PYRIMIDINES

XXI. 5-Substituted 2-Hydroxy-4,6-diphenylpyrimidines*

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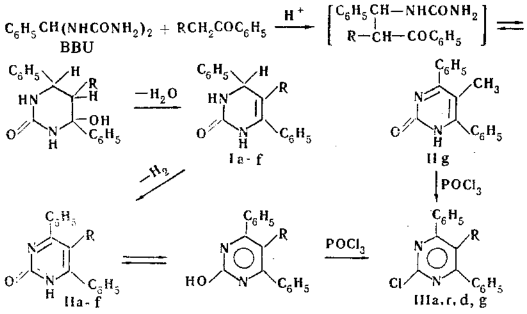
The condensation of ω-substituted acetophenones with benzylidenebisurea in an acid medium has given 5-R-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidones. The analogous condensation of propiophenone forms 5-methyl-2-hydroxy-4,6-diphenylpyrimidine. The tetrahydro derivatives obtained are readily dehydrogenated to 5-R-2-hydroxy-4,6-diphenylpyrimidines.

2-Hydroxypyrimidines having a substituent in position 5 are generally obtained by the condensation of α-substituted β-dicarbonyl compounds or their derivatives with urea [2]. Some 5-acyl- and 5-alkoxycarbonylpyrimidines can be obtained by Biginelli's method [3a]. When strong electron-donating groups are present in the pyrimidine ring, the direct introduction of halogens [3b], and in some cases that of a nitro group [4], into position 5 of the ring is possible.

One of us has shown that the condensation of acetophenone, urea, and benzaldehyde (it is more convenient to use previously-prepared benzylidenebisurea) leads to the formation of 2-hydroxy-4,6-diphenylpyrimidine [5].

When ω-substituted acetophenones are used in the condensation, 5-R-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidines (I) are formed.



R = a Cl, b OCH_3, c OC_6H_5, d p-$NO_2C_6H_4O$, e SC_6H_5, f $NHCOCH_3$, g CH_3

The structure of the compounds was established on the basis of their chemical properties and by analogy with literature information [5, 6], and was confirmed by a consideration of their IR and UV spectra. The properties of compounds I are given in Table 1.

The UV spectra of the compounds I that we obtained are similar to the UV spectrum of 2-hydroxy-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine [5]. Apparently the different substituents in position 5 in compounds I have an insignificant influence on the absorption in UV light (**Fig. 1**).

Additional information on the structure and properties of compounds I was obtained by the dehydrogenation of these compounds to the corresponding 5-R-2-hydroxy-4,6-diphenylpyrimidines (II) (we shall call compounds II 2-hydroxypyrimidines, although they exist in the tautomeric form of 2-oxodihydropyrimidines).

We found that dehydrogenation takes place in good yield when suspensions of I (a-c, e, f) in xylene are boiled with chloranil [7]. Because of its poor solubility in boiling xylene, Id is not dehydrogenated under these conditions. Its dehydrogenation takes place smoothly by successive bromination and dehydrobromination [8, 9]. Information on compounds II is given in Table 2.

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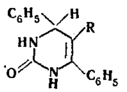
*For part XX, see [1].

Table 1. 5-R-2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidines (I)



R*	Mp, °C (from ethanol)	Molecular weight		UV spectrum		IR spectrum, ν_{CO}, cm^{-1}	Empirical formula	Found, %				Calculated, %				Reaction time, min	Yield, %
		found†	calcu-lated	λ_{max}, nm	log ε			C	H	N	Cl, S	C	H	N	Cl, S		
Cl	202—203			276	3,72	1690	$C_{16}H_{13}ClN_2O$	67,12 67,21	4,35 4,40	10,08 10,10	Cl 12,45 12,56	67,50	4,57	9,86	Cl 12,45	30	34
OCH_3	208—210	280	280	286	3,77	1690	$C_{17}H_{16}N_2O_2$	72,67 72,69	5,75 5,85	9,85 9,86		72,83	5,75	10,00		120	42
OC_6H_5	200—202	342	342	278	3,89	1685	$C_{22}H_{18}N_2O_2$	77,23 77,40	5,33 5,38	8,49 8,54		77,17	5,30	8,18		25	80
$OC_6H_4NO_2$	278(decomp.)			294	4,16	1700	$C_{22}H_{17}N_3O_4$			10,58 10,65				10,80		30	90
SC_6H_5	232—235	358	358	282	3,87	1690	$C_{22}H_{18}N_2OS$	74,21 74,32	4,95 4,82	7,66 7,58	S 8,78 8,68	73,73	5,06	7,82	S 8,92	30	55
$NHCOCH_3$	240—243			280	3,73	1680	$C_{18}H_{17}N_3O_2$	70,84 70,74	6,08 5,97	13,52 13,59		70,35	5,68	13,80		20	50

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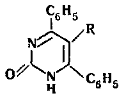
*I (R = H), mp 228-230°C; IR spectrum: 1690 cm^{-1} (ν_{CO}); UV spectrum: λ_{max} 278 nm, log ε 3.75.

