Saturated Heterocycles. 242 [1]. Synthesis of 2-Substituted-6-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one Derivatives

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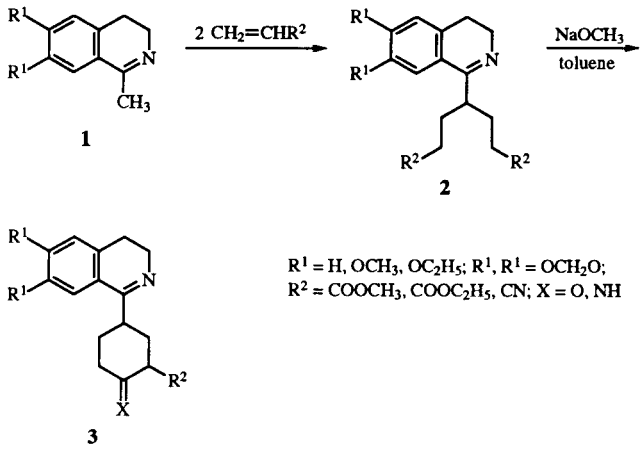
Dedicated to Professor Miha Tišler on the occasion of his 70th birthday

In the reactions of the recently synthesized β-ketoesters 1-[(3'-methoxycarbonyl- and 1-[(3'-ethoxycarbonyl-4'-oxo)-1'-cyclohexyl]-3,4-dihydroisoquinoline **4, 5** with amidines or cyclic guanidines, a number of 2-substituted-6-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one derivatives **6-8** were prepared. The new compounds possess various pharmacological actions.

J. Heterocyclic Chem., **33**, 1983 (1996).

The reactivity of the 1-methyl group of 1-methyl-3,4-dihydroisoquinoline, 1-methyl-6,7-dialkoxy-3,4-dihydroisoquinolines and 1-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline **1** was earlier thoroughly investigated [2-11]. From 1-[bis(hydroxymethyl)methyl]-6,7-dialkoxy-3,4-dihydroisoquinolines, obtained in the reaction of **1** and paraformaldehyde, a number of azeto[2,1-*a*]isoquinoline, 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinoline derivatives have been synthesized for pharmacological screening [6-11].

Scheme 1



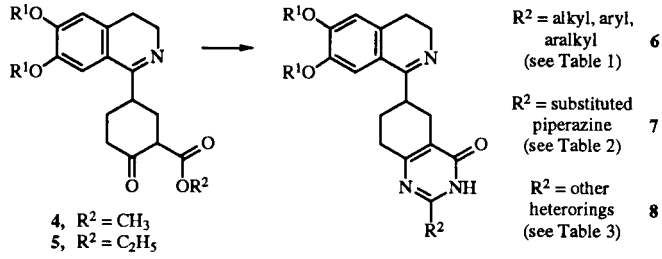
1 **2** **3**

In contrast with earlier literature data [12], it was found that both acrylic esters and acrylonitrile undergo Michael addition to 1-methyl-3,4-dihydroisoquinolines **1** to yield the diesters or the dinitrile **2**, respectively. By Claisen condensation, **2** were transformed to 1-[(3'-methoxycarbonyl- and 1-[(3'-ethoxycarbonyl-4'-oxo)-1'-cyclohexyl]-3,4-dihydroisoquinoline derivatives **3** [13].

Our present aim was to utilize 1-[(3'-methoxycarbonyl- and 1-[(3'-ethoxycarbonyl-4'-oxo)-1'-cyclohexyl]-3,4-dihydroisoquinoline derivatives **4** and **5** for the preparation of potential pharmacons. In our earlier investigations, the condensation of β-ketoesters with amidines resulted in a number of pharmacologically promising derivatives [14-16], and we therefore decided to perform similar transformations starting from the ketoesters **4** and **5**.

In the reactions of ketoesters **4** and **5** with amidines in the presence of sodium ethylate, a number of 2-substituted-6-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one derivatives **6** were obtained in good yields (Scheme 2, Table 1). In the reactions of the ketoesters **4** and **5** with different guanidine derivatives, the condensation reactions likewise took place in good yields (Tables 2 and 3).

