Dihydropyrimidines. Part 6.[1] 5-Acetyldihydropyrimidines *via* Condensation of Olefinic Acetylacetones with Amidines. Reinvestigation of Ruhemann's Reaction.

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The condensation of benzylideneacetylacetone and benzamidine, studied by Ruhemann in 1903, has been reinvestigated in detail, and several new reaction products have been isolated and identified. The influence of varying the conditions of reaction have been studied. By using an aprotic solvent (benzene) with azeotropic removal of the water released, for example, the reaction is directed towards formation of 5-acetyldihydropyrimidine (**5a**). This compound has been obtained in better yields with a two-step approach: initial preparation of the 5-acetyl-6-hydroxytetrahydropyrimidine intermediate (**4a**), followed by dehydration in acidic media. While this tetrahydropyrimidine in $CDCl_3$ solution most probably exists as a mixture of the 1,4,5,6-tetrahydro and 3,4,5,6-tetrahydro compounds, crystallization from acetone gave single crystals of 5-acetyl-6-hydroxy-3,4,5,6-tetrahydropyrimidine (**4aB**) and water in the ratio 2:1. Using the two-step procedure, other tetrahydro- and dihydro-pyrimidine derivatives have been prepared from *m*-nitrobenzylideneacetylacetone and benzamidine. The reaction has also been explored using acetamidine. All isolated 5-acetyldihydropyrimidines exist in the solid state in the 1,4-dihydro form. However, in solution amidinic tautomerism was observed, which also favours the 1,4-dihydro tautomer. These newly prepared dihydropyrimidines easily undergo oxidation to the corresponding pyrimidines. The mechanism of the basic deacetylation observed by Ruhemann in ethanolic solutions, affording the 5-unsubstituted dihydropyrimidine, is also discussed.

Dihydropyridines, particularly those containing electron-withdrawing groups (*e.g.* dihydronicotinamides or Hantsch esters), are materials of extreme interest to chemists and biomedical researchers alike.[2] They can be considered as analogues of cyclohexadienes, in which the lone-ring nitrogen induces substantial perturbations in the behaviour of these molecules that are of considerable theoretical significance. Dihydropyridines also provide new opportunities for the synthesis of natural products; they are essential components in the oxidation–reduction chemistry of all living organisms (NADH and NADPH)[3] and also serve as highly active Ca^{2+}-channel blocking pharmaceuticals (*e.g.* nifedipine, a Hantsch ester derivative).[4] However, a related group of compounds, the 5-functionalized 1,4-dihydropyrimidines (in which the electron-withdrawing fragment C-CO_2R in position 3 or 5 of the Hantsch ester is replaced by a double-bonded ring nitrogen), was then unknown.

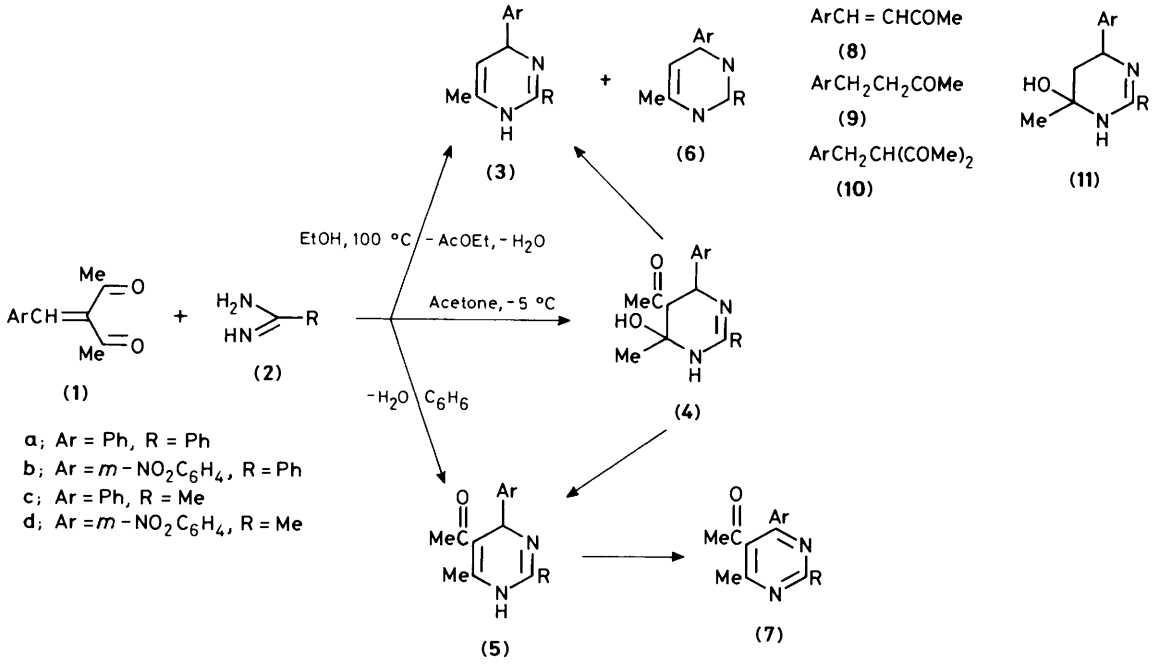
Following successful structural determination and investigation of tautomerism in several dihydropyrimidines,[1,5] as well as the development of a versatile [3 + 3]-fragment synthesis of these substances from α,β-unsaturated carbonyl compounds and amidines,[6] we attempted to use the same methodology to produce 5-functionalized dihydropyrimidines, which, by analogy to the Hantsch esters, should be even more stable[7] than those not functionalized at that position. As a model, we chose the reactions of the easily prepared benzylideneacetylacetone with amidines, and report below on the results of these investigations.

