4-HYDROXYQUINOLONES-2.

5.* SYNTHESIS AND PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF NEW PYRAZOLE DERIVATIVES

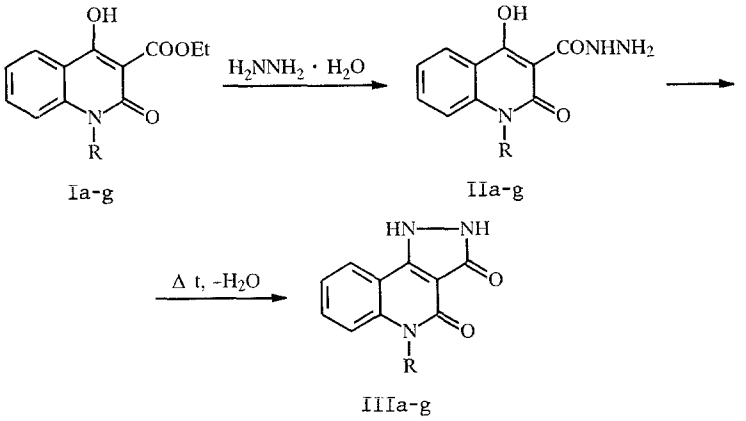
I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, M. Yu. Kornilov, A. V. Turov, A. I. Maslennikov, S. V. Gladchenko, and V. I. Krivobok

Hydrazinolysis of 1-R-3-carbethoxy-4-hydroxyquinolones-2 was used to synthesize the corresponding hydrazides; thermal cyclodehydration of the latter yielded 3-oxopyrazolo-[4,3-c]-5-R-quinolones-4. Findings relating to their analgesic and antiphlogistic activity are outlined.

Among the derivatives of five-membered heterocyclic compounds with two heteroatoms considerable interest in medical practice centers on those of pyrazole, which has served as a basis for synthesizing a wide range of drugs with pain-relieving, antipyretic, and antiphlogistic properties [2].

The importance of quinoline-3-carboxylic acids has also been recognized in this context and substances with significant antibacterial [3], antitumorigenic [4], and analgesic [5] activity have been found among their derivatives.

A combination of the biologically active pyrazole and quinoline-3-carboxylic acid structures in one molecule lays real foundations for synthesizing effective pharmacological preparations of low toxicity. Indeed, it was this that provided the theoretical framework for our research. Hydrazinolysis of the appropriate ethyl esters (I), obtained using a method that we developed in a previous work [6], was employed to synthesize the starting hydrazides of 1-R-4-hydroxyquinoline-3-carboxylic acids (II, Table 1). Subsequent thermolysis of hydrazides II afforded the target pyrazoles III.



I—III a R=Me, b R=Et, c R=C_3H_7, d R=C_5H_{11}, e R=C_6H_{13} f R=C_8H_{17}, g R=C_9H_{19}

In order to establish the thermodynamic characteristics of hydrazides II and study their reactivity and thermal stability, we carried out a derivative graph analysis for this group of compounds under dry heating conditions. The results showed that the thermal behavior of hydrazides II, which we outlined using N-ethyl derivative IIb as an example (Fig. 1), was consistent.

The endothermic peak with minimum at 195°C corresponded to the melting point of hydrazide IIb. As the temperature rose, the substance, in the liquid phase, began to vaporize at an increasing rate: vaporization point = 273°C (the vaporization point is taken as the temperature at which the sample mass decreases by 10% of its initial size). Further heating brought about an exothermic chemical transformation (DTA curve) in the range 283-293°C. Losses in mass per molecule of the starting compound

*For previous report, see [1].

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TABLE 1. Physical Properties and Spectral Data for 1-R-4-Hydroxyquinolone-2-carboxylic-3-acid Hydrazides IIa-g

