Mannich Bases as Synthetic Intermediates: Alkylation of Amines and Diamines with Bis-ketonic Mannich Bases

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The bis-ketonic Mannich base, *N,N*-bis(β-benzoylethyl)methylamine hydrochloride (**1**) reacts with primary arylamines and diamines to give ketonic *sec*-arylamines **3a** – **e** and **4**. The piperidines **7a** – **c** were obtained from **1** and primary alkylamines, whereas the 1,4-diazepine derivative **10** was obtained from **1** and ethylenediamine.

Treatment of the bis-base 1,4-di[β-(*N*-morpholino)propionyl]benzene bis(hydrochloride) (**11**) with primary arylamines gave the corresponding bis-(*sec*-arylamines) **12a** – **b**, whereas its reaction with *o*-phenylenediamine afforded the bis[1,5-benzodiazepine] ring system **14**. The synthesis of the diazacyclophane ring system **15** has been achieved by treating **11** with piperazine. Attempted synthesis of 4-aza-[7]-*para*cyclophane (**16**) from **11** and benzylamine led to **17**. The reaction of **1** or **11** with phenylhydrazine gave the 2-pyrazolines **18** and **19**. Treatment of **3** or **4** with phenylhydrazine and formaldehyde afforded the 2*H*-1,2,4-triazepines **20a** – **c** and the bis[2*H*-1,2,4-triazepine] ring system **21**.

Key words: Bis-(Mannich Bases), Transamination, 1,2,4-Triazepines, Diazacyclophanes

Introduction

Mannich bases and their quaternary salts have been employed frequently as potential synthetic intermediates, particularly in alkylation reactions. The alkylation of various substrates such as amines [1 – 7], enamines [8 – 10], NH-heterocycles [11 – 13] and thiols [1, 7, 14, 15] with ketonic Mannich bases has been the subject of extensive studies. Although the synthetic utility of mono-(Mannich bases) in alkylation reactions was well established [1 – 16], the use of bis-(Mannich bases) in such reactions was less widely recognized and has been limited [17 – 21].

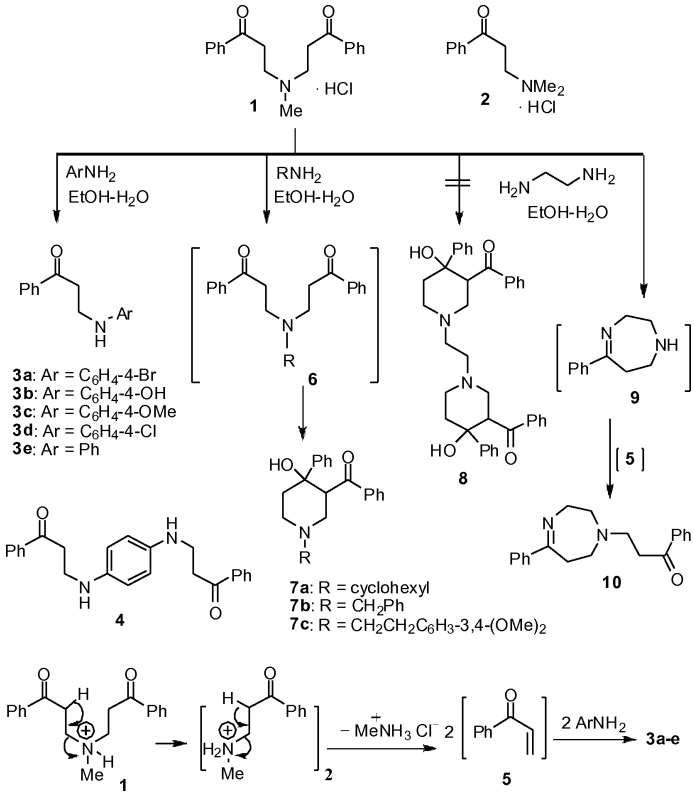
In connection with our studies in this area [7, 21 – 24], and in view of the wide range of biological activities of ketonic Mannich bases such as antimicrobial [25, 26], cytotoxic [27 – 29] and anticancer [28] activities, the present work is concerned with attempts to extend the scope of the *N*-alkylation of amines and diamines with bis-(ketonic Mannich bases) to include the synthesis of some new Mannich bases and related heterocycles of pharmaceutical interest.

Results and Discussion

The bis-(Mannich base) *N,N*-bis(β-benzoylethyl)-methylamine hydrochloride (**1**) was prepared according to an earlier report [30]. Treatment of **1** with the appropriate primary aromatic amine afforded a series of β-(arylamino)propiophenones **3a** – **e** in excellent yields.

