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THE STEREOSPECIFICITY AND STEREOSELECTIVITY OF HYDROGEN TRANSFER IN PHOTOCHEMICAL REACTIONS

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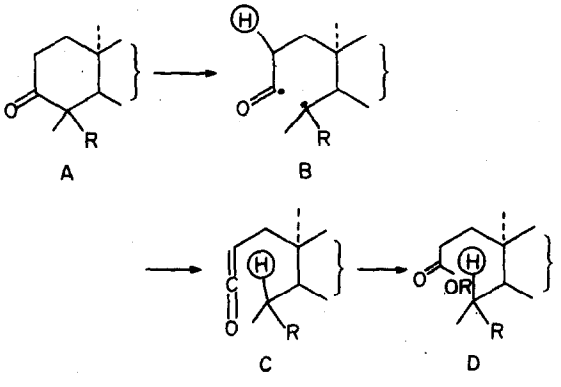
Abstract—The photolysis of methyl *ent*-19-acetoxy-3-oxo-beyer-15-en-17-oate (3) occurs with retention of configuration of C-4 to give the 4*S*-3,4-seco acid. In the phototransformation of 3-ketobeyeranes to 3,4-seco acids the C-2 axial hydrogen is transferred preferentially to C-4.

The photochemical rearrangement of cycloalkanones to ketenes involves a Norrish type 1 cleavage of the cycloalkanone followed by intramolecular disproportionation in which a hydrogen α- to the acyl radical site transfers to the alkyl radical.[1,2] The factors which govern the disproportionation of the intermediate biradical and the stereoselectivity of hydrogen transfer have received a great deal of attention.[2] The reaction is exemplified by the well known photochemical rearrangement of 3 - oxo - 4,4 - disubstituted terpenes to seco acids (A→D).[1] Compounds containing this structural feature are readily available and amenable to stereospecific labelling of the C-2 hydrogens thus providing a system in which the stereoselectivity of hydrogen transfer from C-2 can be investigated. Furthermore, in those cases where the substituents at C-4 are different the stereochemistry of the newly formed chiral centre can be determined.

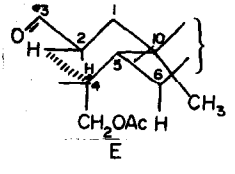


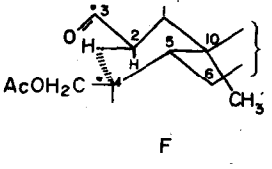
Our interest in this topic arose from the isolation of the seco acid (1) as a single stereoisomer at C-4 (*S*) from the resin of *Beyeria calycina* var. *minor*.[3] Feeding experiments suggest [3,4] that this compound may arise by a photochemical reaction of the congener 2 rather than by an enzymatic pathway. We have now shown that the natural seco acid and the compound synthesised photochemically from 2 have the 4*S*-stereochemistry. Furthermore we have investigated the stereoselectivity of hydrogen transfer from C-2 to C-4 in the phototransformation of the 3-ketobeyerane derivative (5) to the seco acid (6) and found that the C-2 axial hydrogen in 5 is transferred preferentially

RESULTS AND DISCUSSION

In an extension of our work[5] on the diterpene constituents of *B. calycina* var. *minor* we isolated the unusual hydroxy seco acid (1) as a minor component. This acid was shown to have the 4*S*-stereochemistry by comparison of the derived dihydrodiester with a synthetic sample prepared from the acid (4).[3] In an attempt to determine the origin of 1 we have photolysed the methyl ester of the keto acetate (3)[5] expecting the formation of both the 4*R*- and 4*S*-stereoisomers. Surprisingly only one stereoisomer was obtained and by comparison of the dihydrodiester with synthetic samples[3] of both stereoisomers the compound obtained from the photolysis was shown to have the 4*S*-chirality. This result establishes that the photolysis of the methylester (3) proceeds with retention of configuration at C-4 and thus the hydrogen atom at C-2 is transferred to the same side of C-4 as the original 3,4-bond.

