

Mannich Bases as Synthetic Intermediates: Convenient Synthesis of Functionalized 1,2,4-Triazepines, 1,4-Diazepines and 1,5-Diazocines

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Transamination between the ketonic Mannich bases **1a, b** and primary arylamines gave a series of ketonic *sec*-Mannich bases **2a–h**. A variety of tetrahydro-1,2,4-triazepines **3a–f** have been synthesized by treating the arylhydrazones of **2** with formaldehyde. A similar reaction with the benzenesulfonylhydrazone of **2b** afforded **4**. The 3-styryl-2*H*-1,2,4-triazepine **5** was obtained from the phenylhydrazone of **2a** and cinnamaldehyde. Treatment of arylhydrazones of the 4-methoxystyryl keto base **7** with formaldehyde and cinnamaldehyde afforded the 3,4,5,6-tetrahydro-2*H*-1,2,4-triazepines **8a, b**. Mannich reaction with 4-(*p*-hydroxyphenyl)-tetrahydro-1,2,4-triazepine **3d** afforded the Mannich bases **9, 10** and **11**.

The reaction of **1b** with *o*-phenylenediamine leads to the 1,5-benzodiazepine **13**. The new tetrahydro-1,4-diazepine and tetrahydro-1,5-diazocine Mannich bases **15** and **17** were obtained from **1b** and ethylenediamine or 1,3-diaminopropane, respectively. The bi(piperidine) derivative **19** was obtained from **1a** and 1,3-diaminopropane.

Key words: Mannich Bases, 1,2,4-Triazepines, 1,4-Diazepines, 1,5-Diazocines

Introduction

Mannich bases have been used extensively in the synthesis of heterocyclic systems [1–6] and of heterocycles having a potential basic side chain of alkaloidal nature [7–13]. In particular, ketonic *tert*-Mannich bases and their quaternary salts have been employed frequently as potential intermediates in the synthesis of a multitude of heterocycles of pharmaceutical interest, such as pyrazolines [9–11], pyridines [3], piperidines [14–16], 1,5-benzo- or 1,5-hetero-diazepines [16–19], and quinolines [20]. The use of *sec*-Mannich bases as synthetic intermediates has been reported in a limited number of cases for the synthesis of pyrimidines [21], quinolines [22, 23] and isoquinolines [24, 25], and recently we reported [16] the synthesis of the 2*H*-1,2,4-triazepine ring system starting with ketonic *sec*-amine bases.

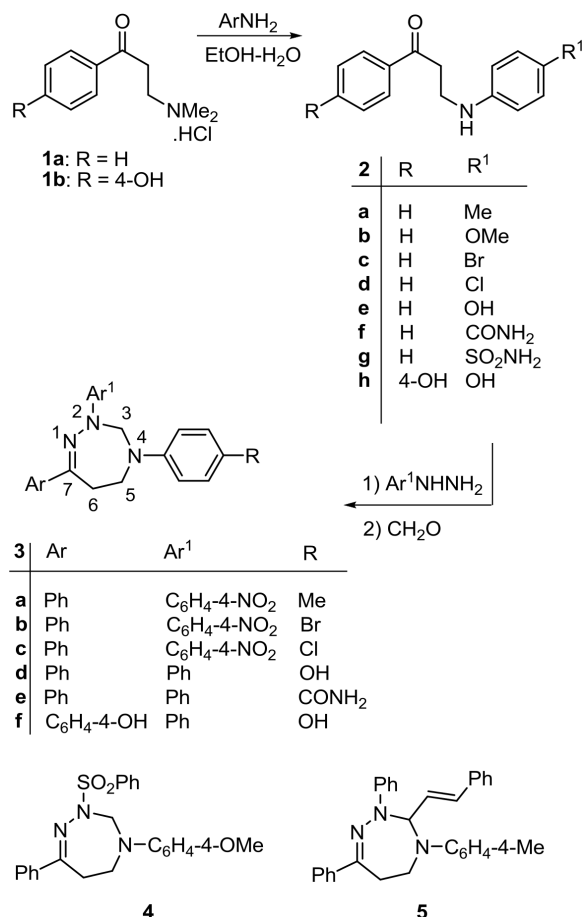
In connection with our studies in the area of Mannich bases [4, 11–13, 16, 26] and in view of the widespread and increasing interest in the chemistry and biological activities of Mannich bases and related compounds, the synthetic potential of ketonic *sec*-Mannich bases as intermediates in heterocyclic synthesis was further investigated. We report here on the synthesis of some new functionalized tetrahydro-1,2,4-tri-

azepines, tetrahydro-1,4-diazepines, tetrahydro-1,5-diazocines, and bi(piperidines), which possess considerable synthetic and pharmaceutical interest.

Results and Discussion

A series of ketonic *sec*-Mannich bases **2a–h** was prepared by transamination reaction between the ketonic *tert*-Mannich base hydrochloride **1a** or **1b** and the appropriate primary aromatic amine, according to an earlier report [27]. Compounds **2f–h** have been reported for the first time by this study. It was found that treatment of the ketonic *sec*-amines of the type **2** with *p*-nitrophenylhydrazine or phenylhydrazine, and subsequently with formaldehyde under mild conditions, afforded a series of 3,4,5,6-tetrahydro-2,4,7-triaryl-2*H*-1,2,4-triazepines (**3a–f**) with different substituents on the 1,2,4-triazepine ring (Scheme 1).

