

Pyrrolo[2,1-*f*]-1,2,4-triazine Derivatives.

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1-Ureidopyrroles of type **6a,b** prepared by the general method previously described (2), readily cyclized under basic conditions giving pyrrolo[2,1-*f*]-1,2,4-triazine-2,4(1*H*,3*H*)dione derivatives.

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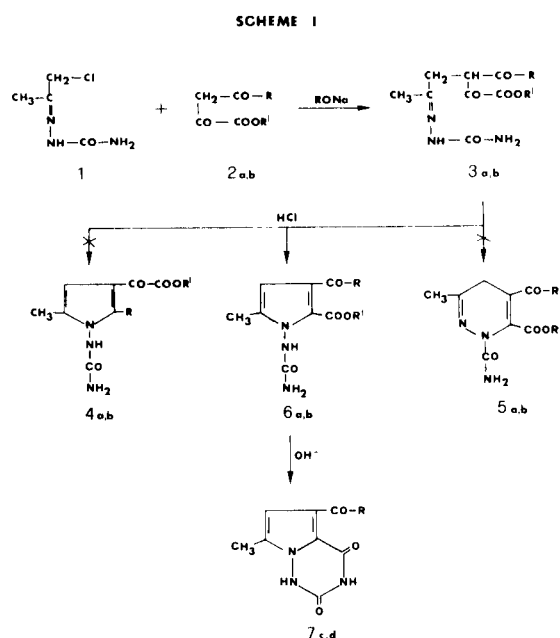
In the development of a synthetic program directed toward the preparation of various fused bridgehead nitrogen ring system derivatives, a number of pyrrolo[2,1-*f*]-1,2,4-triazines were synthesized. Compounds of this type have not been previously reported in the literature. The semicarbazones **3a,b** which were synthesized by the action of chloroacetone semicarbazone (**1**) on the sodium salts of compounds **2a,b** in dry ethanol or methanol, respectively, were used as starting materials.

The cyclodehydration of **3a,b** may be carried out using ethanol or methanol saturated with hydrochloric acid as the condensing agent. Three possible products could be formed from this reaction (see Scheme I). The possible 1-ureidopyrrole structures **6a,b** and **4a,b** were assigned on the basis of nmr spectral data. These compounds showed a doublet at δ 2.00-2.20 [3H, C(5)-CH₃] and a quartet at δ 6.15-6.20 [1H, pyrrole methyne proton at C(4)].

The coupling constant between the C(5)-CH₃ protons and the C(4)-H proton (0.75 Hz) correlated with nmr data for similar 1-ureidopyrroles reported in a previous paper (2). Moreover, the NH₂ and NH absorbances appeared at δ 6.20-6.30 and δ 9.00-9.10, respectively (2). Further, cyclisation of 1-ureidopyrroles **6a,b** in base afforded the bicyclic system **7c,d**, thus eliminating the alternative structures **4a,b**.

The suggested structures, (**7c,d**), have therefore been proven mainly on the basis of physical data, analyses, mass exact measurement, ir spectra and in particular nmr spectra. The nmr clearly shows, besides the signals due to the substituents, a doublet at δ 2.40 (3H) attributable to C(7)-CH₃ ($J \cong 0.75$ Hz), a quartet at δ 6.40-6.80 due to C(6)-H ($J \cong 0.75$ Hz) and broad resonances centered at about δ 12.36 exchangeable with deuterium oxide, for three or two acidic protons, respectively.

Moreover, compound **7c** upon decarboxylation afforded 7-methylpyrrolo[2,1-*f*]-1,2,4-triazine-2,4(1*H*,3*H*)dione (**8**), having spectral data in agreement with the above reported compounds.

