

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

Péter Mátyus^{*}, Nándor Makk, Endre Kasztreiner, and Gyula Jerkovich

Institute for Drug Research, Budapest, P.O.Box 82, H-1325 Hungary

Abstract - The reaction of (6-substituted 3-pyridazinyloxy)alkanols $2a-d$, $3a-d$ and $4a-c$ with thionyl chloride is described. The 2-chloroalkylpyridazinones $5b-d$, $6b-d$ and $15a-c$ were formed from $2b-d$, $3b-d$ and $4a-c$, respectively, while the 3-chloroalkoxy pyridazines $7a$ 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-chloro-propyl-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.

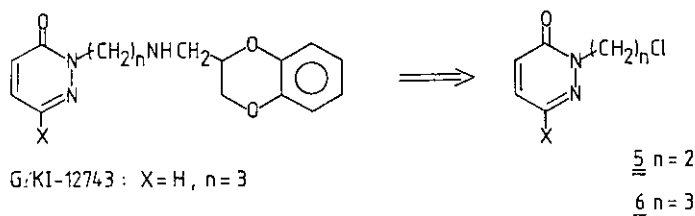
The compounds 2 and 3 were then treated with thionyl chloride in chloroform or mesyl chloride in dimethylformamide in the presence of triethylamine.

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.

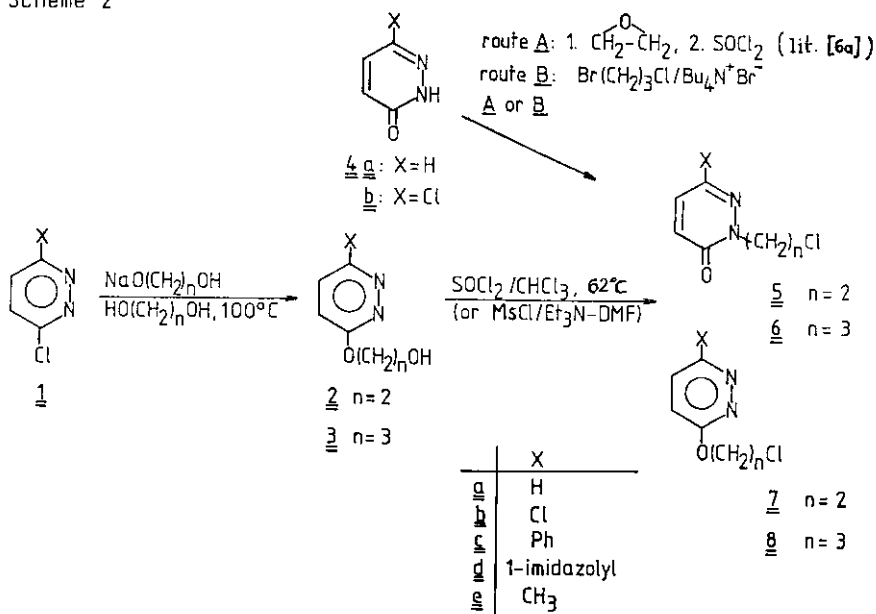
The compounds 5a, 6a and 6b were also synthesized by other ways. Thus, 5a was prepared from 4a by the known method,^{6a} and 6a and 6b were obtained upon treatment of 4a and 4b, respectively, with 1-bromo-3-chloropropane under phase transfer catalysis conditions. Further, 6a could also be prepared from 6b by hydrogenolysis.

(Scheme 2)

