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TWO DIRECTIONS OF THE REACTION OF 4-BROMOBENZALDEHYDE WITH SUBSTITUTED ACETOPHENONES AND UREA. SYNTHESIS OF ARYL-SUBSTITUTED PYRIMIDIN-2-ONE AND HEXAHYDROPYRIMIDO[4,5-*d*]PYRIMIDIN-2,7-DIONE

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Condensation of 4-bromobenzaldehyde, urea, and 4-alkyl-substituted acetophenones gave substituted hexahydro-1H,8H-pyrimido[4,5-d]pyrimidin-2,7-diones or 1H-pyrimidin-2-ones, depending on the substituent on the acetophenone ring and the nature of the solvent (i-PrOH, BuOH, AcOH). The corresponding 5-bromopyrimidin-2-ones were formed on bromination of these compounds. The structures of these compounds were confirmed by IR, UV, and ^{1}H NMR spectroscopy.

Keywords: 4-alkylacetophenones, aminopyrimidines, 4-bromoacetaldehyde, 5-bromo-1H-pyrimidin-2-ones, hexahydro-1H,8H-pyrimido[4,5-*d*]pyrimidin-2,7-diones, 4,6-diaryl-1H-pyrimidin-2-ones, chloropyrimidines, bromination, condensation.

A revived interest in the Biginelli reaction – the three component condensation of aromatic aldehydes, ureas, and carbonyl compounds (β-keto esters, β-diketones, etc.) – which permits the preparation of hydrogenated pyrimidin-2-ones, among which are compounds with high biological activity [1-4], is the reason for our continuation of the investigation of the modification of the Biginelli reaction using aromatic ketones. To synthesize hydrogenated pyrimidin-2-ones [5] we used 4-bromobenzaldehyde (**1**) and a series of aromatic ketones with the aim of preparing 4-bromophenyl derivatives of pyrimidin-2-one. Acetophenone (**2a**), 4-methylacetophenone (**2b**), and 4-butylacetophenone (**2c**)were chosen as the aromatic ketones.

Condensation of the aldehyde **1**, acetophenone **2a**, and urea in a mole ratio of 1:1:4 in 2-propanol in the presence of concentrated HCl did not give the expected products 4-(4-bromophenyl)-6-phenyl-3,4-dihydro-1H-pyrimidin-2-one (**3a**) or 4-(4-bromophenyl)-6-phenyl-1H-pyrimidin-2-one (**4a**). The product of the reaction under these conditions was 4,5-bis(4-bromophenyl)-8a-phenyl-3,4,4a,5,6,8a-hexahydro-1H,8H-pyrimido[4,5-*d*]-pyrimidin-2,7-dione (**5**) (scheme 1, Table 1). Its composition ans structure were confirmed by microanalysis, IR, UV, and ^{1}H NMR spectra. For example, two carbonyl stretching frequencies at 1695 and 1668 cm^{-1} were observed in the IR spectrum and absorptions above 260 nm were absent from the UV spectrum. The latter indicates the presence of unconjugated aromatic groups in the molecule. When the concentration of the solution was increased and the ratio of the reactants change to 1.5:1:3 the pyrimidinone **4a** (Table 1) was isolated from the reaction mixture in addition to compound **5**.

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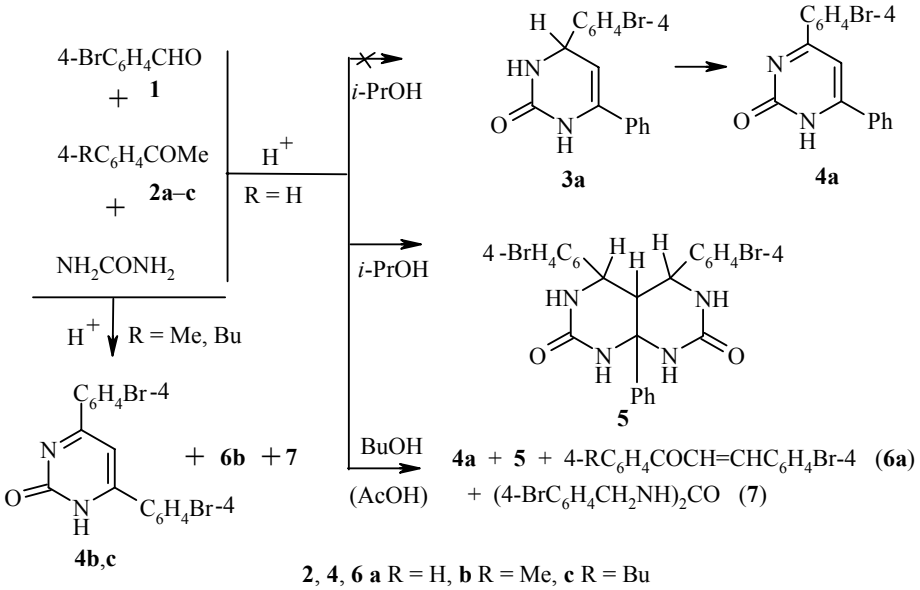
Scheme 1



