Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

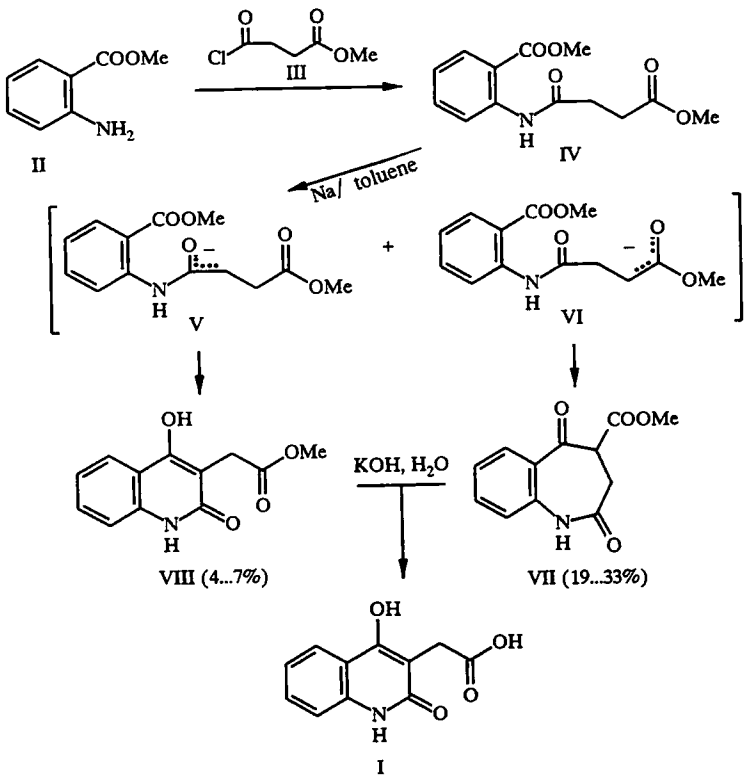
4-HYDROXY-2-QUINOLONES. 33*. NOVEL APPROACH TO SYNTHESIS OF 1H-2-OXO-4-HYDROXYQUINOLINE-3-ACETIC ACID

I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, O. L. Kodolova, and A. V. Turov

We propose a novel method for obtaining the methyl ester of 1H-2-oxo-4-hydroxyquinoline-3-acetic acid.

The method for using 2-oxo-4-hydroxyquinoline-3-acetic acids I used in synthesis of alkaloids of the quinoline series [2,3] has been well known since 1959 [3]. The method includes acylation of methyl anthranilate II by β-carbomethoxypropionyl chloride III followed by Dieckmann cyclization of the anilide IV formed (Scheme 1).

Scheme 1



Literature data and also our experiments duplicating the indicated procedure show that its weakest link is the final stage, i.e., the cyclization. The strategic rule generally accepted in organic synthesis that the riskiest and most questionable stages belong at the beginning of the synthesis scheme [4] stimulated our research to look for a more efficient method for obtaining 2-oxo-4-hydroxyquinoline-3-acetic acids.

*Communication 32, see [1].

Ukrainian Pharmaceutical Academy, Kharkov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 928-932, July, 1997. Original article submitted March 3, 1997.

