*Chemistry of Heterocyclic Compounds, Vol. 30, No. 5, 1994*

# 4-HYDROXY-2-QUINOLONES
# 19.* A NEW SYNTHESIS OF 3-ALKYL-2-OXO-4-HYDROXYQUINOLINES

**I. V. Ukrainets, S. G. Taran,**
**O. A. Evtifeeva, O. V. Gorokhova,**
**P. A. Bezuglyi, A. V. Turov,**
**L. N. Voronina, and N. I. Filimonova**

*3-Alkyl-substituted 2-oxo-4-hydroxyquinolines were obtained in high yields from N,N'-di-2-alkoxycarbonylanilides of alkylmalonic acids under conditions of the Dieckmann condensation. Some types of biological activity were found for the compounds synthesized.*

Known methods for the synthesis of 3-alkyl-2-oxo-4-hydroxyquinolines are based either on the acylation of anilines of alkylmalonic esters with the simultaneous thermal cyclization of the resulting anilides [2, 3], or on the acylation of alkyl anthranilates with acid chlorides of monoethyl esters of alkylmalonic acids and subsequent closure of the quinolone ring according to Dieckmann [4, 5].

The main disadvantages of these methods are associated with the formation of symmetrical dianilides in the first case, and the low accessibility of the acylating agents [6, 7] in the second case. Moreover, the first method does not lead to the desired results in some cases. Thus, for example, the reaction with allylmalonic ester does not allow the isolation of 3-allyl-2-oxo-4-hydroxyquinoline (Ic) [3]. We undertook attempts to improve the methods of synthesis of 3-alkyl-2-oxo-4-hydroxyquinolines.

A previous communication concerned the synthesis of 3,3-disubstituted 2,4-dioxoquinolines by the thermolysis of symmetrical di-2-ethoxycarbonylanilides of alkylmalonic acids [8]. In the presence of bases, i.e. in conditions of the Dieckmann condensation, these compounds form 3-alkyl-2-oxo-4-hydroxyquinolines (I) with high yields. Since the synthesis of N,N'-di-2-alkoxycarbonylanilides of alkylmalonic acids (II) is very simple, the given method can be recommended, on the whole, as a preparative method. One of its disadvantages is the nonrational utilization of alkyl anthranilates. However, this disadvantage is also successfully removed in most cases by the selection of the most optimal proportion of the reagents.

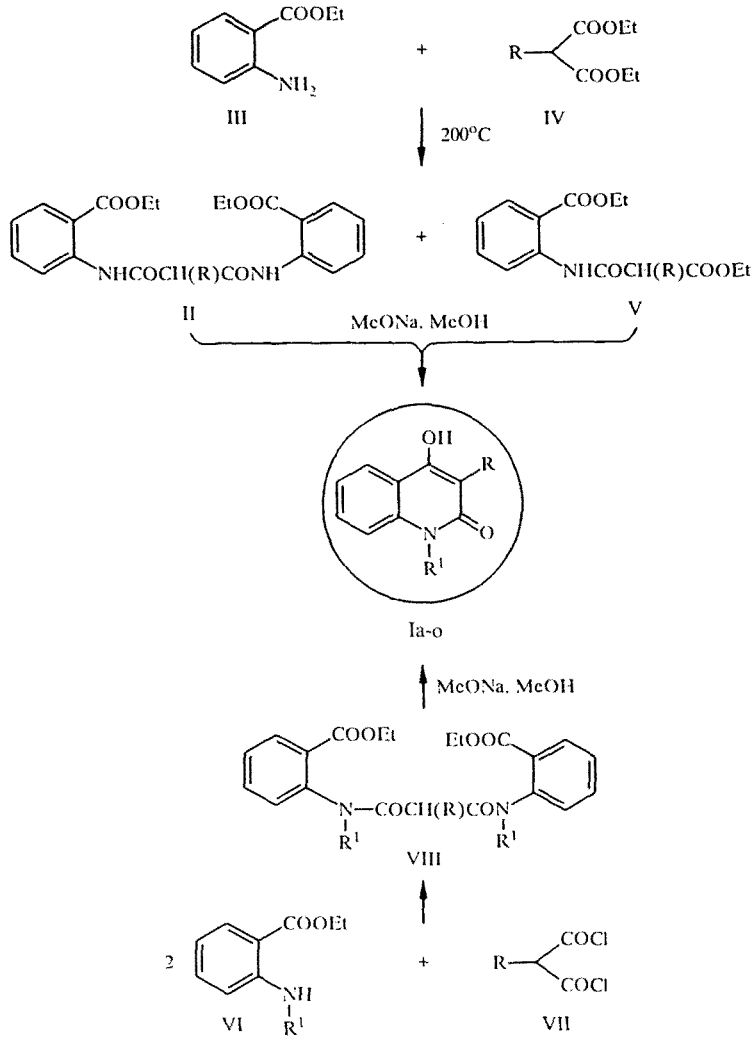
It is known that the acylation of anilines by diethyl malonates is practically always accompanied by the formation of symmetrical dianilides [2, 3, 9-12]. Moreover, it was established experimentally [13] that even ethyl esters of malonanilic acids, isolated in a pure form, are readily converted under analogous conditions (the heating to 170-200°C) to dianilides with the elimination of the corresponding diethyl malonates. Taking all this into account, it is expedient to introduce a twofold excess of the anthranilate into the reaction (Method A) for the acylation of esters of anthranilic acid (III) by diethyl malonates (IV) with lower alkyl substituents. With the lengthening of the hydrocarbon chain of the alkyl substituent, the acylating capacity of the second ethoxycarbonyl group of the malonic esters (IV) falls so much (evidently by reason of steric hindrance) that satisfactory results can also already be obtained with equimolar ratios of the esters (III) and (IV) (Method B).

