A Conveneint Synthesis of 1-Substituted-2,5(4*H*)-piperazinediones

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1-Substituted-2,5(4*H*)-piperazinediones are prepared by the Michael addition of acrylonitrile and methyl-acrylate and glycylglycine, DL-alanyl-DL-alanine and DL-alanyl-DL-phenylalanine followed by cyclohydration in refluxing xylenes.

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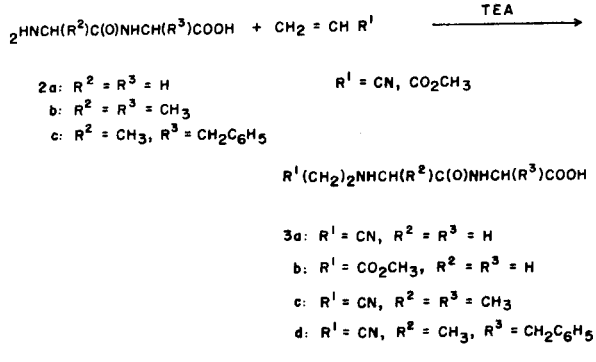
Introduction.

Michael addition by the amino group of a variety of α-amino acids is a well-documented procedure, especially with respect to cyanoethylation [1]. This type of reaction has been extended to a few dipeptides and in one case a tri- and tetrapeptide [2]. We are extremely interested in examining the behavior of a variety of dipeptides and Michael acceptors as a pathway towards the convenient synthesis of mono-*N*-substituted 2,5-diketopiperazines, **4** (Scheme II). Such compounds were of interest for a variety of studies including mutagenicity in the Ames Assay [3], behavior of dianions of 4 towards alkalating agents and finally as potential DNA intercalating agents as suggested by the work of Grafstein [4]. We wish to report the results of our study of the chemical utility of the Michael addition upon selected dipeptides with a number of acceptors and an extremely facile cyclodehydration affording a variety of 2,5-diketopiperazines.

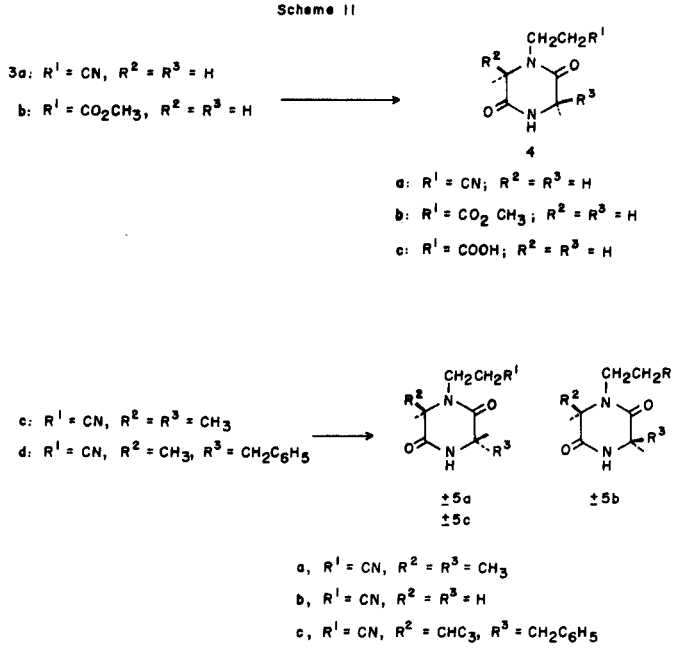
Scheme I



Discussion.

Glyclglycine, **2a**, underwent a facile Michael addition with acrylonitrile (AN) in aqueous triethylamine at room temperature affording *N*-(2-cyanoethyl)glycylglycine, **3a**, in quantitative yield. Compound **3a** was identified by the medium intensity nitrile stretch at 2245 cm^{-1} in the infrared spectrum and two triplets centered at δ 3.2 and 3.65 (J = 7 Hz) respectively in the ^1H nmr spectrum. Carrying out the Michael addition in aqueous sodium hydroxide offered no advantages and, in fact, resulted in a somewhat reduced yield. Compound **3a** was somewhat difficult to handle due to its low melting point and considerable solubility in a variety of solvents.

Scheme II



In a similar fashion **2a** was treated with methyl acrylate (MA) and again Michael addition was observed. This product, **3b**, also proved extremely difficult to handle because of its semicrystalline nature: however sufficient spectral data were obtained to confirm the course of the reaction (see Experimental). The reaction with AN was extended to DL-alanyl-DL-alanine and DL-alanyl-DL-phenylalanine affording **3c** and **3d** respectively. These reactions are summarized in Scheme I.

