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AMIDOALKYLATION OF 2- AND 4-HYDROXY-PYRIMIDINES WITH N-(1,2,2,2-TETRA-CHLOROETHYL)AMIDES OF CARBOXYLIC ACIDS

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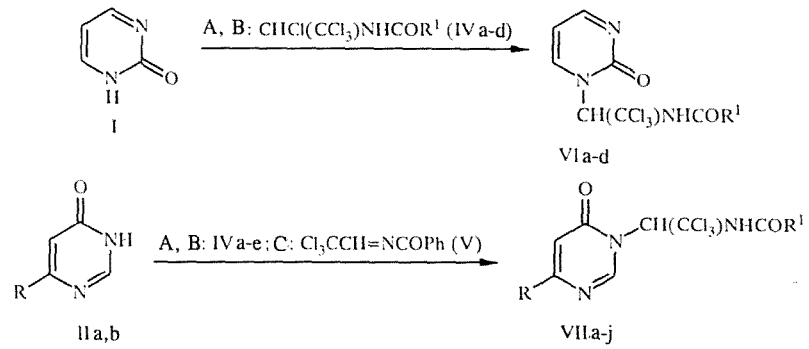
The reaction of 2- and 4-hydroxypyrimidines with N-(1,2,2,2-tetrachloroethyl)amides of carboxylic acids in the presence of sodium hydroxide or triethylamine leads to products of amidoalkylation at the $N_{(1)}$ and $N_{(3)}$ atoms respectively. In addition, 2-alkyl-4-hydroxy-pyrimidines give products of O- or C-amidoalkylation with the reagents indicated, evidently caused by steric factors and by kinetic and thermodynamic control.

Systematic investigation of amidoalkylation of functional derivatives of pyrimidine bases is of significant interest in the development of syntheses of acyclic analogs of nucleosides, among which there are effective antirival preparations and other bioregulators. Previously [1] we investigated the amidoalkylation of uracil and its derivatives and in the present work we have studied the reaction of three types of monohydroxypyrimidines (I)-(III) with typical amidoalkylating agents — N-(1,2,2,2-tetrachloroethyl)amides of carboxylic acids (IVa-e) and N-(benzoyl)trichloroacetaldimine (V) (see scheme). Several methods of amidoalkylation have been used. In method A an alkaline solution of hydroxypyrimidine (I), (II), or (III) was treated with cooling to 0°C with a solution of the tetrachloroamide (IV) in acetone. In method B the reaction was carried out with the same reagents at 20-25°C in acetonitrile in the presence of triethylamine.

In method C the hydroxypyrimidine (II) or (III) was treated with N-(benzoyl)trichloroacetaldimine in acetonitrile at room temperature. As is seen from Table 1, the yields of amidoalkylation products often depended significantly on the method of preparation. However the amidoalkylation conditions have no influence on regioselectivity, which is caused mainly by the nature of the hydroxypyrimidine base.



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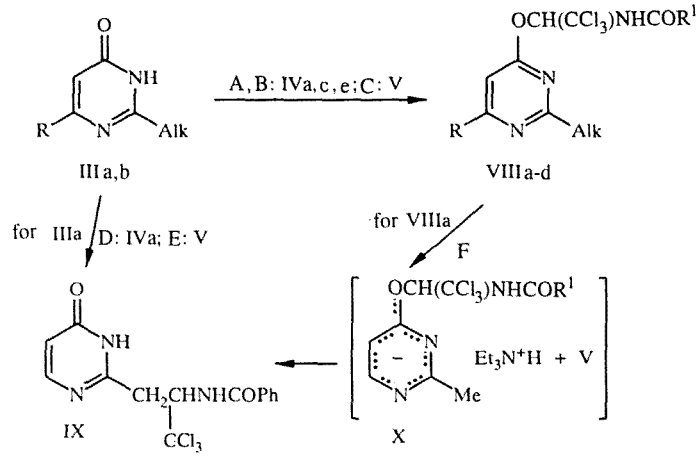


IIa R = H, b R = Me; IIIa Alk = Me, R = H, b Alk = *i*-Pr, R = Me; IV, VIa R^1 = Ph, b R^1 = *t*-Bu, c R^1 = H, d R^1 = furyl -2; IVe R^1 = *p*-Cl-C_6H_4; VIIa–e R = H, a R^1 = Ph, b R^1 = *t*-Bu, c R^1 = H, d R^1 = furyl -2, e R = *p*-Cl-C_6H_4; VIIf–j R = Me, f R^1 = Ph, g R = *t*-Bu, h R^1 = H, i R^1 = = furyl -2, j R = *p*-Cl-C_6H_4; VIIIa Alk = Me, R = H, R^1 = Ph, b Alk = Me, R = R^1 = H, c Alk = *i*-Pr, R = Me, R^1 = Ph, d Alk = *i*-Pr, R = Me, R^1 = *p*-Cl-C_6H_4

