A NOVEL METHOD FOR THE SYNTHESIS OF 2-HALOALKYL-3(2H)-PYRIDAZINONES BY O→N-ALKYL REARRANGEMENT

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Abstract - The reaction of (6-substituted 3-pyridazinyloxy)alkanols 2a-d, 3a-d and 14a-c with thionyl chloride is described. The 2-chloroalkylpyridazinones 5b-d, 6b-d and 15a-c were formed from 2b-d, 3b-d and 14a-c, respectively, while the 3-chloroalkoxypyridazines 7a and 8a were isolated from the reaction of 2a and 3a, respectively. It was shown by chemical and spectroscopic evidences that the rearrangement reaction followed an intramolecular process through bicyclic intermediates.

A great attention has been paid to the compounds containing 3(2H)-pyridazinone moiety due to their potential biological activities.[1-3] Recently, we described the synthesis and antihypertensive effect of a series of 2-aminoalkyl-3(2H)-pyridazinones Based on detailed preclinical investigations the outstanding representative of these substances, GYKI-12 743, seems to be advantageous for the treatment of several types of hypertension.[4] In one of the synthetic approaches of these compounds, 2-chloroalkyl-3(2H)-pyridazinones 5 and 6 were reasonable considered as the key intermediates.[5,6] (Scheme 1)

Based on our earlier observation that the reaction of the 3-pyridazinyloxypropanol derivative 3b with mesyl or thionyl chloride resulted in a formation of the 2-chloropropyl-3(2H)-pyridazinone derivative 6b in high yield, a study on similar reactions of other derivatives was carried out to investigate the mechanism and to explore the scope and limitation of the rearrangement of this type.

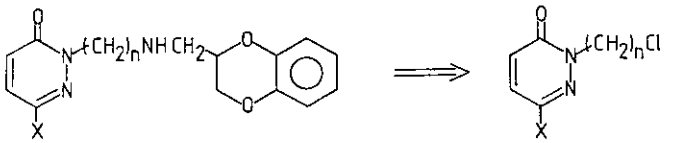
3-Pyridazinyloxyalkanols 2b-d and 3b-d[7] were prepared by the reaction of 6-substituted 3-chloropyridazines 1 with one equivalent of the appropriate alkanediol monosodium salt in an excess of the diol, while 2a and 3a were obtained from 2b and 3b, respectively, by hydrogenolysis.

The compounds 2 and 3 were then treated with thionyl chloride in chloroform or mesyl chloride in dimethylformamide in the presence of triethylamine.

In the reactions of 2b-d, 3b and 3e, the 2-chloroalkyl derivatives 5b-d, 6b and 6e, respectively, were formed as single products. The compounds 3c and 3d also gave the corresponding 2-chloroalkyl derivatives (6c and 6d) as main products, however the 3-chloropropoxy isomers, 8c and 8d, being also detected. In a sharp contrast to these results, 2a and 3a showed a different behaviour and gave the 3-chloroalkoxy derivatives 7a and 8a, respectively, as main products in the form of their hydrochlorides, the 2-chloroalkyl isomers (5a and 6a, respectively) being formed only as by-products.

The compounds 5a, 6a and 6b were also synthetized by other ways. Thus, 5a was prepared from 4a by the known method,[6a] and 6a and 6b were obtained upon treatment of 4a and 4b, respectively, with 1-bromo-3-chloropropane under phase transfer catalysis conditions. Further, 6a could also be prepared from 6b by hydrogenolysis. (Scheme 2)

