ALKYLATION OF 2-, 4-, AND 8-TRIALKYLSILOXY-
QUINOLINES BY METHYL IODIDE

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Trimethyl- and triethylsilyl ethers of 2-, 4-, and 8-hydroxyquinolines have been prepared. The alkylation of these siloxyquinolines by methyl iodide has been studied. In the case of 4-trimethylsiloxyquinaldine, it has been established that both N- and O-alkylation products are formed.

Several earlier studies [1-4] have established that hydroxyquinolines are bifunctional nucleophiles which can react with electrophilic reagents at both the endocyclic nitrogen and the exocyclic oxygen and hence can form both N- and O-alkylation products. The regioselectivity of the reactions is determined by such factors as the nature of the substrate and of the alkylating agent, the temperature, the solvent and several other factors [5-7].

The available information would seem to show that 2- and 4-hydroxyquinoline and 4-hydroxyquinoaldine in the crystalline state exist mainly in the quinolone form (the hydroxy form is a minor component) whereas 8-hydroxyquinoline exists in the quinolinol form [8]. The nature of the solvent influences the tautomeric composition of compounds of this type to a considerable extent. Thus, polar solvents stabilize a lactam form [9, 10] and in nonpolar solvents a lactim form predominates [1, 9-11]. For 2-pyridone and some derivatives of 3-quinolone in chloroform, a dimeric structure has been suggested, arising as a result of hydrogen bonding [12].

Direct quaternization of alkoxyquinolines by methyl iodide takes place readily and with high yield [13, 14]. There is, however, very little published information on the direct interaction of hydroxypyridine ring [14, 15]. UV spectroscopy has revealed the existence of a substituted 4-hydroxyquinolinium cation in methanol under acidic conditions [14, 16]. It has also been shown that trialkylphosphates serve as reagents for the alkylation of 4-substituted (including hydroxy-) quinolines [1]. The methyl iodide alkylation of the sodium salt of 8-hydroxyquinoline has also been described, fairly severe conditions being required (100°C, elevated pressure) [17].

We have verified the possibility of alkylating hydroxyquinolines with methyl iodide using the example of 4-hydroxyquinaldine under different conditions. The reaction was carried out in chloroform, hexane, and ethanol at room temperature (up to 48 h) and on heating (up to 20 h). In all cases the starting material remained unchanged. On heating 4-hydroxyquinaldine with a 30-fold excess of MeI at bp for 20 h in a Pierce reactor, N- and O-alkylation was found to have taken place only to the extent of around 15% forming N-methyl-4-methoxyquinaldinium iodide VIIId. When the reaction was carried out in a flask with a reflux condenser only a trace of VIId was formed over the same time. Möhrle and Gerloff [16] heated 4-hydroxyquinaldine with a 10 times excess of methyl iodide in an autoclave at 100°C for 10 h and also obtained N-methyl-4-methoxyquinaldinium iodides in ~70% yield.

Silylation of the hydroxyquinoline was carried out with hexamethyldisilazane [18] or triethylchlorosilane in the presence of triethylamine in benzene with heating. The reaction gave a reasonably high yield of 70 to 80%. The ethers obtained, with the exception of 2- and 8-trimethylsilyl derivatives, were very sensitive to airborne moisture. The structure of the compounds was confirmed by their PMR spectra. The chemical shifts of the trialkylsilyl groups agreed with published data for the already known-2- and 8-trimethylsiloxyquinolines [18].
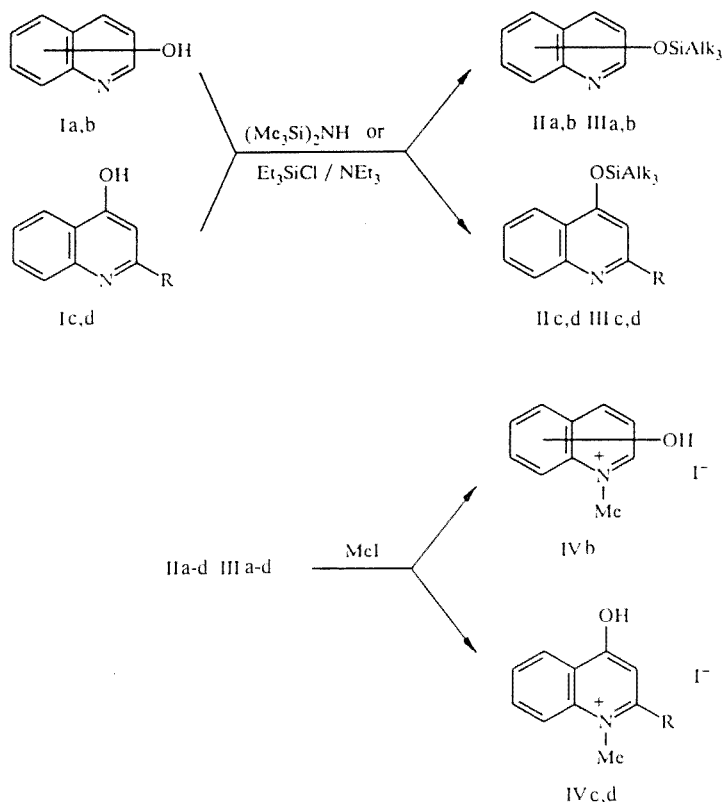
Ia, IIa, IIIa OH group in 2-position; Ib, IIb, IIIb, IVb 8-position; Ic, IIc, IVc R = H; Id, IId, IIId, IVd R = Me; IIa-d Alk$_3$ = Me$_3$; IIIa, b, d Alk$_3$ = Et$_3$

