SYNTHESIS OF 1,2,3,4,6,7,8,9-OCTAHYDROPYRIMIDO[4,5-b]QUINOLINE-2,4-DIONE

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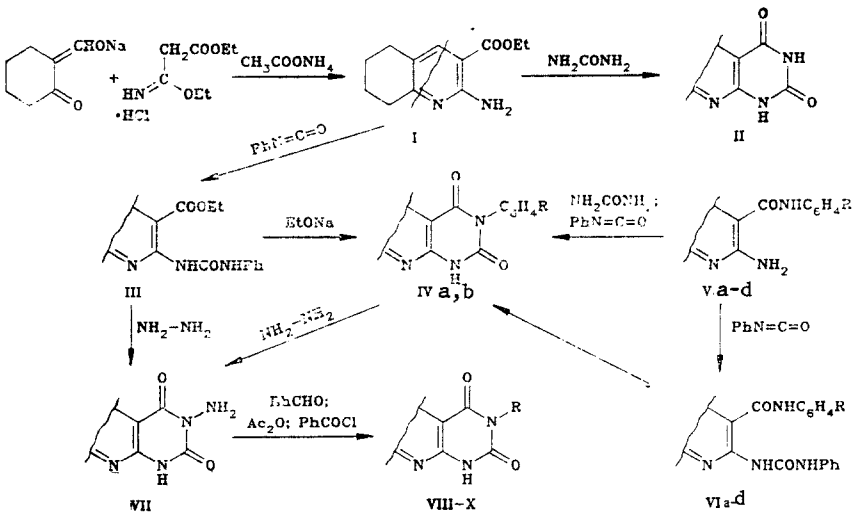
In the presence of hydrazine hydrate or sodium ethylate, ethyl 2-[(N-phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxylate is converted to 3-amino- or 3-phenyl-1,2,3,4,6,7,8,9-octahydropyrimido-[4,5-b]quinoline-2,4-dione. Compounds analogous to the latter are also obtained during heating of 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxylic arylamides with phenyl isocyanate or from their N-phenylcarbamoyl derivatives.

According to the data of [1] and [2], pyrido[2,3-d]pyrimidine-2,4-dione derivatives have fever-reducing and antihistamine actions. It seemed of interest to find routes for the synthesis of previously uninvestigated 1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-diones related to them. For this, we used as the starting substance ethyl 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxylate (I) obtained by the reaction of sodium oxymethylenecyclohexanone with iminomalonic ester hydrochloride.

Heating of ester I with urea is accompanied by the formation of 1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (II). In the reaction of ester I with phenyl isocyanate, ethyl 2-[(N-phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxylate (III) is formed, and, during treatment with sodium ethylate in ethanol, it undergoes cyclization to 3-phenyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (IVa, Table 1). Compound IVa is also obtained during fusion of 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxanilide Va [3] with urea or during boiling with phenyl isocyanate in benzene. If the reaction of anilides Va-d with phenyl isocyanate is carried out at 20°C, 2-[(N-phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxanilides (VIa-d) are formed. Compounds VIa and VId undergo thermal heterocyclization with abstraction of aniline. This suggests that the condensation of arylamide Va with phenyl isocyanate occurs via a step of formation of arylamide VIa.



IV a R = H, b R = o-Cl; V, VI a R = H, b R = p-CH_3, c R = o-Br, d R = o-Cl; VII R = NH_2; VIII R = NHAc; IX R = NHCOPh; X R = N=CHPh

