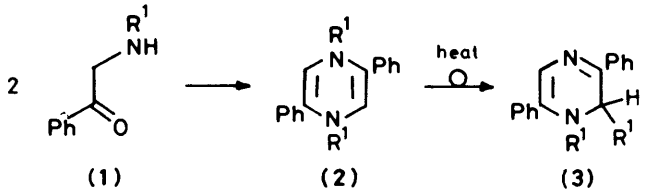
Preparation of Stable 1,4-Dihydropyrazines

Jean-Louis Fourrey *
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France
Josiane Beauhaire and Chun Wei Yuan
Laboratoire associé I.N.R.A., E.N.S.I.A., Avenue des Olympiades, 91305 Massy, France

The *N*-phenacylarylamine (**4**) gives the *N,N*-diphenacyl derivative (**5**) on treatment with phenacyl bromide under phase-transfer catalysis conditions. Condensation of (**5**) with an arylamine results in the formation of the thermally stable 1,4-diaryl-3,5-diphenyl-1,4-dihydropyrazine (**6**) in moderate yield. 1,2-Diaryl-3,6-diphenyl-1,2-dihydropyrazine (**9**) is obtained by heating *N*-phenacylarylamine (**4**). Formation of (**9**) is also promoted by a Lewis acid at lower temperature.

Pyrazines which are known to be formed during food processing *via* Maillard-type reactions have received considerable attention because of their potent flavouring properties.[1] We are currently exploring the pathways which lead to pyrazines in these reactions. Working on a model system,[2] we have detected a 1,4-dihydropyrazine intermediate and become interested in the chemical behaviour of such compounds.

Indeed among six-membered ring heterocycles 1,4-dihydropyrazines are chemically intriguing molecules. They exhibit a delocalized 8π electron system which according to Breslow and Dewar is antiaromatic and poorly stabilized.[3] So far, such systems have only been elaborated in a few instances as it is necessary to choose the ring substituents carefully. Thus, molecules having their nitrogen atoms bound either to electron-deficient substituents or trimethylsilyl groups have been fully characterized.[4] Kaim and other workers have noted that relatively stable 1,4-dialkyl-1,4-dihydropyrazines can be obtained by introducing bulky substituents in the 3 and 5 positions. Steric repulsion between such vicinal substituents in the 3, 4, and 5 positions prevents the conjugation of the free electron pair on N-4 with the rest of the π system, thus rendering the antiaromatic destabilization no longer possible.[4] It is reported in the literature that condensation of two α-amino ketones (**1**) provides a 1,4-dihydropyrazine which is given structure (**2**) or (**6**) depending on the nature of R^1. When R^1 is an alkyl group the product of this reaction is the 1,4-dihydropyrazine (**2**). Such a compound is unstable and it rapidly isomerizes into the corresponding 1,2-dihydropyrazine (**3**).[5]



On the other hand when R^1 is an aryl group Schmidt *et al.*[6] have established that the expected 1,4-dihydropyrazine (**8**) is not formed. Instead, they have isolated its isomer (**6**) in low yield and postulated that the *N,N*-diphenacylarylamine (**5**) should be its precursor. Condensation of (**5**) with an arylamine would furnish the stable 1,4-dihydropyrazine (**6**) which does not rearrange to give the corresponding 1,2-dihydropyrazine (**7**). To date, no experimental data have been presented to support this mechanism. We have succeeded in preparing compounds of structure (**5**) and observed their behaviour in the presence of aromatic amines to give 1,4-dihydropyrazine (**6**).

