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USE OF INTERPHASE CATALYSIS IN THE SYNTHESIS OF 2-ACYL-4-OXOPYRAZINO[2,1-*a*]ISOQUINOLINES AND 4-ACYL-2-PIPERAZINONES

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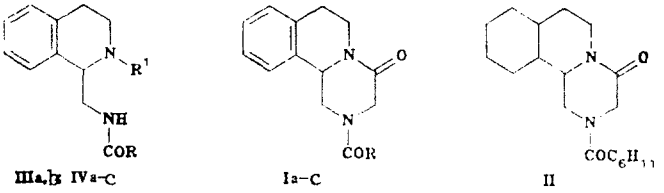
2-Acetyl-4-oxopyrazino[2,1-a]isoquinolines and 4-acyl-2-piperazinones have been synthesized, with interphase catalysis, by the intramolecular N-alkylation of the corresponding diamides.

In the synthesis of the high-efficiency antihelmintic Praziquantel (Ia), which has a tricyclic, pyrazinoisoquinoline structure, an intramolecular cyclization of diamide IVa is used. The cyclization takes place in an anhydrous medium on the action of such strong bases as potassium tert-butylate, sodium hydride, etc. [1].

We have synthesized praziquantel (Ia) and some of its analogs, Ib, c, by cyclization of the corresponding diacyl derivatives, IV, with interphase catalysis.



I a $R=C_6H_{11}$, b $R=C_6H_5$, c $R=CH_2Cl$; III a $R=C_6H_{11}$, $R^1=H$, b $R=C_6H_5$, $R^1=H$; IV a $R=C_6H_{11}$, b $R=C_6H_5$, c $R=CH_2Cl$, a–c $R^1=COCH_2Cl$

Starting materials IVa, b were prepared by acylation of the monoacyl derivatives, III, with chloroacetyl chloride. The conversion of diamides IVa, b to tricyclic Ia, b is carried out in a 50% aqueous solution of NaOH/organic solvent system in the presence of the interphase transfer catalyst TEBAC [triethylbenzylammonium chloride], as described in [2] (method **A**, see Experimental).

Tricyclic compounds Ia, b can be prepared from monoacyl derivatives IIIa, b even without isolating diamines IVa, b. In this case the acylation of compounds IIIa, b with chloroacetyl chloride leads the same system, and after the end of the reaction (monitored by TLC), TEBAC is added to the reaction mixture (method **B**, see Experimental). By the same method, starting from 1-cyclohexylcarbonylaminomethylperhydroisoquinoline, the hydrogenated analog of praziquantel, II, described by us earlier [3], has been synthesized.

In the synthesis of 2-chloroacetylpyrazinoisoquinoline, Ic, 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline, converted to the bischloroacetyl derivative IVc by the action of chloroacetyl chloride, was used as the starting compound. Cyclization of IVc also takes place in the presence of the catalyst without the isolation of the IVc.

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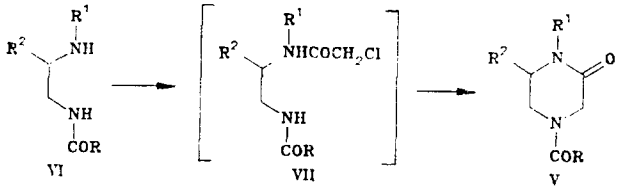
TABLE 1. Preparative Conditions and Yields of Compounds Ia, b, II, and IV

