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CHAIN LENGTH DEPENDENT REACTIVITY OF 2-(ω-HYDROXYALKYL)-4-(ω'-HYDROXYALKYLAMINO)PHTHALAZIN-1(2H)-ONES IN AZEOTROPIC HYDROBROMIC ACID

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Abstract - In boiling 48% HBr conversions of title compounds (5a-f) resulted in 2-(ω-bromoalkyl)-4-(2-hydroxyethylamino)-phthalazinones 8a,c, angular tricycles 7a,c-f and the 14a tricyclic dione, respectively, depending on the lengths of the side chains and the reaction time applied. The large difference between the reactivities of 4-(2-hydroxyethylamino)- and 4-(3-hydroxypropylamino) homologues in the exchange OH → Br was interpreted on the basis of the relative OH-basicities in the N^3-protonated molecules. The proposed mechanism for the conversion to 14a involving a Smiles-type rearrangement was supported by additional experiments with 4-amino-2-(ω-hydroxyalkyl)-phthalazinones 15a,b.

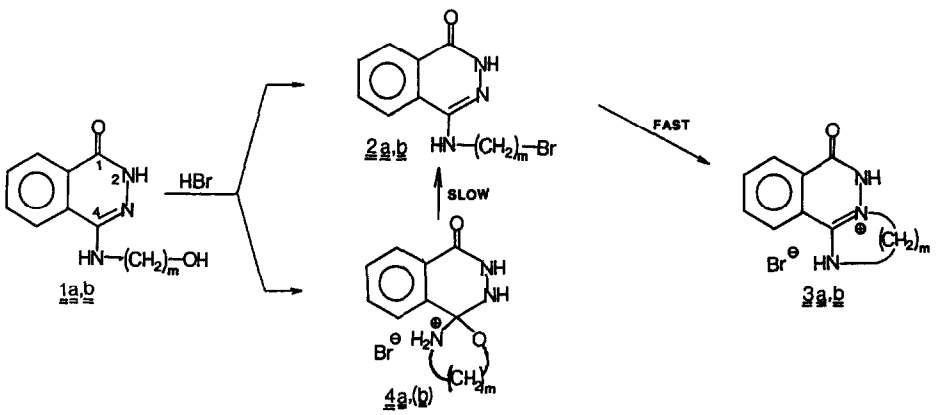
INTRODUCTION

As it has been reported[1], 4-(ω'-hydroxyalkylamino)phthalazin-1(2H)-ones 1a,b can be converted into the angular tricycles 3a,b using azeotropic hydrobromic acid as reagent (Scheme 1). These conversions proceed via the bromoalkylamino intermediates 2a,b. The rate for exchange OH → Br - which is the clue step - has proved to be highly dependent on the length of the side chain: after 5 min of refluxing almost the whole amount of the unchanged 1a can be recovered, while, applying the same reaction time, conversion 1b → 2b → 3b can easily be completed[1]. The reason proposed so far[1] for this strikingly large difference between the reactivities of the homologues has to be re-examined and this will be discussed again in this paper. The same dependence of the reactivity on the length of 4-(ω'-hydroxyalkylamino) chain was reflected in the structure of products when we chose 48% aqueous HBr as a convenient and effective reagent in order to convert bis-hydroxy derivatives 5a-f[2] into condensed bromoalkylphthalazinones of type 7 (Scheme 2). Both the expected and unexpected conversions of 5a-f including a rearrangement followed by the split of the hydroxyethylamino chain will also be dealt with in detail. It has to be mentioned here that bromoalkyl compounds like 7a-f seem to be suitable alkylating agents for amination reactions resulting in condensed aminoalkylphthalazinones of biological interest (cf. Ref. 3).

