Notes

Ring–Chain Isomerism of Tetrahydropyrimido[4,5-*d*]pyrimidines[1a]

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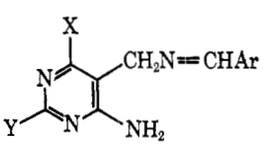
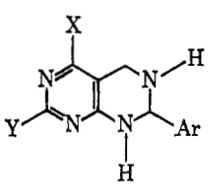
Recent work by McDonagh and Smith[2,3] and Dorman[4] has demonstrated the existence of ring–chain tautomerism involving hydroxyl and imine functions. This paper describes a new type of ring–chain isomerism involving the amine and imine functions of tetrahydropyrimido[4,5-*d*]pyrimidines.

In 1955, Suter and Habicht[5] reported that the reaction of 4-amino-5-(aminomethyl)-2,6-disubstituted pyrimidine with aromatic aldehydes gave two isomers, the Schiff base A or the tetrahydropyrimido[4,5-*d*]pyrimidine B. But they were unable to differentiate between these two isomers. On reinvestigating the re-

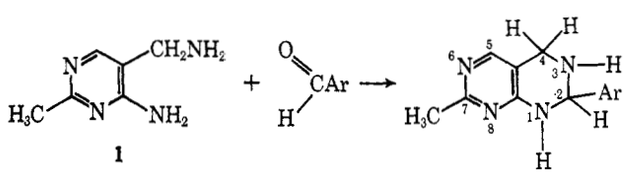


A



B, X = H, NH_2, OH, etc.
Y = CH_3, NH_2, OH, etc.

action of 4-amino-5-(aminomethyl)-2-methylpyrimidine (**1**) with a number of substituted aromatic aldehydes by nmr and ir spectroscopy, we have obtained strong evidence for the existence of a ring–chain isomerism between the two forms A and B. Thus, the reaction of *p*-methoxy, *p*-nitro, 2,4-dichloro- and 3,4-dichlorobenzaldehydes with **1** afforded only the corresponding ring isomers, tetrahydropyrimido(4,5-*d*)pyrimidines **2–5** as outlined below. Their tlc indicated only one spot.

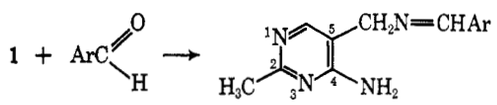


1

2, Ar = *p*-methoxyphenyl
3, Ar = *p*-nitrophenyl
4, Ar = 2,4-dichlorophenyl
5, Ar = 3,4-dichlorophenyl

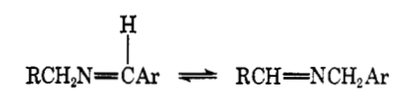
The ir spectra (Nujol) had only one absorption band in the region 3300–3200 cm^{-1}, characteristic of secondary amines. The nmr spectra of these compounds showed a singlet at δ 5.42–5.83, characteristic of the methine proton.[4] In confirmation of the proposed ring structure **2**, the protons on N-1 and N-3 could be exchanged with deuterium.

The reaction of **1** with *p*-chloro- and *p*-bromobenzaldehydes furnished the Schiff bases **6** and **7**, respectively, which were found to be homogenous by tlc.



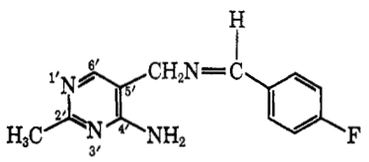
6, Ar = *p*-chlorophenyl
7, Ar = *p*-bromophenyl

Their ir spectra showed two bands at 3400 and 3300 cm^{-1} for the NH_2 group. The nmr spectra of the chain isomers **6** and **7** were considerably different than those of the ring isomers, **2–5**. The most significant difference was the peak for the azomethine proton at δ 8.44. This assignment was confirmed by the nmr spectra of authentic Schiff bases of aniline with *p*-chloro- and *p*-bromobenzaldehydes. As expected, the protons on the 4-NH_2 group in **6** could be exchanged with deuterium. To determine if **6** and **7** were involved in the following type of equilibrium, **6** was hydrolyzed with 1



N hydrochloric acid at room temperature for 15 min. A quantitative yield of *p*-chlorobenzaldehyde appeared to rule out this possibility.[6]

The reaction of **1** with *p*-fluorobenzaldehyde afforded a mixture of the open-chain and the ring isomers, **8** and **9**, respectively, as shown by ir and nmr spectra and tlc of the reaction mixture. Tlc indicated two spots, and the ir spectrum (Nujol) showed three bands in the N–H region at 3400, 3300, and 3250 cm^{-1}. The nmr spectrum showed absorptions characteristic of both **8** and **9**. The