Compound	R	R^1	R^2	Method	Reaction conditions				T_{mp}, °C	Yield, %	
					solvent	n mmoles NaOH	T, °C	duration of cyclization reaction, h		with interphase catalyst	with *t*-BuOK
Ia	C_6H_{11}	—	—	A	Бензол	40	80	0,7	135...137	86	
				B	CH_2Cl_2	60	20...25	0,7	136...138	88	
Ib	C_6H_5	—	—	A	CH_2Cl_2	50	40	2,0	160...161	80	59 [6]
				B	CH_2Cl_2	90	40	2,5	160...161	82	
II	C_6H_{11}	—	—	B	CH_2Cl_2	60	40	4,5	149...151	83	60 [3]
Va	C_6H_{11}	$CH_2C_6H_5$	H	B	Benzene	40	55...60	1,0	87...88	80	65 [5]
Vb	C_6H_5	$CH_2C_6H_5$	H	B	Benzene	40	55...60	1,0	101...102	97	71 [5]
Vc	C_6H_{11}	$(CH_2)_2C_6H_5$	H	B	Benzene	40	55...60	1,0	116...118	72	67 [5]
Vd	C_6H_5	$(CH_2)_2C_6H_5$	H	B	Benzene	40	55...60	1,0	80...82	82	62 [5]
Ve	C_6H_{11}	C_2H_5	C_6H_5	B	CH_2Cl_2	40	40	4,0	152...154	96	64 [5]
Vf	C_6H_5	C_2H_5	C_6H_5	B	CH_2Cl_2	40	40	4,0	72...74	95	66 [5]

The convenient method we have developed for building a piperazine ring is based on the cyclization of the corresponding diamides under conditions of interphase catalysis and has quite a wide range of application. It has been used for the preparation of 4-acylpiperazinones V, previously synthesized using potassium tert-butylate [5] (R, R^1, and R^2, see Table 1). Compounds I, II, and V were obtained in the same way earlier.



The use of interphase catalysis in the synthesis of acylpiperazinones not only simplifies the process of preparing them, but also increases the yield of these compounds (see Table 1).

EXPERIMENTAL

The IR spectra were taken in KBr pellets on a UR-20 instrument. The course of the reactions and the purity of the resultant compounds were monitored by means of TLC on Silufol UV-254 plates in 5:1 ether/acetone developed with iodine vapor.

The elementary analyses agreed with the calculated values.

Preparation of 2-Acyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinolines (Ia, b), 2-Cyclohexylcarbonyl-4-oxoperhydropyrazino[2,1-*a*]isoquinoline (II), and 1-Alkyl(aralkyl)-4-acyl-2-piperaznones (V). A. Add n mmoles of 50% aqueous NaOH solution and 1 mmole (0.23 g) TEBAC to a solution of 10 mmoles of diacyl derivative IVa, b in 30 ml of benzene or methylene chloride. Stir and heat the reaction mixture until the starting compound disappears (monitor by TLC: R_f of starting compound is greater that the R_f of the reaction products). Then cool the mixture, dilute it with 10 ml of water, separate the organic layer, wash it with water (2 × 10 ml), 5% HCl (10 ml), and water again (2 × 5 ml), and dry it with Na_2SO_4. Distill the solvent and recrystallize the residue.

B. Add n moles of 50% aqueous NaOH solution and, over the course of 15-20 min, a solution of 11 mmoles of chloroacetyl chloride in 5 ml of absolute benzene or methylene chloride to a solution of 10 mmoles of the monoacyl derivative (IIIa, b, 1-cyclohexylcarbonylaminomethylperhydroisoquinoline [3], or VI) in 30 ml of benzene or methylene chloride. Stir the reaction mixture at 20°C until the starting compound disappears (30-50 min, monitor by TLC) and add 1 mmole (0.23 g) of TEBAC. Then stir at 20°C or with heating until cyclization stops (monitor by TLC) and work up as described for method **A**.

1-Chloroacetylaminomethyl-2-chloroacetyl-1,2,3,4-tetrahydroisoquinoline (IVc, $C_{14}H_{16}Cl_2N_2O_2$). Add 1 ml (20 mmoles) of 50% aqueous NaOH solution to a solution of 0.47 g (2 mmoles) of the dihydrochloride of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline [4] in 10 ml of methylene chloride. Stir the reaction mixture for 15 min and add over the course of 20 min a solution of 0.33 ml (4.4 mmoles) of chloroacetyl chloride in 3 ml of absolute methylene chloride. Stir the reaction mixture for 30 min at 20°C, dilute it with 10 ml of water, separate the organic layer, wash it with water (2 × 10 ml), 5% HCl (5 ml), again with water (2 × 5 ml), and dry it with Na_2SO_4. Distill off the solvent and recrystallize the residue from ethyl acetate to obtain 0.54 g (88%). Mp 110-112°C. IR spectrum: 3374 (NH), 1662, 1612 cm^{-1} (C=O).

