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CYCLIC HYDRAZIDES. 2.* SYNTHESIS OF SUBSTITUTED 4-HYDROXY-1-OXO-1,2-DIHYDROPYRIDAZINO[4,5-*b*]QUINOLINE 5-OXIDES

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Reaction of N-oxides of dimethyl quinoline-2,3-dicarboxylates with hydrazine and subsequent oxidation with peracetic acid has given quinoline-2,3-dicarboxylic acid hydrazide 5-oxides, from which water soluble-quaternary ammonium salts can be prepared.

In continuation of our study of the synthesis and biological activity of cyclic hydrazides of heterocyclic dicarboxylic acids [1] we now report the preparation of pyridazino[4,5-*b*]quinoline 5-oxides III. This type of compound has not been reported in the literature, hence, we have studied two possible routes of synthesis: 1) reaction of the N-oxides of diesters I with hydrazine hydrate, and 2) direct oxidation of pyridazino[4,5-*b*]quinolines II.

The method we developed for preparation of II [1] had to be significantly changed since reaction of even unsubstituted diester Ia with hydrazine hydrate gave the 5-oxide IIIa along with 3-4% of the reduced form IIa and, when using halo substituted diesters I, the content of II increased sharply. There is one report in the literature [2] of the reduction of a pyridine N-oxide by hydrazine but under more forcing conditions and using a copper catalyst [2]. There has also been described the reduction of the C=N bond when carrying out the reaction with hydrazine hydrate in refluxing ethanol, which is explained by the proposed formation of a diimide in an oxygen containing atmosphere [3]. Hence, in the subsequent reaction of diesters I with hydrazine hydrate, we used an argon atmosphere (in the case of Ia, this reduces the content of IIa to 0.5-1%). Experiments to vary the reaction time (3-8 h), the amount of hydrazine hydrate (2-10 equivalents), and the use of different solvents (ethanol, methanol, isopropanol, and DMF) have shown the optimum conditions for this reaction to be a ratio of I to hydrazine hydrate of 1:3 with refluxing in ethanol solvent under argon for 3 h. In this case, the content of the reduced form II in the product depends on the nature of the substituent in the starting diester I: for R^2 = Cl or R^3 = F, Cl, Br it is 9.5-16%, for R^2 and R^3 = F, Cl, Br 30-55%, for R^4 = Cl 45-70%, and for R^1 and R^4 = F, Cl, Br 85-95%. With a 1:3 ratio of Ie to hydrazine hydrate, a mixture of the cyclic hydrazide IIIe and N-aminoimide IV is formed (1:1 ratio according to the PMR spectrum in which there are a double set of aromatic proton signals and broad signals for NH_2 at δ 5.10 ppm, NH at 12.00 ppm, and OH at 14.70 ppm). Formation of the analogous N-amino derivative (NH_2 at 5.15 ppm) by treatment of the diester of 4-methylquinoline-2,3-dicarboxylic acid with hydrazine hydrate has been reported in the literature [4]. Heating the obtained mixture of IIIe and IV with 15 equivalents of hydrazine hydrate and subsequent treatment with acetic acid gives the N-oxide IIIe with about 2% of the reduced form IIe. With a starting ratio of Ie to hydrazine hydrate of 1:20, the derivative IV is not formed and the obtained product IIIe contains less than 1% of the reduced form IIe. This anomalous result evidently infers that reduction by hydrazine is easier only with the presence of electron acceptor substituents in the N-oxide I. The proposal could not be confirmed since the two other diesters with electron donor substituents Il (R^1 = R^4 = H; R^2 = R^3 = OMe) and Im (R^1 = R^4 = H; R^2, R^3 = O−CH_2−O) have very low solubility and are virtually unreactive towards hydrazine hydrate when refluxed in ethanol for 3 h.

*For Communication 1, see [1].