The analogous reaction of **1** with *p*-phenylenediamine gave *N,N′*-bis(β-benzoylethyl)-*p*-phenylenediamine (**4**). Compounds **3c** – **e** and **4** are identical (m. p., IR and ^{1}H NMR spectra) to authentic samples previously prepared from the mono-(Mannich base) **2** and the appropriate amine [3]. The IR spectra of **3a** – **e** and **4** showed sharp bands around 3392 – 3355 (NH), 1363 – 1317 (C–N stretch of *sec*-arylamine) and 1677 – 1665 cm^{-1} (CO). The ^{1}H NMR spectra revealed the presence of an amine proton at δ = 4.20 – 4.45 and the methylene protons as two triplets at δ = 2.35 – 2.42 (COCH_2) and 3.15 – 3.31 (CH_2NHAr) with J = 7 Hz in both cases. The formation of **3** and **4** from **1** may be rationalized on the basis of a mechanism which involves the elimination-addition sequence that is operative with ketonic Mannich bases [1 – 4] *via* the intermediacy of the enone **5**, which is formed *in situ* through two successive deamination reactions of the bis-(Mannich base) **1**. Nucleophilic addition of the primary aromatic amine to **5** provided **3a** – **e** and **4** (Scheme 1).

On the other hand, the reaction of **1** with primary aliphatic amines such as cyclohexylamine, benzylamine and 2-(3,4-dimethoxyphenyl)ethylamine takes a different course. The products were identified as

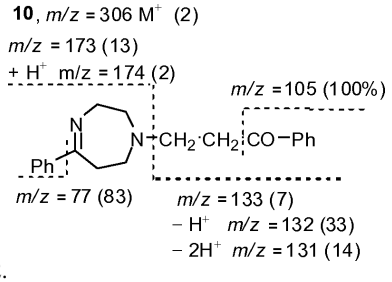


Scheme 1.

the *N*-substituted 3-benzoyl-4-hydroxy-4-phenylpiperidines **7a**–**c**. Compounds **7a**, **b** are identical (m. p., mixed m. p. and spectral data) with authentic samples obtained from the mono-(Mannich base) **2** and the appropriate amine as previously reported [4, 31]. The structure of **7a**–**c** was confirmed on the basis of analytical and spectral data. In each case, the identity of the product as the *N*-substituted piperidinol **7** and not the isomeric diketo base **6**, was shown by the IR spectra which possessed a strong OH band around 3400 cm^{-1} as well as the (CO) absorption band (1675 cm^{-1}).

Obviously, compounds **7a**–**c** were formed *via* the non-isolable diketo bases **6a**–**c**, which were readily converted into **7** by intramolecular aldolization. The double *N*-alkylation of primary aliphatic amines with Mannich bases, leading to **6a**–**c**, can be rationalized by consideration of their strong basicity and nucleophilicity as compared with aromatic amines. Attempts to isolate the intermediates **6a**–**c** were unsuccessful due to the ease with which such bases undergo intramolecular aldolization even at r. t.

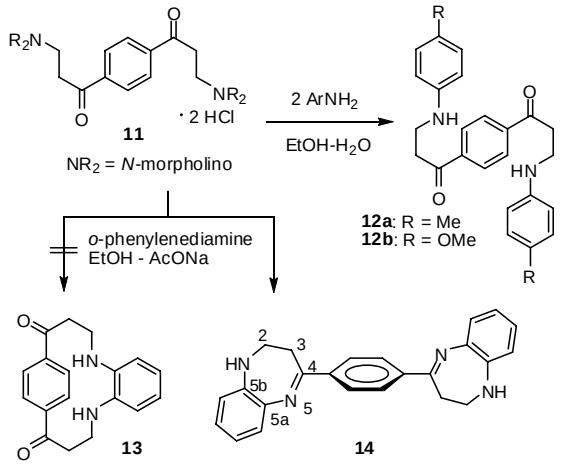
It is interesting in this connection that the reaction of **1** with ethylenediamine does not afford the dip-



Scheme 2.

iperidine derivative **8**, as could have been expected in analogy to the formation of **7a**–**c**. Actually, the product of such a reaction was identified on the basis of its analytical and spectral data as 2,3,6,7-tetrahydro-1-(β-benzoylethyl)-5-phenyl-1*H*-1,4-diazepine (**10**). Its mass spectrum showed the molecular ion at *m/z* = 306. The base peak at *m/z* = 105 (100%) is due to the (PhCO) ion. Two peaks at *m/z* = 174 and 173 identify the 1,4-diazepine unit (Scheme 2).

The ^{1}H NMR spectrum of **10** supported the structure, as it revealed the 1,4-diazepine ring protons as two triplets at δ = 2.96 and 3.32 (6-H_2 and 7-H_2), and a multiplet at 3.38 – 3.42 (2-H_2 and 3-H_2), and the side

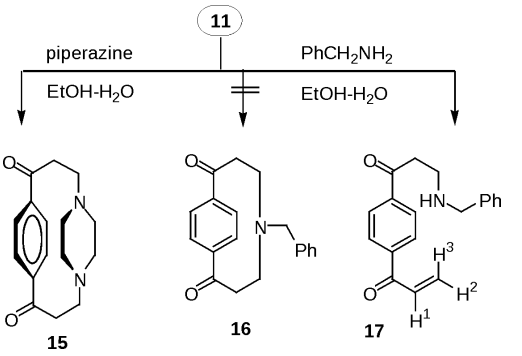


Scheme 3.

chain protons as two triplets at 2.61 ($COCH_2$) and 3.14 (CH_2N). The formation of **10** rather than **8** or **7** (R = $CH_2CH_2NH_2$) may be attributed to the intermediacy of the non-isolable 1*H*-1,4-diazepine **9**, resulting from the cyclocondensation reaction of ethylenediamine with **5**, which readily reacts further with a second molecule of **5** to afford the new Mannich base **10**.