Scheme 1

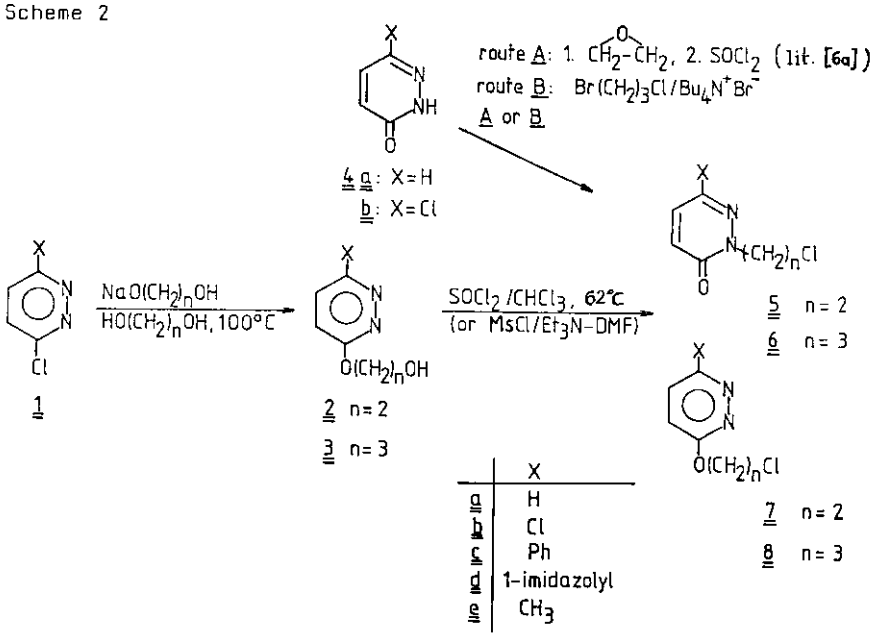


G:KI-12743 : X = H, n = 3

5 n = 2

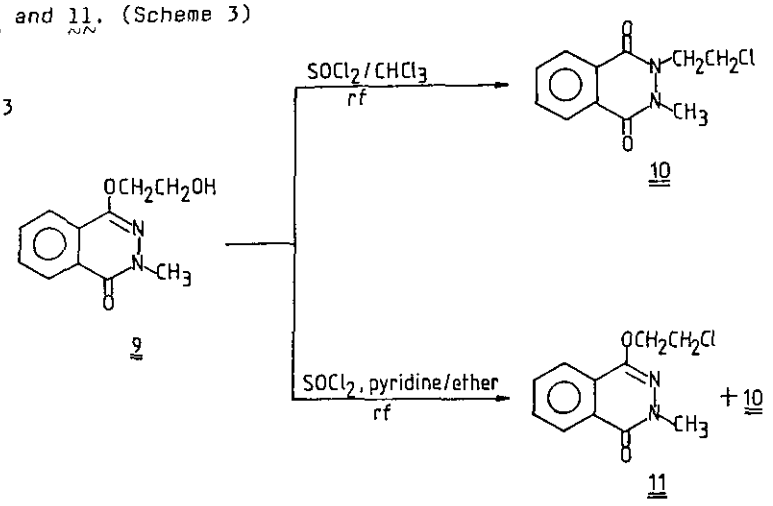
6 n = 3

Scheme 2



Earlier, a similar O→N-alkyl rearrangement was also observed by others.[8] It was reported that the reaction of the phthalazinyloxyethanol derivative 9 with thionyl chloride gave the N-chloroethyl derivative 10 and/or the O-chloroethyl derivative 11 depending on the conditions. It was also postulated that the reaction proceeded via an oxazolinium intermediate which was subsequently attacked by the chloride ion to form 10 and 11. (Scheme 3)