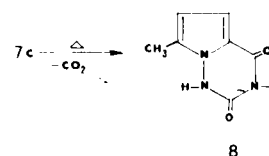


a. R = -OC₂H₅; R' = C₂H₅-

b. R = C₆H₅; R' = CH₃

c. R = -OH

d. R = C₆H₅-



EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer Infracord 137 using nujol mulls. Nmr spectra (DMSO-*d*₆) were measured using TMS as the internal standard, with a Jeol C-60H spectrometer. The mass spectra were measured with a Jeol JMS-O1SG-2 double focusing spectrometer at 75 eV (100 μ A). Exact mass measurement were performed on Ilford Q-2 photoplates; perfluorokerosene was used as a reference at a resolving power better than 15000.

General Procedure for the Preparation of **3a,b**.

To a stirred suspension of the sodium salts of diethyl oxalacetate (**2a**) (3) or oxalylacetophenone (**2b**) (4) (obtained from 0.01 mole of sodium, 100 ml. of absolute ethanol or methanol,

respectively, and 0.01 mole of **2a** or **2b**) chloroacetone semicarbazone (**1**) was added in small portions over a period of 15 minutes. After the addition was completed, the mixture was kept at room temperature for 2-3 additional hours with stirring, and then stored in the refrigerator overnight. The reaction products, precipitated by concentration of the solvent, were filtered off, washed with ice-water and ether and then air dried. The products were recrystallized from ethanol (yield 70% for **2a** and 65% for **2b**).

Diethyl 3-Acetyloxalacetate 3-Semicarbazone (**3a**).

This compound had m.p. 160°; ir: cm^{-1} 3520, 3410 and 3220 (broad) (NH and NH_2), 1750 and 1680 (CO).

Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_6$: C, 47.83; H, 6.36; N, 13.95. Found: C, 47.90; H, 6.48; N, 13.87.

Methyl 2,5-Dioxo-3-benzoylesanoate 5-Semicarbazone (**3b**).

This compound had m.p. 165°; ir: cm^{-1} 3480, 3220 (broad) (NH and NH_2), 1750 and 1680 (CO).

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.52; H, 5.31; N, 13.10.

General Procedure for the Preparation of **6a,b**.

Compounds **3a,b** (3 mmoles) in 20 ml. of ethanol or methanol, respectively, saturated with hydrochloric acid, were stirred at room temperature for 3 hours. After evaporation of the solvent under reduced pressure a solid was obtained, which was washed with ice-water and recrystallized from ethanol (yield 70%).

1-Ureido-5-methyl-2,3-dicarbethoxypyrrole (**6a**).

This compound had m.p. 165°; ir: cm^{-1} 3250 (broad) (NH and NH_2), 1740 and 1650 (CO); nmr: δ 1.20 (6H, t, 2 X $-\text{COOCH}_2\text{CH}_3$, $J \cong 6.00$ Hz), 2.00 (3H, d, C_5-CH_3 , $J \cong 0.75$ Hz), 4.15 (4H, q, 2 X $-\text{COOCH}_2-\text{CH}_3$, $J \cong 6.00$ Hz), 6.20 (3H, m, C_4-H and NH_2 , $J \cong 0.75$ Hz, which became a quartet upon exchange with deuterium oxide), 9.10 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$: 283.1168. Found: 283.1170 (± 0.002).

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.92; H, 6.13; N, 14.97.

1-Ureido-5-methyl-3-benzoyl-2-carbomethoxypyrrole (**6b**).

This compound had m.p. 225°; ir: cm^{-1} 3400, 3200 (NH and NH_2), a set of signals at 1680 (CO); nmr: δ 2.20 (3H, d, C_5-CH_3 , $J \cong 0.75$ Hz), 3.30 (3H, s, $-\text{COOCH}_3$), 6.15 (1H, q, C_4-H , $J \cong 0.75$ Hz), 6.30 (2H, s, NH_2 , exchangeable with deuterium oxide), 7.40-7.80 (5H, m, C_6H_5), 9.00 (1H, s, NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$: 301.1062. Found: 301.1064 (± 0.003).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.90; H, 5.17; N, 14.00.

General Procedure for the Preparation of **7c,d**.

