CYCLOCONDENSATION OF CHALCONES WITH 2-AMINO- AND 1,2-DIAMINO-BENZIMIDAZOLES

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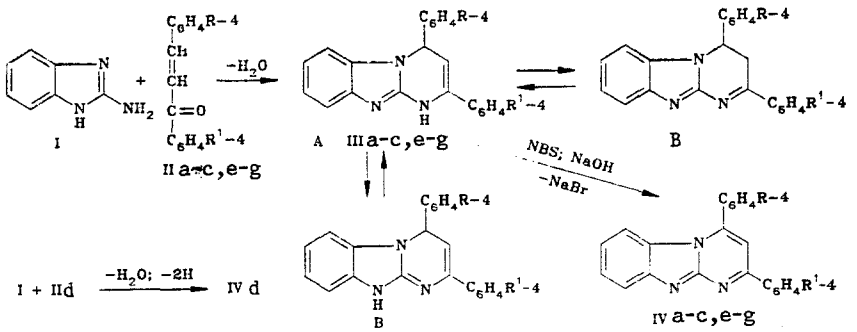
2,4-Diaryl-1,4-dihydropyrimido[1,2-a]benzimidazoles were obtained by the reaction of 2-aminobenzimidazole with chalcones, and their heteroaromatization was accomplished. The condensation of 1,2-diaminobenzimidazole with unsymmetrically substituted chalcones, which leads to substituted pyrimido-[1,2-a]benzimidazoles, was studied. The specificity of this reaction was ascertained by means of alternative synthesis.

Continuing our study of methods for obtaining partially hydrogenated azolopyrimidines and their properties we have investigated the cyclocondensation of 2-aminobenzimidazole (I) with chalcones IIa-g. The formation of precipitates of 2,4-diaryl-1,4-dihydropyrimido-[1,2-a]benzimidazoles IIIa-c, e-g occurred after refluxing solutions of I and IIa-c, e-g in DMF for 5 min; the unchanged starting substances and 2,4-diaryl-pyrimido[1,2-a]benzimidazoles IVa-c, e-g were also identified in the reaction mixtures by TLC. An increase in the condensation time led only to a decrease in the yields of IIIa-c, e-g as a consequence of resinification processes; the formation of appreciable amounts of IVa-c, e-g was not observed.

We were unable to obtain IIId by this method: the starting substances remained the principal components of the reaction mixture after refluxing a solution of I and IId in DMF for 5-30 min. However, an increase in the reaction time to 2 h led to the formation of 4-(4-nitrophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (IVd) along with difficult-to-identify resinous reaction products. The reason for this, in our opinion, is, on the one hand, the previously noted [1, 2] low reactivity of IId with respect to amino azoles (in contrast to, for example, 4'-nitrochalcone IVg) and, on the other, the existence in IId, as in the aromatic nitro derivative, of oxidative properties.

The synthesis of the remaining pyrimido[1,2-a]benzimidazole derivatives IVa-c, e-g was accomplished by the successive treatment of methanol solutions of their dihydro derivatives IIIa-c, e-g with N-bromosuccinimide (NBS) and alkali.



II—IV a, e-g R=H, b R=CH_3, c R=Cl, d R=NO_2; a-d R^1=H, e R^1=CH_3, f R^1=Cl, g R^1=NO_2

Stretching vibrations of C=N, C=C, and NH bonds appear in the IR spectra of IIIa-c, e-g, while only vibrations of C=N bonds show up in the spectra of IVb-g (Table 1). The electronic absorption spectra of dihydro derivatives IIIa-c, e, f are characterized by an

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TABLE 1. Characteristics of IIIa-c, e-g and IVb-g*

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm⁻¹ (in KBr)			UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)**	Yield, %
			C=N	C=C	NH		
IIIa	$C_{22}H_{17}N_3$	249	1627	1671	3420	277 (14,8), 308 (8,2)	62
IIIb	$C_{23}H_{19}N_3$	221...223	1629	1669	3423	280 (16,0), 308 (8,5)	65
IIIc	$C_{22}H_{16}ClN_3$	239	1629	1670	3415	285 (15,0), 307 (8,0)	71
IIIe	$C_{23}H_{19}N_3$	222...224	1628	1665	3420	279 (14,3), 309 (8,0)	73
IIIf	$C_{22}H_{16}ClN_3$	235...237	1626	1672	3413	290 (17,0), 311 (7,8)	54
IIIg	$C_{22}H_{16}N_4O_2$	237	1628	1659	3403	305 (14,0), 378 (7,0)	48
IVb	$C_{23}H_{17}N_3$	299...301	1626	—	—	345 (17,2), 391 (5,6)	60
IVc	$C_{22}H_{14}ClN_3$	273...275	1625	—	—	344 (18,5), 389 (5,7)	37
IVd	$C_{22}H_{14}N_4O_2$	275	1620	—	—	343 (16,5), 389 (5,9)	80
IVe	$C_{23}H_{17}N_3$	275...278	1622	—	—	343 (16,5), 390 (5,5)	54
IVf	$C_{22}H_{14}ClN_3$	280...282	1625	—	—	343 (17,0), 390 (5,6)	40
IVg	$C_{22}H_{14}N_4O_2$	301...303	1625	—	—	344 (17,0), 389 (6,1)	52

