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BROMOALKYLPHTHALAZINONES AND ISOMERIC OXAZOLINIUM SALTS AS INTERMEDIATES AND SYNTHONS

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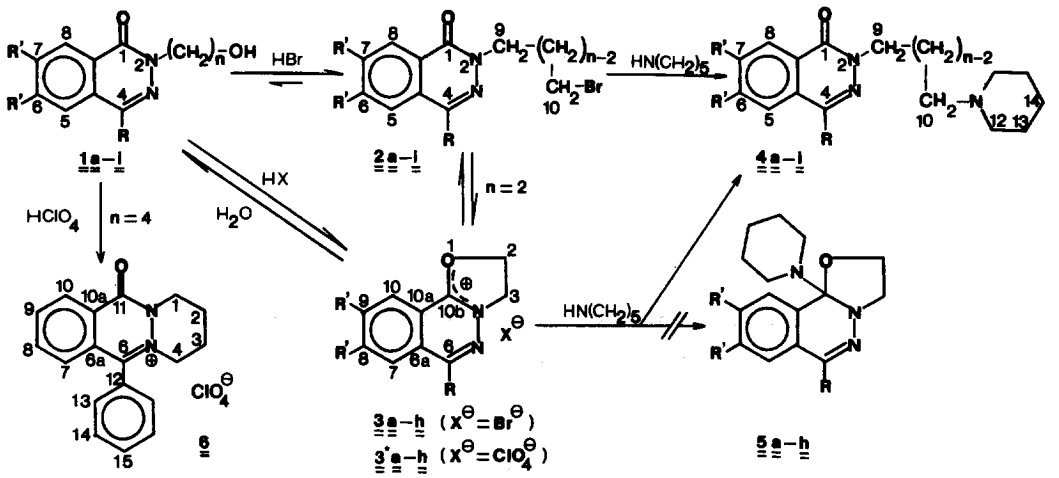
Abstract - 2(ω-Piperidinoalkyl)phthalazin-1(2H)-ones can be prepared from the 2-hydroxyalkyl compounds both via the open-chain 2-bromoalkyl derivatives and via their cyclic isomers. Substitution reactions of bromoalkyl compounds may be assisted by polar solvents and by neighbouring group effect of hydrazinocarbonyl moiety. Nucleophiles attack the condensed oxazolinium ring in tricyclic intermediates at the saturated carbon bonded to the oxygen with ring opening. Addition of piperidine to unsaturated iminohydrine-carbon was only found with a tetracyclic bis cation having both oxazolinium and strong electron-withdrawing amidinium parts.

INTRODUCTION

Piperidinoethylphthalazinones like 4a-h are compounds of pharmacological interest.[1] They can be synthesized from hydroxyethylphthalazinones (1a-h) via bromoethylphthalazinones (2a-h) and/or isomeric tricyclic oxazolinium salts (3a-h) representing a new type of heterocyclic compound. This paper reports on the interconversion of compounds 1-4 (Scheme 1) and on the substituent and solvent dependent neighbouring group effect observed in the reactions. We assumed that the readiness of bromoethyl derivatives to form oxazolinium ring (2 → 3)[2,3] would be reflected both in the different rates of hydrolysis (2 → 3 → 1) and in product distributions referring to the concurrent reactions 2 → 3 → 4 + 1 and 2 → 4. Such neighbouring group participation of hydrazinocarbonyl group has been described only in one case[4] although similar effect of aminocarbonyl group promoting nucleophilic displacements is well known,[2,3] and heterocyclic intermediates have also been prepared.[2,3,5]

RESULTS AND DISCUSSION

2-Bromoalkylphthalazinones - Using 48% HBr 2-hydroxyalkylphthalazinones (1) were converted into the corresponding bromo compounds (2). 1g-i yielded quantitatively 2g-i, but conversions 1a-d → 2a-d were not complete, as the crude products contained 5-20% of the starting material (Experim.: Method A). In contrast, 1e and 1f provided stable tricyclic oxazolinium salts (3e,f) as major products (70% and 80%, respectively), and the isomeric



Scheme 1 n=2 (a-h) and 4 (i); R=H (a), Me (b), Ph (c, i), OH (d, e) NH_2 (f), Cl (g, h); R'=H (a-d, f, h), OMe (e, g)

bromo derivatives (2e,f) together with the hydroxy compounds (1e,f) were obtained only in poor yields (Experim.: Method A).

The above-mentioned product distributions may be ascribed to the neighbouring group participation of hydrazinocarbonyl group which is more or less effective in these reactions. With 2-(4-bromobutyl) or electron-withdrawing R=Cl substituents the negatively polarized carbonyl-oxygen either lies too far or is not active enough to attack the electrophilic carbon carrying the bromine, thus only simple 1g-i → 2g-i conversions take place. In contrast, with shorter 2-(bromoethyl) side chain and powerful electron-releasing substituents tricyclic oxazolinium bromides are formed (2e,f → 3e,f; R=OH, R'=OMe and R=NH_2, R'=H respectively). In case of R=H, Me, Ph, OH (with R'=H) neighbouring group participation seems to be moderate and cyclic intermediates (3a-d) hydrolyze quantitatively to the corresponding hydroxy derivative (1a-d).

