HETEROCYCLES FROM NITRILE IMINES. PART I[1].
1,2,3,4-TETRAHYDRO-1,2,4,5-TETRAZINES

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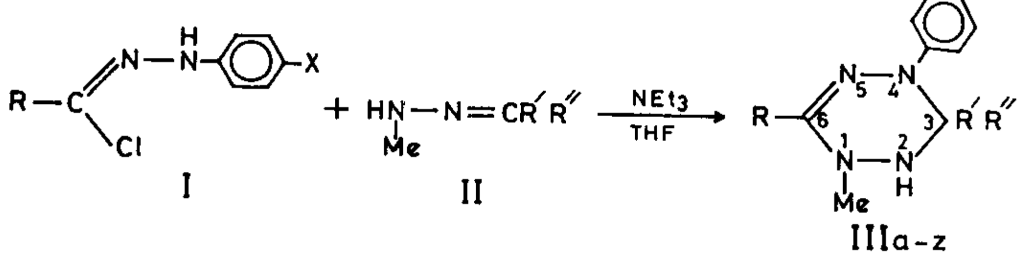
Abstract — The interaction between ketohydrazones and nitrile imines provides a new and direct synthetic route to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines. Elemental analysis and spectral data are consistent with the assigned tetrazine ring system.

Quite recently, we have reported that the reaction of hydrazones with nitrile oxides provides a direct access to 1,2,4,5-oxatriazine derivatives[2]. Accordingly, we anticipate that hydrazones would, as well, react with nitrile imines IV in a similar manner to afford the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazines III. In this work, we find that, in the presence of triethylamine, ketone methylhydrazones II do react readily with hydrazonoyl chlorides I (precursors of IV) giving good yields of the presumed tetrazine derivatives (III) as stable crystalline products (Scheme 1, Table 1).

Scheme 1



IIIa-j : R=CO_2Me ; R′=R″=Me
IIIo-t : R=CO_2Me ; R′+R″=$-(CH_2)_5-$
IIIu-z : R=CO_2Me ; R′+R″=$-(CH_2)_4-$
(for X, see Table 1)

IIIk : R=C_6H_5 ; R′=R″=Me
IIIl : R=p-ClC_6H_4 ; R′=R″=Me
IIIm : R=C_6H_5 ; R′+R″=$-(CH_2)_5-$
IIIn : R=p-ClC_6H_4 ; R′+R″=$-(CH_2)_5-$

Table 1. Physical and Analytical Data of Compounds III.

				% Analysis					
				Calcd.			Found		
Compd.	X	Mp(°C)	%Yield	C	H	N	C	H	N
IIIa	H	88–89[a]	68	59.53	6.92	21.36	59.27	6.99	21.40
IIIb	Me	95–96[a]	53	60.85	7.29	20.27	60.67	7.24	20.36
IIIc	OMe	105–106[a]	60	57.52	6.90	19.17	57.32	6.84	19.33
IIId	F	118–119[a]	67	55.71	6.11	19.99	55.64	6.07	20.31
IIIe	Cl	126–127[a]	88	52.62	5.77	18.88	52.30	5.83	18.92
IIIf	Br	127–128[a]	72	45.76	5.02	16.42	45.45	4.99	16.72
IIIg	I	114–115[b]	65	40.22	4.41	14.43	40.36	4.40	14.40
IIIh	CN	112–113[b]	64	58.53	5.96	24.37	58.43	5.96	24.26
IIIi	Ac	97–98[b]	60	59.20	6.62	18.41	59.05	6.58	18.41
IIIj	NO_2	126–127[b]	55	50.81	5.58	22.79	50.67	5.53	22.65
IIIk	H	144–145[b]	67	72.83	7.19	19.98	72.82	7.09	20.16
IIIl	H	115–116[b]	56	64.86	6.08	17.80	64.63	6.06	17.81
IIIm	H	103–104[b]	60	74.97	7.55	17.48	74.86	7.49	17.37
IIIn	H	134–135[b]	62	67.69	6.53	15.79	67.57	6.48	15.62
IIIo	H	133–134[b]	70	63.56	7.33	18.53	63.61	7.31	18.52
IIIp	Me	122–123[c]	42	64.53	7.64	17.71	64.22	7.59	17.91
IIIq	OMe	126–127[c]	55	61.43	7.28	16.86	61.64	7.17	16.95
IIIr	F	109–110[c]	50	59.99	6.61	17.49	59.67	6.51	17.30
IIIs	Cl	120–121[b]	62	57.06	6.28	16.63	56.88	6.21	16.63
IIIt	Br	119–120[b]	58	50.40	5.55	14.69	50.18	5.43	14.65
IIIu	H	111–112[b]	60	62.48	6.99	19.43	62.34	6.94	19.59
IIIv	Me	97–98[c]	45	63.56	7.33	18.53	63.35	7.26	18.63
IIIw	OMe	99–100[a]	66	60.36	6.96	17.60	60.18	6.86	17.82
IIIx	F	103–104[a]	53	58.81	6.25	18.29	58.59	6.22	18.50
IIIy	Cl	105–106[a]	56	55.81	5.93	17.36	55.45	5.80	17.60
IIIz	Br	115–116[c]	60	49.06	5.21	15.26	48.71	5.10	15.22