RESULTS AND DISCUSSION

1) Exchange OH → Br in the 4-(ω'-hydroxyalkylamino) chain

The above mentioned difference between the reactivities of homologues 1a and 1b has earlier[1] been interpreted with the fast primary formation of the spirocyclic intermediate 4a (Scheme 1) supposed to be less capable to undergo further conversion involving ring cleavage 4a → 2a. In contrast, the formation of the homologue spiro compound 4b has been regarded to be much slower than the direct reaction 1b → 2b → 3b.



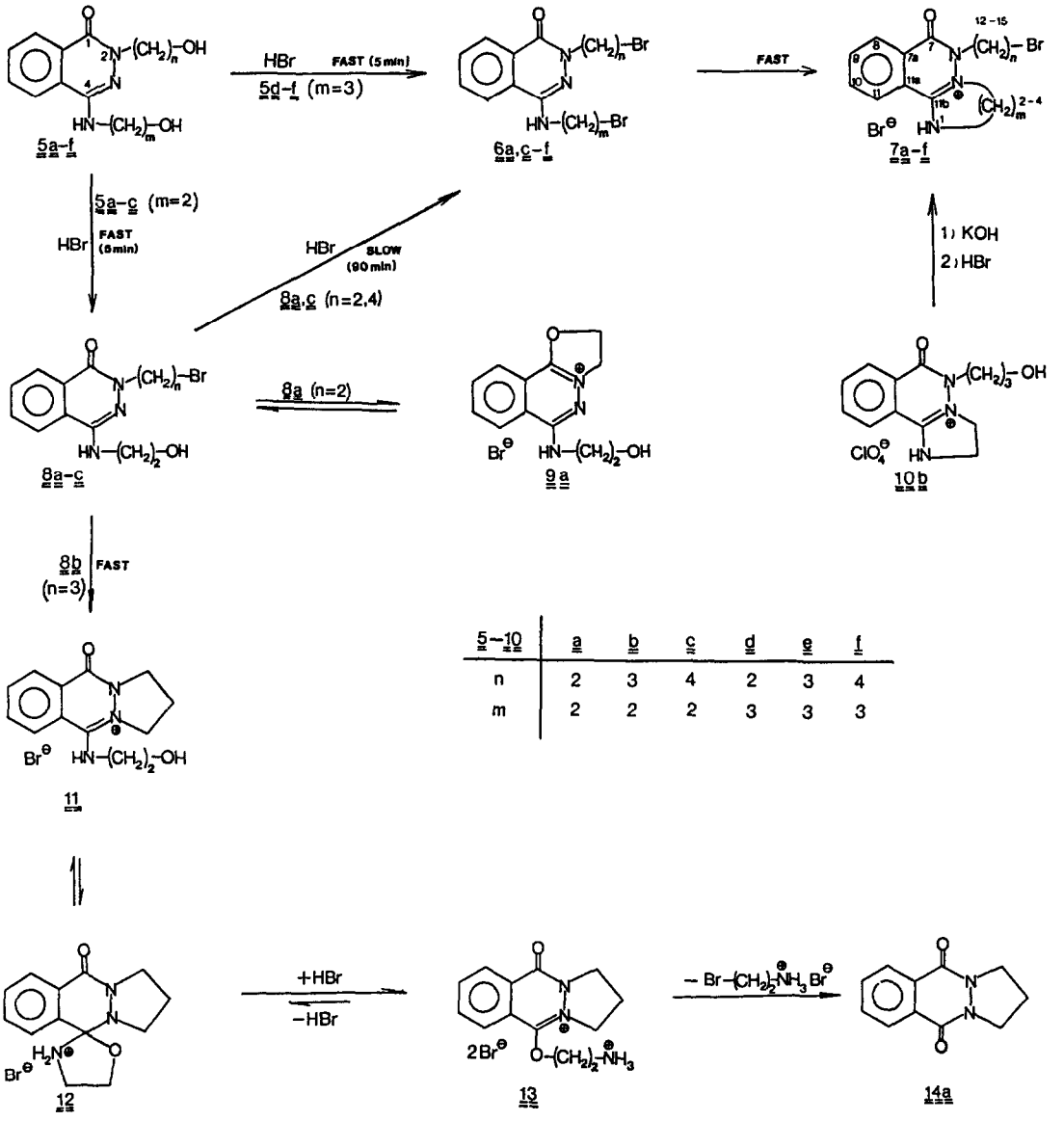
SCHEME 1 — m=2 for a and 3 for b

Recently we carried out comparative nmr studies (solvent 48% DBr) which unambiguously exclude the presence of the spiro compound 4a, although the spectra of 1a were registered after 5 min of boiling of its solution. (In order to avoid the fast conversion 1b → 2b → 3b, the solution of 1b was not refluxed before the registration.) Supporting the open-chain structure for 1a, the following experimental results were obtained: i) in the ^{1}H-nmr spectrum of 1a the typical A_2B_2 part for the $(CH_2)_2$ moiety points to free rotation around the C-C bond, ii) the same signals are discernible in the aromatic region of ^{1}H-nmr spectra of 1a and 1b, respectively; iii) for both homologues the low field regions of ^{13}C-nmr spectra are practically identical, containing two characteristic signals with similar intensity ratio derived from the unsaturated C-1 and C-4 atoms.

Nevertheless, the significant difference between the readinesses of hydroxyethyl- and propylaminophthalazinones to undergo exchange OH → Br can be rationalized with the different basicity of the OH group in the N^{3}-protonated molecules. According to our view, the -I effect of the powerful electron-withdrawing amidinium moiety on the OH group has to be weakened in a smaller degree through two than through three methylene groups (cf. Ref.4). Thus O-protonation, which is crucial for exchange OH → Br, must occur more easily in the longer than in the shorter chain. This electronic effect can be well documented by the proton chemical shifts of the CH_2 groups (in 48% DBr) showing much stronger deshielding in the hydroxyethylamino than in the hydroxypropylamino chain (Experimental b).

2) *Conversions of 2-(ω-hydroxyalkyl)-4-(ω'-hydroxyalkylamino)phthalazinones (5a-f) on treatment with boiling 48% HBr*

For these conversions the yields and the structure of products proved to be highly dependent on the lengths of the side chains and on the reaction time applied (Scheme 2). On the one hand, conversion of 4-(3-hydroxypropylamino) derivatives 5d-f can practically be completed within five minutes, pointing to fast exchange OH → Br in both chains followed by



5–10	a	b	c	d	e	f
n	2	3	4	2	3	4
m	2	2	2	3	3	3

SCHEME 2

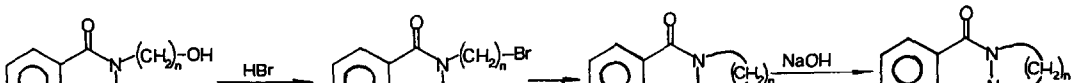
fast angular cyclization (5d-f → 6d-f → 7d-f). On the other hand, with this short reaction time, 4-(2-hydroxyethylamino) homologues 5a-c gave three types of products depending on the length of the 2-(ω-hydroxyalkyl) chain. We found that. i) the 8a bromoethyl- and the 8c bromobutylphthalazinones with unchanged chain in position 4 can be isolated with good yield, ii) contrary to the stable 8c bromobutyl derivative, during the working up of the reaction mixture, the 8a bromoethyl homologue undergoes an equilibrium cycloisomerization (8a ⇌ 9a) unless an excess of NaBr is added to the solution before its evaporation (cf. Ref.5); iii) the 8b bromopropyl derivative primarily formed from 5b cannot be isolated, as its further conversion to the dione 14a and bromoethylamine-hydrobromide takes place very rapidly. The latter product was identified *via* its benzoyl derivative (Experimental c/ii)

Table 1. M.p., anal and ir data of compounds 7a,b,d,e[a]

