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Reaction of 1-substituted 3-aminoquinolinediones with isocyanic and isothiocyanic acid

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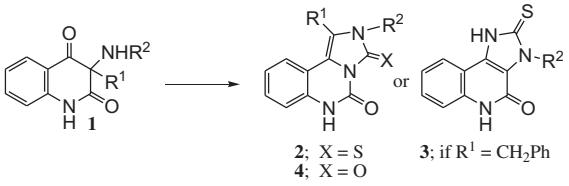
ABSTRACT

1-Substituted-3-aminoquinoline-2,4(1*H*,3*H*)-diones react with potassium cyanate or potassium thiocyanate in boiling acetic acid to give ureido- or thioureidooxindoles, spiro-oxindoles and dihydroimidazoquinolones. However, if the starting compounds are substituted with a benzyl group at position 3, a C-debenzylation proceeds to give imidazoquinolones. According to a proposed reaction mechanism, a molecular rearrangement of the primarily formed mono-substituted urea or thiourea takes place. All compounds were characterized by ^{1}H, ^{13}C and IR spectroscopy and MS data.

1. Introduction

Recently, we published the reaction of 1-unsubstituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **1** with isothiocyanic acid (prepared in situ from potassium thiocyanate) in boiling acetic acid.[1] During a rearrangement of the addition products, novel 2,3-dihydro-3-thioxoimidazo[1,5-*c*]quinazolin-5(6*H*)-ones **2** arose in high yields. However, if the starting compounds were substituted with a benzyl group at position 3, a C-debenzylation proceeded to give 2,3-dihydro-2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones **3**. When using thiourea as a source of thiocyanic acid, the yields of compounds **2** and **3** were substantially lower. The reaction of **1** with urea[2] or potassium cyanate[1] in boiling acetic acid resulted in no observed C-debenzylation; instead, only 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **4** were obtained (Scheme 1).

These interesting results gave us the incentive to perform analogous reactions with 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5**. We had studied the reaction of these compounds with urea in acetic acid earlier[3] and, depending on the type of substitution at position 3 and on the nitrogen atom of the 3-amino group, four novel types of heterocyclic compounds (**6**–**9**) could be obtained (Scheme 2). All of these compounds arose due to rearrangement of the intermediate 3-ureido-1*H*,3*H*-quinoline-2,4-diones or 9b-hydroxy-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-diones, which are obtained by the reaction of **5** with nitrourea and subsequently converted to **6**–**9** by boiling in acetic acid.[4]



Scheme 1.

In this work, we would like to describe the reaction of 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5** with potassium cyanate or potassium thiocyanate in boiling acetic acid. In the reaction of **5** with potassium cyanate, we expect the formation of the same products (**6**–**9**) as those produced in the reaction with urea.[3] The production of novel sulfur analogues of compounds **6**–**9** are expected when using potassium thiocyanate. Finally, the formation of 1-substituted analogues of compounds **3** is expected when the starting compound bears a benzyl group at position 3.

2. Results and discussion

Reactions of 3-aminoquinolinediones **5** with the appropriate reagent (Scheme 2) were performed by boiling the reaction

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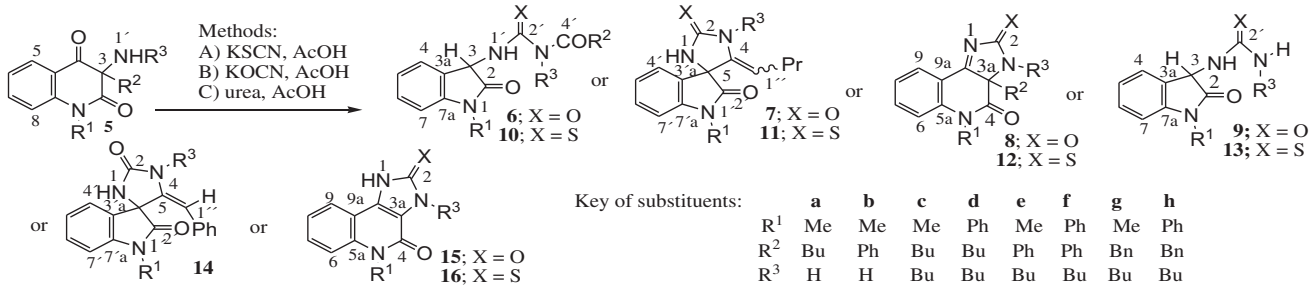


Scheme 2.

components in acetic acid. Starting aminoketones **5** were prepared from the corresponding 3-chloro derivatives in accordance with the procedure described earlier.[5] Potassium thiocyanate (method A) or potassium cyanate (method B) were used as reagents. In two cases (compounds **5g**,**h**), urea was also used. In preliminary experiments, reaction of thiourea with compounds **1**[1] and **5** did not give good results; accordingly, we did not use this reagent further in our work. The trituration of the crude reaction product with sodium hydroxide solution, described in our previous paper[1] to remove traces of cyanuric or 1,3,5-trithiocyanuric acid, was omitted due to the high solubility of some reaction products in an alkaline medium.