Results and Discussion

Benzylideneacetylacetone (BAA; 3-benzylidenepentane-2,4-dione) may be viewed either as a derivative of a β-diketone or as an α-functionalized α,β-unsaturated ketone. However condensations at the β-diketone function occurred only to a very small extent, if at all, and all reactions with amidines investigated took place *via* the α,β-unsaturated fragment.

(*a*) *Reaction of Benzylideneactylacetone* (**10**) *with Benzamidine* (**2a**).—One report by Ruhemann[8] exists in the literature of the reaction of olefinic diketones and amidines. He found that 'on boiling an alcoholic solution of the mixture of benzylideneacetylacetone and benzamidine, the additive product loses water and its acetyl group in the form of ethyl acetate to produce a methyldiphenyldihydropyrimidine.'

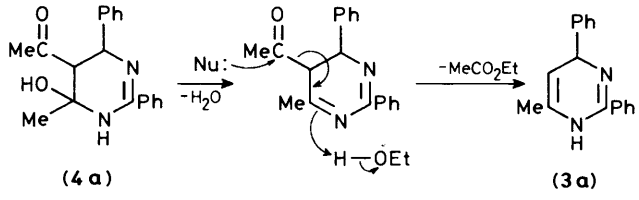
In order to decipher the mechanism of this reaction, we initiated a systematic study, aimed at identifying the reaction products, as well as the factors governing their formation. In order to distinguish between the various possible reaction paths (Scheme 1), the question was posed: does the cleavage of the acetyl group occur before or after cyclization with benzamidine? If the loss precedes cyclization, the operative condensation reaction involves benzylideneacetone and benzamidine as starting materials. This reaction is similar to a previously described condensation carried out in benzene to afford the dihydropyrimidine (**3a**) in high yield. This course is, therefore, theoretically possible. Loss of the acetyl group can also take place following formation of the cyclic adduct (**4**), from the adduct itself or from the dihydropyrimidine final product. To clarify the situation and determine whether deacetylation of the starting material is possible, an ethanolic solution of benzylideneacetylacetone was heated with triethylamine (1 equiv.) for 24 h. No formation of benzylideneacetone was detected, which probably indicates that deacetylation of the starting material does not occur. To determine whether loss of the acetyl group occurs from the cyclic products, it was necessary, first of all, to prepare the purported acetylated dihydropyrimidine. Because the driving force for deacetylation observed in Ruhemann's reaction—independently of when it occurs—might derive from the protic solvent used (ethanol), we attempted the preparation of 5-acetyl-6-methyl-2,4-diphenyl-1,4-(or 1,6)-dihydropyrimidine



Scheme 1.

(**5a**) by direct condensation in an aprotic solvent (benzene) using a Dean-Stark trap for removal of the water formed. After removal of the calculated amount of water (boiling for *ca.* 4 h), a yellowish-green solution was obtained, which was shown by quantitative ^{1}H n.m.r. analyses[9] using the integral intensity of an acetyl peak at δ 2.47, to be the 5-acetyldihydropyrimidine (**5a**) (70%). Isolation by evaporation of the solvent followed by column chromatography, afforded the analytically pure product as a yellow, crystalline, stable solid, m.p. 83—84 °C. Boiling the material in ethanol had no effect on the acetyl group. Therefore, deacetylation, under Ruhemann's conditions, must occur at one of the earlier stages of reaction. To confirm this, it was necessary to prepare the purported intermediate acetylated compounds. This was achieved *via* a two-step process for the preparation of dihydropyrimidines developed earlier in our laboratory.[6] This approach was also hoped to lead to improved yields of 5-acetyldihydropyrimidine than were previously obtained.

The intermediate cyclic adduct 6-hydroxytetrahydropyrimidine (**4a**) was prepared in quantitative yield by the addition of compound (**1**) to an acetone solution of amidine (**2**) at 0—5 °C (for details, see the Experimental section). The white solid thus formed was washed with diethyl ether, to give analytically pure (**4a**) (92%), m.p. 127 °C. Various methods for dehydrating compound (**4a**) to the corresponding dihydropyrimidine were attempted. The best results, providing quantitive yields of the 5-acetyldihydropyrimidine (**5a**), were obtained using glacial acid as a solvent–catalyst, reminiscent of acid-catalysed dehydration in the Schiff base reactions.[10] Using conventional dehydration methods in aprotic solvents (Dean-Stark trap, molecular sieves, *etc.*),[11] formation of (**5a**) was also observed, although at a substantially slower rate and with lower yield. Acid catalysis also accelerated the reaction in aprotic solvents, making possible yields of up to 93%. With the 5-acetyl-6-hydroxytetrahydropyrimidine (**4a**) intermediate in hand, we could examine the effects of ethanol in order to clarify the mechanism of deacetylation. Boiling of the cyclic adduct (**4a**) in 96% ethanol produced no change. However, addition of a base (tertiary amine or benzamidine; 1 equiv.), effectively cleaved the acetyl group at position 5, to form the dihydropyrimidine (**3a**) (*ca.* 30%) and ethyl acetate (by n.m.r. g.c.m.s.). Loss of the acetyl group in ethanol may be explained in terms of solvent participation during the base catalysed dehydration of tetrahydropyrimidine (Scheme 2).

