

## SYNTHESIS OF SUBSTITUTED 4-ANILINOQUINAZOLINES

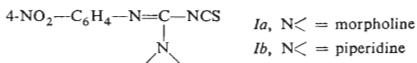
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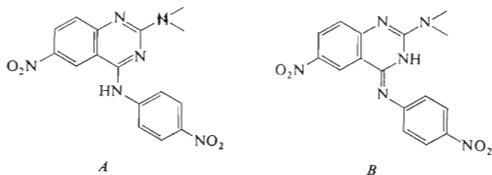
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Synthesis of substituted 4-anilinoquinazolines by means of a reaction of amidinoyl isothiocyanates with aromatic isothiocyanates is described. The probable mechanism of the reaction is discussed and characteristic spectral data of the prepared substances are presented.

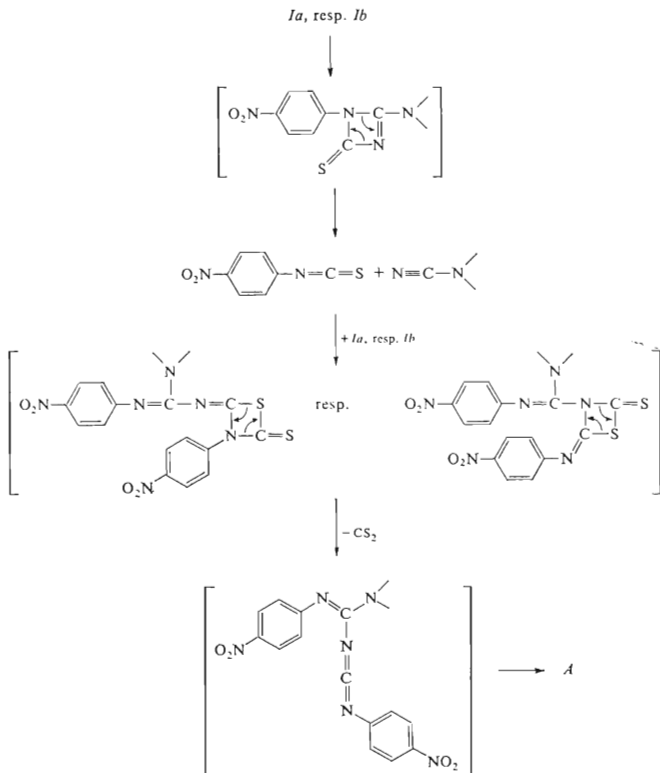
Amidinoyl isothiocyanates<sup>1</sup> and imidoyl isothiocyanates<sup>2-5</sup> are known to isomerize and dimerize spontaneously or on mild heating to give rise to the corresponding quinazoline-4-(3*H*)-thiones or *s*-triazine derivatives. Since electron-withdrawing substituents hinder these conversions such substituted dimeric amidinoyl isothiocyanates have not been described in the literature. With the aim to prepare dimers of nitro derivatives *Ia* and *Ib* we have heated these substances in boiling acetonitrile.



In each case, instead of the expected dimer, two substances were formed one of which was identified as the corresponding 6-nitroquinazoline-4-(3*H*)-thione. The second substance, insoluble in common solvents, was studied by IR and mass spectrometry and its elemental analysis was determined. In this way the molecular weight of the substance was determined and the absence of sulphur in the molecule was confirmed. The mass spectra contained a pronounced molecular ion peak and the mode of disintegration of molecular ions showed the presence of a secondary amine

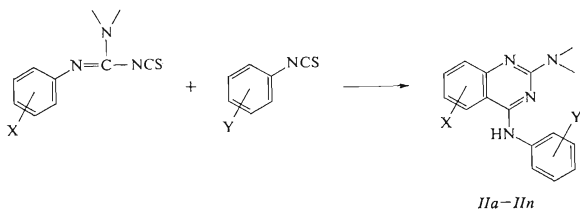


and a 4-nitroanilino residue. Although based on the spectral data the substances can be assumed to possess either of structures *A* or *B*, structure *A* containing stable aromatic skeletons is more probable than the imino group-containing structure *B*. The IR spectral data lead to the same conclusion since the spectra showed an absorption band at  $1630\text{ cm}^{-1}$  assignable to the skeletal  $\text{C}=\text{N}$  vibrations. For an exocyclic  $\text{C}=\text{N}$  group, such as in *B*, the corresponding absorption would be expected to appear at higher wave-number ( $1650\text{--}1670\text{ cm}^{-1}$ ).



