PYRIMIDINES

XXIV. SYNTHESIS OF PYRIMIDOPYRIMIDINES AND THEIR CONVERSION TO 5H-INDENO[1,2-d]PYRIMIDINES*

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Condensation of substituted acetophenones with arylidenebisureas at 50° C has given 2,7-dioxo-4,5,8'-triaryldecahydropyrimido[4,5-d]pyrimidines. The latter, on boiling with CF_3COOH, are converted into 2-oxo-4,5-diaryl-5H-indeno[1,2-d]pyrimidines, whose structure has been confirmed by spectral methods and by independent synthesis from 3-phenyl-1-indanone and arylidenebisureas.

Condensation of substituted acetophenones with arylidenebisureas gives 2-oxo-4,6-diaryl-1,2,3,4-tetrahydropyrimidines (I) or 2-oxo-4,6-diarylpyrimidines (II) [2-4]. Since the formation of II by the dehydrogenation or disproportionation of I during the course of the reaction [5] would be reduced or completely avoided by a reduction in the temperature, we condensed acetophenone with arylidenebisureas (ABU) at 50° C. However, instead of the expected I, or a mixture of I and II, another compound was isolated, with molecular formula $C_{24}H_{20}N_4O_2R_2$ (where R is the substituent in the benzene ring of the ABU). This compound may be considered as having been formed from 1 mole of acetophenone, 2 moles of urea, and 2 moles of the aldehyde, with the elimination of water.

The presence of hydrogenated pyrimidine ring cannot be deduced unambiguously by the positions of the C=O, NH, and CH_{arom} absorption bands in the IR spectra of these compounds. The correspondence

TABLE 1. NMR Spectra* of IVa-d

Compound	Chemical shift, ppm	Ratio of integral intensities †
	$CH_{arom}-C^{4}H(C^{5}H)-C^{4'}H-CH_{CH_3}$	
IVa	A) 6.70 m — 4.36 d — 2.99 tr — — I=6 Hz	2 : 1
	B) — — 4.75 dd — 3.24 tr — — I=6 Hz	2 : 1
IVb	A) 6.75 m — 4.34 d — 2.93 tr — 1.82 s I=6 Hz	2 : 1 : 6
	B) — — 4.75 d — 3.21 tr — 2.10 s I=6 Hz	2 : 1 : 6
IVc	A) 6.66 m — 4 36 d — 2.95 tr — 1.75 s I=6 Hz	2 : 1 : 3
	B) — — 4.65 d — 3.12 m — 1.77 s I=6 Hz	2 : 1 : 3
IVd	A) 6.55 m — 4.21 d — 2.88 tr — — I=6 Hz	2 : 1

* Solvent A) CF_3COOH, B) pyridine; m) multiplet, d) doublet, dd) double doublet, tr) triplet, s) singlet.

† The integral curve in the 7.5-6.0-ppm region (solvent CF_3COOH) corresponds to a greater number of protons than expected for IV, because of protonation of the NH group, and also solvation effects [9].

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* For part XXIII, see [1].

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TABLE 2. 2,7-Dioxo-4,5,8'-triaryldecahydropyrimido[4,5-d]pyrimidines (IV)

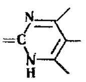
Compound	Reaction time, hr	mp, °C	UV spectra, λ_{max}, log ε, nm	Molecular formula	Found, %				Calculated, %				Yield, %
					C	H	N	F	C	H	N	F	
IVa	15	305—308	254 (2.52) 259 (2.61) 264 (2.53)	$C_{24}H_{22}N_4O_2 \cdot {}^1/_2H_2O$	70.98	5,40	13.78	—	70.80	5.65	13.80	—	59
IVb	7	309—314	264 (2.61)	$C_{26}H_{26}N_4O_2 \cdot {}^1/_2H_2O$	69.76	6.15	12.26	—	70.27	6.30	12.61	—	57
IVc	8,5	301—303	252 (2.65) 258 (2.68) 262 (2.62)	$C_{25}H_{24}N_4O_2 \cdot {}^1/_2H_2O$	70.93	6.03	13.19	—	71.29	5.98	13.30	—	60
IVd	2 (78°)	309—312	264 (3.00) 271 (2.93)	$C_{24}H_{20}F_2N_4O_2$	—	—	12.95	8.72	—	—	12.90	8.75	56
IVe	8,5	270—272	233 (3.84) 259 (3.00) 265 (3.05) 276 (3.02) 283 (3.00)	$C_{25}H_{24}N_4O_3 \cdot {}^1/_2H_2O$	69.04	5.73	12.77	—	68.63	5.76	12.80	—	65

of the UV absorption maxima with those of the substituted toluenes (see Table 2) suggests that the only chromophoric system present is the unconjugated benzene ring.

