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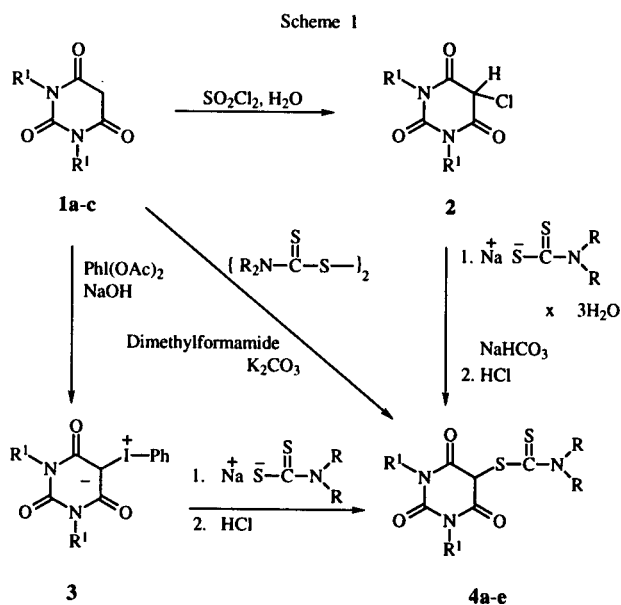
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The title compounds are obtained by three different methods. The aminothiocarbonylthiolation of barbituric acids **1** and aminouracil (**5**) can be accomplished in one step by reaction with thiuram disulfides in the presence of potassium carbonate. On the other hand, compounds **4** can be obtained *via* the salt of chloro derivative **2** or the corresponding iodonium ylides **3**. The aminouracil derivative **7** was obtained in a similar fashion from **5** directly or *via* iodonium betaine **6**.

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In recent years the sulfidation of cyclic 1,3-dione systems has been achieved by different methods. Thus, the diethylaminothiocarbonylthiolation of dimedone has been accomplished by Neilands [1] by converting dimedone into its phenyliodonium betaine, and subsequent reaction of this ylide with sodium diethyldithiocarbamate. The same approach has been used successfully with barbituric acids [2-5]. The compounds obtained in this fashion could be converted to novel tetrathiafulvalene derivatives that are capable to form ion-radical salts [4] or are able to form intermolecular hydrogen bonds of nucleic acid base-pair types [5]. Another method to afford open chain [6], alicyclic, or heterocyclic thiolation is the reaction of anions of 1,3-dicarbonyl system with disulfides [6-9]. This way has been successfully used with aromatic disulfides and with tetraalkylthiuram disulfides [7-9]. Since aliphatic disulfides are less electrophilic than the above mentioned species, and do not react in this fashion, we have developed a method to prepare also aliphatic sulfides of heterocyclic 1,3-dicarbonyl systems by reacting the monohalogeno derivatives of 1,3-dicarbonyl compounds with aliphatic thiolates [7,10]. This paper describes the utilization of the new methods for the synthesis of 5-dialkylaminothiocarbonylthio-barbituric acids **4a-e**, and the preparation of 5-diethylaminothiocarbonylthio-6-aminouracil (**7**).

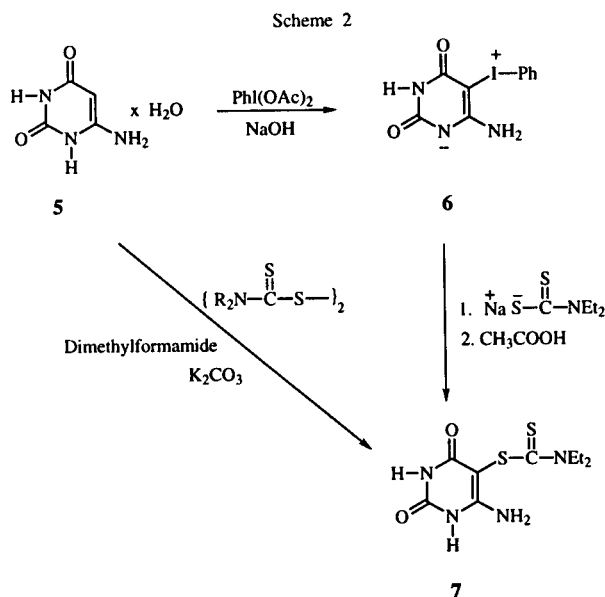
The one-step synthesis of **4a-e** was accomplished by reacting the corresponding barbituric acids with a small excess (5%) of tetraethyl- or tetramethylthiuram disulfides in dimethylformamide at 85-95° in the presence of two equivalents of potassium carbonate for several hours. After concentration and acidification the thiuram sulfides **4a-e** were isolated in good yields. The preparation of **4a** or **4e** by the reaction of the phenyliodonium ylide of 1,3-dimethylbarbituric acid or barbituric acid has been previously described [3,2]. Still another way to obtain compounds of type **4** is the two-step synthesis *via* the



