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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—X

SOME BEYERENE 2 AND 3-ALCOHOLS

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Abstract—Beyer -15,16-en-2α,3α, and 3β-alcohols have been prepared and their stereochemistry assigned. 2α-Hydroxybeyer-15,16-epoxide undergoes reaction with lead tetra-acetate to form a 2-20 ether which may be rearranged to a kaurenoid skeleton. Reduction of 3α-hydroxybeyer-15,16-en-2-one affords the 2α,3α-diol. Treatment of the 3-monotoluene-*p*-sulphonate of this diol with alumina affords the 2-ketone. Beyer-15,16-en-3-one undergoes acetoxylation to furnish the corresponding 2β-acetate which may be reduced to a 2β,3α-diol. The solvent shifts in the NMR spectra of these compounds have been studied.

IN THE course of studies on the chemistry of the tetracyclic diterpenes,[2] we have had occasion to examine some features of ring A in the beyerene series. The preparation and stereochemistry of 2 and 3-mono-ols and diols form the subject of this paper.

Beyer-15,16-en-3-one (stachenone) (1) may be readily isolated[3] from *Spirostachys africana*. On reduction[3] with LAH or sodium in pentanol it affords the 3α-equatorial alcohol. However reduction with aluminium isopropoxide in isopropanol although giving predominantly the 3α-alcohol, also gives some of the 3β-axial alcohol.[cf. 4] As expected in the NMR spectrum the equatorial 3α-proton of the axial alcohol resonates at lower field (τ 6·62) compared to the axial 3β-proton of the equatorial alcohol (τ 6·78) whilst in the IR the axial alcohol shows a group of bands at 950, 990 and 1070 cm^{-1} whilst the equatorial alcohol shows only a band at 1030 cm^{-1} (lit,[3] 1012 cm^{-1}) of comparable intensity.[5] The solvent shift data between $CDCl_3$ and C_5D_5N for these alcohols are set out in Table 1.

In the case of the 3α-alcohol both the C-18 and C-19 methyl groups show large shifts whilst in the case of the 3β-alcohol only the C-18 Me group is affected. On the other hand a 3-ketone shows relatively little solvent shift. However both C-18 and C-19 are deshielded by the CO group.

The preparation of beyer-15,16-en-2-one has been described previously.[6] On reduction with sodium borohydride it affords a 2α-axial alcohol. Comparison of the solvent shift data shows the anticipated shift for the 1,3-diaxial interaction of the 2α-alcohol with the C-19 and C-20 Me groups. This was confirmed by ether formation. Oxidation of 2α-hydroxy-beyerane with lead tetra-acetate afforded a gummy ether and hence the reaction sequence was carried through with the 15,16-epoxide. Treatment of 2α-hydroxybeyer-15,16-epoxide (II) with lead tetraacetate in benzene gave an ether (III) in which one C-Me resonance had been replaced by a methyleneoxy resonance at τ 6·2 (*J* 8 Hz). The 15,16-epoxide underwent rearrangement[6,7] with BF_3 to generate a kauranoid compound (IV) possessing hydroxyl absorption at 3440, 3520 cm^{-1} and terminal methylene absorption at 890 cm^{-1} (τ 4·95). This compound

TABLE 1. NMR SOLVENT SHIFT DATA FOR SOME 3-SUBSTITUTED BEYERENES

Compound	Solvent	C-20	C-19	C-18	C-17	C-15 and C-16		C-3
Beyer-15,16-ene	$CDCl_3$	9·25	9·19	9·14	9·01	4·52	4·25	—
	C_5D_5N	9·25	9·17	9·12	8·98	4·50	4·22	—
Beyer-15,16-en-3α-ol	$CDCl_3$	9·27	9·21	9·02	9·02	4·52	4·22	6·78
	C_5D_5N	9·18	8·96	8·78	8·96	4·50	4·22	6·55
Beyer-15,16-en-3β-ol	$CDCl_3$	9·24	9·16	9·05	9·01	4·56	4·30	6·62
	C_5D_5N	9·17	9·09	8·82	9·00	4·52	4·20	6·48
Beyer-15,16-en-3-one	$CDCl_3$	9·12	8·99	8·94	9·02	4·56	4·30	—
	C_5D_5N	9·18	9·00	8·91	9·00	4·50	4·22	—
15,16-Epoxybeyeran-3α-ol	$CDCl_3$	9·20	9·10	9·02	9·02	6·98	6·58	6·78
	C_5D_5N	9·10	9·02	8·82	8·98	6·98	6·58	6·60
3α-Acetoxybeyer-15,16-ene	$CDCl_3$	9·26	9·17	9·17	9·03	4·56	4·30	5·59
Beyeran-3α-ol	$CDCl_3$	9·04	9·22	9·04	9·00	—	—	6·72
	C_5D_5N	9·02	9·02	8·78	8·98	—	—	6·58

