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Synthesis of Stable Free Radicals : 2, 2, 6, 6-Tetramethyl-4-Hydroxypiperidine-1-Oxyl-4-Derivatives (1)

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This report deals with the synthesis of the stable free radicals : 2, 2, 6, 6-tetramethyl-4-hydroxypiperidine-1-oxyl-4-derivatives : methyl-, ethyl-, isopropyl-, tert. butyl-, cyclohexyl-, phenyl-.

These derivatives were synthesized by means of Grignard reaction. The spectra of U. V. and I. R. for these compounds were also reported.

We have studied the static magnetic susceptibility and the ESR absorption spectra of many organic stable free radicals.[1-3] 2, 2, 6, 6-tetramethylpiperidine-1-oxyl (Fig. 1-a) and 2, 2, 5, 5-tetramethylpyrrolidine-1-oxyl (Fig. 1-b) are very stable free radicals. The derivatives of these radicals are also very stable and easily soluble in most solvents *e. g.* ether, benzene, alcohol and water. Accordingly, these radicals are studied in various aspects such as organic chemical, biochemical and physiochemical ones. We, expressly, have been interested in magnetic property of these radicals. One of the conclusions obtained is that 2, 2, 6, 6-tetramethyl-4-hydroxypiperidine-1-oxyl (TANOL) (Fig. 1-c), one of the

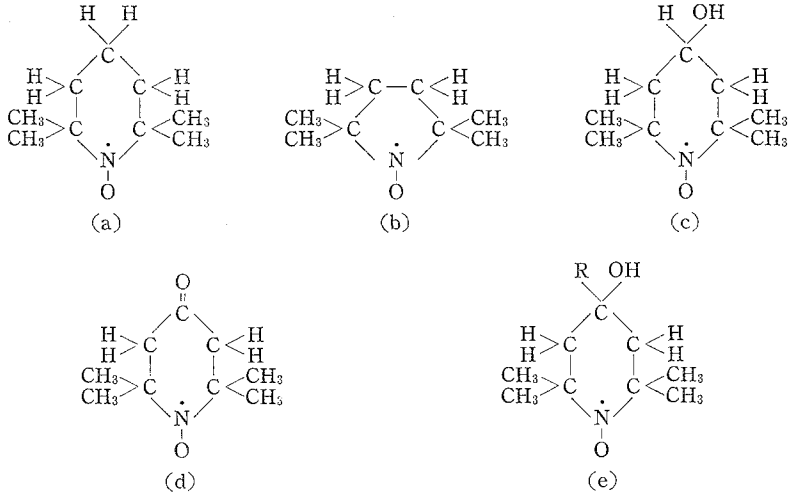

Fig. 1

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hindered organic stable free radicals, is the one-dimensional Heisenberg antiferromagnet according to the static magnetic susceptibility measurments[4-5] and that the exchange antiferromagnetic interaction was large as compared with other organic stable free radicals. The precise determination of the crystallographic structure has been made by Lajzerowicz-Bonneteau,[6] who found that crystals of TANOL are monoclinic and the molecules are associated with hydrogen bonds and form chains. The following problems, however, have not been clarified definitely: whether this one-dimensional magnetic interaction is along this chain or not and if the hydrogen bond bridged between the radical molecules might contribute to this magnetic interaction.

The ESR absorption spectra of 2, 2, 6, 6-tetramethylpiperidine-1-oxyl derivatives have been observed by Rassat *et al.*.[7] Kreilick[8] has observed not only the normal 3 hyperfine lines arising from ^{14}N but also 7 to 13 lines from the protons. In the ESR absorption spectra of 2, 2, 6, 6-tetramethylpiperidine-1-oxyl derivatives the hyperfine coupling constants of both ^{14}N and protons in TANOL have been larger that those of 2, 2, 6, 6-tetramethyl-4-ketopiperidine-1-oxyl (Fig. 1-d) but the hyperfine structures of protons of these derivatives have not been clearly observed. On the other hand, only two of the derivatives of TANOL, *i. e.* methyl and ethyl derivatives, have been synthesized by Rassat *et al.*[7] and Rozantsev *et al.*.[9] It is reported that their ESR absorption spectra including the proton hyperfine lines have been observed only in TANOL.