A mixture of **6a,b** (1.7 mmoles), 10 ml. of ethanol and 16 ml.

of 2% sodium hydroxide was refluxed for 2 hours. After evaporation of the solvent under reduced pressure, the residue was treated with hydrochloric acid (20%). The solid was collected, washed with water and recrystallized from ethanol (yield 60%).

7-Methylpyrrolo[2,1-f]-1,2,4-triazine-2,4(1H,3H)dione-5-Carboxylic Acid (**7c**).

This compound had m.p. 310°; ir: cm^{-1} 3180 (NH), 1700 (CO); nmr: δ 2.40 (3H, d, C_7-CH_3 , $J \cong 0.75$ Hz), 6.80 (1H, q, C_6-H , $J \cong 0.75$ Hz), 12.36 (3H, broad, 2 X NH and C_5-COOH , exchangeable with deuterium oxide); exact mass measurement: Calcd. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_4$: 209.043. Found: 209.045 (± 0.002).

Anal. Calcd. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_4$: C, 45.94; H, 3.37; N, 20.09. Found: C, 46.02; H, 3.41; N, 20.17.

5-Benzoyl-7-methylpyrrolo[2,1-f]-1,2,4-triazine-2,4(1H,3H)dione (**7d**).

This compound had m.p. 275°; ir: cm^{-1} 3200 (NH), 1720 and 1680 (CO); nmr: δ 2.40 (3H, d, C_7-CH_3 , $J \cong 0.75$ Hz), 6.40 (1H, q, C_6-H , $J \cong 0.75$ Hz), 7.60-8.00 (5H, m, C_6H_5), 11.40 (2H, broad, 2 X NH, exchangeable with deuterium oxide); exact mass measurement: Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3$: 269.080. Found: 269.082 (± 0.002).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.40; H, 4.21; N, 15.70.

Pyrolysis of **7c**. 7-Methylpyrrolo[2,1-f]-1,2,4-triazine-2,4(1H,3H)dione (**8**).

Compound **7c** (0.5 g.) was heated at 280° for 10 minutes. The residue was washed with boiling ethanol (5-8 ml.), filtered and recrystallized, m.p. 300° (ethanol); ir: cm^{-1} 3180 (NH), 1680 (CO); nmr: δ 2.34 (3H, d, C_7-CH_3 , $J_{\text{C}_7-\text{CH}_3, \text{C}_6-\text{H}} \cong 0.75$ Hz), 6.15 (1H, doublet-broad, C_6-H , $J_{\text{C}_6-\text{H}, \text{C}_5-\text{H}} \cong 3.30$ Hz), 6.65 (1H, d, C_5-H , $J_{\text{C}_5-\text{H}, \text{C}_6-\text{H}} \cong 3.30$ Hz), 10.80 (2H, broad 2 X NH exchangeable with deuterium oxide); exact mass measurement: Calcd. for $\text{C}_7\text{H}_7\text{N}_3\text{O}_2$: 165.0300. Found: 165.0310.

Anal. Calcd. for $\text{C}_7\text{H}_7\text{N}_3\text{O}_2$: C, 50.91; H, 4.27; N, 25.45. Found: C, 51.08; H, 4.35; N, 25.57.

REFERENCES AND NOTES

- (1) The signal for compound **6a** appeared overlapped by NH_2 group resonances, which, on addition of deuterium oxide, became a sharp quartet.
- (2) V. Sprio and P. Madonia, *Ann. Chim. (Rome)*, **50**, 1791 (1960); V. Sprio, S. Plescia and I. Fabra, *Atti Accad. Sci. Lett. Arti. Palermo, Serie IV*, **31**, 179 (1972); *Chem. Abstr.*, **79**, 105026x (1973).
- (3) L. Claisen and N. Stylos, *Ber.*, **20**, 2188 (1887).
- (4) M. Freri, *Gazz. Chim. Ital.*, **68**, 617 (1938).