Tetrahedron. Vol. 25, pp. 155 to 162 Pergamon Press 1969 Printed in Great Britain

SOLVENT SHIFTS INDUCED BY BENZENE IN TRITERPENES AS AN AID TO STRUCTURE ELUCIDATION

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(*Received in the UK* 22 *July* 1968; *accepted for publication* 12 *August* 1968)

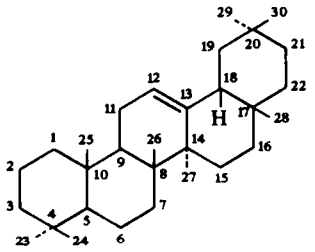
Abstract—Solvent shifts for protons in several derivatives of the triterpenes oleanene and lupane are reported. It is found that in general only those Me groups which are close to a polar group exhibit appreciable solvent shifts. In the compounds examined, an axial proton on the same C atom as an equatorial acetate function exhibits a characteristic downfield shift in benzene solution. In contrast, equatorial protons attached to the same C atom as the oxygen of a γ-lactone bridge exhibit an upfield shift in benzene solution. As a general rule, protons which lie in regions of high electron density tend to be deshielded in benzene solution.

THE use of benzene-induced solvent shifts has been shown to be of value in structural, stereochemical and conformational problems in steroids.[1–4] Certain empirical rules have been deduced concerning the solvent shifts of various protons in ketones.[2–8] The aim of this paper is to show the possibilities for the use of benzene-induced solvent shifts in structural studies of triterpenes.

Derivatives of oleanene (**1**) and lupane (**2**) were examined and in addition a few examples of other triterpenes. The assignment of chemical shift values to the Me groups in deuterochloroform was carried out using criteria discussed in previous work.[9–11] The determination of solvent shifts for the Me protons necessitated the use of dilution studies, i.e. the determination of spectra using $CDCl_3$–C_6D_6 mixtures as solvents. Apart from the Me groups, other protons studied were confined to those adjacent to electronegative functions (i.e. those protons occurring at relatively low field) owing to the fairly wide spread of the methylene envelope. Assignments of chemical shift values to these protons were made by comparison with similar models in the steroid field.[12] The numbering systems for the oleanene and lupane skeletons are given with structures (**1** and **2**). The chemical shifts (δ_{CDCl_3}, $\delta_{C_6D_6}$) and solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$) for protons in compounds (**3–21**) are given in Table 1, together with their structures. Since TMS is employed as an internal reference, one is of course measuring the difference between the solvent effect on a proton in the sample and that on the protons of the internal reference.

DISCUSSION

The protons of a C-24 Me group in the presence of a C-3β acetate function show an appreciable upfield shift (**4**, **8–14**, Δ = +0·08 to +0·19 ppm). If the acetate exists in a *cis* conformation with the C-3α proton eclipsed by the CO group (discussed below), the C-24 protons will lie behind the CO group and so will be shielded by benzene molecules which solvate the carbonyl C atom.[3,5] In the presence of a C-3-oxo function (**6**, **7**) both the C-24 and C-25 protons show positive solvent shifts (+0·14 to +0·22 ppm) while the C-23 protons are only slightly affected (−0·04 to +0·02 ppm), in accord with



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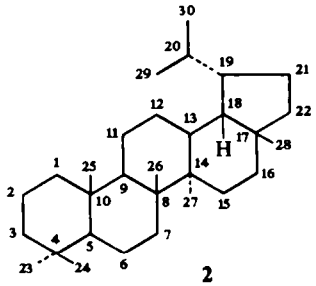


2

3 Methyl oleanate
4 Methyl acetyl glycerrhetate
5 Methyl acetyl oleanate
6 Methyl 3-keto oleanate
7 3,16-Diketo echinocystic acid methyl ester
8 30-Nor-keto thurberogenin acetate
9 Dumortiogenin diacetate
10 Betulin diacetate
11 β-Amyrin acetate-30-ol
12 Longispinogenin acetate
13 Stellatogenin acetate
15 β-Amyrin benzoate
16 Methyl acetyl ursolate
17 α-Amyrin
18 β-Amyrin acetate
19 Methyl acetyl betulinate
20 Myricendiol diacetate
21 3β, 30-Diacetoxy oleanene

previous generalizations;[3,5] the C-24 and C-25 protons lie behind the reference plane of the CO at C-3 while the C-23 protons lie approximately in the reference plane. Since in general the chemical shifts of the protons of C-23, C-24 and C-25 in deuterochloroform are very similar, benzene-induced solvent shifts may be of assistance in distinguishing between them.

