Synthesis of 5-(Functionalized acyl)-1,3-dialkyl-Substituted Barbituric and 2-Thiobarbituric Acids

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A sodium derivative of 1,3-dimethylbarbituric acid or 1,3-diethyl-2-thiobarbituric acid undergoes an efficient monoacylation at C5 by the reaction with ω-chloroalkanoyl chloride or diacid dichloride in the presence of pyridine in tetrahydrofuran. A nucleophilic displacement of the chlorine in a 5-chloroacetylbartiburate can be accomplished by using a one-pot procedure. By contrast, a similar transformation of a 5-(chlorobutanoyl)barbituric acid requires intramolecular cyclization in the presence of a nonnucleophilic base followed by treatment with a nucleophile of the resultant 5-[4,5-dihydro(3*H*)-2-furylidene]barbiturate.

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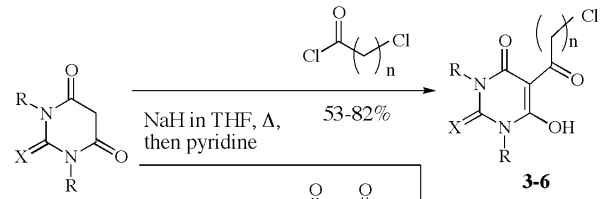
C5-Substituted barbituric and 2-thiobarbituric acids exhibit a wide spectrum of biological activity, and some of them are useful drugs or agrochemicals [1-5]. The major synthetic routes to these compounds involve ring construction because few efficient substitution reactions of the parent barbituric acids are available [1]. In particular, we have reported recently an improved procedure for a selective introduction of either one or two benzyl groups at C5 of 1,3-dimethylbarbituric acid (**1**) [6]. Benzoylation [4] of **1** can be accomplished by treatment with benzoyl chloride in the presence of Et_3N and $Zn(CN)_2$ or by the reaction of its sodium derivative with benzoyl chloride [7]. Compound **1** can also be acetylated by treatment under forcing conditions with a large excess of acetic anhydride [8], but similar preparations of higher alkanoyl derivatives have not been reported. Indeed, our attempted reactions of **1** and 1,3-diethyl-2-thiobarbituric acid (**2**) with either butyric chloride or butyric anhydride under the conditions indicated above produced only traces of the substituted product. On the other hand, compound **1** is efficiently acylated by reaction with an alkanoyl chloride when conducted in pyridine [9]. It appears that pyridine undergoes a reaction with the acid chloride to generate an intermediate *N*-acylpyridinium cation that is more reactive than the starting acid chloride [9, 10]. Unfortunately, this method is not suitable for the preparation of nucleophile-sensitive compounds such as **3-6** (Scheme 1). In our hands, the treatment of **1** with either chloroacetyl chloride or 4-chlorobutanoyl chloride in pyridine produced an inseparable mixture of products.

In a preliminary report [10] we showed that the desired compounds **3-6** are efficiently synthesized by the reaction of the corresponding sodium derivative of **1** and **2** with an alkanoyl chloride in the presence of pyridine under conditions that all three reagents (a sodium derivative of **1** or **2**, an alkanoyl chloride, and pyridine) are present in approximately equimolar amounts. In a subsequent report [11] we described a limited number of transformations of 5-(ω-chloroalkanoyl)-1,3-dimethylbarbituric acids **3** and **4**. In this paper we present a full account of the above mentioned chemistry that includes complete experimental details and a detailed characterization of all products mentioned previously [10, 11]. More importantly, additional examples of the successful derivatization of **1** and **2** are described.