2, **4**, **6 a** R = H, **b** R = Me, **c** R = Bu

When the reaction was carried out in butanol the yield of compound **4a** increased, but the main product remained the pyrimidopyrimidine **5** (Table 1). 4-Bromochalcone **6a** was also isolated and the formation of N,N'-bis(4-bromobenzyl)urea (**7**) was shown by ^{1}H NMR spectroscopy. Increasing the reaction time led to decrease in the yield of **5a** and an increase in the yield of the chalcone **6a** which may be associated with hydrolytic decomposition of the pyrimidopyrimidine **5**. It was shown that when compound **5** was boiled in butanol containing concentrated HCl it was converted completely into the pyrimidine **4a** and the chalcone **6a** (cf. [6]).

Condensation of compounds **1**, **2a**, and urea in acetic acid led to the preferential formation of the pyrimidin-2-one **4a** (Table 1). This compound was also obtained from the addition of urea to chalcone **6a** in acid catalysis conditions analogous to those reported in [7, 8].

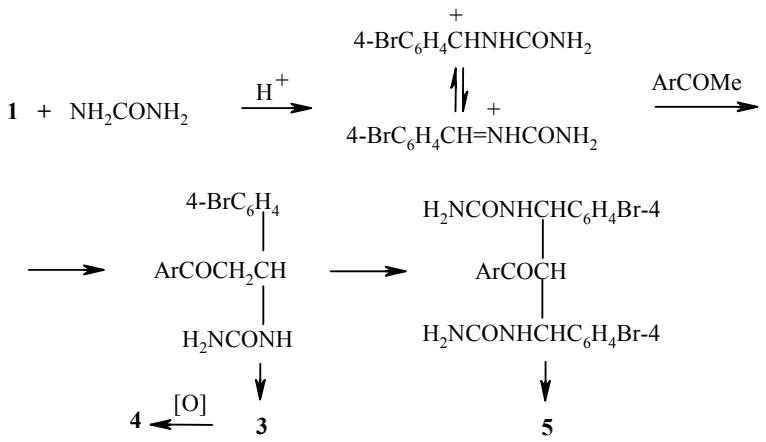
The behavior of acetophenones **2b** and **2c** in the three component condensations differed from that of acetophenone **2a**. The reaction products obtained were, respectively 4-(4-bromophenyl)-6-(4-tolyl)-1H-pyrimidin-2-one (**4b**) and 4-(4-bromophenyl)-6-(4-butylphenyl)-1H-pyrimidin-2-one (**4c**), together with disubstituted ureas **7** and the chalcone (**6b**) (see Scheme 1) (Table 1, experiments 6-8). Pyrimidopyrimidines analogous to compound **5** were not isolated from these experiments.

TABLE 1. Condensation of 4-Bromobenzaldehyde (**1**) with Acetophenones (**2**) and Urea (U)

Experiment	Acetophenone	Reaction conditions			Reaction products and yields, %			
		Medium	Reaction time, h	Reagent ratio **1** : **2** : U	**4**	**5**	**6**	**7**
1	**2a**	*i*-PrOH/HCl	6	1 : 1 : 4	—	63	—	—
2	**2a**	*i*-PrOH/HCl	6	1.5 : 1 : 3	13 (**4a**)	49		
3	**2a**	BuOH/HCl	6	1.5 : 1 : 3	21 (**4a**)	42	16 (**6a**)	
4	**2a**	BuOH/HCl	14	1.5 : 1 : 3	17 (**4a**)	25	23 (**6a**)	
5	**2a**	AcOH/HCl	5	1.5 : 1 : 3	34 (**4a**)	5	4 (**6a**)	7
6	**2b**	*i*-PrOH/HCl	8	1.5 : 1 : 3	48 (**4b**)	—	10 (**6b**)	21
7	**2c**	*i*-PrOH/HCl	6	1.5 : 1 : 3	15 (**4c**)	—	—	7
8	**2c**	BuOH/HCl	6	1.5 : 1 : 3	25 (**4c**)	—	—	10

