Tetrahedron Vol. 46, No. 19, pp. 6895-6902, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

PREPARATION OF HETEROCYCLIC DICATIONS FROM SUBSTITUTED PHTHALAZINONES

A. Csámpai*, †K. Körmendy, P. Sohár×, J. Császár and F. Ruff

Inst. Organic Chemistry, Eötvös University, H-1518 Budapest 112, POB 32.
×Spectroscopic Dept. EGIS Pharmaceuticals, H-1475 Budapest, POB 100, Hungary

(Received in UK 26 June 1990)

Abstract - Using perchloric acid 2-(ω-hydroxyalkyl)-4-(ω'-hydroxyalkylamino)phthalazinones and their 6,7-dimethoxy derivatives were converted into tetracyclic dications containing both iminoether and amidine moieties. The 2-(4-hydroxybutyl) chain avoided the formation of seven-membered ring with either isomerisation or degradation involving cleavage of C-N bond assisted by neighbouring group participation of the hydroxyl group. The sequence of ring closures depends on the ring substituents and the lengths of side chains. The reaction mechanism is also influenced by the site of the protonation. The structures of the new tetracycles were proved by ^{1}H- and ^{13}C-nmr spectroscopy.

INTRODUCTION

We have reported earlier[1] on the preparation of tetracyclic dication 4b and its regioselective reaction with piperidin yielding a tetrahedral orthoacid derivative.

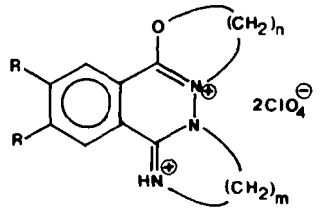
This paper discusses the cyclization reactions of bis-hydroxy compounds 1a-f and 2a-f resulting in tetra- and tricyclic dications of types 3-7 (Scheme 1). The dependence of the reactivity and the structure of the products on substituent R and on the lengths of the side chains (cf. Ref.2) are also dealt with, and alternative mechanisms and sequences are proposed for the ring closures.

RESULTS AND DISCUSSION

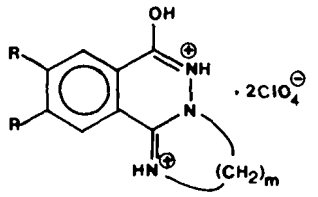
Cyclizations of compounds of types 1 and 2 were effected with 70% $HClO_4$-EtOH (1:1) and 70% aqueous $HClO_4$, respectively (Methods A and B). The yields for conversions 2 → 4 (R=OMe) were much higher even with shorter reaction times (Table 1) indicating that the positively charged heterorings are effectively stabilized by the electron-releasing OMe groups. The most significant difference was observed between the rates for the formation of 3a and 4a dications containing two five-membered heterorings. The reaction 2a → 4a can be carried out with excellent yield even by Method A, but 1a → 3a takes only place under more vigorous conditions (Method B).

1,3,5,8,10,12,14 (R=H)
2,4,6,7,9,11,13,15 (R=OMe)

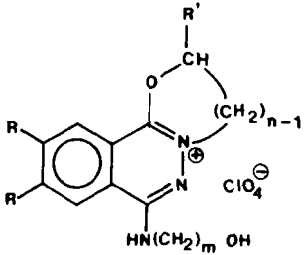
a (n=m=2)
b (n=2, m=3)
c (n=3, m=2)
d (n=m=3)
e (n=4, m=2)
f (n=4, m=3)



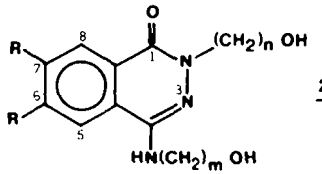
3a-d, 4a-d



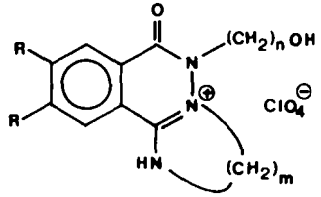
7a, b



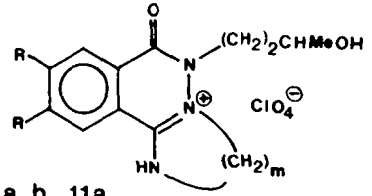
12a-d, 13a,c (R'=H)
14c, d, 15c (R'=Me)



