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RING-CHAIN TAUTOMERISM OF 6-HYDROXY-6-ALKYL-5,6-DIHYDROPYRIMIDO[4,5-b][1,4]-THIAZINES

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Abstract—IR, NMR and UV spectroscopy of 4-chloro-5-amino (methylamino) 6-acylmethylmercaptopyrimidine and of 4-chloro-6-oxy-6-aryl (alkyl) dihydropyrimido [4,5-*b*] [1,4] thiazines has shown that the conversion of 4-chloro-5-methylamino-6-acylmethylmercaptopyrimidine into 4-chloro-5-methyl-6-oxy-6-alkyl-dihydropyrimido [4.5-*b*] [1,4] thiazine (IV–VI) is reversible ring-chain tautomerism. The regularity of this tautomerism has been studied and it has been shown that steric factors play an important role. The steric factors affect the spectral characteristics of these compounds.

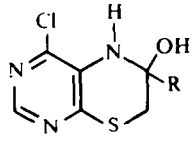
THERE ARE only a few reports in the literature of success in detecting both forms of ring-chain tautomerism [the cyclic carbinolamine. (B) and the open aminocarbonyl form (A)] and observing their mutual transformation.[1]

It has now been found that 6-hydroxy-5.6-dihydropyrimido (4.5-b) (1.4) thiazines can adopt both in forms B and A.

If there is an aryl group at C-6 in carbinolamines. an isomeric open form A can be obtained along with the cyclic form B.[2] In this case form A in neutral solutions is rather stable and can be transformed into B only under the action of catalytic amounts alkali.[3]

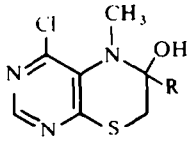
Further it has been noted that carbinolamines having alkyl groups at C-6 are able to form the tautomeric system A⇄B. The position of the tautomeric equilibrium is determined by steric factors and by the nature of the substituent at C-6. Thus it has been found that carbinolamines (I-VI) display dual reaction ability: they can form derivatives of both cyclic (compound VII) and open forms (compounds VIII-X).

However dual reactivity (the formation of derivatives of two different structural formulas) extends beyond tautomerism.[4] Therefore spectral methods have been used to detect the presence of the ring-chain tautomerism A⇄B in the series of compounds I–VI.



B(I-III)

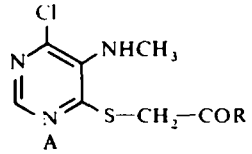
I. IV: R=CH_3;



B

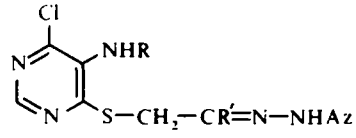
II. V: R=CH_2Cl;

(IV-VI)



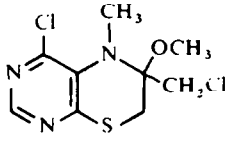
A

III. VI: R=$CH_2COOC_2H_5$



VIII-X

VIII: R=H. R'=CH_3; IX: R=R'=CH_3; X: R=CH_3, R'=CH_2Cl



VII

IR measurements have shown that compounds I–III exist as the cyclic carbinolamines both in the solid state and in solution. The IR spectra of these compounds show only NH absorption bands (3340–3390 cm^{-1}) and OH (3580–3590 cm^{-1}). The situation is quite different with carbinolamines IV–VI having a Me-group in the 5-position. IR spectra of IV–VI in solution show CO bands at 1722–1793 cm^{-1}, NH bands at 3400 cm^{-1} for open chain form A and OH absorption at 3520–3590 cm^{-1} for cyclic form B (Fig. 1). The intensities of the carbonyl absorption changes depending upon the solvent and the nature of the substituent in the 6-position of the thiazine ring. The highest intensity of these bands can be observed in CCl_4 and $CHCl_3$. It decreases in dioxan. CO bands being practically absent in pyridine (Fig. 1).

