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# 4-HYDROXY-2-QUINOLONES. 31.* 3-AMINO-1R-2-OXO-4-HYDROXYQUINOLINES AND THEIR ACYL DERIVATIVES

**I. V. Ukrainets, S. G. Taran, L. V. Sidorenko, O. V. Gorokhova, A. A. Ogirenko, A. V. Turov, and N. I. Filimonova**

*An alternative method has been developed for preparing and studying the antioxidant activity of 3-acylamino-2-oxo-4-hydroxyquinolones. Results are presented from an investigation of the antithyroid and antimicrobial action of the intermediate 2-oxo-3-(1-pyridinio)quinolin-4-olates and the 3-amino-2-oxo-4-hydroxyquinolines.*

A typical method for the preparation of 3-amino-2-oxo-4-hydroxyquinolines I, which are intermediates in the synthesis of biologically active substances, includes the following stages: acylation of esters of anthranilic acids II with chloroacetyl chloride; treatment of the resulting anilides III with pyridine; cyclization of the resulting quaternary salts IV to form 2-oxo-3-(1-pyridinio)quinolin-4-olates VI, the interaction of which with aniline or hydrazine hydrate gives the desired 3-aminoquinolines (method A) [2-5].

As is known [6], quaternary pyridinium salts with electron-acceptor groupings on the nitrogen atom can react with amines along two pathways: the quaternary pyridinium ring may be displaced by the amine that is introduced into the reaction, or the ring may be cleaved with the formation of glutaconic aldehyde (Zincke cleavage), with the nitrogen atom of the pyridine leaving in the form of a primary amino group with the substituent that was located on this atom in the pyridinium salt. In the case of 2-oxo-3-(1-pyridinio)quinolin-4-olates VI, preference should obviously be given to the second path, since the first path is characteristic for reactions of N-R-pyridinium chlorides not with amines, but with their hydrochlorides [6].

On the whole, this method for obtaining 3-aminoquinolines I is fairly simple, and ordinarily does not encounter any particular difficulties. Here we should note only the need for careful monitoring of the completeness of conversion of the sodium salts V to the derivatives VI and their hydrochlorides VII, since they, like the potassium salts of 1-R-2-oxo-3-carbethoxy-4-hydroxyquinolines [7], are extremely resistant to the action of nucleophilic reagents, including hydrazine hydrate. Moreover, the 3-aminoquinolines I are subject to rapid oxidation; therefore, they are best converted immediately to acyl or other derivatives, and to the corresponding hydrochlorides VIII if storage is necessary.

Nonetheless, because of the multistage nature of such syntheses, we have been impelled to search for a more rational scheme of synthesis. We investigated the possibility of obtaining 2-oxo-3-(1-pyridinio)quinolin-4-olates VI by treatment of the readily available 3-bromo-2-oxo-4-hydroxyquinolines IX [8] with boiling pyridine. Unfortunately, however, this reaction leads only to the 3H-2-oxo-4-hydroxyquinolines X, the structure of which was proven by counter-synthesis — decarboxylation of the corresponding 1-R-2,4-dioxoquinoline-3-carboxylic acids [9].

An extremely attractive path for the assembly of 3-aminoquinolines appeared to be the cyclization of N-glycylanthranilates. However, for closure of the quinoline ring, the substituent at the methylene group of the N-acyl radical must be an electron acceptor (phenyl [10], ethoxycarbonyl [11, 12], cyano [13-15], a pyridine ring in salts IV, etc.), as such a grouping provides the possibility of generating an intermediate carbanion. If such a group is not present, the reaction proceeds in different directions; and the use of N-glycylanthranilates leads to 3H-1,4-benzodiazepine-2,5-diones [16]. Protection of the

*For communication 30, see [1].