Compound	m.p.[b] (°C)	Anal. (%)[c] C	H	N	Br	νN⁺-H[d]	Ir (cm^{-1}) amide-I	νC=N
7a	256-9	38.4 38.5	3.5 3.5	11.2 11.0	42.6 42.6	3150-2600	1671	1612
7b	220-2	40.1 40.0	3.9 3.7	10.8 10.8	41.1 41.0	3150-2500	1668	1610
7d	232-4	40.1 40.3	3.9 4.0	10.8 11.0	41 1 40.9	3200-2700	1665	1616 1600
7e	157-60	41.7 41.8	4.3 4.4	10.4 10.6	39.6 39.6	3200-2650	1666	1620 1605

[a]Data for 7c,f see in Ref.2. [b]After recryst. from abs. EtOH. [c]Upper row. calculated, lower row. found. [d]Broad band.

A possible mechanism for this conversion shown in Scheme 2 involves the fast 8b → 11 cycloalkylation to N-3 atom followed by a Smiles-type rearrangement[6] *via* a spirocyclic intermediate (11 ⇌ 12 ⇌ 13) and finally, by the irreversible splitting of the CH_2-O bond in the 13 aminoethyl ether. (However, it has to be noted that original Smiles rearrangements occur in basic media[6].) This assumption for the mechanism gains support from the following experiments underlining the role of the 4-hydroxyethylamino chain. i) on an extended treatment (reaction time. 5 h) with 48% HBr, 4-amino-2-(ω-hydroxyalkyl)phthalazinones 15a,b exclusively resulted in the 17a,b tricyclic salts as end-products (Scheme 3); ii) conversions 17a,b → 14a,b took only place in basic solution On the other hand, these experiments also



SCHEME 3 — n=3 for a and 4 for b

exclude the formation of the 4a spirocyclic intermediate (Scheme 1) which then would undergo a conversion analogous to that of 12 (cf. Scheme 2) to yield phthalic hydrazide and bromoethylamine-hydrobromide.

The fast conversion of 15a into 17a can be completed even with five minutes of boiling. The open chain intermediate (16a) could not be isolated at all. In contrast, with the same reaction time, 15b gave the 16b bromobutyl homologue as the major product. As expected, with longer reaction times the ratio 16b . 17b shifted toward the tricyclic salt (Exp. c/viii). These findings are also in correlation with the different readinesses of 4-(2-hydroxyethylamino) analogues 8b and 8c to form linear tricycles. However, on an extended treatment with 48% HBr, instead of conversion to the homologue 14b dione, 8c underwent a slow exchange OH → Br followed by fast angular cyclization (8c → 6c → 7c, Scheme 2). Similarly to 8c, both 8a and 9a can be converted into 7a (Scheme 2).

Since, using 48% HBr as reagent, homologue 5b cannot be transformed into 7b at all, this tricyclic salt was prepared from the 10b tricyclic hydroxypropyl compound (Scheme 2) easily obtainable from 5b by a described method[2].

EXPERIMENTAL

M.p.s were measured on a Boetius hot stage. Ir spectra were obtained on a Zeiss IR-75 instrument in KBr pellet. ^{1}H- and ^{13}C-nmr spectra were registered on a Bruker AC-80 PFT spectrometer using TMS or DSS as reference.

a) 4-Amino-2-(ω-hydroxyalkyl)phthalazin-1(2H)-ones (15a,b)

Using the corresp. hydrazinoalcohol[7], 15a and 15b were prepared by the method described for 4-amino-2-(2-hydroxyethyl)phthalazin-1(2H)-one[8]. Yield: 62% for 15a and 50% for 15b.
15a. m.p. 164-5°C, anal. (calc/found %) C 60.3/60.5, H 6.0/6.1, N 19.2/19.2, ir(cm^{-1}) νNH_2, OH 3375 3330 3220, amide-I 1620, νC=N 1574.
15b: m.p. 135-7°C, anal. C 61.8/61.8, H 6.5/6.3, N 18.0/17.9; ir νNH_2, OH 3400 3325 3260, amide-I 1612, νC=N 1570.