[a] Crystallized from diethyl ether/petroleum ether. [b] From ethanol. [c] From chloroform/petroleum ether.

The hydrazonoyl chlorides, employed in this study (Table 2), have been prepared via the Japp-Klingemann reaction[3], or by the action of phosphorus pentachloride on the respective hydrizides[4,5].

Table 2. Physical and Analytical Data for the Hydrazonoyl Chlorides (I)[a].

		% Analysis					
		Calcd.			Found		
Compd	Mp (°C)	C	H	N	C	H	N
Ib	139–140[b]	52.99	4.89	12.36	53.03	5.02	12.23
Id	113–114[b]	46.87	3.50	12.15	46.96	3.66	12.18
If	159–160[b]	37.08	2.77	9.61	37.18	2.71	9.40
Ih	194–195[c]	50.54	3.39	17.68	50.46	3.37	17.65
Ii	188–189[c]	51.88	4.35	11.00	51.78	4.30	10.92

[a] For X and R, see Table 1 and Scheme 1; Literature melting points (°C) for the following known compounds are given only when there are marked differences from our values: Ia[7], mp 101–102; Ic[8], mp 105–106; Ie[8], mp 152–153 (Lit.[8] mp 135); Ig[9], mp 169–170; Ij[10], mp 218–220; Ik[4,5], mp 130–131; Il[6], mp 151–152. [b] Crystallized from chloroform/pet. ether. [c] Crystallized from THF/petroleum ether.

