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Reaction of 3,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline-1-thiones with Amines in the Presence of Mercury(II) Chloride

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Abstract—Amidines of the 3,4-dihydroisoquinoline series were synthesized by reaction of 1,2,3,4-tetrahydroisoquinoline-1-thiones with amines in the presence of mercury(II) chloride.

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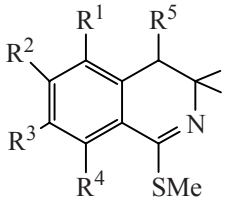
It is known that heterocyclic amidines exhibit diverse pharmacological activity. Examples are such widely used drugs as Naphazoline, Xylometazoline, Phentolamine, and Chlordiazepoxide [1]. Aliphatic amidines are starting compounds for the preparation of various heterocycles; they are commonly synthesized by the Pinner reaction, reaction of thioamides with amine hydrochlorides, reaction of ortho esters with amides, etc. [2]. Only a few published data are available on the transformations of a heterocyclic fragment, leading to the formation of amidines. For instance, Mikhailovskii et al. [3] described the synthesis and biological activity of a series of amidines, which were obtained by reaction of 6-chlorophenanthridine with various primary and secondary amines.

We previously showed that amidines of the 3,4-dihydroisoquinoline series can be synthesized by reaction of amines with 3,3-dialkyl-1-methylsulfanyl-3,4-dihydroisoquinoline (**Ia**); the reactions with secondary amines required heating with excess amine without a solvent [4]. Imidothioates like **I** having a substituent in the 9-position of the aromatic ring reacted with both primary and secondary amines much more difficultly [5], and the experimental conditions strongly differed from those given in [4].

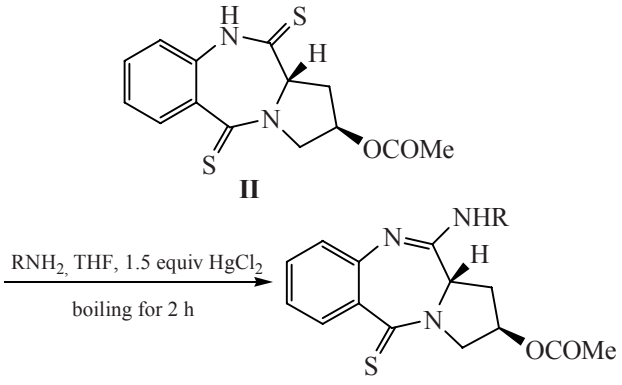
Gillard and Rault [6] proposed a procedure for the preparation of amidines by reaction of thiolactams like **II** with primary amines in the presence of mercury(II) chloride in tetrahydrofuran (Scheme 1). The procedure is characterized by experi-mental simplicity and mild conditions. It was interesting to examine analogous transformation in the series of 1,2,3,4-tetrahydroisoquinoline-1-thione derivatives **III**. Furthermore, on the basis of the data of [6] it remained unclear whether lactams **III** are capable of reacting under the given conditions: in all cases described in [6] the reaction involved only the thioimidoyl group that was not conjugated with the aromatic ring.



Ia–Id

$R^1 = R^2 = R^3 = R^4 = R^5 = H$ (**a**); $R^1 = R^2 = H$, R^3R^4 = benzo, R^5 = Me (**b**); $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$ (**c**); R^1R^2 = benzo, $R^3 = R^4 = H$, R^5 = Me (**d**).

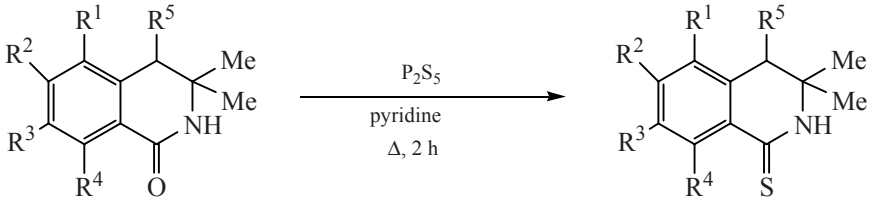
Scheme 1.



II

Thiolactams **IIIa**–**IIId** are readily obtained by treatment of the corresponding 1,2,3,4-tetrahydroisoquinolin-1-ones with phosphorus(V) sulfide in pyridine on heating (Scheme 2). The procedures for the synthesis of 1,2,3,4-tetrahydroisoquinolin-1-ones were described in [4, 7].

