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4-HYDROXY-2-QUINOLONES.
36.* SYNTHESIS OF 2-R-OXAZOLO[4,5-*c*]QUINOLIN-4(5H)-ONES

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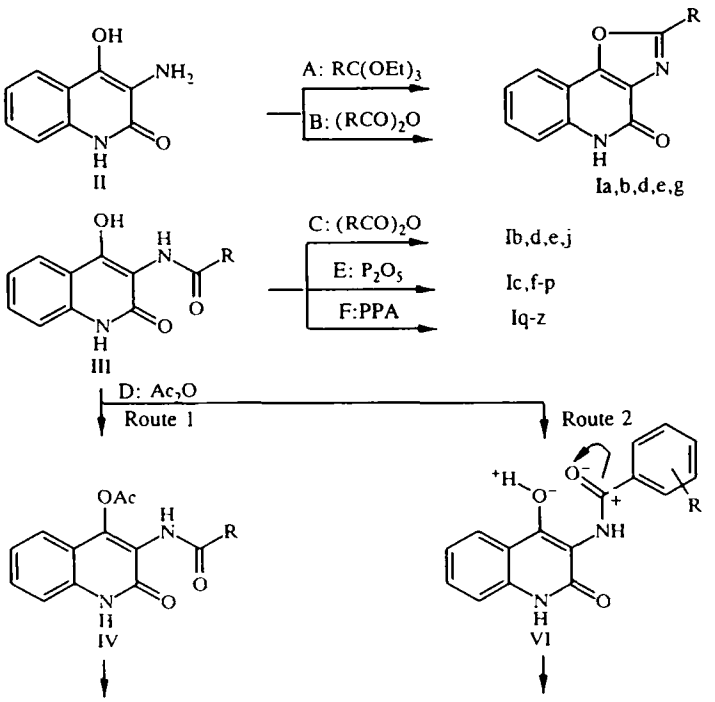
We consider different variants for synthesis of 2-R-oxazolo[4,5-c]quinolin-4(5H)-ones based on 3-amino-1H-2-oxo-4-hydroxyquinolines and their 3-N-acyl derivatives. We show that in the latter case, formation of the oxazole ring is possible via two routes, depending on the nature of the substituent on the acyl residue.

2-Aryl-substituted oxazolo[4,5-*c*]quinolin-4(5H)-ones, obtained from the corresponding isatoic anhydrides, are of interest in medical practice as stimulators or antagonists of GABA-receptors of the brain, and can be used for treatment of anxiety states and sleep disorders and for memory improvement [2].

We know that the main sources for obtaining benzoxazoles and molecular systems related to them are *o*-aminophenols and carboxylic acids [3]. So it seems advisable to synthesize 2-R-oxazolo-[4,5-*c*]quinolin-4(5H)-ones I based on the 3-amino-1H-2-oxo-4-hydroxyquinolines II and their acyl derivatives III which we described earlier in [4].

Unsubstituted oxazoloquinoline Ia is obtained in high yield by treatment of aminoquinoline II with triethylorthoformate [5] (method A).



*For Communication 35, see [1].

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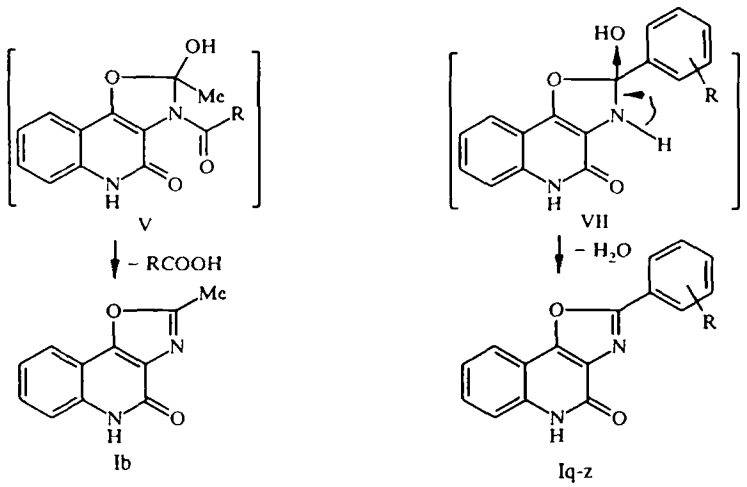

