

manner, the compounds shown in Table I were prepared.

All of the compounds reported had infrared spectra which exhibited a nitrile band at  $2195 \pm 10 \text{ cm.}^{-1}$  and an ester band at  $1700 \pm 10 \text{ cm.}^{-1}$

#### EXPERIMENTAL

*Reagents.* The author thanks Kay-Fries Chemicals, Inc. for a generous gift of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification or were prepared by standard literature methods. Thanks go to the Antara Chemicals Division of General Aniline and Film Corp. for a sample of *p*-diethylaminobenzaldehyde.

*Typical condensation.* To a mixture of 22.6 g. (0.2 mole) of ethyl cyanoacetate and 0.2 mole of aldehyde in about 60 ml. of dry dioxane at  $0^\circ$  was added dropwise 0.8 ml. of piperidine. After standing overnight at room temperature, crystals had formed (in a few cases cooling was needed to promote crystallization). The solids were filtered, washed, dried, and recrystallized several times from an appropriate solvent.

DEPARTMENT OF CHEMISTRY  
UNIVERSITY OF MIAMI  
CORAL GABLES, FLA.

### Preparation of Various Substituted Pyrimidines<sup>1</sup>

RAYMOND P. MARIELLA AND JAMES J. ZELKO<sup>2</sup>

Received October 29, 1959

During the last decade, numerous pyrimidines and purines have been investigated which might be useful in human cancer chemotherapy, and several have been found to possess tumor-inhibiting properties.<sup>3,4</sup> The pharmacological activity of these compounds has prompted the preparation of various substituted pyrimidines.

The substituted pyrimidines synthesized during the course of this investigation have incorporated the physiologically active ring systems of pyridine and thiophene and were prepared in hopes that some of them would exhibit physiological activity of some type, since they are related to a number of the biological and medicinal agents, such as nucleic acids, several vitamins and enzymes, uric acid, and sulfadiazine.

Pharmacological tests of these substituted pyrimidines are being made.

(1) This work is based on a thesis submitted by James J. Zelko in partial fulfillment for the degree of Master of Science at Loyola University, Chicago, Ill.

(2) Cooperative National Science Foundation Fellow, Summer 1959.

(3) C. Heidelberger, N. C. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Plevin, and J. Scheiner, *Nature*, **179**, 663 (1957).

(4) R. Duschinsky, E. Plevin, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957)

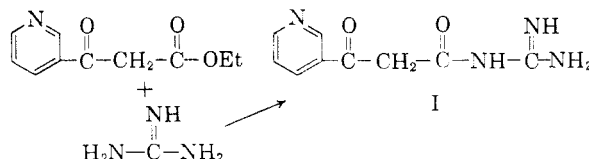
The substituted pyrimidines synthesized are listed in Table I and Table II and were prepared by condensing the appropriate  $\beta$ -diketone or  $\beta$ -keto ester with guanidine carbonate. The general procedure is given in the experimental section.

The 2-amino-4-alkyl-6-( $\alpha$ -thienyl)pyrimidines were prepared by condensing the appropriate acyl-2-thienylmethane with guanidine carbonate.

The 2-amino-4-alkyl-6-( $\beta$ -pyridyl)pyrimidines were prepared by the same method, but the appropriate nicotinylacetylmethane was employed.

In the case of 2-amino-4-hydroxy-6-( $\alpha$ -thienyl)pyrimidines, ethyl  $\beta$ -keto-( $\alpha$ -thienyl)propionate was condensed with guanidine carbonate.

In the attempted preparation of 2-amino-4-hydroxy-6-( $\beta$ -pyridyl)pyrimidine, ethyl nicotinylacetate was treated with guanidine carbonate, but ring closure did not occur as the intermediate product (I) was obtained instead.



The infrared spectra of these pyrimidines have been recorded and showed prominent peaks near  $3200\text{--}3100 \text{ cm.}^{-1}$  due to CH stretching vibrations. In addition, strong peaks were noted in the region near  $1665 \text{ cm.}^{-1}$ ,  $1600\text{--}1565 \text{ cm.}^{-1}$  and  $1555\text{--}1540 \text{ cm.}^{-1}$  which are due to C=C and C=N vibrations, respectively, in this aromatic system. There is some belief that the higher frequency bands are due to  $\text{NH}_2$  deformations modes rather than C=C and C=N vibrations themselves.<sup>5</sup> There is also a strong band near  $3320 \text{ cm.}^{-1}$  and this is assigned to the  $\text{NH}_2$  group.