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	R_f*	Yield, %
II	$C_{11}H_{11}N_3O_2$	294...296	0,79	33
III	$C_{19}H_{21}N_3O_3$	218...220	0,83	80
IVa	$C_{17}H_{15}N_3O_2$	306...308	0,85	93
IVb	$C_{17}H_{14}ClN_3O_2$	255...257	0,84	81
VIa	$C_{23}H_{22}N_4O_2$	194...196	0,51	87
VIb	$C_{24}H_{24}N_4O_2$	245...247	0,84	76
VIc	$C_{23}H_{21}BrN_4O_2$	204...206	—	56
VId	$C_{23}H_{21}ClN_4O_2$	181...183	0,28	74
VII	$C_{11}H_{12}N_4O_2$	207...209	0,45	80 (87)**
VIII	$C_{13}H_{14}N_4O_3$	226...228	0,92	87
IX	$C_{18}H_{16}N_4O_3$	182...184	—	61
X	$C_{18}H_{16}N_4O_2$	268...269	0,49	93

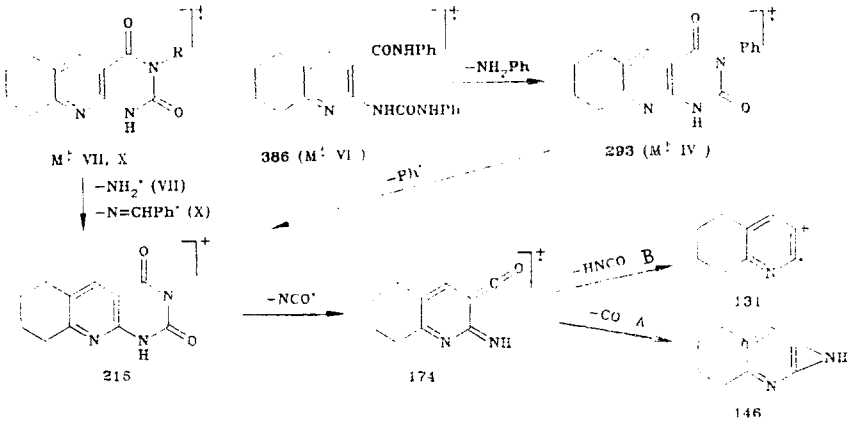
*In the 1:1 butanol—benzene system.
**The yield according to method B is indicated in parentheses.

Heating of compound III with excess hydrazine hydrate affords 3-amino-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (VII). This same compound is also obtained in the reaction of derivative IVa with hydrazine hydrate. Compound VII was converted to N-acetyl (VIII), N-benzoyl (IX), and N-benzylidene (X) derivatives. Compound X is hydrolyzed to compound VII.

The structure of the synthesized compounds was confirmed by PMR (see Table 2) and IR spectra (see the experimental part). The UV spectra of compounds II, IVa, VII, and X are similar and have absorption maximums at 245-275 nm and a maximum or inflection for IVa at 315-320 nm. The UV spectrum of Va is characterized by one maximum at 270 nm.

The mass spectra of IVa, VIa, VII, and X (see the scheme and Table 3) contain peaks

Scheme



of M^+ ions. The molecular ion of carbamoyl derivative VIa abstracts an aniline molecule, and in this case, apparently, cyclization occurs, and an ion with m/z 293, corresponding to M^+ of compound IVa, is formed. Cleavage of VIa under the effect of electron impact occurs just as during heating. Both these facts indicate low strength of the NH—CO bond in the carbamoyl group in compounds of this type. The 293 ion eliminates a Ph· species, and the 216 ion is formed. During electron impact, the molecular ions of compounds VII and X lose NH_2· and N=CHPh·, being converted also to the 216 ion, which, during abstraction of NCO·, is converted to the 174 ion. The latter decomposes by two routes. Route A is accompanied by the formation of the 146, 119, 118, 91, and 64 ions. During fragmentation by route B, the 131, 104, 79, and 77 ions are formed.

