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4-HYDROXY-2-QUINOLONES. 153*. SYNTHESIS OF HETARYLAMIDES OF 4-METHYL-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID

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4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hetarylamides can be prepared by two fundamentally different routes with allowance made for the thermal stability of the starting hetarylamines.

Keywords: 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid, amidation, intramolecular cyclization.

We have previously proposed the preparation of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamides and this has been introduced satisfactorily into the synthesis of N-alkyl- [2], arylalkyl- [3], and aryl- [4] substituted derivatives. There are differences in some details of carrying out the experiment but a common feature is shared, i.e. all are based on the initial separation of the corresponding quinoline-3-carboxylic acid. In most cases such a course was justified even though the method of activating the carbonyl carbon atom of the carboxyl group in the starting quinoline-3-carboxylic acid has to be modified each time based on the properties of the starting amine.

One of the reported methods can evidently also be used for synthesis of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hetarylamides **1**. It should immediately be noted, however, that when 2-oxo-1,2-dihydroquinoline-3-carboxylic acid chlorides react with azahetarylamines they frequently form stable N-acylhetarylamine salts rather than the amides [5]. For this reason we have not studied the "acid chloride" variant in this work. The use here of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid imidazolide (**2)** as the acylating agent appears more promising and, in fact, shows fully satisfactory results (method A, Table 1). None the less it has been noted before [4] that the imidazolide **2** is unusually unreactive and thus needs the use of high boiling solvents and in some cases has led to serious complications. Hence, for example, with acylation of the thermally unstable 2-amino-5-isobutyl-1,3,4-thiadiazole under these conditions the corresponding hetarylamide **1n** could be obtained, but due to the low reaction rate it proved to be so strongly charged with gray-brown colored degradation products of the free amine that purification of the final product proved impossible even

* For Communication 152 see [1].

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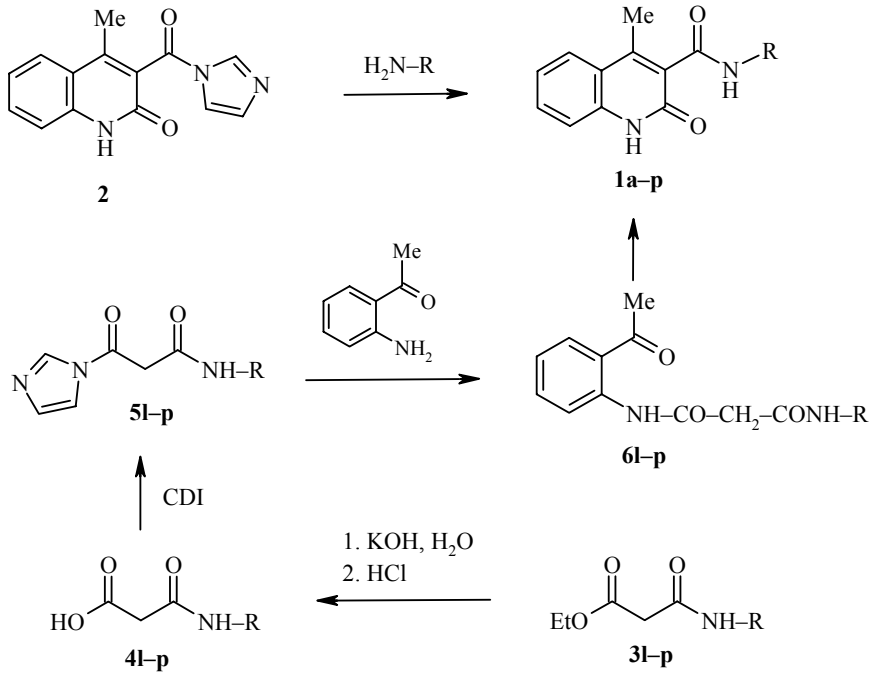
after many recrystallizations. The situation was not improved by carrying out the synthesis under an argon atmosphere. In fact for similar examples we have proposed a totally different scheme for creating the target structures allowing the possibility of synthesizing hetarylamides of type **1n** in good yields and, specially importantly, with a high degree of purity. For this purporse ethyl esters of the corresponding N-hetarylmalonamic acids **3l-p** (method B) are obtained initially on the basis of hetarylamines by one of the suitable methods [6, 7]. Subsequent basic hydrolysis gives acids **4** which react with N,N'-carbonyldiimidazole to give the imidazolides **5** immediately used for acylating *ortho*-aminoacetophenone. In principle the basic properties of the free imidazole formed as a result of successive formation of imidazolides **5l-p** and then the diamides **6l-p** are quite enough for closure of a quinolone ring so addition of more powerful basic catalysts are not needed in the final stage.