The following reaction mechanism (Scheme 1) is proposed for the conversion of amidinoyl isothiocyanates to the discussed substances: The formation of an aromatic isothiocyanate from an imidoyl isothiocyanate has been described<sup>4</sup>. Although reactions of imidoyl isothiocyanates with aromatic isothiocyanates have not been observed<sup>4</sup> it can be assumed that the more reactive amidinoyl isothiocyanates would be amenable to this type of reactions and, by means of a 2 + 2 cycloaddition, could give rise to an unstable intermediate. On heating carbon disulphide would be liberated to give amidinoyl carbodiimide. Unlike their imidoyl analogues<sup>6</sup> amidinoyl carbodiimides have not been described in the literature. In the second stage of the reaction a cyclisation of the unstable amidinoyl carbodiimide takes place *via* the common electrocyclic mechanism involving 6 $\pi$  electrons and a 1,7-sigmatropic transfer of hydrogen to afford the corresponding anilinoquinazoline. Reactions of this type have been observed with many imidoyl heterocumulenes<sup>6,7</sup>. These reactions, as we have found, take place more easily in more highly-boiling dimethylformamide. When a mixture of aromatic isothiocyanates and amidinoyl isothiocyanates was heated in boiling dimethylformamide 4-anilinoquinazolines (Table I) were obtained.

The possibility of the formation of amidinoylcarbodiimide as an intermediate of the discussed reactions was verified in the following manner: By means of the reaction of [N<sup>1</sup>,N<sup>1</sup>-(3-oxapentamethylene)-N<sup>2</sup>-4-chlorophenyl]amidinoyl isothiocyanate with aniline in benzene the corresponding thiourea derivative was prepared and this was allowed to react with yellow mercuric oxide. Hydrogen disulphide was eliminated but the corresponding carbodiimide could not be isolated since, even at room temperature, fast cyclisation occurred. The product formed was identical with the one obtained by the reaction of the corresponding amidinoyl isothiocyanate with phenyl isothiocyanate in dimethylformamide, namely 6-chloro-2-morpholino-4-anilino-3*H*-quinazoline<sup>8</sup>.



A number of unstable imidoylcarbodiimides react in a similar manner. For instance, when a solution of *N*-phenyl-*N'*-(*N*-phenyl-benzimidoyl)thiourea was shaken with mercuric oxide the corresponding carbodiimide could not be isolated either. Instead, the cyclisation product, namely 4-anilino-2-phenyl-3*H*-quinazoline, was isolated although a series of stable imidoylcarbodiimides was prepared in this this



