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NEW METHOD OF SYNTHESIS OF 5-ACETYL-3-CYANO-6-METHYLPYRIDINE-2(1H)-THIONE AND ITS PROPERTIES

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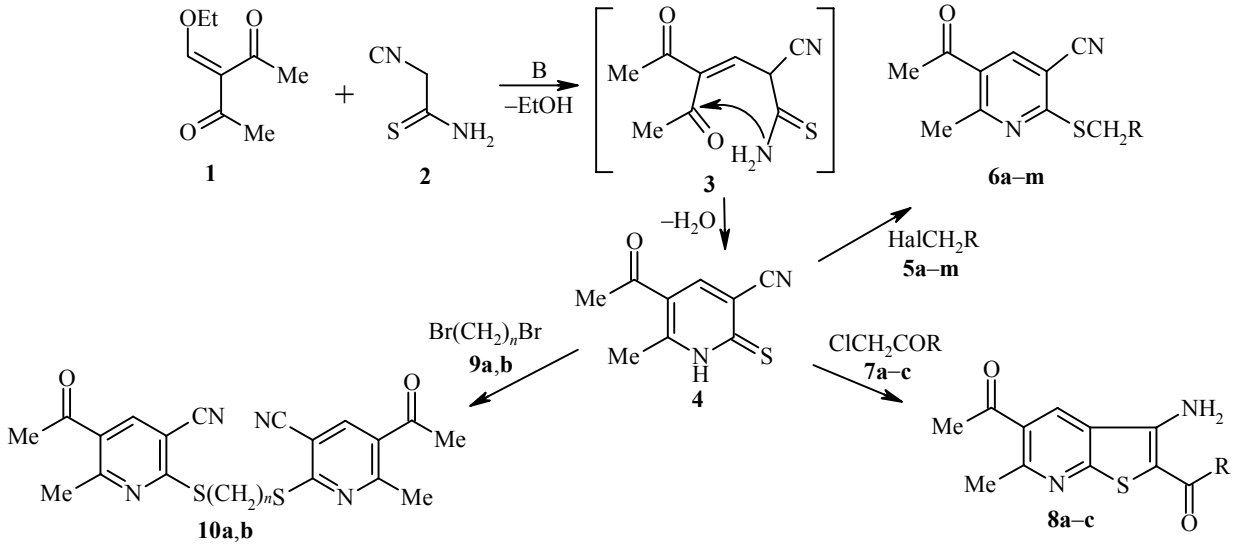
5-Acetyl-3-cyano-6-methylpyridine-2(1H)-thione was obtained by the reaction of ethoxymethyleneacetylacetone with cyanothioacetamide in the presence of N-methylmorpholine. Its alkylation, bromination of the 2-methylthio derivative, and the conversions of its 5-bromoacetyl derivative have been studied.

Keywords: 5-acetyl-3-cyano-6-methylpyridine-2(1H)-thione, alkylation.

5-Acetyl-3-cyano-6-methylpyrid-2(1H)-one, obtained by the interaction of dimethylaminomethylene-acetylacetone [1-4], ethoxymethyleneacetylacetone [5], or isopropylmethyleneacetylacetone [6] with cyanoacetamide, and as well as their derivatives possess cardiotonic properties.



5, 6 a R = H**,** Hal = I; **b** R = Et**,** Hal = I; **c** R = Pr, Hal = Br; **d** R = CH_2=CH, Hal = Br; **e** R = Ph, Hal =Cl; **f** R = $H_2NC(O)$, Hal = Cl; **g** R = $Me_2CHOC(O)$, Hal = Cl; **h** R = 4-Br–$C_6H_4NHC(O)$, Hal = Cl; **i** R = HC≡C, Hal =Br; **j** R = 3,4-$(HO)_2C_6H_3C(O)$, Hal = Br; **k** R = 3-coumarinylcarbonyl, Hal = Br; **l** R = 7-hydroxy-3-coumarinylcarbonyl, Hal = Br; **m** R = benzo[*f*]-3-coumarinylcarbonyl, Hal = Br; **7, 8 a** R = 4-Br-C_6H_4; **b** R = 4-Ph–C_6H_4; **c** R = PrO. **9, 10 a** *n* = 2**, b** *n* = 4. B = N-methylmorpholine

