4-Hydroxy-1(2*H*)-isoquinolone-3-carboxamides Synthesis and Properties

Celia B. Schapira, María I. Abasolo and Isabel A. Perillo*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica,
Universidad Nacional de Buenos Aires, Junín 956,
Buenos Aires, República Argentina

Received November 29, 1983

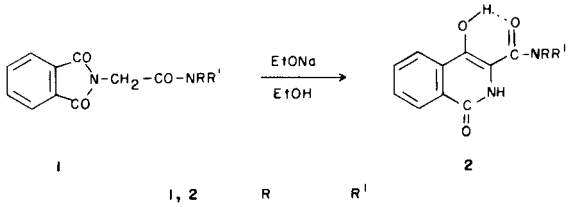
Reaction of some α-phthalimidoacetamides **1a-i** with sodium ethoxide was carried out under drastic conditions. Compounds **1b-g** afforded 4-hydroxy-1(2*H*)-isoquinolone-3-carboxamides **2b-g**, while **1h-i** afforded the acid **3a-b** together with the expected isoquinolones **2h-i**. Compound **1a** gave phthalimide as the major product. Compounds **2** are acidic and unstable in basic media. The most acidic compounds presented the longest half-life. An explanation of these results was given.

J. Heterocyclic Chem., **22**, 577 (1985).

Several 4-hydroxy-2-methyl-1(2*H*)-isoquinolone-3-carboxanilides were prepared by Lombardino from 4-hydroxy-2-methyl-1(2*H*)-isoquinolone and aryl isocyanates and their spectral properties were described [1]. However, there were no isoquinolone-3-carboxamides reported with a 2*H* substituent. This fact has led us to synthesize some isoquinolones **2** applying the Gabriel Colman rearrangement [2-8], as has been described for the sulfone analogs [9-11].

Treatment of α-phthalimidoacetamides **1b-g** with sodium ethoxide in drastic conditions afforded 4-hydroxy-1(2*H*)-isoquinolone-3-carboxamides **2b-g** in variable amounts (Scheme I). Compounds **1h-i** gave together with the expected isoquinolones **2h-i**, *o*-(*N*-arylcarboxamidomethylcarbamoyl)benzoic acid **3a-b**. In some cases 4-hydroxy-1(2*H*)-isoquinolone-3-carboxylic acid ethyl ester **4** was also observed. In the same conditions compound **1a** afforded only phthalimide and traces of **4**.

Scheme I



1 2

1, 2	R	R'
a	H	H
b	CH_3	H
c	i-C_3H_7	H
d	C_6H_{11}	H
e	C_2H_5	C_2H_5
f	CH_3	C_6H_5
g	C_2H_5	C_6H_5
h	C_6H_5	H
i		H

The fact that the ester **4** could not be obtained by alcoholysis of compounds **2**, and never phthalimidoacetic acid ethyl ester was observed from reaction of compounds **1** and sodium ethoxide, suggest that, as in the benzoisothiazoline series [10-13], alcoholysis presumably occurs in the open phthalamic esters **5** (Scheme II). However, like in rearrangement of *N*-phenacylphthalimides [14] these open intermediates were not detected.

As in the 2-methyl analogs [1], spectral properties support the enol ("4-hydroxy") structure for carboxamides **2** [15] (Table II).

All of isoquinolones **2** proved to be acidic as was pointed out by Lombardino [1] who reported for the 2-methyl analogs of compound **2h** a pK'_a of 7.7 in 2:1 dioxane-water. The pK'_a values were found to be 1.1-1.3 units higher in 1:1 dioxane-water than in water (Table III). *N,N*-Disubstituted compounds **2e-g** show the highest pK'_a. One amidic hydrogen was found to increase acidity and *N*-aryl derivatives are more acidic than *N*-alkyl derivatives. The enhanced acidity may be explained by invoking stabilization of

Scheme II

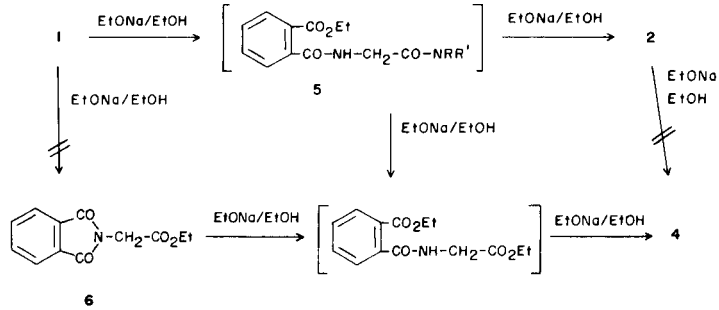
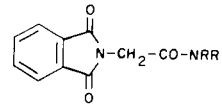


