Studies of Pyridazine Compounds. XXVI [1]. The Synthesis of Pyridazino[4,5-*b*]pyrrolo[1,2-*d*][1,4]oxazines and a Pyridazino[4,5-*b*]pyrrolo[1,2-*d*][1,4]thiazine

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The tricyclic oxazines **3** and **5** were obtained by ring closure of (2-hydroxymethyl-1-pyrrolidinyl)-3(2*H*)-pyridazinones **2d,e,g**, respectively, prepared from 4,5-dichloro-3(2*H*)-pyridazinones with L-prolinol. The synthesis of the thiazine analogue **4a** was achieved by treatment of **2d** with thionyl chloride and the subsequent reaction with sodium sulfide. The structures of the compounds were supported by spectroscopic evidence.

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As a part of our program directed toward the synthesis of antihypertensive pyridazine derivatives, we have recently described a novel series of 2-aminoalkyl-3(2*H*)-pyridazinones [2]. One of these compounds, GYKI-12 743 (**1**), has been selected for clinical investigation as a promising agent for treatment of hypertension [3].

In our structure-activity study, preparation of some fused derivatives of the parent pyridazinones was also desired in order to examine the contribution of substitution at the 4- and 5-position of the pyridazine moiety to the biological effects.

As appropriate starting materials for constructing such systems, 4,5-dichloro-3(2*H*)-pyridazinone (**2a**) and/or its congeners were considered, because of their relatively high reactivity toward nucleophiles (see *e.g.* [4-6]).

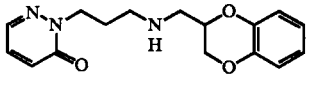
When **2a** was reacted with L-prolinol in 1-butanol, the 5-substituted pyridazinone derivative **2c** was obtained. However, our attempts (in ethanol or 1-butanol/sodium alcoholate) have failed to cyclize it to the desired tricyclic product (**3**, R = H), which could have served as a convenient precursor for 2-*N*-functionalization. Thus we applied a reverse reaction sequence. Treatment of **2c** with 3-[*N*-(2-[1,4]benzodioxanylmethyl)-*N*-benzyl)]aminopropyl chloride (**6**) under phase transfer catalysis conditions afforded **2g**, which cyclized smoothly to **3b** upon heating with sodium butylate in 1-butanol. This latter compound was converted to **3c**, *i.e.*, the tricyclic analogue of **1**, by catalytic debenzylation. (Scheme I).

Next we looked at the reaction of **2b** with L-prolinol. Monosubstitution occured at the 5- and 4-position resulting in **2d** and **2e**, respectively, which could be separated by column chromatography in a ratio of *ca.* 10. Their subsequent ring closure reactions to the pyridazino[4,5-*b*]pyrrolo[1,2-*d*][1,4]oxazine derivatives, **3a** and **5**, respectively, were easily achieved by an analogous manner as described above for **2g**.

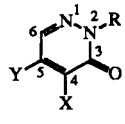
The significant difference observed in the cyclization tendency of **2c** *vs.* **2d,e,g** may be due to the lack of substitution at 2-*N* (*cf.* [7]). Compound **4a**, the thiazine analogue of **3a**, was prepared from **2d**, as illustrated in Scheme I. Treatment of the 5-(2-hydroxymethyl-1-pyrrolidinyl)-3(2*H*)-pyridazinone derivative **2d** with thionyl chloride gave the corresponding chloromethyl derivative **2f**, which on reacting with sodium sulfide in ethanol at reflux afforded **4a**.

The structures of these compounds were derived by spectroscopic methods.

Scheme I

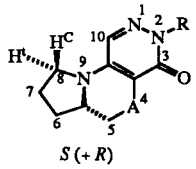


1



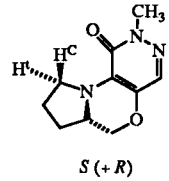
2

a, R = H, X = Y = Cl
b, R = CH_3, X = Y = Cl
c, R = H, X = Cl, Y = PyrOH
d, R = CH_3, X = Cl, Y = PyrOH
e, R = CH_3, X = PyrOH, Y = Cl
f, R = CH_3, X = Cl, Y = PyrCl
g, R = Bd-CH_2-N(Ph)-$CH_2CH_2CH_2$,
X = Cl, Y = PyrOH