*Compound IVa was characterized in [3, 4].
**The spectra of solutions in methanol with substance concentrations of $(3\text{-}5)\cdot10^{-5}$ mole/liter were recorded.

absorption band at 307-311 nm; a substantial bathochromic shift of it is observed in the spectrum of nitro derivative IIIg (Table 1). It has been noted [2] that dihydroazolopyrimidines can exist in two tautomeric forms (A and B) that differ substantially with respect to the position and intensity of the long-wave absorption band. Since the realization also of 4,9-dihydro form C is possible for the investigated dihydropyrimidobenzimidazoles IIIa-c, e-g, we accomplished quantum-chemical calculations of the electronic absorption spectra of planar models of the principal chromophore groupings of forms A-C of IIIa, g by the MO LCAO SCF CI method in the Pariser–Parr–Pople (PPP) variant with the standard set of parameters [5] (Table 2). The calculation made for 1,4-dihydro form A is in good agreement with the experimental values of λ_{max} and the oscillator force (f) of the long-wave absorption band of IIIa, while for forms B and C the calculation predicts longer-wave and more intense absorption (Table 2). Considering the results of the calculations, as well as the fact that dihydropyrimido[1,2-a]benzimidazoles IIIa-c, e, f have rather similar electronic absorption spectra, it may be concluded that these compounds exist in methanol solutions exclusively in 1,4-dihydro form A. The results of calculation of dihydro forms A and C are, on the whole, in agreement with the long-wave part of the spectrum of IIIg. However, an analysis of the data on the second transition (Table 2) indicates that 1,4-dihydro form A is more preferable in this case also.

The electronic absorption spectra of IVb-g are similar to the spectra of other substituted pyrimido[1,2-a]benzimidazoles [3] and are characterized by the presence in the long-wave region of two absorption bands with λ_{max} 343-346 nm and 389-390 nm (Table 1). The results of quantum-chemical calculation of the spectrum of IVa, being in good agreement with the experimental data (Table 2), indicate substantial localization of the first and second long-wave transitions on the pyrimidobenzimidazole fragment of this molecule; this also explains the weak effect of substituents in the aryl rings on the absorption of IVb-g.

The low solubilities of IIIa-c, e-g hindered the study of their PMR spectra. We were able to record the PMR spectrum of IIIa in CF_3COOH; in it, in addition to a multiplet of aromatic protons at 6.60-8.00 ppm, we observed signals of the protons of the CH–CH group of dihydro form A (C)* [5.95 (1H, d, CH), 5.06 ppm (1H, d, CH), J = 3 Hz] and the $CH–CH_2$ group of dihydro form B [ABX system: 5.60 (1H, t, H_X), 3.66 (1H, dd, H_B), 3.44 ppm (1H, dd, H_A), $J_{AX} = J_{BX} = 7.5$ Hz, $J_{AB} = 15$ Hz]. The concentration of dihydro form B evaluated from data on the integral intensities of the corresponding groups of signals is ~50%.

The realization of two cyclocondensation pathways, to which the formation of isomeric dihydropyrimidobenzimidazoles that differ with respect to the positions of the 4-R–C_6H_4–

*Under the conditions of the measurements one should expect protonation of IIIa. Since the most probable protonation center of this compound in 1,4-dihydro form A is the $N_{(9)}$ atom while the $N_{(1)}$ atom is the most likely protonation center in 4,9-dihydro form C, the same cation should correspond to tautomers A and C.