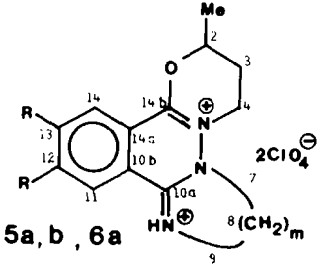
1a-f, 2a-f



8a-f, 9a-f



10a, b, 11a



5a, b, 6a

12a-d, 13a, c / $HClO_4$

1a-f, 2a, c, e / $HClO_4$

2b, d, f / $HClO_4$

8a-d, 9a-d / $HClO_4$ / $+H_2O$ / $-H_2O$

9e, f / $HClO_4$ / $-THF$

14c, d / 15c / $HClO_4$

H_2O / $HClO_4$

8e, f / $HClO_4$

SCHEME 1

Table 1. Reaction times and yields for reactions effected by $HClO_4$

Reaction	React. time (min.)	Yield (%) Method A	B	Reaction	React. time (min.)	Yield (%) Method A	B	Reaction	React. time (min.)	Yield (%) Method A	B
1a ⟶ 3a	120	-	20	1e ⟶ 5a	600	32[a]	40[a]	2c ⟶ 4c	60	96	97
	720	-	66	8e ⟶ 5a	600	35[a]	39[a]	9c ⟶ 4c	5	98	99
8a ⟶ 3a	720	-	70	10a ⟶ 5a	366	62	78	2d ⟶ 4d	5	18	32
12a ⟶ 3a	30	-	75	1f ⟶ 5b	120	12[a]	20[a]		60	99	98
1b ⟶ 3b	60	20	31		600	42[a]	54[a]	9d ⟶ 4d	5	97	98
	360	59	84	8f ⟶ 5b	600	42[a]	51[a]	2e ⟶ 6a	30	10[a]	14[a]
8b ⟶ 3b	360	62	80	10b ⟶ 5b	360	73	87		300	60[a]	64[a]
1c ⟶ 3c	60	24	34	2a ⟶ 4a	5	12	20	11a ⟶ 6a	5	98	95
	360	61	86		60	95	98	9e ⟶ 7a	5	96	96
8c ⟶ 3c	360	64	84	9a ⟶ 4a	5	97	98	2f ⟶ 7b	5	11	16
1d ⟶ 3d	30	18	27	2b ⟶ 4b	5	15	27		60	98	94
	360	77	94		60	98	99	9f ⟶ 7b	5	95	94
8d ⟶ 3d	360	78	93	9b ⟶ 4b	5	97	97	17b ⟶ 18	5	9	13
1e ⟶ 5a	120	9[a]	13[a]	2c ⟶ 4c	5	14	30		90	92	97

[a] Products were recrystallized from EtOH-70% $HClO_4$ (1:1), using charcoal, see text.

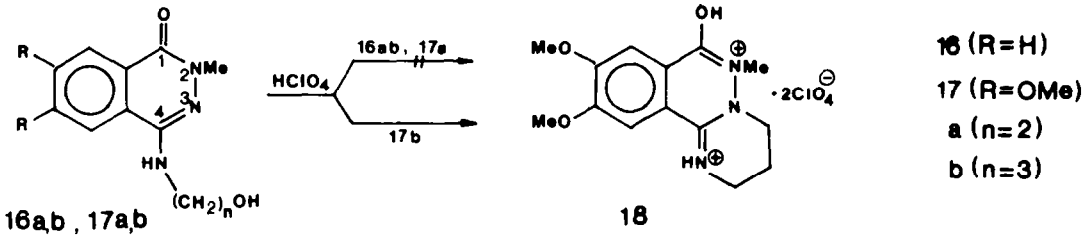
2-Hydroxyethyl- and propyl derivatives (1a-d, 2a-d) yielded the expected tetracycles (3a-d, 4a-d), while under the same conditions avoiding the formation of the seven-membered heteroring reactions of hydroxybutyl homologues 1e,f and 2e,f produced anomalous products. In case of R=OMe, either a methyl-oxazonium ring was formed (2e → 6a) or the reaction yielded tricyclic product and THF (2f → 7b). When R=H, only the closure of the isomeric ring was observed (1e,f → 5a,b). Ring closures to 5 and 6 were not accompanied by chain--degradation.

In order to study the structural conditions of the anomalous reactions, experiments with tricyclic hydroxyalkyl compounds were carried out: (i) 8a-d, 9a-d, 10a,b, and 11a obtained by hydrolysis of tetracycles were easily recyclized; (ii) homologues 8e,f - similarly to 1e,f - gave 5a,b, with neither of these reactions being accompanied by chain--degradation (cf. Exp.); (iii) under the same conditions, the 9e,f dimethoxy analogues underwent fast chain-degradation to 7a,b. On this basis it can be concluded that the conversion of 2f proceeds *via* 9f, while the conversion of 2e must proceed *via* 15c (Scheme 1), because otherwise chain-degradation 9e → 7a would take place.

