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Single-step conversion of aliphatic, aromatic and heteroaromatic primary amines into piperazine-2,6-diones

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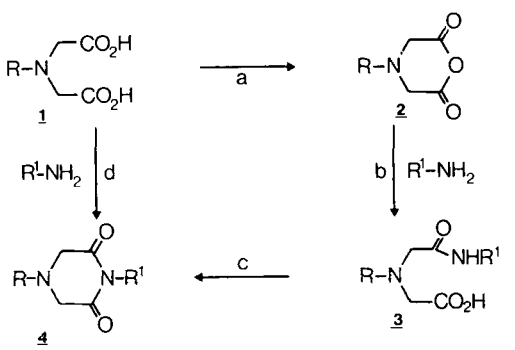
Abstract. The development of a facile, single-step method for the synthesis of 1,4-disubstituted piperazine-2,6-diones (**4**) in excellent yields from the corresponding aliphatic, aromatic and heteroaromatic primary amines and iminodiacetic acids (**1**) is described. A possible mechanism is discussed and the presence of intermediate **6a** is confirmed by high-resolution proton NMR spectroscopy. The subsequent two-step conversion of dione **4a** into the deoxygenated 4-unsubstituted piperazine **10** in high yield provides an attractive alternative to the currently available (hetero)arylpiperazine synthetic methods.

Introduction

A number of synthetic methods for piperazine-2,6-diones (2,6-dioxopiperazines) **4** have appeared in patents and in the literature[1-5]. Representative structures of this class of compounds have attracted attention because of their biological (*e.g.* antitumour)[6] properties and because of the possibility of being able to convert them into mesoionic structures[3c]. They may also serve as precursors for the synthesis of the corresponding piperazines, with manifold pharmacological and pharmacotherapeutic applications[3,5,7].

Henry[3a] investigated the possibility of using commercially available *N*-substituted iminodiacetic acids as building blocks in the construction of the piperazine-2,6-dione ring system (Scheme 1). He found that the preferred procedure consisted of first converting iminodiacetic acids **1** into cyclic anhydrides **2** (step *a*), followed by reaction with primary amines R^1NH_2 to give the diacid monoamides **3** (step *b*). Subsequent ring closure produced 1,4-disubstituted piperazine-2,6-diones **4** (step *c*).

Disadvantages of this three-step method are the necessity to isolate the unstable morpholine-2,6-diones **2**, the moderate overall yields of **4** (20–50%) and the limited scope, because neither heterocyclic nor sterically hindered primary amines could be converted into the corresponding cyclic imides **4**[3a]. Methods of converting **1** and primary amines



Scheme 1

directly into **4** (step *d*) by reaction at high temperatures (150–200 °C) have also been described, but in these cases the scope is even more limited[1,2,3a,f].

In this paper we describe the development of a facile and efficient method for the synthesis of a wide variety of piperazine-2,6-diones from iminodiacetic acids **1** and aliphatic, aromatic and heteroaromatic primary amines under mild reaction conditions in a single-step process (Scheme 3). A new methodology is also presented for the transformation of **4** (R = benzyl) into the corresponding deoxygenated 1-monosubstituted piperazines[8] (Scheme 4).

Results and discussion

Optimization via diacid monoamides 3

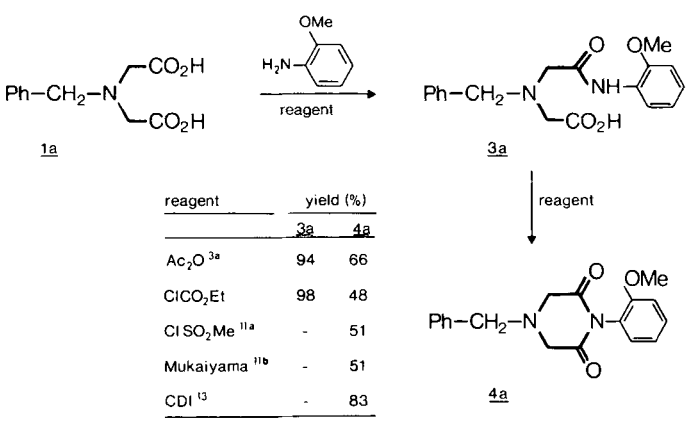
Commercially available (benzylimino)diacetic acid **1a** (R = benzyl) and *o*-anisidine (R^1 = *o*-$OMeC_6H_4$, 2-methoxyaniline) were chosen as standard reagents for finding optimal methodology for the synthesis of **4**. Application of the stepwise procedure of *Henry*[3a] (Scheme 1), using acetic anhydride as solvent and dehydrating agent in both steps *(a)* (reflux, 1h) and *(c)* (reflux, 6h) resulted, via diacid monoamide **3a** (94% yield), in 4-benzyl-1-(2-methoxyphenyl)-piperazine-2,6-dione **4a** (62% overall yield, Scheme 2) after a necessary chromatographic purification[9].

