Synthesis of Some New Pyrimido[1,6-*a*]pyrimidines. Isolation of Stable Covalent Hydrated Pyrimido[1,6-*a*]pyrimidines

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4-Amino-5-phenylpyrimidine **2** reacts with alkyl malonic acids **3** in acetic anhydride under reflux to give 2(4)*H*-pyrimido[1,6-*a*]pyrimidines **4**. From these reactions some covalent hydrated pyrimido[1,6-*a*]pyrimidines **5** were also isolated, where the addition of the water molecule occurred to the 6,7 C=N bond. This covalent hydration is irreversible.

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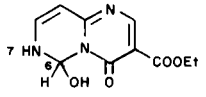
Derivatives of 4-aminopyrimidine have been used [1,2,3] in reactions with malonic acid or alkyl malonates [4,5,6] for the preparation of pyrimido[1,6-*a*]pyrimidine systems.

On the other hand, the phenomenon of covalent hydration in heterocyclic rings is of great interest and has been studied in pteridine systems [7-11], in quinazolines [12,13] and recently in pyrimido[4,5-*d*]pyrimidines [14]. Covalent hydrated pyrimido[1,6-*a*]pyrimidines **1** have been prepared and studied by Matsumoto *et al.* [5].



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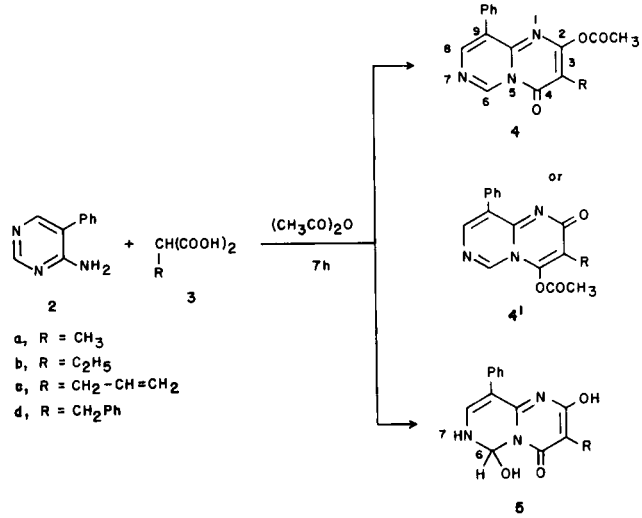
This work provides another example of covalent hydration in pyrimido[1,6-*a*]pyrimidine systems.

The reactions of 4-amino-5-phenylpyrimidine **2** with 2-alkylmalonic acids **3** (Scheme 1) were carried out with isomolecular amounts under reflux in excess of acetic anhydride [15] for 7 hours to give the condensation products 2(4)-oxo-3-alkyl-4(2)-acetoxy-9-phenylpyrimido[1,6-*a*]-pyrimidines **4a,b,c** and 2(4)-hydroxy-3-alkyl-4(2)-oxo-6-hydroxy-9-phenylpyrimido[1,6-*a*]pyrimidines **5a,b,c,d**. In the case of the reaction with **3d** only the product **5d** was isolated.

Scheme I



The structural assignment of the isolated compounds **4** and **5** was made on the basis of the elemental analysis and spectroscopic data (ir, nmr, ms), which are summarized in Table I.

The compounds **4** showed in ir two peaks at 1770 and 1700 cm^{-1} for acetoxy- and CO group respectively [16], whereas the compounds **5** showed a peak at 3380-3200 cm^{-1} (NH), a peak at 2650 cm^{-1} (chelated OH) [5] and a peak at 1700 cm^{-1} (CO).

The ^1H nmr spectrum of the reaction products **4** gave for pyrimido protons peaks at δ 8.23-8.78 and δ 9.17-9.6 which were analogous to those of the compounds **2** whereas for R group protons the signals were analogous to those of the compounds **3** [6].