The C-27 protons, which being homoallylic in the oleanenes occur at lower field than the other methyls, show a positive solvent shift (+0·08 to +0·23 ppm) in the presence of proximate polar substituents e.g. C-11 oxo(**4**), C-16 oxo(**7**), C-21β, C-28 lactone (**8, 13, 14**) and C-15β, C-28 lactone (**9**). In other cases the solvent shifts are very small (−0·04 to +0·03 ppm).

In lupane derivatives which have a functional group at C-20 (**8, 10, 13, 14**), the C-29 and C-30 Me protons will occur at lower field in deuterochloroform than will protons of the other Me groups. Consequently the solvent shifts of these protons are easily observed. In 30-nor-keto thurberogenin acetate (**8**), the C-29 protons show a large upfield shift (+0·60 ppm) and the C-29 and C-30 protons of stellatogenin acetate (**13**) also show relatively large solvent shifts (+0·38 to +0·46 ppm). In both cases, benzene association with the CO of the lactone bridge probably contributes to the magnitude of the observed solvent shifts. This is suggested by comparing the solvent shifts for the C-29 protons in betulin diacetate (**10**, +0·02 ppm) and in thurberogenin acetate (**14**, +0·28 ppm), both of which contain a C-30 methylene group but only **14** contains a C-21β, C-28 lactone bridge.

In the presence of a C-3β OH group (**3, 17**), a C-3α proton shows a positive solvent shift (+0·16, +0·17 ppm). However, in the presence of a C-3β acetate function (**4–16, 18–21**, Fig. 1), the C-3α proton is deshielded (−0·11 to −0·22 ppm). This suggests that the acetate function exists predominantly in a *cis* conformation, probably with the C-3α hydrogen (axial) eclipsed by the CO group. It has been shown that, in general, acetates tend to exist in a *cis* conformation;[13] the solvent shift of the C-3α proton in 3β-cholestanyl acetate (−0·14 ppm), in which there are no Me groups at C-4, is of the