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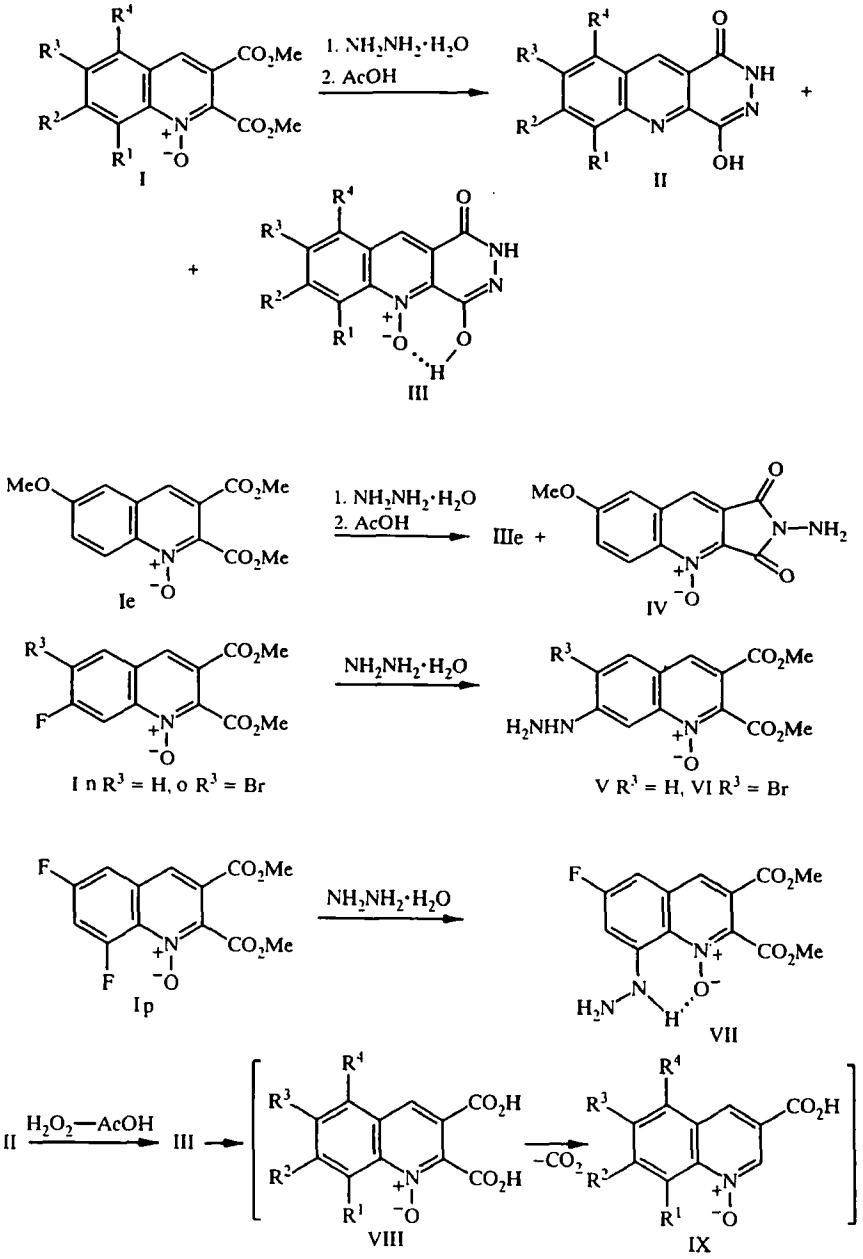
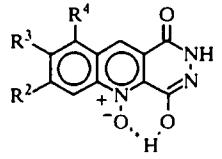


It is known that nucleophilic substitution of halogens in N-oxides occurs more readily than in the corresponding heterocycles [5]. We observed a similar reaction for some fluoro containing N-oxides I. Hence, treatment of diesters In (R^1 = R^3 = R^4 = H; R^2 = F), Io (R^1 = R^4 = H; R^2 = F; R^3 = Br) or Ip (R^2 = R^4 = H; R^1 = R^3 = F) with hydrazine hydrate leads to rapid substitution of the fluorine by the hydrazino group, moreover, the hydrazide is not formed since V, VI, or VII precipitate out and do not react further with hydrazine hydrate. In the case of the Br, F derivative substitution of the same fluorine atom is unambiguously identified by the nature of the 5-H and 8-H PMR signals in the spectrum of VI since they occur as two singlets with no H,F spin coupling. For the F,F derivative, the hydrazino group substitutes the fluorine at C_8 since the PMR spectrum of the product VII shows an $N\underline{H}NH_2$ signal which is strongly shifted to low field due to formation of an intramolecular hydrogen bond with the N-oxide oxygen (δ 10.28 ppm compared with 8.49 and 8.01 ppm for V and VI). In addition, the fixed trans configuration of the N–H and C–F bonds causes a five σ-bond coupling between the H and F atoms (J = 2.5 Hz).

