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

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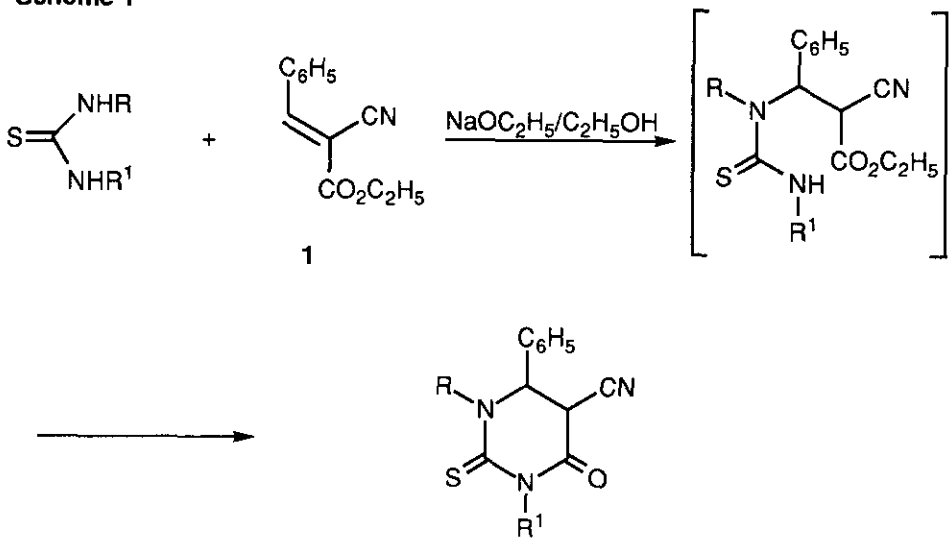
Abstract- Synthetic and conformational studies on dihydro-2-thiouracils obtained from thioureas and 2-cyano-3-phenylpropenamide or ethyl 2-cyano-3-phenylpropenoates are reported.

The utility of thioureas to the synthesis of heterocyclic compounds has been described in the literature.[1,2] In preceeding papers[3-5] 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.

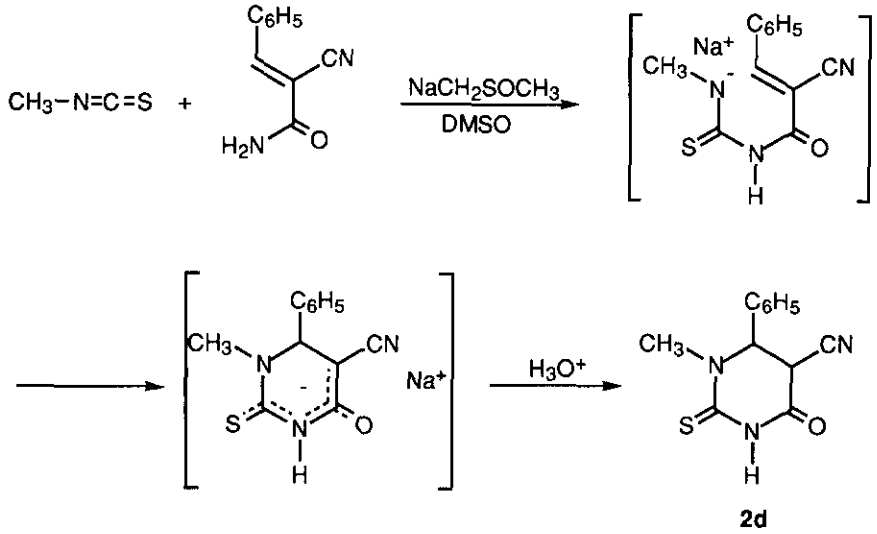
Scheme 1



2b: R =H, R^1=CH_3
2c: R =R^1=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 the following process.

Scheme 2



2d

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. Ir[6] and nmr[7-11] studies afford evidence for a distorted half-chair conformation of these compounds in which the NH-CO-NH-CO part of the molecule is aproximately 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 ^{1}H nmr data.

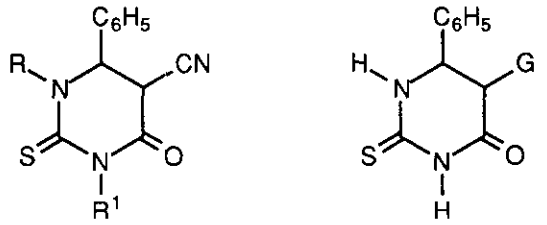


Figure 1

2a R=R^1=H
2b R=H, R^1=CH_3
2c R=R^1=CH_3
2d R=CH_3, R^1=H

3a G =$CO_2C_2H_5$
3b G =$CONH_2$
3c G =C_6H_5
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 (**3 d**) appear as a four-spin ABMX system that was analysed by means of the LAOCOON III program.[14] Assignments of resonances are unambigous, 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}	%*5e6a*
cis-**2a**	acetone	5.01	5.39	6.23	4.03	87[c]
cis-**2b**	acetone	5.11	5.30	6.23	4.03[b]	87[d]
cis-**2c**	acetone	5.27	5.53	6.41	——	90[d]
cis-**2d**	acetone	5.28	5.56	6.59	——	90[d]
cis-**3a**	acetone	4.05	5.19	7.69	2.74	50[c]
cis-**3b**	acetone	3.85	5.23	6.04	2.56	45[c]
cis-**3c**	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]
						%*5e6e*
trans-**2a**	acetone	4.74	5.30	11.17	not observed	97[d]
trans-**2b**	acetone	4.84	5.23	11.54	not observed	100[d]
trans-**2c**	acetone	4.65	5.65	3.84	——	20[d]
trans-**2d**	acetone	4.58	5.64	4.40	——	23[d]
trans-**3c**	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 $^3J_{16}$. [d] Calculated from $^3J_{56}$. [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}H5-^{1}H6 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 $^{3}J_{16e}$ (4.5 Hz), $^{3}J_{16a}$ (1 Hz), $^{3}J_{5e6e}$ (2 Hz) and $^{3}J_{5a6a}$ (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 monoconformational with the phenyl and* cyano groups in axial and equatorial, respectively, in agreement with the $^{3}J_{56}$ and $^{3}J_{16}$ 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.

