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THE FORMYLATION OF 3-ALKYLINDOLE-2-ACETIC ESTERS

C. F. JONES, D. A. TAYLOR* and D. P. BOWYER
Dept of Chemistry, University of Rhodesia, Salisbury, Rhodesia

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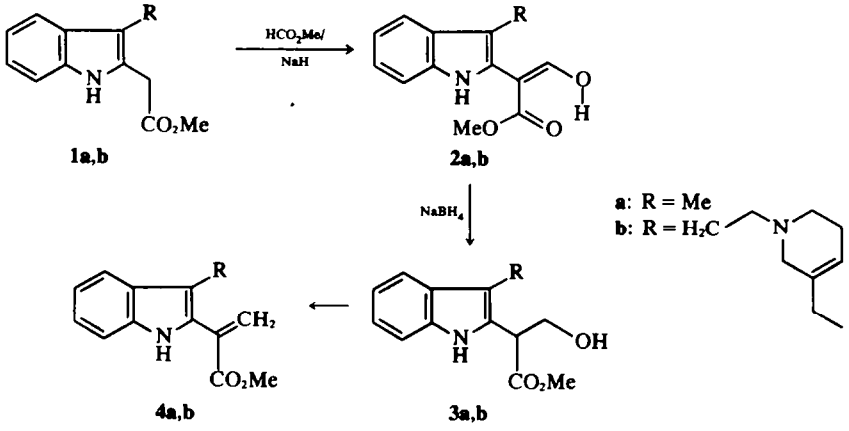
Abstract—Methyl 2[2 - (3 - methyl)indolyl]acetate (**1a**), on treatment with sodium hydride and methyl formate, gives methyl (Z) - 2[2 - (3 - methyl)indolyl] - 3 - hydroxyacrylate (**2a**), which is in tautomeric solvent-dependent equilibrium with methyl 2[2 - (3 - methyl)indolinylidene] - 3 - oxopropanoate (**6**). On reaction with phosphoryl chloride in dimethyl formamide, (**1a**) yields methyl (Z) - 2[2 - (3 - methyl)indolyl] - 3 - N,N - dimethylaminoacrylate (**9**) as expected, together with a more complex product derived from (**9**).

In connection with our interest[1,2] in the synthesis of the secodine skeleton (**4b**), the formylation of the model indolylacetic ester (**1a**) under Vilsmeier–Haack and Claisen conditions was investigated. Formylation of the complex indole-2-acetic ester (**1b**) has already been accomplished with methyl formate in the presence of sodium hydride[3] and trityl sodium.[4] The resulting compound was described simply as an enol (**2b**), which was reduced[3,4] to the β-hydroxyester (**3b**) and thence transformed to secodine (**4b**).[3]

use of the products of these reactions in the study of indole alkaloid biogenesis. Thus, from (**3b**), processes involving oxidation of the piperideine ring, dehydration of the hydroxyester to acrylate, and various Michael, Mannich and Diels-Alder intramolecular interactions of the resulting functionalities may be invoked to generate the quite dissimilar *Aspidosperma* and *Iboga* skeleta.[5] Further, the indole-2-acrylic ester system (**4**) possesses an extremely interesting propensity for intermolecular Diels-Alder dimerisation,[6] the diene being defined



1a,b **2a,b** **3a,b** **4a,b**

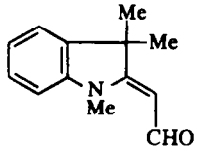
The complex nature of the indole 3-substituent depicted in the **b** series of compounds related to the by the acrylate C=C and the indole 2,3-double bonds, and the dienophile by the acrylate residue itself.

In order to prepare a simpler case for study of this 1,4-cycloaddition, and to examine the formylation *per se* of simple indole-2-acetic esters blocked at the 3-position, the **a** series compound (**1a**) was chosen.†

Our model compound was prepared from 3-methylindole (skatole) by successive acetylation,[8]

†During the course of this work, Drs. G. F. Smith and G. A. Cordell informed us that they had carried out the transformation of (**1a**) to (**4a**),[7] and had conducted studies on (**4a**) which effectively anticipated the investigations we had in mind. Accordingly, work in our laboratory on the topic of the cycloaddition properties of (**4a**) was terminated.