2-Hydroxypyrimidine (I) and 4-hydroxypyrimidines (IIa, b), which contain no substituent in position 2 of the ring, form amidoalkylation products at the $N_{(1)}$ (VI) and $N_{(3)}$ (VII) atoms respectively. In the case of 2-alkyl-4-hydroxypyrimidines (III) the reaction usually proceeds at the oxygen atom with the formation of compounds (VIII). On carrying out the amidoalkylation by methods A and B it is definitely not possible to link its direction with the protonated forms of the hydroxypyrimidines, since the latter are deprotonated in the presence of strong bases and an important role is then played by mesomeric anions in which the excess electron density is centered mainly on the nitrogen and oxygen atoms. The regioselectivity of the subsequent amidoalkylation is brought about by the differences in electron density distribution in the deprotonated forms of the hydroxypyrimidines (I)-(III) and by steric hindrance. These enable the different direction of amidoalkylation of 4-hydroxypyrimidines (II) and (III) to be explained. Unlike the N-amidoalkylation of (II) → (VII), an O-aminoalkylation (III) → (VIII) is a characteristic of 2-alkyl-4-hydroxypyrimidines. This is probably linked with steric shielding of both nucleophilic centers at the nitrogen atoms of compounds (III) by the methyl or isopropyl group. C-amidoalkylation occurs on extended boiling of 4-hydroxy-2-methylpyrimidine (IIIa) with amide (IVa) in acetonitrile in the presence of triethylamine (method D) or with the aldimine (V) (method E) with the formation of product (IX). Probably the conversion (IIIa) → (VIIIa), occurring under mild conditions, is under kinetic control and the conversion (IIIa) → (IX), effected under conditions of extended heating, is under thermodynamic control. It may be suggested that in the latter case the O-amidoalkylation product (VIIIa) is formed first and is decomposed under the more forcing conditions in the presence of triethylamine. This forms N-(benzoyl)-trichloroacetaldimine, which is a very reactive amidoalkylating agent capable of reacting with the methyl group of the intermediate mesomeric ion (X), and leads to the stable C-amidoalkylation product (IX). It was confirmed experimentally that compound (IX) is in fact obtained not only from 4-hydroxy-2-methylpyrimidine (methods D and E) but also from its O-substituted derivative (VIIIa) on boiling with triethylamine (method F). It is interesting that C-amidoalkylation of 4-hydroxy-6-methylpyrimidine does not occur even under forcing conditions.

In conclusion we demonstrated the effectiveness of using ^{13}C NMR spectroscopy for confirming the structure of the N- and O-amidoalkylation products of hydroxypyrimidines. This procedure was used previously for investigating the structure of similar compounds obtained from 2-thiouracil [2]. The chemical shift of the α-carbon atom of the amidoalkyl fragment in compounds (VI) and (VII) was 65-70 and in compounds (VIII) 81-82 ppm which permits the fragments N–CH–N and O–CH–N to be distinguished reliably. The structure of the C-amidoalkylation product (IX) follows from consideration of the PMR spectra in which a doublet signal was detected for a methylene group (3.32 ppm) and a signal for the methine group proton (5.56 ppm) as a doublet of triplets which is caused by coupling with the CH_2 and NH group protons. Additional confirmation of the structure of compounds (VI)-(VIII) was obtained with the aid of PMR spectra (see Table 2). A low=field displacement ($\Delta\delta$ 0.37 ppm) of the signal of the proton in position 2 of the pyrimidine ring of compound (VIIa) compared to the starting material was observed in the PMR spectrum. No displacement of the signal of the position 6 proton was observed, which proves substitution to be at the $N_{(3)}$ atom.

TABLE 1. Characteristics of Compounds (VI)-(IX)

