ALKYLATION OF SOME 6-SUBSTITUTED PURINES UNDER INTERPHASE CATALYSIS CONDITIONS*

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The mixture of 9-, 3-, and 7-benzyl-6-substituted purines is formed in almost quantitative yield by the alkylation of 6-benzylamino-, 6-furfurylamino-, 6-methylthio-, and 6-chloropurine with benzyl halides in the biphasic system of the liquid–liquid or liquid–solid type in the presence of interphase catalysts (quaternary ammonium salts, 18-crown-6). The catalytic activity of the quaternary ammonium salts increases with the increase in the lipophilicity of the cation. Taking the alkylation of 6-benzylaminopurine as an example, the possibility of the application of "triphasic catalysis" in the alkylation reaction of purines is indicated. The alkylation of 6-substituted purines with isopropyl bromide proceeds regioselectively under the conditions of the interphase catalysis with the formation of the corresponding 9-isopropylpurines.

A large number of biologically active compounds having a wide spectrum of action (antineoplastic [2] and antiviral [3] agents, cytokinins [4], etc.) have been observed among the 9-substituted purine derivatives. Therefore, the development of new synthetic methods, which are more preparatively simple and convenient for the compounds of this class, remains one of the important tasks of the chemistry of the purines.

The main method for the synthesis of 9-substituted purines is the N-alkylation in dry bipolar aprotic solvents in the presence of bases; this leads, in the majority of cases, to a mixture of isomeric substances with the predominance of the $N_{(9)}$-isomer [5-7]. The regioselectivity of the alkylation depends on the conditions of the reaction, the structure of the alkylating agent, and the nature of the substituents in the purine ring [6-11]. Thus, the alkylation of adenine or its sodium salt leads to the formation of the mixture of the $N_{(9)}$- and $N_{(3)}$-isomers in the ratio of 80:20 independently of the reaction conditions [8, 9]. The benzylation of 6-alkylaminopurines under standard conditions (DMF–K_2CO_3 or NaH) gives the 67:33 mixture of the $N_{(9)}$- and $N_{(3)}$-isomers [10]; 6-chloropurine is benzylated with the formation of the 72:28 mixture of the $N_{(9)}$- and $N_{(7)}$-isomers [12]. The alkylation of 6-methylthiopurine by benzyl bromide (DMF–K_2CO_3, 100°C, 15 h) gives the mixture of the 7- and 9-benzyl derivatives in the low respective yields of 8 and 13% [13].

The possibility of the application of interphase catalysis in this reaction was recently shown for the alkylation of adenine, xanthine, theobromine, and theophylline by primary alkyl and benzyl halides [14-16]. Thus, the alkylation of adenine goes through at 20-80°C in 3-24 h in the biphasic liquid–liquid (organic solvent and 10-40% aqueous NaOH) [14, 15] or liquid–solid (without the solvent; alkylating agent and the solid alkali) [16] systems in the presence of the interphase catalyst; the yield of the mixture of the isomeric alkyladenines is 50-98%.

In the present work, the alkylation of 6-benzylamino-6-furfurylamino-, 6-methylthio-, and 6-chloropurine with benzyl halides and isopropyl bromide was studied in the conditions of interphase catalysis. There are no literature data on the alkylation of these compounds in a biphasic catalytic system.

The alkylation of 6-benzylaminopurine (Ia) by benzyl bromide in the liquid–liquid or liquid–solid biphasic system in the presence of an interphase catalyst results in the forma-

*For the preliminary communication, see [1].

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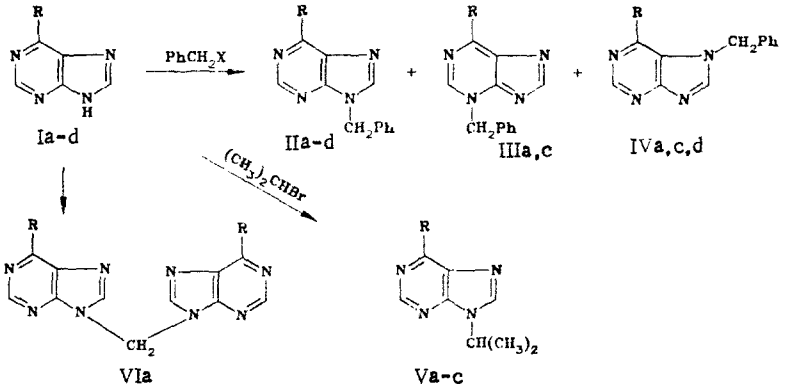
TABLE 1. Alkylation of 6-Substituted Purines by Benzyl Bromide in the Conditions of Interphase Catalysis