Scheme 2.

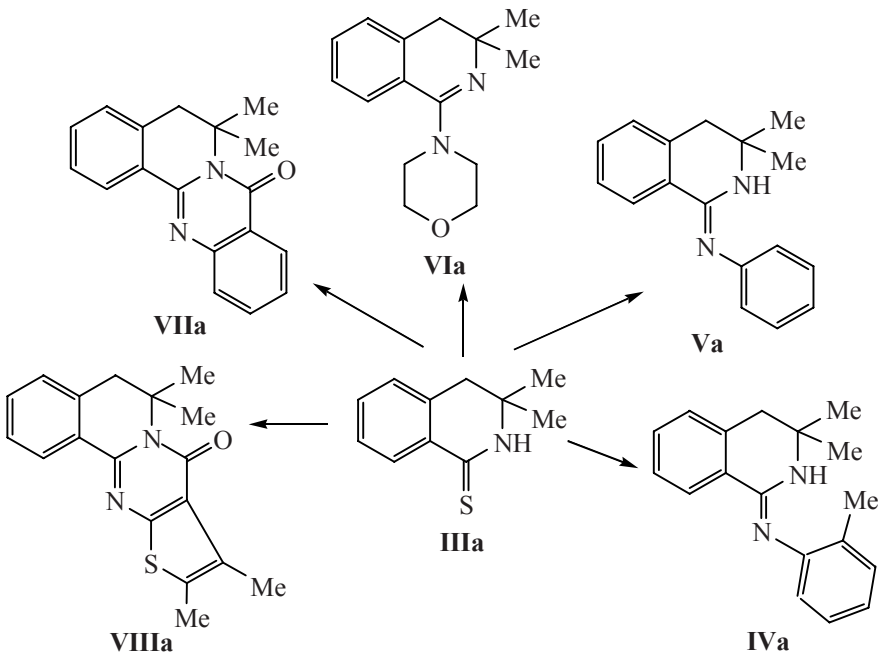


IIIa–IIId

$R^1 = R^2 = R^3 = R^4 = R^5 = H$ (**a**); $R^1 = R^2 = H$, R^3R^4 = benzo, R^5 = Me (**b**); $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$ (**c**); R^1R^2 = benzo, $R^3 = R^4 = H$, R^5 = Me (**d**).

In fact, 3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-thione (**IIIa**) taken as a model compound readily reacted with *o*-xylidine, anilinom, morpholine, anthranilic acid, and ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate to produce amidines **IVa**–**VIIIa** (Scheme 3). Unfortunately, compound **IIIa** failed to react with diethylamine (methylsulfanyl derivative **I** also failed to react with excess diethylamine on heating) and CH nucleophiles such as dimedone, diethyl malonate, and malononitrile.

Scheme 3.