S (+ R)

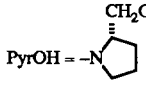
3, A = O, 4, A = S



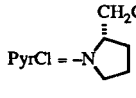
S (+ R)

5

a, R = CH_3
b, R = Bd-CH_2-N(Ph)-$CH_2CH_2CH_2$
c, R = Bd-CH_2-NH$CH_2CH_2CH_2$



PyrOH = –N



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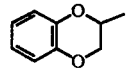

Bd =

Table 1
Physical and Analytical Data of Compounds **2c-g, 3a-c, 4a** and **5**

Compound	mp (°C) (Crystallized from)	a_D^{20} (°) (cl MeOH)	Yield (%)	Molecular Formula	Analysis C	(%) H	(Found/Calcd.) N
2c	183-185	-16.3	60	$C_9H_{12}ClN_3O_2$	46.97	5.21	17.93
				(229.67)	47.07	5.27	18.30
2d	94-96	-5.4	73	$C_{10}H_{14}ClN_3O_2$	49.38	5.82	17.07
	[a]			(243.69)	49.29	5.79	17.24
2e	oil		7	$C_{10}H_{14}ClN_3O_2$	48.96	5.87	17.49
				(243.69)	49.29	5.79	17.24
2f	73-74	-27.8	82	$C_{10}H_{13}Cl_2N_3O$	45.78	5.10	16.02
				(262.14)	45.82	5.00	16.03
2g	oil		95	$C_{28}H_{33}ClN_4O_4$	63.90	6.21	10.48
				(525.06)	64.05	6.33	10.67
3a	155-156	-128.0	76	$C_{10}H_{13}N_3O_2$	57.60	6.53	20.15
	[b]			(207.23)	57.96	6.32	20.28
3c [c]	230-233	-61.9	53	$C_{21}H_{27}ClN_4O_4$	58.12	6.12	12.98
	(2-Propanol)			(434.93)	57.99	6.26	12.88
4a	137-138		6	$C_{10}H_{13}N_3OS$	53.61	5.87	18.85
	[b]			(223.30)	53.79	5.87	18.82
5	68-70	-47.6	24	$C_{10}H_{13}N_3O_2$	57.95	6.50	20.04
	[b]			(207.25)	57.96	6.32	20.28

[a] Ether-ethanol 1:1. [b] Isopropyl ether. [c] As the hydrogen chloride salt.

The types of compounds **3**, **4** and **5** can be well distinguished by ^{1}H nmr data. In DNOE experiments, irradiations of 8-CH_2 in **3a,c**, **4a** and **5** resulted in an enhancement at the signal of pyridazinone moiety (10-C*H*) in the cases of **3a,c** and **4a**, whereas no enhancement was observed at the intensity of the signal of 3-C*H* in the case of **5**. The chemical shifts of the C_8-protons are of diagnostic value, also. As a consequence of anisotropic effect of the neighbouring carbonyl group, both signals are shifted upfield in the cases of **3a,c** and **4a** compared to the corresponding signals of **5**. Similarly, a characteristic difference in the chemical shifts of the 2-C*H* signal of the pyrrolidine moiety was served for **2d** and **2e**.

The ^{13}C nmr data are also in agreement with the structures proposed.

The novel compounds tested for antihypertensive effect were practically inactive.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets on a Bruker IFS 85 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on Bruker AC-250 spectrometer in deuteriochloroform (unless otherwise stated) at ambient temperature using TMS as internal reference.

For assignment of signals of the tricyclic compounds, COSY and ^{13}C, ^{1}H-heterocorrelation spectra were taken.

DNOE and COSY experiments were performed with the Bruker microprogram.

Syntheses of compounds **2a,b** [8] and **6** [2] were performed according to the quoted literature.

General Method for the Preparation of (2-Hydroxymethyl-1-pyrrolidinyl)-3(2*H*)-pyridazinones **2c-e**.

