SYNTHESIS AND STRUCTURE OF 1-ARYL-2-ACETONYL(2-PHENACYL)-6,7,8,9-TETRAHYDROPYRIMIDO[4,5-b]QUINOLIN-4-ONES

M. Yu. Gavrilov, M. I. Vakhrin, and M. E. Konshin

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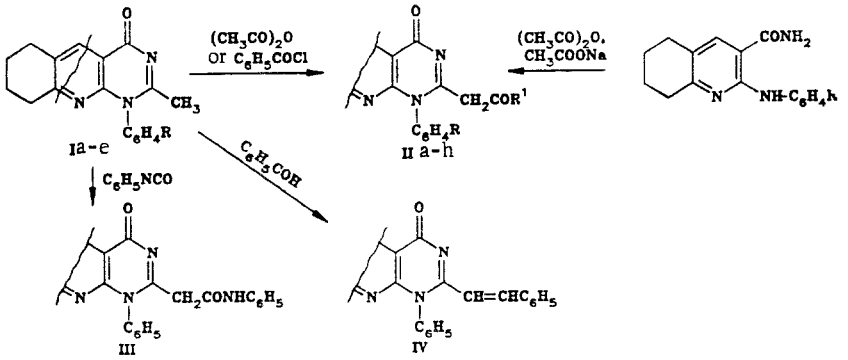
On reaction with acylating agents 1-aryl-2-methyl-6,7,8,9-tetrahydropyrimido-[4,5-b]quinolin-4-ones are acylated at the methyl group; they also react with benzaldehyde. On the basis of the PMR and UV spectra it was concluded that 1-aryl-2-acetonyl(2-phenacyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones exist in two tautomeric forms with strong intramolecular hydrogen bonds of the chelate type — enaminocarbonyl and enol.

1-Aryl-2,7-dimethyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines are relatively readily acetylated by acetic anhydride at the methyl group in the 2 position to give acetonyl derivatives [1]. We have studied the reactivity of the methyl group in the structurally similar 1-aryl-2-methyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (I).



IIa R=H, $R^1=CH_3$; II b R=*p*-CH_3, $R^1=CH_3$; II c R=*o*-CH_3, $R^1=CH_3$; II d R=*m*-CH_3, $R^1=CH_3$; II e R=*p*-CH_3O, $R^1=CH_3$; II f R=H, $R^1=C_6H_5$; II g R=*m*-CH_3, $R^1=C_6H_5$; II h R=*p*-CH_3O, $R^1=C_6H_5$

Compounds Ia-e on heating with excess acetic anhydride (method A) are, in fact, converted to 1-aryl-2-acetonyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones IIa-e (Table 1). Compounds IIa, b, d, e are obtained in lower yields when 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid amides are refluxed with acetic anhydride in the presence of anhydrous sodium acetate (method B).

Heating Ia, d, e with benzoyl chloride in pyridine leads to 1-aryl-2-phenacyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones IIf-h. The reaction also proceeds successfully when a solution of Ia, benzoyl chloride, and triethylamine in benzene is refluxed. The desired product IIf is formed in 56% yield. However, the reaction does not proceed with acetyl chloride under these conditions; this is evidently due to conversion of the acetyl chloride to an inactive ketene in the presence of bases.

Compound IIf can be obtained by the reaction of Ia with methyl benzoate under the conditions of the Claisen reaction. Refluxing Ia with phenyl isocyanate in benzene leads to 1-phenyl-2-(N-phenylcarbamoylmethyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (III).

Compound Ia forms 1-phenyl-2-styryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (IV) when it is heated with benzaldehyde.

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TABLE 1. Characteristics of the Synthesized Compounds