We have found that the reaction of **5a**–**f** with potassium cyanate (method B) proceed in the same manner as those with urea.[3] Compounds **6a**,**b**,**e**,**f**, **7c**,**d**, **8e**,**f** and **9e** were isolated (Table 1) in yields comparable to those obtained from the reaction of **5a**–**f** with urea.[3] In addition, a new compound (*Z*)-**7a** was isolated. In the presence of potassium thiocyanate (method A), the reaction of compounds **5a**–**f** proceed as expected affording the novel compounds **10b**,**f**, **11a**,**c**,**d**, **12e** and **13f**, sulfur analogues of compounds **6**, **7**, **8** and **9**; all of these compounds were obtained in good yields except for **10f** and **12e**, both having a phenyl group as substituent R^2. The NMR spectra of these new compounds are very similar to those of compounds **6**–**9** (Tables 2–4), with the only significant difference between them being the shift of the C=S group signals to 179–196 ppm compared to the C=O group signals.[3]

Table 1
Reaction of 3-aminoquinolinediones **5** with potassium thiocyanate (method A), potassium cyanate (method B) and urea (method C)

Entry	5	Substituents			Method	Time (min)	Product (yield, %)
		R^1	R^2	R^3			
1	**a**	Me	Bu	H	A	30	(*E*/*Z*)-**11a** (30)
2					B	60	**6a** (43)[a], (*Z*)-**7a** (11)
3	**b**	Me	Ph	H	A	35	**10b** (74)
4					B	50	**6b** (39)[b]
5	**c**	Me	Bu	Bu	A	30	(*E*)-**11c** (68)
6					B	50	(*E*)-**7c** (70)[a]
7	**d**	Ph	Bu	Bu	A	50	(*E*)-**11d** (79)
8					B	60	(*E*)-**7d** (72)[a]
9	**e**	Me	Ph	Bu	A	45	**12e** (7)
10					B	40	**8e** (47)[a], **6e** (5)[a], **9e** (4)[a]
11	**f**	Ph	Ph	Bu	A	40	**10f** (13), **13f** (8), **NPI** (6)[c]
12					B	45	**8f** (36)[a], **6f** (2)[a]
13	**g**	Me	Bn	Bu	A	30	**16g** (33)
14					B	60	**15g** (43), (*E*)-**14g** (13)
15					C	60	**15g** (38), (*E*)-**14g** (14)
16	**h**	Ph	Bn	Bu	A	50	**16h** (27)
17					B	60	**15h** (42), (*E*)-**14h** (16)
18					C	60	**15h** (42), (*E*)-**14h** (12)

[a] Identical in all respects to the authentic compound.[3]
[b] Mp 178–179 °C (benzene/hexane), identical in all respects to the authentic compound, for which incorrect mp 83–86 °C was formerly published.[3]
[c] *N*-Phenylisatin.

Compounds **5g**,**h**, bearing the benzyl group at position 3, react with potassium cyanate (method B) differently to give only small amounts of the expected compounds **14g**,**h**. In the NMR spectra of the observed products (Table 4), no signals corresponding to a benzyl group are seen. Mass spectra of these products also indicate that no benzyl group is present, leading us to identify these products as structures **15g**,**h**. The loss of the *C*-benzyl group is surprising, as we do not observe this phenomenon in the potassium cyanate reaction method with the analogous compounds unsubstituted at position 1.[1] This observation indicates that not only the very strong isothiocyanic acid (pK_a −1.3),[6,7] arising by isomerization of weak thiocyanic acid (pK_a 5.4),[6] but also mesoscale isocyanic acid (pK_a 3.9), arising from isomerization of weak thiocyanic acid (pK_a 5.4),[6] can eliminate the benzyl group from compounds **5g**,**h**. Thus, not only the acidity of the reaction medium, but also the type of substituent at position 1 of the starting compounds **5** influence the course of the reaction. In the reaction of **5g**,**h** with isothiocyanic acid (method A), *C*-debenzylated compounds **16g**,**h** were obtained in moderate yields as the only reaction products. This result is in agreement with our expectation based on the results of the same reaction using 1-unsubstituted analogues.[1] However, these reactions afforded approximately half the expected yields for **16g**,**h** compared to reactions of 1-unsubstituted analogues[1] indicating that other transformations are able to produce side products, which seemingly have not been isolated. The NMR spectra comparison of compounds **15** and **16** (Table 4) shows a significant difference only in the chemical shifts of the C=S and C=O groups. The same difference is seen in the comparison of NMR spectra for **11** and **14** (Table 3). However, these compounds can differ in their configuration at the butylidene or benzylidene double bonds. The stereochemistry of the individual compounds **7**, **11** and **14** was established by 2D-NOESY experiments.

In our opinion, the formation of an *E*- or *Z*-isomer is dependent on the steric conditions of intermediate **D** (Scheme 3). If **D** contains a butyl group, a strong steric interaction exists between the *N*(3)-butyl and *C*(4)-butyl or -benzyl groups, resulting unambiguously in the formation of the isomers (*E*)-**7c**,**d**, (*E*)-**11c**,**d** and (*E*)-**14g**,**h**. If there is a hydrogen atom at N(3), such a steric interaction does not exist, and elimination of the proton occurs preferentially to give the (*Z*)-**7a** and (*Z*)-**11a** isomers. We have observed similar behaviour in analogous compounds isolated from the reaction of 3-butylquinolinediones with isothiocyanates.[8] In the case of compound **11a**, a mixture of both stereoisomers was isolated, but with a significantly greater quantity of the *Z*-isomer (Table 3). Our proposal for the reaction mechanism of the conversion of compounds **5** to the products **6**–**16** (Scheme 3) is different from that described earlier.[3] In our original proposal we thought to describe the mechanism of the transformation of compounds **5** during their reaction with urea by means of two different paths, depending on whether starting compound **5** bore a primary or secondary amino group. However, afterwards we prepared[4] addition products of **5** with nitrourea, whose structures corresponded to intermediates **A** and **B** in

Table 2
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **5**, **10** and **13** in DMSO-d_6