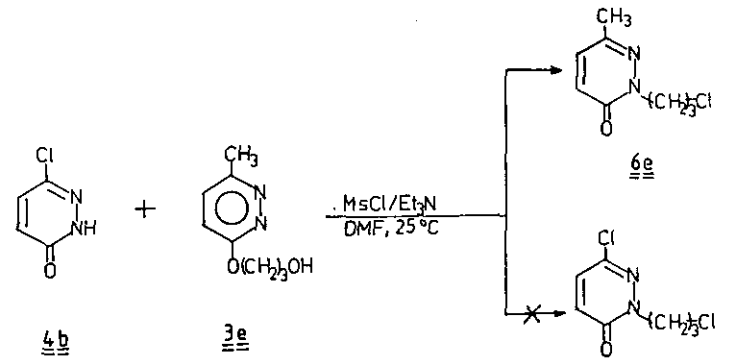
Scheme 3



9 10 11

We carried out the following experiments in order to get an insight into the mechanism of the rearrangement. A mixture containing 3e and 4b was treated with mesyl chloride. In this crossover experiment 6e could only be detected, supporting an intramolecular pathway. If the reaction (also) took place in an intermolecular manner, both 6b and 6e should have been formed. (Scheme 4)

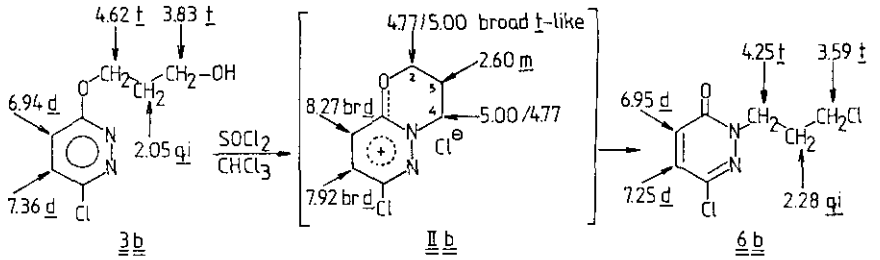
Scheme 4



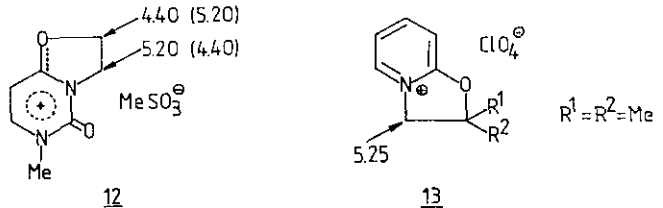
4b 3e 6e 6b

To obtain some information about the intermediate(s), the reaction of 3b with thionyl chloride was monitored by ^{1}H nmr spectroscopy. In the course of the reaction one set of signals could be identified which significantly differs from the set of both 3b and 6b. The values of the chemical shifts and the pattern of the multiplicity prove the structure of the supposed intermediate IIb. The good approximations of the values of the chemical shifts of H-2/H-4 of IIb to those of the corresponding signals in the structurally related compounds 12[9] and 13[10] also supports this constitution. (Scheme 5)

Scheme 5



3b IIb 6b



12 13

The intramolecular process through the bicyclic intermediates was also shown by the following observation.

Treatment of a 2:1 mixture of pyridazinyloxyalkanols 14a and 14b with thionyl chloride gave a 2:1 mixture of the 2-chloroalkyl derivatives 15a and 15b.

An important conclusion could also be drawn from the following experiment. The trans-pyridazinyloxycyclohexanol derivative 14c (prepared from 1b and trans-cyclohexanediol) reacted with thionyl chloride to give the trans-2-chlorocyclohexyl-pyridazinone 15c, proving that the rearrangement took place with inversion at both C-1 and C-2. The trans-diaxial configurations of H-1 and H-2 were unambiguously proved by the proton-proton coupling constant.[11] (Scheme 6)