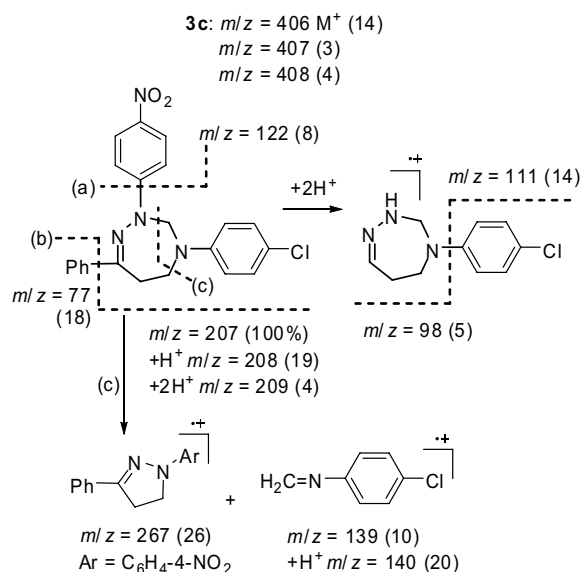
In line with this, the 2-benzenesulfonyl-tetrahydro-1,2,4-triazepine derivative **4** was obtained by treating **2b** with benzenesulfonyl hydrazide and formaldehyde. The synthesis of the 3-styryl-tetrahydro-1,2,4-triazepine **5** was achieved by treating the phenylhydrazone of **2a** with cinnamaldehyde. A practical advantage of the reactions leading to the 3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine derivatives **3–5** is that it is



Scheme 1.

often unnecessary to isolate the arylhydrazone intermediates of the ketonic *sec*-Mannich bases. The mass and ¹H NMR spectra of compounds **3–5** are consistent with their structures. The main characteristic features of the ¹H NMR spectrum of **3a** are a singlet at $\delta = 5.35$ assignable to 3-H₂ and two triplets at $\delta = 3.65$ (5-H₂) and 3.38 (6-H₂), and a singlet at $\delta = 2.33$ (Ar-CH₃). The mass spectra of **3a–f**, **4** and **5** contain peaks of the respective molecular ions, and fragmentation patterns which supported their structures. As an example the fragmentation pattern of **3c** is depicted in Scheme 2.

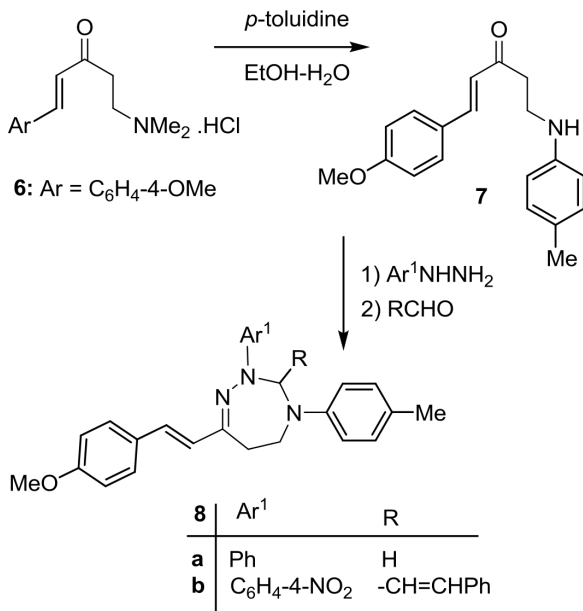
The scope of the above reaction has been broadened by treatment of the arylhydrazones derived from 1-(*p*-anisyl)-5-(*p*-tolylamino)-1-penten-3-one (**7**) with formaldehyde or cinnamaldehyde to afford 7-(4-methoxystyryl)-tetrahydro-2-phenyl-4-(*p*-tolyl)-2*H*-1,2,4-triazepine (**8a**) and 7-(4-methoxystyryl)-3-styryl-tetrahydro-2*H*-1,2,4-triazepine (**8b**), re-



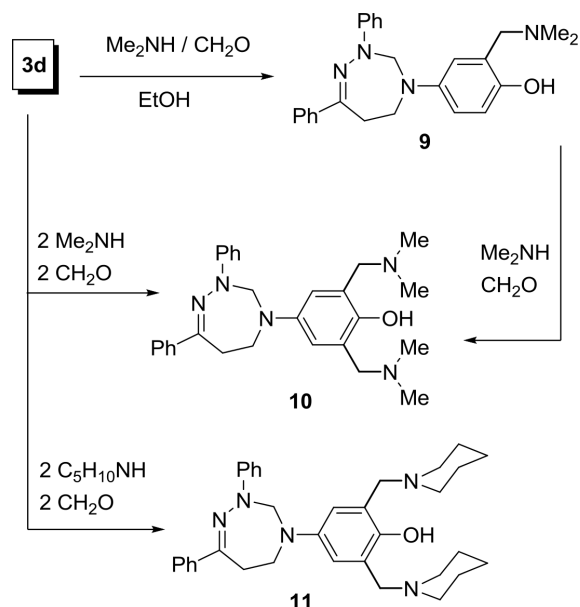
Scheme 2.

spectively (Scheme 3). The analytical and spectral data of **8a** and **8b** are consistent with their structures.

The Mannich reaction of the 4-(*p*-hydroxyphenyl)-tetrahydro-2*H*-1,2,4-triazepine (**3d**) is of particular interest, because it provides access to tetrahydro-2*H*-1,2,4-triazepines having a phenolic Mannich base as a structural unit. This has been achieved by treating **3d** with dimethylamine or piperidine and formaldehyde to



Scheme 3.



Scheme 4.

give the mono-(Mannich base) **9** or the bis-(Mannich bases) **10** and **11** depending on the molar ratio of the reactants (Scheme 4).

The structures of compounds **9–11** are supported by analytical and spectral data. The ^1H NMR spectrum of **9** displays four singlets at $\delta = 2.38$ (NMe_2), 3.67 ($\text{Ar-CH}_2\text{N}$), 5.17 (3-H_2), and 6.71 (ArOH), and two triplets at $\delta = 3.62$ (5-H_2) and 3.34 (6-H_2). The mass spectra of **9**, **10** and **11** revealed molecular ion peaks at $m/z = 400$, 458 [$\text{M}+1$] $^+$ and 537, respectively, and fragmentation patterns which supported their structures.