Compound	Empirical formula	mp, °C	Crystallization solvent	Yield, % (method)
VIa	$C_{13}H_{10}Cl_3N_3O_2$	203...205	MeCN	83,5(A)
VIb	$C_{11}H_{14}Cl_3N_3O_2$	205...206	MeCN	92,0(A), 38,0(B)
VIc	$C_7H_6Cl_3N_3O_2$	189...190	MeCN	16,0(A)
VId	$C_{11}H_8Cl_3N_3O_3$	197...200	MeOH	61,0(A)
VIIa	$C_{13}H_{10}Cl_3N_3O_2$	198...200	EtOH	70,0(A), 34,0(B), 45,0(C)
VIIb	$C_{11}H_{14}Cl_3N_3O_2$	205...207	MeCN	79,5(A)
VIIc	$C_7H_6Cl_3N_3O_2$	181...183	MeCN	26,3(B)
VIId	$C_{11}H_8Cl_3N_3O_3$	199...201	MeOH	32,7(B)
VIIe	$C_{13}H_9Cl_4N_3O_2$	211...213	CCl_4	63,0(A), 66,0(B)
VIIf	$C_{14}H_{12}Cl_3N_3O_2$	201...202	MeCN	79,0(A), 58,0(B), 80,0(C)
VIIg	$C_{12}H_{16}Cl_3N_3O_2$	186...187	MeCN	66,0(A)
VIIh	$C_8H_8Cl_3N_3O_2$	209...210	MeCN	70,4(B)
VIIi	$C_{12}H_{10}Cl_3N_3O_3$	206...207	MeOH	25,3(B)
VIIj	$C_{14}H_{11}Cl_4N_3O_2$	192...193	EtOH	75,0(A), 72,1(B)
VIIIa	$C_{14}H_{12}Cl_3N_3O_2$	143...145	*	56,7(A), 72,0(B), 48,0(C)
VIIIb	$C_8H_8Cl_3N_3O_2$	158...159	*	38,7(B)
VIIIc	$C_{17}H_{18}Cl_3N_3O_2$	128...130	*	75,0(A), 97,0(B), 80,0(C)
VIIId	$C_{17}H_{17}Cl_4N_3O_2$	141...143	*	41,0(A), 25,0(B)
IX	$C_{14}H_{12}Cl_3N_3O_2$	226...227	EtOH	38,0(D), 32,0(E), 37,0(F)

*The O-substituted derivatives (VIIIa-d) did not crystallize since they were unstable.

TABLE 2. Data of the PMR Spectra of Compounds (I)-(III) and (VI)-(IX)

Compound	Chemical shifts, δ, ppm*					
	2-H, s (4-H, d)	5-H	6-H, d	CHN, d	NH—CO, d	Other signals*2
I	(8,24)	6,34 t	8,24	—	—	
IIa	8,20	6,31 d	7,90	—	—	
IIb	8,02	6,22 s	—	—	—	2,24 (3H, s, CH_3), 9,23 (1H, s, NH)
IIIa	—	6,26 d	7,87	—	—	2,42 (3H, s, CH_3), 13,20 (1H, br.s, OH)
IIIb	—	6,07 s	—	—	—	1,23 [6H, d, $CH(CH_3)_2$], 2,20 (3H, s, CH_3), 2,83 (1H, br, CH), 13,07 (1H, s, OH)
VIa	(8,70)	6,63 t	8,72	*3	9,75	
VIb	(8,65)	6,60 t	8,71	7,71	8,54	1,61 (9H, s, $3CH_3$)
VIc	(8,25)	6,63 t	8,68	7,52	10,1 τ	8,33 (1H, d, CHO)
VIIa	8,57	6,39 d	7,85	7,97	9,44	
VIIf	8,15	6,25 s	—	6,69	9,56	2,25 (3H, s, CH_3)
VIIi	8,13	6,25 s	—	6,60	9,51	2,23 (3H, s, CH_3), 7,19...7,23 (2H, q, 3-and 4-H furyl), 7,74 (1H, d, 5-H furyl)
VIIj	8,15	6,27 s	—	6,69	9,60	2,26 (3H, s, CH_3)
VIIIc	—	6,46 s	—	6,80	7,96	1,26 [6H, d, $CH(CH_3)_2$], 2,38 (3H, s, CH_3), 3,02 (1H, m, CH)
IX	—	6,11 d	—	5,56 dt	8,79	3,32 (2H, d, CH_2), 12,48 (1H, s, OH)

*The spectra of compounds (IIa), (VIa-c), and (IX) were obtained in DMSO-D_6, and of (IIb), (IIIa, b), (VIIIa, f, i, j), and (VIIIc) in $CDCl_3$.

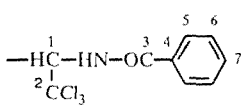
*2The aromatic protons resonate at 7.36-7.87 ppm

*3Signal is overlapped by the multiplet of the aromatic protons.