When compound **2a** was treated with methyl vinyl ketone or acrolein dimethyl acetate under the above conditions and at 80°, no addition to the vinyl group was detected. Likewise vinyl acetate and methacrylamide failed to react at room or elevated temperatures. It should be noted that glycine undergoes a facile addition with methyl vinyl ketone and a variety of similar acceptors [2] and the

inability of **2a** to react may be attributed to the diminished nucleophilicity of the amino group of the anion formed under the basic conditions employed in the addition reaction [5].

When compound **3a** was heated at 160-180° in a mixture of xylenes, a clean cyclodehydration affording 1-(2'-cyanoethyl)-(4*H*)-piperazinedione, **4a** in excellent yield. The product was identified by spectral means in that the infrared spectrum contained NH stretching at 3250 cm^{-1}, with strong CN stretch at 2240 cm^{-1} and amide carbonyl stretching at 1670 cm^{-1}. The ^1H nmr spectrum was also invaluable in identifying **4a** illustrating the piperazine ring methylenes as non-equivalent resonances at δ 3.69 and 3.79 respectively. Also the exocyclic methylenes of the cyanoethyl group appeared as triplets at δ 2.75 and 3.79 (J = 9 Hz). In addition, the mass spectrum which contained the molecular ion, m/z 167 (100%), possessed a major fragment at m/z 127 corresponding to the loss of CH_2-CN.

The cyclodehydration of **3a** (and all other Michael adducts examined) was quite sensitive to temperature. For example, attempts to effect ring closure in refluxing toluene were unsuccessful with starting material recovered in greater than 90% yield. Also, the ability of the solvent (xylenes) to effect azeotropic removal of water was important since heating **3a** in the absence of solvent lead to significantly diminished yields. The optimum procedure employed the use of a Dean-Stark receiver to further displace the equilibrium.

Attempts to bring about ring-closure of **3a** with dicyclohexylcarbodiimide (DCC) were unsuccessful. While dicyclohexylurea was produced in the reaction, only oily, intractable residues could be isolated. An examination of the oily material by ir did not reveal the presence of a nitrile group and further attempts to employ DCC as a means of effecting cyclization were abandoned.

When the cyclodehydration was extended to **3b** the course of the reaction was slightly modified. In this case two products were isolated, one soluble in the xylenes (**4b**) and the other insoluble (**4c**). Isolation and purification of **4b** permitted spectral evaluation of the material and both ir (C=O at 1735 cm^{-1}, C-O-R at 1220 and 1125 cm^{-1}) and ^1H nmr (OCH_3 at δ 3.55) demonstrated the presence of an ester group. Ring closure was also indicated by the triplet centered at δ 2.43 (J = 7 Hz) upfield relative to the starting material. Compound **4b** was assigned the structure methyl 3-(1',(4'*H*)-2',5'-piperazinedionyl)propanoate. Compound **4c** was identified mainly by the strong carbonyl at 1720 cm^{-1} and broad absorption between 3000 and 2400 cm^{-1}, all typical of a carboxylic acid. Also an exchangeable broad resonance at δ 12.0 was indicative of the carboxylic acid group. Thus **4c** was assigned the structure 3-(1',(4'*H*)-2',5'-piperazinedionyl)propanoic acid. The overall yield of **4b** and **4c** varied from experiment to experiment; however the amount of **4b** always exceeded the amount of **4c** that could be recovered after the reflux period and the ratio was quite constant at 2:1 **4b/4c**. These observations led to the speculation that **4c** results from the *in situ* hydrolysis of **4b** by water entrapped in the crude **3b** employed or water evolved during the course of the cyclization reaction and quite likely a combination of both.

Next, the cyclization was extended to **3c** and **3d** with similar results. Yields were reasonably high and product isolation was readily accomplished as **5a-c** crystallized from the reaction solvent. Ring closure of the Michael adducts was deduced from spectral data as before. However, ring closure in these examples affords diastereomeric products (see Scheme II) and close examination of the ^1H nmr confirmed this fact. For example, examination of the methyl resonance region of **5a,b** revealed a complex multiplet centered at δ 1.3. Scale expansion of this region of the spectrum indicated the presence of a series of four doublets (J = 7.5 Hz) resulting from the chemical shift non-equivalence of the methyl groups in each diasteromer. The methine region appeared as an extremely complex multiplet with one exocyclic triplet superimposed. Scale expansion could not resolve this region into the predicted sixteen lines when the ^1H nmr experiment was accomplished at 60 MHz.

