7.7 Å) was quite close to that found analytically in the known triazolopyridazine ligands of the benzodiazepine receptor [24], the compounds were tested *in vitro* for receptor affinity in competition with ^{3}H-flunitrazepam [25,26]. Inhibition of the labeled ligand binding was, however, very low (<10%). The failure was considered to be caused either by non-planarity of the hydropyridazine ring, which is not a π-electron structure, or by adverse position of the aryl substituent, which may be directed towards an inaccessible region of the receptor protein [27]. Further research is being carried on to account for that problem.

EXPERIMENTAL

General Methods.

Melting points were determined in a Büchi apparatus and are reported uncorrected. The ir spectra were recorded in potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were taken with Varian 300 and 200 MHz instruments with TMS as internal standard. Microanalyses were carried out by Mrs. E. Godzisz, Warsaw University of Technology, on a Perkin-Elmer C-H-N analyzer. Merck DC-Plastikfolien with Kieselgel 60 were used in tlc purity checking; the chloroform-methanol-ethyl acetate-saturated aqueous ammonia 3:2:1:0.1 developing system was used. The yield data refer to recrystallized, chromatographically homogeneous compounds.

General Procedure for the Preparation of Ethyl 2-[(4-Aryl-6-oxo-3-tetrahydropyridazinylidene)hydrazono]propanoates **2a-d**.

Ethyl pyruvate (0.55 mole) was added to the suspension of the appropriate 4-aryltetrahydropyridazine-3,6-dione 3-hydrazone (0.05 mole) in 100 ml of methanol. Within 10-20 minutes the mixture became homogeneous but another product began to precipitate soon. The mixture was refluxed gently for four hours, cooled and filtered to yield **2**. Crude products were purified by recrystallization from ethanol.

Ethyl 2-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]propanoate (**2a**).

This compound was obtained from **1a** as colorless crystals, mp 195-196°, yield 79%; ir: ν 3340 and 3180 (NH), 1695 (ester C=O), 1660 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 1.44 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.17 (s, 3H, CH_3), 3.07-3.47 (m, 2H, CH_2), 4.34 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.81-4.92 (m, 1H, CH), 7.34-7.69 (m, 5H, arom), 10.48 (s, 1H, NH), 10.56 ppm (s,1H, NH).

Anal. Calcd. for $C_{15}H_{18}N_4O_3$ (302.33): C, 59.59; H, 6.00; N, 18.53. Found: C, 59.62; H, 6.12; N, 18.41.

Ethyl 2-{[4-(4-Chlorophenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}propanoate (**2b**).

This compound was obtained from **1b** as colorless crystals, mp 164-165°, yield 83%;. ir: ν 3330 and 3170 (NH), 1690 (ester C=O), 1660 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.26 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.03 (s, 3H, CH_3), 3.17-3.38 (m, 2H, CH_2), 4.17 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.94-5.00 (m, 1H, CH), 7.04-7.33 (m, 4H, arom), 10.53 (s, 1H, NH), 10.59 ppm (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{17}ClN_4O_3$ (336.78): C, 53.50; H, 5.09; N, 16.64. Found: C, 53.44; H, 5.23; N, 16.41.

Ethyl 2-{[4-(4-Methoxyphenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}propanoate (**2c**).

This compound was obtained from **1c** as colorless crystals, mp 163-164°, yield 78%; ir: ν 3330 and 3210 (NH), 1675 (ester C=O), 1640 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.26 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.04 (s, 3H, CH_3), 2.98-3.29 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.84-4.95 (m, 1H, CH), 6.58-7.38 (m, 4H, arom), 10.59 ppm (broad s, 2H, NH and NH).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$ (332.36): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.73; H, 6.05; N, 16.80.

Ethyl 2-{[4-(4-Methylphenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}propanoate (**2d**).

This compound was obtained from **1d** as colorless crystals, mp 193-194°, yield 75%; ir: 3330 and 3240 (NH), 1670 (ester C=O), 1640 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.03 (s, 3H, CH_3C=N), 2.21 (s, 3H, $CH_3C_6H_4$), 3.04-3.31 (m, 2H, CH_2), 4.18 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.92-5.08 (m, 1H, CH), 6.74-7.43 (m, 4H, arom), 10.67 ppm (broad s, 2H, NH and NH).