As expected, derivatives of quinoline II proved inert to the action of most oxidizing agents conventionally used for the synthesis of N-oxides of π-deficient heterocycles, e.g., m-chloroperbenzoic acid [6], oxone [7], and the system HF–DMF–methanol [8]. There is a published report of the oxidation of the cyclic hydrazide of pyridine-2,3-dicarboxylic acid by peracetic acid at 95°C and it was shown that hydrolysis and decarboxylation occur under these conditions with an N-

TABLE 1. Parameters for 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline 5-Oxides IIIa-k



Compound	R^2	R^3	R^4	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum (DMSO-D_6), δ, ppm, J, Hz		Yield, %*
					C	H	N		aromatic protons	NH, OH (exchange with D_2O)	
1	2	3	4	5	6	7	8	9	10	11	12
IIIa	H	H	H	$C_{11}H_7N_3O_3$	57,56 / 57,65	2,98 / 3,08	18,22 / 18,33	>300	7,88...8,28 (2H, m); 8,46...8,79 (2H, m); 9,07 (1H, s)	12,02 (1H, br. s); 14,83 (1H, br. s)	65,0
IIIb	H	Cl	H	$C_{11}H_6ClN_3O_3$	49,34 / 50,11	2,29 / 2,29	15,40 / 15,94	>300	8,12 (1H, d. d J_1 = 9,0, J_2 = 2,5); 8,60...8,73 (2H, m); 8,96 (1H, s)	12,10 (1H, br. s); 14,55 (1H, br. s)	88,0
IIIc	H	Br	H	$C_{11}H_6BrN_3O_3$	42,57 / 42,88	1,91 / 1,96	13,40 / 13,64	>300	8,27 (1H, d. d J_1 = 9,5, J_2 = 2,0); 8,60 (1H, d, J = 9,0); 8,82 (1H, d, J = 2,0); 9,00 (1H, s)	12,00 (1H, br. s); 14,40 (1H, br. s)	78,0
IIId	H	F	H	$C_{11}H_6FN_3O_3$	53,43 / 53,45	2,35 / 2,45	16,90 / 17,00	297...298	8,07 (1H, d.d.d, J_1 = 9,5, J_2 = 8,5, J_3 = 2,5); 8,36 (1H, d. d J_1 = 9,5, J_2 = 2,5); 8,75 (1H, d. d J_1 = 9,5, J_2 = 5,0); 9,02 (1H, s)	12,00 (1H, br. s); 14,58 (1H, br. s)	37,0

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
IIIe*2	H	OMe	H	$C_{12}H_9N_3O_4$	55,21 55,60	3,48 3,50	16,08 16,21	>300	7,79 (1H,d. d, J_1 = 9,5, J_2 = 2,5); 7,93 (1H, d, J = 2,5); 8,59 (1H, d, J = 9,5); 8,89 (1H, s)	11,95 (1H, br. s); 14,70 (1H, br. s)	68,0
IIIf	Cl	Cl	H	$C_{11}H_5Cl_2N_3O_3$	44,17 44,32	1,75 1,69	14,14 14,10	>300	8,83 (1H, s); 8,90 (1H, s); 9,06 (1H, s)	12,06 (1H, br. s); 14,32 (1H, br. s)	16,0
IIIg	Cl	Br	H	$C_{11}H_5BrClN_3O_3$	37,98 38,57	1,43 1,47	11,97 12,27	>300	8,80 (1H, s); 9,00 (1H, s); 9,01 (1H, s)	12,06 (1H, br. s); 14,28 (1H, br. s)	15,0
IIIh	Br	Cl	H	$C_{11}H_5BrClN_3O_3$	38,36 38,57	1,41 1,47	12,08 12,27	>300	8,90 (1H, s); 9,01 (1H, s); 9,04 (1H, s)	12,13 (1H, br. s); 14,32 (1H, br. s)	17,0
IIIi	Cl	H	H	$C_{11}H_6ClN_3O_3$	49,76 50,11	2,26 2,29	15,85 15,94	>300	8,07 (1H,d. d, J_1 = 9,0, J_2 = 2,5); 8,59 (1H, d, J = 9,0); 8,69 (1H,d, J = 2,5); 9,11 (1H,s)	12,05 (1H, br. s); 14,60 (1H, br. s)	31,5
IIIj	H	H	Cl	$C_{11}H_6ClN_3O_3$	49,89 50,11	2,25 2,29	15,79 15,94	>300	8,00...8,31 (2H,m); 8,68 (1H,d. d, J_1 = 9,0, J_2 = 2,0); 8,93 (1H, s)	12,16 (1H, br. s); 14,64 (1H, br. s)	33,5
IIIk	H	Cl	Cl	$C_{11}H_5Cl_2N_3O_3$	43,90 44,32	1,71 1,69	13,90 14,10	>300	8,30 (1H, d, J = 9,5); 8,68 (1H, d, J = 9,5); 8,88 (1H, s)	12,20 (1H, br. s); 14,12 (1H, br. s)	20,0

*After oxidation and recrystallization from DMF.

