HETROCYCLES FROM NITRILE IMINES. PART III.[1] SUBSTITUENT EFFECT ON RING-CHAIN TAUTOMERISM OF 1,2,3,4-TETRAHYDRO-*s*-TETRAZINES

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Abstract —— Selected series of 6-substituted 4-aryl-3-heteroaryl-1-methyl-1,2,3,4-tetrahydro-*s*-tetrazines (V:1-12) were synthesized *via* direct interaction between appropriate nitrile imine and model methylhydrazones. The extent of "ring-chain" tautomerism, as evidenced from nmr spectral data of V, is dependent on the nature of substituents at N-4, C-3, and C-6. The results reveal that: (i) The concentration of the cyclic tautomer tends to decrease as the basicity of the arylated N-4 decreases. (ii) For C-3 substituents, the cyclic tautomer ratio decreases in the order: phenyl $\rangle$ pyridyl $\rangle$ furyl $\rangle$ thienyl. (iii) For C-6 substituents, the cyclic ratio decreases in the order: $C_6H_5 \rangle CO_2Me \rangle$ COMe. These trends are interpreted in terms of conjugative and electronic effects.

Recently, we have reported the synthesis of 1,2,3,4-tetrahydro-*s*-tetrazines *via* the reaction of nitrile imines (1,3-dipoles) with a variety of alkanone/cycloalkanone and alkanal monomethylhydrazones.[1,2] Tetrahydro-*s*-Tetrazines derived from benzaldehyde methylhydrazones exhibit, in solution, "ring-chain" tautomerism as evidenced from their nmr spectral data.[1] The ratio of the "ring" form, equilibrating with the "chain" tautomer, is dependent

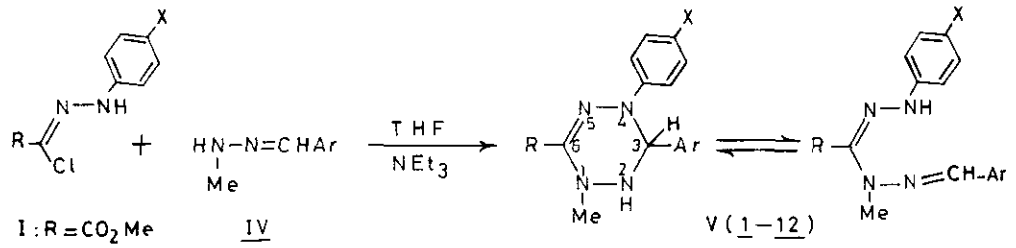
on the nature of substituent at C-3, as indicated from few sporadic ^{1}H-nmr spectral results.[1]

The main objectives of the present work are to further investigate the dependence of "ring-chain" tautomeric ratio onto: (i) the relative aromatic character of groupings at 3-carbon, (ii) the relative basicity of the 4-nitrogen, and (iii) the nature of substituents at 6-carbon.

Accordingly, we synthesized selected sets of 6-methoxycarbonyl-1,2,3,4-tetrahydro-*s*-tetrazines V(1-4) with varying heteroaryls at C-3, and serverl *p*-substituted phenyls at N-4, as well as sets of the 6-acetyl (V:5-8), and 6-phenyl analogues (V:9-12); their syntheses (Scheme 1) followed the aforementioned route[1,2] invloving direct interaction between the corresponding hydrazonoyl chloride (I-III) and the partner methylhydrazone (IV). The appropriate nitrile imines were generated *in situ* by the action of triethylamine onto the respective *N*-arylhydrazonoyl chlorides. The latter precursors (I),[2] (II),[35] and (III),[6] used in this study (Scheme 1), were prepared by the methods previously described. The monomethylhydrazones (IV) of thiophene-2-carboxaldehyde,[7] Furan-2-carboxaldehyde,[8] pyridine-2-carboxaldehyde,[7] and benzaldehyde,[8] employed in the present work, were prepared according to reported methods.