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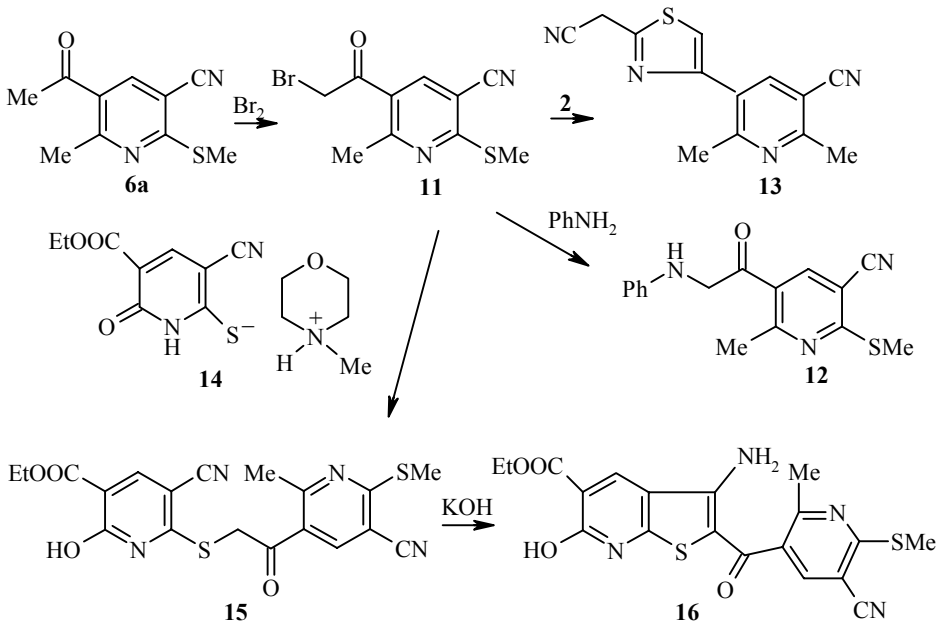
The interaction of dimethylaminomethyleneacetylacetone with cyanothioacetamide leads to the formation of 5-acetyl-3-cyano-6-methylpyridine-3(1H)-thione [7]. However the similar reaction with ethoxymethyleneacetylacetone, according to literature data [8], gives the isomeric 5-acetyl-3-cyano-4-methylpyridine-2(1H)-thione, but that is doubtful. With the aim of resolving this inconsistency and searching for new biologically active compounds we have developed a new synthesis of 5-acetyl-3-cyano-6-methylpyridine-2(1H)-thione and have studied its properties.

We have found that the reaction of ethoxymethyleneacetylacetone (**1**) with cyanothioacetamide (**2**) in the presence of N-methylmorpholine in abs. ethanol at 25°C leads, probably through the intermediate **3**, to 5-acetyl-3-cyano-6-methylpyridine-2(1H)-thione (**4**) but not to the 4-methyl isomer. This was confirmed by physico-chemical data, which are in agreement with the literature data of [7], and by its further conversions. Alkylation of thione **4** with halides **5a-m** in DMF in the presence of an equimolar amount of KOH occurs regioselectively and leads to the formation of the corresponding 5-acetyl-3-cyano-6-methyl-2-(R-methylthio)pyridines (**6a-m**). The use of chlorides **7a-c** for the alkylation of thione **4** in the presence of a twofold excess of KOH leads, without isolation of the linear products, to the corresponding 5-acetyl-3-amino-2-(R-carbonyl)-6-methylthieno[2,3-*b*]pyridines (**8a-c**). 1,2-Dibromoethane (**9a**) and 1,4-dibromobutane (**9b**) alkylate thione **4** (DMF, 10% KOH solution) to give di(2-pyridinylthio)alkanes (**10a,b**).

The structures of the sulfides obtained **6a-m**, **9a,b** and thienopyridines **8a-c** were in agreement with the data of physicochemical investigations (Table 1).



Bromination of the 2-methylthiopyridine **6a** in acetic acid in the light leads to 5-bromoacetyl-3-cyano-6-methyl-2-methylthiopyridine (**11**), which gives compounds **12** and **13** in reactions with nucleophilic reagents (see Experimental).