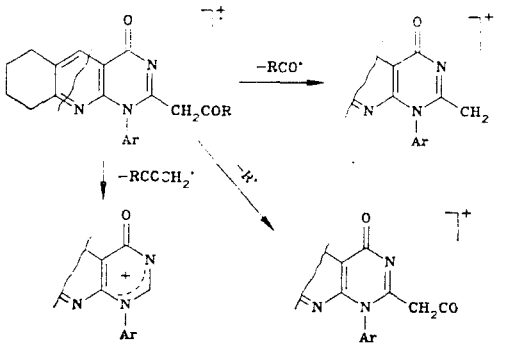
Compound*	mp, °C	TLC, R_f	PMR spectrum, chemical shifts, ppm						$H_{chelate\ ring}$	Found, %			Empirical formula	Calc., %			Yield, † %
			CH_2 (5,8)	CH_2 (6,7)	CH_3	=CH	H_{arom}	$H_{pyridine}$		C	H	N		C	H	N	
IIa	278...280	0,86	2,6	1,7	1,83	4,28	7,2	7,8	13,6	72,2	5,7	12,8	$C_{20}H_{19}N_3O_2$	72,1	5,7	12,6	50 (58)
IIb	259...260	0,90	2,67	1,76	1,9; 2,41	4,38	7,1	7,8	14,1	72,9	5,9	12,2	$C_{21}H_{21}N_3O_2$	72,6	6,1	12,1	60 (34)
IIc	240...242	0,93	2,65	1,65	1,84; 1,94	4,2	7,1	7,86	13,9	72,8	6,0	12,4	$C_{21}H_{21}N_3O_2$	72,6	6,1	12,1	30
IId	226...227	0,88	2,6	1,73	1,9; 2,36	4,2	7,0	7,83	13,83	72,8	6,3	12,0	$C_{21}H_{21}N_3O_2$	72,6	6,1	12,1	54 (38)
IIe	218...220	0,92	1,9	1,7	1,9; 3,85	4,35	7,0	7,9	13,8	70,0	6,0	11,4	$C_{21}H_{21}N_3O_3$	69,4	5,8	11,6	65 (33)
IIf	252...253	0,91	2,67	1,73	—	5,16	7,3	8,0	14,67	75,8	5,2	10,5	$C_{25}H_{21}N_3O_2$	75,9	5,4	10,6	40
IIg	274...275	0,68	2,66	1,73	2,36	5,0	7,2	7,96	13,6	75,9	5,3	10,0	$C_{26}H_{23}N_3O_2$	76,3	5,7	10,3	58
IIh	286...288	0,73	2,4	1,67	3,85	4,93	7,0	7,9	13,3	73,8	5,7	10,0	$C_{26}H_{23}N_3O_3$	73,4	5,5	9,9	53
III	237...239	0,92	2,5	1,66	—	4,03	7,03	7,7	13,1	73,4	5,3	13,6	$C_{25}H_{22}N_4O_2$	73,2	5,4	13,6	62
IV	280...282	0,81	2,68	1,66	—	6,1; 6,54	7,3	8,0	—	78,8	5,5	11,0	$C_{25}H_{21}N_3O$	79,1	5,6	11,1	71

*UV spectra, λ_{max} (log ε): IIa 250 (4.15), 312 (4.56), 350 (4.56); IIf 255 (4.55), 334 inflection (4.55), 372 (4.89); III 250 inflection (3.65), 318 (4.30), 360 (3.63); IV 230 (4.70), 300 inflection (4.74), 338 (4.98).

†The yields of IIa-e obtained by method B are given in parentheses.

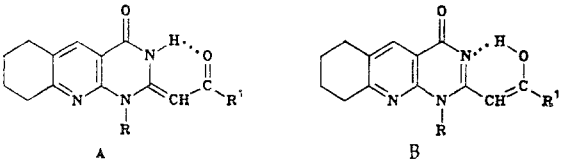
All of this constitutes evidence for the high lability of the hydrogen atoms in the methyl group of Ia-e, which is due to hyperconjugation in the O=C–N=C–CH_3 system. Calculations by the LCAO MO method within the Hückel approximation show that the negative charge (the residual electron density is −0.099) is concentrated on the carbon atom of the CH_3 group in the Ia molecule, while the hydrogen atom is protonated and has a charge of +0.128, which is in agreement with the experimental data.

The molecular ions M^+ in the mass spectra* of IIa, d, e, f (Table 2) undergo fragmentation via three pathways:



The charge in the M^+ ion is concentrated chiefly on the oxygen atom of the acetonyl (phenacyl) group; this causes further fragmentation of M^+ via cleavage of the α- or β-C–C bonds in these residues. Cleavage, which is accompanied by separation of the acyl residue, is the primary process. The higher intensity of the peak of the M^+ ion in the mass spectrum of IIf is probably associated with its greater stability as compared with the M^+ ions of IIa, d, e; this is ensured by the stabilizing effect of the phenyl group due to its conjugation with the group that bears the charge.