The EI mass spectra of compounds V(1-12) displayed the correct molecular ions suggested by the molecular formulae for which satisfactory analytical data were also obtained (Table 1). The ir spectra of compounds (V) exhibited absorption bands characteristic of the C=N-(1600-1630 cm^{-1}), N-H(3200-3250 cm^{-1}), the ester carbonyl (1720-1750 cm^{-1}) in compounds (1-4), and the acetyl carbonyl (1690-1710 cm^{-1}) in compounds (5-8).

Scheme 1



Ar	1	2	3	4	R
No	5	6	7	8	COMe
	9	10	11	12	C_6H_5

	a	b	c	d	e	f	g	h	i	j	k
X	H	Me	OMe	F	Cl	Br	I	CN	COMe	NO_2	CO_2Me

^{1}N-Nmr Spectral Data

Signal doubling of the various protons in the ^{1}H-nmr spectra of compounds (V) demonstrated that the these compounds exist, in solution, as "ring-chain" tautomers (VA⇌VB) (Scheme 1 and Table 2). Ring tautomer (VA) was characterized by the presence of two doublets arising from the vicinal, mutually coupled protons at N-2 (4.2-4.7 ppm) and C-3 (5.8-6.2 ppm) ($J_{CH-NH} \sim 3$ Hz); upon addition of D_2O, the former doublet disappeared, while the latter collasped to a singlet. The existence of the chain tautomer (VB) was revealed by the presence of two singlets for its two distant, deshielded protons in the range 9.1-11.6 ppm (exchangeable N-H) and 7.2-7.7 ppm (azomethine -N=CH-). Likewise, the 1-methyl protons showed up as two singlets at 2.6-2.8 ppm (ring tautomer VA) and 3.2-3.4 ppm (chain tautomer VB). Signal doubling was also observed for the ester methyl protons at C-6

Table 1. Physical and Analytical Data of Compounds (V1-11)

Compd No.	Yield[a] (%)	mp (°C)	Molecular Formulae	[M]+	Calcd/Found (%) C	H	N
1a	60	133-134	$C_{15}H_{16}N_4O_2S$	316	56.95 56.83	5.10 5.26	17.71 18.02
1b	55	100-101	$C_{16}H_{18}N_4O_2S$	330	58.16 57.95	5.49 5.49	16.96 16.85
1c	42	108-109	$C_{16}H_{18}N_4O_3S$	346	55.48 55.41	5.24 5.18	16.17 16.10
1d	50	124-125	$C_{15}H_{15}N_4O_2FS$	334	53.88 53.95	4.52 4.54	16.76 16.75
1e	75	126-127	$C_{15}H_{15}N_4O_2ClS$	350/ 352	51.36 51.19	4.31 4.35	15.97 16.24
1f	65	131-132	$C_{15}H_{15}N_4O_2BrS$	394/ 396	45.58 45.52	3.82 4.00	14.17 14.18
1g	56	150-151	$C_{15}H_{15}N_4O_2IS$	422	40.74 40.90	3.42 3.47	12.67 12.60
1h	72	148-149	$C_{16}H_{15}N_5O_2S$	341	56.29 56.27	4.43 4.45	20.51 20.65
1i	70	157-158	$C_{17}H_{18}N_4O_3S$	358	56.97 57.06	5.06 4.81	15.63 15.70
1j	62	163-164	$C_{15}H_{15}N_5O_4S$	361	49.86 49.50	4.18 4.17	19.38 19.35
1k	68	144-145	$C_{17}H_{18}N_4O_4S$	374	54.54 54.52	4.85 4.84	14.96 14.90
2a	55	132-133	$C_{15}H_{16}N_4O_3$	300	59.99 59.62	5.37 5.39	18.66 18.70
2b	50	116-117	$C_{16}H_{18}N_4O_3$	314	61.14 61.10	5.77 5.74	17.82 17.85
2c	40	135-136	$C_{16}H_{18}N_4O_4$	330	58.18 57.99	5.49 5.46	16.96 16.90
2d	45	121-122	$C_{15}H_{15}N_4O_3F$	318	56.60 56.56	4.75 4.89	17.60 17.67