The tautomerism of IV–VI and its absence in I–III are supported by NMR data (Fig. 2). Thus, in the NMR spectra of I–III there are proton signals of only cyclic form B in both deuteropyridine and $CDCl_3$ (Table I) NMR spectra of IV–VI in

TABLE 1. CHEMICAL SHIFTS IN NMR SPECTRA OF COMPOUNDS I-III

N	Groups	Chemical shifts in p.p.m. (δ); coupling constants in Hz (J)	
		in $CDCl_3$. B form	in C_5D_5N. B form
I	6—Me	1·71 (s*)	1·71 (s)
	7—S—CH_2	$\nu_A = 3{\cdot}21$; $\nu_B = 3{\cdot}05$; $J = 14{\cdot}0$ (q*)	3·17 (s)
II	6—CH_2Cl	$\nu_A = 3{\cdot}90$; $\nu_B = 3{\cdot}78$; $J = 11{\cdot}0$ (q)	$\nu_A = 4{\cdot}32$; $\nu_B = 4{\cdot}21$; $J = 11{\cdot}0$ (q)
	7—S—CH_2	$\nu_A = 3{\cdot}28$; $\nu_B = 3{\cdot}11$; $J = 12{\cdot}0$ (q)	$\nu_A = 3{\cdot}67$; $\nu_B = 3{\cdot}49$; $J = 13{\cdot}0$ (q)
III	CH_3 } $CO_2C_2H_5$	1·3(t*)	1·02(t)
	CH_2 } $CO_2C_2H_5$	4·26(9)	4·15(9)
	6—CH_2—CO_2R	$\nu_A = 3{\cdot}0$; $\nu_B = 2{\cdot}89$; $J = 15{\cdot}0$ (q)	3·04 (s)
	7—S—CH_2	$\nu_A = 3{\cdot}25$; $\nu_B = 3{\cdot}12$; $J = 14{\cdot}0$ (q)	4·05 (s)

* s = singlet; q = quartet; t = triplet.

$CDCl_3$ showed separate signals for all the various groups of protons in the two tautomers (A and B). In deuteropyridine solutions only signals of cyclic forms of IV–VI can be detected (Fig. 2 Table 2).

A $\rightleftarrows$ B conversion for IV–VI is reversible. Thus, the percentage of cyclic form B increased when deuteriopyrine was added to the solutions of IV–VI in $CDCl_3$. On the contrary the content of form B decreased when the pyridine solutions of these compounds were diluted with $CDCl_3$. NMR spectra obtained in both cases finally prove the same. From NMR evidence it is concluded further that the tautomeric equilibrium A $\rightleftarrows$ B in $CDCl_3$ for 6-CH_3 derivative (IV) is shifted to open form A and for 6-chloromethyl—and 6-carbethoxymethyl-6-hydroxypyrimido-thiazines (V and VI)—to the cyclic form B.

Thus, the ring-chain tautomerism A $\rightleftarrows$ B was detected only for carbinolamines IV–VI having the Me group at N-5. The difference in the properties of compounds I–III and IV–VI is understandable if one considers steric molecular models and calculates inter-atomic distances in I–III and in the corresponding 5-Me derivatives IV–VI. The dihydrothiazine ring can exist in two half-chair conformations. The substituent at N-5 in one conformation is in an axial position whereas the other one is equatorial. It is known that nitrogen linked with the aromatic ring is not in a pure sp^3 hybridization but is approaching sp^2 hybridization owing to which the pyramidal bonds