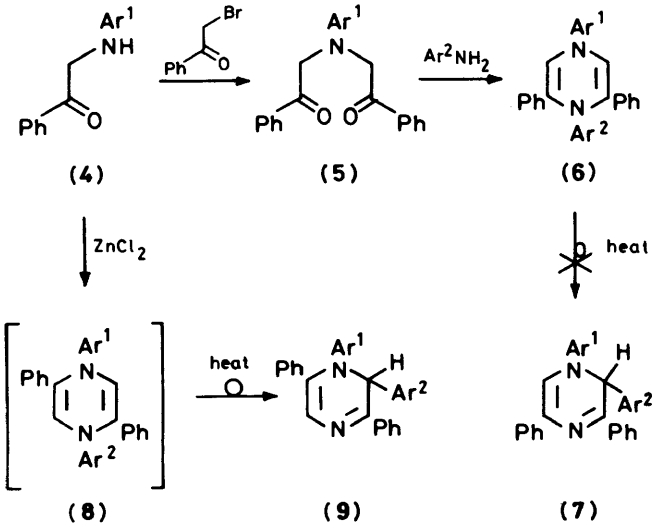
Literature methods for the preparation of the *N,N*-diphenacyl derivatives of toluidine[7,8] and aniline[9] gave in our hands only low and unsatisfactory yields. Thus we followed a recently reported phase-transfer catalysis procedure[10] in which condensation of phenacyl bromide with *N*-phenacylarylamine (**4**) gives the *N,N*-diphenacylarylamine (**5**) (in 36% yield for Ar^1 = *p*-tolyl and 34% yield for Ar^1 = Ph). These compounds are poorly soluble in the usual organic solvents. Their spectral and analytical data are in full agreement with the proposed structures.

N,N-Diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl) was condensed with *p*-toluidine in refluxing toluene in the presence of toluene-*p*-sulphonic acid under azeotropic distillation conditions to give the 1,4-dihydropyrazine (**6**; $Ar^1 = Ar^2$ = *p*-tolyl) in 35% yield. Condensation of (**5**; Ar^1 = Ph) with *p*-toluidine in the same conditions resulted in the formation of 1,4-dihydropyrazine (**6**; Ar^1 = Ph, Ar^2 = *p*-tolyl) in 40% yield. It is noteworthy that *N*-phenacylarylamine (**4**) is a side-product in these reactions and that it is probably formed *via* acid-catalyzed hydrolysis. The spectral and analytical data are fully consistent with the proposed structure for compound (**6**; $Ar^1 = Ar^2$ = *p*-tolyl). Its ^{1}H n.m.r. spectrum exhibits two methyl signals at 2.00 and 2.11 p.p.m. in accordance with the data given by Schmidt *et al.*[6] for a related product. The methyl group localized between the two phenyls was at lower field as indicated by the spectrum of dihydropyrazine (**6**; Ar^1 = Ph, Ar^2 = *p*-tolyl) in which the chemical shift of the methyl group is at 2.16 p.p.m. This indication that the *p*-tolyl methyls are not identical suggests that the thereby obtained molecule possesses a plane of symmetry. Further structural evidence is given from the ^{13}C n.m.r. spectrum which exhibits 16 resonances, two of them at high field being attributed to the two methyl carbons. No other sp^3 carbon resonance was observed; this confirms that the compound is indeed a 1,4-dihydropyrazine and has not rearranged to a 1,2-dihydropyrazine.

After we established the validity of the hypothesis of Schmidt *et al.*[6] which rationalizes the formation of the stable 1,4-dihydropyrazine (**6**), we were interested in investigating the behaviour of *N*-phenacylarylamines (**4**) under conditions which do not lead to indoles according to Bischler.[11] Indeed simple thermal treatment of *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) at 140 °C gave rise to 3,6-diphenyl-1,2-di-*p*-tolyl-1,2-dihydropyrazine (**9**; $Ar^1 = Ar^2$ = *p*-tolyl) which is different from 2,6-diphenyl-1,4-di-*p*-tolyl-1,4-dihydropyrazine (**6**; $Ar^1 = Ar^2$ = *p*-tolyl). In its ^{1}H n.m.r. spectrum the methyl signals appears at 2.21 and 2.33 p.p.m. instead of 2.00 and 2.11

p.p.m.; a singlet at 5.05 p.p.m. can be attributed to 2-H. The presence of an sp^3 carbon in the molecules is confirmed by the observation of a resonance at 68.04 p.p.m. in the ^{13}C n.m.r. spin echo spectrum. Compounds (**9**; $Ar^1 = Ar^2$ = *p*-tolyl) results probably from a suprafacial 1,3-sigmatropic shift of one of the *p*-tolyl groups of 2,5-diphenyl-1,4-di-*p*-tolyl-1,4-dihydropyrazine (**8**; $Ar^1 = Ar^2$ = *p*-tolyl) as explained by Lown *et al.*[5] in the case of the 1,4-dibenzyl-1,4-dihydropyrazine.