As shown by ^{1}H-nmr measurements in 48% DBr, each hydroxyethyl compound (1a-h) gets completely converted into bromo derivatives (2a-h) after five minutes of boiling, independently of the substituents. However, it should also be considered that, on the one hand, in such strong acid media deuteration of N^3 atom will markedly decrease the electron-density on the carbonyl-group independently of ring substituents, and on the other, bromide ions in large excess also suppress ring closures 2 → 3, (cf. Ref.2). Thus the starting hydroxy compounds (1a-f) and tricyclic salts (3e,f) could only be formed during the isolation of the products. These assumptions have been supported by additional experimental findings. (i) The equilibrium cyclization, presumably the key step for the reverse hydrolysis (2 ⇄ 3 ⇄ 1), too can be suppressed by adding an excess (1:3) of NaBr to the reaction mixture, thus the bromoethyl derivatives were obtained as only product (Experim.: Method B). (ii) The equilibrium

isomerizations 2d-f ⇌ 3d-f directly observable at room temperature in DMSO-d_6 (Experim.: Method D) can be shifted to the left by adding NaBr to the solutions. Under same conditions other 2-bromoethylphthalazinones with less electron-releasing R groups fail to undergo any spontaneous cyclization. (iii) Equilibrium isomerizations 2e,f ⇌ 3e,f are shifted in $CHCl_3$ to the right, since crystalline oxazolinium bromides separate slowly from the solution. A slow cycloisomerization can also take place in the solid state, pointing to the thermodynamic stability of tricyclic oxazolinium salts 3e,f, although they do not contain hydrazinocarbonyl group. Similar formation of cyclic iminoether halides in solid state have been reported.[6] (iv) Substituent-dependent readiness of 2-bromoethylphthalazinones to undergo cycloisomerization is also shown in their hydrolysis (2 → 1) carried out in hot EtOH-water (4:1) requiring different reaction times (Experim.: Method E). The observed hydrolysis rates 2h ≪ 2g ≪ 2a-c < 2d∼2e∼2f follow the order of neighbouring group assistance; the 2-(4-bromobutyl) derivative (2i) does not hydrolyze at all. This order of reactivity suggests the reaction sequence 2 ⇌ 3 → 1, where the first step is rate-determining. The hydrolysis of tricyclic oxazolinium perchlorates 3*a-h (see below) is consistent with this scheme: under same conditions reactions proceed in ca. 10 sec in all cases. Solvent effect gives further support for reactions involving cyclic salt intermediates. The hydrolysis is faster in EtOH-water (4:1) than in less polar $CHCl_3$-EtOH-water (10:10:1). (Cf. the different rates of formation of oxazolinium halides in solvents of different polarity in Ref. 7.).

For 2-bromoethylphthalazinones (2a-h) the effectivity of neighbouring group assistance increases with the negative polarity of carbonyl-oxygen which can be characterized by the frequency of amide-I band[8] (Table 1). The significant electronic effect of distant 4-R group on the polarity of carbonyl-oxygen is transmitted by the interaction between the lone pairs of N^2 and N^3 atoms (thermodynamic α-effect: cf. Ref. 9). It is noticeable that the electron-withdrawing effect of substituent R=Cl is not overcompensated by the electron-releasing effect of R'=OMe groups (in 2g). On the other hand, when R=OH, R'=OMe groups are necessary for the spontaneous cyclization taking place in solid state.

Cyclic intermediates - 2-Hydroxyethylphthalazinones (1a-h) were dehydrated at 100°C by 70% $HClO_4$ to give oxazolinium perchlorates (3*a-h) in good yields (Experim.: Method G). Using EtOH-70% $HClO_4$ (10:1) (cf. the analogous synthesis of 2,3-dihydro-oxazolo[2,3-a] isoquinolinium perchlorates in Ref. 10) the yields became much poorer (Experim.: Method H), but their variety pointed to relative stability of products. Since in case of 1i an angular cyclization might lead to an unfavourable seven membered ring, dehydration results in the formation of 6 with linearly condensed rings (Scheme 1). Tricyclic oxazolinium perchlorates (3*a-h) can easily be hydrolyzed to the hydroxy compounds 1a-h.

Reactions with piperidine - 2-Piperidinoalkylphthalazinones (4a-i) were prepared in excellent yields by treating the corresponding bromoalkyl derivatives (2a-i) with an excess of piperidine at room temperature (Experim.: Method I). The same products were also obtained from 3*a-h. In hot $CHCl_3$ the reactivity of compounds 2a-i differs: 2d-f gave amine products in 30 min., while the others require ca. 6 hr for complete conversion. With $CHCl_3$-

-EtOH-water (10:10:1), hydroxy compounds 1d-f were obtained as only products; in other cases analogous compounds were produced only in small amount contaminating the isolated piperidino derivatives (4a-c,g-i) (Table 3: Method K). Using hot abs. (99%) ethanol as solvent, even with an excess of piperidine, the hydroxy compounds 1a-f were formed from 2a-f as major products, and only 2g-i were converted almost quantitatively into the amines 4g-i (Table 3: Method L).