1 a R = pyridin-4-yl, **b** R = pyridin-3-yl, **c** R = pyridin-2-yl, **d** R = 5-chloropyridin-2-yl, **e** R = 3,5-dichloropyridin-2-yl, **f** R = 3-methylpyridin-2-yl, **g** R = 4-methylpyridin-2-yl, **h** R = 5-methylpyridin-2-yl, **i** R = 6-methylpyridin-2-yl, **j** R = pyrazin-2-yl, **k** R = benzimidazol-2-yl, **1, 3-6 l** R = thiazol-2-yl, **m** = 5-isopropyl-1,3,4-thiadiazol-2-yl, **n** R = isobutyl-1,3,4-thiadiazol-2-yl, **o** R = benzothiazol-2-yl, **p** R = 6-bromobenzothiazol-2-yl, CDI = N,N'-carbonyldiimidazole

Hetarylamides **1a-p** are crystalline materials which are colorless or white with a yellowish tinge. The unusual property of a so called *one-pot* reaction as occurring in contemporary scientific literature was noted for the 3,5-dichloropyridin-2-ylamide **1e**. When crystallized from DMF this compound formed two different crystalline types simultaneously, i.e. fine colorless needles and light-yellow stacked plates. After a simple mechanical separation the ^{1}H NMR spectra of both forms were completely identical but their melting point differed by several degrees (Table 1). These facts serve to confirm that one is dealing with the same compound existing in different polymorphic modifications.

TABLE 1. Characteristics of the 4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Hetarylamides **1a-p**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (with dec.)	Yield*, %
		C	H	N		
1a	$C_{16}H_{13}N_3O_2$	68.73 / 68.81	4.57 / 4.69	14.95 / 15.04	339.2	79
1b	$C_{16}H_{13}N_3O_2$	68.70 / 68.81	4.78 / 4.69	15.13 / 15.04	278.5	80
1c	$C_{16}H_{13}N_3O_2$	68.89 / 68.81	4.82 / 4.69	15.15 / 15.04	292.6	73
1d	$C_{16}H_{12}ClN_3O_2$	61.13 / 61.25	3.75 / 3.86	13.47 / 13.39	366.0	75
1e	$C_{16}H_{11}Cl_2N_3O_2$	55.28 / 55.19	3.28 / 3.18	11.93 / 12.07	261.5*[2] 66.8*[3]	71
1f	$C_{17}H_{15}N_3O_2$	69.72 / 69.61	5.23 / 5.15	14.20 / 14.33	297.4	68
1g	$C_{17}H_{15}N_3O_2$	69.74 / 69.61	5.22 / 5.15	14.25 / 14.33	305.1	76
1h	$C_{17}H_{15}N_3O_2$	69.55 / 69.61	5.10 / 5.15	14.41 / 14.33	373.3	77
1i	$C_{17}H_{15}N_3O_2$	69.76 / 69.61	5.28 / 5.15	14.43 / 14.33	285.7	81
1j	$C_{15}H_{12}N_4O_2$	64.17 / 64.28	4.40 / 4.32	20.08 / 19.99	324.6	78
1k	$C_{18}H_{14}N_4O_2$	67.83 / 67.92	4.54 / 4.43	17.72 / 17.60	348.2	73
1l	$C_{14}H_{11}N_3O_2S$	59.05 / 58.93	3.97 / 3.89	14.65 / 14.73	296.5	75
1m	$C_{16}H_{16}N_4O_2S$	58.59 / 58.52	4.86 / 4.91	16.93 / 17.06	321.9	77
1n	$C_{17}H_{18}N_4O_2S$	59.55 / 59.63	5.41 / 5.30	16.47 / 16.36	397.0	74
1o	$C_{18}H_{13}N_3O_2S$	64.59 / 64.46	4.02 / 3.91	12.46 / 12.53	370.2	82
1p	$C_{18}H_{12}BrN_3O_2S$	52.24 / 52.19	2.99 / 2.92	10.05 / 10.14	379.5	85

* Compounds **1a-k** were prepared by method A and **1l-p** by method B.
*[2] Crystal form – needles
*[3] Crystal form – stacked plates

The ^{1}H NMR spectra of all of the synthesized hetarylamides **1a-p** (Table 2) satisfactorily provide confirmation of their chemical structure. No complications demanding additional discussion and explanation were observed although one feature should be mentioned. This concerns the spectrum of the benzimidazol-2-ylamide **1k** in which the signals for the H-4 and H-7 protons of the benzimidazole ring appear as a totally unresolved broadened multiplet of overall intensity 2H while the protons H-5 and H-6 show the usual, well resolved sextet with spin-spin coupling constant of 3.0 Hz, typical of benzimidazoles. The ^{1}H NMR spectra of the very closely structurally related 3-(benzimidazol-2-yl)-4-hydroxy-2-oxo-1,2-dihydroquinolines [8, 9] do not show similar anomalies hence the only source of this observed effect has to be the carbamide group separating the quinolone and benzimidazole fragments. More precisely it is not this group but the whole 2-amino-benzimidazole fragment which is not overall a conventional amine (as reported in [10]) and in some respects resembles an imino derivative of benzimidazolone. It is likely that this type or tautomerism occurs in the solution of amide **1k** and the observed broadening of the signals for protons H-4 and H-7 is explained by a slow exchange between its imide and amide tautomeric forms.