The possible sequences for ring closures are summarized in Scheme 1. We assume that the condensation of the amidine ring is the primary process only in reactions of dimethoxy derivatives 2b,d,f leading to six-membered ring (m=3). This is confirmed by experiments with N-methyl analogues 16a,b and 17a,b (Scheme 2). Applying the same conditions the ring closure occures only when m=3 and R=OMe (17b → 18). No cyclization of 16a,b and 17a were effected by either of the methods used: with longer reaction time (20 h), 66-90% of the $HClO_4$ salt of the unchanged materials were recovered. We can not offer any explanation for the unique reactivity of 17b.

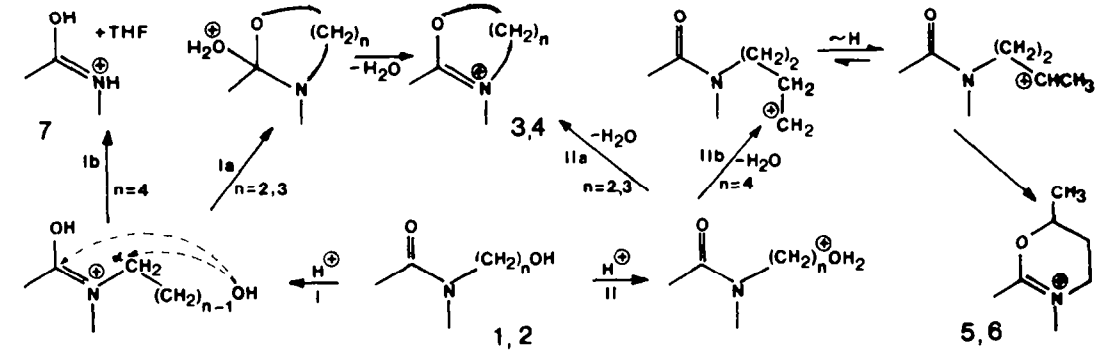
In shorter reaction times conversions of bis-hydroxy compounds resulted exclusively in end-products 3a-d, 4a-d, 5a,b, 6a and 7b, but the yields were much poorer (Table 1). These experiments suggest that relatively slow formations of the supposed intermediates 9b,d,f,

12a-d, 13a,c and 15c are followed by fast formations of the end-products. This assumption can be supported by additional experimental findings: in shorter reaction times tricycles 9b,d,f and 12a were converted into the corresponding end-products with excellent yields, but cyclization to 18 took place only with poor yield (Table 1).



SCHEME 2

For the formation of the three different types of products (3+4, 5+6 and 7) four mechanisms (Ia,b and IIa,b) may be taken into consideration depending on the site of the protonation and on the size of the ring formed (Scheme 3). It can be seen that only conversions of the hydroxybutyl chain are governed by the site of the primary protonation (mech. Ib and IIb).



SCHEME 3

Mechanism Ia which is analogues to N → O acyl-migration with retention[3] involves the protonation of carbonyl oxygen followed by nucleophilic addition of the OH group, finally, by the elimination of water. If n=4, this addition would lead to a seven-membered ring, thus the OH group only attacks on the C-α atom (mech. Ib). In case of shorter chains, the attack on the C-α atom would result in strained cyclic ethers. If n=2,3, the positively charged ring can also be formed by mechanism IIa, comparable to N → O acyl-migration with inversion[3], while the closure of the methyl-oxazinium ring occurs after a carbocation rearrangement[4] by mechanism IIb. This assumption is in keeping with observations by Oláh et al[5] that carbocations formed from 1,3- and 1,2-dibromobutane in SbF_5-SO_2 at -70°C cyclize to the favoured five-membered tetramethylene-bromonium ion after a series of 1,2-hydride-shifts.

By the above considerations, for every single cyclization leading to products of types 3 and 4 no alternative Ia or IIa mechanisms can be unambiguously adopted. On the other hand, it is very likely that in fast reactions 9a-d → 4a-d mainly mechanism Ia operates, which assumption may be supported by the fact that tricycles 7a,b and 18 containing R=OMe groups precipitate with two molecules of perchloric acid (cf. Table 3). This is also in accord with mechanism Ib considered as probable for reactions 9e,f → 7a,b. So far we have failed to carry out the N-deprotonation of the tetracyclic dications without any other conversions of the molecules.

EXPERIMENTAL

M.p.'s (uncorrected) were determined on a Boetius micro-hot-stage. Ir spectra were obtained on a Zeiss UR-75 instrument in KBr pellets. Nmr spectra were recorded on a Varian A-60P instrument and a Brucker WM-250 (^{1}H) or WP 80-SY (^{13}C) FT spectrometer at RT using TMS as reference. For gaschromatography a G.C.H.F. 18.3 instrument was used.