8

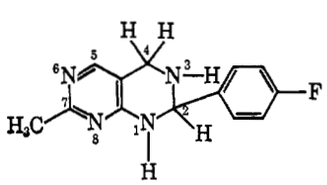


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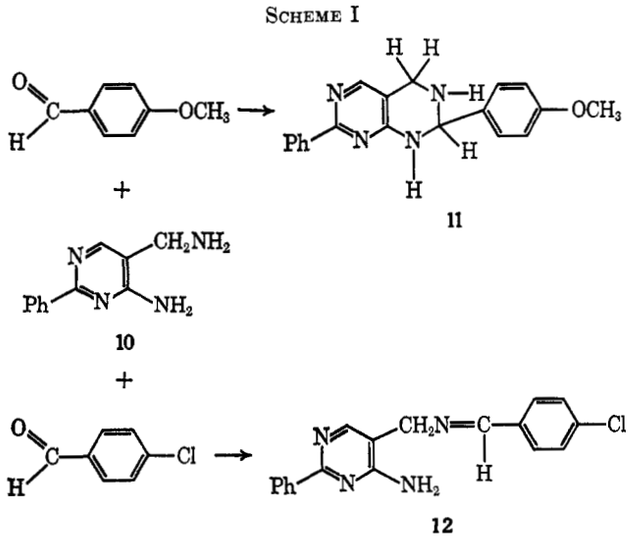
TABLE I

Compd	Mp, °C	Empirical formula	Analysis		Nmr data	
			Calcd, %	Found, %	Solvent	δ
2	142–143	$C_{14}H_{16}N_4O$	C 65.60 H 6.29 N 21.89	65.40 6.17 22.12	$CHCl_3$-*d*	2.0 (m, 1, 3 H); 2.35 (s, 3, CH_3); 3.80 (s, 3, OCH_3); 3.87 (m, 2, 4 CH_2); 5.42 (s, 1, 2 H); 6.55 (s, 1, 1 H); 7.13 (m, 4, aromatics); 7.83 (s, 1, 5 H)
3	189–190	$C_{13}H_{13}N_5O_2$	C 57.56 H 4.83 N 25.82	57.80 5.02 25.58	DMSO-*d*	2.32 (s, 3, CH_3); 3.23 (m, 2, CH_2); 5.50 (s, 1, 2 H); 7.98 (m, 4, aromatics); 8.04 (m, 1, 5 H)
4	179–180	$C_{13}H_{12}Cl_2N_4$	C 52.90 H 4.10 N 18.98	52.89 4.19 18.74	$CHCl_3$-*d*	2.13 (m, 1, 3 H); 2.41 (s, 3, CH_3); 3.90 (d, 2, J = 3.0, CH_2); 5.83 (s, 1, 2 H); 6.21 (s, 1, 1 H); 7.38 (m, 4, aromatics); 7.93 (m, 1, 5 H)
5	163–165	$C_{13}H_{12}Cl_2N_2$	C 52.90 H 4.10 N 18.98	52.85 4.32 19.24	$CHCl_3$-*d*	2.48 (s, 3, CH_3); 3.86 (d, 2, J = 2.0, CH_2); 5.50 (s, 1, 2 H); 7.37 (m, 4, aromatics); 7.55 (m, 1, 5 H)
6	169–170	$C_{13}H_{13}N_4Cl$	C 59.88 H 5.02 N 21.49	59.73 5.10 21.27	$CHCl_3$-*d*	2.30 (s, 3, CH_3); 4.82 (s, 2, CH_2); 6.06 (s, 2, NH_2); 7.60 (m, 4, aromatics); 8.16 (s, 1, 6 H); 8.44 (s, 1, azomethine H)
7	170–172	$C_{13}H_{13}BrN_4$	C 51.16 H 4.29 N 18.36	51.27 4.39 18.64	$CHCl_3$-*d*	2.46 (s, 3, CH_3); 4.60 (s, 2, CH_2); 5.92 (s, 2, NH_2); 7.52 (m, 4, aromatics); 7.98 (2, 1, 6 H); 8.26 (s, 1, azomethine H)
8 and 9	163–170	$C_{13}H_{13}FN_4$	C 63.92 H 5.36 N 22.94	63.72 5.47 23.09	DMSO-*d*	2.34 (s, 3, CH_3); 3.60 (s, 0.7, 4 CH_2); 4.54 (s, 1.3, 5 CH2); 5.36 (m, 0.33, 2 CH); 6.60 (s, 1.2, 4 NH_2); 7.20 (m, 2.6, chain aromatics); 7.78 (m, 1.4, ring aromatics); 7.92 (m, 1, 5, and 6 CH); 8.44 (m, 0.66, azomethine H)
11	132.5–133	$C_{19}H_{18}N_4O$	C 71.78 H 5.70 N 17.60	71.77 5.74 17.68	DMSO-*d*	3.78 (s, 5, OCH_3 and CH_2); 5.42 (s, 1, 2 H); 7.44 (m, 8, aromatics)
12	182–182.5	$C_{18}H_{15}ClN_4$	C 66.97 H 4.68 N 17.36	67.21 4.81 17.51	DMSO-*d*	4.66 (s, 2, CH_2); 6.80 (s, 2, NH_2); 7.80 (m, 8, aromatics); 8.48 (s, 1, azomethine H)