Cont. Table 1

2e	72	129-130	$C_{15}H_{15}N_4O_3Cl$	334/ 336	53.82 53.55	4.52 4.59	16.74 17.06
2f	63	141-142	$C_{15}H_{15}N_4O_3Br$	378/ 380	47.51 47.38	3.99 3.99	14.77 14.46
2g	60	160-161	$C_{15}H_{15}N_4O_3I$	426	42.27 42.34	3.55 3.54	13.14 13.30
2h	65	142-143	$C_{16}H_{15}N_5O_3$	325	59.07 58.96	4.65 4.68	21.53 21.26
2i	75	116-117	$C_{17}H_{18}N_4O$	342	59.64 59.82	5.30 5.46	16.37 16.37
2j	66	164-165	$C_{15}H_{15}N_5O_5$	345	52.17 51.99	4.38 4.32	20.28 20.40
2k	68	149-150	$C_{17}H_{18}N_4O_5$	358	56.98 57.01	5.06 5.12	15.63 15.63
3a	40	137-138	$C_{16}H_{17}N_5O_2$	311	61.73 61.41	5.50 5.44	22.49 22.29
3c	30	121-122	$C_{17}H_{19}N_5O_3$	341	59.81 59.63	5.61 5.52	20.52 20.40
3e	32	100-101	$C_{16}H_{16}N_5O_2Cl$	345/ 347	55.58 55.21	4.66 4.45	20.25 19.98
3j	36	177-178	$C_{16}H_{16}N_6O_4$	356	53.93 53.58	4.53 4.40	23.58 23.25
4a	85	155-156	$C_{17}H_{18}N_4O_2$	310	65.79 65.60	5.85 5.78	18.05 18.28
5a	85	149-150	$C_{15}H_{16}N_4OS$	300	59.98 60.04	5.37 5.28	18.65 18.52
5c	60	113-114	$C_{16}H_{18}N_4O_2S$	330	58.16 57.83	5.49 5.36	16.96 16.59
5e	80	145-146	$C_{15}H_{15}N_4OClS$	334/ 336	53.81 53.84	4.52 4.61	16.73 16.82
6a	60	126-127	$C_{15}H_{16}N_4O_2$	284	63.37 63.18	5.67 5.57	19.71 19.53

Cont. Table 1

6c	57	108-109	$C_{16}H_{18}N_4O_3$	314	61.14 60.98	5.77 5.82	17.82 17.89
6e	70	151-152	$C_{15}H_{15}N_4O_2Cl$	318/ 320	56.52 56.36	4.74 4.49	17.58 17.29
7a	28	138-139	$C_{16}H_{17}N_5O$	295	65.07 65.17	5.80 5.72	23.71 23.70
8a	92	103-104	$C_{17}H_{18}N_4O$	294	69.37 69.59	6.16 6.34	19.03 19.00
9a	55	118-119	$C_{19}H_{18}N_4S$	334	68.24 68.18	5.42 5.52	16.75 16.94
10a	62	141-142	$C_{19}H_{18}N_4O$	318	71.68 71.31	5.70 5.79	17.60 17.93
11a	40	152-153	$C_{20}H_{19}N_5$	329	72.93 72.80	5.81 5.75	21.26 21.18

[a]Based on recrystallized product. Compounds (1j, 2j, and 3j) were recrystallized from chloroform/pet. ether (bp 40-60°C); all other compounds were recrystallized from ethanol (90 %). Compound (12a) was previously characterized.[1]

(1-4), the acetyl methyl protons at C-6 (5-8), and for the methyl protons in the X-portion of the N-4 aromatic moiety.

^{13}C-Nmr Spectral Data

The proton-decoupled ^{13}C-nmr spectra of compounds (V) also displayed signal doubling of the various carbons as a result of "ring-chain" tautomerism. Thus, the sp^3-hybridized C-3 ring carbon resonated at 65-71 ppm, and was diagnostic of the existence of the cyclic tautomer VA (Table 3). The 1-methyl carbon showed up as two signals at about 43 and 37 ppm belonging to the cyclic VA and acyclic VB tautomers, respectively. Similarly, each of the ester methyl carbon and the ester carbonyl carbon, positioned at C-6 (1-4), showed signal doubling around 52 and 161 ppm, respectively. Signal doubling was likewise observed for the carbons comprising the X-portion of the aromatic moiety at N-4.

