

SYNTHESIS OF 1,2,4-TRIAZINE-3,5(2*H*,4*H*)-DIONES CONTAINING ELECTRONEGATIVE SUBSTITUENTS IN POSITION 6

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Reaction of fluorine with 1,2,4-triazine-3,5(2*H*,4*H*)-dione (*I*) in acetic acid afforded the 6-fluoro derivative *II* in low yield. The 6-nitro compound *III* was prepared by oxidation of the 6-amino derivative of compound *I* with hydrogen peroxide in trifluoroacetic acid. Synthesis of the 6-cyano compound *IV* was accomplished by treatment of the 6-bromo derivative with cuprous cyanide in *N,N,N',N'*-tetramethylurea. The effect of substituents on the carbonyl frequencies for 6-substituted derivatives of *I* was studied.

In connection with the investigations on biological activity of 1,2,4-triazine-3,5(2*H*,4*H*)-dione<sup>1</sup> (6-azauracil, *I*) many of its 6-substituted derivatives have been prepared<sup>2</sup>. Among them there were derivatives with alkyl groups<sup>3</sup> or various hetero atoms, bonded either directly (halogens<sup>4,5</sup>, amino<sup>5</sup>, dimethylamino<sup>6</sup>, methoxy<sup>7</sup>, thio<sup>6</sup>, alkylthio<sup>8</sup> or alkylsulfonyl groups<sup>9</sup>) or by means of a carbon atom (fluoromethyl<sup>10,11</sup>, trifluoromethyl<sup>12,13</sup>, chloromethyl<sup>14</sup>, aminomethyl<sup>15</sup> or hydroxymethyl groups<sup>16</sup>).

In this communication we describe the preparation of 6-fluoro-, 6-nitro- and 6-cyano-1,2,4-triazine-3,5(2*H*,4*H*)-diones (*II-IV*) which we considered missing links for a systematic biological research\*.

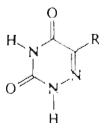
Chang<sup>5</sup> attempted to prepare the compound *II* by diazotation of 6-amino-1,2,4-triazine-3,5(2*H*,4*H*)-dione in fluoroboric acid but the obtained reaction mixture did not contain any UV-absorbing compound. Also attempts to prepare *II* by reaction of 6-bromo-1,2,4-triazine-3,5-(2*H*,4*H*)-dione with potassium fluoride failed<sup>17</sup>. (This kind of substitution was successful only with 6-bromo-2,4-dimethyl-1,2,4-triazine-3,5-dione.) In the light of these negative results we turned our attention to the direct fluorination of the compound *I*. Whereas the direct fluorination<sup>18,19</sup> of uracil affords high yield of 5-fluorouracil, fluorination of *I* proceeds with great difficulty. Treatment of compound *I*, suspended in acetic acid, with fluorine for 2 h at 15°C, followed by chromatography, afforded only 0.3% of the desired fluoro derivative *II* and almost 50% of the starting compound *I* was recovered. The difficult fluorination of com-

\* After finishing the manuscript of this paper, a synthesis of compound *II*, starting from 3,5,6-trifluoro-1,2,4-triazine, has been published<sup>29</sup>.

compound *I* is obviously due to its low reactivity towards electrophilic reagents. As shown by kinetic studies<sup>20</sup>, also the bromination of *I* is by several orders of magnitude slower than bromination of uracil.

Another example of the low reactivity of compound *I* towards electrophilic reagents is given by the unsuccessful<sup>22</sup> attempts to nitrate directly the compound *I* to the nitro compound *III* under conditions described for nitration of uracil<sup>21</sup> (fuming nitric acid at 60–65°C). We utilized therefore the fact that substituted anilines can be oxidized to the corresponding nitrobenzenes with trifluoroperoxyacetic acid in dichloromethane or with a mixture of 30% hydrogen peroxide and trifluoroacetic acid (the latter reaction, however, affording substantially lower yields<sup>23</sup>). Since the 6-amino derivative of compound *I* was insoluble in dichloromethane, we had to use the less advantageous alternative which gave the 6-nitro derivative *III* in 23% yield.

Although 6-chloro-, 6-bromo- and 6-iodo-1,2,4-triazine-3,5(2*H*,4*H*)-diones react with benzylamine to give well crystallizable salts which are sparingly water-soluble, we obtained no crystalline benzylammonium salts of compounds *II* and *III*.