b) Comparative structure determination of 4-(ω'-hydroxyalkylamino)phthalazinones 1a,b in DBr

0.25 mmol of the corresponding homologue was dissolved in 48% DBr (0.5 ml). The soln of 1a was refluxed for 5 min, then cooled and examined with ^{1}H- and ^{13}C-nmr, respectively. Spectra from the soln of 1b were taken without any refluxing. No signals related to spirocyclic isomer 4a were observed in either of the spectra taken from the soln of 1a.
1a: ^{1}H-nmr: NCH_2, OCH_2 4.26 and 4.13 (A_2B_2, J = 5.2 Hz, 2x2H), ArH 8.2-8.6 (m, 4H); ^{13}C-nmr C(1,4) 158.2 152.6, C(4a) 127.4, C(5) 132.6, C(6) 124.8, C(7) 135.7, C(8) 129.0, OCH_2 61.2, NCH_2 53.9.
1b ^{1}H-nmr. NCH_2, OCH_2 3.97 and 3.74 (2xt, J = 6.5 Hz, 2x2H), C-CH_2-C 2.30 (qi, J = 6.5 Hz, 2H), ArH 8.2-8.6 (m, 4H), ^{13}C-nmr: C(1,4) 157.9 151 3, C(4a) 127 7, C(5) 133.1, C(6) 125.1, C(7) 135.4, C(8) 128.7, OCH_2 60.3, NCH_2 51.5, C-CH_2-C 32.1.

c) Reactions effected by 48% HBr and some conversions of the products

Generalizations for sections c/i-iii, vi, viii: 0.01 M of the corresp. hydroxy compound (5a-f, 8a,c, 9a, 15a,b) was dissolved in 48% HBr (10 ml). Reactions were carried out by refluxing the solns obtained The reagent was removed by distillation in vacuo Products were dried over P_2O_5 in all cases.

i) *Hydrobromides of 5-(ω-bromoalkyl)-2,3-dihydroimidazo[2,1-a]phthalazin-6(5H)-ones (7a,e) and 6-(ω-bromoalkyl)-3,4-dihydro-2H-pyrimido[2,1-a]phthalazin-7(6H)-ones (7d-f)*

Reaction times: 90 min for 5a → 7a, 8a → 7a, 9a → 7a, 5c → 7c, 8c → 7c; 5 min for 5d-f → 7d-f.

Evaporation of the reaction mixture was carried out in presence of NaBr (3.1 g, 0.03 M) The residue was extracted with 80 ml of hot, freshly absolutized EtOH. After filtration of NaBr, the ethanolic soln was concentrated to about a quarter of its volume. To the suspensio obtained Et_2O (4 ml) was slowly added, then the crystalline product was filtered off and dried. Yields: 76-91%. M.p., anal., ir and nmr for 7a-f are found in Tables 1 and 2.

ii) *Conversion of 5b into 2,3-dihydro-1H-pyrazolo[1,2-b]phthalazin-5,10(4H,11H)-dione (14a) and 2-bromoethylamine*

Reaction of 5b was interrupted after 5 min of boiling. The residue obtained by removing of the reagent was triturated with water (5 ml), then the crystalline product (14a) was filtered off and dried: 1.87 g (92%). M.p. (crude): 204-5°C. After recryst. from $CHCl_3$-petroleum ether, the product proved to be identical with the sample obtained by hydrolysis of 17a, as shown by m.p., anal., ir and ^{1}H-nmr (section c/ix).

The aqueous mother liqueur was diluted with water (5 ml), then intensively shaken with benzene containing benzoylchloride (1.50 g/4 ml of solvent).

