Triterpenes. The HBr Catalysed Rearrangement of Lupenyl Acetate and Stereochemistry of the Epoxidation of the Products

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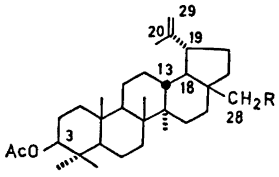
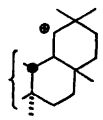
The acid catalysed rearrangement of lupenyl acetate (*1a*) is known [1] to proceed *via* the skeletally rearranged carbocation *2*. We reported previously [2] an HBr catalysed rearrangement of betulin diacetate (*1b*), giving *3b*, where the carbon skeleton is not altered. It was recently claimed [3] that lupenyl acetate (*1a*) does not



1a R = H
b R = OAc



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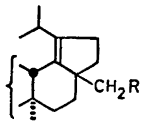
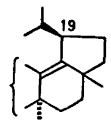


3a R = H
b R = OAc



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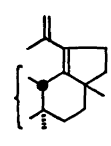
give *3a* on HBr treatment. However, we have found that *3a* is formed, when *1a* is treated with HBr in Ac_2O-AcOH-benzene solution and can be isolated, but is also readily isomerised to *4*.*

Compound *3a* has been reported previously [4] as a component of the preparatively unseparable mixture of products from the PtO_2 catalysed hydrogenation of *5*. We have now isolated and characterised *3a* along with the tetrahydro derivative *12* from this mixture. Compound *3a* has also been reported [5] to occur in Nature but the reported physical data differ from those now obtained for *3a*. The natural product is probably correctly formulated *3a* but impure, according to the close similarity of the mass spectra.

When the diene *5* is first isomerised [6] to the mixture of compounds *6** and *7*, and these products hydrogenated,[6] the same dihydro compound, identical with *4*, is obtained in both cases. Compound *4* from these reactions gave the epoxide *8*. X-Ray crystallographic measurements [7] gave the 13α,18α-epoxy-19α(H)-structure *8* for this epoxide. This establishes the 19α(H)-structures for *4* and *6*.



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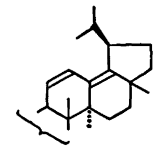

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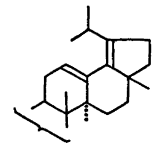

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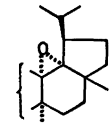

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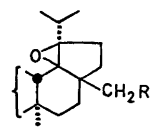
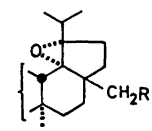
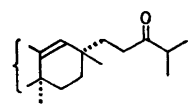
The epoxidation of *3a* with *m*-chloroperbenzoic acid gives the β-epoxide *9a*, also obtained from the corresponding betulin derivative *9b* of known [8] β-epoxy structure. Thus the isomeric epoxide obtained [8,9] from *3a* with ozone has α-epoxy structure *10a*.



9a R = H
b R = OAc
c R = OH
d R = OTos



10a R = H
b R = OAc



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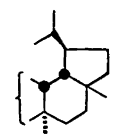

12

Both epoxides *9a* and *10a* give the baccharane derivative *11* on a BF_3 treatment in analogy with the corresponding betulin epoxides *9b* and *10b*.[8]

Experimental. Melting points are uncorrected. ^1H NMR spectra were recorded on a Jeol JNM-PMX 60 spectrometer, IR spectra on a Perkin-Elmer 125 spectrometer using KBr pellets, mass spectra on a Perkin-Elmer 270 B mass spectrometer, specific rotations in $CHCl_3$ solution on a Perkin-Elmer 141 polarimeter.

* For the stereostructure at C-19 see below.