Position	**5g**		**5h**		**10b**		**10f**		**13f**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	—	171.8	—	172.0	—	172.3	—	173.4	—	174.1
3	—	74.4	—	74.4	6.09	56.6	5.72	58.4	5.70	58.8
3a	—	—	—	—	—	125.6	—	[b]	—	127.1
4	—	195.2	—	195.5	7.35	123.5	[a]	[b]	7.36	129.7
4a	—	121.0	—	120.7	—	—	—	—	—	—
5	7.82	126.7	7.91	126.9	7.05	122.1	[a]	[b]	7.11	123.0
6	7.18	122.9	7.16	123.2	7.35	128.8	[a]	[b]	7.11	127.7
7	7.62	136.4	7.43	136.2	7.03	108.6	[a]	[b]	7.32	121.8
7a	—	—	—	—	—	144.3	—	142.5	—	142.5
8	7.12	115.5	6.14	116.4	—	—	—	—	—	—
8a	—	142.5	—	143.4	—	—	—	—	—	—
1′(R^1)	3.33	29.6	—	137.4	3.20	26.5	—	135.7	—	144.6
2′(R^1)	—	—	7.30	129.2	—	—	[a]	[b]	6.93	116.7
			7.05	128.8						
3′(R^1)	—	—	7.64	130.5	—	—	[a]	[b]	7.25	129.2
			7.59	130.3						
4′(R^1)	—	—	7.57	128.9	—	—	[a]	[b]	6.86	119.9
1′(R^2)	3.09	47.0	3.27	46.7	—	132.2	—	132.1	—	—
			3.21							
2′(R^2)	—	133.7	—	133.8	8.01	128.7	[a]	[b]	—	—
3′(R^2)	6.89	129.8	7.04	130.2	7.59	128.5	a	[b]	—	—
4′(R^2)	7.10	127.6	7.19	128.0	7.71	133.1	[a]	[b]	—	—
5′(R^2)	7.10	127.0	7.19	127.2	—	—	—	—	—	—
1′(R^3)	2.27	44.1	2.42	44.1	11.67	—	3.75	40.3	3.73	40.2
2′(R^3)	1.38	32.2	1.39	32.2	—	—	1.62	29.4	1.57	29.4
3′(R^3)	1.31	19.8	1.30	19.8	—	—	1.33	19.5	1.29	19.5
4′(R^3)	0.86	13.9	0.87	13.9	—	—	0.94	13.7	0.90	13.7
1′(NH)	2.50	—	2.60	—	11.32	—	10.75	—	10.72[c]	—
2′(C=S)	—	—	—	—	—	181.3	—	183.7	—	182.9
4′(C=O)	—	—	—	—	—	167.9	—	170.1	—	—

[a] δ_H=7.18–7.64.
[b] δ_C=126.2–130.3.
[c] δ_H=7.51 (N***H***C_6H_5).

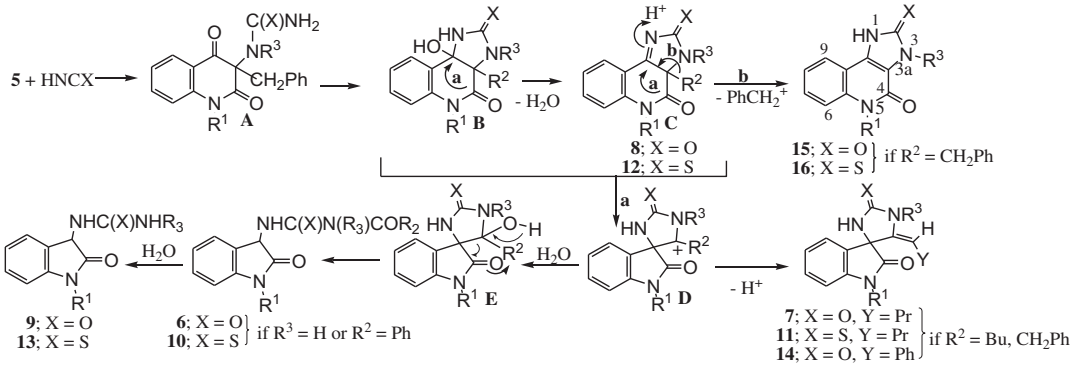
Table 3
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **7**, **11** and **14** in DMSO-d_6

