Chemistry of Heterocyclic Compounds, Vol. 30, No. 10, 1994

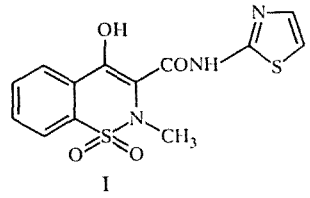
4-HYDROXY-2-QUINOLONES. 23.* N-(2-THIAZOLYL)AMIDES OF 1-R-2-OXO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACIDS - A NEW GROUP OF POTENTIAL ANTIINFLAMMATORY AGENTS

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

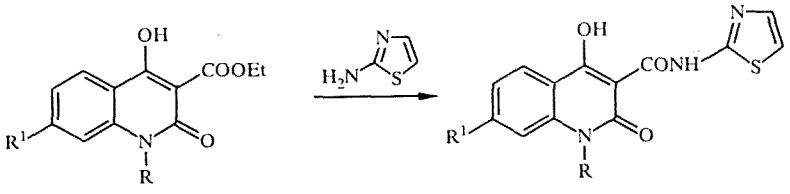
By thermolysis of equimolar quantities of 1-R-2-oxo-3-carbethoxy-4-hydroxyquinolines and 2-aminothiazole in diphenyl oxide, we have synthesized N-(2-thiazolyl)amides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids. Some of the substances that were obtained have high antiexudative activity (carrageenan edema), higher than the activity of sudoxicam.

Even though a broad arsenal of antiinflammatory agents is available today [2, 3], there is still an urgent need for the development of new, highly effective preparations with this type of pharmacological action.

Among the ranks of the new nonsteroidal antiinflammatory preparations that do not have any analogs among the previously used antirheumatic agents, we find the oxicams — isoxicam, sudoxicam (I), and piroxicam [4]. The structural similarity with these compounds and also the favorable results obtained in a pharmacological study of hetarylamides of 4-hydroxyquinoline-3-carboxylic acids [5] and 1-R-2-oxy-4-hydroxyquinoline-3-carboxylic acids [6], have served as the theoretical grounds for undertaking the research described in this article.



I



II IIIa-k

II, III) R^1 = H: a) R = H; b) R = CH_3; c) R = C_2H_5; d) R = C_3H_7; e) R = C_4H_9; f) R = C_5H_{11}; g) R = C_6H_{13}; h) R = C_8H_{17}; i) R = C_9H_{19}; j) R = $C_{10}H_{21}$; R^1 = Cl: k) R = 3,4-$(CH_3)_2C_6H_3$

We had shown previously [6] that the most rational method for the synthesis of hetarylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids is the thermolysis of equimolar quantities of the amine and the ester II. This method can also be used in synthesizing the corresponding N-(2-thiazolyl)amides IIIa-k. However, as the 2-aminothiazole is highly susceptible to thermal decomposition, it is better to carry out this reaction in a medium of a high-boiling, inert solvent such as diphenyl oxide; with this method of synthesis, the final products can be obtained in a higher degree of purity.

*For Communication 22, see [1].

Ukrainian Pharmaceutical Academy, Khar'kov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1397-1399, October, 1994. Original article submitted November 8, 1994.

0009-3122/94/3010-1211$12.50

TABLE 1. Characteristics of N-(2-thiazolyl)amides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids IIIa-k