It should be noted that one more positive feature is that the given method does not require the separation of the mono- and dianilides of alkylmalonic acids (V) and (II), which are always present in different proportions in the reaction mixture (see the scheme).

*For Communication 18, see [1].

Ukrainian Pharmaceutical Academy, Khar'kov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 673-678, May, 1994. Original article submitted May 6, 1994.

0009-3122/94/3005-0591$12.50 



I $R^1$ = H: a R = $CH_3$; b R = $C_2H_5$; n R = $CH_2CH{=}CH_2$; d R = $C_3H_7$; e R = *i*-$C_3H_7$; f R = $C_4H_9$; 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 = $C_{12}H_{25}$; n R = $CH_2C_6H_5$, $R^1$ = $CH_3$; o R = $C_4H_9$

The utilization of the available alkylmalonic dichlorides (VII) as the acylating agents significantly widens the possibilities of the method (Method C), allowing the ready synthesis of both the 1H-2-oxo-3-alkyl-4-hydroxyquinolines (Ia-n) and their 1-substituted analogs (Io).

In spite of their wide distribution in nature [14], 3-alkyl-2-oxo-4-hydroxyquinolines remain, as before, practically unstudied in a pharmaceutical connection. Works relating to this subject and associated mainly with the isolation from plant raw material and the establishment of the structure of alkaloids of the given group [15-19] were devoted to synthetic methods for their isolation [20, 21]. Information on the study of biological properties of 3-alkyl-2-oxo-4-hydroxyquinolines, more often their antimicrobial and fungicidal activity [3, 14], is only presented in a few publications. The quinolones (Ia-o), which we synthesized, were tested for antiinflammatory, antioxidant, and antimicrobial activity. The influence of these compounds on the excretory function of the kidneys and the coagulant system of the blood was also studied. As a result of the biological testing carried out, it was established that the 3-alkylquinolones (Ia-o) do not show marked antiinflammatory action using the model of carragenin edema. These compounds proved to be practically inactive (the MICs $\geq$ 60 $\mu$g/ml) toward *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 78857), and *Bacillus subtilis* (ATCC 6633). In the entire group of substances, an insignificant anticoagulant effect was only noted for the 3-benzyl-substituted derivative (In), whereas the remaining compounds did not influence humoral hemostasis. An interesting regularity was found in the study of the influence of the quinolones (Ia-o) on the excretory function of the kidneys. It was shown that