The use of the 5-bromoacetylpyridine **11** as an alkylating agent in the reaction with thiolate **14** [9] leads sequentially to sulfide **15** and thienopyridine **16**.

The structures of compounds **11-13** and **15**, **16** were confirmed by data of physicochemical investigations (Table 1).

TABLE 1. Characteristics of the Synthesized Compounds **6a-m**, **8a-c**, **10a,b**, **11-13**, **15**, and **16**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C, (solvent for crystallization)	IR spectrum, cm^{-1}		^{1}H NMR spectrum, δ, ppm, *J* (Hz)	Yield, %
		C	H	N		C≡N	C=O, NH_2		
1	2	3	4	5	6	7	8	9	10
6a	$C_{10}H_{10}N_2OS$	58.03 / 58.23	4.55 / 4.89	13.69 / 13.58	143-145 (EtOH)	2210	1680	2.57 (3H, s, CH_3); 2.64 (3H, s, CH_3S); 2.70 (3H, s, CH_3CO); 8.66 (1H, s, C(4)H)	70
6b	$C_{12}H_{14}N_2OS$	61.42 / 61.51	6.21 / 6.02	11.75 / 11.96	117-119 (EtOH)	2200	1690	0.98 (3H, t, *J* = 6.16, $\underline{CH_3}CH_2$); 1.69 (2H, m, $CH_3C\underline{H_2}$); 2.57 (3H, s, 6-CH_3); 2.68 (3H, s, CH_3CO); 3.28 (2H, m, SCH_2); 8.65 (1H, s, C(4)H)	66
6c	$C_{13}H_{16}N_2OS$	62.58 / 62.87	6.26 / 6.49	11.37 / 11.28	64-66 (EtOH)	2220	1670	0.91 (3H, t, *J* = 6.72, $\underline{CH_3}(CH_2)_2$); 1.05-1.90 (4H, m, $CH_3(\underline{CH_2})_2$); 2.57 (3H, s, 6-CH_3); 2.69 (3H, s, CH_3CO); 3.31 (2H, m, SCH_2); 8.66 (1H, s, C(4)H)	58
6d	$C_{12}H_{12}N_2OS$	61.89 / 62.04	5.30 / 5.21	11.90 / 12.06	103-105 (EtOH)	2220	1690	2.57 (3H, s, CH_3); 2.70 (3H, s, CH_3CO); 3.98 (2H, d, *J* = 6, SCH_2); 5.15 d, *J* = 10, and 5.35 d, *J* = 16.8, (1H, CH_2=); 5.90 (1H, m, CH=); 8.67 (1H, s, C(4)H)	58
6e	$C_{16}H_{14}N_2OS$	67.83 / 68.06	5.11 / 5.00	9.74 / 9.92	92-94 (EtOH)	2220	1690	2.57 (3H, s, CH_3); 2.73 (3H, s, CH_3CO); 4.58 (2H, s, SCH_2); 7.42 (5H, m, Ph); 8.66 (1H, s, C(4)H)	58
6f	$C_{11}H_{11}N_3O_2S$	52.79 / 53.00	4.23 / 4.45	16.56 / 16.86	165-168 (EtOH)	2210	1680	2.58 (3H, s, CH_3); 2.67 (3H, s, CH_3CO); 4.01 (2H, s, SCH_2); 7.19 br. s and 7.64 br. s (1H, NH_2); 8.68 (1H, s, C(4)H)	85
6g	$C_{14}H_{16}N_2O_3S$	57.33 / 57.52	5.33 / 5.52	9.69 / 9.58	136-138 (DMF)	2200	1680	1.19 s and 1.27 s (3H, $(C\underline{H_3})_2CH$); 2.58 (3H, s, CH_3); 2.64 (3H, s, CH_3CO); 4.13 (2H, s, SCH_2); 4.93 (1H, m $(CH_3)_2\underline{CH}$); 8.70 (1H, s, (4)H)	60