We have synthesized several 4-alkyl and 4-aryl derivatives of TANOL (Fig. 1-e) in order to investigate the effect of the substituted group on the hydrogen bond formation in the crystal and the ESR absorption spectra in solution. The observation of these hyperfine structures of protons will result in the evidence of direct interaction of an unpaired electron on the NO group with the protons, because these compounds have no π system except the NO group. Furthermore, we might expect that the hydroxyl and 4-substituted groups would affect the hyperfine coupling constants of ^{14}N and protons. In the present paper we shall report synthetic methods and properties of radicals thus obtained.

EXPERIMENTAL

(1) Preparation of the substances was as follows:

a) 2, 2, 6, 6-tetramethyl-4-ketopiperidine was synthesized following the same process as that of Leonard *et al.*.[10] In a 1-l. three -necked flask was placed 500 g. (8.62 moles) of acetone and 160 g. of crashed calcium chloride and passed ammonia for 30 minutes. More ammonia was introduced for 15 minutes period at intervals of 3 hours for 3 days. The mixture was allowed to stand at room temperature. It was poured into 250 ml of 50 % sodium hydroxide. The upper layer was decanted from the heavy white sludge of calcium hydroxide which was then rinsed with ether. The combined ether layers were dried over potassium carbonate and distilled to give 120 g. yellow liquid, boiling 75-105°/15 mmHg. Careful fractionation of this material through a short column gave 85 g. 2, 2, 6, 6-tetramethyl-4-ketopiperidine, yielding 12.8 %, lit. 20 %,[10] b. p. 95-102°/13 mmHg, lit.

