POTENTIAL ANTIDEPRESSANTS: 3-METHYL-6-DIMETHYLAMINO--1,2-DIPHENYLHEXAN-3-OL AND RELATED COMPOUNDS

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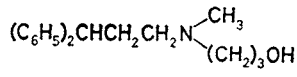
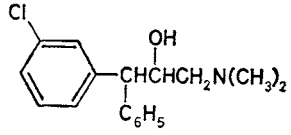
3,4-Diphenylbutan-2-one (*III*) and 3-methyl-3-phenylbutan-2-one were transformed by treatment with 3-dimethylaminopropylmagnesium chloride and 1-methyl-4-piperidylmagnesium chloride to the amino alcohols *VI*, *VII*, and *X*. Compound *VI* was dehydrated to the olefinic amine *VIII*, and reduced to the saturated amine *IX*. 2-(3-Fluoro-4-hydroxyphenyl)ethylamine (*XI*) was prepared by a modified route *via* the methoxy precursor *XV*. Only the amino alcohol *VI* showed antireserpine activity in one test. The fluoro analogue of dopamine *XI* did show neither the dopaminomimetic nor the antidopaminergic character.

The structurally rather unspecific antidepressant activity was found within series of diarylalkylamines and diarylaminoalkanols, especially of the 3,3-diarylpropylamine type[1-4]. Examples of such substances are the experimental antidepressant drugs PF-82 (*I*) (ref.[5]) and clemeprol (*II*) (refs[6-8]) which exhibit antireserpine activity in animal tests, inhibit the neuronal uptake of noradrenaline, and partly proved their therapeutic efficacy in depressive patients. The purpose of the present paper was to test the importance of the distance between the aromatic nuclei and the amino group for the potential antidepressant activity. For this reason the title compound and some related substances have been prepared.



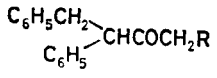
I



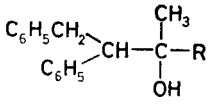
II

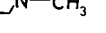
Reactions of phenylacetone with benzyl bromide or benzyl chloride in the presence of powdered sodium hydroxide afforded 3,4-diphenylbutan-2-one (*III*) in yields of 76 and 78%, respectively (*cf.* refs[9,10]). Its reduction with sodium borohydride in a mixture of aqueous ethanol and benzene gave the secondary alcohol *V* which was obtained as the mixture of stereoisomers. Mannich reaction of *III* with dimethylamine hydrochloride and paraformaldehyde in boiling ethanol (method[11]) led to the

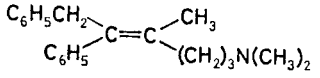
known base *IV* (refs[12,13]) whose hydrochloride was prepared for pharmacological testing. The ketone *III* was subjected to treatment with 3-dimethylaminopropylmagnesium chloride in boiling tetrahydrofuran; an important part of the crude product crystallized and evidently represents one homogeneous tertiary alcohol *VI* (homogeneity was confirmed by the ^{1}H NMR spectrum) which afforded a homogeneous hydrochloride. The acid catalyzed dehydration of *VI* (heating with dilute sulfuric acid) gave the olefinic amine *VIII* as a (*Z*, *E*)-mixture. The alcohol *VI* was reduced with hydroiodic acid in boiling acetic acid to give the amine *IX* as the mixture of two racemates. The hydrochloride needed many recrystallizations for getting the constantly melting product. The mass spectrum confirmed the elemental composition $C_{21}H_{29}N$ for the base. Reaction of the ketone *III* with 1-methyl-4-piperidylmagnesium chloride[14] in tetrahydrofuran gave a mixture which was separated by chromatography. From the less polar fractions, the secondary alcohol *V* was isolated being formed by reduction of *III* by the Grignard reagent (*cf.* ref.[15]). The most polar fractions represent a mixture of stereoisomeric amino alcohols *VII* (low yield) from which a part crystallized and is considered to be homogeneous (in agreement with the ^{1}H NMR spectrum); this afforded a homogeneous hydrochloride.



