Synthesis of Novel Dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones

László Ürögdi* and Lajos Kisfaludy†

Chemical Works of Gedeon Richter Ltd.,
H-1475 Budapest 10, P. O. Box 27, Hungary

Ágnes Patthy

Institute of Organic Chemistry, Semmelweis Medical University,
H-1092 Budapest, Hőgyes E.u. 7., Hungary

+ Ernő Moravcsik, Helga Tüdős, Zsuzsanna Tegyei and László Ötvös

Central Research Institute for Chemistry of the Hungarian Academy of Sciences,
H-1525 Budapest, P. O. Box 17, Hungary

Received November 4, 1987

The title compounds **4** were synthesized *via* the acid-catalyzed reaction of α-(acylaminooxy)carboxylic acid amides **6** with carbonyl compounds, and controlled catalytic hydrogenation of the resulting 2-benzyloxycarbonyldihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **7** (R^6 = $PhCH_2O$).

J. Heterocyclic Chem., **26**, 129 (1989).

In earlier work we intensely studied the synthesis and the chemical and biological properties of α-aminooxycarboxylic acids and their derivatives [1]. These bifunctional compounds, producible in relatively good yields, offer a number of possibilities for the syntheses of known and new heterocycles. For instance, starting from an α-aminooxycarboxylic acid amide **1**, the formal incorporation of a carbon atom will give rise to 1,2,4-oxadiazines **2** [2a-b], **3** [3a-d] and **4** (Figure 1); of these, in this paper we report the synthesis of dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones, compounds of type **4**, hitherto not described in the literature.

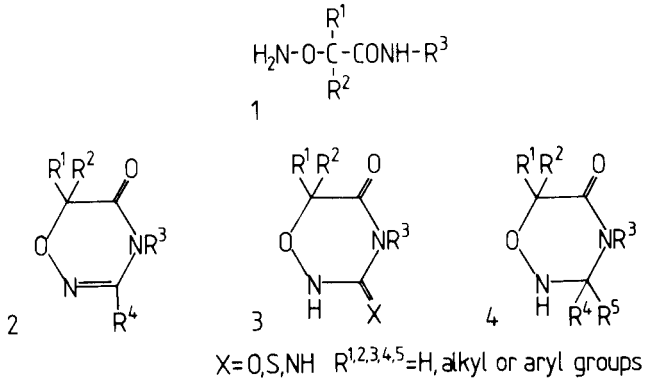


Figure 1

Results and Discussion.

The direct reaction of α-aminooxycarboxylic acid amides **1** with carbonyl compounds led to the formation of a *syn-anti* mixture of the corresponding oxime ethers **5** (Figure 2). Reactions leading to ring closure of these products to obtain compounds of type **4** have remained hitherto unsuccessful. In acetic anhydride and with acid catalysis, **5** afforded the N^2-acetyl derivative **7** only in a very low yield.

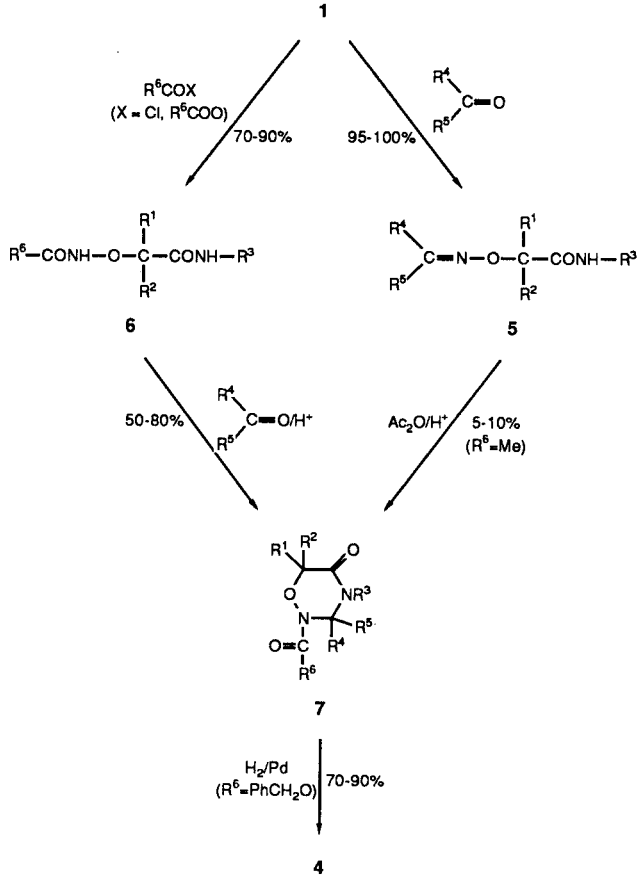
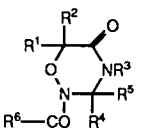