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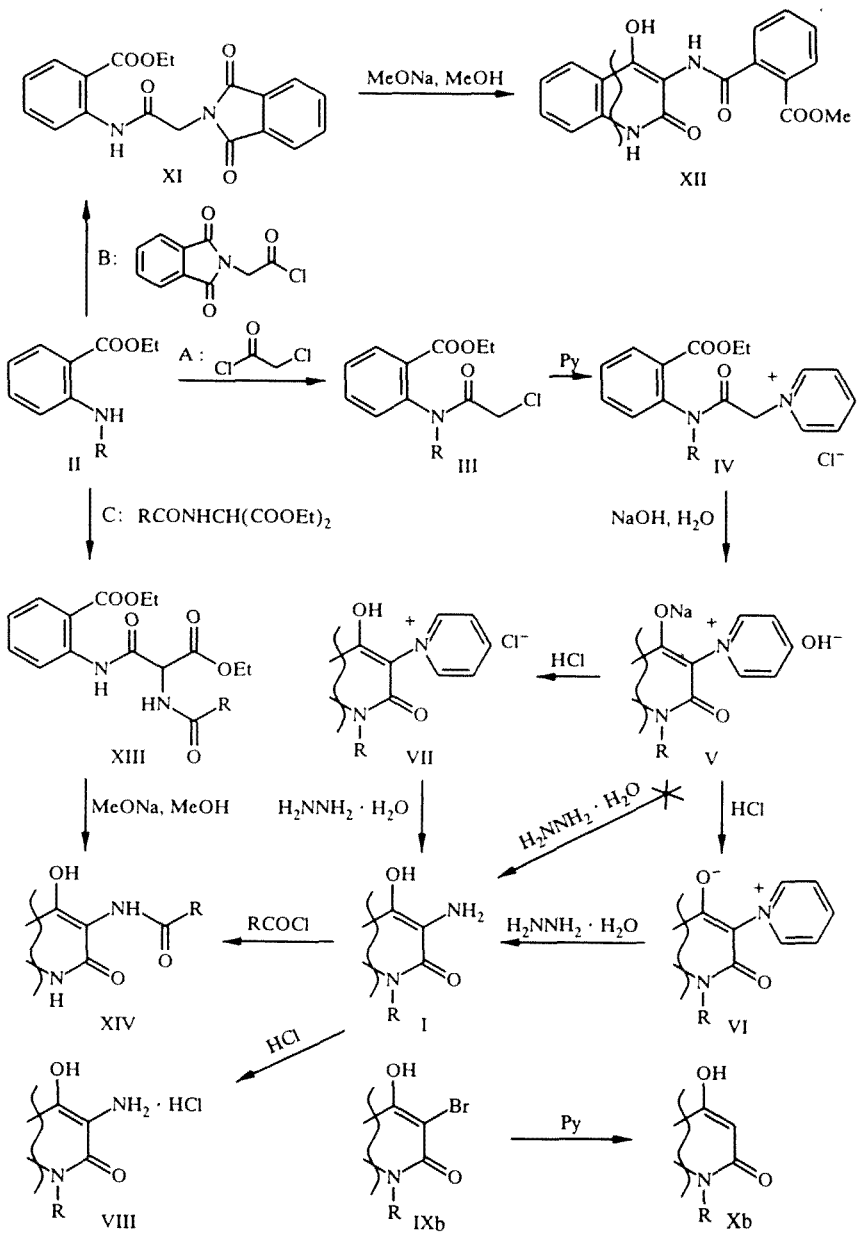

I—X a)R = H;b)R = Me;c)R = Et;d)R = Pr;e)R = Bu; f)R = *i*-Bu; g)R = $C_6H_{13}$
XIV a)R = Me;b)R = Et;c)R = Pr;d)R = *i*-Pr;e)R = Bu; f)R = *i*-Bu; g)R = $C_5H_{11}$;
h)R = $C_6H_{13}$; i)R = $C_7H_{15}$; j)R = $C_8H_{17}$; k)R = $C_9H_{19}$; l)R = $C_{10}H_{21}$; m)R = $C_{11}H_{23}$; n)R = $C_{12}H_{25}$;
o)R = $C_{15}H_{31}$; p)R = $CH_2$—Ph; q)R = Ph; r)R = *p*-$MeC_6H_4$; s)R = *m*-$MeC_6H_4$; t)R = *o*-$FC_6H_4$;
u)R = *o*-$ClC_6H_4$; v)R = *m*-$ClC_6H_4$; w)R = *o*-$BrC_6H_4$; x)R = *p*-$BrC_6H_4$;
y)R = 4-pyridyl; z)R = 3-pyridyl

amino group in N-glycylanthranilates with a phthalic acid group is still inadequate to increase the acidic properties of the methylene group to the required degree; and as a result, the 2-carbethoxyanilide of phthalylaminoacetic acid (XI) is readily cyclized in the presence of sodium methylate to the quinolone XII (method B). It is obviously possible in principle to convert from these compounds to the 3-amino-quinolones I; however, this version of the synthesis can hardly be regarded as any simpler or more rational than method A.

In this connection, a method given in [17] for the preparation of 3-alkyl-2-oxo-4-hydroxyquinolones is of interest. The replacement of monoalkylated diethyl malonates as the acylating agents by N-acylaminomalonic esters, with subsequent treatment of the anilides XIII with sodium methylate in methanol, offers a means for obtaining the final 3-acylaminoquinolines XIV through a shorter scheme of reactions (method C), without isolating the intermediate products, while still obtaining high yields (see Table 3). Still another substantial advantage of this method is that it is not the 3-aminoquinolines I themselves that are of interest as potentially biologically active substances, but rather their derivatives (acyl derivatives, Schiff bases, and so

