Kinetic and Thermodynamic Control of the Reaction of 5-Amino-11H-isoindolo[2,1-*a*]quinazoline with *N*-phenylmaleimide

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The reaction of 5-amino-11H-isoindolo[2,1-*a*]quinazolIne with maleimides is not a typical Michael reaction but proceeds through a more complex rearrangement. Depending on the type of control, the reaction with *N*-phenylmaleimide can follow two different pathways. Probable reaction mechanisms have been proposed for both kinetic and thermodynamic control. The structures of the reaction products were confirmed, in particular, by COSY and HMBC methods.

Introduction

Isoindole derivatives have long attracted the attention of scientists due to their unique properties, both in terms of fundamental research and practical applications [1, 2]. In particular, they show promise in medicinal chemistry [3] and solar energy [4]. One of the most characteristic reactions of isoindoles is the Diels–Alder reaction [1]. In the course of studying [4+2]-cycloaddition, our research group discovered five new rearrangements for isoindoles [5, 6] and for condensed isoindoles [7, 8, 9]. These findings provide synthetic diversity in using this reaction to obtain:

1. Norbornene-type Diels–Alder adducts, which can serve as rigid linkers [10];
2. Michael adducts, interesting not only as potential anti-tuberculosis agents [11] but also for passivating surface defects in perovskite-based devices [12];
3. Conjugated aromatic rearranged adducts, which are of interest from the standpoint of combining stereochemical effects.

This work is a continuation of studies on the reaction of isoindolo[2,1-*a*]quinazolones with maleimides.

Experimental part

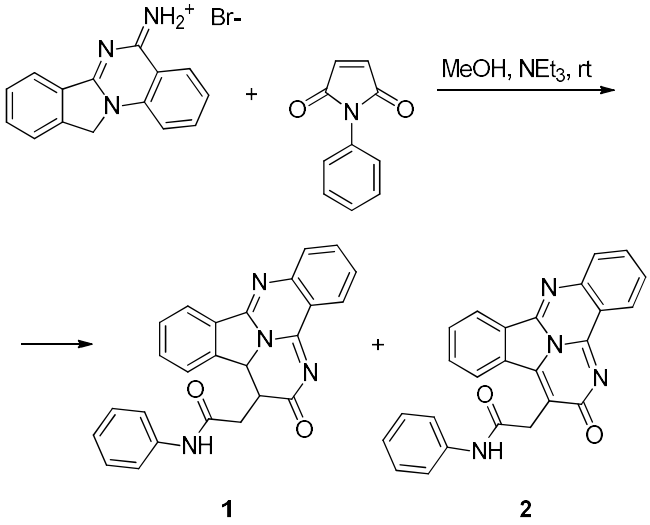
Methods

^{1}H and ^{13}C NMR spectra were recorded on the Mercury 400 Varian (at 400 and 101 MHz). IR spectra were recorded on the PerkinElmer Spectrum BX. The purity of the obtained compounds was confirmed by using an Agilent 1100 Series mass-chromatograph equipped with an Agilent LC/MSD SL selective detector. The samples were introduced in a trifluoroacetic acid matrix, and electron ionization (EI) was used. The numerical m/z

values are provided, as well as the [M+1] peak, which corresponds to the molecular ion.