Ring-Chain Tautomerism; Substituent Effects

The "ring-chain" tautomeric ratio [A]/[B] in these compounds V1-12 was calculated directly from the integrated peak areas of the respective 1-methyl protons' signals (Table 2).

N-4 Substituent Effect

The nature of *para*-substituents of the 4-phenyl group is expected to influence the relative basicity of the 4-nitrogen (and hence the tautomeric ratio). In compound 1c (X = OMe), and to a lesser extent 1b (X = Me), electron releasing substituents tend to increase the cyclic ratio as compared to the unsubstituted parent compound 1a (X=H). Conversely, electron-withdrawing groups, in compounds: 1d-k, tend to bring about a decrease in the concentration of the cyclic tautomer whose ratio decreases in the following order:

OMe $\rangle$ Me $\rangle$ H $\rangle$ Halogen $\rangle$ CN, COMe, $CO_2Me \gg NO_2$

Table 2. ^{1}H-nmr Data (δ-values in ppm) of Compounds (V1-12)

Compd	% Tautomer ratio	N-Me	N-H[b]	C_3-H[b]	Ester-Me at C-6(s)	-Me (in X) (s)
1a(A):	28	2.83(s)	4.46(d)	6.18(d)	3.86	
(B):	72	3.31(s)	9.87(s)	7.59(s)	3.88	
1b(A):	30	2.81(s)	4.38(d)	6.14(d)	3.84	2.28
(B):	70	(3.29/3.30)[a]	9.64(s)	7.54(s)	3.86	2.30
1c(A):	32	2.80(s)	4.36(d)	6.06(d)	3.86	3.75
(B):	68	3.29(s)	9.58(s)	7.53(s)		3.78
1d(A):	27	2.82(s)	4.41(d)	6.09(d)	3.86	
(B):	73	3.30(s)	9.87(s)	7.59(s)	3.87	
1e(A):	27	2.83(s)	4.47(d)	6.11(d)	3.86	
(B):	73	(3.29/3.31)[a]	10.02(s)	7.60(s)	3.88	
1f(A):	28	2.84(s)	4.47(d)	6.13(d)	3.86	
(B):	72	(3.29/3.30)[a]	10.07(s)	7.61(s)	3.88	
1g(A):	27	2.84(s)	4.44(d)	6.10(d)	3.86	
(B):	73	(3.29/3.31)[a]	10.06(s)	7.61(s)	3.87	
1h(A):	25	2.90(s)	4.62(d)	6.23(d)	3.87	
(B):	75	(3.32/3.33)[a]	10.77(s)	7.69(s)	3.90	
1i(A):	24	2.85(s)	4.60(d)	6.20(d)	3.84	2.48
(B):	76	(3.29/3.30)[a]	10.56(s)	7.66(s)	3.86	2.50
1j(A):	12	2.86(s)	2.64(d)	6.18(d)	3.84	
(B):	88	3.30(s)	11.07(s)	7.70(s)		
1k(A):	26	2.86(s)	4.58(d)	6.20(d)	3.86	3.90
(B):	74	3.31(s)	10.48(s)	7.65(s)		
2a(A):	52	2.65(s)	4.36(d)	6.00(d)	3.85	
(B):	48	3.29(s)	9.76(s)	7.18(s)	3.87	
2b(A):	53	2.62(s)	4.25(d)	5.95(d)	3.85	2.25
(B):	47	3.27(s)	9.50(s)	7.18(s)		2.27
2c(A):	55	2.62(s)	4.23(d)	5.85(d)	3.84	3.74
(B):	45	3.28(s)	9.43(s)	7.16(s)	3.85	3.76
2d(A):	50	2.64(s)	4.31(d)	5.87(d)	3.84	
(B):	50	3.26(s)	9.83(s)	7.21(s)		