2-(ω-hydroxyalkyl)-4-(ω'-hydroxyalkylamino)phthalazin-1(2H)-ones 1c-f and 2c-f

Using the corresponding phthalimide and hydroxyalkylhydrazine, 1c-f and 2c-f were prepared by the methods described for 1a,b[6] and 2a,b[7], respectively. Yield: 68-95%. Ir bands (cm^{-1}): νNH, OH: 3450-3190 (1-3 bands); amide-I: 1640-1620.

$HClO_4$ salt of 2,3,6,7-tetrahydro-10,11-dimethoxy-oxazolo[2,3-a]imidazo[1,2-c]phthalazin-4-ium-perchlorate (4a), 2,3,7,8-tetrahydro-6H-oxazolo[2,3-a]pyrimido[1,2-c]phthalazin-4-ium-perchlorate (3b), 3,4,7,8-tetrahydro-2H-[1,3]-oxazino[2,3-a]imidazo[1,2-c]-phthalazin-5-ium-perchlorate (3c), 3,4,8,9-tetrahydro-2H,7H-[1,3]-oxazino[2,3-a]pyrimido-[1,2-c]phthalazin-5-ium-perchlorate (3d) and 2-methyl derivs. of 3c,d (5a,b), 2-methyl--11,12-dimethoxy deriv. of 3c (6a), 11,12-dimethoxy derivs. of 3b,c (4b,c), 12,13-dimethoxy deriv. of 3d (4d) - METHOD A

0.01 M of the corresp. precursor (1a-f, 2a-e, 8a-f, 9a-d, 10a,b, 11a, 12a) was dissolved in EtOH-70% $HClO_4$ (5-5 ml) then the soln. was refluxed for the time as shown in Table 1. In case of 4a-d, after 2-3 min of reflux the crystalline product started to precipitate from the reaction mixture. After cooling, to the solutions 8 ml of Et_2O, to the suspensions 5 ml of Et_2O was slowly added. (Using 1a or 12a as precursor, no crystals were obtained by dilution even with 20 ml of Et_2O and only some precipitation of a viscose oil was observed. After ~30 min some more Et_2O (4 ml) was added, then the crystals were filtered off, and washed with cold EtOH-Et_2O (2-5 ml). The products 5a,b and 6a were precipitated as grey crystals from the darkened reaction mixtures and purified as follows: the crude product was dissolved in 3-7 ml of hot EtOH-70% $HClO_4$ (1:1), and to the soln. a small amount of charcoal was added. After several minutes of reflux the charcoal was removed by filtration on glass-filter. To the clear soln. Et_2O (4-9 ml) was added to obtain the colourless pure product. In case of other products no purification was necessary.

$HClO_4$ salt of 2,3,6,7-tetrahydrooxazolo[2,3-a]imidazo[1,2-c]phthalazin-4-ium-perchlorate (3a) + 3b-d, 4a-d, 5a,b, 6a - METHOD B

0.01 M of the corresp. precursor mentioned in Method A was dissolved in 70% $HClO_4$ (6 ml). The soln. was warmed on steam-bath for the time given in Table 1, then cooled and diluted with 1 ml of EtOH. To the obtained suspension cooled with ice-water, Et_2O (7 ml) was slowly added. After ~30 min an additional amount of Et_2O (3 ml) was poured into the thick suspension. The crystalline product was filtered off and washed with cold EtOH-Et_2O (2-5 ml). The grey crystals of 5a,b and 6a were purified as described in Method A.

Dihydrcperchlorate of 2,3-dihydro-8,9-dimethoxy-imidazo[2,1-a]phthalazin-6(5H)-one (7a), 3,4-dihydro-9,10-dimethoxy-2H-pyrimido[2,1-a]phthalazin-7(6H)-one (7b) and its 6-methyl derivative (18).

Starting materials: as shown in Table 1. Reactions and isolation: by Methods A and B, respectively.

7a: ^{1}H-nmr (TFA): $(CH_2)_2$: 5.15 and 4.61 (2 x t, J = 10.5 Hz, 2 x 2H); 8,9-OMe: 4.25 (s, 6H); ArH: 7.79 and 7.70 (2 x s, 2 x 1H).

7b: ^{1}H-nmr (TFA): N-CH_2 groups: 4.67 (t, J = 5.0 Hz, 2H) and 3.86 (t, J = 6.0 Hz, 2H); C-CH_2-C: 2.51 (~qi, 2H); 9,10-OMe: 4.20 and 4.11 (2 x s, 2 x 3H); ArH: 7.82 and 7.70 (2 x s, 2 x 1H). (Description of base derived from 7b can be found in Ref.8.)