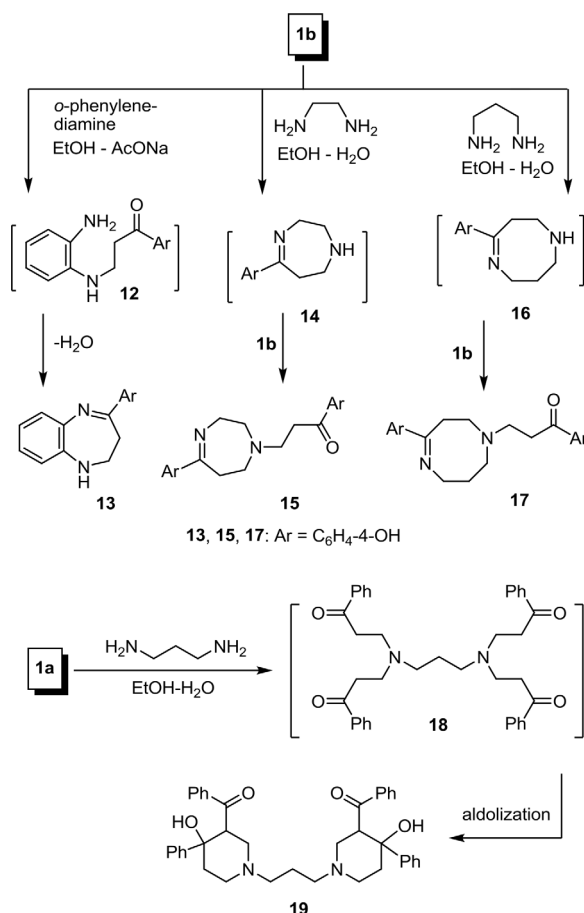
In connection with the present study, the transamination reaction between **1b** and *o*-phenylenediamine afforded the 2,3-dihydro-4-(*p*-hydroxyphenyl)-1*H*-1,5-benzodiazepine **13**. It is believed that the initially formed intermediate **12** readily undergoes cyclodehydration to give **13**, as confirmed by analytical and spectral data (Scheme 5).

On the other hand, the reaction of **1b** with ethylenediamine led to the formation of 2,3,6,7-tetrahydro-1-(β -4-hydroxybenzoyl-ethyl)-5-(4-hydroxyphenyl)-1*H*-1,4-diazepine (**15**) rather than the tetrahydro-1,4-diazepine **14**, which would be the expected product. Obviously, **15** was formed *via* the intermediacy of the non-isolable tetrahydro-1,4-diazepine **14**, resulting from the cyclocondensation reaction of ethylenediamine with **1b**, which readily reacts further with a second molecule of **1b** *via* transamination to afford the

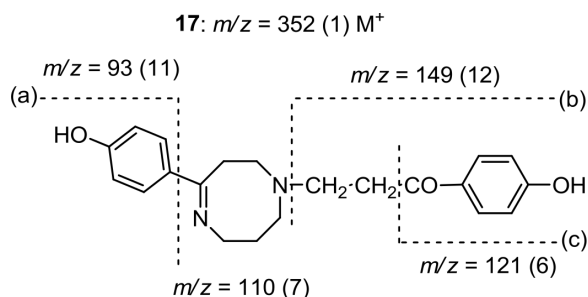
new Mannich base **15**. The reaction of **1b** with 1,3-diaminopropane proceeded quite analogously to afford 3,4,7,8-tetrahydro-1-(β -4-hydroxybenzoyl-ethyl)-6-(4-hydroxyphenyl)-2*H*-1,5-diazocine (**17**). The reaction of **1b** with ethylenediamine and 1,3-diaminopropane is of particular interest, because it offers access with good yields to the new tetrahydro-1,4-diazepine and tetrahydro-1,5-diazocine Mannich bases **15** and **17**, respectively.

The mass spectrum of **17** exhibited a molecular ion peak at $m/z = 352$ [M] $^+$ and a peak at $m/z = 110$ due to the tetrahydro-1,5-diazocine unit. The side chain can be identified by two peaks at $m/z = 121$ and 149 (Scheme 6). The formation of **15** and **17** is in line with our recent report [16] on the reaction of bis-ketonic Mannich bases with ethylenediamine.

On the other hand, the reaction of **1a** with 1,3-diaminopropane in a molar ratio of 4:1 takes a different course. The reaction proceeded smoothly to



Scheme 5.



Scheme 6.

give 1,3-bis(3-benzoyl-4-hydroxy-4-phenylpiperidin-1-yl)propane (**19**), via the intermediacy of *N,N,N',N'*-tetra(β -benzoylethyl)-1,3-diaminopropane (**18**), which undergoes intramolecular aldolization to give **19** as the end product. The identity of the product as the bi-(piperidinol) **19**, and not the isomeric tetraketo base **18**, was shown by the IR spectrum which displayed a strong OH band at 3421 cm^{-1} as well as the absorption band at 1629 cm^{-1} for C=O. The tendency of primary alkyl amines to undergo double *N*-alkylation with ketonic Mannich bases, and subsequent aldolization of the resulting bis-(ketonic Mannich bases) to *N*-alkyl piperidinols, has been previously reported [14–16]. Attempts to isolate the intermediate tetraketo base **18** were unsuccessful due to the ease with which such bases undergo aldolization even at r. t.