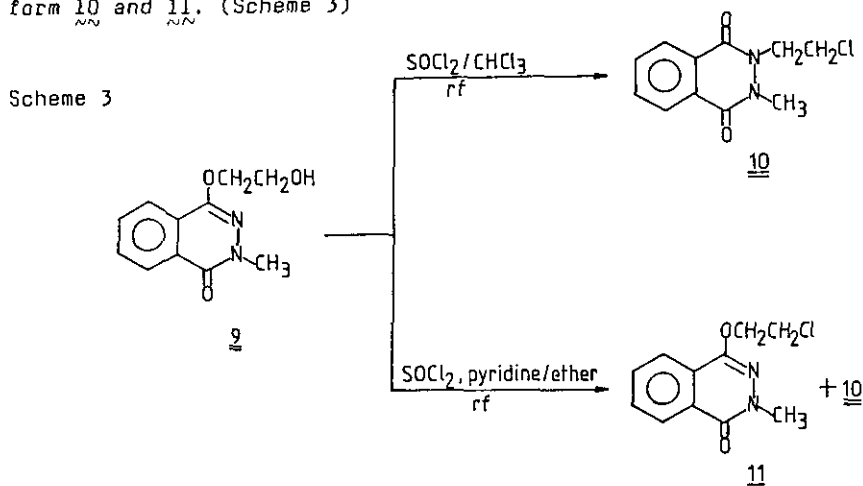
Scheme 1



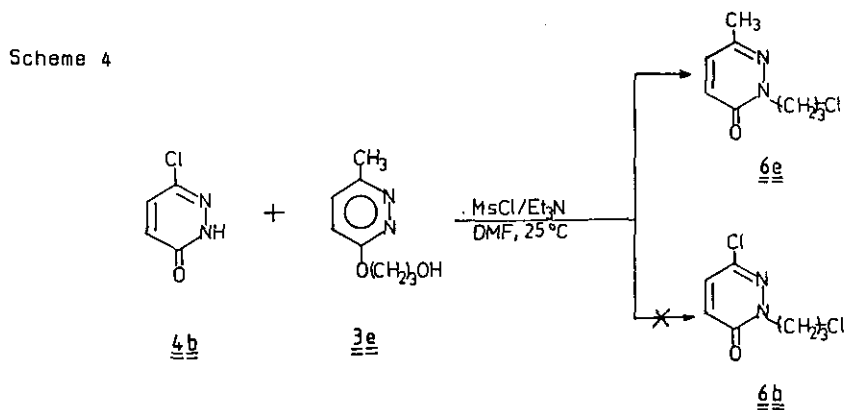
Scheme 2



Earlier, a similar $O \rightarrow N$ -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)

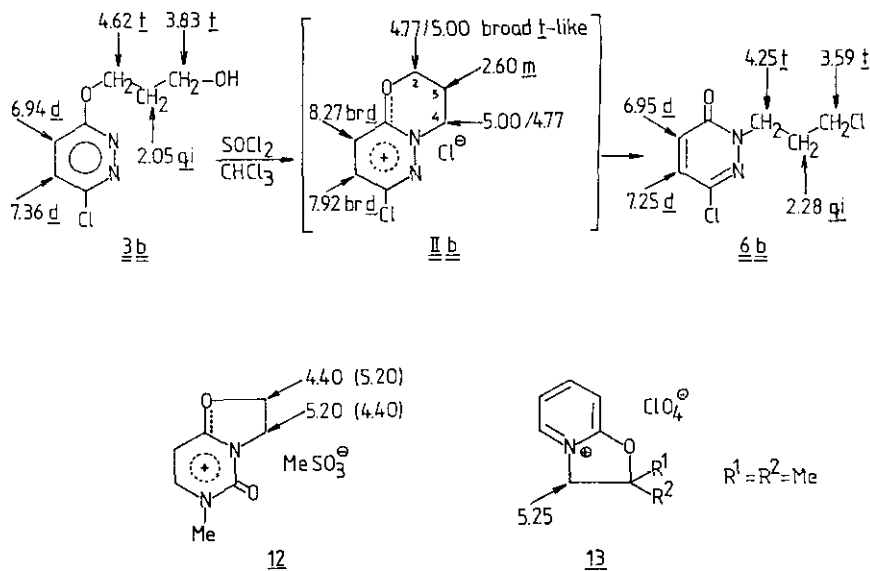


We carried out the following experiments in order to get an insight into the mechanism of the rearrangement. A mixture containing 3e and 4b was treated with mesyl chloride. In this crossover experiment 6e could only be detected, supporting an intramolecular pathway. If the reaction (also) took place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



To obtain some information about the intermediate(s), the reaction of 3b with thionyl chloride was monitored by ^1H 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 12⁹ and 13¹⁰ also supports this constitution. (Scheme 5)

Scheme 5



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-pyridazinyloxy cyclohexanol derivative 14c (prepared from 1b and trans-cyclohexanediol) reacted with thionyl chloride to give the trans-2-chlorocyclohexylpyridazinone 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)