TABLE 1. Characteristics of 1-R-2-Oxo-3-(1-pyridinio)quinolin-4-olates VIa-g

| Compound | Empirical formula | mp, °C (ethanol)* | PMR spectra, δ, ppm | | | | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $H_{arom}$ | | | | | | R | |
| | | | 2',6'-H (2H, d, J, Hz) | 4'-H (1H, t, J, Hz) | 5,5',3'-H (3H, m) | 7-H (1H, t, J, Hz) | 8-H (1H, d, J, Hz) | 6-H (1H, t, J, Hz) | | |
| VIa | $C_{14}H_{10}N_2O_2$ | >320 (220...222) | 9,12 (6,0) | 8,74 (7,5) | 8,40...8,22 | 7,67 (7,0) | 7,45 (8,0) | 7,28 (7,5) | 12,11 (1H, s, NH) | 76 |
| VIb | $C_{15}H_{12}N_2O_2$ | 194...196 (156...158) | 8,91 (6,0) | 8,74 (7,4) | 8,17...7,94 | 7,54 (7,0) | 7,33 (8,0) | 7,21 (7,5) | 3,50 (3H, s, $CH_3$) | 73 |
| VIc | $C_{16}H_{14}N_2O_2$ | 133...135 (186...188) | 9,12 (6,0) | 8,75 (7,5) | 8,39...8,20 | 7,55 (7,1) | 7,38 (8,0) | 7,12 (7,0) | 4,19 (2H, q, $NCH_2$); 1,19 (3H, s, $CH_3$) | 71 |
| VId | $C_{17}H_{16}N_2O_2$ | 191...193 (174...176) | 9,06 (6,0) | 8,65 (7,5) | 8,37...8,18 | 7,78 (7,0) | 7,64 (8,0) | 7,35 (7,0) | 4,15 (2H, t, $NCH_2$); 1,65 (2H, m, $C\underline{H}_2CH_3$); 0,96 (3H, t, $CH_3$) | 69 |
| VIe | $C_{18}H_{18}N_2O_2$ | 206...208 (178...180) | 8,93 (6,0) | 8,48 (7,6) | 8,19...7,98 | 7,55 (7,4) | 7,35 (8,0) | 7,12 (7,4) | 4,16 (2H, t, $NCH_2$); 1,70...1,21 (4H, m, $(C\underline{H}_2)_2CH_3$); 0,93 (3H, t, $CH_3$) | 66 |
| VIf | $C_{18}H_{18}N_2O_2$ | 198...200 (186...188) | 8,91 (6,0) | 8,49 (7,6) | 8,18...7,98 | 7,53 (7,5) | 7,37 (8,0) | 7,12 (7,3) | 4,04 (2H, d, $NCH_2$); 2,13 (1H, m, $C\underline{H}(CH_3)_2$); 0,92 (6H, d, $CH_3$×2) | 60 |
| VIg | $C_{20}H_{22}N_2O_2$ | 139...141 (97...98) | 8,91 (6,0) | 8,48 (7,5) | 8,18...7,96 | 7,55 (7,0) | 7,36 (8,0) | 7,12 (7,3) | 4,13 (2H, t, $NCH_2$); 1,62 (2H, qu, $NCH_2C\underline{H}_2$); 1,32 (6H, m, $(C\underline{H}_2)_3CH_3$); 0,87 (3H, t, $CH_3$) | 62 |

*Melting points of corresponding hydrochlorides VIIa-g are shown in parentheses.

TABLE 2. Characteristics of 3-Amino-1-R-2-oxo-4-hydroxyquinolines Ia-g

| Compound | Empirical formula | mp, °C* | PMR spectra, δ, ppm† | | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|
| | | | $H_{arom}$ | | | $NH_2$ (2H, s) | R | |
| | | | 5-H (1H, d) | 7, 8-H (2H, m) | 6-H (1H, t) | | | |
| Ia | $C_9H_8N_2O_2$ | 320‡ (subl.) (>320) | 7,71 | 7,32...7,17 | 7,08 | 4,98 | 11,59 (1H, s, NH) | 83 |
| Ib | $C_{10}H_{10}N_2O_2$ | 256...258 (264...266) | 7,77 | 7,40...7,28 | 7,12 | 5,00 | 3,51 (3H, s, $CH_3$) | 77 |
| Ic | $C_{11}H_{12}N_2O_2$ | 240...242 (248...250) | 7,79 | 7,41...7,30 | 7,13 | 4,99 | 4,20 (2H, q, $NCH_2$); 1,21 (3H, s, $CH_3$) | 70 |
| Id | $C_{12}H_{14}N_2O_2$ | 198...200 (208...210) | 7,82 | 7,48...7,31 | 7,16 | 5,10 | 4,22 (2H, t, $NCH_2$); 1,62 (2H, m, $C\underline{H}_2CH_3$); 0,92 (3H, t, $CH_3$) | 75 |
| Ie | $C_{13}H_{16}N_2O_2$ | 194...196 (199...201) | 8,17 | 7,65...7,50 | 7,34 | 5,08 | 4,27 (2H, t, $NCH_2$); 1,76...1,20 (4H, m, $(C\underline{H}_2)_2CH_3$); 0,92 (3H, t, $CH_3$) | 80 |
| If | $C_{13}H_{16}N_2O_2$ | 172...176 (206...208) | 8,16 | 7,70...7,54 | 7,32 | 5,03 | 4,15 (2H, d, $NCH_2$); 2,10 (1H, m, $C\underline{H}(CH_3)_2$); 0,88 (6H, d, $CH_3$×2) | 73 |
| Ig | $C_{15}H_{20}N_2O_2$ | 146...148 (165...167) | 8,18 | 7,79...7,55 | 7,34 | 5,05 | 4,26 (2H, t, $NCH_2$); 1,58 (2H, qu, $NCH_2C\underline{H}_2$); 1,40...1,10 (6H, m, $(C\underline{H}_2)_3CH_3$); 0,84 (3H, t, $CH_3$) | 71 |

*Melting points of corresponding hydrochlorides VIIIa-g are shown in parentheses.

