Synthesis of S-((Arylamino)formimidoyl)-2-thiobarbituric Acid Hydrochloride Antituberculous Agents

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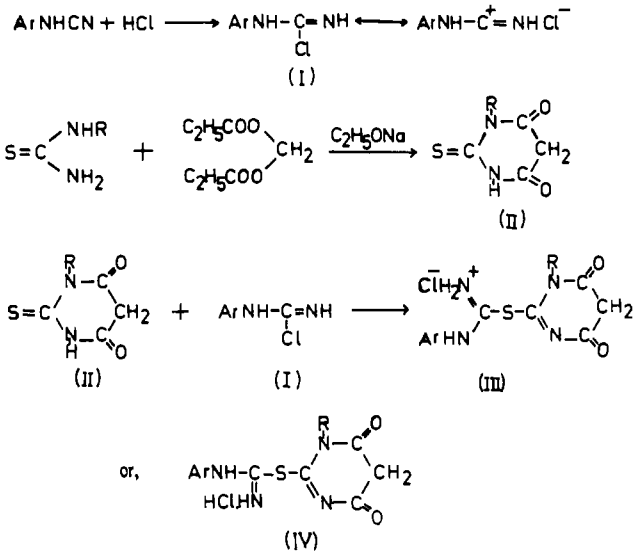
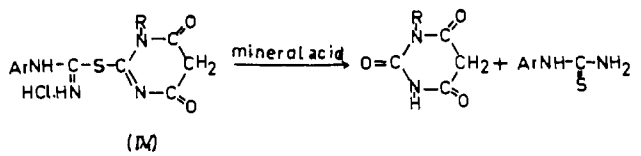
Various S-((arylamino)formimidoyl)-2-thiobarbituric acid hydrochlorides have been synthesized by the condensation of corresponding arylcyanamides with 2-thiobarbituric acid and 1-substituted-2-thiobarbituric acids. Precursors required in these syntheses were prepared by already known methods.

The present communication deals with the preparation of new S-((arylamino)formimidoyl)-2-thiobarbituric acid hydrochlorides and S-((arylamino)formimidoyl)1-substituted-2-thiobarbituric acid hydrochlorides. S-((Arylamino)formimidoyl)-2-thiobarbituric acids (IV) are all light yellow crystalline com-



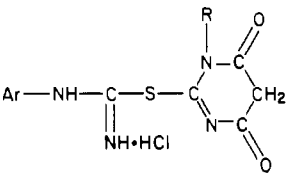
pounds and S-((arylamino)formimidoyl)-1-substituted-2-thiobarbituric acid hydrochlorides are white crystalline compounds and are soluble in hot water. These formimidoyl-2-thiobarbituric acid hydrochlorides (IV) could not be crystallized without decomposition and hence purification was achieved by repeated washings with acetone, petroleum ether.

The structures of the compounds have been confirmed on the basis of their elemental analysis, spectral data, and chemical behavior. The conversion of acetone-soluble reactant into acetone-insoluble product further confirmed the formation of hydrochloride salt. In addition to this, hydrolysis of the S-((arylamino)formimidoyl)-2-thiobarbituric acid hydrochloride by mineral acids yielding barbituric acid and arylthiourea also confirmed the structure of S-((arylamino)formimidoyl-2-thiobarbituric acid.



The above-mentioned compounds have been submitted for pharmacological screening and the results will be published elsewhere.

Table I.
S-((Arylamino)formimidoyl)-1-substituted-2-thiobarbituric Acid Hydrochlorides[a]



IV

Ar	R	mp, °C	yield, %
C_6H_5	H	150	80
o-$CH_3C_6H_4$	H	250	75
m-$CH_3C_6H_4$	H	220	78
p-$CH_3C_6H_4$	H	215	82
o-ClC_6H_4	H	230	74
m-ClC_6H_4	H	145	75
p-ClC_6H_4	H	210	78
o-$CH_3OC_6H_4$	H	225	76
p-$CH_3OC_6H_4$	H	140	72
C_6H_5	p-ClC_6H_4	155	78
m-$CH_3OC_6H_4$	p-ClC_6H_4	138	72
p-$CH_3OC_6H_4$	p-ClC_6H_4	152	80
m-ClC_6H_4	p-ClC_6H_4	157	78
p-ClC_6H_4	p-ClC_6H_4	145	75

[a] All these compounds gave elemental analyses (C, H, N, S) within ±0.30 of the calculated values.