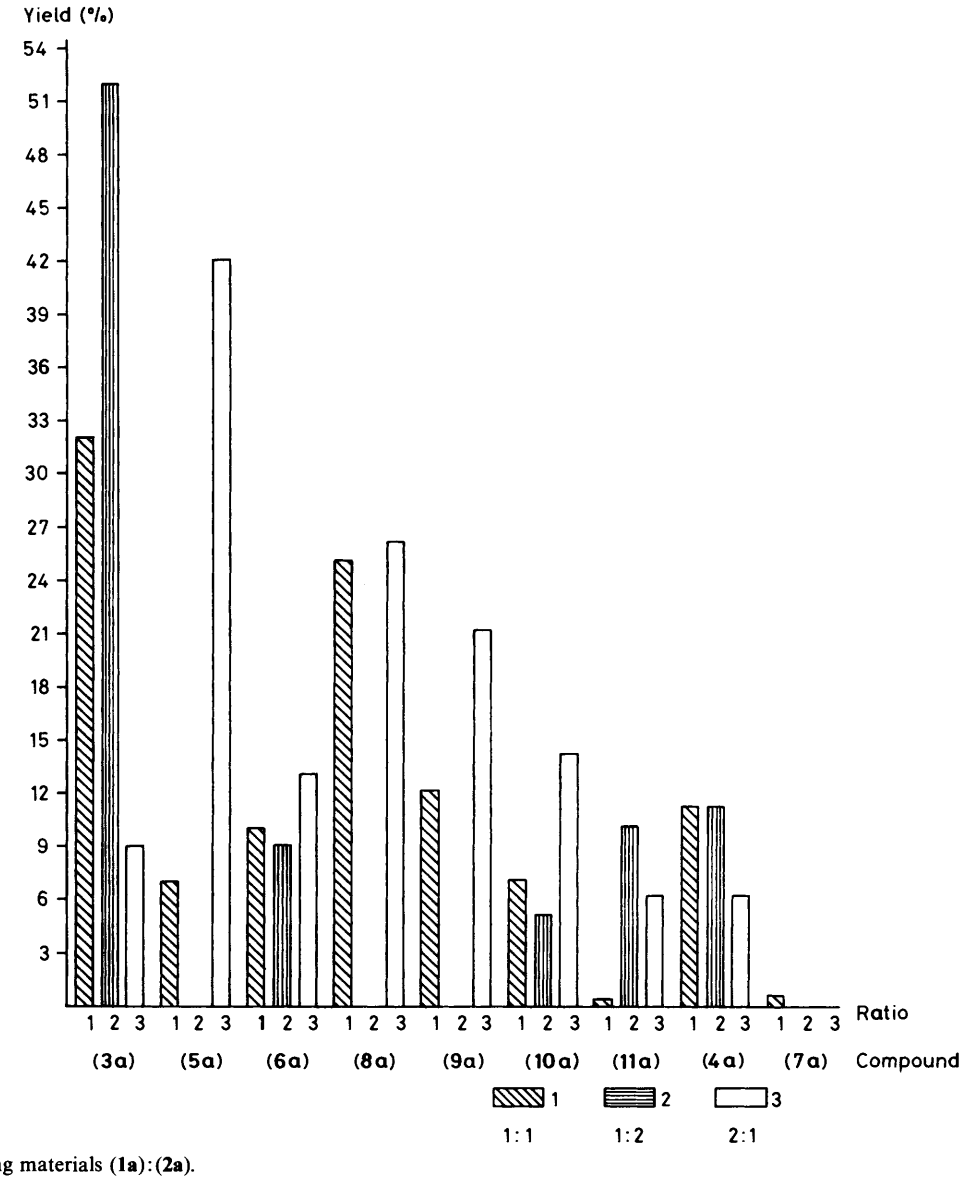


Scheme 2.

Therefore, it became clear that according to the proposed mechanism, the initial product formed in this reaction is the hydroxytetrahydropyrimidine (**4a**), which, depending upon reaction conditions, may be transformed into the 5-acetyldihydropyrimidine (**5a**) or lose the acetyl group.

Some 10 years ago, we repeated Ruhemann's work in order to prepare an authentic sample of 6-methyl-2,6-diphenyldihydropyrimidine (**3a**).[12] At that time, we noted that, aside from (**3a**), the complex reaction mixture contained over 15 individual components, among them a small amount of 4-methyl-2,6-diphenylpyrimidine (**6a**). The then widely accepted opinion was that dihydropyrimidines are highly unstable and easily oxidizable, and so we initially ascribed the appearance of the pyrimidine (**6a**) to the facile spontaneous oxidation of (**3a**) in air. However, repetition of the reaction under a dry, inert atmosphere, also led to a similar amount of (**6a**). Moreover, we were later able to prepare pure dihydropyrimidine (**3a**) crystals having the 1,4-dihydro structure,[13] which do not deteriorate over years of storage. In order to clarify the origin of the pyrimidine (**6a**), we initiated a detailed, systematic study of this reaction, trying to identify as many of the reaction products as

Table 1. Yields of the main products of reaction of benzylideneacetylacetone (**1a**) with benzamidine (**2a**) under Ruhemann's conditions.*



Ratio of starting materials (**1a**):(**2a**).

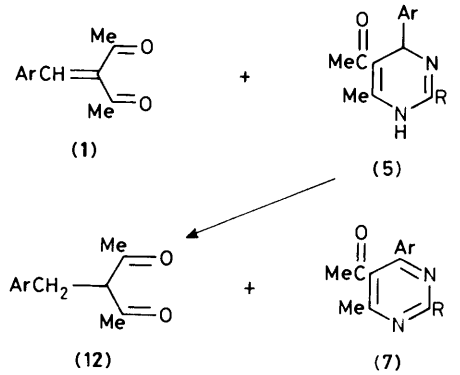
* These results are averages of 30 experiments carried out for each ratio of starting materials. Yields were calculated by quantitative ^{1}H n.m.r. and physical separation of materials by chromatography.

possible and the factors governing their formation. Multi-fold repetition of the original Ruhemann reaction enabled us to isolate and identify most of the products formed under Ruhemann's conditions.

Table 1 presents the results of isolation of the major compounds of the mixture, along with their relative concentrations as determined using quantitative ^{1}H n.m.r. analysis. In addition, the effect of changing the ratio of starting materials on the distribution of the final products was studied. As can be seen, a two-fold excess of benzylideneacetylacetone increases the yield of 5-acetyldihydropyrimidine substantially. In contrast, a two-fold excess of benzamidine produces significant deacetylation, with formation of 5-unsubstituted dihydropyrimidine (**3a**) as the main product. These results support our suggested mechanism of a base-catalyzed deacetylation.