†Signals of protons of 4-OH groups are not manifested in the PMR spectra, evidently because of rapid deuterium exchange. Signals of protons of $NH_2 \cdot HCl$ groups in salts VIIIa-g have the form of a broadened singlet in the 8.86-9.33 ppm region.

‡According to [2], mp 360°C.

TABLE 3. Characteristics of 3-Acylamino-2-oxo-4-hydroxyquinolines XIVa-z

| Compound | Empirical formula | mp, °C* | PMR spectra, δ, ppm† | | | | | | Yield, %, by indicated method‡ |
|---|---|---|---|---|---|---|---|---|---|
| | | | NHCOR (1H, s) | $H_{arom}$ | | | | R | |
| | | | | 5-H (1H, d) | 7-H (1H, t) | 8-H (1H, d) | 6-H (1H, t) | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| XIVa | $C_{11}H_{10}N_2O_3$ | 244...246 | 9,71 | 7,86 | 7,51 | 7,31 | 7,21 | 2,24 (3H, s, $CH_3$) | A 53, B 81 |
| XIVb | $C_{12}H_{12}N_2O_3$ | 234...236 | 9,59 | 7,87 | 7,50 | 7,28 | 7,20 | 2,58 (2H, q, $COCH_2$); 1,11 (3H, t, $CH_3$) | A 51, B 84 |
| XIVc | $C_{13}H_{14}N_2O_3$ | 188...190 | 9,70 | 7,85 | 7,50 | 7,29 | 7,20 | 2,54 (2H, t, $COCH_2$); 1,61 (2H, m, $CH_2CH_3$); 0,92 (3H, t, $CH_3$) | A 50, B 79 |
| XIVd | $C_{13}H_{14}N_2O_3$ | 204...206 | 9,64 | 7,86 | 7,50 | 7,29 | 7,20 | 3,00 (1H, m, $CH(CH_3)_2$); 1,13 (6H, d, $CH(CH_3)_2$) | A 50 |
| XIVe | $C_{14}H_{16}N_2O_3$ | 182...184 | 9,66 | 7,86 | 7,50 | 7,30 | 7,20 | 2,58 (2H, t, $COCH_2$); 1,55 (2H, qu, $COCH_2CH_2$); 1,29 (2H, m, $CH_2CH_3$); 0,89 (3H, t, $CH_3$) | A 49, B 78 |
| XIVf | $C_{14}H_{16}N_2O_3$ | 200...202 | 9,74 | 7,85 | 7,51 | 7,29 | 7,20 | 2,50 (2H, d, $COCH_2$); 2,09 (1H, m, $CH(CH_3)_2$); 0,94 (6H, d, $CH(CH_3)_2$) | A 47 |
| XIVg | $C_{15}H_{18}N_2O_3$ | 160...162 | 9,66 | 7,85 | 7,50 | 7,28 | 7,20 | 2,56 (2H, t, $COCH_2$); 1,59 (2H, qu, $COCH_2CH_2$); 1,40...1,12 (4H, m, $CH_2CH_2CH_3$); 0,86 (3H, t, $CH_3$) | A 53 |

TABLE 3. (Continued)

