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The synthesis of 1-hydroxy-2,4-diphenylpyrrolo[2,3-d]pyridazin-7(6H)one is described.

J. Heterocyclic Chem., 16, 203 (1979).

Sir:

Recently several pyrrolo[2,3-d]pyridazines have been prepared as potential antineoplastic agents (1-3). The more recent paper described the preparation of a number of interesting derivatives of pyrrolo[2,3-d]pyridazine 5-oxides (4). Furthermore, we wish to devise a synthetic sequence which would lead to the unknown 1-hydroxy-pyrrolo[2,3-d]pyridazine derivatives.

By stirring at room temperature a solution of methyl 3,4-dibenzoyl-2-oxobutyrates 4-oxime (1) (5) in methanol saturated with hydrochloric acid for 6 hours, upon evaporation to dryness under reduced pressure, 1-hydroxy-3-benzoyl-5-phenyl-2-carbomethoxypyrrole (2) was obtained in high yield (80%), employing the method previously described (6). The physical, analytical and spectral data (7) for 2 are as follows: m.p. 160° (ethanol); exact mass measurement (8): Calcd. for C₁₉H₁₅NO₄: 321.100. Found: 301.102 (± 0.003); nmr, δ: 3.30 (3H, s, -COOCH₃), 6.60 (1H, s, C₄-H); 7.35-8.00 (10H, m, 2 x C₆H₅), 12.00 (1H, s, OH, exchangeable with deuterium oxide); ir cm⁻¹: broad centered at 3100 (OH), 1670 and 1650 (CO).

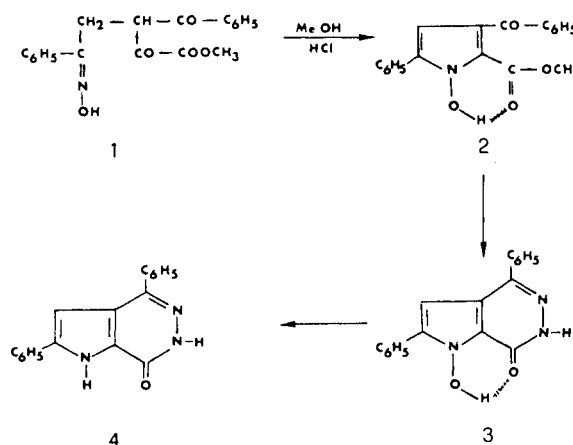
Anal. Calcd. for C₁₉H₁₅NO₄: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.19; H, 4.85; N, 4.35.

In the ir spectra of compound 2 there are observed broad bands centered at 3100 cm⁻¹ for the OH stretching frequency and bands at 1670 and 1650 cm⁻¹. These low frequency bands due to the carbonyl groups agree with a structure intramolecularly hydrogen bonded in a six membered ring system of low energy. By refluxing equimolar amounts of 2 and hydrazine hydrochloride in ethanol for 3 hours, 1-hydroxy-2,4-diphenylpyrrolo[2,3-d]pyridazin-7(6H)one (3) was obtained in 75% yield, m.p. 240° (ethanol). Exact mass measurement: Calcd. for C₁₈H₁₃N₃O₂: 303.101. Found: 303.103 (± 0.003).

Anal. Calcd. for C₁₈H₁₃N₃O₂: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.19; H, 4.45; N, 13.92.

The nmr spectrum of 3 showed a singlet at 6.80 δ attributable to the C₃-H proton, at 7.20-8.40 δ (11H) for the aromatic protons and lactamic NH, at 12.40 δ (1H) OH, exchangeable with deuterium oxide. The ir spectrum exhibited a weak broad band, centered at 3180 cm⁻¹ (OH and NH) and a strong absorption at 1640 cm⁻¹ low frequency carbonyl groups intramolecularly hydrogen bonded. The simple refluxing of 0.1 g. of 3 in 85%

SCHEME 1



hydrazine hydrate (5 ml.) and in ethanol (20 ml.) for 10 hours lead to 2,4-diphenylpyrrolo[2,3-d]pyridazine-7(6H)-one (4), m.p. 275° (ethanol). Exact mass measurement: Calcd. for C₁₈H₁₃N₃O: 287.105. Found: 287.103 (± 0.002); ir cm⁻¹: broad centered at 3180 (NH) and 1670 (CO); nmr δ: 7.15 (1H, s, C₃-H), 7.30-8.30 (11H, m, 2 x C₆H₅ and lactamic NH), 12.35 (1H, s, pyrrole NH).

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- (7) Ir absorption spectra were determined with a Perkin-Elmer Infracord 137 using nujol mulls. Nmr spectra (DMSO-d₆) were measured with a Jeol C-60H spectrometer (TMS as the internal standard).
- (8) Exact masses were measured on Ilford Q-2 photoplates with a Jeol JMS-OISG-2 double focusing spectrometer at 75 eV (100μA); perfluorokerosene was used as a reference at a resolving power better than 15,000.

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