To improve these results, the application of other dehydrating agents was studied, both in the coupling step (**1a** → **3a**) and in the cyclization step (**3a** → **4a**).

An improvement in the coupling step was readily achieved by treating **1a** with ethyl chloroformate/triethylamine in acetonitrile under mild conditions (0°C). Without isolating the mixed anhydride intermediate, product **3a** was obtained almost quantitatively after addition of *o*-anisidine in a one-pot procedure (see Experimental).

In the cyclization step, a number of reagents were tested[10], again giving the desired (dehydration) reaction under appreciably milder conditions than refluxing acetic anhydride (Scheme 2). However, with ethyl chloroformate, methanesulfonyl chloride and *Mukaiyama* reagent, other products were also formed; in the case of ethyl chloroformate, the major side-product was isolated (*ca.* 10% yield) and identified as **5**, the *N*-(ethoxycarbonyl) derivative of **3a** (see Experimental). This result may be rationalized by assuming that the weakly nucleophilic amide-*N* can attack both carbonyl groups of the mixed anhydride intermediate, leading to either the desired cyclic product **4a** or the acyclic product **5**[12]. The moderate yields obtained with the other acyl-activating agents described above can be similarly explained, since they all introduce an additonal electrophilic centre into the reactive intermediate.

These difficulties can be circumvented by using *N,N'*-carbonyldiimidazole (CDI)[13]. Ring closure of **3a** proceeded efficiently (83% yield) and cleanly in THF at reflux temperature after addition of 1 equiv. of CDI (see Experimental). During the course of our investigations, *Harfenist*[3e] reported unique qualities of CDI in the cyclization of a *N*-(ethoxycarbonyl)iminodiacid monoamide. The modest yields (*ca.* 50%) reported by him are in line with our observation that [(*tert*-butoxycarbonyl)imino]diacetic acid (**1c**, R = *t*-BuOOC)[14] gave poor results in comparison to **1a** in both the coupling and in the cyclization steps. Apparently, carbonyl-containing substituents on the imino-*N* have a negative influence upon the electrophilicity of the reactive carbonyl intermediates.

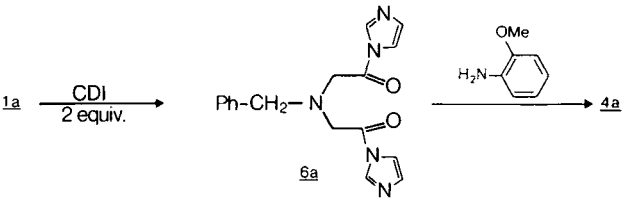


reagent	yield (%)	
	3a	4a
Ac_2O [3a]	94	66
$ClCO_2Et$	98	48
$ClSO_2Me$ [11a]	-	51
Mukaiyama [11b]	-	51
CDI [13]	-	83

Scheme 2

Single-step procedure to piperazine-2,6-diones

The successful application of CDI to the cyclization step **3a** → **4a** led us to investigate the possibility of simultaneously activating *both* carboxyl groups of iminodiacid **1a**. Treatment of **1a** with 2 equiv. of CDI can result in the formation of iminodiacyl intermediate **6a** (Scheme 3).



Scheme 3

Indeed, **4a** was obtained as the sole product in high yield in a one-pot procedure by treating **1a** first with CDI (2.2 equiv.) in THF (reflux, 15 min), followed by the addition of *o*-anisidine (reflux, 2h).

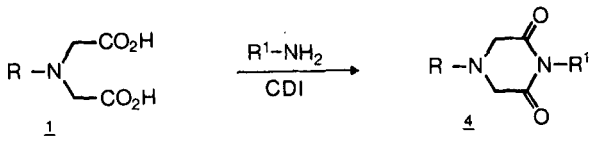
To ascertain the structure of the reactive intermediate **6a**, the homogeneous solution formed after addition of CDI (2.0 equiv.) to **1a** in THF was studied by high-resolution (400 MHz) proton NMR spectroscopy. The spectrum revealed the presence of imidazole and 1,1'-[benzyliminobis(1-oxo-1,2-ethanediyl)]diimidazole **6a** (in a molar ratio of 2:1)[15] as the only reaction products, indicating that *both* carbonyl groups had been activated. The 2- and 5-imidazole-H of **6a** showed a characteristic downfield shift of 0.53 and 0.51 ppm, respectively, in comparison to the corresponding imidazole signals.