| Compound | Empirical formula | mp, °C* | PMR spectra, δ, ppm† | | | | | | Yield, %, by indicated method‡ |
|---|---|---|---|---|---|---|---|---|---|
| | | | NHCOR (1H, s) | $H_{arom}$ | | | | R | |
| | | | | 5-H (1H, d) | 7-H (1H, t) | 8-H (1H, d) | 6-H (1H, t) | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| XIVh | $C_{16}H_{20}N_2O_3$ | 158...160 | 9,71 | 7,87 | 7,51 | 7,30 | 7,21 | 2,58 (2H, t, $COCH_2$); 1,57 (2H, qu, $COCH_2CH_2$); 1,41...1,10 (6H, m, $(CH_2)_3CH_3$); 0,87 (3H, t, $CH_3$) | A 54 |
| XIVi | $C_{17}H_{22}N_2O_3$ | 152...154 | 9,66 | 7,86 | 7,52 | 7,28 | 7,19 | 2,57 (2H, t, $COCH_2$); 1,59 (2H, qu, $COCH_2CH_2$); 1,40...1,10 (8H, m, $(CH_2)_4CH_3$); 0,87 (3H, t, $CH_3$) | A 50, B 80 |
| XIVj | $C_{18}H_{24}N_2O_3$ | 146...148 | 9,58 | 7,86 | 7,51 | 7,30 | 7,20 | 2,58 (2H, t, $COCH_2$); 1,59 (2H, qu, $COCH_2CH_2$); 1,40...1,12 (10H, m, $(CH_2)_5CH_3$); 0,85 (3H, t, $CH_3$) | A 52 |
| XIVk | $C_{19}H_{26}N_2O_3$ | 144...146 | 9,55 | 7,87 | 7,50 | 7,31 | 7,20 | 2,57 (2H, t, $COCH_2$); 1,62 (2H, qu, $COCH_2CH_2$); 1,40...1,11 (12H, m, $(CH_2)_6CH_3$); 0,85 (3H, t, $CH_3$) | A 54 |
| XIVl | $C_{20}H_{28}N_2O_3$ | 140...142 | 9,70 | 7,89 | 7,52 | 7,30 | 7,20 | 2,59 (2H, t, $COCH_2$); 1,61 (2H, qu, $COCH_2CH_2$); 1,40...1,10 (14H, m, $(CH_2)_7CH_3$); 0,84 (3H, t, $CH_3$) | A 53, B 76 |
| XIVm | $C_{21}H_{30}N_2O_3$ | 138...140 | 9,67 | 7,84 | 7,49 | 7,29 | 7,20 | 2,58 (2H, t, $COCH_2$); 1,56 (2H, qu, $COCH_2CH_2$); 1,40...1,10 (16H, m, $(CH_2)_8CH_3$); 0,83 (3H, t, $CH_3$) | A 55 |
| XIVn | $C_{22}H_{32}N_2O_3$ | 134...136 | 9,69 | 7,85 | 7,50 | 7,28 | 7,19 | 2,57 (2H, t, $COCH_2$); 1,57 (2H, qu, $COCH_2CH_2$); 1,40...1,11 (18H, m, $(CH_2)_9CH_3$); 0,83 (3H, t, $CH_3$) | A 54 |
| XIVo | $C_{25}H_{38}N_2O_3$ | 124...126 | 9,59 | 7,83 | 7,48 | 7,29 | 7,19 | 2,58 (2H, t, $COCH_2$); 1,60 (2H, qu, $COCH_2CH_2$); 1,40...1,10 (24H, m, $(CH_2)_{12}CH_3$); 0,84 (3H, t, $CH_3$) | A 52 |
| XIVp | $C_{17}H_{14}N_2O_3$ | 264...266 | 9,85 | 7,85 | 7,60...7,04 (8H, m, 7,8,6-H + Ph) | | | 3,93 (2H, s, $CH_2$ Ph); Ph mx.$H_{arom}$ | A 51, B 79 |
| XIVq | $C_{16}H_{12}N_2O_3$ | 314...316 | 9,59 | 7,91 | 7,51 | 7,31 | 7,22 | 8,05 (2H, d, 2',6'-H); 7,60 (3H, t, 3',4',5'-H) | A 53, B 62 |

TABLE 3. (Continued)

| Compound | Empirical formula | mp. °C* | PMR spectra, δ, ppm† | | | | | | Yield, %, by indicated method‡ |
|---|---|---|---|---|---|---|---|---|---|
| | | | NHCOR (1H, s) | $H_{arom}$ | | | | R | |
| | | | | 5-H (1H, d) | 7-H (1H, t) | 8-H (1H, d) | 6-H (1H, t) | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| XIV r | $C_{17}H_{14}N_2O_3$ | 310...312 | 9,56 | 7,99 (3H, m, 5-H + 2',6'-H) | 7,52 | 7,30 | 7,21 | 2,40 (3H, t, $CH_3$); 7,66 (2H, d, 3',5'-H); 2',6'-H mx.$H_{arom}$ | A 54 |
| XIV s | $C_{17}H_{14}N_2O_3$ | 316...318 | 9,49 | 7,92 (3H, m, 5-H + 2',6'-H) | 7,68...7,10 (5H, m, 7,8,6-H + 4',5'-H) | | | 2,41 (3H, c, $CH_3$); 2',4',5',6'-H mx. H arom. | A 50 |
| XIV t | $C_{16}H_{11}FN_2O_3$ | 294...298 | 9,82 | 8,11...7,80 (2H, m, 5-H + 3'-H) | 7,78...7,14 (6H, m, 7,8,6-H + 4',6',5'-H) | | | Mx. H arom. | A 48 |
| XIV u | $C_{16}H_{11}ClN_2O_3$ | 296...298 | 9,86 | 8,03...7,76 (2H, m, 5-H + 3'-H) | 7,74...7,21 (6H, m, 7,8,6-H + 4',6',5'-H) | | | Mx. $H_{arom}$ | A 54 |
| XIV v | $C_{16}H_{11}ClN_2O_3$ | 292...294 | 9,63 | 7,88 | 7,54 | 7,31 | 7,22 | 8,10 (1H, s, 2'-H); 8,98 (1H, d, 6'-H); 7,63 (2H, t, 4',5'-H) | A 49 |
| XIV w | $C_{16}H_{11}BrN_2O_3$ | 286...288 | 9,84 | 7,94 | 7,69...7,42 (3H, m, 7-H + 4',5'-H) | 7,32 | 7,20 | 7,76 (2H, d, 3',6'-H); 4',5'-H mx.7-H | A 51 |
| XIV x | $C_{16}H_{11}BrN_2O_3$ | >320 | 9,61 | 7,89 | 7,53 | 7,31 | 7,21 | 7,97 (2H, d, 2',6'-H); 7,75 (2H, d, 3',5'-H) | A 47 |
| XIV y | $C_{15}H_{11}N_3O_3$ | 316...318 | 9,75 | 7,88 | 7,55 | 7,32 | 7,21 | 8,78 (2H, d, 2',6'-H); 7,96 (2H, d, 3',5'-H) | A 53 |
| XIV z | $C_{15}H_{11}N_3O_3$ | 300...302 | 9,72 | 7,90 | 7,65...7,46 (2H, m, 7-H + 5'-H) | 7,33 | 7,22 | 9,17 (1H, s, 2'-H); 8,77 (1H, d, 6'-H); 8,36 (1H, d, 4'-H); 5'-H mx.7-H | A 51 |

*Compounds XIVa-o were crystallized from ethanol, XIVp from dioxane, others from DMF.