Scheme 2



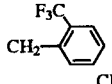
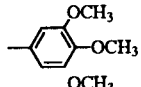
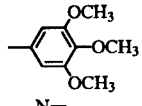
4, $R^2 = CH_3$
5, $R^2 = C_2H_5$

The amidines used in the above reactions were prepared by the Pinner method, starting from the corresponding nitriles, *via* iminoethers, and subsequent ammonia treatment [17]. The *N*-substituted guanidines were prepared from *S*-methylisothiouronium sulfate and the corresponding secondary amines [17].

When the 2-phenyl-substituted derivative **6a** was heated with 40% aqueous hydrobromic acid, demethylation took

Table 1

Physical and Analytical Data on Compounds **6**

Compound	Yield(%)	Mp (°C) Solvent	R^1	R^2	Formula Molecular mass	Analysis% Calcd./Found C	H	N
6a	52	260-261 ethanol	CH_3	CH_3	$C_{20}H_{23}N_3O_3$ 353.43	67.97 67.85	6.56 6.72	11.89 11.66
6b	48	225 [a] ethanol	C_2H_5	CH_3	$C_{22}H_{27}N_3O_3$ 381.48	69.27 68.97	7.13 7.15	11.02 10.80
6c	66	248 toluene	CH_3		$C_{25}H_{25}N_3O_3$ 415.50	72.27 72.13	6.07 6.38	10.11 9.98
6d	62	226-228 ethanol	C_2H_5		$C_{27}H_{29}N_3O_3$ 449.94	73.11 73.22	6.59 6.73	9.47 9.61
6e	72	154-155 DMF	CH_3		$C_{25}H_{29}ClN_3O_3$ 443.55	66.74 66.50	5.38 5.68	9.34 9.07
6f	55	198 [a] ethanol	C_2H_5		$C_{27}H_{28}ClN_3O_3$ 478.00	67.85 68.02	5.90 6.19	8.79 8.37
6g	58	234-235 DMF	CH_3		$C_{26}H_{27}ClN_3O_3$ 429.53	72.71 72.41	6.34 6.48	9.78 10.05
6h	57	269-270 DMF	CH_3		$C_{27}H_{26}F_3N_3O_3$ 497.52	65.18 65.29	5.27 5.41	8.45 8.30
6i	60	243 ethanol	CH_3		$C_{26}H_{24}F_3N_3O_3$ 483 50	64.59 64.72	5.00 5.31	8.69 9.06
6j	70	275 toluene	CH_3		$C_{27}H_{29}N_3O_5$ 475 55	68.20 67.86	6.15 6.25	8.84 8.88
6k	60	293-295 ethanol	CH_3		$C_{28}H_{31}N_3O_6$ 505.58	66.52 66.63	6.18 6.50	8.31 8.07
6l [b]	54	204-206 ethanol	CH_3		$C_{24}H_{26}Cl_2N_4O_3$ 489.41	58.90 58.56	5.36 5.72	11.45 11.08
6m	56	221-222 ethanol	CH_3		$C_{24}H_{24}N_4O_3$ 416.49	69.21 69.41	5.81 6.12	13.45 13.22
6n	55	244-245 ethanol	C_2H_5		$C_{26}H_{28}N_4O_3$ 444.54	70.25 70.28	6.35 6.64	12.60 13.03
6o	54	258-259 toluene	CH_3		$C_{24}H_{24}N_4O_3$ 416.49	69.21 68.86	5.81 6.17	13.45 13.28
6p	78	286-287 DMF	CH_3		$C_{26}H_{26}ClN_3O_3$ 463.97	67.31 67.56	5.65 5.90	9.06 9.09
6q	58	250 [a] DMF	C_2H_5		$C_{28}H_{30}ClN_3O_3$ 492.02	68.35 68.35	6.15 6.35	8.54 8.56

[a] With decomposition. [b] Dihydrochloride.

[a] With decomposition. [b] Dihydrochloride.

