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1-Substituted 1,4,5,6-Tetrahydropyridazines and 1-(N-Substituted)-aminopyrrolidines from Hydrazines and 2,5-Dimethoxytetrahydrofuran

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Abstract: N-Substituted 1,4,5,6-tetrahydropyridazines (3) can be prepared in a one pot procedure from a hydrazine 1 and 2,5-dimethoxytetrahydrofuran (2) using $NaBH_4$ in aqueous-THF acidic medium in fair yields. Variable amounts of two side products are also formed: hexahydropyridazines 5, likely produced by a route other than the direct reduction of 3, and 1-aminopyrrolidines 4. A direct reduction-N-reductive ethylation of 3 could be achieved in AcOH with $NaBH_4$.

Although the parent system 1,4,5,6-tetrahydropyridazine and its either C- or N,N'- or C,N- alkyl or aryl substituted derivatives have been described in many instances, perusal of the literature revealed that simple N-monosubstituted 3 were not described. A classical approach to the pyridazine ring is the 4+2 atom fragment procedure employing 1,4-dicarbonyl compounds and hydrazines.[1]

RESULTS AND DISCUSSION

The commercial availability of a masked succinaldehyde, namely 2,5-dimethoxytetrahydrofuran (2), prompted us to use it in combination with monosubstituted hydrazines (1) in the synthetic approach we have previously used for the reductive alkylation of amines.[2]

The results are summarised in Tables 1, 2 and 3. The yields of 3 are rather poor and these products are always accompanied by variable amounts of polycondensation products from which they can be easily separated by a combination of conventional methods and, eventually, the treatment of a mixture containing the fully saturated products 1-pyrrolidinamines 4 and hexahydropyridazines 5 with copper(II) acetate or simple extraction with diluted mineral acid.

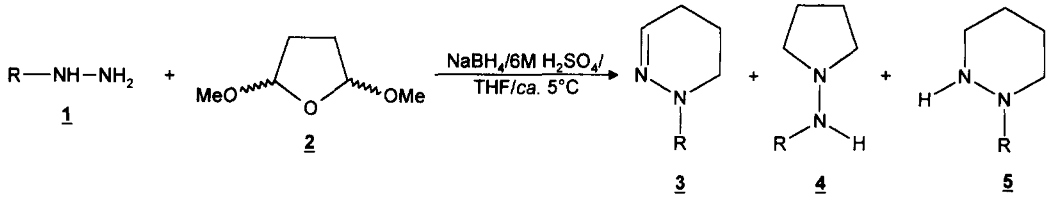
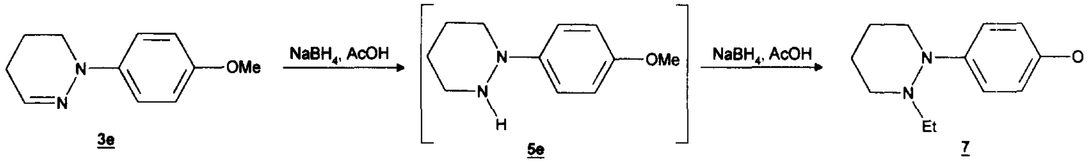


Table 1. Products from the reaction between hydrazines (1) and 2,5-dimethoxytetrahydrofuran (2).

R	1	3[a]	4[a]	5[a]
Ph	a	72	4	24
2-MeC_6H_4	b	79	8	19
3-MeC_6H_4	c	85	2	13
4-MeC_6H_4	d	93	1	6
4-$MeOC_6H_4$	e	100	0	0
2-ClC_6H_4	f	40	56	4
3-ClC_6H_4	g	88	10	2
4-ClC_6H_4	h	82	8	10
2-$NO_2C_6H_4$	i	0	100	0
3-$NO_2C_6H_4$	j	50	45	5
4-$NO_2C_6H_4$	k	20	80	0
$PhCH_2$	l	100	0	0

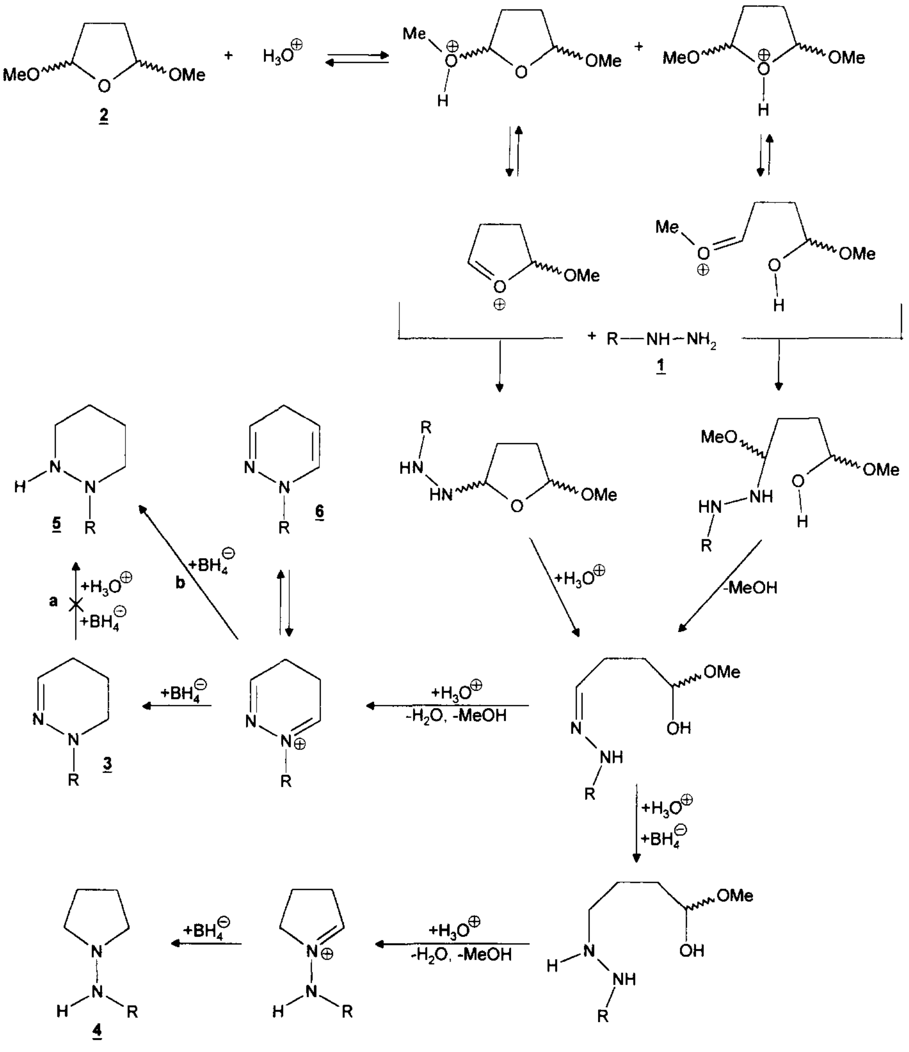
[a] GC concentration in whole mixtures expressed as % of total ion current from GC-MS peaks.