Table 1. Analytical, ir (cm^{-1}, KBr) and ^{1}H-nmr (δ ppm, $CDCl_3$)[a] data for compounds 2a-i

	m.p. °C	Elemental analysis % (calc/found) C	H	N	Br	amide-I ir-band	9/10-H t[b](2x2H)	R s[c]
2a	73-4	47.5/47.6	3.6/3.5	11.1/11.0	31.6/31.4	1642	4.62/3.78	8.24
2b	101-2	49.5/49.3	4.2/4.1	10.5/10.6	29.9/29.8	1640	4.61/3.76	2.60
2c	119-21	58.4/58.3	4.0/3.8	8.5/8.6	24.3/24.2	1640	4.70/3.81	7.6[d]
2d	176-9	44.6/44.6	3.4/3.4	10.4/10.5	29.7/29.8	1634	4.60/3.76	12.90
2e	213-6[e]	43.8/44.0	4.0/4.2	8.5/8.4	24.3/24.4	1630	4.60/3.76	12.10
2f	164-7[e]	44.8/44.9	3.8/3.8	15.7/15.4	29.8/29.6	1622	4.59[f]/3.77	4.45[f]
2g	176-8	41.5/41.4	3.5/3.6	8.1/7.9	23.0/23.1[g]	1658	4.60/3.76	-
2h	115-6	41.8/41.5	2.8/2.9	9.7/9.8	27.8/28.0[g]	1668	4.63/3.76	-
2i	100-1	60.5/60.5	4.8/4.7	7.8/7.9	22.4/22.4	1640	4.38/3.57	7.6[d]

[a]Further ^{1}H-nmr data: Ar-H-(5-8) 7.7-7.9 m(3H) and 8.45 dd(1H) for 2a-d,f,h,i; H-5,8 7.38 and 7.80 for 2e, 7.26 and 7.77 2xs(2x1H) for 2g, -C-$(CH_2)_2$-C 1.9-2.3 m(4H) for 2i; OMe 4.03 s(6H) for 2e and 4.08 s(6H) for 2g. [b]J 7.0 Hz for 2a-h and 6.5 Hz for 2i. [c]Intensity: 1H for 2a,d,e; 3H for 2b; 2H for 2f; 5H for 2c,i. [d]~s. [e]Due to fast isomerizations 2e,f → 3e,f taking place without melting, m.p.-s of 3e,f were measured. [f]Partly overlapping signals. [g]Total halogen content 33.2/33.2 for 2g and 40.1/40.1 for 2h.

These experiments suggest that conversion of 2-bromoalkylphthalazinones by piperidine takes place in a one-step (2 → 4) or two step reaction (2 ⇄ 3 → 4), depending on the nature of ring substituents and the solvent used. Both mechanism may occur when the reaction is carried out in piperidine. On the other hand, the fast conversion of 2d-f in hot $CHCl_3$ must be associated with an initial cycloisomerization assisted by strong electron-releasing R and R' groups. Dilution of the solvent with more polar EtOH and some water promotes only slightly the cyclization yielding ions as predominant hydrolysis occurs only in the conversion of 2d-f. (The formation of a small amount of 1i hydroxybutyl derivative can be ascribed to the nucleophilic attack of hydroxide ions on the open-chain 2i bromo compound.) Cyclization predominates in most reactions conducted in 99% EtOH. This view gains support from the observed reactions of oxazolinium perchlorates. For these compounds, including 3*g,h hydrolysis overcomes amination in all cases (Table 3: Method L, cf. Ref. 11).

The very similar distribution of products obtained after reactions of 2a-f and the corresponding cyclic perchlorates points to fast primer cyclization (2 → 3) preceding the

Table 2. Analytical, ^{1}H- and ^{13}C-nmr data (TFA, δ ppm)[a] of compounds 3*a-h

	m.p. °C	Elemental analysis %[b] C	H	N	Cl	2,3-H t[c](2x2H)	C(2) C(3)	C(6) C(10b)	C(6a) C(10a)	C(7)[d] C(10)	C(8)[d] C(9)
3*a	229-31	44.1	3.3	10.3	13.0	5.34	76.6	158.3	121.0	139.9	132.5
		44.0	3.5	10.4	13.1	5.03	55.6	165.0	135.0	142.9	129.2
3*b	226-8	46.1	3.9	9.8	12.4	5.52	74.6	161.5[d]	119.1	137.5	128.2
		46.3	4.1	9.7	12.4	5.19	54.3	162.7	133.4	141.3	129.4
3*c	276-9	55.1	3.8	8.0	10.2	5.55	75.3	163.8[d]	120.7	138.2	132.1
		55.1	3.9	8.2	10.2	5.26	54.9	163.1	134.5	141.5	128.7
3*d	208-11	41.6	3.1	9.7	12.3	5.31	74.6	161.2[d]	127.5	138.7	128.6
		41.4	3.2	9.6	12.3	5.01	54.7	163.3	121.2	141.3	129.1
3*e	264-7	41.3	3.8	8.0	10.2	5.45	73.2	161.2[d]	116.3	106.6	159.0
		41.2	3.5	7.9	10.2	5.04	53.7	160.2	125.2	106.7	157.8
3*f	227-30	41.8	3.5	14.6	12.3	5.42	75.1	160.5[d]	121.7	139.1	130.2
		42.0	3.6	14.8	12.4	5.02	56.0	159.9	127.7	142.1	128.5
3*g	214-7	39.3	3.3	7.6	19.3	5.55	74.0	151.6	114.7	106.5	160.7
		39.2	3.5	7.6	19.2	5.18	53.7	158.3	128.9	108.5	161.0
3*h	238-40	39.1	2.6	9.1	23.1	5.33	75.0	154.8	119.5	138.5	129.7
		39.1	2.9	9.0	23.3	4.96	54.0	162.8	132.1	141.7	128.3

[a]Further nmr signals: ArH(7-10): 8.1-8.5 m(4H) for 3*a-d,f,e, ArH(7,10): 7.73 s(2H) for 3*e and 7.79, 7.88 2xs(2x1H) for 3*g; 6-H: 8.99 s(1H) for 3*a; CH_3($^{1}H/^{13}C$): 3.10 s(3H)/21.1 for 3*b; C_6H_5($^{1}H/^{13}C$): 7.6 ~s(5H)/134.0, 133.6, 132.3, 131.7 for 3*c; OCH_3($^{1}H/^{13}C$): 4.25, 4.28 2xs(2x3H)/58.2, 58.3 for 3*e and 4.25, 4.29 3xs(2x3H)/58.2 (overlapping lines) for 3*g. [b]Upper row "calculated", lower row "found". [c]J 9.5±0.2 Hz. [d]Assignments may also be reversed for the signed line pairs.

