Synthesis of Some New Pyrrolo Heterocycles of Pharmaceutical Interest from 1,4-Diphenylpyrrolidine-2,3,5-trione⁺

Mohamed Abbas Metwally* and M. A. Sofan

Department of Chemistry, Faculty of Science, University of Mansoura, Mansoura, Egypt

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Pyrrolo Heterocycles, 1,4-Diphenylpyrrolidine-2,3,5-trione

Continuing earlier studies designed to obtain derivatives of pharmacological interest, some novel compounds **2**, **5**, **6**, **7** and **8** were prepared using 1,4-diphenylpyrrolidine-2,3,5-trione (**1**) and 1,2-phenylenediamines, *o*-aminophenol, 1,3-diphenylacetone and thiosemicarbazide, respectively. The hydrazino derivative (**8**) was obtained from **7** and hydrazine hydrate. Structural identification was obtained by ¹H NMR, mass spectra and IR spectral data.

Pyrrolidines are reported to act as a respiratory stimulant and anticonvulsant agents [1, 2]. A search of the literature showed that condensed heterocycles having a fused pyrrolo nucleus have attracted little attention, but some interest has come from alkaloids bearing this ring system.

This work has focussed on exploring the synthetic potentialities of the heterocyclic 1,4-diphenylpyrrolidine-2,3,5-trione (**1**) [3] as a key intermediate for the synthesis of some condensed heterocycles having a pyrrolo nucleus.

A survey of the literature showed that no reactions of **1** with 1,2-diamines has been reported.

Continuing our earlier [4] studies designed to obtain derivatives of pharmacological interest, some novel compounds (**2**, **5**, **6**, **7** and **8**) were prepared using 1,4-diphenylpyrrolidine-2,3,5-trione (**1**) and 1,2-phenylenediamines, *o*-aminophenol, 1,3-diphenylacetone and thiosemicarbazide.

Reaction of **1** with 1,2-phenylenediamines yielded the pyrroloquinoxalines **2**, **3** or **4**. In principle these compounds could be expected to exist in tautomeric forms. The IR and ¹H NMR spectra favours structure **2a–d** rather than **3** or **4**. These compounds showed absorption bands at 1570–1595 cm⁻¹ (C=N), 1660–1680 cm⁻¹ (C=O) and 3090–3230 cm⁻¹ (enolized OH). The ¹H NMR (400 MHz) of *e.g.* **2a** displayed signals at δ 7.0–7.6 (m, ArH), 5.6 (s, 1 H, Ph–H–C=O) and 10.28

- a: R¹ = R² = H;
- b: R¹ = Me, R² = H;
- c: R¹ = H, R² = Cl;
- d: R¹ = H, R² = NO₂

(s, 1 H, OH). The mass spectrum of **2a** gave an M⁺ at *m/z* 337 fitted exactly with the obtained molecular weight.

In connection with the above successful reactions, it was the intention to examine the reaction of **1** with *o*-aminophenol. Thus, condensation of **1** with *o*-aminophenol in glacial acetic acid afforded the pyrrolobenzoxazine (**5**) in quantitative yield.

The formation of **5** finds support from its correct analytical and spectral data, the IR spectrum showed absorption bands at 1605 (C=N) and 1665 cm⁻¹ (C=O). The ¹H NMR spectrum displayed signals at δ 7.4–8.07 (m, ArH). Further evidence for the formation of **5** was proved from the mass spectrum which revealed the M⁺ at *m/z* 338 fitted exactly with the obtained molecular weight.

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* Reprint requests to Prof. Dr. M. A. Metwally.

Compound **1** condensed with 1,3-diphenylacetone in presence of 20% aqueous potassium hydroxide to give the pyrrolocyclopentenone (**6**) in a good yield. Assignment of the product as **6** rather than **7** was partly based on the appearance in the IR spectrum of a peak at 3235 cm^{-1} , characteristic of enolized carbonyl.

1,4-Diphenylpyrrolidine-2,3,5-trione (**1**) was allowed to react with thiosemicarbazide to afford 1,2,4-triazino[5,6-*b*]pyrrole-3-thione (**7**). The latter, on refluxing with hydrazine hydrate, afforded the corresponding 3-hydrazino-1,2,4-triazino[5,6-*b*]pyrrole (**8**). In addition to the correct analytical data, the IR spectrum of **7** showed characteristic bands at 1060 (C=S) , 1670 (C=O) and $3250\text{ cm}^{-1}\text{ (NH)}$. In the IR spectrum of **9** no absorption bands for C=S has been observed.