TABLE 2. ^{1}H NMR Spectra of Hetarylamides **1a–p**

Compound	Chemical shifts, δ, ppm (*J*, Hz)							
	NH (1H, s)	NH–R (1H, s)	Quinoline nucleus				4-CH_3 (3H, s)	R
			H-5 (1H, dd)	H-7 (1H, td)	H-8 (1H, d)	H-6 (1H, td)		
1	2	3	4	5	6	7	8	9
1a	12.04	10.78	7.83 (*J* = 8.1, *J* = 1.1)	7.56 (*J* = 7.7, *J* = 1.3)	7.34 (*J* = 8.2)	7.25 (*J* = 7.7, *J* = 1.3)	2.42	8.46 (2H, dd, *J* = 4.6, *J* = 1.5, H-2',6'); 7.64 (2H, dd, *J* = 4.6, *J* = 1.5, H-3',4')
1b	12.02	10.63	7.82 (*J* = 8.2, *J* = 1.0)	7.57 (*J* = 7.7, *J* = 1.3)	7.39 (*J* = 8.1)	7.25 (*J* = 7.7, *J* = 1.1)	2.43	8.81 (1H, d, *J* = 2.5, H-2'); 8.30 (1H, dd, *J* = 4.8, *J* = 1.3, H-6'); 8.15 (1H, dd, *J* = 8.3, *J* = 1.5, H-4'); 7.33 (1H, t, *J* = 7.6, H-5')
1c	11.94	10.93	See R	7.55 (*J* = 7.6, *J* = 1.0)	7.32 (*J* = 8.1)	7.23 (*J* = 7.5, *J* = 1.2)	2.43	8.32 (1H, d, *J* = 4.6, H-6'); 8.24 (1H, d, *J* = 8.5, H-3'); 7.83 (2H, m, H-5 quinolone + H-4'); 7.13 (1H, td, *J* = 6.2, *J* = 1.0, H-5')
1d	11.96	11.13	7.82 (*J* = 8.2, *J* = 1.0)	7.54 (*J* = 7.5, *J* = 1.1)	7.32 (*J* = 8.2)	7.24 (*J* = 7.7, *J* = 1.1)	2.43	8.38 (1H, d, *J* = 2.4, H-6'); 8.27 (1H, d, *J* = 9.0, H-3'); 7.95 (1H, dd, *J* = 9.0, *J* = 2.8, H-4')
1e	11.97	10.87	7.83 (*J* = 8.1, *J* = 1.2)	7.55 (*J* = 7.7, *J* = 1.1)	7.32 (*J* = 8.2)	7.24 (*J* = 7.7, *J* = 1.1)	2.54	8.47 (1H, d, *J* = 2.2, H-6'); 8.31 (1H, d, *J* = 2.2, H-4')
1f	11.88	10.43	7.82 (*J* = 8.2, *J* = 1.1)	7.54 (*J* = 7.6, *J* = 1.2)	7.33 (*J* = 8.0)	See R	2.44	8.24 (1H, d, *J* = 4.5, H-6'); 7.69 (1H, d, *J* = 7.5, H-4'); 7.28–7.16 (2H, m, H-6 quinolone + H-5'); 2.33 (3H, s, CH_3)
1g	11.93	10.85	7.81 (*J* = 8.1, *J* = 1.2)	7.55 (*J* = 7.7, *J* = 1.3)	7.31 (*J* = 8.2)	7.25 (*J* = 7.6, *J* = 1.1)	2.42	8.17 (1H, d, *J* = 5.0, H-6'); 8.09 (1H, s, H-3'); 6.97 (1H, d, *J* = 5.1, H-5'); 2.35 (3H, s, CH_3)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
1h	11.92	10.81	7.82 (J = 8.0, J = 1.0)	7.54 (J = 7.7, J = 1.1)	7.30 (J = 8.2)	7.23 (J = 7.8, J = 1.0)	2.42	8.16 (1H, s, H-6'); 8.11 (1H, d, J = 8.5, H-3'); 7.65 (1H, dd, J = 8.5, J = 2.1, H-4'); 2.26 (3H, s, CH_3)
1i	11.89	10.84	7.80 (J = 8.1, J = 1.2)	7.54 (J = 7.6, J = 1.1)	7.31 (J = 8.0)	7.23 (J = 7.7, J = 1.1)	2.41	8.03 (1H, d, J = 7.9, H-3'); 7.70 (1H, t, J = 7.9, H-4'); 6.98 (1H, d, J = 7.6, H-5'); 2.38 (3H, s, CH_3)
1j	12.01	11.27	7.83 (J = 8.1, J = 1.2)	7.57 (J = 7.8, J = 1.2)	7.33 (J = 8.2)	7.25 (J = 7.7, J = 1.2)	2.45	9.48 (1H, s, H-3'); 8.41 (2H, m, H-5',6')
1k	12.24	See R	7.85 (J = 8.1, J = 1.1)	7.58 (J = 7.7, J = 1.2)	7.34 (J = 8.1)	7.26 (J = 7.6, J = 1.2)	2.53	12.03 (2H, br. s, 2NH); 7.47 (2H, br. m, H-4',7'); 7.09 (2H, m, H-5',6')
1l	12.93	12.08	7.85 (J = 8.1, J = 1.2)	7.58 (J = 7.7, J = 1.0)	7.35 (J = 8.2)	7.27 (J = 7.6, J = 1.0)	2.43	7.51 (1H, d, J = 3.8, H-5'); 7.31 (1H, d, J = 3.8, H-4')
1m	12.86	12.12	7.86 (J = 8.1, J = 1.1)	7.60 (J = 7.6, J = 1.1)	7.33 (J = 8.2)	7.25 (J = 7.5, J = 1.1)	2.42	3.40 (1H, m, CH); 1.45 (6H, d, J = 6.6, $2CH_3$)
1n	12.88	12.09	7.84 (J = 8.1, J = 1.1)	7.59 (J = 7.6, J = 1.0)	7.34 (J = 8.2)	7.26 (J = 7.5, J = 1.0)	2.42	2.89 (2H, d, J = 7.0, CH_2); 2.03 (1H, m, CH); 0.95 (6H, d, J = 6.5, $2CH_3$)
1o	12.81	12.10	7.86 (J = 8.0, J = 1.2)	7.60 (J = 7.7, J = 1.2)	See R	7.27 (J = 7.8, J = 1.3)	2.44	8.02 (1H, d, J = 8.0, H-7'); 7.77 (1H, d, J = 7.9, H-4'); 7.45 (1H, t, J = 7.9, H-6'); 7.38–7.30 (2H, m, H-8 quinolone + H-5')
1p	12.92	12.11	7.86 (J = 8.0, J = 1.1)	See R	7.35 (J = 8.1)	7.27 (J = 7.7, J = 1.1)	2.43	8.30 (1H, d, J = 1.9, H-7'); 7.70 (1H, d, J = 8.6, H-4'); 7.60 (2H, m, H-7 quinolone + H-5')