Undoubtedly, the formation of the saturated ketones (**9a**) and (**10a**), and the pyrimidines (**6a**) and (**7a**) can be ascribed to the reducing properties of dihydropyrimidines (Scheme 3). Dihydropyridines are well known reducing agents, but the corresponding dihydropyrimidines—which have similar properties—require further study.

(*b*) *Reaction of* m-*Nitrobenzylideneacetylacetone* (**1b**) *with Benzamidine and Acetamidine.*—Ruhemann claimed that 'the behaviour of *m*-nitrobenzylideneacetylacetone towards benzamidine is of special interest because the additive compound, which may be supposed to be first found, loses its acetyl group and yields *m*-nitrodiphenylmethylpyrimidine, and not its dihydro derivatives.' Indeed, reconstructing his original reaction conditions, we obtained the same pyrimidine (**6b**), as the main



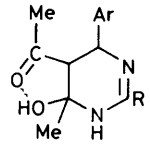
Scheme 3.

product. It should be noted that, to our surprise, azeotropic removal of water in benzene also gave the pyrimidine and only trace amounts of the corresponding 5-acetyldihydropyrimidine. The same disappointing results were obtained utilizing acetamidine (**2b**) instead of benzamidine, both with compounds (**1a**) and (**1b**).

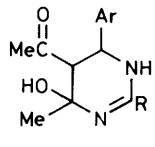
Therefore, we applied the above-mentioned two-step method of dihydropyrimidine preparation and were able to isolate separately the intermediate 5-acetyl-6-hydroxytetrahydropyrimidine, and, after dehydration, the desired yellow 5-acetyldihydropyrimidines. Yields with selected physical and spectral data are given in Tables 2 and 3. ^{1}H N.m.r. spectral assignments were made from standard chemical shift and coupling constant data.[14]

All prepared dihydropyrimidines were easily oxidized to the corresponding pyrimidines by titration with acetone–$KMnO_4$. The prepared hydroxytetrahydropyrimidines and dihydropyrimidines easily formed hydrochlorides, hexachloroplatinates, and picrates with the corresponding acids.

(*c*) *Structure of the 5-Acetyl-6-hydroxytetrahydropyrimidines* (**4**).—A Dreiding molecular model of compound (**4a**) showed that there are a large number of possible stereoisomers induced by the three asymmetric centres of this compound, in addition to its ability to undergo amidinic tautomerism, ring and nitrogen inversions, *etc.* However, analysis of the ^{1}H and ^{13}C n.m.r. (see Table 3) spectra of compound (**4a**) has shown that in $CDCl_3$ there are at least two isomers (ratio 1:1), which were tentatively assigned as half-chair structures with pseudoaxial protons at positions 4 and 5 as confirmed by their spin-spin coupling constant of J 12 Hz, a typical value for *trans*-disposed pseudoaxial protons.[4] However, such isomeric pairs can be diastereoisomers, tautomers, conformers, *etc.*



4 A



4 B

In order to elucidate the detailed structures of compound (**4a**) single crystals of the compound were prepared for *X*-ray diffraction. The solid formed in water had the hydrated structure $C_{19}H_{20}N_2O_2 \cdot 0.5H_2O$. The analysis showed a hydrogen-bonded cluster of four molecules of the 5-acetyl-6-hydroxytetrahydropyrimidine (**4aB**) with one molecule of water (Figure 1). Two enantiomers of only one stereoisomer were present. The water molecule, lying on a two-fold axis, forms hydrogen bonds with the hydroxy groups and NH groups of four pyrimidine molecules. Moreover, the two molecules hydrogen bond with one another to link a hydroxy group of one molecule with the lone electron pair of the N(sp^2) of the second molecule (see Figure 2). The hydroxytetrahydropyrimidine molecules have a half-chair conformation (Figure 3). Bond lengths between C(2)–N(1), and C(2)–N(3) were found to be 1.29 and 1.345 Å respectively, indicating that the double bond of the amidinic fragment of the molecule lies between C(2) and N(1). The phenyl and acetyl groups at C-4 and C-5, respectively, occupy equatorial positions, and their protons have an axial *trans* disposition, which confirms the n.m.r. data. It is interesting that the methyl group at C-6 is axial, whereas the hydroxy group is equatorial, in contrast to the situation described previously[6] for the 5-unsubstituted hydroxytetrahydropyrimidines. This difference is probably due to hydrogen bond

Table 2. Analytical data for the hydroxytetrahydropyrimidines (**4**) and dihydropyrimidines (**5**)

Compd.	R^2	R^4	R^5	Yield (%)	M.p. (°C) (solvent)	Molecular formula	M (M^+)	Found (%)* (Required) C	H	N
(**4a**)	Ph	Ph	COMe	>98	137—138	$C_{19}H_{20}N_2O_2$	308.4 (308)	73.91 (74.00)	6.38 (6.54)	9.26 (9.08)
(**4b**)	Ph	*m*-$NO_2C_6H_4$	COMe	75	142—144	$C_{19}H_{19}N_3O_4$	353.4 (353)	64.62 (64.58)	5.72 (5.42)	11.88 (11.89)
(**4c**)	Me	Ph	COMe	84	120—121.5	$C_{14}H_{18}N_2O_2$	246.3 (246)	68.14 (68.27)	7.20 (7.37)	11.21 (11.37)
(**4d**)	Me	*m*-$NO_2C_6H_4$	COMe	78	104—106	$C_{14}H_{17}N_3O_4$	291.3 (291)	57.48 (57.72)	5.67 (5.88)	14.12 (14.42)
(**5a**)	Ph	Ph	COMe	93	83—84	$C_{19}H_{18}N_2O$	290.4 (290)	78.40 (78.59)	6.18 (6.25)	9.54 (9.65)
(**5b**)	Ph	*m*-$NO_2C_6H_4$	COMe	85	153—156	$C_{19}H_{17}N_3O_3$	335.4 (335)	67.92 (68.05)	5.18 (5.11)	12.23 (12.53)
(**5c**)	Me	Ph	COMe	84	118—120	$C_{14}H_{16}N_2O$	228.3 (228)	73.84 (73.66)	7.29 (7.06)	11.84 (12.27)
(**5d**)	Me	*m*-$NO_2C_6H_4$	COMe	82	138—139	$C_{14}H_{15}N_3O_3$	273.3 (273)	61.75 (61.53)	5.62 (5.53)	15.27 (15.38)

* Calculated values were taken from ref. 17.