TABLE 1

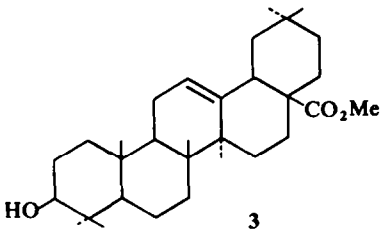
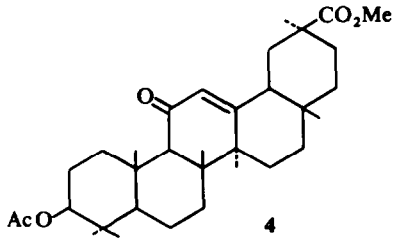
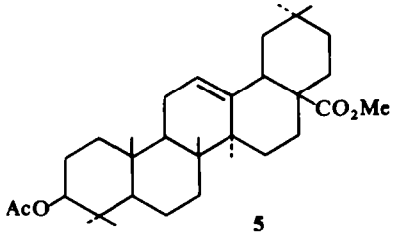
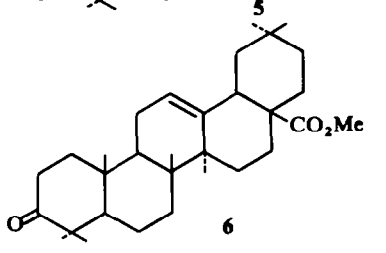
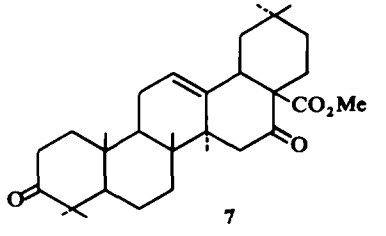
	Proton	δ_{CDCl_3}	$\delta_{C_6D_6}$	Δ
 3	12	5·27	5·39	−0·12
	3α	3·20	3·03	+0·17
	17β-CO_2Me	3·60	3·42	+0·18
	23, 24	0·80	0·81	−0·01
	25	0·92	0·96	−0·04
		1·00	1·03	−0·03
	26	0·75	0·86	−0·11
	27	1·14	1·18	−0·04
	29, 30	0·92 (2)	0·90 (2)	+0·02
 4	12	5·66	5·92	−0·26
	3α	4·56	4·76	−0·20
	17β-CO_2Me	3·67	3·32	+0·35
	23, 25	0·90 (2)	0·90	0·00 to
			0·92	−0·02
	24	1·14	1·06	+0·08 to +0·12
	26	1·16	1·02	+0·12 to +0·16
	29	1·18	1·25	−0·11 to −0·07
	27	1·37	1·14	+0·23
 5	12	5·27	5·40	−0·13
	3α	4·49	4·67	−0·18
	17β-CO_2Me	3·60	3·42	+0·18
	23, 24	0·88 (2)	0·88	−0·08 to
	25	0·91	0·90 (3)	+0·03
	29, 30	0·94 (2)	0·96	−0·02 to +0·06
	26	0·75	0·84	−0·09
	27	1·14	1·18	−0·04
 6	12	5·30	5·37	−0·07
	17β-CO_2Me	3·62	3·42	+0·20
	23	1·10	1·14	−0·04
	24, 25	1·06 (2)	0·87	+0·19
			0·91	+0·15
	26	0·81	0·83	−0·02
	27	1·16	1·14	+0·02
	29, 30	0·92	0·97 (2)	−0·05
		0·95		−0·02
 7	12	5·55	5·45	+0·10
	17β-CO_2Me	3·65	3·30	+0·35
	23	1·10	1·08	+0·02
	24	1·08	0·86	+0·22
	25	1·08	0·94	+0·14
	26	0·89	0·76	+0·13
	27	1·22	1·14	+0·08
	29, 30	0·92	0·82	+0·10
		0·95	0·91	+0·04

TABLE 1—*continued*

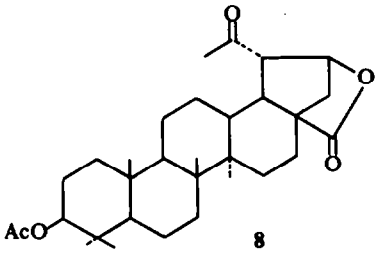
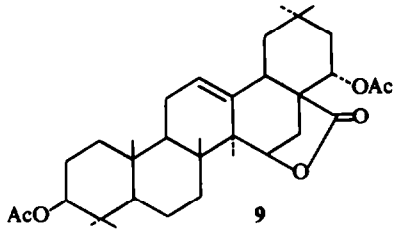
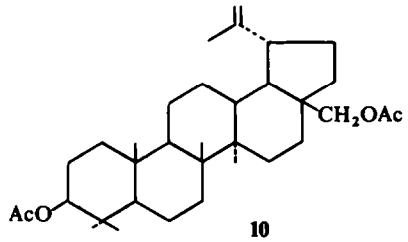
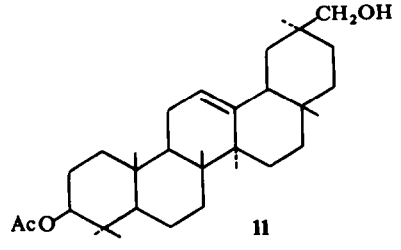
	Proton	δ_{CDCl_3}	$\delta_{C_6D_6}$	Δ
 **8**	21	4·68	4·08	+0·60
	3α	4·46	4·64	−0·18
	19β	3·79	3·48	+0·31
	29	2·30	1·70	+0·60
	23, 25	0·87 (2)	0·89 (2)	−0·02
	24	0·87	0·76	+0·11
	26	1·00	0·98	+0·02
	27	1·00	0·84	+0·16
 **9**	12	5·53	5·16	+0·37
	15α	4·54	4·25	+0·29
	3α	4·50	4·64	−0·14
	22β	5·20	5·61	−0·41
	23, 25	0·90 (2)	0·91 (2)	−0·01
	24, 26	0·99 (2)	0·80 (2)	+0·19
	27	1·20	0·94	+0·26
	29	1·07	0·94	+0·13 to +0·16
	30	1·10	1·18	−0·08 to −0·11
 **10**	30	4·58	4·71	−0·13
		4·68	4·79	−0·11
	29	1·70	1·68	+0·02
	28	3·85	3·95	−0·10
		4·25	4·47	−0·22
	23, 25	0·86 (2)	0·90 (2)	−0·04
	24	0·86	0·76	+0·10
	27	0·98	0·95	+0·03
	3α	4·50	4·66	−0·16
	26	1·04	0·95	+0·09
 **11**	12	5·07	5·20	−0·13
	3α	4·49	4·65	−0·16
	30	3·50	3·32	+0·18
	23	0·98	1·00	−0·02
	24	0·98	0·86	+0·12
	25	0·92	0·93	−0·01
	26	0·85	0·93	−0·08
	27	1·16	1·22	−0·06
	28	0·89	0·93	−0·04
	29	0·89	0·93	−0·04