Anal. Calcd. for $C_{16}H_{20}N_4O_3$ (316.36): C, 60.75; H, 6.37; N, 17.71. Found: C, 60.66; H, 6.21; N, 17.68.

General Procedure for Preparation of 2-[(4-Aryl-6-oxo-3-tetrahydropyridazinylidene)hydrazono]propanoic Acids **3a-d**.

The appropriate **2** (0.02 mole) was added with stirring to a sodium ethoxide solution prepared from 0.022 mole of sodium and 60 ml of anhydrous ethanol. The mixture was refluxed 3 hours, cooled, diluted with 100 ml of anhydrous diethyl ether and left standing overnight in a refrigerator. The sodium salt (almost quantitative yield) was filtered off, dissolved in 50 ml of water and the solution acidified under cooling with 20 ml of acetic acid. The filtered product was thoroughly dried (vacuum over phosphorus pentoxide) and purified by recrystallization from nitromethane.

2-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]-propanoic Acid **3a**.

This compound was obtained from **2a** as colorless crystals, mp 190-191° dec, yield 95%; ir: 3330 and 3210 (NH), 1685 (acid C=O), 1645 (amide C=O) cm^{-1}. ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 1.93 (s, 3H, CH_3), 2.85-3.19 (m, 2H, CH_2), 4.68-4.82 (m, 1H, C*H*), 7.19-7.42 (m, 5H, arom), 9.47-10.51 ppm (broad signal, 3H, N*H* and COO*H*).

Anal. Calcd. for $C_{13}H_{14}N_4O_3$ (274.28): C, 56.93; H, 5.14; N, 20.43. Found: C, 56.53; H, 5.22; N, 20.19.

2-{[4-(4-Chlorophenyl)-6-oxo-3-tetrahydropyridazinylidene]-hydrazono}propanoic Acid (**3b**).

This compound was obtained from **2b** as off-white crystals, mp 190-191° dec, yield 85%.

Anal. Calcd. for $C_{13}H_{13}ClN_4O_3$ (308.72): C, 50.58; H, 4.24; N, 18.15. Found: C, 50.48; H, 4.08; N, 18.05.

2-{[4-(4-Methoxyphenyl)-6-oxo-3-tetrahydropyridazinylidene]-hydrazono}propanoic Acid (**3c**).

This compound was obtained from **2c** as yellowish crystals, mp 194-195° dec, yield 78%.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$ (304.31): C, 55.26; H, 5.30; N,18.41. Found: C, 55.11; H, 5.24; N, 18.48.

2-{[4-(4-Methylphenyl)-6-oxo-3-tetrahydropyridazinylidene]-hydrazono}propanoic Acid (**3d**).

This compound was obtained from **2d** as colorless crystals, mp 196-197° dec, yield 78%.

Anal. Calcd. for $C_{14}H_{16}N_4O_3$ (288.31): C, 58.32; H, 5.59; N, 19.43. Found: C, 58.36; H, 5.47; N, 19.35.

General Procedure for Preparation of 9-Aryl-8.9-dihydro-3-methyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazine-4,7(6*H*)-diones **4a-d**.

A solution of 0.01 mole of **2** in 50 ml of 2-(2-ethoxy-ethoxy)ethanol was refluxed 4 hours and the solvent distilled *in vacuo*. The tan, thick residue was treated with 15 ml of ethanol and cooled in dry ice. The crystalline product was filtered off and recrystallized from ethanol.

An analogous procedure applied to the acid **3a** gave a crude mixture consisting of at least 3 compounds (tlc). Upon repeated recrystallization from butanol, **4a** was obtained in the yield as low as 20%.

8,9-Dihydro-3-methyl-9-phenyl-4*H*-pyridazino[6,1-*c*][1,2,4]-triazine-4,7(6*H*)-dione (**4a**).