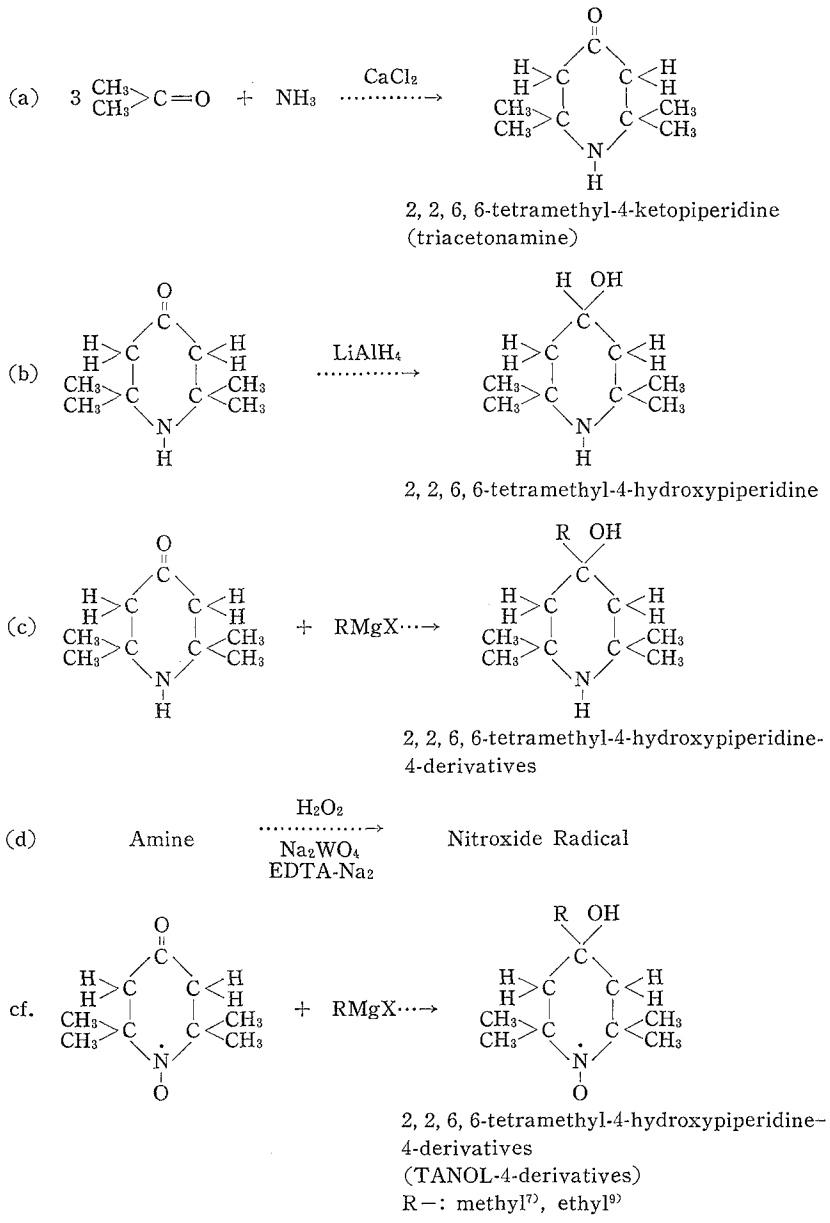


Fig. 2

102-105°/18 mmHg,[10] m. p. 35.0-36.0°, lit. 34-36°.[10] (These boiling point and melting point are not corrected.)

(b) 2, 2, 6, 6-tetramethyl-4-hydroxypiperidine was snythesized following the same process as that of Rassat *et al.*.[7] In a 300-ml three-necked flask equipped with a reflux condenser and dropping funnel, both protected by drying tube, was placed a suspension of 2.5 g. (0.07 mole) of litium aluminum hydride in 100 ml of anhydrous ether. The mixture was stirred with a mechanical sealed stirrer. A solution of 10 g. (0.06 mole) of 2, 2, 6, 6-tetramethyl-4-ketopiperidine in 100 ml of

anhydrous ether is added at such a rate as to maintain gentle reflux. The mixture was then stirred and heated under reflux for 6 hours. The heater was replaced by an ice bath. 2.5 ml of water was added slowly with vigorous stirring. Stirring was continued for 30 minutes after the addition of water was complete. A cold solution of 2.5 ml of 15 % sodium hydroxide was added at once, filtered with suction and solid was washed with several portions of ether. After the ether was removed from the filtrates, the residue was recrystallized from benzene, yielding 35.5 % (3.6 g.), lit. 39.4 %,[7] m. p. 128.5-130.0°, lit. 128.5-129°.[7]

(c) 2,2,6,6-tetramethyl-4-hydroxypiperidine-4-derivatives were synthesized by means of Grignard reaction. In a 100-ml three-necked flask was placed 1.6 g. (0.07 mole) of magnesium turnings and 20 ml of anhydrous ether. The stirring was started, and a solution of 7.9 g. (0.06 mole) of isopropyl bromide [or methyl bromide, ethyl bromide, tert. butyl bromide, cyclohexyl bromide or phenyl bromide] in 20 ml of anhydrous ehter was then added. The reaction was practically complete when all the halides had been added, but the reaction mixture was refluxed on a heater for 30 minutes longer. The flask was cooled and a solution of 5 g. (0.03 mole) of 2, 2, 6, 6-tetramethyl-4-ketopiperidine in 20 ml of anhydrous ether was slowly added to the reacting mixture. After the 2,2,6,6-tetramethyl-4-ketopiperidine had been added, the flask was heated on a heater and stirring was continued for 4 hours, and then left to stand over night. After removal of ether the solid reacting mass was dissolved with cooling in 15 % hydrogen chloride, then saturated with sodium hydroxide and extracted with ether. The combined ether extracts were dried with potassium carbonate and ether removed, the residue was recrystallized from petroleum ether, yielding 50–70 %.

Methyl-derivative: m. p. 78.0-79.0°. Ethyl-derivative: m. p. 65.0-66.0°, lit. 66.6°.[9] isoPropyl-derivative: m. p. 45-50° (This compound may be contaminated by trace of the initial ketone but it does not matter, because we can separate the ketone with column chromathography as ketone radical on next step.) tert. Butyl-derivative: m. p. 135.0-136.5°. cycloHexyl-derivative: m. p. 92.5-93.5°. Phenyl-derivative: m. p. 135.0-136.5°, lit. 130°.[10]

(d) TANOL and its derivatives were synthesized following the same process as that of Rozantsev *et al.*.[9] 0.1 g. of ethylenediaminetetraacetic acid disodium salt, 0.1 g. of sodium tungstate, 50 ml of water and 15 ml of 30 % hydrogen peroxide were added to 0.05 mole of 2, 2, 6, 6-tetramethyl-4-hydroxylpiperidine or its derivatives in 50 ml of methanol. The mixture was stirred for 2 days and then saturated with potassiun carbonate and extracted with ether and the extracts combined and dried with potassium carbonate. After removal of ether the residual solid or oil were recrystallized from petroleum ether or benzene, or were redissolved in a little ether, isolated by chromathography on aluminium oxide and recrystallized from petroleum ether or benzene, yielding 70-80 %.