Experimental Section

Melting points were determined by using the hot stage Kofler method and are uncorrected.

Arylcyanamides (I). Arylcyanamide hydrochlorides were prepared as reported in the literature (*1*).

2-Thiobarbituric Acids (II) (2-5). 2-Thiobarbituric acids were prepared by the reaction of diethyl malonate with the corresponding arylthioureas in sodium ethoxide.

S-((Phenylamino)formimidoyl)-2-thiobarbituric Acid Hydrochloride. 2-Thiobarbituric acid (1.44 g, 0.01 mol) was dissolved in acetone (15 mL) and the solution was cooled in an ice–salt mixture. To this cooled solution, phenylcyanamide hydrochloride (1.54 g, 0.01 mol) dissolved in acetone was added slowly with constant shaking. After the solution was kept in the ice–salt mixture for 1 h, crystalline pure S-((phenylamino)formimidoyl)-2-thiobarbituric acid hydrochloride was separated. It was filtered and washed with acetone and petroleum ether to remove the unreacted constituents: yield 80%, mp 150 °C (dec). The structure of the compound was confirmed by the spectral data: IR (Nujol) 3260 (NH), 1670 (C=O), 1630 (C=N), 760 (C=S) cm^{-1}; NMR (Me_2SO-d_6) δ 1.50 (s, 2 H, CH_2), 6.16 (bs, 1 H, NH), 7.03 (bs, 1 H, NH), 7.26–7.66 (m, 5 H, Ar–H), 7.80 (bs, 1 H, NH).

S-((Phenylamino)formimidoyl)-1-(*p*-tolyl)-2-thiobarbituric acid hydrochloride has been prepared and confirmed by the spectral data: IR (Nujol) 3480 (OH), 3270 (NH), 1670 (C=O), 1620 (C=N), 760 (C=S); NMR (Me_2SO-d_6) δ 2.12 (s, 3 H, tolyl CH_3), 2.20–2.66 (s, 1 H, CH), 6.66 (bs, 2 H, NH), 6.80–7.86 (m, 9 H, Ar–H), 8.40 (bs, 1 H, OH).

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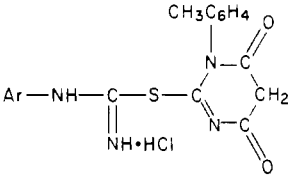
Table II.
***S*-((Arylamino)formimidoyl)-1-(*p*-tolyl)-2-thiobarbituric Acid Hydrochlorides**[a]



Ar	mp, °C	yield, %
C_6H_5	140	85
o-$CH_3C_6H_4$	157	82
p-$CH_3C_6H_4$	150	80
p-$CH_3OC_6H_4$	143	79
o-$CH_3OC_6H_4$	149	75
p-ClC_6H_4	143	81

[a] All these compounds gave elemental analyses (C, H, N, S) within ±0.30 of the calculated values.

Other *S*-((arylamino)formimidoyl)-2-thiobarbituric acid hydrochlorides and *S*-((arylamino)formimidoyl-1-(*p*-chlorophenyl)-2-thiobarbituric acid hydrochlorides synthesized by condensing 2-thiobarbituric acid and 1-(*p*-chlorophenyl)-2-thiobarbituric acid with different arylcyanamide hydrochlorides are summarized in Table I.

By a similar procedure several *S*-((arylamino)formimidoyl-1-(*p*-tolyl)-2-thiobarbituric acid hydrochlorides were synthesized and are given in Table II.

Acknowledgment

We are thankful to Prof. R. C. Aggrawal, Head of the Department of Chemistry, Banaras Hindu University, Varanasi, India, for providing the laboratory facilities.