In connection with the present study, the *N*-alkylation of amines with bis-(Mannich bases) was further extended to the use of 1,4-di[β-(*N*-morpholino) propionyl]benzene bis(hydrochloride) (**11**), and some interesting results were obtained. Treatment of **11** with *p*-toluidine or *p*-anisidine gave the expected 1,4-di[β-(arylamino)propionyl]benzenes (**12a**, **b**) respectively, *via* a double transamination reaction (Scheme 3). The bis-base **12a** was again the sole product when the reaction conditions were modified in the hope of isolating a mixed bis-base, in which one *N*-morpholino group is replaced by a *sec*-arylamino group.

On the other hand, the reaction of **11** with *o*-phenylenediamine afforded 4,4′-[*p*-phenylene-bis(2,3-dihydro-1*H*-1,5-benzodiazepine)] (**14**) rather than the macrocyclic compound **13**, which would be the expected product. The IR spectrum of **14** revealed the absence of a carbonyl group and showed strong bands at 3394 (NH) and 1612 cm^{-1} (C=N). The mass spectrum exhibited a molecular ion peak at *m/z* = 366 (M^+) (100 %). The benzodiazepine moiety could be identified by two peaks at *m/z* = 145 and 143. The formation of **14** is in line with the work of Roman *et al.* [32], who obtained 4-aryl-2,3-dihydro-1*H*-1,5-benzodiazepine *via* cyclocondensation of the mono-base **2** with *o*-phenylenediamine.



Scheme 4.

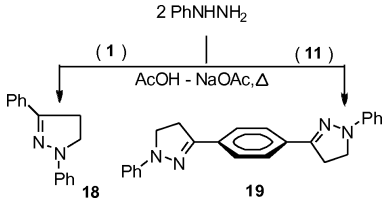
In order to extend the scope of the reaction of **11** with diamines, the synthetic possibilities afforded by replacing *o*-phenylenediamine with piperazine have been investigated as a possible route to the new diazacyclophane ring system **15**. The synthesis of **15** has been achieved by treating **11** with an equimolar amount of piperazine to afford 1,12-diaza-tricyclo[10.2.2.$2^{5,8}$]octadeca-5(18), 8(17)-triene-4,9-dione (**15**) (Scheme 4).

The mass spectrum of **15** indicated the molecular ion peak at *m/z* = 272 (M^+). The base peak at *m/z* = 159 (100 %) is due to the $[CH_2{=}CH\text{-}CO\text{-}C_6H_4\text{-}CO]^+$ fragment. The ^{1}H NMR spectrum supported the structure as it revealed a broad singlet at $\delta = 2.61$ assignable to [N(CH_2CH_2)$_2$N] of the piperazine ring, and a multiplet at 3.12 – 3.56 (2 × $COCH_2CH_2N$).

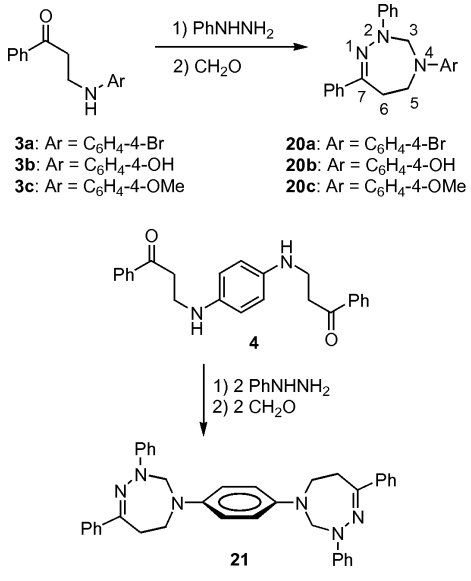
The tendency of primary aliphatic amines to undergo double *N*-alkylation with Mannich bases prompted us to investigate the reaction of **11** with benzylamine as a possible route to the 4-aza-[7]-paracyclophane ring system **16**, but this has not been realized. Actually, the reaction product was identified on the basis of its analytical and spectral data as 4-[β-(benzylamino)propionyl]acrylophenone (**17**).

In an extension of this study, the reaction of the di-keto base **1** with phenylhydrazine in boiling acetic acid containing sodium acetate afforded 1,3-diphenyl-2-pyrazoline (**18**), which is identical (m. p., mixed m.p. and spectral data) with an authentic sample obtained from **2** and phenylhydrazine as previously reported [33]. A similar reaction takes place with **11** yielding 3,3′-[*p*-phenylene-bis(1-phenyl-2-pyrazoline)] (**19**) (Scheme 5).

It is believed that the initially formed phenylhydrazones of **1** or **11** cyclized readily *via* an intramolecular amine exchange reaction, leading to **18** and **19**, as confirmed by analytical and spectral data.



Scheme 5.



Scheme 6.

In addition, it has been found that a convenient new route to the 2*H*-1,2,4-triazepine ring system starts with the ketonic *sec*-amine bases of the type **3**, which were treated with phenylhydrazine and subsequently with formaldehyde under mild conditions to give 3,4,5,6-tetrahydro-4-aryl-2,7-diphenyl-2*H*-1,2,4-triazepines **20a**–**c**. A similar reaction takes place on treating the diphenylhydrazone of the bis-(*sec*-amine base) **4** with formaldehyde yielding 4,4′-[*p*-phenylene-bis(3,4,5,6-tetrahydro-2,7- diphenyl-2*H*-1,2,4-triazepine)] (**21**) (Scheme 6).