TANOL: m. p. 72.0-72.5°, lit. 71.5°.[7] Methyl-TANOL: m. p. 103.5-104.5°, lit 104°.[7] Ethyl-TANOL: m. p. 67.5-68.5°, lit. 67-68°.[9]

isoPropyl-TANOL: orange red plate from *n*-hexane; m. p. 88.5-89.5°, Anal. Calcd. for $C_{12}H_{24}NO_2$: C, 68.24; H, 11.29; N, 6.54. Found: C, 67.84; H, 11.61;

N, 6.58.

tert. Butyl-TANOL: orange red needle from *n*-hexane; m. p. 150.0-150.5°, Anal. Calcd. for $C_{13}H_{26}NO_2$: C, 68.34; H, 11.48; N, 6.13. Found: C, 68.41; H, 11.92; N, 6.02.

cycloHexy-TANOL: orange red needle from *n*-hexane; m. p. 110.5-111.5°, Anal. Calcd. for $C_{15}H_{28}NO_2$: C, 70.82; H, 11.10; N, 5.51. Found: C, 70.53; H, 11.40; N, 5.74.

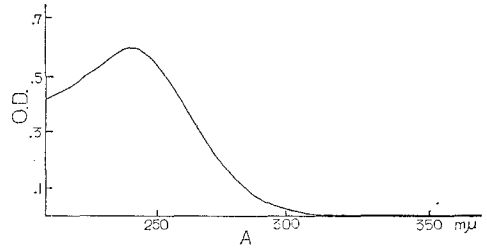
Phenyl-TANOL: orange leaf from benzene; m. p. 119.5-120.5°, Anal. Calcd. for $C_{15}H_{22}NO_2$: C, 72.54; H, 8.93; N, 5.64. Found: C, 72.75; H, 9.39; N, 5.84.

(2) Ultraviolet absorption spectra

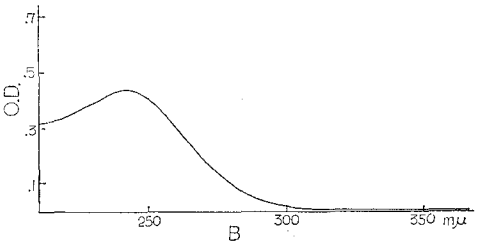
TANOL: λ=240 mμ (ε=1260) [dioxane], λ=239 mμ (ε=1720) [methanol][7]

Methyl-TANOL: λ_{max}=239-242 mμ (ε/M=4960) [cyclohexane][7]

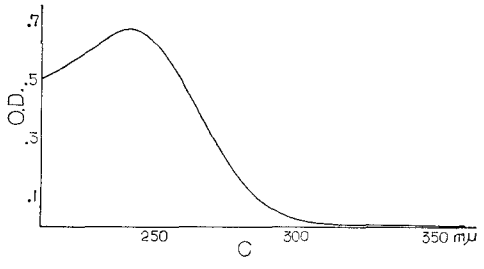
Ethyl-TANOL: λ_{max}=227 mμ, 235 mμ [*n*-heptane][9]



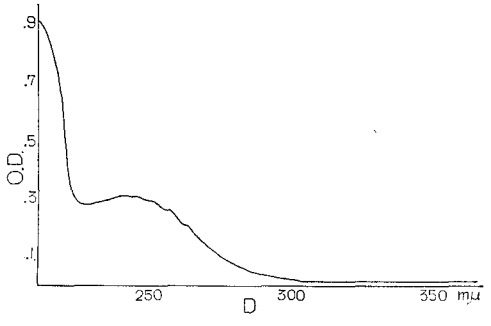
isoPropyl-TANOL
λ_{max}=242 mμ (ε/M=1970) [*n*-hexane]



tert. Butyl-TANOL
λ_{max}=242 mμ (ε/M=2070) [*n*-hexane]