Compound	Empirical formula	mp, °C	PMR spectra,* δ, ppm		IR spectra, $\nu_{C=O}$	Yield, %	Antiexudative activity, % inhibition of edema
			H_{arom} (m)	R			
IIIa	$C_{13}H_9N_3O_3S$	305...307	8,14...7,28 (6H)	12,30 (1H, s, NH)	1650, 1621	94	27,4
IIIb	$C_{14}H_{11}N_3O_3S$	249...251	8,27...7,33 (6H)	3,68 (3H, s, CH_3) 1640, 1621	1640, 1621	89	18,8
IIIc	$C_{15}H_{13}N_3O_3S$	200...202	8,26...7,37 (6H)	4,40 (2H, q, NCH_2); 1,28 (3H, s, CH_3)	1641, 1623	91	5,0
IIId	$C_{16}H_{15}N_3O_3S$	182...184	8,25...7,36 (6H)	4,32 (2H, t, NCH_2); 1,69 (2H, m, $NCH_2\underline{CH_2}$); 0,99 (3H, t, CH_3)	1644, 1630	88	14,9
IIIe	$C_{17}H_{17}N_3O_3S$	190...192	8,24...7,29 (6H)	4,29 (2H, t, NCH_2); 1,55 (4H, m, $(\underline{CH_2})_2CH_3$); 0,95 (3H, t, CH_3)	1640, 1622	87	7,0
IIIf	$C_{18}H_{19}N_3O_3S$	168...169	8,25...7,28 (6H)	4,24 (2H, t, NCH_2); 1,58 (2H, q, $NCH_2\underline{CH_2}$); 1,33 (4H, s, $(\underline{CH_2})_2CH_3$); 0,90 (3H, s, CH_3)	1640, 1626	84	57,6
IIIg	$C_{19}H_{21}N_3O_3S$	164...166	8,23...7,16 (6H)	4,19 (2H, t, NCH_2); 1,59 (2H, q, $NCH_2\underline{CH_2}$); 1,40 (6H, s, $(\underline{CH_2})_3CH_3$); 0,89 (3H, t, CH_3)	1640, 1621	85	33,8
IIIh	$C_{21}H_{25}N_3O_3S$	136...138	8,22...7,24 (6H)	4,27 (2H, t, NCH_2); 1,60 (2H, q, $NCH_2\underline{CH_2}$); 1,31 (10H, s, $(\underline{CH_2})_5CH_3$); 0,88 (3H, t, CH_3)	1636, 1619	84	14,5
IIIi	$C_{22}H_{27}N_3O_3S$	121...123	8,26...7,25 (6H)	4,30 (2H, t, NCH_2); 1,62 (2H, q, $NCH_2\underline{CH_2}$); 1,34 (12H, s, $(\underline{CH2})_6CH_3$); 0,89 (3H, t, CH_3)	1640, 1626	89	72,8
IIIj	$C_{23}H_{29}N_3O_3S$	117...119	8,24...7,19 (6H)	4,29 (2H, t, NCH_2); 1,63 (2H, q, $NCH_2\underline{CH_2}$); 1,32 (14H, s, $(\underline{CH_2})_7CH_3$); 0,87 (3H, t, CH_3)	1644, 1630	90	46,8
IIIk	$C_{21}H_{15}ClN_3O_3S$	276...278	8,24...6,58 (8H)	N—Ar mx.H_{arom} 2,36 (3H, s, CH_3); 2,33 (3H, s, CH_3)	1645, 1620	93	15,7
Sudoxicam							51,0

*The signals of the protons of 4-OH groups are manifested in the form of a singlet in the 15.37-15.00 ppm region, those of the protons of NH groups of the thiazolylamide fragment in the form of a singlet in the 14.32-13.40 ppm region.

The antiinflammatory (antiexudative) action of the amides IIIa-k was investigated in the model of acute carrageenan inflammation (edema) of the feet of male white rats (weight 140-160 g) [7]. The test substances and the reference preparation (sudoxicam) were introduced in a dose of 20 mg/kg in the form of a finely dispersed aqueous suspension stabilized with Tween 80, administered perorally 1 h before introducing the carrageenan.

This comparative evaluation of the antiinflammatory activity of the amides IIIa-k (Table 1) showed that the greatest retardation of the exudative reaction was given by the 1-amyl (IIIf) and 1-nonyl (IIIi) derivatives, the introduction of which gave a 57-72% inhibition of carrageenan edema. At an analogous dose, the sudoxicam manifested activity at the level of 51%.

Thus, our studies have demonstrated the need for expanding research on heterylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids with the aim of creating new, highly effective, nonsteroidal antiinflammatory agents.

EXPERIMENTAL

The IR spectra of the synthesized compounds were registered on a Specord M-80 instrument in KBr tablets, substance concentration 1%. The PMR spectra were recorded on a Bruker WP-100 SY instrument (100 MHz), solvent DMSO-d_6, internal standard TMS.

Elemental analyses (C, H, N, and S) were in satisfactory agreement with the calculated values.

General Method of Synthesis of N-(2-Thiazolyl)amides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic acids (IIIa-k). A mixture of 0.01 mole of the ethyl ester of the appropriate 1-R-2-oxo-4-hydroxyquinoline-3-carboxy acid and 1.00 g (0.01 mole) of 2-aminothiazole in 15 ml of diphenyl oxide was held for 15-20 min at 150-160°C. The reaction mixture was cooled, diluted with 30 ml of 2-propanol, and thoroughly mixed. The precipitate of the amide III was filtered off, washed with 2-propanol, and dried, after which it was crystallized from DMF.

REFERENCES

1. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, Khim. Geterotsikl. Soedin., No. 7, 958 (1994).
2. M. A. Klyuev (ed.), Pharmaceuticals Used in Medical Practice in the USSR [in Russian], Meditsina, Moscow (1989).
3. Pharmaceutical Preparations of Foreign Firms in Russia (Handbook) [in Russian], Astrafarmservis, Moscow (1993).
4. Ya. A. Sigidin, G. Ya. Shvarts, A. P. Arzamastsev, and S. S. Liberman, Drug Therapy of the Inflammation Process [in Russian], Meditsina, Moscow (1988).
5. F. Clemence, O. Martret, F. Delevallee, J. Benzoni, A. Jouanen, S. Jouquey, M. Mouren, and R. Deraedt, J. Med. Chem., **31**, 1453 (1988).
6. I. V. Ukrainets, S. G. Taran, O. A. Evtifeeva, and A. V. Turov, Khim. Geterotsikl. Soedin., No. 8, 1101 (1993).
7. C. A. Winter, E. A. Risley, and G. W. Nuss, Proc. Soc. Exp. Biol. Med. (N.Y.), **111**, 544 (1962).