Cont. Table 2

2e(A):	48	2.63(s)	4.36(d)	5.92(d)	3.82	
(B):	52	3.25(s)	10.08(s)	7.20(s)	3.84	
2f(A):	48	2.64(s)	4.35(d)	5.92(d)	3.84	
(B):	52	3.26(s)	10.10(s)	7.24(s)	3.85	
2g(A):	48	2.64(s)	4.33(d)	5.92(d)	3.84	
(B):	52	3.26(s)	10.23(s)	7.25(s)	3.85	
2h(A):	47	2.70(s)	4.49(d)	6.02(d)	3.84	
(B):	53	3.28(s)	11.12(s)	7.32(s)	3.87	
2i(A):	46	2.72(s)	4.46(d)	6.10(d)	3.89	2.53
(B):	54	3.31(s)	10.84(s)	7.33(s)	3.90	2.54
2j(A):	20	2.73(s)	4.56(d)	6.10(d)	3.88	
(B):	80	3.32(s)	11.57(s)	7.38(s)		
2k(A):	44	2.66(s)	4.47(d)	6.06(d)	3.84	
(B):	56	3.27(s)	10.71(s)	7.29(s)		
3a(A):	62	2.58(s)	4.53(d)	5.94(d)	3.86	
(B):	38	3.32(s)	9.78(s)	7.53(s)		
3c(A):	66	2.60(s)	4.55(d)	5.95(d)	3.86	3.73
(B):	34	3.31(s)	9.80(s)	7.56(s)	3.88	3.76
3e(A):	63	2.60(s)	4.59(d)	5.96(d)	3.86	
(B):	37	3.33(s)	9.81(s)	7.55(s)	3.88	
3j(A):	45	2.65(s)	4.71(d)	6.14(d)	3.86	
(B):	55	3.37(s)	11.48(s)	7.59(s)		
4a(A):	72	2.58(s)	4.52(d)	5.94(d)	3.84	
(B):	28	3.30(s)	9.75(s)	7.52(s)		
5a(A):	20	2.84(s)	4.42(d)	6.23(d)	2.50	
(B):	80	(3.31/3.33)[a]	10.32(s)	7.50(s)	2.53	
5c(A):	22	2.82(s)	4.37(d)	6.12(d)	2.48	3.78
(B):	78	(3.31/3.32)[a]	10.14(s)	7.56(s)	2.52	3.80
5e(A):	-	-	-	-	-	-
(B):	100	(3.29/3.30)[a]	10.48(s)	7.60(s)	2.49	
6a(A):	37	2.69(s)	4.30(d)	6.02(d)	2.47	
(B):	63	(3.28/3.29)[a]	10.36(s)	7.42(s)	2.50	

Cont. Table 2

6c(A):	42	2.67(s)	4.27(d)	5.90(d)	2.47	3.78
(B):	58	3.28(s)	10.10(s)	7.43(s)	2.49	3.80
6e(A):	18	2.70(s)	4.39(d)	6.00(d)	2.47	
(B):	82	(3.28/3.29)[a]	10.63(s)	7.47(s)	2.50	
7a(A):	45	2.68(s)	4.29(d)	5.94(d)	2.49	
(B):	55	3.29(s)	10.35(s)	7.52(s)		
8a(A):	63	2.62(s)	4.38(d)	6.01(d)	2.52	
(B):	37	3.35(s)	10.06(s)	7.35(s)	2.56	
9a(A):	74	2.64(s)	4.65(d)	6.20(d)		
(B):	26	3.26(s)	9.38(s)	7.59(s)		
10a(A):	77	2.48(s)	4.55(d)	6.00(d)		
(B):	23	3.29(s)	9.14(s)	7.20(s)		
11a(A):	78	2.66(s)	4.32(d)	5.96(d)		
(B):	22	3.30(s)	10.23(s)	7.50(s)		

[a] These two singlets, of almost equal intensity, probably belong to two different stereoisomers of the acyclic tautomer (VB).