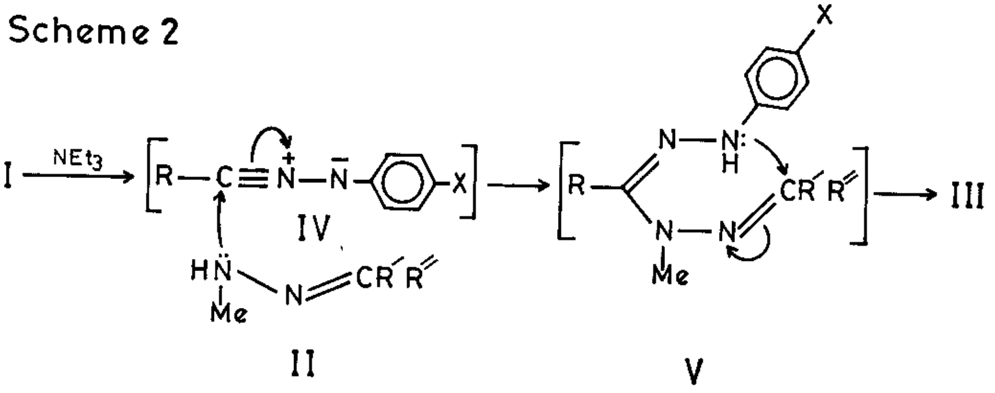
RESULTS AND DISCUSSION

A. Mechanism

The formation of compounds III is assumed to involve nucleophilic addition of the hydrazone to the nitrile imine (generated in situ from I by the action of triethylamine) to give the corresponding acyclic adducts V. The latter intermediates ultimately undergo intramolecular cyclization, involving the azomethine and the N-H termini, to yield the tetrazine derivatives (Scheme 2).

Examples of related intramolecular cyclizations, following the initial 1,3-nucleophilic addition step of suitably functionalized nucleophilic substrates onto nitrile imines, are cited in the literature[11].

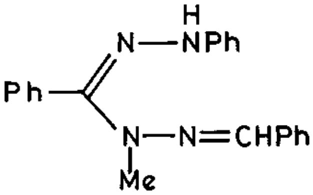
Scheme 2

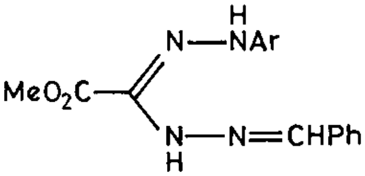


B. Spectral Data

The assignment of a tetrazine structure to the products III is based on elemental analysis (Table 1), and spectral data that rule out the alternative acyclic structure V. The ir spectra of compounds III revealed the presence of an N-H absorption in the range 3260–3280 cm^{-1} and a C=N bond stretching band at about 1620 cm^{-1}. The ms spectra display peaks for the correct molecular ions $[M]^{+\cdot}$ as well as fragment ions corresponding to the partner nitrile imines, and their characteristic $[X\text{-}C_6H_4N]^+$ / $[RCNH]^+$ daughter ions[12]. Ring contraction of $[M]^{+\cdot}$ to the respective triazolium ion, via expulsion of $X\text{-}C_6H_4\dot{N}$, is also a favourable fragmentation mode. In their pmr spectra, compounds III exhibit an exchangable broadened singlet (1 H) in the range 4.0–4.3 ppm, attributed to the NH proton. Compounds IIIa–l show the protons of the two methyls at C-3 as one singlet at 1.3 ppm (6 H), indicating them to be equivalent. In the parent hydrazone (II, R = R = Me) these protons are non-equivalent and appear as two singlets at a significantly lower field (1.84 and 1.64 ppm)[13], a pattern that would also be observed for the alternative acyclic structure V. The tetrahydrotetrazines IIIm–t and IIIu–z, derived from cyclohexanone and cylopentanone methylhydrazones, exhibit one signal for the methylene protons, centered at 1.6–1.7 (10 H) and 1.7–1.8 (8 H), respectively. By analogy to their parent hydrazones[14], these protons would appear in the acyclic structure V as two distinct signals at 2.2 and 1.8 ppm, of which the lower field signal (4 H) belongs to the α-methylene protons directly attached to the azomethine carbon. The ^{13}C-nmr spectra of compounds III exhibit a signal at 70–80 ppm, indicative of an sp^3-carbon, flanked by two nitrogen atoms[15,16]. This signal shows no splitting in the off-resonance spectra and is therefore assigned to the quaternary C-3 carbon atom. The signal located at about 137 ppm is assigned to the C-6 carbon atom. This assignment is in good agreement with literature data for azomethine carbons[16,17]. The acyclic adducts V would exhibit two such azomethine signals, but lack the ^{13}C signal at around 70-80 ppm.

Literature reports on the reaction between hydrazonoyl halides and hydrazones are limited to a few cases. Grashey et al.[18], assumed structure VI for the reaction product obtained from benzaldehyde methylhydrazone and I (R = Ph). Ehrhardt et al.[19], also identified the reaction products from I (R = COOMe) and benzaldehyde hydrazone as methyl-2-benzylidenehydrazino-2-arylhydrazonoacetates VII.