An examination of Dreiding models suggests that during photolysis of the keto acetoxy ester (3) the transition state (E) contains a somewhat greater degree of unfavourable non-bonding interactions than (F) due largely to the 1,3-diaxial interactions between the acetoxyl group and the 10-methyl and 6α-proton. This would also apply to a lesser extent to transition states with a half chair conformation. The reaction pathway therefore proceeds through the sterically more unfavourable transition state and must be controlled by other factors as well as those depending on the conformational stability of the transition state involved.[6–9] Thus the life time of the biradical may not be sufficient to allow rotation about the C-4,5 bond although rotation about the C-1,2-bond must still occur before hydrogen transfer can take place. In this case, rotation about the C-1,2 bond may be easier than rotation about the C-4,5 bond, because of lower energy barriers with the former.





As expected, an examination of the reaction mixture obtained from photolysis of the keto acetoxy ester (3) failed to reveal any product arising from epimerisation about C-4 which would have to take place by ring opening, rotation about the C-4,5 bond and then ring closure again. Epimerisation has been observed[1,10] with the photolysis of some cyclic ketones and might be expected on the grounds of formation of the less sterically hindered product but not in view of the absence of inversion at C-4 during the seco acid formation.

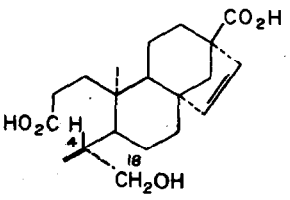
We then turned our attention to the stereochemistry of the transfer of hydrogen from C-2 to the alkyl radical site. Where there are two non-equivalent H atoms in this position there may be some preference for transfer of one or the other. During the photolysis of carvonecamphor (7) it is the *exo*-hydrogen which migrates almost exclusively.[9] In the photolysis of a 3-ketobeyerene some stereoselectivity of hydrogen transfer may also take place although the intermediate biradical is considerably less rigid than that formed during photolytic cleavage of carvonecamphor. If there is any preference for hydrogen transfer then a consideration of the factors discussed above suggests that it should be for the 2α-hydrogen. In a transition state with a chair conformation the CO group experiences greater non-bonding interactions during transfer of the 2β-hydrogen than during the transfer of the 2α-H.

The difference in stability for transition states with half chair conformations would be somewhat less and again due mainly to an unfavourable interaction between the CO group and the 10-Me during transfer of the 2β-hydrogen.

Alternatively if the hydrogen shift is very rapid then any stereoselectivity may depend on a preference for the CO group to rotate in one direction or another. If this were the case transfer of the 2α-hydrogen would still be expected to predominate as this involves rotation of the CO away from the 10- and 4α-Me groups rather than towards them which would bring the 2β-hydrogen in the proximity of the alkyl radical.

The question of the stereoselectivity of hydrogen transfer during the photolytic conversion of a 3-ketobeyerane to the corresponding seco acid was investigated using the known[5] keto acid (5) as a substrate. This compound was chosen rather than the naturally occurring keto acetate (2) because of the anticipated ease of functional group manipulation with 5 during the specific labelling at C-2 with deuterium. Photolysis of 5 in dioxan-water gave the known[5] seco diacid (6) which was purified *via* the seco diester (8 31% yield). Photolysis of the 2-d_2-keto acid (9), prepared by treatment of 5 with D_2O under basic conditions, followed by methylation of the reaction mixture gave the diester (10). The NMR spectrum of 10 included a 6H singlet at δ 0.91, assigned to C-10 and one of the secondary Me groups, by comparison with the NMR spectrum of 8, and a 3H singlet at δ 0.80 assigned to the other secondary Me. This is consistent with the expected transfer of deuterium from C-2 to C-4 during ketene formation.

The 2α-d-keto acid (16) was prepared first, as outlined in Scheme 1. Reduction of the keto acid (5) with sodium borohydride followed by methylation gave the known[5] hydroxy ester (11) which was dehydrated to the unsaturated ester (12). Treatment of 12 with *m*-chloroperbenzoic acid gave the epoxide (13) which, after reduction by LAH, gave a diol (14). The diol (14) was not the known[5] 3α,17-dihydroxybeyerane but was obviously



