

SYNTHETIC AND CONFORMATIONAL STUDIES ON
5,6-SUBSTITUTED DIHYDRO-2-THIOURACILS

Antonio Lorente* and Luis María Aurrecoechea

Departamento de Química Orgánica, Universidad de Alcalá. 28871
Alcalá de Henares (Madrid), Spain

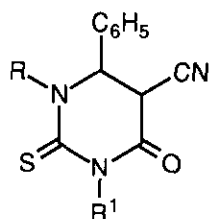
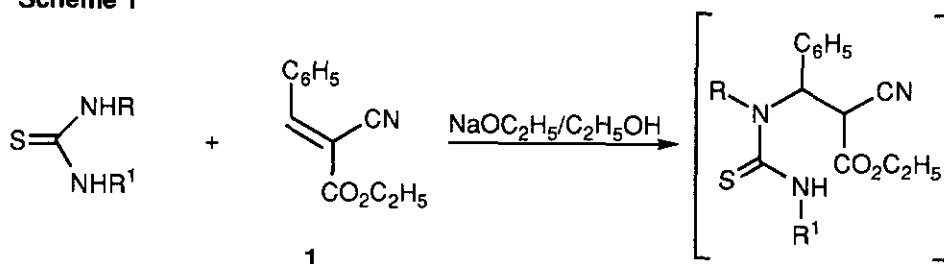
Abstract- Synthetic and conformational studies on dihydro-2-thiouracils obtained from thioureas and 2-cyano-3-phenylpropenamide or ethyl 2-cyano-3-phenylpropenoates are reported.

The utility of thioureas to the synthesis of heterocyclic compounds has been described in the literature.^{1,2} In preceding papers³⁻⁵ we reported a synthesis of different 2-thioxopyrimidines from thiourea and 2-cyano-3-phenylpropenenitriles (or ethyl 2-cyano-3-phenylpropenoates). In this paper we report a synthetic and conformational studies on 4-oxo-2-thioxohexahydropyrimidines (dihydro-2-thiouracils) from different thiourea derivatives.

SYNTHESIS OF 5-CYANO-4-OXO-2-THIOXOHEXAHYDROPYRIMIDINES (DIHYDRO-2-THIOURACILS)

The reactions of ethyl 2-cyano-3-phenylpropenoate (**1**) with methylated thioureas afford 5-cyano-4-oxo-6-phenyl-2-thioxohexahydropyrimidines (**2b,c**) according the process depicted in Scheme 1. In all cases cyclization of the intermediate Michael type adduct occurs regioselectively by attack of the nitrogen to the ethoxycarbonyl group.

Scheme 1

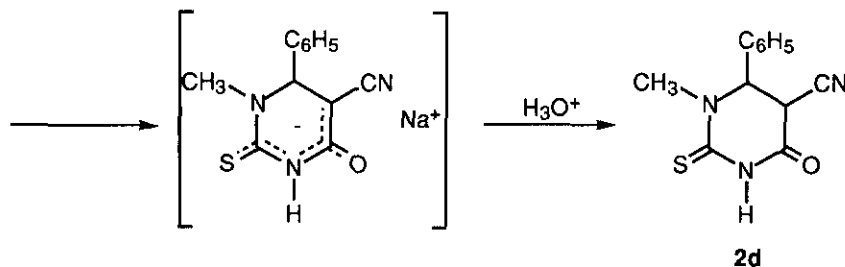
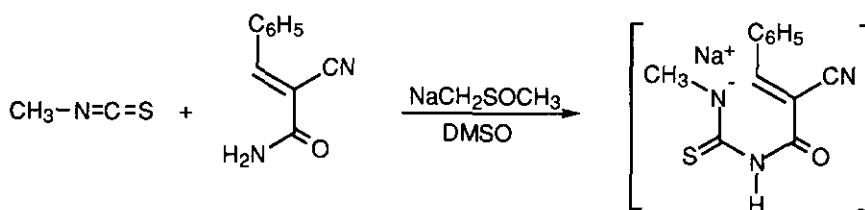


2b: $\text{R}=\text{H}$, $\text{R}^1=\text{CH}_3$

2c: $\text{R}=\text{R}^1=\text{CH}_3$

The synthesis of the 5-cyano-1-methyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (**2d**) was achieved from 2-cyano-3-phenylpropenamide and methyl isothiocyanate according to the following process.