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^1H and ^{13}C NMR data were obtained in CDCl_3 or $[\text{D}_6]\text{DMSO}$ solution on a Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a GC-MS QP-1000 EX Shimadzu instrument. The course of the reaction and the purity of the synthesized compounds were monitored by TLC using EM science silica gel-coated plates with visualization by irradiation with an ultraviolet lamp. Compounds **3f**, **8b**, **17**, and **19** are of limited solubility in common ^1H NMR solvents. Compounds **1b** [28], **2a–d** [27], **2c** and **e** [16], **3d** [16], and **6** [9] were prepared as previously described.

β -Arylamino propiophenones **2f–h**

A mixture of **1a** (2.13 g, 10 mmol) or **1b** (2.29 g, 10 mmol) and the appropriate amine (10 mmol) in

50 % aqueous ethanol (80 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **2f–h**.

4-(3-Oxo-3-phenylpropylamino)benzamide (**2f**)

M. p. 198°C . Yield 75 % (colorless crystals). – IR (KBr): $\nu = 3399$ (NH), 3360 (CONH), 1666 (CO), 1592 , 1388 , 1326 , 1060 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.46$ (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 3.31 (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 4.40 (s, 1H, ArNH), 7.19 – 7.73 (m, 9H, aromatic), 8.11 (br. s, 2H, CONH_2). – MS (EI, 70 eV): m/z (%) = 268 (18) $[M]^+$, 267 (2) $[M-1]^+$, 149 (100) $[\text{CH}_2\text{NH}-\text{C}_6\text{H}_4-\text{CONH}_2]^+$, 136 (7), 133 (3), 132 (12), 120 (11), 105 (37), 77 (32). – $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ (268.31): calcd. C 71.62, H 6.01, N 10.44; found C 71.59, H 5.58, N 10.21.

4-(3-Oxo-3-phenylpropylamino)benzenesulfonamide (**2g**)

M. p. 220°C . Yield 60 % (colorless crystals). – IR (KBr): $\nu = 3410$ (NH), 3380 (SO_2NH), 1671 (CO), 1469 , 1330 , 1226 , 1145 cm^{-1} . – MS (EI, 70 eV): m/z (%) = 304 (14) $[M]^+$, 305 (3) $[M+1]^+$, 303 (2) $[M-1]^+$, 185 (100) $[\text{CH}_2\text{NH}-\text{C}_6\text{H}_4-\text{SO}_2\text{NH}_2]^+$, 172 (10), 156 (6), 133 (4), 119 (10) $[\text{PhCOCH}_2]^+$, 105 (56) $[\text{PhCO}]^+$, 77 (39). – $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ (304.36): calcd. C 59.19, H 5.30, N 9.20; found C 59.09, H 5.21, N 9.11.

3-(4-Hydroxyphenylamino)-1-(4-hydroxyphenyl)propan-1-one (**2h**)

M. p. 185°C . Yield 57 % (yellow crystals). – IR (KBr): $\nu = 3439$ (OH), 3366 (NH), 1664 (CO), 1492 , 1338 , 1226 , 1120 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.34$ (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 3.42 (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 4.46 (s, 1H, ArNH), 7.11 – 7.82 (m, 8H, aromatic), 11.77 (s, 2H, $2\times\text{OH}$). – MS (EI, 70 eV): m/z (%) = 257 (10) $[M]^+$, 148 (37) $[\text{HO}-\text{C}_6\text{H}_4-\text{COCH}=\text{CH}_2]^+$, 121 (100) $[\text{HO}-\text{C}_6\text{H}_4-\text{CO}]^+$, 109 (43), 93 (25). – $\text{C}_{15}\text{H}_{15}\text{NO}_3$ (257.28): calcd. C 70.02, H 5.88, N 5.44; found C 69.95, H 5.82, N 5.31.

3,4,5,6-Tetrahydro-2,4,7-triaryl-2H-1,2,4-triazepines **3a–f**

A solution of the appropriate β -(arylamino)propiophenone (**2a–h**) (5 mmol) and *p*-nitrophenylhydrazine (0.77 g, 5 mmol) or phenylhydrazine (0.54 g, 5 mmol) in ethanol (30 mL) was heated on a steam bath for 20 min, then formalin (37 %, 0.6 mL, 8 mmol) and acetic acid (0.1 mL) were added. The reaction mixture was heated for 5 min, and the product obtained on cooling was filtered and crystallized from the appropriate solvent to give **3a–f**.

3,4,5,6-Tetrahydro-2-(*p*-nitrophenyl)-7-phenyl-4-*p*-tolyl-2H-1,2,4-triazepine (**3a**)

M. p. 196°C (ethanol). Yield 71 % (yellow crystals). – IR (KBr): $\nu = 1610$ (C=N), 1520 , 1365 , 1238 , 1210 ,

870 cm^{-1} . – ^1H NMR (CDCl_3): δ = 2.33 (s, 3H, ArMe), 3.38 (t, 2H, 6- H_2), 3.65 (t, 2H, 5- H_2), 5.35 (s, 2H, 3- H_2), 6.88–8.08 (m, 13H, aromatic). – ^{13}C NMR (CDCl_3): δ = 20.51 (CH_3), 30.98 (C-6), 45.64 (C-5), 71.62 (C-3), 112.88, 116.60, 126.40, 128.54, 129.14, 130.12, 132.47, 138.10, 140.03, 146.01, 152.31 (all Ar-C), 154.94 (C-7). – MS (EI, 70 eV): m/z (%) = 386 (3) $[\text{M}]^+$, 387 (1) $[\text{M}+1]^+$, 268 (17), 309 (5), 236 (100) $[\text{M}-(\text{NO}_2-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2)]^+$, 218 (11), 173 (3), 150 (4), 122 (12), 119 (62) $[\text{Me}-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2]^+$, 120 (31), 105 (54), 91 (79), 77 (36). – $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2$ (386.45): calcd. C 71.48, H 5.74, N 14.50; found C 71.40, H 5.68, N 14.44.