Willgerodt reaction of the resulting 2-acetylskatole (*cf* Ref 9) using morpholine, and acid-catalysed methanolysis of the resulting thiomorpholide. Formylation under nitrogen in dry tetrahydrofuran using methyl formate and sodium hydride provided a compound which crystallised slowly after workup, and could be recrystallised without difficulty from non-polar solvents. This compound gave a weakly positive ferric chloride test in chloroform.



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The solvent dependence of the ultraviolet spectrum is shown in Fig 1. On dissolving the crystalline compound in hexane, the chromophore strongly resembled that of β-anilinoacrylate models typified by (**5**).[10] Immediately after dissolving the compound in methanol, the spectrum closely duplicated that in hexane, but slowly altered until, after 90 sec at a concentration of 0·01 mg per ml, it

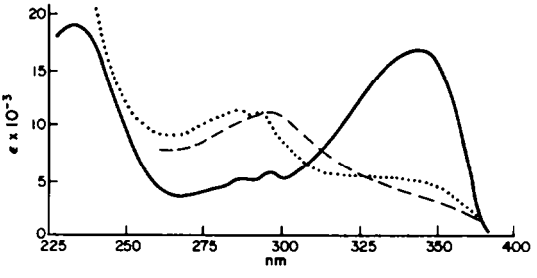
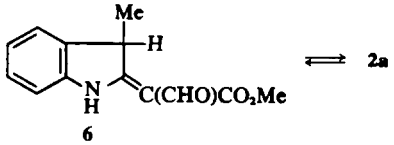


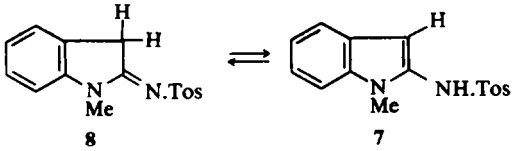
Fig 1. UV spectrum of **2a** ⇄ **6** —in Hexane, --in DMSO, . . . in MeOH

reached final equilibrium, whereupon the chromophore was more nearly that of an indole with a tail to longer wavelength. This tail is slowly eliminated on addition of sodium borohydride to the cell, resulting in conversion to the compound (**3a**).[7]



⇌ **2a**

6



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The hypothesis that a tautomeric equilibrium exists between the species with exocyclic double bond (**6**), favoured in non-polar solvents, and a species with endocyclic double bond (**2a**), favoured in polar solvents, was confirmed and quantified by examination of the NMR and IR spectra of the substance.

The NMR of the compound in $CDCl_3$, in which both forms are present, is shown in Fig 2. The doublet at 8·54τ is due to the methyl group of the tautomer (**6**), coupled to the benzylic hydrogen quartet at 5·35τ ($J = 8$ Hz). The singlet at 7·78τ arises from the aromatic methyl of the tautomer (**2a**). On addition of D_2O or in deuteromethanol, the doublet collapses to a singlet and the quartet vanishes. OH and two NH signals are seen well downfield, and the OMe singlet at 6·26τ. The vinyl proton of the enolic form is located in the aromatic multiplet.

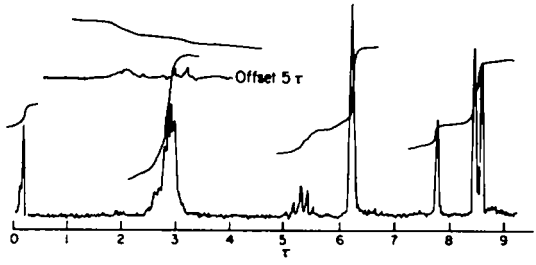


Fig 2. NMR spectrum of **2a** ⇄ **6** in $CDCl_3$

By comparing the integral due to the benzylic methyl with that due to the aromatic Me singlet in various solvents, it was possible to arrive at the equilibrium ratios shown in the Table. It is not possible to say whether the tautomer with the exocyclic double bond occurs as the Z isomer or the E.

The IR spectrum of the solid in KBr has peaks appropriate for NH, acrylate ester carbonyl, acraldehyde carbonyl and the exocyclic C=C (3160, 1692, 1611 and 1605 cm^{-1} respectively), whereas the IR spectrum in DMSO shows the peaks expected of the enolic β-ketoester—the chelated OH occurring as a broad singlet at 2600 cm^{-1}, and the ester carbonyl at 1705 cm^{-1}.[11] The NH appears at 3300 cm^{-1}.