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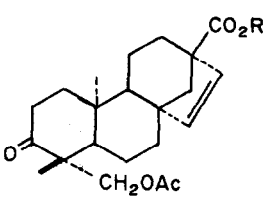
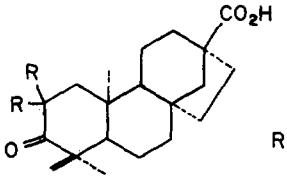
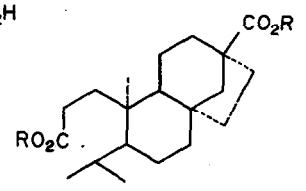
4: $\Delta^{4,18}$



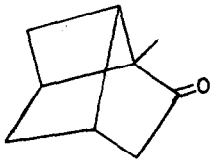
2: R = H
3: R = CH_3



5: R = H
9: R = D



R
6: H
8: CH_3



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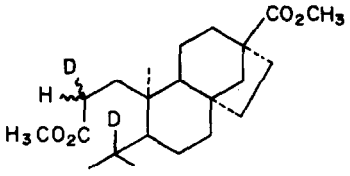

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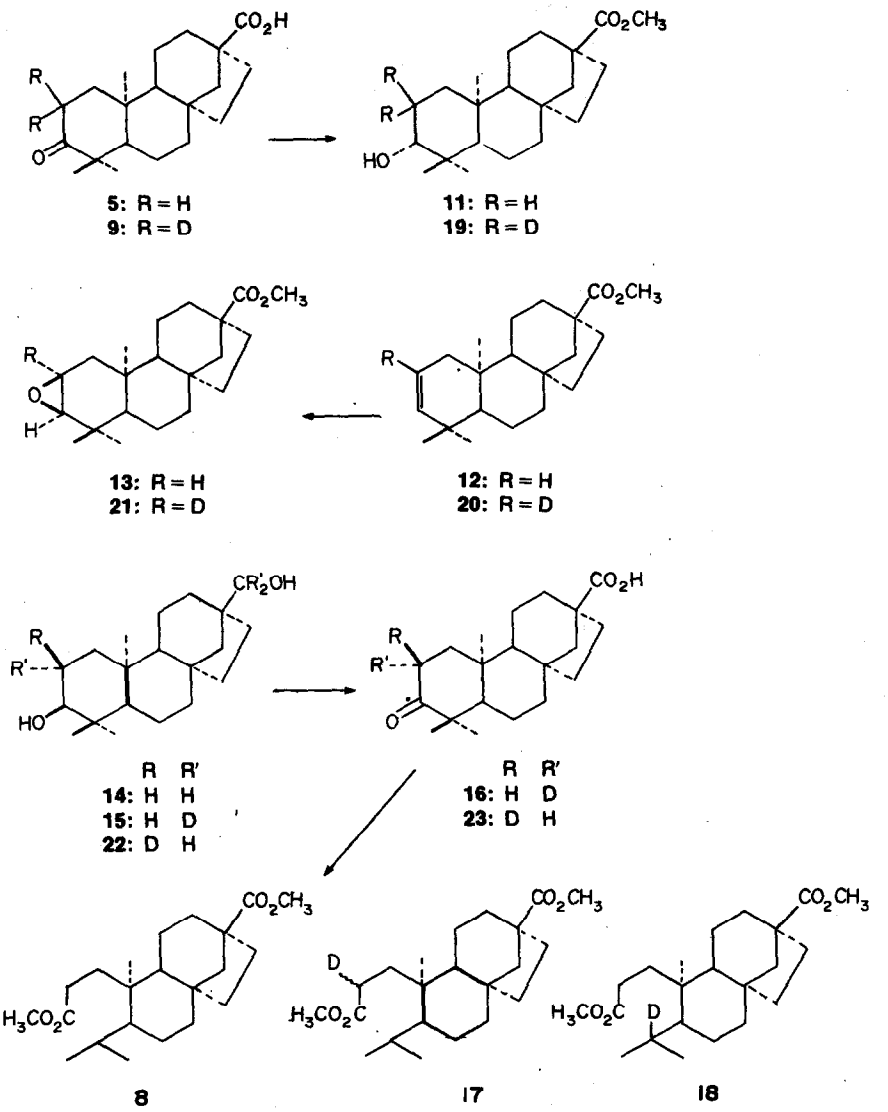
oxygenated at C-3 and C-17 since oxidation of 14 regenerated the keto acid (5). Hence 14 was the 3β,17-diol and 13 the β-epoxide, as might be expected.[11] Reductive opening of the epoxide (12) must then be by attack at C-2 from the α-face and thus reduction of 13 with LAD leads to the d_3-diol (15). Oxidation of 15 gave the keto acid (16) which contained 5% of the undeuterated acid (5, mass spectrum).

