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CYCLIC HYDRAZIDES
1. SYNTHESIS OF 4-HYDROXY-1-OXO-1,2-DIHYDROPYRIDAZINO[4,5-b]QUINOLINES

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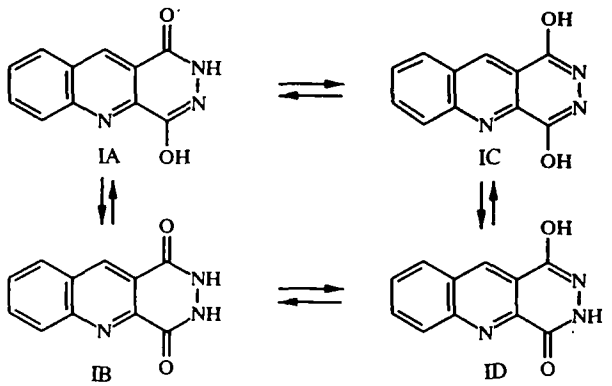
A series of dimethyl esters and cyclic hydrazides of quinoline-2,3-dicarboxylic acid has been synthesized with different substituents in the benzene ring.

This study is the first in a series of investigations of the synthesis of cyclic hydrazides of heterocyclic dicarboxylic acids and a study of their biological activity. As the first object of our study we chose quinoline-2,3-dicarboxylic acids, containing substituents in different positions of the benzene ring, with the aim of a detailed examination of a structure-activity relationship. It should be noted that this class of compound can exist as four tautomeric forms (A-D) which can form an equilibrium mixture in solvents. Comparison of the IR and PMR spectra of I and of model compounds has shown that form IA [1] predominates, hence, all of the analogous compounds synthesized by us will be assigned the 4-hydroxy-1-oxo form.



Only the unsubstituted compound I [1] and the 7-chloro derivative [2] have been described in the literature, however, in both cases the method of preparing the intermediate dimethyl quinoline-2,3-dicarboxylate esters was hardly adequate for the synthesis of substituted derivatives. Of the methods for the synthesis of similar diesters described in the literature, the most universal is the reaction of o-nitrobenzaldehydes with diethoxyphosphinylsuccinate and subsequent reduction of the N-oxide formed with phosphorus trichloride [3]. This is due, in the first place, to the availability and stability of substituted o-nitrobenzaldehydes and, in the second, to the feasibility of preparing the N-oxide which is difficult to obtain in the quinoline series. We have studied in detail this reaction, which has been reported only for the synthesis of diethyl esters and only with a few substituent variations [3]. The o-nitrobenzaldehydes not reported in the literature were synthesized by traditional methods (see Experimental section).

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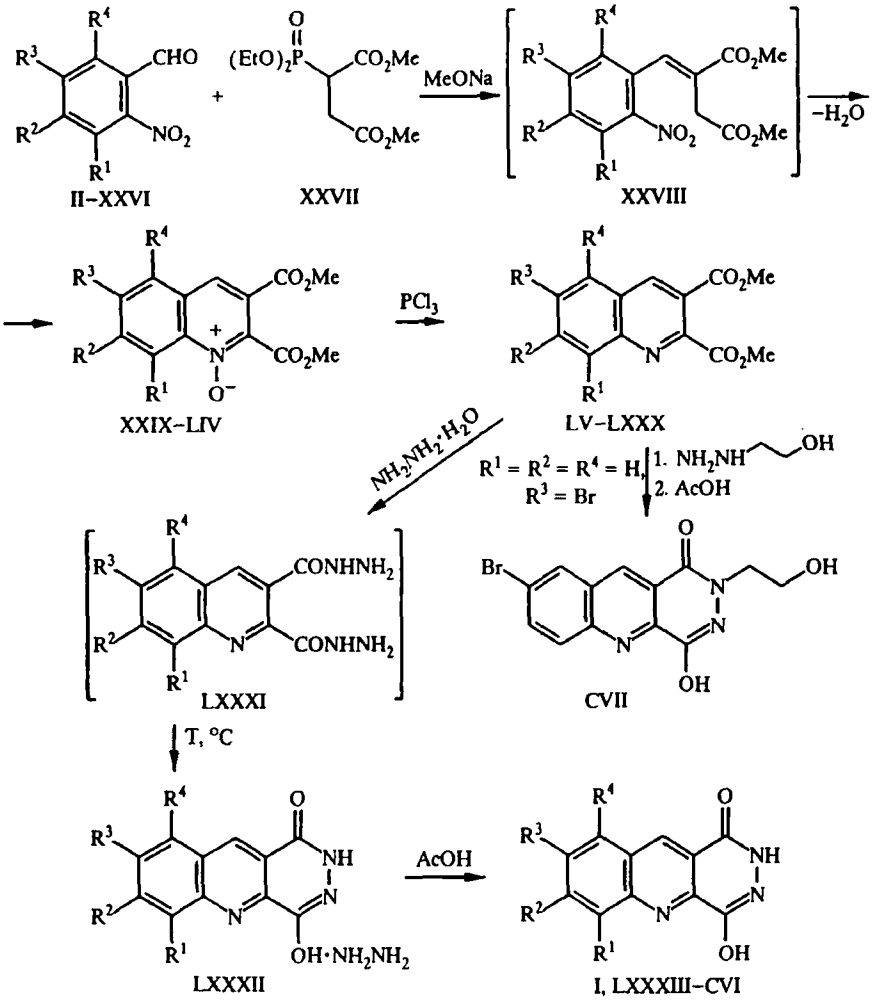
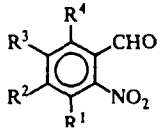