Signals of the protons of methyl groups at 1.8-1.9 ppm (for IIa-e), methylene groups in the 6 and 7 positions (1.73-1.80 ppm) and the 5 and 8 positions (2.60-2.67 ppm), a multiplet of aromatic rings centered at 7.1-8.0 ppm, and signals of protons of a pyridine ring (7.3-7.8 ppm) are observed in the PMR spectra of acetonyl and phenacyl derivatives IIa-h in deuterochloroform. In addition, singlets at 4.28-5.16 (1H) and 13.60-14.67 ppm (1H) are present. Similarly, in the PMR spectrum of III, in addition to signals at 1.66 and 2.5 ppm (8H, CH_2), 7.03 (10H, Ph), 7.7 (1H, pyridine), and 9.03 ppm (1H, amide), there are also singlets at 4.03 (1H) and 13.1 ppm (1H). The absorption at 4.03-5.16 ppm is due to an ethylene proton, while that at 13.1-14.67 ppm is due to the proton of the chelate ring of tautomers A or B.



Calculations by the Hückel MO method show that the A form is energetically more favorable by 56.7 kcal/mole for IIb than the B form, while for IIf the A form is more favorable by 57.4 kcal/mole than the B form.

The bathochromic shift in the UV spectra of IIa, f as compared with Ia constitute evidence for an increase in the conjugation chain; tautomeric forms B should absorb in the longer-wave region, since the conjugation chain in them is greater than in the A forms. Because of the slight enolizability of the carbonyl group in III the A form is probably the primary form for it. This assumption is in agreement with the UV spectrum of III, in which the long-wave maximum at 360 nm has a low intensity.

The IR spectra of IIa-f contain bands at 1610-1620, 1680-1700 (CO), 2940-2950 (CH_2), and 3040-3070 cm^{-1} (=CH). Vibrations of O–H or N–H bonds, which might have been expected in the case of nonchelate OH or NH tautomers, are not observed. Thus, the PMR and IR spectroscopic

*We thank S. N. Shurov for participating in the discussion of the mass spectra.

TABLE 2. Mass Spectra of IIa, d, e, f

Compound	m/z (relative intensity, %)*				
	M^+	$[M-R]^+$	$[M-RCO]^+$	$[M-RCOCH_2]^+$	other fragments
IIa	333 (53)	318 (52)	290 (100)	276 (21)	230 (20), 93 (12), 86 (20), 77 (19), 56 (15), 48 (10)
IId	347 (44)	332 (33)	304 (100)	290 (8)	108 (11), 93 (14), 87 (17), 86 (20), 77 (17), 68 (36), 65 (18), 56 (12)
IIe	363 (37)	348 (18)	320 (100)	306 (39)	102 (6), 88 (8), 86 (9), 77 (5), 56 (9)
IIf	395 (100)	318 (62)	290 (60)	276 (12)	230 (18), 105 (42), 93 (19), 86 (30), 77 (92), 56 (76)

*The peaks of ions with intensities ≥5% are presented.

data make it possible to conclude that nonchelate OH and NH tautomers are virtually absent for IIa-h.

At 25°C in the PMR spectrum of IIf in deuterochloroform one observes a singlet of an ethylene proton at 5.16 ppm. With a decrease in the temperature to 0 to −10°C two singlets centered at 5.16 ppm that differ clearly with respect to a difference in the chemical shifts of 0.10 ppm and an intensity ratio of 1:1. The form of the signals at 14.67 ppm does not change. In the presence of traces of CF_3COOH over the temperature range from 59 to 32°C signals of an ethylene proton at 5.16 ppm and signals at 14.67 ppm are not observed. Commencing at 32°C one signal appears, while at −15°C there are two signals of an ethylene proton with a difference in the chemical shifts of 0.16 ppm and an intensity ratio of 1:3. At temperatures of −10°C to −34°C there is also a signal at 14.67 ppm. The doubling of the signals at 5 ppm makes it possible to make an assumption that IIf exists in the form of two isomers – A and B. For the enol form one might assume the existence of a chelate stereoisomer in which the hydrogen bond is formed through the $N_{(1)}$ atom. However, in view of the slight basicity of the latter, this is unlikely. In the case of IIf the residual electron density on the $N_{(3)}$ atom is −0.483, as compared with +0.317 on the $N_{(1)}$ atom.

An examination of the stereoisomers of the enol form of IIf with Stuart–Briegleb models shows that the double bond of the chelate ring that includes the $N_{(1)}$ atom is not conjugated with the pyrimidine ring, while in the B isomer this conjugation is present; this is also in agreement with the conclusion regarding the structure of IIf.