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Varian Mercury VX-200 spectrometer (200 MHz) using DMSO-d_6 solvent and with TMS as internal standard. Melting point for amides **1a-p** were determined on a Mettler Toledo FP62 instrument (gradient temperature regime 2ºC/min). The synthesis of imidazolide **2** has been reported in [4]. N-Hetarylmalonamic acids **4** and their ethyl esters **3** were prepared by known methods [6, 7]. For the syntheses, anhydrous DMF for peptide synthesis and N,N'-carbonyl-diimidazole were obtained from Fluka and *ortho*-aminoacetophenone from the Aldrich company.

4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Pyridin-4-ylamide (1a). 4-Aminopyridine (0.94 g, 0.01 mol) was added to a solution of the imidazolide **2** (2.53 g, 0.01 mol) in anhydrous DMF (10 ml) and refluxed with the exclusion of atmospheric moisture for 8 h. The product was cooled, diluted with cold water, and acidified with acetic acid to pH ~ 5.5. The precipitated residue of amide **1a** was filtered off, washed with water, dried, and crystallized from a mixture of DMF and ethanol.

Hetarylamides 1b-k were prepared similarly.

4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Thiazol-2-ylamide (1l). N,N'-Carbonyl-diimidazole (1.78 g, 0.011 mol) was added to a solution of N-thiazol-2-ylmalonamic acid **4l** (1.86 g, 0.01 mol) in anhydrous DMF (10 ml). With protection from atmospheric moisture it was held at 55-60ºC until carbon dioxide evolution had ceased (~4 h). The temperature of the reaction mixture should not be increased at this stage because of the high tendency of the N-hetarylmalonamic acids (especially in solution) towards decarboxylation. Ortho-aminoacetophenone (1.35 g, 0.01 mol) was added to the imidazolide **5l** obtained in this way and refluxed for 12 h. The reaction mixture was diluted with cold water and acidified with dilute (1:1) HCl to pH ~ 5.5. The precipitated thiazol-2-ylamide **1l** was filtered off, washed with cold water, dried, and crystallized from a mixture of DMF and ethanol.

Hetarylamides 1m-p were prepared similarly.

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