Isomerisation of lupenyl acetate (1a). (a) Lupenyl acetate (*1a*) (0.5 g) in benzene (17 g), Ac_2O (7 g), and 36 % HBr in AcOH (13 g) was allowed to stand at ambient temperature for 50 h. Work up and chromatography on 10 % $AgNO_3$ impregnated silica plates (eluent: $CHCl_3$ – light petroleum b.p. 60 – 80 °C, 2:1) gave 3β-acetoxy-19α(H)-lup)-13(18)-ene (*4*) (0.2 g), m.p. (EtOH) 177 °C, $[\alpha]_D$ −21° (*c* 0.82). (Ref. 6, m.p. 184 – 185 °C *in vacuo*, $[\alpha]_D$ −20.7°). *ν* 1730, 1235. *δ* (CCl_4) 4.4 (1 H, m), 3.7 – 2.1 (3 H, m), 1.97 (3 H, s), 1.1 – 0.83 (8 methyls). *m/e* 468 (M^+), 205 (100 %).

(b) Lupenyl acetate (*1a*) (0.5 g) in benzene (17 g), Ac_2O (7 g), and 36 % HBr in AcOH (11 g) was allowed to stand at room temperature for ten days. The reaction is sensitive to the concentration of HBr. Work up and chromatography on 10 % $AgNO_3$ impregnated silica plates gave 3β-acetoxy-19α(H)-lup-13(18)-ene (*4*) (0.1 g) as above and 3β-acetoxy-lup-18-ene (*3a*) (0.1 g), m.p. (EtOH) 238 °C, $[\alpha]_D$ +13° (*c* 1.0). (Ref. 5, m.p. 210 – 212 °C, $[\alpha]_D$ +6.8°.) *ν* 1730, 1245. *δ* (CCl_4) 4.4 (1 H, m), 3.05 (1 H, sept. *J* 7 Hz), 2.6 – 2.0 (4 H, m), 1.96 (3 H, s), 1.1 – 0.8 (8 methyls). *m/e* (% rel. int.) 468 (32, M^+), 204 (94), 189 (100), 177 (64). This compound was identical (m.p., mixed m.p., $[\alpha]_D$, TLC, MS, IR, ^{1}H NMR) with the compound obtained from the hydrogenation of diene *5* (see below).

Isomerisation of 3β-acetoxy-lup-18-ene (3a). 3β-Acetoxy-lup-18-ene (*3a*) was treated as lupenyl acetate (*1a*) above with an HBr – Ac_2O – AcOH – benzene mixture. Work up gave 3β-acetoxy-19α(H)-lup-13(18)-ene (*4*), identical with the compound obtained above.

Hydrogenation of 3β-acetoxy-lupa-18,20(29)-diene (5). 3β-Acetoxy-lupa-18,20(29)-diene (*5*) (1 g) was hydrogenated over PtO_2 according to Ref. 4. Chromatography on 10 % $AgNO_3$ impregnated silica plates (eluent: $CHCl_3$ – light petroleum b.p. 60 – 80 °C, 3:1) gave 3β-acetoxy-18β(H),19α(H)-lupane [6,10] (*12*) (0.25 g), m.p. (EtOH) 271 °C. $[\alpha]_D$ +21° (*c* 1.0) (Ref. 6, m.p. 272 – 274 °C, $[\alpha]_D$ +24°) and 3β-acetoxy-lup-18-ene (*3a*) (0.63 g) identical with the compound from the isomerisation of lupenyl acetate (*1a*).

Epoxidation of 3β-acetoxy-19α(H)-lup-13(18)-ene (4). 3β-Acetoxy-19α(H)-lup-13(18)-ene (*4*) (0.2 g) from the isomerisation of *1a*, or from the hydrogenation of the dienes *6* and *7* was stirred with $NaHCO_3$ (0.5 g) and *m*-chloroperbenzoic acid (0.15 g) in CH_2Cl_2 (10 ml) for 30 min. The mixtures were washed with water and Na_2SO_3 solution, dried and chromatographed on silica plates ($CHCl_3$ eluent). Each reaction gave the same main product 3β-acetoxy-13α,18α-epoxy-19α(H)-lupane (*8*) (80 – 100 mg), m.p. (EtOH) 194 °C, $[\alpha]_D$ +25° (*c* 0.92). *ν* 1730, 1245, 1095, 1010, 980, 870. *δ* (CCl_4) 4.45 (1 H, m), 1.98 (3 H, s), 1.16 – 0.84 (8 methyls). *m/e* 484 (M^+), 140 (100 %).

