A Synthesis of Lumazine Derivatives

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Treatment of 6-amino-1,3-dimethyl-5-nitrosouracil (Ia) with dimethyl acetylenedicarboxylate (DMAD) in dimethylformamide (DMF) afforded 6,7-bis(dimethoxycarbonyl)-1,3-dimethyllumazine (II). Similarly, the reaction of 6-amino-1,3-dimethyl-5-phenylazouracil with DMAD gave also II. Hydrolysis of II with hydrochloric acid gave 1,3-dimethyllumazine-6-carboxylic acid (III). III was chlorinated with thionyl chloride and then aminated with ethanolic ammonia to give rise to 6-carbamoyl-1,3-dimethyllumazine (V). V was alternatively synthesized by the treatment of Ia with propiolamide in DMF.

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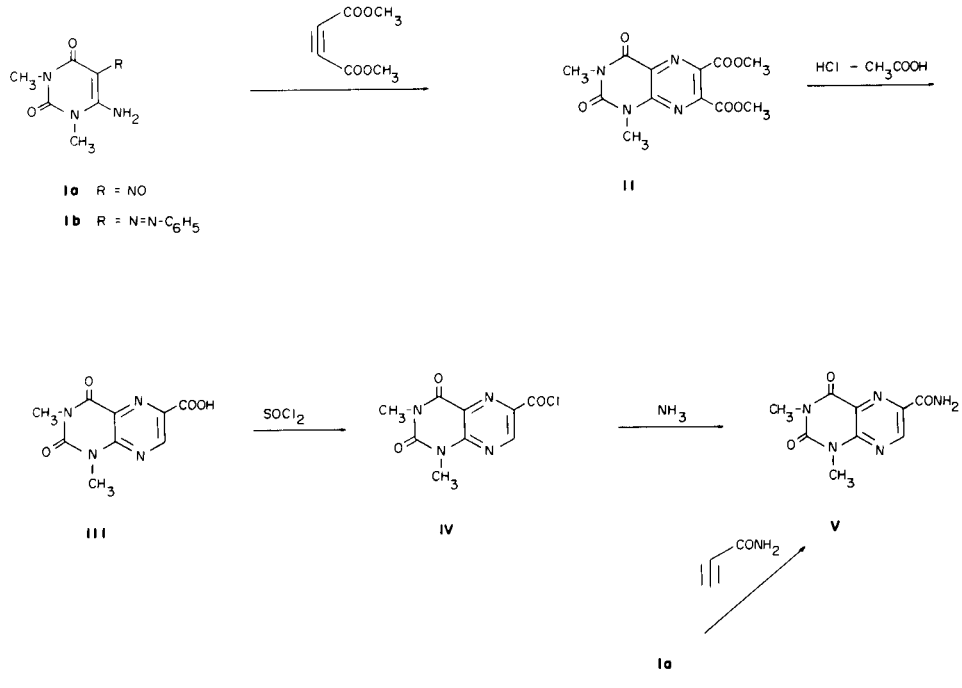
6-Amino-5-nitroso- and 6-amino-5-phenylazopyrimidines have often been used as the precursors of 5,6-diaminopyrimidines, which were conventional starting materials for the preparation of biologically interesting fused pyrimidine derivatives. Since Timmis (1) used 6-amino-5-nitrosopyrimidines for the first time as the direct starting material (without their conversion into 5,6-diaminopyrimidines) for the preparation of pteridines, several new synthetic routes to purines (2-9) and pteridines (10-12) from 6-amino-5-nitrosopyrimidines have been developed. Subsequently, 5-amino-6-phenylazopyrimidines which possess similar reactivity to 5-amino-6-nitrosopyrimidines have been shown to be used as the direct starting material for the synthesis of purines (13) and pteridines (14,15).

In the present paper, we report another utilization of 6-amino-5-nitroso- and 6-amino-5-phenylazo-pyrimidines as the direct starting material for the synthesis of pteridines (16). This synthesis consists of the reaction of 6-amino-1,3-dimethyl-5-nitroso- (Ia) and 6-amino-1,3-dimethyl-5-phenylazo-uracil (Ib) with acetylene derivatives.

Thus, refluxing of Ia with dimethyl acetylenedicarboxylate (DMAD) in dimethylformamide (DMF) afforded 6,7-bis(methoxycarbonyl)-1,3-dimethyllumazine (II) in 63% yield. The structure of II was confirmed by the satisfactory elemental anaysis and spectral data. This reaction presumably proceeds through the initial formation of the Michael-type adduct, followed by intramolecular cyclization and subsequent aromatization by the loss of water, as

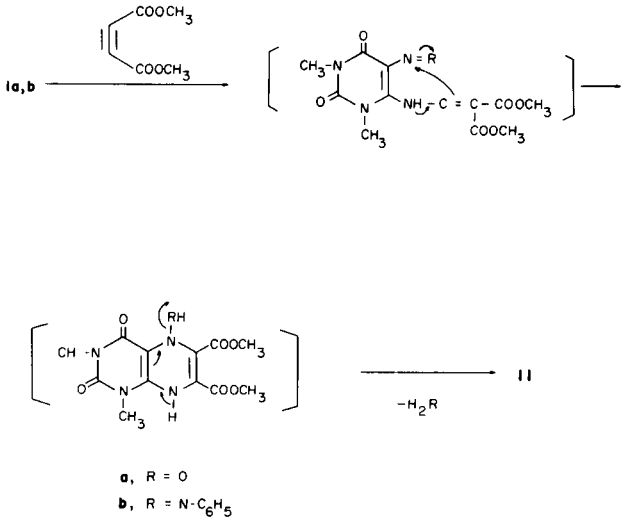
Scheme I



depicted in Scheme 2.