Position	(*Z*)-**7a**		(*Z*)-**11a**[a]		(*E*)-**11a**[a]		(*E*)-**11c**		(*E*)-**11d**		(*E*)-**14g**		(*E*)-**14h**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1 (NH)	7.54	—	9.22	—	9.15	—	9.45	—	9.60	—	7.94	—	8.12	—
2	—	159.8	—	181.6	—	179.6	—	179.8	—	179.6	—	157.7	—	157.5
4	—	138.2	—	139.9	—	139.6	—	139.0	—	139.1	—	140.1	—	139.5
5	—	65.9	—	69.7	—	68.6	—	66.7	—	66.9	—	63.6	—	63.7
2′	—	174.7	—	173.4	—	172.4	—	172.3	—	171.9	—	173.3	—	172.5
3a′	—	130.2	—	128.4	—	128.1	—	128.2	—	128.0	—	129.2	—	129.1
4′	7.27	124.1	7.25	124.3	7.31	124.5	7.21	124.3	7.32	124.9	7.19	123.7	7.36	124.5
5′	7.14	123.2	7.17	123.4	7.17	123.5	7.17	123.6	7.23	124.2	7.02	122.9	7.15	123.7
6′	7.41	129.8	7.43	130.3	7.46	130.4	7.47	130.5	7.41	130.5	7.23	129.8	7.27	130.0
7	7.10	109.0	7.12	109.3	7.12	109.3	7.17	109.3	6.85	109.7	6.64	108.8	6.51	109.4
7a′	—	143.9	—	143.8	—	143.4	—	143.5	—	143.3	—	143.4	—	143.3
1′(R^1)	3.17	26.5	3.18	22.3	3.22	22.4	3.24	26.6	—	133.8	2.80	26.1	—	133.7
2′(R^1)	—	—	—	—	—	—	—	—	7.43	126.3	—	—	7.05	126.1
3′(R^1)	—	—	—	—	—	—	—	—	7.68	130.1	—	—	7.57	129.5
4′(R^1)	—	—	—	—	—	—	—	—	7.58	128.7	—	—	7.47	128.2
1″	3.61	96.2	3.81	99.2	4.77 [b]	101.5	4.84[b]	102.7	4.93[b]	103.1	5.82[b]	99.4	5.94[b]	100.2
2″	1.90 [b]	27.5	2.03[b]	27.4	1.24	27.1	1.42	27.2	1.64	27.5	—	134.3	—	134.6
					1.16		1.27		1.41					
3″	1.19	22.4	1.22	22.3	1.00	22.4	1.07	22.4	1.15	22.5	6.52	129.2	6.64	129.0
					0.90		0.98		1.06					
4″	0.77	13.3	0.78	13.3	0.52	13.5	0.55	13.4	0.60	13.5	6.98	127.2	7.01	127.6
5″	—	—	—	—	—	—	—	—	—	—	6.98	125.9	7.01	126.1
1′(R^3)	9.34[b]	—	10.77[b]	—	10.71 [b]	—	3.90 [b]	42.2	3.93[b]	42.3	3.64[b]	39.3	3.67[b]	39.3
							3.78 [b]		3.81[b]		3.56[b]		3.59[b]	
2′(R^3)	—	—	—	—	—	—	1.59	27.9	1.49	27.9	1.67[b]	28.1	1.69[b]	28.1
3′(R^3)	—	—	—	—	—	—	1.40	19.4	1.40	19.4	1.45	19.3	1.47	19.5
4′(R^3)	—	—	—	—	—	—	0.98	14.0	0.99	13.9	1.01	13.9	1.02	13.9

[a] Measured as a 2.6:1 mixture of (*Z*)- and (*E*)-isomers.
[b] Through-space interaction observed in NOESY allowing geometrical isomer determination and, for (*Z*)-**7a**, also the assignment of NH protons.

Table 4
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **12**, **15** and **16** in DMSO-d_6

Position	**12e**		**15g**		**15h**		**16g**		**16h**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1 (NH)	—	—	12.01	—	12.17	—	13.78	—	13.39	—
2	—	194.3	—	153.7	—	153.8	—	166.8	—	167.0
3a	—	83.6	—	113.1	—	113.1	—	110.1	—	110.1
4	—	165.1	—	152.8	—	152.9	—	152.4	—	152.5
5a	—	141.3	—	136.5	—	137.6	—	137.0	—	138.4
6	7.43	116.9	7.59	115.6	6.60	116.4	7.62	115.9	6.59	117.5
7	7.69	135.5	7.56	128.5	7.34	128.3	7.62	122.6	7.43	122.8
8	7.31	124.2	7.34	122.2	7.32	122.5	7.38	122.3	7.34	122.2
9	7.96	126.2	7.89	121.5	7.98	121.5	8.12	129.5	8.20	129.0
9a	—	116.9	—	110.9	—	110.8	—	117.4	—	117.5
9b	—	182.8	—	128.1	—	129.0	—	131.8	—	132.5
1′(R^1)	3.48	30.3	3.69	28.8	—	137.8	3.70	29.1	—	137.4
2′(R^1)	—	—	—	—	7.38	129.6	—	—	7.39	129.5
3′(R^1)	—	—	—	—	7.67	130.0	—	—	7.67	130.1
4′(R^1)	—	—	—	—	7.60	128.9	—	—	7.62	129.3
1′(R^2)	—	131.9	—	—	—	—	—	—	—	—
2′(R^2)	7.06	126.1	—	—	—	—	—	—	—	—
3′(R^2)	7.51	130.1	—	—	—	—	—	—	—	—
4′(R^2)	7.51	130.4	—	—	—	—	—	—	—	—
1′(R^3)	3.83 3.53	45.9	4.05	40.9	4.03	41.0	4.48	44.4	4.45	44.5
2′(R^3)	1.76 1.29	28.1	1.68	31.9	1.68	31.9	1.75	30.9	1.70	30.8
3′(R^3)	1.20	19.8	1.32	19.4	1.32	19.4	1.28	19.4	1.35	19.4
4′(R^3)	0.82	13.6	0.93	13.7	0.92	13.7	0.98	13.8	0.92	13.7



Scheme 3.

Scheme 3. Both identically substituted compounds **A**, **B** and also **8** (prepared by dehydration of **B**) were rearranged in boiling acetic acid under formation of the same reaction product. Compounds of type **8** derived from primary amines **5** (R^3=H) could not be obtained by dehydrating compounds **B** (R^3=H). Hence, it was considered that the rearrangement occurs with these compounds already in the stage of aminocarbinol **B**.