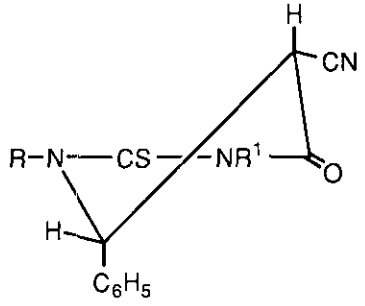


Figure 2. Preferred conformation for *cis*-**2a-d**

The $^{3}J_{16}$ value of dihydro-2-thiouracil (**3a**) assesses that both *ea* and *ae* forms are equally populated. The experimental value of $^{3}J_{56}$ 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	$J_i(40°)$[a]	$J_i(-40°)$[a]	%*5e6a*	Jcalcd[b]
cis-**2a**	6.35	5.61	87	6.25
cis-**2b**	6.35	5.61	87	6.25
cis-**2c**	6.34	5.74	90	6.29
cis-**2d**	6.34	5.74	90	6.29
cis-**3a**	6.60	5.94	50	6.27
cis-**3b**	6.53	5.86	45	6.16
cis-**3c**	6.34	5.60	47	5.94
			55 (DMSO)	6.01
	$J_i(167°)$[a]	$J_i(62°)$[a]	%*5e6e*	Jcalcd[b]
trans-**2a**	11.47	2.19	97	11.47
trans-**2b**	11.47	2.19	100	11.47
trans-**2c**	11.55	2.26	20	4.12
trans-**2d**	11.55	2.26	23	4.39
trans-**3c**	11.45	2.19	50	6.82
			35 (DMSO)	5.43

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

[b] Calculated from $J = \Sigma N_i J_i°$. 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.

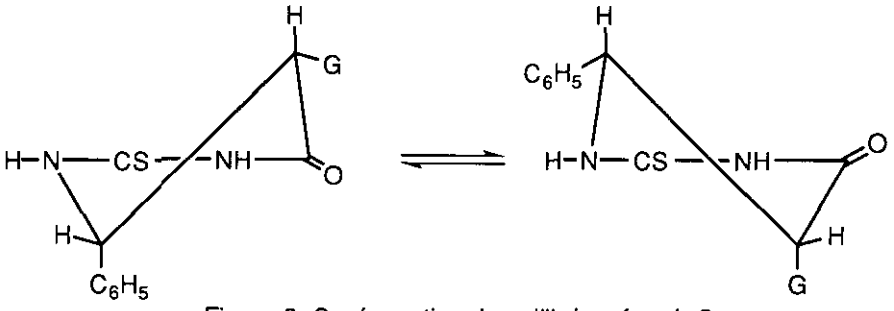


Figure 3. Conformational equilibrium for *cis*-**3a-c**

Trans-Isomers

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

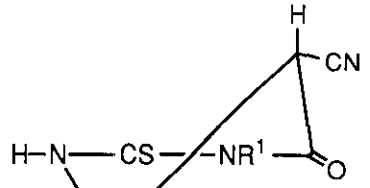


Figure 4. Predominant conformer for *trans*-**2a,b**

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.

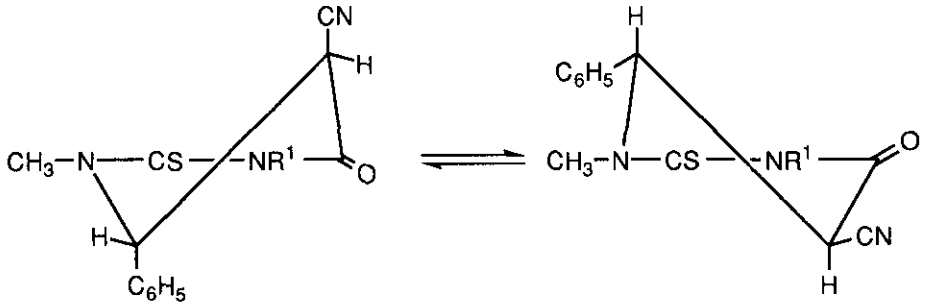


Figure 5. Conformational equilibrium for *trans*-**2c**,**d**

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 $^{3}J_{56}$ value in trifluoracetic 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 literature[11] 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 μs. 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 ^{1}H 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) υ 3304 (NH), 2260 (C≡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 $C_{12}H_{11}N_3OS$: 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) υ 2257 (C≡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 $C_{13}H_{13}N_3OS$: 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 dimsylsodium 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) υ 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 $C_{12}H_{11}N_3OS$: C, 58.75; H, 4.52; N, 17.13. Found: C, 58.61; H, 4.40; N, 17.35.

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