#### EXPERIMENTAL

*Preparation of substituted pyrimidines.* The substituted pyrimidines were prepared by heating 3.5 g. of the appropriate  $\beta$ -diketone or  $\beta$ -keto ester with 1.5 g. of guanidine carbonate at  $130\text{--}140^\circ$  for 3–4 hr. according to the method of Evans.<sup>6</sup> The molten mass was allowed to cool and then dissolved in hydrochloric acid. The substituted pyrimidine was then precipitated upon the addition of dilute ammonium hydroxide.

The substituted pyrimidine was recrystallized three times from absolute alcohol, and white crystals were obtained. The average yield was 20%.

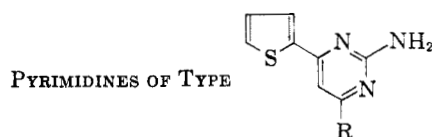
The respective picrates were prepared by dissolving 0.1 g. of the pyrimidine in 5 ml. of absolute alcohol and adding a saturated solution of picric acid dissolved in absolute alcohol. Upon standing, the picrate settled out and was recrystallized from absolute alcohol.

In the case of the 2-amino-4-hydroxy-6-( $\alpha$ -thienyl)pyrimidine, the acid-base technique was not employed, but the pyrimidine was recrystallized from 80% alcohol.

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Second Edition, John Wiley and Sons, (New York, 1956), p. 282.

(6) P. N. Evans, *J. prakt. Chem.* [2] **48**, 513 (1893).

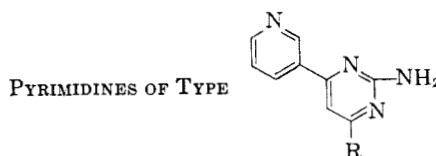
TABLE I



| R   | Molecular Formula                                | M.P.      | % Nitrogen |                    | Molecular Formula   | M.P. <sup>b</sup> | % Nitrogen |                    |
|---|--|-----------|------------|--------------------|---|-------------------|------------|--------------------|
|   |  |           | Calcd.     | Found <sup>a</sup> |   |                   | Calcd.     | Found <sup>a</sup> |
| —CH <sub>3</sub>                          | C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> S   | 172°      | 21.97      | 21.50              | C <sub>15</sub> H <sub>12</sub> N <sub>6</sub> O <sub>7</sub> S | 243–248°          | 19.93      | 19.94              |
| —C <sub>2</sub> H <sub>5</sub>            | C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> S | 139°      | 20.47      | 20.32              | C <sub>16</sub> H <sub>14</sub> N <sub>6</sub> O <sub>7</sub> S | 233–237°          | 19.34      | 19.25              |
| — <i>n</i> -C <sub>3</sub> H <sub>7</sub> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> S | 116°      | 19.16      | 19.13              | C <sub>17</sub> H <sub>16</sub> N <sub>6</sub> O <sub>7</sub> S | 213–214°          | 18.74      | 18.81              |
| — <i>i</i> -C <sub>3</sub> H <sub>7</sub> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> S | 115°      | 19.16      | 19.03              | C <sub>17</sub> H <sub>16</sub> N <sub>6</sub> O <sub>7</sub> S | 220–222°          | 18.74      | 18.65              |
| <i>n</i> -C <sub>4</sub> H <sub>9</sub>   | C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> S | 79°       | 18.01      | 18.27              | C <sub>18</sub> H <sub>18</sub> N <sub>6</sub> O <sub>7</sub> S | 196–199°          | 18.17      | 18.00–             |
| <i>i</i> -C <sub>4</sub> H <sub>9</sub>   | C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> S | 110°      | 18.01      | 18.17              | C <sub>18</sub> H <sub>18</sub> N <sub>6</sub> O <sub>7</sub> S | 175–176°          | 18.17      | 17.92              |
| <i>n</i> -C <sub>5</sub> H <sub>11</sub>  | C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> S | 82°       | 16.99      | 16.88              | C <sub>19</sub> H <sub>20</sub> N <sub>6</sub> O <sub>7</sub> S | 163–164°          | 17.64      | 17.60              |
| —OH                                       | C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> OS  | 306° dec. | 21.74      | 21.95              | C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> O <sub>8</sub> S   | 241–248°          | 19.90      | 19.72              |