Therefore, we suppose that compounds **5** react with isocyanic or isothiocyanic acid to give intermediate **A** that cyclizes to form intermediate **B** and subsequently dehydrates to give intermediate **C**. This intermediate is one of the final products in cases where R^2=Ph (compounds **8** and **12**). The crucial step in the mechanism is the acid-catalyzed migration of the amide group in **B** or **C** to the C(9b), to form intermediate **D** (path **a**). If a hydrogen atom is present on the first carbon atom of the substituent R^2 (R^2=Bu or CH_2Ph), it is eliminated to form compounds **7**, **11** and **13**. If R^2 is a phenyl group, the addition of water to intermediate **D** leads to the formation of intermediate **E**, in which the imidazolidine ring opens to afford compounds **6** and **10**, and their hydrolytic products **9** and **13**. It is interesting to note that compounds **6** and **10** arise via intermediate **E** even in cases where R^3=H. We never observed the elimination of the hydrogen from the N(3) atom of intermediate **D** to give a C=N bond.

The alternative path **b**, which is dominant in the reactions of **5g**,**h** with isothiocyanic acid (method A), leads to debenzylated compounds **15g**,**h** and **16g**,**h**. It is still unclear why compounds **5g**,**h** are debenzylated also by the weak isocyanic acid, considering such reactions were not observed when using analogous 1-unsubstituted compounds **1**.[1]

3. Conclusions

In conclusion, we would like to emphasize that the described reaction of 3-aminoquinolinediones **5** with isocyanic or isothiocyanic acid allows the preparation of 3-ureido- or thioureidooxindoles and different types of spiro-oxindole derivatives in good yields. While many biologically active compounds contain sulfur atoms,[9,10] compounds **10**–**13** could also be interesting structures for further studies.

The C-debenzylation of starting compounds **5** bearing a benzyl group at position 3 not only has theoretical significance but also enables the targeted preparation of compounds **15** and **16** by a simple procedure. To our surprise, only one compound **15**, described as the –OH tautomer (5-butyl-2-hydroxy-1-methyl-1,5-dihydro-imidazo[4,5-*c*]quinolin-4-one), and only one compound

16, described as the –SH tautomer (5-butyl-2-mercapto-1-methyl-1,5-dihydro-imidazo[4,5-*c*]quinolin-4-one), were found in the literature.[11] Both of these compounds, which induce contraction in tracheal strips of passively sensitized guinea pigs, were prepared by five different multi-step reactions starting from 3-nitro-quinolin-2-ones bearing the hydroxy, chloro, or methylamino substituents in position 4 and also from *N*-butylisatoic anhydride.

4. Experimental

4.1. General

Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C and 50.68 MHz for ^{15}N) in DMSO-d_6. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. All 2D experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton spectra were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC. Quaternary carbons were assigned by gs-HMBC. The positive-ion EI mass spectra were measured on a Shimadzu QP-2010 instrument within the mass range m/z=50–600 using direct inlet probe (DI). Samples were dissolved in dichloromethane (30 μg/mL) and 10 μL of the solution was evaporated in DI cuvette at 50 °C. The ion source temperature was 200 °C; the energy of electrons was 70 eV. Only signals exceeding relative abundance of 9% are listed. Column chromatography was carried out on Silica gel (Merck, grade 60, 70–230 mesh) using chloroform and then successive mixtures of chloroform/ethanol (in rations from 99:1 to 8:2) or benzene and then successive mixtures of benzene/ethyl acetate (in rations from 99:1 to 8:2). Reactions as well as the course of separation and also the purity of substances were monitored by TLC in elution systems benzene/ethyl acetate (4:1), chloroform/ethanol (9:1 and/or 19:1) and chloroform/ethyl acetate (7:3) on Alugram® SIL G/UV$_{254}$ foils (Macherey–Nagel). Elemental analyses (C, H and N) were performed with a EA 1108 Elemental Analyzer (Fisons Instrument).

4.2. Preparation of 3-aminoquinoline-2,4(1*H*,3*H*)-diones (5)

Starting 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5a**–**h** were prepared from corresponding 3-chloro derivatives according to the general procedure described in literature.[5] Two new derivatives (**5g**,**h**) were prepared.

*4.2.1. 3-Benzyl-3-butylamino-1-methyl-1H,3H-quinoline-2,4-dione (**5g**).* Compound was prepared from 3-benzyl-3-chloro-1-methyl-1*H*,3*H*-quinoline-2,4-dione and butyl-amine in 53% yield. Colourless crystals, mp 70–71 °C (cyclohexane); IR: 3312, 3032, 2961, 2928, 2861, 2824, 1691, 1652, 1599, 1492, 1472, 1435, 1412, 1362, 1302, 1282, 1245, 1207, 1179, 1149, 1121, 1079, 1051, 1033, 939, 917, 845, 769, 750, 735, 701, 661, 633, 587, 526 cm^{-1}. EIMS (*m*/*z*, %): 336 (M^{+}, 2), 246 (16), 245 (100), 203 (7), 191 (12), 190 (15), 189 (7), 161 (15), 146 (7), 118 (6), 104 (5), 91 (26), 77 (8), 65 (6). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{21}H_{24}N_2O_2$: C 74.97 (75.09); H 7.19 (7.23); N 8.33 (8.14).