Initial compound	Solvent–base	Catalyst	Time of reaction, min	T, °C	Ratio of the isomers, $N_{(9)}$–$N_{(3)}$–$N_{(7)}$*
Ia	Benzene–50% NaOH	Bu_4NBr	10	80	53 : 42 : 5
	Benzene–50% NaOH	$(C_8H_{17})_4NBr$	5	80	55 : 42 : 3
	CH_2Cl_2–50% NaOH	Bu_4NBr	5	40	66 : 30 : 4
	CH_2Cl_2–50% NaOH	$(C_8H_{17})_4NBr$	5	20	72 : 27 : 1
	CH_2Cl_2–50% NaOH	P-$(CH_2)_6P(C_4H_9)_3Br$**	10	40	53 : 45 : 2
	Benzene –60% KOH	18-Crown-6	20	80	43 : 55 : 2
	CH_2Cl_2–60% KOH	18-Crown-6	5	40	45 : 50 : 5
	Benzene– solid KOH	18-Crown-6	60	80	17 : 37 : 46
	CH_2Cl_2–20% NaOH	$(C_8H_{17})_4NBr$	30	40	45 : 52 : 3
Ib	CH_2Cl_2–50% NaOH	Bu_4NBr	10	40	—
Ic	Benzene –50% NaOH	Bu_4NBr	10	40	58 : 9 : 33
	CH_2Cl_2–50% NaOH	Bu_4NBr	20	40	58 : 9 : 33
	Benzene–50% NaOH	$(C_8H_{17})_4NBr$	5	60	44 : 14 : 42
	CH_2Cl_2–50% NaOH	$(C_8H_{17})_4NBr$	10	40	62 : 5 : 33
Id	Benzene–50% NaOH	Bu_4NBr	30	80	65 : 35
	CH_2Cl_2–50% NaOH	Bu_4NBr	60	40	72 : 28
	Benzene –50% NaOH	$(C_8H_{17})_4NBr$	10	60	60 : 40
	CH_2Cl_2–50% NaOH	$(C_8H_{17})_4NBr$	20	40	69 : 31
Ia***	Benzene–50% NaOH	Bu_4NBr	90	80	58 : 38 : 4
	Benzene–50% NaOH	$(C_8H_{17})_4NBr$	40	80	60 : 39 : 1

*The ratio of the isomers is presented according to the data of HPLC. The ratio of the isomers was not determined for compound (Ib). The yield of the $N_{(9)}$-isomer (IIb) comprises 60%. Only the ratio of the $N_{(9)}$- and $N_{(7)}$-isomers was determined for the compound (Id).
**P is hexyltributylphosphonium bromide on a polymeric support; 0.83 mmole Br/g (a product of the firm Fluka).
***The alkylation was with benzyl chloride.

tion of an almost quantitative yield of the mixture of the 9-, 3-, and 7-benzyl-6-benzylaminopurines (IIa), (IIIa), and (IVa). The duration of the reaction and the proportion of the isomers depend on the solvent, the nature of the base, and the type of the catalyst (Table 1).



I-VI *a* R = $NHCH_2Ph$; b R = $NHCH_2$ (2-furyl); c R = SCH_3; d R = Cl; X = Cl or Br

The system of CH_2Cl_2–50% aqueous NaOH, with the utilization of tetraoctylammonium bromide as the catalyst, is the most effective. The activity of the latter, which is higher than that of tetrabutylammonium bromide, is evidently explained by the greater lipophilicity of the $(C_8H_{17})_4N^+$ cation in comparison with $(C_4H_9)_4N^+$; this facilitates the transfer of the anion, which is generated by the deprotonation of the compound being alkylated at the interphase boundary, into the organic phase [17]. Moreover, the anion occurring in the nonpolar

TABLE 2. PMR Spectra of the Compounds (II)-(V)