The compounds **5** gave a peak at δ 7.95-8.35 for the C_6 proton, whereas the analogous proton in the compound **1** resonates at δ 8.45-8.76.

The C_6-OH, $C_{2(4)}$-OH and N_7-H protons of compounds **5** gave two broad peaks at δ 10.12-11.12 and δ 3.0-4.07 which disappeared with addition of deuteriumoxide. It is suggested that the C_6-OH and N_7-H protons gave the broad peak at δ 10.12-11.12 (2H). It is mentioned that the compound **1** gave for the analogous protons two broad peaks at δ 12.74 and δ 11.56 respectively [5].

Furthermore, the C_8 proton of **1** gave a peak at δ 7.5. The signal of the analogous proton of **5** was included into the aromatic area of the phenyl group.

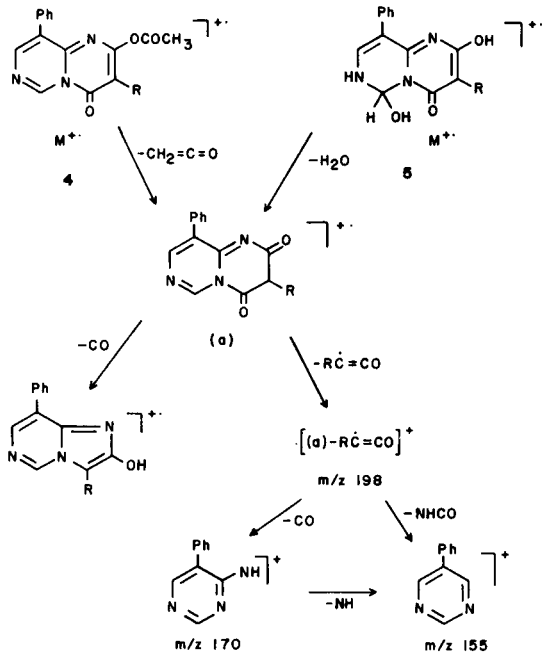
These data are in accordance with the assigned structure **5** for the hydrate, corresponding to the covalent addition of a molecule of water across the 6,7 C=N bond in the pyrimido[1,6-*a*]pyrimidine **5**. This covalent hydration was irreversible, since no loss of water was observed after staying for one day in anhydrous chloroform solution and even after addition of *N,N*-dicyclohexylcarbodiimide.

Examination of mass spectrum of **4** in comparison with that of **5** provided further evidence in support of the structure **5**.

Compounds **4** showed the base peak (a) which resulted from $M^{+\cdot}$ with loss of C_2H_2O. The same peak (a) resulted from $M^{+\cdot}$ of compounds **5** with loss of water. The fragmentation pattern after the ion peak (a) was almost the same

for both compounds **4** and **5** (Scheme 2).

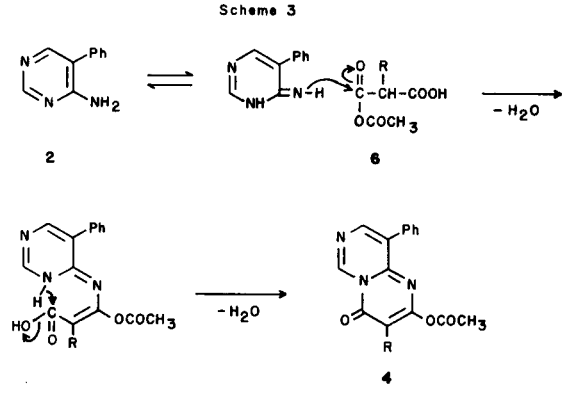
Scheme 2



The formation of the reaction products **4** and **5** could be explained by the mechanistic Schemes 3 and 4 respectively.

According to Scheme 3 initial nucleophilic substitution takes place on the mixed acetic anhydride **6** [17] and after elimination of two water molecules compounds **4** are formed.