<sup>a</sup> Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. <sup>b</sup> Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

TABLE II



| R                | Molecular Formula                              | M.P. | % Nitrogen |                    | Molecular Formula   | M.P. <sup>b</sup> | % Nitrogen |                    |
|------------------|--|------|------------|--------------------|---|-------------------|------------|--------------------|
|                  |  |      | Calcd.     | Found <sup>a</sup> |   |                   | Calcd.     | Found <sup>a</sup> |
| —CH <sub>3</sub> | C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> | 205° | 30.09      | 29.83              | C <sub>16</sub> H <sub>13</sub> N <sub>7</sub> O <sub>7</sub> | 245–249°          | 23.60      | 23.75              |
| <i>t</i> -Butyl  | C <sub>13</sub> H <sub>16</sub> N <sub>4</sub> | 138° | 24.43      | 24.43              | C <sub>19</sub> H <sub>19</sub> N <sub>7</sub> O <sub>7</sub> | 210–212°          | 21.43      | 21.34              |
| <i>i</i> -Butyl  | C <sub>13</sub> H <sub>16</sub> N <sub>4</sub> | 149° | 24.66      | 24.66              | C <sub>19</sub> H <sub>19</sub> N <sub>7</sub> O <sub>7</sub> | 206–207°          | 21.43      | 21.38              |
| Phenyl           | C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> | 166° | 22.57      | 22.57              | C <sub>21</sub> H <sub>15</sub> N <sub>7</sub> O <sub>7</sub> | 223–225°          | 20.53      | 20.78              |

<sup>a</sup> Nitrogen analyses by Micro-Tech Laboratories, Skokie, Ill. <sup>b</sup> Melting points of the picrates were taken in a sealed evacuated capillary tube, are uncorrected, and all melt with decomposition.

*Preparation of I.* A 3.5-g. sample of ethylnicotinoylacetate and 5 g. of guanidine carbonate was heated at 140° for 1 hr. The molten mass was allowed to cool and recrystallized from 80% alcohol, and light colored crystals were obtained melting at 283–288° dec.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>N<sub>4</sub>: N, 27.37. Found: N, 27.17.

DEPARTMENT OF CHEMISTRY  
LOYOLA UNIVERSITY  
CHICAGO 26, ILL.

composition of some *N*-methyl-*N,N*-di-*n*-propylanilinium salts. The tertiary bases, used as starting materials in this investigation, were prepared by propylation of the corresponding primary aromatic amines with tri-*n*-propyl phosphate as recommended by Bilman *et al.*<sup>4</sup> for the preparation of dipropylaniline. The dipropylanilines obtained were identified through the picrate. The boiling points and the yields of the tertiary bases are recorded in Table I.

#### Quaternary Ammonium Salts. IV. Synthesis and Decomposition of *N*-Methyl-*N,N*-di-*n*-propylanilinium Salts

HUSSEIN A. FAHIM, ABDALLAH M. FLEIFEL AND (MRS.) FAWZIA FAHIM

Received August 18, 1959

In continuation of the research done by Fahim and Galaby,<sup>1</sup> Fahim and Fleifel,<sup>2</sup> and Fahim *et al.*,<sup>3</sup> we now have studied the synthesis and de-

TABLE I  
TERTIARY BASES

| Primary aromatic amine | Boiling point of the dipropylaniline | Yield, % |
|------------------------|--------------------------------------|----------|
| <i>p</i> -Anisidine    | 158–160/15 mm.                       | 70       |
| <i>o</i> -Anisidine    | 142–145/15 mm.                       | 45       |
| <i>p</i> -Phenetidine  | 166–168/60 mm.                       | 44       |
| <i>o</i> -Phenetidine  | 173–175/60 mm.                       | 45       |
| <i>p</i> -Toluidine    | 165–168/65 mm.                       | 51       |
| <i>m</i> -Toluidine    | 170–173/60 mm.                       | 51       |
| <i>o</i> -Toluidine    | 144–146/55 mm.                       | 58       |

(1) H. A. Fahim and M. Galaby, *J. Chem. Soc.*, 3529 (1950).

(2) H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, 2761 (1951).

(3) H. A. Fahim, F. G. Baddar, and M. Galaby, *J. Chem. Soc.*, 317 (1955).

(4) J. H. Bilman, A. Radike, and A. W. Mundy, *J. Am. Chem. Soc.*, 64, 2977 (1942).