VI


VII

Corresponding acyclic structures have likewise been assigned for the products isolated from the reaction of I (R = Ar) with benzaldehyde hydrazones[20], phenylhydrazones[21], or with hydrazones of acetophenone, benzophenone and fluorenone[22]. In contrast, our present findings document the first examples of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines, obtained via direct interaction between ketone methylhydrazones and hydrazonoyl chlorides.

Currently, we are continuing exploration of the scope and potential of this reaction as a new preparative method of unsymmetrical tetrahydrotetrazines, a class of heterocycles for which only limited synthetic routes are available[23].

EXPERIMENTAL

Melting points were obtained on an electrothermal Mel-Temp. apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 577 spectrophotometer, using KBr pellets. Pmr spectra were obtained with a Varian T-60A spectrometer for solutions in $CDCl_3$ containing TMS as internal reference. ^{13}C-Nmr spectra (FT mode) were measured on a Bruker WM-250 spectrometer at 26.97 MHz in $CDCl_3$ with tetramethylsilane as internal reference. Ms spectra were run on a Finnigan MAT 112 mass spectrometer (70 eV). Microanalysis was performed at the Mikroanalytisches Labor, Pascher, Remagen, W. Germany.

Preparation of the Hydrazonoyl Chlorides I (Precursors of IV).

i) Methyl 2-arylhydrazono-2-chloroacetates (Ia-j, Table 2). These compounds were prepared via the Japp-Klingemann reaction[3] involving coupling of arenediazonium salts to methyl 2-chloroacetoacetate. The following procedure was adopted: A fresh cold solution of the appropriate arenediazonium chloride (0.11 mol) was added to a stirred solution of methyl 2-chloroacetoacetate (0.10 mol, Fluka) in 50% aqueous pyridine (120 ml) at zero to 5°C. The reaction mixture was then stirred for 15-20 minutes, the precipitated yellow-orange solid was collected, washed several times with cold water, dried, and recrystallized from the suitable solvent. Yields were in the range 85-95%. No attempt was made to isolate the intermediate methyl 2-arylazo-2-chloroacetoacetates, which are convertible rather readily to the corresponding hydrazones I, via preferential hydrolytic cleavage of the acetyl group.

(ii) N-Phenylbenzohydrazonoyl chloride (Ik)[4,5] and N-Phenyl-p-chlorobenzohydrazonoyl chloride (Il)[6]. These compounds were obtained by the action of phosphorus pentachloride on β-benzoylphenylhydrazine, or β-(p-chlorobenzoyl)phenylhydrazine, respectively, according to literature methods[4-6].

Monomethylhydrazones (II). Acetone methylhydrazone, cyclopentanone methylhydrazone, and cyclohexanone methylhydrazone, employed in this work, have been prepared according to literature methods[24].

Preparation of 1-Methyl-4-aryl-6-methoxycarbonyl-3,3-disubstituted-1,2,3,4-tetrahydro-1,2,4,5-tetrazines (IIIa-j, IIIo-z) and 1-Metyl-4,6-diaryl-3,3-disubstituted-1,2,3,4-tetrahydro-1,2,4,5-tetrazines (IIIk-n).

General Procedure: To a solution of the appropriate hydrazonoyl chloride (I, 0.01 mol) in tetrahydrofuran (20 ml) was added the respective ketone methylhydrazone (0.01 mol) and triethylamine (0.03 mol) in tetrahydrofuran (20 ml). The resulting mixture was then refluxed for 2-3 h. The precipitated triethylammonium chloride was filtered off from the cold mixture, and the solvent was removed in vacuo. The residue was washed with water, and triturated with ethanol (5-10 ml). The solid product, thus obtained, was collected and recrystallized from the appropriate solvent. Comparable yields of III were also obtained when the above reaction was conducted at room temparature (28°C) for 2-4 days.

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