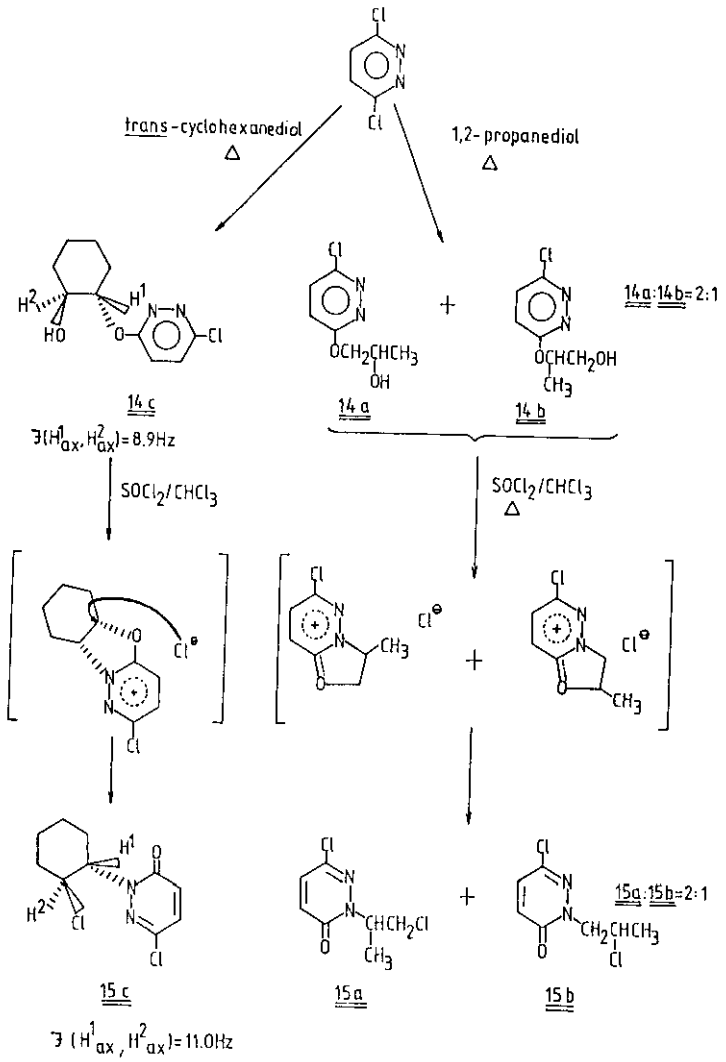
Table 1

Characteristic ir (KBr, cm^{-1}), ^1H nmr ($COCl_3$, δ ppm) and uv (96 % ethanol) data of 2a-d, 3a-e, 5b, 5d, 6a-e, 7a, 8a, 8c, 8d, 16 and 17