I a R = H; b R = Me; c R = CH_2Cl; d R = Et; e R = Pr; f R = *i*-Pr; g R = Bu; h R = *i*-Bu; i R = C_5H_{11}; j R = C_6H_{13}; k R = C_7H_{15}; l R = C_8H_{17}; m R = C_9H_{19}; n R = $C_{11}H_{21}$; o R = $C_{11}H_{23}$; p R = $C_{12}H_{25}$; q R = CH_2Ph; r R = Ph; s R = 4-MeC_6H_4; t R = 3-MeC_6H_4; u R = 2-FC_6H_4; v R = 2-ClC_6H_4; w R = 3-ClC_6H_4; x R = 2-BrC_6H_4; z R = 4-BrC_6H_4

Use of carboxylic acid anhydrides as acylating agents and simultaneously as condensing agents also easily allows us to obtain the 2-alkyl-substituted analogs Ib, d, e (method B). However, considering the instability of 3-amino-2-oxo-4-hydroxyquinolines [6], it is more expedient for the previously obtained 3-acylaminoquinolines III to undergo cyclization (method C). We should however note that in practice, methods B and C are sufficiently effective only when using anhydrides of lower aliphatic acids. As the hydrocarbon chain becomes longer ($C_{(6)}$ or more), isolation of the final oxazoloquinolines I becomes considerably more complicated, which results in lower yields.

Closure of the oxazole ring in N-acylquinolines III when treated with cheap and readily available acetic anhydride (method D) requires more detailed consideration. The results of our investigations showed that this reaction can occur via two routes, determined by the nature of the N-acyl moiety. Thus in the case of acylquinolines III with alkyl substituents, cyclization occurs exclusively according to the mechanism proposed by Landenburg back in [3]. As we know, the first stage of such a cyclization is formation of 4-O-acetyl derivatives IV. Subsequent nucleophilic attack on the acetoxyl group by the amide nitrogen leads to formation of the oxazole ring. Clearly the result of realization of such a mechanism can only be 2-methyloxazolo[4,5-*c*]quinolin-4(5H)-one (Ib), since stabilization of the intermediates V is possible only in the case of cleavage of the N-acyl residue.

We observe a different pattern when treating 3-N-phenacyl- and benzoylquinolines III with acetic anhydride. In this case, along with 2-methyloxazole Ib, the corresponding 3-phenacyl(aryl)oxazoles Iq-z are formed in 8-40% yield. This fact suggests the possibility of another route for closure of the oxazole ring, which obviously (due to the electron-acceptor properties of the aryl substituents) occurs according to a mechanism similar to the formation of benzimidazoles under thermolysis conditions [3]. The dihydro derivatives VII formed in this case go to the final oxazoloquinolines Iq-z, losing a water molecule, which immediately is bound by acetic anhydride. By and large, method D, even though it allows us to synthesize 3-aryl-substituted oxazoloquinolines, is of more theoretical than practical interest.

Using as condensing agents either phosphorus pentoxide (for the alkyl derivatives III, easily soluble in carbon tetrachloride, method E) or polyphosphoric acid (for their benzoyl analogs, method F) allows us to obtain the target oxazoloquinolines Ic-z in high preparative yields.

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY instrument in DMSO-D_6, internal standard TMS. The mass spectra were recorded on a Finnigan MAT Incos 50 quadrupole spectrometer with full scanning in the 33-700 *m/z* range, electron-impact ionization at 70 eV, direct injection, heating rate ~5°C.