Table 3. Product distribution for conversions of compounds 2a-i and 3*a-h by piperidine in solvents containing water

Pre-cursor	Method	Yields of isolated products (%) 1a:4a	1b:4b	1c:4c	1d:4d	1e:4e	1f:4f	1g:4g	1h:4h	1i:4i
2a-i	K	6:81	9:71	9:81	83:0	94:0	98:0	2:93	2:92	3:95
2a-i	L	75:21	79:14	88:7	82:10	88:10	90:7	0:96	0:99	0:99
3*a-h	L	75:22	81:14	90:6	80:10	90:8	90:6	92:7	92:6	-

attack of piperidine on open-chain bromoethyl derivatives. Only compounds 2g-i which are less capable of neighbouring group participation (owing to the electron-withdrawing R group or too long 2-bromoalkyl chain) are converted directly into amines. It seems very likely that in solvents containing water amination with piperidine cannot compete with hydrolysis if tricyclic oxazolinium salts are the substrates.

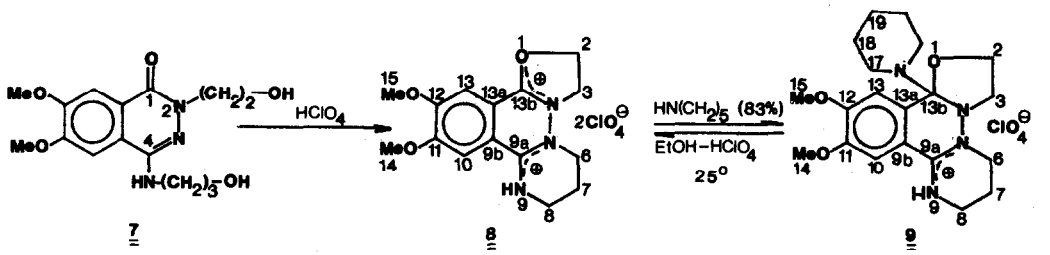
Addition of piperidine to oxazolinium salts - Although the structure of tricyclic oxazolinium salts (3a-h) as ambient electrophiles (cf. Ref. 5) may allow the formation of adducts 5a-h (Scheme 1), these compounds were not formed at all. However, the potential

Table 4. Analytical, ir (cm^{-1}, KBr) and ^{1}H-nmr (δ ppm, in $CDCl_3$)[a] data of compounds 4a-i

	m.p. °C	Analysis (calc/found) (%) C	H	N	amide-I ir-band	9/10-H t[b](2x2H)	12-H t[c](4H)	13,14-H s(6H)	R_d s[d]
4a	110-2[e]	70.0/70.2	7.4/7.3	16.3/16.3	1648	4.45/2.83	2.58	1.7	8.21
4b	75-7	70.8/70.9	7.8/7.9	15.5/15.2	1650	4.34/2.79	2.56	1.6	2.57
4c	159-60	75.6/75.4	7.0/6.9	12.6/12.7	1652	4.50/2.89	2.59	1.7	7.6[f]
4d	210-4	65.9/66.0	7.0/7.2	15.4/15.5	1653	4.43/3.15[g]	2.90[g]	1.7	9.3
4e	253-6	61.2/61.1	7.0/6.9	12.6/12.6	1644	4.40/3.18[g]	2.90[g]	1.7	9.6
4f	147-8	66.2/66.2	7.0/6.9	20.6/20.8	1630	4.28/2.79	2.56	1.6	4.75
4g[h]	158-9	58.0/58.1	6.3/6.0	11.9/12.0	1658	4.36/2.77	2.55	1.6	-
4h[h]	84-5	61.7/61.5	6.2/6.4	14.4/14.3	1668	4.39/2.81	2.55	1.6	-
4i	100-1	76.4/76.4	7.5/7.5	11.6/11.7	1652	4.46/2.40[i]	2.40[i]	1.3-2.2[j]	7.6[f]

[a]Further ^{1}H-nmr data: ArH(5-8) 7.6-8.0 m(3H) and 8.45 dd(1H) for 4a-d,f,h,i; H-5,8 7.70, 6.45g for 4e and 7.76, 7.23 2xs(2x1H) for 4g; OMe: 4.04, 3.70 2xs(2x3H) for 4e and 4.05 s(6H) for 4g. [b]J 7.5 Hz for 4a-c,f,h and 5.0 Hz for 4d,e and 7.0 Hz for 4i. [c]J 5.0 Hz. [d]Intensity: 1H for 4a,d,e, 3H for 4b, 2H for 4f and 5H for 4c,i. [e]112° in Ref. 21a. [f]~s. [g]These chemical shifts point to zwitterionic structure of 4d,e. [h]Cl% 10.1/10.1 for 4g and 12.1/12.2 for 4h. [i]Not resolved m(6H). [j]m 10H (overlapping with signals of $-C-(CH_2)_2-C-$).