3β-Acetoxy-18β,19β-epoxylupane (9a). (a) 3β-Acetoxy-lup-18-ene (*3a*) was epoxidised with *m*-chloroperbenzoic acid as *4* above to give 3β-acetoxy-18β,19β-epoxylupane (*9a*), m.p. (EtOH) 235 °C, $[\alpha]_D$ +37° (*c* 1.0). (Ref. 6, m.p. 236 – 238 °C, $[\alpha]_D$ +32°.)

(b) 3β,28-Diacetoxy-18β,19β-epoxylupane [8] (*9b*) (1.0 g) and KOH (0.12 g) in EtOH (100 ml) were refluxed for 1 h. Work up and chromatography gave as the main product 3β-acetoxy-28-hydroxy-18β,19β-epoxylupane (*9c*) (0.52 g), m.p. (EtOH) 246 °C, $[\alpha]_D$ +38° (*c* 1.0).

Hydroxyacetate *9c* (0.2 g), *p*-toluenesulfonylchloride (0.4 g), and pyridine (3 g) were stirred overnight and worked up. Chromatography on a silica plate gave 3β-acetoxy-28-tosyloxy-18β,19β-epoxylupane (*9d*) (0.14 g), m.p. (EtOH) 160 °C (decomp.), $[\alpha]_D$ +12° (*c* 1.1). *δ* (CCl_4) 7.78 and 7.30 (à 2 H, d, *J* 8 Hz), 4.4 (1 H, m), 4.3 and 3.77 (à 1 H, d, *J* 9 Hz), 2.45 (3 H, s), 2.05 (3 H, s), 1.1 – 0.8 (8 methyls).

Tosylate *9d* (100 mg), NaI (220 mg), Zn (300 mg), $(Me_2N)_3PO$ (2 ml), and $MeOCH_2CH_2OMe$ (2 ml) were kept at 100 °C overnight (*cf.* Ref. 11). Work up and crystallisation from EtOH gave 3β-acetoxy-18β,19β-epoxylupane (*9a*), identical (m.p., mixed m.p., $[\alpha]_D$, IR, ^{1}H NMR, TLC) with the compound above.

3β-Acetoxy-18α,19α-epoxylupane (10a). 3β-Acetoxy-lup-18-ene (*3a*) (200 mg) was ozonised in CH_2Cl_2 (20 ml) at −75 °C until the solution remained faintly blue. Excess ozone was driven off with a nitrogen stream and the solution allowed to reach room temperature. Chromatography on a silica plate ($CHCl_3$ eluent) gave 3β-acetoxy-18α,19α-epoxylupane (*10a*) (130 mg), m.p. (MeOH) 242 °C, $[\alpha]_D$ +40° (*c* 0.8). (Ref. 9, m.p. 238 °C, $[\alpha]_D$ +40°). *ν* 1730, 1240, 1130, 1100, 1023, 1000, 980. *δ* ($CDCl_3$) 4.5 (1 H, m), 2.3 (2 H, m), 2.05 (3 H, s), 1.1 – 0.85 (8 methyls). M^+ 484.

Rearrangement of 3β-acetoxy-18,19-epoxylupanes (9a) *and* (10a). Both 3β-acetoxy-18α,19α-epoxylupane (*10a*) and 18β,19β-epoxy isomer (*9a*) (0.2 g) were treated with BF_3-etherate (5 drops) in dry benzene (3 ml) for 5 min. Work up and chromatography on silica plates ($CHCl_3$ eluent) gave 3β-acetoxy-18,19-secolup-13(18)-en-19-one (*11*) (yields 80 – 95 %), m.p. (EtOH) 130 °C, $[\alpha]_D$ −5° (*c* 0.72). *ν* 1725, 1710, 1245. *δ* ($CDCl_3$) 4.96 (1 H, br. s), 4.53 (1 H, m), 2.9 – 2.0 (7 H, m), 2.04 (3 H, s), 1.15 – 0.85 (8 methyls). M^+ 484.