Compd.	ir amide-I	ir νOH	$ArOCH_2$ (2H)	$CH_2CH_2CH_2OH$ (2H)	CH_2OH (2H)	CH_2Cl (2H)	NCH_2 (2H)	H-4 (1H)	H-5 (1H)	Other signals	uv λmax (ε)
2a	-	3302	4.66 t(J=4.5Hz)	-	4.00 t(4.5)	-	-	7.05 d(9)	7.44 dd(9,4.5)	8.81(1H,d(4.5),H-6)	269 (2400)
2b	-	3416	4.60 t(4.5)	-	3.98 t(4.5)	-	-	7.05 d(9)	7.40 d(9)	-	282 (2080)(d)
2c	-	3285	4.68 t(5)	-	3.99 t(5)	-	-	7.05 d(9)	7.75 d(9)	7.43(3H,m,m+p-PhH) 7.95(2H,m,o-PhH)	250 (19280)
2d	-	3204	4.47(c) t(5)	-	~3.9	-	-	7.45 d(9)	8.11 d(9)	7.17(1H,s,H-4') 7.93(1H,s,H-5') 8.50(1H,s,H-2')	240 (14660)(d) 285 (7270)
3a	-	3396 (e)	4.67 t(6)	2.05 qi(6)	3.83 t(6)	-	-	7.01 d(9)	7.43 dd(9,4.5)	8.81(1H,d(4.5),H-6)	270 (2420)
3b	-	3371	4.62 t(6)	2.05 qi(6)	3.83 t(6)	-	-	6.94 d(9)	7.36 d(9)	-	282 (1090)
3c	-	3285	4.70 t(6)	2.09 qi(6)	3.79 t(6)	-	-	6.99 d(9)	7.72 d(9)	7.42(3H,m,m+p-PhH), 7.91(2H,m,o-PhH)	250 (20340)
3d	-	3198	4.56 t(6)	2.03 qi(6)	3.69 t(6)	-	-	7.13 d(9)	7.79 d(9)	7.10(1H,s,H-4'), 7.73(1H,s,H-5'), 8.33(1H,s,H-2')	240 (15860) 285 (2439)
3e	-	3358	4.60 t(6)	2.07 qi(6)	3.76 t(6)	-	-	6.77 d(9)	7.23 d(9)	2.61(3H,s,CH_3)	275 (2080)
5b	1670					3.87 t(6)	4.45 t(6)	6.95 d(10)	7.25 d(10)		306 (3010)(d)
5d (a)	1664	-	-	-	-	4.05 t(4.5)	4.40 t(4.5)	7.30 d(9)	8.24 d(9)	7.03(1H,s,H-5'), 8.30(1H,s,H-4'), 9.93(1H,s,H-2)	310 (2640)(d)
6a	1663 (e)	-	-	2.32 qi(6)	-	3.62 t(6)	4.35 t(6)	6.98 dd(9,4)	7.30 dd(9,2)	7.87(1H,dd(4.2),H-6)	297 (3620)
6b	1666	-	-	2.28 qi(7)	-	3.59 t(7)	4.25 t(7)	6.95 d(10)	7.25 d(10)		306 (3110)
6c	1666 (e)	-	-	2.25 qi(6)	-	3.54 t(6)	4.27 t(6)	6.90 d(10)	7.55 d(10)	~7.3(3H,m,m+p-PhH) ~7.7(2H,m,o-PhH)	259 (22800)(d) 313 (3080)
6d (a)	1666	-	-	2.25 qi(6)	-	3.71 t(6)	4.21 t(6)	7.30 d(10)	8.22 d(10)	7.90(1H,s,H-5'), 8.25(1H,s,H-4'), 9.96(1H,s,H-2')	312 (2840)
6e	1663 (e)	-	-	2.25 qi(7)	-	355 t(7)	4.21 t(7)	6.82 d(10)	7.06 d(10)	2.30(3H,s,CH_3)	302 (17600)(d)
7a	-	-	4.80 t(4.5)	-	-	3.90 t(4.5)	-	7.02 d(8)	7.39 dd(8,4)	8.85(1H,d(4),H-6)	268 (2690)(d)
8a	-	-	4.58 t(6)	2.25 qi(6)	-	3.80 t(6)	-	7.10 dd(9,2)	7.50 dd(9,4)	8.82(1H,dd(4,2)H-6)	269 (2200)(d)
8c	-	-	4.70 t(6)	2.30 qi(6)	-	3.70 t(6)	-	7.06 d(9)	7.80 d(9)	7.45(3H,m,m+p-PhH), 7.95(2H,m,o-PhH)	251 (18500)
8d (a)	-	-	4.62(c) t(6)	2.25 qi(6)	-	3.82 t(6)	-	7.67 d(10)	8.47 d(10)	~7.9(1H,s,H-5'), 8.51(1H,s,H-4'), 9.95(1H,s,H-2')	
16	1736		~4.8 m	-	-	~4.8 m	-	7.05 d(9)	7.45 d(9)	8.20(4H,s,(NO_2)Ph-H)	260 (12500)(d)
17	1720 (b)	-	4.56 (c) t(6)	2.35 qi(6)	-	4.66 t(6)	-	6.95 d(9)	7.39 d(9)	8.22(4H,m,(NO_2)Ph-H)	260 (13900)