This compound was obtained as colorless crystals, mp 181-182° dec, yield 83% from **2a** and 20% from **3a**; ir: ν 3260 (NH), 1730 and 1680 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.67 (s, 3H, CH_3), 3.38-3.77 (m, 2H, CH_2), 4.98-5.27 (m, 1H, C*H*), 7.30-7.77 ppm (m, 5H, arom).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$ (256.26): C, 60.93; H, 4.72; N, 21.86; Found: C, 60.82; H, 4.72; N, 21.77.

9-(4-Chlorophenyl)-8,9-dihydro-3-methyl-4*H*-pyridazino[6,1-*c*]-[1,2,4]triazine-4,7(6*H*)-dione (**4b**).

This compound was obtained from **2b** as lightly tan crystals, mp 225-226° dec, yield 75%; ir: ν 3160 (NH), 1720 and 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.68 (s, 3H, CH_3), 3.32-3.62 (m, 2H, CH_2), 4.94-5.27 (m, 1H, C*H*), 7.36-7.61 ppm (m, 4H, arom).

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$ (290.71): C, 53,71; H, 3.81; N, 19.27. Found: C, 53.67; H, 3.86; N, 19.12.

8,9-Dihydro-9-(4-methoxyphenyl)-3-methyl-4*H*-pyridazino[6,1-*c*]-[1,2,4]triazine-4,7(6*H*)-dione (**4c**).

This compound was obtained from **2c** as lightly tan crystals, mp 199-201° dec, yield 62%; ir: ν 3160 (NH), 1705 and 1685 (C=O) cm^{-1}. ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.65 (s, 3H, CH_3), 3.32-3.67 (m, 2H, CH_2), 3.97 (s, 3H, OCH_3), 4.97-5.18 (m, 1H, C*H*), 6.99-7.54 ppm (m, 4H, arom).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$ (286.29); C, 58.74; H, 4.93; N, 19.57. Found: C, 58.32; H, 4.71; N, 19.24.

8,9-Dihydro-3-methyl-9-(4-methylphenyl)-4*H*-pyridazino[6,1-*c*]-[1,2,4]triazine-4,7(6*H*)-dione (**4d**).

This compound was obtained from **2d** as colorless crystals, mp 222-224° dec, yield 76%; ir: ν 3170 (NH), 1710 and 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.41 (s, 3H, $CH_3C_6H_4$), 2.64 (s, 3H, CH_3C=N), 3.25-3.62 (m, 2H, CH_2), 4.88-5.25 (m, 1H, C*H*), 7.11-7.38 ppm (m, 4H, arom).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$ (270.29): C, 62.21; H, 5.22; N, 20.73. Found: C, 62.06; H, 5.13; N, 20.54.

6-Benzyl-8,9-dihydro-3-methyl-9-phenyl-4*H*-pyridazino[6,1-*c*]-[1,2,4]triazine-4,7(6*H*)-dione (**5**).

Tetrabutylammonium bromide (0.13 g, 0.0004 mole), powdered potassium hydroxide (0.1 g, 0.002 mole) and benzyl bromide (0.39 g, 0.0023 mole) were added to the solution of 0.5 g (0.002 mole) of **4a** in 7.5 ml of anhydrous DMF. The mixture was stirred 6 hours at room temperature, the solvent was distilled *in vacuo* and the oily residue was treated with chloroform. Filtration removed some inorganic salts and the filtrate was repeatedly washed with saline and water. Evaporation of the chloroform left a yellowish oil which slowly solidified. Recrystallization from ethanol yielded 46% of **5** as colorless crystals, mp 148-150; ir: ν 1700 and 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.65 (s, 3H, CH_3), 3.40-3.75 (m, 2H, endocyclic CH_2), 4.62-4.84 (m, 1H, C*H*), 5.08 (d, ^2J =15.7 Hz, 1H, benzyl CH_2), 5.29 (d, ^2J =15.7 Hz, 1H, benzyl CH_2), 7.38-7.69 ppm (m, 10H, arom).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$(346.39): C, 69.35; H, 5.24; N, 16.17. Found: C, 69.22; H, 5.29; N, 16.21.

General Procedure for Preparation of Ethyl α-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]arylacetates **2e-f**.

