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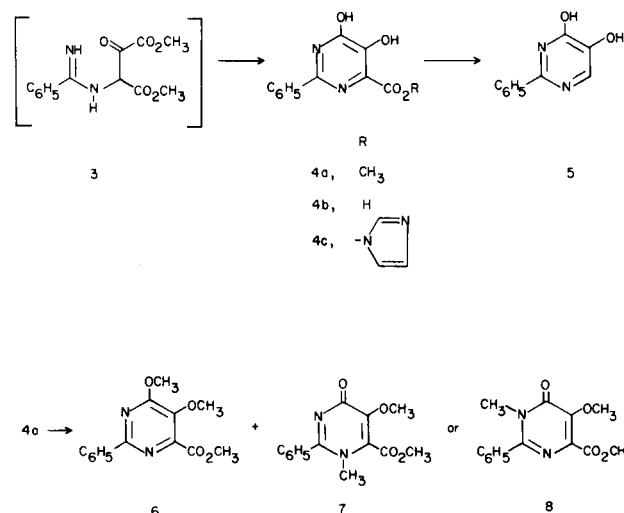
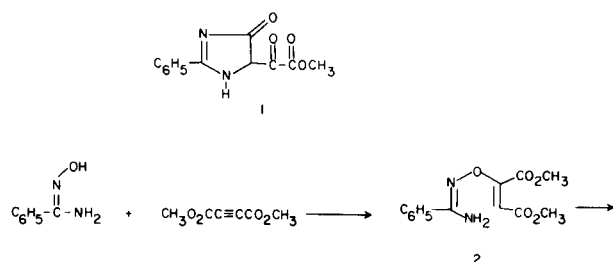
Received May 28, 1979

Pyrolysis of the adduct of benzamide oxime and dimethyl acetylenedicarboxylate leads to 5,6-dihydroxy-2-phenyl-4-pyrimidinecarboxylic acid methyl ester (**4a**) rather than 4,5-dihydro- α ,4-dioxo-2-phenyl-1*H*-imidazole-5-acetic acid, methyl ester (**1**).

J. Heterocyclic Chem., **16**, 1423 (1979).

In an attempt to prepare the α -ketoester **1** we followed the procedure of Heindel and Chun (1). Benzamide oxime was reacted with dimethyl acetylenedicarboxylate to afford the adduct **2** as a mixture of *cis-trans* isomers (1:3 ratio), which when heated in refluxing xylene solution (2) afforded a compound, m.p. 236-238°, molecular ion *m/e* 246, pmr (DMSO-*d*₆): δ 3.86 (s, 3H), 7.50 (m, 3H), 7.88 (m, 2H) corresponding to the methyl ester previously described. This compound hydrolyzed to a carboxylic acid by heating with two equivalents of sodium hydroxide, but attempts to react the expected α -keto group with methoxyamine hydrochloride to form a methoxyimine derivative gave only unreacted starting material. Upon heating the acid with 6*N* hydrochloric acid, a new compound was isolated which exhibited an elemental analysis, molecular ion *m/e* 188 and pmr (DMSO-*d*₆): δ 7.53 (m, 3H), 7.63 (s, 1H), 8.06 (m, 2H) corresponding to 2-phenyl-4,5-pyrimidinediol (**5**) derived from decarboxylation of 5,6-dihydroxy-2-phenyl-2-pyrimidinecarboxylic acid (**4b**). The correct structure of the decarboxylation product was further established by comparison with a sample of **5** prepared by the method of O'Brien, *et al.*, (3) and was found to be identical by mixed melting point and spectral data.

The pyrolysis reaction apparently proceeds *via* tautomerization and Claisen rearrangement of the oxime adduct **2** to the amidine **3** which then cyclizes by lactam formation with the more reactive α -ketoester group to afford 5,6-dihydroxy-2-phenyl-4-pyrimidinecarboxylic acid, methyl ester (**4a**). Heindel and Chun suggested **4a** as a possible structure for the product of the cyclization reaction but rejected it on the basis of the mass spectrum of its *o*-phenylenediamine adduct (**1**).



Compound **4b** could be converted into the imidazolidone with carbonyldiimidazole which then reacted with methanol to regenerate **4a**. Treatment of **4a** with diazomethane afforded a mixture of methyl ethers **6** and **7** (**8**) (2:1 ratio) which were separated by chromatography.