Table 3. Selected spectral data for compounds (**4**) and (**5**).

Compd.	Ratio	$\delta_H(CDCl_3)$ R²	R⁴	R⁴′	R⁵	R⁵′	R⁶	(NH,OH)	$\nu_{max.}/cm^{-1}$ $CHCl_3$ solution	KBr pellets	$\lambda_{max.}$(EtOH/nm)(ε)
(4a)	1 A	7.40—7.79	7.33	4.80	1.67	2.86	1.52		3 438, 1 705, 1 696,	3 424, 1 708, 1 631,	
	1 B	(m, 5 H)	(s, 5 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	4.29	1 635, 1 579, 1 506,	1 626, 1 510, 1 487,	223(15 680)
			7.33	4.87	2.03	3.10	1.41	(br s, 2 H)	1 494, 1 480, 1 454,	1 457, 1 372, 1 356,	206 (18 410)
			(s, 5 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)		1 380, 1 362	1 252, 1 145	
(4b)	4 A	7.32—8.29		5.04	1.73	2.86	1.53		3 435, 1 696, 1 635,	3 398, 1 697, 1 632,	
	1 B	(m, 9 H)		(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	3.84	1 580, 1 533, 1 506,	1 537, 1 513, 1 488,	250 (13 450)
				5.01	2.11	3.12	1.42	(br s, 2 H)	1 480, 1 381, 1 353,	1 352, 1 315, 1 238,	210 (22 250)
				(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)		1 324, 1 313	1 145	
(4c)	1 A	1.96	7.29	4.65	1.66	2.78	1.42		3 439, 1 691, 1 655,	3 308, 1 687, 1 622,	258 (760)
	1 B	(s, 3 H)	(s, 6 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	4.81	1 603, 1 494, 1 454,	1 602, 1 542, 1 456,	252 (700)
				4.65	2.07	3.05	1.38	(br s, 2 H)	1 432, 1 380, 1 364,	1 377, 1 359, 1 239,	202 (18 270)
				(d, 11.5 Hz, 1 H)		(d, 11.5 Hz, 1 H)			1 345, 1 326	1 156	
(4d)		2.01	7.47—8.23	4.82	1.68	2.82	1.45	3.49	3 454, 1 710, 1 695,	3 420, 3 244, 3 127,	
		(s, 3 H)	(m, 4 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	(d, 11.5 Hz, 1 H)	(s, 3 H)	(br s, 2 H)	1 653, 1 533, 1 494,	1 718, 1 630, 1 548,	254 (7 100)
									1 444, 1 430, 1 419,	1 525, 1 456, 1 410,	202 (18 680)
									1 381, 1 356	1 396, 1 381, 1 385,	
										1 246, 1 162, 255	
(5a)		7.32—7.75		5.80	2.17		2.46	6.70	3 433, 1 674, 1 653,	3 276, 1 657, 1 649,	
		(m, 9 H)		(s, 1 H)	(s, 3 H)		(s, 3 H)	(br s)	1 600, 1 795, 1 534,	1 632, 1 620, 1 602,	329 (3 870)
									1 491, 1 460, 1 442,	1 579, 1 476, 1 443,	248 (24 600)
									1 374, 1 360	1 240	
(5b)		7.36—8.22		5.97	2.21		2.50	6.77	3 428, 1 676, 1 653,	3 274, 3 218, 3 060,	
		(m, 9 H)		(s, 1 H)	(s, 3 H)		(s, 3 H)	(br s)	1 602, 1 532, 1 499,	1 655, 1 605, 1 579,	324 (4 980)
									1 458, 1 444, 1 382,	1 528, 1 476, 1 444,	245 (22 520)
									1 375, 1 350	1 372, 1 347, 1244	
(5c)		2.35	7.29	5.55	2.08		1.95	6.6	3 428, 1 686, 1 666,	3 024, 2 896, 1 672,	
		(s, 3 H)	(s, 5 H)	(s, 1 H)	(s, 3 H)		(s, 3 H)	(br s, 1 H)	1 600, 1 550, 1 491,	1 453, 1 381, 1 360,	322 (6 790)
									1 464, 1 434, 1 379,	1 262, 1 252, 1 239	228 (8 620)
									1 360, 1 300		
(5d)		2.37	7.46—8.14	5.71	2.15		2.00	6.90	3 428, 1 686, 1 668,	3 258, 3 077, 2 920,	
		(s, 3 H)	(m, 4 H)	(s, 1 H)	(s, 3 H)		(s, 3 H)	(br s, 1 H)	1 618, 1 601, 1 532,	1 674, 1 616, 1 534,	308 (6 500)
									1 462, 1 430, 1 380,	1 507, 1 428, 1 375,	255 (9 640)
									1 352, 1 300	1 350, 1 331, 1 249,	
										1 024	

The ^{13}C n.m.r spectrum of compound (**4a**) shows the following pairs of signals: 214.25, 208.56 (C=O); 153.29, 152.04 (C-2); 84.27, 80.05 (C-6); 60.70, 60.63 (C-4); 58.91, 55.19 (C-5); 33.70, 33.48 (Me); 28.73, 24.63 (Me-C=O).