Photolysis of the keto acid (16) followed by methylation gave a mixture of the seco diesters (17, 18 and 8), the last of these arising from cleavage of the 5% undeuterated keto acid in the substate (16). The percentage composition of this mixture was determined from the NMR spectrum which included a singlet and doublet at δ 0.80 of relative areas of 62 and 38% respectively. The former was attributed to 18 in the mixture while the latter was attributed to 17 and undeuterated 8, these assignments being based on the spectra of 8 and 10. Thus, taking into account the proportion (5%) of undeuterated material in the substrate, the photolytic conversion of the deuterated keto acid (16) to the corresponding esters proceeds with approx 65% axial hydrogen (i.e. deuterium) transfer.

This degree of stereoselectivity would reflect that stereoselectivity of hydrogen transfer during photolysis of the undeuterated analogue (5) only if there was no isotope effect operating during deuterium transfer. Hence the 2β-d-keto acid (23) was prepared from 9 as shown in Scheme 1 in an analogous manner to the synthesis of the 2α-isomer (16) and gave, after photolysis and methylation, a mixture of the seco diesters (17, 18 and 8). The ratio of the area of the doublet to that of the singlet at δ 0.80 in the NMR spectrum of this mixture indicated that at least 85% of the axial hydrogen (i.e.



Scheme 1.

protium) is transferred during the photolytic conversion of **23** to the esters.

From these results, both the isotope effect operating during hydrogen transfer and the degree of stereoselectivity favouring transfer of the axial hydrogen can be calculated on the assumption that the isotopic effects for the two epimerically deuterated ketones are similar. Using the formalism of Curtin and Kellom[14] a value of 1.8 for the isotope effect is obtained and the preference for transfer of the axial over the equatorial hydrogen is estimated to be *ca.* 3:1. These figures are only approximate because of the error (5%) involved in measuring peak intensities in NMR spectra. (Attempts to obtain a more accurate assessment from mass spectral data proved fruitless). The value of the isotope effect is within the range (1.5–2.1) observed for hydrogen disproportionations.[2] The moderate degree of stereoselectivity favouring transfer of the axial hydrogen during photolysis of this system is as predicted although the degree of selectivity is not as great as that observed[9] with the more rigid carvonecamphor (**7**).

EXPERIMENTAL

General experimental details have been described.[13]

Photolysis of methyl - ent - 19 - *acetoxy* - 3 - *oxobeyer* - 15 - *en* - 17 - *oate* (**3**). A soln of **3** (0.15 g) in AcOH (9 ml) –H_2O (1 ml) was refluxed under N_2 in a pyrex vessel for 5 days while being irradiated by an external Hanovia 1L photochemical reactor. The solvent was removed *in vacuo* and the crude product was treated with CH_2N_2. Preparative TLC of the product gave **3** (120 mg) and a fraction which was saponified then methylated to give **4** (20 mg), the NMR and MS of which were identical to those of (4*S*) - dimethyl - *ent* - 18 - hydroxy - 3,4 - secobeyerane - 3,17 - dioate isolated from *B. calycina* var. *minor*.[3] The hydroxy diester (**4**), prepared by photolysis of **3** in EtOH, was hydrogenated over Pd/C for 3 hr giving the dihydro diester identical with a sample of the compound prepared from *ent* - 3,4 - secobeyer - 4(18),15 - diene - 3,17 - diol.[3] The NMR spectra of the 4*R*- and 4*S*-stereoisomeric diesters are significantly different. In particular the resonance signals of the 19-H_3 appear at δ 0.78 and 1.04 respectively. For the pair of diacids similar differences are noted (19-H_3 at δ 0.95 and 1.25 respectively in C_5H_5N). The corresponding diacid crystallized from EtOAc as plates, m.p. 102–106° undepressed with a sample of the diacid prepared as described previously.[3]

Ent-2-d_2-3-*ketobeyeran*-17-*oic acid* (**9**). Na (150 mg) was added to a soln of **5** (1 g)[5] in dioxan (30 ml) and D_2O (10 ml) and the soln stirred at 50° under N_2 for 12 hr. The organic material was recovered with ether and evaporation of the solvent left **9** as a white crystalline solid; MS: *m/e* (%) 320 (M^+, 43), 319 (5) 232 (100), 221 (15), 220 (15), 219 (15), 187 (30).

