Synthesis of Some New Pyrimido[1,6-*a*]pyrimidines

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4-Amino-5-arylpyrimidines **1** react with diethyl alkylmalonates **2** to give pyrimido[1,6-*a*]pyrimidines **4** in satisfactory yields. A possible mechanistic scheme and the spectral data of the reaction products are discussed.

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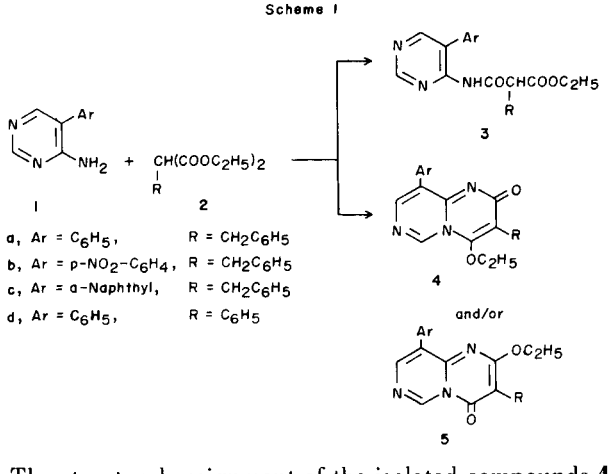
Condensed bicyclic systems, mostly pyrido[1,2-*a*]pyrimidines [1] or pyrido[2,3-*d*]pyrimidines [2] have been used as antibacterial agents. These systems are prepared from derivatives of 4-aminopyrimidine [2,3,4] and diethyl alkylmalonates [1,2,5]. The same reagents, have been recently used by Matsumoto *et al.* [6] for the preparation of some pyrimido[1,6-*a*]pyrimidines. However, the little known chemistry of these compounds led us to prepare and study such systems.

The reactions of 4-aminopyrimidines **1** with diethyl alkylmalonates **2** in excess (Scheme 1) were carried out under reflux for 3 hours to give when R = $CH_2C_6H_5$ the condensation products 2-oxo-3-benzyl-4-ethoxy-9-arylpyrimido[1,6-*a*]pyrimidines **4a,b,c** in satisfactory yields (45-55%). In one case, after 90 minutes reflux, the condensation product **3a** was also isolated. When R = C_6H_5 the reaction gave after prolonged reflux (20 hours) only in the case of **1d** the corresponding condensation product **4d** in low yield (25%), whereas no condensation product was isolated from the reactions with several other substituted diethyl malonates **2** (R = methyl, ethyl, propyl, butyl, allyl) even under more drastic conditions (heating in a Carius tube at 150-300° for 3-20 hours).

Scheme 1

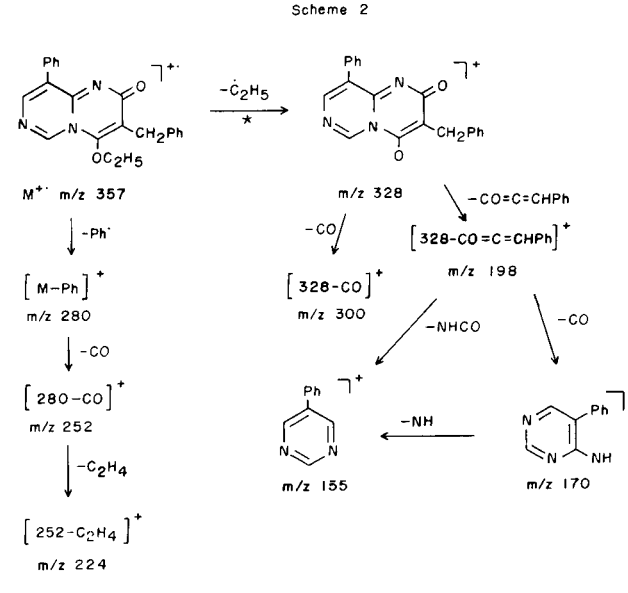


The structural assignment of the isolated compounds **4** was made on the basis of the elemental analysis and spectroscopic data (ir, nmr, ms), which are summarized in Table I. The compounds **4** showed an ir peak at 1680 cm^{-1} (C=O) and a peak at 1600 cm^{-1} (C=N), whereas the compound **3a** showed a peak at 3100 cm^{-1} (NH) and two peaks at 1700 and 1650 cm^{-1} (C=O).

The ^1H nmr spectrum of the reaction products **4** gave for pyrimido protons peaks at δ 8.23-8.38 and δ 9.72-9.88 which were analogous to those of the compounds **1**, whereas for R group protons, the signals were analogous to those of the compounds **2**.

In the mass spectra, the pyrimido[1,6-*a*]pyrimidines **4** gave besides the molecular ion M^+ which was the base peak, also peaks corresponding to ions $[M-29]^+$, $[M-29-CO]^+$, $[M-Ar-CO]^+$. A possible fragmentation pattern for compound **4a** is given in Scheme 2. Compound **3a** gave besides the peak for molecular ion, also a peak for the ion $[M-18]^+$ whereas the pyrimidine ring had a pattern similar to that of the compound **4a**.