Silylation of 4-hydroxyquinaldine Id by trimethylchlorosilane in different molar ratios from 1:0.5 to 1.0 in chloroform under an inert atmosphere (to allow for the lability of the Si−O bond in trialkylsiloxyquinolines) with reaction times between 1 h and 1 day at room temperature led to the formation of the hydrochloride of 4-trimethylsiloxyquinaldine Vd which readily hydrolyzed into the hydrochloride of 4-hydroxyquinaldine VId. The formation of the siloxy derivative Vd which is unstable in air was confirmed from its PMR spectrum.
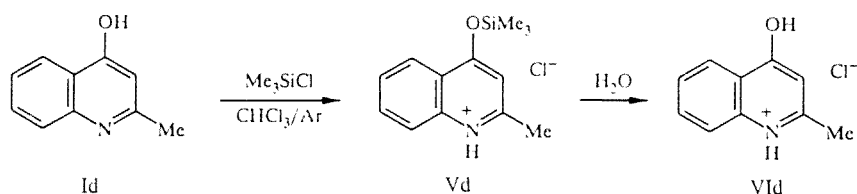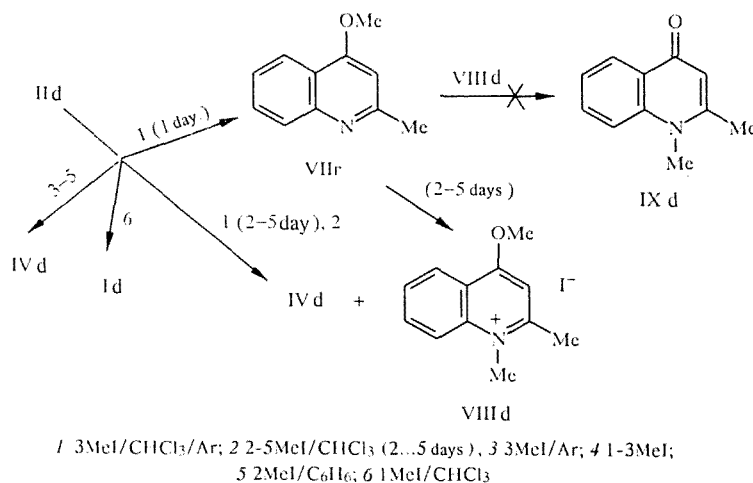

Alkylation of 4-hydroxyquinaldine was also carried out with the successive introduction of two alkylating reagents − trimethylchlorosilane and methyl iodide in molar ratio 1:(0.5 to 1):(1 to 2). The reaction was carried out in an atmosphere of argon at room temperature in chloroform over a period of one day. In all cases the formation of the hydrochloride Vd was also established by PMR spectroscopy; this led to blocking of the nitrogen, thereby impeding its methylation. The spectrum showed no signals characteristic of a methoxy group in 4-methoxyquinaldine or for an N−Me group in 1,2-dimethyl-4-quinoline (respectively δ_{OMe} = 3.89 ppm (CDCl$_3$) and δ_{NMe} = 3.52 [14], 3.59 [19], 3.67 [20] (CDCl$_3$)).