†The molecular weight was determined mass spectrometrically.

Table 2. 5-R-2-Hydroxy-4,6-diphenylpyrimidines (II)



R*	Mp, °C (form ethanol)	UV spectra		IR spectrum, ν_{CO}, cm^{-1}	Empirical formula	Found, %			Calculated, %			Time of dehydrogenation, min	Yield, %
		λ_{max}, nm	log ε			C	H	N	C	H	N		
CH_3 †	238—240	250 345	4,15 4,10	1640	$C_{17}H_{14}N_2O$	77,52	5,39	10,52	77,80	5,35	10,70	660†	42†
Cl	235—236	250 350	4,16 3,85	1670	$C_{16}H_{11}ClN_2O$	68,12	4,01	10,20	68,05	3,92	9,90	40	90
OCH_3	238—240	252 354	4,11 4,00	1650	$C_{17}H_{14}N_2O_2$	—	—	10,24	—	—	10,17	60	64
OC_6H_5	257—260	250 354	4,17 3,94	1650	$C_{22}H_{16}N_2O_2$	77,50	4,70	8,21	77,50	4,70	8,24	90	94
$OC_6H_4NO_2$	288—290 ‡	252 300	4,16 4,20	1660	$C_{22}H_{15}N_3O_4$	68,32	3,93	10,85	68,60	3,90	10,92	—	80
SC_6H_5	275—277	250 320	4,31 3,78	1650	$C_{22}H_{16}N_2OS$	73,87	4,38	—	73,96	4,49	—	40	90
$NHCOCH_3$	302—304	238 334	4,14 3,91	1650	$C_{18}H_{15}N_3O_2$	70,76	5,02	—	70,80	4,92	—	60	90

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*II (R = H), mp 237-239°C; IR spectrum: ν_{CO} 1640 cm^{-1}; UV spectrum: λ_{max}, nm (log ε): 252, (4.17), 345 (4.11).

†The times and yields are given for the condensation reaction.

‡From acetic acid.

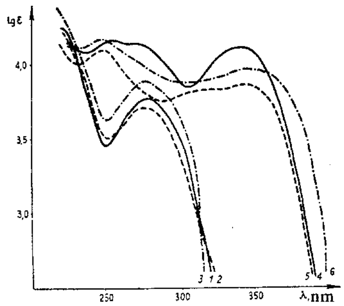

Fig. 1. UV spectra: 1) 2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine; 2) Ia; 3) Ic; 4) 2-hydroxy-4,6-diphenylpyrimidine; 5) IIa; 6) IIc.

In the IR spectra of II, the absorption band of the CO group is shifted in the low-frequency direction as compared with I. This shift is caused by the formation of a new double bond conjugated with the CO group [5]. In the UV spectra of II, the absorption maximum is shifted in the long-wave direction as compared with I.

A comparison of the spectral characteristics of I and II (Tables 1 and 2) shows that they change regularly on passing from the 2-oxotetrahydropyrimidines to the 2-hydroxypyrimidines. It is obvious that the positions of the absorption bands of the CO groups in the IR spectra and the positions of the absorption maxima in the UV spectra can be used to determine the structure of these groups of compounds.

It is known that, on being heated with phosphorus oxychloride, hydroxypyrimidines are converted into chloropyrimidines [10]. On being boiled with phosphorus oxychloride, compounds II (a, d, g) are also converted into 5-R-2-chloro-4,6-diphenylpyrimidines (IIIa, d, g).

The ω-substituted acetophenones react with BBU with different degrees of readiness according to the nature of the substituent R. In the case of acceptor substituents R, the condensation takes place under mild conditions with the formation of I. Propiophenone reacts less readily than acetophenone (the reaction time must be increased twofold), forming 2-hydroxy-5-methyl-4,6-diphenylpyrimidine (IIg).

It is interesting that the condensation of ω-chloroacetophenone with BBU gave 5-chloro-2-oxo-4,6-diphenylpyrimidine (Ia). At the same time, the condensation of ω-bromoacetophenone with BBU gave a substance containing no halogen. This product was identified as 2-hydroxy-4,6-diphenylpyrimidine. Its formation is possibly connected with the ready dehydrobromination of the condensation product. The use of hydrogen bromide as catalyst in place of hydrogen chloride in order to decrease the possibility of dehydrobromination did not change the course of the reaction. The large volume of the bromine atom also apparently plays a certain part in this reaction.

EXPERIMENTAL

The UV spectra were recorded on an SF-4 spectrophotometer in ethanolic solution. The IR spectra were recorded on UR-10 and UR-20 spectrophotometers. Tablets of KBr with c 0.5 and 0.25% were used.

The melting points of the substances were determined on a Kofler block. Typical experiments are described below, the other compounds being obtained similarly.