When the substituent was a bulky benzyl group as in the case of **5c**, only one diastereomer seemed to form at least with respect to the detection limits of nmr. It is presumed that steric factors account for the observed course of the reaction and that the relative stereochemistry of **5c** has the methyl and benzyl groups trans with respect to each other. Unfortunately we were unable to cleanly separate **5a** and **5b** by tlc (silica or microcrystalline cellulose), and therefore cannot estimate the relative amounts of **5a** and **5b** that form under the above conditions.

Summary.

Selected dipeptides undergo Michael addition with reactive acceptors such as acrylonitrile and methyl acrylate to afford monoadducts in excellent yield. These adducts may then be subjected to cyclodehydration in refluxing xylenes to produce a corresponding series of mono-*N*-substituted 2,5-diketopiperazines in excellent yield. In addition to cyclodehydration, ester hydrolysis was also noted under the reaction conditions affording the corresponding 2,5-diketopiperazine with an exocyclic carboxylic acid group. All compounds synthesized were completely characterized by spectral methods.

EXPERIMENTAL

General.

All solvents were dried and purified prior to use by standard methods. All reagents were employed as received except when otherwise noted. Infrared spectra were recorded on a Beckman Acculab 2 as potassium

bromide discs. Proton spectra were measured on a Perkin-Elmer R24B spectrometer and chemical shifts are reported on the δ scale relative to TMS as an internal standard. Mass spectra were recorded on a Hewlett-Packard Model 5982 A dual source instrument. Melting points are uncorrected and were obtained on a Mel-Temp device. Elemental analyses were performed by Atlantic Microlab Inc. Atlanta, Georgia.

Reaction of **2a** with Acrylonitrile.

To a stirred solution of 2.5 g (0.02 mole) of **2a** in 50 ml of water, 1.2 g (0.01 mole) of triethylamine and 1.2 g (0.022 mole) of acrylonitrile were added and the resulting solution stirred at room temperature for 24 hours. The solvents were removed under reduced presure and the viscous oil that remained was triturated with 25 ml of 2-propanol. The white crystals of **3a** that resulted were collected, affording 3.30 g (94%); ir (potassium bromide): 3500 cm^{-1} (NH), 2245 (CN), 1695 (C=O); nmr (deuterium oxide): δ 3.20 (t, 2H, CH_2, J = 7 Hz), 3.65 (t, 2H, CH_2, J = 7 Hz), 4.00 (s, 2,H, CH_2), 4.22 (s, 2H, CH_2). This material was employed in subsequent reactions without further purification. In a similar fashion the following were prepared from **2a,b,c** (see Scheme I).

Compound **3b** was obtained in 53% yield; ir (potassium bromide): 3400 cm^{-1} (NH), 1725 (ester C=O), 1650 (amide C=O), nmr (deuterium oxide): δ 2.85 (t, 2H, CH_2, J = 8 Hz), 3.39 (t, 2H, CH_2, J = 8 Hz), 3.7 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 3.91 (s, 2H, CH_2).

Compound **3c** was obtained in 52% yield; ir (potassium bromide): 3300 cm^{-1} (NH), 2240 (CN), 1650 (C=O), nmr (deuterium oxide): δ 1.35 (d, 3H, CH_3, J = 7 Hz), 1.55 (d, 3H, CH_3, J = 6 Hz), 3.0 (t, 2H, CH_2, J = 6 Hz), 3.3 (t, 2H, CH_2, J = 6 Hz), complex multiplet centered around 4.2 (6H) with overlapping doublet at 4.1.

Compound **3d** was obtained in 95% yield; ir (potassium bromide): 3300 cm^{-1} (NH), 2260 (CN), 1650 (C=O).

As in the case of **3a**, the above compounds were employed in subsequent reactions without further purification.

1-(2'-Cyanoethyl)-2,5(4*H*)-piperazinedione (**4a**).