carbonium centre in bis-perchlorate 8 prepared from the corresponding hydroxy derivative 7 has proved to be active enough to form the adduct 9 at room temperature in good yield (Scheme 2). The addition reaction yielding 9 which is effectively stabilized by the electron-withdrawing amidinium group (cf. Refs. 5, 12), was not accompanied by a nucleophilic attack at the saturated carbon bonded to positive oxygen resulting in the opening of oxazolinium ring. Only a few instances have been reported on similar conversions of cyclic iminoether salts with enhanced electrophilicity.[5,11] Using EtOH-70% $HClO_4$ (1:1) at room temperature adduct 9 can be easily desaminated to bis-perchlorate 8 in accordance with its structure proved by the ^{13}C-nmr chemical shift of C-13b which is much lower in 9 than in 8 (130.0 and 160.2 ppm, respectively), due to the order of the corresponding carbons.



7 8 9

Scheme 2

EXPERIMENTAL

2-(ω-Hydroxyalkyl)phthalazin-1(2H)-ones 1a-f,i - 1a,[13] 1b,[14] 1d,[15] 1f,[16] and 7[17] are known compounds. Based on the description for 1a, 1b was prepared from o-acetylbenzoic acid[18] and 2-hydrazinoethanol, and in a similar way 1c and 1i from o-benzoylbenzoic acid using 2-hydrazinoethanol or 2-hydrazinobutanol[19]; 81, 95 and 98%, m.p. 152-3°, 155-8° and 107-9°, respectively, after recryst. from water. Anal. (calc/found %): 1b, C 64.7/64.9 H 5.9/6.0 N 13.7/13.6; 1c, C 72.2/72.3 H 5.3/5.1 N 10.5/10.6; 1i, C 73.5/73.3 H 6.2/6.2 N 9.5/9.5. Ir (cm^{-1}): 1b, νOH 3340, amide-I 1629; 1c/1i, νOH 3434/3375, amide-I 1630/1630.

4-Chloro-2-(2-hydroxyethyl)phthalazin-1(2H)-one (1h) - 2.06 g of 1d (10 mmol) and PCl_5 (6.2 g, 30 mmol) were boiled in $POCl_3$ (40 ml) for 3 h at 110°, then half of the solvent was removed by distillation in vacuo. The residue was slowly poured into cracked ice (500 g). To the suspension Na_2CO_3 (15 g) was added, and next day the crystals of 4-chloro-2-(2-chloroethyl)phthalazin-1(2H)-one were filtered off, washed with water (100 ml), then dried (P_2O_5); 78%, m.p. 103-5°. Recryst. from $CHCl_3$-petroleum ether (10:6 ml); m.p. 107-8°. Anal. (calc/found %): C 49.4/49.6 H 3.3/3.2 N 11.5/11.3 Cl 29.2/29.3. Ir (cm^{-1}): amide-I 1670.

The dichloro compound (2.43 g, 10 mmol) and KOH (0.65 g, 11.6 mmol) were boiled in a mixture of EtOH-water (20:5 ml) for 5 h , then the solvent was removed. The residue was triturated with water (8 ml) and the suspension was neutralized with cc.HCl. The crystals were filtered off, washed with water (5 ml) then dried (80%, m.p. 123-6°). Recryst. from EtOH-water (6:6 ml); m.p. 127-9°. Anal. (calc/found %): C 53.5/53.5 H 4.0/3.8 N 12.5/12.5 Cl 15.8/15.8. Ir (cm^{-1}): νOH 3395, amide-I 1631.

4-Chloro-2-(2-hydroxyethyl)-6,7-dimethoxyphthalazin-1(2H)-one (1g) - 2.66 g (10 mmol) of 1e (see: next section) was converted into 4-chloro-2-(2-chloroethyl)-6,7-dimethoxyphthalazin-1(2H)-one by the method described above (90%, m.p. 169-72°). Recryst. from $CHCl_3$-petroleum ether (20:9 ml); m.p. 171-2°. Anal. (calc/found %): C 47.5/47.6 H 4.0/3.8 N 9.2/9.4 Cl 23.4/23.4. Ir in (cm^{-1}): amide-I 1660. The dichloro compound was hydrolized to 1g by the method described above (92%; m.p. 176-9°). Recryst. from EtOH-water (11:8 ml); m.p. 178-80°. Anal. (calc/found %): C 50.6/50.3 H 4.6/4.7 N 9.8/10.0 Cl 12.5/12.5. Ir (cm^{-1}): νOH 3435, amide-I 1656.

4-Hydroxy-2-(2-hydroxyethyl)-6,7-dimethoxyphthalazin-1(2H)-one (1e) - 4,5-Dimethoxyphthalic anhydride[20] (2.08 g, 10 mmol) and 2-hydrazinoethanol (1.52 g, 20 mmol) were boiled in EtOH (50 ml) for 1 h. After cooling the crystals were filtered off and washed with water (5 ml); 97%, m.p. 265-8°. Recryst. from AcOH; m.p. 267-70°. Anal. (calc/found %): C 54.1/54.0 H 5.3/5.3 N 10.5/10.5. Ir (cm^{-1}): νOH 3400-2300 (for hydroxyethyl and iminohydrine moieties), amide-I 1635.