3,4,5,6-Tetrahydro-4-(p-bromophenyl)-2-(p-nitrophenyl)-7-phenyl-2H-1,2,4-triazepine (3b)

M.p. 188 °C (ethanol). Yield 60 % (reddish crystals). – IR (KBr): ν = 1615 (C=N), 1529, 1355, 1218, 1110, 875 cm^{-1} . – ^1H NMR (CDCl_3): δ = 3.32 (t, 2H, 6- H_2), 3.57 (t, 2H, 5- H_2), 5.15 (s, 2H, 3- H_2), 7.17–8.24 (m, 13H, aromatic). – MS (EI, 70 eV): m/z (%) = 451 (14) $[\text{M}]^+$, 452 (9) $[\text{M}+1]^+$, 301 (100), 300 (93) $[\text{M}-(\text{NO}_2-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2)]^+$, 267 (38) $[\text{M}-(\text{Br}-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2)]^+$, 220 (27), 207 (73), 184 (25), 156 (12), 77 (43). – $\text{C}_{22}\text{H}_{19}\text{BrN}_4\text{O}_2$ (451.32): calcd. C 58.55, H 4.24, N 12.41; found C 58.48, H 4.18, N 12.21.

3,4,5,6-Tetrahydro-4-(p-chlorophenyl)-2-(p-nitrophenyl)-7-phenyl-2H-1,2,4-triazepine (3c)

M.p. 190 °C (ethanol). Yield 65 % (reddish crystals). – IR (KBr): ν = 1617 (C=N), 1537, 1326, 1209, 1100, 855 cm^{-1} . – ^1H NMR (CDCl_3): δ = 3.28 (t, 2H, 6- H_2), 3.51 (t, 2H, 5- H_2), 4.86 (s, 2H, 3- H_2), 7.21–8.12 (m, 13H, aromatic). – MS (EI, 70 eV): m/z (%) = 406 (14) $[\text{M}]^+$, 407 (3) $[\text{M}+1]^+$, 408 (4) $[\text{M}+2]^+$, 267 (26), 208 (19), 207 (100) $[\text{M}-(\text{Ph}+\text{C}_6\text{H}_4-\text{NO}_2)]^+$, 139 (10), 122 (8), 111 (14), 77 (16). – $\text{C}_{22}\text{H}_{19}\text{ClN}_4\text{O}_2$ (406.86): calcd. C 64.94, H 4.71, N 13.77; found C 64.88, H 4.60, N 13.65.

4-(2,3,5,6-Tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)-benzamide (3e)

M.p. 215 °C (DMF). Yield 53 % (pale-yellow crystals). – IR (KBr): ν = 3359 (CONH₂), 1645 (CO), 1610 (C=N), 1517, 1436, 1225, 1142, 879 cm^{-1} . – ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 3.26 (t, 2H, 6- H_2), 3.87 (t, 2H, 5- H_2), 5.43 (s, 2H, 3- H_2), 6.66 (br. s, 2H, CONH₂), 7.25–7.84 (m, 14H, aromatic). – MS (EI, 70 eV): m/z (%) = 370 (4) $[\text{M}]^+$, 371 (2) $[\text{M}+1]^+$, 369 (1) $[\text{M}-1]^+$, 265 (100) $[\text{M}-\text{PhN}=\text{N}]^+$, 222 (65), 221 (93), 149 (53), 105 (35), 77 (81). – $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}$ (370.45): calcd. C 74.57, H 5.99, N 15.12; found C 74.50, H 6.01, N 15.04.

3,4,5,6-Tetrahydro-4,7-di(p-hydroxyphenyl)-2-phenyl-2H-1,2,4-triazepine (3f)

M.p. 199 °C (washed with boiling ethanol). Yield 50 % (dark-brown powder). – IR (KBr): ν = 3410–3329 (OH), 1610 (C=N), 1523, 1456, 1215, 1112, 956 cm^{-1} . – MS (EI, 70 eV): m/z (%) = 360 (51) $[\text{M}+1]^+$, 238 (62) $[\text{M}-(\text{HO}-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2)]^+$, 173 (58), 121 (33) $[\text{HO}-\text{C}_6\text{H}_4-\text{N}=\text{CH}_2]^+$, 97 (100), 96 (67), 95 (56), 93 (83), 77 (15). – $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2$ (359.42): calcd. C 73.52, H 5.89, N 11.69; found C 73.49, H 5.80, N 11.62.

3,4,5,6-Tetrahydro-4-(p-methoxyphenyl)-2-benzenesulfonyl-7-phenyl-2H-1,2,4-triazepine (4)

A solution of **2b** (0.64 g, 2.5 mmol) and benzenesulfonyl hydrazide (0.43 g, 2.5 mmol) in ethanol (30 mL) was heated on a steam bath for 20 min. After standing at r. t. for 2 h, formalin (37 %, 0.3 mL, 4 mmol) and acetic acid (0.1 mL) were added. The reaction mixture was heated for 5 min, and the product obtained on cooling was filtered and crystallized from ethanol to give **4**. M.p. 134 °C. Yield 60 % (pale-yellow crystals). – IR (KBr): ν = 1614 (C=N), 1515, 1478, 1362, 1165, 849 cm^{-1} . – ^1H NMR (CDCl_3): δ = 3.22 (t, 2H, 6- H_2), 3.52 (t, 2H, 5- H_2), 3.83 (s, 3H, OMe), 5.51 (s, 2H, 3- H_2), 7.12–7.77 (m, 14H, aromatic). – ^{13}C NMR (CDCl_3): δ = 54.67 (OMe), 29.97 (C-6), 46.76 (C-5), 72.78 (C-3), 111.98, 116.10, 126.34, 128.14, 129.10, 130.11, 132.17, 138.11, 146.22, 152.41 (all Ar-C), 156.44 (C-7). – MS (EI, 70 eV): m/z (%) = 421 (2) $[\text{M}]^+$, 422 (1) $[\text{M}+1]^+$, 252 (40), 251 (100), 173 (48), 174 (18), 142 (30), 107 (16) $[\text{C}_6\text{H}_4-\text{OMe}]^+$, 97 (8), 77 (59). – $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ (421.51): calcd. C 65.54, H 5.50, N 9.97; found C 65.48, H 5.47, N 9.88.