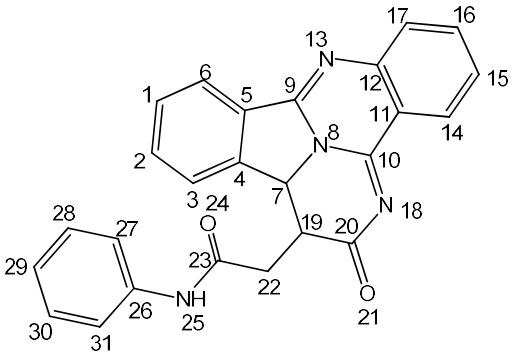
Synthesis

Kinetic Control Conditions



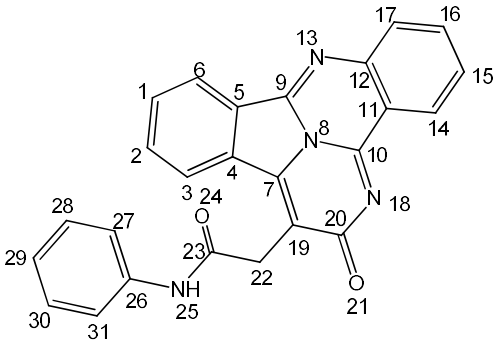
A suspension of 2 mmol of 5-amino-11H-isoindolo[2,1-*a*]quinazoline hydrobromide and 4.2 mmol of *N*-phenylmaleimide in 5 mL of absolute methanol is prepared. Then 1 mL of triethylamine is added, and the flask is tightly sealed. After one week, the resulting precipitate is filtered off and washed with methanol. The solid is then boiled in a 50:50 acetone/methanol mixture and filtered. The filtrate is evaporated, yielding compound **1**. The residue remaining after filtration is compound **2**.

Compound **1**. Yield: 27%; mp > 300°C. IR (KBr) (ν_{max}, $см^{-1}$): 3284, 3244, 3184, 3128, 3076, 3052, 2904, 1652, 1620,1592, 1544, 1504, 1448, 1432, 1300, 1210, 1148, 1128, 772. MS (EI): found 406. $C_{25}H_{18}N_4O_2$ calculated 406.



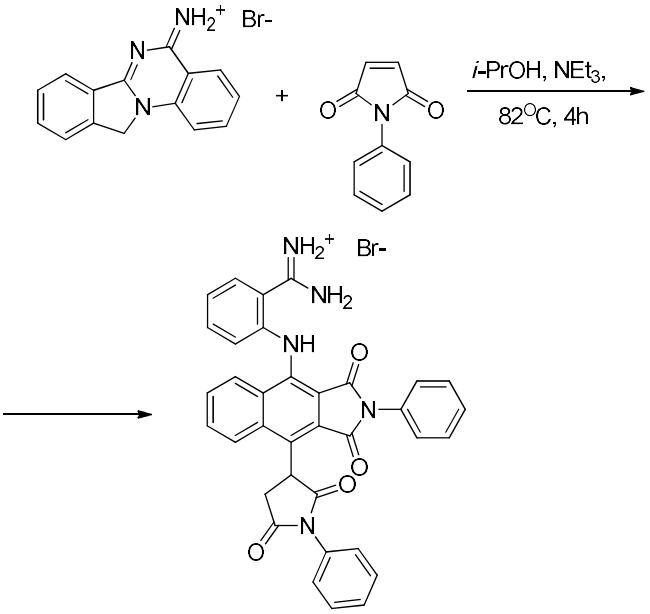
№	H	C	COSY	HMBC
1	7.73	130.1	2, 6	3, 5
2	7.76	133.3	1, 3	4, 6
3	7.91	125.0	2	1, 5, 7
4	-	143.1	-	-
5	-	132.4	-	-
6	8.21	124.0	1	2, 4, 9
7	5.99	61.6	19	4, 19, 20
9	-	152.3	-	-
10	-	157.0	-	-
11	-	119.0	-	-
12	-	148.8	-	-
14	8.36	126.8	15	10, 12, 16
15	7.64	127.7	14, 16	11, 17
16	7.95	135.6	15, 17	12, 14
17	7.87	127.9	16	11, 15
19	3.34	38.6	7, 22	7, 20, 23
20	-	178.7	-	-
22	3.16	32.5	19	7, 19, 20, 23
23	-	170.2	-	-
25	10.24	-	-	23, 26, 27, 31
26	-	139.9	-	-
27, 31	7.66	119.5	28, 30	27, 29, 31
28, 30	7.32	129.2	27, 29, 31	26, 28, 30
29	7.05	123.5	28, 30	27, 31

Compound **2**. Yield: 68%; mp > 300°C. IR (KBr) (ν_{max}, $см^{-1}$): 3276, 3244, 3184, 3124, 3076, 3008, 2912, 1656, 1636, 1612, 1544, 1516, 1456, 1432, 1408, 1352, 1340, 1308, 1244, 1152, 1108, 956, 768.MS (EI): found 404. $C_{25}H_{16}N_4O_2$ calculated 404.