Ethyl aroylformate (0.011 mole) and **1a** (0.023 mole) were dissolved in 2 ml of methanol and left standing at room temperature for 7 days and next at 0° for 5 days. The precipitated product was recrystallized from methanol.

Ethyl α-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]phenylacetate (**2e**).

This compound was obtained from **1a** and ethyl benzoylformate as colorless crystals, mp 192-194°, yield 30%; ir: ν 3290, 3180 and 3120 (NH), 1700 and 1670 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.57-2.80 (m, 2H, $CHCH_2$), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.67-4.80 (m, 1H, $CHCH_2$), 7.04-7.50 ppm (m, 10H, arom).

Anal. Calcd. for $C_{20}H_{20}N_4O_3$ (364.40): C, 65.92; H, 5.53; N, 15.37. Found: C, 65.70; H, 5.57; N,15.30.

Ethyl α-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]-3-nitrophenylacetate (**2f**).

This compound was obtained from **1a** and ethyl 3-nitrobenzoylformate as light yellow crystals, mp 167-169°, yield 35%; ir: ν 3290 and 3190 (NH), 1720 and 1670 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.30 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.42-2.79 (m, 2H, $CHCH_2$), 4.24 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.62-4.89 (m, 1H, $CHCH_2$), 7.29-8.11 ppm (m, 9H, arom).

Anal. Calcd. for $C_{20}H_{19}N_5O_5$ (409.40): C, 58.68; H, 4.68; N, 17.11. Found: C, 58.36; H, 4.70; N, 16.97.

General Procedure for Preparation of 3-Aryl-8,9-dihydro-9-phenyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazine-4,7(6*H*)-diones **4e-f**.

These compounds were prepared from **2e-f** analogously as described for **4a-d** or directly from **1a** and the appropriate aroylformate as follows: **1a** (0.0023 mole) and 0.0112 mole of ethyl aroylformate were refluxed for 30 minutes in 5 ml of 2-(ethoxyethoxy)ethanol. The crystals which separated on cooling were filtered off and purified by recrystallization.

8,9-Dihydro-3,9-diphenyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazine-4,7(6*H*)-dione (**4e**).

This compound was obtained as lightly yellow crystals, mp 251-251° (nitromethane), yield 85% from **2e** and 56% from **1a**; ir: ν 3180 (NH), 1715 and 1680 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 3.07-3.54 (m, 2H, CH_2), 4.85-5.30 (m, 1H, CH), 7.12-8.15 ppm (m, 10H, arom).

Anal. Calcd. for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.92; H, 4.43; N, 17.60. Found: C, 67.80; H, 4.42; N, 17.51.

8,9-Dihydro-3-(3-nitrophenyl)-9-phenyl-4*H*-pyridazino[6,1-*c*]-[1,2,4]triazine-4,7(6H)-dione (**4f**).

This compound was obtained as yellow crystals, mp 250-251° (methanol), yield 55% from **2f** and 38% from **1a**; ir: ν 3190 (NH) 1710 and 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 3.20-3.52 (m, 2H, CH_2), 4.85-5.19 (m, 1H, CH), 7.25-8.02 ppm (m, 9H, arom).

Anal. Calcd. for $C_{18}H_{13}N_5O_4$ (363.33): C, 59.50; H, 3.61; N, 19.28. Found: C, 59.65; H, 3.79; N, 19.30.

General Procedure for Preparation of Ethyl 3-[(4-Aryl-6-oxo-3-tetrahydropyridazinylidene)hydrazono]butanoates **6a-d**.

A mixture of 0.05 mole of the appropriate **1** and 0.075 mole (9.76 g) of ethyl acetoacetate in 100 ml of methanol was refluxed gently for 4 hours. Evaporation of the solvent left a solid product which was washed with a small volume of thoroughly cooled ethyl ether and then with hexane and finally recrystallized to yield **6**.

Ethyl 3-[(6-Oxo-4-phenyl-3-tetrahydropyridazinylidene)hydrazono]butanoate (**6a**).