The pmr spectrum (deuteriochloroform) of the major component showed singlets for O-CH₃ at δ 3.97, 4.03 and 4.20 corresponding to 5,6-dimethoxy-2-phenyl-4-pyrimidinecarboxylic acid, methyl ester (**6**). For the minor product there appeared two singlets for O-CH₃ (δ 3.90 and 4.03) and one for N-CH₃ (δ 3.43), but it was not possible to clearly establish which of two possible dienone structures, 3,6-dihydro-5-methoxy-3-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid, methyl ester (**7**) or 1,6-dihydro-5-methoxy-1-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid, methyl ester (**8**) was correct.

EXPERIMENTAL

Infrared spectra were obtained in potassium bromide discs on a Digilab FTS-14 spectrophotometer. The pmr spectra were performed on a Varian EM-390 90/MHz spectrometer in the solvent indicated with TMS as an internal standard. Mass spectra were obtained from a Finnigan 1015 quadrupole mass spectrometer. Ultraviolet spectra were recorded on a Cary 118C spectrophotometer. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected.

Thin layer chromatography (tlc) was performed on E. Merck pre-coated 0.2 mm sheets of silica gel 60 F₂₅₄ and spots viewed under a short wave length ultraviolet lamp. Column chromatography was carried out using E. Merck silica gel 60 70-230 mesh.

Adduct **2** from Benzamide Oxime and Dimethyl Acetylenedicarboxylate.

A solution of 1.36 g. (10 mmoles) of benzamide oxime and 1.42 g. (10 mmoles) of dimethyl acetylenedicarboxylate in 25 ml. of methanol was refluxed three hours, treated with Darco G-60, and evaporated *in vacuo* to give 4.7 g. of pale orange oil. Tlc with ethyl acetate-hexane (3:1) showed one major spot (Rf 0.56) and minor spots at Rf 0.22, 0.31, 0.41. Isolation of the major spot material by column chromatography with ethyl acetate-hexane (3:2) gave 1.3 g. of a colorless sirup; pmr (deuteriochloroform): δ 3.70 (S, 3H, OCH₃), 3.85 and 3.90 (S,S, 3:1 ratio, 3H total, OCH₃), 5.20 and 5.48 (broad singlets, 1:3 ratio, 2H total, NH₂), 5.87 and 6.00 (S,S, 3:1 ratio, 1H total, viny), 7.4 (m, 3H, phenyl), 7.7 (m, 2H, phenyl).

When the reaction was carried out in refluxing chloroform for one hour, tlc of the crude product showed the same major spot with relatively less of the minor spots. Material from either method worked equally well in the subsequent reaction.

5,6-Dihydroxy-2-phenyl-4-pyrimidinecarboxylic Acid, Methyl Ester (**4a**).

A solution of 65.5 g. (0.461 mole) of dimethyl acetylenedicarboxylate and 61.8 g. (0.454 mole) of benzamide oxime in 300 ml. of chloroform was refluxed 40 minutes and evaporated *in vacuo*. The residual sirup was dissolved in 530 ml. of xylene (b.p. 137-144°) and refluxed with a Dean-Stark trap. The trap was emptied of 25 ml. after periods of 0.5, 1.5 and 3 hours. After standing overnight a light brown solid was filtered, washed with hexane and dried to give 49.4 g. crude product (**4a**). Crystallization from methanol afforded 23.8 g. yellowish solid, m.p. 232-235° dec. Recrystallization from methanol twice more afforded material with m.p. 236-238°; ms: molecular ion *m/e* 246; uv (methanol): 318 nm ($\epsilon = 11,300$); ir: 1700, 1675 cm⁻¹; pmr (DMSO-*d*₆): δ 3.86 (S, 3H), 7.50 (m, 3H), 7.88 (m, 2H).

Anal. Calcd. for C₁₂H₁₀N₂O₄: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.32; H, 4.42; N, 11.71.

5,6-Dihydroxy-2-phenyl-4-pyrimidinecarboxylic Acid (**4b**).

A solution 9.84 g. (40 mmoles) of ester **4a** in 160 ml. of 0.5*N* sodium hydroxide was heated on a steam bath 0.5 hour, cooled to 45° and neutralized by addition of 80 ml. of 1*N* hydrochloric acid. After crystallizing at 0° the product was filtered, washed with water and dried *in vacuo* to afford 8.60 g. of acid **4b**, m.p. 216-217° dec.; titration in 50% aqueous methanol: p*K*_a 2.7, 9.4; pmr (DMSO-*d*₆): δ 7.5 (m, 3H), 8.1 (m, 2H); uv (methanol): 314 nm ($\epsilon = 10,184$), 277 (10,092); ir: 1700, 1655 cm⁻¹.