peak at δ 8.44 (azomethine proton, structure **8**) integrated for 0.66 H, whereas the peak at δ 5.36 (methine proton, structure **9**) integrated for 0.33 H. This suggested the approximate composition of the mixture to be 33% **9** and 67% **8**.

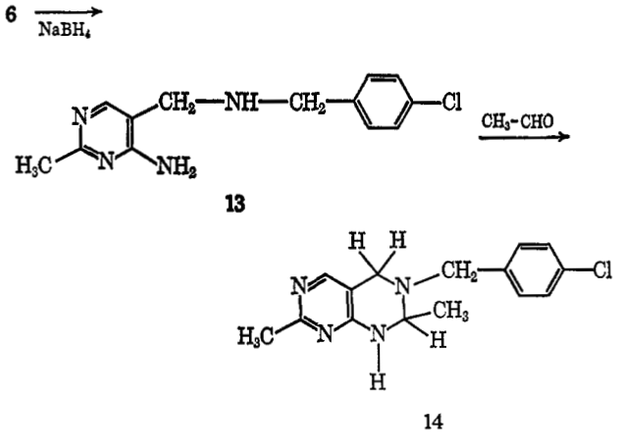
The reaction of 4-amino-5-(aminomethyl)-2-phenylpyrimidine (**10**) with *p*-chloro- and *p*-methoxybenzaldehydes furnished products (shown in Scheme I) similar to those obtained from **1**.

SCHEME I



Sodium borohydride reduction of the Schiff base **6** afforded 4-amino-5-(*p*-chlorobenzylaminomethyl)-2-methylpyrimidine (**13**). Reaction of **13** with acetaldehyde gave the ring isomer **14** as shown in Scheme II. The nmr and ir spectra of **14** were consistent with the structure.

SCHEME II



The conclusion is that the reaction of 4-amino-5-(aminomethyl)-2-methylpyrimidine with substituted aromatic aldehydes afforded Schiff bases, tetrahydropy-

rimido(4,5-*d*)pyrimidines, or a mixture of both, depending on the aldehyde substituent.

Experimental Section

The melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were obtained with a Varian A-60 spectrometer. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. Glass plates coated with silica gel G were used for tlc in ethanol–water.

General Procedure for the Reaction of 4-Amino-5-(aminomethyl)-2-methylpyrimidine (1)[7] and 4-Amino-5-(aminomethyl)-2-phenylpyrimidine (10) with Substituted Benzaldehydes.—To a solution of 0.075 mol of the benzaldehyde in 150 ml of benzene was added 0.075 mol of the pyrimidine with stirring. The mixture was heated under reflux for 8–12 hr in the presence of a Dean–Stark trap. The reaction mixture was filtered while hot to remove any unreacted pyrimidine. The product, the Schiff base or the tetrahydropyrimido(4,5-*d*)pyrimidine, was obtained in 70–90% yield by either cooling the filtrate or by evaporating it to dryness and triturating the residue with petroleum ether (bp 30–60°). The analytical samples were obtained by three or four recrystallizations from benzene or ethanol. The analyses as well as the nmr data are summarized in Table I.

Hydrolysis of 4-Amino-5-(*p*-chlorobenzylideneaminomethyl)-2-methylpyrimidine (6).—A solution of 2.06 g (0.008 mol) of **6** in 50 ml of 1 *N* hydrochloric acid was kept at room temperature for 15–20 min. Colorless crystals, mp 45–48°, of *p*-chlorobenzaldehyde were obtained by filtration of the reaction mixture. Extraction of the mother liquors with ether furnished an additional yield of *p*-chlorobenzaldehyde, mp 45–48°. The *p*-chlorobenzaldehyde thus obtained was dissolved in ether and treated with a solution of 2,4-dinitrophenylhydrazine in ether. Filtration afforded 2.3 g (93%) crystals of *p*-chlorobenzaldehyde-2,4-dinitrophenylhydrazone, mp 264–267° (lit.[8] mp 266°).