Compound	Chemical shifts of the protons, δ, ppm (in $CDCl_3$)
IIa	4.87 (d, 2H, J=6 Hz, $NHCH_2Ph$); 5.33 (s, 2H, CH_2Ph), 6.15 (br.t, 1H, $NHCH_2$), 7.27 (m 10H, C_6H_5), 7.60 (s) and 8.38 (s) (1H and 1H purine ring)
IIIa	4.89 (br.s, 2H, $NHCH_2Ph$), 5.55 (s, 2H, CH_2Ph), 5.72 (br.s 1H, $NHCH_2$), 7.30 (m 10H, C_6H_5), 7.96 (s) and 8.01 (s) (1H and 1H purine ring)
IVa	5.22 (br.s 3H, $NHCH_2Ph$), 5.33 (s, 2H, CH_2Ph), 7.25 (m, 10H, C_6H_5), 7.64 (s) and 8.39 (s) (1H and 1H purine ring)
Va	1.62 (d, 6H, J=7 Hz $(CH_3)_2CH$), 4.87 (m 3H, $NHCH_2Ph$ and $CH(CH_3)_2$), 6.40 (br.s 1H, $NHCH_2$), 7.31 (m, 5H, C_6H_5), 7.58 (s) and 8.37 (s) (1H and 1H purine ring)
IIb	4.87 (d, 2H, J=6 Hz $NHCH_2$), 5.33 (s, 2H, CH_2Ph), 6.26 (m 3H, $NHCH_2$ + + H^3, H^4 furan ring), 7.28 (m CH, C_6H_5 + H^5 furan ring), 7.67 (s) and 8.40 (s) (1H and 1H purine ring)
Vb	1.62 (d 6H, J=7 Hz $(CH_3)_2CH$), 4.87 (m 3H, $NHCH_2$ and $CH(CH_3)_2$), 6.26 (m 3H, $NHCH_2$ + H^3, H^4 furan ring), 7.33 (m, 1H, H^5 furan ring) 7.76 (s) and 8.38 (s) (1H and 1H purine ring)
IIc	2.71 (s, 3H, SCH_3), 5.36 (s, 2H, CH_2), 7.26 (m 5H, C_6H_5), 7.86 (s) and 8.71 (s) (1H and 1H purine ring)
IIIc	2.76 (s, 3H, SCH_3), 5.64 (s) 2H, CH_2), 7.26 (s, 5H, C_6H_5), 8.22 (s) and 8.26 (s) (1H and 1H purine ring)
IVc	2.66 (s, 3H, SCH_3), 5.61 (s, 2H, CH_2), 7.24 (m 5H, C_6H_5), 7.95 (s) and 8.80 (s) (1H and 1H purine ring)
Vc	1.62 (d, 6H, J=7 Hz $(CH_3)_2CH$), 2.71 (s, 3H, SCH_3), 4.87 (heptet 1H, J=7 Hz, $CH(CH_3)_2$), 7.96 (s) and 8.69 (s) (1H and 1H purine ring)
IId	5.42 (s, 2H, CH_2), 7.31 (m 5H, C_6H_5), 8.06 (s) and 8.74 (s) (1H and 1H purine ring)
IVd	5.64 (s, 2H, CH_2), 7.31 (m 5H, C_6H_5), 8.15 (s) and 8.82 (s) (1H and 1H purine ring)

medium as an ion pair with a more bulky cation is more reactive owing to the decrease in the cation–anion interaction [17].

When a solvent less polar than benzene is utilized, the reaction proceeds more slowly and requires a higher temperature; the regioselectivity for the $N_{(9)}$-isomer thereby decreases somewhat. The application of aqueous KOH as the base in the presence of 18-crown-6 also proved to be less effective (the reaction time increases; the regioselectivity for the $N_{(9)}$-isomer decreases). The utilization of solid KOH leads to the anomalous increase in the content of the $N_{(7)}$-isomer in the mixture of the products. The benzylation of the purine (Ia) under the conditions which are analogous to those proposed for the alkylation of adenine using dilute aqueous alkali [14] does not contribute to an increase in the selectivity of the formation of the isomer (IIa). The alkylation of 6-benzyl-aminopurine with benzyl chloride under the conditions of interphase catalysis proceeds significantly more slowly than with the utilization of benzyl bromide; the regioselectivity changes insignificantly. The study of the possible utilization of the "triphasic catalysis" [18] for the alkylation of compound (Ia) showed that the phosphonium salt, attached to the insoluble polymer, catalyzes the reaction effectively, and has an activity close to that of the soluble onium salts. The polymer-bound catalyst is readily separated from the reaction mixture by filtration, and it can be utilized repeatedly.