TABLE I

Properties of the Prepared 4-Anilinoquinazolines

Compound	X Y	N <sup>a</sup>	Molecular formula (m.w.)	Calculated/Found			Yield, % m.p., °C
				% C	% H	% N	
<i>IIa</i>	H	Pi	C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> (349.4)	65.31	5.48	20.04	20
	4-NO <sub>2</sub>			65.72	5.41	20.18	237—239
<i>IIb</i>	H	Mo	C <sub>18</sub> H <sub>17</sub> N <sub>5</sub> O <sub>3</sub> (351.4)	61.53	4.87	19.93	32
	4-NO <sub>2</sub>			61.32	4.53	19.67	309—310
<i>IIc</i>	H	Mo	C <sub>18</sub> H <sub>17</sub> BrN <sub>4</sub> O (385.3)	56.11	4.45	14.54	47
	4-Br			56.10	4.27	14.37	286—288
<i>II d</i>	Cl	Mo	C <sub>18</sub> H <sub>16</sub> BrClN <sub>4</sub> O (419.7)	51.50	3.84	13.35	60
	4-Br			51.38	3.57	13.18	270—272
<i>IIe</i>	Cl	Mo	C <sub>18</sub> H <sub>17</sub> ClN <sub>4</sub> O (340.8)	63.43	5.03	16.44	60
	H			63.21	4.97	16.23	262—264
<i>II f</i>	Cl	Mo	C <sub>18</sub> H <sub>16</sub> ClN <sub>5</sub> O <sub>3</sub> (385.8)	56.03	4.18	18.15	60
	4-NO <sub>2</sub>			55.92	4.03	17.98	301—305
<i>II g</i>	Br	Di	C <sub>16</sub> H <sub>14</sub> BrN <sub>5</sub> O <sub>2</sub> (388.2)	49.50	3.63	18.03	26
	4-NO <sub>2</sub>			49.90	3.86	18.02	237—239
<i>II h</i>	Br	Mo	C <sub>18</sub> H <sub>16</sub> BrN <sub>5</sub> O <sub>3</sub> (430.3)	50.24	3.74	16.27	42
	4-NO <sub>2</sub>			49.87	3.71	16.45	305—307
<i>II i</i>	Br	Di	C <sub>16</sub> H <sub>14</sub> BrN <sub>5</sub> O <sub>2</sub> (388.2)	49.50	3.63	18.03	38
	2-NO <sub>2</sub>			49.84	3.84	18.26	241—242
<i>II j</i>	Br	Mo	C <sub>18</sub> H <sub>16</sub> BrN <sub>5</sub> O <sub>3</sub> (430.3)	50.24	3.74	16.27	45
	2-NO <sub>2</sub>			50.01	3.69	16.30	238—240
<i>II k</i>	Br	Mo	C <sub>18</sub> H <sub>17</sub> BrN <sub>4</sub> O (385.3)	56.11	4.45	14.54	60
	H			56.03	4.32	14.27	273—275
<i>II l</i>	Br	Mo	C <sub>18</sub> H <sub>16</sub> Br <sub>2</sub> N <sub>4</sub> O (464.2)	46.57	3.47	12.07	40
	4-Br			46.32	3.28	11.92	262—265
<i>II m</i>	NO <sub>2</sub>	Mo	C <sub>18</sub> H <sub>16</sub> N <sub>6</sub> O <sub>5</sub> (396.4)	54.54	4.07	21.20	60
	4-NO <sub>2</sub>			54.34	4.00	21.15	332—335
<i>II n</i>	NO <sub>2</sub>	Pi	C <sub>19</sub> H <sub>18</sub> N <sub>6</sub> O <sub>4</sub> (394.4)	57.85	4.57	21.30	65
	4-NO <sub>2</sub>			57.43	4.45	21.20	252—353

<sup>a</sup> Pi piperidine, Mo morpholine, Di dimethylamine.

way<sup>6</sup>. The reaction appears to be suitable for convenient preparation of 4-anilino-3*H*-quinazolines which, otherwise obtainable only with difficulties, are normally prepared by the substitution of chlorine in 4-chloro-3*H*-quinazolines with reactive amines<sup>9</sup> or, in very low yields, by a reaction of chloroformamidines with phenylcyanoamides.

TABLE II

Spectral Properties of the Prepared 4-Anilinoquinazolines

Compound	$\nu_{(\text{C}=\text{N})}$ $\text{cm}^{-1}$	$\nu_{(\text{NH})}$ $\text{cm}^{-1}$	$\lambda_{\text{max}}$ , nm log $\epsilon$	
<i>Ila</i>	1 617	3 410	248 (4.29)	342 (4.11)
	1 632		295 (4.38)	402 (4.03)
<i>Ilb</i>	1 613	3 390	247 (4.28)	340 (3.93)
	1 635		294 (4.19)	396 (3.92)
<i>Ilc</i>	1 611	3 340	248 (4.51)	292 (4.44)
	1 628		285 (4.42)	339 (3.97)
<i>Ild</i>	1 610	3 368	243 (4.61)	377 (3.94)
	1 623		288 (4.52)	
<i>Ile</i>	1 603	3 325	242 (4.59)	375 (3.87)
	1 624		288 (4.47)	
<i>Ilf</i>	1 611	3 410	247 (4.45)	340 (4.15)
	1 629		293 (4.39)	393 (4.14)
<i>Ilg</i>	1 616	3 425	250 (4.45)	292 (4.32)
	1 642		285 (4.32)	402 (3.60)
<i>Ilh</i>	1 612	3 408	249 (4.48)	342 (4.14)
	1 628		295 (4.39)	396 (4.12)
<i>Ili</i>	1 605	3 436	244 (4.52)	294 (4.51)
	1 627		287 (4.54)	354 (3.75)
<i>Ilj</i>	1 603	3 310	246 (4.59)	294 (4.53)
	1 630		287 (4.55)	352 (3.75)
<i>Ilk</i>	1 603	3 317	245 (4.59)	377 (3.85)
	1 620		290 (4.49)	
<i>Ill</i>	1 603	3 375	246 (4.61)	380 (3.90)
	1 621		290 (4.51)	
<i>IIm</i>	1 600	3 397	260 (4.35)	360 (4.26)
	1 632			404 (4.30)
<i>Iln</i>	1 600	3 400	253 (4.47)	360 (4.76)
	1 630			407 (4.29)

The data in Table I show that the discussed reactions are not quantitative. Thin-layer chromatography of the reaction mixtures on silica gel revealed the presence of products of competing reactions, *i.e.* the corresponding quinazoline-4(3*H*)-thiones and aromatic isothiocyanates.