Alkylation of silyl ethers by methyl iodide was studied in great detail for the example of 4-trimethylsiloxyquinaldine. The reaction was carried out under different conditions − in air and in an inert atmosphere, varying the solvent, the temperature, the reaction time, and the ratio of the starting materials.

On treating 4-trimethylsiloxyquinaldine with a three times excess of methyl iodide in the absence of solvent over a period of one day in an atmosphere of argon, the PMR spectrum showed the formation of N-methyl-4-hydroxyquinaldinium iodide in ~60% yield. In air over the same period the yield of the iodide IVd was 100% with a three times excess of methyl

iodide and ~80% with equimolar quantities. In the same way, reaction of 4-trimethylsiloxyquinoline with methyl iodide gave a quantitative yield of 4-hydroxyquinolinium iodide IVe.

When 4-trimethylsiloxyquinaldine was reacted with an excess of methyl iodide in chloroform under argon for a period of one day, the PMR spectrum recorded the formation of around 13% of 4-methoxyquinaldine VIId. In addition to signals attributed to the initial 4-trimethylsiloxyquinaldine there were also signals at δ = 2.55 ppm (2-Me), δ = 3.78 ppm (OMe), δ = 6.25 ppm (3-H). For 4-methoxyquinaldine in CDCl$_3$, the following results are given in [14]: δ = 2.64 ppm (2-Me), 3.89 ppm (4-OMe), 6.50 ppm (3-H). Further evidence in support of the identity of the product is the observation that the reaction will proceed further with the formation of 4-methoxyquinaldine VIIId. If one assumes further reaction of VIIId with 4-methoxyquinaldine by a process similar to that described in [1], then one would expect to find 1,2-dimethyl-4-quinolone IXd present in the final product together with 4-methoxy- and 4-hydroxyquinaldinium iodide. However, we were unable to establish the formation of dimethylquinolone IXd. Published results for the PMR spectrum of 1,2-dimethyl-4-quinolone IXd in CDCl$_3$ are found as follows (δ in ppm): δ = 2.29 [14], 2.34 [19], 2.40 [20] (2-Me), δ = 3.52 [14], 3.59 [19], 3.67 [20] (N−Me), and δ = 6.00 [14], 6.05 [19], 6.17 [20] (3-H).

1 3MeI/CHCl$_3$/Ar; *2* 2-5MeI/CHCl$_3$ (2...5 days), *3* 3MeI/Ar; *4* 1-3MeI;
5 2MeI/C$_6$H$_6$; *6* 1MeI/CHCl$_3$

In the reaction of 4-trimethylsiloxyquinaldine with methyl iodide (using a 2-5 times excess of the latter) in chloroform under air over a period of 2-5 days the quaternary iodide VIIId was formed to the extent of 10% or less and was isolated in pure form; up to 45% of the iodide IVd was also formed. In benzene over the same period ~10% IVd was formed. In ether or hexane IVd was not formed and the product of desilylation (4-hydroxyquinaldine) was isolated. Likewise, the quaternary iodide IVd was not formed in chloroform when the methyl iodide was reduced to 1 equivalent per equivalent of 4-trimethylsiloxyquinaldine. 4-Hydroxyquinaldine was detected in the reaction mixture.

When 4-triethylsiloxyquinaldine (IIId) was treated with a two-times excess of methyl iodide in chloroform under an inert atmosphere over a period of one day, as in the case of the trimethyl derivative, the PMR spectrum showed the formation of ~7% of the methoxy derivative VIId. Extending the reaction time to several days under the same conditions resulted in the formation of ~5% VIId and around 50% quaternary iodide IVd.

Reaction of 8-trimethylsiloxyquinoline IIb with a 2-3-times excess of methyl iodide over one day at room temperature gave 8-hydroxy-N-methylquinolinium iodide IVb in ~25% yield. In chloroform, the reaction led to the formation of quaternary iodide on heating for 1 h, the yield amounting to ~28%. By keeping the reaction mixture for a prolonged period at room temperature it was possible to achieve a yield of the quaternary iodide close to quantitative. Reaction of 8-triethylsiloxyquinoline IIIb with a two-times excess of methyl iodide in chloroform over several days also gave the quaternary iodide IVb (~60%). In an inert atmosphere in chloroform, the PMR spectrum showed only 6% IVb after one day.