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
6h	$C_{17}H_{14}BrN_3O_2S$	50.30 / 50.51	3.21 / 3.49	10.17 / 10.39	233-235 (DMF)	2217	1680 sh, 3270	2.56 (3H, s, CH_3); 2.60 (3H, s, CH_3CO); 4.24 (2H, s, SCH_2); 7.51 (4H, m, C_6H_4); 8.68 (1H, s, C(4)H); 10.48 (1H, br. s, NH)	68
6i	$C_{12}H_{10}N_2OS$	62.40 / 62.59	4.29 / 4.38	12.25 / 12.16	119-121 (AcOH)	2219	1710	2.58 (3H, s, CH_3); 2.74 (3H, s, CH_3CO); 2.87 (1H, s, HC≡); 4.14 (2H, s, SCH_2); 8.66 (1H, s, C(4)H)	74
6j	$C_{17}H_{14}N_2O_4S$	59.33 / 59.64	4.22 / 4.12	8.25 / 8.18	285-287 (DMF)	2222	1674	2.43 (3H, s, CH_3); 2.56 (3H, s, CH_3CO); 4.83 (2H, s, SCH_2); 6.87 d, J = 7, and 7.43 d, J = 7.9, (1H, C(5)H and $C(6)H_{1\text{-pyrocatechinyl}}$); 7.52 (1H, s, $C(2)H_{1\text{-pyrocatechinyl}}$); 8.68 (1H, s, C(4)H); 9.50 br. s and 9.95 br. s (1H, $(OH)_2$)	72
6k	$C_{20}H_{14}N_2O_4S$	63.26 / 63.48	3.55 / 3.73	7.52 / 7.40	203-205 (DMF)	2224	1680, 1722	2.48 (3H, s, CH_3); 2.56 (3H, s, CH_3CO); 4.90 (2H, s, SCH_2); 7.47-7.98 m (4H, H_{arom}); 8.70 (1H, s, C(4)H); 8.80 (1H, s, $C(4)H_{3\text{-coumarinyl}}$)	77
6l	$C_{20}H_{14}N_2O_5S$	60.82 / 60.91	3.39 / 3.58	7.23 / 7.10	230 dec. (DMF)	2228	1675, 1710	2.48 (3H, s, CH_3); 2.54 (3H, s, CH_3CO); 4.86 (2H, s, SCH_2); 6.80 (2H, m, H_{arom}); 7.79 (1H, d, J = 8, H_{arom}); 8.66 (2H, s, C(4)H and $C(4)H_{3\text{-coumarinyl}}$); 11.25 (1H, br. s, OH)	81
6m	$C_{24}H_{16}N_2O_4S$	67.07 / 67.28	3.67 / 3.76	6.65 / 6.54	225 dec. (DMF)	2225	1680, 1704	2.51 (3H, s, CH_3); 2.53 (3H, s, CH_3CO); 4.96 (2H, s, SCH_2); 7.49-8.68 (7H, m, H_{arom}); 9.35 (1H, s, $C(4)H_{benzo\text{-}3\text{-coumarinyl}}$)	92
8a	$C_{17}H_{13}BrN_2O_2S$	52.14 / 52.45	3.08 / 3.37	7.31 / 7.20	186-188 (AcOH)	—	1670, 3180	2.63 (3H, s, CH_3); 2.69 (3H, s, CH_3CO); 7.71 (4H, s, C_6H_4); 8.51 (2H, br. s, NH_2); 9.14 (1H, s, C(4)H)	60
8b	$C_{23}H_{18}N_2O_2S$	71.25 / 71.48	4.45 / 4.69	7.14 / 7.25	88-90 (AcOH)	—	1600, 1700, 3280	2.67 (3H, s, CH_3); 2.74 (3H, s, CH_3CO); 7.49-7.87 (9H, m, H_{arom}); 8.53 (2H, br. s, NH_2); 9.21 (1H, s, C(4)H)	75