The mass and ^{1}H NMR spectra of compounds **20** and **21** are consistent with the proposed structures. The main characteristic features of the ^{1}H NMR spectrum of **20a** are a singlet at δ = 4.96 assignable to 3-H_2 and two triplets at δ = 3.51 (5-H_2) and 3.13 (6-H_2). Similar signals appeared in the spectrum of **20b**, **c** and **21**. A practical advantage of the reactions leading to compounds **20** and **21** is that it is often unnecessary to isolate the phenylhydrazone intermediates. The reactions described in Scheme 6 provide an important entry into the 1,2,4-triazepine series. The simplicity of the procedure is an attractive feature.

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. ^{1}H and ^{13}C NMR data were obtained in $CDCl_3$ 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 **1** [30] and **2** [34] were prepared as previously described.

*β-Arylaminopropiophenones **3a–e***

A mixture of **1** (1.66 g, 5 mmol) and the appropriate amine (10 mmol) in 50 % aqueous ethanol (60 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **3a**–**e**.

*β-(p-Bromophenylamino)propiophenone (**3a**)*

M. p. 141 °C. – Yield 85 % (white crystals). – IR (KBr): ν = 3392 (NH), 1668 (CO), 1594, 1388, 1317, 1068 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.42 (t, J = 6.7 Hz, 2H, COCH_2CH$_2$N), 3.29 (t, J = 6.7 Hz, 2H, COCH$_2$CH_2N), 4.38 (s, 1H, ArN*H*), 7.21 – 7.83 (m, 9H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 304 (6) [M]$^+$, 303 (30) [M–1]$^+$, 199 (5) [M–PhCO]$^+$, 185 (96) [Br-C$_6$H$_4$-NHCH$_2$]$^+$, 184 (100) [Br-C$_6$H$_4$-N=CH$_2$]$^+$, 133 (4) [PhCOCH$_2$CH$_2$]$^+$, 119 (7) [PhCOCH$_2$]$^+$, 105 (46) [PhCO]$^+$, 77 (54) [Ph]$^+$. – $C_{15}H_{14}BrNO$ (304.18): calcd. C 59.23, H 4.64, N 4.60; found C 59.13, H 4.52, N 4.47.

*β-(p-Hydroxyphenylamino)propiophenone (**3b**)*

M. p. 144 °C. – Yield 91 % (pale brown crystals). – IR (KBr): ν = 3405 (OH), 3274 (NH), 1677 (CO), 1517, 1427, 1363, 1222 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.40 (t, J = 7 Hz, 2H, COCH_2CH$_2$N), 3.30 (t, J = 7 Hz, 2H, COCH$_2$CH_2N), 4.45 (s, 1H, ArN*H*), 7.15 – 7.88 (m, 9H, aromatic), 11.85 (s, 1H, O*H*). – MS (EI, 70 eV): *m/z* (%) = 241 (25) [M]$^+$, 242 (4) [M+1]$^+$, 136 (3) [HO-C$_6$H$_4$-NHCH$_2$CH$_2$]$^+$, 132 (13) [PhCOCH=CH$_2$]$^+$, 122 (100) [HO-C$_6$H$_4$-NHCH$_2$]$^+$, 105 (42) [PhCO]$^+$, 77 (47) [Ph]$^+$. – $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.60, H 6.11, N 5.45.

*β-(p-Anisylamino)propiophenone (**3c**)*

M. p. 112 °C (112 °C [3]). Yield 94 % (white crystals). – IR (KBr): ν = 3355 (NH), 1662 (CO), 1568, 1370, 1322, 1109 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.38 (t, J = 6.8 Hz, 2H, $COCH_2CH_2N$), 3.22 (t, J = 6.8 Hz, 2H, $COCH_2CH_2N$), 3.81 (s, 3H, O*Me*), 4.31 (s, 1H, ArN*H*), 7.30 – 7.91 (m, 9H, aromatic).

*β-(p-Chlorophenylamino)propiophenone (**3d**)*

M. p. 135 °C (134 °C [3]). Yield 91 % (white crystals). – IR (KBr): ν = 3368 (NH), 1668 (CO), 1605, 1375, 1319, 1110 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.41 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 3.30 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 4.42 (s, 1H, ArN*H*), 7.18 – 7.88 (m, 9H, aromatic).

*β-(Phenylamino)propiophenone (**3e**)*

M. p. 114 °C (113 °C [3]). Yield 81 % (white crystals). – IR (KBr): ν = 3359 (NH), 1665 (CO), 1665, 1385, 1318, 1207 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.35 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 3.15 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 4.20 (s, 1H, PhN*H*), 7.11 – 7.73 (m, 10H, aromatic).