L-2-Hydroxymethylpyrrolidine (L-prolinol) (0.125 mole) was added to a stirred solution of 4,5-dichloro-3(2*H*)-pyridazinone (**2a**) or its *N*-methyl derivative **2b** (0.05 mole) in 1-butanol or ethanol (100 ml), respectively, at room temperature. After stirring for *ca.* 4 hours (monitored by tlc) under reflux, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel using ethyl acetate as eluent, to give **2c** or **2d** and **2e**, respectively.

(*S*)-4-Chloro-5-(2-hydroxymethyl-1-pyrrolidinyl)-3(2*H*)-pyridazinone (**2c**).

This compound had ir: 3380 (OH), 1620 (amide-I) cm^{-1}; ^{1}H nmr (DMSO d_6): δ 1.90 (m, 4H, 3-CH_2 + 4-CH_2), 3.45 (m, 2H, 5-CH_2), 3.75 (m, 2H, CH_2O), 4.2 (m, 1H, 2CH), 7.75 (s, 1H, 6-CH), 12.50 (s, 1H, NH).

(*S*)-4-Chloro-5-(2-hydroxymethyl-1-pyrrolidinyl)-2-methyl-3(2*H*)-pyridazinone (**2d**).

This compound had ir: 3414 (OH), 1610 (amide-I) cm^{-1}; ^{1}H nmr: δ 1.75-2.20 (m, 4H, 3 CH_2 + 4-CH_2), 3.2 (br, 1H, OH), 3.63 (m, 3H, 5-CH^t + CH_2O), 3.68 (s, 3H, *N*-CH_3) 3.90 (m, 1H, 5-CH^c), 4.52 (m, 1H, 2-CH), 7.70 (s, 1H, 6-CH).

5-Chloro-4-(2-hydroxymethyl-1-pyrrolidinyl-2-methyl)-3(2*H*)-pyridazinone (**2e**).

This compound had ir: 3430 (OH), 1640 (amide-I) cm^{-1}; ^{1}H nmr: δ 1.70-2.25 (m, 5H, 3-CH_2 + 4-CH_2, + OH), 3.21 (m, 1H, 5-CH^c), 3.36 (dd, J_{vic} = 5.3, J_{gem} = 11.3 Hz, CHO), 3.49 (dd, J_{vic} = 4.0, J_{gem} = 11.3, 1H, CHO), 3.70 (s, 3H, *N*-CH_3), 3.97 (m, 1H, 5-CH^c), 5.15 (m, 1H, 2-CH), 7.55 (s, 1H, 6-CH).

(*S*)-4-Chloro-5-(2-chloromethyl-1-pyrrolidinyl)-2-methyl-3(2*H*)-pyridazinone (**2f**).

Compound **2d** (3.50 g, 0.014 mole) was added to thionyl chloride (4.40 g, 0.036 mole) with stirring at 0-5° and the mixture was stirred at 60° for 3 hours. Then the excess of thionyl chloride was removed *in vacuo* and the residue was treated with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic phase was evaporated to dryness and the residue was taken up in hot ether (200 ml) and filtered. The filtrate was evaporated and the residue was crystallized. This compound had ir: 1626 (amide-I) cm^{-1}; ^1H nmr: δ 2.1 (m, 4H, 3-CH_2 + 4-CH_2), 3.5 (dd, 2H, CH_2O), 3.7 (s, 3H, *N*-CH_3), 3.75 (m, 2H, 5-CH_2), 4.78 (m, 1H, 2-CH), 7.53 (s, 1H, 6-CH).

2-[3-[*N*-(2-[1,4]Benzodioxanylmethyl)-*N*-benzyl]aminopropyl]-4-chloro-5-(2-hydroxymethyl-1-pyrrolidinyl)-3(2*H*)-pyridazinone (**2g**).