Condensation of aliphatic aldehydes with urea yields hydrogenated pyrimidines [7,8], probably by a double aminoalkylation at the activated CH_2 group, followed by cyclization onto the carbonyl group. Acetophenone is known to give a bisaminomethyl derivative on aminomethylation [6]. Therefore, we suggest that, under the reaction conditions, acetophenone and 2 moles of the benzylidenebisurea (BBU) yield the diureido derivative, which cyclizes to give 2,7-dioxo-4,5,8'-triphenyldecahydropyrimido[4,5-d]pyrimidine (IVa). The NMR spectral data are in agreement with the proposed structure (see Table 1) (in view of the low solubilities of IV, the spectra were obtained in CF_3COOH and in pyridine).

Compounds IVb-e were obtained from the substituted acetophenones and ABM at 50° C (see Table 1 and 2).

Acid hydrolysis of IVa gave, in addition to urea and benzaldehyde, chalcone and 2-oxo-4,6-diphenylpyrimidine, while IVb gave p-methylchalcone and 2-oxo-4-phenyl-6-tolylpyrimidine.

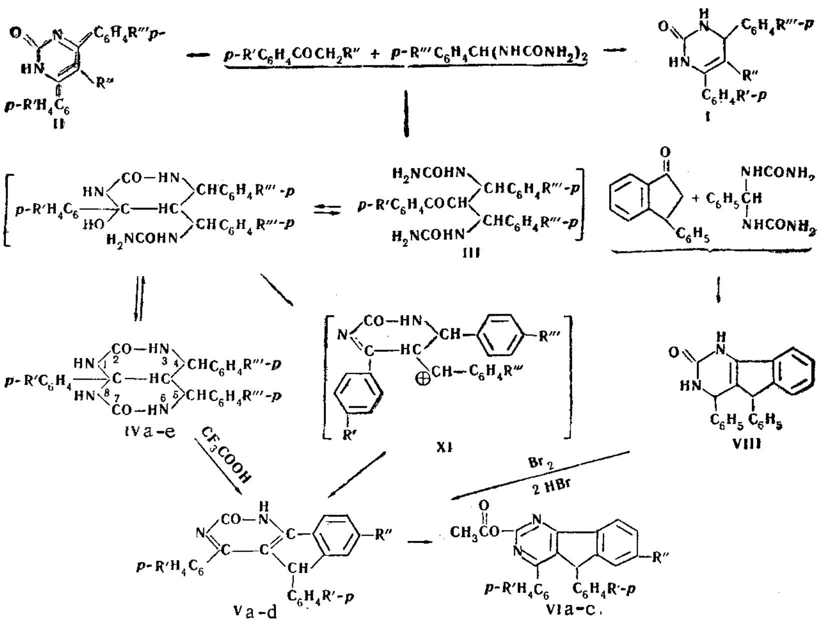
It has been shown that solutions of IV in CF_3COOH, on standing, undergo an irreversible change, which is speeded up considerably by heat. On boiling IVa in CF_3COOH, a compound was isolated with the composition $C_{23}H_{16-18}N_2O$, having an IR absorption band at 1640 cm^{-1} ($\nu_{C=O}$) characteristic of dehydrogenated pyrimidine derivative of type II. The UV spectrum of the compound (λ_{max} (log ε), nm: 275 (4.12) and 355 (4.16) is similar to that of 2-oxo-4,6-diphenylpyrimidine [2-4]. From the structure of IVa, and the analytical and comparative spectral data, we suggest that two compounds possessing the  :

fragment could be formed, namely, 2-oxo-4,6-diphenyl-5-benzylpyrimidine (VII, mol. wt. 338), or 2-oxo-4,5-diphenyl-5H-indeno[1,2-d]pyrimidine (Va, mol. wt. 336) (see scheme on top of page following). The mol. wt., as determined by mass spectrometry, was 336, which supports structure Va.