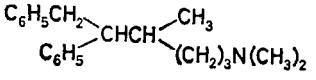
III, R = H
IV, R = $CH_2N(CH_3)_2$



V, R = H
VI, R = $(CH_2)_3N(CH_2)_3$
VII, R = 

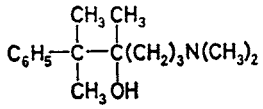


VIII



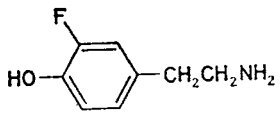
IX

3-Methyl-3-phenylbutan-2-one, obtained by repeated treatment of phenylacetone with sodium hydride and methyl iodide in dimethyl sulfoxide[16], was also reacted with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran, and the obtained mixture was separated by chromatography. The amino alcohol *X* formed the most polar fraction.

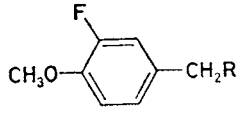


X

In a different connection we needed for pharmacological testing a sample of 2-(3--fluoro-4-hydroxyphenyl)ethylamine (*XI*) whose synthesis was described by Kraft[17]. We contributed by modifications in some of the steps. Our synthesis started first from methyl 3-fluoro-4-methoxybenzoate[18] which was reduced with aluminium hydride in ether to the alcohol *XII*. Its transformation to the chloride *XIII* by treatment with thionyl chloride was accompanied by a partial decomposition and the yield was low. The described[17] chloromethylation of 2-fluoroanisole was found to be much more advantageous for obtaining *XIII* which was converted to the nitrile *XIV* by the known method[17]. For reducing this nitrile to the amine *XV*, Kraft[17] used pressure hydrogenation on a nickel–cobalt–silica gel catalyst; we used reduction with lithium aluminium hydride in ether which afforded 50% of the amine *XV* at the maximum. The oily base *XV* was characterized by the NMR spectra and gave the hydrochloride which is evidently identical with that of the Kraft's product[17]. Demethylation to *XI* was carried out by refluxing with hydrobromic acid (*cf.* ref.[17]).



XI



XII, R = OH
XIII, R = Cl
XIV, R = CN
XV, R = CH_2NH_2

Compounds *IV*, *VI*, *VII*, *IX*, *X*, and *XI* were tested in a battery of tests for psychopharmacological activity. The compounds were adminstered orally in the form of salts, described in the Experimental; the doses given were calculated *per* bases. Acute toxicity in mice, LD_{50} in mg/kg: *IV*, 614; *VI*, 454; *XI*, 86. *IV*, *VI*, *VII*, and *IX* in doses of 25 mg/kg were inactive in the test of reserpine ptosis in mice. In the dose of 50 mg/kg, *VI* had significant effect against the reserpine-induced gastric ulcers in rats; in the same doses, *IV*, *VII*, and *IX* were inactive in this test. In concentrations of 500 nmol l^{-1} *IV*, *VI*, *VII*, and *IX* and *X* in concentration of 100 nmol l^{-1} did not influence the binding of 4 nmol l^{-1} [^{3}H]imipramine in the hypothalamus of the rat brain; similarly *IV*, *VI*, *VII*, and *IX* in concentrations of 100 nmol l^{-1} did not influence the binding of 4 nmol l^{-1} [^{3}H]desipramine in the same medium. *VI* in the dose of 10 mg/kg had not anticonvulsant or protective effect in the electroshock test

in mice. *X* until the subtoxic dose of 250 mg/kg had not discoordinating effect in the rotarod test in mice; in the same dose it had no cataleptic effect in rats and it had only very weak effect in the test of potentiation of yohimbine toxicity in mice (lethality only with 20% animals); in the test of apomorphine-induced climbing behaviour (verticalization) in mice, it was inactive in the dose of 300 mg/kg. The dopamine analogue *XI* showed some anticataleptic activity in rats: The dose of 50 mg/kg reduced the perphenazine catalepsy by 20%. In the same dose it was not cataleptic in rats and did not influence the apomorphine stereotypies in rats. It had no affinity to dopamine D_2 receptors in corpus striatum of the rat brain: $IC_{50} > 30\ \mu mol\ l^{-1}$. In conclusion, only *VI* showed some antireserpine effect in one test, and *XI* did show neither signs of dopaminomimetic nor antidopaminergic character of effects.