[b] J_{CH-NH} Values for the mutually coupled protons at 2-nitrogen and 3-carbon of the ring tautomer (VA), in compounds (V1-11) are as follows:

J ~ 2.5 Hz in compounds (V1, 5, 9);

J ~ 3.0 Hz in compounds (V2, 6, 10);

J ~ 3.3 Hz in compounds (V3, 7, 11);

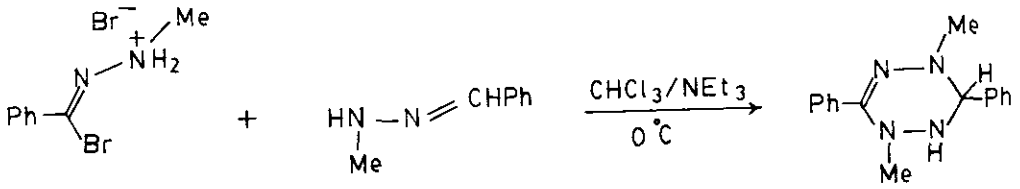
J ~ 2.8 Hz in compounds (V4, 8).

Compound (12a) was reported[1] to have the cyclic/acyclic ratio: 80/20.

Except for the case of p-NO_2 group, the increments were, however, rather small (few percent). A comparable trend for *para*-substituent electronic effects was also observed in each of the related 6-methoxycarbonyl sets: 2a-k and 3a, c, e, i, as well as in the 6-acetyl analogues: 5a, c, e, and 6a, c, e (Table 2).

In this respect, it is worthnoting that the 4-methyl-1,2,3,4-tetrahydro-*s*-tetrazine (14), prepared from (13)[9] as depicted in Scheme 2, exists

Scheme 2



(13) (14)

exclusively in the cyclic form (100 %). This was evidenced from its ^{1}H-nmr spectrum which showed each of the 1-Me and 4-Me protons as a sharp singlet at 2.6 ppm (3H) and 2.8 ppm (3H), respectively. On the other hand, the 4-phenyl analogue V12a was reported[1] to display, in solution, "ring-chain" tatomerism whereby the concentration of the cyclic tautomer was 80 %. This large difference can be attributed to increased basicity of the methylated 4-nitrogen compared to the 4-phenyl analogue.

C-3 Substituent Effect

The nature of the heteroaryl substituents at 3-carbon was found to exert a profound effect on the "ring-chain" tautomeric ratio. Thus, in compounds V1a-V4a (X=H) the ratio of the cyclic tautomer decreased in the following order :

Table 3. ^{13}C-Chemical Shifts (δ-values, in ppm) for Selected Carbons in Compounds (V1-3)

Compd	N-Me	C=O	-O-Me	C-3	X
1b(A):	43.20	162.04	52.24	66.77	20.53 (-Me)
(B):	37.80	161.79			20.37
1d(A):	43.23	162.08	52.39	67.05	
(B):	37.40	161.72			
1e(A):	43.29	162.14	52.57	66.66	
(B):	37.28	161.67			
1f(A):	43.30	162.16	52.61	66.58	
(B):	37.27	161.67	52.43		
1g(A):	43.32	162.16	52.63	66.44	
(B):	37.27	161.66	52.43		
1h(A):	43.20	162.09	52.85	65.92	119.97 (-CN)
(B):	36.71	161.47	52.69		119.81
1i(A):	43.32	162.25	52.84	66.22	26.23 (C-Me, 196.60)
(B):	36.97	161.55	52.77		26.15
1k(A):	43.29	162.20	52.76	66.25	166.92 (C-OMe) 51.69
(B):	36.29	161.55	52.69		166.86
2b(A):	42.82	162.04	52.47		20.67 (- Me)
(B):	38.48	161.94	52.36		20.52
2c(A):	42.86	162.02	52.47	65.02	55.52 (-OMe)
(B):	38.60	161.94	52.31		55.50