The interesting tautomeric behaviour that may thus be inferred for 2(2-indolyl)malonates generally is paralleled by the observations of Harmon[12] and

Table

State	% 6	% 2a
Solid, m.p. 107°	100	—
Solution*, CCl_4	85	15
$CHCl_3$	75	25
d_4-MeOH	20	80
d_6-DMSO	—	100

*Concentration: 70 mg/ml.

Bailey[13] in relation to the N(2-indolyl)sulphonamide system, 7, which is in solvent-dependent equilibrium with 8, the former similarly predominating in polar solvents.

It has been shown[14] that carboxylic acids of the type RCH_2CO_2H, where R is an aromatic homo- or heterocyclic residue, gave β-dialdehyde derivatives under mild Vilsmeier conditions. Despite the dependence of this reaction upon the use of an acid substrate, the susceptibility of indoles such as 1,2,3-trimethylindole to electrophilic attack at the α-methylene position under Mannich conditions[15] indicated that a similar electrophilic attack might still be possible with Vilsmeier reagent ($CHCl{=}N^+Me_2$ $Cl_2PO.O^-$)[16] in the case of β-blocked indole-α-acetic esters. Vilsmeier formylation of 9 - methyl - 1, 2, 3, 4 - tetrahydrocarbazole has been reported to yield 3 - formyl - 1, 9 - dimethylcarbazole. A complex series of reactions of unknown mechanism is involved, possibly initiated by attack of the formylating species at C(1) of the tetrahydrocarbazole. Redox reactions perhaps generate a 1,9-dimethylcarbazole which is subsequently formylated.[17]

shown in Fig 3 compared with spectra of starting material and intermediate. The chromophore is not altered by base or borohydride, but an addition of acid, undergoes a hypsochromic shift and degrades fairly rapidly. The empirical formula shows that a second N, N-dimethylaminomethylene residue has been introduced into the molecule. Work is in hand

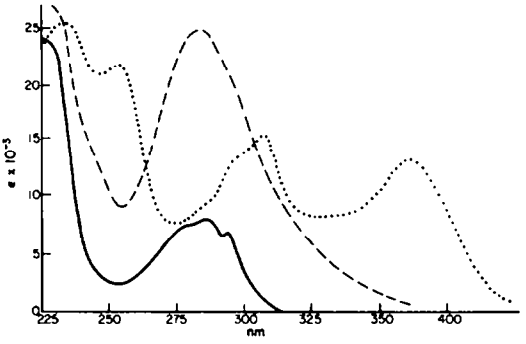
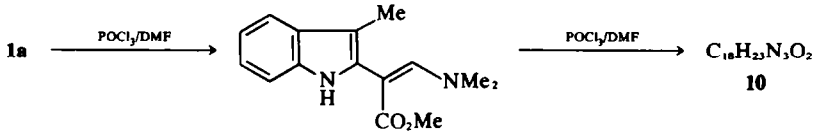


Fig 3. UV spectra of **1a**, **9** and **10** in EtOH —**1a**, ---**9**, ...**10**



The ester (**1a**) was initially warmed with phosphoryl chloride/N,N-dimethylformamide ($POCl_3$/DMF) at 45°, but was recovered unchanged. By performing the reaction at 70° for 3 h using three equivalents of $POCl_3$/DMF in excess DMF, a 59% yield of the (Z)-dimethylaminoacrylate (**9**) was isolated after chromatography and recrystallisation. A second compound, $C_{18}H_{23}N_3O_2$ (**10**), representing a 4% yield from starting ester, was obtained as a less polar fraction from the same TLC plate. In all reactions, this yellow compound was contaminated with a bright red impurity present in minute amount, which ran slightly ahead of it on TLC and whose presence made the crystallisation of the other exceedingly difficult. Repeated chromatography, followed by careful multiple recrystallisations from aqueous ethanol, succeeded in purifying the yellow compound.