3,4,5,6-Tetrahydro-2,7-diphenyl-3-styryl-4-p-tolyl-2H-1,2,4-triazepine (5)

This compound was obtained from **2a** (0.60 g, 2.5 mmol) and phenylhydrazine (0.27 g, 2.5 mmol) in the manner described for the synthesis of **3a–f**, except for the use of cinnamaldehyde (0.40 g, 3 mmol) instead of formaldehyde. The product was crystallized from ethanol to give **5**. M.p. 180 °C. Yield 65 % (pale-yellow crystals). – IR (KBr): ν = 1610 (C=N), 1577, 1458, 1322, 1222, 1145, 870 cm^{-1} . – ^1H NMR (CDCl_3): δ = 2.31 (s, 3H, ArMe), 3.36 (t, 2H, 6- H_2), 3.58 (t, 2H, 5- H_2), 4.87 (d, 2H, 3- H_2), 6.22 (d, 1H, -CH=CH-Ph), 6.61 (d, 1H, -CH=CH-Ph), 6.83–7.68 (m, 19H, aromatic). – ^{13}C NMR (CDCl_3): δ = 21.81 (Me), 31.10 (C-6), 47.56 (C-5), 72.18 (C-3), 113.44, 114.36, 117.18, 124.44 (Ph-CH=CH), 127.12, 128.11, 129.12, 131.22 (Ph-CH=CH), 134.44, 138.33, 142.63, 147.41 (all Ar-C), 157.27 (C-7). – MS (EI, 70 eV): m/z (%) = 443 (58) $[\text{M}]^+$, 442 (50) $[\text{M}-1]^+$, 350 (59) $[\text{M}-(\text{p-tolyl})]^+$, 264 (55), 131 (29), 119 (100) $[\text{PhC}(\text{=NH})\text{Me}]^+$, 117 (88), 103 (47), 91 (45) $[\text{C}_6\text{H}_4-$

$\text{Me}]^+$. – $\text{C}_{31}\text{H}_{29}\text{N}_3$ (443.58): calcd. C 83.94, H 6.59, N 9.47; found C 83.88, H 6.56, N 9.39.

1-(p-Anisyl)-5-(p-tolylamino)-1-penten-3-one (7)

A mixture of **6** (2.15 g, 8 mmol) and *p*-toluidine (0.85 g, 8 mmol) in 50 % aqueous ethanol (80 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **6**. M. p. 110 °C. Yield 85 % (yellow crystals). – IR (KBr): $\nu = 3382$ (NH), 1653 (CO), 1605, 1557, 1460, 1319, 1209, 1105, 868 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.24$ (s, 3H, ArMe), 2.96 (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 3.52 (t, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 3.52 (s, 3H OMe), 6.64 (s, 1H, ArNH), 6.59 (d, 2H, Ar-CH=CH-CO), 6.93 (d, 2H, Ar-CH=CH-CO), 7.12–7.58 (m, 8H, aromatic). – $\text{C}_{19}\text{H}_{21}\text{NO}_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.18, H 7.10, N 4.69.

7-(4-Methoxystyryl)-3,4,5,6-tetrahydro-2-phenyl-4-p-tolyl-2H-1,2,4-triazepine (8a)

This compound was obtained from equimolar amounts of **6**, phenylhydrazine and formaldehyde (5 mmol) in ethanol (40 mL), following the procedure described for the synthesis of **3a–f**. The product was crystallized from ethanol to give **8a**. M. p. 184 °C. Yield 55 % (yellow crystals). – IR (KBr): $\nu = 1617$ (C=N), 1597, 1489, 1308, 1229, 1114, 1082, 847 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.28$ (s, 3H, ArMe), 3.42 (t, 2H, 6- H_2), 3.60 (s, 3H, OMe), 3.94 (t, 2H, 5- H_2), 4.58 (s, 2H, 3- H_2), 6.89 (d, 2H, Ar-CH=CH-), 6.96 (d, 2H, Ar-CH=CH-), 7.02–7.33 (m, 8H, aromatic). – ^{13}C NMR (CDCl_3): $\delta = 22.11$ (Me), 32.18 (C-6), 48.44 (C-5), 54.23 (OMe), 79.89 (C-3), 113.33, 114.28, 116.88, 127.14, 129.44, 130.10, 136.47 (Ar-CH=CH), 138.33 (Ar-CH=CH), 142.63, 146.41, 156.10, 158.31 (all Ar-C), 154.77 (C-7). – $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}$ (397.51): calcd. C 78.56, H 6.85, N 10.57; found C 78.50, H 6.77, N 10.49.

7-(4-Methoxystyryl)-3,4,5,6-tetrahydro-2-(4-nitrophenyl)3-styryl-4-p-tolyl-2H-1,2,4-triazepine (8b)

This compound was obtained from equimolar amounts of **6**, *p*-nitrophenylhydrazine and cinnamaldehyde (5 mmol) in ethanol (80 mL), in the manner described for the synthesis of **3a–f**. The product obtained was filtered and washed with boiling ethanol (3×15 mL) to give **8b**. M. p. 265 °C. Yield 33 % (yellow powder). – IR (KBr): $\nu = 1622$ (C=N), 1588, 1459, 1326, 1232, 1119, 1066, 865 cm^{-1} . – MS (EI, 70 eV): m/z (%) = 530 (46) $[\text{M}-\text{Me}]^+$, 213 (67), 134 (52), 107 (6), 103 (61), 98 (70) [triazepine unit] $^+$, 84 (100) [triazepine unit-(CH_2)] $^+$. – $\text{C}_{34}\text{H}_{32}\text{N}_4\text{O}_3$ (544.64): calcd. C 74.98, H 5.92, N 10.29; found C 74.91, H 5.89, N 10.21.