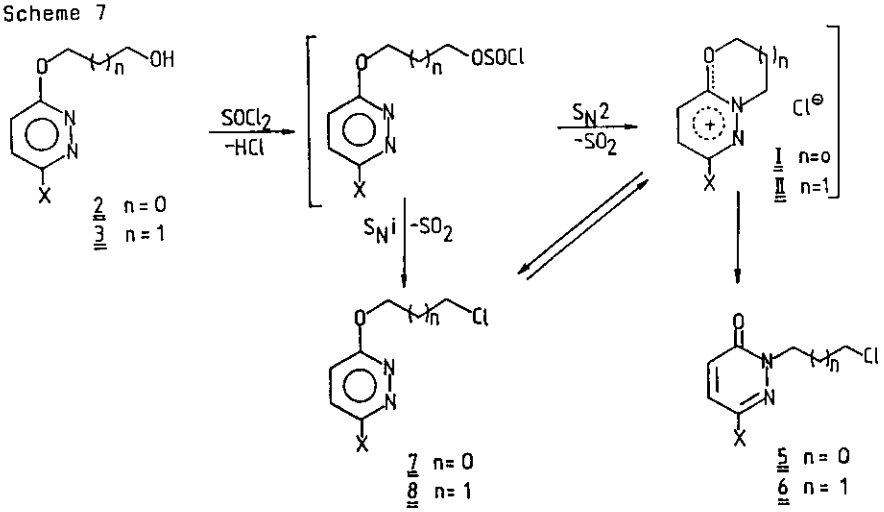
(a) as HCl salt; (b) νC=O (ester); (c) ^1H nmr in DMSO-d_6; (d) uv in ethanol; (e) ir in film

Scheme 6



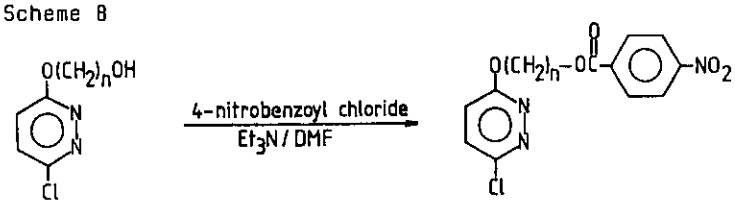
All of the above results suggest that the formation of 2-chloroethyl or 2-chloropropylpyridazinones from 3-pyridazinyloxyethanols or -propanols with thionyl or mesyl chloride involves the bicyclic intermediate of type I or II, respectively. On the other hand the 3-chloroalkoxypyridazines may also be formed from the chlorosulfite ester by an S_Ni mechanism. (Scheme 7)

Scheme 7



When p-nitrobenzoyl chloride was used instead of mesyl or thionyl chloride in the reaction of 2b or 3b, the corresponding p-nitrobenzoates 16 and 17 could be separated. A separate experiment showed that 17 is thermally stable (toluene, 110 °C). (Scheme 8).

Scheme 8



EXPERIMENTAL

Melting points were determined on a Boetius apparatus. None of melting and boiling points are corrected. The following apparatus were used to obtain spectral data. Ir: Bruker IFS 85; ^1H nmr: Bruker AC-250 at 250.13 MHz, using TMS as internal reference; uv: Cary 118.

Compounds 1c,[12] 1d,[13] 1e,[14] 4a[15] and 4b[16] were prepared by the methods reported in the literature. The other starting materials are commercially available.

Preparation of 3-pyridazinyloxyalkanols (2b-d, 3b-e and 14a,b) (Method I)

Sodium (2.30 g, 0.10 mol) was dissolved in 1,2-ethane- or 1,3-propanediol under nitrogen atmosphere. Then, the appropriate 3-chloropyridazine (0.09 mol) was added to the solution. The reaction mixture was stirred at 100 °C for the given time, the solvent was removed in vacuo and the residue dissolved in H_2O and extracted with $CHCl_3$. The crude product was purified by destillation and/or recrystallization.

The reaction of 1b with 1,2-propanediol under similar conditions gave a 2:1 mixture of 14a and 14b (bp 128-129 °C/1.5 torr, total yield: 70 %) which was used for the reaction with thionyl chloride.