Scheme 2



CONFORMATIONAL STUDY ON 4-OXO-2-THIOXOHEXAHYDOPYRIMIDINES

Biological interest of 2,4-dioxohexahydropyrimidines (dihydrouracils) has promoted the study of conformational preferences of these class of compounds. Ir⁶ and nmr⁷⁻¹¹ studies afford evidence for a distorted half-chair conformation of these compounds in which the NH-CO-NH-CO part of the molecule is approximately planar. The assumption of a half-chair conformation of the dihydrouracil ring has been confirmed by X-ray analysis of dihydrothimine.¹² The NH-CO-NH-CO portion of the ring is planar while the C-5 and C-6 atoms are 0.42 and 0.31 Å out of plane on opposite sides with a dihedral angle of ca. 30° between the bonds on the C-5 and C-6 atoms. The crystallographic study of the dihydro-2-thiouracil affords analogous results.¹³ The base exhibits a half-chair conformation with a dihedral angle C4-C5-C6-N1 of -36.9°.

In this paper we report the conformational study of 5,6-substituted 4-oxo-2-thioxohexahydropyrimidines (dihydro-2-thiouracils) (2) and (3) (Figure 1) from ¹H nmr data.

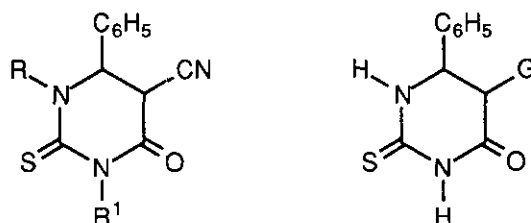


Figure 1

2a	R=R ¹ =H	3a	G =CO ₂ C ₂ H ₅
2b	R=H, R ¹ =CH ₃	3b	G =CONH ₂
2c	R=R ¹ =CH ₃	3c	G =C ₆ H ₅
2d	R=CH ₃ , R ¹ =H	3d	G =H

Chemical shift and coupling constant data are summarized in Table 1. Most spectra were sufficiently first order to allow direct determination of coupling constants from observed splittings. The aliphatic protons of 6-phenyldihydro-2-thiouracil (**3d**) appear as a four-spin ABMX system that was analysed by means of the LAOCOON III program.¹⁴ Assignments of resonances are unambiguous, H6 is coupled to H1 and appears at lower field than H5.

Table 1. Selected proton magnetic parameters and conformer distribution of dihydro-2-thiouracils (2) and (3)

Compound	Solvent	H-5	H-6	J ₅₆	J ₁₆	% <i>5e6a</i>
<i>cis-2a</i>	acetone	5.01	5.39	6.23	4.03	87 ^c
<i>cis-2b</i>	acetone	5.11	5.30	6.23	4.03 ^b	87 ^d
<i>cis-2c</i>	acetone	5.27	5.53	6.41	—	90 ^d
<i>cis-2d</i>	acetone	5.28	5.56	6.59	—	90 ^d
<i>cis-3a</i>	acetone	4.05	5.19	7.69	2.74	50 ^c
<i>cis-3b</i>	acetone	3.85	5.23	6.04	2.56	45 ^c
<i>cis-3c</i>	acetone	4.35	5.21	6.04	2.65	47 ^c
	DMSO	4.41	4.96	6.22	2.93	55 ^c
	TFA	4.24	5.07	5.80	—	27 ^d
						%<i>5e6e</i>
<i>trans-2a</i>	acetone	4.74	5.30	11.17	not observed	97 ^d
<i>trans-2b</i>	acetone	4.84	5.23	11.54	not observed	100 ^d
<i>trans-2c</i>	acetone	4.65	5.65	3.84	—	20 ^d
<i>trans-2d</i>	acetone	4.58	5.64	4.40	—	23 ^d
<i>trans-3c</i>	acetone	4.18	5.08	6.96	2.75	50 ^c
	DMSO	4.13	4.92	5.86	3.29	35 ^c
	TFA	4.35	5.31	11.9	—	100 ^d
3d^a	acetone	2.86; 3.05	5.01	6.26; 6.56	3.11	60 ^e
	DMSO	2.69; 3.02	4.80	4.71; 6.48	4.03	87 ^e