TABLE 1. 2-R-Oxazolo[4,5-*c*]quinolin-4(5H)-ones Ia-z

Compound	Empirical formula	Found, % / Calculated, %			T_{mp}*, °C	Yield by method, %
		C	H	N		
Ia	$C_{10}H_6N_2O_2$	64,57 / 64,52	3,24 / 3,25	15,08 / 15,05	280 (sublimes)	A 93
Ib	$C_{11}H_8N_2O_2$	66,09 / 66,00	4,12 / 4,03	13,44 / 13,99	260 (sublimes)	B 90, C 92
Ic	$C_{11}H_7ClN_2O_2$	56,27 / 56,31	3,05 / 3,01	11,92 / 11,94	248 (sublimes)	E 96
Id	$C_{12}H_{10}N_2O_2$	67,36 / 67,28	4,77 / 4,71	13,01 / 13,08	280...282	B 87, C 91
Ie	$C_{13}H_{12}N_2O_2$	68,40 / 68,41	5,35 / 5,30	12,20 / 12,27	254...256	B 84 C 90
If	$C_{13}H_{12}N_2O_2$	68,48 / 68,41	5,26 / 5,30	12,34 / 12,27	238 (sublimes)	E 85
Ig	$C_{14}H_{14}N_2O_2$	69,40 / 69,41	5,77 / 5,82	11,55 / 11,56	226 (sublimes)	E 83
Ih	$C_{14}H_{14}N_2O_2$	69,44 / 69,41	5,80 / 5,82	11,64 / 11,56	242 (sublimes)	E 87
Ii	$C_{15}H_{16}N_2O_2$	70,33 / 70,29	6,27 / 6,29	10,91 / 10,93	232...234	E 85
Ij	$C_{16}H_{18}N_2O_2$	71,15 / 71,09	6,70 / 6,71	10,42 / 10,36	228...230	B 64, C 71, E 86
Ik	$C_{17}H_{20}N_2O_2$	71,78 / 71,81	7,16 / 7,09	9,88 / 9,85	238...240	E 80
Il	$C_{18}H_{22}N_2O_2$	72,40 / 72,46	7,57 / 7,43	9,42 / 9,39	227...229	E 77
Im	$C_{19}H_{24}N_2O_2$	73,16 / 73,05	7,70 / 7,74	8,91 / 8,97	208...210	E 79
In	$C_{20}H_{26}N_2O_2$	73,64 / 73,59	8,00 / 8,03	8,66 / 8,58	195...197	E 84
Io	$C_{21}H_{28}N_2O_2$	74,11 / 74,08	8,24 / 8,29	8,25 / 8,23	186...188	E 81
Ip	$C_{22}H_{30}N_2O_2$	74,50 / 74,54	8,59 / 8,53	7,94 / 7,90	166...170	E 89,
Iq	$C_{17}H_{12}N_2O_2$	73,83 / 73,90	4,45 / 4,38	10,10 / 10,14	279 (sublimes)	D 8, F 90
Ir	$C_{16}H_{10}N_2O_2$	73,30 / 73,27	3,93 / 3,84	10,55 / 10,68	268 (sublimes)	D 26, F 94
Is	$C_{17}H_{12}N_2O_2$	73,94 / 73,90	4,27 / 4,38	10,11 / 10,14	290 (sublimes)	F 95
It	$C_{17}H_{12}N_2O_2$	73,89 / 73,90	4,40 / 4,38	10,10 / 10,14	281 (sublimes)	D 30, F 92
Iu	$C_{16}H_9FN_2O_2$	68,66 / 68,57	3,21 / 3,24	10,07 / 10,00	273 (sublimes)	D 28, F 90
Iv	$C_{16}H_9ClN_2O_2$	64,81 / 64,77	3,12 / 3,06	9,36 / 9,44	283 (sublimes)	D 24, F 87
Iw	$C_{16}H_9ClN_2O_2$	64,79 / 64,77	3,10 / 3,06	9,40 / 9,44	276 (sublimes)	D 40, F 93
Ix	$C_{16}H_9BrN_2O_2$	56,39 / 56,33	2,71 / 2,66	8,28 / 8,21	284 (sublimes)	F 89
Iz	$C_{16}H_9BrN_2O_2$	56,41 / 56,33	2,62 / 2,66	8,17 / 8,21	291 (sublimes)	F 96

*Compounds Id-p were crystallized from 2-propanol; the rest were crystallized from glacial AcOH.