Table 2

Physical and Analytical Data on Compounds **7**

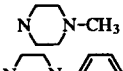
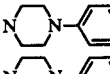
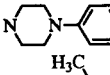
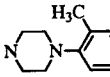
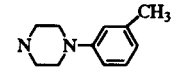
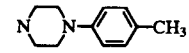
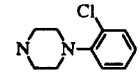
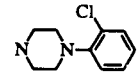
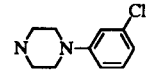
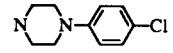
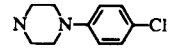
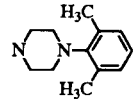
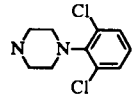
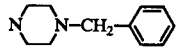
Compound	Yield(%)	Mp (°C) Solvent	R^1	R^2	Formula Molecular mass	Analysis % Calcd./Found C	H	N
7a	58	241 ethanol	CH_3		$C_{24}H_{31}N_5O_3$ 437.55	65.88 66.17	7.14 7.50	16.01 15.72
7b	65	241-242 DMF	CH_3		$C_{29}H_{33}N_5O_3$ 499.62	69.72 70.08	6.66 6.82	14.02 13.89
7c	61	225-226 [a] ethanol	C_2H_5		$C_{31}H_{37}N_5O_3$ 527.67	70.56 70.70	7.07 6.87	13.27 13.00
7d	51	234-235 DMF	CH_3		$C_{30}H_{35}N_5O_3$ 513.65	70.15 70.30	6.87 6.99	13.63 13.87

Table 2 (continued)

Compound	Yield(%)	Mp (°C) Solvent	R^1	R^2	Formula Molecular mass	Analysis % Calcd./Found C	H	N
7e [b]	49	286-287 ethanol	C_2H_5		$C_{32}H_{41}Cl_2N_5O_3$ 614.62	62.54 62.80	6.72 6.86	11.39 11.44
7f	60	290-292 DMF	CH_3		$C_{30}H_{35}N_5O_3$ 513.65	70.15 70.38	6.87 7.06	13.63 13.59
7g	57	254 [a] DMF	CH_3		$C_{29}H_{32}ClN_5O_3$ 534.07	65.22 64.95	6.04 6.27	13.11 13.03
7h	58	226-228 DMF	C_2H_5		$C_{31}H_{36}ClN_5O_3$ 562.12	66.24 65.84	6.46 6.50	12.46 12.50
7i	60	260-261 DMF	CH_3		$C_{29}H_{32}ClN_5O_3$ 534.07	65.22 65.45	6.04 6.28	13.11 13.09
7j	60	263-264 DMF	CH_3		$C_{29}H_{32}ClN_5O_3$ 534.07	65.22 64.92	6.04 6.25	13.11 12 87
7k	64	248-255 [a] DMF	C_2H_5		$C_{31}H_{36}ClN_5O_3$ 562.12	65.22 65.45	6.04 6.28	13.11 13.09
71 [b]	49	210-212 DMF	CH_3		$C_{31}H_{39}Cl_2N_5O_3$ 600.60	62 00 61.71	6.55 6.80	11.66 11.83
7m [b]	58	255-258 DMF	CH_3		$C_{29}H_{33}Cl_4N_5O_3$ 641.43	54.30 54.73	5.19 5.61	10.92 10.47
7n [c]	60	222-224 DMF	CH_3		$C_{30}H_{38}Cl_3N_5O_3$ 623.03	57.84 57.47	6.15 6.50	11.24 11.30

[a] With decomposition. [b] Dihydrochloride. [c] Trihydrochloride.