When 2-trimethylsiloxyquinoline IIa was treated with methyl iodide both in chloroform and in absence of solvent, desilylation of IIa occurred and no quaternary nitrogen compound was formed. On keeping a mixture of 2-triethylsiloxyquinoline with two equivalent of methyl iodide in chloroform for one day under an inert atmosphere no change was observed. This result was in agreement with published results [21] concerning the impossibility of preparing quaternary salts of 2-methoxyquinoline under different conditions.

Bearing in mind the published results on the alkylation of 4-substituted quinolines by trimethyl phosphate [1, 22] and on concurrent N- and O-alkylation of ambient anions [7], we put forward the following possibilities.

Reaction of 4-trimethylsiloxyquinaldine with methyl iodide can proceed in two directions, depending on the reaction conditions, and products of N- and O-alkylation are formed as a result. The 4-methoxyquinaldine formed in the O-alkylation process can be further alkylated to the corresponding quaternary onium salt. The critical factor influencing the process is the presence or absence of solvent and its type, together with the presence of the alkylating agent, methyl iodide, in excess. It was found that the O-alkylation product was formed only in chloroform.

The main product of the reaction of 4-trimethylsiloxyquinaldine with methyl iodide is 4-hydroxyquinaldinium iodide. It could be suggested that in this case direct N-alkylation by methyl iodide takes place with the formation of 4-trimethylsiloxyquinaldinium iodide and the latter is readily hydrolyzed by moisture in the air to give the corresponding 4-hydroxy compound. However, the presence of 4-trimethylsiloxyquinaldinium iodide has not been recorded in this reaction, either with or without solvent. In the presence of a solvent the N-methylated products (quaternary salts of 4-methoxy- and 4-hydroxyquinaldine) are detected only with a twofold excess of methyl iodide, further increase in the quantity of methyl iodide (in chloroform) having no fundamental effect. The presence of a solvent apparently retards the N-methylation process to a greater or lesser extent, depending on the nature of the solvent. It seems to us most probable that the formation of the $N^+ - Me$ fragment takes place at the moment of rupture of the Si—O bond since otherwise the formation of the silyl-substituted quaternary salt would be recorded, especially in a solvent because obviously the presence of a solvent will slow down the rupture of the Si—O bond. It should also be noted that the readily accessible 4-trimethylsiloxyquinolines can be used to prepare quaternary ammonium salts of 4-hydroxyquinolines.

EXPERIMENTAL

PMR spectra were run on a Bruker WH-90/DS instrument in $CDCl_3$ or DMSO-D_6 with TMS internal standard; the accuracy of the measurements was ± 0.05 ppm. IR spectra were recorded on a Perkin Elmer 580B instrument as mulls in mineral oil. GLC was carried out on a Khrom-4 (Czechoslovak) chromatograph with a flame-ionization detector and a glass column 1.2 m by 3 mm packed with 5% OV-17 on Chromosorb W-HP (80-100 mesh) carrier.

The results of elemental analysis for C, H, N, Cl were in agreement with those calculated.

2-Trimethylsiloxyquinoline (IIa) was prepared by the method of [18].

8-Trimethylsiloxyquinoline (IIb) was prepared by the method of [18].

4-Trimethylsiloxyquinoline (IIc, $C_{12}H_{15}NOSi$). A mixture of 4.35 g (0.03 mole)-4-hydroxyquinoline and 50 ml hexamethyldisilazane was heated with stirring for several hours until the solid had dissolved completely. The evolved ammonia was trapped in hydrochloric acid solution. The progress of the reaction was monitored by glc. When the reaction was complete, the excess hexamethyldisilazane was removed in a rotary evaporator under vacuum and the residue distilled in vacuum (115°C, 3 hPa). The yield was 5.0 g (76.6%) compound IIc. PMR spectrum ($CDCl_3$, δ, ppm): 8.60 (1H, d, 2-H), 8.00 (1H, d, 8-H), 7.91 (1H, d, 5-H), 7.56 (1H, t, 7-H), 7.36 (1H, t, 6-H), 6.64 (1H, d, 3-H), 0.31 (9H, s, SiMe$_3$).