Table I

α-Phthalimidoacetamides



Compound No.	Yield (%)	Mp (°C)	Recrystallization Solvent	Previous Reference	Analyses % Calcd./Found C	H	N	IR ν, cm⁻¹ NH	CH	CO (imide)	CO (amide)	C=C	amide II
1a	75	264	ethanol	[22]				3400		1760 1710	1660	1600	
1b	80	252	methanol		60.55 60.33	4.59 4.75	12.84 12.81	3300	2950	1780 1710	1680		1550
1c	78	226	ethanol		63.41 63.30	5.69 5.80	11.38 11.43	3300	2900	1788 1710	1620		1525
1d	83	235	methanol		67.13 66.98	6.29 6.34	9.79 9.75	3310	2900	1790 1710	1630		1580
1e	80	151	methanol		64.62 64.49	6.15 6.01	10.77 10.83		2940	1780 1710	1650		
1f	83	177	ethanol		69.39 69.24	4.76 4.90	9.52 9.60		2950	1785 1715	1680	1600	
1g	78	161	ethanol		70.13 70.31	5.19 5.32	9.09 9.03		2950	1785 1710	1665		
1h	80	231	ethanol	[23]				3280	3000	1785 1720	1650	1600	1530
1i	70	191	ethanol	[24]				3200	2950	1790 1710	1690	1595	1540

the enolate anion through hydrogen bonding. When the amine basicity is lower, higher stabilization could be expected. However, although aniline (pK_b 9.42) is a weaker base than 2-aminopyridine (pK_b 7.29) [19], compound **2i** is more acidic than **2h**. The fact was explained taking into account a tautomeric structure which may import further stability to the enolate anion of **2i**. Similar results were observed in the related 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides [20].

Compounds **2** were found to be unstable in basic media [21]. Decomposition was followed by uv spectrophotometry. Rate constants and half-lives are listed in Table IV. A quantitative evaluation of the structure-stability relationship indicates that stability in basic media increases on decreasing pK'_a values. Disubstituted compounds **2e-g**, which exhibit the highest pK'_a values were found to be the most unstable; decomposition occurs immediately at p*H* 11 and rates of reaction were studied at p*H* 8. Among the other carboxamides, the most acidic compound **2i** presents the longest half-life. According to these results, stabilization of the enolate anion increases not only the acidity but also the stability of these compounds in alkaline media.

EXPERIMENTAL

Melting points were taken on a Buchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 A spectrometer using potassium bromide pellets. The nmr spectra were obtained on a Perkin Elmer R 12 A (60 MHz) spectrometer with tetramethylsilane as internal reference using DMSO-d_6 as solvent. Chemical shifts are reported in parts per million (δ) and signals are quoted as: S (singlet), D (doublet), T (triplet), Q (quartet) and M (multiplet). The presence of exchangeable protons was confirmed by use of deuterium oxide. The uv spectra were recorded with a Perkin Elmer 202 spectrophotometer and absorbances were read on a Beckman DB-G Grating spectrophotometer. The p*H* values of the buffer solutions were measured in a Beckman Zeromatic II p*H* meter using standardized glass electrode. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures. Analytical tlc was carried out on aluminium sheets silica gel 60 F_{254} using 9:1 benzene-methanol as solvent.

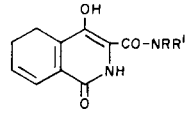
α-Phthalimidoacetamides **1a-i**. General Procedure.

A mixture of 0.12 mole of potassium phthalimide, 0.08 mole of the corresponding 2-chloroacetamide and 15 ml of *N,N*-dimethylformamide was heated at 120° for 4 hours. The reaction mixture was poured into ice-water and the resulting solid was filtered, washed with water, dried and recrystallized. Yields, melting points, recrystallization solvents, elemental analyses and spectroscopic data of the compounds are given in Table I.

4-Hydroxy-1(2*H*)-isoquinolone-3-carboxamides **2b-g**. General Procedure.