*2For OCH_3 δ 3.83 (3H, s).

TABLE 2. Parameters for 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline salts XI-XVIII

Compound	R^2	R^3	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum (CD_3OD), δ, ppm, J, Hz		Yield, %
				C	H	N		aliphatic protons	aromatic protons	
1	2	3	4	5	6	7	8	9	10	11
XIa	H	H	$C_{16}H_{20}N_4O_3 \cdot H_2O \cdot 2CH_3OH$	54,23 / 54,26	7,39 / 7,59	14,15 / 14,06	102...110 (decomp.)	3,21 (9H, br. s); 3,38...3,64 (2H, m); 3,89...4,13 (2H, m)	7,64...8,02 (2H, m); 8,09...8,57 (2H, m); 9,17 (1H, s)	81,5
XIb	H	Cl	$C_{16}H_{19}ClN_4O_3 \cdot 0,25H_2O$	54,10 / 54,08	5,55 / 5,53	15,61 / 15,76	189...191	3,25 (9H, br. s); 3,37...3,67 (2H, m); 3,87...4,17 (2H, m)	7,89 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,23 (1H, d, J = 2,5); 8,34 (1H, d, J = 9,0); 9,13 (1H, s)	84,0
XIc	H	Br	$C_{16}H_{19}BrN_4O_3 \cdot 2,5H_2O$	44,07 / 43,65	5,14 / 5,49	12,73 / 12,72	234...236	3,22 (9H, br. s); 3,38...3,67 (2H, m); 3,88...4,08 (2H, m)	7,99 (1H, d. d, J_1 = 9,0, J_2 = 2,0); 8,26 (1H, d, J = 9,0); 8,41 (1H, d, J = 2,0); 9,09 (1H, s)	61,0
XId	H	F	$C_{16}H_{19}FN_4O_3 \cdot 2H_2O$	52,08 / 51,89	6,23 / 6,26	15,19 / 15,13	229...230	3,20 (9H, br. s); 3,40...3,58 (2H, m); 3,88...4,08 (2H, m)	7,64...7,91 (2H, m); 8,39 (1H, d. d, J_1 = 9,0, J_2 = 5,0); 9,12 (1H, s)	95,0
XIe	H	OMe	$C_{17}H_{22}N_4O_4 \cdot 3H_2O$	51,18 / 50,99	6,89 / 7,05	14,01 / 13,99	202...203	3,20 (9H, br. s); 3,39...3,59 (2H, m); 3,89...4,11 (5H*, m)	7,45...7,67 (2H, m); 8,22 (1H, d, J = 9,5); 9,01 (1H, s)	77,5
XIf	Cl	Cl	$C_{16}H_{18}Cl_2N_4O_3 \cdot H_2O$	47,24 / 47,65	5,00 / 4,99	13,60 / 13,89	205...208	3,22 (9H, br. s); 3,40...3,62 (2H, m); 3,89...4,15 (2H, m)	8,46 (1H, s); 8,55 (1H, s); 9,14 (1H, s)	83,0
XIg	Cl	Br	$C_{16}H_{18}BrClN_4O_3 \cdot H_2O$	42,78 / 42,92	4,60 / 4,50	12,44 / 12,51	207...209	3,22 (9H, br. s); 3,34...3,66 (2H, m); 3,84...4,16 (2H, m)	8,53 (1H, s); 8,64 (1H, s); 9,13 (1H, s)	90,5