TABLE 3. Data of the ^{13}C NMR Spectra of Compounds (II), (III), and (VI)-(IX) in DMSO-D_6

Compound	Chemical shifts, δ, ppm*											Other signals
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C'_{(1)}$	$C'_{(2)}$	$C'_{(3)}$	$C'_{(4)}$	$C'_{(5)}$	$C'_{(6)}$	$C'_{(7)}$	
IIb	148,23	164,32	112,93	165,91	–	–	–	–	–	–	–	23,59 (CH_3)
IIIa	160,39	162,87	113,03	154,59	–	–	–	–	–	–	–	21,35 (CH_3)
IIIb	166,61	166,29	110,30	167,38	–	–	–	–	–	–	–	20,54 and 24,22 ($2CH_3$), 34,66 (CH)
VIa	145,28	154,57	104,55	168,06	68,44	98,54	167,46	128,52	128,18	128,26	132,56	
VIIj	148,74	159,71	112,22	167,07	65,69	98,90	164,47	138,06	129,13	130,64	131,60	23,36 (CH_3)
VIIIa	160,29	162,87	113,0	154,40	81,56	102,93	167,33	133,78	127,97	128,34	132,94	21,23 (CH_3)
VIIIc	174,47	167,45	104,21	169,60	81,99	99,63	167,37	133,44	128,33	128,63	132,43	21,32, 21,42, 23,66 ($3CH_3$), 36,79 (CH)
IX	159,12	162,64	113,86	154,35	61,96	102,93	134,10	128,00	128,82	128,82	132,25	35,78 (CH_2)

*Chemical shifts of carbon atoms $C_{(2)}$, $C_{(4)}-C_{(6)}$ of the pyridine ring and of carbon atoms $C'_{(1)}-C'_{(7)}$ of the amidoalkyl group.



EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXP 300 spectrometer in DMSO-D_6 and $CDCl_3$, internal standard was RMS.

The data of elemental analysis for C, H, Cl, and N for the compounds synthesized corresponded to calculated values.

The characteristics of the compounds synthesized are given in Tables 1-3.

1-(1-Benzoylamino-2,2,2-trichloroethyl)-2-oxopyrimidine (VIa). A. A solution of compound (IVa) (2.87 g, 10 mmole) in acetone (20 ml) was added dropewise with stirring to a solution of 2-hydroxypyrimidine hydrochloride (1.33 g; 10 mmole) in 4% NaOH (20 ml) at 0°C. A solid precipitated immediately, and was filtered off, washed with water, dried in the air, and crystallized.

1-(1-Pivaloylamino-2,2,2-trichloroethyl)-2-oxopyrimidine (VIb). B. A solution of compound (IVb) (2.67 g: 10 mmole) in absolute acetonitrile (50 ml) was added dropwise with stirring to a suspension of 2-hydroxypyrimidine hydrochloride (1.33 g, 10 mmole) and triethylamine (2.0 g, 20 mmole) in absolute acetonitrile (20 ml) at room temperature. The product which separated was treated as for (VIa) and crystallized.

3-(1-Benzoylamino-2,2,2-trichloroethyl)-4-oxopyrimidine (VIIa). C. A solution of N-(benzoyl)-trichloroacetaldimine (1.25 g, 5 mmole) in absolute acetonitrile (15 ml) was added dropwise with stirring to a suspension of 4-hydroxypyrimidine (0.48 g, 5 mmole) in absolute acetonitrile (15 ml) at room temperature. After adding the aldimine a solution was formed, 5 min later a solid was precipitated, which was treated as for (VIa).

1-(1-Acylamino-2,2,2-trichloroethyl)-2-oxopyrimidines(VIa-d),3-(1-acylamino-2,2,2-trichloroethyl)-4-oxopyrimidines (VIIa-j), and 4-(1-acylamino-2,2,2-trichloroethyloxy)-2-alkylpyrimidines (VIIIa-d) were synthesized by the proecdures described above (see Table 1).

2-(2-Benzoylamino-3,3,3-trichloropropyl)-4-hydroxypyrimidine (IX). D. A solution of compound (IVa) (11.4 g, 40 mmole) in absolute acetonitrile (100 ml) was added with stirring to a suspension of compound (IIIa) (4.4 g, 40 mmole) and triethylamine (4 g; 40 mmole) in absolute acetonitrile (40 ml). The suspension was cooled, the precipitated solid was filtered off, and crystallized.

E. A solution of N-(benzoyl)trichloroacetaldimine (2.5 g, 10 mmole) in absolute acetonitrile (25 ml) was added with stirring to a suspension of compound (IIIa) (1.1 g, 10 mmole) in absolute acetonitrile (25 ml). The suspension was boiled for 20 h to complete solution. The reaction mixture had darkened considerably. On cooling a solid was precipitated, which was filtered off, and crystallized.

F. A suspension of compound (VIIIa) (0.54 g: 1.5 mmole) and triethylamine (0.15 g, 1.5 mmole) in absolute acetonitrile (15 ml) was boiled for 20 h. A dark brown solution was formed, which was evaporated in vacuum and the residue crystallized.

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