Condensation of ω-chloroacetophenone with benzylidenebisurea (BBU). A mixture of 5.0 g (0.03 mole) of ω-chloroacetophenone, 6.23 g (0.03 mole) of BBU, and 20 ml of absolute n-butanol containing 1.09 g (0.03 mole) of hydrogen chloride was heated until a solution had been formed (bath temperature 120°C). The solvent was distilled off in vacuum and the residual oil was treated with ether to extract the unchanged ketone and benzaldehyde and was then triturated with 5% $NaHCO_3$ solution. The precipitate that formed was filtered off, washed with water to eliminate urea (negative reaction with p-dimethylaminobenzaldehyde), and dried in vacuum over P_2O_5. The dry product was washed with absolute ethanol, giving 2.62 g of Ia. An additional amount of the same product (0.57 g) precipitated when the ethereal solution was allowed to stand. The total yield was 3.19 g. The product is sparingly soluble in ether, petroleum ether, benzene, and chloroform, moderately soluble in ethanol, and soluble in methanol, acetone, dioxane, and β-ethoxyethanol.

When the condensation was carried out in acetic acid, Ia was again formed, but in lower yield.

Condensation of propiophenone with BBU. Under the conditions of the experiment described above, 7.3 ml of propiophenone and 11.4 g of BBU in 50 ml of absolute n-butanol containing 2.3 g of hydrogen chloride gave 6.0 g of IIg. It was purified by recrystallization from ethanol.

Condensation of ω-bromoacetophenone with BBU. A mixture of 5.0 g (0.041 mole) of ω-bromoacetophenone, 8.53 g (0.041 mole) of BBU, and 20 ml of absolute n-butanol containing 3.31 g (0.041 mole) of hydrogen bromide was boiled for 30 min (bath temperature 120°C). The precipitate was filtered off, washed with ether, ethanol, 5% $NaHCO_3$, solution and water, and was then dried in vacuum over P_2O_5 and recrystallized from ethanol. This gave 2.2 g of 2-hydroxy-4,6-diphenylpyrimidine with mp 235-238°C, which was identified by comparison with an authentic sample [5].

5-Chloro-2-hydroxy-4,6-diphenylpyrimidine (IIa). A mixture of 1.0 g (3.52 mM) of Ia, 1.04 g (4.18 mM) of chloranil, and 14 ml of xylene was boiled until a solution had been formed. On cooling, a white precipitate deposited; it was filtered off and washed with absolute ether. The yield of crude product was 0.96 g. The substance is insoluble in ether, n-heptane, and water, moderately soluble in chloroform, dioxane, and ethanol, and less soluble in acetic acid.

2-Hydroxy-5-(p-nitrophenoxy)-4,6-diphenylpyrimidine (IId). At room temperature, a solution of 0.3 ml (6 mM) of bromine in 6 ml of acetic acid was added to a solution of 1.5 g (3.9 mM) of Id in 60 ml of acetic acid. The mixture was boiled for 15 min and the solvent was distilled off in vacuum. The residue was treated with 3 ml of ethanol and 6 ml of pyridine and was boiled for 1 hr. After cooling, 30 ml of water was added to the mixture and the precipitate that deposited was filtered off and washed with 5% HCl solution, water, ethanol, and ether. Weight 1.2 g.

2,5-Dichloro-4,6-diphenylpyrimidine (IIIa). A mixture of 1.0 g (3.54 mM) of IIa and 35 ml (35.4 mM) of phosphorus oxychloride was boiled for 7 hr. The excess of $POCl_3$ was distilled off in vacuum. A few pieces of ice were added to the resinous residue and it was treated with 5% $NaHCO_3$ solution. The solid product was washed with water to neutrality and dried in vacuum over P_2O_5. Weight 0.42 g (70%). After sublimation in vacuum and recrystallization from ethanol, mp 143-146°C. Found %: C 63.53; H 3.22; Cl 22.88; N 9.20. $C_{16}H_{10}Cl_2N_2$. Calculated %: C 63.59; H 3.31; Cl 23.46; N 9.30. UV spectrum: λ_{max} 302 nm; log ε 4.14.

2-Chloro-5-methyl-4,6-diphenylpyrimidine (IIIg). A mixture of 2.6 g of IIg and 12.5 ml of phosphorus oxychloride was boiled for 5 hr. The further treatment and isolation of the product were carried out as described in the preceding experiment. This gave 1.7 g (60%) of IIIg. Mp 136-138°C (from ethanol). Found %: Cl 12.67. $C_{17}H_{13}ClN_2$. Calculated %: Cl 12.61.

2-Chloro-5-(p-nitrophenoxy)-4,6-diphenylpyrimidine (IIId). A mixture of 1.0 g of IId, 4 ml of phosphorus oxychloride, and 0.3 ml of dimethylaniline was boiled for 3 hr. The product was worked up as in the preceding experiment. Yield 0.84 g (80%). Mp 218-220°C (from ethanol). Found %: Cl 8.35. $C_{22}H_{14}ClN_3O_3$. Calculated %: Cl 8.70. UV spectrum: λ_{max} 302 nm, log ε 4.51.

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