The scope of this one-pot synthesis of 1,4-disubstituted piperazine-2,6-diones of type **4** was studied by varying both *N* substituents[16]. The results of the reaction of **1a** with a wide variety of primary amines leading to the corresponding 4-benzylpiperazine-2,6-diones (**4a-4s**) with 1-aryl (entry 1–7), 1-alkyl (entry 8–14) and 1-heteroaryl (entry 15–19) substituents and of similar transformations of (phenylimino)diacetic acid **1b** (R = phenyl, entry 20–25) into 4-phenylpiperazine-2,6-diones (**4t-4y**) are summarized in Table I.

Good to excellent yields were obtained in all cases with both aliphatic and aromatic 1- and 4-substituents, clearly improving the efficiency and extending the scope of the existing procedures[1-3]. Furthermore, this one-pot procedure could be carried out conveniently on a multigram scale (see Experimental, also for a description of the pertinent MS, IR and NMR data of the products).

The superior electrophilic properties of the *N*-acylimidazole moieties in **6a** and **6b** (N-phenyl) are reflected by the following observations (Table I):

Table I Products of the reaction of N-*substituted iminodiacetic acids* (**1**) *with primary amines and their physical properties.*



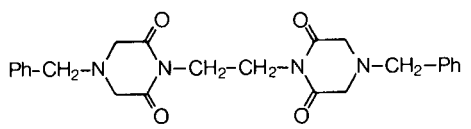
Entry	Prod.	R	R^1	Yield[a] (in %)	M.p. (°C)	NMR data (DMSO-d_6), δ (ppm)[b]			
						R–H		3,5-H	R^1–H
						C_6H_5	CH_2		
1	**4a**	benzyl	2-methoxyphenyl	97	109–110	7.36	3.84	3.64	7.07, 7.02 (m, 4H, C_6H_4), 3.76 (s, 3H, OCH_3)
2	**4b**	benzyl	phenyl	88	129–130[c]	7.4	3.82	3.62	7.0–7.4 (m, 5H)
3	**4c**	benzyl	4-methoxyphenyl	98	146	7.32	3.74	3.56	7.05, 6.93 (AA'BB', 4H, C_6H_4), 3.76 (s, 3H, OCH_3)
4	**4d**	benzyl	4-chlorophenyl	98	112–113	7.34	3.78	3.58	7.50, 7.18 (AA'BB', 4H)
5	**4e**	benzyl	4-nitrophenyl	94	120–121	7.36	3.84	3.62	8.28, 7.48 (AA'BB', 4H)
6	**4f**	benzyl	2,6-dimethylphenyl	79	144–145	7.38	3.82	3.67	7.19 (m, 3H, C_6H_3), 2.03 (s, 6H, CH_3)
7	**4g**	benzyl	2,6-dichlorophenyl	90[d]	162–163	7.28	3.80	3.38	7.28 (m, 3H)
8	**4h**	benzyl	*n*-propyl	80	–	7.28	3.64	3.41	3.56 (t, 2H, 1-H), 2.2–2.6 (m, 2H, 2-H), 1.82 (t, 3H, 3-H)
9	**4i**	benzyl	*n*-octyl	92	–	7.30	3.65	3.43	3.6 (t, 2H, 1-H), 1.25 (broad s, 12H, CH_2), 0.86 (t, 3H, 8-H)
10	**4j**	benzyl	allyl	85	–	7.30	3.66	3.45	5.86 (m, 1H, 2-H), 4.9–5.1 (m, 2H, 3-H), 4.22 (d, 2H, 1-H)
11	**4k**	benzyl	*tert*-butyl	70[d]	–	7.27	3.60	3.31	1.49 (s, 9H)
12	**4l**	benzyl	1-adamantyl	65[d]	125–127	7.30	3.60	3.32	2.1 (broad s, 3H, CH), 1.65 (broad s, 12H, CH_2)
13	**4m**	benzyl	cyclohexyl	91	183	7.28	3.60	3.34	0.8–2.3 (broad, 10H), 4.25 (broad, 1H)
14	**4n**	benzyl	benzyl	89	56[e]	7.29	3.65	3.48	7.24 (s, 5H, C_6H_5), 4.80 (s, 2H, CH_2)
15	**4o**	benzyl	2-thiazolyl	99	128	7.30	3.76	3.60	7.80 (m, 2H, 4- and 5-H)
16	**4p**	benzyl	3-isoxazolyl	92	–[f]	7.39	3.78	3.63	8.55 and 6.41 (AB, 2H, 5- and 4-H)
17	**4q**	benzyl	2-pyridyl	98	128–129	7.28	3.78	3.58	8.50 (d, 1H, 6-H), 7.92 (dd, 1H, 4-H), 7.48 (d, 1H, 3-H), 7.28 (dd, 1H, 5-H)
18	**4r**	benzyl	7-indolyl[g]	92	–[f]	7.41	3.86	3.68	7.59 (dd, 1H, 4-H), 7.29 (dd, 1H, 2-H), 7.05 (t, 1H, 5-H), 6.85 (dd, 1H, 6-H), 6.48 (dd, 1H, 3-H)
19	**4s**	benzyl	5-quinoxalinyl	93	–[f]	7.39	3.83	3.73	8.86 and 8.79 (AB, 2H, 2- and 3-H), 8.12 (dd, 1H, 8-H), 7.84 (t, 1H, 7-H), 7.63 (dd, 1H, 6-H)
20	**4t**	phenyl	*tert*-butyl	63[d]	76–77	6.8–7.1 (m)		4.14	1.44 (s, 9H)
21	**4u**	phenyl	cyclohexyl	97	136–137	6.8–7.3 (m)		4.18	1.0–2.35 (broad, 10H), 4.25 (broad, 1H)
22	**4v**	phenyl	benzyl	92	104–105[h]	6.8–7.3 (m)		4.32	6.8–7.3 (m, 5H, C_6H_5), 4.82 (s, 2H, CH_2)
23	**4w**	phenyl	2-methoxyphenyl	89	162–163	6.9–7.4 (m)		4.40	6.9–7.4 (m, 4H, C_6H_4), 3.56 (s, 3H, OCH_3)
24	**4x**	phenyl	4-cyanophenyl	85[d]	203–204	6.9–7.4 (m)		4.14	7.92, 7.32 (AA'BB', 4H)
25	**4y**	phenyl	2-pyridyl	87	184–185	6.8–7.5 (m)		4.42	8.52 (d, 1H, 6-H), 7.94 (t, 1H, 4-H), 6.8–7.5 (2H, 3- and 5-H)