The higher basicity of 4 and 5 resulted in their preferential protonation and, therefore, extraction into the aqueous phase, whereas the tetrahydroderivatives 3 were kept in the organic solvent used. Washing with aqueous copper(II) ions also caused the disappearance of 4 and 5 from the organic phase. In most instances excess $NaBH_4$ did not cause the formation of 5 to be increased, perhaps because it was not product 3 which underwent reduction (route **a**, Scheme 1), but the process deviated somewhere under way to 5 (e.g., route **b**, Scheme 1). This rationale is consistent with the observation that separated 3 under the reaction conditions employed for its synthesis resisted further reduction to 5. Even the action of $LiAlH_4$ in refluxing THF on 1-(3-chlorophenyl)-1,4,5,6-tetrahydropyridazine (3g) was not able to lead to 5g. However, when $NaBH_4$ was used in acetic acid on 1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (3e) a surprising, but not fully unprecedented,[3] reduction plus reductive N-al-kylation took place quantitatively.

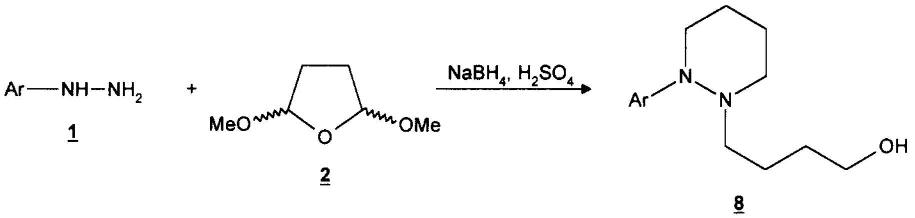


It is likely that a different borohydride species formed in solution[4] is the effective reductant of **3e** to **5e** which subsequently underwent the known reductive N-alkylation to 1-(4-methoxyphenyl)-2-ethylhexahydropyridazine (**7**) by the combined action of acetaldehyde and $NaBH_4$.

Scheme 1



It is to be noted that yields in 3 and 4 were drastically reduced when the synthetic procedure was changed, i.e., 2 was added to a solution of a hydrazine, while NaBH$_4$ pellets were being added. Then, a new product, namely 1-aryl-2-(4-hydroxybutyl)hexahydropyridazine (8), was formed in low yield from further reductive alkylation of 5, as shown by GC-MS.



In most instances, as shown above, variable amounts of the saturated heterocycle 4 and/or 5 were produced; in fact with 2-nitrophenylhydrazine (1i) 4i was the sole monomeric outcome of the reaction, as shown by GC-MS analysis. The acid-base separation of 3 (see above) allowed us to obtain mixtures enriched in compounds 4, which were obtained as homogeneous materials and fully characterised in three instances (4f, 4j, 4k) by repetitive acid-base extraction followed by absorption chromatography. Low yields of compounds having the general structure 4 were obtained by the reaction of benzofuroxan and pyrrolidine.[5]

It may be noticed that the five membered heterocycles 4 were the prevalent products in the cases where either σ or π-electron withdrawing ring substituents could make their effect felt (2-Cl, 2-NO$_2$, 4-NO$_2$). Electron releasing substituents, on the other hand, caused the six membered products 3 to be formed preferentially. Benzylhydrazine (1l) yielded only the monounsaturated cyclic compound 3l. These results can be rationalised in view of the lowered nucleophilicity of the nitrogen bearing the phenyl group with EW substituents.

Each reaction mixture was made basic (pH = 8/9) with sodium hydroxide and extracted with Et$_2$O: a preliminary quantitative GC-MS analysis, whose results are summarised in Table 1, allowed us to establish the presence of 3, 4 and 5. The structure of 4 was arrived at by the study of their ^{1}H-decoupled ^{13}C NMR spectra, exhibiting only two aliphatic carbon resonances at *ca.* 22.0 and 55.5 ppm in the products 4f, i, j and k, which were obtained as homogeneous separated materials. Their ^{1}H NMR spectra consistently showed a much broadened peak devoid of any fine structure for the protons of the methylenes linked to the nitrogen atom, which constituted one of the two sets of carbon bonded aliphatic protons at *ca.* 3.0 ppm. On the other hand, in the six member N,N'-disubstituted hexahydropyridazines 7 the sets of ring protons are three neatly separated multiplets, respectively centred for the EtNCH$_2$ at *ca.* 3.0 ppm, in the close neighbourhood of the methylene of the ethyl group, for the other N-methylene group at 3.4 ppm and for the remaining aliphatic protons at 1.7 ppm. The two equivalent methylene group not attached to the nitrogen atoms of the aliphatic ring in 4 showed up at 1.8-1.9 ppm. The NH group usually exhibiting the H-resonance as a relatively sharp peak in the range 4.6-5.1 ppm with the notable exception of the 2-NO_2 derivative **4i** (8.4 ppm). Of course, the IR spectra of compounds **4** also gave a clearcut evidence for the presence of the NH group with a strong absorption at 3290-3330 cm^{-1}. The 1,4,5,6-tetrahydropyridazines **3** obtained were characterised by ^1H NMR spectra with a complex pattern centred around 3.1-3.7 ppm for the methylene group adjacent to one of the nitrogen atoms; the methine hydrogen showed up at 6.7-6.8 ppm with a pattern often resembling that of a triplet of triplets. The other two pairs of methylene protons were usually separated in the ^1H NMR spectra, where they appeared in the range 1.8-2.3 ppm. The NH absorption was completely absent in all the derivatives **3** consistent with the absence of isomers. It was not possible to associate any C=N absorption with the observed characteristics of the infrared spectra of **3**.