№	H	C	COSY	HMBC
1	7.91	132.6	2, 6	3, 5
2	7.99	134.0	1, 3	4, 6
3	8.92	126.4	2	1, 5, 7
4	-	132.4	-	-
5	-	130.3	-	-
6	8.47	124.1	1	2, 4, 9
7	-	139.9	-	-
9	-	146.5	-	-
10	-	148.9	-	-
11	-	118.0	-	-
12	-	146.0	-	-
14	9.02	126.4	15	10, 12, 16
15	7.84	129.3	14, 16	11, 17
16	8.04	135.3	15, 17	12, 14
17	8.15	128.9	16	11, 15
19	-	117.8	-	-
20	-	166.7	-	-
22	4.26	36.6	-	7, 19, 20, 23
23	-	172.8	-	-
25	9.62	-	-	27, 31
26	-	138.1	-	-
27, 31	7.59	119.6	28, 30	27, 29, 31
28, 30	7.29	128.9	27, 29, 31	26, 28, 30
29	7.07	124.1	28, 30	27, 31

Thermodynamic Control Conditions



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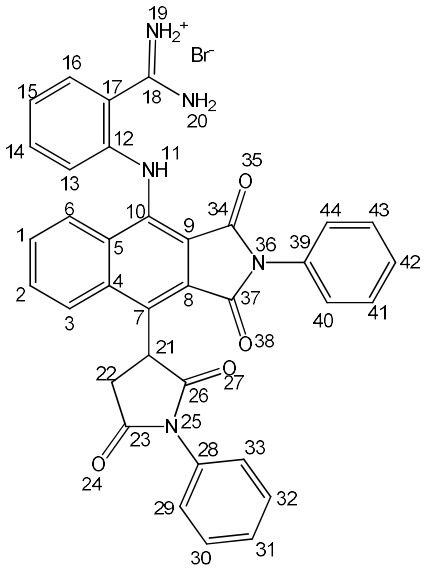
A mixture of 2 mmol of 5-amino-11H-isoindolo[2,1-*a*]quinazoline hydrobromide, 4.2 mmol of *N*-phenylmaleimide, and 1 mL of triethylamine is refluxed in isopropanol for 4 hours. The resulting precipitate is filtered off and washed with isopropanol, yielding compound **3**.

Compound **3**. Yield: 72%; mp > 300°C. IR (KBr) (ν_{max}, $см^{-1}$): 3388, 3272, 3052, 2972, 1744, 1692, 1588, 1484, 1372, 1168, 768. MS (EI): found 580. $C_{35}H_{26}N_5O_4$ calculated 580.



№	H	C	COSY	HMBC
1	7.76	129.2	2, 6	3, 5
2	7.92	131.0	1, 3	4, 6
3	8.70	126.5	2	1, 5, 7
4	-	136.9	-	-
5	-	130.6	-	-
6	8.39	127.3	1	2, 4, 10
7	-	129.9	-	-
8	-	125.2	-	-
9	-	133.4	-	-
10	-	140.3	-	-
11	8.82	-	-	-
12	-	143.4	-	-
13	6.81	121.0	14	15, 17
14	7.38	133.2	13, 15	12, 16
15	7.20	123.0	14, 16	13, 17
16	7.60	130.0	15	14, 15, 18
17	-	121.9	-	-
18	-	166.0	-	-
19	9.30	-	-	-
20	9.30	-	-	-
21	5.71	39.2	22	4, 7, 8, 22, 23
22	3.19; 3.49	37.1	21, 22	7, 21, 23, 26
23	-	177.2	-	-
26	-	175.9	-	-
28	-	133.5	-	-
29, 33	7.34	127.4	30, 32	29, 31, 33
30, 32	7.53	129.0	29, 31, 33	28, 30, 32
31	7.44	127.8	30, 32	29, 33
34	-	167.0	-	-
37	-	167.0	-	-
39	-	132.0	-	-
40, 44	7.34	127.4	41, 43	40, 42, 44
41, 43	7.53	129.0	40, 42, 44	39, 41, 43
42	7.44	128.5	41, 43	40, 44