4-Trimethylsiloxyquinaldine (IId, $C_{13}H_{17}NOSi$) was prepared by a method similar to that for IIc from 4.35 g (0.027 mole)-4-hydroxyquinaldine Id and 20 ml hexamethyldisilazane. The yield was 5.0 g (81%), bp 114°C (2 hPa). PMR spectrum ($CDCl_3$, internal standard TsG, δ ppm): 8.07 (1H, d, 8-H), 7.96 (1H, d, 5-H), 7.66 (1H, t, 7-H), 7.45 (1H, t, 6-H), 6.67 (1H, s, 3-H), 2.69 (3H, s, 2-Me), 0.42 (9H, s, SiMe$_3$).

2-Triethylsiloxyquinoline (IIIa, $C_{15}H_{21}NOSi$). A mixture of 3.62 g (0.025 mole) 2-hydroxyquinoline, 4 ml triethylamine (2.9 g = 0.029 mole), and 10 ml benzene was warmed and 4.35 ml (3.9 g = 0.025 mole) triethylchlorosilane added dropwise with stirring. When addition was complete the mixture was heated at bp for a further hour. The following day, the solid deposit was filtered off, the filtrate evaporated, and the residue distilled in vacuum (163°C, 9 hPa) to yield 4.4 g (68%) compound IIIa. PMR spectrum ($CDCl_3$, δ, ppm calculated relative to $\delta_{CDCl_3} = 7.26$ ppm): 7.98 (1H, d, 8-H), 7.75 (1H, d, 4-H), 7.66 (1H, t, 7-H), 7.62 (1H, d, 3-H), 7,42 (1H, t, 6-H), 6.88 (1H, d, 5-H), 0.73 to 1.26 (15H, m, SiEt$_3$).

8-Triethylsiloxyquinoline (IIIb, $C_{15}H_{21}NOSi$) was prepared by a method similar to that for IIIa from 3.62 g (0.025 mole) 8-hydroxyquinoline and 4.35 ml (3.9 g = 0.025 mole) Et$_3$SiCl. Yield 4.5 g (70%), bp 138-142°C (4 hPa). PMR spectrum ($CDCl_3$, δ, ppm): 8.80 (1H, d.d, 2-H), 8.02 (1H, d.d, 7-H), 7.07-7.49 (4H, m, 3,4,5,6-H), 0.60-1.29 (15H, m, SiEt$_3$).

4-Triethylsiloxyquinaldine (IIId, $C_{16}H_{23}NOSi$) was prepared by the above method from 3.98 g (0.025 mole) 4-hydroxyquinaldine and 4.35 ml (3.9 g = 0.025 mole) Et_3SiCl. Yield 5.7 g (83%), bp 177°C (7 hPa). PMR spectrum ($CDCl_3$, δ ppm calculated relative to $δ_{CDCl_3}$ = 7.26 ppm): 8.10 (1H, d, 8-H), 7.94 (1H, d, 5-H), 7.65 (1H, t, 7-H), 7.44 (1H, t, 6-H), 6.63 (1H, s, 3-H), 2.67 (3H, s, 2-Me), 0.60-1.34 (15h, m, $SiEt_3$).

8-Hydroxy-N-methylquinolinium iodide (IVb). A mixture of 0.6 g (2.8 mmole) 8-trimethylsiloxyquinoline IIb and 0.4 ml (0.9 g = 6.4 mmole) MeI was kept for 1 day at room temperature. The deposit which formed was filtered off and washed with ether. Yield 0.2 g (25%) compound IVb, mp 175-178°C. PMR spectrum (DMSO-D_6, δ, ppm): 11.6 (1H, br.s, OH), 9.31 (1H, d, 2-H), 9.07 (1H, d, 4-H), 7.99 (1H, d.d, 3-H), 7.80 (1H, d, 7-H), 7.78 (1H, d, 5-H), 7.55 (1H, m, 6-H), 4.82 (3H, s, N^+Me). IR spectrum: 3340 cm^{-1} (O−H).