The isolated 1,4,5,6-tetrahydropyridazines **3a-h**, **j**, **k** exhibited mass spectra (electron impact, 70 eV) with intense parent ions, often accompanied by the ion at one less unit. Very typically, there was a cascade of ions formed by different losses of fragments containing carbon and hydrogen atoms from the parent ion and the peak for the formal N-methylene imine ions **9** (Scheme 2).

Scheme 2

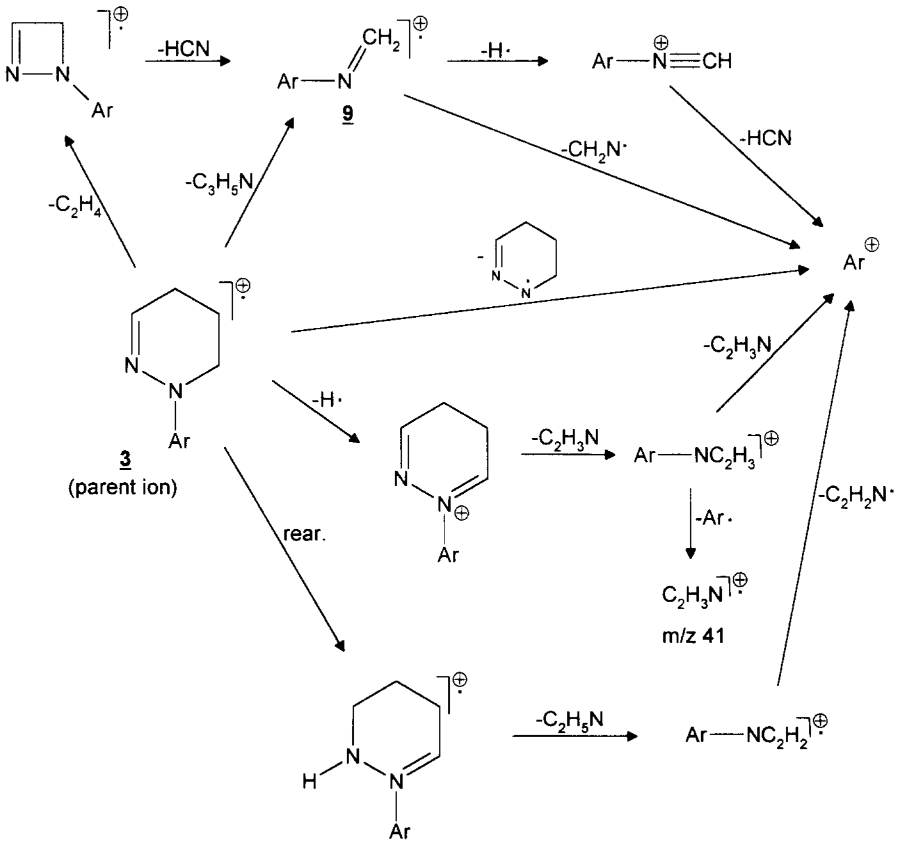


Table 2. Yields and some properties of the products of the reactions between hydrazines (**1**) and 2,5-dimethoxytetrahydrofuran (**2**).

$RNHNH_2$	Reaction products	Separated yield (%)	mp[a](°C) or bp[a](°C)/Pa	Formula	Elemental analysis
1a	**3a**	30	90/40	$C_{10}H_{12}N_2$	Calcd: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.90; H, 7.60; N, 17.41
1b	**3b**	32	70/30	$C_{11}H_{14}N_2$	Calcd: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.78; H, 8.10; N, 16.12
1c	**3c**	40	100/35	$C_{11}H_{14}N_2$	Calcd: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.80; H, 8.15; N, 16.00
1d	**3d**	33	111/45	$C_{11}H_{14}N_2$	Calcd: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.88; H, 8.01; N, 15.98
1e	**3e**	24	77[c]	$C_{11}H_{14}N_2O$	Calcd: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.40; H, 7.50; N, 14.65
1f	**3f**	30	87/40	$C_{10}H_{11}N_2Cl$	Calcd: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.63; H, 5.73; N, 14.32
	4f	40	90/40	$C_{10}H_{13}N_2Cl$	Calcd: C, 61.07; H, 6.66; N, 14.24. Found: C, 61.00; H, 6.58; N, 14.30
1g	**3g**	44	105/40	$C_{10}H_{11}N_2Cl$	Calcd: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.63; H, 5.74; N, 14.33
1h	**3h**	14	63[b]	$C_{10}H_{11}N_2Cl$	Calcd: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.74; H, 5.70; N, 14.31
1i	**4i**	35	30[b]	$C_{10}H_{13}N_3O_2$	Calcd: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.90; H, 6.36; N, 20.32
1j	**3j**	38	dec.[c]	$C_{10}H_{11}N_3O_2$	Calcd: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.50; H, 5.43; N, 20.50
	4j	24	97[c]	$C_{10}H_{13}N_3O_2$	Calcd: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.83; H, 6.40; N, 20.28
1k	**3k**	10	173[c]	$C_{10}H_{11}N_3O_2$	Calcd: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.56; H, 5.40; N, 20.51
	4k	40	122[c]	$C_{10}H_{13}N_3O_2$	Calcd: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.01; H, 6.41; N, 20.20

[a] Uncorrected. [b] Crystallizated from EtOH. [c] Thermal instability of the product prevented its distillation.

Table 3. Infrared, ^{1}H and ^{13}C NMR spectra and electron impact mass spectra of 1,4,5,6-tetrahydropyridazines (3) and 1-aminopyrrolidines (4).