[a] See Experimental; solvent THF unless noted otherwise. [b] Data for ^3J nd ^4J (Hz) were in full agreement with standard values. [c] Lit.[3a] m.p. 127–128.5°C. [d] Solvent 1,4-dioxane. [e] Lit.[3a] m.p. 55.5–57.5°C. [f] No analytical sample prepared; product used in subsequent reactions. [g] NMR data in 1:4 $CDCl_3$/DMSO-d_6. [h] Lit.[3a] m.p. 105–107°C.

(i) The efficiency of the method is not influenced by the basicity of R^1NH_2, since a wide range of pK_a values (*ca.* 1 for the anilines in entries 5 and 24 up to *ca.* 11 for the aliphatic amines in entries 8–13 and 20–22)[17] is allowed.

(ii) A variety of 1-heteroarylpiperazine-2,6-diones (**4o-4s** and **4y**), originating from highly electron-deficient heterocyclic amines, in each case carrying an additional nucleophilic nitrogen centre, were formed in excellent yields. Products containing 5- (**4o**, **4p**) and 6-membered (**4q**, **4y**), as well as bicyclic (**4r**, **4s**) heteroaromatic substituents, are now accessible.

(iii) Primary amines with sterically highly demanding R^1 groups can also be converted into the corresponding piperazine-2,6-diones. For the products with *tert*-butyl (**4k**, **4t**), 1-adamantyl (**4l**) and 2,6-disubstituted phenyl (**4f**, **4g**) substituents, a higher-boiling solvent (1,4-dioxane) was usually required in order to obtain high yields.



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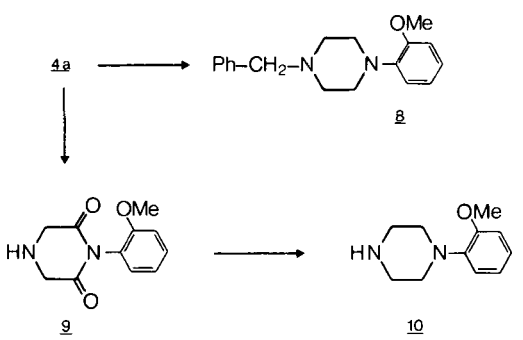
Finally, the reaction of **1a** with ethylenediamine as a bifunctional substrate afforded the ethylenedipiperazine derivative **7** in good yield, once more proving the versatility of this single-step synthetic method.