Anal. Calcd. for C₁₁H₈N₂O₄: C, 56.90; H, 3.47; N, 12.07. Found: C, 57.35; H, 3.67; N, 12.21.

2-Phenyl-4,5-pyrimidinediol (**5**).

A suspension of 0.60 g. (2.59 mmoles) of acid **4b** in 18 ml. of 6*N* hydrochloric acid was stirred at reflux 45 minutes. Evaporation to dryness afforded a crude solid which crystallized from aqueous methanol to afford a 0.24 g. of 2-phenyl-4,5-pyrimidinediol (**5**), m.p. 216-218°; ms: molecular ion *m/e* 188; uv: (pH 1) 290 nm (ϵ 11,100), 244 (9550); (pH 11)

315 (11,600), 222 (15,200, shoulder); pmr (DMSO-*d*₆): δ 7.50 (m, 3H), 7.62 (s, 1H), 8.05 (m, 2H).

Anal. Calcd. for C₁₀H₈N₂O₂: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.74; H, 4.32; N, 14.82.

Conversion of Acid **4b** to Ester **4a**.

To a solution of 1.20 g. (5.17 mmoles) of acid **4b** in 15 ml. of *N,N*-dimethylformamide stirred in an ice bath was added 0.90 g. (5.56 mmoles) of carbonyldiimidazole. After standing one hour at 0° and overnight at room temperature the mixture containing a yellow solid was diluted with 30 ml. of ethyl acetate and filtered. After washing with ethyl acetate and ether there was obtained 1.57 g. of imidazolide **4c**; ir: 1685, 1660 cm⁻¹.

A suspension of 100 mg. (0.355 mmole) of imidazolide **4c** in 5 ml. of methanol was stirred at reflux 10 minutes. Cooling the colorless solution to room temperature afforded 48 mg. of ester **4a**, m.p. 236-238°. Mixed melting point with the ester isolated from the pyrolysis reaction was undepressed.

Methylation of Ester **4a**.

A suspension of 1.50 g. (6.10 mmoles) ester **4a** in 50 ml. of methanol stirred in an ice bath was treated with excess diazomethane solution in ether. After stirring 30 minutes at 0° the resulting solution was evaporated *in vacuo* to a sirup. The (chloroform-methanol, 20:1) showed spots at Rf 0.83 (stronger) and 0.55 (weaker) and these components were separated by column chromatography on 25 g. of silica gel with chloroform. Evaporation of the combined upper spot fractions afforded 1.17 g. of 5,6-dimethoxy-2-phenyl-4-pyrimidinecarboxylic acid, methyl ester (**6**) which was recrystallized from hexane, m.p. 64-65°; ms: molecular ion *m/e* 274; uv (methanol): 264 nm ($\epsilon = 19,400$); ir: 1740 cm⁻¹; pmr (deuteriochloroform): δ 3.97 (S, 3H, OCH₃ ester), 4.03 (S, 3H, OCH₃ ether), 4.20 (S, 3H, OCH₃ ether), 7.50 (m, 3H, phenyl), 8.40 (m, 2H, phenyl).

Anal. Calcd. for C₁₄H₁₄N₂O₄: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.09; H, 5.17; N, 10.05.

Evaporation of the combined lower spot fractions afforded 0.24 g. of compound **7** or **8** which was recrystallized twice from chloroform-hexane, m.p. 109-110°; ir: 1735, 1665 cm⁻¹; uv (methanol): 298 nm ($\epsilon = 7,700$), 237 (6,494); nmr (deuteriochloroform): δ 3.43 (S, 3H, N-CH₃), 3.90 (S, 3H, OCH₃ ester), 4.03 (S, 3H, OCH₃ ether), 7.43 (S, 5H, phenyl).

Anal. Calcd. for C₁₄H₁₄N₂O₄: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.36; H, 5.30; N, 10.34.

By comparing integrations of the aromatic resonances at δ 7.4 and 8.4 the crude reaction product was determined to contain **6** and **7** (or **8**) in a 2:1 ratio.

REFERENCES AND NOTES

- (1) N. D. Heindel and M. C. Chun, *Chem. Commun.*, 664 (1971).
- (2) It was possible to carry out the reaction in diphenyl ether if the temperature was not allowed to rise above ca 190°; otherwise, an intractable tar resulted.
- (3) D. E. O'Brien, L. T. Weinstock, R. H. Springer and C. C. Chung, *J. Heterocyclic Chem.*, **4**, 49 (1967).