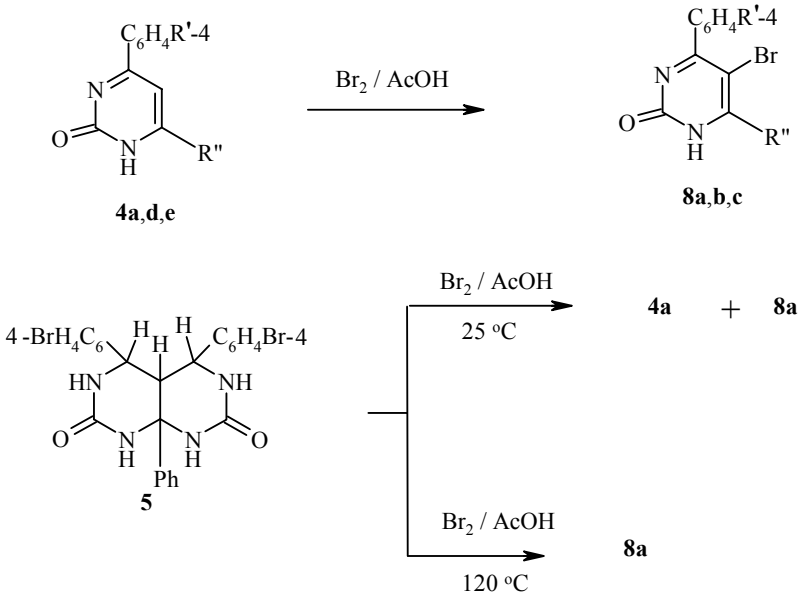
A scheme for this reaction can be proposed in agreement with data from [5, 9]. In the first stage an acid catalysed condensation of the aldehyde with urea occurs to give an intermediate immonium ion. This ion reacts further with the acetophenones to give an open chain intermediate which cyclizes stepwise into the dihydropyrimidinones **3** (Scheme 2).

Scheme 2



Depending on the reaction conditions and the increased reactivity of the immonium ion and the relatively low reactivity of the carbonyl groups in the intermediates diureidoalkylation may occur at the same time as formation of compound **3** with subsequent cyclization to the pyrimidopyrimidines **5**. During the reaction the immonium ion is the hydrogen acceptor for the dehydrogenation of the dihydropyrimidinones **3** which are converted in this way into the substituted benzyl- or dibenzylureas **7** [10].

Scheme 3



4a, **8a** R' = Br, R" = Ph; **4d**, **8b** R' = H, R" = Ph; **4e**, **8c** R' = R" = H

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %					mp, °C (solvent)	Yield, %
		C	H	Br (Cl)	N	$[M]^+$*, *m/z*		
1	2	3	4	5	6	7	8	9
4a	$C_{16}H_{11}BrN_2O$	58.44 / 58.73	3.40 / 3.39	24.30 / 24.43	8.42 / 8.56	326.0055 / 326.0055	272-275 (EtOH–dioxane)	34
4b	$C_{17}H_{13}BrN_2O$	59.98 / 59.83	3.76 / 3.84	23.50 / 23.42	8.49 / 8.21	340.0199 / 340.0212	335-337 (EtOH–DMF)	47
4c	$C_{20}H_{19}BrN_2O$	62.57 / 62.67	4.86 / 4.99	20.40 / 20.85	7.19 / 7.31	382.0675 / 382.0681	310-312 (EtOH–DMF)	25
5	$C_{24}H_{20}Br_2N_4O_2$	51.42 / 51.82	3.71 / 3.62	29.30 / 28.73	9.77 / 10.07	*	327-329 (80% AcOH)	63
6b	$C_{16}H_{13}BrO$	62.97 / 63.80	4.40 / 4.35	27.60 / 26.53	—	300.0 / 300.0	157-159 (EtOH)	23
7	$C_{15}H_{14}Br_2N_2O$	45.52 / 45.25	3.52 / 3.54	39.90 / 40.15	6.79 / 7.04	395.9499 / 395.9474	265–267 [14] (EtOH)	21
8a	$C_{16}H_{10}Br_2N_2O$	47.47 / 47.32	2.69 / 2.48	39.06 / 39.35	6.36 / 6.90	403.9185 / 403.9161	268-272 (EtOH–dioxane)	55
8d	$C_{16}H_{11}BrN_2O$	58.43 / 58.73	3.44 / 3.39	25.10 / 24.43	8.79 / 8.56	326.0066 / 326.0055	246-251 (EtOH)	57