Conversion of **4** *into 1-monosubstituted piperazines*

In view of the important role which *N*-substituted piperazines play in pharmacotherapy we also investigated the possibility of transforming 4-benzylpiperazine-2,6-diones (**4**, R = $PhCH_2$) into the corresponding deoxygenated 4-unsubstituted piperazines. This is especially interesting for substrates with (hetero)aromatic R^1 groups, as in **4a–4g**, **4o–4s** and **4w–4y**. Currently available procedurees all require highly toxic reagents (nitrogen-mustard type) or intermediates[8]. We therefore studied the efficiency of this conversion with **4a** as a standard substrate.



Scheme 4

Deoxygenation of 1,4-disubstituted piperazine-2,6-diones **4** has been described by a number of authors with yields varying between 50% and 80%[1,3,5]. Accordingly, carbonyl reduction of **4a**, both with $LiAlH_4$ and $BH_3 \cdot Me_2S$[18], gave piperazine **8** in moderate yields (49–64%, see Experimental)[19]. Better results were obtained by *first* carrying out the debenzylation step (H_2, Pd/C)[20] to give 4-unsubstituted **9** (98% yield), and then performing the deoxygenation with $BH_3 \cdot Me_2S$, giving 1-(2-methoxyphenyl)piperazine **10** in 86% yield (Scheme 4). Both reactions proceeded rapidly and in excellent yields (see Experimental).

Thus, the combination of the single-step CDI-promoted cyclization method and the two-step deprotection sequence may constitute an attractive alternative to the current 4-unsubstituted 1-(hetero)arylpiperazine syntheses from the corresponding (hetero)aryl amines.

Experimental

General remarks

Melting points are uncorrected. IR spectra(KBr disc or liquid film) were recorded on a Pye Unicam SP3–200 Spectrometer. ^1H NMR spectra were taken in DMSO-d_6 solution (unless noted otherwise) using either a JEOL PS-100 or a Bruker WP-200 instrument; δ is expressed in ppm relative to internal tetramethylsilane; J in Hz. Mass spectra were obtained using a Kratos MS 9/50 apparatus with RP 12,000 static ion source in EI mode, operating at 150°C above ambient temperature. Samples were introduced via HDIS. Elemental analyses of crystalline products were performed at TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands or at Dr. *P. Pascher*'s Laboratory, Bonn, Federal Republic of Germany. All experiments described below were carried out in an atmosphere of dry nitrogen.

Materials

Solvents THF, acetonitrile and 1,4-dioxane were purified and dried according to standard procedures. (Benzylimino)diacetic acid, *N,N'*-carbonyldiimidazole, primary amines and further reagents were used as high-grade commercial products. (Phenylimino)diacetic acid[16], 7-aminoindole[21a] and 5-aminoquinoxaline[21b] were prepared according to known procedures. For normal-pressure and flash chromatography, Merck silica gel type 60 (size 70–230 and 230–400 mesh, respectively) was used.

General procedure for the single-step conversion of primary amines into piperazine-2,6-diones (**4**)

CDI (3.58 g, 22 mmol) was added in portions to a stirred suspension of **1a** or **1b** (10 mmol) in dry solvent (THF or 1,4-dioxane, 30 ml). The reaction mixture was heated at reflux temperature until the evolution of CO_2 ceased (*ca.* 15 min), giving a clear solution of reagent **6a** or its *N*-phenyl analogue **6b** and imidazole. Primary amine (10 mmol) was then added and stirring at reflux was continued for 16 h (in the case of entries 11, 12 and 20 for 72 h).

In most cases, TLC analysis (3:1 ether/petroleum ether) showed complete conversion. If not, an additional amount of CDI (2 mmol) was added and heating at reflux was continued for 2 h. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate. The organic layer was washed successively with 0.5 N HCl (100 ml and 2 x 25 ml) in order to remove all imidazole and H_2O (100 ml). After drying ($MgSO_4$) and evaporating the solvent, products **4** were obtained in a purity of at least 90%. The yields indicated in Table I refer to pure substances (calculated from NMR spectra). These products can be used in following reactions without purification.

In the case of **4a**, the yield of an analytically pure sample, obtained after flash chromatography (3:1 ether/petroleum ether), amounted to 93%. In a large-scale experiment (0.22 mol **1a** and *o*-anisidine), the above procedure yielded **4a** in 84% (57.3 g) yield after crystallization from isopropanol. Analytical samples of the other products were obtained by repeated crystallization or, in the case of **4h–4k**, by short-path distillation.

In the IR spectra, all piperazine-2,6-diones showed the characteristic imide-carbonyl absorptions at 1680–1710 (strong) and 1740–1760 (weak) cm^{-1} [3a]. In the mass spectra of all products with R = benzyl, a fragment with m/z 119 was present, apparently from the *N*-benzylaziridinium radical ion.