Compound	Empirical formula	mp, °C	Vap. point, °C	Thermolysis point, °C	IR spectrum, cm^{-1} C=O	PMR spectrum, δ, ppm*			Yield, %
						NH (1H, s)	NH_2 (2H, s)	R	
IIa	$C_{11}H_{11}N_3O_3$	228		228...247	1662, 1616	11,39	4,94	3,63 (3H, s, CH_3)	98
IIb	$C_{12}H_{13}N_3O_3$	195	273	283...293	1653, 1617	11,02	4,93	4,29 (2H, q, CH_2); 1,22 (3H, t, CH_3)	98
IIc	$C_{13}H_{15}N_3O_3$	125	240	262...291	1646, 1620	10,26	5,69	4,22 (2H, t, NCH_2); 1,65 (2H, m, CH_2CH_3); 0,96 (3H, t, CH_3)	97
IId	$C_{15}H_{19}N_3O_3$	104	274	290...304	1654, 1622	11,06	4,83	4,24 (2H, t, NCH_2); 1,60 (2H, q, NCH_2CH_2); 1,35 (4H, m, $(CH_2)_2CH_3$); 0,88 (3H, t, CH_3)	92
IIe	$C_{16}H_{21}N_3O_3$	90	265	285...300	1647, 1621	11,01	5,14	4,22 (2H, t, NCH_2); 1,62 (2H, q, NCH_2CH_2); 1,31 (6H, m, $(CH_2)_3CH_3$); 0,85 (3H, t, CH_3)	96
IIf	$C_{18}H_{25}N_3O_3$	86	270	286...302	1644, 1620	11,03	4,96	4,23 (2H, t, NCH_2); 1,52 (2H, q, NCH_2CH_2); 1,26 (10H, m, $(CH_2)_5CH_3$); 0,84 (3H, t, CH_3)	94
IIg	$C_{19}H_{27}N_3O_3$	68	255	273...290	1654, 1625	10,99	4,88	4,23 (2H, t, NCH_2); 1,60 (2H, q, NCH_2CH_2); 1,24 (12H, m, $(CH_2)_6CH_3$); 0,85 (3H, t, CH_3)	96

*4-OH group proton signals had singlet form in the 17.10-17.98 ppm region. 5-H (d.d) aromatic proton signals were found in the vicinity of 8.01-8.09 ppm; 6-H (t.d) at 7.35-7.42; 7-H (t.d) at 7.82-7.89; and 8-H (d) at 7.61-7.68 ppm.

TABLE 2. Physical Properties and Spectral Data for 3-Oxopyrazolo-[4,3-c]-5-R-quinolones-4 (IIIa-g)

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1} C=O	PMR spectrum, δ, ppm					Yield, %
				H_{arom}				R	
				9-H 1H, d.d	7-H 1H, t.d	6-H 1H, d	8-H 1H, t		
IIIa	$C_{11}H_9N_3O_2$	346...348	1644	8,45	7,98	7,70	7,57	3,90 (1H,s; CH_3)	86
IIIb	$C_{12}H_{11}N_3O_2$	324...326	1649	8,44	7,97	7,70	7,56	4,52 (2H,q, NCH_2); 1,53 (3H,t, CH_3)	82
IIIc	$C_{13}H_{13}N_3O_2$	329...331	1630	8,45	7,97	7,69	7,56	4,40 (2H,t, NCH_2); 1,95 (2H,m, $C\underline{H}_2CH_3$); 1,19 (3H,t, CH_3)	80
IIId	$C_{15}H_{17}N_3O_2$	242...244	1653	8,46	7,96	7,67	7,56	4,44 (2H,t, NCH_2); 1,93 (2H,m, $NCH_2C\underline{H}_2$); 1,59 (4H,m, $(C\underline{H}_2)_2CH_3$); 1,03 (3H,t, CH_3)	84
IIIe	$C_{16}H_{19}N_3O_2$	224...226	1632	8,46	7,96	7,67	7,55	4,43 (2H,t, NCH_2); 1,90 (2H,m, $NCH_2C\underline{H}_2$); 1,52 (6H,s, $(C\underline{H}_2)_3CH_3$); 0,98 (3H,t, CH_3)	87
IIIf	$C_{18}H_{23}N_3O_2$	184...186	1646	8,46	7,96	7,68	7,55	4,42 (2H,t, NCH_2); 1,90 (2H,m, $NCH_2C\underline{H}_2$); 1,42 (10H,s, $(C\underline{H}_2)_5CH_3$) 0,94 (3H,t, CH_3)	81
IIIg	$C_{19}H_{25}N_3O_2$	180...182	1629	8,46	7,96	7,68	7,55	4,42 (2H,t, NCH_2); 1,94 (2H,m, $NCH_2C\underline{H}_2$); 1,39 (12H,s, $(C\underline{H}_2)_6CH_3$); 0,92 (3H,t, CH_3)	87

