HETEROCYCLES FROM NITRILE IMINES. PART II[1]. SYNTHESIS AND RING-CHAIN TAUTOMERISM OF 1,2,3,4-TETRAHYDRO-*s*-TETRAZINES

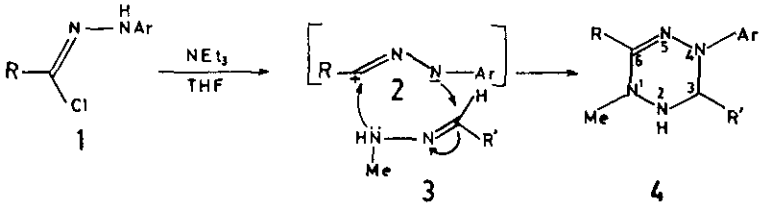
Ahmad Q. Hussein*, Mustafa M. El-Abadelah, and
Khalid Al-Adhami
Chemistry Department, University of Jordan, Amman, Jordan

Ahmad S. Abushamleh
Natural Sciences Department, Mutah University, Karak, Jordan

Abstract—Alkanal methylhydrazones react with nitrile imines to give 1,2,3,4-tetrahydro-*s*-tetrazines. Tetrazines obtained from the reaction of nitrile imines with methylhydrazones of aromatic aldehydes and ketones exhibit ring-chain tautomerism in solution. The extent of such tautomerism is influenced both by steric and electronic effects of substituents.

Recently[1], we reported on the synthesis of 1,2,3,4-tetrahydro-*s*-tetrazines by direct interaction between nitrile imines 2 and aliphatic ketone methylhydrazones. Our desire to explore the scope and potential of this new synthetic route led us to pursue the reaction of 2 with methylhydrazones of aldehydes and aromatic ketones. Alkanal methylhydrazones 3 are found to add readily onto 2, generated *in situ* from the respective hydrazonoyl chlorides 1, giving the corresponding tetrahydro-*s*-tetrazines 4 (Scheme 1) in good yields.

Scheme 1



The assignment of structure 4 to these compounds is based on elemental analysis (Table 1) and spectral data. Their ir spectra revealed an N-H absorption in the range 3260-3280 cm^{-1} and C=N bond stretching at *ca.*1620 cm^{-1}. The ^1H-nmr spectra (Table 2) of these compounds exhibited a sharp singlet at about 3.0-3.3 ppm (3H), assigned to the N-methyl protons. The C-3 proton signal shows splitting patterns that indicate coupling with the vicinal N-2 (J=3 Hz) and R'-protons(J=7-9 Hz); upon addition of D_2O, this pattern is reduced to a quartet (4a-c), triplet (4d,e), or a doublet (4f-k). The diastereotopic methyls of the isopropyl group at C-3 in compounds 4f-k appear as two doublets, centered at ca. 0.92 and 1.18 ppm. The ^{13}C-nmr spectra of 4a-k exhibit, besides other expected signals, two signals in the range 136-142 and 69-74 ppm, ascribed respectively to C-6 and C-3. The latter signal shows up as a doublet in the off-resonance spectra. These assignments[1,2] confirm the tetrazine structure for these compounds. Their mass spectra display peaks corresponding to the correct molecular ions, and fragment ions that confirm structure 4[1].

In contrast to these findings, Grashey *et al.*[3] assumed the acyclic structure 6a(B) for the reaction product obtained from 1 (R = Ar = C_6H_5) and benzaldehyde methylhydrazone. On the other hand, Ehrhardt *et al.*[4] mentioned that tetrahydrotetrazines were formed only as by-products from the reaction of benzaldehyde alkylhydrazones with 1 (R = CO_2Me); the major products being the acyclic adducts. This controversy prompted us to further investigate the reaction of 2 with methylhydrazones (5) of aromatic aldehydes and ketones.