While shaking, 1N NaOH (11 ml) was poured in small portions into the mixture, keeping it temperature under 30°C. After about 20 min of shaking the precipitated N-(2-bromoethyl)-benzamide was filtered off, washed with water and dried 1.76 g (77%). M.p. (from benzene). m.p 104-5°C (105-6°C in Ref.9a); anal. C 47.4/47.3, H 4.4/4.4, N 6.1/6.0, Br 35.0/35.1, ir νN-H 3200-2700, amide-I 1648, amide-II 1562. (The method for acylation described in this section has been reported in Ref.9b).

iii) *Conversion of 5a into 2-(2-bromoethyl)-4-(2-hydroxyethylamino)phthalazin-1(2H)-one (8a) and 2,3-dihydro-6-(2-hydroxyethylamino)-oxazolo[2,3-a]phthalazin-4-ium-bromide (9a)*

Reaction of 5a was interrupted after 5 min of boiling. To the residue obtained by evaporation of the reaction mixture water (8 ml) was added, then the insoluble part (8a and 5a) was filtered off, washed with water and dried. The mixture of 8a and 5a was extracted with $CHCl_3$ (3 ml) at RT. 5a (insoluble in $CHCl_3$) was filtered off. 0.25 g. To the organic filtrat petroleumether (2 ml) was slowly added to obtain 8a: 0.22 g. Without addition of petroleum-ether, on standing at RT for one day, tricyclic salt 9a (0.28 g) was precipitated from the soln. By evaporation of the fresh chloroformic soln, 9a was obtained quantitatively (0.30 g) as the only product due to the cyclization 8a → 9a.

The aqueous filtrate (see above) showing acidic character was neutralized with cc NH_4OH then the precipitated 5a was filtered off and dried (1.64 g). The aqueous mother liqueour was evaporated to obtain the second crop of 5a (0.34 g).

The approximate ratio of the products (mol %) 5a 8a : 9a ≈ 7 10 . 83. (The weight of 9a was calc from the amount of 5a obtained from the aqueous phase.)

When the reaction mixture was evaporated in presence of NaBr (3.1 g, 0.03 M), 8a was the only product (3.12 g, 100%) isolated by treating the residue with water. On standing for four months at RT, the product soluble in $CHCl_3$ became soluble in water and insoluble in $CHCl_3$, due to the cycloisomerisation 8a → 9a.On heating this cyclization had to take place without melt, since 157-160°C was measured as m.p. for both 8a and 9a.Cyclization 8a → 9a was also reflected in ir spectra: 8a. νNH,OH 3335, amide-I 1629, νC=N, νN-H 1570 1543; 9a.νNH,OH 3345 3225, further characteristic bands 1609 1570 1550 and 1530.
Anal for 8a(9a)C 46.2/46.3(46.2), H 4.5/4 4(4.4), N 13 5/13.7(13 4), Br 25.6/25.6(25.7).
(Prepn. of the perchlorate analogue of 9a has been reported in Ref.2.).

iv) *Conversion 5a → 8a in 48% DBr*

62 mg (0.25 mmol) of 5a was refluxed in azeotropic DBr for 5 min. After cooling the mixture the ^{1}H-nmr spectrum was taken directly. The open chain spectrum indicated the formation of 8a CO-N-CH_2 4.60 (t, J = 6.0 Hz, 2H), Br-CH_2 3.82 (t, 6.0 Hz, 2H), $(CH_2)_2$ in the hydroxy ethylamino chain 4.27 and 4.13 (A_2B_2, 5.2 Hz, 2x2H), ArH 8.2-8.6 (m, 4H).

v) *Determination of the equilibrium 8a ⇌ 9a in DMSO-d_6 at RT*

8a (78 mg, 0.25 mmol) was dissolved in DMSO-d_6 (1 ml), and the soln was investigated by ^{1}H-nmr. The characteristic signals related to the equilibrium 8a ⇌ 9a (65 . 35) were assigned 4 44 (t, 6.5 Hz) for CO-N-CH_2 in 8a, 5.29 and 4.92 (A_2B_2, 9.5 Hz) for the oxazoline ring in 9a. The same signals characteristic of the equilibrium were also registered when 9a was dis-

solved in DMSO-d_6. By adding NaBr (51 mg, 0.5 mmol) to the soln, the equilibrium was shifted to the left.