CycloHexyl-TANOL
λ_{max}=241 mμ (ε/M=1890) [*n*-hexane]



Phenyl-TANOL
λ_{max}=241 mμ (ε/M=2560), λ_s=245 mμ, λ_s=250 mμ, λ_s=256 mμ, λ_s=262 mμ. [*n*-hexane]

Fig. 3

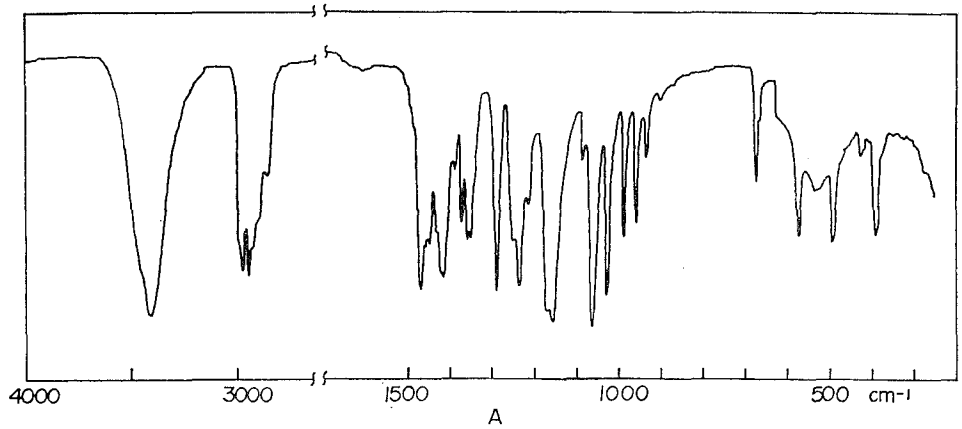
(3) Infrared absorption spectra

TANOL: 3620(OH) or 3430-3450(OH) cm^{-1} [CCl_4] 1240 cm^{-1} [CS_2].[7]

Methyl-TANOL: 3500(OH), 1310, 1200, 1090, 960, 905, 810 cm^{-1} [nujol].[7]

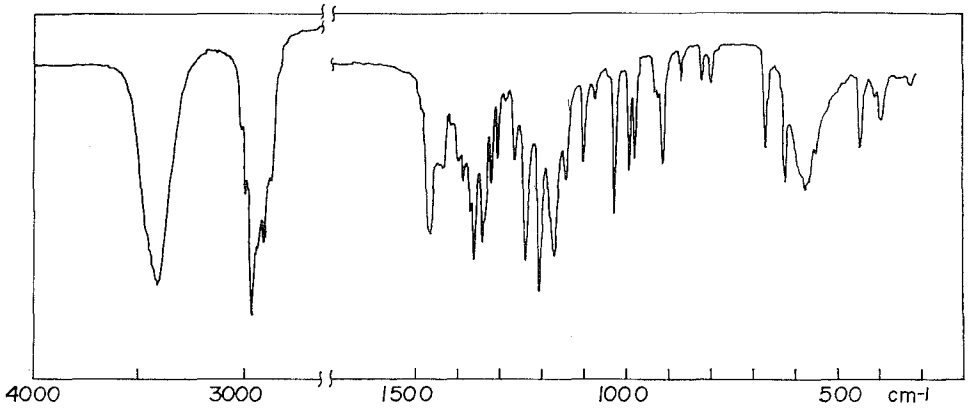
Ethyl-TANOL: 3445 cm^{-1} (broad band), 3605 cm^{-1} (narrow band)[9]

In Fig. 3, little difference is found in the spectra of TANOL and its derivatives. And in Fig. 4, the broad band between 3400 and 3600 cm^{-1} indicates the