Compounds *VI* and *IX* showed some antimicrobial effects *in vitro* (minimum inhibitory concentration in μg/ml given): *Streptococcus β-haemolyticus, IX* 50; *Streptococcus faecalis, IX* 50; *Staphylococcus pyogenes aureus, IX* 25; *Trichophyton mentagrophytes. VI* 50, *IX* 50.

EXPERIMENTAL

The melting points were determined in the Kofler block and were not corrécted. The samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. IR spectra (liquids as films, solids in Nujol; ν in cm^{-1}) were recorded with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3; δ, J in Hz) with a Tesla BS 487 C (80 MHz spectrometer), ^{19}F NMR spectrum ($CHCl_3$, δ ($CFCl_3$) = 0) with the same instrument, and the mass spectrum (m/z, %) with Varian MAT 44S spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). Preparative chromatographic separations used neutral Al_2O_3 (activity II). The extracts in organic solvents were dried with K_2CO_3, Na_2SO_4 or $MgSO_4$, and were evaporated under reduced pressure on a rotating evaporator.

3,4-Diphenylbutan-2-one (*III*)

A part of the mixture of 20·1 g phenylacetone and 29·9 g benzyl bromide was added to 8·2 g powdered NaOH, the stirring was started and the second part of the mixture was added dropwise over 20 min at 90—94°C. The mixture was then stirred and heated for 9 h in a boiling water bath, cooled, treated under stirring with 25 ml water, stirred for 10 min under cooling, treated with 5 ml hydrochloric acid, and extracted with ether. The extract was washed with 3M-HCl and water, dried and evaporated. Distillation of the residue gave 25·5 g (76%) *III*, b.p. 146 to 152°C/0·25 kPa. A similar reaction of 80·5 g phenylacetone, 83·6 g benzyl chloride, and 32·8 g NaOH gave 105 g (78%) *III*, b.p. 168—170°C/1·3 kPa. Refs[9,10] gave the yield of 62% for a similar preparation (not explicitly described), b.p. 119—122°C/0·13 kPa, and 122—124°C/40 Pa, respectively.

3,4-Diphenylbutan-2-ol (*V*)

A solution of 6·73 g *III* in a mixture of 50 ml ethanol and 15 ml benzene was treated with a solution of 0·6 g 95% $NaBH_4$ in 6 ml water containing 0·6 ml 20% NaOH, and the mixture was

refluxed for 4·5 h. The solvents were evaporated *in vacuo*, the residue was distributed between benzene and water, the aqueous layer was extracted with ether, the combined organic layers were dried, and evaporated; 6·8 g (theoretical) *V* (stereoisomeric mixture), b.p. 148°C/80 Pa. IR spectrum: 700, 732, 752 (5 adjacent Ar—H); 1 068, 1 115 (CHOH); 1 491, 1 581, 1 600, 3 020, 3 075, 3 080 (Ar); 3 400, 3 560 (OH). ^{1}H NMR spectrum: 1·12 d, 3 H (CH_3, J = 6·0); 1·40 bs, 1 H (OH); 2·70—3·30 m, 3 H ($ArCH_2CHAr$); 3·95 bm, 1 H (CH—O); 6·80—7·30 m, 10 H (2 C_6H_5). For $C_{16}H_{18}O$ (226·3) calculated: 84·91% C, 8·02% H; found: 84·99% C, 8·03% H.

5-Dimethylamino-1,2-diphenylpentan-3-one (*IV*)

A mixture of 11·2 g *III*, 2·4 g paraformaldehyde, 6·5 g dimethylamine hydrochloride, and 30 ml ethanol was treated with 0·3 ml hydrochloric acid and refluxed under stirring for 12 h. After addition of 30 ml ethanol, refluxing was continued for further 6 h. Ethanol was evaporated, the residue was dissolved in 25 ml water and the solution was washed with ether. Processing of these washings recovered 4·9 g *III*. The aqueous solution was made alkaline with NH_4OH and the product was extracted with ether. Processing of the extract gave 4·9 g crude *IV* which was dissolved in ether and neutralized with HCl in ether; 7·5 g (84% *per* conversion) crude hydrochloride which was crystallized from acetone, m.p. 137—140°C. For $C_{19}H_{24}ClNO$ (317·8) calculated 71·79% C, 7·61% H, 11·16% Cl, 4·41% N; found: 71·90% C, 7·50% H, 11·38% Cl, 4·31% N. Refs[12,13], m.p. 129—130°C.