Figure 2

In contrast, the acid-catalysed reaction of the corresponding α-(acylaminooxy)carboxylic acid amides **6** with oxo compounds gave the 2-acyldihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **7** in good yields. Without removal of the water liberated, the reaction comes to equilibrium; therefore the conversions were effected (a) in benzene or

Table 1

Some Representatives of 2-Acyldihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **7** [e]



No.	R^1	R^2	R^3	R^4	R^5	R^6 [b]	Method	Yield %	Mp, °C	Crystallization solvent	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
7a	H	H	H	H	Ph	Z	a	76	130-133	EtOH	$C_{17}H_{16}N_2O_4$	65.38	5.16	8.97	65.11	5.43	8.85
b	H	H	H	H	Ph	MeCO	b	52	166-168	EtOH	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.7	60.12	5.92	12.7
c	H	H	H	H	3,4,5-$(MeO)_3$Ph	Z	a	88	152-153	Et_2O [c]	$C_{20}H_{22}N_2O_7$	59.70	5.51	6.96	60.03	5.40	6.76
d	H	H	H	H	1-naphtyl	MeCO	a	28	218-220	EtOH	$C_{15}H_{14}N_2O_3$	66.66	5.22	10.4	66.37	5.40	10.4
e	H	H	H	H	Ph-CH=CH-	Z	a	50	109-112	EtOH	$C_{19}H_{18}N_2O_4$	67.44	5.36	8.28	67.50	5.18	8.42
f	H	H	H	H	5-NO_2-2-furyl	Z	b	16	152-153	EtOH	$C_{15}H_{13}N_3O_7$	51.88	3.77	12.1	51.58	3.92	11.8
g	H	H	H	H	2-thienyl	MeCO	b	18	176-177	EtOH	$C_9H_{10}N_2O_3S$	47.78	4.45	12.3	47.89	4.15	12.4
h	H	Me	H	H	Me	Z	b	15	97-98	iPr_2O [c]	$C_{13}H_{16}N_2O_4$	59.31	5.74	10.6	59.10	5.57	10.5
i	H	H	H	H	*n*-Pr	Z	b	57	105-106	iPr_2O [c]	$C_{14}H_{18}N_2O_4$	60.42	6.52	10.1	60.69	6.60	9.83
j [a]	H	H	H		-$(CH_2)_5$-	Z	a	33	158-160	EtOH	$C_{16}H_{20}N_2O_4$	63.14	6.62	9.20	62.76	6.69	9.05
k	H	H	Me	H	Ph	Z	a	50	83-84	Et_2O-hexane	$C_{18}H_{18}N_2O_4$	66.25	5.56	8.58	66.27	5.30	8.52
l	H	Me	H	H	4-F-Ph	PhCO	a	55	105-108	iPr_2O [c]	$C_{18}H_{17}N_2O_4F$	64.96	4.81	8.91	65.32	5.03	9.20
m	H	Et	H	H	4-Cl-Ph	Z	a	64	118-121	EtOAc-hexane	$C_{19}H_{19}N_2O_4Cl$	60.88	5.11	7.47	60.82	5.00	7.62
n	H	$PhCH_2$	H	H	4-NO_2-Ph	Z	a	67	145-147	Et_2O [c]	$C_{14}H_{21}N_3O_6$	64.42	4.73	9.39	64.26	4.45	9.08
o	H	Ph	H	H	2,5-$(MeO)_2$Ph	Z	a	70	160-163	EtOH	$C_{25}H_{24}N_2O_6$	66.95	5.39	6.25	66.64	5.11	6.19
p	Me	Me	H	H	Ph	Z	a	67	128-129	Et_2O [c]	$C_{19}H_{20}N_2O_4$	67.04	5.92	8.23	66.85	5.63	8.20
r	Ph	Ph	H	H	Ph	Z	a	25	162-164	Et_2O [c]	$C_{29}H_{24}N_2O_4$	74.98	5.21	6.03	75.12	5.07	6.15