TABLE 2. CHEMICAL SHIFTS IN NMR SPECTRA OF COMPOUNDS IV-VI

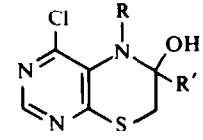
N N Groups		Chemical shifts in p.p.m. (δ); coupling constants in Hz(J)		
		$CDCl_3$		C_5D_5N
		A form	B form	B form
	6—Me	2·30	1·51	1·52
IV	N-- Me	2·96	2·77	2·64
	S—CH_2	3·97 (s)	3·21 (s)	3·23 (s)
	6—CH_2Cl	4·32 (s)	3·74 (s)	3·83 (s)
V	N—Me	2·98	2·90	2·73
	S—CH_2	4·09 (s)	3·16 (s)	3·39 (s)
	CH_3	1·32 (t)	1·27 (t)	1·0 (t)
VI	$CO_2C_2H_5$	4·24(9)	4·24(9)	4·12(9)
	CH_2			
	N—Me	3·02	2·78	2·70
	CH_2CO_2R	3·72	$\nu_A = 2·93$; $\nu_B = 2·77$ $J = 15·0$ (q)	2·90
	S—CH_2	4·14 (s)	$\nu_A = 3·48$; $\nu_B = 3·2$; $J = 13·0$ (q)	3·64

TABLE 3. CHEMICAL SHIFTS IN NMR SPECTRA OF COMPOUNDS VII

Groups	Chemical shifts in ppm (δ); coupling constants in Hz(J)		
	$CDCl_3$ t = − 53°	$CDCl_3$ t = + 20°	C_5D_5N t = + 20°
NMe	2·63	2·65	2·51
OMe	3·24	3·27	3·12
SCH_2	$\nu_A = 3·43$; $\nu_B = 3·33$ $J = 12·0$ (q)	3·27	3·39 (s)
CH_2Cl	$\nu_A = 3·95$; $\nu_B = 3·71$ $J = 12·0$ (q)	$\nu_A = 3·79$; $\nu_B = 3·67$ $J = 13·0$ (q)	$\nu_A = 4·02$; $\nu_B = 3·93$ $J = 12·0$ (q)

arrangement at N-5 becomes more planar. In this case the equatorially oriented substituent is disposed almost in the plane of the pyrimidine ring and the lone pair electrons of the nitrogen atom in the 5-position come into maximum conjugation with the π-electronic system of the pyrimidine ring. When a hydrogen atom is at N-5 (I–III) there are no steric hindrances to such an arrangement or they are very small since the distance between Cl atom at C-4 and the hydrogen atom at N-5 is sufficiently large. (2·8 Å with the Van der Waals radii amounting to 3·0 Å). The situation changes when the Me group is the substituent at N-5. In this case the distance between the Cl at C-4 and the hydrogen atom of the Me group amounts only to 1·6 Å resulting in a significant steric repulsion of these groups. Consequently a different conformation in which the Me group occupies an axial position becomes more advantageous. In this conformation the nitrogen atom approaches sp^3 hybridization and conjugation of its undivided pair with the π-electrons of the pyrimidine ring is practically absent.

The examined steric hindrances in the carbinolamines IV–VI appear to decrease

TABLE 4.  I–VI

NN	R	R'	Bruttoformula	Yield in %	m.p.	Calculated					Found %				
						C	H	Cl	N	S	C	H	Cl	N	S
I	H	Me	$C_7H_8ClN_3OS$	76	101–3	38·62	3·70	16·29	19·3	14·73	38·78	3·99	16·02	19·28	15·04
II	H	CH_2Cl	$C_7H_7Cl_2N_3OS$	93	89–91	33·34	2·8	28·12	16·67	12·72	33·1	2·85	28·37	16·34	12·4
III	H	CH_2CO_2Et	$C_{10}H_{12}ClN_3O_3S$	83	107–9	41·45	4·17	12·24	14·5	11·07	41·41	4·17	12·36	14·51	11·2
IV	Me	Me	$C_8H_{10}ClN_3OS$	67	73–75	41·46	4·35	15·30	18·14	13·84	41·43	4·47	15·60	17·84	13·62
V	Me	CH_2Cl	$C_8H_9Cl_2N_3OS$	87	94–96	36·1	3·4	26·64	15·8	12·05	36·1	3·7	26·9	16·02	12·3
VI	Me	CH_2CO_2Et	$C_{11}H_{14}ClN_3O_3S$	91	94–96	43·5	4·64	11·67	13·83	10·56	43·74	4·73	11·94	14·08	10·3

Compounds I.III.VI.V recrystallized from MeOH. II—from $CHCl_3$ VI–EtOH.

the stability of the thiazine ring and to make its transition into tautomeric form A much easier. This steric factor essentially influences the spectral characteristics of substances IV–VI in particular, the UV. As can be seen from Fig. 3, the absorption intensity of the band at about 320 coupled with the altered absorption in the other regions and sharp decreases in the UV spectra of IV–VI and VII (with a fixed cyclic form B) is a contrast to I–III having no Me group at N–5.