Table 3

Physical and Analytical Data on Compounds **8**

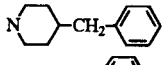
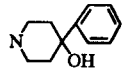
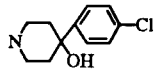
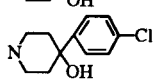
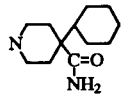
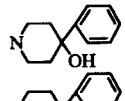
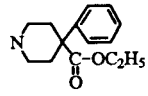
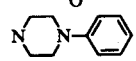
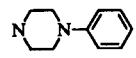
Compound	Yield(%)	Mp (°C) Solvent	R^1	R^2	Formula Molecular mass	Analysis% Calcd./Found C	H	N
8a	62	274-275 ethanol	CH_3		$C_{23}H_{28}N_4O_3$ 408.51	67.63 67.85	6.91 7.20	13.72 13.55
8b [a] [b]	64	266 ethanol	C_2H_5		$C_{25}H_{34}Cl_2N_4O_3$ 509.48	58.94 58.62	6.73 7.12	11.00 10.65
8c	64	278-279 ethanol	CH_3		$C_{24}H_{30}N_4O_3$ 422.53	68.22 68.33	7,16 7.37	13.26 13.48
8d	50	279-280 ethanol	CH_3		$C_{26}H_{34}N_4O_3$ 450.59	69.31 68.95	7.61 7.88	12.43 12.64
8e	52	286 [b] ethanol	CH_3		$C_{23}H_{28}N_4O_4$ 424.51	65.08 65.45	6.65 6.52	13.20 13.49
8f	56	269 ethanol	C_2H_5		$C_{25}H_{32}N_4O_4$ 452.56	66.35 66.56	7.13 7.51	12.38 12.34
8g	60	229-230 ethanol	CH_3		$C_{31}H_{36}N_4O_3$ 512.66	72.63 72.20	7.08 7.45	10.93 10.65
8h [c]	61	160-162 DMF	CH_3		$C_{30}H_{34}ClN_4O_4$ 550.09	65.51 65.87	6.23 6.55	10.19 9.88
8i	65	163-165 ethanol	CH_3		$C_{30}H_{33}ClN_4O_4$ 549.09	65.63 65.94	6.06 6.42	10.20 10.32
8j	59	147-149 ethanol	C_2H_5		$C_{32}H_{37}ClN_4O_4$ 577.13	66.60 67.00	6.46 6.18	9.71 9.66

Table 3 (continued)

Compound	Yield(%)	Mp (°C) Solvent	R^1	R^2	Formula Molecular mass	Analysis% Calcd./Found C	H	N
8k [d]	61	243-245 ethanol	CH_3		$C_{30}H_{43}Cl_3N_6O_4$ 658.08	54.76 54 43	6.59 6.97	12.77 12.80
8l	54	244-246 ethanol	CH_3		$C_{30}H_{34}N_4O_4$ 514.63	70.02 70.28	6.66 6.60	10.89 10.90
8m [a]	49	262-265	CH_3		$C_{33}H_{40}Cl_2N_4O_5$ 643.62	61.58 61.69	6.26 6.48	8.70 8.42
8n	64	217-218 toluene	CH_3		$C_{30}H_{32}O_3N_4$ 496.62	72.56 72.82	6.50 6.70	11.28 11.44
8o	60	210-213 DMF	C_2H_5		$C_{32}H_{36}N_4O_3$ 524.67	73.26 73.60	6.92 7.04	10.68 11.08

[a] With decomposition. [b] Dihydrochloride. [c] Hydrochloride. [d] Trihydrochloride.

place, resulting in the dihydroxy derivative **9**. Condensation of the ketoester **4** with thiourea or with *S*-methylisothiouronium sulfate afforded the 2-thioxo **10** and the 2-methylthio derivative **11**, respectively. However, the transformation of **11** with secondary amines to compounds of type **7** or **8** proceeded only in very low yields.

Some of the compounds of types **6-8** possess marked sedatohypnotic, antiulcer, antihypertensive and immunosuppressive effects [18].

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The homogeneity of the compounds prepared was tested by tlc (silica gel G layer; developing solvent: benzene-ethanol 4:1, detection in iodine vapour).

The structures of the compounds were confirmed by ir and ^{1}H- and ^{13}C-nmr spectroscopy. The ir spectra were recorded in potassium bromide pellets on a Spectromom 2000 instrument. The ^{1}H nmr spectra were recorded on a Bruker spectrometer at 400 MHz, with tetramethylsilane as internal standard. The spectra obtained corresponded to the structures given in the Schemes. The EI mass spectra were recorded at 70 EV on a Finnigen TSQ-7000 spectrometer. All peaks with relative intensities greater than 12% of the base peak are given. The physical data on the synthesized compounds are listed in Tables 1, 2 and 3.

2-Phenyl-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**6c**). General Method A.

A mixture of 1-(4'-oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (16.7 g, 0.05 mole) and benzamidine hydrochloride (8.6 g, 0.055 mole) was suspended in ethanol (200 ml), and sodium ethylate (3.74 g, 0.055 mole) was added in 50 ml of ethanol. The mixture was stirred and refluxed for 6 hours, and the solvent was then evaporated off. The residue was suspended in water (100 ml) and the precipitated product was filtered off and washed with water and acetone; ms: m/z (relative intensity) 415 (M^+, 100), 414 (50), 400 (48), 387 (28), 386 (48), 384 (30), 225 (14), 205 (20), 194 (78), 192 (32), 190 (14), 104 (12), 77 (16).