*N,N′-Bis(β-benzoylethyl)-p-phenylenediamine (**4**)*

This compound was prepared from equimolar amounts of **1** and *p*-phenylenediamine (5 mmol) in ethanol (60 mL), following the same procedure as described above. Crystallization of the product from chloroform gave **4**. M. p. 178 °C (179 °C [3]). Yield 54 % (buff leaflets). – IR (KBr): ν = 3351 (NH), 1667 (CO), 1331, 1222, 1120 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.41 [t, J = 6.8 Hz, 4H, 2 × ($COCH_2CH_2N$)], 3.24 [t, J = 6.8 Hz, 4H, 2 × ($COCH_2CH_2N$)], 4.22 (s, 1H, N*H*), 4.36 (s, 1H, N*H*), 7.31 – 7.94 (m, 14H, aromatic).

*N-Substituted 3-benzoyl-4-hydroxy-4-phenylpiperidines **7a – c***

A mixture of **1** (1.66 g, 5 mmol) and the appropriate amine (10 mmol) in 50 % aqueous ethanol (60 mL) was refluxed for 90 min, and allowed to stand at r. t. for 24 h. The reaction mixture was diluted with water (20 mL), and the product obtained was filtered and crystallized from ethanol or aqueous ethanol to give **7a – c**. Compounds **7a**, **b** are identical (m. p., mixed m. p., IR and TLC) with authentic samples obtained from the mono-(Mannich base) **2** and the appropriate amine as previously reported [4, 31].

*N-Cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (**7a**)*

M. p. 136 °C (aqueous ethanol) (137 °C [4]). Yield 81 % (colorless needles). – IR (KBr): ν = 3400 (OH), 1675 (CO), 1515, 1380, 1211 cm^{-1}.

*N-Benzyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (**7b**)*

M. p. 118 °C (ethanol) (119 °C [31]). Yield 87 % (colorless crystals). – IR (KBr): ν = 3421 (OH), 1670 (CO), 1492, 1377, 1231, 1115 cm^{-1}.

*N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-benzoyl-4-hydroxy-4-phenylpiperidine (**7c**)*

M. p. 142 °C (ethanol). Yield 77 % (white crystals). – IR (KBr): ν = 3410 (OH), 1673 (CO), 1447, 1365, 1217, 1119 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.96 (m, 1H, 5-*H ax*), 2.51 – 2.70 (m, 4H, $ArCH_2CH_2N$), 2.78 (m, 1H, 5-*H eq*), 3.48 (m, 4H, 2-H_2 and 6-H_2), 3.80 (s, 3H, O*Me*), 3.83 (s, 3H, O*Me*), 5.17 (d, J = 2.9 Hz, 1H, O*H*), 5.43 (dd, J = 4 Hz, J = 10.8 Hz, 1H, 3-*H*), 7.05 – 8.20 (m, 13H, aromatic). – $C_{28}H_{31}NO_4$ (445.55): calcd. C 75.48, H 7.01, N 3.14; found C 75.35, H 6.88, N 3.01.

*2,3,6,7-Tetrahydro-1-(β-benzoylethyl)-5-phenyl-1H-1,4-diazepine (**10**)*

A solution of **1** (1.66 g, 5 mmol) and ethylenediamine (0.15 g, 2.5 mmol) in 50 % aqueous ethanol (60 mL) was refluxed for 2 h, and allowed to stand at r. t. for 24 h. The product obtained was filtered and purified by preparative chromatography on Al_2O_3 using pet. ether 40 – 60 °C / ethyl acetate (2 : 1) as eluent. The product was crystallized from ethanol to give **10**. M. p. 192 °C. Yield 25 % (white crystals). – IR (KBr): ν = 3430 (NH), 1670 (CO), 1625 (C=N), 1445, 1273, 1122 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.61 (t, J = 6.4 Hz, 2H, $COCH_2CH_2N$), 2.96 (t, J = 5.6 Hz, 2H, 6-H_2), 3.14 (t, J = 6.4 Hz, 2H, $COCH_2CH_2N$), 3.32 (t, J = 5.6 Hz, 2H, 7-H_2), 3.38 – 3.42 (m, 4H, 2-H_2 and 3-H_2), 6.92 – 7.75 (m, 10H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 306 (2) $[M]^+$, 173 (13) $[M–PhCOCH_2CH_2]^+$, 133 (7) $[PhCOCH_2CH_2]^+$, 132 (33) $[PhCOCH{=}CH_2]^+$, 131 (14) $[PhCOCH_2CH_2–2H]^+$, 105 (100) $[PhCO]^+$, 77 (83) $[Ph]^+$. – $C_{20}H_{22}N_2O$ (306.40): calcd. C 78.40, H 7.24, N 9.14; found C 78.25, H 7.08, N 8.91.