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
8e	$C_{10}H_7BrN_2O$	47.35 47.83	2.74 2.81	32.00 31.83	10.82 11.16	249.9741 249.9742	207-211 (EtOH)	68
9a	$C_{16}H_{10}BrClN_2$	55.67 55.59	2.83 2.92	(10.00) (10.26)	8.01 8.11	343.9715 343.9716	154-155 (EtOH)	74
9b	$C_{17}H_{12}BrClN_2$	56.96 56.77	3.33 3.36	(10.08) (9.86)	7.68 7.79	357.9873 357.9873	156-159 (EtOH)	68
9c	$C_{20}H_{18}BrClN_2$	60.10 59.79	4.61 4.51	(9.02) (8.82)	6.99 6.97	400.0343 400.0342	74-76 (EtOH)	50
9d	$C_{16}H_9Br_2ClN_2$	45.74 45.26	2.37 2.14	(8.20) (8.35)	6.40 6.60	421.8818 421.8822	205-207 (EtOH)	70
10a	$C_{21}H_{20}BrN_3$	64.32 63.96	5.18 5.11	20.99 20.27	10.80 10.66	393.0837 393.0841	159-161 (EtOH)	75
10b	$C_{22}H_{22}BrN_3$	64.08 64.71	5.28 5.43	19.20 19.57	10.42 10.29	407.0989 407.0997	178-180 (EtOH)	94
10c	$C_{25}H_{28}BrN_3$	67.16 66.66	6.19 6.26	17.40 17.74	9.46 9.33	449.1474 449.1467	112-113 (EtOH)	88
10d	$C_{21}H_{19}Br_2N_3$	53.31 53.30	4.07 4.05	33.90 33.76	8.85 8.88	470.9939 470.9947	170-174 (EtOH)	80

***** High resolution mass spectra, except for compound **6b**. In addition to $[M^+]$ (*m/z* 554), compound **5** gave a fragment ion (*m/z* 327.0113), calculated for $C_{16}H_{12}BrN_2O$ [M - $BrC_6H_4CH{=}NHCONH_2]^+$ *m/z* 327.0133.

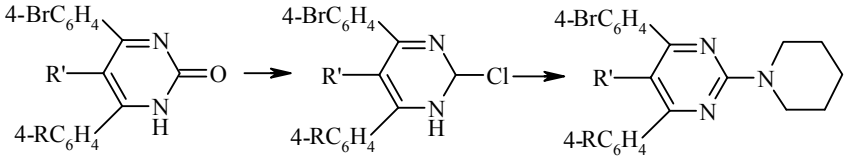
Bromination of pyrimidine derivatives at position 5 of the ring occurred readily in the presence of donor substituents [11]. An example of bromination of unsubstituted pyrimidin-2-one is known [12]. It was shown that preliminary covalent hydration facilitated bromination. There are no reports of the behavior of aryl-substituted pyrimidin-2-ones in the literature.

We have established that ready bromination of aryl-substituted pyrimidinones is a general phenomenon. For example, 4,6-diphenyl- (**4d**) and 4-phenyl-1H-pyrimidin-2-ones (**4e**) are brominated to give the corresponding 5-bromoderivatives **8b** and **8c** (Scheme 3).

Compound **5** underwent no change on treatment with bromine in chloroform. It appeared to be unstable to bromination in acetic acid and two products which appeared to be aryl-substituted pyrimidin-2-ones were isolated from the reaction mixture. One of these was compound **4a** while the second was the product of bromination of **4a** which was confirmed by bromination of **4a.** The structure 5-bromo-4-(4-bromophenyl)-6-phenyl-1H-pyrimidin-2-one (**8a**) was assigned to this compound on the basis of its ^{1}H and ^{13}C NMR spectra. The signal of the carbon atom $C_{(5)}$–Br of the pyrimidine ring was observed to strong field at 101.59 ppm in the ^{13}C NMR spectrum.