We separated the isomers (IIa)-(IVa) by the method of preparative TLC; the UV spectral parameters and the mp's of these compounds correspond with the data of [19]. The PMR spectra also confirm the structure of these compounds (Table 2).

The reactivity of 6-furfurylaminopurine (kinetin, Ib) is close to that observed for the compound (Ia) for its alkylation by benzyl bromide in the system of CH_2Cl_2–50% aqueous NaOH in the presence of the catalyst $Bu_4N^+Br^-$. However, the reaction proceeds less selectively. The marked resinification of the reaction mixture, from which only 9-benzyl-6-furfurylaminopurine (IIb) was isolated in 60% yield, was noted (Tables 2 and 3). The position of the absorption maximum at 270 nm in the UV spectrum is characteristic of 6-benzylamino-9-benzylpurine [19], and indicates that (IIb) is the $N_{(9)}$-isomer.

TABLE 3. Characteristics of the Purines (IIb) and (Va-c)

Compound	mp, °C	R_f*		Mass spectrum, m/z (M^+)	UV spectrum, λ_{max}, nm (ethanol)	Found, %			Empirical formula	Calculated, %		
		a	b			C	H	N		C	H	N
IIb	141—142	0,11	0,81	305	270	66,9	4,9	23,0	$C_{17}H_{15}N_5O$	66,9	4,9	22,9
Va	109—110		0,91	267	273	67,4	6,5	26,2	$C_{15}H_{17}N_5$	67,4	6,4	26,2
Vb	125—127	0,21	0,88	257	270	60,5	5,9	26,7	$C_{13}H_{15}N_5O$	60,7	5,8	27,2
Bc	116—117	0,23	0,90	208	286	51,5	5,7	26,5	$C_9H_{12}N_4S$	51,9	5,8	26,9

*a) Chloroform—ethyl acetate, 1:1; b) chloroform—ethanol, 9:1.

The 6-methylthio- and 6-chloropurines (Ic) and (Id) are alkylated by benzyl bromide under the conditions of interphase catalysis of the liquid—liquid type giving, as also for the purine (Ia), an almost quantitative yield of the mixture of isomers with the predominance of the corresponding 9-benzylpurine (IIc,d) and the relatively high content of the 7-benzyl derivatives (IVc,d) (Table 1). This agrees with the data on the benzylation of the compounds (Ic) [13] and (Id) [12] by a standard method utilizing K_2CO_3 as the base. The products of the alkylation of the purines (Ic) and (Id) were separated by the method of preparative TLC, and were identified by the coincidence of the UV spectral parameters and the values of the mp's with those presented in the works [12, 13, 20]. The PMR spectra of the compounds (IIc, d), (IIIc), and (IVc, d) are presented in Table 2. The $N_{(3)}$-isomer could not be isolated in the crystalline state by the alkylation of the purine (Id) due to its low content in the reaction mixtures. Therefore, only the ratio of the $N_{(9)}$- and $N_{(7)}$-isomers (IId) and (IVd) was determined by the method of high-performance liquid chromatography (HPLC) in the given case. The comparison of the data obtained with the literature data [12, 13] indicates that the method of interphase catalysis is considerably more effective than the traditional method for the alkylation of the purines (Ic) and (Id): The yield increases twofold to fourfold with the simultaneous decrease in the reaction time.

Further, we first studied the possible alkylation of purines by sec-alkyl halides under the conditions of interphase catalysis taking as an example the alkylation of the compounds (Ia-c) by isopropyl bromide. In the systems of CH_2Cl_2—50% aqueous NaOH or benzene—50% aqueous NaOH, the reaction proceeds regioselectively with the formation of the corresponding 9-isopropylpurines (Va-c) in 58-75% yield. It is known [17] that the sec-alkyl halides are less reactive than the benzyl halides, and the reaction requires the application of a large excess of the alkylating agent and prolonged boiling, and is accompanied by the marked resinification of the reaction mixtures.