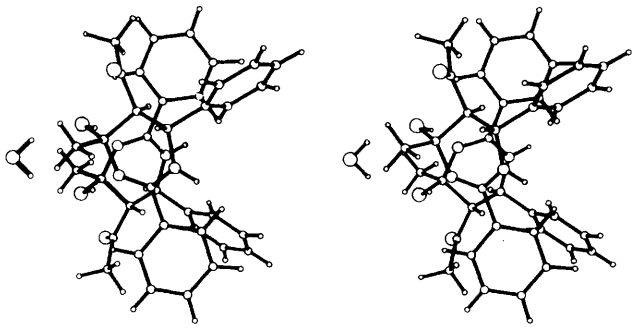


Figure 1. Stereoview of dimolecular cluster of (**4aB**).

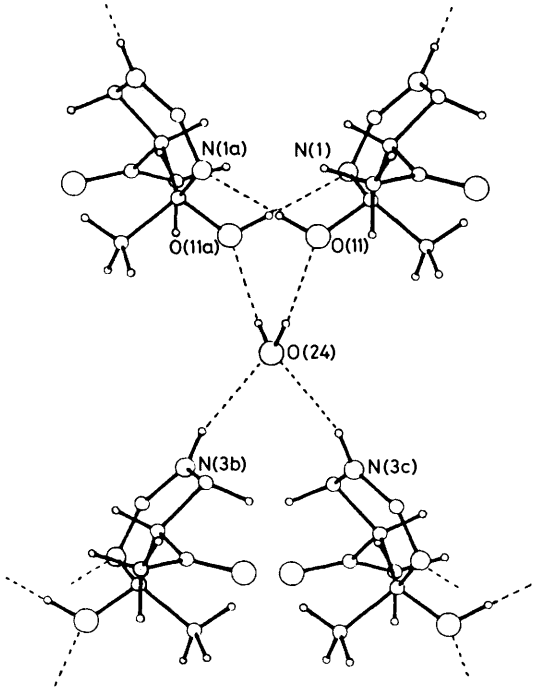


Figure 2. Hydrogen bonding in crystal structure (**4aB**). (The phenyl groups are omitted for clarity).

stabilization and the presence of water. FT-i.r. data on finely ground hydrated single crystals of (**4aB**) in KBr were similar to those obtained from the anhydrous product which precipitated during the condensation. In chloroform solution, in contrast to the crystal data, and in agreement with ^1H and ^{13}C n.m.r. measurements, the FT-i.r. spectra showed the appearance of a set of new signals due to formation of a second isomer. The observation of two distinct isomers in solution at room temperature is unlikely to result from ring inversion (or other conformational interconversions), which are usually in rapid equilibrium under these conditions. This suggestion is supported by ^1H n.m.r. data, which show that the protons at positions 4 and 5 are *trans*, pseudoaxial (J 12 Hz), and by the solution i.r. data which shows the new C=O stretching band at lower frequency (1 693 cm^{-1}) indicating hydrogen bond formation.[15] These data strongly suggest that the second isomer observed in solution is most probably the hydroxytetrahydropyrimidine (**4aA**), which represents the second amidinic tautomeric form with a hydroxy group that intramolecularly hydrogen bonds with the pseudoequatorial acetyl group at position 5. This conclusion is feasible, since only the methyl

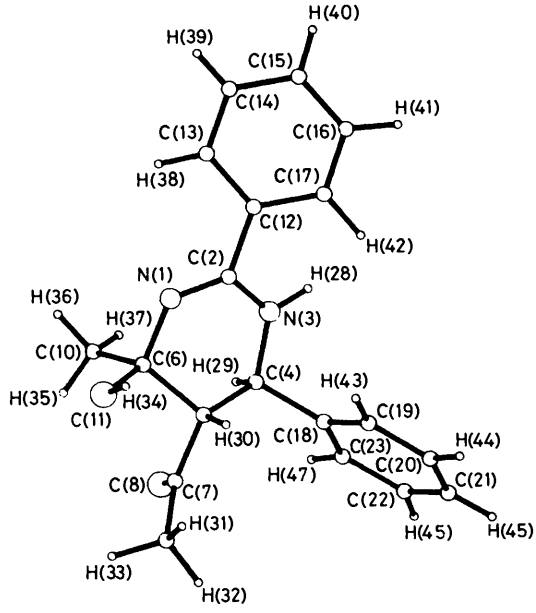
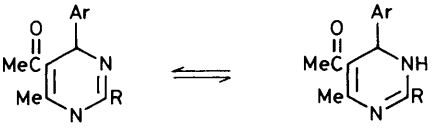


Figure 3. Computer-drawn molecular structure of (**4aB**).

group at position 5 is substantially shifted, whereas the methyl group at position 6 and 4-H and C-4 are only slightly shifted. The data in Table 3 show that the ratio of the two isomers depends upon the ring substituents, very probably due to their effects upon the strength of the hydrogen bonds formed. An analogous situation was noted in the case of 5-carboxylic acid derivatives of hydroxytetrahydropyrimidines.[16] A detailed structural investigation of this class of compounds is in progress.

5-*Acetyldihydropyrimidines* (**5**).—All of the 5-acetyldihydropyrimidines prepared (see Table) exist in the solid state in the 1,4-dihydropyrimidinic form. In solution, however, only an average n.m.r. spectrum of the equilibrium between 1,4- and 1,6-tautomers can be observed (see Table 3). Under special conditions—ultrapure deuteriochloroform or [$^2H_6$] DMSO, low concentration, and low temperature—the ^1H n.m.r. spectrum of the two individual tautomers could be recorded for (**5a**). At —50 °C (0.01M), the following signals were observed. 1,4-dihydropyrimidine, (**5aA**): 7.10 (NH), 5.82 (4-H), 2.50