NMR data are compiled in Table I. For products with R = benzyl, the methylene signals of both 3,5-H and the benzylic substituent are influenced by the electronic properties of the 1-substituent. Aliphatic groups result in δ ranging from 3.31–3.48 and 3.60–3.66 for 3,5-H and benzylic CH_2, respectively. Aromatic and heteroaromatic groups consistently give a 0.2 ppm downfield shift for *both* signals (exception **4g**). In products **4a-4e**, **4p-4s** and **4w-4y**, the

chemical shift of the aromatic *ortho* protons indicate that the aromatic and the piperazine rings are considerably twisted away from coplanarity[22].

N-Benzyl-N-[[N-(2-methoxyphenyl)carbamoyl]methyl]glycine (**3a**)

(a) With acetic anhydride[3a]. Following *Henry*'s two-step procedure, **1a** (10 mmol) was treated first with excess Ac_2O (reflux, 1 h) and then with *o*-anisidine (10 mmol) to give **3a** (3.09 g, 94%).

(b) With ethyl chloroformate. Triethylamine (7.0 ml, 50.2 mmol) was added to a stirred suspension of **1a** (10.3 g, 46 mmol) in acetonitrile (50 ml). After cooling to 0°C, ethyl chloroformate (4.63 ml, 48.3 mmol) was added dropwise, keeping the temperature below 10°C. After stirring for 30 min, a solution of *o*-anisidine (5.51 g, 44.7 mmol) in acetonitrile (10 ml) was added, giving rise to a slightly exothermic reaction. Stirring was continued for 30 min at room temperature and then the solvent was evaporated. After addition of ethyl acetate (300 ml), the precipitate ($Et_3N \cdot HCl$) was filtered off. The filtrate was washed successively with H_2O (100 ml, pH between 6 and 7) and brine. After drying ($MgSO_4$) and evaporating the solvent, **3a** was isolated (14.45 g, 98,3%) as an almost pure substance (NMR, TLC). Chromatography (9:1 methylene chloride/methanol) yielded a pure sample as a foamy substance. NMR: broadened signals at δ 9.75 (1H, CO_2H), 8.08 (1H, *o*-H), 7.4–7.5 (5H, C_6H_5), 7.09 (1H, *p*-H), 6.9 (2H, *m*-H), 4.2–4.95 (6H, NCH_2), 3.75 (3H, OCH_3).

4-Benzyl-1-(2-methoxyphenyl)piperazine-2,6-dione (**4a**)

(a) From **3a** *and acetic anhydride*[3a]. A solution of **3a** (3.09 g, 9.3 mmol) in Ac_2O (12 ml) was heated at reflux temperature for 6 h. After cooling, the solvent was evaporated *in vacuo.*

(b) From **3a** *and ethyl chloroformate.* A solution of **3a** (10 mmol) in acetonitrile (20 ml), obtained after successive treatment of **1a** with triethylamine, ethyl chloroformate and *o*-anisidine as described above, was cooled to 2°C. Triethylamine (1.45 ml, 10.4 mmol) was then added dropwise causing a slightly exothermic reaction. The resulting suspension was heated at reflux temperature for 30 min. After cooling and evaporating the solvent, the residue was extracted with Et_2O (3 × 50 ml) and the combined extracts were concentrated *in vacuo.*

(c) From **3a** *and methanesulfonyl chloride*[11a]. A stirred solution of **3a** (10 mmol) and triethylamine (10.4 mmol) in THF (25 ml) was cooled to −40°C. Methanesulfonyl chloride (0.81 ml, 10.4 mmol) in THF (5 ml) was added dropwise, keeping the temperature below −30°C. Stirring was continued at room temperature for 1 h. Triethylamine (10.4 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.31 g, 2 mmol) were then added and the ensuing mixture was stirred at reflux for 3 h, followed by a standard work-up.

(d) From **3a** *and* Mukaiyama*'s reagent*[11b]. To a stirred solution of **3a** (10 mmol) and triethylamine (24 mmol) in THF (25 ml) was added 2-chloro-1-methylpyridinium iodide (3.09 g, 12 mmol) in small portions at −20°C. After stirring at room temperature for 30 min and at reflux for 16 h, the reaction mixture was worked-up by a standard procedure.

In all cases *(a)–(d)* the crude product contained, in addition to **4a**, several side-products. Flash-chromatographic purification was necessary in order to obtain pure **4a** in the yields indicated in Scheme 2 [an additional 10% of **5** was isolated in the case of (b)].