Oxazolo[4,5-*c*]quinolin-4(5H)-one (Ia). A. A mixture of 1.76 g (0.01 moles) 3-aminoquinoline II and 50 ml triethylorthoformate was boiled for 5 h, driving off the ethanol liberated during the reaction. The excess triethylorthoformate was driven off under reduced pressure. The residue was cooled and treated with diethyl ether. The precipitate of oxazoloquinoline Ia was filtered off, washed with diethyl ether, and dried.

2-Hexyloxazolo[4,5-*c*]quinolin-4(5H)-one (Ij). Methods B and C are carried out by treatment of respectively 3-aminoquinoline II or 3-N-heptanoylaminoquinoline III (R = C_6H_{13}) with excess heptanoic anhydride according to the procedure of the preceding experiment.

TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	PMR spectra, δ, ppm						Mass spectrum,* $[M]^+$ (relative intensity, %)
	NH (1H, s)	H_{arom}				R	
		9-H (1H, d)	7-H (1H, t)	6-H (1H, d)	8-H (1H, t)		
1	2	3	4	5	6	7	8
Ia	12,00	7,91	7,60	7,49	7,31	8,82 (1H, s, =CH)	186 (100)
Ib	11,91	7,75	7,54	7,43	7,25	2,63 (3H, s, Me	200 (100)
Ic	12,06	7,88	7,61	7,48	7,32	5,14 (2H, s, CH_2Cl)	234 (48)
Id	11,91	7,85	7,58	7,45	7,30	2,99 (2H, q, CH_2); 1,36 (3H, t, Me)	214 (100)
Ie	11,92	7,84	7,56	7,45	7,28	2,94 (2H, t, CH_2); 1,85 (2H, m, $C\underline{H}_2Me$); 0,98 (3H, t, Me)	228 (70)
If	11,91	7,86	7,59	7,48	7,30	3,31 (1H, m, CH); 1,40 (6H, d, $(Me)_2$)	228 (62)
Ig	11,89	7,83	7,57	7,44	7,29	2,97 (2H, t, CH_2); 1,80 (2H, q, $C\underline{H}_2Et$); 1,40 (2H, m, $C\underline{H}_2Me$); 0,92 (3H, t, Me)	242 (60)
Ih	11,94	7,84	7,58	7,45	7,29	2,84 (2H, d, CH_2); 2,20 (1H, m, CH); 0,98 (6H, d, $(Me)_2$)	242 (60)
Ii	11,92	7,84	7,57	7,47	7,30	2,97 (2H, t, CH_2); 1,79 (2H, q, $CH_2C\underline{H}_2$); 1,34 (4H, m, $(C\underline{H}_2)_2Me$); 0,88 (3H, t, Me)	256 (48)
Ij	11,79	7,83	7,56	7,48	7,29	2,97 (2H, t, CH_2); 1,83 (2H, q, $CH_2C\underline{H}_2$); 1,35 (6H, m, $(C\underline{H}_2)_3Me$); 0,88 (3H, t, Me)	270 (37)
Ik	11,82	7,82	7,55	7,47	7,27	2,95 (2H, t, CH_2); 1,81 (2H, q, $CH_2C\underline{H}_2$); 1,30 (8H, m, $(C\underline{H}_2)_4Me$); 0,85 (3H, t, Me)	284 (40)
Il	11,72	7,86	7,58	7,48	7,30	2,97 (2H, t, CH_2); 1,81 (2H, q, $CH_2C\underline{H}_2$); 1,29 (10H, m, $(C\underline{H}_2)_5Me$); 0,85 (3H, t, Me)	298 (32)
Im	11,81	7,84	7,56	7,47	7,30	2,96 (2H, t, CH_2); 1,82 (2H, q, $CH_2C\underline{H}_2$); 1,25 (12H, m, $(C\underline{H}_2)_6Me$); 0,83 (3H, t, Me)	312 (20)

TABLE 2 (continued)