TABLE 2. Spectra of Compounds II-IV, VI-VIII, and X

Compound	δ, ppm (in DMSO-D_6)					
	CH (5,8), m	CH (6,7), m	CH_3	H_{arom}, multiplet	H_γ of pyridine, singlet	NH, s
II	2,30...2,83	1,46...1,90	—	—	7,67	11,5 (2H)
III*	2,40...2,90	1,56...1,93	1,27 t	6,76...7,46	7,80	9,83; 12,00
IVa	2,46...2,83	1,63...2,23	—	7,03...7,36	7,80	11,50
IVb	2,50...2,86	1,53...1,86	—	7,10...7,41	7,70	11,60
VIa	2,33...2,86	1,56...1,91	—	6,66...7,46	7,67	8,05; 10,20; 11,93
VIb	2,53...2,86	1,60...1,83	2,30 s	6,80...7,33	7,73	8,27; 9,63; 11,48
VIc	2,35...2,88	1,54...1,87	—	7,15...7,51	7,76	8,19; 9,74; 11,82
VId	2,63...3,16	1,66...2,16	—	7,00...7,30	7,77	8,27; 9,17; 11,47
VII**	2,45...2,89	1,62...2,19	—	—	7,77	5,33
VIII	2,49...2,90	1,59...1,81	2,31 s	—	7,85	12,08
X***	2,36...2,82	1,55...1,91	—	7,30...7,61	7,80	11,73

*The spectrum of compound III was obtained in $CDCl_3$; quadruplet of the CH_2 group at 4.20 ppm.
**Broadened NH_2 peak at 6.61 ppm.
***CH singlet at 8.60 ppm.

TABLE 3. Mass Spectra of Compounds IVa, VIa, VII, and X

Compound	Values of m/z* (I_{rel}, %)
IVa	293 (39), 265 (7), 216 (5), 174 (24), 173 (9), 146 (27), 131 (12), 119 (100), 118 (89), 91 (77), 79 (34), 77 (27), 64 (36)
VIa	386 (3), 293 (45), 265 (36), 216 (25), 174 (51), 173 (48), 146 (99), 131 (19), 119 (47), 118 (100), 104 (85), 91 (66), 79 (41), 77 (54), 64 (71)
VII	323 (100), 216 (3), 174 (9), 173 (9), 146 (14), 131 (9), 119 (10), 118 (19), 104 (8), 91 (17), 79 (8), 77 (12), 64 (9)
X	320 (4), 216 (100), 174 (52), 146 (25), 131 (5), 119 (46), 118 (38), 104 (21), 91 (84), 79 (16), 77 (4), 64 (5)

*The peaks of the ions with intensity ≥3% of the maximum are given (the peaks of the isotopic ions are not given).

EXPERIMENTAL

The UV spectra were recorded on an SF-16 instrument in ethanol with $c = 10^{-5}$ M. The IR spectra were obtained on a UR-20 instrument for a paste of the compounds in mineral oil, the PMR spectra were obtained on an RYa-2310 spectrometer (60 MHz) for 5% solutions of the compounds, and the internal standard was HMDS. The mass spectra were recorded on an MKh-1303 instrument with direct feed of the sample into an ion source with ionizing voltage 70 eV, and thin-layer chromatography was carried out on Silufol UV-254 plates. The data of elemental analysis of compounds II-X for C, H, N, and Hal corresponded to the calculated values.

Ethyl 2-Amino-5,6,7,8-tetrahydroquinoline-3-carboxylate (I). A solution of 14.8 g (0.1 mole) of sodium 2-oxymethylenecyclohexanone, 19.5 g (0.1 mole) of iminomalonic ester hydrochloride, and 7.7 g of ammonium acetate in 150 ml of ethanol was boiled for 1 h, cooled, and poured into water. It was neutralized with a 10% ammonia solution to an alkaline medium, and the precipitate was filtered and crystallized. According to the data of [4], the yield is 11.5 g (78%) with mp 124-125°C.

1,2,3,4,6,7,8,9-Octahydropyrimido[4,5-b]quinoline-2,4-dione (II). A mixture of 2.2 g (0.01 mole) of ester I and 3 g (0.05 mole) of urea was heated at 190°C for 6 h and treated with boiling water, and the residue was crystallized from butanol. IR spectrum: 1660, 1715 (CO), 3170, and 3200 cm^{-1} (NH).