(e) From **3a** *and CDI.* A solution of CDI (1.63 g, 10 mmol) in THF (10 ml) was added dropwise to a stirred solution of **3a** (10 mmol) in THF (25 ml) at −30°C. The temperature was then raised to 65°C. After stirring for 1 h, TLC analysis (3:1 ether/petroleum ether) indicated an almost complete conversion. Stirring was continued for 16 h. Work-up consisted of cooling, addition of ethyl acetate and H_2O. After the extraction procedure, the organic layer was washed twice with H_2O (to remove residual imidazole) and brine. Drying ($MgSO_4$), filtration over a short silica-gel column and concentrating *in vacuo* gave a pure sample of **4a** (2.58 g, 83%).

N-Benzyl-N-[[N-(ethoxycarbonyl)-N-(2-methoxyphenyl)carbamoyl]methyl]glycine (**5**)

Triethylamine (10.4 mmol) was added to a stirred solution of **3a** (10 mmol) in THF (10 ml). After cooling, a solution of ethyl chloroformate (10.4 mmol) in THF (5 ml) was added dropwise, keeping the temperature below −30°C. DMAP (1 mmol) was then added and the reaction mixture was stirred at room temperature for 16 h. Work-up consisted of evaporating the solvent followed by an extraction procedure after the addition of ethyl acetate and H_2O. The crude product was crystallized from diisopropyl ether, yielding white crystals of **5** (2.3 g, 60%); m.p. 61.5–63°C. NMR δ 9.9 (s, 1H, CO_2H), 8.43 (dd, 1H, ^3J 8 and ^4J 2, *o*-H), 7.30–7.45 (m, 5H, C_6H_5), 7.06 (dt, 1H, ^3J 8 and ^4J 2, *p*-H), 6.98 and 6.94 (dd and dt, 2H, *m*-H), 4.17 (q, 2H, ^3J 7.5, OCH_2), 3.95 (s, 3H, OCH_3), 3.89 (s, 2H, $C\underline{H}_2C_6H_5$), 3.49 and 3.40 (2 × s, 2H, NCH_2CO), 1.23 (t, 3H, ^3J 7.5, $CH_2C\underline{H}_3$).

1,1'-Ethylenebis(4-benzylpiperazine-2,6-dione) (**7**)

To a solution of reagent **6a** (10 mmol) in THF (25 ml), prepared as described above, was added ethylenediamine (0.30 g, 5 mmol). Stirring at reflux temperature was continued for 16 h. After work-up as described above in the general procedure, **7** was isolated in 64% yield (1.39 g). An analytically pure sample *(m/z)* was obtained as a viscous oil after short-path distillation. NMR δ: 7.24 (m, 5H, C_6H_5), 3.80 (s, 2H, $C\underline{H}_2C_6H_5$), 3.6 (s, 4H, NCH_2CH_2N), 3.30 (s, 4H, 3,5-H).

4-Benzyl-1-(2-methoxyphenyl)piperazine (**8**)

(a) Reduction with $BH_3 \cdot Me_2S$[18]. A stirred solution of **4a** (1.71 g, 5 mmol) in THF (20 ml) was heated at 60°C. $BH_3 \cdot Me_2S$ (1.84 ml, 18.4 mmol) was then added dropwise over 10 min. A mixture of THF and Me_2S was distilled off over 30 min, while keeping the total volume of the reaction mixture constant by addition of THF. After cooling to room temperature, 6 N HCl (10 ml) was added and hydrolysis was completed by heating at 100°C for 30 min. The reaction mixture was cooled to room temperature and extracted with Et_2O (3 × 50 ml) after addition of 2 N NaOH (50 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue (1.2 g) was purified by flash chromatography (3:1 ether/petroleum ether) giving 0.99 g (64%) of **8**, contaminated with *ca.* 10 mol% of the corresponding 2-hydroxyphenyl compound[19].

(b) Reduction with $LiAlH_4$. $LiAlH_4$ (0.68 g, 18 mmol) was added to a suspension of **4a** (8.3 mmol) in THF (20 ml) with efficient stirring. The reaction mixture was heated at reflux temperature for 2 h. A further portion of $LiAlH_4$ (18 mmol) was then added and stirring at reflux was continued for a further 2 h. Work-up consisted of the addition of H_2O (1.4 ml), 2 N NaOH (2.8 ml) and again H_2O (2.8 ml). After 10 min at reflux temperature, the suspension was cooled, filtered and concentrated *in vacuo*, giving crude **8** (2.12 g); this was purified by flash chromatography yielding 1.16 g (49%) of pure **8** as a colourless oil. This material was identical (TLC, NMR) with a sample prepared by benzylation of **10** (benzyl chloride and triethylamine in THF). NMR δ: 7.25–7.35 (m, 5H, C_6H_5), 6.85–7.00 (m, 4H, C_6H_4), 3.85 (s, 3H, OCH_3), 3.59 (s, 2H, $C\underline{H}_2C_6H_5$), 3.09 and 2.66 (m, 2 × 4H, piperazine-H).