This compound was obtained from **1a** as colorless crystals, mp 139-141° (nitromethane), yield 92%; ir: ν 3240 and 3255 (NH), 1740 (ester C=O), 1660 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform) of the major isomer: δ 1.20 (t, ^{3}J = 7.15 Hz, 3H, CH_2CH_3), 1.88 (s, 3H, $=CCH_3$), 2.79 and 2.81 (2 dd, ^{2}J = 16.7 Hz, ^{3}J = 3.8 and 7.5 Hz, 2 non-equivalent H, endocyclic CH_2), 3.20 (s, 2H, $=CCH_2$), 4.08 and 4.10 (4 dd, ^{2}J = 11.0 Hz, ^{3}J = 7.2 Hz, 2 non-equivalent H, CH_2CH_3), 4.73 (m, 1H, CH), 7.29-7.32 (m, 5H, arom), 9.43 (s, 1H, NH), 10.23 ppm (s, 1H, NH); ^{13}C-nmr (deuteriochloroform) of the major isomer: δ 14.1 (CH_2CH_3), 15.9 ($=CCH_3$), 34.2 (endocyclic CH_2), 36.7 (CH), 44.7 ($=CCH_2$), 60.9 (CH_2CH_3), 127.4, 127.6, and 129.0 (arom CH), 137.5 (arom C), 143.9 (exocyclic C=N), 154.7 (endocyclic C=N), 167.3 (ester C=O), 170.0 ppm (pyridazine C=O); ^{1}H-nmr (deuteriochloroform) of the minor isomer: δ 1.17 (t, ^{3}J = 7.2 Hz, 3H, CH_2CH_3), 1.98 (s, 3H, $=CCH_3$), 2.81 and 2.83 (2 dd, 2 non-equivalent H, ^{2}J = 16.8 Hz, ^{3}J = 3.9 and 7.4 Hz, endocyclic CH_2), 3.25 (s, 2H, $=CCH_2$), 4.04 (q, ^{3}J = 7.2 Hz, 2H, CH_2CH_3), 4.55 (m, 1H, CH), 7.29-7.32 ppm (m, 5H, arom); ^{13}C-nmr (deuteriochloroform) of the minor isomer: 14.1 (CH_2CH_3), 24.3 ($=CCH_3$), 34.4 (endocyclic CH_2), 37.5 (CH), 46.3 ($=CCH_2$), 61.5 (CH_2CH_3), 127.5, 127.7, and 129.1 (arom CH), 137.36 (arom C), 143.9 (exocyclic C=N), 153.7 (endocyclic C=N), 167.1 (ester C=O), 168.3 ppm (pyridazine C=O).

Anal. Calcd. for $C_{16}H_{20}N_4O_3$ (316.36): C, 60.75; H, 6.37; N, 17.71. Found: C, 60.67; H, 6.31; N, 17.88.

Ethyl 3-{[4-(4-Chlorophenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}butanoate (**6b**).

This compound was obtained from **2b** as colorless crystals, mp 146-148° (ethanol), yield 75%; ir: ν 3260 (NH), 1740 (ester C=O), 1665 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.15 (t, 3H, CH_2CH_3), 1.88 (s, 3H, $=CCH_3$), 2.63-2.78 (m, 2H, endocyclic CH_2), 3.08 (s, 2H, $=CCH_2$), 3.97 (q, 2H, CH_2CH_3), 4.71-4.76 (m, 1H, CH), 7.12-7.37 (m, 4H, arom), 9.93 (s, 1H, NH), 10.63 ppm (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{19}ClN_4O_3$ (350.80): C, 54.78; H, 5.46; N, 15.97. Found: C, 55.02; H, 5.50; N, 15.89.

Ethyl 3-{[4-(4-Methoxyphenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}butanoate (**6c**).

This compound was obtained from **2c** as colorless crystals, mp 184-185° (ethanol-2-methoxyethanol 1:3), yield 91%; ir: ν 3240 (NH), 1735 (ester C=O), 1655 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.18 (t, 3H, CH_2CH_3), 1.90 (s, 3H, $=CCH_3$), 2.61-2.80 (m, 2H, endocyclic CH_2), 3.15 (s, 2H, $=CCH_2$), 3.60 (s, 3H, OCH_3), 3.84 (q, 2H, CH_2CH_3), 4.70-4.76 (m, 1H, CH), 6.92-7.04 (m, 4H, arom), 9.83 (s, 1H, NH), 10.52 ppm (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{22}N_4O_4$ (346.39): C, 58.95; H, 6.40; N, 16.17. Found: C, 58.79; H, 6.57; N, 15.97.