2-(Dimethylaminomethyl)-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (9)

A solution of **3d** [16] (1.37 g, 4 mmol), formalin (37 %, 0.4 mL, 5 mmol) and dimethylamine (40 %, 0.56 mL, 5 mmol) in ethanol (50 mL) was refluxed for 6 h. After standing at r.t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **9**. M. p. 145 °C. – Yield 72 % (colorless crystals). – IR (KBr): $\nu = 3373$ (OH), 1605 (C=N), 1588, 1454, 1371, 1271, 1113, 1073 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.38$ (s, 6H, $\text{N}(\text{Me})_2$), 3.33 (t, 2H, 6- H_2), 3.60 (t, 2H, 5- H_2), 3.67 (s, 2H, CH_2N), 5.17 (s, 2H, 3- H_2), 12.01 (s, 1H, OH), 6.88–7.85 (m, 13H, aromatic). – ^{13}C NMR (CDCl_3): $\delta = 30.98$ (C-6), 44.21 (C-5), 46.61 (NMe), 62.44 (CH_2N), 74.89 (C-3), 115.32, 117.12, 118.89, 119.42, 120.54, 126.11, 126.29, 128.29, 128.56, 128.84, 139.42, 141.74, 148.33, (all Ar-C), 152.09 (C-7). – MS (EI, 70 eV): m/z (%) = 400 (4) $[\text{M}]^+$, 401 (1) $[\text{M}+1]^+$, 250 (59) $[\text{M}-(\text{C}_6\text{H}_3-\text{OH}+\text{CH}_2\text{Me}_2)]^+$, 251 (13), 93 (7), 77 (100), 58 (15) $[\text{CH}_2\text{NMe}_2]^+$. – $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}$ (400.52): calcd. C 74.97, H 7.05, N 13.99; found C 74.91, H 6.97, N 13.90.

2,6-Bis-(dimethylaminomethyl)-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (10)

Procedure A: This compound was obtained from equimolar amounts of **9**, formalin and dimethylamine (5 mmol) in ethanol (50 mL), following the procedure described for the synthesis of **9**. The product was crystallized from ethanol to give **10**. M. p. 190 °C. Yield 55 % (colorless crystals). – IR (KBr): $\nu = 3370$ (OH), 1612 (C=N), 1577, 1446, 1335, 1221, 1108, 1079 cm^{-1} . – ^1H NMR (CDCl_3): $\delta = 2.30$ (s, 12H, $2 \times \text{NMe}_2$), 3.34 (t, 2H, 6- H_2), 3.96 (t, 2H, 5- H_2), 4.17 (s, 4H, $2 \times \text{CH}_2\text{N}$), 5.31 (s, 2H, 3- H_2), 12.11 (s, 1H, OH), 6.94–7.75 (m, 12H, aromatic). – MS (EI, 70 eV): m/z (%) = 457 (6) $[\text{M}]^+$, 456 (18) $[\text{M}-1]^+$, 370 (6), 222 (40), 233 (27), 248 (10), 263 (100) $[\text{M}-(\text{Ph}=\text{N}-\text{NPh})]^+$, 264 (75), 104 (23), 77 (19), 57 (34). – $\text{C}_{28}\text{H}_{35}\text{N}_5\text{O}$ (457.61): calcd. C 73.49, H 7.71, N 15.30; found C 73.41, H 7.69, N 15.22.

Procedure B: A solution of **3d** (1.37 g, 4 mmol), formalin (37 %, 0.8 mL, 10 mmol) and dimethylamine (40 %, 1.12 mL, 10 mmol) in ethanol (50 mL) was refluxed for 8 h. After standing at r.t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **10**. M. p. 190–192 °C. Yield 60 %. The structure was confirmed by a comparison of ^1H NMR data, m. p. and TLC with that from Procedure A.

2,6-[Bis-(piperidin-1-ylmethyl)]-4-(2,3,5,6-tetrahydro-2,7-diphenyl-1,2,4-triazepin-4-yl)phenol (11)

This compound was obtained from **3d** (1.37 g, 4 mmol), formalin (37 %, 1 mL, 12 mmol) and piperidine (1 g, 12 mmol), following the procedure described for the syn-

thesis of **9**. The product was crystallized from ethanol to give **11**. M.p. 142 °C. Yield 49 % (colorless crystals). – IR (KBr): ν = 3377 (OH), 1618 (C=N), 1557, 1426, 1355, 1216, 1100, 1050 cm^{-1} . – ^1H NMR (CDCl_3): δ = 1.52–1.67 [m, 12H, $2\times$ (3- H_2 , 4- H_2 , 5- H_2) of piperidine], 2.55 (m, 4H, 2- H_2 , 6- H_2 of piperidine), 3.35 (t, 2H, 6- H_2), 3.60 (t, 2H, 5- H_2), 3.68 (s, 4H, $2\times$ CH_2N), 5.16 (s, 2H, 3- H_2), 11.11 (s, 1H, OH), 6.85–7.86 (m, 12H, aromatic). – ^{13}C NMR (CDCl_3): δ = 23.92 (C-3, C-4, C-5 of piperidine), 25.72 (C-6), 31.21 (C-5), 46.65 (C-2, C-6 of piperidine), 53.85 (CH_2N), 75.10 (C-3), 115.33, 118.82, 120.54, 126.12, 126.29, 128.28, 128.54, 128.82, 139.45, 142.45, 148.98 (all Ar-C), 150.54 (C-7). – MS (EI, 70 eV): m/z (%) = 537 (1) $[\text{M}]^+$, 440 (61) $[\text{M}-(\text{CH}_2\text{NC}_5\text{H}_{10})+\text{H}]^+$, 250 (100) $[\text{M}-(\text{C}_6\text{H}_2\text{OH}(\text{CH}_2\text{NC}_5\text{H}_{10})_2)^+]$, 251 (22), 222 (16), 204 (10), 84 (4) $[\text{NC}_5\text{H}_{10}]^+$. – $\text{C}_{34}\text{H}_{43}\text{N}_5\text{O}$ (537.74): calcd. C 75.94, H 8.06, N 13.02; found C 75.91, H 7.98, N 12.97.