is assigned the 2–20 ether structure by analogy with comparable reactions in the 2β-hydroxymanoyl oxide series.[8] Furthermore there is a dramatic change in the C-15 and C-16 proton resonances which become equivalent [τ 6·50 and 6·95 in (II) and 7·02 in (III)]. Only C-20 is sufficiently close to affect C-15 in the beyerane skeleton.

The ketol (V) gives a diol[3] on reduction with sodium borohydride. This diol forms an acetonide precluding a diaxial conformation, a diacetate and on epoxidation, a 15,16-epoxide. The 2α,3α-stereochemistry of the diol may be defined in the following manner. In each compound the axial 3-proton may be distinguished as a doublet (J = 4 Hz) corresponding to a gauche interaction with the C-2 proton. The latter resonates at 0·4–0·5 ppm to lower field in accordance with its equatorial conformation. The multiplicity of this resonance (quartet J 4 Hz) is also in accord with gauche interactions with the protons at C-1. We had previously assigned[3] a diequatorial 2β,3α-structure to this diol on the basis of its formation by osmylation of a 2,3-ene.

TABLE 2. NMR SOLVENT SHIFT DATA FOR SOME 2-SUBSTITUTED BEYERENES

Compound	Solvent	C-20		C-19	C-18	C-17	C-15 and C-16		C-2
Beyer-15,16-en-2α-ol	$CDCl_3$	8·96		9·00	9·08	9·00	4·55	4·25	5·83
	C_5D_5N	8·76		8·76	9·05	8·98	4·52	4·22	5·62
Beyer-15,16-en-2-one	$CDCl_3$	9·23		9·12	8·93	8·98	4·48	4·28	—
	C_5D_5N	9·24		9·13	9·02	8·98	4·53	4·33	—
15,16-Epoxybeyeran-2α-ol	$CDCl_3$	8·80		8·94	9·08	8·98	6·95	6·50	5·85
	C_5D_5N	8·62		8·76	9·05	8·98	6·95	6·50	5·68
15,16-Epoxybeyeran-2,20-oxide	$CDCl_3$	6·36	6·10	8·98	9·08	8·98	7·02		5·80
	C_5D_5N	6·36	6·06	8·90	9·05	8·98	7·02		5·75

However this is also compatible with the 2α,3α structure. Reduction of the corresponding ketol 3-acetate with sodium borohydride afforded the 2α-monohydroxy-3α-acetate. The diequatorial diol was prepared as follows. Acetoxylation of beyer-15,16-en-3-one with lead tetraacetate and boron trifluoride etherate gave a 2-acetoxy-3-ketone. This is assigned the equatorial 2β-acetoxyl conformation by analogy with the corresponding compounds[9] in the triterpene and 4,4-dimethyl steroid series. The CHOAc proton resonance shows a comparable chemical shift and coupling constant (τ 4·6; *J*, 6 and 13 Hz) to these compounds. Reduction with lithium aluminium hydride affords the 2β,3α-diequatorial diol. The solvent shift data for these alcohols are set out in the following table.

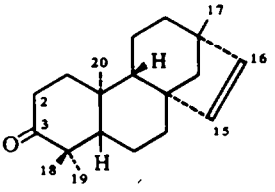
TABLE 3. NMR SOLVENT SHIFT DATA FOR SOME 2,3-DISUBSTITUTED BEYERENES

Compound	Solvent	C-20	C-19	C-18	C-17	C-15 and C-16		C-2	C-3
Beyer-15,16-en-2α,3α-diol	$CDCl_3$	8·98	8·95	9·04	8·98	4·56	4·28	5·95	6·90
	C_5D_5N	8·65	8·68	8·76	8·98	4·52	4·20	5·63	6·60
Beyer-15,16-en-2β,3α-diol	$CDCl_3$	9·16	9·16	9·02	8·98	4·55	4·30	7·00 (br)	7·00 (br)
	C_5D_5N	9·14	9·02	8·78	8·96	4·55	4·25	6·85 (br)	6·65 (br)
15,16-Epoxybeyeran-2α,3α-diol	$CDCl_3$	8·76	8·95	8·95	8·98	6·98	6·58	5·92	6·80
	C_5D_5N	8·51	8·68	8·76	8·98	6·95	6·40	5·55	6·52
2α,3α-Diacetoxybeyer-15,16-ene	$CDCl_3$	8·92	9·00	9·10	9·00	4·58	4·30	4·71	5·42
	C_5D_5N	8·82	8·99	9·06	8·99	4·50	4·22	4·40	5·22

Examination of the influence of the OH groups on the proton resonances of the Me groups of ring A is in accord with the assigned stereochemistry. Although the effect of a diol is clearly not the sum of the two monohydroxy components nevertheless these shifts may have some diagnostic value in structural studies in this field. The effects of the hydroxyl groups are diminished by acetylation.