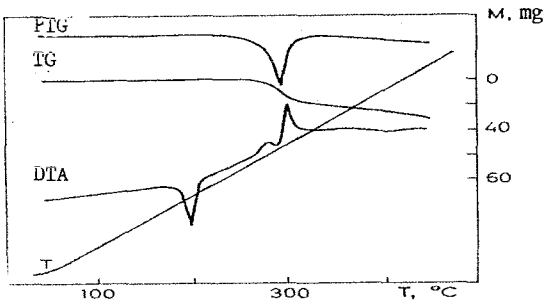

Fig. 1. Derivatogram for 1-ethyl-4-hydroxyquinolone-2-carboxylic-3-acid hydrazide IIb: T) thermal analysis curve; DTA) differential thermal analysis curve; TG) thermogravimetric curve; DTG) differential thermogravimetric curve. Sample weighing 100 mg.

were about 18 amu in this instance, i.e., hydrazide IIb cyclodehydrates into pyrazole IIIb in this temperature range. Heating beyond 293°C did not produce any perceptible chemical changes.

Data from analogous derivative graph analysis in the hydrazide II series is shown in Table 1. It is interesting to note that for almost the entire series of compounds investigated (with the exception of hydrazide IIa) the thermally active cyclodehydration process is linked with the vaporization of the substance. The growth in the internal energy of the molecule up to a point that is sufficient for vaporization to occur would appear to produce a large conformational lability, steric hindrances to intramolecular cyclization being reduced in the process.

The analgesic activity of pyrazoles IIIa-g was studied by means of convulsion simulation using the method described by Shvarts and Syubaev [7]. Compounds IIId and IIIf proved to be the most active, intragastric administration of a 25.0 mg/kg dose reducing convulsions by 22-30% against the control. These same two compounds also exhibited the most pronounced antiphlogistic properties, which were evaluated by means of a peritonitis model to determine peritoneal exudate quantity and mesentery condition [8]. As well as possessing marked antiexudative activity (the volume of intraperitoneal fluid was reduced by 32-40%), pyrazoles IIId and IIIf also inhibited perivascular infiltration of the mesentery.

EXPERIMENTAL

IR spectra of synthesized compounds were taken in KBr tablets on a UR-20 instrument, substance concentration 1%. PMR spectra were recorded with a Bruker WP-100 SY (100 MHz), DMSO-D_6 (hydrazides IIa-g) or CF_3COOD (pyrazoles IIIa-g) solvent, internal standard TMS. Derivative graph analysis and determination of melting points for hydrazides IIIa-g were carried out in a covered platinum crucible using a Derivatograf Q-1500D complex thermochemical instrument, heating rate 5°C/min. Melting points of pyrazoles IIIa-g were determined in a capillary.

Elemental analysis data on C, H, and N for compounds IIa-g and IIIa-g were in line with calculated values.

General Methodology for Synthesizing Hydrazides of 1-R-4-Hydroxyquinolone-2-carboxylic-3-acids (IIa-g). To a solution of 0.01 mole of the corresponding ethyl ester in 15 ml of ethanol was added 0.02 moles of hydrazine hydrate; the mixture was left overnight at room temperature. It was then diluted with water and acidified with HCl to pH ~5. The resultant hydrazide precipitate was filtered off, washed with water, and dried.

General Methodology for Synthesizing 3-Oxopyrazolo-[4,3-c]-5-R-quinolones-4 (IIIa-g). Hydrazide IIa-g was kept at 40-50°C above the melting point (Table 1) for 30 min, then cooled. The product was recrystallized from a DMF—water mixture.

REFERENCES

1. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, No. 5, 640 (1992).
2. M. D. Mashkovskii, *Medicinal Preparations*, Vol. 1 [in Russian], Meditsina, Moscow (1988), p. 181.
3. M. Tsukamura, *Microbiol. Immunol.*, **27**, No. 12, 1129 (1983).
4. N. M. Sukhova, T. V. Lapina, and M. Yu. Lidak, *Khim. Geterotsikl. Soedin.*, No. 11, 1521 (1983).
5. F. Clemence, C. Martret, F. Delevallee, J. Benzoni, A. Jouanen, S. Jouquey, M. Mouren, and R. Deraedt, *J. Med. Chem.*, **31**, No. 7, 1453 (1988).

6. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, A. V. Turov, and S. V. Slobodzyan, *Khim. Geterotsikl. Soedin.*, No. 5, 636 (1992).
7. G. Ya. Shvarts and R. D. Syubaev, *Farmakol. Toksikol.*, **45**, No. 1, 46 (1982).
8. P. N. Aleksandrov and G. V. Speranskaya, *Byull. Éksp. Biol.*, **3**, No. 2, 188 (1987).