TABLE 1. Characteristics of the 3-Alkyl-2-oxo-4-hydroxyquinolones

| Compound | Empirical formula | mp, °C (ethanol) | PMR spectral parameters, δ, ppm | | | | | | | Method | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NH (1H, s) | OH* (1H, s) | $H_{arom}$ | | | | R | | |
| | | | | | 5-H (1H, d.d, J, Hz) | 7-H (1H, t.d, J, Hz) | 8-H (1H, d.d, J, Hz) | 6-H (1H, t.d, J, Hz) | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Ia | $C_{10}H_9NO_2$ | 264...266 | 11,32 | 10,08 | 7,97 (8,0; 1,3) | 7,45 (7,5; 1,4) | 7,27 (8,0; 1,3) | 7,13 (7,2; 1,6) | 2,01 (3H, s, $CH_3$) | A | 94 |
| Ib | $C_{11}H_{11}NO_2$ | 260...261 | 11,27 | 10,03 | 7,86 (8,0; 1,2) | 7,43 (7,4; 1,8) | 7,24 (8,0; 1,3) | 7,12 (7,3; 1,5) | 2,57 (2H, q, $CH_2$); 1,01 (3H, t, $CH_3$) | A | 92 |
| Ic | $C_{12}H_{11}NO_2$ | 198...200 | 11,33 | 10,14 | 7,90 (7,8; 1,4) | 7,46 (7,7; 1,5) | 7,26 (7,9; 1,3) | 7,12 (7,0; 1,9 | 6,09...5,68 (1H,m, $CH{=}CH_2$); 5,12...4,83 (2H,m, $CH{=}CH_2$) | A C | 61 88 |
| Id | $C_{12}H_{13}NO_2$ | 234...236 | 11,26 | 9,99 | 7,96 (8,0; 1,3) | 7,47 (7,3; 1,4) | 7,26 (8,0; 1,2) | 7,13 (7,3; 1,8) | 2,54 (2H, t, $CH_2C_2H_5$); 1,45 (2H, m, $CH_2CH_2CH_3$); 0,90 (3H, t, $CH_3$) | A | 93 |
| Ie | $C_{12}H_{13}NO_2$ | 194...195 | 11,17 | 9,96 | 7,91 (8,0; 1,4) | 7,43 (7,5; 1,5) | 7,24 (8,0; 1,2) | 7,11 (7,5; 1,2) | 3,44 (1H,m, CH); 1,28 (6H, d, $CH_3 \times 2$) | B C | 67 90 |
| If | $C_{13}H_{15}NO_2$ | 190...192 | 11,29 | 9,99 | 7,89 (8,0; 1,3) | 7,43 (7,3; 1,4) | 7,25 (8,0; 1,2) | 7,12 (7,4; 1,8) | 2,57 (2H, t, $CH_2C_3H_7$); 1,40 (4H,m, $(CH_2)_2CH_3$); 0,87 (3H, t, $CH_3$) | B | 83 |
| Ig | $C_{14}H_{17}NO_2$ | 182...184 | 11,28 | 9,98 | 7,89 (7,9; 1,5) | 7,46 (7,1; 1,3) | 7,26 (7,9; 1,1) | 7,14 (7,2; 1,8) | 2,56 (2H, t, $CH_2C_4H_9$); 1,35 (6H, m, $(CH_2)_3CH_3$); 0,87 (3H, t, $CH_3$) | B | 87 |
| Ih | $C_{15}H_{19}NO_2$ | 213...214 | 11,26 | 9,96 | 7,88 (7,8; 1,3) | 7,46 (7,1; 1,3) | 7,26 (7,8; 1,2) | 7,13 (7,0; 1,5) | 2,55 (2H, t, $CH_2C_5H_{11}$); 1,30 (8H,m, $(CH_2)_4CH_3$); 0,86 (3H, t, $CH_3$) | B | 86 |
| Ii | $C_{16}H_{21}NO_2$ | 174...176 | 11,25 | 9,96 | 7,85 (7,9; 1,5) | 7,47 (7,1; 1,4) | 7,25 (7,9; 1,6) | 7,11 (7,1; 1,6) | 2,52 (2H, t, $CH_2C_6H_{13}$); 1,26 (10H, m, $(CH_2)_5CH_3$); 0,84 (3H, t, $CH_3$) | B | 79 |
| Ij | $C_{17}H_{23}NO_2$ | 177...178 | 11,26 | 9,97 | 7,86 (7,9; 1,6) | 7,46 (7,2; 1,5) | 7,26 (7,9; 1,6) | 7,12 (7,2; 1,7) | 2,53 (2H, t, $CH_2C_7H_{15}$); 1,24 (12H,m, $(CH_2)_6CH_3$); 0,84 (3H, t, $CH_3$) | B | 83 |
| Ik | $C_{18}H_{25}NO_2$ | 173...175 | 11,24 | 9,94 | 7,85 (8,0; 1,6) | 7,44 (7,2; 1,6) | 7,24 (8,0; 1,6) | 7,12 (7,4; 1,8) | 2,52 (2H, t, $CH_2C_8H_{17}$); 1,23 (14H,m, $(CH_2)_7CH_3$); 0,84 (3H, t, $CH_3$) | B | 76 |
| Il | $C_{19}H_{27}NO_2$ | 147...149 | 11,22 | 9,95 | 7,86 (8,0; 1,5) | 7,44 (7,3; 1,8) | 7,24 (8,0; 1,5) | 7,12 (7,1; 1,7) | 2,53 (2H, t, $CH_2C_9H_{19}$); 1,23 (16H,m, $(CH_2)_8CH_3$); 0,85 (3H, t, $CH_3$) | B | 74 |
| Im | $C_{21}H_{31}NO_2$ | 164...166 | 11,24 | 9,92 | 7,86 (8,0; 1,5) | 7,43 (7,3; 1,7) | 7,24 (8,0; 1,5) | 7,12 (7,1; 1,8) | 2,52 (2H, t, $CH_2C_{11}H_{23}$); 1,22 (20H,m, $(CH_2)_{10}CH_3$); 0,84 (3H, t, $CH_3$) | B | 70 |
| In | $C_{16}H_{13}NO_2$ | 218...219 | 11,39 | 10,38 | 7,98 (8,0; 1,6) | 7,48 (7,3; 1,7) | 7,33...7,00 (7H,m, 6,8-H + $H_{Ph}$ | | 3,94 (2H, s, $CH_2$–Ph) | B C | 72 89 |
| Io | $C_{14}H_{17}NO_2$ | 118...120 | – | 9,98 | 7,97 (8,0; 1,6) | 7,56 (7,0; 2,0) | 7,41 (8,0; 1,5) | 7,22 (7,0; 2,0) | 3,57 (3H, s, N–$CH_3$); 2,61 (2H, t, $CH_2C_3H_7$); 1,38 (4H,m, $(CH_2)_2CH_3$); 0,87 (3H, t, $CH_3$) | C | 90 |