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
8c	$C_{14}H_{16}N_2O_3S$	57.23 / 57.52	5.64 / 5.52	9.67 / 9.58	162-164 (AcOH)	—	1680, 3360	1.03 (3H, t, *J* = 6.8, CH_3); 1.78 (2H, m, CH_2); 2.67 (3H, s, 6-CH_3); 2.76 (3H, s, CH_3CO); 4.22 (2H, t, *J* = 5.6, OCH_2); 7.25 (2H, br. s, NH_2); 9.04 (1H, s, C(4)H)	63
10a	$C_{20}H_{18}N_4O_2S_2$	58.36 / 58.52	4.23 / 4.42	13.56 / 13.65	195-197 (BuOH)	2210	1680	2.59 (6H, s, $(CH_3)_2$); 2.68 (6H, s, $(CH_3CO)_2$); 3.69 (4H, s, $(SCH_2)_2$); 8.64 (2H, s, $(C(4)H)_2$)	88
10b	$C_{22}H_{22}N_4O_2S_2$	59.95 / 60.25	4.86 / 5.06	12.62 / 12.78	218-220 (AcOH)	2217	1694	1.89 (4H, m, $(CH_2)_2$); 2.58 (6H, s, $(CH_3)_2$); 2,73 (6H, s, $(CH_3CO)_2$); 3.38 (4H, m, $(SCH_2)_2$); 8.60 (2H, s, $(C(4)H)_2$)	91
11	$C_{10}H_9BrN_2OS$	42.04 / 42.12	2.98 / 3.18	9.93 / 9.82	132-134 (EtOH)	2210	1700	2.66 (3H, s, CH_3); 2.69 (3H, s, SCH_3); 4.91 (2H, s, CH_2CO); 8.73 (1H, s, C(4)H)	71
12	$C_{16}H_{15}N_3OS$	64.36 / 64.62	5.15 / 5.08	13.92 / 14.13	180-182 (AcOH)	2220	1680, 3200	2.66 (6H, br. s, 6-CH_3 and SCH_3); 4.54 (2H, s, CH_2CO); 6.68 m and 7.08 m (3H and $2H_{arom}$); 8.81 (1H, s, C(4)H)	55
13	$C_{13}H_{10}N_4S_2$	54.30 / 54.52	3.36 / 3.52	19.45 / 19.56	175-177 (AcOH)	2217, 2250	—	2.65 (3H, s, CH_3); 2.73 (3H, s, SCH_3); 4.46 (2H, s, CH_2CN); 8.05 (1H, s, $C(5)H_{5\text{-thiazolyl}}$); 8.36 (1H, s, C(4)H)	60
15	$C_{19}H_{16}N_4O_4S_2$	53.02 / 53.26	3.58 / 3.76	13.17 / 13.08	158-160 (EtOH)	2230 sh.	1680 sh.	1.30 (3H, t, *J* = 6.2, $\underline{CH_3}CH_2O$); 2.64 (3H, s, SCH_3); 2.68 (3H, s, 6-CH_3); 4.27 (2H, q, *J* = 7.1, $CH_3\underline{CH_2}O$); 4.85 (2H, s, SCH_2); 8.45 s and 8.82 s (1H, C(4)H and C(4')H)	83
16	$C_{19}H_{16}N_4O_4S_2$	53.04 / 53.26	3.57 / 3.76	13.28 / 13.08	294-296 (DMF)	2220	1670, 3360	1.49 (3H, t, *J* = 2.9, $\underline{CH_3}CH_2O$); 2.52 (3H, s, SCH_3); 2.57 (3H, s, 6-CH_3); 4.33 (2H, q, *J* = 2.5, $CH_3\underline{CH_2}O$); 8.09 s and 8.92 s (1H, C(4)H and C(4')H); 8.46 (2H, br. s, NH_2); 12.80 (1H, br. s, OH)	79

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on an IKS 29 instrument (in nujol). The ^{1}H NMR spectra were recorded on a Bruker WP-100SY (100 MHz) instrument [for compounds **6i,8c,10a,b** on a Bruker WM-250 (250.13 MHz)] in DMSO-d_6, internal standard was Me_4Si. The course of reactions was monitored by TLC (Silufol UV 254, acetone–heptane 3 : 5, visualization by iodine vapor).

5-Acetyl-3-cyano-6-methylpyridine-2(1H)-thione (4). A mixture of ethoxymethyleneacetylacetone **1** (15 g, 96 mmol), cyanoacetamide **2** (9.6 g, 96 mmol), and N-methylmorpholine (10.8 ml, 96 mmol) in abs. ethanol was stirred for 2 h at 25°C. The precipitate formed was filtered off, washed with abs. ethanol, and with hexane. Compound **4** was obtained, identical with that described previously in [7].