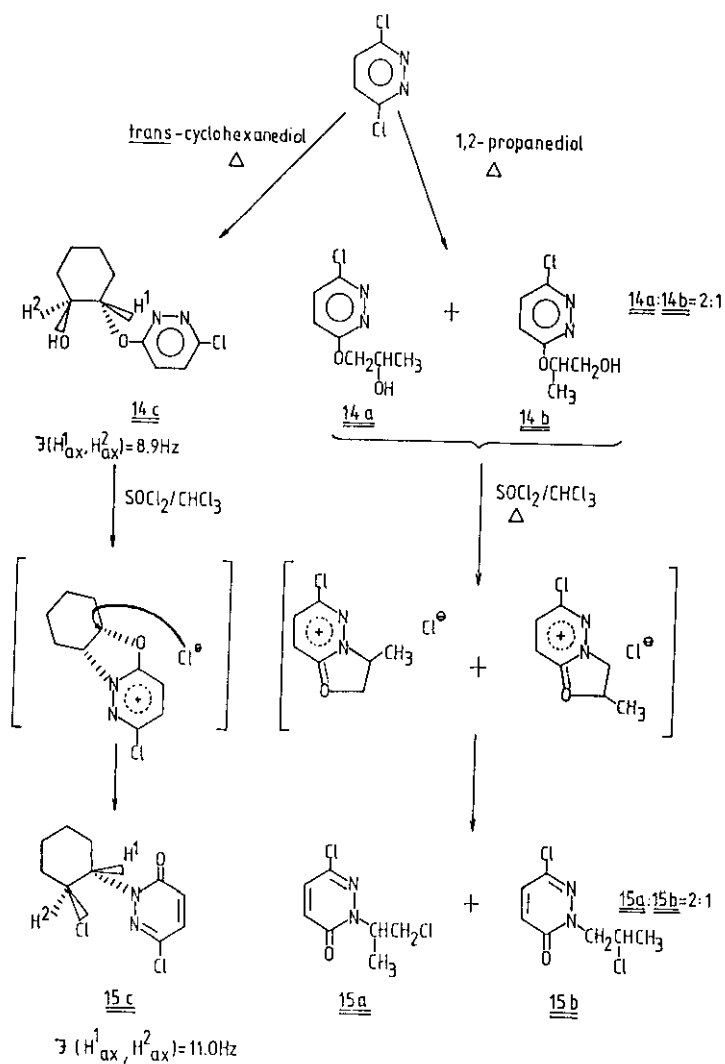
Table 1

Characteristic ir (KBr, cm^{-1}), ^1H nmr (CDCl_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.	amide-I	ir	ν_{OH}	ArOCH_2 (2H)	$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ (2H)	CH_2OH (2H)	CH_2Cl (2H)	NCH_2 (2H)	H-4 (1H)	H-5 (1H)	Other signals	uv λ_{max} (ϵ)
2a	-	3302	-	4.66 t(3-4.5Hz)	-	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,q-PrH) 7.95(2H,m,q-PrH)	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)(a) 285 (2270)
3a	-	3396 (e)	-	4.67 t(6)	2.05 q(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 q(6)	3.83 t(6)	-	-	6.94 d(9)	7.36 d(9)	-	282 (1090)
3c	-	3285	-	4.70 t(6)	2.09 q(6)	3.79 t(6)	-	-	6.99 d(9)	7.72 d(9)	7.42(3H,m,m,q-PrH), 7.91(2H,m,q-PrH)	250 (20340)
3d	-	3198	-	4.56 t(6)	2.03 q(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 q(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)(a)
6a	1663 (w)	-	-	2.32 q(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 q(7)	-	3.59 t(7)	4.25 t(7)	6.95 d(10)	7.25 d(10)	-	-	306 (3110)
6c	1666 (e)	-	-	2.25 q(6)	-	3.54 t(6)	4.27 t(6)	6.90 d(10)	7.55 d(10)	-	~7.3(3H,m,m,q-PrH) ~7.7(2H,m,q-PrH)	259 (27800)(a) 313 (3080)
6d (a)	1666	-	-	2.25 q(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 q(7)	-	3.55 t(7)	4.21 t(7)	6.82 d(10)	7.06 d(10)	-	2.30(3H,s,CH ₃)	302 (1760)(a)
7a	-	-	-	4.80 t(4.5)	-	3.90 t(4.5)	-	-	7.02 d(9)	7.39 dd(8,4)	8.85(1H,d(4),H-6)	268 (2690)(d)
8a	-	-	-	4.58 t(6)	2.25 q(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 q(6)	3.70 t(6)	-	-	7.06 d(9)	7.80 d(9)	7.45(3H,m,m,q-PrH), 7.95(2H,m,q-PrH)	251 (18500)
8d (a)	-	-	-	4.62(c) t(6)	2.25 q(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 q(6)	4.66 t(6)	-	-	6.95 d(9)	7.39 d(9)	8.22(4H,s,(NO ₂)Ph-H)	260 (13900)