Herein, the latter reaction is found to yield the expected tetrahydro-*s*-tetrazines 6(A), that in solution coexist in equilibrium with the acyclic tautomers 6(B) (Scheme 2, Table 1). This is evidenced from their nmr spectra which reveal signal doubling indicative of "ring-chain" tautomerism (A⇌B). Thus, the ^1H-nmr spectra of 6a-e show the protons at N-2 and C-3 each as a doublet at 4.4 and 5.8 ppm, respectively. The former doublet disappears upon addition of D_2O, while the latter collapses to a singlet. This confirms the presence of the cyclic tautomer 6(A), which is further characterised by a ^{13}C-nmr signal appearing at *ca.* 70 ppm, characteristic of the C-3 ring carbon[1]. In addition, the ^1H-nmr spectra show another exchangeable singlet at 9-11 ppm, assigned to the N-H of the acyclic tautomer 6B. Signal doubling is likewise observed for the remaining protons; in particular the N-1 methyl protons give rise to two singlets of unequal intensities at *ca.* 2.3-2.6

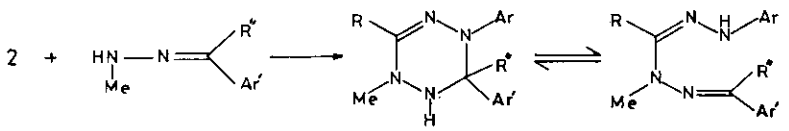
Table 1. Yields and Physical Data of Compounds 4 and 6.

Compd	R	R′/Ar′	R″	Ar	Yield (%)[a]	mp (°C)	Calcd / Found C	H	N
4a	CO_2Me	Me	–	p-NO_2-C_6H_4	68	192–194	49.14 48.98	5.15 5.14	23.88 23.94
4b	Ac	Me	–	p-Cl-C_6H_4	70	102–103	54.04 53.80	5.67 5.74	21.00 21.28
4c	p-Cl-C_6H_4	Me	–	C_6H_5	67	156–158	63.89 63.90	5.70 5.60	18.60 18.25
4d	CO_2Me	Et	–	p-Br-C_6H_4	65	131–133	45.76 46.02	5.02 5.15	16.42 16.34
4e	Ac	Et	–	p-Cl-C_6H_4	72	111–113	55.62 55.41	6.10 6.18	19.96 20.12
4f	p-NO_2-C_6H_4	i-Pr	–	C_6H_5	77	157–159	63.70 63.65	6.24 6.17	20.63 20.55
4g	CO_2Me	i-Pr	–	p-Ac-C_6H_4	60	164–166	60.36 60.29	6.96 7.17	17.60 17.35
4h	CO_2Me	i-Pr	–	p-CN-C_6H_4	63	119–120	59.79 59.72	6.35 6.49	23.24 23.14
4i	CO_2Me	i-Pr	–	p-I-C_6H_4	68	101–102	41.81 41.87	4.76 4.75	13.93 13.74
4j	CO_2Me	i-Pr	–	p-NO_2-C_6H_4	70	139–140	52.33 52.20	5.96 5.98	21.79 21.70
4k	Ac	i-Pr	–	p-Cl-C_6H_4	75	140–142	57.04 57.19	6.50 6.72	19.01 19.26
6a	C_6H_5	C_6H_5	H	C_6H_5	72	125–126	76.80 76.92	6.14 6.24	17.06 17.15
6b	Ac	C_6H_5	H	p-Cl-C_6H_4	78	150–152	62.10 61.80	5.21 5.32	17.04 17.04
6c	CO_2Me	p-Cl-C_6H_4	H	p-Br-C_6H_4	75	137–138	48.19 48.36	3.81 3.77	13.22 12.97
6d	CO_2Me	p-Cl-C_6H_4	H	p-MeO-C_6H_4	76	135–136	57.68 57.70	5.11 5.11	14.95 14.95
6e	p-Cl-C_6H_4	p-Cl-C_6H_4	H	C_6H_5	70	146–147	63.49 63.54	4.57 4.55	14.10 14.12
6f	Ac	C_6H_5	Me	p-Cl-C_6H_4	76	118–119	63.06 62.87	5.59 5.42	16.34 16.18
6g	CO_2Me	2,2′-C_6H_4.C_6H_4		p-Me-C_6H_4	74	127–129	72.34 72.19	5.56 5.67	14.06 14.08
6h	CO_2Me	2,2′-C_6H_4.C_6H_4		C_6H_5	78	116–117	71.86 71.58	5.24 5.42	14.57 14.30

[a]Yields refer to crystallized products.

and 3.2-3.4 ppm, belonging to the cyclic 6(A) and acyclic 6(B) tautomers, respectively (Table 2). A similar trend is observed in the ^{13}C-nmr spectra of compounds 6; the N-1 methyl, for example, appears at ca. 37 (tautomeric form A) and 43 ppm (form B). The ring-chain tautomeric ratio in these compounds, inferred from the relative intensities of the respective ^{1}H-nmr signals at 35°C, ranges from 20:80% in compound 6a, up to about 60:40% in 6h.