5-Acetyl-3-cyano-6-methyl-2-(R-methylthio)pyridines 6a-m. Thione **4** (1 g, 5.2 mmol) was dissolved in DMF (8 ml) and 10% KOH solution (2.9 ml, 5.2 mmol) was added with stirring. The appropriate halogen derivative **5a-m** (5.2 mmol) was introduced into the reaction mixture after 5 min, the mixture was filtered through a folded filter, and stirred for 4 h. The precipitate was filtered off, and washed with ethanol. Compounds **6a-m** were obtained (Table 1).

5-Acetyl-3-amino-6-methyl-2-(R-carbonyl)thieno[2,3-b]pyridines (8a-c). Thione **4** (1 g, 5.2 mmol) was dissolved in DMF (8 ml) and 10% KOH solution (2.9 ml, 5.2 mmol) was added with stirring. After 5 min the appropriate chloride **7a-c** (5.2 mmol) was introduced into the reaction mixture, and stirring continued for 0.5 h, then 10% KOH solution (2.9 ml) was again added to the reaction mixture. The solution was stirred for 4 h. The precipitate was filtered off, and washed with ethanol. Compounds **8a-c** were obtained (Table 1).

Di(5-acetyl-3-cyano-6-methyl-2-pyridinylthio)alkanes (10a,b). Thione **4** (1 g, 5.2 mmol) was dissolved in DMF (8 ml) and 10% KOH solution (2.9 ml, 5.2 mmol) was added with stirring. After 5 min the appropriate dibromoalkane **9a,b** (2.6 mmol) was added to the reaction mixture, the mixture was filtered through a folded filter, and stirred for 4 h. The precipitate was separated, and washed with ethanol. Compounds **10a,b** were obtained (Table 1).

5-Bromoacetyl-3-cyano-6-methyl-2-methylthiopyridine (11). The 2-methylthiopyridine **6a** (1 g, 4.8 mmol) was dissolved in glacial acetic acid (8 ml) and bromine (0.25 ml, 4.8 mmol) was introduced to the solution dropwise with stirring in the light. The reaction mixture was stirred until decolorized, then cooled with ice. The resulting precipitate was filtered off, and washed with ethanol. Compound **11** was obtained (Table 1).

5-Anilinoacetyl-3-cyano-6-methyl-2-methylthiopyridine (12). The bromoacetylpyridine **11** (1 g, 3.9 mmol) was dissolved in ethanol (5 ml) and aniline (0.44 ml, 4.8 mmol) was added with stirring. The reaction mixture was stirred for 2 h. The resulting solid was filtered off, and washed with ethanol. Pyridine **12** was obtained (Table 1).

3-Cyano-5-(2-cyanomethyl-4-thiazolyl)-6-methyl-2-methylthiopyridine (13). A mixture of bromoacetyl-pyridine **11** (1 g, 3.9 mmol) and cyanothioacetamide **2** (0.48 g, 4.8 mmol) in DMF (8 ml) was stirred for 2 h. The precipitate formed was filtered off, and washed with ethanol. Compound **13** was obtained (Table 1).

3-Cyano-2-(3-cyano-6-methyl-2-methylthio-5-pyridylcarbonylmethylthio)-5-ethoxycarbonyl-6-hydroxypyridine (15). A mixture of thiolate **14** (1 g, 3 mmol) and bromide **11** (0.88 g, 3 mmol) in ethanol (10 ml) was brought to boiling and filtered through a folded filter. The solid which precipitated on cooling the filtrate was separated, and washed with ethanol. Pyridine **15** was obtained (Table 1).

3-Amino-2-(3-cyano-6-methyl-2-methylthio-5-pyridylcarbonyl)-5-ethoxycarbonyl-6-hydroxythieno-[2,3-*b*]pyridine (16). Compound **15** (1 g, 2.3 mmol) was dissolved in DMF (8 ml) and 10% KOH solution (1.3 ml, 2.3 mmol) was added with stirring. The reaction mixture was stirred for a further 2 h. The precipitate was filtered off, and washed with ethanol. Compound **16** was obtained (Table 1).

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