In order to confirm their structures, V and VII were synthesized independently. Starting from 3-phenyl-1-indanone and ω-benzylacetophenone, condensation with BBU gave 2-oxo-4,5-diphenyl-1,2,3,4-tetrahydro-5H-indeno[1,2-d]pyrimidine (VIII) and 2-oxo-4,6-diphenyl-5-benzyl-1,2,3,4-tetrahydropyrimidine (IX), respectively, which were dehydrogenated by the bromination—dehydrobromination method. Compound VIII gave a product identical with Va obtained by treatment of IVa with CF_3COOH.

Acetylation of the compound obtained gave 2-acetoxy-4,5-diphenyl-5H-indeno[1,2-d]pyrimidine (VIa). The IR and UV spectral data are given in Table 4 and in the Experimental.

Dehydrogenation of IX gave VII, which on acetylation gave 2-acetoxy-4,6-diphenyl-5-benzylpyrimidine (X). Both compounds differed from Va and VIa.



IV a $R'=R'''=H$; b $R'=H$, $R'''=CH_3$; c $R'=CH_3$, $R'''=H$ d $R'=H$, $R'''=F$; e $R'=OCH_3$, $R'''=H$. V a $R'=R''=H$; b $R'=H$, $R''=CH_3$; c $R'=F$, $R''=H$; d $R'=H$, $R''=OCH_3$. VI a $R'=R''=H$, b $R'=H$, $R''=CH_3$; c $R'=F$, $R''=H$

It would appear that the indenopyrimidine Va is obtained by the cyclization of the carbonium ion XI under acid conditions, and that this could be formed from the ureido derivative. Carbonium ions of a similar type in the aromatic hydrocarbon series are known to cyclize to fluorene derivatives [10-13].

Compounds Vb-d (Table 3) and their 2-acetoxy derivatives (Table 4) were prepared in a manner similar to Va and VIa.

Cyclization of the corresponding carbonium ions in Vb-d could give two isomers, depending on which of the aryl residues in the 4- and 6-positions of the pyrimidine ring is involved in cyclization. Independent synthesis, and a consideration of mass spectral data, allow us to draw conclusions concerning the structure of these compounds.

Compounds Vf and Ve [f) $R=CH_3O$, $R'=R''=H$; and e) $R=CH_3$, $R'=R''=H$] were synthesized by condensation of 3-phenyl-1-indanone with p-methoxy- and p-methylbenzylidenebisurea, and were found to differ from Vb and Vd (Table 3).

In the mass spectrum of Va* ($R_4=C_6H_5$), the only lines occurring at high mass number were those with m/e 336 and 233 (mol. wt. 103). In the spectra of Vf ($R_4=CH_3C_6H_4$) and Ve ($R_4=CH_3OC_6H_4$) lines were observed with respective m/e values of 350 and 233 (mol. wt. 127), and 366 and 233 (mol. wt. 133). In the

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* The mass spectra were determined on a modernized MI-1305 instrument (the sample being introduced into the ion source) by L. Yu. Ivanovskii, to whom the authors express their sincere thanks. R_4 is the substituent in the 4-position of the indenopyrimidine.

TABLE 3. 2-Oxo-4,5-diaryl-5H-indeno[1,2-d]pyrimidines (V)

Compound	R	R'	R''	mp, °C	Molecular formula	Found, %				Calculated, %				Yield, %
						C	H	N	F	C	H	N	F	
Va	H	H	H	280—282	$C_{23}H_{16}N_2O$	81.99	4.81	8.44	—	82.14	4.76	8.33	—	65
Vb	H	H	CH_3	280—285	$C_{24}H_{18}N_2O$	82,25	5.21	8.26	—	82.26	5.17	7.99	—	75
Vc	F	F	H	279—280	$C_{23}H_{14}F_2N_2O$	74,77	3.89	7,65	10.32	74.48	4.08	7.52	10,20	67
Vd	H	H	OCH_3	295—298	$C_{24}H_{18}N_2O_2$	79.14	4.94	7,80	—	78.66	4.95	7.65	—	58
Ve	OCH_3	H	H	270—271	$C_{24}H_{18}N_2O_2 \cdot H_2O$	74.93	5.49	7.32	—	75.00	5.24	7.28	—	77
Vf	CH_3	H	H	309—312	$C_{24}H_{18}N_2O \cdot H_2O$	78,11	5.17	7,60	—	78.26	5.43	7.60	—	60