TABLE 1—*continued*

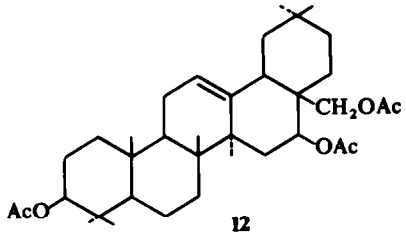
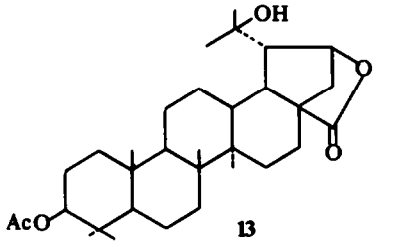
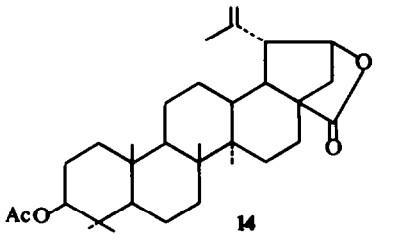
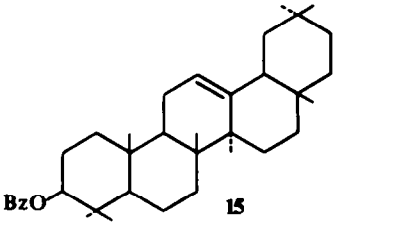
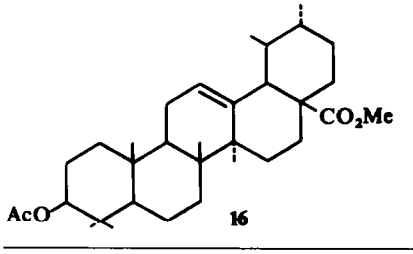
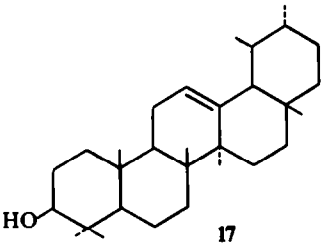
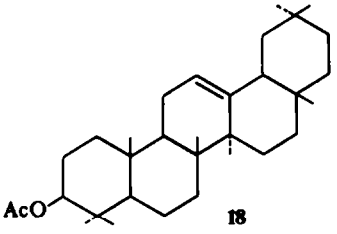
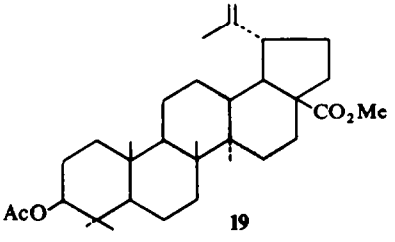
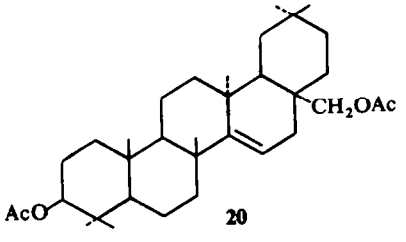
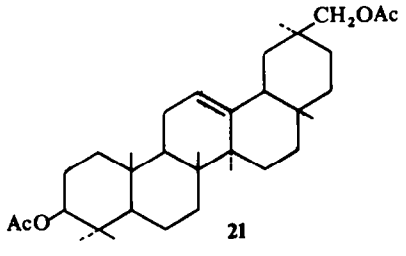
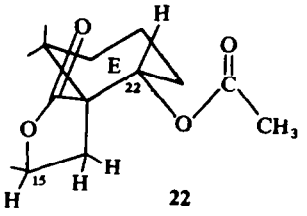
	Proton	δ_{CDCl_3}	$\delta_{C_6D_6}$	Δ
 12	12	5·26	5·24	+0·02
	3α	4·49	4·60	−0·11
	16α	5·53	5·87	−0·34
	28	4·09	4·44	−0·35
		3·99	4·24	−0·25
	23	0·92	0·99	−0·07
	24	0·92	0·78	+0·14
	25, 26	0·88 (2)	0·88 (2)	0·00
	27	1·28	1·32	−0·04
	29	1·02	1·01	+0·01
	30	0·97	0·93	+0·04
 13	3α	4·48	4·62	−0·14
	21α	4·68	4·38	+0·30
	23, 25	0·87 (2)	0·88 to 0·90	−0·01 to −0·03
	24	0·87	0·76	+0·11
	27	1·01	0·88 to 0·90	+0·11 to +0·13
	26	1·01	1·07	−0·06
	29, 30	1·28	0·88 to	+0·38 to +0·46
		1·34	0·90	
 14	30	4·82	4·67	+0·15
		4·93	4·79	+0·14
	3α	4·48	4·66	−0·18
	21α	4·50	4·16	+0·34
	29	1·86	1·58	+0·28
	23, 25	0·88 (2)	0·90 (2)	−0·02
	24	0·88	0·78	+0·10
	26	1·02	1·01	+0·01
	27	1·02	0·90	+0·12
 15	12	5·19	5·22	−0·03
	3α	4·74	4·91	−0·17
	24	1·03	0·85	+0·18
	27	1·17	1·23	−0·06
 16	12	5·27	5·38	−0·11
	3α	4·49	4·68	−0·19
	17β-CO_2Me	3·62	3·46	+0·16