Recently Walkup and Linder[12] have reported that the formation of a 1,4-diaryl-2,5-diphenyl-1,4-dihydropyrazine (**8**) can be promoted by a Lewis acid such as $ZnCl_2$ starting from *N*-phenacylarylamine. However no details have been given to establish firmly the structural identification of the reaction product.



In our hands, treatment of *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) under the same conditions provided the 1,2-dihydropyrazine (**9**; $Ar^1 = Ar^2$ = *p*-tolyl) together with traces of *N,N*-diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl). When *N,N*-diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl) is treated with *p*-toluidine according to the same procedure, a mixture of the dihydropyrazines (**6**; $Ar^1 = Ar^2$ = *p*-tolyl) and (**9**; $Ar^1 = Ar^2$ = *p*-tolyl) is observed indicating that, as already pointed out *N,N*-diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl) gives back *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) when treated under acidic conditions.

Experimental

M.p.s were determined with a Reichert hot-stage microscope and are uncorrected. U.v. spectra were measured in ethanol on a Kontron Uvicon 810 spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer 297 instrument. High- and low-resolution electron impact (e.i.) mass spectra were obtained with an A.E.I. MS 50 instrument. The ^1H n.m.r. spectra were obtained on a Bruker WP-80 (80 MHz) or WP-200-SY (200 MHz) spectrometer using tetramethylsilane as the internal standard. ^{13}C N.m.r. spectra were recorded on a Bruker WP-200-SY spectrometer operating at 50.30 MHz in the pulsed f.t. mode. Thin layer chromatography (t.l.c.) was performed on Schleicher and Schüll silica gel F 1500 LS 254 plates. Tetrahydrofuran (THF) was distilled prior to use from sodium–benzophenone. *p*-Toluidine was distilled under atomospheric pressure.

N-Phenacyl-p-*toluidine* (**4**; Ar^1 = p-tolyl).—A solution of phenacyl bromide (1.99 g, 10 mmol) and *p*-toluidine (2.14 g, 20 mmol) in ether was stirred overnight at room temperature. Precipitated *p*-toluidine hydrobromide was filtered off and the filtrate evaporated under reduced pressure to give the title compound as a yellow solid (1.95 g, 86%) which crystallized from methanol, m.p. 126—128 °C (lit.,[7] 134 °C); *m/z* (e.i.) 225 ($M^{+\cdot}$) (Found: C, 79.95; H, 6.65; N, 5.95. $C_{15}H_{15}NO$ requires C, 79.97; H, 6.71; N, 6.22%); δ_H (80 MHz, $CDCl_3$) 2.25 (3 H, s), 4.52 (2 H, s), and 6.87, 7.75 (9 H, ArH); $\delta_C(CDCl_3)$ 20.42, 50.76, 27.01, 135.16, 145.04, and 195.37.

N-Phenacylaniline (**4**; Ar^1 = Ph).—This was obtained as a yellow solid from methanol, m.p. 95—97 °C (lit.,[7] 93 °C); *m/z* (e.i.) 211 ($M^{+\cdot}$); δ_H (80 MHz, $CDCl_3$) 4.51 (2 H, s), 4.66 (1 H, NH), and 6.57, 8.02 (10 H, ArH).

N,N-*Diphenacyl*-p-*toluidine* (**5**; Ar^1 = p-*tolyl*).—A powdery mixture of *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) (990 mg, 4.4 mmol), phenacyl bromide (995 mg, 5 mmol), $KHCO_3$ (880 mg, 8.8 mmol), and tetrabutylammonium hydrogen sulphate (45 mg, 0.13 mmol) was kept for 1 h at 80 °C. After this, the mixture was carefully partitioned between water and a large volume of dichloromethane to solubilize the *N,N*-diphenacyl compound. The organic layer was separated, dried (Na_2SO_4), and concentrated to leave the title product as a white crystalline compound (553 mg, 36%), m.p. 242—244 °C (lit.,[7] 255 °C); *m/z* (e.i.) 343 ($M^{+\cdot}$) (Found: C, 80.5; H, 6.3; N, 4.2. $C_{23}H_{21}NO_2$ requires C, 80.44; H, 6.16; N, 4.08%); δ_H (80 MHz, $CDCl_3$ + CF_3CO_2D) 2.37 (3 H, s), 5.50 (4 H, s), 7.65 (m, ArH); $\nu_{max.}$(Nujol) 1 680 cm^{-1} (C=O).