*1,4-Bis[β-(N-morpholino)propionyl]benzene bis(hydrochloride) (**11**)*

To a solution of 1,4-diacetylbenzene (4 g, 25 mmol) and morpholine hydrochloride (6.2 g, 50 mmol) in absolute ethanol (80 mL), paraformaldehyde (1.65 g, 55 mmol) was added, followed by hydrochloric acid (37 % w/v, 0.2 mL), and the mixture was refluxed for 6 h. The product obtained on cooling was filtered and crystallized from ethanol to give **11**. M. p. 220 °C (dec). Yield 61 % (pale brown crystals). – IR (KBr): ν = 1670 (CO), 1605, 1458, 1330, 1239, 1143 cm^{-1}. – ^1H NMR (200 MHz, D_2O, 25 °C, TMS): δ = 2.91 – 3.33 [m, 8H, 2 × (CH_2-N-CH_2) of morpholine], 4.01 – 4.20 [m, 8H, 2 × (CH_2-O-CH_2) of morpholine], 3.42 [t, J = 6.9 Hz, 4H, 2 × ($COCH_2CH_2N$)], 3.76 [t, J = 6.9 Hz,

4H, 2 × ($COCH_2CH_2N$)], 6.69 – 7.66 (m, 4H, aromatic). – $C_{20}H_{30}N_2O_4Cl_2$ (433.37): calcd. C 55.43, H 6.97, N 6.46; found C 55.25, H 6.88, N 6.29.

1,4-Bis[β-(arylamino)propionyl]benzenes ***12a, b***

A mixture of **11** (1.08 g, 2.5 mmol) and the appropriate amine (5 mmol) in 50 % aqueous ethanol (60 mL) was refluxed for 3 h. The product obtained on cooling was filtered and crystallized from DMF to give **12a**, **b**.

*1,4-Bis[β-(p-tolylamino)propionyl]benzene (**12a**)*

M. p. 205 °C (dec). – Yield 70 % (reddish crystals). – IR (KBr): ν = 3392 (NH), 1678 (CO), 1617, 1517, 1402, 1301, 1207, 1123 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.27 (s, 3H, Ar*Me*), 2.92 (s, 3H, Ar*Me*), 3.58 – 3.73 [m, 8H, 2 × ($COCH_2CH_2N$)], 4.22 (s, 1H, ArN*H*), 4.24 (s, 1H, ArN*H*), 7.11 – 7.89 (m, 12H, aromatic). – $C_{26}H_{28}N_2O_2$ (400.51): calcd. C 77.97, H 7.05, N 6.99; found C 77.88, H 6.98, N 6.79.

*1,4-Bis[β-(p-anisylamino)propionyl]benzene (**12b**)*

M. p. 195 °C. – Yield 73 % (dark red crystals). – IR (KBr): ν = 3388 (NH), 1677 (CO), 1513, 1402, 1376, 1240, 1035 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.55 – 3.76 [m, 8H, 2 × ($COCH_2CH_2N$)], 3.79 (s, 3H, O*Me*), 3.82 (s, 3H, OMe), 4.18 (s, 1H, ArN*H*), 4.21 (s, 1H, ArN*H*), 6.91 – 7.86 (m, 12H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 432 (0.4) $[M]^+$, 309 (17) $[M–MeO\text{-}C_6H_4\text{-}NH_2]^+$, 159 (18) $[CO\text{-}C_6H_4\text{-}COCH{=}CH_2]^+$, 136 (100) $[MeO\text{-}C_6H_4\text{-}NHCH_2]^+$, 123 (25) $[MeO\text{-}C_6H_4\text{-}NH_2]^+$. – $C_{26}H_{28}N_2O_4$ (432.51): calcd. C 72.20, H 6.53, N 6.48; found C 72.08, H 6.48, N 6.35.

*4,4′-[p-Phenylene-bis(2,3-dihydro-1H-1,5-benzodiazepine)] (**14**)*

A mixture of **11** (1.08 g, 2.5 mmol), *o*-phenylenediamine (0.54 g, 5 mmol) and fused sodium acetate (1.5 g) in absolute ethanol (80 mL) was refluxed for 10 h. The crystalline product was filtered and washed with boiling ethanol-acetone (1 : 1) to give **14**. M. p. 272 °C. Yield 65 % (yellow crystals). – IR (KBr): ν = 3394 (NH), 1612 (C=N), 1490, 1373, 1328, 1261, 1106 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.95 (t, J = 5.7 Hz, 4H, 2 × 3-H_2), 3.71 (t, J = 5.7 Hz, 4H, 2 × 2-H_2), 3.83 (s, 1H, N*H*), 3.84 (s, 1H, N*H*), 6.94 – 7.83 (m, 12H, aromatic). – ^{13}C NMR (200 MHz, $CDCl_3$): δ = 32.66 (C-3), 49.12 (C-2), 113.84, 119.22, 123.84, 127.88, 130.15, 134.55 (all Ar-*C*), 138.01 (C-5a), 138.83 (C-5b), 167.61 (C-4). – MS (EI, 70 eV): *m/z* (%) = 366 (100) $[M]^+$, 367 (25) $[M+1]^+$, 365 (34), 337 (15), 310 (21), 248 (7), 182 (13), 145 (14), 128 (7), 119 (34). – $C_{24}H_{22}N_4$ (366.46): calcd. C 78.66, H 6.05, N 15.29; found C 78.48, H 6.00, N 15.05.