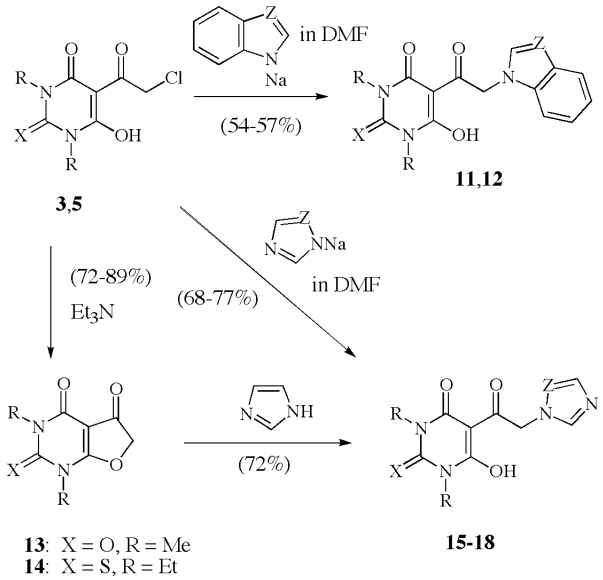
The highest efficiency of the acylation reaction of **1** and **2** to give the corresponding product **3-6** is observed when one equivalent of a sodium derivative of **1** or **2** and one equivalent of pyridine are used. This implies the formation

Scheme 1



3-6	7-10	X	R	n
3		O	Me	1
4	**7**	O	Me	3
	8	O	Me	6
5		S	Et	1
6	**9**	S	Et	3
	10	S	Et	6

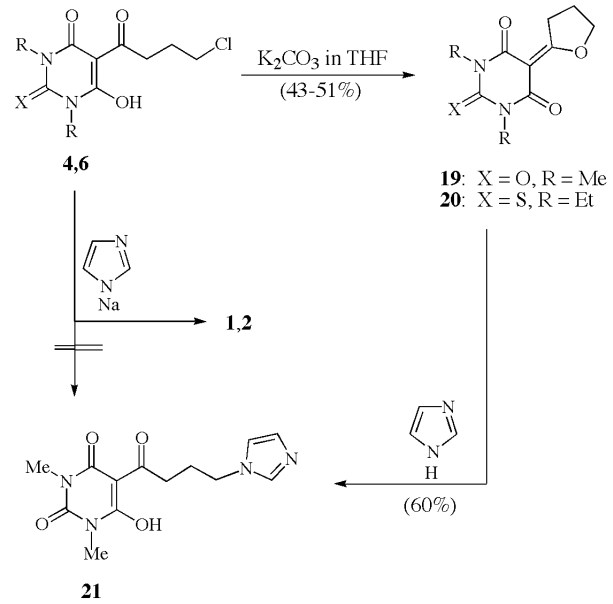
Scheme 2



11,12,15-18	X	Z	R
11,15	O	CH	Me
16	O	N	Me
17	S	CH	Et
12,18	S	N	Et

of an enolate of **3-6**. After quenching the mixture with acid the product **3-6** also exists in an enol form. Thus, the ^{1}H nmr spectra of **3-6** taken in anhydrous deuteriochloroform show the presence of a single enol form that absorbs at δ 18.1 ± 0.2. The suggested enolization of the carbonyl group at position 6 of the pyrimidine is in excellent agreement with the observed (δ 94.6-96.8) chemical shifts for C5 in the ^{13}C nmr spectra and the corresponding computer simulated values (δ 94.5-96.7) using an ACD/Labs™ program [12]. By comparison, the calculated chemical shift for C5 in the alternative tautomer with the acyl carbonyl enolized is δ 107±2 and the predicted value for the all-carbonyl tautomer is δ 80±3 for all compounds **3-6**.

Scheme 3



The synthesis of bis-barbituryl derivatives **7-10** is given in Scheme 1. Although these compounds can be obtained by conducting the reaction in pyridine, the modified method as described above greatly facilitates workup and isolation of these relatively water-soluble products. Again, compounds **7-10** exist in a single enol form as shown.

Since many substituted azoles exhibit potent biological activity [13-17], it was of interest to substitute the ω-chloro atom in **3-6** with the azole functionality. The reactions of **3** and **5** with sodium derivatives of indole, benzimidazole, imidazole, and 1,2,4-triazole furnished the corresponding products **11**, **12**, **15-18** in good yields (Scheme 2). A gc-ms analysis revealed that the 1,2,4-triazoles **16**, **18** were not accompanied by isomeric 1,3,4-triazoles. On the other hand, the treatment of **3**, **5** with triethylamine resulted in cyclization and gave the respective furanouracils **13**, **14**. These structures were derived from spectral data and then confirmed by an x-ray crystallographic analysis of **13**. The furan subsystem of **13**, **14** undergoes a facile ring opening in the presence of a nucleophile, as exemplified in Scheme 2 by the reaction of **13** with imidazole.

