# Cyclocondensation of 3-Amino-2-hydrazino-4(3*H*)-pyrimidinones with Dimethyl Acetylenedicarboxylate. Formation of 1-Amino-2,6-dihydro-2,6-dioxo-1*H*-pyrimido[1,2-*b*][1,2,4]triazine-3-acetic Acid Esters



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[(1-Amino-6-hydroxy-2(1*H*)-pyrimidinylidene)hydrazone]butanedioic acid dimethyl esters **3**, formed from 3-amino-2-hydrazino-4(3*H*)-pyrimidinones and dimethyl acetylenedicarboxylate in acetic acid at room temperature, underwent a facile, thermal rearrangement to 1-amino-2,6-dihydro-2,6-dioxo-1*H*-pyrimido-[1,2-*b*]-[1,2,4]triazine-3-acetic acid methyl esters **6** in hot acetic acid.

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The 3-Amino-2-hydrazino-4(3*H*)-pyrimidinones **1** were recently shown [1-3] to be versatile intermediates for the synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidin-7(8*H*)ones and 6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones. We have now found that their reactions with dimethyl acetylenedicarboxylate yield the title ring system **6** *via* facile thermal rearrangement of isolable intermediate hydrazones **3**.

The pyrimidinones **1** and dimethyl acetylenedicarboxylate in acetic acid at room temperature underwent a ready exothermic reaction to give the [(1-amino-6-hydroxy-2(1*H*)-pyrimidinylidene)hydrazone]butanedioic acid dimethyl esters **3**, formed by tautomerism from the initial 1:1-adducts **2**. Addition of the hydrazino $NH_2$ group to the acetylene instead of addition of the ring N-$NH_2$ group is consistent with the greater nucleophilic character of the former when compared to the latter group [1-3]. Although the addition of amino groups to electron deficient acetylenes is well documented [4], the formation of the hydrazones **3** is unique. Their extended chromophores were indicated by their uv spectra [λ max (methanol) 323-339 mμ, log ε = 4.36891-3.98342] and their spectral data (Table I) were consistent with the assigned structures. In addition, the structure of the hydrazone **3a** was established unequivocally by a single crystal X-ray analysis.

When the hydrazones **3** were heated under reflux in acetic acid for three hours, the pyrimido-1,2,4-triazinones **6** were obtained. The structure of **6c** was also established by a single crystal X-ray determination and the physical characteristics of these rearrangement products **6** are shown in Table I.

Crystallography [5].

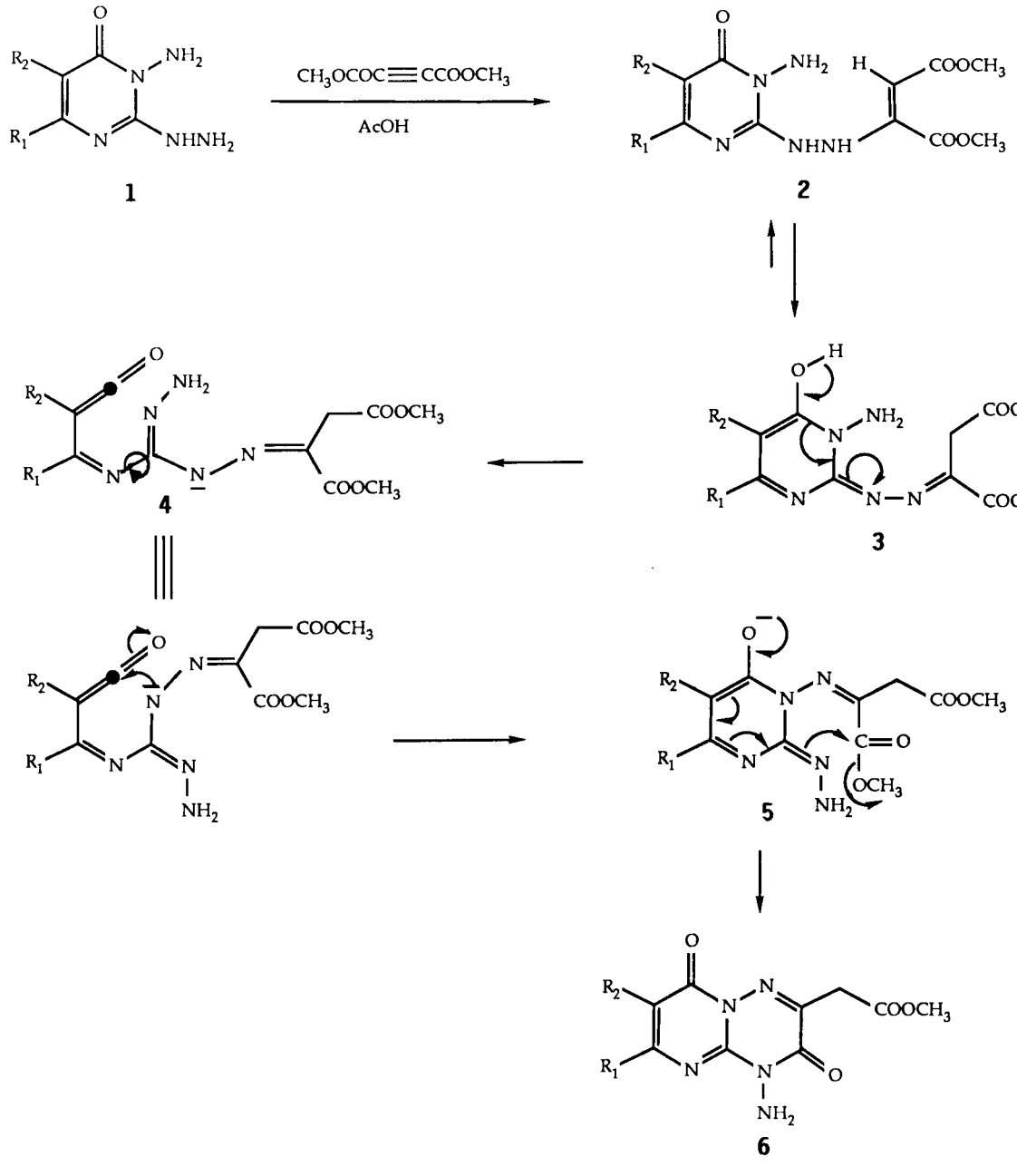
Crystals of **3a** and **6c** were obtained from tetrahydro-