The 4,6-diaryl-5R'-2-chloropyrimidines **9a-d** were obtained by treatment of compounds **4a-c** and **8a** with $POCl_3$. Compounds **9a-d** were converted into the 4,6-diaryl-5'-2-piperidinopyrimidines **10a-d** by nucleophilic substitution with piperidine (Scheme 4).

Scheme 4



4a–c, **8a** **9a–d** **10a–d**

9a, 10a R = R' = H, **9b,10b** R = Me, R' = H, **9c, 10c** R= Bu, R' = H; **9d, 10d** R= H, R' = Br

We have shown that acetophenone and its 4-alkyl-substituted analogs behave differently in condensation with 4-bromobenzaldehyde and urea. It has been established that bromination of aryl-substituted pyrimidin-2-ones with bromine in acetic acid occurs readily and identically to give the corresponding 5-bromopyrimidin-2-ones.

TABLE 3. Spectroscopic Characteristics of the Compounds Synthesized

Com-pound	IR spectrum, $\nu_{C=O}$, cm^{-1}	UV spectrum (EtOH), λ_{max}, nm (log ε)	^{1}H NMR spectrum, δ, ppm (*J*, Hz) in CF_3COOH
1	2	3	4
4a	1625	278.6 (4.062), 348.4 (3.994)	7.74 (1H, s, $C_{(5)}$–H); 7.87 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 8.02 (5H, s, Ph); 8.16 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4)
4b	1618	7.6 (3.928), 349.9 (3.880)	2.66 (3H, s, CH_3); 7.70 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.77 (1H, s, $C_{(5)}$–H); 8.02 (4H, s, *p*-$CH_3C_6H_4$); 8.12 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4)
4c	1615	7.1 (4.310), 349.4 (4.272)	1.08 (3H, t, *J* = 7.0, CH_3); 1.56 (2H, m, CH_2); 1.83 (2H, m, CH_2); 2.95 (2H, t, *J* = 8.0, CH_2); 7.72 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.78 (1H, s, $C_{(5)}$–H); 7.96-8.10 (4H, m, *p*-$C_4H_9C_6H_4$); 8.15 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4)

TABLE 3 (continued)