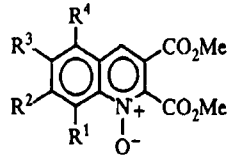
For interaction of the aldehydes II-XXVI with succinate XXVII (prepared by addition of diethylphosphite to dimethylmaleate using method [4]) there initially occurred a Horner reaction (which demands one equivalent of base). The intermediate XXVIII then cyclizes via addition of the carbanion to the nitro group with the elimination of a molecule of water. Repeating the literature method with use of 1.08 equivalents of sodium methylate [3] showed that formation of the N-oxide begins before complete addition of all of the succinate (particularly with large batches). This implies that formation of water at the second stage must partially hydrolyze the sodium methylate needed in an equimolar amount in the first stage and thus lowering the product yield. We have shown the optimum ratio to be 1.5-2 equivalents of sodium methylate to aldehyde. We have also been able to simplify significantly the method for work up of the reaction mixture. It was found that the formed N-oxides XXIX-LIV are poorly soluble in methanol at 0°C and can be separated by filtration from the reaction mixture almost without loss. The yields of the N-oxide depend on the number and nature of the substituents in the starting aldehydes II-XXVI. In the majority of cases the yields when $R^1 = R^4 = H$ are 50-75%, the exceptions being $R^2 = F$ or NO_2 (25-30%). For R^1 and (or) R^4 = Hal, the yields are lowered to 10-30%; while their decrease depends on the substituent volume (F, Cl, Br): with R^1 = F, Cl, Br and R^4 = Br they are 32, 11, and 9% respectively and with $R^1 = R^4$ = Cl and R^1 = Cl, R^4 = Br they are 28 and 11%. This is evidently due to an unfavorable steric interaction of R^1 and R^4 with the aldehyde and nitro groups on the reaction course. For $R^4 = NO_2$, the aldehyde group does not generally react and the single reaction product is 1,3-dinitrobenzene (analogous to the decarbonylation of 2,6-dinitrobenzaldehyde using base as described in [5]). With the use of 4-fluoro-5-chloro-2-nitrobenzaldehyde XXVI in the usual conditions the basic product is the methoxy derivative LIV; only by changing the order of mixing the reagents was it possible to obtain the fluoro product LIII. Nucleophilic substitution of fluorine by a methoxy group evidently occurs in diester LIII since the starting aldehyde XXVI does not react with sodium methylate under the conditions for carrying out the reaction. Confirmation of substitution of the indicated fluorine atom comes from the form of the 5-H and 8-H signals in the PMR spectra, appearing as two doublets ($J_{H,F}$ coupling = 8.0 and 10.0 Hz) in LIII and two

TABLE 1. Parameters for o-Nitrobenzaldehydes XVII-XXVI



Compound	R1	R2	R3	R4	Empirical formula	Found, % / Calculated, %			mp, °C	PMR Spectrum ($CDCl_3$), δ, ppm, J, Hz		Yield, %
						C	H	N		aromatic protons	CHO	
XVII	H	Cl	Br	H	$C_7H_3BrClNO_3$	31,55 / 31,79	0,98 / 1,14	5,09 / 5,29	81...82	8,22 (1H, s); 8,23 (1H, s)	10,39 (1H, s)	51,5
XVIII	H	Br	Cl	H	$C_7H_3BrClNO_3$	31,60 / 31,79	1,01 / 1,14	5,11 / 5,29	95...98	8,02 (1H, s); 8,43 (1H, s)	10,39 (1H, s)	53,0
XIX	H	Br	F	H	$C_7H_3BrFNO_3$	33,62 / 33,90	1,25 / 1,22	5,51 / 5,65	43...45	7,64 (1H, д, J = 8,0); 8,38 (1H, d, J = 6,0)	10,33 (1H, d, J = 2,0)	64,0
XX	Cl	H	H	Br	$C_7H_3BrClNO_3$	31,81 / 31,79	1,10 / 1,14	5,17 / 5,29	145...146	7,58 (1H, d, J = 8,5); 7,72 (1H, d, J = 8,5)	10,20 (1H, s)	35,0
XXI	Br	H	H	Br	$C_7H_3Br_2NO_3$	27,00 / 27,22	1,00 / 0,98	4,41 / 4,53	134...135	7,60...7,80 (2H, m)	10,18 (1H, s)	50,0
XXII	F	H	H	Br	$C_7H_3BrFNO_3$	34,00 / 33,90	1,09 / 1,22	5,60 / 5,65	102,5...104	7,37 (1H, d. d, J_1 = 9,0, J_2 = 8,5); 7,78 (1H, d. d, J_1 = 9,0, J_2 = 4,5)	10,19 (1H, d, J = 2,0)	25,0
XXIII	Cl	H	Cl	Cl	$C_7H_2Cl_3NO_3$	33,11 / 33,04	0,84 / 0,79	5,34 / 5,51	119...121	7,86 (1H, s)	10,35 (1H, s)	94,0
XXIV	H	F	Br	H	$C_7H_3BrFNO_3$	33,71 / 33,90	1,30 / 1,22	5,48 / 5,65	56...58	7,86 (1H, d, J = 7,5); 8,19 (1H, d, J = 7,0)	10,33 (1H, s)	60,0
XXV	F	H	F	H	$C_7H_3F_2NO_3$	44,61 / 44,94	1,64 / 1,62	7,24 / 7,49	57...59	7,16...7,38 (1H, m); 7,42...7,57 (1H, m)	10,01 (1H, d, J = 2,0)	73,0
XXVI	H	F	Cl	H	$C_7H_3ClFNO_3$	40,80 / 41,30	1,55 / 1,49	6,69 / 6,88	46...49	7,94 (1H, d, J = 7,5); 8,05 (1H, d, J = 7,0)	10,37 (1H, s)	74,5

TABLE 2. Parameters for Synthesized N-Oxide Dimethyl Esters of Quinoline-2,3-dicarboxylic Acids XXIX-LIV