On carrying out the reaction at 90° for 2 h using six equivalents of $POCl_3$/DMF, the yield of (**9**) dropped to 31%, and that of the yellow material rose to 25%. That the latter is formed from the former was established by heating (**9**) with three equivalents of the Vilsmeier reagent under the same conditions, whereupon, along with 25% of recovered starting material, 28% of the yellow compound was obtained.

The UV spectrum of the unknown compound is to verify a hypothesis[18] for the structure of this compound, further discussion of which is therefore deferred.

EXPERIMENTAL

IR spectra were run in Nujol on a Unicam SP200 Spectrometer, unless otherwise stated; UV spectra were obtained on a Unicam SP800 Spectrometer with samples in EtOH. Mass spectra were obtained on an AEI MS-9 Spectrometer, 60 MHz NMR spectra on a Perkin–Elmer R12 Spectrometer, and 100 MHz spectra, where specified, on a Varian HA100 Spectrometer. Unless otherwise specified, NMR samples were made up in $CDCl_3$. Silica TLC plates used were Eastman Chromagram 6060, and Alumina TLC plates Merck 5726/0012, and for preparative chromatography, 5727/0025. Phosphoryl chloride was distilled from sodium wire, and DMF distilled under reduced pressure from Linde Type 4A molecular sieve, over which the distillate was stored. Otherwise, Fluka "Practical" grade reagents were used throughout without further purification. M.ps are uncorrected, and were determined on a Kofler hot-stage.

2 - *Acetyl* - 3 - *methylindole.* 3 - Methylindole (13·0 g, 0·1 mole) in Na-dried ether (80 ml) was added to $ZnCl_2$ (36·0 g, 0·26 mole) in a flask fitted with a reflux condenser, dropping funnel, drying tube and mechanical stirrer. The mixture was cooled in ice, stirring vigorously, and acetyl chloride (7 ml, 0·1 mole) in dry ether (100 ml) added dropwise over 30 min. The reaction was removed from the icebath and stirred a further 30 min. Water (75 ml) was

added, maintaining the stirring, and the mixture filtered. The aqueous phase was separated from the organic, washed with ether, the organic phases combined and evaporated. The residue was combined with the solids removed by filtration, water (200 ml) added, sat aq KOH stirred into the mixture until the pH was 7, and steam distillation carried out until no further 3-methylindole contaminated the distillate. The non-volatile residue was filtered, washed with water and dried at 90° to give 10·4 g (61%) of crude product, m.p. 145°. This material could be recrystallised from $CHCl_3$/hexane, affording off-white rods, m.p. 147°,[8] and ran as a single spot, $R_f = 0{\cdot}40$ on silica in benzene. (Found: C, 76·4; H, 6·2; N, 7·8. $C_{11}H_{11}NO$ requires: C, 76·3; H, 6·4; N, 8·1%) λ_{max} 237, and 311 nm (log ϵ 4·14, and 4·22), ν_{max} 3320, and 1640 cm^{-1}, *m/e* 173 (M^+), 158, and 130 (12, 40, and 100%), τ 7·43 (s, 2 × Me).

2(2 - *Thio* - 2 - *morpholino)ethyl* - 3 - *methylindole.* 2 - Acetyl - 3 - methylindole (7·07 g, 41 m mole), sulphur (1·32 g, 41 m mole) and excess morpholine (8 ml) were heated together in a sealed tube overnight at 130°. The excess morpholine was removed on a rotary evaporator and the residue triturated with EtOAc until pale brown, yielding 6·06 g (52%) of insoluble crystalline product, m.p. 191–4°. This showed $R_f = 0{\cdot}47$, on silica in benzene and was sufficiently pure for use in the methanolysis described below. It could be crystallised from DMF, raising the m.p. to 194–7°. λ_{max} 225, 280, and 290(sh) nm (log ϵ 4·22, 3·93, and 3·81), ν_{max} 3320, 1500, 1108, and 1090 cm^{-1}, τ(d_6-DMSO, 100 MHz), 7·81 (s, CH_2), 5·67 (s, Me), 6·57, 6·37, 6·24, and 5·78 (four triplets, each integrating for 2H, J = 4–5 Hz. Restricted rotation due to partial double-bond character of the C(S)—N bond causes the ring methylene groups to have different spatial relationships to the C=S group, resulting in two A_2X_2 pairs), *m/e* 274 (M^+), 187, 144, 130, and 96 (25, 20, 100, 30, and 30%) (Found: M^+ 274·112853. $C_{15}H_{18}N_2OS$ requires: 274·113985).