Table II

4-Hydroxy-1(2*H*)-isoquinolone-3-carboxamides **2a-i**



Compound No.	Reaction Time (minutes)	Yield (%)	Mp [a] (°C)	Recrystallization Solvent	Analyses % Calcd./Found C	H	N	IR ν (cm^{-1}) [b]	δ (ppm)	^{1}H NMR Multiplicity	Assignment	UV in 0.1*N* HCl λ max (nm)	log ϵ	UV in 0.1*N*NaOH λ max (nm)	log ϵ
2a	[c]		237-262	ethanol	58.82	3.92	13.72	3400 (NH)		[d]		212	4.39	222	4.39
					58.70	3.99	13.65	3250 (NH)				260 (sh)	3.68	260 (sh)	3.75
								1680 (CO)				325	4.01	363	4.04
								1595 (C=C)							
2b	15	30	246-265	DMF	60.55	4.59	12.84	3350 (NH)		[d]		215	4.36	220	4.34
					60.38	4.80	12.80	1680 (CO)				260 (sh)	3.75	240	4.06
								1600 (C=C)				322	3.95	365	3.99
								1560 (amide II)							
2c	30	21	242-257	DMSO	63.41	5.69	11.38	3350 (NH)		[d]		215	4.28	225	4.19
					63.28	5.81	11.30	1670 (CO)				260 (sh)	3.72	365	3.99
								1605 (C=C)				325	3.97		
								1560 (amide II)							
2d	20	42	250-265	methanol	67.13	6.29	9.79	3350 (NH)		[d]		220	4.27	220	4.15
					67.27	6.40	9.85	1670 (CO)				260 (sh)	3.85	375	3.95
								1600 (C=C)				333	3.95		
								1550 (amide II)							
2e	7	37	206-208	benzene	64.62	6.15	10.77	[e]	11.23	S [f]	OH	210	4.41	220	4.04
					64.50	6.30	10.71	1660 (CO)	8.87	S [f]	NH	230 (sh)	4.10	350	3.83
								1600 (C=C)	8.39-7.59	M	aromatics	295	3.84		
									3.50	Q	CH_2				
									1.25	T	CH_3				
2f	5	51	222-228	ethanol	69.39	4.76	9.52	[e]	11.00	S [f]	OH	210	4.54	220	4.42
					69.20	4.89	9.55	1640 (CO)	8.92	S [f]	NH	260 (sh)	3.88	370	3.91
								1600 (C=C)	8.30-7.00	M	aromatics	310	3.92		
									3.40	S	CH_3				
2g	10	71	192	ethyl acetate	70.13	5.19	9.09	[e]	11.04	S [f]	OH	210	4.46	230	4.09
					70.01	5.30	9.18	1630 (CO)	8.81	S [f]	NH	260 (sh)	3.81	260 (sh)	4.02
								1580 (C=C)	8.12	D	=CH(C=)CO	310	3.80	370	3.74
									7.94-7.00	M	aromatics				
									4.16	Q	CH_2				
									1.12	T	CH_3				
2h	120	50	260-270	DMF	68.57	4.29	10.00	3350 (NH)		[d]		247	4.14	247	4.12
					68.50	4.42	10.05	1680 (CO)				335	3.83	270 (sh)	3.94
								1630 (CO)						380	3.99
								1600 (C=C)							
								1560 (amide II)							
2i	180	8	255-266	DMSO	64.05	3.91	14.94	3400 (NH)		[d]		242	3.98	240	4.00
					63.90	4.07	14.90	3250 (NH)				290 (sh)	3.87	393	4.11
								1660 (CO)				350	4.10		
								1600 (C=C)							
								1560 (amide II)							

[a] All of these compounds exhibit high and, except those *N,N*-disubstituted species, wide ranges of melting points. [b] OH-Absorptions appear as broad bands in the range of 3500-2500 cm^{-1}. [c] This compound was obtained by ammonolysis of **4**. [d] Insolubility of the species in every solvent enable the nmr spectra to be performed. [e] The absence of NH absorption could be attributed to a superimposition upon the broad OH band. [f] Exchangeable.

A solution of sodium ethoxide (0.92 g of sodium in 13 ml of absolute ethanol) was refluxed in an oil bath (140°) and 0.01 mole of α-phthalimidoacetamide **1b-g** was added all at once as the powder. When the reaction was completed, the mixture was poured into ice-concentrated hydrochloric acid. The solid was filtered off, washed with water and recrystallized affording compounds **2b-g**. Reaction times, yields, melting points, recrystallization solvents, analyses and spectroscopic data of compounds are given in Table II. Following the reaction at different times by tlc, nevertheless was observed some intermediate.

4-Hydroxy-1(2*H*)-isoquinolone-3-carboxylic acid ethyl ester (**4**) was isolated from the reaction of **1b** with sodium ethoxide as follows: the crude product was boiled with ethanol, the hot suspension was filtered off to remove **2b** and the filtrate was evaporated to dryness, affording **4** (3% yield). Structure was confirmed by comparison with an authentic sample [2,3], mp and mixture mp 194°.