Scheme 3



Concerning the formation of hydrated products **5** it is suggested (Scheme 4) that they could be produced from an intramolecular migration of the acetoxy group after the

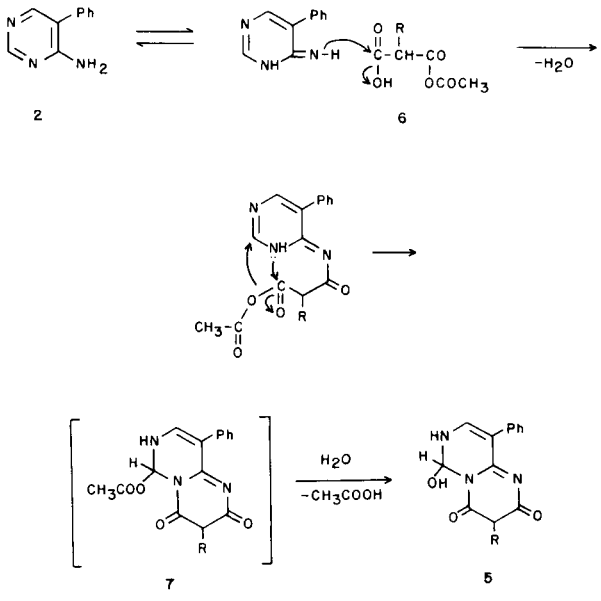
Table I

Physical, Analytical and Spectral Data of Compounds **4** and **5**

Compound	M p, °C recryst. from	Yield %	Molecular Formula MW	Analysis % Calcd/Found C	H	N	Spectral Data
4a	120-121 ethyl ether	4	$C_{16}H_{13}O_3N_3$ 295	65.08 64.98	4.44 4.46	14.24 14.54	ir (nujol): cm^{-1} 1770 (C=O), 1700 (C=O); nmr (deuteriochloroform): δ 2.1 (s, 3H), 2.3 (s, 3H), 7.13-7.8 (m, 5H), 8.23 (s, 1H), 9.58 (s, 1H); ms: m/z 295 (15) $M^{+\cdot}$, 253 (100), 225 (60), 198 (25), 170 (8)
4b	115-117 ethyl ether	7	$C_{17}H_{15}O_3N_3$ 309	66.02 65.98	4.89 4.85	13.59 13.26	ir (nujol): cm^{-1} 1770 (C=O), 1700 (C=O); nmr (deuteriochloroform): δ 1.17 (t, 3H), 2.13-2.78 (q, 2H), 2.28 (s, 3H), 7.17-7.78 (m, 5H), 8.25 (s, 1H), 9.6 (s, 1H); ms: m/z 309 (12) $M^{+\cdot}$, 267 (100), 252 (100), 239 (7), 224 (30), 198 (37)
4c	124-126 ethyl ether	3	$C_{18}H_{15}O_3N_3$ 321	67.29 67.04	4.71 5.01	13.08 13.01	ir (nujol): cm^{-1} 1750 (C=O), 1700 (C=O); nmr (deuteriochloroform): δ 2.17 (s, 3H), 2.47 (d, 2H), 4.63-5.33 (m, 2H), 5.33-6.05 (m, 1H), 7.07-7.58 (m, 5H), 8.78 (s, 1H), 9.17 (s, 1H); ms: m/z 321 (2) $M^{+\cdot}$, 279 (100), 269 (20), 198 (29), 170 (10)
5a	145-147 ethanol	11	$C_{14}H_{13}O_3N_3$ 271	61.99 61.49	4.83 4.66	15.49 15.27	ir (nujol): cm^{-1} 3200 (NH), 2640 (OH), 1700 (C=O); nmr (DMSO): δ 2.48 (s, 3H), 3.27 (s, br, 1H), 6.93-7.5 (m, 6H), 8.0 (s, 1H), 10.12 (s, v.br, 2H); ms: m/z 271 (2) $M^{+\cdot}$, 253 (79), 225 (39), 198 (100), 170 (23)
5b	136-138 ethanol	15	$C_{15}H_{15}O_3N_3$ 285	63.16 63.23	5.30 5.29	14.73 14.77	ir (nujol): cm^{-1} 3360-3180 (NH), 2650 (OH), 1700 (C=O); nmr (DMSO): δ 1.02 (t, 3H), 2.1-2.6 (q, 2H), 3.0 (s, br, 1H), 6.93-7.48 (m, 6H), 8.35 (s, 1H), 11 (s, v.br, 2H); ms: m/z 285 (5) $M^{+\cdot}$, 267 (92), 252 (100), 224 (20), 198 (71), 170 (7)
5c	132-134 ethanol	20	$C_{16}H_{15}O_3N_3$ 297	64.63 64.47	5.09 5.11	14.14 14.33	ir (nujol): cm^{-1} 3380-3200 (NH), 2650 (OH), 1700 (C=O); nmr (DMSO): δ 3.07 (d, 2H), 4.73-5.23 (m, 2H), 5.23-6.38 (m, 1H), 7.0-7.6 (m, 6H), 8.32 (s, 1H), 11.12 (s, v.br, 2H); ms: m/z 297 (2) $M^{+\cdot}$, 279 (7), 269 (4), 198 (9), 170 (8)
5d	128-130 chloroform	19	$C_{20}H_{17}O_3N_3$ 347	69.15 68.96	4.93 5.01	12.10 11.99	ir (nujol): cm^{-1} 3350-3200 (NH), 2650 (OH), 1700 (C=O); nmr (DMSO): δ 3.35 (s, 2H), 4.07 (s, v.br, 1H), 6.67-7.18 (m, 11H), 7.95 (s, 1H), 11.23 (s, v.br, 2H); ms: m/z 247 (4) $M^{+\cdot}$, 329 (38), 301 (5), 260 (8), 198 (12), 170 (38)