Cont. Table 3

2d(A):	42.85	162.05	52.55	64.69		
(B):	37.83	161.80	52.45			
2e(A):	42.69	161.93	52.40	63.91		
(B):	37.23	161.58	52.27			
2g(A):	42.83	162.08	52.66	63.94		
(B):	37.47	161.69	52.61			
2h(A):	42.56	161.88	52.68	63.13		119.73 (-CN)
(B):	36.35	161.20	52.62			119.42
2k(A):	42.73	162.18	52.66	63.63	166.86 (-C(=O)-)	51.64 (-CMe)
(B):	36.90	161.52	52.62		166.78	51.58
3a(A):	42.95	162.00	52.61	70.62		
(B):	37.45	161.67				

V4a (72%) > V3a (62%) > V2a (52%) > V1a (28%)

This trend was consistently observed for the other sets of the 6-methoxycarbonyl series (1c-3c; 1e-3e; 1j-3j) having identical *p*-substituents of the aryl groups at N-4. Comparable trend also held for the related 6-acetyl (5a-8a) and, to lesser extent for the 6-phenyl analogues (9a-12a) (Table 2). These results can be explained as follows: extended conjugation with the aryl/heteroaryl moiety at C-3 confers a degree of enhanced stability to the acyclic tautomer. As the aromatic character of the C-3 substituent increases, its conjugative ability (with the neighboring C=N π-system in

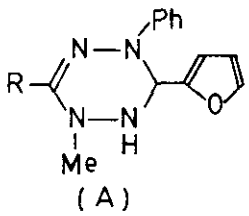
the acyclic tautomer) decreases, leading to a decreased stability of the acyclic tautomer, and hence to a decrease in its ratio. This explains the decreased ratio of the acyclic tautomer in 4a compared to 3a.

Thiophene and furan are less aromatic than either benzene or pyridine. Accordingly, the tetrahydro-*s*-tetrazines (1a and 2a) are expected to have, in solution, a higher concentration of the acyclic tautomer as compared to 3a or 4a. In experiment, this expectation was found to be true. Based on the above arguments, the acyclic concentration of 1a is expected to be less than that of 2a, since thiophene is more aromatic than furan (the latter has more of the diene-like character). However, the opposite was observed experimentally in all parallel sets of 1 and 2 as well as for 5a, 6a and 9a, 10a (Table 2). This latter result indicated the presence of other electronic factors besides conjugation. Possibly a stronger electron-withdrawing effect of the furan moiety compared to thiophene would enhance the electrophilicity of the neighbouring azomethine carbon, and hence leads to increased ratio of the cyclic tautomer (A).

C-6 Substituent Effect

The extent of "ring-chain" tautomeric ratio in 1,2,3,4-tetrahydro-*s*-tetrazines (V: 1-12) was also dependent on the nature of substituents at C-6. It can be seen from the data, shown below for the C-3 furyl set, that the ratio of the cyclic tautomer (A) decreased in the following order:

R :	C_6H_5-	$MeOC(=O)-$	$Me-C(=O)-$
No :	10a	2a	6a
ratio of (A) :	(77%)	(52%)	(37%)



(A)

This trend was also observed for the 3-thienyl (9a, 1a, 5a), 3-pyridyl (11a, 3a, 7a), and the 3-phenyl (12a, 4a, 8a) sets. Comparable results

were also obtained for each of the following pairs whereby the cyclic ratio of the 6-methoxycarbonyl derivative was always higher than that of the corresponding 6-acetyl analogue (Table 2):

(1c > 5c; (1e > 5e); (2c > 6c); (2e > 6e)

These results may be explained on the basis of the electron-withdrawing ability of the R-group at C-6. Apparently, the electron-withdrawing ability of the acetyl or the ester group is greater than that of the phenyl group. This effect is reflected on the basicity of the hydrazone nitrogen (4-nitrogen) which in turn affects the ratio of the cyclic tautomer (A) in the same above order.

EXPERIMENTAL

Melting points were measured on an electrothermal Mel-Temp apparatus and are uncorrected. Ir spectra were recorded as KBr discs on a Perkin Elmer 577 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker WH 250 and AM 400 instruments, for solutions in $CDCl_3$. Electron impact mass spectra were run on a Finnigan MAT 731 and MS 50 spectrometers at 70 eV. Elemental microanalyses were performed at M. H. W. Laboratories, Phoenix, Arizona, U. S. A., and at Butterworth Laboratories Ltd., Middlesex, England.