*1,12-Diaza-tricyclo[10.2.2.2^{5,8}]octadeca-5(18),8(17)-triene-4,9-dione (**15**)*

A solution of **11** (1.08 g, 2.5 mmol) and piperazine (0.22 g, 2.5 mmol) in 50 % aqueous ethanol (50 mL) was refluxed for 4 h, and allowed to stand at r. t. for 24 h. The product obtained was filtered and crystallized from ethanol-chloroform (1 : 1) to give **15**. M. p. 230 °C (dec.). Yield 73 % (beige powder). – IR (KBr): ν = 1677 (CO), 1404, 1314, 1266, 1211, 853 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.61 [br s, 8H, N(CH_2CH_2)$_2$N)], 3.12 – 3.56 [m, 8H, 2 × ($COCH_2CH_2N$)], 7.96 – 8.08 (m, 4H, aromatic). – ^{13}C NMR (200 MHz, $CDCl_3$): δ = 39.11 (all $COCH_2$), 46.98 (all CH_2N), 56.35 (all piperazine-*C*), 129.62, 144.26 (all Ar-*C*), 203.26 (CO). – MS (EI, 70 eV): *m/z* (%) = 273 (1) $[M–1]^+$, 272 (3) $[M]^+$, 230 (52) $[CO\text{-}C_6H_4\text{-}CO(CH_2)_2N(CH_2)_4]^+$, 186 (22) $[C_6H_4\text{-}(COCH{=}CH_2)_2]^+$, 159 (100) $[CO\text{-}C_6H_4\text{-}COCH{=}CH_2]^+$, 131 (9) $[C_6H_4\text{-}COCH{=}CH_2]^+$, 104 (10) $[C_6H_4\text{-}CO]^+$, 86 (7) [piperazine]$^+$, 76 (11) $[C_6H_4]^+$, 55 (20) $[COCH{=}CH_2]^+$. – $C_{16}H_{20}N_2O_2$ (272.34): calcd. C 70.56, H 7.40, N 10.29; found C 70.49, H 7.22, N 10.16.

*4-[β-(Benzylamino)propionyl]acrylophenone (**17**)*

This compound was obtained from equimolar amounts of **11** and benzylamine (2 mmol) in 50 % aqueous ethanol (40 mL), following the same procedure as described above. Crystallization of the product from ethanol gave **17**. M. p. 148 °C. Yield 49 % (pale yellow crystals). – IR (KBr): ν = 3435 (NH), 1673 (CO), 1603 (α,β-unsaturated CO), 1452, 1360, 1208, 1071 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.62 – 2.94 [m, 4H, ($COCH_2CH_2N$)], 3.66 (s, 2H, PhCH_2N), 1.44 (s, 1H, N*H*), 5.78 (dd, J = 10.5, 1.8 Hz, 1H, H^2), 6.48 (dd, J = 16.8, 1.8 Hz, 1H, H^3), 7.16 (dd, J = 16.8, 10.5 Hz, 1H, H^1), 7.21 – 8.05 (m, 9H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 293 (3) $[M]^+$, 186 (20) $[C_6H_4(COCH{=}CH_2)_2]^+$, 159 (99) $[CO\text{-}C_6H_4\text{-}COCH{=}CH_2]^+$, 131 (12) $[C_6H_4\text{-}COCH{=}CH_2]^+$, 107 (22) $[PhCH_2NH_2]^+$, 106 (73) $[PhCH_2NH]^+$, 91 (34) $[PhCH_2]^+$, 55 (100) $[COCH{=}CH_2]^+$. – $C_{19}H_{19}NO_2$ (293.36): calcd. C 77.79, H 6.53, N 4.77; found C 77.73, H 6.11, N 4.34.

*1,3-Diphenyl-2-pyrazoline (**18**)*

A solution of **1** (1.66 g, 5 mmol), phenylhydrazine (1.08 g, 10 mmol) and sodium acetate (2 g) in 50 % acetic acid (50 mL) was refluxed for 3 h, then poured onto water (100 mL). The product was filtered off and recrystallized from ethanol to give **18**. M. p. 150 °C (151 °C [33]). Yield 54 % (white crystals). The structure was confirmed by a com-

parison of IR data, m. p. and TLC with an authentic sample obtained from **2** and phenylhydrazine as previously reported [33].

*3,3′-[p-Phenylene-bis(1-phenyl-2-pyrazoline)] (**19**)*

This compound was obtained from **11** (1.08 g, 2.5 mmol) and phenylhydrazine (0.54 g, 5 mmol), following the same procedure as described above. The product precipitated from the reaction mixture was filtered and crystallized from methanol-chloroform (1 : 1) to give **19**. M. p. 272 °C. Yield 82 % (orange crystals). – IR (KBr): ν = 1622 (C=N), 1552, 1382, 1301, 1122 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.12 [m, 4H, 2 × (5-H_2)], 3.68 [m, 4H, 2 × (4-H_2)], 7.12 – 8.20 (m, 14H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 367 (27) $[M+1]^+$, 366 (100) $[M]^+$, 365 (10) $[M–1]^+$, 364 (23) $[M–2]^+$, 260 (4) $[M–PhN=NH]^+$, 221 (5) [M–(1-phenylpyrazoline)]$^+$, 77 (23) $[Ph]^+$. – $C_{24}H_{22}N_4$ (366.46): calcd. C 78.66, H 6.05, N 15.29; found C 78.59, H 5.90, N 15.04.

*3,4,5,6-Tetrahydro-4-aryl-2,7-diphenyl-2H-1,2,4-triazepines **20a – c***

A solution of the β-(arylamino)propiophenone (**3a – c**) (5 mmol) and 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 ethanol-chloroform (1 : 1) to give **20a – c**.