4a: R¹ = Me R² = Et
4b: R¹ = Me R² = Me
4c: R¹ = Ph R² = Et
4d: R¹ = Ph R² = Me
4e: R¹ = H R² = Et

monochloro barbituric acid **2**. This intermediate is easily prepared in 80% yield by the chlorination of barbituric acid with sulfuryl chloride in water [11] or by reaction of the phenyliodonium ylide **3** (R¹ = H) with hydrochloric acid in ethanol [12]. The conversion of **2** to **4e** is also performed in water: Thus the mixture of **2** and sodium hydrogen carbonate with a small excess of diethylaminothiocarbamate trihydrate is heated for 1.5 hours under reflux and acidified to give **4e**. Compound **2**, being a strong acid, decomposes the diethylaminodithiocarbamate; therefore it is necessary to add sodium bicarbonate to the solution of

of **2**. A reaction of 5-bromouracil with benzylmercaptan to yield the corresponding 5-benzylthiouracil has recently been described [13]. We have successfully performed analog reactions with a number of chloromalonylheterocycles, such as for instance 3-chloro-4-hydroxy-2-quinolones, with various aliphatic mercaptanes [7,10].



The synthesis of the 5-diethylaminothiocarbonylthio-6-aminouracil (**7**) was accomplished by two methods. The one-step reaction of 6-aminouracil (**5**) with tetraethylthiuram disulfide in dry dimethylformamide in the presence of potassium carbonate yielded **7** in 55% yield. The two-step reaction *via* the iodonium betaine **6** [14], obtained from **5** in 96% yield, afforded **7** in 30% yield. In this case the reaction was carried out at room temperature in one week.

In conclusion, we have demonstrated that there are three, fundamentally different, procedures to obtain sulfides from 1,3-dicarbonyl compounds (using barbituric acids and 6-aminouracil as model compounds): The first one uses the electrophilic property of disulfides (such as thiuram disulfides). Here, the anion of the 1,3-dicarbonyl system reacts with the electrophilic reagent. The second one first converts the 1,3-dicarbonyl system into a betaine containing a weakly nucleophilic anionic part and an electrophilic iodonium part (iodobenzene is a good leaving group). The mechanism of this nucleophilic substitution has not been investigated. Probably, a single electron transfer process or formation of a dioxocarbene intermediate is involved. In the case of betaine **6** we observe an usual nucleophilic substitution at a sp^2 carbon atom. The third method makes use of 2-chloro-1,3-dicarbonyl compounds. The reaction of nonionized **2** seems to be a nucleophilic substitution at the tetragonal carbon atom in

2-position by the strong anionic *S*-nucleophile. However 5-chlorobarbituric acid is a strong acid ($pK_a = 0.0$), therefore the concentration of nonionized **2** is about 10⁻⁷%. Thus a reaction path *via* a carbene intermediate derived from the anion of **2** seems also possible.

It should be stressed that all starting barbituric acids are easily available. The sodium salts of dialkylaminodithiocarbamates are easily obtained by mixing secondary amines, carbon disulfide, and sodium hydroxide. If ammonium salts (which are usually more soluble in organic solvents) are used, carbon disulfide is just mixed with two equivalents of the secondary amine. Finally, the thiuram disulfides are easily obtained in a one pot reaction by oxidizing the dithiocarbamate salts with hydrogen peroxide. The best choice of the reaction pathway will be dependent upon the availability of the starting materials and the yields.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. The ¹H nmr spectra (200 MHz) were obtained on a Varian Gemini 200 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ -units. The solvent for nmr was hexadeuteriodimethyl sulfoxide unless otherwise stated. Microanalyses were performed on a Fisons elemental analyzer, Model EA 1108. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer in potassium bromide pellets. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection.

1,3-Dimethyl-5-diethylaminothiocarbonylthio-barbituric Acid (**4a**).