TABLE 2. Results of Calculation of the Electronic Absorption Spectra of IIIa, g and IVa

Compound	Exptl.		Calc.			
	λ_{max}, nm	f	tautomer	λ_{max}, nm	f	L^*
IIIa	277	0,69	A	284	0,57	0,81
	308	0,17		312	0,25	0,86
			B	303	0,10	0,90
				356	0,94	0,82
			C	296	0,08	0,82
				348	0,53	0,90
IIIg	305	0,61	A	308	0,78	
	378	0,12		382	0,08	
			B	331	0,18	
				384	0,92	
			C	332	0,83	
				375	0,08	
IVa	343	0,73	—	337	0,66	0,94
	390	0,16		387	0,17	0,95

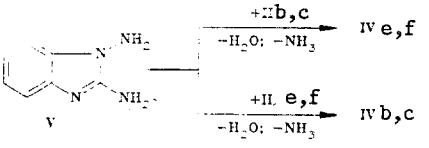
*L is the number of localization of the transitions [6] on the pyrimidobenzimidazole fragment.

and 4-R^1–C_6H_4– substituents in the pyrimidine ring corresponds in the case $R \neq R^1$, is possible in the reaction of I with chalcones. We assumed the positions of the substituents in IIIa-c, e-g and IVa-g presented in the scheme proceeding from the analogy between the investigated condensation and the reactions of chalcones with 3-amino-1,2,4-triazole and 5-aminotetrazole [1, 2]. Confirmation of this structure was obtained in an analysis of the PMR spectra of IVa, d, g and the mass spectra of dihydro derivatives IIIa, c, f.

The PMR spectra of IVa, d, g recorded in d_6-DMSO contain signals of aromatic protons (6.7-8.7 ppm); the signal of the proton of the pyrimidine ring among them cannot be unequivocally identified. An intense slightly split signal of protons of one of the phenyl rings (7.79 ppm, 5H) stands out in the spectrum of IVa in the indicated region. In conformity with the data obtained for analogous azolopyrimidine systems [7, 8] this signal should be ascribed to the protons of the phenyl substituent in the 4 position of the pyrimidine ring. A similar signal is also retained in the spectrum of nitro derivative IVg (7.80 ppm, 5H); however, in the spectrum of IVd instead of a slightly split signal one observes two doublets that characterize the protons of the nitrophenyl ring: 8.60 (2H, d), 8.05 ppm (2H, d), J = 8 Hz. Thus, the PMR spectra confirm the proposed position of the p-nitrophenyl substituent in IVd, g.

The mass spectrum of IIIa contains a molecular-ion peak with m/z 323 (66%). The principal pathway of its fragmentation involves the detachment of one of the phenyl rings [$(M - 77)^+$, 100%]. Splitting out of the substituent bonded to the sp^3-hybrid carbon atom (i.e., in the 4 position of the pyrimidine ring [9]) is most likely. In this case splitting out of the chlorophenyl radical and the formation of an ion with m/z 246 should be the principal pathway of fragmentation of IIIc, and detachment of a phenyl ring (isotopic ions with m/z 282 and 280) should be the principal process for IIIf, which is observed experimentally (Table 3).

Compound IVa is also formed in the reaction of chalcone IIa with 1,2-diaminobenzimidazole (V), which proceeds with splitting out of a molecule of ammonia [4]. In an attempt to obtain information regarding the pathway of this condensation, we studied the reaction of V with unsymmetrically substituted chalcones IIb, c, e, f.



It was found that the reaction of V with IIb, c leads to the formation of IVe, f and that, on the other hand, IVb, c are formed from ketones IIe, f. Thus, the cyclocondensation

TABLE 3. Mass Spectra of IIIa, c, f

Compound	m/z values (I, % of the maximum peak)*
IIIa	323 (66), 322 (21), 247 (26), 246 (100), 219 (11), 133 (17), 132 (10), 108 (29), 107 (11), 103 (10), 90 (11), 77 (19), 72 (22)
IIIc	359 (25), 358 (26), 357 (75), 356 (25), 280 (10), 247 (34), 246 (100), 161 (11), 103 (13), 90 (16), 77 (19)
IIIf	359 (24), 358 (21), 357 (52), 356 (16), 282 (34), 281 (21), 280 (100), 161 (10), 90 (10)

*The peaks with m/z ≥ 70 and intensities ≥ 10% are presented.

of 1,2-diaminobenzimidazole with ketones IIb, c, e, f and the analogous process on the basis of 2-aminobenzimidazole have opposite specificities.

EXPERIMENTAL

The IR spectra of the compounds were obtained with a Specord IR-75 spectrometer. The electronic spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in CF_3COOH were recorded with a Varian XL-100 spectrometer (in the case of IIIa), while the PMR spectra of solutions in d_6-DMSO were recorded with a Tesla BS-487B spectrometer (in the case of IVa, d, g). The mass spectra of IIIa, c, f were recorded with a Varian MAT-212 spectrometer at an ionizing voltage of 70 eV. The individuality of the compounds and the compositions of the reaction mixtures were monitored by TLC on Silufol UV-254 plates with chloroform and acetone as the eluents. The percentages of nitrogen in IIIa-c, e-g and IVb-g were in agreement with the calculated values.