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
XIh	Br	Cl	$C_{16}H_{18}BrClN_4O_3 \cdot H_2O$	42,66 / 42,92	4,57 / 4,50	12,37 / 12,51	201...203	3,22 (9H, br. s); 3,34...3,66 (2H, m); 3,87...4,13 (2H, m)	8,43 (1H, s); 8,73 (1H, s); 9,13 (1H, s)	92,0
XIi	Cl	H	$C_{16}H_{19}ClN_4O_3 \cdot 0,5H_2O$	53,88 / 53,41	5,59 / 5,60	15,57 / 15,57	184...185	3,22 (9H, br. s); 3,35...3,66 (2H, m); 3,87...4,13 (2H, m)	7,71 (1H, d. d, J_1 = 9,0, J_2 = 2,0); 8,20 (1H, d, J = 9,0); 8,38 (1H, d, J = 2,0); 9,19 (1H, s)	97,0
XIj	OMe	OMe	$C_{18}H_{24}N_4O_5 \cdot 2,5H_2O$	51,59 / 51,30	6,88 / 6,94	13,16 / 13,29	195...197	3,20 (9H, br. s); 3,38...3,60 (2H, m); 3,92...4,14 (8H*, m)	7,47 (1H, s); 7,68 (1H, s); 8,92 (1H, s)	89,0
XIm	O–CH$_2$–O		$C_{17}H_{20}N_4O_5 \cdot 2,5H_2O$	50,61 / 50,37	6,11 / 6,22	13,50 / 13,82	212...214	3,20 (9H, br. s); 3,36...3,60 (2H, m); 3,87...4,13 (2H, m); 6,20 (2H, s)	7,38 (1H, s); 7,54 (1H, s); 8,85 (1H, s)	89,0
XIn	F	H	$C_{16}H_{19}FN_4O_3 \cdot 2H_2O$	52,22 / 51,89	6,01 / 6,26	15,09 / 15,13	215...216	3,18 (9H, br. s); 3,33...3,55 (2H, m); 3,86...4,14 (2H, m)	7,59 (1H, d.d.d , J_1 = 9,5, J_2 = 8,5, J_3 = 2,5); 7,99 (1H, d. d J_1 = 10,5, J_2 = 2,5); 8,27 (1H, d. d, J_1 = 9,5, J_2 = 6,5); 9,22 (1H, s)	57,5
XII	H	Cl	$C_{15}H_{17}ClN_4O_2 \cdot H_2O$	53,58 / 53,17	5,55 / 5,65	16,64 / 16,33	194...195	3,21 (12H, br. s)	7,89 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,24 (1H, d, J = 2,5); 8,34 (1H, d, J = 9,0); 9,12 (1H, s)	79,0
XIII	H	Cl	$C_{19}H_{25}ClN_4O_2 \cdot 2,5H_2O$	54,45 / 54,08	7,48 / 7,16	12,88 / 13,27	195...196	1,16...1,38 (12H, m); 3,14...3,40 (8H, m)	7,89 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,24 (1H, d, J = 2,5); 8,34 (1H, d, J = 9,0); 9,12 (1H, s)	83,5
XIV	H	Cl	$C_{21}H_{32}ClN_5O_4 \cdot H_2O$	52,81 / 53,44	6,99 / 7,26	14,61 / 14,84	182...185	3,36 (18H, br. s); 3,50...3,76 (4H, m); 3,99...4,27 (4H, m)	8,04 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,39 (1H, d, J = 2,5), 8,47 (1H, d, J = 9,0); 9,26 (1H, s)	94,0
XVa	H	H	$C_{16}H_{20}N_4O_4 \cdot H_2O$	54,76 / 54,85	6,32 / 6,33	15,86 / 15,99	179...180	3,20 (9H, br. s); 3,40...3,64 (2H, m); 3,88...4,14 (2H, m)	7,69...8,00 (2H, m); 8,18 (1H, br. d, J = 8,0); 8,59 (1H, s); 8,76 (1H, br. d, J = 8,5)	91,0

TABLE 2 (continued)