*3,4,5,6-Tetrahydro-4-(p-bromophenyl)-2,7-diphenyl-2H-1,2,4-triazepine (**20a**)*

M. p. 174 °C. Yield 78 % (gray crystals). – IR (KBr): ν = 1612 (C=N), 1595, 1332, 1201, 1072 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.13 (t, 2H, 6-H_2), 3.51 (t, 2H, 5-H_2), 4.96 (s, 2H, 3-H_2), 7.03 – 8.22 (m, 14H, aromatic). – ^{13}C NMR (200 MHz, $CDCl_3$): δ = 29.66 (C-6), 53.12 (C-5), 82.22 (C-3), 112.48, 113.77, 115.65, 117.52, 128.86, 129.14, 130.33, 132.47, 144.63, 145.52 (all Ar-*C*), 164.67 (C-7). – MS (EI, 70 eV): *m/z* (%) = 407 (3) $[M+1]^+$, 405 (2) $[M–1]^+$, 301 (21) [M–(PhN_2)]$^+$, 222 (30) [M–(Br-C_6H_4-N=CH_2)]$^+$, 184 (16) [Br-C_6H_4-N=CH_2]$^+$, 105 (21) $[PhN_2]^+$, 91 (49) $[PhN]^+$, 77 (100) $[Ph]^+$. – $C_{22}H_{20}BrN_3$ (406.32): calcd. C 65.03, H 4.96, N 10.34; found C 65.21, H 4.81, N 10.08.

*3,4,5,6-Tetrahydro-4-(p-hydroxyphenyl)-2,7-diphenyl-2H-1,2,4-triazepine (**20b**)*

M. p. 197 °C. Yield 75 % (yellow crystals). – IR (KBr): ν = 3332 (OH), 1610 (C=N), 1554, 1457, 1334, 1234, 1068 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.15 (t, 2H, 6-H_2), 3.47 (t, 2H, 5-H_2), 4.98 (s, 2H, 3-H_2), 7.05 – 8.31 (m, 14H, aromatic), 14.86 (s, 1H, O*H*). – MS (EI, 70 eV): *m/z* (%) = 344 (2) $[M+1]^+$, 343 (8) $[M]^+$, 238 (100) $[M–PhN_2]^+$, 237 (60) $[M–PhN=NH]^+$, 222 (33) [M–(HO-C_6H_4-N=CH_2)]$^+$, 121 (10) [HO-C_6H_4-N=CH_2]$^+$, 93 (9) [C_6H_4-OH]$^+$, 77 (27) $[Ph]^+$. – $C_{22}H_{21}N_3O$ (343.42): calcd. C 76.94, H 6.16, N 12.24; found C 76.81, H 6.03, N 11.94.

*3,4,5,6-Tetrahydro-4-(p-anisyl)-2,7-diphenyl-2H-1,2,4-triazepine (**20c**)*

M. p. 183 °C. Yield 81 % (yellow crystals). – IR (KBr): ν = 1613 (C=N), 1557, 1461, 1326, 1240, 1118, 1029 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.17 (t, 2H, 6-H_2), 3.54 (t, 2H, 5-H_2), 3.83 (s, 3H, O*Me*), 5.10 (s, 2H, 3-H_2), 7.01 – 8.40 (m, 14H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 358 (2) $[M+1]^+$, 357 (9) $[M]^+$, 252 (100) $[M–PhN_2]^+$, 222 (28) [M–(MeO-C_6H_4-N=CH_2)]$^+$, 135 (24) [MeO-C_6H_4-N=CH_2]$^+$, 105 (12) $[PhN_2]^+$, 91 (45) $[PhN]^+$, 77 (90) $[Ph]^+$. – $C_{23}H_{23}N_3O$ (357.45): calcd. C 77.28, H 6.49, N 11.76; found C 77.32, H 6.33, N 11.55.

*4,4′-[p-Phenylene-bis(3,4,5,6-tetrahydro-2,7-diphenyl-2H-1,2,4-triazepine)] (**21**)*

A solution of **4** (0.93 g, 2.5 mmol) and phenylhydrazine (0.54 g, 5 mmol) in ethanol (25 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 1 h, and the product obtained on cooling was filtered and crystallized from dioxane to give **21**. M. p. 228 °C. Yield 66 % (white powder). – IR (KBr): ν = 1617 (C=N), 1559, 1455, 1328, 1203, 1115, 1068 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.15 (t, 4H, 6-H_2, 6′-H_2), 3.59 (t, 4H, 5-H_2, 5′-H_2), 5.12 (s, 4H, 3-H_2, 3′-H_2), 7.02 – 7.98 (m, 24H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 576 (2) $[M]^+$, 366 (16) $[M–2PhN_2]^+$, 250 (13) [diphenyltriazepine–H]$^+$, 249 (50) $[C_{16}H_{15}N_3]^+$, 132 (11) $[H_2C$=N-C_6H_4-N=$CH_2]^+$, 105 (13) $[PhN_2]^+$, 91 (41) $[PhN]^+$, 77 (100) $[Ph]^+$. – $C_{38}H_{36}N_6$ (576.73): calcd. C 79.14, H 6.29, N 14.57; found C 79.01, H 6.13, N 14.25.

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