Ethyl 2-[(N-Phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxylate (III). A solution of 2.2 g (0.01 mole) of ester I and 1.2 g (0.01 mole) of phenyl isocyanate in 30 ml of anhydrous benzene was heated for 5 h. The precipitate was filtered and crystallized from DMFA. IR spectrum: 1625, 1690 (CO), 3200, and 3315 cm^{-1} (NH).

3-Phenyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinoline-2,4-dione (IVa). A. A solution of 3.4 g (0.01 mole) of compound III and 0.68 g (0.01 mole) of sodium ethylate in 50 ml of ethanol was boiled for 8 h, poured into water, and neutralized with acetic acid, and the precipitate was filtered and crystallized from butanol. Yield 2.52 g (74%), mp 306-308°C. IR spectrum: 1655, 1715 (CO), and 3280 cm^{-1} (NH).

B. For 5 h at 180°C, 2.6 g (0.01 mole) of 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxanilide (Va) and 3 g (0.05 mole) of urea were fused, the whole was treated with hot water, and the residue was crystallized from butanol. Yield 0.87 g (33%), mp 306-308°C. A mixed sample obtained from melting with the substance obtained in the preceding experiment gave no depression.

C. A benzene solution of 2.6 g (0.01 mole) of anilide Va and 1.2 g (0.01 mole) of phenyl isocyanate was boiled for 5 h. The precipitate was filtered, washed with benzene, and crystallized. We obtained 2.08 g (80%) of compound IVa, which was identical to the sample obtained in the preceding experiments.

Cyclization of 2-[(N-Phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxylic Arylamides. For 3 h at 80°C, 0.01 mole of arylamide VIa and VId was heated in 50 ml of benzene. The precipitate was filtered, washed with benzene, and crystallized from butanol. Compounds IVa and IVb were obtained.

2-[(N-Phenylcarbamoyl)amino]-5,6,7,8-tetrahydroquinoline-3-carboxylic Arylamides (VIa-d). To a solution of 0.01 mole of arylamide Va-d in pyridine was added 1.2 g of phenyl isocyanate, and the whole was kept at 20°C for 5 days, poured into water, washed, and crystallized from DMFA.

3-Amino-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (VII). A. To a solution of 3.4 g (0.01 mole) of compound III in 20 ml of isopropyl alcohol was added 5 ml of hydrazine hydrate, the whole was boiled for 6 h and cooled, and the precipitate was filtered and crystallized from butanol.

B. To a solution of 2.93 g (0.01 mole) of compound IVa in 20 ml of isopropyl alcohol was added 5 ml of hydrazine hydrate, the whole was boiled for 8 h and cooled, and the precipitate was filtered and crystallized. A mixed sample obtained from melting with the sample obtained in the preceding experiment gave no depression. IR spectrum: 1660, 1715 (CO), 3130, 3320, and 3500 cm^{-1} (NH and NH_2).

3-(N-Acetylamino)-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (VIII). A solution of 2.32 g (0.01 mole) of compound VII in a mixture of 10 ml of acetic anhydride and 10 ml of pyridine was heated for 2 h at 100°C, cooled, and poured into water, and the precipitate was filtered and crystallized from butanol.

3-(N-Benzoylamino)-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline-2,4-dione (IX). This compound was obtained similarly to VIII from 2.32 g (0.01 mole) of VII and 10 ml of benzoyl chloride. It was crystallized from DMFA.

3-(N-Benzylideneamino)-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinoline 2,4-dione (X). A mixture of 2.32 g of compound VII, 2 ml of benzaldehyde, and 5 drops of piperidine in 20 ml of benzene was boiled for 3 h and cooled, and the precipitate was filtered and crystallized from DMFA. IR spectrum: 1650, 1710 (CO), and 3140 cm^{-1} (NH). During 3-h boiling in 20% HCl, compound X underwent hydrolysis to the starting VII.

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