18: ^{1}H-nmr (TFA): N-CH_2 groups: 4.70 (t, J = 5.5 Hz, 2H) and 3.80 (t, J = 6.0 Hz, 2H); C-CH_2-C: 2.49 (~qi, 2H); 9,10-OMe: 4.18 (s, 6H); 6-Me: 3.98 (s, 3H); ArH: 7.83 and 7.76 (2 x s, 2 x 1H).

Table 2. ^{1}H- and ^{13}C-nmr data of compounds 3a-d, 4a,c,d, 5a,b and 6a in TFA solution (δ, ppm) at 250 (^{1}H) and 20 MHz (^{13}C).[a]

Compound	2-H[b] 4-H[b]	3-H[c] 8-H[c]	7-H[d] 9-H[d]	ArH(11-14)[e] NH, s(1H)	C(14b) C(10a)	C(10b)[f] C(14a)[f]	C(11)[f] C(14)[f]	C(12)[f] C(13)[f]	C(2) C(9)	C(4)[f] C(7)[f]	C(3) C(8)
3a	5.66	-	5.17	8.4-8.6	163.6	122.0	142.8	133.0	78.3	55.1	-
	5.33	-	4.62	9.48	159.3	124.1	144.2	132.6	48.8	55.7	-
3b	5.57	-	4.70	8.3-8.6	162.6	120.4	141.6	132.6	77.3	55.1	-
	5.34	2.57	3.92	9.22	154.3	127.9	144.2	129.8	43.5	53.8	21.4
3c	5.11[g]	2.83	5.18[g]	8.4-8.6	161.4	122.4	142.6	131.5	74.4	52.9	23.1
	4.82	-	4.55	9.25	158.2	126.6	143.1	132.2	47.9	55.1	-
3d	5.07	2.74	4.70	8.3-8.6	162.1	124.5	141.3	131.9	74.0.	53.1[h]	23.5
	4.82	2.49	3.88	9.15	154.2	126.0	143.2	128.5	43.2	53.1[h]	21.9
4a	5.59	-	5.14	7.91, 7.79	161.6	110.7	122.9	160.1	75.6	53.6	-
	5.28	-	4.57	11.2	160.2	110.0	119.3	156.1	46.3	52.9	-
4c	5.08	2.83	5.16	7.87, 7.83	161.1	110.1[h]	121.0	158.6	72.5	51.3	21.9
	4.81	-	4.53	8.85	160.4	110.1[h]	118.3	155.6	46.2	53.6	-
4d	5.03	2.73	4.70	7.83, 7.75	161.9	110.4	120.9	160.0	72.8	52.2[h]	22.9
	4.80	2.49	3.87	8.85	160.0	108.5	118.7	152.3	42.3	52.2[h]	21.3
5a	~5.2[g]	2.56	5.10[g]	8.3-8.6	160.9	122.2	142.3	131.9	84.7	52.6	29.5
	4.80	2.80	4.50	9.35	158.0	126.4	142.8	131.3	47.6	54.8	-
5b	5.26	~2.7[i]	~4.7[g]	8.3-8.6	153.1[h]	123.5	140.4	130.9	83.5	51.9	29.2
	~4.7[g]	2.4	~3.9	9.02	153.1[h]	125.0	142.2	127.5	42.1	52.1	20.9
6a	~5.2[g]	~2.7[i]	~5.2[g]	7.84, 7.80	155.6	110.1[h]	120.4	160.3	82.8	51.3	28.5
	4.68	-	4.51	8.83	161.1	110.1[h]	116.5	158.3	46.3	53.7	-

[a] The numbering of atoms are given in Scheme 1 on Formulas 5-6. Assignments of the carbon lines were proved by DEPT measurements for 5a,b and 6a. Data for 4b see in Ref. 1. Further signals: CH_3 (^{1}H, d, J Hz/^{13}C): 1.80, 6.2/21.6 (5a), 1.84, 6.3/20.7 (5b) and 1.84, 6.4/20.7 (6a). OCH_3 (^{1}H, 2xs (2x3H)/^{13}C): 4.23, 4.24/58.7, 59.2 (4a), 4.22[h]/59.0, 59.4 (4c), 4.17, 4.19/59.7, 60.3 (4d) and 4.21[h]/59.0, 59.6 (6a); [b] t (2H), J = 9.5 ± 0.3 Hz (3a,b, 4a) and 5-6 Hz (3c,d). The H-2 signal is not resolved m for 4c,d, 5a,b; intensity is 3H for 5a,b and 6a; [c] Not resolved m's (2H for 3b,c and 4c, 2x2H for 3d and 4d, 2x1H for 5a and 6a and 1+1+2H for 5b); [d] t (2H), J = 10.4 ± 0.2 Hz (3a,c, 4a,c, 5a, 6a); not resolved m's. 2xm (2x2H) for 3b and 4d, 3xm (2+1+1H) for 5b, [e] Partly overlapping two dd and two dt of 1-1H intensity for 3a-d and 5a,b, 2xs (2x1H) for 4a,c,d and 6a. [f] Assignments may also be reversed for the signed line pairs, [g] Overlapping signals; [h] Two coalesced lines, in overlapp with a TFA-line for 4c and 6a; [i] Two not resolved m's.