Preparation of Monomethylhydrazones. The methylhydrazones of thiophene-2-carboxaldehyde,[7] furan-2-carboxaldehyde,[8] and benzaldehyde,[7] were prepared following literature procedure. Pyridine-2-carboxaldehyde methylhydrazone was prepared from pyridine-2-carboxaldehyde and methylhydrazine following the procedure reported for the isomeric pyridin-3-carboxaldehyde methylhydrazone.[7] Yield 68 %; bp 104°C/0.1 mm Hg. Anal. Calcd for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.15; H, 6.68; N, 31.02.

Preparation of the Hydrazonoyl Chlorides (I-III). Methyl 2-arylhydrazono-2-chloroacetates (Ia-j)[2] were prepared as previously reported. Compound (Ik) was likewise prepared by reaction of methyl 2-chloroacetoacetate

with diazotized methyl *p*-aminobenzoate. The product was recrystallized from chloroform/pet. ether (bp 40-60°C). Yield 85 %; mp 193-194°C. Anal. Calcd for $C_{11}H_{11}N_2O_4Cl$: C, 48.81; H, 4.10; N, 10.35. Found: C, 48.90; H, 4.03; N, 10.32.

1-Arylhydrazono-1-chloroacetones (II) were similarly prepared via direct diazo-coupling reaction between 3-chloro-2,4-pentanedione and the particular arenediazonium chloride. The physical properties of (IIa),[3,4] (IIb),[3] (IIc),[3,5] and (IIe),[3] employed in this study, are in agreement with the reported data. *N*-phenylbenzenecarbohydrazonoyl chloride (IIIa) was prepared according to literature procedure.[6]

Preparation of *N*-Methylbenzenecarbohydrazonoyl Bromide Hydrobromide (13). To a stirred and cooled solution (8°C) of benzaldehyde methylhydrazone (100 mmol) in glacial acetic acid (45 ml) was added bromine (100 mmol) in glacial acetic acid (40 ml) during 1 h. The reaction mixture was then allowed to warm up to room temperature. Stirring was continued for 1-2 h and the resulting yellow precipitate was filtered, triturated with acetic acid (10 ml) and acetonitrile (5 ml), and recrystallized from acetonitrile. The title product was obtained as colourless needles. Yield 60 %; mp 142-143°C (Lit.[9] mp 141-143°C).

Preparation of Compounds V (1-12). Triethylamine (100 mmol) was added to a stirred solution of the appropriate *N*-arylhydrazonoyl chloride (20 mmol) and the partner methylhydrazone (22 mmol) in tetrahydrofuran (80 ml). The resulting reaction mixture was set aside at ambient temperature for 1-2 days and worked up. The precipitated triethylammonium chloride was filtered off, and the organic solvent was removed from the filtrate under reduced pressure; the solid residue (or oily/gummy product in few cases) was then triturated with ethanol, collected, and recrystallized from the appropriate solvent.

Alternatively, the above reaction was conducted at the refluxing temperature, and was completed within 1-2 h. In either case, comparable yields of the title compounds were obtained.

Preparation of 1,4-Dimethyl-3,6-diphenyl-1,2,3,4-tetrahydro-s-tetrazine (14). To a stirred, ice-cooled solution of benzaldehyde methylhydrazone (20 mmol) and triethylamine (60 mmol) in chloroform (40 ml) was dropwise added a solution of N-methyl-benzenecarbohydrazonoyl chloride (20 mmol) in chloroform (20 ml). The resulting solution was then allowed to warm up slowly to room temperature (1-2 h); stirring was continued for 5-8 h. The reaction mixture was then washed with water (40 ml), the organic layer was separated, dried ($MgSO_4$), and chloroform was removed in vacuo. The residue (product 14) was then recrystallized from acetonitrile. Yield 55 %; mp 112-113°C. Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.01; H, 6.77; N, 21.02.

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