Conversion of 2-(ω-hydroxyalkyl)phthalazin-1(2H)-ones with HBr (1 → 2 *and* 1 → 3) -

Method A. The hydroxyalkyl compounds 1a-i (10 mmol) and 48% HBr (10 ml, 88 mmol) were boiled for 5 min, then the reagent was removed by distillation in vacuo. The oily residue was triturated with water (5 ml), the crystalline product was filtered off, washed with water (5 ml) then dried (P_2O_5). To the crude product $CHCl_3$ (10 ml) was added, the solid hydroxyalkyl compound (insoluble both in $CHCl_3$ and water) was filtered off, (5-20% for 1a-f), and the solvent was distilled from the filtrate to yield the bromoalkyl derivatives (80-90% for 2a-d, 10-25% for 2e,f and 98-100% for 2g,i). With the conversion of 1e,f, oxazolinium bromides 3e,f were formed as major products (70-80%). These salts dissolved in water when crude products were triturated and washed. Yields for 3e,f were calculated from the molar amount of hydroxy compounds 1e,f isolated by evaporation of the neutralized (NH_4OH aq.) aqueous soln.

Method B. To the above reaction mixture NaBr (3.4 g, 30 mmol) was also added and procedure A was carried out. In these cases only open-chain bromoalkyl compounds were isolated (~99%). Analytical and spectral data for 2-(ω-bromoalkyl)phthalazin-1(2H)-ones (2a-i) prepared by this method and recryst. from $CHCl_3$-petroleum ether at 25° are listed in Table 1.

Method C. The hydroxyethyl compounds 1a-h (0.25 mmol) were boiled in azeotropic DBr (1 ml, 9 mmol) for 5 min. After cooling the mixture to 20°, the ^1H-nmr spectra were taken directly. Based on signals of 9-H and 10-H (cf. Table 1) all bromoethyl compounds formed gave "open-chain" spectra. No signals were observed related to cyclic isomers.

Cycloisomerization of 2-(2-bromoethyl)phthalazin-1(2H)-ones (2 ⇄ 3) - As expected, the crude products 2a-h obtained by Method B dissolved quantitatively in $CHCl_3$, but 2e and 2f isomerized completely in 3 months to yield 3e and 3f cyclic salts which were insoluble in $CHCl_3$ and well soluble in water. Characteristic ir bands in KBr for 3e and 3f cyclic bromides: 1627, 1600, 1583, 1540 cm^{-1} and 1653, 1603, 1568, 1535 cm^{-1}, respectively; the corresponding bands for the analogous 3*e and 3*f perchlorates (see later): 1637, 1607, 1588, 1540 cm^{-1} and 1640, 1606, 1572, 1538 cm^{-1}, respectively.

Method D. The bromoethyl derivatives 2a-h (0.25 mmol) were dissolved in DMSO-d_6 (1 ml) and the solns were investigated by ^{1}H-nmr. In case of 2d-f the CH_2-signals related to the equilibria 2d ⇄ 3d (95:5), 2e ⇄ 3e (80:20) and 2f ⇄ 3f (65:35) were observed. By adding NaBr (51 mg, 0.5 mmol) to the soln., equilibria were shifted to the left. The same signals characteristic of the two latter equilibria were also registered when the salts 3e and 3f were dissolved in DMSO-d_6.

Hydrolysis of 2-(ω-bromoalkyl)phthalazin-1(2H)-ones (2 → 1) -

Method E. The bromoalkyl derivatives 2a-i (5 mmol) were boiled in EtOH-water (16:4 ml). After cooling the mixture containing methylorange indicator was neutralized with 1N-NaOH (5 ml), the solvent was removed by distillation, the residue was triturated with water (6 ml), filtered off, washed with water (10 ml) then dried (P_2O_5). Yields and reaction times required for complete hydrolysis were: 1a: 89%, 10 min; 1b: 95%, 10 min; 1c: 97%, 10 min; 1d: 90%, 10 sec; 1e: 95%, 10 sec; 1f: 92%, 10 sec; 1g: 92%, 2 h; 1h: 98%, 8 h. Under same conditions 2i did not hydrolize: the starting material was quantitatively recovered even after a reaction time of 50 h.

Method F. The bromoethyl derivatives 2a-h (10 mmol) were boiled in $CHCl_3$-EtOH-water (10:10:1 ml) and the hydrolysis products 1a-h were isolated as shown above; the yields were about the same. Reaction times required for complete hydrolysis: 2 min for 2d-f; 30 min for 2a-c; 18 h for 2g and 60 h for 2h.

*2,3-Dihydrooxazolo[2,3-a]phthalazin-4-ium perchlorates (3*a-h)* -

Method G. 2-Hydroxyethylphthalazinones (1a-h; 10 mmol) were treated with 70% $HClO_4$ (5 ml) at 100° for 3 h. To the cooled mixture EtOH (1 ml) then Et_2O (4 ml) were added dropwise. After standing 1 h the crystals were filtered off, washed with EtOH-Et_2O (1:6 ml) to yield products requiring no further purification. (Analytical data and nmr spectra are shown in Table 2.) Yields were between 86-99%.

Method H. 2-Hydroxyethylphthalazinones (1a-h; 10 mmol) and EtOH-70% $HClO_4$ (10:1 ml) were boiled for 5 h, the EtOH was removed by distillation. The oily residue was triturated with EtOH-Et_2O (3:5 ml). After standing 1 h the crystals were filtered off and washed with EtOH-Et_2O (1:6 ml). In case of 1g and 1h no crystalline product was obtained. Yields: 3*a: 9%; 3*b: 12%; 3*c: 14%; 3*d: 31%; 3*e: 40%; 3*f: 42%; 3*g,h: -.