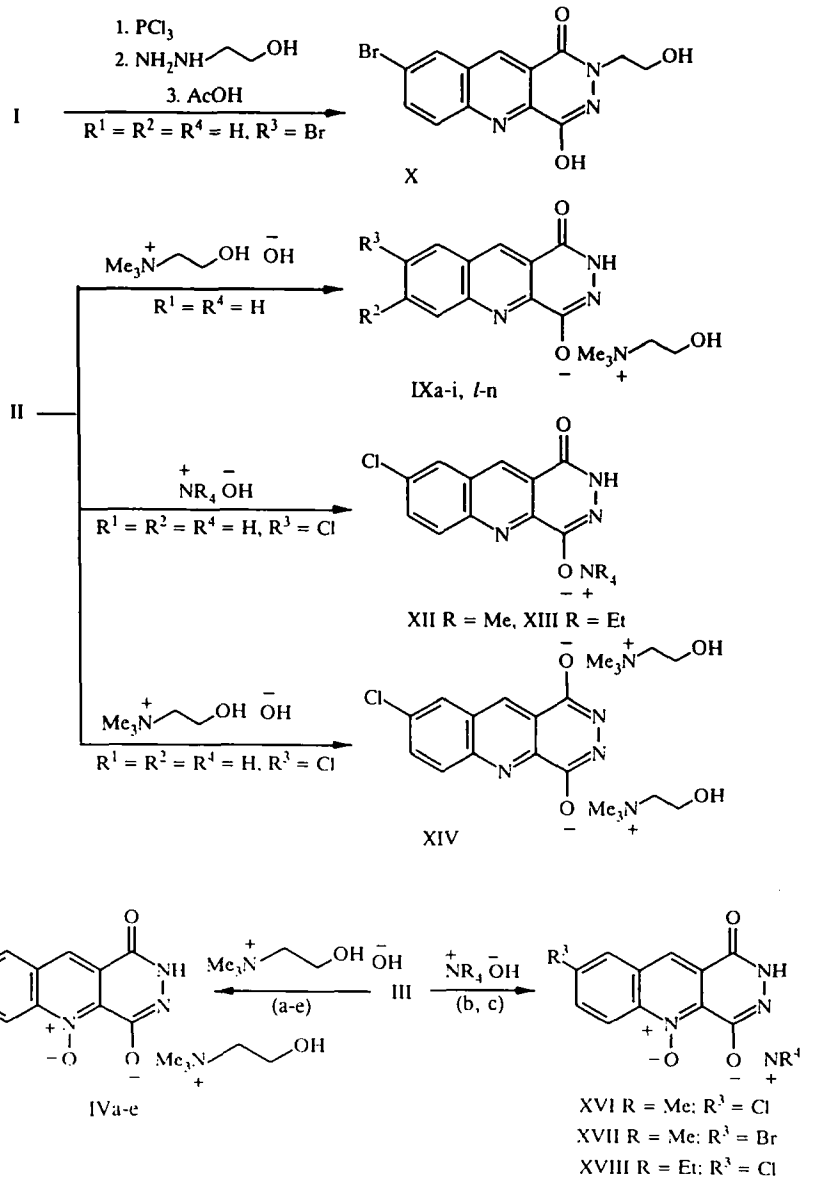
1	2	3	4	5	6	7	8	9	10	11
XVb	H	Cl	$C_{16}H_{19}ClN_4O_4 \cdot H_2O$	49,30 / 49,93	5,46 / 5,50	14,24 / 14,55	185...188	3,22 (9H, br. s); 3,41...3,59 (2H, m); 3,90...4,10 (2H, m)	7,88 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,27 (1H, d, J = 2,5); 8,52 (1H, s); 8,76 (1H, d, J = 9,0)	87,5
XVc	H	Br	$C_{16}H_{19}BrN_4O_4 \cdot H_2O$	44,85 / 44,75	4,93 / 4,92	12,96 / 13,04	191...193	3,20 (9H, br. s); 3,40...3,56 (2H, m); 3,90...4,08 (2H, m)	7,99 (1H, d. d, J_1 = 9,5, J_2 = 2,0); 8,41 (1H, d, J = 2,0); 8,53 (1H, s); 8,64 (1H, d, J = 9,5)	71,5
XVd	H	F	$C_{16}H_{19}FN_4O_4 \cdot H_2O$	51,84 / 52,17	5,67 / 5,75	15,05 / 15,20	203...204	3,22 (9H, br. s); 3,41...3,61 (2H, m); 3,92...4,12 (2H, m)	7,64...7,98 (2H, m); 8,62 (1H, s); 8,87 (1H, d. d, J_1 = 10,0, J_2 = 5,0)	37,0*2
XVe	H	OMe	$C_{17}H_{22}N_4O_5 \cdot H_2O$	53,23 / 53,68	6,37 / 6,36	14,60 / 14,73	193...194	3,20 (9H, br. s); 3,41...3,57 (2H, m); 3,92...4,12 (5H*, m)	7,44...7,60 (2H, m); 8,51 (1H, s); 8,69 (1H, d, J = 9,5)	77,5
XVI	H	Cl	$C_{15}H_{17}ClN_4O_3 \cdot 3H_2O$	46,05 / 46,10	5,81 / 5,93	14,17 / 14,34	228...229	3,20 (12H, br. s)	7,87 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,27 (1H, d, J = 2,5); 8,54 (1H, s); 8,77 (1H, d, J = 9,0)	73,0
XVII	H	Br	$C_{15}H_{17}BrN_4O_3 \cdot 3H_2O$	41,36 / 41,39	5,29 / 5,33	12,80 / 12,87	218...219	3,23 (12H, br. s)	7,81...8,00 (1H, m); 8,37 (1H, br. s); 8,45 (1H, s); 8,64 (1H, d, J = 9,5)	42,0*2
XVIII	H	Cl	$C_{19}H_{25}ClN_4O_3 \cdot 2H_2O$	53,49 / 53,21	6,79 / 6,82	13,08 / 13,06	145...147	1,16...1,38 (12H, m); 3,18...3,40 (8H, m)	7,85 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,24 (1H, d, J = 2,5); 8,51 (1H, s); 8,76 (1H, d, J = 9,0)	38,0*2