Preparation of trans -2-(6-chloro-3-pyridazinyloxy)cyclohexanol (14c)

Sodium (0.46 g, 0.02 mol) was added to a solution of trans-1,2-cyclohexanediol (5.80 g, 0.05 mol) in dry toluene (70 ml) and the suspension formed was gently heated to 90 °C under nitrogen atmosphere. After all the sodium had reacted, 3,6-dichloropyridazine (2.98 g, 0.02 mol) was added to the solution at 50 °C. The reaction mixture was stirred at 110 °C for 2 h, then cooled and filtered. The filtrate was evaporated in vacuo, the residue washed with H_2O and recrystallized.

Hydrogenolysis of the 6-chloro substitutent: preparation of 2a, 3a and 6a (Method II)

A suspension of 2b, 3b or 6b (0.25 mol) and 10 % Pd-C catalyst (1 g) in a mixture of EtOH (60 ml) and ammonia solution (15 ml, d = 0.91) was shaken with H_2 in a Parr apparatus until the calculated H_2-uptake was reached. The solvent was evaporated in vacuo, the residue was dissolved in H_2O and extracted with CH_2Cl_2. The crude product was recrystallized.

Table 2

List of compounds 2a-d, 3a-e, 5b-5d, 6a-e, 7a, 8a, 8c, 14c, 15c, 16 and 17[+]

Compd.	Method (reaction time, h)	Solvent of cryst.	mp (°C)	Yield %	Molecular formula
2a	II	petrol ether	59-60	52	$C_6H_8N_2O_2$
2b	I (1)	isopropanol-petrol ether 1:1	98-100[++++]	70	$C_6H_7ClN_2O_2$
2c	I (5)	ethanol	102-103	40	$C_{12}H_{12}N_2O_2$
2d	I (7)	ethanol	157-159	53	$C_9H_{10}N_4O_2$
3a	II		oil	56	$C_7H_{10}N_2O_2$
3b	I (1)	petrol ether	39-41	71	$C_7H_9ClN_2O_2$
3c	I (4)	ethanol	109-110	45	$C_{13}H_{14}N_2O_2$
3d	I (4)	water	131-133	29	$C_{10}H_{12}N_4O_2$
3e	I (4)		oil[+++]	60	$C_8H_{12}N_2O_2$
5b	III (1)	petrol ether	55-57	73	$C_6H_6Cl_2N_2O$
5c	III (3.5)	diethyl ether	69-70[++++]	52	$C_{12}H_{11}ClN_2O$
5d[++]	III (1)	ethanol	202-205	91	$C_9H_{10}Cl_2N_4O$
6a	III (5)		oil	60	$C_7H_9ClN_2O$
	V (5)			73	
6b	III (2)			80	$C_7H_8Cl_2N_2O$
	IV	isopropyl ether		75	
	V (8)			50	
6c	III (1.5)		oil	20	$C_{13}H_{13}ClN_2O$
6d[++]	III (1)	ethanol	193-195	70	$C_{10}H_{12}Cl_2N_4O$
6e	III		oil	64	$C_8H_{11}ClN_2O$
7a	III (1)	petrol ether	59-61	80	$C_6H_7ClN_2O$
8a[++]	III (1)	diethyl ether	110-112	60	$C_7H_{10}Cl_2N_2O$
8c	III (1.5)	diethyl ether	82-83	8	$C_{13}H_{13}ClN_2O$
14c		isopropanol	126-128	70	$C_{10}H_{13}ClN_2O_2$
15c	III (5)	ethanol	97-100	87	$C_{10}H_{12}Cl_2N_2O$
16	IV	diethyl ether	167-169	55	$C_{13}H_{10}ClN_3O_5$
17	IV	diethyl ether	118-120	60	$C_{14}H_{12}ClN_3O_5$

[+]Satisfactory elemental analyses (C,H,N,Cl) were obtained for all the newly synthetized compounds.

[++]As HCl salt.

[+++] bp : 160 °C/0.6 torr

[++++]Reported values 102 °C (2b)[7] and 57-59 °C (5c)[6b].