The assignment of the previously unknown 9-isopropylpurines (Va-c) as the $N_{(9)}$-isomers was made on the basis of the UV spectral data (Table 3). The value of the λ_{max} in the spectra of these compounds conforms well with the known values which are characteristic of the 6,9-disubstituted purines [19, 20].

It should be kept in mind that when methylene chloride is utilized as the organic phase, it may play the role of the alkylating agent. Thus, bis(6-benzylaminopurin-9-yl)methane (VIa) is formed in the isolated yield of 30% when the purine (Ia) is subjected to the prolonged boiling in the system of CH_2Cl_2—50% aqueous NaOH in the presence of $Bu_4N^+Br^-$.

Therefore, interphase catalysis is effective in the N-alkylation reaction of different 6-substituted purines; it permits the isolation of various 6,9-disubstituted purines in yields which are sufficiently high, and under mild conditions. The utilization of the liquid—liquid system greatly simplifies the monitoring of the course of the reaction. The alkylation can be regarded as completed right after the disappearance of the suspension of the salt of the initial purine, which is formed as the result of its deprotonation at the phase boundary, and is insoluble in the reaction medium. The solubilization of this salt with the aid of the interphase catalyst gradually draws it into the reaction, the products of which are soluble in the organic phase.

EXPERIMENTAL

The analytical TLC was performed on plates of Silufol-254. The preparative separation by the method of TLC was carried out on PSC-prepared plates of kieselgel 60 F_{254}, having 2 mm thickness, in the 1:1 system of chloroform—EtOAc; the development was performed in UV

light using a UPM instrument. The UV spectra were obtained on a Pye-Unicam SP 1800 spectrophotometer, in ethanol. The PMR spectra were obtained on a Bruker WH-90 spectrometer, in $CDCl_3$; the internal standard was TMS. The mass spectra were obtained on an MS-50 (AEI) mass spectrometer with 70 eV energy of ionization and the direct input of the substance into the ionization region.

The determination of the ratio of the isomers was performed by the method of HPLC on a DuPont-850 chromatograph with a column 4.6 by 150 mm, the sorbent was Silasorb C184C, and the mobile phase was a 65:2.5:32.5 mixture of acetonitrile—acetic acid (0.02 M) and a solution of the sodium salt of dodecylsulfonic acid.

The characteristics of the substances synthesized are presented in the Tables 2 and 3.

Alkylation of the Purines (Ia, c, d) by Benzyl Halides (General Method). To the suspension of 1 mmole of the 6-substituted purine in 10 ml of the organic solvent, containing 0.1 mmole of the catalyst, is added 4 ml of the aqueous solution of the alkali or the solid alkali with stirring. The mixture is stirred for 30 min at 20°C prior to the addition of 1.2 mmole of the benzyl halide and heating it with intense stirring until the disappearance of the suspension of the salt of the corresponding purine is achieved (the reaction conditions are presented in Table 1). The reaction mixture is diluted with 20 ml of water and 30 ml of the corresponding organic solvent; the organic layer is separated, washed with water, dried with $MgSO_4$ or Na_2SO_4, and concentrated to dryness. The analytically pure isomers are obtained by the separation on preparative plates in the 1:1 system of chloroform—EtOAc; the elution is carried out with chloroform, and the crystallization is carried out from hexane. The substances obtained were utilized as calibration standards for the determination of the ratio of the isomers by the method of HPLC.

6-Furfurylamino-9-benzylpurine (IIb). To the suspension of 0.6 g (3 mmole) of 6-furfurylaminopurine and 0.09 g (0.3 mmole) of Bu_4NBr in 30 ml of methylene chloride is added, with stirring, 12 ml of 50% aqueous NaOH. The mixture is stirred for 10 min. Benzyl bromide (0.6 ml, 4.5 mmole) is added, and the mixture is boiled for 10 min prior to the dilution with 50 ml of CH_2Cl_2 and 30 ml of water. The organic layer is separated, dried with $MgSO_4$, and concentrated to dryness. The residue is recrystallized twice from ethanol; 0.55 g of the compound (IIb) is obtained in 60% yield.