1	2	3	4
5*	1695, 1668	253.5 (3.336)	2.91 (1H, t, *J* = 6.0, ArCH–CH–CHAr); 4.21 (2H, d, *J* = 6.0, Ar–CH–); 6.76 (2H, s, 2NH); 6.94 (4H, d, *J* = 8.5, *o*,*o*'-H, 2*p*-BrC_6H_4); 6.99–7.01 (5H, m, *m*,*m*'-H, *p*-H, C_6H_5, NH); 7.11-7.19 (2H, m, *o*,*o*'-H, C_6H_5); 7.27 (4H, d, *J* = 8.5, *m*,*m*'-H, 2*p*-BrC_6H_4)
6b	1658	225 (3.436), 317 (3.700)	2.56 (3H, s, CH_3); 7.48 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.58-7.76 (5H, m, *p*-$CH_3C_6H_4$, –COCH=CH–); 7.97 (1H, d, *J* = 15.0, –COCH=CH–); 8.01 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4)
7	1665	261 (3.070), 270 (3.070), 276 (2.861)	4.55 (4H, s, $2CH_2$); 7.16 (4H, d, *J* = 8.0, *o*,*o*'-H, 2*p*-BrC_6H_4); 7.56 (4H, d, *J* = 8.0, *m*,*m*'-H, 2*p*-BrC_6H_4)
8a*[2]	1675	248 (4.062), 343 (3.725)	7.95 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.94 (2H, d, *J* = 7.5, *o*,*o*'-H, C_6H_5); 7.83 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4); 7.74-7.94 (3H, m, *m*,*m*'-H, *p*-H, C_6H_5)
8d	1668	244 (4.110), 345 (3.844)	7.75-7.97 (6H, m, *m*,*m*'-H, *p*-H, $2C_6H_5$); 7.99 (4H, d, *J* = 8.0, *o*,*o*'-H, $2C_6H_5$)
8e	1662	228 (4.045), 338 (3.616)	7.76-7.96 (3H, m, *m*,*m*'-H, *p*-H, C_6H_5); 8.00 (2H, d, *J* = 8.0, *o*,*o*'-H, C_6H_5); 9.09 (1H, s, $C_{(6)}$–H)
9a	—	257 (4.395), 313 (4.410)	7.83 (2H, d, *J* = 7.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.90–8.10 (3H, m, *m*,*m*'-H, *p*-H, C_6H_5); 8.22 (2H, d, *J* = 7.0, *m*,*m*'-H, *p*-BrC_6H_4); 8.26 (2H, d, *J* = 8.0, *o*,*o*'-H, C_6H_5); 8.57 (1H, s, $C_{(5)}$–H)
9b	—	261 (4.075), 285 (3.994), 316 (4.125)	2.62 (3H, s, CH_3); 7.63 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.93 (2H, d, *J* = 8.5, *o*,*o*'-H, *p*-$CH_3C_6H_4$); 8.13 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4); 8.23 (2H, d, *J*=8.5, *m*,*m*'-H, *p*-$CH_3C_6H_4$); 8.51 (1H, s, $C_{(5)}$–H)
9c	—	262 (4.376), 285 (4.298), 317 (4.420)	1.09 (3H, t, *J* = 7.0, CH_3); 1.56 (2H, m, CH_2); 1.83 (2H, m, CH_2); 2.91 (2H, t, *J* = 8.0, CH_2); 7.67 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.93 (2H, d, *J* = 8.5, *o*,*o*'-H, *p*-$C_4H_9C_6H_4$); 8.18 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4); 8.25 (2H, d, *J* = 8.5, *m*,*m*'-H, *p*-$C_4H_9C_6H_4$); 8.54 (1H, s, $C_{(5)}$–H)
9d*[2]	—	256 (4.243), 304 (4.130)	7.68-7.83 (3H, m, *m*,*m*'-H, *p*-H, C_6H_5); 7.86 (4H, s, *o*,*o*'-H, *m*,*m*'-H, *p*-BrC_6H_4); 7.87 (2H, d, *J* = 8.0, *o*,*o*'-H, C_6H_5)
10a	—	229 (4.527), 270 (4.660), 366 (3.855)	1.98 (6H, s, $3CH_2$); 4.17 (4H, s, $2CH_2$); 7.58 (1H, s, $C_{(5)}$–H); 7.74 (2H, d, *J* = 7.5, *o*,*o*'-H, *p*-BrC_6H_4); 7.75-7.91 (3H, m, *m*,*m*'-H, *p*-H, C_6H_5); 8.00 (2H, d, *J* = 7.5, *m*,*m*'-H, *p*-BrC_6H_4); 8.08 (2H, d, *J* = 8.0, *o*,*o*'-H, C_6H_5)
10b	—	232 (4.399), 270 (4.453), 366 (3.710)	1.98 (6H, s, $3CH_2$); 2.58 (3H, s, CH_3); 4.16 (4H, s, $2CH_2$); 7.48 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.57 (1H, s, $C_{(5)}$–H); 7.73 (2H, d, *J* = 8.5, *o*,*o*'-H, *p*-$CH_3C_6H_4$); 8.02 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4); 8.17 (2H, d, *J* = 8.5, *m*,*m*'-H, *p*-$CH_3C_6H_4$)
10c	—	232 (4.466), 267 (4.560), 366 (3.854)	1.07 (3H, t, *J* = 7.5, CH_3); 1.52 (2H, m, CH_2); 1.77 (2H, m, CH_2); 1.99 (6H, c, $3CH_2$); 2.88 (2H, t, *J* = 8.0, CH_2); 4.18 (4H, c, $2CH_2$); 7.57 (1H, s, $C_{(5)}$–H); 7.58 (2H, d, *J* = 8.0, *o*,*o*'-H, *p*-BrC_6H_4); 7.84 (2H, d, *J* = 8.5, *o*,*o*'-H, *p*-$C_4H_9C_6H_4$); 7.93 (2H, d, *J* = 8.0, *m*,*m*'-H, *p*-BrC_6H_4); 8.08 (2H, d, *J* = 8.5, *m*,*m*'-H, *p*-$C_4H_9C_6H_4$)
10d	—	267 (4.535), 360 (3.667)	1.94 (6H, s, $3CH_2$); 4.08 (4H, s, $2CH_2$); 7.63-7.76 (4H, m, C_6H_4); 7.76-7.98 (5H, m, C_6H_4)

* ^{1}H NMR spectrum recorded in DMSO-d_6.