In contrast to the facile nucleophilic displacement of chlorine of the chloroacetyl group in **3**, **5**, the ω-chlorobutanoyl-substituted barbituric acids **4**, **6** undergo deacylation under similar conditions to give **1**, **2** in nearly quantitative yields (Scheme 3). The facile loss of the acyl group from **4**, **6** can be explained in terms of a nucleophile addition to the acyl carbonyl group followed by retro aldol-type fragmentation of the resultant adduct.

The desired compound **21** was obtained by cyclization of **4** in the presence of potassium carbonate and then opening of the furylidene subunit in the resultant product **19** by treatment with imidazole. The 2-thio analog **6** undergoes a similar cyclization to **20**. Since on the basis of spectral data alone the structures of **19** and its 2-thioxo analog **20** could not be determined unambiguously, the molecular structure of the selected compound **19** was solved by x-ray crystallographic analysis.

In summary, we have described a simple method for the introduction of an ω-chloroalkanoyl group at C5 of 1,3-dialkyl-substituted barbituric and 2-thiobarbituric acids. While chlorine in chloroacetyl-substituted products can be displaced by nucleophiles in a one-pot reaction, a similar transformation of ω-chlorobutanoyl derivatives requires a two-step procedure. It is important to note that no chromatography was involved and analytically pure

products were obtained by crystallization in all cases studied. Several substituted azoles obtained as part of this work were screened by DuPont and were shown to be insecticides against southern corn rootworm, two-spotted spider mite, green peach aphid or corn planthopper [18]. The biological results will be published in due course.

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. All reactions were conducted under a nitrogen atmosphere. The progress of the reactions was monitored, and mass spectra of pure products were obtained on a gc-ms instrument equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column, and a mass selective detector operating at 70 eV. The lack of mass spectral data indicates a nonvolatile compound. Melting points are not corrected. ^{1}H and ^{13}C nmr spectra were obtained at 400 MHz and 100 MHz, respectively. Unless otherwise indicated the nmr spectra were taken in deuteriochloroform at 25°.

5-Acylbarbiturates, **3-6**.

A solution of **1** or **2** (10 mmoles) in tetrahydrofuran (10 ml) was added to a suspension of sodium hydride (0.3 g, 95%, 12 mmoles) in tetrahydrofuran (50 ml) and the mixture was heated under reflux for 2.5 hours. After cooling the mixture was treated with pyridine (1 ml, 12 mmoles) followed by addition of an acid chloride (12 mmoles) and stirring at 40° for 24 hours. After concentration under reduced pressure the residue was extracted with chloroform (3 x 20 ml). The extract was dried with magnesium sulfate and concentrated, and the resultant product was crystallized from ethanol (**3**) or ether/pentanes (1:1, **4-6**).

5-Chloroacetyl-1,3-dimethylbarbituric Acid (**3**).

This compound was obtained in 82% yield, mp 101-102°; ^{1}H nmr: δ 3.33 (s, 3H), 3.40 (s, 3H), 4.96 (s, 2H), 17.91 (br s, exchangeable with deuterium oxide, 1H); ^{13}C nmr: δ 28.1, 28.2, 44.1, 94.6, 149.8, 160.3, 169.7, 190.9; ms: m/z 81 (100), 196 (80, M^+-HCl).

Anal. Calcd. for $C_8H_9ClN_2O_4$: C, 41.31; H, 3.90; N, 12.04. Found: C, 41.29; H, 3.75; N, 11.91.

5-(4-Chlorobutanoyl)-1,3-dimethylbarbituric Acid (**4**).

This compound was obtained in 67% yield, mp 56-57°; ^{1}H nmr: δ 2.17 (m, 2H), 3.32 (t, J = 8 Hz, 2H), 3.37 (s, 6H), 3.63 (t, J = 6.8 Hz, 2H), 17.87 (br s, exchangeable with deuterium oxide, 1H); ^{13}C nmr: δ 27.8, 28.0, 28.1, 34.2, 44.1, 95.3, 150.2, 160.7, 169.7, 198.0; ms: m/z 42 (100), 224 (80, M^+-HCl).