A signal of an ethylene proton at 4.38 ppm and a signal of a proton of a chelate ring at 14.1 ppm, which is converted from a slighly broadened signal to a sharp lone signal with a decrease in the temperature from 48 to −49°C. The addition to CF_3COOH leads to disappearance of the signals at 4.38 and 14.1 ppm. Splitting of the signal at 4.38 ppm is not observed.

EXPERIMENTAL

The IR spectra of solutions of the compounds in CCl_4 (c = 0.05 M) were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol ($c = 1 \cdot 10^{-5}$ M) were obtained with an SF-16 spectrophotometer. The PMR spectra of 5% solutions of the compounds were obtained with an RS-60 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 eV with ^{200}Hg as the reference. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates [acetone–chloroform (1:1)].

The characteristics of the synthesized compounds are presented in Table 1.

1-Aryl-2-acetonyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one IIa-e. A) A solution of 0.01 mole of 1-aryl-2-methyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one [2] in 10 ml of acetic anhydride was heated at 140°C for 2 h, after which the mixture was poured into water, and the precipitate was removed by filtration and crystallized from ethanol.

B) A mixture of 0.01 mole of the 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid amide, 0.8 g (0.01 mole) of anhydrous sodium acetate, and 10 ml of acetic anhydride was refluxed for 9 h, after which it was poured into water, and the resulting precipitate was crystallized.

1-Aryl-2-phenacyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones (IIf-h). The solution of 0.01 mole of Ia, d, e with 3 g (0.02 mole) of benzoyl chloride in 10 ml of pyridine was heated at 140°C for 3 h after which it was poured into water, and the resulting precipitate was crystallized from ethanol.

1-Phenyl-2-phenacyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (IIf). A solution of 2.9 g (0.01 mole) of Ia, 1.1 g (0.01 mole) of methylbenzoate, and 0.54 g (0.01 mole) of sodium methoxide in 10 ml of dry methanol was refluxed for 10 h, after which it was cooled and diluted with water, and the resulting precipitate was removed by filtration and crystallized to give 1.45 g (50%) of a product with mp 252-253°C. No melting-point depression was observed for a mixture of this product with a sample of IIf obtained in the preceding experiment.

1-Phenyl-2-(N-phenylcarbamoylmethyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (III). A solution of 2.9 g (0.01 mole) of Ia and 1.2 g (0.01 mole) of phenyl isocyanate in 20 ml of dry benzene was refluxed for 30 min, after which the solvent was removed by distillation, and the residue was crystallized from ethanol.

1-Phenyl-2-styryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (IV). A solution of 2.9 g (0.01 mole) of Ia, 3.2 g (0.03 mole) of benzaldehyde, and 0.43 g (0.005 mole) of piperidine in 15 ml of ethanol was refluxed for 10 h, after which the solvent and volatile impurities were removed by steam distillation, and the residue was crystallized from ethyl acetate.

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STRUCTURES OF THE COVALENT HYDRATES AND PRODUCTS OF ACIDIC HYDROLYSIS OF RHEUMYCIN AND FERVENULIN

S. V. Shorshnev, G. G. Aleksandrov, S. E. Esipov, N. A. Klyuev, and A. I. Chernyshev

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It is shown that pyrimido[5,4-e]-1,2,4-triazinediones are hydrated at the $N_{(4)}$–$C_{(4a)}$ bond in aqueous acidic media. The equilibrium constants of these processes were measured by PMR spectroscopy. The structure of the covalent adduct of fervenulin was established by x-ray diffraction analysis. Formic, 5-diazo-3-methylbarbituric, and methylparabanic acids were identified among the products of destruction of the hydrates in acidic media.

It has been shown that pyrimido[5,4-e]-1,2,4-triazines (7-azapteridines) in neutral aqueous and alcohol solutions form covalent adducts due to the addition of water or alcohol to the $C_{(5)}$–$N_{(6)}$ bond [1, 2]. The three-dimensional structures of these products have not been established. A study of the behavior of 6-methyl- [rheumycin (Ia)] and 6,8-dimethyl- [fervenulin (Ib)] pyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-diones in aqueous media provides evidence for the chemical stability of these compounds over a wide range of pH values (1-9) [3]. The stability of 7-azalumazines Ia, b as compared with 7-azapteridine under the indicated conditions can be explained by the saturated character of the pyrimidine ring. At pH > 9 one observes the addition of water to Ia, b at the $C_{(5)}$–$N_{(6)}$ bond with its subsequent cleavage and cyclization of the ureido group to give an imidazolidine ring [4]. An investi-

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