Detection of THF

After reactions by Method A resulting in 7a,b, the suspension was cooled, then the crystalline product was filtered off and washed with EtOH (3 ml). Yield (without addition of Et_2O): 76-82%. To the mother liqeour cooled with ice-water, KOH (4.5 g) was slowly added. $KClO_4$ was filtered off, then washed with EtOH (1 ml) and sucked thoroughly (The suction vessel was cooled with salt-ice.) The filtrate was slowly distilled under atmospheric pressure. (The collector was cooled with salt-ice.) About 4-5 ml of the distillate was collected. G.C.: 3 m 10% Carbowax 20M/Gaschrom Q, 100-120 mesh; 60°C. Reference: EtOH (5 ml) + THF (0.72 g; 0.01 M). Min. 60% of the calculated amount of THF was detected in

the samples. In Method B detection was carried out with an increased amount of KOH (6.0 g). Min. 70% of the calculated amount of the THF was detected in these samples. In samples obtained from reactions of 1e,f, 8e,f and 2e, in either Method A or B, no THF was found even in traces.

2,3-dihydro-6-(2-hydroxyethylamino)-oxazolo[2,3-a]phthalazin-4-ium-perchlorate (12a)

2.49 g (0.01 M) of 1a was dissolved in 48% HBr (10 ml). The solution was refluxed for 5 min, then evaporated in vacuo in presence of 3.1 g NaBr. To the residue cold EtOH (10 ml) was added, the insoluble salts were filtered off. 70% $HClO_4$ - Et_2O (1-3 ml) was slowly poured into the filtrate cooled with ice-water. After 1 h the precipitated crystals were washed with EtOH-Et_2O (2-4 ml): 2.28 g (69%); ir (cm^{-1}): νN-H, O-H: 3550, 3400 and 3280; ^1H-nmr (TFA): $(CH_2)_2$ (ring): 5.47 and 5.08 (2 x t, J = 9.5 Hz, 2 x 2H); $(CH_2)_2$ (chain): 4.24 and 4.00 (2 x t, J = 5.0 Hz, 2 x 2H); ArH: 8.1-8.3 (m, 4H).

$HClO_4$ salt of 2,3-dihydroimidazo[2,1-a]phthalazin-6(5H)-ones: -5-(2-hydroxyethyl) (8a), -5-(3-hydroxypropyl) (8c), -5-(3-hydroxybutyl) (10a), their 8,9-dimethoxy analogues (9a,c and 11a) and 3,4-dihydro-2H-pyrimido[2,1-a]phthalazin-7(6H)-ones: -6-(2-hydroxyethyl) (8b), -6-(3-hydroxypropyl) (8d), -6-(3-hydroxybutyl) (10b) and the 9,10-dimethoxy analogues of 8b,d (9b,d)

0.01 M of the dications (3a-d, 4a-d, 5a-b, 6a) was suspended in water (20 ml). The suspension was stirred at RT for ca 30 min. The soln. obtained was neutralized with 1N NaOH (10 ml) then concentrated. The precipitated crystals were washed with EtOH (5 ml) then dried over P_2O_5. Yield: 70-97%.

$HClO_4$ salt of 2,3-dihydro-5-(4-hydroxybutyl)-imidazo[2,1-a]phthalazin-6(5H)-one (8e) and 3,4-dihydro-6-(4-hydroxybutyl)-2H-pyrimido[2,1-a]phthalazin-7(6H)-one (8f):

a) HBr salt of 5-(4-bromobutyl)-2,3-dihydroimidazo[2,1-a]phthalazin-6(5H)-one (19) and 6-(4-bromobutyl)-3,4-dihydro-2H-pyrimido[2,1-a]phthalazin-7(6H)-one (20)

0.01 M of 1e/1f was dissolved in 48% HBr (15 ml). The soln. was refluxed for 90 (1e) or 5 min (1f), then evaporated in vacuo in presence of NaBr (3.1 g). The residue was extracted with hot abs. EtOH (80 ml). After filtration the soln. was concentrated. To the suspension obtained Et_2O (4 ml) was slowly added. The crystals were washed with EtOH-Et_2O (5-1 ml) and recryst. from abs. EtOH. Yield: 77-79%.

