Chemistry of Heterocyclic Compounds, Vol. 30, No. 7, 1994

INVESTIGATION OF BIS-HETERYL DERIVATIVES OF PIPERAZINE AND ITS ANALOGS

1. SYNTHESIS AND CONVERSIONS OF N,N′-BIS(2-R-5-NITRO-6-PYRIMIDINYL)PIPERAZINES AND N,N^3-BIS(2-R-5-NITRO-6-PYRIMIDINYL)DISPIROTRIPIPERAZINIUM DICHLORIDE

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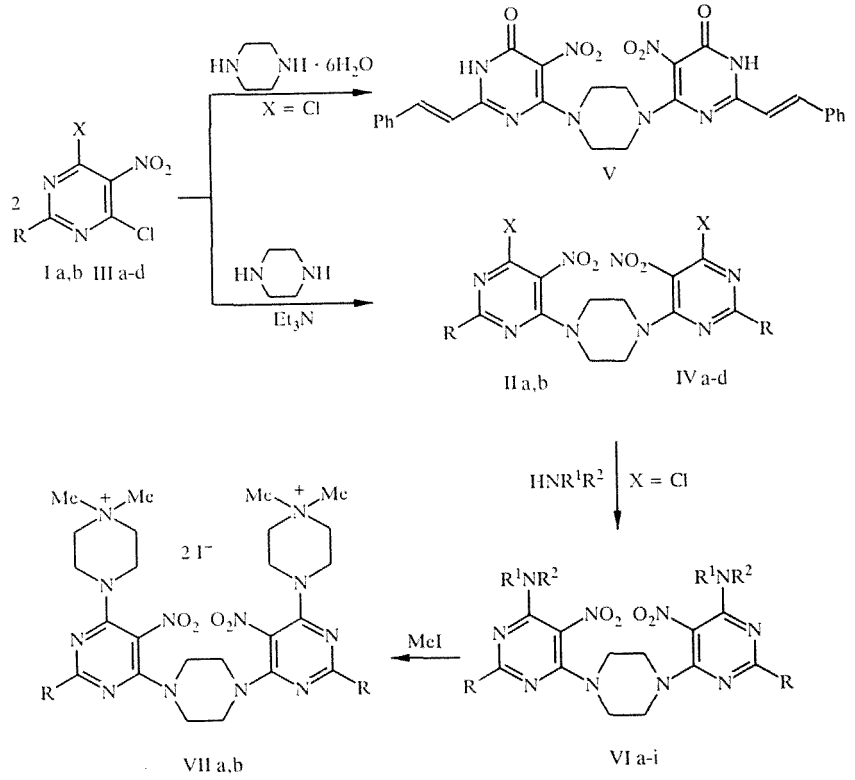
A method has been developed for the synthesis of some N,N′-bis(5-nitro-6-pyrimidinyl) derivatives of piperazine and dispirotripiperazinium dichloride containing a chlorine atom in the 4 position of the pyrimidine ring. It has been shown possible to react them with various nucleophilic reagents with the formation of the corresponding dialkylamino derivatives.

In continuation of our studies on the reaction of 5-nitropyrimidines with nucleophilic reagents we undertook the synthesis of symmetrical N,N′-bis-pyrimidinyl substituted piperazines and 3,12-diaza-6,9-diazoniadispiro[5.2.5.2]hexadecane dichlorides (referred to henceforth as dispirotripiperazinium dichloride). The reaction of halogen substituted 5-nitropyrimidines



I, II R = H, a X = OMe, b X = NMe$_2$; III, IV X = Cl, a R = H, b R = Me, c R = SMe, d R = CH = CHPh; VI a-f R = H; a $R^1 = R^2$ = Pr, b $R^1 + R^2$ = $(CH_2)_2O(CH_2)_2$, c $R^1 + R^2$ = $(CH_2)_2NMe(CH_2)_2$, d $R^1 + R^2$ = $=(CH_2)_2N(COPh)(CH_2)_2$, e $R^1 + R^2$ = $(CH_2)_2N(CONEt_2)(CH_2)_2$, f $R^1 + R^2$ = $=(CH_2)_2N(CHPh_2)(CH_2)_2$; VI g-i R = Me, g $R^1 + R^2$ = $(CH_2)_2O(CH_2)_2$; h $R^1 + R^2$ = $=(CH_2)_2NMe(CH_2)_2$, i $R^1 + R^2$ = $(CH_2)_2NH(COEt_2)(CH_2)_2$; VII a R = H, b R = Me