0009-3122/97/3307-0811$18.00

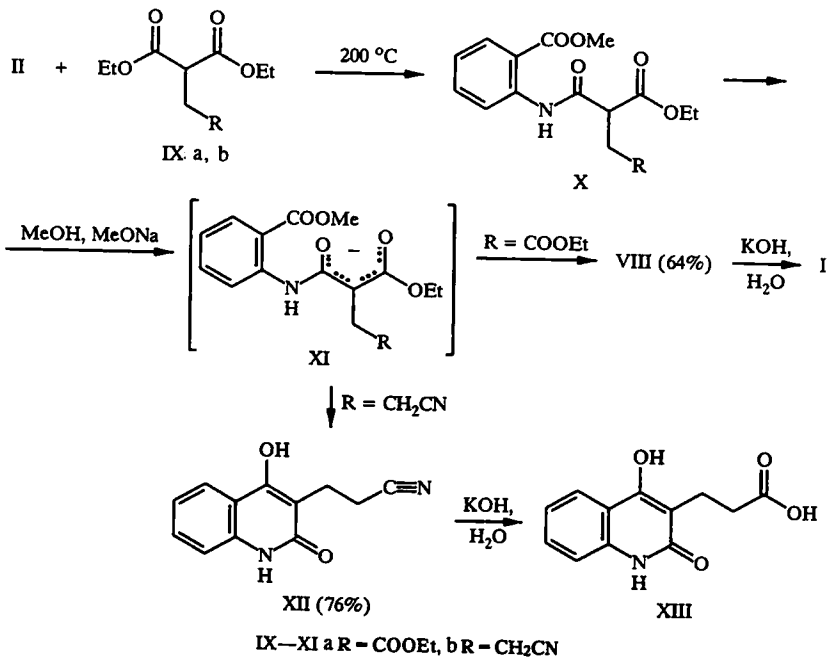
TABLE 1. Electronic Absorption Spectra of Synthesized Compounds in Ethanol

Compound	$\nu \cdot 10^{-3}$, cm^{-1}	λ, nm	$\varepsilon \cdot 10^{-3}$, $moles^{-1} \cdot cm^{-1} \cdot liter$	Compound	$\nu \cdot 10^{-3}$, cm^{-1}	λ, nm	$\varepsilon \cdot 10^{-3}$, $moles^{-1} \cdot cm^{-1} \cdot liter$
I	43,6	229	40,3	XIV	43,1	232	45,9
	36,5	274	7,6		36,2	276	7,0
	35,5	282	7,8		35,1	285	7,4
	31,7	315	7,4		31,4	318	6,3
	30,5	328	5,8		30,4	329	4,9
VIII	43,9	228	45,9	XV	43,2	231	49,4
	36,8	272	8,3		36,3	275	7,6
	35,6	281	8,2		35,2	284	7,9
	31,6	316	7,6		31,4	318	6,7
	30,5	328	5,7		30,3	330	5,1
XIII	43,6	229	36,1				
	36,6	273	6,9				
	35,5	282	6,9				
	31,7	315	6,6				
	30,6	327	5,2				

Detailed analysis of the described reaction indicates that anilide IV in the presence of bases can form two types of carbanions: V and VI (generation of the dianion in the presence of metallic sodium is unlikely). However, since the carbonyl group in esters is more effective with respect to its electron-acceptor and delocalizing action than the carbonyl group in amides [5], anion VI should be predominant. Therefore it is understandable why the major product of such reactions is the esters of 3-azabenzocycloheptene-4,7-dione-6-carboxylic acids VII, while the esters of 2-oxo-4-hydroxyquinoline-3-acetic acids VIII can be isolated in only 4-7% yield. Base hydrolysis of ester VIII yields acid I [2,3,6]. It is interesting that compound VII also undergoes recyclization under the same conditions to acid I, but the total yield (calculated on the basis of anilide IV) is no greater than 25%.

From the above it follows that we can increase the yield of quinoline VIII only for the condition of additional activation in anilide IV of the methylene group adjacent to the carbamide group. In this case, the ethoxycarbonyl group proves to be quite effective and furthermore is easy to introduce (synthesis of the triethyl ester of ethane-1,1,2-tricarboxylic acid IXa is extremely simple) and is removed again during cyclization of anilide X (Scheme 2). Obviously, closure of the quinolone ring with removal of the ethoxycarbonyl group is analogous to the mechanism for the formation of 3-alkyl-substituted 2-oxo-4-hydroxyquinolines [7].