Scheme 2



5 (A) 6 (B)

Compounds 6 are colorless to pale yellow crystalline compounds, give sharp melting points, and show single spots upon tlc examination using different eluents and adsorbents. Neither of their physical characteristics nor the ^{1}H-nmr spectra were altered upon repeated crystallizations from various solvents. In solution, these compounds acquire intense yellow coloration[5].

Evidently, these compounds exist in one form in the solid phase, whereas both cyclic and acyclic tautomers equilibrate in solution. Apparently, the acyclic tautomers B gain stabilization through extended conjugation of the aryl moiety at C-3 with the neighbouring C=N bond, absent in the cyclic tautomers A. Introduction of an additional aryl group at C-3, such as in compounds 6g and 6h (derived from fluorenone), enhances such conjugation and, therefore, shifts the equilibrium more in favour of the acyclic tautomers. Ring-chain tautomerism is documented for related heterocycles[6].

Acylating agents, such as ethyl chloroformate and acetyl chloride, selectively react with the cyclic tautomer at N-2, and thereby shift the equilibrium towards this tautomer, leading eventually to the consumption of the acyclic form . As a model compound, 6a gave high yields of the 2-acyl derivatives 7a and 7b (Scheme 3), neither of which exhibits ring-chain tautomerism in solution, as shown in their ^{1}H-nmr as well as ^{13}C-nmr spectra (experimental part). Deacylation of 7b, by mild hydrolysis, regenerated the parent tetrahydrotetrazine 6a, which, according to ^{1}H-nmr and ^{13}C-nmr spectra, coexists in equilibrium with the acyclic tautomer, in a

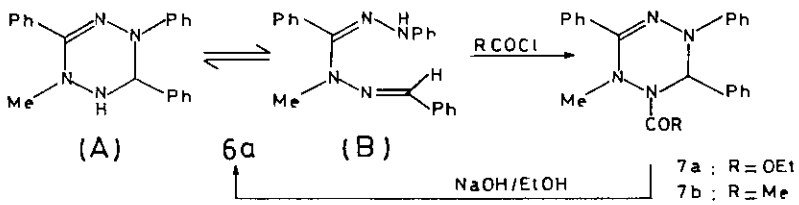
Table 2. ^{1}H-Nmr Data (ppm, in $CDCl_3$) of Compounds 4 and 6.

Compd	Me in R	(R')[a]	(C^3-H / R*)[b]	N-Me	(N-H)[c]	% Tautomer ratio
4a[d]	3.83	1.37 (3H, d)	5.32 (dq)	3.19	5.95 (d)	–
4b	2.42	1.38 (3H, d)	4.95 (dq)	3.24	4.26 (d)	–
4c	–	1.40 (3H, d)	4.83 (dq)	2.96	4.33 (d)	–
4d	3.76	1.05 (3H, t) 1.60 (2H, dq)	4.63 (dt)	3.17	4.22 (d)	–
4e	2.39	1.08 (3H, t) 1.62 (2H, dq)	4.64 (dt)	3.20	4.12 (d)	–
4f	–	1.03 (3H, d) 1.12 (3H, d) 2.15 (1H, m)	4.50 (dd)	3.02	4.04 (d)	–
4g	3.86	0.92 (3H, d) 1.20 (3H, d) 2.00 (1H, m)	4.67 (dd)	3.26	4.34 (d)	–
4h	3.86	0.92 (3H, d) 1.18 (3H, d) 2.00 (1H, m)	4.65 (dd)	3.26	4.24 (d)	–
4i	3.80	0.92 (3H, d) 1.15 (3H, d) 2.00 (1H, m)	4.47 (dd)	3.18	3.93 (d)	–
4j	3.83	0.92 (3H, d) 1.15 (3H, d) 2.00 (1H, m)	4.68 (dd)	3.24	4.40 (d)	–
4k	2.43	0.92 (3H, d) 1.15 (3H, d) 2.00 (1H, m)	4.58 (dd)	3.26	4.00 (d)	–
6a(A):	–	–	5.88 (d)	2.36	4.48 (d)	80
(B):				3.23	9.16 (s)	20
6b(A):	2.43	–	5.87 (d)	2.58	4.42 (d)	60
(B):	2.48			3.25	10.20 (s)	40
6c(A):	3.83	–	5.87 (d)	2.63	4.43 (d)	67
(B):	3.83			3.30	9.50 (s)	33
6d(A):	3.83	–	5.82 (d)	2.60	4.32 (d)	72
(B):	3.83			3.30	9.12 (s)	28
6e(A):	–	–	5.82 (d)	2.40	4.47 (d)	80
(B):				3.23	8.80 (s)	20
6f(A):	2.42	–	1.80 (s)	2.68	3.97 (s)	56
(B):	2.47		1.97 (s)	3.22	9.90 (s)	44
6g(A):	3.83	–	6.55-7.75[e]	3.17	4.72 (s)	45
(B):	3.90		(m)	3.36	9.77 (s)	55
6h(A):	3.83	–	6.68-7.92[e]	3.17	4.90 (s)	40
(B):	3.92		(m)	3.36	10.00 (s)	60