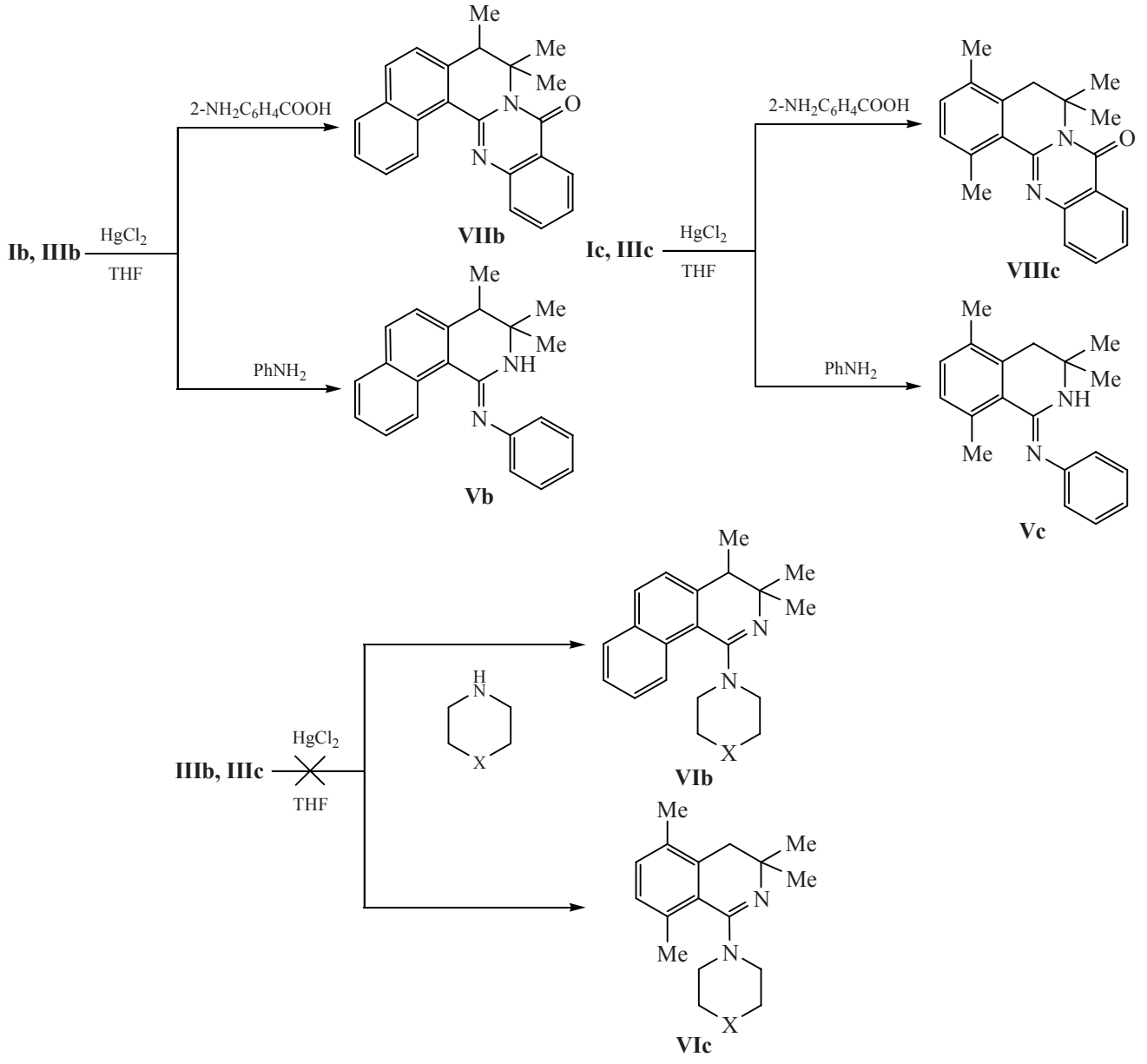


It should be noted that mutual arrangement of the aryl and lactam fragments affects the character of the C=N bond. In the amidine molecules described in [6] the C=N bond is endocyclic, whereas the corresponding bond in the condensation products of lacatms **III** with primary amines is exocyclic. This follows from the downfield shift of the 10-H signal in the ^{1}H NMR spectra of compounds **IIIb**, **VIIb**, and **IX** relative to the corresponding signal of **Ia**. The effect of the exocyclic double bond in structurally related compounds on the chemical shift of proton in position *8* of the isoquinoline ring was considered in [5].

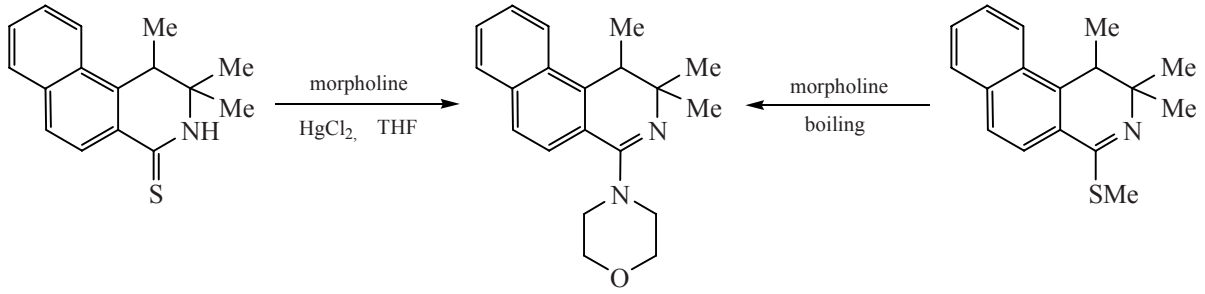
Our numerous attempts to react compound **IIIa** with 2,6-disubstituted anilines (2,6-dichloro-, 2,6-dimethyl-, and 2,6-dimethoxyanilines) were unsuccessful; compound **Ia** also failed to react with the above sterically hindered anilines [4]. A quite different pattern was observed when a substituent was present in the 8-position of the isoquinoline fragment. Primary amines, including anthranilic acid, readily reacted with tetrahydroisoquinoline-1-thiones **IIIb** and **IIIc** to give the corresponding amidines, while secondary amines did not react (Scheme 4).