Scheme 2



IX—XI a R = COOEt, b R = CH_2CN

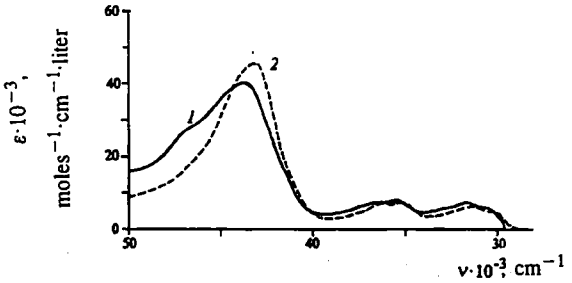


Fig. 1. Electronic absorption spectrum in ethanol: *1*) 1H-quinoline-3-acetic acid I; *2*) 1-propylquinoline-3-acetic acid XIV.

On the whole, the method we propose allows us to increase the yield of the methyl ester (cyclization of anilide Xa in the methanol–sodium methoxide system is accompanied by transesterification) of 1H-2-oxo-4-hydroxyquinoline-3-acetic acid (VIII) by almost an order of magnitude compared with the familiar method, and so can be recommended as a preparative method. We have successfully extended this method also to 1H-2-oxo-3-(2′-cyanoethyl)-4-hydroxyquinoline (XII), the base hydrolysis of which leads to the corresponding quinoline-3-propionic acid XIII.

In the literature, 1H-2-oxo-4-hydroxyquinoline-3-acetic acids are characterized as derivatives of 2,4-dihydroxyquinoline [3] or 4-hydroxy-2-quinolone [2]. In order resolve this question, we obtained 1-propyl-2-oxo-4-hydroxyquinoline-3-acetic acid (XIV) and its ethyl ester XV. The appearance of the electronic absorption spectra of acid I, its methyl ester VIII, and their N-alkyl analogs shows that they all exist in the 2-oxo-4-hydroxy form. The same conclusion can be drawn also with respect to quinoline-3-propionic acid XIII (see Fig. 1 and Table 1).

EXPERIMENTAL

The electronic absorption spectra were recorded on a Specord M-40 spectrometer in ethanol solution (10^{-4} to 10^{-3} moles/liter). The PMR spectra were recorded on a Bruker WP-100 SY in DMSO-D_6, internal standard TMS. The IR and mass spectra of nitrile XII and acid XIII were recorded respectively on a Specord M-80 in KBr pellets and a Finnigan MAT-4615 B, ionizing potential 70 eV, with ballistic heating of the sample.

The triethyl ester of ethane-1,1,2-tricarboxylic acid (IXa) was obtained by alkylation of the diethylmalonate with ethylchloroacetate in the DMF–NaOH system according to the procedure in [8].

1H-2-Oxo-4-hydroxyquinoline-3-acetic Acid (I, $C_{11}H_9NO_4$). A solution of 2.33 g (0.01 moles) of ester VIII in 20 ml of a 10% aqueous KOH solution was boiled for 2 h. This was cooled and acidified with HCl to pH 3. The precipitate of acid I was filtered off and then washed with water and dried. Yield, 2.10 g (96%). After recrystallization from dioxane, T_{mp} 313°C (decomp.). According to the data in [3], T_{mp} 290-295°C (decomp.). PMR spectrum: 11.38 (1H, s, NH); 7.90 (1H, dd, J = 8.0 and 1.9 Hz, 5-H); 7.49 (1H, td, J = 7.5 and 1.9 Hz, 7-H); 7.27 (1H, d, J = 7.0 Hz, 8-H); 7.16 (1H, td, J = 7.5 and 1.9 Hz, 6-H); 3.54 ppm (2H, d, CH_2). Splitting of the signal from the methylene group of the acetic acid residue in quinolones I and XIV into a doublet obviously happens due to formation of an intramolecular hydrogen bond involving the OH groups of the carboxyl and carbonyl group at the 2 position of the quinoline ring, since in the corresponding esters VIII and XV we do not observe such a phenomenon.