^a Calculated by means of LAOCOON III program. ^b Deduced from double resonance experiments.

^c Calculated from ³J₁₆. ^d Calculated from ³J₅₆. ^e % of *6a* conformer.

The resonance of H6 in *cis*- and *trans*-**2c,d** occurs at lower field than the same proton of *cis* and *trans*-**2a,b**. This deshielding ($\Delta\delta \cong 0.25$ ppm) can be explained by the interaction with the methyl on N1.

The calculation of the $^1\text{H}_5$ - $^1\text{H}_6$ vicinal coupling constants (Table 2) has been carried out by means of the empirical equation proposed by Haasnoot *et al.*¹⁵ This empirical equation relates the vicinal coupling constants between the protons of a H-C-C-H fragment with the values of the dihedral angles, the electronegativity of the substituents attached to the rotational system and their orientation with respect to the considered protons.

Conformational analysis of dihydro-2-thiouracils (**2**) and (**3**) was carried out from standard values of the coupling constants $^3\text{J}_{16e}$ (4.5 Hz), $^3\text{J}_{16a}$ (1 Hz), $^3\text{J}_{5e6e}$ (2 Hz) and $^3\text{J}_{5a6a}$ (11.5 Hz) used by Katritzky *et al.*¹¹ for semiquantitative conformational analysis of 5,6-substituted dihydrouracils.

Cis-Isomers

The dihydro-2-thiouracils (**2a**) and (**2b**) are nearly monokonformational with the phenyl and cyano groups in axial and equatorial, respectively, in agreement with the $^3\text{J}_{56}$ and $^3\text{J}_{16}$ values which fit with the ones calculated for a dihedral angle H5-C5-C6-H6 of ca. 40°. The dihydro-2-thiouracils (**2c**) and (**2d**) adopt the same conformation.

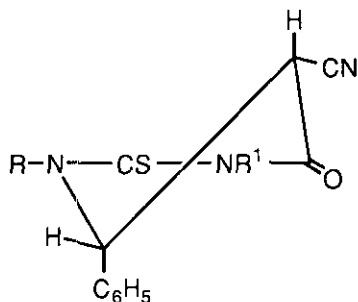


Figure 2. Preferred conformation for *cis*-**2a-d**

The $^3\text{J}_{16}$ value of dihydro-2-thiouracil (**3a**) assesses that both *ea* and *ae* forms are equally populated. The experimental value of $^3\text{J}_{56}$ is not in agreement with the one calculated for

standard values of the torsional angle H5-C5-C6-H6 but it is similar to the described for the 6-methoxycarbonyldihydrouracil.¹¹

Table 2. Experimental and calculated $^3J_{56}$ (Hz) of dihydro-2-thiouracils (2) and (3).