Generally speaking, a methyl group on C^8 creates greater steric hindrances than benzene ring fused at the 7,8-positions. On the other hand, aromatic naphthalene system provides more effective delocalization of positive charge on the thiocarbonyl carbon atom, as follows from ready formation of tetrahydroisoquinoline-1-thione from the corresponding imidothioate [5]. To elucidate probable reasons for the failure of thiones **IIIb** and **IIIc** to react with secondary amines (increased basicity as compared to **IIIa** or steric factor), we examined reactions of 1,2,2-trimethyl-1,2,3,4-tetra-

Scheme 4.



Scheme 5.



IIId **VId** **Id**

hydrobenzo[*f*]isoquinoline-1-thione (**IIId**) and 1,2,2-trimethyl-4-methylsulfanyl-1,2-dihydrobenzo[*f*]isoquinoline (**Ib**) with morpholine. In both cases, the reactions smoothly afforded the corresponding amidine **VId** (Scheme 5).

Thus the inertness of 8-substituted 1,2,3,4-tetrahydroisoquinoline-1-thiones toward secondary amines is determined exclusively by steric factor. When $HgCl_2$ was preliminarily stirred with amine for 15 min at 65°C (before addition of **IIIa**), the results were the same as in the reaction with 1.5 equiv of $HgCl_2$ according to the procedure described in [6]. Presumably, the main factors responsible for the reaction of thiolactams of the tetrahydroisoquinoline series with amines are (1) the possibility for complex formation of $HgCl_2$ with amine and (2) steric hindrances related to the presence of a substituent in position *8* of the quinoline ring.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer (300 MHz) in DMSO-d_6 using tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–acetone (9:1) as eluent; the chromatograms were developed by treatment with a 0.5% solution of chloranil in toluene.

Compounds **IVa**–**VIIIa** were reported previously [4], and their yields differed within experimental error from those given in [4]. Compounds **Ia**, **VIIa** [4], **Ib**, **IIIb**, **VIIb** [5], **Ic** [9], and **Id** [10] were also described previously.

3,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline-1-thione (IIIa) [5]**.** A mixture of 4.06 g of 3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-one and 6.66 g of phosphorus(V) sulfide in 30 ml of anhydrous pyridine was heated for 2 h. The mixture was left overnight, the solution was separated from the solid material and poured into 150 ml of water under stirring, and the precipitate was filtered off, dried, and recrystallized from appropriate solvent. Yield 73%. The physical constants of the product coincided with those given in [8].

Compounds **IIIb**–**IIIe** were synthesized in a similar way.

Reaction of 3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-thione (IIIa) with aniline. Mercury(II) chloride, 5.44 g, was added in several portions to a solution of 2.19 g of compound **IIIa** and 0.93 g of freshly distilled aniline in 30 ml of anhydrous THF at 50°C. The mixture was heated for 2–2.5 h and filtered, the solvent was removed from the filtrate under reduced pressure, the residue was dissolved in 30–40 ml of ethyl acetate, and the solution was washed with aqueous sodium thiosulfate. The organic phase was separated, dried over magnesium sulfate, and filtered, and the filtrate was evaporated on heating on a water bath. Yield of **VIa** 62%. The physical constants of the product coincided with those given in [4].

Reactions of compounds **IIIa**–**IIIe** with other amines were carried out following an analogous procedure.

1,2,2-Trimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-1-one (IX). A mixture of 5 g of compound **Id** [9] and 20 ml of 90% acetic acid containing 3 drops of triethylamine was treated as described in [4]. Yield 3.7 g (87%), mp 269–271°C. Compound **IX** was then converted into **IIId** as described above for the synthesis of thione **IIIa**.