[a] Characterized by ^{13}C-nmr spectrum (DMSO-d_6): δ ppm 22.16, 24.34, 36.66 (CH_2), 67.48, 68.76 (OCH_2 signals [d]), 74.02 (C-3), 123.03, 123.17, 133.43 (Ph), 154.26, 165.14 (C=O signals [d]). [b] Z = $PhCH_2OCO$. [c] Triturated. [d] Interchangeable. [e] All compounds are racemates; the C(3)-C(6) dichiral ones were diastereo-homogeneous; their relative configurations will be published later.

toluene with azeotropic elimination of water, or (b) in a mixture of acetic anhydride and acetic acid. The best catalyst under non-polar conditions (a) was 10-camphorsulfonic acid, which is soluble in benzene or toluene; using method (b), the catalyst of choice was concentrated sulfuric acid. Highest yields were obtained in the reactions of type (a), using the *N*-benzyloxycarbonyl derivatives **6** (R = $PhCH_2O$) that are also readily soluble in benzene or toluene. The synthesis of compounds **7** containing an R^6 substituent other than $PhCH_2O$, can be more conveniently achieved by the usual acylation reactions [4] of compounds **4**.

As oxo components, first of all aromatic aldehydes should be considered. In these compounds, electron-releasing substituents (MeO, OH) promote the condensation reaction, and electron-attracting groups (*e.g.* NO_2) will have a slowing effect. A few characteristic compounds with formula **7** are shown in Table 1.

Attempted removal by hydrolysis or acidolysis of the N^2-acyl group of compounds **7** resulted in ring cleavage to give oxime ethers **5**. However, controlled catalytic hydrogenation of the appropriate benzyloxycarbonyl derivatives **7** (R^6 = $PhCH_2O$) led to the required dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones, **4** (Table 2). The correct end-point of the hydrogenation can be found by tlc; further hydrogenation will result in decomposition of the product involving ring cleavage with the formation of glycolic acid amide as the end product (Figure 3).

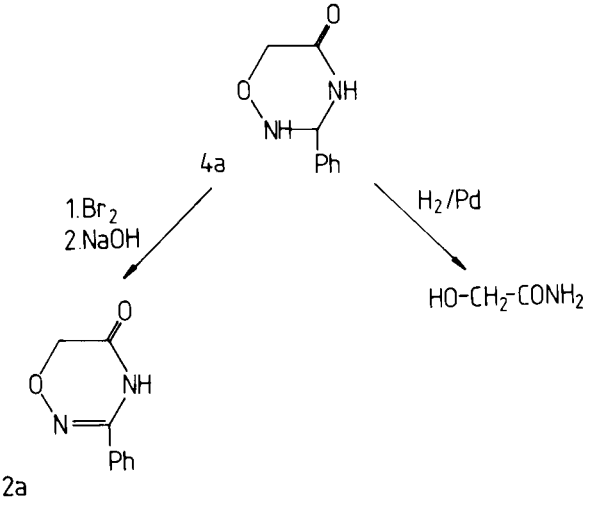


Figure 3

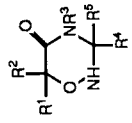
In addition to spectroscopic evidence, the structures of compounds **4** were supported by chemical conversions, too. For instance, the bromination of **4a** and subsequent hydrogen bromide elimination [5] furnished 3-phenyl-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**2a**), a compound described in the literature [2] (Figure 3).

Spectroscopic Characterization of the Dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-one Ring.

In the ir spectra - for both compounds **7** and **4** - there are two characteristic skeletal vibration bands at wavenumbers 1420 ± 20 cm^{-1} and 820 ± 20 cm^{-1}, which appear with varying intensities.