Photolysis of **9**. The photolysis of **9** (85 mg) followed by methylation as above gave **10** (21 mg); NMR (90 MHz, $CDCl_3$): δ 0.80 (s, 18- or 19-H_3), 0.91 (s, 18- or 19-H_3 and 20-H_3), 3.64 and 3.67 (s, $-OCH_3$); MS: *m/e* (%) 366 (M^+, 9%), 307 (48), 306 (41), 279 (43), 278 (100).

Photolysis of ent - 3 - *ketobeyeran* - 17 - *oic acid* (**5**). A soln of **5** (150 mg) in dioxan (15 ml) – H_2O (5 ml) under N_2 in a quartz vessel was irradiated with an Hanovia 1L Photochemical Reactor for 3 days at room temp. The organic material recovered with ether was methylated with CH_2N_2. Preparative TLC of the product gave **8**, (53 mg) as a gum; NMR (90 MHz; $CDCl_3$): δ 0.80, 0.91 (d, J 6.5 Hz, 18-, 19-H_3), 0.90 (20-H_3), 3.63 and 3.66 (s, $-OCH_3$); MS: *m/e* (%) 364 (M^+, 5), 305 (28), 304 (19), 278 (61), 277 (100). A portion (30 mg) of **8** was saponified to give **6** which crystallised from benzene as prisms, m.p. 195–196° undepressed on admixture with an authentic sample.[5]

Synthesis of ent - 2β - d - 3 - *ketobeyeran* - 17 - *oic acid* (**16**). The ester **11** (0.8 g)[5] and $POCl_3$ (8 g) were dissolved in pyridine (10 ml) and the soln stood at room temp. overnight. The soln was then heated to 80° for 2 hr, poured into H_2O (200 ml) and the organic material recovered with ether. The solvent was evaporated *in vacuo*, leaving the *ester* (**12**, 0.6 g) which crystallised from MeOH as plates, m.p. 91–95°, $[\alpha]_D$ – 27° (*c*, 0.3, $CHCl_3$) (Found: C, 79.4; H, 9.9. $C_{21}H_{32}O_2$ requires: C, 79.7; H, 9.8%). $\nu_{max}^{CS_2}$ cm^{-1}: 1725, 725, 714; NMR: δ 0.87 (3H) 0.95 (6H), (18-, 19-, 20-H_3), 3.62 (s, $-OCH_3$), 5.37 (s, 2-, 3-H); MS: *m/e* (%) 316 (M^+, 100), 301 (55), 261 (55), 233 (40), 201 (35), 175 (65). The ester (**12**, 0.5 g) and *m*-chloroperbenzoic acid (0.5 g) were dissolved in EtOH-free $CHCl_3$ (10 ml) and the soln stood at –5° overnight. The soln was poured into Et_2O (50 ml) and the ether soln washed with 5% NaOH aq (2 × 50 ml), H_2O, dried and the Et_2O evaporated leaving the *epoxide* (**13**) which crystallized from n-pentane as cubes, m.p. 104–107°, $[\alpha]_D$ + 12° (*c*, 0.5, $CHCl_3$) (Found: C, 75.9; H, 9.7. $C_{21}H_{32}O_3$ requires: C, 75.9; H, 9.7%). $\nu_{max}^{CS_2}$ cm^{-1}: 1725; NMR: δ 0.92, 1.00, 1.08 (s, 18–, 19-, 20-H_3), 2.48 (A part of an ABXY system, J_{AB} 3.5 Hz, 3-H), 3.18 (B part of an ABXY system, $W_{1/2}$ 12 Hz, 2-H), 3.64 (s, $-OCH_3$); MS: *m/e* (%) 332 (M^+, 30), 317 (55), 314 (70), 275 (100). A soln of **13** (450 mg) and LAH (2 eq) in dry Et_2O (10 ml) was refluxed for 12 hr. The organic material recovered with Et_2O was purified by preparative TLC to give the *diol* (**14**, 250 mg) which crystallized from benzene as cubes, m.p. 159–162°, $[\alpha]_D$ + 12 (*c*, 1.3, $CHCl_3$) (Found: C, 78.5; H, 11.2. $C_{20}H_{34}O_2$ requires: C, 78.4; H, 11.2%). $\nu_{max}^{CS_2}$ cm^{-1}: 3620; NMR: δ 0.83 (3H) and 0.95 (6H) (18-, 19-, 20-H_3), 3.48 (br m, 3-H and 17-H_2); MS: *m/e* (%) 306 (M^+, 25), 288 (75), 273 (40), 136 (100). Reduction of a sample of **13** with LAD gave the corresponding d_3-diol (**15**); NMR: δ 0.83 (3H) and 0.95 (6H) (18-, 19-, 20-H_3), 3.48 (d, J 3 Hz, 3-H); MS: *m/e* (%) 309 (M^+, 95), 291 (100), 276 (70), 137 (100). The d_3-diol (**15**, 150 mg) in acetone (10 ml) was oxidized with Jones reagent for 5 min at room temp. The soln was poured into H_2O and the organic material recovered with Et_2O. Evaporation of the solvent gave **16**; MS: *m/e* (%) 319 (M^+, 100), 318 (6).