A mixture of **1a** (3.12 g, 0.02 mole), tetraethylthiuram disulfide (6.21 g, 0.021 mole), potassium carbonate (5.52 g, 0.04 mole) and 120 ml of dimethylformamide was heated under stirring for 4 hours at 85°. After removing half of the solvent *in vacuo* the solution was poured into ice-water. After standing for 3 hours it was filtered and the filtrate slowly acidified with diluted hydrochloric acid. The solution was kept for 6 hours at 4° and the precipitate was collected. The yield was 3.00 g (50%), mp 123-126° (toluene) (lit [3] mp 125-130°, from ethanol or 2-propanol); ir: ν 3600-3300 wb, 2980 m, 2850 m, 1720 s, 1680 s, 1500 s cm^{-1} ; ¹H nmr: δ 1.13 (t, $J = 7$ Hz, 3H, CH₃) 1.28 (t, $J = 7$ Hz, 3H, CH₃), 3.17 (s, 6H, N-CH₃), 3.76-3.89 (m, 4H, CH₂), 5.00 (sb, OH-H₂O).

Anal. Calcd. for C₁₁H₁₇N₃O₃S₂ (303.40): C, 43.55; H, 5.65; N, 13.85. Found: C, 43.16; H, 5.53; N, 13.74.

1,3-Dimethyl-5-dimethylaminothiocarbonylthio-barbituric Acid (**4b**).

A mixture of **1a** (3.12 g, 0.02 mole), tetramethylthiuram disulfide (5.30 g, 0.022 mole), potassium carbonate (5.52 g, 0.04 mole) and 140 ml of dimethylformamide was heated under stir-

ring for 10 hours at 85°. After removing half of the solvent *in vacuo* the solution was poured into ice-water. After standing for 3 hours it was filtered and the filtrate slowly acidified with diluted hydrochloric acid. The solution was kept for 6 hours at 4° and the precipitate was collected. The yield was 4.68 g (85%), mp 167-169° (ethanol); ¹H nmr: δ 3.18 (s, 6H, N-CH₃-barbituric acid), 3.43 (s, 6H, N-CH₃-methylaminothiocarbonylthio).

Anal. Calcd. for C₉H₁₃N₃O₃S₂ (275.40): C, 39.26; H, 4.76; N, 15.26. Found: C, 38.91; H, 4.70; N, 14.88.

1,3-Diphenyl-5-diethylaminothiocarbonylthiobarbituric Acid (4c).

A mixture of **1b** (5.60 g, 0.02 mole), tetraethylthiuram disulfide (6.21 g, 0.021 mole), potassium carbonate (5.52 g, 0.04 mole) and 140 ml of dimethylformamide was heated under stirring for 10 hours at 85°. After removing half of the solvent *in vacuo* the solution was poured into ice-water. After standing for 3 hours it was filtered and the filtrate slowly acidified with diluted hydrochloric acid. The solution was kept for 6 hours at 4° and the precipitate was collected. The yield was 6.29 g (73%), mp 139-140° (ethanol); ir: ν 2980 w, 2915 w, 1710 s, 1700 s, 1590 w, 1490 s cm⁻¹; ¹H nmr: δ 1.20 (t, J = 7 Hz, 3H, CH₃), 1.30 (t, J = 7 Hz, 3H, CH₃), 3.75-4.02 (m, 4H, CH₂), 4.28 (sb, OH-H₂O), 7.20-7.52 (m, 10H, ArH).

Anal. Calcd. for C₂₁H₂₁N₃O₃S₂ (427.53): C, 58.99; H, 4.95; N, 9.83. Found: C, 58.66; H, 4.90; N, 9.73.

1,3-Diphenyl-5-dimethylaminothiocarbonylthiobarbituric Acid (4d).

A mixture of **1b** (5.60 g, 0.02 mole), tetramethylthiuram disulfide (5.30 g, 0.022 mole), potassium carbonate (5.52 g, 0.04 mole) and 150 ml of dimethylformamide was heated under stirring for 4 hours at 85°. After removing half of the solvent *in vacuo* the solution was poured into ice-water. After standing for 3 hours it was filtered and the filtrate slowly acidified with diluted hydrochloric acid. The solution was kept for 6 hours at 4° and the precipitate was collected. The yield was 6.39 g (80%), mp 193-196° (ethanol); ir: ν 1700 s, 1590 w, 1510 m, 1490 w cm⁻¹; ¹H nmr: δ 3.42 (s, 6H, CH₃) 7.20-7.50 (m, 10H, ArH).

Anal. Calcd. for C₁₉H₁₇N₃O₃S₂·H₂O (417.50): C, 54.61; H, 4.55; N, 10.05. Found: C, 55.00; H, 4.25; N, 10.23.

5-Diethylaminothiocarbonylthiobarbituric Acid (4e).

Method A.