Results and discussion

As with 1H-isoindol-3-amine derivatives [5, 13], 5-amino-11H-isoindolo[2,1-*a*]quinazoline exists in tautomeric forms, which significantly affects the course of its reactions, in particular making possible the application of the Curtin–Hammett principle [14]. According to the ^{1}H NMR spectrum, the main tautomeric form of 5-amino-11H-isoindolo[2,1-*a*]quinazoline is the isoindole form **4a** (80%) (**Figure 1**).

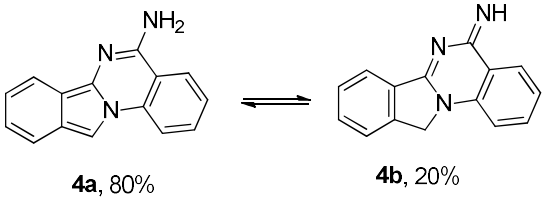
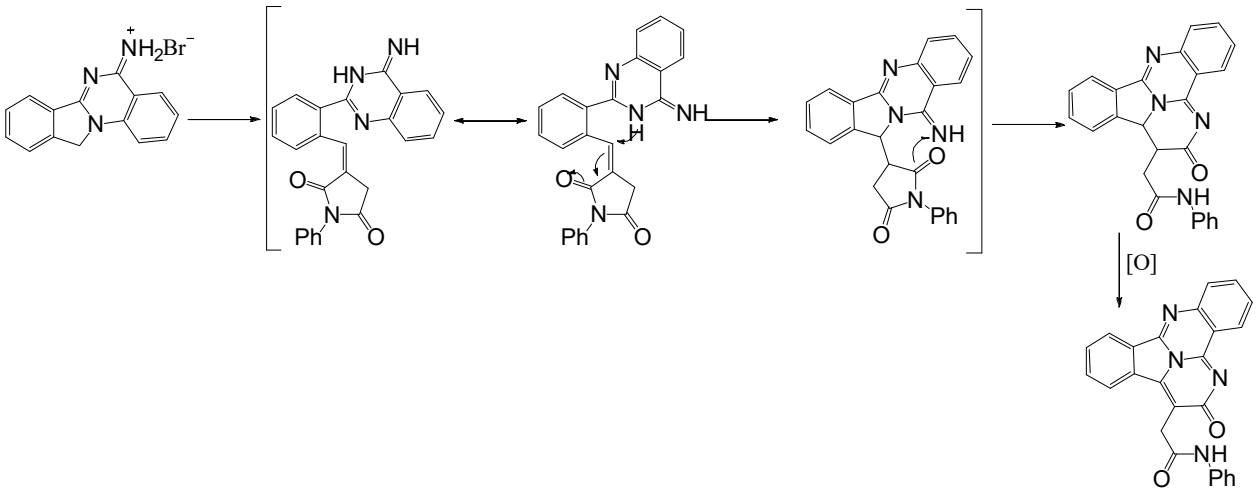


Figure 1. Tautomeric forms of 5-amino-11H-isoindolo[2,1-*a*]quinazoline.