*4.2.2. 3-Benzyl-3-butylamino-1-phenyl-1H,3H-quinoline-2,4-dione (**5h**).* Compound was prepared from 3-benzyl-3-chloro-1-phenyl-1*H*,3*H*-quinoline-2,4-dione and butyl-amine in 61% yield. Colourless crystals, mp 137–139 °C (benzene/hexane); IR: 3310, 3061, 3032, 2948, 2926, 2869, 2823, 1696, 1660, 1598, 1494, 1466, 1454, 1438, 1347, 1303, 1268, 1241, 1205, 1183, 1162, 1112, 1089, 1073, 1026, 942, 917, 843, 780, 767, 735, 701, 664, 651, 557, 542, 525 cm^{-1}. EIMS (*m*/*z*, %): 398 (M^{+}, 2), 307 (100), 252 (13), 223 (13), 196 (8), 195 (7), 167 (8), 91 (25), 77 (9), 65 (5). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{26}H_{26}N_2O_2$: C 78.36 (78.55); H 6.58 (6.65); N 7.03 (7.12).

4.3. General procedure for the preparation of compounds 6–15

A mixture of the appropriate 3-aminoquinolinedione (**5a**–**h**) (2.5 mmol) and the appropriate reagent (see below) in acetic acid (3 mL) was heated to reflux for the time given in Table 1. The course of the reaction was monitored by TLC. After cooling, the reaction mixture was poured onto ice (50 g). The precipitated product was filtered off with suction, washed with water, dried and crystallized from an appropriate solvent or column chromatographed.

Reagents: method A: potassium thiocyanate (583 mg, 6 mmol); method B: potassium cyanate (487 mg, 6 mmol); method C: urea, see Ref. 3.

*4.3.1. (Z)-4-Butylidene-1′-methyl-1′H-spiro[imidazolidine-5,3′-indole]-2,2′-indole (**7a**).* Compound was prepared besides **6a** from **5a** in 11% yield (method B). Colourless crystals, mp 236–238 °C (ethyl acetate/hexane); IR: 3254, 3104, 2950, 2929, 2869, 1724, 1713, 1694, 1617, 1496, 1472, 1450, 1391, 1370, 1355, 1314, 1239, 1192, 1161, 1130, 1106, 1060, 1022, 973, 896, 848, 801, 757, 728, 697, 679, 539 cm^{-1}. EIMS (*m*/*z*, %): 271 (M^{+}, 86), 242 (82), 228 (39), 214 (14), 200 (100), 188 (82), 171 (16), 160 (45), 146 (31), 132 (50), 117 (14), 104 (24), 84 (17), 77 (23), 54 (22), 41 (12). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{15}H_{17}N_3O_2$: C 66.40 (66.24); H 6.32 (6.32); N 15.49 (15.54).

*4.3.2. 3-(3′-Benzoylthioureido)-1-methyl-2-oxo-2,3-di-hydro-1H-indole (**10b**).* Compound was prepared from **5b** in 74% yield (method A). Yellowish crystals, mp 219–220 °C (benzene); IR: 3245, 3060, 3033, 2934, 2900, 1709, 1684, 1613, 1532, 1494, 1469, 1449, 1423, 1375, 1353, 1311, 1259, 1197, 1169, 1125, 1087, 1074, 1054, 1019, 981, 940, 932, 913, 879, 821, 786, 753, 697, 664, 643, 594, 539 cm^{-1}. EIMS (*m*/*z*, %): 325 (17), 204 (18), 188 (6), 161 (15), 146 (13), 118 (16), 105 (100), 91 (10), 77 (54), 51 (16). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{17}H_{15}N_3O_2S$: C 62.75 (62.66); H 4.65 (4.63); N 12.91 (12.93); S 9.85 (9.79).

*4.3.3. 3-(3′-Benzoyl-3′-butyl-thioureido)-1-phenyl-2-oxo-2,3-dihydro-1H-indole (**10f**).* Compound was prepared from **5f** besides **13f** and *N*-phenylisatin in 13% yield (method A). Colourless crystals, mp 173–176 °C (benzene/hexane); IR: 3187, 3061, 3050, 2957, 2930, 2870, 1749, 1629, 1592, 1576, 1506, 1492, 1447, 1436, 1405, 1353, 1313, 1288, 1232, 1223, 1181, 1161, 1123, 1079, 1027, 966, 949, 924, 855, 822, 792, 759, 729, 697, 659, 625, 550, 518 cm^{-1}. EIMS (*m*/*z*, %): 443 (M^{+}, 14), 279 (22), 180 (8), 105 (100), 77 (38). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{26}H_{25}N_3O_2S$: C 70.40 (70.36); H 5.68 (5.69); N 9.47 (9.61); S 7.23 (7.14).

*4.3.4. (E/Z)-4-Butylidene-1′-methyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11a**).* Compound was prepared from **5a** in 30% yield (method A). Colourless crystals, mp 182–187 °C (ethyl acetate/hexane); IR: 3241, 3156, 2957, 2928, 2867, 1731, 1709, 1612, 1518, 1470, 1416, 1366, 1349, 1302, 1205, 1158, 1125, 1102, 1006, 952, 753, 695, 593, 539 cm^{-1}. EIMS (*m*/*z*, %): 288 (19), 287 (M^{+}, 100), 258 (39), 244 (22), 216 (55), 200 (53), 184 (13), 172 (11), 146 (12), 143 (10), 118 (12), 117 (14), 116 (11), 115 (10), 102 (10), 77 (12), 41 (11). For NMR spectra of both stereoisomers see Table 3. Anal. Calcd (found) for $C_{15}H_{17}N_3OS$: C 62.69 (62.62); H 5.96 (6.04); N 14.62 (14.51); S 11.16 (10.85).

