Chemistry of Heterocyclic Compounds, Vol. 36, No. 7, 2000

REACTIONS OF AMINOQUINOLINES WITH UNSATURATED CARBOXYLIC ACIDS. 4*. SYNTHESIS OF 4-CARBOXY-1-QUINOLYL-2-PYRROLIDINONES

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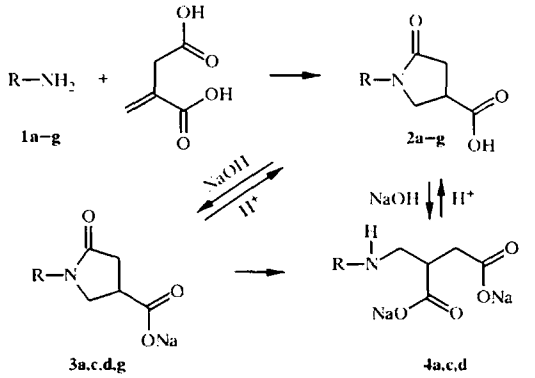
1-Quinolyl-4-carboxy-2-pyrrolidinones have been synthesized by the reaction of aminoquinolines with itaconic acid. Decyclization of the products gave 2-(quinolylaminomethyl)succinic acids.

Keywords: quinolylaminobutanoic acid, 1-quinolyl-4-carboxy-2-pyrrolidinones, biological activity.

Pyrrolidinone derivatives are of interest as compounds possessing a wide range of valuable properties. They show growth regulating [2], psychotropic and antitumor [3] effects, and they are used for the synthesis of medicinals [4].

It seemed to us to be interesting to prepare the previously undescribed 1-quinolyl-3-carboxy-2-pyrrolidinones **2**. These compounds were synthesized in 30-60% yields by heating the corresponding aminoquinolines **1** with itaconic acid in water or toluene.



a R = 4-C_9H_6N; **b** R = 5-C_9H_6N;**c** R = 2-CH_3-5-C_9H_5N; **d** R = 6-C_9H_6N; **e** R = 2-CH_3-6-C_9H_5N; **f** R = 4-CH_3-8-C_9H_5N; **g** R = 5-Br-8-C_9H_5N

Pyrrolidinones **2** are stable to acid hydrolysis. The sodium salts of carboxypyrrolidinones **3** are obtained by treatment of compounds **2** with an equivalent amount of alkali, but heating with an excess of alkali caused opening of the pyrrolidinone ring to give disodium salts of 2-(quinolylaminomethyl)succinic acid **4**. The free 2-(quinolylaminomethyl)succinic acids were not isolated: neutralization or acidification of salts **4** solutions gave the cyclic compounds **2**.

* For Communication 3, see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 932-935, July, 2000. Original article submitted February 15, 1999.

 0009-3122/00/3607-0818$25.00©2000 KluwerAcademic/Plenum Publishers

TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (dec.), solvent	^{1}H NMR spectrum*, δ, ppm (coupling constants, Hz)					Yield, %
		C	H	N		CH_3 (s)	CH_2CO (d)	CH (m)	NCH_2 (d)	arom., m	
1	2	3	4	5	6	7	8	9	10	11	12
2a	$C_{14}H_{12}N_2O_3$	65.90 / 65.62	4.51 / 4.72	10.78 / 10.93	176, water		2.63-2.85 (m)	3.18-3.60	4.63 (J = 6)	6.40-8.33 (6H)	59
2b	$C_{14}H_{12}N_2O_3$	65.47 / 65.62	4.61 / 4.72	10.84 / 10.93	273, ethanol		2.81 (J = 6)	3.20-3.68	4.10 (J = 8)	6.69-9.08 (6H)	30
2c	$C_{15}H_{14}N_2O_3$	66.48 / 66.66	5.40 / 5.22	10.19 / 10.36	244, ethanol	2.63	2.84 (J = 6)	3.22-3.72	4.12 (J = 7)	6.6-8.18 (5H)	47
2d	$C_{14}H_{12}N_2O_3$	65.31 / 65.62	4.82 / 4.72	10.93 / 10.93	265, ethanol		2.95 (J = 6)	3.21-3.65	4.19 (J = 7)	7.6-9.05 (6H)	52
2e	$C_{15}H_{14}N_2O_3$	65.85 / 66.66	5.39 / 5.22	10.14 / 10.36	219, ethanol	2.60	2.79 (J = 8)	3.18-3.58	4.13 (J = 7)	7.25-8.28 (5H)	56
2f	$C_{15}H_{14}N_2O_3$	66.95 / 66.66	5.10 / 5.22	10.26 / 10.36	202, ethanol	2.76	2.94 (J = 6)	3.18-3.61	4.09 (J = 7)	7.4-8.85 (5H)	36
2g	$C_{14}H_{11}BrN_2O_3$	49.62 / 50.17	3.28 / 3.31	8.38 / 8.36	206, propanol-2		2.81 (J = 9)	3.36-3.53	4.08-4.38 (m)	7.58-9.09 (5H)	31