4-Amino-5-(*p*-chlorobenzylaminomethyl)-2-methylpyrimidine (13).—To a solution of 2.0 g (0.008 mol) of **2** in 40 ml of absolute MeOH at −5° was added slowly and with stirring 0.43 g (0.012 mol) of sodium borohydride. The reaction mixture was heated under reflux for 20 min and then made basic by the addition of 45 ml of 1.0 *N* sodium hydroxide with vigorous stirring. Extraction with six 25-ml portions of ether and evaporation of the ether extract to dryness afforded 1.7 g (84%) of crystals of **13**, mp 97–100°. Three recrystallizations from benzene furnished the analytical sample: mp 101.5–102.5°; nmr ($CHCl_3$-*d*) δ 1.50 (m, 1, **NH**), 2.43 (s, 3, CH_3), 3.64 (s, 2, 5 CH_2), 3.75 (m, 2, benzylic CH_2), 6.23 (s, 2, NH_2), 7.30 (m, 4, aromatics), and 7.92 (s, 1, 6 H); ir ν_{max}^{Nujol} 3400 and 3300 cm^{-1} (NH_2).

Anal. Calcd for $C_{13}H_{15}ClN_4$: C, 59.42; H, 5.75; N, 21.33. Found: C, 59.36; H, 5.82; N, 21.48.

3-(*p*-Chlorobenzyl)-2,7-dimethyl-1,2,3,4-tetrahydropyrimido(4,5-*d*)pyrimidine (14).—Two drops of concentrated HCl was added to a solution of 2.0 g (0.008 mol) of **13** and 2.5 g (0.06 mol) of acetaldehyde in 75 ml of benzene. The reaction mixture was heated under reflux for 6 hr. Evaporation to dryness afforded 1.6 g (73%) of crystals of **14**, mp 144–146°. Recrystallization from benzene gave the analytical sample: mp 146–147°; nmr ($CHCl_3$-*d*) δ 1.40 (d, 3, J = 7.0, 2 CH_3), 2.47 (s, 3, 7 CH_3), 3.57 (d, 2, J = 2.0, 3 CH_2), 3.73 (d, 2, J = 7.0, 4 CH_2), 5.71 (m, 1, 1 NH), 7.31 (m, 4, aromatics), and 7.85 (s, 1, 5 H); ir ν_{max}^{Nujol} 3230 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.92; H, 5.88; N, 19.40. Found: C, 63.25; H, 6.10; N, 19.23.

Registry No.—**2**, 20352-37-8; **3**, 20352-38-9; **4**, 20352-39-0; **5**, 20352-40-3; **6**, 20352-46-9; **7**, 20352-47-0; **8**, 20352-48-1; **9**, 20352-41-4; **11**, 20352-42-5; **12**, 20352-43-6; **13**, 20352-44-7; **14**, 20352-45-8.

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Preparation of Substituted 5,6-Dihydro-1,4-dithiins

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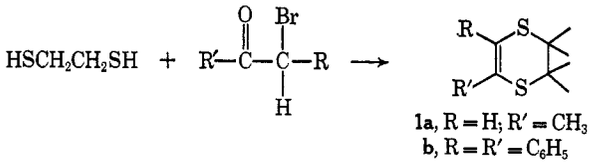
There is a great deal of interest in the chemistry of 1,4-dithiins and 1,4 dithianes.[1] Unsubstituted dithiins and dithianes can be prepared by relatively straightforward procedures.[2,3] There are, however, few good methods for the preparation of simple alkyl or aryl dithianes or dithiins. Of the existing methods, the usual procedures give 2,5-disubstituted or 2,3,5,6-tetrasubstituted derivatives.[4-9] The reported methods for the preparation of monoalkyl and aryl substituted dithiins usually involve multistep syntheses and proceed with poor yields.[10,11] There are no reports in the literature of simple procedures for the preparation of 2,3-disubstituted dithianes or dithiins except for benz-1,4-dithianes.[12]

We report here a novel synthesis of 2- and 2,3-mono- and disubstituted 5,6-dihydro-1,4-dithiins (**1**). These compounds can readily be prepared by treating ethanedithiol with an α-bromo ketone.



1a, R = H; R′ = CH_3
b, R = R′ = C_6H_5

When α-bromoacetone is treated with ethanedithiol, the resulting 2-methyl-5,6-dihydro-1,4-dithiin (**1a**) is obtained in 60% yield. This compound has previously been reported in a multistep synthesis which resulted in 10% yields[10] of **1a**. As an example of the formation of 2,3-disubstituted dithiins, 2-bromo-2-phenylacetophenone gives the corresponding 2,3-diphenyl-5,6-dihydro-1,4-dithiin (**1b**) in 50% yield.

The dihydrodithiins resulting from these reactions may be reduced to the dithianes[12] or oxidized to the dithiins[13] by established procedures.

Experimental Section

Micro analyses were carried out by Werby Laboratories, Boston, Massachusetts. Melting points are corrected. Nuclear

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