Center for Drug Chemistry, Moscow 119815. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 971-975, July, 1994. Original article submitted May 30, 1994.

0009-3122/94/3007-0841$12.50

with the amines named above has therefore been investigated. The reaction of 4(6)-chloro- and 4,6-dichloropyrimidines with aliphatic diamines has been studied fairly completely [1, 2]. However the use of piperazine, and its derivatives and analogs, in these reactions has been investigated less.

We have established that the reaction of 6-chloro-4-methoxy- and 6-chloro-4-dimethylamino-5-nitropyrimidines (Ia, b) with piperazine hexahydrate in aqueous dioxan in the presence of triethylamine gives exclusively N,N′-bis(5-nitro-6-pyrimidinyl)piperazines (IIa, b). Analogous results were obtained under the same conditions in the presence of an equimolar quantity of triethylamine in the reaction of 4,6-dichloro-5-nitropyrimidine (IIIa) and its 2-substituted analogs (IIIb-d) with piperazine. From the literature data a mixture of products consisting of mono- and disubstituted piperazine derivatives might be expected. However the use of double quantities of substituted pyrimidines relative to piperazine led to the exclusive preparation of the corresponding bispyrimidinyl substituted piperazines (IVa-d) in 60-93% yield.

The reaction of 4,6-dichloro-5-nitro-2-styryl-pyrimidine (IIId) with piperazine hexahydrate in aqueous methanol leads to N,N′-bis(4-oxo-5-nitro-6-pyrimidinyl)-piperazine (V), formed evidently by hydrolysis of the chlorine at the $C_{(4)}$ atom of the pyrimidine ring. Carrying out this reaction in aqueous dioxan enabled the chloro compound (IVd) to be obtained.

It must be noted that, due to the presence of labile chlorine atoms, compounds (IVa-d) were used as key synthons for a whole series of substances of interest in the search for compounds with biological activity. For example, N-substituted piperazines corresponding to the bispiperazine derivatives (VIa-i) were obtained by the reaction of the dichloro substituted compounds (IVa, b) with such nucleophilic reagents as dipropylamine or morpholine.

Compounds (VIa-i) were insoluble or poorly soluble in water. The iodomethylates of (VIc, h) were synthesized with the purpose of obtaining water-soluble bis-pyrimidinylpiperazines. Boiling compounds (VIc, h) with MeI in acetonitrile led to the readily water-soluble compounds (VIIa, b), enabling assessment of their biological activity.

It is known that various substituted 5-nitro-pyrimidines undergo fission of the pyrimidine ring on reaction with hydrazine leading, after subsequent recyclization, to 4-nitropyrazole derivatives [3, 4]. On attempting to extend this conversion to bis(5-nitro-6-pyrimidinyl)piperazine (IVa) we discovered that either the 4,6-bishydrazino-5-nitropyrimidine (VIII) described previously [6] or the 4-nitropyrazole derivative (IX) were obtained, depending on the solvent, reaction temperature, and reactant ratio. The IR spectrum of the latter is characterized by the presence of intense absorption bands at 3330, 3240, and 3140 cm^{-1}, corresponding to the stretching vibrations of NH_2 and NH (ring) groups. Signals were observed in the PMR spectrum for piperazine ring protons (3.63 ppm) as a singlet, two signals at 5.29 and 8.10 were assigned to the NH_2 group, and the signal at 9.83 ppm was assigned to the NH fragment of the pyrazole ring. The formation of compound (IX), by analogy with the results of [5], may be explained by hydrazinolysis of the pyrimidine ring followed by recyclization. In the case of the known compound (VIII), nucleophilic replacement of the chlorine atom by a hydrazine residue also took place with transamination of the pyrimidine fragment at position 6 with the displacement of piperazine.