Photolysis of **16**. The compound (74 mg) was photolysed as described above. Methylation of the crude product and preparative TLC gave a mixture of diesters (**17**, **18** and **8**, 31 mg). NMR (90 MHz, $CDCl_3$): δ 0.80 (s, 18- or 19-H_3 of **18**, 62%), 0.80 (d, J 6.5 Hz, 18- or 19-H_3 of **17** and **8**, 38%); MS: *m/e* (%) 365 (M^+, 5), 279 (36), 278 (100), 277 (66), 276 (15), 263 (4), 262 (12), 261 (35), 260 (32), 220 (5), 219 (13), 218 (71), 217 (43).

Synthesis of ent - 2α - d - 3 - *ketobeyeran* - 17 - *oic acid* (**23**). The same sequence as that used for the synthesis of **16** was used starting from the 2-d_2-keto acid (**9**). The 2-d_2-hydroxy ester (**19**) had the following spectroscopic properties; NMR: δ 0.77, 0.93 and 0.98 (18-, 19-, 20-H_3), 3.18 (br s, 3-H), 3.64 (s, $-OCH_3$); the 2-*d*-2-ene intermediate (**20**); NMR: δ 0.87 (3H) and 0.94 (6H) (18-, 19-, 20-H_3) 3.62 (s, $-OCH_3$), 5.37 (s, 3-H); MS: *m/e* (%) 317 (M^+, 100), 302 (50), 261 (55), 233 (30), 201 (15), 175 (30); the 2-*d*-epoxide (**21**): NMR δ 0.91, 1.0 and 1.09 (18-, 19-, 20-H_3), 2.75 (br s, 3-H), 3.60 (s, $-OCH_3$); the 2-*d*-diol (**22**); NMR (C_5H_5N): δ 0.88, 0.90 and 1.13 (18-, 19-, 20-H_3), 3.57 (D, 3-H, partly obscured by OMe group signal) 3.60 (s, $-OCH_3$).

The diol (**22**) was oxidized to **23** as described above; MS: *m/e* (%) 319 (55), 318 (5), 232 (100), 219 (30), 187 (25). The intensity of the ion at *m/e* 318 is 9.2% of that at *m/e* 319.

Photolysis of **23**. The compound (100 mg) was photolysed at 25° as described above. The product was methylated and preparative TLC gave a mixture of **17**, **18** and **8** (35 mg); NMR (90 MHz, $CDCl_3$): δ 0.80 (s, 18- or 19-H_3 of **18**, 18%), 0.80 (d, J 6.5 Hz, 18- or 19-H_3 of **17** and **8**, 82%); MS: *m/e* (%) 365 (M^+, 5), 279 (28), 278 (67), 277 (100), 276 (7).

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