Methyl 2[2(3 - *methyl)indolyl]acetate* (**1a**). Abs MeOH (100 ml) was saturated with dry HCl gas, and the thiomorpholide described above (6·06 g, 22 m mole) added. The mixture was magnetically stirred and refluxed for 6 h in an apparatus protected from adventitious moisture. Longer periods of reflux increased the contamination of the product with 2,3-dimethylindole. The mixture was cooled and filtered, resulting in the recovery of some insoluble morpholide (1·83 g). The filtrate was evaporated on a rotary evaporator at 40°, and the residue swirled with ether (30 ml). Filtration resulted in the recovery of precipitated morpholide (0·91 g). The filtrate was washed with water (3 × 25 ml), dried (Na_2CO_3), filtered and evaporated to give 2·65 g of crude crystalline product. The recovered morpholide was recycled, scaling quantities proportionately, and gave a further 0·94 g of product. The combined product fractions were columned on 100 mesh silica, eluting with benzene/hexane 4:1. 2,3-Dimethylindole (0·54 g) eluted first, followed by the acetate (**1a**) (2·84 g), which was crystallised from hexane to give 2·39 g (53%) as off-white prisms, m.p. 77–8°, $R_f = 0{\cdot}52$ on alumina, eluting with benzene/EtOAc 9:1. (Found: C, 71·1; H, 6·6; N, 6·4. $C_{12}H_{13}NO_2$ requires: C, 70·9; H, 6·4; N, 6·9%), λ_{max} shown in Fig 3, ν_{max} 3357, and 1720 cm^{-1}, *m/e* 203 (M^+), and 144 (20, and 100%), τ 7·77 (s, CMe), 6·32 (s, OMe), and 6·26 (s, CH_2).

Methyl (Z) - 2[2 - (3 - methyl)indolyl] - 3 - hydroxyacrylate (**2a**). NaH/60% oil (80 mg, 2 m mole) was placed in a 10 ml flask fitted with a magnetic stirrer head. The flask was flushed with N_2 and sealed with a vaccine cap pierced by a syringe needle connected to a static head of N_2. HCO_2Me (0·12 ml, approx. 2 m mole) in THF (2 ml, distilled from NaH) was added by syringe and the mixture stirred at 0°. Methyl 2[2 - (3 - methyl)indolyl]acetate (200 mg, 1 m mole) dissolved in dry THF (1 ml) was added dropwise by syringe over a period of 2 min and the stirred mixture allowed to stand a further 15 min in the icebath. The bright yellow soln was removed from the bath and stirring continued a further 10 min at room temp. The soln, which became a dark greenish-red, was cooled back to 0°, quenched with water, and evaporated to dryness at 30° on a rotary evaporator. The residue was partitioned between 2N KOH/Et_2O, the aqueous phase washed with Et_2O, acidified with 5N HCl and extracted with Et_2O. The organic phase, after drying ($MgSO_4$), filtration and evaporation gave 199 mg of an oil which slowly crystallised. Recrystallisation from benzene/hexane gave 140 mg (61%) of final product, m.p. 105–7°. The compound streaked on all TLC systems tried. (Found: C, 67·6; H, 5·7; N, 5·8. $C_{13}H_{13}NO_3$ requires: C, 67·6; H, 5·6; N, 6·1%); λ_{max}, τ shown in Figs 1 and 2 respectively, ν_{max} discussed in text. *m/e* 231 (M^+), 199, 171, 143 (90, 100, 90 and 86%, metastable peaks showing loss of 32, 28 and 28 mu is sequential).

Methyl (Z) - 2[2 - (3 - methyl)indolyl] - 3 - N,N - dimethylaminoacrylate (**9**) *and the di-Vilsmeier product* $C_{18}H_{23}N_3O_2$ (**10**).