The compounds synthesized by this method are listed in Table 1.

The hydrochlorides were prepared from ethanolic suspensions of the bases by treatment with aqueous hydrochloric acid, followed by evaporation and ethanolic treatment.

2-Morpholinyl-6-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**8e**). General Method B.

This reaction was performed according to General Method A, but instead of benzamidine hydrochloride, the corresponding guanidinium sulfate was used; ms: m/z (relative intensity) 424 (M^+, 24), 409 (20), 395 (12), 195 (14), 194 (100), 193 (12), 192 (13), 91 (12) 77 (16), 50 (32).

The compounds synthesized by this method are listed in Tables 2 and 3.

2-Phenyl-6-(6',7'-dihydroxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one Hydrobromide (**9**).

2-Phenyl-6-(6',7'-dimethoxy-3',4'-dihydro-1'-isoquinolyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (0.42 g, 1 mmole) was suspended in aqueous hydrobromic acid (10 ml, 40%) and stirred and gently refluxed for 1 hour. The product **9** slowly precipitated out. The solvent was evaporated off and the product was recrystallized from 80% ethanol, yield 0.36 g, 78%, mp 293-295°; ms: m/z (relative intensity) 387 (M^+, 8), 96 (60), 94 (64), 82 (98), 84 (41), 80 (100), 78 (40).

Anal. Calcd. for $C_{23}H_{20}N_3O_3$ (386.44): C, 59.11; H, 453; N, 8.99. Found: C, 59.32; H, 4.55; N 8.78.

6-(6',7'-Dimethoxy-3',4'-dihydro-1'-isoquinolyl)-2-thioxo-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**10**).

A mixture of 1-(4'-oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (1.67 g, 5 mmoles) and thiourea (0.38 g, 5 mmoles) was suspended in ethanol (20 ml), and sodium ethylate (0.37 g, 5.5 mmoles) was added in 10 ml of ethanol. The mixture was stirred and refluxed for 12 hours, and the solvent was then evaporated off. Water (100 ml) was added to the residue and the mixture was neutralized under cooling with hydrochloric acid (10 *M* aqueous solution). The precipitated product was filtered off, washed with water and recrystallized from ethanol:dimethylformamide, yield 0.84 g, 48%, mp 229-231°; ms: m/z (relative intensity) 372 (M+H, 24), 371 (M^+, 100), 370

(65), 356 (34), 342 (14), 341 (16), 340 (20), 205 (22), 192 (22), 191 (12), 190 (20).

Anal. Calcd. for $C_{19}H_{21}N_3O_3S$ (371.46): C, 61.44; H, 5.70; N, 11.31. Found: C, 61.23; H, 5.44; N 11.45.

6-(6',7'-Dimethoxy-3',4'-dihydro-1'-isoquinolyl)-2-methylthio-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**11**).

A mixture of 1-(4'-oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (1.67 g, 5 mmoles) and *S*-methylisothiuronium sulfate (1.39 g, 5 mmoles) was suspended in ethanol (20 ml), and sodium ethylate (0.37 g, 5.5 mmoles) was added in 10 ml of ethanol. The mixture was stirred and refluxed for 12 hours, and the solvent was then evaporated off. Water (15 ml) was added to the residue and the precipitated product was filtered off, washed with water and recrystallized from ethanol:dimethylformamide, yield 9.81 g, 51%, mp 225-228°; ms: m/z (relative intensity) 386 (M+H, 15), 385 (M^+, 60) 384 (45), 383 (42), 382 (26), 371 (13), 370 (57), 368 (20), 357 (13), 356 (30), 355 (34), 354 (100), 340 (16), 337 (21), 326 (16), 311 (13), 259 (20), 244 (17), 205 (28), 192 (32), 190 (20), 176 (13).

Anal. Calcd. for $C_{20}H_{23}N_3O_3S$ (385.49): C, 62.32; H, 6.01; N, 10.90. Found: C, 62.43; H, 5.89; N 10.78.

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