*[2] ^{1}H NMR spectrum at 400.13 MHz.

EXPERIMENTAL

IR spectra of the compounds synthesized were recorded in KBr disks on a Bruker Vector 22 spectrophotometer. UV spectra of ethanol solutions were recorded on Specord M-40 spectrophotometer. Mass spectra were recorded with a Finnigan MAT-8200 by direct insertion of samples into the ion source. ^{1}H NMR spectra in trifluoroacetic acid with CH_2Cl_2 as internal standard (5.32 ppm) were recorded on Bruker AC-200 (200 MHz) and Bruker WP-200 SY (200 MHz) instruments. The spectra of compounds **8a** and **8d** were recorded with a Bruker AM-400 (400 MHz) instrument. The ^{13}C NMR spectrum of compound **8a** in DMSO-d_6 was recorded on a Bruker AM-400 spectrometer (100 MHz). The course of reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 strips with $CHCl_3$ as eluent. Data for new compounds are cited in Tables 2 and 3.

4,5-Bis(4-bromophenyl-8a-phenyl-3,4,4q,5,6,8-hexahydro-1H,8H-pyrimido[4,5-*d*]pyrimidin-2,7-dione (5) and 4-(-bromophenyl)-6-phenyl-1H-pyrimidin-2-one (4a). 4-Bromobenzaldehyde (9.2 g, 50 mmol) was added to a solution of urea (9.0 g, 150 mmol) in 2-propanol (70 ml) and conc. HCl (5 ml). The reaction mixture was stirred and kept at room temperature overnight. A voluminous precipitate formed. Acetophenone (6.0 g, 50 mmol) was added to the reaction mixture which was boiled for 3 h, more urea (3.0 g, 50 mmol) was added and boiling was continued for 3 h. The precipitate was removed after cooling, and was washed successively with methanol, $NaHCO_3$ solution, water, and ethanol, and then dried to give the pyrimidopyrimidine **5** (6.9 g). A further amount of **5** (1.85 g) was obtained by dilution of the filtrate with methanol or ethanol. Overall yield 8.75 g (63%) (experiment 1, Table 1).

Experiments 2-4 were carried out analogously. In experiment 2 treatment of the filtrate with ethanol gave compound **4a** (2.5 g, 13%). In experiments 3 and 4 the precipitate consisted of a mixture of compounds **4a**, **5**, and **6a**. The precipitate was boiled with methanol (75 ml) and filtered. A precipitate of 4-bromochalcone **6a**, mp 127-129°C [13], was formed from the filtrate. An additional quantity of the chalcone was precipitated from the methanol filtrate with water. The solid which did not dissolve in methanol was heated with 2:1 ethanol–dioxane (50 ml) and filtered. The pyrimidine **4a** precipitated from the filtrate. The insoluble residue was dissolved on boiling in 1:2 ethanol–acetic acid. The precipitate which formed on cooling was filtered off, washed with $NaHCO_3$ solution, water, and ethanol, then dried to give compound **5**. More **5** can be obtained by adding an equal volume of ethanol to the filtrate.

When the reaction was carried out in acetic acid (experiment 5), the precipitate obtained was substituted dibenzylurea **7**. The precipitate obtained by addition of an equal volume of methanol to the filtrate was filtered off and washed with methanol to give pyrimidine **4a**. Water (150 ml) was added to the filtrate, the precipitate which formed was separated, boiled with ethanol and filtered. Chalcone **6a** precipitated from the ethanol filtrate. The residue insoluble in ethanol was a mixture of compounds **5** and **7** according to the ^{1}H NMR spectrum

4-4-Bromophenyl)-6-phenyl-1H-pyrimidinone (4a). A. A mixture of 4-bromochalcone **6a** (4.6 g, 16 mmol) and urea (3.0 g, 50 mmol) in 2-propanol (30 ml) and conc. HCl (5 ml) was boiled for 7.5 h. The precipitate was filtered off, washed with ethanol, $NaHCO_3$ solution, water, and again with ethanol to give pyrimidine **4a** (3.0 g, 49%).