Compound	$J_i(40^\circ)^a$	$J_i(-40^\circ)^a$	%5e6a	Jcalcd ^b
<i>cis-2 a</i>	6.35	5.61	87	6.25
<i>cis-2 b</i>	6.35	5.61	87	6.25
<i>cis-2 c</i>	6.34	5.74	90	6.29
<i>cis-2 d</i>	6.34	5.74	90	6.29
<i>cis-3 a</i>	6.60	5.94	50	6.27
<i>cis-3 b</i>	6.53	5.86	45	6.16
<i>cis-3 c</i>	6.34	5.60	47	5.94
			55 (DMSO)	6.01
	$J_i(167^\circ)^a$	$J_i(62^\circ)^a$	%5e6e	Jcalcd ^b
<i>trans-2 a</i>	11.47	2.19	97	11.47
<i>trans-2 b</i>	11.47	2.19	100	11.47
<i>trans-2 c</i>	11.55	2.26	20	4.12
<i>trans-2 d</i>	11.55	2.26	23	4.39
<i>trans-3 c</i>	11.45	2.19	50	6.82
			35 (DMSO)	5.43

$$^a \quad ^3J_{HH} = 13.22 \cos^2\phi - 0.91 \cos\phi + \sum \Delta x_i [0.87 - 2.41 \cos^2(\xi_i\phi + 15.5|\Delta x_i|)]$$

^b Calculated from $J = \sum N_i J_i^\circ$. N_i is the molar fraction of each conformer.

In acetone the *ea* and *ae* forms of **3b** and **3c** are nearly equal populated according with the $^3J_{16}$ values. The calculated values of $^3J_{56}$ are in agreement with the experimental value for a dihedral angle of 40° . Changing the solvent from acetone to dimethyl sulphoxide shifts the equilibrium of **3c** in favour of the *5e6a* conformer. On the contrary in TFA as solvent the *5a6e* conformer is predominant.

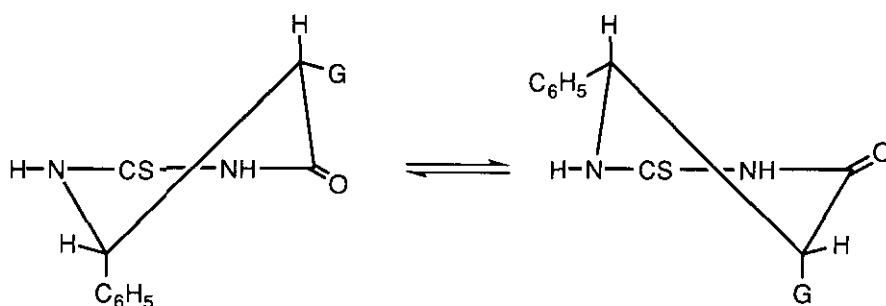


Figure 3. Conformational equilibrium for *cis-3a-c*

Trans-Isomers

From $^3J_{56}$ and $^3J_{16}$ values we can assess that compounds (**2a**) and (**2b**) are nearly monokonformational with the phenyl and cyano groups in equatorial.

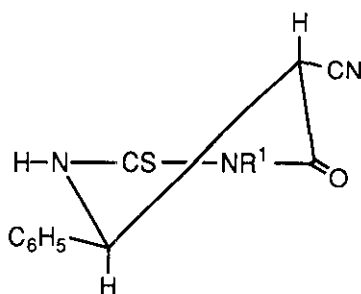


Figure 4. Predominant conformer for *trans-2a,b*

Experimental values of $^3J_{56}$ for **2a** and **2b** are in agreement with the ones calculated for a dihedral angle of 167°

Dihydro-2-thiouracils (**2c**) and (**2d**) exist in two conformers with a predominance of the form *5a6a*. This preference can be explained by the interaction between equatorial phenyl and methyl on N1.