Initially, we attempted to carry out the reaction of 5-amino-11H-isoindolo[2,1-*a*]quinazoline hydrobromide with *N*-phenylmaleimide under conditions similar to those described in [5]: the reaction mixture was kept in methanol at room temperature for a week. 5-Amino-11H-isoindolo[2,1-*a*]quinazoline was generated *in situ* by the addition of triethylamine. Under these conditions, we obtained two compounds, **1** and **2**, with **2** being the major product. Compound **1** was separated by boiling in a methanol-acetone mixture, after which the filtrate was evaporated, leaving behind the insoluble compound **2**. It was also observed that upon standing in air for a prolonged period, **1** gradually oxidizes and is converted into **2**.

Based on the analysis of these results and the literature data [15], we propose a probable mechanism for this reaction (**Scheme 1**).

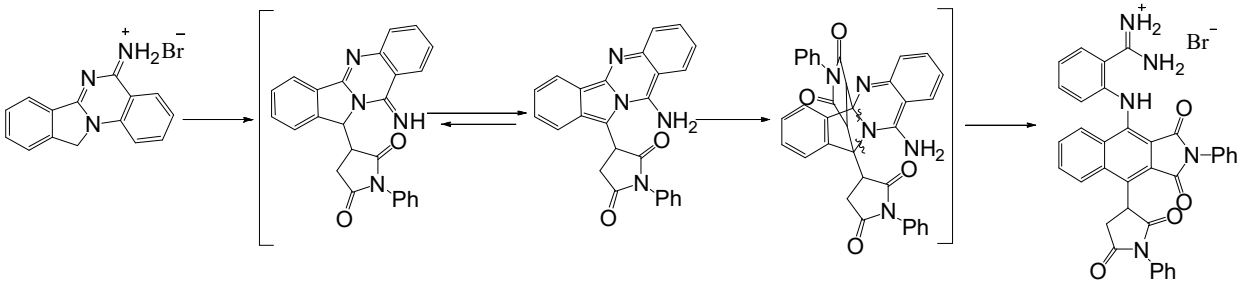


Scheme 1. Probable mechanism of the reaction of 5-amino-11H-isoindolo[2,1-*a*]quinazoline with *N*-phenylmaleimide under kinetic control.

The reaction proceeds via opening of the isoindole fragment and subsequent rearrangement. Next, owing to the presence of an exocyclic imine group located in direct proximity to the succinimide fragment, rearrangement occurs, leading to the formation of a dihydropyrimidone ring, which then undergoes oxidative aromatization to give a pyrimidone ring.

We also attempted a similar reaction under thermodynamic control by refluxing in isopropanol. Under these conditions, we obtained a different product — naphthalene derivative **3**, similar to the one formed in the reaction of 2,4-dimethylpyrimido[2,1-*a*]isoindole with maleimides [8].

For this transformation, we also propose a plausible mechanism (**Scheme 2**). Initially, the reaction proceeds via opening of the isoindole fragment and rearrangement as in the previous case (**Scheme 1**). However, instead of opening the succinimide fragment, another equivalent of maleimide undergoes a Diels–Alder reaction, followed by cleavage of the azanorbornene fragment.



Scheme 2. Probable mechanism of the reaction of 5-amino-11H-isoindolo[2,1-*a*]quinazoline under thermodynamic control.

Conclusions

Thus, depending on the type of control, the reaction with *N*-phenylmaleimide can proceed via two pathways. In the case of kinetic control, the reaction takes place with only one molecule of maleimide and apparently does not stop at the stage of forming an intermediate product. Due to the presence of an exocyclic imine group located next to the succinimide fragment, a rearrangement occurs, leading to the formation of a dihydropyrimidone ring, which then undergoes oxidative aromatization to a pyrimidone ring.

Under thermodynamic control, the reaction resembles the reaction of 2,4-dimethylpyrimido[2,1-*a*]isoindole. The initial steps of the reaction are the same as under kinetic control, but the key difference is an additional reaction with another maleimide molecule via a Diels–Alder reaction, followed by rearrangement.

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