[a] J=7 Hz. [b] J for C^3-H with the exocyclic C-H in R is 7 Hz in 4a-e, 6a-e and 9 Hz in 4f-k. [c] J=3 Hz. [d] Measured in DMSO-d_6. [e] Overlapped with Ar signal in both tautomers.

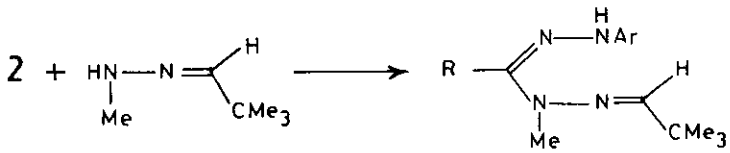
ratio exactly matching that prior to acylation. This could be considered as a chemical evidence in support of the *hitherto* undescribed ring-chain tautomerism in 1,2,3,4-tetrahydro-*s*-tetrazines.

Scheme 3



As indicated by ^{1}H-nmr and ^{13}C-nmr, products 9, obtained from 2 and pivalaldehyde methylhydrazone 8, exist exclusively in the acyclic form (Scheme 4). This is presumably due to excessive steric hindrance caused by the bulky *tert*-butyl group at the azomethine terminus, a factor which disfavours intracyclization thereon.

Scheme 4



8 9

9a : R = p−NO_2-C_6H_4 ; Ar = C_6H_5

9b : R = MeOCO ; Ar = C_6H_5

9c : R = MeCO ; Ar = p−Cl-C_6H_4

EXPERIMENTAL

Melting points (uncorrected) were determined on a Mel-Temp apparatus. Ir spectra (KBr pellets) were obtained on a Perkin Elmer 577 Spectrophotometer. Nmr spectra (in $CDCl_3$) were recorded on a Bruker WM-250, with tetramethylsilane as internal standard. Mass spectra were run on a Finnigan MAT 112 at 70 eV. Microanalyses were performed at Butterworth Laboratories, Midelsex, England. All chemicals and solvents were of commercial grade. Methylhydrazones[7] and hydrazonoyl chlorides[1,8] were prepared according to known procedures.

Preparation of Compounds 4,6 and 9. To a solution of the appropriate hydrazonoyl chloride (0.01 mol) in tetrahydrofuran (20 ml) was added a solution of the methylhydrazone (0.01 mol) and triethylamine (0.03 mol) in tetrahydrofuran (30 ml). The

mixture was stirred for 24-30 h at room temperature. The white precipitate of triethylammonium chloride was filtered off, and the solvent was evaporated in vacuo. The residue was washed with water, and, if oily, triturated with little ethanol (10-15 ml). The insoluble solid was collected and recrystallized from ethanol. Compound 9a: Yield 82%. mp 121-122° C. ^{1}H-Nmr($CDCl_3$): 1.18 (9H, s), 3.10 (3H, s), 6.67 (1H, s), 9.50 (N-H, br s) ppm. Calcd: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.61; H, 6.69; N, 19.97.

Compound 9b: Yield 77%. mp 83-84° C. ^{1}H-Nmr ($CDCl_3$): 1.14 (9H, s), 3.10 (3H, s), 3.80 (Me-N, s), 6.62 (1H, s), 10.70 (N-H, s) ppm. Calcd: C, 62.05; H, 7.64; N, 19.30. Found: C, 61.88; H, 7.54; N, 19.58.