Table 2

Some Representatives of Dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **4** [b]



No.	R^1	R^2	R^3	R^4	R^5	Yield %	Mp, °C	Crystallization solvent	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
4a	H	H	H	H	Ph	77	118-119	EtOAc-hexane	$C_9H_{10}N_2O_2$	60.66	5.66	15.72	60.33	5.57	15.94
c	H	H	H	H	2,5-$(MeO)_2$Ph	91	149-150	EtOH	$C_{11}H_{14}N_2O_4$	55.46	5.92	11.76	55.66	6.08	11.94
d	H	H	H	H	3,4,5-$(MeO)_3$Ph	72	150-151	EtOH	$C_{12}H_{16}N_2O_5$	53.73	6.01	10.44	53.78	6.28	11.20
j	H	H	H	H	*n*-Pr	88	98-99	EtOAc-hexane	$C_6H_{12}N_2O_2$	49.49	8.39	19.43	49.74	8.29	19.31
k	H	H	H	-$(CH_2)_5$-		68	172-173	EtOAc	$C_8H_{14}N_2O_2$	56.45	8.29	16.46	52.42	8.03	16.70
p	H	Ph	H	H	2,5-$(MeO)_2$Ph	91	158-160	Et_2O [a]	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	64.78	5.90	8.92
s	Ph	Ph	H	H	Ph	64	184-185	EtOH	$C_{21}H_{18}N_2O_2$	76.34	5.49	8.48	76.39	5.08	8.53

[a] Triturated. [b] All compounds are racemates.

In the ^{1}H-nmr spectra, in the most frequent cases, when R^4 is aryl and R^5 is hydrogen, the signal of the R^5 proton is found at δ 6.5-7 ppm. The coupling of this signal with the neighboring NH proton(s) disappearing on the addition of deuterium oxide, affords evidence of the cyclic structure.

The characteristic of the ^{13}C nmr spectra again in the most frequent case when R^4 is aryl, are that for compounds **7** the C-3 signal is between 63 and 66 ppm, and the C-6 signal at 80-81 ppm; for compounds **4**, the C-3 and C-6 signals are found in the ranges 70-74 and 77-78 ppm, respectively. The carbonyl (C-5) signal appears, as usual, at about 170 ppm.

The mass spectra of the compounds differ characteristically depending on type **4** or **7** and, within this, whether an R^4 = aryl or alkyl compound is examined. The main fragmentation pathways are shown in Figure 4.

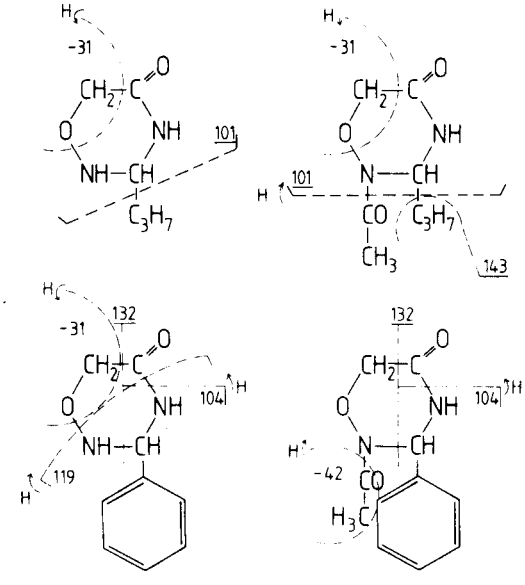


Figure 4

Biological Actions.

Some of the synthesized dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-one derivatives exerted remarkable anticonvulsive effect. Detailed results of the biological tests will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. The ^{1}H-nmr spectra were taken on a Varian EM-60 instrument using TMS as the internal standard. The reactions were followed and the purity of products checked by tlc on precoated Merck plates (Kieselgel 60 F_{254}, 5714).

2-Acyldihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **7**.

Method "a".

A solution or suspension of the acylaminooxycarboxylic acid amide (**6**, 0.1 mole) the appropriate oxo-compound (0.12 mole) and 10-camphorsulfonic acid (0.01 mole) was refluxed in 250 ml of benzene or toluene for 2-10 hours. The water formed was removed using a Marcusson adapter. After completion of the reaction (tlc), the solvent was removed *in vacuo*. The residue was rubbed with ether or diisopropyl ether to obtain **7**.

Method "b".