The yields, melting points, and elemental analyses of newly synthesized compounds are given in Table 1,

Table 1. Yields, melting points, and elemental analyses of compounds **IIIb**–**IIId**, **Vb**–**Vd**, **VId**, **VIIc**, and **IX**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIb	88	164–165 (ethanol)	75.39	6.59	5.41	$C_{16}H_{17}NS$	75.25	6.71	5.48
IIIc	79	166–167 (ethanol)	71.03	7.87	6.20	$C_{13}H_{17}NS$	71.18	7.81	6.39
IIId	85	216–217 (ethanol)	75.36	6.55	5.43	$C_{16}H_{17}NS$	75.25	6.71	5.48
Vb	53	167–168 (hexane–benzene, 2 : 1)	84.21	6.95	8.84	$C_{22}H_{22}N_2$	84.04	7.05	8.91
Vc	61	174–175 (methanol)	82.15	7.86	9.99	$C_{19}H_{22}N_2$	81.97	7.97	10.06
VId	51	57–58 (hexane)	77.81	7.89	9.16	$C_{20}H_{24}N_2O$	77.89	7.84	9.08
VIIc	54	192–193 (ethyl acetate)	78.81	6.63	9.33	$C_{20}H_{20}N_2O$	78.92	6.62	9.20
IX	87	269–271 (benzene)	80.20	7.19	5.80	$C_{16}H_{17}NO$	80.33	7.11	5.86

Table 2. IR and 1H NMR spectra of compounds **IIIb**–**IIId**, **Vb**, **Vc**, **VId**, **VIIc**, and **IX**

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
IIIb	3180; 1645; 1595; 1550	1.29 d (3H, 4-Me); 1.36 s [6H, $(CH_3)_2$.; 2.88 q (1H, 4-CH); 7.24 s (1H, NH); 7.50–7.87 m (5H, H_{arom}); 9.55 d (1H, 10-H)
IIIc	3185; 1640; 1600	1.22 s [6H, $(CH_3)_2$.; 2.23 s (3H, 5-Me); 2.75 s (3H, 8-Me); 3.08 s (2H, 4-CH_2); 7.03 d (1H, 6-N); 7.12 d (1H, 7-H); 9.98 s (1H, NH)
IIId	3180; 1640; 1596	1.23 s (3H, CH_3, pseudoaxial); 1.29 s (3H, CH_3, pseudoequatorial); 1.46 d (3H, 1-Me); 3.48 q (1H, 4-CH); 7.51–8.16 m (6H, H_{arom}); 8.66 s (1H, NH)
Vb	1605; 1570; 1510	1.26 s (3H, CH_3, pseudoaxial); 1.30 d (3H, 4-Me); 1.33 s (3H, CH_3, pseudoequatorial); 2.83 q (1H, 4-CH); 7.10–7.87 m (11H, H_{arom})
Vc	1605; 1570; 1510	1.25 s [6H, $(CH_3)_2$.; 2.24 s (3H, 5-Me); 2.29 s (3H, 8-Me); 6.77 s (1H, NH); 6.98–7.65 m (7H, H_{arom})
VId	1610; 1600;1580	1.20 s (3H, CH_3, pseudoaxial); 1.29 s (3H, CH_3, pseudoequatorial); 1.44 d (3H, 1-Me); 2.84 t [4N, $(CH_2)_2$N.; 3.43 t [4H, $(CH_2)_2$O.; 3.51 q (1H, 4-CH); 7.13–787 m (6H, H_{arom})
VIIc	1658; 1605; 1580; 1500	1.33 s [6H, $(CH_3)_2$.; 2.29 s (3H, 5-Me); 2.38 s (3H, 8-Me); 7.13–7.87 m (6H, H_{arom})
IX	3190; 1660; 1600	1.25 s (3H, CH_3, pseudoaxial); 1.29 s (3H, CH_3, pseudoequatorial); 1.41 d (3H, 1-Me); 3.49 q (1H, 1-CH); 7.26 s (1H, NH); 7.50–8.22 m (6H, H_{arom})

and their IR and ^1H NMR spectra are collected in Table 2.

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