*Obscured by $-OCH_2-$ and OCH_3.

*2After recrystallization from 2-propanol.

oxide yield of only 33% [9]. Similar processes evidently occur with oxidation of quinolines II (although we were not able to separate the decomposition products VIII or IX). In place of 32% peracetic acid it was preferable to use a mixture of acetic acid and 30% hydrogen peroxide (1:1) at 70-75°C. However, for halo substituted compounds of II, the rate of hydrolysis is evidently close to the rate of oxidation so that the yield of N-oxide III is no greater than a few percent. The efficiency of the method could be improved through use of, as starting material, not the pure quinolines II but our previously prepared mixture of II and III with the content of reduced form II not more than 60%. In this way, the content of N-oxide in the product can be increased to 80-95% (although with large losses through hydrolysis) and the pure products obtained by multiple recrystallizations from DMF. Hence, we were able to synthesize a series of N-oxides IIIa-k, although with a more limited substituent variation than for pyridazino[4,5-b]quinolines II [1]. The predominant 4-hydroxy-1-oxo form for derivatives of II can be further stabilized in the 5-oxides III by an intramolecular hydrogen bond, and this is confirmed by PMR spectral data for IIIa-k, which show two broadened signals in the region δ 11.95-12.20 (NH) and 14.12-14.83 ppm (OH).

A major problem is the very low solubility of compounds II and III (at room temperature only in DMSO in very low concentration). Introduction of an additional hydrophilic substituent had virtually no effect on increasing the solubility of X when compared with the N-unsubstituted derivative IIc [1]. Attempts to prepare salts of II with primary, secondary, or tertiary amines showed that such salts decompose to starting components when their solutions are evaporated. The problem can be resolved by changing the amines to the quaternary ammonium hydroxides of the bases (a similar method has been reported for preparation of salts of the 10-hydroxy derivatives of the pyridazino[4,5-*b*]quinolines [10]). Hence, treatment of



II with one equivalent of choline hydroxide in methanol caused loss of a molecule of water and formation of the choline salt XI, and with tetramethylammonium or tetraethylammonium hydroxide there were formed salts XII, XIII. Two equivalents of choline hydroxide gave the dicholinium salt XIV, which confirms the presence of the 1,4-dihydroxy form for IIb in solution. Similarly, the 5-oxides of the pyridazino[4,5-*b*]quinolines III are converted to the cholinium salts XV or tetraalkylammonium salts XVI-XVIII. All the salts obtained XI-XVIII are very hygroscopic (see Table 2), are extremely stable, can be stored at room temperature without change for several months, and are readily soluble in water, methanol, and ethanol. Acidification of methanol solutions of salts XI-XVIII gives the starting pyridazino[4,5-*b*]quinolines II or N-oxides III in almost quantitative yields. We assign the 4-hydroxy-1-oxo form to the salts XI-XIII and XV-XVIII in agreement with the most stable tautomers for the base compounds II [1] and III, however, an exact proof of the structure of these salts needs further investigation.

The compounds IIIa-k, XVa-e, and XVI-XVIII synthesized by us show high activity as NMDA-receptor antagonists. For most tests, they outperform II and XI-XIV with identical substituents in the benzene ring. Detailed results of the biological experiments will be published later.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90/DS (90 MHz) spectrometer with TMS internal standard. Melting points were determined on a Boetius micro heating block and are not corrected. The purity of the compounds was determined by HPLC (Zorbax Pro 10 C_8 4.6 × 250 mm) using 40% acetonitrile — 60% 0.1 molar phosphate buffer solution of pH 2.5 as mobile phase and a UV-254 detector.

General Method for Synthesis of 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline 5-Oxides (IIIa-k).