Reaction of pyridazinyloxyalkanols (2a-d, 3a-e and 14a-c) with acid chlorides

Method (III): reaction with thionyl chloride - To a stirred solution of the appropriate 3-pyridazinyloxyalkanol (0.01 mol) in $CHCl_3$ (10 fold by vol.), thionyl chloride (0.02 mol) was slowly dropped at room temperature. The reaction mixture was heated under reflux for several hours. Then, the solvent was removed in vacuo and the crude product was suspended in Et_2O, recrystallized or column chromatographed on silica gel using EtOAc as eluent (for 6c and 8c).

Method (IV): reaction with mesyl chloride or 4-nitrobenzoyl chloride

To a stirred solution of the appropriate 3-pyridazinyloxyalkanol (0.01 mol) and Et_3N (0.01 mol) in dimethylformamide (8 fold by vol.), the acid chloride (0.011 mol) was added at 5 °C in 15 min. Then, the reaction mixture was poured onto ice-water and extracted or filtered. The crude product was recrystallized.

N-Alkylation of pyridazinones (4a,b). Preparation of 6a and 6b (Method V)

A suspension of the Na-salt of 4a or 4b (0.02 mol) and $Bu_4N^+Br^-$ (4 mmol) in dry benzene (100 ml) was treated with 1-bromo-3-chloropropane (0.02 mol). The reaction mixture was stirred for several hours at 50 °C, then filtered. The filtrate was washed with NaOH solution. The crude product was recrystallized.

Spectroscopic data of 14a-c and 15a-c

Ir (cm^{-1}): 15a, b: 1666, 15c: 1672 (amide-I).

^1H NMR ($CDCl_3$ δ, ppm):

14a: 1.37 (d(J=6 Hz), 3H, CH_3), 4.15-4.60 (m, 3H, OCH_2CH), 7.05 (d(J=9 Hz), 1H, H-4), 7.40 (d(J=9 Hz), 1H, H-5);

14b: 1.43 (d(J=6 Hz), 3H, CH_3), 3.83 (d(broad, J=5 Hz), 2H, CH_2OH), 5.46 (m, 1H, OCH), 7.00 (d(J=9 Hz), 1H, H-4), 7.40 (d(J=9 Hz), 1H, H-5);

14c: 1.40 (m, 4H, H-3-6 (ax)), 1.75 (m, 2H, H-4, H-5 (eq)), 2.10 (m, 1H, H-6 (eq)), 2.30 (m, 1H, H-3 (eq)), 3.74 (ddd(J=10.3, 8.9, 4.5), 1H, H-1 (ax)), 5.09 (ddd(J=2x9.5, 4.6), 1H, H-2 (ax)), 7.00 (d(J=9 Hz), 1H, H-4'), 7.40 (d(J=9 Hz), 1H, H-5');

15a: 1.56 (d(J=6 Hz), 3H,CH_3) ~3.5-3.9 (m, 2H, CH_2Cl), 5.30 (m, 1H, NCH), 6.85 (d(J=10 Hz) 1H, H-4), 7.12 (d(J=10 Hz), 1H, H-5);

15b: 1.73 (d(J=6 Hz), 3H, CH_3), 4.10-4.60 (m, 3H, $CHCl+NCH_2$), 6.85 (d(J=10 Hz), 1H, H-4), 7.15 (d(10), 1H, H-5);

15c: 1.45 (m, 2H, H-4, H-5 (ax)), 1.80 (m, 4H, H-4 (ax), H-6 (ax), H-4 (eq), H-5 (eq)), 2.00 (m, 1H, H-3 (eq)), 2.40 (m, 1H, H-6 (eq)), 4.24 (ddd(J=2x11, 4.4 Hz) 1H, H-1), 4.98 (ddd(J=2x11, 4.1 Hz), 1H, H-4 (ax)), 6.94 (d(J=10 Hz), 1H, H-4'), 7.17 (d(J(10 Hz), 1H, H-5').

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