*4.3.5. (E)-3-Butyl-4-butylidene-1′-methyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11c**).* Compound was prepared from **5c** in 68% yield (method A). Colourless crystals, mp 152–154 °C

(benzene/hexane); IR: 3405, 3314, 3058, 2955, 2930, 2868, 1735, 1723, 1677, 1609, 1492, 1468, 1438, 1418, 1368, 1343, 1303, 1291, 1251, 1194, 1156, 1129, 1109, 1279, 1021, 985, 942, 878, 853, 760, 693, 668, 565, 539 cm^{-1}. EIMS (*m*/*z*, %): 343 (M^+, 100), 314 (52), 310 (36), 298 (14), 286 (51), 282 (35), 272 (23), 258 (55), 256 (20), 244 (11), 226 (14), 216 (28), 213 (24), 204 (20), 200 (29), 184 (25), 143 (14), 140 (11), 130 (11), 115 (15), 77 (10), 55 (17), 41 (40). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{19}H_{25}N_3OS$: C 66.44 (66.40); H 7.34 (7.35); N 12.23 (12.22); S 9.34 (9.13).

*4.3.6. (E)-3-Butyl-4-butylidene-1′-phenyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11d**).* Compound was prepared from **5d** in 79% yield (method A). Colourless crystals, mp 147–150 °C (benzene/hexane); IR: 3406, 3056, 3013, 2957, 2930, 2869, 1720, 1669, 1615, 1596, 1500, 1464, 1417, 1355, 1327, 1297, 1287, 1260, 1227, 1213, 1199, 1175, 1150, 1114, 1092, 1049, 1028, 1003, 978, 938, 820, 774, 751, 702, 666, 618, 559, 510 cm^{-1}. EIMS (*m*/*z*, %): 406 (29), 405 (M^+, 100), 378 (26), 377 (98), 376 (48), 373 (33), 372 (56), 360 (12), 350 (11), 349 (30), 348 (57), 345 (17), 344 (67), 335 (24), 334 (42), 321 (10), 320 (23), 318 (18), 316 (11), 289 (15), 288 (13), 279 (14), 278 (73), 276 (12), 275 (35), 274 (15), 266 (17), 262 (17), 261 (15), 247 (14), 246 (30), 219 (10), 218 (10), 217 (13), 205 (11), 204 (15), 180 (15), 140 (14), 128 (10), 115 (12), 77 (34), 55 (18), 54 (17), 51 (12), 41 (44). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{24}H_{27}N_3OS$: C 71.08 (71.00); H 6.71 (6.73); N 10.36 (10.43); S 7.91 (7.78).

*4.3.7. 3-Butyl-5-methyl-3a-phenyl-2-thioxo-3,3a-dihydro-5H-imidazo[4,5-c]quinoline-2-one (**12e**).* Compound was prepared from **5e** in 7% yield (method A). Yellow crystals, mp 175–180 °C (benzene/hexane); IR: 2957, 2936, 2894, 2873, 2855, 1689, 1609, 1589, 1469, 1448, 1399, 1356, 1324, 1283, 1270, 1253, 1219, 1165, 1126, 1064, 1043, 1013, 993, 969, 860, 776, 751, 726, 697, 659, 619, 612, 571, 529 cm^{-1}. EIMS (*m*/*z*, %): 363 (M^+, 29), 331 (25), 330 (100), 320 (10), 307 (31), 293 (12), 292 (24), 248 (10), 204 (19), 118 (12), 104 (48), 103 (10), 77 (16), 41 (13). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{21}H_{21}N_3OS$: C 69.39 (69.49); H 5.82 (5.85); N 11.56 (11.49); S 8.82 (8.65).

*4.3.8. 1-Butyl-3-(2-oxo-1-phenylindolin-3-yl)thiourea (**13f**).* Compound was prepared besides **10f** and *N*-phenylisatin from **5f** in 8% yield (method A). Colourless crystals, mp 111–114 °C (cyclohexane), get blue on air and light; IR: 3330, 3166, 3048, 2959, 2932, 2871, 1745, 1598, 1580, 1510, 1499, 1455, 1438, 1413, 1352, 1283, 1260, 1229, 1190, 1174, 1129, 1110, 1081, 1033, 923, 878, 826, 797, 748, 693, 649, 637, 618, 577, 540 cm^{-1}. EIMS (*m*/*z*, %): 340 (23), 339 (M^+, 100), 337 (12), 266 (31), 250 (10), 237 (13), 224 (29), 223 (12), 209 (13), 208 (33), 195 (29), 181 (16), 180 (92), 179 (19), 77 (18), 74 (16), 72 (16), 66 (7), 51 (7), 41 (11). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{19}H_{21}N_3OS$: C 67.23 (67.37); H 6.24 (6.33); N 12.38 (12.43); S 9.45 (9.39).

*4.3.9. (E)-4-Benzylidene-3-butyl-1′-methyl-1′H-spiro-[imidazolidine-5,3′-indole]-2,2′-indole (**14g**).* Compound was prepared from **5g** besides **15g** in respective yields 13% (method B) or 14% (method C). Colourless crystals, mp 198–200 °C (benzene/hexane); IR: 3216, 3085, 3012, 2960, 2932, 2873, 1734, 1719, 1666, 1613, 1494, 1470, 1456, 1426, 1371, 1342, 1305, 1261, 1229, 1175, 1155, 1127, 1088, 1066, 1011, 945, 923, 898, 863, 824, 786, 751, 700, 674, 666, 620, 539 cm^{-1}. EIMS (*m*/*z*, %): 362 (25), 361 (M^+, 100), 319 (15), 276 (10), 270 (15), 256 (39), 247 (14), 228 (51), 215 (13), 200 (41), 189 (13), 188 (99), 160 (34), 132 (42), 131 (25), 118 (14), 117 (50), 116 (16), 104 (14), 91 (62), 90 (17), 89 (14), 77 (15), 41 (30). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{22}H_{23}N_3O_2$: C 73.11 (72.92); H 6.41 (6.41); N 11.63 (11.58).