TABLE 4. 2-Acetoxy-4,5-diaryl-5H-indeno[1,2-d]pyrimidines (VI)

	R	R′	R″	mp, °C	Molecular formula	Found, %				Calculated, %				UV spectra, λ_{max} (log ε), nm	NMR spectra in $CDCl_3$				Yield, %
						C	H	N	F	C	H	N	F		CH_{arom}	CH_{benzyl}	CH_{CH_3}	Ratio of integral intensities	
VIa	H	H	H	205—206	$C_{25}H_{18}N_2O_2$	79.93	5.00	7.56	—	79.35	4.79	7.40	—	196 (4,84); 244 (4,04); 300 (4,11); 318 (4,20)	7.20 m	5.60 s	2.35 s	14 : 1 : 3	98
VIb	H	H	CH_3	205—207	$C_{26}H_{20}N_2O_2$	80,00	5.38	7.57	—	79.57	5.13	7.14	—	198 (4,72); 263 (4,03); 257 (4,13); 322 (4,29)	7.22 m	5.62 s	2.36 s	13 : 1 : 6	98
VIc	F	F	H	194—196	$C_{25}H_{16}F_2N_2O_2$	72.84	3.73	7.04	9.18	72.45	3.89	6.76	9.17	244 (4,10); 274 (3,98); 318 (4,27)	7.44 m	5.71 s	2.36 s	12 : 1 : 3	96

spectra of Vb ($R_4 = C_6H_5$) and Vd ($R_4 = C_6H_5$), which are isomeric with the last two compounds, the difference in the mass numbers of the lines in question amounted to 103 m/e, as was also the case with Va. Since, in the mass spectrum of Vc, this difference was equal to 121 m/ e, of the two possible structures, this compound corresponds to 2-oxo-4,5-di(p-fluorophenyl)-5H-indeno[1,2-d]pyrimidine. Consequently, formation of the indene system from the carbonium ion XI involves an aromatic ring which possesses donor substituents, the presence of acceptor substituents apparently hinders the cyclization.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer in KBr disks, c 0.25%. The UV spectra were registered on an Unicam SP-700 C instrument, with alcohol as solvent. The NMR spectra were taken on a Varian A-60 instrument, using HMSO as standard (δ = 0).

The identity of the samples was established by comparison of their IR specta, and by the absence of depression of the mixed mp's.

2,7-Dioxo-4,5,8′-triphenyldecahydropyrimido[4,5-d]pyrimidine (IVa). A 2.0-g (16.6 mmole) quantity of acetophenone and 3.5 g (16.6 mmole) of benzylidenebisurea were heated with stirring in 25 ml of alcohol containing 0.6 g (16.6 mmole) of dry HCl, at 50° C for 15 hr. The precipitate was filtered off, washed with ether and then with sodium bicarbonate solution and water until neutral, to give 0.9 g of IVa, mp 270-276° C. Mp after recrystallization from alcohol, 305-308° C. On standing in the refrigerator, an additional 1.0 g of IVa separated from the filtrate, giving an over-all yield of 59%.

In some experiments, no precipitate separated. In such case, the mixture was evaporated, the residue carefully triturated with ether until there was no reaction with 2,4-dinitrophenylhydrazine and then with water (the oil crystallized). The solid was filtered off and washed with sodium bicarbonate solution and alcohol, mp 260-270° C. Recrystallization from alcohol gave 55-60% , mp 300-306° C.

Compounds IVb-e were obtained in a similar manner from p-substituted acetophenones and arylidenebisureas (Table 2).

Acid Hydrolysis of IVb. A 1.0-g (2.5 mmole) of IVb was boiled in 20 ml of butanol containing 0.5 ml of conc HCl for 4 hr. The oil which remained after removal of the solvent was treated with sodium bicarbonate solution and ether, leaving a residue of 0.45 g of 2-oxo-4-phenyl-6-tolylpyrimidine, mp 303-306° C (according to [4], mp 309-310° C). p-Methylchalcone was isolated from the filtrate.

From IVa there was similarly obtained 2-oxo-4,6-diphenylpyrimidine and chalcone.

