Saturated Heterocycles, Part 161 [1]. Synthesis of 2-Hydroxycycloalkyl-substituted 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Triazoles

Ferenc Fülöp, Éva Semega, György Dombi, and Gábor Bernáth*

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121, Hungary

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A number of 2-hydroxycycloalkyl-substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives were prepared by different methods from *cis*- and *trans*-2-hydroxy-1-cycloalkanecarbohydrazides and their isocyanate or isothiocyanate adducts. In contrast with the related ring-closure reactions of 2-aminobenzoylhydrazides, no condensed skeleton heterocycles were formed in this case.

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Introduction.

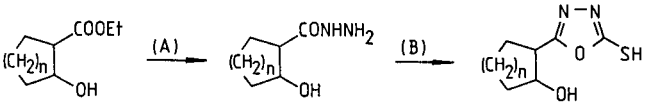
The ring-closure reactions of carbohydrazides are well-known and have been thoroughly studied. In these reactions five-membered heterocycles with three heteroatoms are formed, such as 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles [2].

These types of molecules are important for both chemical and pharmacological purposes. A number of these compounds show analgetic, antidepressive, anticonvulsive and bactericidal activity [3]. As a continuation of our earlier work on the alicyclic 1,2-disubstituted 1,3-difunctional systems [4-6], our aim was the investigation of the ring-closure reactions of *cis*- and *trans*-2-hydroxy-1-cyclopentane- and cyclohexane carbohydrazides **5-8**. Another aim was to study the effects of the *cis* and *trans* configurations of the functional groups, the ring size and the hydroxy group of the 1,2-disubstituted alicycles on the ring closure.

Results.

The starting materials were *cis*- and *trans*-2-hydroxy-1-cycloalkanecarboxylates **1-4** prepared according to literature methods [7,8]. Reduction of the corresponding ethyl β-ketocarboxylates and subsequent fractional distillation on a column with a large number of theoretical plates gave the compounds **1-4**. The corresponding carbohydrazides **5-8** were obtained in good yields by reacting **1-4** with hydrazine hydrate [9-11]. For the ring-closure reactions of the hydrazide derivatives, a number of different literature methods [12-19] were used.

Scheme 1



n = 1, cis : 1	n = 1, cis : 5	n = 2, cis : 9
n = 1, trans : 2	n = 1, trans : 6	n = 2, trans : 10
n = 2, cis : 3	n = 2, cis : 7	
n = 2, trans : 4	n = 2, trans : 8	

Compounds **5-8** could be transformed directly to oxadiazoles. In the reactions of **5-8** with carbon disulfide in the presence of potassium hydroxide, oxadiazole derivatives **9** and **10** were obtained in good yields.

Synthetic methods for preparation of the title heterocycles from the isocyanate and isothiocyanate adducts of hydrazides are known. The treatment of **5-8** with isocyanates or isothiocyanates gave thiosemicarbazides **11-14** and semicarbazides **15-16**, respectively, in nearly quantitative yields (Scheme 2).

On the treatment of thiosemicarbazides **11-14** with aqueous sodium hydroxide, 1,2,4-triazole derivatives **17-20** were obtained in 50-70% yields. A short reflux of thiosemicarbazides **11-14** in ethanolic hydrogen chloride, furnished the thiadiazole derivatives **21-24**, *via* water elimination. The same products were obtained when methanesulfonic acid was used according to a recently published method [16].