Treatment of the 2α,3α-diol with toluene-*p*-sulphonyl chloride in pyridine, and chromatography of the product on alumina afforded the 2-ketone. Presumably the equatorial 3α-OH forms a monotoluene-*p*-sulphonate and this is eliminated either during the basic reaction conditions or on chromatography on alumina. A small amount of the ditoluene-*p*-sulphonate is also formed during this reaction. Reduction of the 2-ketol 3-toluene-*p*-sulphonate which on heating with alumina is smoothly converted to the 2-ketone. Elimination of 3-equatorial toluene-*p*-sulphonates has been described as a method of forming triterpene Δ^2-olefins.[10] It also provides a satisfactory method in this series. Thus the toluene-*p*-sulphonate of beyer-15,16-en-3α-ol gave an oily diolefin which was characterized as its crystalline diepoxide formed

with *m*-chloroperbenzoic acid. Attack of the reagent from the less-hindered β-face of the molecule would be expected to form the 2β,3β-epoxide.[cf. 10]



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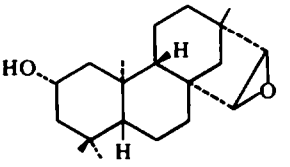

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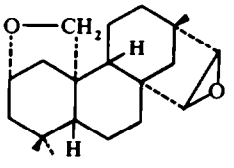

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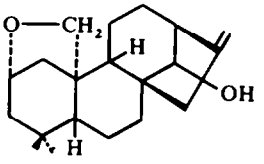

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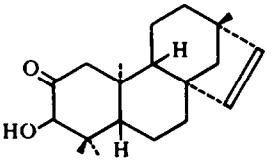

V

EXPERIMENTAL

General details have been described previously.[11]

Meerwein-Ponndorf reduction of beyer-15,16-en-3-one. The ketone (350 mg) and aluminium isopropoxide (1 g) in isopropanol (25 ml) were heated under reflux for 4 hr. The soln was poured into water, acidified and the product recovered in Et_2O. Chromatography on Al_2O_3 gave, in the fraction eluted with 5% Et_2O: light petroleum, *beyer-15,16-en-3β-ol* (80 mg) which crystallized from aq. MeOH as needles, m.p. 88–90°. (Found: C, 82·9; H, 10·9. $C_{20}H_{32}O$ requires: C, 83·3; H, 11·2%); ν_{max} 3380, 760 cm^{-1}. Subsequent fractions eluted with 15% Et_2O: light petroleum gave beyer-15,16-en-3α-ol (210 mg) identified by its IR spectrum.

15β,16β-Epoxybeyeran-2α-ol. Beyer-15,16-en-2α-ol (1·0 g) in $CHCl_3$ (50 ml) was treated with *m*-chloroperbenzoic acid (1·25 g) at room temp overnight. The product was recovered in $CHCl_3$, washed with aq. $FeSo_4$, dil HCl, aq. $NaHCO_3$, water and dried. Evaporation of the solvent and chromatography of the product on alumina gave 15β,16β-*epoxybeyeran-2α-ol* which crystallized from light petroleum as prisms, m.p. 149–151°. (Found: C, 78·8; H, 10·5. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%); ν_{max} 3400 cm^{-1}.

Oxidation with lead tetraacetate. The above alcohol (170 mg) and freshly purified, dried lead tetraacetate (500 mg) in A.R. benzene (5 ml) were heated under reflux for 4 hr. The soln was poured into water, recovered in ether and chromatographed on alumina. Elution with light petroleum gave 15β,16β-*epoxybeyeran-2α-20-oxide* (55 mg: III) which crystallized from acetone as needles, m.p. 130–135° (with sublimation). (Found: C, 79·2; H, 9·9. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

Rearrangement of the ether (III). The above ether (400 mg) in Et_2O (10 ml) was treated with BF_3 etherate (0·5 ml) for 1 hr. The soln was poured into water and extracted with Et_2O. The extract was washed with aq. $NaHCO_3$, dried and evaporated to give a gum which was chromatographed on alumina. Elution with

20% Et_2O: light petroleum gave 2α, 20-*epoxy*-(−)-*kaur*-16-*en*-15β-*ol* which crystallized as needles from light petroleum, m.p. 137–138°. (Found: C, 79·0; H, 9·95. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%); ν_{max} 3520, 3440, 890 cm^{-1}.