first elimination of a water molecule, leading to the acetyl derivatives **7**. This nucleophilic attack is analogous to that observed in the addition of barbituric acid, ethylacetoacetate, acetylacetone and other Michael reagents to purines, 8-azapurines and pteridines [18-21].

Scheme 4



The products intermediates **7** are probably hydrolyzed to the compounds **5** during the work up of the reaction mixture.

EXPERIMENTAL

All melting points were uncorrected and they were obtained with a Kofler hot-stage apparatus. The ir spectra were obtained with a Perkin-Elmer 281B spectrophotometer. The nmr spectra, reported in δ units, were obtained with a Varian A-60A spectrometer with tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi-Perkin-Elmer Model RMU-6L spectrometer, with an ionization energy of 70 eV. Elemental analysis were performed with a Perkin-Elmer analyzer Model 240-B.

Preparation of Starting Materials.

4-Amino-5-phenylpyrimidine **2** was prepared according to the procedure described in the literature [22].

General Procedure for the Preparation of **4** and **5**.

Compound **2** (0.01 mole, 1.71 g) and 0.01 mole of the substituted malonic acid **3** were added in 3 g of acetic anhydride and the mixture was refluxed with stirring for 7 hours. The excess of solvent was distilled in a rotator and the black resin obtained was chromatographed on a silica gel column with chloroform-ethyl acetate 1:1 as the eluant. The analytical and spectral data are summarized in Table I.

A byproduct from all the reactions was produced, namely 4-acetamido-5-phenylpyrimidine [23,24] in yield 40%, mp 132-133°, recrystallization from chloroform; ir (Nujol): cm^{-1} 3100-3140 (NH), 1760 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 2.55 (s, 3H), 7.1-7.63 (m, 5H), 7.73 (s, br, 1H), 8.37 (s, 1H), 8.78 (s, 1H); ms: m/z 213 (37) M^+, 198 (2), 170 (100), 144 (12), 117 (8).

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