*The signals disappear after the addition of $D_2O$ due to deuterium exchange.

substances containing an even number of carbon atoms in the alkyl substituent exhibit a marked diuretic action, which is albeit inferior to that of hypothiazide. At the same time, the quinolones (I) with an odd number of carbon atoms in the alkyl chains either do not influence urination at all, or induce a strong decrease in diuresis, surpassing in activity [e.g. the quinolones (Ie, n)] the antidiuretic hormone adiurekrin.

The antioxidant activity of the investigated compounds was determined from the rate of the spontaneous noninduced peroxide oxidation of lipids using the model of the toxic injury to the liver of rats by tetrachloromethane. The rate of peroxide oxidation of the lipids was judged from the amount of malonic dialdehyde formed in the liver homogenates [22]. It was thereby established that all the quinolones (I) possess marked antioxidant action, which reliably exceeds the activity of the comparison preparation, Vitamin E, in most cases.

## EXPERIMENTAL

The PMR spectra were recorded on the Bruker WP-100 SY instrument in DMSO-$D_6$ using TMS as the internal standard.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

The antiinflammatory, antimicrobial, diuretic, and anticoagulant activities of the quinolones (Ia-o) were studied by known methods [23-26].

**3-Alkyl-substituted 1H-2-Oxo-4-hydroxyquinolines. A.** The mixture of 3.3 g (0.02 mole) of ethyl anthranilate and 0.01 mole of the corresponding manolinic ester (IV) is maintained for 4 h at 200-210°C. The reaction mixture is cooled prior to the addition of the solution of sodium methoxide [from 0.92 g (0.04 mole) of metallic sodium and 20 ml of abs. methanol] and the boiling for 5 h. Water (50 ml) is added, and the methanol is distilled off. The mixture is cooled and acidified with HCl to the pH 3-4. The precipitated residue of the quinolone (I) is filtered off, washed with water, and dried.

**B.** The method is performed analogously with the utilization of equimolar amounts of ethyl anthranilate and the alkyl-substituted malonic ester (IV).

**C.** To the solution of 0.02 mole of the N-alkyl-substituted ethyl anthranilate (VI) in 20 ml of methylene chloride are added 2.8 ml (0.02 mole) of triethylamine prior to the addition, dropwise with stirring and cooling, of 0.01 mole of the alkylmalonic dichloride (VII). The reaction mixture is maintained at room temperature for 5 h, after which 100 ml of water are added, and the mixture is stirred. The organic layer is separated, and the solvent is distilled off (toward the end at decreased pressure); the residue is treated by analogy with the method A.