N,N-*Diphenacylaniline* (**5**; Ar^1 = Ph).—This was obtained as a white solid from dichloromethane, m.p. 235—237 °C (lit.,[9] 236—240 °C); *m/z* (e.i.) 329 ($M^{+\cdot}$); δ_H (80 MHz, $CDCl_3$ + CF_3CO_2D) 5.50 (4 H, s) and 7.50, 8.07 (15 H, ArH).

2,6-*Diphenyl*-1,4-*di*-p-*tolyl*-1,4-*dihydropyrazine* (**6**; $Ar^1 = Ar^2$ = p-*tolyl*).—Following the procedure previously used by Schmidt *et al.*[6] a mixture of the *N,N*-diphenacyl compound (**5**) (343 mg, 1 mmol), *p*-toluidine (107 mg, 1 mmol), and toluene-*p*-sulphonic acid (10 mg, 0.05 mmol) was refluxed for 5 h under azeotropic distillation conditions (toluene 5 ml). 2,6-Diphenyl-1,4-di-*p*-tolyl-1,4-dihydropyrazine (**6**; $Ar^1 = Ar^2$ = *p*-tolyl) was purified by chromatography on a silica gel column with dichloromethane as eluant; yield 147 mg, (35%), m.p. 164—166 °C (EtOH–benzene, 1:1) *m/z* (e.i.) 414 ($M^{+\cdot}$) (Found: C, 86.75; H, 6.4; N, 6.85. $C_{30}H_{26}N_2$ requires C, 86.92; H, 6.32; N, 6.77%); $\lambda_{max.}$ 253 nm (ε 42 930); δ_H((200 MHz, C_6D_6) 2.00 (3 H, s), 2.11 (3 H, s), and 6.83—7.83 (ArH); $\delta_C(C_6D_6)$ 20.40, 20.56, 117.37, 117.55, 124.49, 125.74, 126.46, 127.53, 128.50, 129.10, 129.54, 130.19, 132.80, 137.86, 140.89, and 149.03.

2,4,6-*Triphenyl*-1-p-*tolyl*-1,4-*dihydropyrazine* (**6**; Ar^1 = Ph, Ar^2 = p-*tolyl*).—This had m.p. 135—137 °C (MeOH) *m/z* (e.i.) 400 ($M^{+\cdot}$) (Found: C, 86.8; H, 5.65; N, 6.75. $C_{29}H_{24}N_2$ requires C, 86.96; H, 6.04; N, 7.00%); δ_H (80 MHz, $CDCl_3$) 2.16 (3 H, s) and 6.75, 7.85 (21 H, ArH).

3,6-*Diphenyl*-1,2-*di*-p-*tolyl*-1,2-*dihydropyrazine* (**9**; $Ar^1 = Ar^2$ = p-*tolyl*).—*Thermal treatment of* N-*phenacyl*-p-*toluidine* (**4**; Ar^1 = p-*tolyl*). Neat *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) (225 mg, 1 mmol) was heated under nitrogen at 140 °C for 16 h. Purification on a silica gel column with dichloromethane as eluant gave the 1,2-dihydropyrazine (**9**; $Ar^1 = Ar^2$ = *p*-tolyl) as a white crystalline compound (50 mg, 18%) and unchanged *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) (76 mg).

3,6-Diphenyl-1,2-di-*p*-tolyl-1,2-dihydropyrazine (**9**) had m.p.

143—144 °C (EtOH); *m/z* (e.i.) 414 ($M^{+\cdot}$) (Found: C, 86.65; H, 6.3; N, 6.75. $C_{30}H_{26}N_2$ requires C, 86.92; H, 6.32; N, 6.77%); $\lambda_{max.}$ 253 nm (ε 36 800); δ_H (200 MHz, $CDCl_3$) 2.21 (3 H, s), 2.33 (3 H, s), 5.05 (1 H, s), and 6.80—7.63 (ArH); δ_C($CDCl_3$) 20.56, 21.05, 68.04, 114.07, 120.00, 122.96, 123.10, 125.41, 125.96, 126.81, 126.95, 128.15, 128.46, 128.60, 129.75, 129.91, 130.26, 131.31, 134.75, 136.43, 138.19, and 146.59.