Beyer-15,16-*en*-2α,3α-*diol*. The ketol V (1·2 g) in MeOH (25 ml) was treated with $NaBH_4$ (0·5 g) for 1 hr. The soln was acidified with dil HCl, concentrated, poured into water and the diol recovered in EtAc. The diol (0·9 g) crystallized from acetone–light petroleum as needles, m.p. 180–182°, [lit.[3] 181–182°]. The *diacetate* prepared with Ac_2O in pyridine, crystallized from light petroleum as needles, m.p. 129–132°. (Found: C, 74·3; H, 9·2. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·3%); ν_{max} 1740 (br), 760 cm^{-1}. The *acetonide* prepared by treatment of the diol with refluxing acetone containing a trace of $HClO_4$, crystallized from acetone as prisms, m.p. 96–98°. (Found: C, 79·4; H, 10·6. $C_{22}H_{36}O_2$ requires: C, 79·5; H, 10·9%). The *epoxide* prepared with *m*-chloroperbenzoic acid in chloroform, crystallized from acetone–light petroleum as needles, m.p. 202–204°. (Found: C, 74·6; H, 9·8. $C_{20}H_{32}O_3$ requires: C, 74·9; H, 10·0%); ν_{max} 3400 (br) cm^{-1}.

Beyer-15,16-*en*-2-*one*. The diol (1·3 g) in pyridine (20 ml) was treated with toluene-*p*-sulphonyl chloride (2 g) for 24 hr at room temp. The product was poured into water, acidified and recovered in Et_2O and chromatographed on alumina. Elution with light petroleum gave beyer-15,16-en-2-one (0·7 g), m.p. 116–118° (lit.[6] 119–120°) identical to an authentic sample. In some reactions a small amount of the 2α,3α-*ditoluene*-p-*sulphonate*, m.p. 188–190°. (Found: C, 66·2; H, 7·4. $C_{34}H_{44}S_2O_6$ requires: C, 66·65; H, 7·2%) ν_{max} 1600, 700 cm^{-1}, was also isolated.

The 3-*monotoluene*-p-*sulphonate of beyer*-15,16-*en*-2α-3α-*diol*. The toluene-*p*-sulphonate[6] of V (300 mg) in MeOH (25 ml) was treated with $NaBH_4$ (200 mg) at room temp for 1 hr. Dil HCl was added, the 3-*monotoluene*-p-*sulphonate* of beyer-15,16-en-2α,3α-diol filtered and recrystallized from aqueous MeOH as needles, m.p. 131–132°. (Found: C, 69·9; H, 8·3. $C_{27}H_{38}SO_4$ requires: C, 69·75; H, 8·4%); ν_{max} 3360 (br), 1600, 760 cm^{-1}.

Elimination of toluene-p-*sulphonic acid*. The above toluene-*p*-sulphonate (50 mg) was absorbed onto alumina from $CHCl_3$ and gently warmed for 1 hr. Elution with 5% Et_2O: light petroleum gave beyer-15,16-en-2-one (20 mg), m.p. 115–118° identified by its IR spectrum.

2β,3β: 15β,16β-*Diepoxy beyerane*. Beyer-15,16-em-3α-ol toluene-*p*-sulphonate (1 g) was absorbed onto alumina (10 g) from $CHCl_3$ and heated at 80° for 1 hr. Elution with light petroleum gave the diolefin (250 mg) ν_{max} 760, 745 cm^{-1} as a gum. This was taken up in $CHCl_3$ (5 ml) and treated with *m*-chloroperbenzoic acid (540 mg) overnight. The product was recovered in $CHCl_3$, rinsed with $FeSO_4$aq, dil HCl, $NaHCO_3$aq, dried and evaporated to give a gum which was chromatographed on alumina. Elution with 20% Et_2O–light petroleum gave the *diepoxide* (53 mg) which crystallized from aqueous MeOH as plates, m.p. 123–124°. (Found: C, 78·8; H, 10·0. $C_2oH_{30}O_2$ requires: C, 79·4; H, 10·0%).

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