2-Chloroacetyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (Ic, $C_{14}H_{15}ClN_2O_2$). Add with mixing 2 ml (40 mmoles) of 50% aqueous NaOH solution to a suspension of 0.47 g (2 mmoles) of the dihydrochloride of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline in 10 ml of methylene chloride. Stir the reaction mixture for 30 min and add over the curse of 20 min 0.33 ml (4.4 mmoles) of a solution of chloroacetyl chloride in 3 ml of absolute methylene chloride. Then stir the mixture for 40 min at 20°C, add 0.09 (0.4 mmoles) of TEBAC, and continue stirring for another 3 h at 20°C. Add 5 ml of water, separate the organic layer, wash it with water (2 × 5 ml), 5% HCl (5 ml), and again with water (5 ml), and dry it with Na_2SO_4. Distill off the solvent and recrystallize the residue from alcohol to obtain 0.45 g (81%). Mp 164-165°C. IR spectrum: 1660, 1645 cm^{-1} (C=O).

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CHEMICAL PROPERTIES OF YLIDENE DERIVATIVES OF AZINES.
5.* BROMINATION OF DIHYDROPYRIDYLIDENE- AND DIHYDROPYRIMIDINYLIDENECYANOACETIC ESTERS

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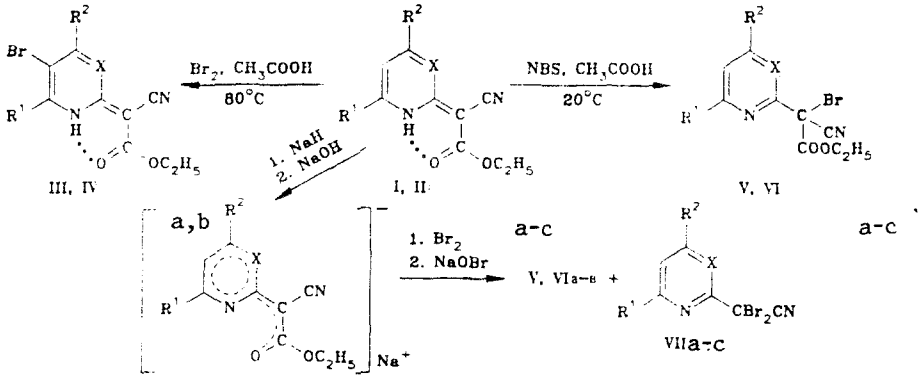
The bromination of dihydro-2-pyridylidene- and dihydro-2-pyrimidinylidenecyanoacetic esters proceeds at the 5-position of the dihydroazine ring under thermodynamically controlled conditions. By using the "kinetically" controlled conditions the products of monobromination in the side chain can be obtained in high yields. By the action of bromine on the sodium salts of substituted dihydro-2-pyrimidinylidenecyanoacetic esters in dimethoxyethane, a mixture of mono- and dibrominated derivatives is formed at the exocyclic carbon atom, while only the corresponding 2-pyrimidinyldibromoacetonitriles are formed by the action of sodium hypobromite in water.

The presence of several nucleophilic reaction centers in the ylidene derivatives of dihydropyridine and -pyrimidine, their possible heteroaromatic tautomers, and the corresponding mesomeric anions may result in their displaying ambient properties in the reactions with electrophilic reagents [2, 3]. We studied the reaction of dihydro-2-pyridylidene- and dihydro-2-pyrimidinylidenecyanoacetic esters (I and IIa-c) with various brominating agents: bromine, N-bromosuccinimide (NBS), and sodium hypobromite.



I, III, V X=CH, $R^1=R^2=H$; II, IV, VI, VII X=N, a $R^1=R^2=H$, b $R^1=H$, $R^2=C_6H_5$, c $R^1=R^2=C_6H_5$

2(1H)-Pyridones, 2(1H)-pyrimidinones, and their N-methyl derivatives react rapidly with bromine in solutions; the bromination in the ring proceeds under mild conditions as a result of a fast reaction of their covalent hydrates with bromine [4, 5].

*For Communication 4, see [1].

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