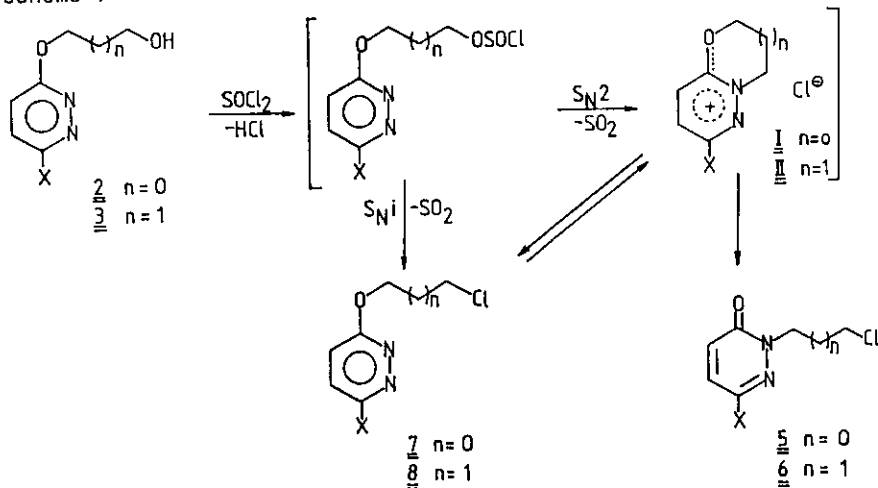
(a) as HCl salt; (b) VC-O (aster); (c) ^1H nmr in DMSO-d_6 ; (d) uv in ethanol; (e) ir in EtOH

Scheme 6



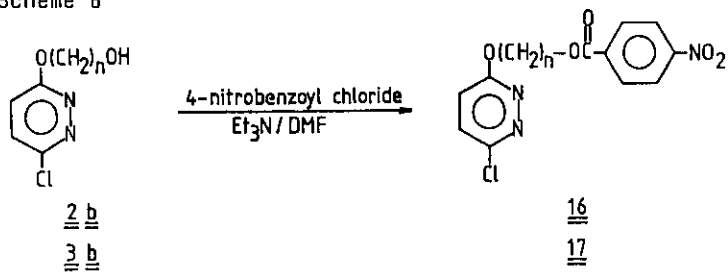
All of the above results suggest that the formation of 2-chloroethyl or 2-chloropropylpyridazinones from 3-pyridazinylxyethanols or -propanols with thionyl or mesyl chloride involves the bicyclic intermediate of type I or II, respectively. On the other hand the 3-chloroalkoxy-pyridazines may also be 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 distillation 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 substituent: 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 ₆ H ₈ N ₂ O ₂
2b	I (1)	isopropanol-petrol ether 1:1	98-100 ⁺⁺⁺	70	C ₆ H ₇ ClN ₂ O ₂
2c	I (5)	ethanol	102-103	40	C ₁₂ H ₁₄ N ₂ O ₂
2d	I (7)	ethanol	157-159	53	C ₉ H ₁₀ N ₄ O ₂
3a	II	oil	oil	56	C ₇ H ₁₀ N ₂ O ₂
3b	I (1)	petrol ether	39-41	71	C ₇ H ₉ ClN ₂ O ₂
3c	I (4)	ethanol	109-110	45	C ₁₃ H ₁₄ N ₂ O ₂
3d	I (4)	water	131-133	29	C ₁₀ H ₁₂ N ₄ O ₂
3e	I (4)	oil	oil ⁺⁺⁺	60	C ₈ H ₁₂ N ₂ O ₂
5b	III (1)	petrol ether	55-57	73	C ₆ H ₆ Cl ₂ N ₂ O
5c	III (3.5)	diethyl ether	69-70 ⁺⁺⁺⁺	52	C ₁₂ H ₁₁ ClN ₂ O
5d ⁺⁺	III (1)	ethanol	202-205	91	C ₉ H ₁₀ Cl ₂ N ₄ O
6a	III (5)	oil	oil	60	C ₇ H ₉ ClN ₂ O
	V (5)			73	
6b	III (2)			80	C ₇ H ₈ Cl ₂ N ₂ O
	IV	isopropyl ether		75	
	V (8)			50	
6c	III (1.5)	oil	oil	20	C ₁₃ H ₁₃ ClN ₂ O
6d ⁺⁺	III (1)	ethanol	193-195	70	C ₁₀ H ₁₂ Cl ₂ N ₄ O
6e	III	oil	oil	64	C ₈ H ₁₁ ClN ₂ O
7a	III (1)	petrol ether	59-61	80	C ₆ H ₇ ClN ₂ O
8a ⁺⁺	III (1)	diethyl ether	110-112	60	C ₇ H ₁₀ Cl ₂ N ₂ O
8c	III (1.5)	diethyl ether	82-83	8	C ₁₃ H ₁₃ ClN ₂ O
14c		isopropanol	126-128	70	C ₁₀ H ₁₃ ClN ₂ O ₂
15c	III (5)	ethanol	97-100	87	C ₁₀ H ₁₂ Cl ₂ N ₂ O
16	IV	diethyl ether	167-169	55	C ₁₃ H ₁₀ ClN ₃ O ₅
17	IV	diethyl ether	118-120	60	C ₁₄ H ₁₂ ClN ₃ O ₅