B. Compound **5** (10.0 g, 18 mmol) was boiled in butanol (60 ml) and conc. HCl (10 ml) for 13 h. The precipitate was filtered off and washed with water to give chalcone **6a** (1.1 g). Methanol (100 ml) was added to the filtrate and further chalcone (1.2 g) precipitated. Overall yield of chalcone **6a** 45%. Pyrimidine **4a** (2.6 g, 44%) precipitated on addition of water (150 ml) to the methanol filtrate.

4-(4-Bromophenyl)-6-(4-tolyl)-1H-pyrimidin-2-one (4b). The reaction was carried out analogously to experiments 1 and 2 above. A mixture (12.8 g) of pyrimidine **4b**, chalcone **6b**, and urea **7** (63:13:24 from ^{1}H NMR spectroscopic data) was obtained. The residue was boiled in ethanol (50 ml) and filtered. Chalcone **6b** separated from the filtrate. Crystallization of the insoluble residue from a mixture of ethanol and DMF gave the pyrimidine **4b**.

4-(4-Bromophenyl)-6-(4-butylphenyl)-1H-pyrimidin-2-one (4c) was prepared analogously to compound **4b** (experiments 7 and 8, Table 1).

Bromination of Compound 5. A. Bromine (10.4 g, 65 mmol) was added dropwise to a solution of compound **5** (18.0 g, 320 mmol) in acetic acid (90 ml) and the mixture was stirred for 8 h at room temperature. The reaction mixture was evaporated, methanol (100 ml) and pyridine (20 ml) added, the mixture boiled for 1 h, cooled, the precipitate filtered off and washed with water and methanol to give pyrimidine **4a** (6.8 g).

An equal volume of water was added to the filtrate. The precipitate was filtered off and washed with ethanol to give **5-bromo-4-(4-bromophenyl)-6-phenyl-1H-pyrimidin-2-one (8a)** (3.0 g, 24%). ^{13}C NMR (100.61 MHz), DMSO-d $_6$, δ, ppm: 101.59 ($C_{(5)}$), 122.44 (C-Br, C_6H_4Br), 127.44 ($C_{m,m'}$,C_6H_5), 128.52 ($C_{o,o'}$, C_6H_5) 128.85 (C_p, C_6H_5), 130.52, 130.71 ($C_{o,o}$, $C_{m,m'}$, C_6H_4Br), 137.93 (C_i, C_6H_4Br), 138.66 (C_i, C_6H_5), 158.82 ($C_{(4)}$), 164.86 ($C_{(6)}$), 166.16 (C=O).

B. The reaction mixture obtained by adding bromine to compound **5** in acetic acid, as in the preceding experiment, was boiled for 0.5 h and treated analogously to give compound **8a** (7.1 g, 55%).

5-Bromo-4,6-diphenyl-1H-pyrimidin-2-one (8b). A solution of bromine (0.8 g, 5 mmol) in acetic acid (5 ml) was added to a solution of compound **4d** (1.0 g, 4 mmol) in acetic acid (10 ml). A precipitate formed in 1-2 min. The mixture was boiled for 1 h, cooled, and the precipitate was filtered off. Methanol (15 ml) and pyridine (1 ml) were added to the residue, the mixture was heated for 15 min, cooled, and 10% HCl added until the solution was acidic. The precipitate was filtered off, washed with water and dried to give pyrimidine **8d** (0.75 g).

Compounds **8a** and **8c** were made analogously.

2-Chloro-4-(4-bromophenyl)-6-phenylpyrimidine (9a). A mixture of pyrimidine **4a** (21.0 g, 64 mmol) and $POCl_3$ (75 ml) was boiled for 4h, the excess of $POCl_3$ was evaporated in vacuum, the residue was poured onto ice, triturated, and kept for several hours at room temperature. The precipitate was filtered off, washed with $NaHCO_3$ solution and water to give chloropyrimidine **9a** (16.4 g, 74%).

Compounds **9b,c,** and **d** were made analogously.

4-(4-Bromophenyl)-6-phenyl-2-piperidinopyrimidine (10a). A mixture of chloropyrimidine **9a** (1.0 g, 2.9 mmol), piperidine (0.8 g, 9.0 mmol), and ethanol (10 ml) was boiled for 5 h, the precipitate was filtered off and washed with water and ethanol to give compound **10a** (0.85 g, 75%).

Compounds **10b, c,** and **d** were prepared analogously.

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