Whereas 3,5-dioxo-1,2,4-triazine(2*H*,4*H*)-5-carboxylic acid is known for a long time<sup>24</sup>, its nitrile *IV* remained hitherto undescribed; however, some of its substituted 1-aryl derivatives (ref.<sup>25</sup> and references therein) are known. We prepared the nitrile *IV* by heating the 6-bromo derivative of *I* with cuprous cyanide in *N,N,N',N'*-tetramethylurea.

The C=O stretching vibration frequencies in the IR spectra of compounds *II–IV* (in dioxane) are significantly higher than those of the unsubstituted compound *I* (ref.<sup>26</sup>). Comparison of IR spectra of a whole series of known 6-substituted derivatives of *I* (Table I) shows that with increasing electronegativity the frequency of the carbonyl bands is shifted to higher values, similarly as in the case of substituted esters<sup>27</sup> or amides<sup>28</sup> of acetic acid. We observed a qualitatively similar dependence also for solutions in dimethyl sulfoxide (Table II). For the unexpectedly low frequency of the 6-methylsulfonyl derivative we can give no suitable explanation. In both solvents, the C=N frequency at 1750 cm<sup>-1</sup> in the studied 1,2,4-triazines varies substantially but the polarity of the substituents is not the dominant factor.

The compounds *II–IV* did not inhibit significantly the growth of *Escherichia coli* B in concentration 100 µg/ml.

## EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 25°C and 6.5 Pa for 8 h. UV spectra were taken on a Specord UV VIS spectrometer, IR spectra on a UR-20 instrument (both Zeiss, Jena, GDR). Mass spectroscopic data were obtained with an AEI 902 double-focusing spectrometer (Associated Electric Industries, Manchester).

6-Fluoro-1,2,4-triazine-3,5(2*H*,4*H*)-dione (*II*)

A gentle stream of fluorine was introduced at 15°C into a stirred suspension of the compound *I* (22.6 g, 0.2 mol) in acetic acid (150 ml) for 2 h. Prolonged introduction resulted usually in explosions of acetic acid vapour with fluorine. After standing for 12 h at room temperature, the unreacted compound *I* (7.4 g) was filtered off, the filtrate was concentrated *in vacuo* and the residue dissolved in water (25 ml), neutralized with aqueous ammonia and applied on a column (1.5 × 30 cm) of Dowex 1 (acetate). The column was washed with water (500 ml) and the unreacted starting compound (2.5 g) was eluted with 1% acetic acid (250 ml). The product *II* was eluted with 10% acetic acid (250 ml), the eluate taken down and the residue chromatographed on a column of silica gel in ethyl acetate-toluene (2 : 1). Evaporation of the UV-absorbing fraction afforded 74.5 mg of material which was crystallized from water to give 45.2 mg (0.3%) of the analytically pure compound *II*, melting at 228–231°C. UV spectrum (0.05M-HCl):  $\lambda_{\max}$

TABLE I

Infrared spectra of 6-substituted 1,2,4-triazine-3,5(2*H*,4*H*)-diones in dioxane (2% solution, 0.1 mm cell), wavenumbers in  $\text{cm}^{-1}$

R	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$
H	1 731 vs	1 709 s
F <sup>a</sup>	1 740 vs	1 715 s, sh
Cl <sup>b</sup>	1 737 vs, br	1 715 s, sh
Br	1 741 s	1 725 s, sh, 1 715 s, sh
I	1 741 s	1 730 s, sh, 1 715 s
CN <sup>c</sup>	1 746 vs, sh	1 731 cs
CF <sub>3</sub> <sup>d</sup>	1 752 s	1 725 s
CH <sub>2</sub> F	1 741 vs	1 718 vs
CH <sub>3</sub> <sup>e</sup>	1 729 vs	1 714 vs
C(CH <sub>3</sub> ) <sub>3</sub> <sup>f</sup>	1 732 vs	1 708 s
NO <sub>2</sub> <sup>g</sup>	1 760 vs	1 744 vs, sh
NH <sub>2</sub> <sup>h,k</sup>	1 721 w	—
SCH <sub>3</sub> <sup>i</sup>	1 730 vs	1 717 s, sh
SO <sub>2</sub> CH <sub>3</sub> <sup>j</sup>	1 755 s	1 742 s, sh 1 718 s

<sup>a</sup> 1 308 m, 814 m (C—F); <sup>b</sup> 664 (C—Cl); <sup>c</sup> 2 247 vw (C≡N); <sup>d</sup> 1 349 w, 1 205, 1 163 w (C—F); <sup>e</sup> 1 372 w (CH<sub>3</sub>); <sup>f</sup> 1 396, sh (CH<sub>3</sub>); <sup>g</sup> 1 554 s, 1 346 m, sh (NO<sub>2</sub>); <sup>h</sup> 1 652 w, sh, 1 634 w (NH<sub>2</sub>); <sup>i</sup> 1 428 m (CH<sub>3</sub>), 660 m (C—S); <sup>j</sup> 1 337 (SO<sub>2</sub>); <sup>k</sup> in saturated solution.