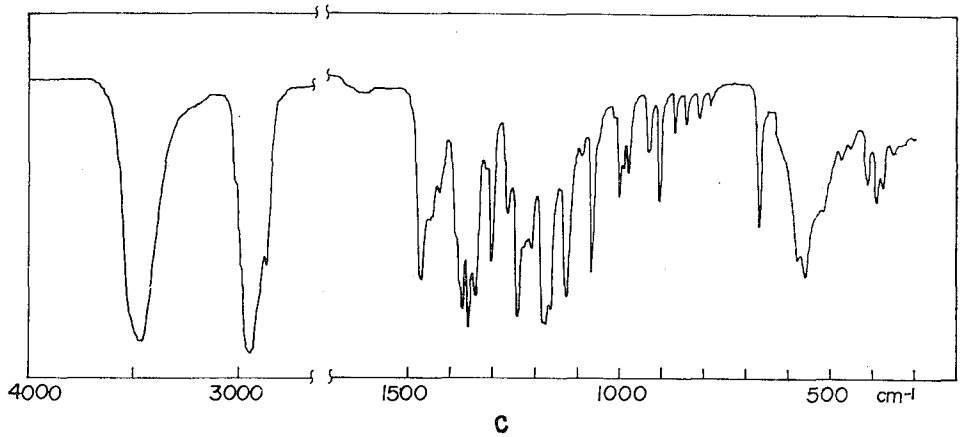
A

TANOL [KBr]



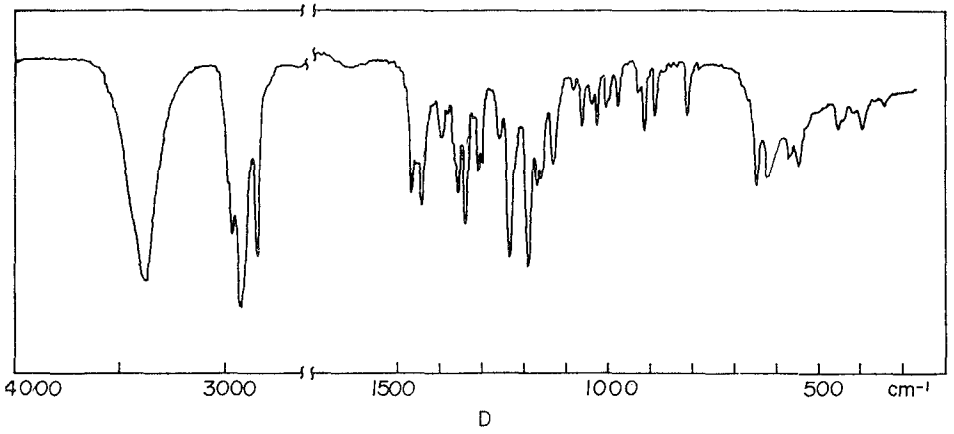
B

isoPropyl-TANOL [KBr]

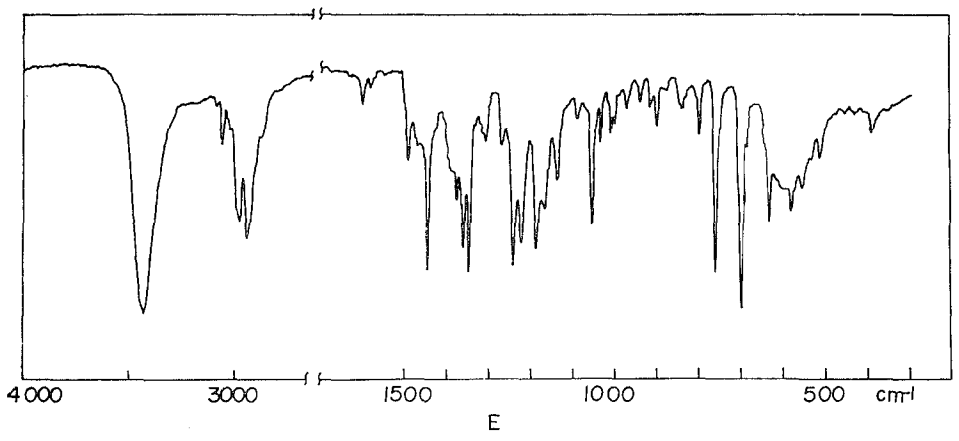


C

tert. Butyl-TANOL [KBr]



cycloHexyl-TANOL [KBr]



Phenyl-TANOL [KBr]

Fig. 4

formation of hydrogen bonds in TANOL and all its derivatives. ESR absorption spectra were also observed in TANOL and all its derivatives.

We are now analysing the ESR absorption spectra and measuring temperature dependence of static magnetic susceptibility of these radicals. These results will be published in succeeding papers.

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