A. Reaction of Dimethyl Quinoline-2,3-dicarboxylate N-Oxides I with Hydrazine Hydrate. Hydrazine hydrate (15 mmole, 100 mmole for diester Ie) was added to a solution (or suspension) of the diester Ia-k (5 mmole) [1] in refluxing ethanol under an argon atmosphere and the product was refluxed with stirring for 3 h. After cooling, the reaction mixture was held for a day at room temperature and the precipitate filtered and washed on the filter with ethanol and ether. By holding the filtrate for several weeks, it was possible to obtain more hydrazinium salt. The obtained salt was treated without purification with acetic acid (15 ml) and the mixture stirred for 3 h at 70-100°C and then cooled to room temperature. The precipitate was filtered and washed on the filter with ethanol and ether to give a mixture of II and III, which was analyzed by HPLC. The products with more than 15% of II were put through an additional oxidation.

B. Oxidation of a Mixture of II and III with Hydrogen Peroxide in Acetic Acid. The mixture of II and III prepared in method A was added to a mixture of acetic acid (10 ml) and hydrogen peroxide (30%, 10 ml). The product was stirred at 70-75°C for 1-6 h (depending on the II content), rapidly cooled to room temperature, and immediately filtered. The precipitate on the filter was washed with water, dried in air, and analyzed by HPLC (components additional to II and III were observed in the mixture). The products with a II content more than 15% underwent a repeat oxidation and products less than 15% were recrystallized from DMF (sometimes several times) to give the 5-oxides III with 97-99.5% purity. The physicochemical parameters for IIIa-k are given in Table 1.

General Method for Synthesis of Cholinium Salts of 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines XI and 5-Oxides XV. A 45% solution of choline hydroxide (10.5 mmole) in methanol was added with stirring to a suspension of II [1] or III (10 mmole) in methanol (50 ml). The mixture was stirred to solution of the precipitate and the solution was evaporated to dryness *in vacuo*. The residue was ground with acetonitrile and the residue filtered, washed on the filter with acetonitrile and absolute ether, and dried *in vacuo* (1-2 mm Hg) at 40-50°C. The cholinium salts XI and XV were obtained as intensely colored hygroscopic powders which corresponded in purity to the starting compounds II or III. If needed, they can be recrystallized from isopropanol. The physicochemical parameters for XIa-i, *l*-n and XVa-e are given in Table 2.

Tetraalkylammonium Salts of 4-Hydroxyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines XII, XIII and 5-Oxides XVI-XVIII. These were prepared similarly to the above method from 10 mmole of starting IIb [1] or IIIb,c and 10.5 mmole of a 25% solution of tetramethylammonium hydroxide in methanol or a 35% solution of tetraethylammonium hydroxide in water. The physicochemical parameters for XII, XIII, and XVI-XVIII are given in Table 2.

Dicholinium Salt of 1,4-Dihydroxy-8-chloropyridazino[4,5-*b*]quinoline XIV. Obtained similarly to the above method from 10 mmole of IIb [1] and 21 mmole of a 45% solution of choline hydroxide in methanol. The physicochemical parameters for XIV are given in Table 2.

REFERENCES

1. E. Rozhkov, I. Piskunova, M. Gol'd, and I. Kalvin'sh, Khim. Geterotsikl. Soedin., No. 1, 86 (1998).
2. S. Kubota and T. Akita, Yakugaku Zasshi, **78**, 248 (1958); Chem. Abstr., **52**, 11834 (1958).
3. D. B. Paul, Austral. J. Chem., **27**, 1331 (1974).
4. Y. Kurasawa and A. Takada, Chem. Pharm. Bull., **28**, 3457 (1980).
5. E. Ochiai, Aromatic Amine Oxides, Elsevier Publishing Co.; Amsterdam (1967), p. 340.
6. K. C. Nicolaou, P. Maligres, T. Suzuki, S. V. Wendeborn, W.-M. Dai, and R. K. Chadha, J. Am. Chem. Soc., **114**, 8890 (1992).
7. G. J. Robke and E. J. Behrman, J. Chem. Res. (S), No. 10, 412 (1993).
8. S. Y. Rhie and E. K. Ryu, Heterocycles, **41**, 323 (1995).
9. D. B. Paul, Austral. J. Chem., **37**, 87 (1984).
10. T. M. Bare and R. B. Sparks, European Patent 0.516.297; Chem. Abstr., **119**, 8821 (1993).