Product	IR (KBr or neat) ν (cm^{-1})	^{1}H NMR (CDCl$_3$/TMS) δ, *J* (Hz)	^{13}C NMR (CDCl$_3$) δ	MS (70 eV) m/z (%)
3a	3059w, 2936m, 2850m, 1598vs, 1578s, 1499vs, 1457m, 1377m, 1330s, 1315m, 1255s, 1136s, 934s, 751s, 692s	1.85-2.00(m, 2H, CH$_2$), 2.05-2.15(m, 2H, CH$_2$), 3.43-3.57(m, 2H, CH$_2$-N), 6.70(t, 1H, CH=N, *J*=3.0), 6.50-7.00 (m, 1H, H$_{arom}$), 7.05-7.30(m, 4H, H$_{arom}$)	17.93, 22.42, 42.92, 113.31, 114.37, 119.35, 128.59, 136.08	160(M$^+$, 90), 159(24), 132(8), 118(9), 117 (13), 106(15), 105(40), 104(34), 91 (15), 78(16), 77(100), 65(7), 64(6), 56(8), 55(9), 51(35), 39(15)
3b	3020m, 2953m, 2832m, 1599s, 1580m, 1491vs, 1455vs, 1310s, 1245s, 1123m, 1101s, 1018s, 927s, 760vs, 721s	1.90-2.05(m, 2H, CH$_2$), 2.05-2.15(m, 2H, CH$_2$), 2.28(s, 3H, CH$_3$), 3.10-3.18(m, 2H, CH$_2$-N), 6.76 (t, 1H, CH=N, *J*=2.7), 6.95-7.05(m, 1H, H$_{arom}$), 7.05-7.17(m, 3H, H$_{arom}$)	17.86, 19.51, 22.53, 47.90, 121.46, 123.90, 126.00, 130.49, 131.13, 138.27, 148.75	174(M$^+$, 94), 173(18), 146(15), 131(34), 130 (77), 119(24), 118(100), 117(23), 106(20), 104(15), 91(92), 77(17), 65(60), 56 (19), 51(19), 41(16) 39(33)
3c	3026m, 2938m, 2921m, 2880w, 2862w, 2836w, 1601vs, 1582vs, 1492vs, 1448s, 1428m, 1376s, 1328vs, 1259s, 1231m, 1182m, 1136s, 1064m, 1037m, 992s, 953vs, 877m, 805m, 773s, 744m, 692s	1.95-2.05(m, 2H, CH$_2$), 2.15-2.25(m, 2H, CH$_2$), 2.35(s, 3H, CH$_3$), 3.49-3.58(m, 2H, CH$_2$-N), 6.64-6.72(m, 1H, H$_{arom}$), 6.74(*app* t, 1H, CH=N, *J*=2.9), 6.87-6.96(m, 1H, H$_{arom}$), 7.01-7.07(m, 1H, H$_{arom}$), 7.10-7.20 (m, 1H, H$_{arom}$)	18.16, 21.64, 22.63, 43.22, 110.50, 114.39, 120.48, 128.58, 136.03, 138.48, 147.83	174(M$^+$, 99), 173(23), 132(10), 131(18), 119(22), 118(26), 91(100), 87(8), 77(8), 65(32), 41(8), 39(17)
3d	3027w, 2938m, 2921m, 2860w, 2836w, 1617m, 1514vs, 1459m, 1376m, 1321s, 1256s, 1140s, 1021m, 935s, 809m	1.87-2.05(m, 2H, CH$_2$), 2.10-2.20(m, 2H, CH$_2$), 2.26(s, 3H, CH$_3$), 3.43-3.53(m, 2H, CH$_2$-N), 6.71(tt, 1H, CH=N, J_1=2.9, J_2=0.6), 7.05(*app* s, 4H, H$_{arom}$)	18.19, 20.27, 22.54, 43.40, 113.66, 128.73, 129.23, 135.74, 145.79	174(M$^+$, 90), 173(26), 146(21), 132 (28), 131(55), 120(40), 119(45), 118(63), 106(25), 105(24), 91(100), 77 (24), 65(72), 63(20), 51(25), 41(26), 39(47)