Sodium (0.115 g, 0.005 mole) was dissolved in ethanol (10 ml) and a solution of **2c** (1.15 g, 0.005 mole) in ethanol (10 ml) was added to it. After stirring at room temperature for 10 minutes, the solvent was evaporated *in vacuo* and anhydrous toluene was added to the residue. The solvent was distilled off under reduced pressure to remove the traces of ethanol. The residue was suspended in toluene (20 ml) and a solution of **6** (1.84 g, 0.005 mole) in toluene (20 ml) and then tetrabutylammonium bromide (0.32 g, 0.001 mole) were added to the suspension. The mixture was stirred under reflux for 7 hours, then cooled and diluted with toluene (100 ml). After filtration the filtrate was washed with water and dried. The solvent was evaporated *in vacuo* to afford **2g**. This compound had ir: 3387 (OH), 1620 (amide-I) cm^{-1}; ^1H nmr: δ 1.8-2.20 (m, 7H, OH, 3-CH_2 + 4-CH_2 pyrr., 2-CH_2 propyl), 2.62 (m, 2H, 3-CH_2 propyl), 2.75 (d, J = 7, CH_2-Bd), 3.55 (m, 2H, CH_2OH), 3.60 (s, 2H, $PhCH_2$), 3.80 (q, J = 7, 2H, 5-CH_2 and m, 1H, OCH Bd), 4.05 (m, 1H, OCH^{ax} Bd), 4.25 (m, 3H, N-CH_2 + OCH^{eq} Bd), 4.50 (m, 1H, 2-CH pyrrolidine), 6.80 (br s, 4H, aromatic Bd), 7.30 (m, 5H, aromatic benzyl), 7.60 (s, 1H, 6-CH).

General Method for the Preparation of Pyridazino[4,5-*b*]pyrrolo-[1,2-d][1,4]oxazines **3a** and **5**.

To a stirred solution of sodium butylate in 1-butanol (prepared from 0.03 mole of sodium in 1-butanol), a solution of **2d** or **2e** 0.01 mole) in 1-butanol (10 ml) was added. The mixture was heated under reflux for *ca* 4 hours (monitored by tlc) then filtered. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using ethyl acetate as eluent.

2-Methyl-3-oxo-5,5a,6,7-tetrahydro-2*H*,8*H*-pyridazino[4,5-*b*]pyrrolo[1,2-*d*][1,4]oxazine (**3a**).

This compound had ir: 1616 (amide-I) cm^{-1}; ^1H nmr: δ 1.50 (m, 1H, 6-CH^t), 2.10 (m, 2H, 7-CH_2), 2.20 (m, 1H, 6-CH^c), 3.25 (dd, 2H, 5-CH^t + 8-CH^t), 3.50 (m, 1H, 5a-CH), 3.65 (m, 1H, 8-CH^c), 3.70 (s, 3H, *N*-CH_3), 4.60 (dd, J_{vic} = 3, J_{gem} = 10, 1H, 5-CH^c), 7.50 (s, 1H, 10-CH); ^{13}C nmr: δ 24.0 (7-C), 27.7 (6-C), 39.5 (*N*-CH_3), 47.6 (8-C), 55.2 (5a-C), 68.2 (5-C), 128.4 (10-C), 131.6 (9a-C), 132.2 (3a-C), 156.1 (3-C).

1-Methyl-10-oxo-5,5a,6,7-tetrahydro-1*H*,8*H*-pyridazino[4,5-*b*]-pyrrolo[1,2-*d*][1,4]oxazine (**5**).

This compound had ir: 1620 (amide-I) cm^{-1}; ^1H nmr: δ 1.4-2.23 (m, 4H, 6-CH_2 + 7-CH_2), 3.24 (dd, J_{vic} = 9.1, J_{gem} = 10.2, 1H, 5-CH^t), 3.35 (m, 1H, 5a-CH), 3.45 (m, 1H, 8-CH^t), 3.68 (s, 3H, *N*-CH_3), 4.39 (dd, J_{vic} = 3.2, J_{gem} = 10.2, 1H, 5-CH^c), 4.51 (m, 1H, 8-CH^c), 7.55 (s, 1H, 3-CH); ^{13}C nmr: δ 24.9 (7-C), 27.0 (6-C), 39.7 (*N*-CH_3), 50.4 (8-C), 55.2 (5a-C), 67.3 (5-C), 127.6 (9a-C), 131.2 (3a-C), 139.1 (3C), 158.5 (10-C).

2-[3-*N*-(2-[1,4]benzodioxanylmethyl)aminopropyl]-3-oxo-5,5a,6,7-tetrahydro-2*H*,8*H*-pyridazino[4,5-*b*]pyrrolo[1,2-*d*][1,4]oxazine (**3c**).