Compound 9c: Yield 85%. mp 115-117° C. ^{1}H-Nmr($CDCl_3$): 1.14 (9H, s), 2.46 (Me-CO, s), 3.10 (3H, s), 6.60 (1H, s), 10.50 (N-H, brs) ppm. Calcd: C, 58.34; H, 6.85; N, 18.14. Found: C, 58.36; H, 7.08; N, 18.22.

Preparation of Compound 7a.

Ethyl chloroformate (6 mmol) in dry tetrahydrofuran (10 ml) was added dropwise to an ice-cold mixture of compound 6a (5 mmol) and triethylamine (10 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 0.5 h at 0° C, and then allowed to stand for 2 h at room temperature. The solvent was evaporated, and the solid residue was washed with water, dried and recrystallized from ethanol. Yield, 88%. mp 153-154° C. Calcd: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.86; H, 6.14; N, 13.80. Ir(KBr): 1715 cm^{-1} (C=O). ^{1}H-Nmr($CDCl_3$): 2.23 (Me-N, s), 1.27 (3H, t, J=7 Hz), 4.18 (2H, q, J=7 Hz) ppm.

Preparation of Compound 7b.

This compound was prepared from 6a and acetyl chloride as described for compound 7a. Yield 75%. mp 150-152° C. Calcd: C, 74.54; H, 5.99; N, 15.12. Found: C, 74.36; H, 6.16; N, 14.89. Ir(KBr): 1672 cm^{-1} (C=O). ^{1}H-Nmr($CDCl_3$): 2.33 (3H, s), 2.38 (3H, s), 7.68 (^{3}C-H, s) ppm. ^{13}C-Nmr($CDCl_3$): 63.1 (C-3 ring carbon; doublet in the off-resonance spectrum), 172.5 (C=O) ppm.

Hydrolysis of Compound 7b.

To a solution of 7b (0.5 g) in ethanol (30 ml) was added 10% aqueous sodium hydroxide (10 ml). The reaction mixture was then refluxed for 5 minutes and then cooled in ice. The resulting precipitate was collected, dried and recrystallized from ethanol. The product was identical (mp, mixture mp, ir, and ^{1}H-nmr) with compound 6a. Yield 70%.

ACKNOWLEDGEMENTS

The authors wish to thank Mutah University, Karak, Jordan, for financial support.

REFERENCES

1. M. M. El-Abadelah, A. Q. Hussein, M. R. Kamal, and K. H. Al-Adhami, Heterocycles, 1988, 27, 917.
2. A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, J. Chem. Soc., Perkin Trans. I, 1979, 143; A. Counotte-Potman, H. C. van der Plas, and B. van Veldhuizen, J. Org. Chem., 1981, 46, 3805; J. Plenkiewicz and T. Zdrojewski, Pol. J. Chem., 1981, 55, 1411; E. Breitmaier and W. Voelter, 'Carbon-13 NMR Spectroscopy', Verlag Chemie, Weinheim, 1978, p. 196.
3. R. Grashey, M. Baumann, and H. Bauer, Chem. Ztg., 1972, 96, 224.
4. H. Ehrhardt, G. Heubach, and H. Mildenberger, Liebigs Ann. Chem., 1982,994.
5. Coloration which develops upon dissolution of these compounds is obviously due to the highly conjugated acyclic tautomer, which equilibrates with the cyclic tautomer in solution. This tautomer is presumably absent in the solid phase.
6. R. E. Valter, Russ. Chem. Rev. (Engl. Transl.), 1974, 43, 665; J. E. Whiting and J. T. Edward, Can. J. Chem., 1971, 49, 3799; K. Vaughan, R. L. LaFrance, and Y. Tang, Can. J. Chem., 1985, 63, 2455.
7. G. J. Karabatsos and R. A. Taller, Tetrahedron, 1968, 24, 3557; R. H. Weiley and G. Irick, J. Org. Chem., 1959, 24, 1925; W. Sucrow, C. Mentzel, and M. Slopianka, Chem. Ber., 1973, 106, 450.
8. N. F. Eweiss and A. Osman, J. Heterocycl. Chem., 1980, 17, 1713, and refs. therein.

Received, January 20th, 1989