Experimental

All melting points ($^{\circ}\text{C}$) are uncorrected and were taken in a Fisher electric melting point apparatus.

Infrared spectra were performed on a Unicam SP 2000 Infrared spectrophotometer using KBr pillet technique. ^1H NMR spectra were obtained in DMSO (d_6) on Bruker 400 MHz apparatus. Mass spectra were measured on Varian MAT 711, direct inlet at 70 eV .

1,4-Diphenylpyrrolidine-2,3,5-trione (**1**)

This compound was prepared according to methods reported previously [3].

Pyrroloquinoxalines (**2a–d**)

A mixture of **1** (0.004 mole) and 1,2-phenylenediamines, namely *o*-phenylenediamine, 3-methyl-1,2-phenylenediamine, 4-chloro-1,2-phenylenediamine and/or 4-nitro-1,2-phenylenediamine (0.004 mole) in (30 ml) glacial acetic acid was heated at $90\text{--}100\text{ }^{\circ}\text{C}$ for 30–60 min and filtered while hot. The solid product that separated in each case was filtered off and recrystallized from acetic acid to give compounds **2a–d**. The results are given in Table I.

Pyrrolobenzoxazine (**5**)

The method followed for the preparation of compounds **2a–d** were adapted. Compound **5** was crystallized from acetic acid to give compound **5** (*cf.* Table I).

Pyrrolocyclopentenone (**6**)

A mixture of **1** (0.01 mole) and 1,3-diphenylacetone (0.015 mole) in ethanol (25 ml) was treated with 20% aqueous potassium hydroxide solution (10 ml), then set aside at room temperature for 2–3 days. The reaction mixture was poured into ice-cold water, and the solid separated was filtered off, crystallized from ethanol to give compound **6** (*cf.* Table I).

1,2,4-Triazino[5,6-*b*]pyrrole-3-thione (**7**)

This compound was prepared by refluxing the corresponding 2,3,5-trione with thiosemicarbazide in alkaline medium by following the method of Gladych, *et al.* [5] (*cf.* Table I).

3-Hydrazino-1,2,4-triazino[5,6-*b*]pyrrole (**8**)

1,2,4-Triazino[5,6-*b*]pyrrole-3-thione (**7**, 1 g) was refluxed with hydrazine hydrate (8 ml), for 4–5 h. On cooling, crystals separated, which were filtered and crystallized from ethanol to give compound **8** (*cf.* Table I).

Table I. Characterization data of compounds **2a–d**, **5**, **6**, **7** and **8**.

Compd.	Colour	Yield [%]	M. p. [°C]	Mol. formula (M. wt.)	Found [%], (Calcd) [%]		
					C	H	N
2a*	Pale yellow	80	>270	C ₂₂ H ₁₅ N ₃ O (337.36)	78.31 (78.39)	4.48 4.35	12.45 12.39
2b	Brown	75	205	C ₂₃ H ₁₇ N ₃ O (351.39)	78.61 (78.52)	4.87 4.69	11.95 12.05
2c	Brownish yellow	78	260	C ₂₂ H ₁₄ N ₃ OC1 (371.807)	71.06 (71.15)	3.79 3.92	11.3 11.51
2d	Reddish brown	85	220	C ₂₂ H ₁₄ N ₄ O ₃ (382.36)	69.1 (69.32)	3.69 3.52	14.65 14.73
5⁺	Brownish yellow	65	178	C ₂₂ H ₁₄ N ₂ O ₂ (338.35)	78.09 (78.16)	4.17 4.30	8.28 8.21
6	Yellow	68	117	C ₃₁ H ₂₁ NO ₂ (439.488)	84.71 (84.55)	4.81 4.73	3.18 3.42
7	Pale yellow	72	120	C ₁₇ H ₁₂ N ₄ SO (320.364)	62.79 (62.85)	3.77 3.59	17.48 17.39
8	Colourless	63	125	C ₁₇ H ₁₄ N ₆ O (318.33)	64.13 (64.23)	4.43 4.59	26.4 26.11

* MS: *m/z* 337 (M⁺; 5%), 308 (3%), 262 (8%), 236 (100%), 207 (20%), 176 (12%); + MS: *m/z* 338 (M⁺; 4%), 265 (100%), 236 (22%), 209 (18%), 145 (60%).

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