A solution of **2g** (2.62 g, 0.005 mole) in 1 butanol (4 ml) was added to a stirred solution of sodium butylate in 1-butanol (prepared from 0.015 mole of sodium in 8 ml of 1-butanol). The mixture was heated under reflux for 5 hours. After filtration, the solvent was removed *in vacuo* to afford 2-[3-[*N*-(2-[1,4]benzodioxanylmethyl)-*N*-benzyl]aminopropyl]-3-oxo-5,5a,6,7-tetrahydro-2*H*,8H-pyridazino[4,5-*b*]pyrrolo[1,2-d][1,4]oxazine (**3b**) (2.17 g, 93%) as a yellowish oil, which was used for the next step without further purification.

Anal. Calcd. for $C_{28}H_{32}N_4O_4$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.30; H, 7.00; N, 10.90.

This compound was dissolved in ethanol (30 ml). The solution was placed in a Parr apparatus containing 10% palladium on charcoal (0.20 g), ethanol (30 ml) and 12*N* hydrochloric acid (0.6 ml). The mixture was hydrogenated at atmospheric pressure until the hydrogen uptake had ceased (*ca.* 10 hours). The catalyst was filtered off and washed with ethanol. The solvent was evaporated *in vacuo* and the crude product was recrystallized to afford **3c** as hydrogen chloride salt. The free base was obtained by treatment of this salt with aqueous sodium hydroxide solution and extraction with ethyl acetate. The base had ir: 1620 (amide-I) cm^{-1}; ^1H nmr: δ 1.55 (m, 1H, 6CH^t), 2.10 (m, 2H, 7-CH_2), 2.15 (m, 2H, 2-CH_2-Bd), 3.25 (m, 2H, 5-CH^t + 8CH^t), 3.50 (m, 1H, 5a-CH), 3.65 (m, 1H, 8-CH^c), 4.05 (m, 1H, OCH^{ax} Bd), 4.25 (m, 3H, 1-CH_2 propyl + OCH^{eq} Bd), 4.50 (m, 1H, OCH Bd) 4.78 (dd, J_{vic} = 3.3 J_{gem} = 10.3, 1H, 5-CH^c), 6.85 (m, 4H, aromatic Bd), 7.50 (s, 1H, 10-CH); ^{13}C nmr: δ 24.0 (7C), 27.5 (2-C propyl), 27.9 (6-C), 46.4 (3-C propyl), 47.5 (8-C), 49.0 (1-C propyl), 49.1 (CH_2-Bd), 55.2 (5a-C), 66.1 (OCH_2 Bd), 66.2 (5-C), 71.4 (OCH Bd), 117.1, 117.5, 121.4, 121.5 (aromatic Bd), 129.0 (10-C), 131.7, 131.9, 142.6, 143.2 (aromatic Bd + 9a-C + 3a-C), 156.3 (3-C).

1-Methyl-3-oxo-5,5a,6,7-tetrahydro-2*H*,8*H*-pyridazino[4,5-*b*]-pyrrolo[1,2-*d*][1,4]thiazine (**4a**).

A suspension of **2f** (1.50 g, 0.006 mole) and sodium sulfide nonahydrate (1.65 g, 0.007 mole) in ethanol (7 ml), under nitrogen atmosphere was heated under reflux for 1 hour. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using ethyl acetate as eluent. This compound had ir: 1613-1620 (amide-I) cm^{-1}; ^1H nmr: δ 1.60 (m, 1H, 6-CH^t), 2.10 (m, 2H, 7-CH_2), 2.30 (m, 1H, 6-CH^c), 2.50 (dd, J_{vic} = 9, J_{gem} = 12, 1H, 5-CH^t), 3.17 (dd, J_{vic} = 3, J_{gem} = 12, 1H, 5-CH^c), 3.35 (m, 1H, 8-CH^t), 3.65 (m, 2H, 8-CH^c + 5a-CH), 3.73 (s, 3H, *N*-CH_3), 7.38 (s, 1H, 10-CH); ^{13}C nmr: δ 23.3 (7-C) 28.2 (5-C), 32.2 (6-C), 39.3 (*N*-CH_3) 47.3 (8-C), 57.6 (5a-C), 106.6 (3a-C), 126.2 (10-C), 140.2 (9a-C), 158.1 (C-3).

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