1,2,3,4-Tetrahydro-6-phenyl-pyridazino[1,2-b]phthalazin-11(10H)-one-5-ium-perchlorate (6), 2,3,7,8-tetrahydro-11,12-dimethoxy-6H-oxazolo[2,3-a]pyrimido[1,2-c]phthalazin-4-ium-perchlorate.HClO$_4$ (8) - These compounds were prepared by Method G (82% for 6 and 99% for 8). 6: m.p. 284-6°; anal. (calc/found %): C 57.4/57.7 H 4.5/4.6 N 7.4/7.4 Cl 9.4/9.4; ^{1}H-nmr in TFA: 1-H 4.71 t(2H) 2,3-H 2.35 m(4H) 4-H 4.90 t(2H) (7,13-15)-H 7.6-7.9 m(6H) 8,9-H 8.29 t and 8.10 t(2x1H) 10-H 8.74 d(1H); ^{13}C-nmr in TFA: C(1) 45.1 C(2,3) 20.4, 21.1 C(4) 58.2 C(6,11) 157.7, 161.2 C(6a,10a) 130.5, 129.4 C(7,15) 134.5, 135.3 C(8,9) 140,7, 138.2 C(10,12-14) 130.3 (two overlapping signals), 130.9, 132.6.

8: m.p. 311-3° (decomp.); anal. (calc/found %): C 36.9/37.0 H 3.9/4.0 N 8.6/8.4 Cl 14.5/14.6; ^{1}H-nmr in TFA: 2-H 5.50 t 9.2 Hz(2H) 3-H 5.29 t 9.2 Hz(2H) 6,8-H 4.68 t 5.3 Hz(2H) and 3.90 not resolved m(2H) 7-H 2.55 not resolved m(2H) 10,13-H 7.81 and 7.72 2xs(2x1H) 14,15-H 4.20 and 4.18 2xs(2x3H); ^{13}C-nmr in TFA: C(2) 75.9 C(3) 54.2 C(6) 53.3 C(7) 20.9 C(8) 42.6 C(9a,13b) 162.8, 160.2 C(9b,13a) 110.8, 109.6 C(10,13) 122.8, 114.3 C(11,12) 159.5, 158.2 C(14,15) 60.5, 59.9.

Hydrolysis of tricyclic oxazolinium perchlorates (3 → 1)* - The reactions were carried out by Method E, as described for bromoethylphthalazinones. Reaction time was ca. 10 sec in all cases; the yields were about the same.

Conversion of 2-(ω-bromoalkyl)phthalazinones and 2,3-dihydrooxazolo[2,3-a]phthalazin-4-ium perchlorates with piperidine (2 → 4 and 3 → 4)* –

Method I. The bromoalkyl derivatives 2a-i (10 mmol) or tricyclic oxazolinium perchlorates 3*a-h (10 mmol) were dissolved in piperidine (8 ml, 80 mmol) and the soln was kept at r.t. for 24 h. The excess of piperidine was removed by distillation in vacuo, the residue was triturated with water (10 ml) and filtered off. The crude amines (4a-i) were washed with water (5 ml), dried (P_2O_5), then recryst. from Et_2O-petroleum ether; m.p.-s raised by max. 2°. Yields changed between 78% and 98%. Analytical and spectral data are listed in Table 4. This method proved very suitable to prepare piperidino derivatives. (Prepn. of dialkylaminoalkylphthalazinones in most cases have been carried out by N^2 alkylation of phthalazinones with dialkylaminoalkyl halides.[21])

In case of the conversions of 2d,e and 3*d,e, by Methods I-L, the residue obtained by evaporation of the reaction mixture was worked up as follows. To the crude product 10% HCl (10 ml) was added, the insoluble part (1d,e) was filtered off and the soln was neutralized to pH 8 with cc. NaOH. Next day the major part of product (4d,e) separated as zwitterion was filtered off. The filtrate was evaporated then mixed with $CHCl_3$ (4 ml). Insoluble salts were filtered off and the filtrate was evaporated to give a second crop of betaine. Crude prodcuts were washed with EtOH-Et_2O (2:3 ml), dried (P_2O_5) and recryst. from $CHCl_3$-Et_2O.

Method J. The bromoalkyl compounds 2a-i (10 mmol) and piperidine (2.55 g, 30 mmol) were dissolved in $CHCl_3$ (20 ml) and boiled for 6 h (2d-f only for 30 min). The crude amines were obtained by the method described in the previous section. Yields were about the same.

Method K. Conversions described in the above section were carried out in $CHCl_3$-EtOH-water (10:10:1 ml). Dry crude products were triturated with Et_2O (10 ml) then the insoluble parts were filtered off, washed with water (8 ml) and dried (P_2O_5) to yield hydroxyalkyl derivatives 1a-i. The filtrate was evaporated, the amine was triturated with water (10 ml), filtered off, dried, then purified as shown above (Tables 3 and 4).

Method L. The bromoalkyl compounds 2a-i (10 mmol) or tricyclic oxazolinium perchlorates 3*a-h (10 mmol) were dissolved in a mixture of 99% EtOH (30 ml) and piperidine (2.55 g, 30 mmol), then boiled for 1 h. The separation of amines (4a-i) and hydroxyalkyl compounds (1a-i) was carried out by Method K (Tables 3 and 4). Using 50-70 mmol of piperidine the yields of amines 4a-f increased only by 2-8%.