19: m.p.: 233-6°C; anal.: C 41.7/41.8, H 4.3/4.1, N 10.4/10.3, Br 39.6/39.5; ir (cm^{-1}): νN-H^+: 3150-2500, amide-I: 1662.

20: m.p.: 200-3°C; anal.: C 43.2/43.2, H 4.6/4.7, N 10.1/10.0, Br 38.3/38.1; ir (cm^{-1}): νN-H^+: 3200-2700, amide-I: 1665.

b) Conversion of 19 and 20 to 8e and 8f, respectively

0.01 M of the corresp. bromobutyl deriv. was suspended in water (30 ml). To the suspension KOH (0.86 g) was added. The yellow oil separated from the aqueous phase was dissolved in n-BuOH (60 ml). In presence of KOAc (5.0 g) the soln. was refluxed for 3 h then evaporated. The residue was triturated with EtOAc (20 ml), the insoluble salts were filtered off and washed with EtOAc (5 ml). After evaporation of the combined filtrate, the oily residue was dissolved in EtOH-70% $HClO_4$ (30-1 ml). The soln. was refluxed for 2 h, then evaporated to obtain the crystalline product washed with EtOH-Et_2O (3-1 ml). Yield: 58-65%.

$HClO_4$ salt of 2,3-dihydro-5-(4-hydroxybutyl)-8,9-dimethoxy-imidazo[2,1-a]phthalazin-6(5H)--one (9e) and 3,4-dihydro-6-(4-hydroxybutyl)-9,10-dimethoxy-2H-pyrimido[2,1-a]phthalazin--7(6H)-one (9f):

a) 2-(4-acetoxybutyl)-4-(2-acetoxyethylamino)-6,7-dimethoxyphthalazin-1(2H)-one (21) and its 4-(3-hydroxypropylamino) homologue (22)

0.01 M of 2e/2f and Ac_2O (3 ml) were dissolved in pyridine (80 ml). The soln. was kept at RT for one day, then diluted with water (20 ml) and evaporated. The residue was tritur-

ated with water. Next day the diester was filtered off, washed with water and recryst. from $CHCl_3$-Et_2O. Yield: 63-71%.

21: m.p.: 81-2°C; anal.: C 57.0/57.1, H 6.5/6.6, N 10.0/9.8; ir (cm^{-1}): νN-H: 3340, 3275, νC=O(ester): 1737, amide-I: 1618.

22: m.p.: 70-2°C; anal.: C 57.9/58.0, H 6.7/6.7, N 9.6/9.7; ir (cm^{-1}): νN-H: 3335, 3270, νC=O(ester): 1735, amide-I: 1620.

b) Conversion of 21 and 22 to 9e and 9f, respectively

The mixture of the corresp. diester (5 mmol) and $TsOH.H_2O$ (0.9 g) was fused in vacuo for 30 min at 200°C (cf. Ref. 9) then dissolved in EtOH (60 ml). The soln. was refluxed for 2 h and evaporated. The oily residue was dissolved in water (15 ml). After addition of solid NaOH to pH ~11, the soln. was extracted with $CHCl_3$ (5 x 10 ml). The combined organic phase was evaporated. The oily residue was dissolved in EtOH-H_2O-70% $HClO_4$ (4-3 - 0.3 ml). After 1 h the salt was filtered off and recryst. from EtOH-H_2O. Yield: 38-48%. Characteristic ir bands (cm^{-1}) for $HClO_4$ salts 8a-f, 9a-f, 10a,b and 11a are: νO-H: 3575-3340, νN-H^+: 3350-2650 (broad band), amide-I: 1678-1660.

Table 3 Anal. data on compd. 1c-f, 2c-f, 3a-d, 4a,c,d, 5a,b, 6a, 7a,b, 8a-f, 9a-f, 10a,b, 11a, 12a and 18.[a]