Anal. Calcd. for $C_{10}H_{13}ClN_2O_4$: C, 46.08; H, 5.03; N, 10.75. Found: C, 46.29; H, 5.12; N, 10.47.

5-Chloroacetyl-1,3-diethyl-2-thiobarbituric Acid (**5**).

This compound was obtained in 65% yield, mp 91-92°; ^{1}H nmr: δ 1.40 (m, 6H), 4.60 (m, 4H), 5.00 (s, 2H), 18.20 (br s, exchangeable with deuterium oxide, 1H); ^{13}C nmr: δ 11.7, 12.1, 43.5, 45.4, 95.8, 158.0, 167.9, 176.5, 193.1; ms: m/z 42 (100), 240 (90, M^+-HCl).

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3S$: C, 43.40; H, 4.73; N, 10.12. Found: C, 43.13; H, 4.57; N, 9.95.

5-(4-Chlorobutanoyl)-1,3-diethyl-2-thiobarbituric Acid (**6**).

This compound was obtained in 57% yield, mp 48-49°; ^{1}H nmr: δ 1.30 (m, 6H), 2.20 (m, 2H), 3.35 (t, J = 7.5 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 4.50 (m, 4H), 18.1 (br s, exchangeable with deuterium oxide, 1H); ^{13}C nmr: δ 11.8, 12.2, 27.7, 35.1, 43.1, 43.3, 44.1, 96.7, 158.0, 167.0, 177.0, 200.1; ms: m/z 69 (100), 268 (60, M^+-HCl).

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3S$: C, 47.29; H, 5.62; N, 9.19. Found: C, 47.24; H, 5.53; N, 9.17.

5-Acylbarbiturates, **7-10**.

In the procedure described above a diacid dichloride (6 mmoles) was substituted for the acid chloride under otherwise identical conditions including workup. The product **7-10** was crystallized from ethanol/chloroform (1:1).

1,5-Bis(1,3-dimethyl-5-barbituryl)pentane-1,5-dione (**7**).

This compound was obtained in 75% yield, mp 181-182°; ^{1}H nmr: δ 2.10 (m, 2H), 3.28 (t, J = 7.8 Hz, 4H), 3.32 (s, 6H), 3.37 (s, 6H), 17.90 (br s, exchangeable with deuterium oxide, 2H); ^{13}C nmr: δ 20.9, 27.9, 28.0, 36.1, 95.4, 150.3, 160.8, 169.7, 198.4.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.87; H, 4.86; N, 13.54.

1,5-Bis-(1,3-dimethyl-5-barbituryl)octane-1,8-dione (**8**).

This compound was obtained in 72% yield, mp 157-158°; ^{1}H nmr: δ 1.47 (m, 4H), 1.71 (m, 4H), 3.14 (t, J = 7.8 Hz, 4H), 3.32 (s, 6H), 3.37 (s, 6H), 17.80 (br s, exchangeable with deuterium oxide, 2H); ^{13}C nmr: δ 25.6, 27.8, 28.0, 29.1, 36.6, 95.2, 150.3, 160.8, 169.7, 199.6.

Anal. Calcd. for $C_{20}H_{26}N_4O_8$: C, 53.33; H, 5.82; N, 12.44. Found: C, 53.20; H, 5.71; N, 12.41.

1,5-Bis-[1,3-diethyl-5-(2-thiobarbituryl)]pentane-1,5-dione (**9**).

This compound was obtained in 59% yield, mp 133-134°; ^{1}H nmr: δ 1.29 (m, 12H), 2.22 (m, 2H), 3.30 (t, J = 7.5 Hz, 4H), 4.54 (m, 8H), 18.10 (br s, exchangeable with deuterium oxide, 2H); ^{13}C nmr: δ 11.9, 12.2, 20.2, 36.9, 43.0, 43.3, 96.8, 158.4, 167.9, 177.1, 200.4.