†Signals of protons of 4-OH groups are manifested in the form of a singlet in the 12.14-11.66 ppm region. Singlet signals of NH group protons of the quinoline ring are located in the 11.86-11.03 ppm region.

‡Yields are calculated on the basis of the original ethyl anthranilate (II).

TABLE 4. Data from Elemental Analyses

| Compound | Found, % | | | Calculated, % | | |
|---|---|---|---|---|---|---|
| | C | H | N | C | H | N |
| XIV a | 60,57 | 4,58 | 12,86 | 60,55 | 4,62 | 12,84 |
| XIV b | 62,07 | 5,20 | 12,09 | 62,06 | 5,21 | 12,06 |
| XIV c | 63,41 | 5,73 | 11,35 | 63,40 | 5,73 | 11,38 |
| XIV d | 63,37 | 5,71 | 11,34 | 63,40 | 5,73 | 11,38 |
| XIV e | 64,57 | 6,24 | 10,77 | 64,60 | 6,20 | 10,76 |
| XIV f | 64,63 | 6,21 | 10,74 | 64,60 | 6,20 | 10,76 |
| XIV g | 65,72 | 6,59 | 10,19 | 65,68 | 6,61 | 10,21 |
| XIV h | 66,63 | 6,70 | 9,81 | 66,65 | 6,99 | 9,72 |
| XIV i | 67,50 | 7,27 | 9,33 | 67,53 | 7,33 | 9,26 |
| XIV j | 68,30 | 7,67 | 8,88 | 68,33 | 7,65 | 8,85 |
| XIV k | 69,04 | 7,90 | 8,49 | 69,06 | 7,93 | 8,48 |
| XIV l | 69,72 | 8,26 | 8,16 | 60,74 | 8,19 | 8,13 |
| XIV m | 70,34 | 8,45 | 7,83 | 70,36 | 8,44 | 7,81 |
| XIV n | 70,99 | 8,65 | 7,50 | 70,94 | 8,66 | 7,52 |
| XIV o | 72,46 | 9,20 | 6,78 | 72,43 | 9,24 | 6,76 |
| XIV p | 69,40 | 4,83 | 9,50 | 69,38 | 4,79 | 9,52 |
| XIV q | 68,60 | 4,30 | 9,94 | 68,57 | 4,32 | 9,99 |
| XIV r | 69,40 | 4,80 | 9,50 | 69,38 | 4,79 | 9,52 |
| XIV s | 69,39 | 4,77 | 9,53 | 69,38 | 4,79 | 9,52 |
| XIV t | 64,44 | 3,70 | 9,42 | 64,43 | 3,72 | 9,39 |
| XIV u | 61,02 | 3,55 | 8,93 | 61,06 | 3,52 | 8,90 |
| XIV v | 61,10 | 3,50 | 8,88 | 61,01 | 3,52 | 8,90 |
| XIV w | 53,47 | 3,13 | 7,84 | 53,50 | 3,09 | 7,80 |
| XIV x | 53,49 | 3,10 | 7,82 | 53,50 | 3,09 | 7,80 |
| XIV y | 64,01 | 3,98 | 14,99 | 64,05 | 3,94 | 14,94 |
| XIV z | 64,08 | 3,93 | 14,90 | 64,05 | 3,94 | 14,94 |

on [18-20]); and, in contrast to the traditional path, the required substituent is introduced during the stage of synthesizing the corresponding N-acylaminomalonic ester. On the whole, we can state that the convergent scheme of obtaining the 3-acylaminoquinolines XIV is more effective than the usual linear scheme, and hence can be recommended as a preparative method.

The rather easy oxidizability of derivatives of 2-oxo-4-hydroxyquinoline [21] served as the theoretical basis for studying the antioxidant activity of 3-acylamino-2-oxo-4-hydroxyquinolines XIV *in vitro*, following procedures given in [22]. It was established that some of the synthesized compounds XIVe,r,v have higher activities than vitamin E and are not inferior to Ionol. We also investigated the antimicrobial activities of the intermediate 2-oxo-3-(1-pyridinio)quinolin-4-olates VI, their hydrochlorides VII, and hydrochlorides of 3-amino-1R-2-oxo-4-hydroxyquinolines VIII with respect to the following test cultures: *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25853), and *Bacillus subtilis* (ATCC 6633). Note should be taken of the stronger antimicrobial effect of the hydrochlorides VII in comparison with the corresponding 2-oxo-3-(1-pyridinio)quinolin-4-olates VI, probably because of their better solubility; on the whole, however, this group of substances is not of practical interest, since their *MPK* is no less than 60 μg/ml.* The antithyroid activity of the 2-oxo-3-(1-pyridinio)quinolin-4-olates VI can be classified as relatively weak. Their intragastric injection in a dose of 10 mg/kg produces an appreciable lowering of the triiodothyronine and thyroxine concentrations in the blood serum of animals. However, the comparison preparation, mercazolyl, gives a considerably greater effect.