Compound	R^1	R^2	R^3	R^4	Empirical formula	Found, % / Calculated, %			mp, °C	PMR Spectrum ($CDCl_3$), δ, ppm, J, Hz		Yield, %
						C	H	N		aliphatic protons	aromatic protons	
1	2	3	4	5	6	7	8	9	10	11	12	13
XXIX	H	H	H	H	$C_{13}H_{11}NO_5$	59,83 / 59,77	4,10 / 4,24	5,28 / 5,36	173...176	3,98 (3H, s); 4,11 (3H, s)	7,66...8,05 (3H,m); 8,43 (1H, s); 8,75 (1H, d.d, J_1 = 8,5, J_2 = 2,0)	61,5
XXX	H	H	Cl	H	$C_{13}H_{10}ClNO_5$	52,80 / 52,81	3,31 / 3,41	4,78 / 4,74	126...127	3,96 (3H, s); 4,08 (3H, s)	7,79 (1H, d.d, J_1 = 10,0, J_2 = 2,0); 7,93 (1H, d, J = 2,0); 8,27 (1H, s); 8,67 (1H, d, J = 10,0)	49,0
XXXI	H	H	Br	H	$C_{13}H_{10}BrNO_5$	45,72 / 45,91	2,85 / 2,96	3,99 / 4,12	168...170	3,91 (3H, s); 4,07 (3H, s)	7,93 (1H, d.d, J_1 = 9,5, J_2 = 2,0); 8,11 (1H, d, J = 2,0); 8,28 (1H, s); 8,58 (1H, d, J = 9,5)	72,0
XXXII	H	H	F	H	$C_{13}H_{10}FNO_5$	55,83 / 55,92	3,62 / 3,61	5,05 / 5,02	194...196	3,98 (3H, s); 4,11 (3H, s)	7,48...7,72 (2H, m); 8,31 (1H, s); 8,73 (1H, d.d, J_1 = 10,0, J_2 = 5,0)	49,0
XXXIII	H	H	OMe	H	$C_{14}H_{13}NO_6$	57,55 / 57,73	4,38 / 4,50	4,71 / 4,81	192...194	3,91 (6H, s); 4,07 (3H, s)	7,13 (1H, d, J = 2,5); 7,44 (1H, d. d, J_1 = 9,5, J_2 = 2,5); 8,22 (1H, s); 8,58 d, J = 9,5)	67,0
XXXIV	H	Cl	Cl	H	$C_{13}H_9Cl_2NO_5$	47,35 / 47,30	2,75 / 2,75	4,17 / 4,24	183...186	3,97 (3H, s); 4,10 (3H, s)	8,08 (1H, s); 8,28 (1H, s); 8,83 (1H, s)	41,0

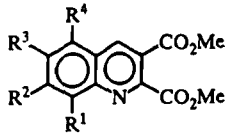
TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
XXXV	H	Cl	Br	H	$C_{13}H_9BrClNO_5$	41,36 41,69	2,23 2,42	3,64 3,74	171...173	3,97 (3H, s); 4,09 (3H, s)	8,26 (2H, s); 8,82 (1H, s)	60,0
XXXVI	H	Br	Cl	H	$C_{13}H_9BrClNO_5$	41,68 41,69	2,25 2,42	3,75 3,74	206...208	3,97 (3H, s); 4,09 (3H, s)	8,06 (1H, s); 8,27 (1H, s); 9,02 (1H, s)	62,5
XXXVII	H	OMe	OMe	H	$C_{15}H_{15}NO_7$	55,71 56,08	4,52 4,71	4,13 4,36	235...237,5	3,95 (3H, s); 4,04 (3H, s); 4,10 (6H, s)	7,16 (1H, s); 8,08 (1H, s); 8,28 (1H, s)	75,5
XXXVIII	H	$O-CH_2-O$		H	$C_{14}H_{11}NO_7$	54,55 55,09	3,60 3,63	4,38 4,59	217...219	3,93 (3H, s); 4,08 (3H, s); 6,21 (2H, s)	7,13 (1H, s); 8,00 (1H, s); 8,18 (1H, s)	47,0
XXXIX	H	Cl	H	H	$C_{13}H_{10}ClNO_5$	52,48 52,81	3,40 3,41	4,59 4,74	187...189	3,98 (3H, s); 4,11 (3H, s)	7,71 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 7,91 (1H, d, J = 9,0); 8,38 (1H, s); 8,74 (1H, d, J = 2,5)	53,5
XL	H	F	H	H	$C_{13}H_{10}FNO_5$	55,56 55,92	3,58 3,61	5,00 5,02	164...165	3,98 (3H, s); 4,11 (3H, s)	7,51 (1H, d.d.d, J_1 = 9,0, J_2 = 8,0, J_3 = 2,5); 8,02 (1H, d.d, J_1 = 9,0, J_2 = 5,5); 8,40 (1H, d.d, J_1 = 9,5, J_2 = 2,5); 8,42 (1H, s)	33,0
XLI	H	H	H	Cl	$C_{13}H_{10}ClNO_5$	52,90 52,81	3,42 3,41	4,62 4,74	145...148	3,99 (3H, s); 4,09 (3H, s)	7,68...7,87 (2H, m); 8,58...8,76 (2H, m)	35,0
XLII	H	NO_2	H	H	$C_{13}H_{10}N_2O_7$	50,97 50,99	3,30 3,29	9,40 9,15	191...193,5	4,02 (3H, s); 4,12 (3H, s)	8,17 (1H, d, J = 9,0); 8,45 (1H, s); 8,49 (1H, d.d, J_1 = 9,0, J_2 = 2,5); 9,56 (1H, br. s)	34,5
XLIII	H	Br	Br	H	$C_{13}H_9Br_2NO_5$	36,96 37,26	1,99 2,16	3,25 3,34	193...195	3,97 (3H, s); 4,09 (3H, s)	8,26 (2H, s); 8,99 (1H, s)	39,0
XLIV	H	Br	F	H	$C_{13}H_9BrFNO_5$	42,91 43,60	2,50 2,53	3,68 3,91	190...192	3,94 (3H, s); 4,07 (3H, s)	7,60 (1H, d, J = 8,0); 8,26 (1H, s); 8,97 (1H, d, J = 7,0)	48,0