Ethyl 3-{[4-(4-Methylphenyl)-6-oxo-3-tetrahydropyridazinylidene]hydrazono}butanoate (**6d**).

This compound was obtained from **2d** as colorless crystals, mp 149-150° (ethanol), yield 71%; ir: ν 3250 (NH), 1735 (ester C=O), 1670 (amide C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.13 (t, 3H, CH_2CH_3), 1.84 (s, 3H, $=CCH_3$), 2.22 (s, 3H, $C_6H_4CH_3$), 2.63-2.76 (m, 2H, endocyclic CH_2), 3.11 (s, 2H, $=CCH_2$), 4.00 (q, 2H, CH_2CH_3), 4.62-4.74 (m, 1H, CH), 6.97-7.09 (m, 4H, arom), 9.73 (s, 1H, NH), 10.49 ppm (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{22}N_4O_3$ (330.39): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.66; H, 6.60; N, 16.89.

General Procedure for Preparation of 3-(2,4-dihydro-5-methyl-3-oxo-3*H*-pyrazol-2-yl)-4-aryl-4,5-dihydropyridazin-6(1*H*)-ones (**7a-d**).

The appropriate **6** (0.02 mole) was added portionwise to a sodium ethoxide solution prepared from 0.51 g (0.022 mole) of sodium and 50 ml of ethanol. The mixture was refluxed with stirring for 3 hours, cooled and filtered. The obtained sodium salt (approximately 90% yields) was dissolved in 50 ml of water and the solution acidified with 2*N* hydrochloric acid. The crude product was dissolved in methanol and the solution was passed through a silica gel column. Recrystallization from methanol gave pure products.

3-(2,4-dihydro-5-methyl-3-oxo-3*H*-pyrazol-2-yl)-4,5-dihydro-4-phenylpyridazin-6(1*H*)-one (**7a**).

This compound was obtained from **6a** as colorless crystals, mp 209-210°, yield 92%; ir: ν 3170 (NH), 1665 and 1630 (C=O) cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.08 (s, 3H,CH_3), 2.55 (s, 2H, CH_2), 3.07-3.13 (m, 2H, CHCH_2), 5.41-5.47 (m, 1H, C*H*CH_2), 7.19-7.36 (m, 5H, arom), 10.72 ppm (s,1H, N*H*).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$ (270.29): C, 62.21; H, 5.22; N, 20.73; Found: C, 62.07; H, 5.20; N, 20.68.

3-(2,4-Dihydro-5-methyl-3-oxo-3*H*-pyrazol-2-yl)-4-(4-chlorophenyl)-4,5-dihydropyridazin-6(1*H*)-one (**7b**).

This compound was obtained from **6b** as colorless crystals, mp 210-211°, yield 82%; ir: ν 3170 (NH), 1670 and 1620 (C=O) cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.08 (s, 3H, CH_3), 2.55 (s, 2H, CH_2), 3.07-3.15 (m, 2H, CHCH_2), 5.42-5.47 (m, 1H, C*H*CH_2), 7.20-7.43 (m, 4H, arom), 10.75 ppm (s, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{13}ClN_4O_2$ (304.74): C, 55.18; H, 4.30; N, 18.39. Found: C, 55.23; H, 4.37; N, 18.49.

3-(2,4-Dihydro-5-methyl-3-oxo-3*H*-pyrazol-2-yl)-4,5-dihydro-4-(4-methoxyphenyl)pyridazin-6(1*H*)-one (**7c**).

This compound was obtained from **6c** as colorless crystals, mp 229-230°, yield 95%; ir: ν 3160 (NH), 1665 and 1615 (C=O) cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.08 (s, 3H, CH_3), 2.56 (s, 2H, CH_2), 3.04-3.08 (m, 2H, CHCH_2), 3.72 (s, 3H, OCH_3), 5.35-5.41 (m, 1H, C*H*CH_2), 6.88-7.17 (m, 4H, arom), 10.70 ppm (s, 1H, N*H*).