4-Hydroxy-1(2*H*)-isoquinolone-3-carboxamide (**2a**).

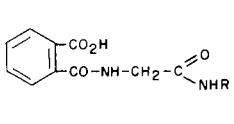
A solution of **4** (2.33 g) in 100 ml of aqueous ammonia (58%) was allowed to stand at room temperature for 2 days. Removal of the excess ammonia *in vacuo*, pouring into ice-hydrochloric acid and recrystallization of the resulting solid gave 1.6 g (80% yield) of pure **2a** (Table II).

Attempts to prepare the carboxamide **2a** by rearrangement of **1a** with sodium ethoxide produced only phthalimide (50% yield) and little amounts of **4**.

Table III

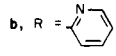
Acidity of 4-Hydroxy-1(2*H*)-isoquinolone-3-carboxamides

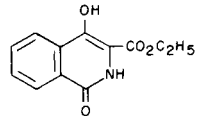
Compound	pK'_a in water	pK'_a in dioxane-water (1:1)
2a	5.03	6.34
2b	5.59	
2c	4.91	6.12
2d		6.00
2e	7.31	8.45
2f	7.30	
2g	7.48	
2h		5.06
2i		4.59



3

a, R = C_6H_5

b, R = 



4

Reaction of **1h** with Sodium Ethoxide Under Drastic Conditions.

When **1h** was treated with sodium ethoxide under the same conditions as **1b-g**, the reaction was completed after 2 hours. The mixture was poured into ice-hydrochloric acid and filtered off. The crude product was boiled with ethanol and the hot suspension was filtered affording **2h** (43% yield) (Table II). Upon cooling the ethanolic filtrate gave a second crop of **2h** (7%). The ethanolic solution was evaporated to dryness, the residue was triturated with saturated sodium bicarbonate solution, filtered off some insoluble and acidified with hydrochloric acid. The precipitate was filtered, washed with water and recrystallized to give *o*-(*N*-phenylcarboxamidomethylcarbamoyl)benzoic acid **3a** (20% yield), melting point 228° (ethyl acetate); ir: 3350 (NH), 1700 (CO), 1680 (CO), 1620 (CO), 1600 (C=C) and 1540 cm^{-1} (amide II); ^1H nmr: δ 9.65 (S, 1, exchangeable, CO_2H), 8.70 (T, 1, exchangeable, -N*H*-CH_2), 7.00-8.00 (M, 10, aromatics and NH), 3.92 (D, 2, CH_2, upon deuteration the doublet collapsed into a singlet).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.39; H, 4.85; N, 9.37.

Reaction of **1i** with Sodium Ethoxide Under Drastic Conditions.

Compound **1i** was treated with sodium ethoxide under the same conditions as **1b-g**. After 3 hours, the reaction mixture was poured into ice-acetic acid and filtered off. The crude product was boiled with ethanol and the insoluble was collected affording **2i** (Table II). The ethanolic solution was evaporated to dryness. The crude product showed (tlc) to be a mixture of little amounts of **4** and another product which was purified by several recrystallizations from ethanol affording *o*-[*N*-(2-pyridyl)carboxamidomethylcarbamoyl]benzoic acid (**3b**) (38% yield), mp 194°; ir: 3300 (NH), 1780 (CO), 1730 (CO), 1650 (CO), 1600 (C=C) and 1550 cm^{-1} (amide II); ^1H nmr: δ 10.40 (S, 1, exchangeable, CO_2H), 8.65 (T, 1, exchangeable, -N*H*-CH_2), 8.30 (D, 1, aromatic, -N=CH-), 8.20-7.00 (M, 8, aromatics and NH) and 4.10 (D, 2, CH_2, upon deuteration the doublet collapsed into a singlet).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.35; N, 14.04. Found: C, 60.31; H, 4.28; N, 13.98.

pK'_a Determinations.

The pK'_a values for compounds **2a-i** were determined by uv spectrophotometry [25] in water or 1:1 dioxane-water, according to solubility of the compounds (Table III).

General Kinetic Procedure.

Two tenths ml of an ethanolic solution of compounds **2** was placed in the cell of the spectrophotometer uv-visible and diluted with the appropriate buffer solution (Table IV) to a known final concentration ($5.8 \times 10^{-5}M$). This solution was immediately read at two selected wavelengths against the corresponding blank. Readings were repeated at known intervals until complete disappearance of absorption at those wavelengths was observed. At constant p*H* the rates of disappearance of compounds were found to be first order. Plots of log (absorbance) against time showed that linearity held up to 100% of the reaction. Pseudo-first order rate constant (k') were calculated from the relationship $k = \ln 2/t_{1/2}$.

