

NEW SYNTHESIS OF 2-ARYL-1,2,4-TRIAZINE-3,5(2H,4H)-DIONES  
(1-ARYL-6-AZAUACILS)

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Treatment of 6-amino-5-arylaazo-1,3-dimethyluracils with urea gave the respective 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones, which were hydrolyzed with alkali to afford 2-aryl-1,2,4-triazine-3,5(2H,4H)-dione-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids). Thermal decarboxylation of these carboxylic acids gave the corresponding 2-aryl-1,2,4-triazine-3,5(2H,4H)-diones (1-aryl-6-azauracils).

1,2,4-Triazine-3,5(2H,4H)-dione (6-Azauracil) and its derivatives<sup>1</sup> are biologically interesting compounds, because of their demonstrated antitumor activity.<sup>2</sup> However, the 6-azauracils possessing aryl substituents at the 1-position have not been widely investigated. The only known synthetic method for the preparation of the 1-aryl-6-azauracils has involved the cyclization of arylhydrazones of N-acetylurethan derivatives.<sup>3,4</sup> Here we

report a new synthetic approach to 1-aryl-6-azauracils which consists of the hydrolysis of 6-azalumazine-7(6H)-one derivatives followed by decarboxylation.

The key intermediates, 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones (IIa-e)<sup>5</sup> were prepared by the reaction of the appropriate 6-amino-5-arylo-1,3-dimethyluracils (Ia-e)<sup>6</sup> with excess urea at 200-220° for 1.5 hr (Table 1).

TABLE 1. 6-Aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones

| Starting material | Substituent (R)  | Product           | Mp (°C) <sup>a)</sup> | Yield (%) |
|-------------------|--|-------------------|-----------------------|-----------|
| Ia                | C <sub>6</sub> H <sub>5</sub>                                      | IIa <sup>b)</sup> | 219                   | 70        |
| Ib                | 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | IIb <sup>b)</sup> | 227                   | 61        |
| Ic                | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | IIc               | 195                   | 62        |
| Id                | 3-Cl-C <sub>6</sub> H <sub>4</sub>                                 | IId               | 199                   | 49        |
| Ie                | 3,4-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> | IIe               | 220                   | 55        |

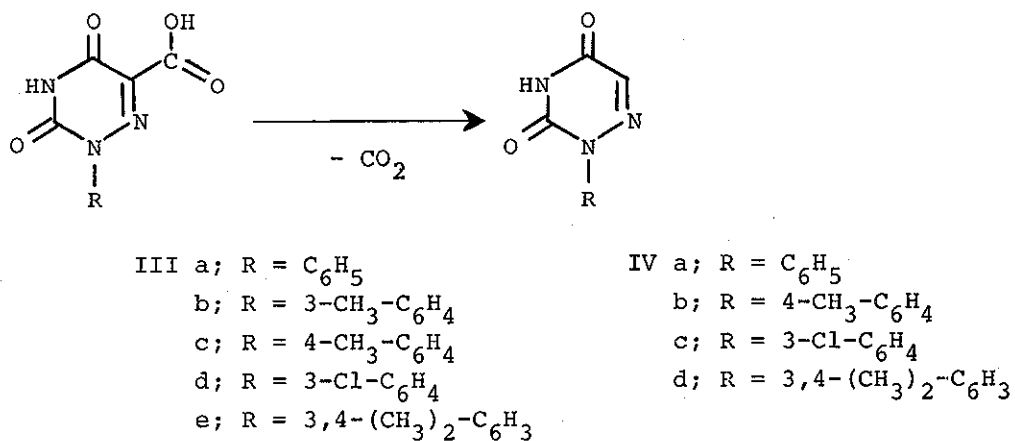
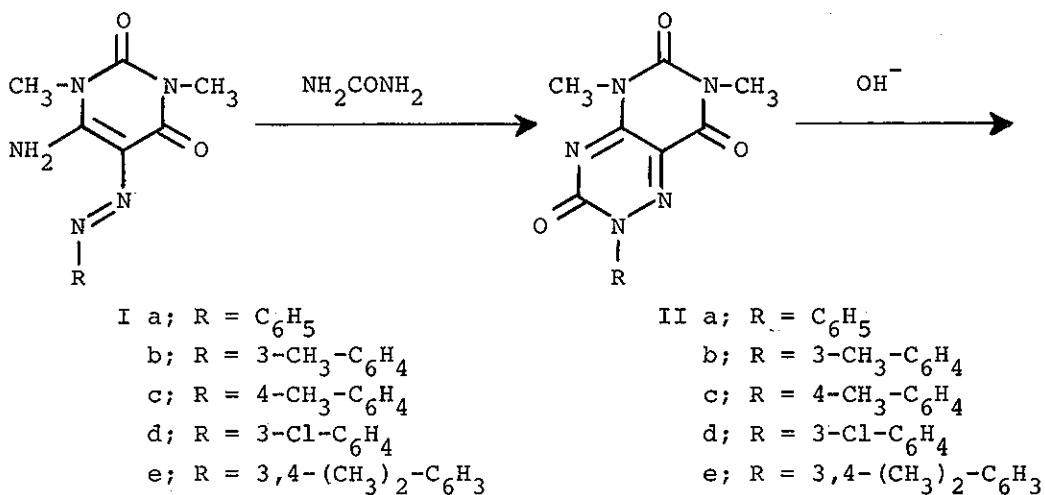
a) All compounds were recrystallized from ethanol to yield yellow crystals.

b) see reference 7.

Treatment of the 6-azalumazine-7(6H)-ones (IIa-e) (0.001 mol) with 10% potassium hydroxide in ethanol and water (3:1) (50 ml) at 90° for 1 hr, followed by acidification with hot hydrochloric acid caused the separation of colorless crystals which were filtered off and recrystallized from hot water to give the monohydrates of the corresponding 2-aryl-1,2,4-triazine-3,5(2H,4H)-dione-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids) (IIIa-e) (Table 2).

Heating of these carboxylic acids (IIIa-d) in diphenyl ether at 200-220° for 1.5 hr, followed by dilution of the reaction

mixture with ethyl ether, caused the separation of crystals, which were purified by sublimation or by recrystallization from ethanol to give the respective 2-aryl-1,2,4-triazine-3,5(2H,4H)-diones (1-aryl-6-azauracils) (IVa-d) as colorless crystals (Table 2).



The structures of compounds IVa-d were characterized by the presence of C<sup>6</sup>-H [for example, sharp singlet at 7.80 ppm (in CF<sub>3</sub>COOH) for IVa] in NMR.

TABLE 2. 1-Aryl-6-azauracil Derivatives

| Compound No. | Substituent (R)  | Mp (°C) | Yield (%) |
|--------------|--|---------|-----------|
| IIIa         | C <sub>6</sub> H <sub>5</sub>                                      | 205     | 72        |
| IIIb         | 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | 206     | 48        |
| IIIc         | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | 200     | 49        |
| IIId         | 3-Cl-C <sub>6</sub> H <sub>4</sub>                                 | 181     | 73        |
| IIIe         | 3,4-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> | 222     | 76        |
| IVa          | C <sub>6</sub> H <sub>5</sub>                                      | 215     | 61        |
| IVb          | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | 212     | 59        |
| IVc          | 3-Cl-C <sub>6</sub> H <sub>4</sub>                                 | 222     | 60        |
| IVd          | 3,4-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> | 153     | 57        |

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