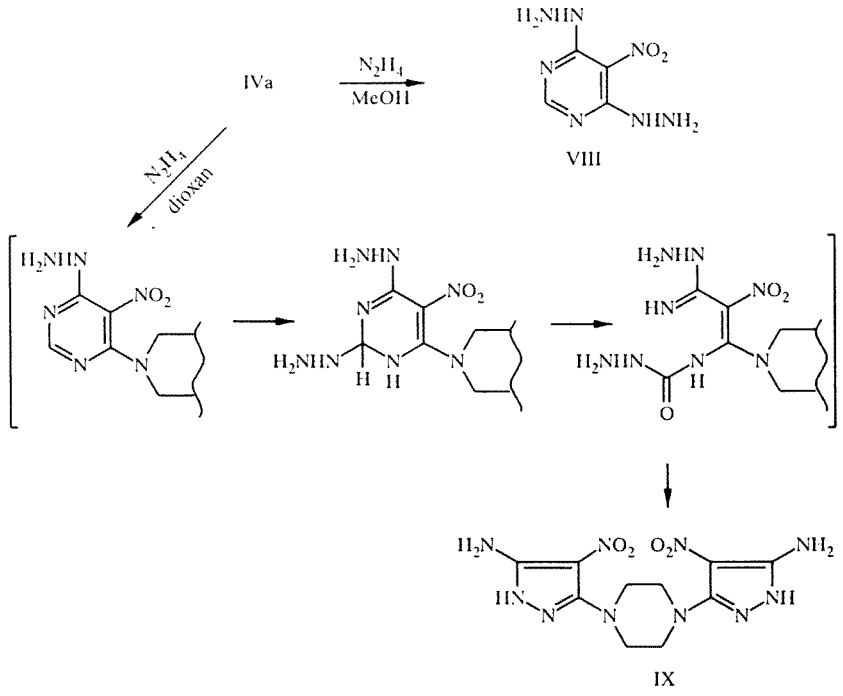
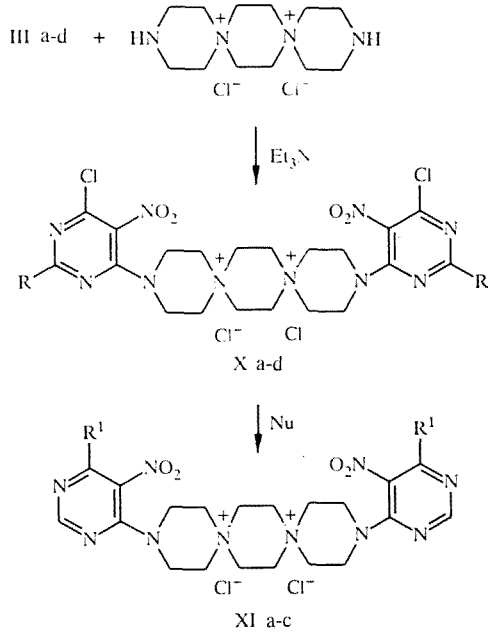


TABLE 1. Characteristics of Compounds (II), (IV)-(VII), and (IX)-(XI)