Methyl Ester of 2-Carbomethoxysuccinanilic Acid (IV, $C_{13}H_{15}NO_5$). 1.4 ml (0.01 moles) triethylamine was added to a solution of 1.51 g (0.01 moles) methyl anthranilate in 10 ml dioxane, and then on cooling 1.65 g (0.011 moles) β-carbomethoxypropionyl chloride III was added dropwise. This was allowed to stand for 3-4 h at room temperature. The reaction mixture was diluted with water. The precipitate of ester IV was filtered off, washed with water, and dried. Yield, 2.52 g (94%). T_{mp} 70-72°C (ethanol). According to the data in [3], T_{mp} 67-70°C. PMR spectrum: 10.62 (1H, s, NH); 8.21 (1H, dd, J = 8.0 and 1.2 Hz, 3-H); 7.90 (1H, dd, J = 7.3 and 1.5 Hz, 6-H); 7.60 (1H, td, J = 7.3 and 1.5 Hz, 5-H); 7.17 (1H, td, J = 7.3 and 1.2 Hz, 4-H); 3.85 (3H, s, Ar-$COOCH_3$); 3.60 (3H, s, CH_3); 2.65 ppm (4H, s, $COCH_2CH_2CO$).

Methyl Ester of 1H-2-oxo-4-hydroxyquinoline-3-acetic Acid (VIII, $C_{12}H_{11}NO_4$). A mixture of 1.51 g (0.01 moles) methyl anthranilate II and 2.58 g (0.01 moles) triethyl ester of ethane-1,1,2-tricarboxylic acid IXa was held at a temperature of 190-200°C for 5 h. This was cooled and a solution of sodium methoxide in methanol [from 1.15 g (0.05 moles) metallic sodium and 50 ml methanol] was added and it was boiled for 4 h. After cooling, the reaction mixture was poured into water acidified with HCl. The precipitate of ester VIII was filtered off, washed with water, and dried. Yield, 1.49 g (64%). T_{mp} 203-204°C (methanol). According to the data in [3], T_{mp} 185-190°C. PMR spectrum: 11.42 (1H, s, NH); 10.51 (1H, s, OH); 7.91 (1H, dd, J = 8.0 and 1.8 Hz, 5-H); 7.49 (1H, td, J = 70 and 1.8 Hz, 7-H); 7.27 (1H, d, J = 7.0 Hz, 8-H); 7.16 (1H, td, J = 7.0 and 1.8 Hz, 6-H); 3.59 ppm (5H, s, CH_2+CH_3).

A sample mixed with a sample of ester VIII obtained by cyclization of anilide IV according to the procedure in [3] does not give a depression of the melting point. The PMR spectra of these compounds are identical.

1H-2-Oxo-3-(2′-cyanoethyl)-4-hydroxyquinoline (XII). Obtained from methyl anthranilate II and cyanoethylmalonic ester IXb according to the synthesis procedure for ester VIII. Yield, 76%. T_{mp} 214-216°C (ethanol). PMR spectrum: 11.44 (1H, s, NH); 7.92 (1H, d, J = 8.0 Hz, 5-H); 7.55 (1H, t, J = 7.2 Hz, 7-H); 7.26 (1H, d, J = 7.2 Hz, 8-H); 7.15 (1H, t, J = 7.2 Hz, 6-H); 2.85 (2H, t, CH_2); 2.68 ppm (2H, t, CH_2). IR spectrum: 2250 (C≡N), 1674 (C=O), 1610 (C−C), 1400 cm^{-1} (CH_2). Mass spectrum, m/z (relative intensity, %): 214 (48) $[M]^+$, 174 (100) $[M-CH_2CN]^+$, 120 (17), 92 (20), 77 (18), 65 (14), 55 (44), 40 (90). Found, %: C 67.22; H 4.73; N 13.06. $C_{12}H_{10}N_2O_2$. Calculated, %: C 67.28; H 4.70; N 13.08.