vi) *Conversion of 5c into 2-(4-bromobutyl)-4-(2-hydroxyethylamino)phthalazin-1(2H)-one (8c)*

Reaction of 5c was interrupted after 5 min of boiling. The residue obtained by removing of the reagent was triturated with water (10 ml), then the crystalline product was filtered off and recryst from EtOH-H_2O to obtain 8c (2.65 g; 78%). As shown by m.p., anal., and ir, the product proved to be identical with that obtained by alkylation of 1a with 1,4-dibromobutane as described in Ref. 10

Table 2 - ^{1}H- and ^{13}C-nmr data for compounds 7a-f in DMSO-d_6 solution (δ, ppm) at 80 (^{1}H) and 20 MHz (^{13}C) [a]

com-pound	2-H[b] 4-H[b]	3-H[c]	12-H[d] 15-H[d]	C(7) C(11b)	C(7a)[e] C(11a)[e]	C(9)[f] C(10)[f]	C(8) C(11)	C(2) C(4)	C(12) C(15)	C(3)
7a	4 24 4 86	-	4 56 3 87	160 1 155 2	129 4 127 0	136 8 136 2	129 2 125 0	45 3 53 0	47 0 29 8	-
7b	4 25 4 84	-	4 43 3 76	158 7 156 0	130 9 126 0	137 0 136 8	129 5 124 7	45 6 52 9	45 4 30 0	-
7c	4 24[g] 4 84	-	4 27[g] 3 70	159 4 154 9	128 1 125 6	136 1 135 7	129 6 124 1	45 6 52 2	45 9 31 2	-
7d	3 63 4 28	2 21	4 61 3 89	159 3 150 0	129 2 127 0	137 1 136 1	129 5 124 3	39 3 51 0	47 3 30 9	20 0
7e	3 65 4 25	2 27	4.42 3 80	157 7 149 7	130.3 126 1	137 2 136 5	129 5 124 0	39 8 50 5	45 8 30 3	20 3
7f	3 62 4 25[g]	2 24	4 28[g] 3 72	158 3 148 6	131 4 127 2	136 3 135 4	129 2 124 1	39 7 49 9	46 0 29.9	20 4

[a] The numbering of atoms is given in Scheme 2 on Formula 7. Further signals, ArH(8-11) 8 2-8 6 (m, 4H) for 7a-f, N-H 10 2-10 5 (s, 1H) for 7a-f, 13-H 2 01 (~q$_1$, 2H) for 7b and 2 05 (~q$_1$, 2H) for 7e, 13,14-H 1 8-2 0 (m, 4H) for 7c,f, C(13) 30.1 for 7b and 29.9 for 7e, C(13,14) 28 4, 33 9 for 7c and 28.2, 35 0 for 7f [b] t(2H), J=10 2±0 3 Hz for 7a-c and 6.0±0 2 Hz for 7d-f [c] ~q$_1$(2H) [d] t(2H), J=6 3±0 2 Hz [e] Assignments of the C(7a, 11a) carbon lines were proved by DEPT measurements [f] Assignments may also be reversed for the signed line pairs [g] Overlapping signals assigned by DR measurements

vii) *Conversion of 10b into hydrobromide of 5-(3-bromopropyl)-2,3-dihydroimidazo[2,1-a]phthalazin-6(5H)-one (7b)*

While cooling with ice-water, the tricyclic perchlorate (3.6 g, 0.01 M) was suspended in 1N KOH (10 ml), then $KClO_4$ was removed by filtration and washed with EtOH (5 ml). The combined yellow filtrate was evaporated, the residue was dissolved in 48% HBr and refluxed for 5 min. Isolation of 7b was carried out as described in section c/i: 2.74 g (70%). M.p., anal., ir, ^{1}H- and ^{13}C-nmr spectra are shown in Tables 1 and 2.