Table I

Physical, Analytical and Spectroscopic Data for Products **3** and **6**

| Compound | $R_1$ | $R_2$ | Yield, % | mp, °C | Formula | $^1$H nmr data (δ) [a] $R_1$ | $R_2$ | OH | $NH_2$ | $CH_2$ | $OCH_3$ | Elemental Analysis Calcd. (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | $CH_3$ | H | 68 | 93-95 | $C_{11}H_{15}N_5O_5 \cdot H_2O$ | 2.2 | 5.6 | 13.2 | 5.8 | 3.6 | 3.8 (2) | 41.9 (41.9) | 5.4 (5.3) | 22.2 (22.5) |
| **3b** | $C_2H_5$ | H | 80 | 95-98 | $C_{12}H_{17}N_5O_5$ | 1.1 t 2.5 q | 5.6 | 13.2 | 5.7 | 3.6 | 3.8 (2) | 46.3 (46.4) | 5.5 (5.4) | 22.5 (22.2) |
| **3c** | $CH_3$ | $C_2H_5$ | 85 | 128-130 | $C_{13}H_{19}N_5O_5$ | 2.2 | 1.0 t 2.4 q | 13.2 | 5.7 | 3.7 | 3.8 (2) | 48.0 (47.8) | 5.9 (5.9) | 21.5 (21.8) |
| **3d** | $C_6H_5$ | H | 66 | 170-172 | $C_{16}H_{17}N_5O_5$ | 7.5 m 8.0 m | 6.7 | 13.3 | 5.7 | 3.7 | 3.8 (2) | 53.4 (53.1) | 4.8 (4.7) | 19.5 (19.9) |
| **6a** | $CH_3$ | H | 34 | 166-168 | $C_{10}H_{11}N_5O_4 \cdot \frac{1}{2}H_2O$ | 2.3 | 6.2 | -- | 6.3 | 3.9 | 3.7 (1) | 43.8 (44.2) | 4.4 (4.5) | 25.5 (25.3) |
| **6b** | $CH_3$ | $C_2H_5$ | 90 | 83-85 | $C_{12}H_{15}N_5O_4 \cdot \frac{1}{2}HOAc$ | 2.3 | 1.0 t 2.0 q | -- | 6.3 | 3.9 | 3.7 (1) | 48.3 (48.6) | 5.3 (5.2) | 21.7 (21.4) |
| **6c** | $C_6H_5$ | H | 60 | 215-216 | $C_{15}H_{13}N_5O_4 \cdot \frac{1}{2}H_2O$ | 7.6 m 8.3 m | 6.9 | -- | 6.5 | 3.9 | 3.7 (1) | 53.7 (53.9) | 4.2 (3.9) | 20.8 (20.9) |

[a] All nmr spectra were taken in DMSO-$d_6$.




furan/1,2-dichloroethane and tetrahydrofuran/methanol, respectively. All intensity measurements were performed with Cuka radiation (λ = 1.54184A) on an Enraf-Nonius CAD4 computer controlled Kappa axis difractometer equipped with a graphite crystal, incident beam monochromator. Both structures were solved by direct methods and all calculations were performed on a PDP-11/60 based TEXRAY® [6] system. The crystal data are given in Table II.