Anal. Calcd. for $C_{21}H_{28}N_4O_6S_2$: C, 50.79; H, 5.68; N, 11.28. Found: C, 50.63; H, 5.81; N, 11.16.

1,5-Bis-[1,3-diethyl-5-(2-thiobarbituryl)]octane-1,8-dione (**10**).

This compound was obtained in 51% yield, mp 123-124°; ^{1}H nmr: δ 1.27 (m, 12H), 1.48 (m, 4H), 1.73 (m, 4H), 3.15 (t, J = 7.8 Hz, 4H), 4.53 (m, 8H), 18.02 (br s, exchangeable with deuterium oxide, 2H); ^{13}C nmr: δ 11.9,12.2, 25.2, 29.0, 37.5, 43.0, 43.3, 96.7, 158.4, 167.9, 177.2, 201.5.

Anal. Calcd. for $C_{24}H_{34}N_4O_6S_2$: C, 53.51; H, 6.36; N, 10.40. Found: C, 53.47; H, 6.52; N, 10.30.

5-(Azolylacetyl)barbiturates, **11**, **12**, **15-18**.

A mixture of sodium hydride (95%, 38 mg, 1.5 mmoles) and an azole (1.5 mmoles) in *N,N*-dimethylformamide (10 ml) was stirred at 23° for 1 hour and then treated with **3**,**5** (1 mmole). The stirring was continued at 80° for 16 hours. Following concentration on a rotary evaporator, the residue was dissolved in water (10 ml) and the solution was neutralized by dropwise addition of 2 *M* hydrochloric acid. The resulting precipitate was filtered, washed with water, dried, and crystallized from ethanol (**11**), chloroform/-methanol (**12**), water (**15**) or ethanol/methanol (**16-18**).

5-(Indol-1-ylacetyl)-1,3-dimethylbarbituric Acid (**11**).

This compound was obtained in 57% yield, mp 206-207°; ^{1}H nmr: δ 3.35 (s, 3H), 3.38 (s, 3H), 5.74 (s, 2H), 6.59 (d, J = 3.3 Hz, 1H), 7.16 (m, 4H), 7.64 (d, J = 3.3 Hz, 1H), 17.90 (br s, exchangeable with deuterium oxide, 1H); ^{13}C nmr: δ 28.0, 28.1, 50.1, 94.3, 102.4, 108.9, 119.9, 121.1, 122.0, 128.4, 128.8, 136.7, 149.9, 160.8, 169.5, 193.4; ms: m/z 130 (100), 313 (70, M$^+$).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.31; H, 4.64; N, 13.40.

5-(Benzimidazol-1-ylacetyl)-1,3-diethyl-2-thiobarbituric acid (**12**).

This compound was obtained in 54% yield, mp 274-276° (dec); ^{1}H nmr: δ 1.41 (t, J = 6.6 Hz, 6H), 4.70 (q, J = 6.6 Hz, 4H), 5.79 (s, 2H), 7.70 (m, 4H), 8.90 (s, 1H), no signal for the enol proton is observed; ms: m/z 132 (100), 358 (80, M$^+$). High-resolution ms: Calcd. for $C_{17}H_{18}N_4O_3S$ m/z 358.1100; observed m/z 358.1110.

Anal. Calcd. for $C_{17}H_{18}N_4O_3S•H_2O$: C, 54.24; H, 5.36; N, 14.88. Found: C, 54.41; H, 5.28; N, 14.86.

5-(Imidazol-1-ylacetyl)-1,3-dimethylbarbituric Acid (**15**).

This compound was obtained in 77% yield, mp 255-256°; ^{1}H nmr: (deuterium oxide, 50°) δ 2.99 (s, 6H), 5.32 (s, 2H), 7.23 (d, J = 1.5 Hz, 1H), 7.28 (d, J = 1.5 Hz, 1H), 8.49 (s, 1H); ms: m/z 82 (100), 264 (80, M$^+$).

Anal. Calcd. for $C_{11}H_{12}N_4O_4•H_2O$: C, 46.80; H, 4.96; N, 19.86. Found: C, 46.49; H, 4.88; N, 19.74.