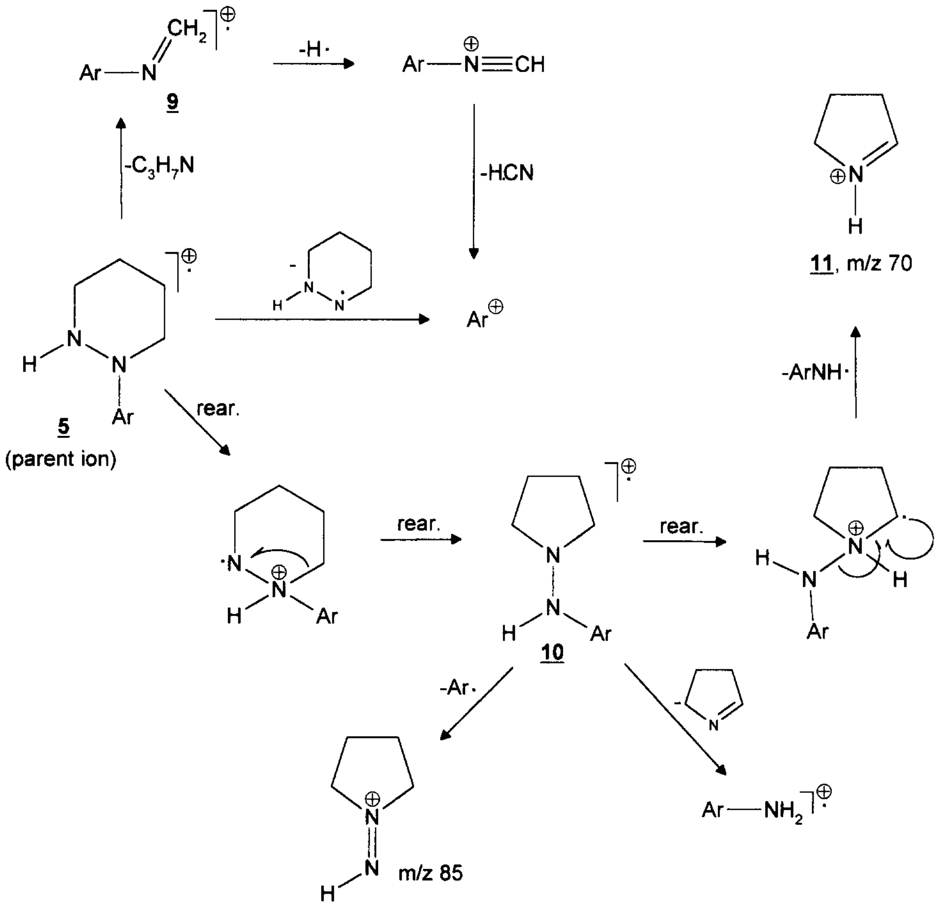
3e	2953m, 2919m, 2833m, 1606m, 1511vs, 1467s, 1454m, 1442s, 1328m,1294s, 1249vs, 1182s, 1140s, 1038vs, 1019s, 936s, 826vs, 795s	1.97-2.13(m, 2H, CH_2), 2.15-2.27(m, 2H, CH_2), 3.47-3.58(m, 2H, CH_2-N), 3.75(s, 3H, O-CH_3), 6.74(*app* t, 1H, CH=N, J=2.9), 6.85(*app* d, 2H, H_{arom}, J=9.3), 7.10(*app* d, 2H, H_{arom}, J=9.3)	18.60, 22.67, 44.31, 55.65, 114.32, 115.59, 136.08, 142.70, 153.80	190(M^+, 100), 175(58), 162(15), 147(49), 136(33), 135(35), 134(29), 132(25), 120(76), 108(30), 107(24), 92(38), 77(39), 64(30), 41(27)
3f	3065w, 3020w,2957m, 2830m, 1618m, 1589s, 1477vs, 1444s, 1426s,1369m,1338m,1309m, 1245m,1128vs, 1110s, 1071s, 1035s, 1017s, 928s, 757vs, 722m, 667w, 584s	1.95-2.05(m, 2H, CH_2), 2.07-2.15(m, 2H, CH_2), 3.20-3.30(m, 2H, CH_2-N), 6.82 (t, 1H, CH=N, J=2.5) 6.90-7.02 (m, 1H, H_{arom}), 7.10-7.30 (m, 3H, H_{arom})	19.39, 22.85, 48.51, 124.13, 124.97, 127.09, 127.26, 129.94, 140.55, 147.18	196(M^+, 51), 195(26), 194(M^+, 93), 193(34), 151(21), 141(35), 140(48), 139(83), 138(68), 130(20), 125(25), 113(68), 112(19), 111(100), 90(21), 77(58), 76(23), 75(76), 63(27), 56(27), 55(49), 51(49), 50(38), 41(29), 39(51)
3g	2970w, 2939w, 2836w, 1595vs, 1568s, 1487vs,1428s, 1376m, 1333s, 1322s, 1230m, 1138s, 1099m, 1064m, 988s, 945vs, 773s, 682m	1.85-2.00(m, 2H, CH_2), 2.05-2.20 (m, 2H, CH_2), 3.40-3.51(m, 2H, CH_2-N), 6.70-6.82(m, 2H, H_{arom} and CH=N), 6.94 (ddd, 1H, H_{arom}, J_1=8.5, J_2=2.4, J_3=0.5), 7.08-7.13(m, 1H, H_{arom}), 7.16-7.20(m, 1H, H_{arom})	17.73, 22.40, 42.83, 110.98, 113.28, 118.93, 129.60, 134.51, 137.15, 148.68	196(M^+, 47), 195(29), 194(M^+, 87), 193(41), 141(21), 140(34), 139(62), 138(51), 125(17), 113(70), 112(24) 111(100), 77(30), 76(20), 75(73), 63(26), 56(22), 55(55), 51(35), 50(30), 41(30), 39(43)
3h	2940m, 2864m, 1596s, 1569m, 1492vs, 1448m, 1324s, 1259s, 1139s, 1020s, 934s, 821s, 750s	1.95-2.10(m, 2H, CH_2), 2.15-2.30 (m, 2H, CH_2), 3.50-3.56(m, 2H, CH_2-N), 6.77(*app* t, 1H, CH=N, J=3.0), 7.06(*app* d, 2H, H_{arom}, J=9.3), 7.20(*app* d, 2H, H_{arom}, J=9.3)	18.06, 22.55, 43.21, 114.62, 124.42, 128.65, 136.92, 146.49	196(M^+, 48), 195(24), 194(M^+, 100), 193(24), 166(10), 151(28), 141(19), 140(41), 139(54), 138(53), 125(21), 113(49), 111(98), 90(13), 75(63), 63(19), 55(20), 51(24), 50(24),

3j	3099w, 2941m, 2860m, 1616vs, 1572s, 1522vs, 1487vs, 1450s, 1346vs, 1258vs, 1232s, 1138vs, 1064s,992vs, 954vs, 893s, 881vs, 871s, 855vs, 735vs, 673s	1.95-2.13 (m, 2H, CH_2), 2.17-2.30 (m, 2H, CH_2), 3.55-3.65(m, 2H, CH_2-N), 6.85(*app* t, 1H, CH=N, *J*=3), 7.25-7.50(m, 2H, H_{arom}), 7.60-7.65(m, 1H, H_{arom}), 7.92(*app* t, 1H, H_{arom}, *J*=2.1)	17.58, 22.36, 42.87, 107.29, 113.42, 118.55, 129.21, 138.33, 148.30, 148.82	205(M^+, 100), 159(11), 150(12), 131(21), 122(38), 104(14), 92(13), 77(28), 76(19), 68(13), 65(11), 63(14), 55(23), 51(17), 50(12), 41(17), 39(17)
3k	3107w, 2966w, 2907w, 2868w, 1600vs, 1586vs, 1494vs, 1453s, 1425s, 1380vs, 1340vs, 1307vs, 1185s, 1134s, 1116vs, 1073s, 1021s, 929vs, 837vs, 751vs	2.00-2.15 (m, 2H, CH_2), 2.20-2.35 (m, 2H, CH_2), 3.65-3.75(m, 2H, CH_2-N), 6.95(*app* t, 1H, CH=N, *J*=3.0), 7.18(*app* d, 2H, H_{arom}, *J*=9.5), 8.15(*app* d, 2H, H_{arom}, *J*=9.6)	17.60, 22.63, 42.98, 111.78, 125.56, 139.68, 140.46, 151.90	205(M^+, 100), 175 (17), 150(12), 131(13), 122(41), 92(12), 77(23), 76(26), 63(13), 55(22), 51(17), 50(18), 41(18), 39(18)
3l		1.85-2.10 (m, 4H, CH_2), 2.70-2.75 (m, 2H, CH_2-N), 4.17 (s, 2H, Ar-CH_2-N), 6.74 (*app* t, 1H, CH=N, *J*=2.6) 7.25-7.4 (m,5H, H_{arom})	19.62, 22.65, 49.53, 62.58, 127.06, 128.13, 128.75, 137.70, 139.53	174(M^+, 72), 173(34), 97(70), 92(25), 91(100), 73(61), 65(57), 55(25), 41(28), 39(37)
4f	3336m, 3065w, 2940s, 2872s, 2816s, 1596vs, 1497vs, 1479vs, 1456vs, 1310m, 1304m, 1288m, 1046s, 1032s, 895m,748vs, 717m, 679m	1.75-1.90 (m, 4H, CH_2), 2.70-2.83 (m, 4H, CH_2-N), 4.87 (s, 1H, N-H), 6.63(ddd, 1H, H_{arom}, J_1=7.8, J_2=7.3, J_3=1.7), 7.05-7.20(m, 2H, H_{arom}), 7.28 (*app* dd, 1H, H_{arom}, J_1=8.1, J_2=1.7)	21.84, 55.57, 114.24, 117.33, 118.47, 127.62, 128.74, 144.28	198(M^+, 27), 196(M^+, 100), 159(26), 139(19), 128(22), 127(42), 126(63), 113(16), 111(68), 99(45), 85(35), 75(15), 70(49), 65(17), 43(21), 42(72), 41(58), 39(28)