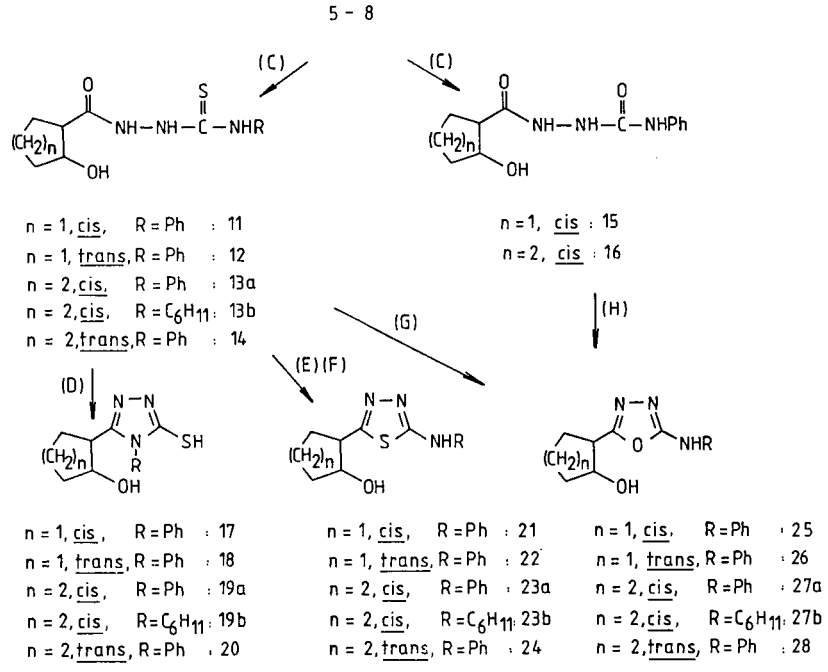
With thionyl chloride in chloroform, compounds **15-16** could be cyclized to oxadiazoles in good yields. When thiosemicarbazides **11-14** were stirred with methyl iodide, followed by treatment with alkali, methyl mercaptan elimination took place, resulting in oxadiazoles **25-28**. The physical data on these compounds are the same as those on the products **25-28** obtained from thiosemicarbazides with methyl iodide.

No significant difference could be found in the reactivities of the *cis* and *trans* isomers or cyclopentane and cyclohexane derivatives. Therefore, it was concluded that the hydroxy group on the cycloalkane ring does not participate in the ring-closure reactions.

It has recently been reported by different authors [20-22] that the treatment of substituted 2-aminobenzoylhydrazides with *ortho*-esters results in different products, depending upon the type of *ortho*-ester employed and the reaction conditions. In the condensation reactions, benzotriazepinones, 1,3,4-oxadiazoles or quinazolinones were obtained. In contrast with these findings, in the reactions discussed in the present paper, only a single product, with the given structure, was isolated in all cases.

The bactericidal, fungicidal and analgetic activities of the synthesized compounds were tested. None of them proved to have a significant activity.

Scheme 2



Spectroscopic Results.

All the compounds prepared were characterized by means of their ^{1}H nmr spectra, which confirmed the structures given. Here, only four representative *cis*-cyclohexane derivatives are discussed, one from each type of heterocycle, **9**, **17**, **21**, **25**, (Table 1).

Of the two possible conformations of the cyclohexane ring, with *axial* or *equatorial* hydroxy group, the predominant conformation is that having an *axial* hydroxy group. The C*H*OH anellation proton has three very similar couplings, which means that this proton is *equatorial*, having a dihedral angle of ~60° with the neighboring protons. The other anellation proton has one coupling above 10 Hz

Table 1

^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) for Compounds **9**, **17**, **21** and **25**

No	H-1	(1H)	H-2	(1H)	H-3-6 (8H)	H-Ar (5H)	OH [a] (1H)	NH [a] (1H)
	δ	J	δ	J	δ	δ	δ	δ
9	2.89	~11 ~7	4.32	~9 [b]	1.1-2.1	–	3.6	10.05
17	2.56	11.3 ~8 [b]	4.08	~9 [b]	1.1-2.2	7.51-7.72	2.0	2.0
21	3.13	11.2 3.7 2.5	4.34	~2.3 ~2.3 ~2.3	1.3-2.1	7.12-7.3	2.5	2.5
25	2.97	10.7 4.0 2.7	4.31	~2.4 ~2.4 ~2.4	1.2-2.2	7.1-7.4	2.0	2.0

[a] Broad. [b] Half-band width.