262.5 nm ( $\log \epsilon$  3.62); (0.05M-NaOH): 289.1 nm ( $\log \epsilon$  3.59). IR spectrum (KBr),  $\text{cm}^{-1}$ : 3 404 sh, 3 160 (NH); 1 746, 1 728, 1 597 (C=O); 1 650 (C=N). Mass spectrum:  $m/z$  131 ( $\text{M}^+$ ), 88, 86, 60;  $\text{M}^+$  131.0127; calculated: 131.0131. For  $\text{C}_3\text{H}_2\text{FN}_3\text{O}_2$  (131.1) calculated: 27.49% C, 1.54% H, 14.50% F, 32.06% N; found: 27.86% C, 1.55% H, 14.46% F, 32.03% N.

6-Nitro-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (*III*)

6-Amino-1,2,4-triazine-3,5(2*H*,4*H*)-dione (1.28 g; 0.01 mol) was added to a stirred mixture of trifluoroacetic acid (15 ml) and 30% hydrogen peroxide (5 ml). After heating to 60°C for 5 h, the mixture was taken down, the residue dissolved in water (10 ml), neutralized with aqueous ammonia and applied on a column (1.5 × 20 cm) of Dowex 1 (acetate form). The column was washed with water (200 ml) and 1% acetic acid (200 ml) and the product was eluted with 10% acetic acid. Evaporation of the solvent gave 350 mg (23%) of chromatographically pure compound *III*. An analytical sample was obtained by crystallization from diethyl ether-toluene (1 : 5); m.p. 180–181°C, with softening at 170°C. UV spectrum (0.05M-HCl):  $\lambda_{\text{max}}$  281 nm ( $\log \epsilon$  3.66); (0.05M-NaOH):  $\lambda_{\text{max}}$  263 nm ( $\log \epsilon$  3.21), 356 nm ( $\log \epsilon$  3.75). IR spectrum (KBr),  $\text{cm}^{-1}$ , 3 337, 3 225, 3 161, 3 100 (NH); 1 750, 1 714 (C=O); 1 589 (C=N); 1 531, 1 351 ( $\text{NO}_2$ ). Mass spectrum:  $m/z$  158 ( $\text{M}^+$ ), 114, 112, 86, 69, 43.  $\text{M}^+$  158.0069, calculated: 158.0076. For  $\text{C}_3\text{H}_2\text{N}_4\text{O}_4$  (158.1) calculated: 22.79% C, 1.28% H, 35.45% N; found: 23.58% C, 1.31% H, 33.62% N. Neither further crystallizations nor prolonged drying improved the analytical data. According to HPLC in dichloromethane — 2-propanol, the analytical samples were homogeneous.

TABLE II

Infrared spectra of 6-substituted 1,2,4-triazine-3,5(2*H*,4*H*)-diones, measured in dimethyl sulfoxide (4% solution, 0.04 mm cell), wavenumbers in  $\text{cm}^{-1}$

R	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$
H	1 723 s	1 700 vs 1 595 w
F <sup>a</sup>	1 727 vs, sh	1 713 vs 1 653 w
Cl <sup>b</sup>	1 733 s, sh	1 715 w 1 583 w
Br	1 723 s, sh	1 713 vs 1 576 w
I	1 720 s	1 706 s 1 566 w
CN	1 733 s, sh	1 721 vs 1 575 w
CF <sub>3</sub> <sup>c</sup>	1 730 s, sh	1 713 vs 1 603 w
CH <sub>2</sub> F	1 722 s, sh	1 705 s 1 602 w
CH <sub>3</sub>	1 712 vs, br	1 696 vs, sh 1 613 w
C(CH <sub>3</sub> ) <sub>3</sub> <sup>d</sup>	1 721 s	1 697 s 1 588 w
NO <sub>2</sub> <sup>e</sup>	1 749 vs	1 721 vs 1 599 m
NH <sub>2</sub> <sup>f</sup>	1 710 vs	1 696 s, sh 1 587 w
SCH <sub>3</sub> <sup>g</sup>	1 712 vs	1 697 s, sh 1 569 w, 1 576 w, sh
SO <sub>2</sub> CH <sub>3</sub> <sup>h</sup>	1 728 s, sh	1 710 s 1 580 w