A sample of the pure hydrochloride was decomposed with NH_4OH and the oily base *IV* was isolated by extraction with ether. ^{1}H NMR spectrum: 2·05 d, 6 H ($N(CH_3)_2$); 2·45 bs, 4 H ($COCH_2CH_2N$); 2·90 dd, 1 H and 3·45 dd, 1 H ($ArCH_2$, J = 13·0; 7·0 and 13·0; 7·0); 3·95 t, 1 H (ArCHCO, J = 7·0); c. 7·15 m, 10 H (2 C_6H_5).

3-Methyl-6-dimethylamino-1,2-diphenylhexan-3-ol (*VI*)

Reaction of 9·2 g Mg and 46·5 g 3-dimethylaminopropyl chloride in 120 ml boiling tetrahydrofuran (addition of small amounts of iodine and 1,2-dibromoethane) gave the Grignard reagent which was stirred and refluxed for 1·5 h. After cooling there were added with stirring 42·6 g *III*, dissolved in 120 ml tetrahydrofuran. The mixture was stirred and refluxed for 2·5 h, allowed to stand at room temperature for 48 h, decomposed then with 250 ml 20% NH_4Cl, and extracted with ether. Processing of the extract gave 51·6 g crude oily prouct. A sample was chromatographed on a column of Al_2O_3; benezene eluted the less polar impurities and a mixture of benzene and chloroform eluted the desired product which partly crystallized. Seeding of the main quantity of the crude product with these crystals led to crystallization of 24·4 g (41%) homogeneous stereoisomer of *VI*, m.p. 72—74°C (hexane). ^{1}H NMR spectrum: 1·20 s, 3 H ($C—CH_3$); 1·55 bm, 4 H (4,5-CH_2CH_2 in the hexane chain); 2·22 s, 6 H ($N(CH_3)_2$); 2·22 bm, 2 H (CH_2N); 2·90 m, 2 H ($ArCH_2$); 3·45 m, 1 H (ArCH); 6·20 bs, 1 H (OH); 6·80—7·30 m, 10 H (2 C_6H_5). For $C_{21}H_{29}NO$ (311·5) calculated: 80·98% C, 9·38% H, 4·50% N; found: 81·38% C, 9·53% H, 4·61% N.

Hydrochloride, m.p. 187—189°C (ethanol–ether). IR spectrum: 700, 705, 740 (C_6H_5); 1 120 (C—OH); 1 480, 1 490, 1 580, 1 600, 3 020, 3 045, 3 080 (Ar); 2 480, 2 520, 2 620 (NH^+); 3 330 (OH). For $C_{21}H_{30}ClNO$ (347·9) calculated: 72·49% C, 8·69% H, 10·19% Cl, 4·03% N; found: 71·96% C, 8·73% H, 10·28% Cl, 3·94% N.

2-(1-Methyl-4-piperidyl)-3,4-diphenylbutan-2-ol (*VII*)

Grignard reagent[14], which was prepared by reaction of 2·9 Mg and 17·0 g 4-chloro-1-methyl-

piperidine in 80 ml tetrahydofuran, was stirred and treated at 10—13°C with 15·8 g *III*, added in small portions. The mixture was stirred for 1 h at room temperature and allowed to stand overnight. It was decomposed with 135 ml 20% NH_4Cl and extracted with benzene and ether. Processing of the extract gave 17·0 g crude product which was chromatographed on 420 g Al_2O_3. Elution with benzene and benzene–chloroform mixtures removed neutral components which were rechromatographed on silica gel; one more important fraction was identified as *V*, (IR spectrum identical with that of authentic *V*). Elution with a 1 : 1 mixture of chloroform and methanol gave 2·5 g (11%) homogeneous basic product which crystallized from a mixture of benzene and light petroleum, m.p. 161—162°C. IR spectrum: 700, 740, 752, 767 (C_6H_5); 1 141 (C—OH); 1 491, 1 580, 1 600, 3 020, 3 058, 3 080 (Ar); 2 700 (N—CH_3); 3 200 (OH). ^{1}H NMR spectrum: 0·90 s, 3 H (C—CH_3); 1·30—2·10 m, 8 H (OH and 7 H in positions 2,3,3,4,5,5,6 of piperidine); 2·20 s, 3 H (NCH_3); 2·80—3·40 m, 5 H ($ArCH_2CHAr$ and remaining H-2 and H-6 of piperidine); 6·70—7·40 m, 10 H (2 C_6H_5). For $C_{22}H_{29}NO$ (323·5) calculated: 81·68% C, 9·04% H, 4·33% N; found: 82·07% C. 8·90% H, 3·86% N.