Table 2

Analytical Data of Products **5-28**

No	Method	Yield (%)	Mp (°C) Solvent	Formula M.W.	Analysis Calcd/Found (%) C	H	N	IR υ max (cm^{-1})
5	A	90	152-154 [a] EtOAc	$C_6H_{12}N_2O_2$ 144.18	49.98 50.03	8.39 8.09	19.43 19.34	3300 2960 1635
6	A	91	135-136 EtOH	$C_6H_{12}N_2O_2$ 144.18	49.98 50.05	8.39 8.49	19.43 19.24	3260 2950 1625
7	A	90	123-125 [b] EtOAc	$C_7H_{14}N_2O_2$ 158.20	53.14 53.36	8.92 9.19	17.71 17.49	3335 3295 2925 1625
8	A	87	207-209 [c] EtOH	$C_7H_{14}N_2O_2$ 158.20	53.14 53.32	8.92 9.10	17.71 17.49	3290 2925 1625 1080
9	B	65	176-179 EtOAc	$C_8H_{12}N_2O_2S$ 200.27	47.98 48.04	6.04 6.16	13.99 13.77	3340 2930 1490 1165
10	B	71	122-124 Hexane/Benzene	$C_8H_{12}N_2O_2S$ 200.27	47.98 48.06	6.04 6.03	13.99 13.78	2925 1490 1140 1030
11	C	93	159-163 EtOH	$C_{13}H_{17}N_3O_2S$ 279.36	55.89 56.00	6.13 5.91	15.04 15.25	3250 1665 1520 1415
12	C	88	150-152 [b] EtOH	$C_{13}H_{17}N_3O_2S$ 279.36	55.89 56.06	6.13 6.10	15.04 15.07	3280 1670 1555 1500
13a	C	90	157-159 [c] EtOH	$C_{14}H_{17}N_3O_2S$ 293.38	57.31 57.60	6.53 6.32	14.32 14.61	3280 2925 1540
13b	C	58	183-185 EtOH	$C_{14}H_{25}N_3O_2S$ 299.43	56.15 56.31	8.42 8.66	14.03 14.06	3230 2910 1680 1040
14	C	91	170-172 EtOH	$C_{14}H_{19}N_3O_2S$ 293.38	57.31 57.56	6.53 6.31	14.32 14.70	3280 2920 1620 1070
15	C	90	205-207 EtOH	$C_{13}H_{17}N_3O_3$ 263.29	59.30 59.60	6.51 6.84	15.96 16.10	3335 3250 1670 1530
16	C	97	181-185 EtOH	$C_{14}H_{19}N_3O_3$ 277.31	60.63 60.35	6.90 6.62	15.15 14.90	3240 1650 1590
17	D	67	221-223 EtOH	$C_{13}H_{15}N_3OS$ 261.34	59.74 60.00	5.79 5.85	16.08 16.30	3070 2920 1490
18	D	50	243-245 EtOH	$C_{13}H_{15}N_3OS$ 261.34	59.74 59.80	5.79 6.21	16.08 16.50	3085 2925 1480 1560
19a	D	69	224-227 EtOH	$C_{14}H_{17}N_3OS$ 275.37	61.06 61.18	6.22 6.44	15.26 14.94	3285 2940 1495
19b	D	58	181-184 EtOH	$C_{14}H_{23}N_3OS$ 281.41	59.75 59.31	8.24 8.32	14.93 14.67	2960 2870 1515 1305
20	D	54	117-120 Hexane	$C_{14}H_{17}N_3OS$ 275.34	61.06 61.20	6.22 6.34	15.26 15.44	3330 2920 1480
21	E	75	183-186 EtOH	$C_{13}H_{15}N_3OS$ 261.34	59.74 59.80	5.78 5.69	16.08 16.57	3050 1590 1540 1490
22	E	46	141.144 Nitromethane	$C_{13}H_{15}N_3OS$ 261.34	59.74 59.84	5.78 5.82	16.08 15.92	2945 1550 1500 1435
23a	E F	57 36	199-200 EtOH	$C_{14}H_{17}N_3OS$ 275.37	61.06 61.03	6.22 6.23	15.26 15.46	2930 1530 1500 1440
23b	E	61	208-209 EtOH	$C_{14}H_{23}N_3OS$ 281.41	59.75 59.61	8.24 8.34	14.93 15.10	3370 2940 2870 1545
24	E F	43 36	178-181 EtOH	$C_{14}H_{17}N_3OS$ 275.37	61.06 61.17	6.22 6.46	15.26 15.37	2930 1590 1550 1435

Table 2 (continued)