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The Formation of Barbaralone Derivatives from the Reaction between Triazolinediones and Cyclooctatetraene-iron Tricarbonyl

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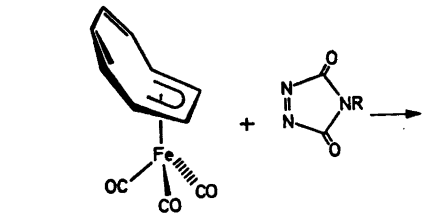
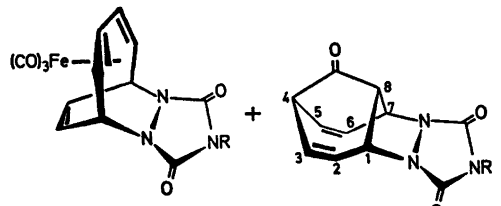
Coordination of a polyene to a metal center can lead to drastic modification of its reactivity. Thus cyclooctatetraene (COT) cycloadds to tetracyanoethylene (TCNE) *via* its [4.2.0]-bicyclic valence isomer in classic Diels-Alder fashion,[1] while the iron tricarbonyl complex *1* yields a 1,3-addition product containing an Fe–C σ bond.[2] The even more powerful dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (*2*, R = Ph, PTAD) is reported to combine with *1* in low yield at 25 °C to give the 1,4-adduct *3*.[3] Apart from the $Fe(CO)_3$ moiety the reaction appears to be completely analogous to that between PTAD and COT under ambient conditions.[4] We have reinvestigated the transformation with both MTAD and PTAD (*2*, R = CH_3, Ph) and have found that the barbaralone derivative *4* is formed along with complex *3*. The result implies carbonyl insertion into an intermediate 1,3-addition product.



1 *2*



3 *4*

Mixing of equimolar quantities of MTAD and *1* (in CH_2Cl_2, 25 °C, 30 min) followed by chromatography (silica gel, ethyl acetate) leads to the isolation of three compounds. Besides unreacted *1* (22 %) and *3* (R = CH_3, 34 %, m.p. 185 °C, dec.) the barbaralone derivative *4* was obtained (R = CH_3, 16 %, m.p. 214–215 °C). The latter gave a satisfactory elemental analysis and molecular weight (MS). The presence of the keto group was substantiated by derivatization (2,4-DNP) and IR ($CHCl_3$): 1750 (m), 1772 (s) and 1714 (s) cm^{-1} (C=O and N–CO–N). ^1H NMR spectrometry (90 MHz, $CDCl_3$) established the symmetry and structure of *4* by revealing six signals readily analyzable by spin decoupling. The absorption at lowest field is an AB quartet showing additional fine structure [δ 6.41 (2 H, H-3 and H-5) 5.99 (2 H, H-2 and H-6); $J_{23} = J_{56} = 9$ Hz; $J_{12} = J_{67} = 4$ Hz; $J_{34} = J_{54} = 6.5$ Hz; $J_{31} = J_{57} = 1$ Hz]. The bridgehead protons α to nitrogen resonate at δ 5.11 (2 H, H-1 and H-7, dd, $J_{18} = J_{78} = 8$ Hz). At high field the remaining absorption consists of two doublets of triplets centered at δ 3.68 (1 H, H-8, $J_{48} = 2$ Hz) and 3.39 (1 H, H-4) and a singlet at δ 3.08 (N-CH_3). The broad band decoupled ^{13}C NMR spectrum (22.63 MHz, $CDCl_3$) is in complete agreement with structure *4* exhibiting only eight peaks: δ 201.1, 156.2, 134.5, 126.2, 61.7, 50.9, 45.3 and 25.8.

The corresponding reaction with PTAD yielded *1* (22 %), the previously characterized *3* (R = Ph, 33 %, m.p. 156–157 °C; lit.[3] m.p. 155 °C) and the barbaralone system *4* (R = Ph, 14 %, m.p. 225–226 °C). The N-phenylbarbaralone was characterized as above, its spectro-