4i	3313m, 3086w, 3041w, 2963s, 2878m, 2823m, 1616vs, 1573s, 1499vs, 1442s,1416s, 1338s, 1266vs, 1219s, 1126s, 1073s, 1034s, 954m, 893m, 853m, 781m, 743s, 526m	1.80-2.00 (m, 4H, CH_2), 2.90(*app* broad s, 4H, CH_2-N), 6.56-6.68(m, 1H, H_{arom}),7.34-7.47(m, 1H, H_{arom}), 7.62(dd, 1H, H_{arom}, J_1=8.7, J_2=1.2), 8.07(dd, 1H, H_{arom}, J_1=8.6, J_2=8.5), 8.40 (s, 1H, N-H)	21.90, 55.40, 115.44, 115.77, 125.78, 130.21, 135.93, 145.83	207(M^+,100), 190(34), 173(18), 159(46), 146(17), 145(10), 131(13), 120(16), 91(12), 77(12), 70(15)
4j	3296m, 3104w, 2973m, 2879m, 2830m, 2810m, 1619vs, 1578s, 1528vs, 1497s, 1347vs, 1271vs, 1200m, 1071m, 991m, 898s, 827m, 788s, 735vs, 681m	1.85-1.95 (m, 4H, CH_2), 2.75-2.90 (m, 4H, CH_2-N), 4.63(s, 1H, N-H), 7.11(ddd, 1H, H_{arom}, J_1=8.2, J_2=2.2, J_3=1.0), 7.28(*app* t, 1H, H_{arom}, J=6.0), 7.57(ddd, 1H, H_{arom}, J_1=8.0, J_2=2.3, J_3=1.0), 7.75(*app* t, 1H, H_{arom}, J=2.3)	21.92, 55.62, 107.23, 113.36, 118.47, 129.54, 149.42, 149.85	207 (M^+, 100), 206(14), 161(8), 150(12), 137(10), 132(11), 122(70), 92(20), 91(18), 85(57), 76(10), 70(98), 68(11), 65(19), 64(21), 63(15), 44(14), 43(32), 42(81), 41(67), 39(23), 36(26)
4k	3313m,2966w, 2837m, 1600vs, 1492s, 1459s, 1303vs, 1276vs, 1202m, 1169m, 1105s, 969m, 891m, 840m, 812m, 752m, 698w, 499m	1.80-2.00 (m, 4H, CH_2), 2.83(*app* broad s, 4H, CH_2-N), 5.12(s, 1H, N-H), 6.83(*app* d, 2H, H_{arom}, J=9.2), 8.08(*app* d, 2H, H_{arom}, J=9.3)	21.90, 55.52, 110.77, 126.23, 138.82, 153.84	207(M^+, 100), 161(7), 150(11), 122(70), 119(10), 92(13), 91(13), 90(21), 85(28), 76(14), 70(58), 68(10), 65(15), 64(22), 63(19), 43(26), 42(67), 41(51), 39(20)

The isomeric saturated compounds **5a-h**, **j**, **k** present in the reaction mixtures from **1a-h**, **j**, **k** were not isolated, but their mass spectra were in agreement with the proposed structures (Scheme 3). A rearrangement of the parent ion to **10** induced subsequent fragmentations reminiscent of 5-member ring system 4. In these spectra the loss of a 57 u fragment (not necessarily in a single step) to yield 9 was a prominent feature.

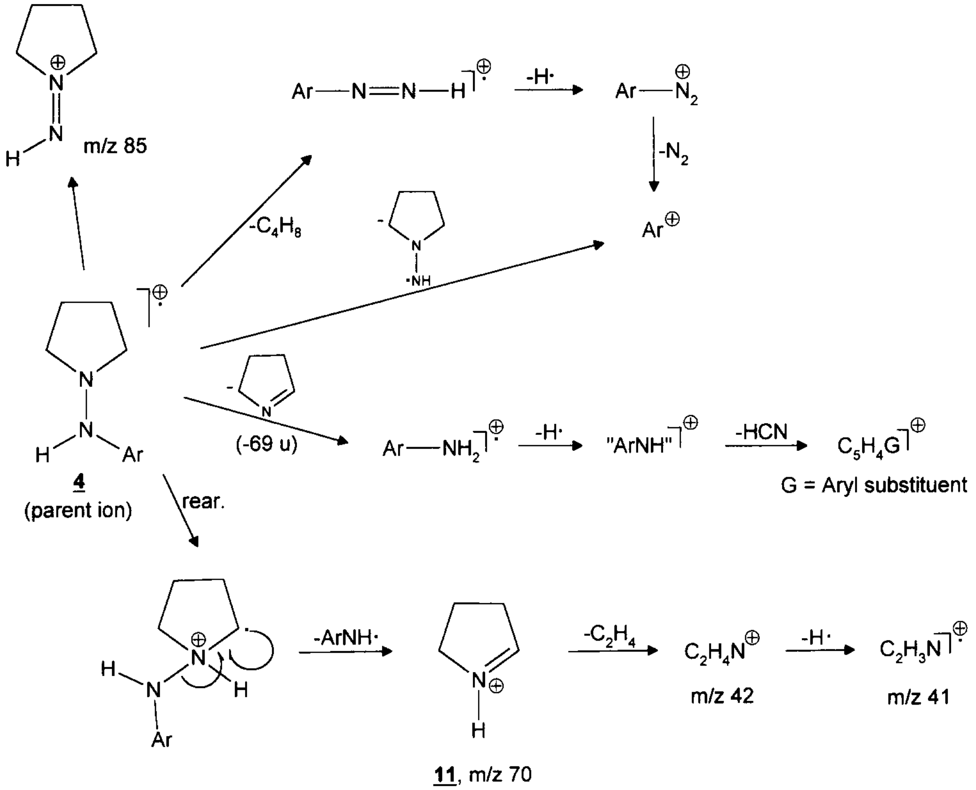
Scheme 3



Some common features in the mass spectra of 4 were revealed (Scheme 4). The parent ions were present in all of them, accompanied by the characteristic preferential losses of either a fragment of 69 u or yielding the ion 11 at m/z 70.