5A **5B**

(MeCO), 2.14 (Me); 1,6-dihydropyrimidine, (**5aB**): 6.98 (NH), 5.73 (4-H), 2.54 (MeCO), 2.31 (Me), at room temperature. The signals of protons linked to the carbons have almost the same chemical shift value (0.03 p.p.m.), whereas the NH protons shift to notably higher field; thus for (**5aA**), δ_{NH} is 6.67 (NH), and for (**5aB**), it is 6.41. A similar effect was observed during dynamic n.m.r. measurements of amidinic tautomerism.[1] The ratio of the two tautomers (derived from the integrated absorptions) in $CDCl_3$ [(**5aA**)/(**5aB**) = 3, 4:1] can be used to calculate the difference in free energy of the two forms:

$$\Delta G^\circ = -RT\ln(K_{eq})$$

where K_{eq} = [(**5aA**)/(**5aB**)], R = 1.987 cal mol^{-1} K, T = temperature (K), which gives ΔG° = 0.73 kcal mol^{-1}. Qualitatively the rate of tautomerism of 5-acetyldihydropyrimidines is much slower than of 5-unsubstituted compounds. A detailed quantitative report on the influence of the 5-acetyl group in the dihydropyrimidines on the rate and mechanism of amidinic tautomerism, stabilization of tautomers *etc.* will be published separately.

Experimental

Melting points were taken on a modified Fisher-Johns apparatus fitted with a thermocouple and digital thermometer (Lauda) and are uncorrected. Proton n.m.r. spectra were measured with Varian FT-80A and ^{13}C n.m.r. were recorded on a WH-270 Bruker Fourier-Transform spectrometer (67.9 MHz). Microanalyses were performed by the microanalytical laboratory at the Weizmann Institute of Science, and at The Hebrew University of Jerusalem (Dr. S. Blum). Quantitative ^{1}H n.m.r. analysis of reaction mixtures was carried out with pocket-calculator program TI-58 (method of internal standard references). The reference compound used is a precisely weighed amount of bibenzyl [whose CH_2 signal in $CDCl_3$ or [$^{2}H_6$] DMSO appears at δ = 2.99 (4 H, s)].

Benzylideneacetylacetone (b.p. 108 °C/0.04 mmHg) and *m*-nitrobenzylideneacetylacetone (m.p. 101—102 °C) were prepared in *ca.* 90% yield according to a modified procedure.[18] Acetamidine hydrochloride,[19] m.p. 164—166 °C (ethanol) and benzamidine hydrochloride,[20] m.p. 169 °C (acetonitrile) were prepared by standard techniques. The free base of benzamidine or acetamidine was prepared from the corresponding hydrochloride and sodium methoxide in dry methanol, followed by fast filtration of the precipitated NaCl under dry argon and evaporation of the solvent at room temperature under high vacuum.

Preparation of 6-*Hydroxy*-1,4,5,6-*tetrahydropyrimidines* (**4**): *General Procedure.*—A solution of the corresponding α,β-unsaturated carbonyl compound (**1**) (0.02 mol) in dry acetone (15 ml) was added dropwise over 30 min at 0—10 °C to a solution of amidine (0.02 mol) in dry acetone (50 ml) with effective magnetic stirring under a dry inert atmosphere. Following the addition, the mixture was stirred for further 30 min, after which the cooling bath was removed and the reaction mixture stirred at room temperature, the course of the reaction being monitored by t.l.c. A white solid started to precipitate after the first hour. When the starting materials were almost completely dissipated (t.l.c.), the white copious precipitate was filtered off and washed with dry diethyl ether. The mother liquor was evaporated to dryness, the crude residue was triturated with a small amount of dry diethyl ether, and the additional portion of undissolved (**4**) was filtered off. The white solids (**4**) were combined, dried, and recrystallized. Very often crystals were formed which, according to the elemental analysis, contained bound water. For the elemental analysis of the anhydrous pure substances, the t.l.c. homogeneous solid was finely ground in a mortar and dried in a vacuum dessicator at 60 °C.

Preparation of 1,4-*Dihydropyrimidines* (**5**): *General Procedure.*—A solution of the 5-acetyl-6-hydroxytetrahydropyrimidine (**4**) (0.02 mol) in glacial acetic acid (15—20 ml) was heated at 80 °C for *ca.* 48 h. After cooling, ice was added, followed by CH_2Cl_2 (40 ml). 25% Aqueous ammonia was added slowly, with constant stirring until the reaction mixture was basic. The methylene chloride layer was separated off and the upper layer extracted methylene chloride (3 × 50 ml). The organic layers were combined, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue of the dihydropyrimidine (**5**) was purified on a silica gel column (ethyl acetate) and/or recrystallized from ethyl acetate to give colourless prisms.

Crystal data. $C_{19}H_{20}N_2O_2 \cdot 0.5\,H_2O$, M = 317.4, monoclinic, a = 9.261(4), b = 16.119(3), c = 23.453(4) Å, α = 90.0°, β = 100.17(2)°, γ = 90.0°, V = 3 446 Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.710 69 Å), space group $C2/c$(No. 15), Z = 8, D_x = 1.22 g cm^{-3}.

Data Collection and Processing.—CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.80 + 0.35 tan θ, constant ω scan speed 3.3 ° min^{-1}, graphite-monochromatic Mo-K_α radiation; 4 181 reflections measured ($2^{\circ} \leqslant \theta \leqslant 27^{\circ}$, $-h + h,k,l$), 3 442 unique (merging R = 0.022) giving 2 788 with $F_o > 3\sigma(F_o)$.