1	2	3	4	5	6	7	8
In	11,73	7,82	7,55	7,48	7,28	2,96 (2H, t, CH_2); 1,82 (2H, q, CH_2CH_2); 1,24 (14H, m, $(CH_2)_7Me$); 0,83 (3H, t, Me)	326 (26)
Io	11,68	7,83	7,56	7,49	7,29	2,96 (2H, t, CH_2); 1,83 (2H, q, CH_2CH_2); 1,25 (16H, m, $(CH_2)_8Me$); 0,85 (3H, t, Me)	340 (18)
Ip	11,72	7,85	7,56	7,49	7,27	2,96 (2H, t, CH_2); 1,82 (2H, q, CH_2CH_2); 1,23 (18H, m, $(CH_2)_9Me$); 0,84 (3H, t, Me)	354 (20)
Iq	11,79	7,79	7,60...7,22 (8H, m, 6-8-H+P h			4,37 (2H, t, CH_2); Ph vic. H_{arom}	276 (100)
Ir	12,03	8,03	7,65 (4H, m, 7-H+3'-5'-H)	7,50		8,23 (2H, d.d, 2',6'-H); 3'–5' vic. H_{arom}	262 (100)
Is	11,99	8,00	7,60	7,50		8,08 (2H, d, 2',6'-H); 7,43 (2H, d, 3',5'-H); 2,40 (3H, s, Me)	276 (100)
It	12,00	7,98	7,65...7,20 (6H, m, 6-8-H+4'-6'-H)			8,11 (1H, t, 2'-H); 4'–6'-H vic. H_{arom}; 2,38 (3H, s, Me)	276 (100)
Iu	12,04	7,96	7,70...7,45 (5H, m, 6,7-H+4'-6'-H)		7,34	8,27 (1H, d, 3'-H); 4'–6'-H vic. H_{arom}	280 (90)
Iv	11,90	7,97	7,65...7,47 (5H, m, 6,7-H+4'-6'-H)		7,35	8,20 (1H, d, 2',6'-H); 4'–6'-H vic. H_{arom}	296 (85)
Iw	12,06	8,06	7,74...7,58 (3H, m, 7-H+5',6'-H)	7,51	7,32	8,23 (2H, s, 2'-H); 8,14 (1H, d, 4'-H); 5',6' vic. H_{arom}	296 (90)
Ix	12,01	7,92 (2H, t 9-H+4'-H)	7,75...7,46 (4H, m, 6,7-H+5',6'-H)		7,36	8,15 (1H, d, 3'-H); 4'–6'-H vic. H_{arom}	340 (84)
Iz	11,77	7,98	7,61	7,50	7,33	8,12 (2H, d, 3',5'-H); 7,60 (2H, d, 2',6'-H)	340 (88)

*For chloro- and bromo-substituted oxazoloquinolines, we give the *m/z* values only for the ^{35}Cl and ^{79}Br isotopes respectively.

E. 2 g P_2O_5 was added to a solution of 2.88 g (0.01 moles) 3-N-heptanoylaminoquinoline III in 50 ml dry carbon tetrachloride and boiled for 5 h, after which the solvent was driven off under reduced pressure. The reaction mass was treated with ice and neutralized with an aqueous solution of Na_2CO_3. The residue of oxazoloquinoline Ij was filtered off, washed with cold water, and dried.

A mixture of samples of 2-hexyloxazoloquinolines Ij obtained by different methods did not give a depression of the melting point.

2-Phenyloxazolo[4,5-*c*]quinolin-4(5H)-one (Ir). D. A solution of 2.80 g (0.01 moles) 3-benzoylaminoquinoline III (R = Ph) in 50 ml acetic anhydride was boiled for 5 h. The excess Ac_2O was driven off and the residue was treated three times with 50 ml boiling acetone. Obtained: 0.68 g (26%) phenyloxazoloquinoline Ir. After evaporation of the acetone extract, 2-methyloxazoloquinoline Ib was obtained.

F. A mixture of 2.80 g (0.01 moles) 3-benzoylaminoquinoline III and 20 g polyphosphoric acid was held on a metal bath at 110-115°C for 4 h. The reaction mass was cooled and poured over ice, after which it was neutralized with an aqueous solution of Na_2CO_3. The residue of oxazoloquinoline Ir was filtered off, washed with cold water, and dried. Yield: 2.46 g (94%).

The PMR spectra of samples of 2-phenyloxazoloquinoline Ir obtained by different methods are identical.

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