Condensation of N-*phenacyl*-p-*toluidine* (**4**; Ar^1 = p-*tolyl*) *prompted by* $ZnCl_2$.[12] *N*-Phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) (670 mg, 3 mmol) in THF (3 ml) was added, under nitrogen, to a solution of $ZnCl_2$ (1.13 g, 8.3 mmol) in THF (1.5 ml) and the mixture refluxed for 20 min. Chromatographic purification gave compound (**9**; Ar^1 = Ar^2 = *p*-tolyl) (120 mg, 23%), unchanged *N*-phenacyl-*p*-toluidine (**4**; Ar^1 = *p*-tolyl) (100 mg), and *N*,*N*-diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl) (20 mg).

To a suspension of *N*,*N*-diphenacyl-*p*-toluidine (**5**; Ar^1 = *p*-tolyl) (100 mg, 0.3 mmol) in ethanol (2 ml) under nitrogen, was added $ZnCl_2$ (285 mg, 2.1 mmol, 7 equiv.) previously dissolved in ethanol (1.5 ml) and *p*-toluidine (321 mg, 3 mmol, 10 equiv.) in ethanol (2 ml). This mixture was refluxed for 2.5 h and filtered in order to remove the precipitate. Silica gel column chromatography of the residue resulting from evaporation of the filtrate gave a mixture (38 mg, 30%) of the two dihydropyrazines (**9** and **6**; Ar^1 = Ar^2 = *p*-tolyl) in a ratio of 3:1 as indicated by ^1H n.m.r. (200 MHz, C_6D_6); *m/z* (e.i.) 414 ($M^{+\cdot}$).

Acknowledgements

We thank Dr. A. Loupy for useful discussions and the m.s. and n.m.r. services of I.C.S.N. (Gif-sur-Yvette) for skilful assistance. We are grateful to Professor H. Richard for encouragement throughout this work.

References

1 For a review see 'The Maillard Reaction in Foods and Nutrition,' eds. G. R. Waller and M. S. Feather; A.C.S. Symposium Series 1983, **215** and 'Chemistry of Heterocyclic Compounds in Flavours and Aromas,' ed. G. Vernin, Wiley & Sons, New York, 1982.
2 J. Beauhaire, J. L. Fourrey, and C. W. Yuan, unpublished work.
3 R. Brewslow, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 565; M. J. S. Dewar, *ibid.*, 1971, **10**, 761.
4 W. Kaim, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 171; W. Kaim, *J. Am. Chem. Soc.*, 1983, **105**, 707.
5 S. J. Chen and F. W. Fowler, *J. Org. Chem.*, 1970, **35**, 3987; J. W. Lown and M. H. Akhtar, *J. Chem., Soc., Chem. Commun.*, 1973, 511; J. W. Lown, M. H. Akhtar, and R. S. McDaniel, *J. Org. Chem.*, 1974, **39**, 1998; J. W. Lown and M. H. Akhtar, *Tetrahdron Lett.*, 1974, 179.
6 R. R. Schmidt, M. Dimmler, and P. Hemmerich, *Chem. Ber.*, 1976, **109**, 2395.
7 E. Lellman and A. Donner, *Chem. Ber.*, 1890, **23**, 166.
8 R. Mohlau, *Chem. Ber.*, 1881, **14**, 171.
9 G. K. Almstrom, *Liebigs Ann. Chem.*, 1916, **411**, 350.
10 E. V. Dehmlow, R. Thieser, Y. Sasson, and H. A. Zahaalka, *Tetrahedron Lett.*, 1985, **26**, 297.
11 W. A. Remers, *Heterocycl. Comp.*, 1972, **25**, 317.
12 R. E. Walkup and J. Linder, *Tetrahedron Lett.*, 1985, **26**, 2155.

Received 12*th May* 1986; *Paper* 6/899