We have obtained a preliminary indication that the reaction between 2 and aliphatic hydrazines may be successful: benzylhydrazine (**1l**) gave the corresponding 1-benzyl-1,4,5,6-tetrahydropyridazine (**3l**) as the sole GC-MS product; the mass spectra was consistent with the structural identification. The product **3l** appeared to be relatively unstable both at the distillation temperature (bp 72°C at 15 Pa, oil bath at 150°C) and upon contact with silica gel. All the features of compounds **3** were present in ^{1}H NMR spectrum of a specimen of **3l** of relatively low purity.

Scheme 4



EXPERIMENTAL SECTION

Materials. Phenylhydrazine hydrochloride, benzylhydrazine dihydrochloride and $NaBH_4$ pellets were purchased from Aldrich, Italy, Milan; described procedures were followed in the preparation of **1b**,[6] **1c**,[7] **1d**,[6] **1e**,[8] **1f**,[6] **1g**,[6] **1h**,[6] **1i**,[9] **1j**,[7] **1k**[10] in the form of their HCl salts.

Silica gel (60-120 mesh) was obtained from BDH (Milan, Italy) and CH_2Cl_2 was used as eluent. Thin layer chromatography was performed on silica gel (Kieselgel 60 F_{254}, Merck, Darmstadt, Deutschland) and Et_2O was used as eluent. Solvents were used as received.

Equipment. GC-MS analyses were performed with a Finnigan 1020 gaschromatograph-mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35-450 u. Injector temperature was kept at 250°C and the column (Supelco SPB™-5, 30 m long, 0.32 mm i.d.) temperature was programmed from 60°C to 300°C with a gradient of 10°C/min.

IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using KBr technique for solids and recorded in the range 4000-400 cm^{-1}.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively. NMR peak locations are reported as δ-values from TMS (^{1}H NMR) and the central peak of $CDCl_3$ (^{13}C NMR). Some ^{1}H multiplets are characterised by the term *app* (apparent): this refers only to their appearance and may be an oversimplification.

Elemental analysis were performed with a Carlo Erba Mod. 1106 elemental analyser and were in satisfactory agreement with calculated values.

Melting points were determined with an automatic Mettler (Mod. FP61) and are not corrected.

Boiling points refer to the central cut of small distillations and are uncorrected.

Reductive reaction between hydrazines (1) and 2,5-dimethoxytetrahydrofuran (2). A THF solution of a monosubstituted hydrazine hydrochloride (1, 16.8 mmol) in THF (50 mL) containing 6M H_2SO_4 (66 mmol) was added simultaneously with $NaBH_4$ (50.4 mmol, pellets) to a well stirred solution of 2 (17.6 mmol) in THF (50 mL) and 6M H_2SO_4 (33 mmol) at *ca.* 5°C at a rate which allowed prompt dissolution of the pellets. Additional water had to be added in some cases to favour dissolution of $NaBH_4$. About half an hour after the end of the addition, the mixture was made strongly basic with solid NaOH and extracted with Et_2O (2x30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and solvents removed by distillation. GC-MS analysis allowed us to detect 1,4,5,6-tetrahydropyridazines (3), 1-aminopyrrolidines (4) hexahydropyridazines (5) and, when present, dihydropyridazines (6). Both 3 and 4 are generally sensitive to the combined effect of atmospheric oxygen and light. TLC analysis (Et_2O was used as eluent) did not separate adequately the above products, but exhibited the presence of oligomeric product at a much lower R_f value.

Products 3 were obtained from the mixture by extracting the reaction mixture dissolved in Et_2O with diluted H_2SO_4: the saturated products (4 and 5) ended up more or less completely in the aqueous phase together with some 3; the Et_2O solution contained 3 with traces of 4 and 5 and, in some instances, of the oligomeric products. Mixtures containing mainly 4 in addition to 3 may be treated with diluted acid, which extracts most of the component 4 alone in order to purify it. Final purification of 3 and 4 was achieved either by absorption chromatography followed, when suitable, by recrystallization or by vacuum distillation. The results are collected in Tables 2 and 3. Purification of 3 from 4 and 5 could be achieved at any stage by washing an Et_2O solution of the mixture with aqueous copper(II) acetate at room temperature: the Et_2O solution contained only the monounsaturated compounds.

In the case of 2-chloro- and 3- and 4-nitrophenylderivatives a very neat separation of **3** from **4** was achieved according to the above procedure without the need of the action of the copper(II) acetate. The reaction with 2-nitrophenylhydrazine (**1i**) yielded only **4i**.

A pretty extensive number of experimental variations were attempted with the aim of optimising the yield of saturated compounds **5** directly from the original mixture, but the results were not encouraging. In fact **3g**, **3j** and **3h** were found quite unreactive both with $NaBH_4$ and $LiAlH_4$ under a variety of experimental conditions. Zn powder in acetic acid on **3h** during 4 h at 60°C gave the ring contraction compound [N-(4-chlorophenyl)-pyrrolidine] as the only product detected by GC-MS and identified by comparison with an authentic specimen (GV *et al.*, unpublished results).