When the NMR spectra of 6-hydroxy-6-alkyl-dihydropyrimidothiazines are considered attention is drawn to the fact that a singlet and not a quadruplet is observed for a $S-CH_2$ group for compounds IV–VI in deuteriopyridine solution. This does not connect with tautomerism of IV–VI because NMR spectral data do not support the occurrence of rapid tautomeric conversion A $\rightleftarrows$ B. Thus in spectra IV–VI in $CDCl_3$ separate signals of forms A and B are shown. In this case not only sufficiently distant signals are separately seen but even those very near by their chemical shifts. It will be noted that the singlet signal for the SCH_2 group is observed in deuteriopyridine for I and III where no tautomerism occurs, as shown by IR and NMR. Moreover, such a phenomenon takes place for VII (which is incapable of existing in the open chain form), in deuterioacetone and deuteriopyridin solutions (Fig. 4, Table 3). The appearance of singlets for such protons in IV–VI is probably due to fortuitous chemical shift equivalence.

EXPERIMENTAL

NMR spectra were recorded with a Jeol JNM-4H-100. (TMS). The UV spectra were measured with a EPS-3 spectrophotometer. The IR spectra were obtained with a UR–IO for suspensions in vaseline oil or for $CHCl_3$, CCl_4 and dioxane solutions.

4-*Chloro*-5,6-*dimethyl*-6-*hydroxy*-6,7-*dihydropyrimido*[4·5-b] (1.4) *thiazine* (IV). To a solution of 4-chloro-5-methylamino-6-mercaptopyrimidine (5·7 mmol) in 20 ml MeOH containing 0·4 g KOH at $-5°$ was added 0·65 g (7 mmol) of chloroacetone, stirred $-2°$ for 20 hr. the solvent was distilled and the residue treated with water. Yield of IV, 1·0 g (67%). m.p. 73–75° (MeOH). Compounds I–III, V, VI were obtained similarly (Table 4).

4-*Chloro*-5-*methyl*-6-*methoxy*-6-*chloromethyl*-6,7-*dihydropyrimido*[4.5-b] (1.4) *thiazine* (VII). To a solution of 0·9 g V in 140 ml ether was added ethereal CH_2N_2 (obtained from 10 g of nitrosomethylurea) and the mixture allowed to stand at 20° for 72 hr. filtered, the solvent distilled and the residue recrystallized from MeOH. Yield of VII 0·9 g (95%). m.p. 98–100° (Found: C, 38·90; H, 4·09; Cl, 25·57; N, 15·11; S, 11·44. $C_9H_{11}Cl_2N_3OS$ requires C, 38·58; H, 3·96; Cl, 25·31; N, 15·0; S, 11·45%).

2,4-*Dinitrophenylhydrazones* (VII–X). To a solution of 0·4 g V in MeOH was added 0·3 g dinitrophenylhydrazine in MeOH containing several drops of conc. HCl. The precipitate was filtered, yield of VIII 0·55 g (74%). m.p. 134–136 (EtOH). (Found: C, 37·7; H, 2·92; N, 22·30; $C_{14}H_{13}Cl_2N_7O_4S$ requires C, 37·67; H, 2·93; N, 21·97%). IX was obtained similarly, yield 54%, m.p. 195–196 (DMFA). (Found: C, 39·40; H, 3·0; N, 24·8. $C_{13}H_{12}ClN_7O_4S$ requires C, 39·25; H, 3·04; N, 24·65%), and X, yield 56%, m.p. 140–142 (EtOH). (Found: C, 40·91; H, 3·41; N, 24·07; $C_{14}H_{14}ClN_7O_4S$ requires C, 40·83; H, 3·42; N, 23·8%).

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