## REFERENCES


1. I. V. Ukrainets, S. G. Taran, P. A. Bezuglyi, S. N. Kovalenko, A. V. Turov, and N. A. Marusenko, Khim. Geterotsikl. Soedin., No. 9, 1223 (1993).
2. E. A. Clarke and M. F. Grundon, J. Chem. Soc., No. 1, 438 (1964).
3. R. H. Baker, G. R. Lappin, and B. Riegel, J. Am. Chem. Soc., **68**, 1284 (1946).
4. P. A. Bezuglyi, I. V. Ukrainets, V. I. Treskach, and A. V. Turov, Khim. Geterotsikl. Soedin., No. 11, 1533 (1991).
5. A. S. 1,705,286 USSR, I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, and A. V. Turov, B. I., No. 2 (1992).
6. P. A. Bezuglyi, I. V. Ukrainets, V. I. Treskach, V. A. Georgiyants, and N. Yu. Bevz, Khar'kov State Pharmaceutical Inst., Khar'kov (1990). Dep. in the UkrNIINTI 19.02. 90, No. 267 Uk-90.
7. I. V. Ukrainets, O. V. Gorokhova, V. A. Georgiyants, P. A. Bezuglyi, and V. I. Treskach, Khar'kov State Pharmaceutical Inst. Khar'kov (1992). Dep. in the UkrNIINTI 22.03.91, No. 367 Uk-91.
8. I. V. Ukrainets, S. G. Taran, P. A. Bezuglyi, and O. A. Evtifeeva, Khim. Geterotsikl. Soedin., No. 9, 1219 (1993).
9. P. A. Bezuglyi, V. I. Treskach, I. V. Ukrainets, V. V. Grinenko, and N. Yu. Bevz, Zh. Org. Khim., **27**, 1410 (1991).
10. P. A. Petonin and N. T. Panferova, Zh. Obshch. Khim., **21**, 1533 (1951).
11. A. K. Dhawan, V. Hora, and I. M. Hora, J. Indian Chem. Soc., **58**, 199 (1981).
12. P. E. Lutz, G. Ashburn, J. A. Freek, R. H. Jordan, N. H. Leake, T. A. Martin, R. J. Rowlett, and J. W. Wilson, J. Am. Chem. Soc., **68**, 1285 (1946).
13. I. V. Ukrainets, Dis. D-ra Khim. Nauk, Khar'kov (1992).

14. I. V. Ukrainets, P. A. Bezuglyi, S. V. Slobodzyan, O. V. Gorokhova, and V. I. Treskach, Khar'kov State Pharmaceutical Inst., Khar'kov (1991). Dep. in the UkrNIINTI 13.06.91, No. 870 Uk-91.
15. S. Yu. Yunusov, Alkaloids [in Russian], FAN, Tashkent (1968).
16. V. I. Akhmedzhanova, Dis. Kand. Khim. Nauk, Tashkent (1975).
17. I. A. Bessonova, Dis. D-ra Khim. Nauk, Tashkent (1977).
18. Ya. V. Rashkes, Dis. D-ra Khim. Nauk, Tashkent (1974).
19. P. B. Terent'ev and A. Stankyavichyus, Mass-spectrometric Analysis of Biologically Active Nitrogenous Bases [in Russian], Mokslas, Vil'nyus (1987), p. 226.
20. M. Ramesh and P. Shanmugam, Indian J. Chem., **24B**, 602 (1985).
21. S. Masayuki, K. Katsuro, and K. Chikara, Chem. Pharm. Bull., **35**, 1319 (1986).
22. Yu. A. Vladimirov and A. I. Archakov, Peroxide Oxidation of Lipids in Biological Membranes [in Russian], Nauka, Moscow (1972).
23. D. Ya. Shvarts and R. D. Syubaev, Farmakol. Toksikol., No. 1, 46 (1982).
24. R. M. Navashin and N. P. Fomina, Handbook on Antibiotic Therapy [in Russian], Meditsina, Mosow (1974), p. 36.
25. E. B. Berkhin, Farmacol. Toksikol., No. 4, 501 (1964).
26. P. A. Bezuglyi, V. I. Treskach, I. V. Ukrainets, Yu. F. Krylov, M. Yu. Ladinskaya, N. P. Moryakov, and E. G. Lobanova, Khim. Farm. Zh., **24**, 31 (1990).