*Reduction and reductive alkylation of 1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (**3e**).* A quantitative transformation of **3e** into 1-(4-methoxyphenyl)-2-ethylhexahydropyridazine (**7**) could be achieved by allowing $NaBH_4$ pellets (1.5 g, 39.7 mmol) to react with **3e** (0.5 g, 2.6 mmol) in acetic acid (20 mL) under stirring without any temperature control during 12 h. Excess acetic acid was evaporated in vacuum (*ca.* 2700 Pa) and the organic product was taken up by addition of some aqueous $NaHCO_3$ and t-BuOMe. GC- MS and TLC analysis of the organic phase showed the presence of only **7**. The crude product **7** (0.6 g, 97 %) obtained after evaporation of the extraction solvent was purified by distillation (80% yield; bp 115°C at 43 Pa); MS m/z 220(M^+, 80), 191(100), 174(32), 159(15), 135(35), 134(21), 123(26), 122(41), 120(36), 107(18), 92(35), 77(39), 68(69), 65(18), 41(24); IR (KBr) 2934m, 2856m, 2831m, 1506vs, 1462m, 1380m, 1302m, 1237s, 1181m, 1114m, 1103m, 1041s, 999m, 824m, 773m cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, CH_3, J=7.1), 1.55-1.75 (m, 4H, CH_2), 2.89 (q, 2H, N-CH_2, J=7.1), 2.90-3.05 (m, 2H, N-CH_2), 3.35-3.45 (m, 2H, N-CH_2), 3.75 (s, 3H, O-CH_3), 6.80 (*app* d, 2H, H_{arom}, J=9.3), 7.00 (*app* d, 2H, H_{arom}, J=9.3); ^{13}C NMR ($CDCl_3$) δ 13.18, 18.04, 21.88, 38.35, 43.47, 47.35, 55.62, 114.42, 115.13, 144.18, 151.87; Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.85; H, 9.18; N, 12.68.

*1-(2-Chlorophenyl)2-(4-hydroxybutyl)hexahydropyridazine (**8f**).* 1-(2-Chlorophenyl)-2-(4-hydroxybutyl)-hexahydropyridazine (**8f**) was prepared by addition of **2** (6.6 mmol) in THF (15 mL) containing 6M H_2SO_4 (12 mmol) to a well stirred solution of 1-(2-chloro)phenylhydrazine (**1f**, 6.3 mmol) in THF (25 mL) and 6M H_2SO_4 (20 mmol) while $NaBH_4$ pellets (20 mmol) were simultaneously added to the reaction mixture at *ca.* 0°C. About half an hour after the end of the addition the mixture was made strongly basic with solid NaOH and extracted with Et_2O (2x15 mL). The combined organic phases were washed with brine and dried (Na_2SO_4) and solvents removed by distillation. GC-MS analysis detected product **8f** and small amounts of **3f**, **4f** and **5f**. Product **8f** was obtained from the mixture by extracting the reaction mixture dissolved in Et_2O with diluted H_2SO_4: the product ended up more or less completely in the aqueous phase. Final purification of **8f** was obtained by absorption chromatography using Et_2O as eluent and silica gel as stationary phase (10% yield, thermal instability of the product prevented its distillation); MS m/z 270(M$^+$, 27), 268(M$^+$, 75), 211(25), 209(73), 197(32), 195(100), 182(19), 180(61), 178(23), 143(15), 140(25), 138(22), 130(12), 111(17), 77(12), 70(13), 68(32); IR (KBr) 3366m, 2939vs, 2858s, 1587s, 1479vs, 1440s, 1356m, 1327m, 1251m, 1243m, 1185m, 1092m, 1056s, 1040s, 910m, 752vs, 732vs cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38-1.44 (m, 4H, CH_2), 1.61-1.64 (m, 4H, CH_2), 2.79 (*app* t, 2H, CH_2-N, J=6.3), 3.12 (*app* t, 2H, CH_2-N, J= 4.8), 3.26-3.38 (m, 5H, CH_2-N, CH_2-O and H-O), 6.80-6.88 (m, 1H, H_{arom}), 7.08-7.19 (m, 2H, H_{arom}), 7.26 (dd, 1H, H_{arom}, J_1=7.9, J_2=1.4); ^{13}C NMR ($CDCl_3$) δ 17.43, 23.47, 23.98, 30.18, 43.00, 49.05, 49.50, 62.03, 121.06, 122.34, 126.56, 130.35, 147.41; Anal. Calcd for $C_{14}H_{21}ClN_2O$: C, 62.56; H, 7.87; N, 10.49. Found: C, 62.51; H, 7.90; N, 10.38.

Mass spectra of 1-arylhexahydropyridazines **5**:

1-phenylhexahydropyridazine (**5a**): MS m/z 162(M$^+$, 76), 106(13), 105(45), 104(24), 93(17), 92(17), 91(15), 78(21), 77(100), 70(14), 51(31), 41(16), 39(14);

1-(2-methylphenyl)hexahydropyridazine (**5b**): MS m/z 176(M$^+$,100), 146(13), 133(10), 130(12), 120(21), 119(30), 118(73), 117(12), 107(13), 106(35), 104(15), 92(17), 91(75), 77(10), 70(16), 65(17);

1-(3-methylphenyl)hexahydropyridazine (**5c**): MS m/z 176(M$^+$, 50), 175(10), 146(7), 135(7), 133(7), 132(7), 120(18), 119(38), 118(34), 107(23), 106(37), 105(15), 104(15), 91(100), 89(15), 79(15), 78(13), 77(24), 70(26), 68(14), 65(37), 63(16), 56(10), 55(9), 52(10), 51(20), 43(13), 41(30), 39(31);

1-(4-methylphenyl)hexahydropyridazine (**5d**): MS m/z 176(M$^+$,44), 119(14), 118(7), 106(13), 105(5), 92(7), 91(100), 65(13), 41(6), 39(6);

1-(2-chlorophenyl)hexahydropyridazine (**5f**): MS m/z 198(M$^+$, 32), 197(13), 196(M$^+$, 95), 141(16), 140(12), 139(45), 138(15), 127(15), 126(13), 113(32), 111(100), 77(19), 75(17), 70(24);

1-(3-chlorophenyl)hexahydropyridazine (**5g**): MS m/z 198(M$^+$,16), 196(M$^+$,46), 140(13), 139(25), 138(17), 113(27), 111(100), 77(11), 75(19), 70(14), 41(17), 40(16), 39(11);

1-(4-chlorophenyl)hexahydropyridazine (**5h**): MS m/z 198 (M$^+$,13), 196(M$^+$, 41), 141(12), 140(11), 139(34), 138(15), 127(30), 126(11), 113(31), 111(100), 77(10), 75(23), 71(26), 70(20), 51(9), 43(21), 41(20), 39(10);

1-(3-nitrophenyl)hexahydropyridazine (**5j**): MS m/z 207(M$^+$,100), 205(15), 150(24), 122(59), 104(10), 92(16), 77(18), 76(15), 70(23), 65(10), 63(9).

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