Anal. Calcd. for $C_{15}H_{16}N_4O_3$ (300.32): C, 59.99; H, 5.37; N, 18.66. Found: C, 59.88; H, 5.37; N, 18.57.

3-(2,4-Dihydro-5-methyl-3-oxo-3*H*-pyrazol-2-yl)-4,5-dihydro-4-(4-methylphenyl)pyridazin-6(1*H*)-one (**7d**).

This compound was obtained from **6d** as colorless crystals, mp 199-200°, yield 91%; ir: ν 3170 (NH), 1665 and 1620 (C=O) cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.07 (s, 3H, pyrazole CH_3), 2.25 (s, 3H, $C_6H_4CH_3$), 2.56 (s, 2H, CH_2), 3.04-3.10 (m, 2H, CHCH_2), 5.35-5.41 (m, 1H, C*H*CH_2), 7.06-7.15 (m, 4H, arom), 10.69 (s, 1H, N*H*).

Anal. Calcd. for $C_{15}H_{16}N_4O_2$ (284.32): C, 63.37; H, 5.67; N, 19.71. Found: C, 63.24; H, 5.66; N, 19.81.

Crystal X-ray Analysis of **7d**.

Crystals were grown from ethanol. Crystallographic measurements were performed on an Enraf-Nonius CAD-4 diffractometer using CuK_α radiation (λ = 1.54178 Å). The ω/2Θ scan technique was applied with 2Θ 150°. Three reflections monitored every 100 reflections were used as standards and remeasured during the data collection; there was no indication of crystal decomposition. A single crystal of approximate dimensions 0.2 x 0.2 x 0.3 mm was used for intensity data collection with a total of 1101 reflections measured ($-7 \le h \le 6$, $-13 \le k \le 12$, $-15 \le l \le 0$). A total of 1054 (R_{int} = 0.058) independent data were classified as observed ($F > 4\alpha(F)$) and Lorentz polarization corrections were applied to these data. The cell dimensions were obtained and refined by the least-square method involving 25 reflections ($10 < \Theta < 42$). The structure was solved by direct methods using the SHELXS-86 program [28]. It was refined on F^2 by the full-matrix-block least-squares method [29]. The positions of all H atoms were obtained from difference maps calculated at the completion of the anisotropic refinement.

Crystal Data of **7d**.

Mol. formula $C_{15}H_{16}N_4O_2$, mol. mass 284.32, triclinic, $P\bar{1}$ space group; unit cell dimensions: a = 5.7690(10) Å, b = 10.160(2) Å, c = 12.335(2) Å; = 79.56(3), = 85.93(3) , = 84.14(3); V = 706.3(2) Å^3; d_x = 1.337 Mgm^{-3}; Z = 2; $F(000)$ = 300; μ(CuK_α) = 0.753 mm^{-1}. Final R = 0.058 for 1054 independent reflections [20].

Determination of the Affinity for the Benzodiazepine Receptor.

Rat brains were homogenized at 0° in 20 volumes of 50 m*M* tris hydrochloride (pH 7.4) and the homogenates were incubated 1 hour at 37° and centrifuged at 20,000 G. Samples of the homogenate (800 μl corresponding to 13.3 mg of brain tissue) were mixed with 100 μl of ^{3}H-flunitrazepam (specific activity 81 Ci/mmole) and 100 μl of the tested compound (10^{-6} *M*). The mixture was incubated 2 hours at 5° and filtered through a glass fiber filter (Whatman GF/C). The filter was washed twice with 5-μl portions of tris, dried, and immersed in 10 ml of the scintillation liquid [1,4-bis(5-phenyl-2-oxazolyl)benzene 50 mg, 2,5-diphenyloxazole 4 g, methanol 20 ml, and toluene 1000 ml]. Radioactivity was measured in a Betamatic II Kontron β-scintillation counter and expressed as % inhibition of binding of the labeled ligand.

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