	m.p.[b] °C	Elem. anal. (calc/found %) C	H	N	Cl		m.p.[c] °C	Elem. anal. (calc/found %) C	H	N	Cl
1c	152-3	59.3/59.3	6.5/6.4	16.0/15.9		7b	297-9	33.8/33.9	3.7/3.6	9.1/ 9.3	15.3/15.2
1d	135-6	60.6/60.9	6.9/6.8	15.2/15.3		8a	194-6	43.5/43.2	4.3/4.2	12.7/12.7	10.7/10.8
1e	116-7	60.6/60.8	6.9/7.1	15.2/15.2		8b	213-4	45.2/45.2	4.7/4.6	12.2/12.4	10.3/10.2
1f	95-7	61.8/61.6	7.3/7.3	14.4/14.5		8c	188-90	45.2/45.0	4.7/4.8	12.2/12.4	10.3/10.3
2c	198-9	55.7/55.7	6.5/6.3	13.0/13.2		8d	171-3	46.7/46.8	5.0/4.8	11.7/11.9	9.9/ 9.9
2d	188-90	57.0/56.8	6.9/7.0	12.5/12.4		8e	169-71	46.7/46.9	5.0/4.9	11.7/11.6	9.9/10.0
2e	189-90	57.0/57.0	6.9/7.2	12.5/12.4		8f	147-8	48.2/48.0	5.4/5.5	11.2/11.1	9.5/ 9.5
2f	149-50	58.1/58.1	7.2/7.0	12.0/11.9		9a	228-30	42.9/43.0	4.6/4.3	10.7/10.9	9.0/ 9.1
3a	270-3	34.8/34.8	3.2/3.3	10.1/10.2	17.1/17.0	9b	251-4	44.4/44.3	5.0/5.1	10.4/10.7	8.7/ 8.7
3b	284-5	36.5/36.6	3.5/3.4	9.8/10.1	16.6/16.6	9c	245-7	44.4/44.2	5.0/4.9	10.4/10.5	8.7/ 8.8
3c	252-4	36.5/36.3	3.5/3.3	9.8/10.0	16.6/16.6	9d	257-60	45.8/45.8	5.3/5.4	10.0/ 9.9	8.4/ 8.6
3d	277-8	38.0/38.1	3.9/3.7	9.5/ 9.5	16.0/16.1	9e	229-32	45.8/45.5	5.3/5.5	10.0/10.2	8.4/ 8.4
4a	281-4	35.5/35.4	3.6/3.9	8.9/ 8.9	15.0/15.0	9f	210-2	47.1/47.0	5.6/5.7	9.7/ 9.9	8.2/ 8.1
4c	294-6	36.9/37.0	3.9/3.8	8.6/ 8.5	14.5/14.5	10a	136-9	46.7/46.9	5.0/5.0	11.7/12.0	9.9/ 9.8
4d	300-3	38.3/38.3	4.2/4.3	8.4/ 8.3	14.1/14.3	10b	137-9	48.2/48.2	5.4/5.7	11.2/11.0	9.5/ 9.6
5a	225-7	38.0/38.1	3.9/3.9	9.5/ 9.8	16.0/15.8	11a	241-4	45.8/46.0	5.3/5.3	10.0/10.1	8.4/ 8.5
5b	248-50	39.5/39.3	4.2/4.1	9.2/ 9.4	15.5/15.6	12a	167-9	43.5/43.5	4.3/4.5	12.7/12.9	10.7/10.7
6a	264-6	38.3/38.5	4.2/4.2	8.4/ 8.6	14.1/14.0	18	278-81	35.3/35.5	4.0/3.8	8.8/ 8.8	14.9/14.9
7a	271-4	32.3/32.3	3.4/3.6	9.4/ 9.3	15.8/15.7						

a Data of 1a,b, 2a,b, 4b see in Ref. 1,6,7. b,c Recryst. from water (b) or ethanol-water (c).

Acknowledgements. - The authors thank Dr.H.Medzihradszky-Schweiger and Dr.S.Kutassi for analyses, Mrs.Á. Várnagy, Miss M. Sipos, Mrs. J. Csákvári and Mr. A. Fürjes for skilled technical assistance, Mrs.J. Máthé, Miss M. Halász and Miss E. Szentes for preparing the manuscript.

REFERENCES

1. A. Csámpai, K. Körmendy, P. Sohár and F. Ruff, Tetrahedron, 1989, 45, 5539.
2. K. Körmendy and F. Ruff, Acta Chim. Hung., 1983, 112, 65.
3. (a) L.H. Welsh, J. Am. Chem. Soc., 1949, 71, 3500; and references therein.
   (b) G. Fodor and V. Bruckner, Acta Chim. Acad. Sci. Hung., 1951, 1, 130.
4. J. March, Advanced Organic Chemistry p. 958. Wiley-Interscience, New York, 1985.
5. G.A. Oláh, J.M. Bollinger, Y.K. Mo and J.M. Brinich, J. Am. Chem. Soc., 1972, 94, 1164.
6. K. Körmendy, Acta Chim. Acad. Sci. Hung., 1977, 94, 373.
7. K. Körmendy, Acta Chim. Acad. Sci. Hung., 1979, 99, 81.
8. K. Körmendy, A. Kálmán, T. Koritsánszky, I. Kövesdi, P. Sohár and F. Ruff, Acta Chim. Hung., 1986, 123, 15.
9. K. Körmendy, F. Ruff and I. Kövesdi: Acta Chim. Hung., 1988, 125, 99.