2-Oxo-4,5-diphenyl-5H-indeno[1,2-d]pyrimidine (Va). A) A 1.0-g (2.5 mmole) quantity of IVa was boiled in 50 ml of CF_3COOH for 7 hr. The solvent was distilled off in vacuo, and the residual oil neutralized with sodium bicarbonate solution and treated with ether. The solid was filtered off and washed with alcohol to give 0.55 g (65%) of Va, mp 272-280° C (from alcohol). Similarly, from IV we obtained Vb-d (Table 3).

B) A 0.4-g (1.92 mmole) quantity of 3-phenyl-1-indanone [15] and 0.4 g (1.92 mmole) of benzylidenebisurea were boiled in 10 ml of absolute butanol containing 1.92 mmole of dry HCl, for 3 hr. The precipitate was filtered off, and washed with alcohol, ether, and sodium bicarbonate solution.

The product (0.5 g) was suspended in 10 ml of chloroform, and to the solution was added dropwise a solution of 0.2 g of bromine in 3 ml of chloroform. The solution became greenish in color, and a yellow precipitate quickly separated. The latter was filtered off and boiled with 0.5 ml of pyridine in 7 ml of alcohol for 5 min. The white precipitate was filtered off and washed with alcohol to give 0.46 of Va, mp 278-280° C.

2-Oxo-4-(p-methoxyphenyl)-5-phenyl-5H-indeno[1,2-d]pyrimidine (Ve). A 1.0-g (5.5 mmole) quantity of 3-phenyl-1-indanone and 1.3 g (5.5 mmole) of anisylidenebisurea were boiled in 13 ml of absolute butanol in the presence of 0.2 g (5.5 mmole) of dry HCl for 3 hr 30 min. Complete solution occurred at first, followed by the separation of a precipitate. The latter was filtered off and washed with sodium bicarbonate solution and alcohol to give 77% of Ve, mp 270-271° C (from alcohol).

2-Oxo-4-(p-tolyl)-5-phenyl-5H-indeno[1,2-d]pyrimidine (Vf) was obtained in a manner similar to Ve, from 3-phenyl-1-indanone and p-methylbenzylidenebisurea (Table 3).

2-Oxo-4,6-diphenyl-5-benzylpyrimidine (VII). To a suspension of 0.5 g (1.5 mmole) of 2-oxo-4,6-diphenyl-5-benzyl-1,2,3,4-tetrahydropyrimidine (IX) [14] in 15 ml of chloroform was added 0.24 g of bromine in 3 ml of chloroform. On adding the bromine, IX gradually dissolved. The solution was evaporated, and the residue was boiled for 30 min in 5 ml of methanol with the addition of 0.5 ml of pyridine. The resulting solution was evaporated, and the residue washed with water to give VII, mp 285-288° C (from alcohol). Found, %: C 81.47, 81.41; H 5.71, 5.40; N 8.38, 8.10. Mol wt 338 (by mass spectrometry). Calculated for $C_{23}H_{28}N_2O$, %: C 81.63; H 5.36; N 8.25. Ml wt 338. UV spectrum, λ_{max} (log ε) nm: 200 (4.84), 230 (4.16), and 333 (3.91).

2-Acetoxy-4,5-diphenyl-5H-indeno[1,2-d]pyrimidine (VIa). A 0.3-g (0.89 mmole) quantity of Va boiled in 8 ml of acetic anhydride for 2 hr. The solution was evaporated, then treated with water, and the solid was filtered off to give VIa, mp 205-206° C (from alcohol).

Compounds Vb and Vc (Table 4) were obtained in a similar manner. IR spectrum (ν), cm^{-1}: 1780 (C=O) and 1200 (C–O–C).

2-Acetoxy-4,6-diphenyl-5-benzylpyrimidine (X) was obtained in a manner similar to VIa by boiling VII in acetic anhydride, mp 189-192° C (from alcohol). Found, %: C 79.12, 79.14; H 4.96, 5.16; N 7.39, 7.30. Calculated for $C_{25}H_{20}N_2O_2$, %: C 78.92; H 5.29; N 7.36. NMR spectrum (in $CDCl_3$): 7.20 ($C-H_{arom}$), 4.20 ($C-H_{CH_2}$), 2.27 ($CH_{acetoxy}$) (15:2:3). UV spectrum, λ_{max} (log ε), nm : 197 (4.72) and 284 (4.08).

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