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
XLV	H	H	Cl	Cl	$C_{13}H_9Cl_2NO_5$	46,58 47,30	2,64 2,75	4,14 4,24	132...133	3,98 (3H, s); 4,09 (3H, s)	7,87 (1H, d, J = 9,5); 8,59 (1H, d, J = 9,5); 8,70 (1H, s)	21,0
XLVI	Cl	H	H	Cl	$C_{13}H_9Cl_2NO_5$	47,00 47,30	2,59 2,75	4,20 4,24	173...175,5	3,98 (3H, s); 4,06 (3H, s)	7,59 (1H, d, J = 8,0); 7,72 (1H, d, J = 8,0); 8,66 (1H, s)	28,0
XLVII	Cl	H	H	Br	$C_{13}H_9BrClNO_5$	41,23 41,69	2,35 2,42	3,68 3,74	165...166	3,99 (3H, s); 4,07 (3H, s)	7,66 (1H, d, J = 8,0); 7,84 (1H, d, J = 8,0); 8,70 (1H, s)	11,0
XLVIII	Br	H	H	Br	$C_{13}H_9Br_2NO_5$	37,00 37,26	2,10 2,16	3,30 3,34	162...164	3,98 (3H, s); 4,07 (3H, s)	7,72 (1H, d, J = 8,0); 7,93 (1H, d, J = 8,0); 8,71 (1H, s)	9,0
XLIX	F	H	H	Br	$C_{13}H_9BrFNO_5$	43,15 43,60	2,40 2,53	3,90 3,91	150...151	4,00 (1H, s); 4,07 (1H, s)	7,36 (1H, d.d, J_1 = 11,5, J_2 = 8,5); 7,90 (1H, d.d, J_1 = 8,5, J_2 = 4,0); 8,63 (1H, d, J = 1,5)	32,0
L	Cl	H	Cl	Cl	$C_{13}H_8Cl_3NO_5$	42,77 42,83	2,20 2,21	3,64 3,84	214...216	4,01 (3H, s); 4,08 (3H, s)	7,90 (1H, s); 8,72 (1H, s)	6,5
LI	H	F	Br	H	$C_{13}H_9BrFNO_5$	43,61 43,60	2,47 2,53	3,80 3,91	192...195	3,99 (3H, s); 4,11 (3H, s)	8,27 (1H, d, J = 7,0); 8,33 (1H, s); 8,45 (1H, d, J = 9,0)	25,0
LII	F	H	F	H	$C_{13}H_9F_2NO_5$	52,15 52,54	3,02 3,05	4,60 4,71	199...201	3,98 (3H, s); 4,07 (3H, s)	7,16...7,48 (2H, m); 8,26 (1H, d, J = 1,5)	56,0
LIII	H	F	Cl	H	$C_{13}H_9ClFNO_5$	49,58 49,78	2,94 2,89	4,34 4,47	170...172	3,99 (3H, s); 4,11 (3H, s)	8,07 (1H, d, J = 7,0); 8,31 (1H, s); 8,48 (1H, d, J = 9,5)	31,5
LIV	H	OMe	Cl	H	$C_{14}H_{12}ClNO_6$	51,27 51,63	3,49 3,71	4,08 4,30	166...168	3,97 (3H, s); 4,11 (6H, s)	7,98 (1H, s); 8,14 (1H, s); 8,28 (1H, s)	56,0

TABLE 3. Parameters for Synthesized Dimethyl Esters of Quinoline-2,3-dicarboxylic Acids LV-LXXX



Compound	R1	R2	R3	R4	Empirical formula	Found, % / Calculated, %			mp, °C	PMR Spectrum ($CDCl_3$), δ, ppm, J, Hz		Yield, %
						C	H	N		aliphatic protons	aromatic protons	
1	2	3	4	5	6	7	8	9	10	11	12	13
LV	H	H	H	H	$C_{13}H_{11}NO_4$	63,48 / 63,67	4,50 / 4,52	5,63 / 5,71	104...106	3,98 (3H, s); 4,06 (3H, s)	7,58...8,00 (3H, m); 8,21 (1H, d.d, J_1 = 9,5, J_2 = 2,0); 8,77 (1H, s)	88,0
LVI	H	H	Cl	H	$C_{13}H_{10}ClNO_4$	55,74 / 55,83	3,59 / 3,60	5,00 / 5,01	152...154	3,97 (3H, s); 4,06 (3H, s)	7,76 (1H, d.d, J_1 = 9,5, J_2 = 2,0); 7,90 (1H, d, J = 2,0); 8,14 (1H, d, J = 9,5); 8,67 (1H, s)	90,0
LVII	H	H	Br	H	$C_{13}H_{10}BrNO_4$	48,09 / 48,17	3,05 / 3,11	4,26 / 4,32	155...157	3,97 (3H, s); 4,07 (3H, s)	7,90 (1H, d.d, J_1 = 9,5, J_2 = 2,0); 8,02...8,16 (2H, m); 8,66 (1H, s)	81,5
LVIII	H	H	F	H	$C_{13}H_{10}FNO_4$	59,23 / 59,32	3,79 / 3,83	5,26 / 5,32	119...121	3,98 (3H, s); 4,07 (3H, s)	7,49...7,72 (2H, m); 8,20 (1H, d.d, J_1 = 10,0, J_2 = 5,0); 8,69 (1H, s)	85,0
LIX	H	H	OMe	H	$C_{14}H_{13}NO_5$	59,85 / 61,09	4,57 / 4,76	5,01 / 5,09	120...122	3,94 (6H, s); 4,02 (3H, s)	7,12 (1H, d, J = 2,5); 7,46 (1H, d. d, J_1 = 9,0, J_2 = 2,5); 8,09 (1H, d. J = 9,0); 8,56 (1H, s)	99,0
LX	H	Cl	Cl	H	$C_{13}H_9Cl_2NO_4$	49,56 / 49,71	2,87 / 2,89	4,41 / 4,46	113...115	3,97 (3H, s); 4,04 (3H, s)	8,02 (1H, s); 8,31 (1H, s); 8,64 (1H, s)	96,0

TABLE 3 (continued)