Registry No. I (Ar = C_6H_5), 64119-04-6; I (Ar = o-$CH_3C_6H_4$), 64119-05-7; I (Ar = m-$CH_3C_6H_4$), 64119-06-8; I (Ar = p-$CH_3C_6H_4$), 64119-07-9; I (Ar = o-ClC_6H_4), 64119-11-5; I (Ar = m-ClC_6H_4), 64119-12-6; I (Ar = p-ClC_6H_4), 64119-13-7; I (Ar = o-$CH_3OC_6H_4$), 64119-08-0; I (Ar = p-$CH_3OC_6H_4$), 64119-09-1; II (R = H), 504-17-6; II (R = p-ClC_6H_4, 28921-30-4; II (R = $CH_3C_6H_4$), 28921-28-0; IV (Ar = C_6H_5, R = H), 93084-87-8; IV (Ar = o-$CH_3C_6H_4$, R = H), 93084-88-9; IV (Ar = m-$CH_3C_6H_4$, R = H), 93084-89-0; IV (Ar = p-$CH_3C_6H_4$, R = H), 93084-90-3; IV (Ar = o-ClC_6H_4, R = H), 93084-91-4; IV (Ar = m-ClC_6H_4, R = H), 93084-92-5; IV (Ar = p-ClC_6H_4, R = H), 93084-93-6; IV (Ar = o-$CH_3OC_6H_4$, R = H), 93084-94-7; IV (Ar = p-$CH_3OC_6H_4$, R = H), 93084-95-8; IV (Ar = C_6H_5, R = p-ClC_6H_4), 93110-21-5; IV (Ar = m-$CH_3OC_6H_4$, R = p-ClC_6H_4), 93084-96-9; IV (Ar = p-$CH_3OC_6H_4$, R = p-ClC_6H_4), 93084-97-0; IV (Ar = m-ClC_6H_4, R = ClC_6H_4), 93084-98-1; IV (Ar = p-ClC_6H_4, R = p-ClC_6H_4), 93084-99-2; IV (Ar = C_6H_5, R = p-$CH_3C_6H_4$), 93085-00-8; IV (Ar = o-$CH_3C_6H_4$, R = p-$CH_3C_6H_4$), 93085-01-9; IV (Ar = p-$CH_3C_6H_4$, R = p-$CH_3C_6H_4$), 93085-02-0; IV (Ar = p-$CH_3OC_6H_4$, R = p-$CH_3C_6H_4$), 93110-22-6; IV (Ar = o-$CH_3OC_6H_4$, R = p-$CH_3C_6H_4$), 93085-03-1; IV (Ar = p-ClC_6H_4, R = p-$CH_3C_6H_4$), 93110-23-7; acetone, 67-64-1.

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Synthesis of 20-Acetamido-3-aza-*A*-homo-4α-pregnen-4-one

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A synthetic approach for the preparation of 20-acetamido epimers of 3-aza-*A*-homo-4α-pregnen-4-one is described.

When cultures of human leukemia cells were treated with 3β-hydroxy-13α-amino-13,17-seco-5α-androstan-17-oic acid 13,17-lactam, an increased proliferating actvivity was exhibited (*1*). On the other hand, 3,17α-diaza-*A*,*D*-dihomoandrost-4α-ene-4,17-dione showed antitumor activity (*2*).

In view of the importance of such compounds we desired to effect the synthesis of steroidal lactams containing a second CONH group out of the steroid nucleus, namely, 20α-acetamido- and 20β-acetamido-3-aza-*A*-homo-4α-pregnen-4-one.

Experimental Section

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. The IR spectra were recorded with a Perkin-Elmer 521 in solid-phase potassium bromide. The NMR spectra were determined with a Varian Associates XL-100 instrument using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of Nuclear Research Center "Democritos", Analytical results obtained for those elements were within ±0.4% of the theoretical values.

20*α*-Acetamido-4-pregnen-3-one (IV). A 1.3-g sample of 3β-hydroxy-20α-aminopregnene (*3*) was dissolved in 10 mL of pyridine and 10 mL of acetic anhydride and left at room temperature overnight. After that time it was poured into ice water and the precipitate collected by filtration (1.48 g). The crude material was hydrolyzed selectively at $C_{(3)}$, 70 mL of 5% methanolic potassium hydroxide solution at room temperature being used with stirring for 30 min. The reaction mixture was diluted with water and the precipitate collected by filtration to yield 3β-hydroxy-20α-acetamido-5-pregnene, 1.28 g (homogeneous as judged by TLC).

A solution of 6.8 mmol of 3β-hydroxy-20α-acetamido-5-pregnene in 500 mL of dry toluene and 45 mL of cyclohexanone was distilled slowly until 50 mL of solvent was removed. An aluminum isopropoxide solution 2 g in 20 mL of dry

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