Treatment of Ib with DMAD in DMF under the same conditions gave also II in rather better yield (76%). This reaction can be likewise explained by the formation of the Michael-type adduct, followed by cyclization and aromatization with the loss of aniline (Scheme 2).

Scheme 2



The lumazine (II) thus obtained was then brought to hydrolysis with hydrochloric acid to give rise to the sole procduct, 1,3-dimethyllumazine-6-carboxylic acid (III) in 34% yield. Compound III was identical in all respects with the authentic sample synthesized by an alternatice route (17).

Compound III was treated with thionyl chloride to give the corresponding carboxylic acid chloride (IV). As the compound IV was very unstable, without purification it was converted into the 6-carbamoyl-1,3-dimethyllumazine (V) by the treatment with ethanolic ammonia. Compound V showed a characteristic C-7 proton signal at 9.65 ppm in the nuclear magnetic resonance spectra (in trifluoroacetic acid).

Compound V was alternatively prepared by the reaction of Ia with propiolamide in DMF in 95% yield.

EXPERIMENATAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. The nmr spectra were determined with a Hitachi R-24B spectrometer (with tetramethylsilane as an interanl standard). Identity of the compounds was confirmed by comparison of ir spectra determined in Nujol on a JASCO IR-Al spectrometer.

6,7-Bis(methoxycarbonyl)-1,3-dimethyllumazine (II).

Method A.

A mixture of Ia (0.92 g, 0.005 mole) and DMAD (1.42 g. 0.01 mole) in DMF (15 ml) was refluxed at 180° (oil bath temperature) for 3 hours. The reaction mixture was evaporated *in vacuo* and the oily residue was treated with a small amount of methanol to cause the separation of crystals, which were collected by filtration and dried. Recrystallization from ethanol gave yellow needles (0.97 g, 63%), mp 177° (18); ms: m/e 308 (M^+); nmr trifluoroacetic acid): δ ppm 3.72 (N-CH_3), 3.90 (N-CH_3), 4.17 (OCH_3) and 4.23 (OCH_3).

Anal. Calcd. for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.58; H, 3.91; N, 18.01.

Method B.

A mixture of Ib (2g, 0.0077 mole) and DMAD (2.13 g, 0.015 mole) in DMF (20 ml) was refluxed at 180° (oil bath temperature) for 3 hours and then treated as described above to give yellow needles (1.8 g, 76%), mp 177 C°.

1,3-Dimethyllumazine-6-carboxylic Aicd (III).

Compound II (0.92 g, 0.003 mole) was refluxed in a mixture of concentrated hydrocloric acid and acetic acid (1:3) (12 ml) for 8 hours. The reaction mixture was evaporated to dryness *in vacuo* in the residue was recrystallized from ethanol to give colorless powder (0.24 g, 34%), mp 250°; ms: m/e 236 (M^+); nmr (trifluoroacetic acid): δ ppm 3.75 (N-CH_3), 3.97 (N-CH_3) and 9.61 (1H, s, C_7-H).

Anal. Calcd. for $C_9H_8N_4O_4$: C, 45.76; H, 3.41; N, 23.72. Found: C, 46.03; H, 3.30; N, 23.48.

6-Carbamoyl-1,3-dimethyllumazine (V).

Method A.

Compound III (0.54 g, 0.0022 mole) was refluxed in thionyl chloride (4 ml) at 100° for 3 hours. After excess thionyl chloride was evaporated *in vacuo*, the residue was treated with saturated ethanolic ammonia (10 ml) under stirring at room temperature. The crystals thus separated were filtered off, dried and recrystallized from DMF to give colorless needles (0.44 g, 82%), mp > 300 °C; ms: m/e 235 (M^+); mnr (trifluoroacetic acid): δ ppm 3.76 (N-CH_3), 3.96 (N-CH_3) and 9.63 (1H, s, C_7-H).

Anal. Calcd. for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 45.64; H, 3.99; N, 29.58.

Method B.

A mixture of Ia (1.84 g, 0.01 mole) and propiolamide (0.76 g, 0.011 mole) in DMF (20 ml) was refluxed for 3 hours. After the reaction mixture was evaporated to dryness *in vacuo*, the residue was recrystallized from DMF to give colorless needles (2.23 g, 95%), mp > 330°. This compound was identical in all respects with the product synthesized by Method A.

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