Scheme 2



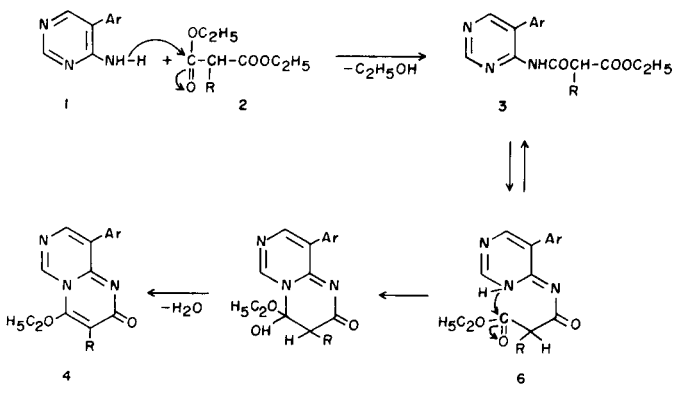
It should be noticed that the above data cannot argue in favor of the proposed structure **4**, instead of the other possible isomer **5**. However, the isolation of the intermediate **3a** which upon further heating gave **4a**, supports the following reaction mechanism (Scheme 3) according to which the condensation product **3** upon further cyclisation and elimination of water, gave the final product **4**.

Table I

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

Compound	Mp, °C recryst from	Yield %	Molecular Formula MW	Analysis % Calcd/Found C	H	N	Spectral Data
4a	127-128 chloroform	45	$C_{22}H_{19}O_2N_3$ 357	73.93 73.94	5.36 5.35	11.76 11.75	ir (nujol): cm^{-1} 1680 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 1.35 (tr, 3H, J = 6 Hz), 3.97 (s, 2H), 4.38 (q, 2H, J = 6 Hz), 7.02-7.85 (m, 10H), 8.28 (s, 1H), 9.72 (s, 1H); ms: m/z 357 (100)M^+, 328 (29), 300 (8), 280 (15), 251 (15), 224 (12), 198 (16), 170 (5), 155 (7), 128 (16)
4b	130-132 chloroform	55	$C_{22}H_{18}O_4N_4$ 402	65.67 65.71	4.47 4.48	13.93 13.97	ir (nujol): cm^{-1} 1680 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 1.4 (tr, 3H, J = 7 Hz), 3.95 (s, 2H), 4.37 (q, 2H, J = 7 Hz), 7.1-7.83 (m, 5H), 7.88 (d, 2H, J = 8 Hz), 8.36 (d, 2H, J = 8 Hz), 8.38 (s, 1H), 9.88 (s, 1H); ms: m/z 402 (100)M^+, 373 (30), 357 (40), 345 (10), 297 (25), 280 (5), 279 (5), 252 (10), 243 (30), 198 (30), 170 (10), 155 (8), 128 (15)
4c	159-160 chloroform	50	$C_{26}H_{21}O_2N_3$ 407	76.65 76.89	5.16 5.28	10.32 10.24	ir (nujol): cm^{-1} 1680 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 1.1 (tr, 3H, J = 7 Hz), 3.92 (s, 2H), 3.97 (q, 2H, J = 7 Hz), 7.2-7.6 (m, 5H), 7.89-8.2 (m, 7H), 8.33 (s, 1H), 9.8 (s, 1H); ms: m/z 407 (100)M^+, 378 (20), 350 (20), 273 (15), 264 (5), 258 (5), 236 (7), 198 (15), 178 (38)
4d	93-95 methanol	25	$C_{21}H_{17}O_2N_3$ 343	73.46 73.41	4.96 5.11	12.24 12.36	ir (nujol): cm^{-1} 1680 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 1.2 (tr, 3H, J = 7 Hz), 4.2 (q, 2H, J = 7 Hz), 7.2-7.7 (m, 10H), 8.23 (s, 1H), 9.78 (s, 1H); ms: m/z 343 (100)M^+, 314 (20), 286 (15), 266 (15), 238 (12), 198 (20), 171 (10), 155 (20), 128 (13)

Scheme 3



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and were uncorrected. The ir spectra were obtained with a Perkin-Elmer 281 B spectrophotometer, nmr spectra reported in δ units were recorded 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.

Preparation of Starting Materials.

4-Amino-5-arylpyrimidines **1a,b,c** were prepared according to the procedure described in the literature [7,8].

Preparation of 2-Oxo-3-alkyl-4-ethoxy-9-arylpyrimido[1,6-*a*]pyrimidines **4a,b,c,d**.

Compound **1** (0.01 mole) was added to excess (10 ml) of diethyl benzylmalonate **2** and the mixture was refluxed with stirring for 3 hours. The black resin obtained was chromatographed on a silica gel column with chloroform-methanol 20:1 as the eluent. In the case of diethyl phenylmalonate the mixture was refluxed for 20 hours. The analytical and spectral data are summarized in Table I.

N-4-(5-Phenylpyrimido)amide of 2-Benzylmonoethyl Malonate **3a**.

This compound was prepared as above, after 90 minutes reflux, mp, 141-142° (from methanol) in 2% yield; ir (Nujol): cm^{-1} 3100 (NH), 1700 (C=O), 1650 (C=O), 1600 (C=N); nmr (deuteriochloroform): δ 1.08-1.52 (m, 3H), 3.72 (s, 1H), 3.92 (s, 1H), 4.03-4.48 (m, 2H), 5.20 (br s, 1H), 6.50-7.52 (m, 10H), 8.18 (s, 1H), 9.60 (s, 1H); ms: m/z 375 (20) M^+, 357 (100), 328 (100), 300 (30), 280 (15), 251 (20), 198 (44), 170 (10), 155 (18), 128 (44).

Anal. Calcd. for $C_{22}H_{21}O_3N_3$ (MW 375): C, 70.38; H, 5.64; N, 11.19. Found: C, 70.39; H, 5.78; N, 10.99.

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