*4.3.10. (E)-3-Butyl-4-benzylidene-1′-phenyl-1′H-spiro-[imidazolidine-5,3′-indole]-2,2′-dione (**14h**).* Compound was prepared besides **15h** from **5h** in respective yields 16% (method B) and 12% (method C). Colourless crystals, mp 161–165 °C (benzene/hexane); IR: 3199, 3080, 2951, 2931, 2870, 1740, 1717, 1663, 1615, 1596, 1501, 1480, 1465, 1445, 1432, 1370, 1327, 1295, 1281, 1251, 1233, 1210, 1177, 1134, 1114, 1089, 1039, 1026, 986, 940, 924, 897, 816, 786, 750, 702, 676, 628, 583, 551 cm^{-1}. EIMS (*m*/*z*, %): 424 (30), 423 (M^+, 100), 395 (10), 381 (12), 319 (19), 318 (80), 290 (30), 277 (13), 263 (11), 262 (56), 251 (13), 250 (75), 194 (26), 117 (34), 91 (31), 90 (10), 77 (23), 66 (10), 41 (16). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{27}H_{25}N_3O_2$: C 76.57 (76.59); H 5.95 (5.95); N 9.92 (9.78).

*4.3.11. 3-Butyl-5-methyl-1H-imidazo[4,5-c]quinoline-2,4(3H,5H)-dione (**15g**).* Compound was prepared from **5g** besides (*E*)-**14g** in respective yields 43% (method B) and 38% (method C). Colourless crystals, mp 289–290 °C (chloroform/ethyl acetate); IR: 2954, 2870, 2824, 2748, 1685, 1657, 1638, 1593, 1571, 1528, 1466, 1376, 1354, 1323, 1294, 1245, 1227, 1168, 1117, 1086, 1044, 968, 940, 903, 881, 857, 826, 746, 726, 710, 665, 650, 551, 539 cm^{-1}. EIMS (*m*/*z*, %): 272 (10), 271 (M^+, 55), 254 (11), 229 (12), 228 (26), 216 (16), 215 (100), 200 (15). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{15}H_{17}N_3O_2$: C 66.40 (66.50); H 6.32 (6.30); N 15.49 (15.70).

*4.3.12. 3-Butyl-5-phenyl-1H-imidazo[4,5-c]quinoline-2,4(3H,5H)-dione (**15h**).* Compound was prepared from **5h** besides (*E*)-**14h** in 42% yield (method B, method C). Colourless crystals, mp 329–333 °C (acetic acid); IR: 3102, 3036, 2955, 2874, 2809, 2727, 1706, 1663, 1636, 1594, 1567, 1520, 1491, 1468, 1453, 1416, 1373, 1324, 1280, 1246, 1226, 1171, 1153, 1118, 1096, 1070, 1050, 1012, 934, 892, 824, 794, 750, 729, 702, 654, 601, 503 cm^{-1}. EIMS (*m*/*z*, %): 334 (15), 333 (M^+, 63), 316 (16), 304 (11), 291 (18), 290 (20), 278 (21), 277 (100), 276 (53), 262 (15), 77 (24). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{20}H_{19}N_3O_2$: C 72.05 (71.91); H 5.74 (5.75); N 12.60 (12.43).

*4.3.13. 3-Butyl-2,3-dihydro-5-methyl-2-thioxo-1H-imid-azo[4,5-c]quinolin-4(5H)-one (**16g**).* Compound was prepared from **5g** in 33% yield (method A). Colourless crystals, mp 299–303 °C (benzene); IR: 3029, 2954, 2927, 1670, 1638, 1588, 1571, 1525, 1481, 1458, 1433, 1392, 1324, 1295, 1245, 1215, 1164, 1115, 1084, 1043, 970, 844, 775, 745, 732, 679, 624, 593, 583, 521 cm^{-1}. EIMS (*m*/*z*, %): 287 (M^+, 60), 255 (16), 254 (84), 244 (11), 243 (10), 232 (29), 231 (100), 203 (11), 202 (36), 117 (12), 116 (13). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{15}H_{17}N_3OS$: C 62.69 (62.51); H 5.96 (5.99); N 14.62 (14.51); S 11.16 (10.85).

*4.3.14. 3-Butyl-2,3-dihydro-5-phenyl-2-thioxo-1H-imid-azo[4,5-c]quinolin-4(5H)-one (**16h**).* Compound was prepared from **5h** in 27% yield (method A). Colourless crystals, mp 349–350 °C (acetic acid); IR: 3154, 3120, 3069, 3055, 2958, 2932, 2871, 2733, 1672, 1634, 1591, 1565, 1518, 1478, 1459, 1393, 1362, 1338, 1323, 1294, 1278, 1258, 1235, 1214, 1160, 1119, 1096, 1071, 1046, 1029, 1004, 943, 852, 836, 755, 733, 699, 681, 662, 605, 561, 513 cm^{-1}. EIMS (*m*/*z*, %): 350(17), 349 (M^+, 71), 317 (34), 316 (100), 307 (11), 306 (10), 294 (37), 293 (97), 292 (68), 277 (11), 275 (10), 274 (10), 261 (12), 260 (20), 205 (14), 77 (32), 51 (14), 41 (14). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{20}H_{19}N_3OS$: C 68.74 (68.92); H 5.48 (5.45); N 12.02 (12.21); S 9.18 (9.12).

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Supplementary data

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