2,3,7,8-Tetrahydro-11,12-dimethoxy-13b-piperidino-6H,13bH-oxazolo[2,3-a]pyrimido[1,2-c]phthalazin.$HClO_4$ (9) –

Method M. Bis-perchlorate 8 (0.98 g, 2 mmol) was dissolved in piperidine (8 ml, 80 mmol) at 25°. After 1 h the excess of piperidine was removed in vacuo. The oily residue was triturated with EtOH (4 ml); the crystals were filtered off and washed with 2 ml of EtOH (0.79 g, 83%, m.p. 158-60°). Recryst. from $CHCl_3$-Et_2O (5:3 ml); m.p. 160-1°. Anal. (calc/found %): C 50.8/50.8 H 6.2/6.2 N 11.8/11.9 Cl 7.5/7.6. ^{1}H-nmr in $CDCl_3$: 2-H 3.65 m, 4.05 m (overlapped by OCH_3 signal) 3,6,8-H 3.8 m(6H) 7-H 2.15 m 2.35 m(2H) 10-H 7.45 s(1H) 13-H 7.02 s(1H) 14,15-H 3.89 s(3H) 4.04 s(3H) 17-H 2.5 m 2.8 m(4H) 18,19-H 1.45 s(6H). ^{13}C-nmr in $CDCl_3$: C(2) 62.1 C(3) 39.1 C(6,8) 47.2, 48.7 C(7) 18.9 C(9a) 154.5 C(9b,13a) 107.3, 109.6 C(10) 111.1 C(11,12) 150.2, 152.7 C(13) 102.1 C(13b) 130.0 C(14,15) 56.1, 56.4 C(17) 45.3 C(18) 25.9 C(19) 24.4.

Desamination of adduct 9

Method N. Adduct 9 (0.47 g, 1 mmol) was dissolved in EtOH-70% $HClO_4$ (1:1 ml) at 25°; an exotherm reaction proceeded. After 1 h the crystals were filtered off, washed with EtOH-Et_2O (0.5:2 ml) then dried to yield bis-perchlorate 8 (0.45 g, 92%, m.p. 310-3°), as shown by analysis and ir.

M.p.-s were measured on a Boetius micro hot stage. Values are uncorrected.

Spectra – Ir spectra were obtained on a Zeiss IR-75 instrument in KBr pellet. ^{1}H-nmr spectra were recorded on a Varian-60D spectrometer (2a-i, 4a-i) and Bruker WM-250 FT instrument (3*a-h, 6, 8 and 9) at 60 and 250 MHz, respectively at r.t. ^{13}C-nmr spectra were measured on a Bruker WP 80-SM spectrometer at 20 MHz using TMS or DSS as int. ref.

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REFERENCES

1. I.D. Lenke, Arzneimittel-Forsch., 1957, 7, 678; C.A. 52, 9439f.
2. H.W. Heine, J. Am. Chem. Soc., 1956, 78, 3708; and refs. therein.
3. The Chemistry of Amides (Ed. by J. Zabicky) Wiley, 1970, pp. 715-724 and refs. therein.
4. T. Taguchi, J. Ishibashi, T. Matsuo and M. Kojima, J. Org. Chem., 1964, 29, 1097.
5. S. Hünig and L. Geldern, J. Prakt. Chem., 1964, 24, 246; and refs. therein.
6. R.M. Lusskin and J.J. Ritter, J. Am. Chem. Soc., 1950, 72, 5577.
7. J. Pocker, J. Org. Chem., 1959, 2319.
8. M.L. Alpert, W.E. Keiser, H.A. Szymanski, Theory and Practice in Infrared Spectroscopy, Plenum Press, New York, 1964, pp. 268-75; S. Holly, P. Sohár, Theoretical and Technical Introduction to the series of Absorption Spectra in the Infrared Region (Eds.: L. Láng, W.H. Prichard) Akadémiai Kiadó, Budapest, 1975, pp. 96-7.
9. J. Gerstein and W.P. Jencks, J. Am. Chem. Soc., 1964, 86, 4655.
10. W. Schneider and B. Müller, Chem. Ber., 1960, 93, 1579.
11. N. Gravitz and W.P. Jencks, J. Am. Chem. Soc., 1974, 96, 489 and 499.
12. H. Meerwein and H. Sönke, Chem. Ber., 1934, 64, 2375; and refs. therein.
13. V. Kolesnikov, E. Bisagni, Chim. Ther., 1967, 250; C.A. 69, 19105j.
14. G.V. Shatalov, S.A. Gridchin and B.I. Mikhaent'ev, Khim. Geterotsikl. Soedin., 1980, 394; C.A. 93, 71681d.
15. H. Cairns, W.H. Hunter, J. King, B.J. Milliard, Brit. Pat. 1,100,911; C.A. 69P, 19181f.
16. K. Körmendy, K.Á. Juhász, É. Lemberkovics, Acta Chim. Acad. Sci. Hung., 1979, 102, 39.
17. K. Körmendy, Acta Chim. Acad. Sci. Hung., 1979, 99, 81.
18. M.S. Newman, Chem. Educ., 1977, 54, 191.
19. G. Gabriel, J. Am. Chem. Soc., 1954, 76, 1283.
20. T. Ikeda, S. Kanahara, T. Ujiie, Kanazawa Daigaku Jakugakubu, Kankyu Nempo, 1958, 8, 1; C. A. 53, 4287i.
21. (a) W. Zerweck, W. Kunze and R.E. Nitz, Brit. Pat. 808,636; C.A. 53P, 14129f,g.
    (b) H.J. Engelbrecht, Ger.(East) Pat. 55,955; C.A. 67P, 90826j.