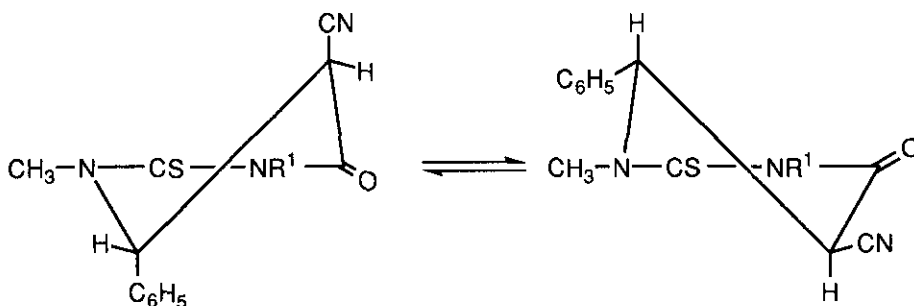


Figure 5. Conformational equilibrium for *trans*-**2c,d**

In acetone the *aa* and *ee* forms of **3c** are either equally populated. This equilibrium is shifted in dimethyl sulphoxide with a predominance of the *aa* conformer. The $^3J_{56}$ value in trifluoroacetic acid shows that in this solvent **3c** is mono-conformational with the phenyl groups in equatorial. This result is analogous to that described in the literature¹¹ for the 5,6-diphenyldihydrouracil.

In acetone the 6-phenyl-2-thiodihydrouracil (**3d**) exists in two conformers with a predominance of the form with phenyl in axial that increases in DMSO as solvent.

EXPERIMENTAL

All melting points were determined with a Büchi SMP-20 and are uncorrected. Ir spectra were recorded on a Perkin Elmer 883 spectrophotometer. Nmr spectra were measured on a Varian UNITY 300 spectrometer at 303 °K. The recording conditions were: 2% w/v solutions, acquisition time 3 s, spectral width 4000 Hz and pulse width 7 μ s. Mass spectra were obtained with a Hewlett Packard HP-5988 at 70eV. Microanalyses were performed in a Perkin Elmer 240. Flash column chromatographies were carried out on silica gel SDS 230-400 mesh. Dihydro-2-thiouracils [**2a** (*cis:trans* ca. 30:70), **3a**, **3b**, **3c** (*cis:trans* ca. 15:85) and **3d**] were obtained according to reported procedures.^{3,4} Diastereomeric ratio (*cis:trans*) of the dihydro-2-thiouracils (**2**) and (**3**) were determined by ^1H nmr.

5-Cyano-3-methyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (2b): To a solution of sodium (230 mg, 10 mmol) in absolute ethanol (30 ml), *N*-methylthiourea (900 mg, 10 mmol) and

ethyl 2-cyano-3-phenylpropenoate (**1**) (2.01 g, 10 mmol) were added. The reaction mixture was stirred at 0 °C for 48 h and then concentrated up to dryness. The residue thus obtained was dissolved in water and acidified with 5% acetic acid affording a precipitate which was collected and recrystallized from ethanol yielding 1.25 g (51%) of **2b** (*cis:trans* ca. 30:70); mp 244-246 °C; ir (KBr) ν 3304 (NH), 2260 (C \equiv N), 1722 (C=O) 1686, 1520, 1456 cm^{-1} ; ^1H nmr (acetone- d_6): δ 3.53 (s, 9/10H, CH $_3$), 3.56 (s, 21/10H, CH $_3$), 4.84 (d, 7/10H, H-5, J=11.54 Hz), 5.11 (d, 3/10H, H-5, J=6.23 Hz), 5.23 (d, 7/10H, H-6, J= 11.54 Hz), 5.30 (dd, 3/10H, H-6, J=4.03 and 6.23 Hz), 7.34-7.58 (m, 5H, arom), 9.27 (br s, 3/10H, N-H), 9.60 (br s, 7/10H, N-H); ms *m/z* 246(M $^{+1}$, 14%), 245(M $^{+}$, 87), 148(100), 130(25), 129(76), 128(22), 116(12), 114(14), 106(23), 105(34), 104(86), 103(20), 102(29), 91(27), 89(16), 79(10), 78(28), 77(61). *Anal.* Calcd for C $_{12}$ H $_{11}$ N $_3$ OS: C, 58.75; H, 4.52; N, 17.13. Found: C, 58.51; H, 4.47; N, 16.86.