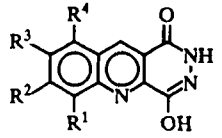
1	2	3	4	5	6	7	8	9	10	11	12	13
LXI	H	Cl	Br	H	$C_{13}H_9BrClNO_4$	43,60 43,54	2,49 2,53	3,85 3,91	128...130	3,98 (3H, s); 4,06 (3H, s)	8,24 (1H, s); 8,33 (1H, s); 8,68 (1H, s)	95,0
LXII	H	Br	Cl	H	$C_{13}H_9BrClNO_4$	43,65 43,54	2,50 2,53	3,85 3,91	142...144	3,96 (3H, s); 4,04 (3H, s)	8,03 (1H, s); 8,53 (1H, s); 8,62 (1H, s)	67,0
LXIII	H	OMe	OMe	H	$C_{15}H_{15}NO_6$	58,64 59,02	4,76 4,95	4,41 4,59	185...187	3,99 (3H, s); 4,09 (3H, s); 4,16 (6H, s)	7,25 (1H, s); 8,27 (1H, s); 8,91 (1H, s)	99,0
LXIV	H	O–CH$_2$–O		H	$C_{14}H_{11}NO_6$	58,09 58,14	3,78 3,83	4,90 4,84	174...176	3,94 (3H, s); 4,01 (3H, s); 6,16 (2H, s)	7,10 (1H, s); 7,42 (1H, s); 8,48 (1H, s)	99,0
LXV*	H	Cl	H	H	$C_{13}H_{10}ClNO_4$	55,65 55,83	3,62 3,60	4,89 5,01	100...102	3,98 (3H, s); 4,06 (3H, s)	7,65 (1H, d.d $J_1 = 9,0$, $J_2 = 2,5$); 7,86 (1H, d. $J = 9,0$); 8,19 (1H, d, $J = 2,5$); 8,75 (1H, s)	98,0
LXVI	H	F	H	H	$C_{13}H_{10}FNO_4$	59,02 59,32	3,80 3,83	5,35 5,32	108...109	3,96 (3H, s); 4,06 (3H, s)	7,48 (1H, d.d.d, $J_1 = 9,0$, $J_2 = 8,0$, $J_3 = 2,5$); 7,76...8.03 (2H, m); 8,79 (1H, s)	89,0
LXVII	H	H	H	Cl	$C_{13}H_{10}ClNO_4$	55,65 55,83	3,61 3,60	4,97 5,01	89...91	4,00 (3H, s); 4,06 (3H, s)	7,67...7,86 (2H, m); 8,02...8,22 (1H, m); 9,13 (1H, s)	88,0
LXVIII	H	NO_2	H	H	$C_{13}H_{10}N_2O_6$	53,57 53,80	3,26 3,47	9,51 9,65	154...156	4,01 (3H, s); 4,09 (3H, s)	8,12 (1H, d, $J = 9,0$); 8,43 (1H, d. d, $J_1 = 9,0$, $J_2 = 2,5$); 8,86 (1H, s); 9,11 (1H, br. s)	87,0
LXIX	H	Br	Br	H	$C_{13}H_9Br_2NO_4$	38,82 38,74	2,16 2,25	3,57 3,48	147...149	3,97 (3H, s); 4,04 (3H, s)	8,20 (1H, s); 8,49 (1H, s); 8,62 (1H, s)	99,0
LXX	H	Br	F	H	$C_{13}H_9BrFNO_4$	45,30 45,64	2,52 2,65	4,03 4,09	122...123	3,96 (3H, s); 4,03 (3H, s)	7,59 (1H, d, $J = 8,0$); 8,47 (1H, d, $J = 7,0$); 8,66 (1H, s)	91,5
LXXI	H	H	Cl	Cl	$C_{13}H_9Cl_2NO_4$	49,31 49,71	2,42 2,89	4,32 4,46	—	3,99 (3H, s); 4,04 (3H, s)	7,89 (1H, d, $J = 8,5$); 8,07 (1H, d, $J = 8,5$); 9,12 (1H, s)	90,5

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
LXXII	Cl	H	H	Cl	$C_{13}H_9Cl_2NO_4$	49,38 / 49,71	2,65 / 2,89	4,41 / 4,46	160...161,5	4,01 (3H, s); 4,06 (3H, s)	7,66 (1H, d, J = 8,0); 7,89 (1H, d, J = 8,0); 9,16 (1H, s)	70,0
LXXIII	Cl	H	H	Br	$C_{13}H_9BrClNO_4$	43,30 / 43,54	2,60 / 2,53	3,80 / 3,91	149...151	3,99 (3H, s); 4,06 (3H, s)	7,82 (2H, br. s); 9,10 (1H, s)	99,0
LXXIV	Br	H	H	Br	$C_{13}H_9Br_2NO_4$	38,46 / 38,74	2,25 / 2,25	3,31 / 3,48	250 (decomp.)	4,01 (3H, s); 4,07 (3H, s)	7,79 (1H, d, J = 8,0); 8,03 (1H, d, J = 8,0); 9,10 (1H, s)	91,0
LXXV	F	H	H	Br	$C_{13}H_9BrFNO_4$	45,10 / 45,64	2,50 / 2,65	4,00 / 4,09	116...118,5	3,97 (3H, s); 4,01 (3H, s)	7,42 (1H, d.d, J_1 = 9,5, J_2 = 8,5); 7,85 (1H, d.d, J_1 = 8,5, J_2 = 4,5); 9,04 (1H, d, J = 1,5)	86,0
LXXVI	Cl	H	Cl	Cl	$C_{13}H_8Cl_3NO_4$	44,57 / 44,80	2,34 / 2,31	3,97 / 4,02	181...183	4,01 (3H, s); 4,06 (3H, s)	8,02 (1H, s); 9,14 (1H, s)	99,0
LXXVII	H	F	Br	H	$C_{13}H_9BrFNO_4$	45,52 / 45,64	2,58 / 2,65	4,03 / 4,09	146...147	3,97 (3H, s); 4,04 (3H, s)	7,88 (1H, d, J = 9,0); 8,18 (1H, d, J = 7,0); 8,67 (1H, s)	88,5
LXXVIII	F	H	F	H	$C_{13}H_9F_2NO_4$	55,66 / 55,52	3,22 / 3,23	5,07 / 4,98	120...122	3,99 (3H, s); 4,05 (3H, s)	7,28...7,49 (2H, m); 8,71 (1H, d, J = 1,5)	73,5
LXXIX	H	F	Cl	H	$C_{13}H_9ClFNO_4$	52,17 / 52,46	3,08 / 3,05	4,57 / 4,71	182...184	3,99 (3H, s); 4,06 (3H, s)	7,94 (1H, d, J = 9,5); 8,03 (1H, d, J = 7,0); 8,71 (1H, s)	97,5
LXXX	H	OMe	Cl	H	$C_{14}H_{12}ClNO_5$	53,92 / 54,29	3,70 / 3,91	4,34 / 4,52	112...114	3,98 (3H, s); 4,09 (6H, s)	7,72 (1H, s); 7,97 (1H, s); 8,71 (1H, s)	98,0

*PMR spectrum of compound LXV in DMSO-D_6 identical to that reported in [2].