Compound	Empirical formula	mp, °C	Recrystallization solvent	IR spectrum, ν, cm^{-1} (in nujol)	Yield, %
IIa	$C_{14}H_{18}N_8O_6$	205...208	Acetone	1595, 1546, 1124, 902	60
IIb	$C_{16}H_{22}N_{10}O_4$	240...243	DMF–H_2O	1588, 1563, 1234, 1005	77
IVa	$C_{12}H_{10}N_8O_4Cl_2$	70...73	Chlorofom	1573, 1530, 986	90
IVb	$C_{14}H_{14}N_8O_4Cl_2$	280...281	DMF–H_2O	1582, 1156, 982	83
IVc	$C_{14}H_{14}N_8O_4Cl_2S_2$	256...258	DMF–H_2O	1572, 1146, 984	67
IVd	$C_{28}H_{22}N_8O_4Cl_2$	234...236	MeOH–dioxan	1456, 1378, 1225, 971	93
V	$C_{28}H_{24}N_8O_6$	208...209	Methanol	1630, 1444, 990, 780	99
VIa	$C_{24}H_{38}N_{10}O_4$	159...160	Methanol	1570, 1520, 1200, 1157	68
VIb	$C_{20}H_{26}N_{10}O_6$	270...272	DMF	1588, 1555, 1220, 1003	56
VIc	$C_{22}H_{32}N_{12}O_4$	246...247	DMSO	1583, 1554, 1218, 1002	95
VId	$C_{34}H_{36}N_{12}O_4$	>300	DMF	1618, 1592, 1215, 849	79
VIe	$C_{30}H_{46}N_{14}O_6$	255...256	Chlorofom	1618, 1583, 1230, 994	83
VIf	$C_{46}H_{48}N_{12}O_4$	200...201	DMF–H_2O	1578, 1545, 1222, 980	68
VIg	$C_{22}H_{30}N_{10}O_4$	135...136	Ethanol	1565, 1512, 1221, 1148	62
VIh	$C_{24}H_{38}N_{12}O_4$	230...234	DMSO–H_2O	1593, 1561, 1230, 1016	72
VIi	$C_{32}H_{50}N_{14}O_6$	240...242	Acetone–H_2O	1623, 1574, 1243, 974	77
VIIa	$C_{24}H_{36}N_{12}O_4I_2$	260...263	H_2O	2800...2600, 1576, 1367	84
VIIb	$C_{26}H_{42}N_{12}O_4I_2$	226...228	H_2O	2800...2600, 1588, 1078	66
IX	$C_{10}H_{14}N_{10}O_4$	172...175	Dioxan	3330, 3240, 3140, 1577	30
Xa	$C_{20}H_{28}N_{10}O_4Cl_4$	240...245	—	3340, 1560, 900	81
Xb	$C_{22}H_{30}N_{10}O_4Cl_4$	270...275	-	3345, 1580, 1299, 1202	64
Xc	$C_{32}H_{30}N_{10}O_4S_2Cl_4$	250...255	—	3450...3350, 1572, 1389	92
Xd	$C_{34}H_{38}N_{10}O_4Cl_4$	245...250	—	1465, 1380, 121, 901	40
XIa	$C_{30}H_{48}N_{12}O_4S_4Cl_2$	251...253	Methanol	1558, 1461, 1201, 965	64
XIb	$C_{30}H_{48}N_{14}O_4Cl_2$	211...214	Methanol	1577, 1234, 1008, 903	54
XIc	$C_{38}H_{62}N_{18}O_6Cl_2$	284...287	Methanol	1623, 1576, 1006, 902	58

The reaction to form symmetrical bispyrimidinylamino derivatives was also further extended by us to dispirotripiperazinium dichloride. Interest in similar families of compounds arose since substances are found among them which possess antitumor and antiviral activity [7-9].



X a R = H, b R = Me, c R = SMe, d R = CH=CHPh; XI a R^1 = SC(S)NEt_2, b R^1 = N$(C_2H_4)_2$NMe, c R^1 = N$(C_2H_4)_2$NCONEt_2

It was established that the symmetrical bispyrimidinyl derivatives (X) were formed on reacting a series of 2,4-substituted 5-nitropyrimidines (IIIa-d) with dispirotripiperazinium dichloride under conditions analogous to those described above. The derivatives (XI) were synthesized by further treatment of compound (Xa) with various nucleophilic reagents.

By studying the special features of the reaction of 4,6-dichloro-5-nitropyrimidine, and derivatives of it 2,4-substituted with such bifunctional amines as piperazine and dispirotripiperazinium dichloride, we have established that under specific reaction conditions and reactant ratios symmetrical bispyrimidinyl derivatives of the amines are obtained exclusively.