Structure Analysis and Refinement.—Direct methods followed by full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens (found from a difference Fourier map) isotropic. The weighting scheme $\omega = 2.123/[\sigma^2(F_o) + 0.000\,61F_o]$, with $\sigma(F_o)$ from counting statistics, gave satisfactory agreement analyses. Final R and R_w values are

Table 4. Atom co-ordinates (× 10^4)

	x/a	*y/b*	*z/c*
N(1)	3 373(2)	1 549(1)	2 618(1)
C(2)	2 819(2)	2 246(1)	2 744(1)
N(3)	1 871(2)	2 716(1)	2 379(1)
C(4)	1 417(2)	2 527(1)	1 766(1)
C(5)	2 465(2)	1 893(1)	1 582(1)
C(6)	2 866(2)	1 197(1)	2 043(1)
C(7)	1 812(3)	1 530(1)	996(1)
O(8)	530(2)	1 359(1)	880(1)
C(9)	2 814(4)	1 402(3)	569(1)
C(10)	1 615(3)	608(2)	2 078(1)
O(11)	4 020(2)	719(1)	1 887(1)
C(12)	3 209(2)	2 569(1)	3 345(1)
C(13)	3 271(3)	2 033(2)	3 807(1)
C(14)	3 610(4)	2 326(2)	4 365(1)
C(15)	3 912(3)	3 150(2)	4 473(1)
C(16)	3 841(3)	3 689(2)	4 019(1)
C(17)	3 482(3)	3 403(2)	3 454(1)
C(18)	1 356(2)	3 315(1)	1 413(1)
C(19)	2 539(3)	3 843(2)	1 472(1)
C(20)	2 466(4)	4 568(2)	1 153(1)
C(21)	1 209(4)	4 768(2)	777(1)
C(22)	30(4)	4 245(2)	720(1)
C(23)	103(3)	3 523(2)	1 033(1)
O(24)	5 000	−806(1)	2 500

Site occupancy factor for atom (0) 24 is equal to 0.500.

Table 5. Bond lengths (Å).

C(2)–N(1)	1.291(3)	C(6)–N(1)	1.461(3)
N(3)–C(2)	1.345(3)	C(12)–C(2)	1.487(3)
C(4)–N(3)	1.456(3)	C(5)–C(4)	1.522(5)
C(18)–C(4)	1.512(5)	C(6)–C(5)	1.557(4)
C(7)–C(5)	1.518(5)	C(10)–C(6)	1.512(5)
O(11)–C(6)	1.418(3)	O(8)–C(7)	1.202(4)
C(9)–C(7)	1.495(5)	C(13)–C(12)	1.380(4)
C(17)–C(12)	1.384(5)	C(14)–C(13)	1.375(4)
C(15)–C(14)	1.370(5)	C(16)–C(15)	1.368(5)
C(17)–C(16)	1.385(4)	C(19)–C(18)	1.375(4)
C(23)–C(18)	1.374(4)	C(20)–C(19)	1.382(4)
C(21)–C(20)	1.369(5)	C(22)–C(21)	1.368(5)
C(23)–C(22)	1.371(4)		

Table 6. Bond angles (°).

C(6)–N(1)–C(2)	118.2(2)	N(3)–C(2)–N(1)	125.8(3)
C(12)–C(2)–N(1)	118.8(3)	C(12)–C(2)–N(3)	115.4(3)
C(4)–N(3)–C(2)	123.5(3)	C(5)–C(4)–N(3)	109.4(2)
C(18)–C(4)–N(3)	109.9(3)	C(18)–C(4)–C(5)	111.9(3)
C(6)–C(5)–C(4)	111.9(3)	C(7)–C(5)–C(4)	110.1(3)
C(7)–C(5)–C(6)	111.0(2)	C(5)–C(6)–N(1)	111.0(2)
C(10)–C(6)–N(1)	108.6(3)	C(10)–C(6)–C(5)	113.5(3)
O(11)–C(6)–N(1)	108.4(2)	O(11)–C(6)–C(5)	108.1(1)
O(11)–C(6)–C(10)	107.0(3)	O(8)–C(7)–C(5)	120.8(3)
C(9)–C(7)–C(5)	117.7(3)	C(9)–C(7)–O(8)	121.5(3)
C(13)–C(12)–C(2)	119.7(3)	C(17)–C(12)–C(2)	121.4(3)
C(17)–C(12)–C(13)	118.8(3)	C(14)–C(13)–C(12)	120.2(3)
C(15)–C(14)–C(13)	120.9(4)	C(16)–C(15)–C(14)	119.4(3)
C(17)–C(16)–C(15)	120.2(4)	C(16)–C(17)–C(12)	120.4(3)
C(19)–C(18)–C(4)	120.9(3)	C(23)–C(18)–C(4)	120.4(3)
C(23)–C(18)–C(19)	118.7(3)	C(20)–C(19)–C(18)	120.5(3)
C(21)–C(20)–C(19)	120.2(4)	C(22)–C(21)–C(20)	119.3(3)
C(23)–C(22)–C(21)	120.6(4)	C(22)–C(23)–C(18)	120.7(4)

Table 7. Geometry of the hydrogen bonds.

$RH^A \cdots R^{10}$	R–H (Å)	$R \cdots R^{10}$ (Å)	$H^A \cdots R^{10}$ (Å)	$RH^A \cdots R^{10}$ (°)
O(11)–H(34) · · · N(1a)	0.915	2.823	1.916	171
O(11a)–H(34a) · · · N(1)	0.915	2.823	1.916	171
N(3b)–H(28b) · · · O(24)	0.921	2.989	2.143	157
N(3c)–H(28c) · · · O(24)	0.921	2.989	2.143	157
O(24)–H(48) · · · O(11)	0.934	2.912	2.029	152
O(24)–H(48a) · · · O(11a)	0.934	2.912	2.029	152

Key to symmetry operations relating designated atoms to reference atoms at (x, y, z): (*a*) 1.0 − x, y, 0.5 − z; (*b*) 0.5 + x, 0.5 + y, +z; (*c*) 0.5 − x, −0.5 + y, 0.5 − z.

0.058 and 0.061. All calculations were performed with the SHELX-76 package of crystallographic programs.[21] (Tables 4—7). Tables of the isotropic and anistropic temperature factors and the hydrogen atom co-ordinates appear as a Supplementary Publication [Sup. No. 56374 (3 pp.)].* The calculated and observed structure factors are available on request from the Editorial Office.

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* For details of the Supplementary Publications scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

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