5-Cyano-1,3-dimethyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (2c): To a solution of sodium ethoxide in absolute ethanol (40 ml) obtained from sodium (230 mg, 10 mmol), *N,N'*-dimethylthiourea (1.04 g, 10 mmol) and ethyl 2-cyano-3-phenylpropenoate (**1**) (2.01 g, 10 mmol) were added. The mixture was stirred at room temperature for 48 h and then the solvent was removed *in vacuo*. The resulting residue was dissolved in 50% aqueous ethanol (60 ml) and acidified with 5% acetic acid. The precipitate formed was collected and washed with water affording 1.27 g (49%) of **2c** (*cis:trans* ca. 70:30) which was recrystallized from ethanol; mp 143-144 °C; ir (KBr) ν 2257 (C \equiv N), 1707 (C=O) cm^{-1} ; ^1H nmr (acetone- d_6): δ 3.47 (s, 21/10H, CH $_3$), 3.51 (s, 9/10H, CH $_3$), 3.56 (s, 9/10H, CH $_3$), 3.57 (s, 21/10H, CH $_3$), 4.65 (d, 3/10H, H-5, J=3.84 Hz), 5.27 (d, 7/10H, H-5, J=6.41 Hz), 5.53 (d, 7/10H, H-6, J=6.41 Hz), 5.65 (d, 3/10H, H-6, J=3.84 Hz), 7.23-7.31 (m, 2H aromatic, o), 7.42-7.48 (m, 3H aromatic, m,p); ms *m/z*: 260(M $^{+1}$, 17%), 259(M $^{+}$, 100), 258(15), 244(25), 168(19), 130(25), 129(28), 128(10), 118(43), 104(11), 103(11), 102(19), 91(23), 77(16). *Anal.* Calcd for C $_{13}$ H $_{13}$ N $_3$ OS: C, 60.21; H, 5.05; N, 16.20. Found: C, 60.50; H, 5.37; N, 16.49.

5-Cyano-1-methyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (2d): To a suspension of dimethylsodium in dimethyl sulphoxide prepared from sodium hydride (15 mmol, 80% in mineral oil) and dimethyl sulphoxide (50 ml), 2-cyano-3-phenylpropenamide (1.78 g, 10.34 mmol) and methyl isothiocyanate (1.09 g, 15 mmol) were added. The reaction mixture was stirred at room

temperature for 3 days, poured into water (500 ml) and acidified with 10% hydrochloric acid. The precipitate thus obtained was collected and the mother liquid were extracted with dichloromethane. The combined extracts were washed with water, dried with magnesium sulfate and concentrated *in vacuo* affording an additional amount of product. The combined solids were purified by flash column (diameter 3 cm) chromatography using hexane-ethyl acetate (3/2, v/v) as eluent yielding 1.53 g (61%) of **2d** (*cis:trans ca. 70:30*) which was recrystallized from hexane-ethyl acetate; mp 209-210 °C; ir (KBr) ν 3217 (NH), 2248 (C=N), 1708 (C=O), 1533, 1454 cm^{-1} ; ^1H nmr (acetone- d_6): δ 3.42 (s, 9/10H, CH_3), 3.47 (s, 21/10H, CH_3), 4.58 (d, 3/10H, H-5, $J=4.40$ Hz), 5.28 (d, 7/10H, H-5, $J=6.59$ Hz), 5.56 (d, 7/10H, H-6, $J=6.59$ Hz), 5.64 (d, 3/10H, H-6, $J=4.40$ Hz), 7.33-7.54 (m, 5H, arom), 10.66 (br s, 7/10H, N-H), 10.78 (br s, 3/10H, N-H); ms m/z 246(M^++1 , 16%), 245(M^+ , 100), 244(18), 230(6), 156(9), 130(39), 129(62), 128(22), 120(19), 118(24), 116(11), 103(13), 102(18), 91(19), 86(9), 77(18). *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{OS}$: C, 58.75; H, 4.52; N, 17.13. Found: C, 58.61; H, 4.40; N, 17.35.

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