<sup>a</sup> 1 257 s, 1 300 m, 801 m (C—F); <sup>b</sup> 661 m (C—Cl); <sup>c</sup> 1 1350 w, 1 200 m, 1 147 s (C—F); <sup>d</sup> 1 392 w, sh, 1 363 w (CH<sub>3</sub>); <sup>e</sup> 1 544 m, 1 558 w, sh, 1 353 m (NO<sub>2</sub>); <sup>f</sup> 1 633 m (NH<sub>2</sub>); <sup>g</sup> 659.5 m (C—S);

<sup>h</sup> 1 325 m, 1 141 m (SO<sub>2</sub>).

6-Cyano-1,2,4-triazine-3,5(2*H*,4*H*)-dione (IV)

A stirred mixture of 6-bromo-1,2,4-triazine-3,5(2*H*,4*H*)-dione (3.84 g; 0.02 mol), cuprous cyanide (3.56 g; 0.04 mol) and N,N,N',N'-tetramethylurea (25 ml) was heated to 150°C for 8 h. The mixture was diluted with 10% acetic acid (100 ml), the separated precipitate was filtered off and washed with 10% acetic acid (20 ml). The combined filtrates were passed through a column (1.5 × 20 cm) of Dowex 50 (H<sup>+</sup>-form), concentrated to about 30 ml, neutralized with aqueous ammonia and applied on a column of Dowex 1 (acetate). After the column had been washed with water (500 ml), the product was eluted with 5% acetic acid and the solvent evaporated. Crystallization from a small volume of water yielded 1.05 g (38%) of compound IV. Another portion of the pure product (0.29 g) was obtained from the mother liquors; m.p. 210–215°C (water). UV spectrum (in 0.05M-HCl):  $\lambda_{\max}$  204 nm (log  $\epsilon$  3.91), 280 nm (log  $\epsilon$  4.20); (in 0.05M-NaOH):  $\lambda_{\max}$  242 nm (log  $\epsilon$  3.99), 313 nm (log  $\epsilon$  4.02). IR spectrum (KBr), cm<sup>-1</sup>: 3 250, 3 179, 3 040 (NH); 2 250 (CN); 1 740, 1 690 (C=O); 1 568 (C=N). Mass spectrum:  $m/z$  138 (M<sup>+</sup>), 67. For C<sub>4</sub>H<sub>2</sub>N<sub>4</sub>O<sub>2</sub> (138.1) calculated: 34.79% C, 1.46% H, 40.58% N; found: 35.09% C, 1.51% H, 40.51% N.

Benzylammonium Salts of 6-Halogeno-1,2,4-triazine-3,5(2*H*,4*H*)-diones

Benzylamine (2.12 g; 0.02 mol) in water (10 ml) was added to a hot solution of the 6-halogeno derivative of compound I (0.01 mol) in water (25 ml). The hot mixture deposited crystals of the benzylammonium salt. After standing for 12 h at 5°C, the product was filtered and crystallized from water.

*6-Chloro derivative*: yield 84%, m.p. 212–213°C (water). For C<sub>10</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub> (254.7) calculated: 47.16% C, 4.35% H, 13.92% Cl, 22.00% N; found: 47.55% C, 4.28% H, 13.86% Cl, 22.11% N.

*6-Bromo derivative*: yield 67%, m.p. 210–211°C (water). For C<sub>10</sub>H<sub>11</sub>BrN<sub>4</sub>O<sub>2</sub> (299.1) calculated: 40.14% C, 3.71% H, 26.71% Br, 18.73% N; found: 39.81% C, 3.48% H, 27.41% Br, 18.60% N.

*6-Iodo derivative*: yield 70%, m.p. 206–207°C (water). For C<sub>10</sub>H<sub>11</sub>IN<sub>4</sub>O<sub>2</sub> (346.1) calculated: 34.70% C, 3.20% H, 36.66% I, 16.19% N; found: 35.25% C, 3.24% H, 36.55% I, 16.68% N.

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