1-(2-Methoxyphenyl)piperazine-2,6-dione (**9**)

Catalyst (10% Pd on C, 400 mg) was added to a solution of **4a** (13.2 mmol) in methanol (50 ml) and hydrogenation proceeded to completion at 25°C within 45 min (330 ml H_2 absorbed). After removing the catalyst by filtration over Hyflo, **9** was obtained as a pure product (TLC, NMR) by evaporating the solvent (2.86 g, 98%). Crystallization from diisopropyl ether afforded an analytical sample, m.p. 168–170°C. NMR δ: 7.40 (dd, 1H ^3J 8 and ^4J 2.5, *o*-H), 7.03–7.10 (m, 3H, *m*- and *p*-H), 3.86 (s, 4H, 3,5-H), 3.79 (s, 3H, OCH_3), 2.04 (s, 1H, 4-H). $C_{11}H_{12}N_2O_3$ (220.23): C, H, N.

1-(2-Methoxyphenyl)piperazine (**10**)

Following the procedure described above, **9** (1.41 g, 6.4 mmol) was deoxygenated with $BH_3 \cdot Me_2S$ (18.8 mmol) in refluxing THF.

Table II Analytical data of the new compounds.

Product	Formula	Anal.			
		m/z calcd. (found)	C (%) calcd. (found)	H (%) calcd. (found)	N (%) calcd. (found)
4a	$C_{18}H_{18}N_2O_3$	310.1317 (310.1311)	69.66 (69.59)	5.85 (5.86)	9.03 (8.82)
4c	$C_{18}H_{18}N_2O_3$		69.66 (69.78)	5.85 (5.86)	9.03 (9.10)
4d	$C_{17}H_{15}N_2O_2Cl$		64.86 (64.85)	4.80 (4.79)	[a]
4e	$C_{17}H_{15}N_3O_4$		62.76 (62.75)	4.65 (4.75)	12.92 (13.10)
4f	$C_{19}H_{20}N_2O_2$		74.00 (73.74)	6.54 (6.53)	9.08 (9.09)
4g	$C_{17}H_{14}N_2O_2Cl_2$		58.47 (58.54)	4.04 (4.17)	[b]
4h	$C_{14}H_{18}N_2O_2$	246.1368 (246.1366)			
4i	$C_{19}H_{28}N_2O_2$	316.2151 (316.2145)			
4j	$C_{14}H_{16}N_2O_2$	244.1212 (244.1219)			
4k	$C_{15}H_{20}N_2O_2$	260.1525 (260.1525)			
4l	$C_{21}H_{26}N_2O_2$	338.1994 (338.1995)			
4m	$C_{17}H_{22}N_2O_2$	286.1681 (286.1683)			
4o	$C_{14}H_{13}N_3O_2S$		58.54 (58.24)	4.53 (4.64)	[c]
4q	$C_{16}H_{15}N_3O_2$		68.31 (68.31)	5.38 (5.42)	14.94 (14.90)
4t	$C_{14}H_{18}N_2O_2$	246.1368 (246.1371)			
4u	$C_{16}H_{20}N_2O_2$		70.56 (70.60)	7.40 (7.41)	10.29 (10.4)
4w	$C_{17}H_{16}N_2O_3$		68.90 (68.40)	5.44 (5.44)	9.45 (9.30)
4x	$C_{17}H_{13}N_3O_2 \cdot H_2O$		66.01 (66.32)	4.89 (4.82)	13.59 (13.6)
4y	$C_{15}H_{13}N_3O_2$		67.40 (67.02)	4.90 (4.93)	15.72 (15.6)
7	$C_{24}H_{26}N_4O_4$	434.1954 (434.1958)			
9	$C_{11}H_{12}N_2O_3$		59.99 (59.51)	5.49 (5.52)	12.72 (12.56)

[a] Calcd.: Cl 11.26; found: Cl 11.30%. [b] Calcd.: Cl 20.30; found: Cl 20.2%. [c] Calcd.: S 11.1; found: S 11.1%.

After acidic hydrolysis (6 N HCl, 10 ml), **10** was obtained by addition of 2 N NaOH (40 ml) and extraction with methylene chloride (1.06 g, 86%). The product was identical (TLC, NMR) with commercially available material.

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