Hydrochloride, m.p. 259—262°C (ethanol–ether). For $C_{22}H_{30}ClNO$ (359·9) calculated: 73·41% C, 8·40% H, 9·85% Cl, 3·89% N; found: 73·17% C, 8·35% H, 10·14% Cl, 3·56% N.

(*Z*, *E*)-N,N,4-Trimethyl-5,6-diphenylhex-4-enylamine (*VIII*)

VI (4·67 g) was added to a solution of 7·0 g H_2SO_4 in 35 ml water and the mixture was refluxed for 2 h. After cooling it was made alkaline with 60 ml 20% NaOH, the base was extracted with benzene, and the extract was processed; 4·3 g (98%) oily *VIII*. Neutralization with HCl in ethanol–ether gave the hydrochloride which crystallized from a mixture of acetone and ether as the hemihydrate. For $C_{21}H_{28}ClN + 0{\cdot}5\,H_2O$ (338·9) calculated: 74·42% C, 8·62% H, 10·46% Cl, 4·13% N; found: 74·35% C, 8·46% H, 10·76% Cl, 3·95% N.

N,N,4-Trimethyl-5,6-diphenylhexylamine (*IX*)

A mixture of 6·23 g *VI*, 20 ml acetic acid, 20 ml hydroiodic acid, and 2·5 g red P was stirred and refluxed for 7 h. The solid was filtered off, the filtrate was diluted with water, made alkaline with 10% NaOH, and extracted with benzene. Processing of the extract gave 5·8 g (98%) oily mixture of bases *IX*. Neutralization with HCl in ether and repeated crystallization of the product from a mixture of ethanol and ether gave the constantly melting hydrochloride, m.p. 151—153°C. Mass spectrum: 295·2311 (M^+, for $C_{21}H_{29}N$ 295·2300, 1·3), 204 (10), 115 (3), 114 (3), 91 (6), 58 (100). For $C_{21}H_{30}ClN$ (331·9) calculated: 75·99% C, 9·11% H, 10·68% Cl, 4·22% N; found: 75·97% C, 9·02% H, 10·83% Cl, 4·07% N.

2,3-Dimethyl-6-dimethylamino-2-phenylhexan-3-ol (*X*)

Grignard reagent, prepared from 5·3 g Mg and 26·9 g 3-dimethylaminopropyl chloride in 70 ml tetrahydrofuran, was treated under stirring over 10 min with a solution of 19·5 g 3-methyl-2-phenylbutan-2-one[16] in 85 ml tetrahydrofuran, and the mixture was refluxed for 1·5 h. After standing overnight it was decomposed with 210 ml 20% NH_4Cl and extracted with ether. Processing of the extract gave 22·4 g inhomogeneous residue which was chromatographed on 450 g Al_2O_3. Elution with benzene and benzene–chloroform removed 13·5 g neutral component. Chloroform and chloroform–methanol eluted 8·4 g (28%) homogeneous oily base *X*. Neutralization with HCl in ether gave the hydrochloride which crystallized from acetone as the hemihydrate, m.p. 164—166°C. For $C_{16}H_{28}ClNO + 0{\cdot}5\,H_2O$ (294·9) calculated: 65·17% C, 9·91% H, 12·03% Cl, 4·75% N; found: 65·60% C, 9·93% H, 12·06% Cl, 4·66% N.