No	Method	Yield (%)	Mp (°C) Solvent	Formula M.W.	Analysis Calcd/Found (%) C	H	N	IR υ max (cm^{-1})
25	G	58	137-140	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	3235 1500 1445
	H	52	EtOAc	245.24	63.42	6.05	17.04	
26	G	23	139-141 Hexane/Benzene	$C_{13}H_{15}N_3O_2$ 245.27	63.66 63.40	6.16 6.36	17.13 17.22	3200 1485 1430
27a	G	57	187-188	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.20	2930 1630 1510 1485
	H	59	EtOAc	259.30	64.63	6.36	16.05	
27b	G	68	131-132 EtOAc	$C_{14}H_{23}N_3O_2$ 265.34	63.37 63.63	8.74 9.01	15.84 15.63	3360 2930 1630 1570
28	G	41	181-183 EtOH/Diisopropyl Ether	$C_{14}H_{17}N_3O_2$ 259.30	64.84 64.84	6.61 6.79	16.20 16.00	2915 1480 1435

[a] Lit [10] mp 153-154°. [b] Lit [11] mp 121-122°. Lit [10] mp 208°.

and two smaller ones, which proves that it is predominantly *axial*.

The two substituents on the cyclohexane ring cause a slight torsion in the chair conformation of the cyclohexane ring since the coupling constant between the two anellation protons is smaller than that for to H_2-H_{3eq} coupling.

All the prepared heterocycles have two tautomeric forms with an *exo* or *endo* C=N or C=S bond. The tautomeric properties of these compounds are under investigation and will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The analytical data on the prepared compounds are listed in Table 2. The ir spectra were determined in potassium bromide pellets on a Unicam SP 200 spectrometer. ^1H nmr spectra were recorded at room temperature in deuteriochloroform solution on a Bruker WM 250 FT instrument, with TMS as internal standard.

Method A.

Ten ml of ethyl 2-hydroxycycloalkanecarboxylate was dissolved in ethanol (50 ml). After the addition of 10 ml of hydrazine hydrate (70% aqueous solution), the mixture was refluxed for 1 hour. After standing for one day in a refrigerator, the crystalline product was filtered off.

Method B.

Two mmoles of hydrazides **5-8** was dissolved in ethanol, potassium hydroxide (0.11 g, 2 mmoles) and carbon disulfide (0.15 g, 2 mmoles) were added, and the mixture was refluxed for 48 hours. After evaporation, the residue was dissolved in water and acidified with acetic acid. After extraction with chloroform (4 × 15 ml), the combined organic layer was dried (sodium sulfate) and evaporated, yielding the target compound.

Method C.

Hydrazides **5-8** (10 mmoles) were refluxed with the corresponding isocyanate or isothiocyanate (11 mmoles) in 30 ml of benzene for half an hour. After evaporation of the solvent, crystalline product was obtained.

Method D.

Thiosemicarbazides **11-14** (2 mmoles) were refluxed for 3 hours in 20 ml of 2 *N* aqueous sodium hydroxide. The mixture was acidified to *p*H 2 after cooling to room temperature. The precipitated product was filtered off and washed several times with water.

Method E.

Thiosemicarbazides **11-14** (2 mmoles) were refluxed in ethanol (15 ml) containing 20% dry hydrogen chloride for 15 minutes. After evaporation, the residue was neutralized with 10% potassium carbonate. The precipitated crystalline product was filtered off and washed with water.

Method F.

Thiosemicarbazide **13** or **14** (2 mmoles) was dissolved in 10 ml of toluene and 3 mmoles (0.19 ml) of methanesulfonic acid was added dropwise in 5 minutes. After a 45-minutes reflux, the mixture was neutralized with ammonium hydroxide under ice cooling. The precipitate was filtered off and washed with water.

Method G.

Thiosemicarbazides **11-14** (2 mmoles) were stirred with methyl iodide (10 mmoles, 0.62 ml) for 3 hours. After evaporation of the methyl iodide excess, the oily residue was dissolved in 20 ml of methanol containing 3 g of potassium hydroxide. The solution was stirred for 3 hours and then evaporated. The residue was dissolved in 30 ml of water and the precipitated product was filtered off.

Method H.

Semicarbazide **15** or **16** (2 mmoles) in chloroform and thionyl chloride (20 mmoles, 1.46 ml) was refluxed for 1 hour. After evaporation of the thionyl chloride excess, 20 ml of saturated sodium hydrogen carbonate was added to the residue and the mixture was extracted with chloroform (4 × 15 ml). The combined extract

was dried (sodium sulfate) and evaporated.

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