*As in Russian original; the Russian initialism *MPK* is presumably equivalent to MOC (maximum oxygen consumption) — Translator.

## EXPERIMENTAL

PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY instrument in DMSO-$d_6$, internal standard TMS. The mass spectrum of the quinolone XII was obtained in a Finnigan MAT-4615 B instrument, ionizing voltage 70 eV, with ballistic heating of the sample.

The results from elemental analyses are given in Table 4.

**General Procedure for Preparing Acylaminomalonic Esters.** A mixture of 2.11 g (0.01 mole) of diethylaminomalonate, 10 ml of water, and 30 ml of methylene chloride was chilled in an ice-water bath; a solution of 2.1 g (0.02 mole) of sodium carbonate in 20 ml of water was added; then, a solution of 0.01 mole of the appropriate acid chloride in 10 ml of methylene chloride was added while stirring, with the addition controlled so as to avoid any severe foaming. The mixture was stirred for 2 h and then acidified with dilute (1:1) HCl to pH 4, after which the organic layer was separated off, treated with activated carbon, and evaporated down. The acylaminomalonic esters that were obtained were used without additional purification in the subsequent syntheses.

**Ethyl N-(Chloroacetyl)anthranilate (IIIa, $C_{11}H_{12}ClNO_3$).** To a solution of 1.65 g (0.01 mole) of ethyl anthranilate in 15 ml of methylene chloride, 1.53 ml (0.011 mole) of triethylamine and 0.88 ml (0.011 mole) of chloroacetyl chloride were added. After 2 h, the reaction mixture was diluted with water, and the organic layer was separated and evaporated to dryness. Yield 2.16 g (90%), mp 74-76°C (ethanol). PMR spectrum, ppm: 11.34 (1H, s, NH); 8.41 (1H, d, J = 8.0 Hz, 3-H); 7.98 (1H, dd, J = 8.0 and 2.0 Hz, 6-H); 7.67 (1H, td, J = 8.0 and 2.0 Hz, 5-H); 7.26 (1H, td, J = 8.0 and 1.7 Hz, 4-H); 4.44 (2H, s, $CH_2Cl$); 4.34 (2H, q, $C\underline{H}_2CH_3$); 1.35 (3H, t, $CH_2C\underline{H}_3$).

**Anilides IIIb-g** were obtained by an analogous procedure; after removing the organic solvent, they were used in the next stage without additional purification.

**1H-2-Oxo-3-(1-pyridinio)quinolin-4-olate (VIa, $C_{14}H_{10}N_2O_2$).** A mixture of 2.41 g (0.01 mole) of the anilide III in 20 ml of pyridine was refluxed for 30 min, after which the mixture was cooled, and 50 ml of acetone was added. The precipitate, consisting of the salt IV, was filtered off, washed with acetone, and then treated with 10 ml of 10% aqueous NaOH and left for 4-5 h at room temperature. The reaction mixture was then acidified with HCl to pH 3 and stirred for 1 h. The pH was checked, and additional acid was added if necessary. The precipitate of the 1H-2-oxo-3-(1-pyridinio)quinolin-4-olate (VIa) was filtered off, washed with water, and dried. Yield 1.82 g (76%).

**1-R-2-Oxo-3-(1-pyridinio)quinolin-4-olates VIb-g** were obtained by analogous procedures (Table 1).

**General Procedure for Preparing 1-R-2-Oxo-4-hydroxyquinoline-3-(1-pyridinium) Chlorides (VIIa-g).** The reaction mixture after acidification (see previous example) was heated to boiling, treated with activated carbon, and filtered. The hydrochloride VII gradually crystallized from the solution. It was filtered off, washed with cold water, and dried.

**1H-3-Amino-2-oxo-4-hydroxyquinoline (Ia, $C_9H_8N_2O_2$).** A solution of 0.01 mole of 1H-2-oxo-3-(1-pyridinio)quinolin-4-olate (VIa) or its hydrochloride VIIa in 20 ml of 50% hydrazine hydrate was refluxed for 4 h, after which it was diluted with water, and the excess hydrazine hydrate was driven off in the form of an azeotropic mixture. After cooling, the reaction mixture was neutralized with acetic acid. The resulting precipitate of the 3-aminoquinoline Ia was filtered off, washed with water, and dried. Yield 1.46 g (83%).

The 1-R-3-amino-2-oxo-4-hydroxyquinolines Ib-g were obtained analogously (Table 2).

**General Procedure for Preparing Hydrochlorides of 1-R-3-Amino-2-oxo-4-hydroxyquinolines (VIIIa-g).** To a suspension of 0.01 mole of the appropriate 3-aminoquinoline I in 10 ml of water, concentrated HCl was added to bring the pH to 3. This resulted in dissolution of the 3-aminoquinoline and, after a few minutes, crystallization of the hydrochloride VIII. It was filtered off rapidly and dried in a vacuum desiccator.