Acknowledgement.

Financial support of this investigation was given by the Subsecretaría de Ciencia y Tecnología.

REFERENCES AND NOTES

[1] J. G. Lombardino, *J. Heterocyclic Chem.*, **7**, 1057 (1970).
[2] S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900).
[3] S. Gabriel and J. Colman, *Ber.*, **33**, 2630 (1900).
[4] S. Gabriel and J. Colman, *Ber.*, **35**, 2421 (1902).
[5] L. R. Caswell and R. D. Campbell, *J. Org. Chem.*, **26**, 4175 (1961).
[6] L. R. Caswell and P. C. Atkinson, *J. Heterocyclic Chem.*, **3**, 328 (1966).

Table IV

Rate Constants and Half-lives for Decomposition of Compounds **2** in Basic Media

Compound	Selected (nm)	*p*H 8 (water) k' (min^{-1})	*p*H 8 (water) $t_{1/2}$ (hours)	*p*H 11 (water) k' ($minutes^{-1}$)	*p*H 11 (water) $t_{1/2}$ (hours)	*p*H 11 (dioxane-water, 1:1) k' ($minutes^{-1}$)	*p*H 11 (dioxane-water, 1:1) $t_{1/2}$ (hours)
2a	330 and 340			1.7×10^{-5}	663.93	9.5×10^{-4}	12.21
2b	340 and 350			1.9×10^{-5}	595.50	1.0×10^{-3}	11.55
2c	370 and 380			5.2×10^{-5}	221.74	2.3×10^{-3}	5.07
2d	340 and 350			5.2×10^{-5}	221.74		
2e	320 and 330	2.5×10^{-3}	4.62				
2f	330 and 340	7.4×10^{-4}	15.72				
2g	360 and 370	3.9×10^{-3}	2.96				
2h	380 and 390					4.2×10^{-4}	27.70
2i	400 and 420					2.0×10^{-4}	57.76

[7] L. R. Caswell and T. Ling-chung Kao, *J. Heterocyclic Chem.*, **3**, 333 (1966).

[8] L. R. Caswell, R. A. Haggard and D. Ching-wing Yung, *J. Heterocyclic Chem.*, **5**, 865 (1968).

[9] H. Zinnes, N. A. Lindo and J. Shavel, Jr., U. S. Patent 4,074,048; *Chem. Abstr.*, **88**, 190.868 (1978).

[10] H. Zinnes, J. C. Sircar, N. Lindo, M. L. Schwartz, A. C. Fabian, J. Shavel, Jr., C. F. Kasulanis, J. D. Genzer, Ch. Lutomski and G. DiPasquale, *J. Med. Chem.*, **25**, 12 (1982).

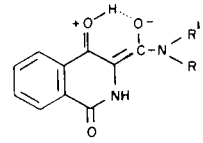
[11] I. A. Perillo, C. B. Schapira and S. Lamdan, *J. Heterocyclic Chem.*, **20**, 155 (1983).

[12] H. Zinnes, R. A. Comes, F. A. Zuleski, A. N. Caro and J. Shavel, Jr., *J. Org. Chem.*, **30**, 2241 (1965).

[13] C. B. Schapira, I. A. Perillo and S. Lamdan, *J. Heterocyclic Chem.*, **17**, 1281 (1980).

[14] J. H. M. Hill, *J. Org. Chem.*, **30**, 620 (1965).

[15] The ir spectra of all of these compounds exhibit broad weak OH absorption bands extending from 3500 to beyond 2500 cm^{-1}. Similar absorption was observed by Lombardino [1] in the 2-methyl isoquinolones and in other conjugated systems [16,17], and can be interpreted according with Rasmussen on the basis of an ionic resonance structure (A) along with the normal covalent structure **2** [18].



A

[16] A. E. Martin, *Nature*, **166**, 474 (1950).

[17] H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

[18] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

[19] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965.

[20] J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.*, **15**, 848 (1972).

[21] The lack of stability in this family of compounds has been reported [1] for the 3-carboxylic methyl ester which slowly decomposed on standing.

[22] M. Bianchi and F. Barzaghi, *Farmaco, Ed. Sci.*, **20**, 611 (1965).

[23] G. W. Anderson, J. Blodinger, R. W. Young and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5304 (1952).

[24] E. J. Browne and J. B. Polya, *J. Chem. Soc. (C)*, 2904 (1968).

[25] B. Fernández, I. A. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. II*, 1416 (1974).