TABLE 1—*continued*

	Proton	δ_{CDCl_3}	$\delta_{C_6D_6}$	Δ
 **17**	3α	3·28	3·12	+0·16
	12	5·18	5·35	−0·17
 **18**	3α	4·53	4·70	−0·17
	12	5·20	5·25	−0·05
 **19**	3α	4·55	4·70	−0·15
	17β-CO_2Me	3·67	3·42	+0·25
 **20**	15	5·47	5·60	−0·13
	3α	4·47	4·62	−0·15
	28	3·73	3·92 }	−0·19 }
			4·05 }	−0·32 }
 **21**	12	5·18	5·16	+0·02
	3α	4·51	4·65	−0·14
	30	4·02	4·17 }	−0·15 }
			4·07 }	−0·05 }

same order as those observed for the triterpenes. This suggests that the presence of two Me groups at C-4 does not appreciably influence the conformation of the C-3β acetate function.

The C-22β proton in dumortiogenin diacetate (**9**) shows an extremely large downfield shift (−0·41 ppm, Fig. 1), which can be explained in terms of two factors. One factor is that which gives rise to the deshielding of the C-3α proton in 3β acetates as discussed above; since the C-22 acetate function is equatorial, a similar effect may be assumed to operate. Secondly, the C-22β proton lies in front of the CO group of the C-15β, C-28 lactone, and hence lies in a region of high electron density which the π-electron cloud of the benzene solvent tends to avoid. The environment of the C-22β proton is shown in **22**.



22

The C-16 proton in longispinogenin acetate (**12**) also shows a large downfield shift (−0·34 ppm). The benzene association at the equatorial C-16β acetate function is again a contributing factor; additional deshielding may result from the presence of a C-28 acetate and from steric inhibition of approach of bulk solvent to the proton in question.[14] The methylene protons of a CH_2OAc grouping (**10**, **12**, **20**, **21**) are generally non-equivalent in both deuterochloroform and hexadeuterobenzene and always show negative solvent shifts. This provides further support for the *cis* conformation of these acetates.