A mixture of barbituric acid (12.8 g, 0.1 mole), tetraethylthiuram disulfide (32.6 g, 0.11 mole), potassium carbonate (27.6 g, 0.2 mole), and dimethylformamide (150 ml) was heated under stirring to 95° for 15 hours. After cooling diethyl ether (300 ml) was added, the precipitate was filtered off and dissolved in water (400 ml). The solution was filtered, glacial acetic acid (20 ml) was added, and then decolorized by charcoal. Concentrated hydrochloric acid (64 ml) was added to the filtrate. After 5 hours the precipitate was filtered, washed with water and dried to give 17.0 g (58%) of monohydrate of **4e** as pale yellow crystals.

Method B.

A mixture of 5-chlorobarbituric acid (**2**, R = H, 0.40 g, 0.0025 mole) [11,12], sodium bicarbonate (0.21 g, 0.0025 mole), and water (10 ml) was heated at 40-50°. To this solution sodium diethylaminodithiocarbamate trihydrate (0.63 g, 0.0028 mole) was added and heated under reflux for 1.5 hours. After cooling

the solution was filtered from some precipitate and neutralized with acetic acid (0.3 ml, 0.005 mole). The turbid solution was filtered and the filtrate acidified with concentrated hydrochloric acid (2 ml) and cooled for 5-6 hours. The yield of **4e** monohydrate as yellowish crystals was 0.44 g (60%).

The melting point of **4e** is not characteristic; at 174-180° **4e** begins to decompose, the solid swells and turns orange, melting occurs at 198-205°; ir (in hexachlorobutadiene): ν 3475 s, 3175 s, 3050 sb, 2480-2500 w; (in nujol): ν 1700 s, 1665 m, 1590 s, 1495 m, cm⁻¹ [2]. After drying for 24 hours; ir (in hexachlorobutadiene): ν 3200 s, 3080 s, 3000-2850 mb, 2600 w; (in nujol): ν 1735 (bend), 1705 s, 1564 w, cm⁻¹; ¹H nmr: δ 1.20 (t, J = 7 Hz, 3H, CH₃), 1.30 (t, J = 7 Hz, 3H, CH₃), 3.80-4.00 (m, 4H, CH₂), 4.10-4.50 (sb, OH-H₂O), 11.10 (s, 2H, NH).

Anal. Calcd. for C₉H₁₃N₃O₃S₂ (275.35): C, 39.26; H, 4.76; N, 15.26. Found: C, 38.87; H, 4.56; N, 15.37.

5-Diethylaminothiocarbonylthio-6-aminouracil (7).

Method A.

A mixture of **5** (5.0 g, 0.032 mole), tetraethylthiuram disulfide (10.0 g, 0.034 mole) and potassium carbonate (5.0 g, 0.036 mole) in 70 ml of dry dimethylformamide was heated to 145° during 25 minutes. After cooling, 100 ml of water was added. The solution was filtered and glacial acetic acid was added. The precipitate was filtered, washed with water and recrystallized from 50% dimethylformamide or 50% ethanol to give 5.20 g (55%), mp >340° dec; ir: ν 3470, 3195, 1733, 1630, 1562, 1528 cm⁻¹; ¹H nmr: δ 1.13 (t, J = 7 Hz, 3H, CH₃), 1.28 (t, J = 7 Hz, 3H, CH₃), 3.77 (q, 2H, CH₂), 3.85 (q, 2H, CH₂), 6.35 (s, 2H, NH₂), 10.26 (s, 1H, NH), 10.39 (s, 1H, NH).

Anal. Calcd. for C₉H₁₄N₄O₂S₂: C, 39.40; H, 5.14; N, 20.42; S, 23.37. Found: C, 39.71; H, 5.12; N, 20.30; S, 23.05.

Method B.

5-Phenyliodonio-6-aminouracil (6).

Phenyliodoso diacetate (32.2 g, 0.1 mole) was dissolved in 150 ml of methanol with heating and filtered. 6-Aminouracil (14.5 g, 0.09 mole) was dissolved in a solution of 8.0 g of sodium hydroxide in 300 ml of water. The solutions were mixed and cooled to 5-10°. After 3 hours the precipitate was filtered, washed with water and ethanol, and dried to give 34.90 g (96%) white crystals, mp >350° dec.

5-Diethylaminothiocarbonylthio-6-aminouracil (7).

5-Phenyliodonio-6-aminouracil (**6**, 32.90 g, 0.1 mole) and sodium diethylaminodithiocarbamate (2.0 g, 0.12 mole) were stirred in 200 ml of dry dimethylformamide for one week at room temperature. The product was precipitated by addition of 300 ml of ether and filtered. The precipitate was dissolved in 400 ml of water with heating and filtered. Glacial acetic acid (20 ml) was added to the solution. The precipitate was filtered, washed with water and recrystallized from 50% ethanol to give 8.14 g (30%) white crystals, identical with the product described above.

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