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
3a	$C_{14}H_{11}N_2O_3Na$	60.31 60.43	3.80 3.99	9.79 10.07	322, ethanol		2.76 (J = 6)	2.91-3.38	3.38 (J = 8)	6.43-8.30 (6H)	100
3c	$C_{15}H_{13}N_2O_3Na$	61.42 61.64	4.37 4.48	9.91 9.59	372, ethanol	2.74	2.84 (J = 8)	3.03-3.48	4.23 (J = 8)	6.7-8.33 (5H)	100
3d	$C_{14}H_{11}N_2O_3Na$	60.28 60.43	3.72 3.99	9.83 10.07	359, ethanol		2.85 (J = 8)	3.28-3.45	3.89 (J = 8)	7.46-8.70 (6H)	100
3e	$C_{15}H_{13}N_2O_3Na$	61.55 61.64	4.42 4.48	9.94 9.58	310, ethanol						100
3g	$C_{14}H_{10}BrN_2O_3Na$	46.84 47.08	2.68 2.82	7.54 7.84	291, ethanol						100
4a	$C_{14}H_{12}N_2O_4Na_2$	52.66 52.84	3.59 3.80	8.59 8.80	367, ethanol		2.55-2.88 (m)	3.18-3.58	3.46 (J = 4)	6.48-8.40 (6H)	44
4c	$C_{15}H_{14}N_2O_4Na_2$	54.02 54.22	4.06 4.25	8.21 8.43	383, ethanol	2.59	2.63-2.88 (m)	3.13-3.40	3.13-3.40 (m)	6.63-8.10 (5H)	51
4d	$C_{14}H_{12}N_2O_4Na_2$	52.60 52.84	3.64 3.80	8.57 8.80	370, ethanol		2.38-2.65 (m)	2.83-3.20	3.20-3.45 (m)	6.58-8.38 (6H)	43

* Spectra of compounds **2a-f** were recorded in CF_3COOH, **2g** in DMSO-d_6, and **3** and **4** in D_2O.

The ^{1}H NMR spectra of pyrrolidinones **2** (in CF_3COOH) and their sodium salts **3** (in D_2O) contain doublets for the protons at $C_{(3)}$ and $C_{(5)}$ in the ranges 2.63-2.95 and 4.08-4.69 ppm, and multiplets for the protons on $C_{(4)}$ in the range 3.18-3.72 ppm. Comparison of the ^{1}H NMR spectra of compounds **3** and **4** shows that the protons of the methylene group in the $NHCH_2$ unit of aminocarboxybutanoic acids are shifted 0.9-1.1 ppm to high field relative to the analogous groups in the cyclic compounds **3**.

Experiments carried out by L. L. Mironova (Dr. Med. Sci.) at the Institute for Poliomyelitis and Viral Encephalitis, Russian Academy of Sciences, showed that compounds **3** and **4** had stimulated the proliferation of isolated simian kidney cells. The decyclized derivatives of pyrrolidinones **3** did not have a significant effect on the proliferation.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Tesla BS-487 C (80 MHz) machine with HMDS as internal standard. The progress of reactions and the purity of products were monitored by TLC on Silufol and Silufol UV-254 strips. Physicochemical data on the compounds synthesized are given in Table 1.

4-Carboxy-1-quinolyl-2-pyrrolidinones 2. Itaconic acid (7.2 g, 55 mmol) and the corresponding aminoquinoline **1a,d,e** (50 mmol) were boiled in water (40 ml) for 6 h, or **1b,c,e** were boiled in toluene (40 ml) for 40 h. The reaction mixtures were then kept for a day at 5°C. The crystals formed were filtered off and recrystallized from ethanol.

Sodium Salts of 4-Carboxy-2-pyrrolidinones 3. The corresponding pyrrolidinone **2** (20 mmol) was dissolved in 90% ethanol (30 ml) containing sodium hydroxide (0.8 g, 20 mmol). The solution was poured into acetone (100 ml). The precipitate was recrystallized from ethanol.

Disodium 2-(Quinolylaminomethyl)succinates 4. Sodium hydroxide (1.2 g, 30 mmol) and pyrrolidinone **2** (14 mmol) were boiled in 60% ethanol (20 ml) for 4 h. The reaction mixture was then kept at 4°C. The crystals formed were filtered off, washed with ethanol and dried.

REFERENCES

1. Z. I. Beresnevicius and V. Viliunas, *Khim. Geterotsikl. Soedin.*, No. 7, 925 (2000).
2. J. Fujiwara, S. Arai, M. Nishida, and M. Oyamada, *Jap. Pat.* 02115161; *Chem. Abs.*, **113**, 110935 (1990).
3. H. Jizuka, T. Oguchi, Y. Aoki, N. Ohto. K. Horikomi, T. Miwa, T. Kamioka, and S. Kawashima, *Eur. Pat. Appl.*, 668275; *Chem. Abs.*, **124**, 8606 (1996).
4. J. W. Lampe, Y. L. Chou, R. G. Hanna, S. V. Di Meo, P. W. Erhardt, W. R. Ingebretsen, and E. Cantor, *J. Med. Chem.*, **36(8)**, 1041 (1993).