EXPERIMENTAL

The IR spectra were taken on Perkin–Elmer spectrophotometers in nujol. The NMR spectra were taken on a Varian XL 200 spectrometer. Chemical shifts are given on the δ scale, internal standard was TMS. Mass spectra were obtained on a MAT 118 spectrometer with direct insertion of substances into the ion source. A check on the purity of products and the progress of reactions was effected by chromatography on Silufol UV 254 plates.

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

The characteristics of the compounds obtained are given in Table 1.

N,N′-Bis(2-R-4-X-5-nitro-6-pyrimidinyl)piperazines (IIa, b), (IVa-d). Piperazine hexahydrate (0.25 g: 1.25 mmole) in water (5 ml) and triethylamine (0.35 ml: 2.5 mmole) was added to a solution of compound (I) or (III) (2.5 mmole) in dioxan (6 ml). Water (80 ml) was added to the reaction mixture after 2 h, the precipitated solid was filtered off, and washed with water (50 ml).

N,N′-Bis(5-nitro-4-oxo-2-styryl-6-pyrimidinyl)-piperazine (V). A solution of piperazine hexahydrate (0.73 g: 3.75 mmole) in water (10 ml) and triethylamine (1 ml: 7.5 mmole) was added to a solution of compound (IIId) (2 g: 7.5 mmole) in methanol (50 ml). After 2 h the reaction mixture was poured into water (60 ml) and the precipitated solid filtered off.

N,N′-Bis(2-R-4-NR^1R^2-5-nitro-6-pyrimidinyl)-piperazines (VIa-i). The appropriate amine (10 mmole) was added with vigorous stirring to a solution of compound (IVa) or (IVb) (5 mmole) in DMSO (40 ml), then 5 min later triethylamine (1.37 ml: 10 mmole) was added. The reaction mixture was kept for 8 h, then poured into cold water (70 ml). The precipitated solid was filtered off and washed with water.

N.N′-Bis[2-R-4-(4-N,N-dimethylpiperazino)-5-nitro-6-pyrimidinyl]piperazine Diiodide (VIIa, b). Methyl iodide (0.29 ml: 4.6 mmole) was added to a suspension of compound (VIc, h) in acetonitrile (100 ml). The reaction mixture was boiled for 15 min, then kept for 24 h at 0°C. The solid was filtered off, and washed with alcohol and with ether.

N,N′-Bis(3-amino-4-nitro-5-pyrazolyl)piperazine (IX). Hydrazine hydrate (0.6 ml: 12.3 mmole) was added to a suspension of compound (IVa) (0.8 g: 1.25 mmole) in dioxan (20 ml). After 10 h the precipitate was filtered off, washed with cold methanol, and recrystallized from dioxan. PMR spectrum (DMSO-D_6): 3.71 (2H, s, CH_2), 5.29, 8.10, 9.83 (3H, all s, NH, NH_2) ppm.

3,12-Bis(2-R-4-chloro-5-nitro-6-pyrimidinyl)-3,12-diaza-6,9-diazoniadispiro[5,2,5,2]hexadecane Dichlorides (Xa-d). A solution of dispirotripiperazinium dichloride (3.4 g: 11.5 mmole) in water (20 ml) was added to a solution of compound (IIIa-d) (23 mmole) in dioxan (50 ml). After 15 min triethylamine (3.3 ml: 23 mmole) was added to the reaction mixture. The mixture was kept for 2 h and then poured into acetone (150 ml). The solid was filtered off and reprecipitated from water with methanol.

3,12-Bis(4-R-5-nitro-6-pyrimidinyl)-3,12-diaza-6,9-diazoniadispiro[5,2,5,2]hexadecane Dichlorides (XIa-c). The appropriate dithiocarbamate or amine (5 mmole) and triethylamine (0.65 ml: 5 mmole) were added to a solution of compound (Xa) (2.5 mmole) in water (50 ml). The reaction mixture was boiled for 1 h, poured into acetone (100 ml), and the precipitated solid filtered off.

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