The hydrazones **3** provide a ready explanation for the ease of formation of **6** *via* an initial thermal ring opening of **3** followed by two cyclocondensation sequences. Breaking of the N1-C6 bond in **3**, the weakest bond in the molecule, leads to iminoketenes **4** which undergo cyclization as shown to give the intermediate pyrimidinones **5**. These intermediates **5** are ideally structured for a second cyclization so that ring annulation occurs leading to **6**. Cyclization of iminoketenes of this general type are known

Table II

Summary of Crystal Data for Compounds **3a** and **6c**

| | **3a** | **6c** |
|---|---|---|
| Formula | $(C_{11}H_{15}N_5O_5(H_2O)\frac{1}{2}(C_2H_4Cl_2)$ $C_{12}H_{19}ClN_5O_6$ | $C_{15}H_{13}N_5O_4$ |
| fw | 364.77 | 327.30 |
| space group | Monoclinic P21/N | Triclinic P1- |
| a | 4.543 (2) Å | 6.884 (1) Å |
| b | 15.220 (3) Å | 7.218 (1) Å |
| c | 24.781 (12) Å | 15.252 (2) Å |
| $\alpha$ | | 91.99 (1)° |
| $\beta$ | 93.89 (3)° | 95.42 (1)° |
| $\gamma$ | | 79.87 (1)° |
| Crystal Dimensions | 0.40 x 0.07 x 0.07 mm | 0.18 x 0.20 x 0.10 mm |
| Peak width at half-height | 0.40° | 0.20° |
| F(000) | 764 | 340 |
| V | 1709.7 $A^3$ | 742.6 $A^3$ |
| Z | 4 | 2 |
| $\rho$ | 1.42 $g/m^3$ | 1.46 $g/cm^3$ |
| $\mu$ | 23.5 $cm^{-1}$ | 9.4 $cm^{-1}$ |

*e.g.*, resulting in quinolones [7], and also of arylimidoyl isothiocyanates which yield quinazolinethiones [8]. However, this is the first instance in which diaminoguanidine derivatives have been involved in such cyclocondensations.

## EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analysis were dried for 1-24 hours under high vacuum. The $^1H$ nmr measurments were obtained on a Varian Model FT-80 spectrometer and chemical shift values are reported in $\delta$ downfield from tetramethylsilane internal standard. All spectra were taken in deuterated dimethylsulfoxide.

Typical Example for [(1-Amino-6-hydroxy-2(1*H*)-pyrimidinylidene)-hydrazone]butanedioic Acid Dimethyl Esters (**3**).

To a solution of 3-amino-2-hydrazino-6-methyl-4(3*H*)-pyrimidone **1a** (10.0 g, 64.4 mmoles) in glacial acetic acid (50 ml) was added dimethyl acetylenedicarboxylate (9.15 g, 64.4 mmoles). An exothermic reaction resulted and the reaction mixture was cooled in an ice bath for 10 minutes and then kept at room temperature overnight. The solution was then evaporated to dryness and the product crystallized from water to give 13.05 g (68%) of [(1-amino-6-hydroxy-4-methyl-2(1*H*)-pyrimidinylidene)hydrazone]butanedioic acid dimethyl ester **3a**, mp 93-95°.

Typical Example for 1-Amino-2,6-dihydro-2,6-dioxo-1*H*-pyrimido[1,2-*b*]-triazine-3-acetic Acid Methyl Esters **6**.

A solution of [(1-amino-6-hydroxy-4-methyl-2(1*H*)pyrimidinylidene)-hydrazone]butanedioic acid, dimethyl ester **3a** (2.0 g) in glacial acetic acid (30 ml) was refluxed for 3 hours and then evaporated to dryness. The product crystallized from water to give 0.6 g (34%) of 1-amino-2,6-dihydro-8-methyl-2,6-dioxo-1*H*-pyrimido[1,2-*b*][1,2,4]triazen-3-acetic acid methyl ester **6a**, mp 166-168°.

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[6] TEXRAY® is a trademark of Molecular Structure Corporation, (1982).

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