TABLE 4. Parameters for Synthesized 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-b]quinolines I, LXXXIII-CVI



Compound	R^1	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		aliphatic protons	aromatic protons	NH / OH (exchange with D_2O)	
1	2	3	4	5	6	7	8	9	10	11	12	13	14
I	H	H	H	H	$C_{11}H_7N_3O_2$	61,43 / 61,97	3,36 / 3,31	19,16 / 19,71	>300	–	7,76...8,16 (2H,m); 8,22...8,47 (2H,m); 9,30 (1H, s)	11,60 (2H, br. s)	86,0
LXXXIII	H	H	Cl	H	$C_{11}H_6ClN_3O_2$	53,33 / 53,35	2,42 / 2,44	16,37 / 16,97	>300	–	8,02 (1H, d.d, J_1 = 9,0, J_2 = 2,5); 8,28 (1H,d, J = 9,0); 8,52 (1H,d, J = 2,5); 9,26 (1H, s)	11,60 (2H, br. s)	88,5
LXXXIV	H	H	Br	H	$C_{11}H_6BrN_3O_2$	44,74 / 45,23	2,10 / 2,07	14,09 / 14,39	>300	–	8,04...8,30 (2H, m); 8,60 (1H, br. s); 9,25 (1H, s)	11,55 (2H, br. s)	82,0
LXXXV	H	H	F	H	$C_{11}H_6FN_3O_2$	56,73 / 57,15	2,47 / 2,62	17,99 / 18,18	>300	–	7,93 (1H, d.d.d , J_1 = 9,5, J_2 = 9,0, J_3 = 2,5); 8,18 (1H, d. d, J_1 = 9,5, J_2 = 2,5); 8,36 (1H,, d.d,. J_1 = 9,5, J_2 = 5,5); 9,24 (1H, s)	11,60 (2H, br. s)	84,0

TABLE 4 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
LXXXVI	H	H	OMe	H	$C_{12}H_9N_3O_3 \cdot 1,6H_2O$	52,30 / 52,98	4,45 / 4,52	15,73 / 15,45	>300	3,97 (3H, s)	7,62...7,80 (2H, m); 8,19 (1H, d, J = 9,0); 9,08 (1H, s)	11,45 (2H, br. s)	74,5
LXXXVII	H	Cl	Cl	H	$C_{11}H_5Cl_2N_3O_2$	46,62 / 46,84	1,73 / 1,79	14,88 / 14,90	>300	–	8,47 (1H, s); 8,67 (1H, s); 9,22 (1H, s)	11,60 (2H, br. s)	82,5
LXXXVIII	H	Cl	Br	H	$C_{11}H_5BrClN_3O_2$	40,23 / 40,46	1,41 / 1,54	12,95 / 12,87	>300	–	8,52 (1H, s); 8,91 (1H, s); 9,28 (1H, s)	11,65 (2H, br. s)	69,5
LXXXIX	H	Br	Cl	H	$C_{11}H_5BrClN_3O_2$	40,14 / 40,46	1,42 / 1,54	12,88 / 12,87	>300	–	8,68 (1H, s); 8,71 (1H, s); 9,26 (1H, s)	11,70 (2H, br. s)	88,0
XC	H	OMe	OMe	H	$C_{13}H_{11}N_3O_4 \cdot H_2O$	53,05 / 53,61	4,30 / 4,50	14,17 / 14,43	>300	3,97 (3H, s); 4,01 (3H, s)	7,57 (1H, s); 7,68 (1H, s); 8,94 (1H, s)	11,35 (2H, br. s)	62,5
XCI	H	O–CH$_2$–O		H	$C_{12}H_7N_3O_4 \cdot 0,5H_2O$	54,01 / 54,14	2,92 / 3,03	15,82 / 15,78	>300	6,31 (2H, s)	7,52 (1H, s); 7,64 (1H, s); 8,92 (1H, s)	11,50 (2H, br. s)	86,5
XCII*	H	Cl	H	H	$C_{11}H_6ClN_3O_2$	53,19 / 53,35	2,34 / 2,44	16,78 / 16,97	>300	–	7,84 (1H, d.d, J_1 = 9,0, J_2 = 2,0); 8,31 (1H, br. s); 8,40 (1H, d, J = 9,0); 9,32 (1H, s)	11,65 (2H, br. s)	50,5
XCIII	H	F	H	H	$C_{11}H_6FN_3O_2$	56,73 / 57,15	2,47 / 2,62	18,00 / 18,18	>300	–	7,78 (1H, d.d.d, J_1 = 9,5, J_2 = 8,5, J_3 = 2,5); 8,00 (1H, d.d, J_1 = 10,5, J_2 = 2,5); 8,49 (1H, d.d, J_1 = 9,5, J_2 = 6,5); 9,36 (1H, s)	11,55 (2H, br. s)	41,5
XCIV	H	H	H	Cl	$C_{11}H_6ClN_3O_2$	52,84 / 53,35	2,36 / 2,44	16,76 / 16,97	>300	–	7,94...8,13 (2H, m); 8,16...8,40 (1H, m); 9,28 (1H, s)	11,70 (2H, br. s)	58,0
XCV	H	NO_2	H	H	$C_{11}H_6N_4O_4 \cdot 0,5H_2O$	49,62 / 49,44	2,66 / 2,64	20,87 / 20,98	>300	–	8,44 (1H, d.d, J_1 = 9,0, J_2 = 2,0); 8,58 (1H, d, J = 9,0); 8,97 (1H, d, J = 2,0); 9,41 (1H, s)	11,70 (2H, br. s)	67,5