[†]Satisfactory elemental analyses (C,H,N,Cl) were obtained for all the newly synthesized 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 $\text{Bu}_4\text{N}^+\text{Br}^-$ (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, $\text{CHCl}+\text{NCH}_2$), 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').

ACKNOWLEDGEMENT

We thank Dr. I. Perczel for help in certain nmr experiments and Mrs. M. Metz for careful typing of the manuscript.

REFERENCES AND NOTES

1. R. Buchman, J. A. Scozzie, Z. S. Ariyan, R. D. Heilman, D. J. Rippin, W. J. Pyne, and L. J. Powers, J. Med. Chem., 1980, 23, 1398.
2. G. Steiner, J. Gries, and D. Lenke, J. Med. Chem., 1981, 24, 59.
3. T. Yamada, Y. Nobuhara, H. Shimamura, Y. Tsukamoto, K. Yoshihara, A. Yamaguchi, and M. Ohki, J. Med. Chem., 1983, 26, 373.
4. Gy. Csókás, L. Jaszlits, and Gy. Rablóczy, J. Mol. Cell. Cardiol., 1987, 19, S14.
5. Eur. Pat. Appl. EP 220, 735; C.A., 1987, 107, 176053m.
6. Among the compounds 5 and 6, 5a^{6a} and 5c^{6b} have already been described: they have been prepared by N-hydroxyethylation of the appropriate 3(2H)-pyridazinone and the subsequent treating with thionyl chloride. Compounds 5e^{6c} and 6c^{6b} have been used as starting materials but without any characterization of their properties.
 - a. G. V. Satalov, S. A. Gridtsin, and B. I. Mihanter, Khim. Get. Soedin., 1980, 3, 394;
 - b. T. Yamada, H. Shimamura, Y. Tsukamoto, A. Yamaguchi, and M. Ohki, J. Med. Chem., 1983, 26, 1144;
 - c. Y. Matsubara, M. Noguchi, M. Yoshihara, and T. Maeshima, Chem. Lett., 1973, 601.
7. Compound 2b has only been described:

Austrian Pat. 204, 560; Beilstein, 23, Suppl. IV. 2456.
8. a. B. G. Pring and C.-G. Swahn, Acta Chem. Scand., 1973, 27, 1891.
 b. Though, in the pyridazine series the rearrangement of some chloroethoxy derivatives was also described, however, these reactions were carried out under basic conditions; R. Jaunin, Chim. Ther., 1967, 2, 317; C.A., 1968, 62, 36054j.
9. D. Lipkin and E. G. Lovett, J. Org. Chem., 1975, 40, 1713.
10. P. S. Mariano and A. A. Leone, J. Am. Chem. Soc., 1979, 101, 3608.
11. L. Verbit and H. C. Price, J. Am. Chem. Soc., 1972, 94, 5143.
12. M. Ogata, Chem. Pharm. Bull., 1963, 11, 1522.
13. G. Steiner, J. Gries, and D. Lenke, J. Med. Chem., 1981, 24, 59.
14. W. G. Overend and L. F. Wiggins, J. Chem. Soc., 1947, 239.
15. C. Grundmann, Chem. Ber., 1948, 81, 1.
16. T. Kuraishi, Pharm. Bull., 1957, 5, 376; C.A., 1958, 52, 14326h.

Received, 6th May, 1988