(*a*) Purified DMF (2·8 ml) and $POCl_3$ (1 ml, 11 m mole) were mixed, cooling in ice. A mixture of **1a** (100 mg, 0·5 m mole) and the formylating soln (0·5 ml, 1·45 m mole reactant) was heated at 70° for 3 h. After removal of the DMF at the vacuum pump at 70°, the residue was taken up in $CHCl_3$ (20 ml) and ice-cold 2N KOH (7 ml) added dropwise with shaking and cooling. The organic phase was separated, washed again in the same manner until the aqueous phase remained basic, washed with water (3 × 10 ml) and dried (Na_2CO_3). Filtration and evaporation yielded 166 mg crude crystalline product. This was triturated with ether (5 × 4 ml) in a centrifuge tube, spinning down the residue each time, leaving 58 mg of undissolved **9**. The mother liquors were evaporated and plated on alumina, eluting with benzene/EtOAc 9:1. 18 mg (4%) of the compound (**10**), $R_f = 0{\cdot}64$, was thereby recovered as a gum, pure by UV criteria, and 29 mg of the crystalline **9**, $R_f = 0{\cdot}38$. 15 mg of the (E) isomer of **9**, $R_f = 0{\cdot}25$, was obtained as a gum. The two crystalline fractions were combined, recrystallised from aqueous DMF and washed with water to give 75 mg (59%) of (Z)-indolylacrylate as white rods, m.p. 247–8°, as the trite-hydrate. (Found: C, 68·1; H, 7·2; N, 10·6. $C_{15}H_{18}O_2N_2$ 0·33 H_2O requires C, 68·2; H, 7·1; N, 10·6%), λ_{max} shown in Fig 3, ν_{max} (KBr) 3400, 2900, 1675, 1580, 1285, 1222, 1100, 775, 742, and 700 cm^{-1}, *m/e* 258 (M^+), 243, 226, 211, 198, 183, and 155 (100, 10, 27, 17, 30, 20, and 20%), τ (d_6-DMSO) 7·98 (s, CMe), 7·35 (s, NMe_2), 6·75 (broad s, H_2O), 6·50 (s, OMe), 2·6–3·2 (m, ArH), and 2·31 (s, vinylic CH. This signal appears at 2·10 τ in the (E) isomer). Properties of **10** are summarised in (*b*).

(*b*) Purified DMF (5·5 ml) and $POCl_3$ (2·8 ml, 31 m mole) were mixed as above, and an aliquot (0·83 ml, 3·1 m mole of reactant) heated with **1a** (100 mg, 0·5 m mole) at 90° for 2 h. Workup as in (*a*) gave 163 mg of crude product as a red oil, which on purification by TLC as before, yielded 41 mg (31%) of the crystalline **9** and 37 mg (25%) of **10** as a red gum, pure by UV criteria, which crystallised over a period of several days. After re-plating 120 mg of this ma-

terial, obtained from several runs, and recrystallising the pale orange product to constant m.p. from aqueous EtOH, 21 mg was finally obtained, m.p. 114–5°, as yellow plates. (Found: c, 69·3; H, 7·5; N, 13·6. $C_{18}H_{23}N_3O_2$ requires: C, 69·0; H, 7·4; N, 13·4%), λ_{max} shown in Fig 3, λ_{max} in EtOH/H$^+$ (run immediately) 250, 270(sh), and 347 nm (log ϵ 4·11, 4·02, and 4·29), in EtOH/H$^+$ (run after 30 min) 269, and 366 nm (log ϵ 4·04, and 3·63), ν_{max} (KBr) 2850, 1680, 1610, 1590, 1565, 1245, 1190, 1150, 1140, and 740 cm^{-1}, *m/e* 313 (M$^+$), 298, 282, 267, 266, and 237 (100, 32, 8, 25, 37, and 57%), τ 7·72 (s, 3H), 7·64 (s, 6H), 6·92 (s, 6H), 6·20 (s, 3H), 4·62 (s, 1H), 2·5–3·2 (m, 4H).

(*c*) The indolylacrylate (**9**) trite-hydrate (39 mg, 0·15 m mole) was heated for 2 h at 90° with the formylating mixture (0·12 ml, 0·45 m mole reactant) prepared as in (*b*). After workup and TLC as before, scaling quantities appropriately, 10 mg starting material (25%) and 13 mg of **10** (28%) were recovered, the latter being spectroscopically and chromatographically indistinguishable from authentic material as obtained in the previous reactions.

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