6-Benzylamino-9-isopropylpurine (Va). To the suspension of 0.46 g (2 mmole) of 6-benzylaminopurine (Ia) and 0.11 g (0.2 mmole) of tetraoctylammonium bromide in 20 ml of benzene is added, with stirring, 8 ml of 50% aqueous NaOH; the mixture is stirred for 10 min. Isopropyl bromide (0.6 ml, 6 mmole) is added, and the mixture is boiled for 3 h. It is then diluted with 40 ml of benzene and 30 ml of water. The benzene layer is separated, dried with Na_2SO_4, and concentrated to dryness. The residue is dissolved in chloroform and applied to a column of silica gel. Compound (Va) is eluted with the 9:1 mixture of chloroform—ethanol, collecting the fraction with the R_f 0.91. The solvent is distilled; the crystallization is performed from hexane. The yield of the compound (Va) is 0.4 g (75%).

Compounds (Vb) (yield 58%) and (Vc) (yield 85%) are obtained analogously.

Bis(6-benzylaminopurin-9-yl)methane (VIa). To the suspension of 0.46 g (2 mmole) of 6-benzylaminopurine (Ia) in 20 ml of CH_2Cl_2 are added, with stirring, 8 ml of 50% aqueous NaOH and 0.06 g (0.2 mmole) of Bu_4NBr. The mixture is boiled for 15 h prior to dilution with 20 ml of water and 20 ml of CH_2Cl_2. The residue is filtered off, washed with water and methylene chloride, and crystallized from ethanol. The compound (VIa) is obtained with a yield of 0.14 g (30%). The spectral characteristics of the methane (VIa) are presented in [1].

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THERMOLYSIS OF SOME 6H-6-OXO-3-AMINOANTHRA[1,9-cd]ISOXAZOLES

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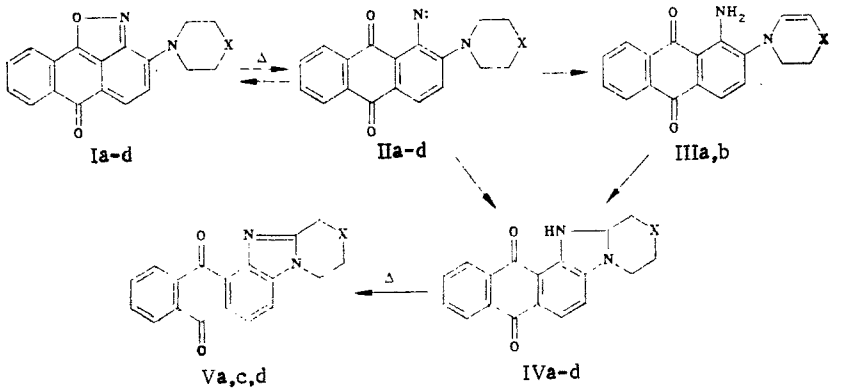
The thermolysis of 6H-6-oxo-3-alkylaminoanthra[1,9-cd]isoxazoles leads to derivatives of anthra[1,2-d]imidazole and 1-amino-9,10-anthraquinone.

In [1] it was demonstrated that 6H-6-oxo-3-morpholinoanthra[1,9-cd]isoxazole (Ia) is converted to 6H,11H,6,11-dioxoanthra[1,2-d]imidazole derivatives IVa and VA when it is heated in various solvents [dioxane, dimethylformamide (DMF), toluene], whereas 1-amino-2-dehydromorpholine-9,10-anthraquinone (IIIa) was isolated when starting Ia was maintained in refluxing pyridine.

In the present research we attempted to determine the structural requirements for substances that undergo this sort of conversion. We studied the transformations of various 6H-6-oxo-3-amino derivatives Ia-d in organic solvents. We found that 6H,11H,6,11-dioxoanthra[1,2-d]imidazoline derivatives IVa-d are the final or intermediate products in all of the investigated examples. Like the starting isoxazolones Ia,c,d, IVa,c,d undergo dehydrogenation to imidazoles Va,c,d at 135-180°C in various solvents.



a X=O; b X=N—C_6H_5; c X=CH_2; d X=$(CH_2)_2$

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