1,3-Dimethyl-5-(1,2,4-triazol-1-ylacetyl)barbituric Acid, (**16**).

This compound was obtained in 74% yield, mp 211-212° (dec); ^{1}H nmr: (dimethyl sulfoxide-d_6, 30°): δ 3.20 (s, 6H), 5.84 (s, 2H), 8.10 (s, 1H), 8.66 (s, 1H); ms: m/z 265 (100, M$^+$). High resolution ms:. Calcd. for $C_{10}H_{11}N_5O_4$ m/z 265.0811, observed m/z 265.0812.

Anal. Calcd. for $C_{10}H_{11}N_5O_4•0.5\ H_2O$: C, 43.79; H, 4.37; N, 25.54. Found: C, 43.82; H, 4.25; N, 25.41.

1,3-Diethyl-5-(imidazol-1-ylacetyl)-2-thiobarbituric Acid, (**17**).

This compound was obtained in 68% yield, mp 249-250°; ^{1}H nmr: δ 1.33 (t, J = 6.9 Hz, 6H), 4.62 (q, J = 6.9 Hz, 4H), 5.60 (s, 2H), 7.06 (d, J = 1.1 Hz, 1H), 7.22 (d, J = 1.1 Hz, 1H), 8.60 (s, 1H), 15.80 (br s, exchangeable with deuterium oxide, 1H); ms: m/z 308 (100, M$^+$). High resolution ms: Calcd. for $C_{13}H_{16}N_4O_3S$ m/z 308.0943, observed m/z 308.0943.

Anal. Calcd. for $C_{13}H_{16}N_4O_3S$: C, 50.64; H, 5.23; N, 18.17. Found: C, 50.66; H, 5.43; N, 18.11.

1,3-Diethyl-5-(1,2,4-triazol-1-ylacetyl)-2-thiobarbituric Acid (**18**).

This compound was obtained in 71% yield, mp 206-208°; ^{1}H nmr: (dimethyl sulfoxide-d_6, 30°) δ 1.16 (t, J = 6.6 Hz, 6H), 4.41 (q, J = 6.6 Hz, 4H), 5.63 (s, 2H), 8.59 (s, 1H), 9.26 (s, 1H).

Anal. Calcd. for $C_{12}H_{15}N_5O_3S$: C, 46.59; H, 4.89; N, 22.65. Found: C, 46.63; H, 4.89; N, 22.88.

Furanouracils, **13** and **14**.

A solution of **3** or **5** (10 mmoles) and triethylamine (1 ml) in absolute ethanol (50 ml) was heated to 50° for 8 hours. After cooling the resultant precipitate was filtered and crystallized from ethanol.

1,3-Dimethylfurano[3,2-*e*]pyrimidine-2,4,5(1*H*,3*H*,6*H*)-trione (**13**).

This compound was obtained in 89% yield, mp 205-206°; ^{1}H nmr: δ 3.25 (s, 3H), 3.50 (s, 3H), 4.80 (s, 2H); ^{13}C nmr: δ 27.9, 28.8, 77.6, 92.1, 150.1, 155.6, 176.9, 187.7; ms: m/z 81 (100), 196 (90, M$^+$).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.09; H, 3.95; N, 14.01.

1,3-Diethylfurano[3,2-*e*]pyrimidine-2(1*H*)-thione-4,5(3*H*,6*H*)-dione (**14**).

This compound was obtained in 72% yield, mp 199-200°; ^{1}H nmr: δ 1.20 (t, J = 7.5 Hz, 3H), 1.40 (t, J = 7.5 Hz, 3H), 4.50 (m, 4H), 4.80 (s, 2H); ^{13}C nmr: δ 11.3, 12.6, 43.1, 43.6, 76.9, 94.3, 153.8, 175.5, 176.0, 188.0; ms: m/z 42 (100), 240 (90, M$^+$).

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 49.72; H, 4.99; N, 11.56.

Furylidenebarbiturates, **19** and **20**.