4-Hydroxy-N-methylquinolinium iodide (IVc, $C_9H_7NO\cdot MeI$) was prepared by the above method from 2.7 g (0.012 mole) IIc and 2 ml (4.6 g = 0.032 mole) MeI. Yield 3.4 g (99%), recrystallized from ether-alcohol mixture, mp 171-174°C. PMR spectrum (DMSO-D_6, δ ppm): 8.67 (1H, d, 2-H), 8.24 (1H, d, 8-H), 8.00 (2H, m, 5.7-H), 7.69 (1H, m, 6-H), 6.84 (1H, d, 3-H), 4.15 (3H, s, N^+Me). IR spectrum: 3300 cm^{-1} (O−H).

4-Hydroxy-N-methylquinaldinium iodide (IVd, $C_{10}H_9NO\cdot MeI$) was prepared in a similar way to IVc from 1.23 g (5.3 mmole) IId and 0.9 ml (2.0 g = 14.4 mmole) MeI. Yield of IVd 1.6g (100%), mp 197-200°C. PMR spectrum (DMSO-D_6, δ, ppm): 8.24 (1H, d, 8-H), 8.15 (1H, d, 5-H), 7.94 (1H, t, 7-H), 7.64 (1H, t, 6-H), 6.89 (1H, s, 3-H), 4.00 (3H, s, N^+Me), 2.74 (3H, s, 2-Me). IR spectrum: 3350 cm^{-1} (O−H).

Hydrochlorides of 4-Trimethylsiloxyquinaldine (Vd, $C_{13}H_{17}NOSi\cdot HCl$) and 4-Hydroxyquinaldine (VId). To 0.32 g (2 mmole) 4-hydroxyquinaldine in 2 ml chloroform in an atmosphere of argon was added 0.27 ml (0.23 g = 2 mmole) Me_3SiCl; heating up of the solution and evaporation of the solvent occurred. The reaction mixture was kept in an inert atmosphere for 1 h and the solvent then removed completely. PMR spectrum ($CDCl_3$, δ, ppm) Vd: 15.5 (1H, br.s, N^+H), 8.37 (1H, d, 8-H), 8.17 (1H, d, 5-H), 7.67 (1H, t, 7-H), 7.45 (1H, t, 6-H), 6.72 (1H, s, 3-H), 2.83 (3H, s, 2-Me), 0.50 (9H, s, $SiMe_3$). The hydrochloride Vd was washed with ether to obtain VId. PMR spectrum (DMSO-D_6, δ, ppm): 14.7 (1H, br.s, N^+H), 8.17 (1H, d, 8-H), 7.97 (2H, m, 5-, 7-H), 7.62 (1H, t, 6-H), 7.02 (1H, s, 3-H), 2.77 (3H, s, 2-Me). IR spectrum 3390 cm^{-1} (O−H).

Alkylation of 4-Trimethylsiloxyquinaldine IId by Methyl Iodide. A. A mixture of 0.5 g (2.2 mmole) IId, 3 ml chloroform, and 0.4 ml (0.9 g = 6.4 mmole) MeI was kept for 1 day at room temperature in an atmosphere of argon. The solvent and excess MeI were then removed in vacuum. The formation of VIId was confirmed from the PMR spectrum. PMR spectrum ($CDCl_3$, δ, ppm calculated relative to $δ_{CDCl_3}$ = 7.26 ppm): 7.3-8.5 (m, Ar, signals overlapped with those of the initial IId), 6.25 (1H, s, 3-H), 3.78 (3H, s, OMe), 2.55 (3H, s, 2-Me).

B. To a solution of 1.56 g (6.8 mmole) IId in 10 ml chloroform was added 1 ml (2.3 g = 16.2 mmole) MeI at room temperature. The deposit which formed after several days was filtered off and washed with ether. Yield 0.1 g (~5%) VIIId, mp 190-192°C (lit. 193-194°C [14], 180-181.5°C [16]). PMR spectrum (DMSO-D_6, δ, ppm): 8.38 (1H, d, 8-H), 8.29 (1H, d, 5-H), 8.07 (1H, m, 7-H), 7.80 (1H, m, 6-H), 7.60 (1H, s, 3-H), 4.20 (3H, s, N^+Me), 4.15 (3H, s, OMe), 2.93 (3H, s, 2-Me). The filtrate was evaporated and the residue washed with ether to obtain IVd, or a mixture of IVd and VIId.

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