## EXPERIMENTAL

The IR spectra were recorded with a double-beam UR-20 (Zeiss) spectrophotometer using the KBr technique. The instrument was calibrated against a polystyrene foil (thickness, 0.25  $\mu\text{m}$ ), and the accuracy of the reading was  $\pm 4 \text{ cm}^{-1}$ . The UV spectra and the spectra in the visible region (200–800 nm) for solutions of the substances in dioxane ( $3\text{--}5 \cdot 10^{-5} \text{ mol l}^{-1}$ ) were obtained with a Specord UV-VIS (Zeiss) spectrometer using 10 mm quartz cells. Characteristic spectral data are in Table II. The mass spectra (70 eV) were measured at an emission of 100  $\mu\text{A}$  with an MS 902–3 (AEI) instrument applying the direct sample introduction technique. The temperature of the ionizing chamber was 180–220°C. The starting amidinoyl isothiocyanates were prepared by the reaction of the corresponding chloroformamides<sup>10</sup> with KSCN as described<sup>1</sup>.

### Attempted Dimerisation of [N<sup>1</sup>,N<sup>1</sup>-(3-Oxapentamethylene) or Pentamethylene-N<sup>2</sup>-4-nitrophenyl]amidinoyl Isothiocyanates (*Ia, b*)

A solution of the respective amidinoyl isothiocyanate (0.01 mol) in acetonitrile (50 ml) was boiled for 5 h and the precipitated products, separated during this time in a crystalline form, were filtered. Since they were insoluble in common organic solvents they were boiled in acetone (100 ml), filtered and identified as 2-morpholino-6-nitro-4-(4-nitroanilino)-3*H*-quinazoline (30%) and 2-piperidino-6-nitro-4-(4-nitroanilino)-3*H*-quinazoline (25%), respectively. Thin-layer chromatography on silica gel of the mother liquors showed, by comparison with standard materials, that the corresponding isomeric products, *i.e.* quinazoline-4(3*H*)-thiones were also present.

### Reactions of Amidinoyl Isothiocyanates with Aromatic Isothiocyanates

A solution of an amidinoyl isothiocyanate (0.005 mol) and a phenyl isothiocyanate (0.005 mol) in dimethylformamide (25 ml) was refluxed for 1 h and then concentrated to 5 ml. The products crystallized on cooling and two recrystallisations from benzene or ethanol gave 4-anilino quinazolines for which the yields, physical constants and spectral characteristics are given in Table I and II.

### Attempted Preparation of N'-(N<sup>1</sup>,N<sup>1</sup>-(3-Oxapentamethylene)-N<sup>2</sup>-4-chlorophenyl)amidino-N<sup>2</sup>-phenylcarbodiimide

A solution of aniline (1.8 g, 0.02 mol) in benzene (25 ml) was added dropwise and with stirring to a solution of [N<sup>1</sup>,N<sup>1</sup>-(3-oxapentamethylene)-N<sup>2</sup>-4-chlorophenyl]amidinoyl isothiocyanate (5.6 g, 0.02 mol) in benzene. The mixture was stirred overnight at room temperature, the precipitate was filtered and recrystallized from ethanol to give the corresponding thiourea derivative (5 g, 67%), m.p. 143°C (lit.<sup>11</sup> m.p. 147–148°C).

A solution of the foregoing compound (3.75 g, 0.01 mol) in dichloromethane (30 ml) was shaken at room temperature with yellow mercuric oxide (4.4 g). After 1 h another portion of mercuric oxide (2.2 g) was added and the mixture was shaken for 1 h. The mixture was filtered through

a short layer of silica gel, to remove colloidal HgS, the layer was washed with acetone (50 ml) and the combined filtrates were concentrated. The yellow material (1.7 g, 50%, m.p. 262—264°C, lit.<sup>8</sup> m.p. 264—265°C) was identified as 2-morpholino-6-chloro-4-anilino-3*H*-quinazoline. It was identical with the product obtained by a reaction of the corresponding amidinoyl isothiocyanate with phenyl isothiocyanate, or the product of the reaction of the corresponding chloroformamidine with phenylcyanoamide<sup>8</sup>.

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