TABLE 4 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
XCVI	H	Br	Br	H	$C_{11}H_5Br_2N_3O_2$	35,34 / 35,61	1,31 / 1,36	11,54 / 11,83	>300	—	8,63 (1H, s); 8,86 (1H, s); 9,24 (1H, s)	11,50 (2H, br. s)	66,0
XCVII	H	Br	F	H	$C_{11}H_5BrFN_3O_2$	42,20 / 42,61	1,69 / 1,63	13,50 / 13,55	>300	—	8,33 (1H, d, J = 9,0); 8,68 (1H, d, J = 7,0); 9,28 (1H, s)	11,60 (2H, br. s)	65,0
XCVIII	H	H	Cl	Cl	$C_{11}H_5Cl_2N_3O_2$	46,46 / 46,84	1,68 / 1,79	14,58 / 14,90	>300	—	8,07...8,33 (2H, m); 9,28 (1H, s)	11,65 (2H, br. s)	67,5
XCIX	Cl	H	H	Cl	$C_{11}H_5Cl_2N_3O_2$	45,65 / 46,84	1,84 / 1,79	14,20 / 14,90	>300	—	7,96 (1H, d, J = 8,0); 8,18 (1H, d, J = 8,0); 9,77 (1H, s)	11,75 (2H, br. s)	39,0
C	Cl	H	H	Br	$C_{11}H_5BrClN_3O_2$	40,04 / 40,46	1,47 / 1,54	12,61 / 12,87	>300	—	8,17 (2H, br. s); 9,26 (1H, s)	11,80 (2H, br. s)	68,0
CI	Br	H	H	Br	$C_{11}H_5Br_2N_3O_2$	34,91 / 35,61	1,30 / 1,36	10,81 / 11,33	>300	—	8,07 (1H, d, J = 8,0); 8,30 (1H, d, J = 8,0); 9,24 (1H, s)	11,70 (2H, br. s)	75,5
CII	F	H	H	Br	$C_{11}H_5BrFN_3O_2$	42,19 / 42,61	1,61 / 1,63	13,45 / 13,55	>300	—	7,82 (1H, d.d, J_1 = 10,0, J_2 = 8,5); 8,16 (1H, d.d, J_1 = 8,5, J_2 = 5,0); 9,20 (1H, d, J = 1,5)	11,80 (2H, br. s)	35,5
CIII	Cl	H	Cl	Cl	$C_{11}H_4Cl_3N_3O_2$	41,49 / 41,74	1,14 / 1,27	13,14 / 13,28	>300	—	8,51 (1H, s); 9,26 (1H, s)	11,80 (2H, br. s)	79,5
CIV	H	F	Br	H	$C_{11}H_5BrFN_3O_2$	42,14 / 42,61	1,52 / 1,63	13,47 / 13,55	>300	—	8,23 (1H, d, J = 10,0); 8,92 (1H, d, J = 8,0); 9,23 (1H, s)	11,60 (2H, br. s)	39,0
CV	F	H	F	H	$C_{11}H_5F_2N_3O_2$	52,91 / 53,02	2,00 / 2,02	17,05 / 16,86	>300	—	7,87...8,20 (2H, m); 9,31 (1H, d, J = 1,5);	11,70 (2H, br. s)	73,5
CVI	H	F	Cl	H	$C_{11}H_5ClFN_3O_2 \cdot 0,5H_2O$	47,72 / 48,11	2,18 / 2,20	15,40 / 15,30	>300	—	8,22 (1H, d, J = 10,5); 8,73 (1H, d, J = 8,0); 9,29 (1H, s)	11,65 (2H, br.s)	40,0

*PMR spectrum for XCII identical to that reported in [2].

singlets in LIV. Reduction of the N-oxides XXIX-LIV occurs readily using phosphorus trichloride in refluxing chloroform and does not depend on the nature of the substitution. In most cases the yields of the products LV-LXXX, are 85-95%.

When going from the N-oxides XXIX-LIV to the corresponding reduced forms LV-LXXX, the characteristic 4-H signals are shifted to low field by 0.34-0.50 ppm and the 8-H signal to higher field by 0.44-0.55 ppm and these are in full agreement with the structures proposed. Certain features of the PMR spectra of the fluorinated aldehydes and diesters were also noted. In addition to the usual interaction of the protons with the fluorine atom in an ortho- or meta- position, there are longer-range interactions through five σ bonds, evidently due to the presence of a fixed trans- configuration for C–H and C–F bonds. Hence, in the meta-fluoroaldehydes XIX, XXII, and XXV the aldehyde proton signal appears as a doublet with coupling $J_{H,F}$ = 2.0 Hz, and in the diesters XLIX, LII, LXXV, and LXXVIII the 4-H signal is a doublet with $J_{H,F}$ = 1.5 Hz (for a similar interaction between 4-H and 8-H in quinolines the coupling is less than 1.0 Hz [6], and in the spectra obtained by us for the diesters with R^1 = H this is shown as a broadening and decreased height for the signals of the corresponding proton signals). In addition, in a series of examples, there are observed deviations of the couplings from standard values: $J_{o\text{-}H,F}$ = 6.2-10.1 and $J_{m\text{-}H,F}$ = 6.2-8.3 Hz [7]. Thus, in the diester XLIX $J_{7H,8F}$ = 11.5, $J_{6H,8F}$ = 4.0 Hz, in aldehyde XXII $J_{5H,3F}$ = 4.5, in diester LXXV $J_{6H,8F}$ = 4.5 Hz, in diesters XXXII and LVIII $J_{8H,6F}$ = 5.0, in diester XL $J_{5H,7F}$ = 5.5 Hz.

Treatment of diesters LV-LXXX with a 4-5 fold excess of hydrazine hydrate in refluxing ethanol gives initially the dihydrazides LXXXI which are then converted to cyclic hydrazides which yield a salt with hydrazine LXXXII. Heating these salts in acetic acid causes fission of hydrazine to form the desired pyridazino[4,5-b]quinolines I, LXXXIII-CVI. In the majority of cases the yields are 60-85% and only for derivatives with R^1 or R^2 = F are they lowered to 40-45% (this may possibly becaused by nucleophilic substitution of fluorine by a hydrazino group and the formed hydrazino derivative remaining in solution upon work-up with acetic acid). A similar reaction of diester LVI with hydrazinoethanol occurs with much greater difficulty than for hydrazine, and the product CVII is obtained in 40% yield. The PMR spectra of I, LXXXIII-CVI show a broad signal at δ 11.35-11.90 ppm (2H, exchanging with D_2O, NH, and OH) pointing to the presence in solution of an equilibrium mixture of some tautomers of the type 1A-1D.

All of the pyridazino[4,5-b]quinolines I, LXXXIII-CVI synthesized by us were studied as potential NMDA receptor antagonists and showed high *in vitro* activity. As proposed, the activity strongly depends on the nature of the substitution in the benzene ring. The most active compounds proved to be those with $R^1 = R^2 = R^4$ = H and R^3 = F, Cl, Br and also those with $R^1 = R^4$ = H, R^3 = Cl, and R^2 = Cl, Br. Detailed results of the biological experiments will be published later.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90 spectrometer (90 MHz) using TMS as internal standard. Melting points were determined on a Boetius microheating block and were not corrected.