A sample of the hydrochloride was decomposed with NH_4OH and the pure base was isolated by extraction with ether. ^{1}H NMR spectrum: 1·03 s, 3 H (O—C—CH_3); 1·35 s, 3 H and 1·40 s, 3 H (CH_3—C—CH_3); c. 1·50 m, 4 H (4,5-CH_2CH_2 in the hexane chain); 2·25 s, 6 H ($N(CH_3)_2$); 2·25 m, 2 H (CH_2N); 4·40 bs, 1 H (OH); 7·10—7·60 m, 5 H (C_6H_5).

3-Fluoro-4-methoxybenzyl Alcohol (*XII*)

A solution of 2·6 g $AlCl_3$ in 40 ml ether was added dropwise to a stirred solution of 2·3 g $LiAlH_4$ in 40 ml ether under nitrogen atmosphere and then, there was slowly added a suspension of 9·2 g methyl 3-fluoro-4-methoxybenzoate[18] in 140 ml ether. The mixture was stirred for 1 h at room temperature and refluxed for 1 h, after cooling decomposed with 20 ml water, added dropwise, and the mixture was poured to ice with dilute H_2SO_4. The product was extracted with ether, the extract was washed with water, dried, and distilled; 5·4 g (69%), b.p. 116°C/0·1 kPa. IR spectrum: 811, 874 (2 adjacent and solitary Ar—H), 1 029 (CH_2OH), 1 278, 2 820 ($ArOCH_3$), 1 462, 1 520, 1 587, 3 029, 3 045 (Ar), 3 310 (OH). For $C_8H_9FO_2$ (156·2) calculated: 61·53% C, 5·81% H, 12·16% F; found: 61·81% C, 5·77% H, 11·96% F.

3-Fluoro-4-methoxybenzyl Chloride (*XIII*)

XII (2·8 g) was shaken and treated with 2·4 ml $SOCl_2$, the mixture was allowed to stand for 2 days at room temperature and then heated for 1 h to 90°C. $SOCl_2$ was evaporated *in vacuo* and the residue was distilled (decomposition observed); 1·7 g (54%), b.p. 95°C/0·3 kPa. The product (analysis confirmed the composition C_8H_8ClFO) is identical with that obtained by chloromethylation of 2-fluoroanisole[17], b.p. 118°C/1·7 kPa.

2-(3-Fluoro-4-methoxyphenyl)ethylamine (*XV*)

A solution of 6·6 g *XIV* (ref.[17]) in 100 ml ether was added dropwise over 40 min to a stirred solution of 4·55 g $LiAlH_4$ in 130 ml ether. The mixture was stirred for 3 h at room temperature and refluxed for 1 h. After standing overnight it was decomposed under stirring by a slow addition of 5 ml water, 5 ml 15% NaOH, and 15 ml water, the mixture was stirred for 30 min, the solid was filtered off and washed with ether, the filtrate was dried, and distilled; 3·1 g (46%), b.p. 150—152°C/4·3 kPa. ^{1}H NMR spectrum: 1·54 s, 2 H (NH_2); 2·64 m, 2 H (CH_2N); 2·90 m, 2 H ($ArCH_2$); 3·82 s, 3 H (OCH_3); c. 6·85 m, 3 H (3 ArH). ^{19}F NMR spectrum: —136·0 m. For $C_9H_{12}FNO$ (169·2) calculated: 63·88% C, 7·15% H, 11·23% F, 8·28% N; found: 63·12% C, 7·21% H, 10·87% F, 8·18% N.

Hydrochloride was obtained by treating the base with HCl in ethanol, m.p. 221—223°C (methanol). Ref.[17], m.p. 219°C.

2-(3-Fluoro-4-hydroxyphenyl)ethylamine (*XI*)

A mixture of 5·9 g *XV* and 40 ml hydrobromic acid was refluxed for 6 h. The solution was diluted with water, filtered with active carbon (this was extracted with boiling ethanol and the extract was added to the filtrate), and the filtrate was evaporated *in vacuo*. The residue was crystallized from a mixture of ethanol and ether to give 4·3 g (52%) hydrobromide, m.p. 228—231°C. For $C_8H_{11}BrFNO$ (236·1) calculated: 40·69% C, 4·70% H, 33·85% Br, 8·05% F, 5·93% N; found: 41·40% C, 4·74% H, 33·90% Br, 7·73% F, 5·89% N. Kraft[17] proceeded similarly but isolated the crystalline base which was then converted to the hydrochloride.

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