Note on the Preparation of Some Thiobarbiturates

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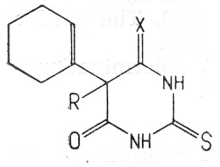
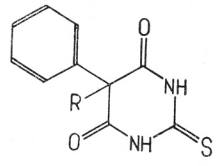
It has been shown that barbituric acid derivatives can be prepared in good yield by gradually adding[1,2] sodium methoxide as condensation catalyst[3,4] to a cyanoacetic or malonic ester reacting with urea or its derivatives. The principle of the gradual addition of sodium methoxide as condensing agent has now been extended to condensations of some substituted cyanoacetic and malonic esters with thiourea. Thus, some thiobarbituric acid derivatives were prepared in moderate yield. The 4-imino-intermediates obtained from the cyanoacetic esters were hydrolized with diluted acid to give the corresponding thiobarbiturates.

The derivatives prepared are listed below:



I

a, R=CH_3; X=NH
b, R=CH_3; X=O
c, R=C_2H_5; X=NH
d, R=C_2H_5; X=O



II

a, R=H
b, R=CH_3
c, R=C_2H_5

EXPERIMENTAL*

General procedure

The General procedure for the preparation of the thiobarbituric acid derivatives is essentially the same as reported earlier for the condensations with urea[4] with the difference that 1,5 mole of thiourea per mole ester was used.

5-(1-cyclohexenyl)-4-imino-5-methyl-2-thiobarbituric acid [I a]

Prepared from ethyl cyclohexenyl-methyl-cyanoacetate and thiourea as described in the General procedure. Yield: 63%. Pale yellow crystalline powder (70% ethanol), m. p. 235—237° with decomposition.

Anal. 1,383 mg subst.: 0,215 ml N_2 (20°, 754 mm)
$C_{11}H_{15}N_3OS$ (237,33) calc'd: N 17,71%
found: N 17,63%

Hydrolysis (eight hours) gave *5-(1-cyclohexenyl)-5-methyl-2-thiobarbituric acid* [I b], m. p. 171—173° (uncorr.). The earlier reported melting point was 172°.[5]

* The melting points were determined with a Kofler micro melting point apparatus unless otherwise indicated.

5-(1-cyclohexenyl)-5-ethyl-4-imino-2-thiobarbituric acid [I c]

Prepared from ethyl cyclohexenyl-ethyl-cyanoacetate and thiourea as described in the General procedure. Yield: 50,8%. Pale yellow crystalline powder (70% ethanol), m. p. 220—225° (uncorr.) with decomposition. The earlier reported melting was 215—220°.[6]

Hydrolysis (ten hours) gave *5-(1-cyclohexenyl)-5-ethyl-2-thiobarbituric acid* [I d], m. p. 182—186° (uncorr.). The earlier reported melting point was 186—188°.[6]

5-phenyl-2-thiobarbituric acid [II a]

Prepared from ethyl phenylmalonate and thiourea as described in the General procedure. Yield: 81,8%. White crystalline powder (80% ethanol), m. p. 254° (uncorr.).

Anal. 3,484 mg subst.: 0,37 ml N_2 (20°, 757 mm)
$C_{10}H_8N_2O_2S$ (220,24) calc'd: N 12,72%
found: N 12,37%

5-methyl-5-phenyl-2-thiobarbituric acid [II b]

Prepared from ethyl methyl-phenylmalonate and thiourea as described in the General procedure with the difference that after refluxing the mixture was cooled and gradually acidified with diluted hydrochloric acid. Yield: 64%. White crystalline powder (absolute ethanol), m. p. 212—213°.

Anal. 3,330 mg subst.: 0,36 ml N_2 (22°, 757 mm)
$C_{11}H_{10}N_2O_2S$ (225,27) calc'd: N 12,42%
found: N 12,20%

5-ethyl-5-phenyl-2-thiobarbituric acid [II c]

Prepared from ethyl ethyl-phenylmalonate and thiourea as described in the General procedure . Yield: 75.6%. (D. Waldi[7] reported an yield of 21%). Pale yellow crystalline powder (ethanol), m. p. 218—220° (uncorr.). The earlier reported melting points were 217°[6, 8], 218°[9] and 211—212°[7] respectively.

The microanalyses and Kofler-melting point determinations were carried out by N. Manger from our Microchemical laboratory.

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IZVOD

Bilješka o pripremi nekih tiobarbiturata

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Nađeno je, da se kondenzacija cijanoctenih i malonskih estera s ureom ili njenim derivatima može provesti u dobrom iskorišćenju, ako se natrium metoksid[3, 4], t. j. kondenzaciono sredstvo, dodaje reakcionoj smjesi postepeno.[1, 2] Sada je taj princip postepenog dodavanja natrium metoksida proširen na kondenzacije nekih cijanoctenih i malonskih estera s tioureom, pa je pripremljeno nekoliko odgovarajućih derivata tiobarbiturne kiseline. 4-Imino-intermedijeri, dobiveni kondenzacijom cijanoctenih estera, dali su hidrolizom u kiselom mediju odgovarajuće tiobarbiturate.

Određivanja tališta mikroskopskom metodom po Kofleru i mikroanalize izvršio je ing. N. Manger u našem mikroanalitičkom laboratoriju.

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