**1-Methyl-2-oxo-4-hydroxyquinoline (Xb, $C_{10}H_9NO_2$). A.** A solution of 2.54 g (0.01 mole) of 1-methyl-2-oxo-3-bromo-4-hydroxyquinoline (IXb) in 15 ml of pyridine was refluxed for 45 min. The reaction mixture was cooled, diluted with water, and acidified with HCl to pH 3. The resulting precipitate of the quinolone Xb was filtered off, washed with water, and dried. Yield 1.68 g (96%), mp 264-266°C (ethanol). According to [23], mp 265-267°C. PMR spectrum, ppm: 11.32 (1H, s, OH); 7.88 (1H, d, J = 8.0 Hz, 5-H); 7.62 (1H, td, J = 7.4 and 2.0 Hz, 7-H); 7.44 (1H, d, J = 7.8 Hz, 8-H); 7.22 (1H, td, J = 7.4 and 2.0 Hz, 6-H); 5.88 (1H, s, 3-H); 3.52 (1H, s, $CH_3$).

**B.** A 2.19-g quantity (0.01 mole) of 1-methyl-2,4-dioxoquinoline-3-carboxylic acid [9] was held in a metal bath at 290-300°C until the end of $CO_2$ evolution (10 min). After cooling, the product was recrystallized from ethanol, obtaining 1.54 g (88%) of the quinolone Xb.

A mixed melting point test on samples of the 1-methyl-2-oxo-4-hydroxyquinoline (Xb) obtained by the different methods did not show any depression of melting point. The PMR spectra of these two samples were identical.

**2-Carbethoxyanilide of Phthalylaminoacetic Acid (XI, $C_{19}H_{16}N_2O_4$).** Obtained by acylation of ethyl anthranilate by phthalylaminoacetyl chloride by the procedure used in the synthesis of the anilides III. Yield 93%, mp 172-174°C (ethanol). PMR spectrum, ppm: 10.82 (1H, s, NH); 8.09 (1H, d, J = 8.0 Hz, 3-H); 7.92 (4H, s, $H_{arom}$ of phthalimide); 7.87 (1H, dd, J = 8.0 and 2.0 Hz, 6-H); 7.60 (1H, td, J = 8.0 and 2.0 Hz, 5-H); 7.21 (1H, t, J = 8.0 Hz, 4-H); 4.49 (2H, s, $CH_2$); 4.22 (2H, q, $C\underline{H}_2CH_3$); 1.28 (3H, t, $CH_3$).

**3-(2-Carbomethoxybenzoylamino)-1H-2-oxo-4-hydroxyquinoline (XII, $C_{18}H_{14}N_2O_5$).** To a solution of 3.36 g (0.01 mole) of the anilide XI in 30 ml of absolute methanol, a solution of sodium methylate in methanol was added [solution prepared from 1.15 g (0.05 mole) of metallic sodium in 30 ml of methanol], and the mixture was refluxed for 4 h. After cooling, the reaction mixture was diluted with HCl-acidified water. The precipitate of the quinolone XII was filtered off, washed with water, and dried. Yield 2.83 g (84%), mp 178-180°C (DMF). PMR spectrum, ppm: 12.13 (1H, s, OH); 10.56 (1H, s, NH); 10.39 (1H, s, NH); 8.32-7.59 (8H, m, $H_{arom}$); 3.91 (3H, s, $CH_3$). Mass spectrum, *m/z* (and relative intensity, %): 338 (24) $[M]^+$, 306 (37) $[M-MeOH]^+$, 151 (100), 119 (66), 104 (30), 76 (38).

**3-Acetylamino-2-oxo-4-hydroxyquinoline (XIVa, $C_{11}H_{10}N_2O_3$). A**. To a mixture of 1.76 g (0.01 mole) of the 3-aminoquinoline Ia and 1.53 ml (0.011 mole) of triethylamine in 20 ml of acetone, 0.86 g (0.011 mole) of acetyl chloride was added, and the mixture was allowed to stand for 2-3 h at room temperature. Then the reaction mixture was diluted with HCl-acidified water. The precipitate of the 3-acetylaminoquinoline XIVa was filtered off, washed with water, and dried. Yield 2.02 g (93%). The yield calculated on the original ethyl anthranilate was 53%.

**B**. A mixture of 1.65 g (0.01 mole) of ethyl anthranilate and 2.17 g (0.01 mole) of acetylaminomalonic ester was held in a metal bath for 5 h at 170-180°C. After cooling the reaction mixture, a solution of sodium methylate in methanol was added [solution prepared from 1.15 g (0.05 mole) of metallic sodium and 50 ml of methanol], and the mixture was refluxed for 4-5 h. After cooling, 100 ml of water was added, and the mixture was acidified with HCl to pH 3-4. The resulting precipitate of the 3-acetylaminoquinoline XIVa was filtered off, washed with water, and dried. Yield 1.76 g (81%).

The identity of the two samples of the 3-acylaminoquinolines XIV obtained by different methods was established by the absence of any melting point depression for a mixed sample, and also on the basis of the PMR spectra.

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