2,3-Dihydro-4-(p-hydroxyphenyl)-1H-1,5-benzodiazepine (13)

A mixture of **1b** (1.14 g, 5 mmol), *o*-phenylenediamine (0.54 g, 5 mmol) and fused sodium acetate (1.5 g) in absolute ethanol (80 mL) was refluxed for 6 h. The crystalline product was filtered and washed with boiling ethanol-acetone (1 : 1) to give **13**. M.p. 134 °C. Yield 60 % (yellow crystals). – IR (KBr): ν = 3394 (OH), 3360 (NH), 1611 (C=N), 1513, 1493, 1344, 1144, 810 cm^{-1} . – ^1H NMR (CDCl_3): δ = 3.11 (m, 2H, 3- H_2), 3.54 (m, 2H, 2- H_2), 6.16 (br. s, 1H, NH), 6.84–7.83 (m, 8H, aromatic), 8.22 (br. s, 1H, OH). – ^{13}C NMR (CDCl_3): δ = 32.16 (C-3), 47.11 (C-2), 113.44, 119.20, 123.24, 127.81, 130.35, 134.45 (all Ar-C), 138.11 (C-5a), 138.55 (C-5b), 168.11 (C-4). – MS (EI, 70 eV): m/z (%) = 238 (1) $[\text{M}]^+$, 222 (2), 210 (4), 121 (9), 120 (100), 119 (12), 107 (31), 106 (27), 92 (19), 77 (35). – $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ (238.28): calcd. C 75.61, H 5.92, N 11.76; found C 75.55, H 5.88, N 11.69.

2,3,6,7-Tetrahydro-1-(β -4-hydroxybenzoyl-ethyl)-5-(4-hydroxyphenyl)-1H-1,4-diazepine (15)

A mixture of **1b** (1.14 g, 5 mmol) and ethylenediamine (0.3 g, 5 mmol) in 50 % aqueous ethanol (50 mL) was re-

fluxed for 3 h. After standing at r.t. for 24 h, the product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **15**. M.p. 255 °C. Yield 52 % (pale-yellow powder). – IR (KBr): ν = 3422 (OH), 1610 (C=N), 1510, 1349, 1036, 1008, 814 cm^{-1} . – ^1H NMR ($[\text{D}_6]$ DMSO): δ = 2.48 (m, 2H, 7- H_2), 2.52 (m, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 2.64 (m, 2H, 2- H_2), 2.96 (m, 2H, $\text{COCH}_2\text{CH}_2\text{N}$), 3.28 (m, 2H, 6- H_2), 3.56 (m, 2H, 3- H_2), 6.78–7.77 (m, 8H, aromatic), 10.11 (br. s, 1H, OH). – $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ (338.40): calcd. C 70.99, H 6.55, N 8.28; found C 70.91, H 6.49, N 8.20.

3,4,7,8-Tetrahydro-1-(β -4-hydroxybenzoyl-ethyl)-6-(4-hydroxyphenyl)-2H-1,5-diazocine (17)

This compound was obtained from equimolar amounts of **1b** and 1,3-diaminopropane (5 mmol), following the procedure described for the synthesis of **15**. The product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **17**. M.p. 260 °C. Yield 33 % (yellow powder). – IR (KBr): ν = 3940 (OH), 1619 (C=N), 1479, 1407, 1336, 1217, 1102 cm^{-1} . – MS (EI, 70 eV): m/z (%) = 352 (1) $[\text{M}]^+$, 149 (12) $[\text{HO}-\text{C}_6\text{H}_4-\text{COCH}_2\text{CH}_2]^+$, 121 (6), 119, 110 (7), 109 (10), 111 (11), 93 (11), 85 (28), 71 (43), 69 (100) $[(\text{C}_4\text{H}_7)\text{N}]^+$, 55 (69). – $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ (352.43): calcd. C 71.57, H 6.86, N 7.95; found C 71.50, H 6.79, N 7.87.

1,3-Bis(3-benzoyl-4-hydroxy-4-phenylpiperidin-1-yl)propane (19)

This compound was obtained from **1a** (3.83 g, 18 mmol) and 1,3-diaminopropane (0.33 g, 4.5 mmol), following the procedure described for the synthesis of **15**. The product obtained was filtered and washed with boiling DMF-ethanol (1 : 1) to give **19**. M.p. 256 °C. Yield 71 % (colorless powder). – IR (KBr): ν = 3421 (OH), 1629 (CO), 1600, 1483, 1407, 1216, 1102, 941 cm^{-1} . – MS (EI, 70 eV): m/z (%) = 601 (58) $[\text{M}-1]^+$, 416 (47), 275 (57), 228 (48), 206 (63), 207 (39), 185 (83), 158 (58), 110 (100), 105 (27), 98 (87), 96 (60), 77 (35). – $\text{C}_{39}\text{H}_{42}\text{N}_2\text{O}_4$ (602.76): calcd. C 77.71, H 7.02, N 4.65; found C 77.70, H 6.98, N 4.58.

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