A mixture of **4** or **6** (5 mmoles) and anhydrous potassium carbonate (2 g, 15 mmoles) in tetrahydrofuran (50 ml) was stirred at 23° for 8 hours, filtered, and the solution was concentrated. The residue was treated with water (30 ml) and extracted with chloroform (3 x 20 ml). The extract was dried with magnesium sulfate, concentrated, and the solid residue was crystallized from toluene/hexanes.

5-[4,5-Dihydro(3*H*)-2-furylidene]-1,3-dimethylbarbituric Acid (**19**).

This compound was obtained in 51% yield, mp 178-179°; ^{1}H nmr: δ 2.23 (m, 2H), 3.32 (s, 6H), 3.58 (t, J = 8.0 Hz, 2H), 4.75 (t, J = 8.0 Hz, 2H); ^{13}C nmr: δ 21.9, 27.9, 28.1, 36.6, 76.9, 97.0, 151.5, 160.4, 163.0, 190.0; ms: m/z 42 (100), 224 (80, M$^+$).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.55; H, 5.38; N, 12.40.

1,3-Diethyl-5-[4,5-dihydro(3*H*)-2-furylidene]-2-thiobarbituric Acid (**20**).

This compound was obtained in 43% yield, mp 140-141°; ^{1}H nmr: δ 1.28 (t, J = 7.0 Hz, 6H), 2.24 (m, 2H), 3.59 (t, J = 7.8 Hz, 2H), 4.53 (q, J = 7.0 Hz, 4H), 4.79 (t, J = 7.5 Hz, 2H); ^{13}C nmr: δ 12.2, 12.4, 21.9, 37.1, 43.1, 43.2, 77.3, 98.4, 158.3, 161.0, 178.8, 191.5; ms: m/z 69 (100), 268 (60, M$^+$).

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.55; H, 6.26; N, 10.38.

Fusion of **13** or **19** with Imidazole.

Heating a mixture of a furanouracil **13** (0.2 g, 1 mmole) or a furylidenebarbituric acid **19** (0.22 g, 1 mmole) and imidazole (0.1 g, 1.5 mmoles) to 125° for 2 hours followed by trituration with ethanol and crystallization of the resultant solid from water gave the respective products **15** (yield 72%) and **21**.

5-[4-(1-Imidazolyl)butanoyl]-1,3-dimethylbarbituric Acid (**21**).

This compound was obtained in 60% yield, mp 203-205°; ^{1}H nmr: (deuterium oxide, 50°) δ 2.02 (m, 2H), 2.71 (t, J = 8.0 Hz, 2H), 3.03 (s, 6H), 4.12 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 1.1 Hz, 1H), 7.37 (d, J = 1.1 Hz, 1H), 8.57 (s, 1H); ms: m/z 183 (100), 292 (70, M$^+$).

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.11; H, 5.59; N, 18.84.

X-ray Structural Data for **13**.

The molecular formula is $C_8H_8N_2O_4$, M = 196.16, the crystal is orthorhombic, space group fold 2, crystal size = 0.187 x 0.034 x 0.034 mm, unit cell dimensions, a = 28.333 (2) Å, $\alpha = \beta = \gamma = 90°$, v = 3409.2 (4) $Å^3$, refinement by full-matrix least-squares on F_2, F (000) = 1632, no. of reflections collected = 4365, no. of independent reflections = 1449 [R (int) = 0.1090]. The complete crystallographic data for **13** have been deposited at the Cambridge Crystallographic Data Centre.

X-ray Structural Data for **19**.

The molecular formula is $C_{10}H_{12}N_2O_4$, M = 224.22, the crystal is monoclinic, space group P2 (1)/C, crystal size = 0.612 x 0.374 x 0.255 mm, unit cell dimensions, a = 12.8616 (11) Å, b = 11.0200 (9) Å, c = 7.2909 (6) Å, $\alpha = 90$, $\beta = 102.8980$ (10) °, $\gamma = 90°$, v = 1007.3 (2) $Å^3$, refinement by full-matrix least-squares on F_2, F (000) = 472, no. of reflections collected = 6277, no. of independent reflections = 2354 [R (int) = 0.0494]. The complete crystallographic data for **21** have been deposited at the Cambridge Crystallographic Data Centre.

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