Elemental analysis for C, H, and N agreed with that calculated.

o-Nitrobenzaldehydes II ($R^1 = R^2 = R^3 = R^4$ = H), III ($R^1 = R^2 = R^4$ = H; R^3 = Cl), IV ($R^1 = R^4$ = H; R^2, R^3 = O–CH_2–O), V ($R^1 = R^2 = R^3$ = H; R^4 = Cl), VI ($R^1 = R^3 = R^4$ = H; R^2 = NO_2) and 2,6-dinitrobenzaldehyde were obtained from the Aldrich company and were used without additional purification.

o-Nitrobenzaldehydes VII ($R^1 = R^2 = R^4$ = H; R^3 = Br) [8], VIII ($R^1 = R^2 = R^4$ = H; R^3 = F) [9], IX ($R^1 = R^2 = R^4$ = H; R^3 = OMe) [10], X ($R^1 = R^4$ = H; $R^2 = R^3$ = Cl) [11], XI ($R^1 = R^4$ = H; $R^2 = R^3$ = OMe) [12], XII ($R^1 = R^3 = R^4$ = H; R^2 = Cl) [13], XIII ($R^1 = R^4$ = H; $R^2 = R^3$ = Br) [14], XIV ($R^1 = R^2$ = H; $R^3 = R^4$ = Cl) [15], XV ($R^2 = R^3$ = H; $R^1 = R^4$ = Cl) [16], and XVI ($R^1 = R^3 = R^4$ = H; R^2 = F) [17] were prepared by literature methods.

o-Nitrobenzaldehydes XVII ($R^1 = R^4$ = H; R^2 = Cl; R^3 = Br) and XVIII ($R^1 = R^4$ = H; R^2 = Br; R^3 = Cl) were obtained correspondingly from 3-nitro-4-chloro- and 4-bromo-3-nitrobenzaldehyde, giving 3-bromo-4-chloro- and 4-bromo-3-chlorobenzaldehyde using method [18] with subsequent nitration by method [10].

o-Nitrobenzaldehydes XIX ($R^1 = R^4$ = H; R^2 = Br; R^3 = F), XX ($R^2 = R^3$ = H; R^1 = Cl; R^4 = Br), XXI ($R^2 = R^3$ = H; $R^1 = R^4$ = Br), and XXII ($R^2 = R^3$ = H; R^1 = F; R^4 = Br) were prepared by oxidation of the corresponding halotoluene to the haloaldehyde by method [13] and subsequent nitration using method [10].

o-Nitrobenzaldehydes XXIII (R^2 = H; $R^1 = R^3 = R^4$ = Cl), XXIV ($R^1 = R^4$ = H; R^2 = F; R^3 = Br), XXV ($R^2 = R^4$ = H; $R^1 = R^3$ = F), and XXVI ($R^1 = R^4$ = H; R^2 = F; R^3 = Cl) were obtained by nitration of the corresponding aldehydes using method [10]. Nitration using this method gave, in all cases, a mixture of nitro isomers from which the desired

isomer was separated by crystallization from isopropanol–water (2:1). The physicochemical parameters for the o-nitro aldehydes synthesized (XVII-XXVI) are given in Table 1.

General Method for Synthesis of N-Oxide Dimethyl Esters of Quinoline-2,3-dicarboxylic Acids XXIX-LIV. A solution of sodium (15 mmoles) in absolute methanol (20 ml) was cooled to 0°C. The o-nitrobenzaldehyde II-XXVI (10 mmole) was added and then diethoxyphosphinylsuccinate XXVII (12 mmole) in absolute methanol (5 ml) added dropwise over 30 min.* The mixture was stirred for a further hour at 0-5°C and the precipitate was washed on the filter with methanol and ether. The diesters XXIX-LIV obtained can be used in the next stage without purification. Analytical samples were prepared by recrystallization from isopropanol. Physicochemical parameters for the N-oxides XXIX-LIV are given in Table 2.

General Method for Synthesis of Dimethyl Esters of Quinoline-2,3-dicarboxylic Acids LV-LXXX. Phosphorus trichloride (30 mmole) was added to a solution of the N-oxide XXIX-LIV (10 mmole) in absolute chloroform (100 ml). The mixture was refluxed for 8 h and evaporated to dryness under vacuum. The residue was dissolved in ethyl acetate (150 ml), washed with a 5% solution of sodium bicarbonate and water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in a vacuum. The residue was then ground with petroleum ether, the precipitate filtered, and the obtained diesters LV-LXXX can be used without purification in the next stage. Analytical samples were obtained by recrystallization from isopropanol. Physicochemical parameters for diesters LV-LXXX are given in Table 3.

General Method for Synthesis of 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-b]quinolines I, LXXXIII-CVI. Hydrazine hydrate (40-50 mmole) was added to a solution (or suspension) of the diester LV-LXXX (5 mmole) in refluxing ethanol (25 ml) and the product refluxed with stirring for 8 h. The mixture was cooled to room temperature and the precipitate filtered and washed on the filter with ethanol and ether. The obtained hydrazinium salt LXXXII was treated without purification with acetic acid (15 ml). The mixture was stirred for 3 h at 70-100°C and cooled to room temperature. The precipitate was filtered and washed on the filter with ethanol and ether to give pyridazino[4,5-b]quinolines I, LXXXIII-CVI which can be crystallized from dimethylformamide if needed. The physicochemical parameters for I, LXXXIII-CVI are given in Table 4.

8-Bromo-4-hydroxy-2-(2-hydroxyethyl)-1-oxo-1,2-dihydropyridazino[4,5-b]quinoline CVII was obtained similarly to the above general method from diether LVI (5 mmole) and hydrazinoethanol (100 mmole) in 40% yield with mp 251-252°C. PMR spectrum (DMSO-D_6): δ 3.77 (2H, t, J = 6.0 Hz, CH_2); 4.07 (2H, t, J = 6.0 Hz, CH_2); 8.14 (2H, m, 6-H, 7-H); 8.69 (1H, s, 9-H); 9.31 ppm (1H, s, 10-H). Found, %: C 46.45; H 3.00; N 12.50. $C_{13}H_{10}BrN_3O_3$. Calculated, %: C 46.47; H 2.91; N 12.53.

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*For derivatives with R^1 and (or) R^4 = Hal, 20 mmole of sodium was taken and the solution of succinate XXVII added over 1 h. For N-oxide LIV, 20 mmole of sodium was used and 10 mmole of aldehyde XXVI. For preparation of N-oxide LIII, there were added simultaneously sodium methylate solution in methanol (10 mmole) and succinate XXVII to aldehyde XXVI (10 mmole).

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