In the four compounds which possess a γ-lactone function (**8**, **9**, **13**, **14**), the proton of the >CH—O—CO— grouping shows a positive solvent shift. The magnitude of the solvent shift in 30-nor-keto thurberogenin acetate (**8**) is larger (+0·60 ppm) than in the other three compounds (+0·29 to +0·34 ppm), probably because of the presence of the C-20 oxo function, which can give rise to an additional shielding effect. Thus the equatorial >CH—O—CO— protons attached to lactone bridges exhibit solvent shifts which are opposite in sign to those observed for axial >CH—O—CO— protons attached to acetate functions. This effect may be systematically employed to resolve the $\delta = 4{\cdot}0$–$5{\cdot}7$ region when overlapping signals associated with lactone and acetate functions occur (Fig. 1).

The wide variations (in sign and magnitude) of solvent shifts observed in the triterpene series emphasize the potential of the method in indicating the proximity of protons to polar groups and, in some cases, the proximity of two functional groups. In effect, the anisotropic benzene molecules are used to probe the local polarizations existing in the solute molecule. In general, the π-electron clouds of the benzene molecules will tend to avoid electron-rich areas and seek electron-deficient areas of the solute.

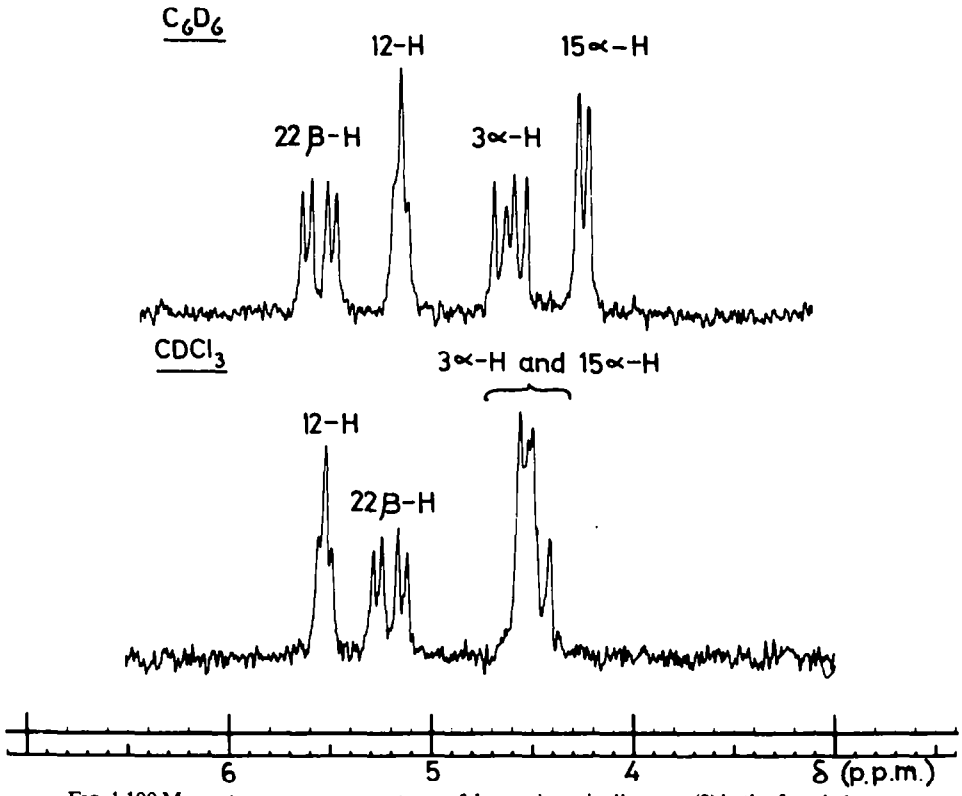


FIG. 1 100 Mc proton resonance spectrum of dumortiogenin diacetate (9) in the δ = 4–6 ppm region in C_6D_6 solution (upper trace) and $CDCl_3$ solution (lower trace).

EXPERIMENTAL

The NMR spectra were determined on a Varian Associates HA 100 Mc/sec instrument at normal probe temps (30–33°C). The concentration of the solns used was 4–5% (w/v) except where the compounds were insufficiently soluble. In these cases saturated solutions were employed.

Acknowledgement—The authors wish to thank Professor C. Djerassi (Stanford University) for generous gifts of triterpenes.

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