To a freshly distilled mixture of xylenes, 0.5 g (3 mmoles) of **3a** was added. The mixture was heated under reflux in a system equipped with a Dean Stark receiver. Reflux was continued until water ceased to codistill (approximately 4 hours). The cooled xylenes afforded a precipitate which upon recrystallization from toluene gave 0.36 g (80%) colorless plates of **4a**, melting at 175-176°; ir (potassium bromide): 3250 cm^{-1} (NH), 2240 (CN), 1670 (C=O); nmr (DMSO-d_6): δ 2.75 (t, 2H, CH_2, J = 6 Hz), 3.54 (t, 2H, CH_2, J = 6 Hz), 3.69 (s, 2H, ring CH_2), 3.79 (s, 2H, ring CH_2); ms: 167 (M^+, 100), 127 (M^+-40, 70).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 45.16; H, 5.42; N, 15.05. Found: C, 45.16; H, 5.44; N, 15.02.

Methyl 3-(1'(4'*H*)-2'-5'-Piperazinedionyl)propanoate (**4b**) and 3-(1'(4'*H*)-2',5'-Piperazinedionyl)propanoic Acid (**4c**).

To a freshly distilled mixtue of xylenes, 2.06 g (9.4 mmoles) of **3b** was added. The mxiture was heated under reflux as described previously. When the reaction period was complete the hot xylenes were decanted and kept at room temperature. The reaction flask contained a brown oil which soon crystallized. Recrystallization from ethanol with charcoal decolorization afforded 0.48 g (26%) of white prisms of **4c**, mp 215° dec; ir (potassium bromide): 3300 cm^{-1} (NH), 3000-2400 (COOH), 1720 (C=O), 1650 (C=O), 1330 (C-O); nmr (DMSO-d_6): δ 2.43 (t, 2H, CH_2, J = 7 Hz), 3.41 (t, 2H, CH_2, J = 7 Hz), 3.72 (s, 2H, ring CH_2), 3.89 (s, 2H, ring CH_2), 12.0 (broad s, exchangeable in deuterium oxide, 1H, COOH); ms: 186 (M^+, 100), 168 (M^+-18, 65).

Anal. Calcd. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.42; N, 15.05. Found: C, 45.16; H, 5.44; N, 15.02.

The xylenes afforded crystals upon cooling. Recrystallization of the same from toluene gave 0.96 g (58%) **4b**, mp 118-120°; ir (potassium bromide): 3195 cm^{-1} (NH), 1735 (ester C=O), 1665 (amide C=O), 1220 (C-O-C); nmr (DMSO-d_6): δ 2.52 (t, 2H, CH_2, J = 7 Hz), 3.48 (t, with s overlap, 5H, CH_2, OCH_3), 3.55 (s, overlap with 3.48t, OCH_3), 3.72 (s, 2H, ring CH_2), 3.89 (s, 2H, ring CH_2); ms: 200 (M^+, 100), 168 (M^+-32, 50).

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.05; N, 14.00. Found: C, 48.03; H, 6.06; N, 13.96.

1-(2'-Cyanoethyl)-3,6-dimethyl-2,5(4*H*)-piperazinediones (±**5a**), (±**5b**).

A mixture of 0.96 g (4.5 mmoles) of **3c** and freshly distilled xylene was heated under reflux as described previously. The isolation and purification of the reaction products was as described before affording 0.73 g (83%) of a mixture of the diastereomers ±**5a** and ±**5b**. The diastereomer nature of this material was based upon the following ^{1}H-nmr spectral data (DMSO-d_6): δ 1.30 (m, 6H, ring CH_3); this multiplet upon scale expansion (100 Hz full scale) demonstrated 4 superimposed doublets, J = 7.5 Hz accounted for by the non-chemical shift equivalence of the ring methyl groups; 2.75 (t, 2H, CH_2, J = 7 Hz), 3.90 (m, 5H, ring H, exocyclic CH_2).

1-(2'-Cyanoethyl)-2-benzyl-6-methyl-2,5(4*H*)-piperazinedione (±**5c**).

A mixture of 1.0 g (3.4 mmoles) of **3d** in freshly distilled xylenes was heated under reflux. The product was isolated and purified as described previously. This gave 0.57 g (66%) of **5c** which melted at 166-167°; ir (potassium bromide): 3200 cm^{-1} (NH), 2250 (C=N), 1670 (C=O); nmr (deuteriochloroform): δ 1.45 (d, 3H, CH_3, J = 6 Hz), 2.51 (t, 2H, CH_2, J = 6 Hz), 3.1 (d, superimposed s, 4H), 3.60 (heptet, 2H, ring methines), 7.18 (m, 5H, aromatic), 7.5 (broad s, exchangeable in deuterium oxide, NH); ms: 271 (M^+, 70), 180 (M^+-91, 40).

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.33; N, 15.49. Found: C, 66.37; H, 6.35; N, 15.47.

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