viii) *5-Amino-2,3-dihydro-1H-pyrazolo[1,2-b]phthalazin-10(11H)-one-4-ium-bromide (17a), 6-amino-1,2,3,4-tetrahydropyridazino[1,2-b]phthalazin-11(12H)-one-5-ium-bromide (17b), and 4-amino-2-(4-bromobutyl)phthalazin-1(2H)-one (16b). (15 → 16 → 17 type of conversions)*

Reaction times: 5 min for 15a → 17a; 5, 20, 60, 90 and 300 min, resp. for 15b → 16b + 17b
The residue was triturated with cold EtOH (8 ml), the insoluble salt (17a,b) was filtered off, washed with EtOH (3 ml) and dried: 2.62 g (93%) for 17a.

After reaction of 15b to the ethanolic filtrate, water (10-15 ml) was added in small portions to obtain 16b. Yields (%) for 16b/17b with different reaction times: 71/27 (5 min), 54/42 (20 min); 40/55 (60 min), 34/61 (90 min), 0/91 (300 min). The total yields for 16b were obtained from the weight of its cyclic isomer 17b isolated almost quantitatively after evaporation of the ethanolic soln. (On heating this soln cyclization 16b → 17b takes place rapidly)

16b (recryst. from CH_2Cl_2-petroleumether at RT). m.p. 88-90°C followed by solidification (16b → 17b) and melting again at 285-7°C, anal. C 48.7/48.5, H 4.8/4.7, N 14.2/14.2, Br 27.0/26.9; ir νNH_2 3430 3295 3185, amide-I 1620, νC=N, δNH_2 1570, νC-Br 695 cm^{-1}.

17a (recryst from EtOH-H_2O): m.p. 360°C, anal. C 46.8/46.7, H 4.3/4.5, N 14.9/14.9, Br 28.3/28 3, ir νNH_2^+ 3330 3270 3150-2600, amide-I 1640, νC=N, δNH_2 1590 (broad).

17b (recryst. from EtOH-H_2O) m.p. 285-7°C; anal. C 48.7/48.7, H 4.8/5.0, N 14.2/14.0, Br 27.0/27.1, ir νNH_2 3230 3175 3200-2600, amide-I 1651, νC=N 1555, δNH_2 1595.

ix) *Conversions* 17a,b → 14a,b

(Prepns of 14a,b have been carried out by different methods, too: see in Ref. 11.)

While heating moderately 0.01 M of the corresp. salt was dissolved in 0.5 N NaOH (20 ml) The soln was kept for 2 h at RT. The crystals were collected, washed with water and dried 1.64 g (14a) m.p. 206-7°C, 1.20 g (14b); m.p. 145-6°C (145.5-6.5°C in Ref. 11b).

The aqueous mother liqueur was evaporated, then the residue was triturated with water (4 ml) to obtain a second crop of the product. Total yield: 94% for 14a and 88% for 14b. Bot 14a and 14b were recryst. from CH_2Cl_2-petroleumether.

14a m.p. 205-6°C; anal. C 65.3/65.4, H 5.0/4.9, N 13.9/14 0, ir amide-I 1625 1599 cm^{-1}, ^{1}H-nmr in $CDCl_3$ ArH, 8.26 and 7.75 (dd's, 6.5 Hz, 3.5 Hz, 2x2H), N-CH_2 4.30 (t, 7.0 Hz, 4H), -C-CH_2-C- 2.43 (qi, 7.0 Hz, 2H).

14b. m.p. 149-50°C, anal. C 66.7/66.9, H 5.6/5.7, N 13.0/13.0, ir amide-I 1666 1636 cm^{-1}, ^{1}H-nmr in $CDCl_3$ ArH 8.47 and 7.94 (dd's, 6.0 Hz, 3.5 Hz, 2x2H), N-CH_2 4.20 (t, 6.0 Hz, 4H) -C-$(CH_2)_2$-C- 1.8-2.2 (m, 4H).

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