To a stirred solution of the acylaminooxycarboxylic acid amide (**6**, 0.1 mole) and the appropriate oxo-compound (0.12 mole) in 100 ml of acetic acid and 15 ml of acetic anhydride was slowly added 5 ml of concentrated sulfuric acid. After stirring at ambient temperature for 5-96 hours (checked by tlc) sodium hydrogencarbonate (7.7 g, 0.092 mole) was added, and the mixture was stirred until *p*H 2 of the solution had been attained. The solvent was removed *in vacuo* and the residue was stirred with water and ether or diisopropyl ether to crystallize the product **7**. It was filtered off, washed with water and ether or diisopropyl ether successively and, if necessary, recrystallized.

2-Unsubstituted Dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones **4**.

Compound **7** (R^6 = $PhCH_2O$, 0.1 mole) was hydrogenated in 200-500 ml of dimethylformamide in the presence of 1.0 g palladium-on-charcoal (5%), bubbling hydrogen through the solution. The hydrogenation was stopped when the amount of the side products, estimated by tlc, had reached the amount of the unreacted starting material. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue solidified on rubbing with ether or diisopropyl ether, to yield the 2-unsubstituted dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-one derivative **4**.

3-Phenyl-4*H*-1,2,4-oxadiazin-5(6*H*)-one (**2a**).

To a solution of 9.0 g (0.05 mole) of **4a** in 90 ml of chloroform was added 2.85 ml (8.35 g, 0.052 mole) of bromine by drops, at 0°. The mixture was stirred at 0° for 45 minutes. Then 105 ml of 1*N* sodium hydroxide solution was added slowly at 0° and the mixture was stirred until the organic layer became neutral. The organic layer was separated. The aqueous phase was saturated with sodiumchloride and extracted with 3 x 60 ml of chloroform. The combined organic layers were dried over sodiumsulfate, then evaporated to dryness. Recrystallization of the residue from ethanol gave **2a** (3.8 g, 42%) mp 150-151° (lit [2] 148-150°); ^{1}H nmr (dimethylsulfoxide-d_6 + deuteriochloroform): 4.40 (s, CH_2), 7.3-8.0 (m, arom) 11.4 (b, NH).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36, H, 4.58; N, 15.9. Found: C, 61.08; H, 4.73; N, 15.8.

REFERENCES AND NOTES

† Deceased.

[1a] L. Kisfaludy, M. Lőw, L. Dancsi, Á. Patthy, O. Nyéki and M. Sárközi, in "Peptides 1972", H. Hanson and H.-Dieter Jakubke, eds, North-Holland Publishing Co, Amsterdam, 1973 p 409. [b] L. Kisfaludy, Á. Patthy, L. Dancsi and E. Klumpp, French Demande 2,150,778 (1973); *Chem. Abstr.*, **79**, 104770y (1973). [c] L. Kisfaludy, Á. Patthy, L. Dancsi, Gy. Fekete, and I. Szabó, German Offen 2,063,966 (1971); *Chem. Abstr.*, **75**, 110073g (1971); German Offen 2,064,061 (1971); *Chem. Abstr.*, **75** 98305z (1971); German Offen 2,064,113 (1971); *Chem. Abstr.* **75** 118234f (1971).

[2a] G. W. Stacy, in "Heterocyclic Compounds", Vol **7**, R. C. Elderfield, ed, John Wiley and Sons, Inc., New York, NY, 1961, p 797. [b] R. L. Mckee, in "Chemistry of Heterocyclic Compounds", Vol **17**, A. Weissberger, ed, John Wiley and Sons, Inc., New York, NY, 1962, p 447.

[3a] H. Kornowski, M. Trichot, B. Delage, *Bull. Soc. Chim. France,* **679** 683 (1966). [b] J. Bernstein and K. A. Losee, US Patent 3,283,200 (1966); *Chem. Abstr.*, **64**, 19645h (1966). [c] P. I. Svirskaya and Ju. A. Bashkakov, *Zh. Org. Khim.*, **6**, 940 (1969). [d] Ch. Bennouna, F. Petrus, and J. Verducci, *J. Heterocyclic Chem.*, **16** 1961 (1979).

[4] L. Ürögdi, Á. Patthy, Cs. Vezér and L. Kisfaludy, in "Bioorganic Heterocycles", H. C. van der Plas, ed, Akadémiai Kiadó, Budapest, 1984, p 323.

[5] L. Kisfaludy, J. Röhricht and M. Lőw, Hungarian Patent 155,373 (1966); *Chem. Abstr.*, **70**, 87865 (1967).