β-(1H-2-Oxo-4-hydroxyquinoline-3-yl)propionic Acid (XIII). A solution of 2.14 g (0.01 moles) nitrile XII in 20 ml of a 20% aqueous KOH solution was boiled until evolution of ammonia stopped (~50 h). The completion of the hydrolysis reaction was determined from the absence of the stretching vibration band for the C≡N group (2250 cm^{-1}) in the IR spectrum of the compound obtained. The reaction mixture was cooled and then acidified with HCl to pH 3. The precipitate of acid XIII was filtered off, washed with water, and dried. Yield, 1.91 g (82%). T_{mp} > 330°C (DMF). PMR spectrum: 11.32 (1H, s, NH); 10.26 (1H, s, 4-OH); 7.89 (1H, d, J = 8.0 Hz, 5-H); 7.46 (1H, t, J = 7.7 Hz, 7-H); 7.25 (1H, d, J = 8.0 Hz, 8-H); 7.14 (1H, t, J = 7.7 Hz, 6-H); 2.80 (2H, t, CH_2); 2.38 ppm (2H, t, CH_2). IR spectrum: 1670 (C=O), 1600 (C−C), 1390 cm^{-1} (CH_2). Mass spectrum: 233 (18) $[M]^+$, 215 (27) $[M-H_2O]^+$, 186 (100) $[M-H_2O-CHO]^+$, 119 (20), 92 (28). Found, %: C 61.83; H 4.71; N 6.05. $C_{12}H_{11}NO_4$. Calculated, %: C 61.80; H 4.75; N 6.01.

1-Propyl-2-oxo-4-hydroxyquinoline-3-acetic Acid (XIV). Obtained according to the procedure in [3]. Yield, 21%. T_{mp} 192-194°C (decomp., ethanol). PMR spectrum: 11.27 (1H, s, OH); 8.00 (1H, d, J = 8.0 Hz, 5-H); 7.70-7.43 (2H, m, 7,8-H); 7.23 (1H, td, J = 7.0 and 2.0 Hz, 6-H); 4.14 (2H, t, NCH_2); 3.57 (2H, d, CH_2COO); 1.58 (2H, m, $NCH_2\underline{CH_2}$); 0.93 ppm (3H, t, CH_3). Found, %: C 64.40; H 5.75; N 5.41. $C_{14}H_{15}NO_4$. Calculated, %: C 64.36; H 5.79; N 5.36.

Ethyl Ester of 1-Propyl-2-oxo-4-hydroxyquinoline-3-acetic Acid (XV). Two or three drops of concentrated sulfuric acid was added to a solution of 2.61 g (0.01 moles) acid XIV in 15 ml ethanol and boiled for 5 h. The reaction mixture was cooled and diluted with cold water. The precipitate of ester XV was filtered off, washed with water, and dried. Yield, 2.25 g (78%). T_{mp} 142-144°C (ethanol). PMR spectrum: 10.52 (1H, s, OH); 8.02 (1H, d, J = 8.0 Hz, 5-H); 7.69-7.44 (2H, m, 7,8-H); 7.24 (1H, td, J = 7.0 and 2.0 Hz, 6-H); 4.16 (2H, t, NCH_2); 4.03 (2H, q, $OC\underline{H_2}CH_3$); 3.62 (2H, s, CH_2COO); 1.58 (2H, m, $NCH_2\underline{CH_2}$); 1.16 (3H, t, $OCH_2\underline{CH_3}$); 0.90 ppm (3H, t, $NCH_2CH_2\underline{CH_3}$). Found, %: C 66.38; H 6.60; N 4.87. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

REFERENCES

1. I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, N. A. Marusenko, and A. V. Turov, Khim. Geterotsikl. Soedin., No. 5, 692 (1997).
2. M. Ramesh and P. Shanmugam, Indian J. Chem., **24B**, 602 (1985).
3. T. A. Geissman and A. K. Cho, J. Org. Chem., **24**, 41 (1959).
4. A. F. Bochkov and V. A. Smit, Organic Synthesis. Goals, Methods, Tactics, Strategy [in Russian], Nauka, Moscow (1987).
5. P. Sykes, A Guidebook to Mechanism in Organic Chemistry [Russian translation], Khimiya, Moscow (1971), p. 224.
6. C. Kunick, Arch. Pharm., **324**, 579 (1991).
7. 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, Khim. Geterotsikl. Soedin., No. 5, 673 (1994).
8. E. Löwe, R. Kirchner, S. Menolow, H. Micke, and R. Müller, Ref. Zh. Khim., 12 O 5P (1986).