2,4-Diphenyl-1,4-dihydropyrimido[1,2-a]benzimidazole (IIIa). A solution of 1.33 g (10 mmole) of 2-aminobenzimidazole and 2.08 g (10 mmole) of the chalcone in 2 ml of DMF was refluxed for 5 min, after which the precipitate was removed by filtration and washed with methanol to give 2.0 g (62%) of crystals of IIIa with mp 249°C [DMF–benzene (1:1)].

Compounds IIIb, c, e-g were similarly obtained.

4-(4-Nitrophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (IVd). A solution of 1.33 g (10 mmole) of 2-aminobenzimidazole and 2.53 g (10 mmole) of 4-nitrochalcone in 2 ml of DMF was refluxed for 2 h, after which it was cooled and mixed with 20 ml of benzene, and the mixture was filtered to give 1.9 g (52%) of crystals of IVd with mp 275°C (from methanol).

4-(4-Methylphenyl)-2-phenylpyrimido[1,2-a]benzimidazole (IVb). A) A solution of 1 g (5.5 mmole) of N-bromosuccinimide (NBS) in 20 ml of methanol was added at a rate of six to eight drops per minute to a suspension of 1.7 g (5 mmole) of IIIb in 80 ml of methanol while maintaining the temperature of the reaction mixture at 50-60°C. The mixture was stirred for another 2 h and filtered, 5 ml of 50% NaOH solution was added to the filtrate, and the resulting solution was mixed with 100 ml of H_2O and filtered to give 1.4 g (83%) of IVb with mp 275-278°C (from methanol).

Compounds IVa, c, e-g were similarly obtained.

B) A solution of 0.6 g (4 mmole) of 1,2-diaminobenzimidazole and 0.89 g (4 mmole) of 4'-methylchalcone IIe in 0.5 ml of DMF was refluxed for 8 h, after which it was cooled and mixed with 10 ml of benzene, and the mixture was filtered to give 0.76 g (54%) of IVb.

Compounds IVc, e, f were similarly obtained from IIf, b, c, respectively.

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ALKYLATION AND REDUCTIVE DETHIONATION OF 2-THIOXO- AND 1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID DERIVATIVES

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2-Methylthio-1,4-dihydropyrimidines were obtained by methylation of 2-thioxo-4-phenyl-5-methoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine or its 1-methyl derivative in a neutral medium. The alkylation of tetrahydropyrimidine-2-thiones in the anionic form leads to S- and S,N-methylation products. Iodoacetamide alkylates pyrimidine-2-thione with the formation of thiazolidino[3,2-a]pyrimidine derivatives. The reductive dethionation of derivatives of tetrahydropyrimidine-2-thiones and 2-methylthio derivatives of 1,4- and 3,4-dihydropyrimidines was accomplished.

It is known [1, 2] that exclusively S-alkyl derivatives are formed in the alkylation of 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives in a neutral medium. In the present research we studied the alkylation of methyl 2-thioxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (I) and its 1-methyl derivative II in a neutral medium and in the presence of a strong base — sodium hydride.

The alkylation of pyrimidine-2-thiones I and II with methyl iodide in a neutral medium leads to the formation of stable salts IIIa, b, which in an aqueous alkaline medium are readily converted to the free bases — 2-methylthio-1,4-dihydropyrimidines IVa, b. It should be noted that only 1,4-dihydropyrimidine IVa was isolated in the alkylation of unsubstituted pyrimidine I; the other possible isomer — 3,4-dihydropyrimidine — is not formed under the conditions described.

It is known that an attempt to alkylate 2-thioxo-1,2,3,4-tetrahydropyrimidine in an aqueous alkaline medium leads only to hydrolysis of the C=S group to a carbonyl group [1].

We have observed the possibility of alkylation of pyrimidine-2-thione I in the presence of a base — sodium hydride; the effects of the solvent [1,2-dimethoxyethane (DME) or hexametapol (HMP)], the nature of the alkylating agent [methyl iodide or dimethyl sulfate (DMS)], and the amount of base, which is responsible for the formation of the 2-thioxo-1,2,3,4-tetrahydropyrimidine anion, were studied.

Thus S-monoalkylation product IVa is formed in the alkylation of pyrimidine-2-thione I in the anionic form (shift of the long-wave maximum in the UV spectrum from 308 nm to 362 nm when one equivalent of NaH is added to a solution of I), regardless of the solvent used and the alkylating agent. A mixture of S-monoalkyl derivative IVa and dialkylation product V, as well as a very small amount of IVb, is the result of alkylation in the presence of two equivalents of NaH. The yields of the products obtained (from the results of liquid chromatography) in different solvents and with different alkylating agents are

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