The Chemistry of Terpenes. Part III.[1] The Conversion of 2β*H*-Pinan-3-one into 2β*H*-Pinan-4-one

By **R. Alan Jones** * and **T. C. Webb**, School of Chemical Sciences, University of East Anglia, Norwich NOR 88C

The ketone transposition sequence for the conversion of 2β*H*-pinan-3-one (pinocamphone) into 2β*H*-pinan-4-one (*trans*-verbanone) *via* the reduction of 4-benzylidene-2β*H*-pinan-3-one with lithium aluminium hydride–lauminium chloride was unsuccessful owing to the failure of the reduction procedure to give 4-benzylidene-2β*H*-pinane. However, an alternative procedure *via* 3-acetoxy-4-benzylidene-2β*H*-pinane readily gave 2β*H*-pinan-4-one.

In connection with our synthetic and deamination studies of the isomeric 4-aminopinanes [2] we required substantial quantities of pure 2β*H*-pinan-4-one (*trans*-verbanone) † (I). The normal route from pin-2-ene *via* pin-2-en-4α-ol leads to a *ca.* 1 : 1 mixture of 2α*H*- and 2β*H*-pinan-4-one [3] and, as in our hands the separation of the isomers by preparative g.l.c. or by distillation using a spinning band column proved to be inefficient, an alternative synthetic route was sought.

Current interest in the ketone transposition reaction [4-9] suggested a possible route to 2β*H*-pinan-4-one (I) from the readily obtained 2β*H*-pinan-3-one (pinocamphone) (II). Having regard for the lability of pinane systems under acidic conditions, the relatively simple and short route *via* the benzylidene derivative (III), using conditions analogous to those described by Jones and his co-workers [4] for the conversion of 17-oxosteroids into 16-oxosteroids, appeared to be the most feasible. The key stage in the transposition is the removal of the 3-oxo-group of the benzylidene derivative (III) using $LiAlH_4$–$AlCl_3$ to give 4-benzylidene-2β*H*-pinane (VII)

† The αβ-notation has been used throughout; the isopropylidene bridge is considered to have the β-configuration.

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[2] R. A. Jones and T. C. Webb, unpublished work.
[3] A. F. Regan, *Tetrahedron*, 1969, **25**, 3801.
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[8] J. E. Bridgeman, C. E. Butchers, Sir Ewart R. H. Jones, A. Kasal, C. D. Meakins, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 244.
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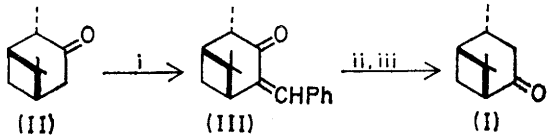
via 1,2-reduction of the ketone to the alcohol (IV). Subsequent ozonolysis of the benzylidenepinane should readily give 2β*H*-pinan-4-one, *i.e.* (II) → (III) → (I).



i, PhCHO–NaOH; ii, $LiAlH_4$–$AlCl_3$; iii, O_3

Although the use of lithium aluminium hydride in the presence of aluminium chloride has been frequently reported to be successful in this type of reduction of αβ-unsaturated ketones,[10-12] the reduction of 4-benzylidene-2β*H*-pinan-3-one led to the formation of seven products (IV)—(X) which were quantitatively estimated by analytical g.l.c. (Table 1). Wherever possible the products were isolated and analysed spectroscopically but minor components were identified by comparison of their retention data and mass spectral data with authentic samples.

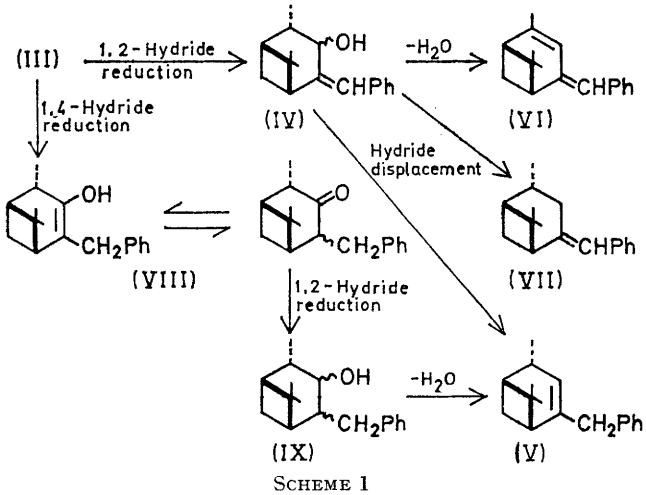
The reaction may take two courses, either *via* an initial 1,2-reduction of the carbonyl group or *via* the alternative 1,4-addition across the αβ-enone system. The first path was preferentially followed in the absence of aluminium chloride but the addition of aluminium chloride subsequent to the addition of the αβ-enone to lithium aluminium hydride (Table 1, Method 2) resulted in further reaction of the initially formed 4-benzylidene-3-hydroxy-2β*H*-pinane (IV). The formation of (V), (VI), and (VII) may be rationalized in terms of a complex of the initially formed 3-hydroxy-compound with aluminium chloride, which facilitated the nucleophilic displacement of the hydroxy-group by the hydride ion (XI) and (XII) and also aided the elimination reaction (XIII). The 2β*H*-pin-3-ene (V) could also have been formed from 4-benzyl-2β*H*-pinan-3-one (VIII), but a comparison with reactions in which the initial 1,4-reduction path is favoured suggests that this mode of formation is of lesser importance. Simultaneous addition of the αβ-enone and aluminium chloride to lithium aluminium hydride or, alternatively, addition of the αβ-enone to the premixed lithium aluminium hydride–aluminium chloride complex[14] (Table 1, Methods, 1, 3, and 4) appeared to favour an initial 1,4-reduction of the αβ-unsaturated ketone, presumably due to an enhanced polarization of the enone system by the formation of complex (XIV). These results reaffirm the report by

TABLE 1

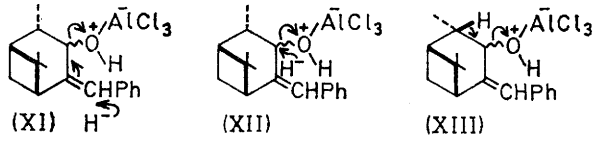
Percentage yields of reaction products from the reduction of 4-benzylidene-2β*H*-pinan-3-one with $LiAlH_4$ in the presence of $AlCl_3$ [a]

Compound	Kovat's retention index [b]	Method 1 [c,f,i]	Method 2 [d,h,i]	Method 3 [e,g,i]	Method 4 [e,g,j]	Method 5 [i] $LiAlH_4$ alone	Identification [k]
(X)	1552	Trace	Trace	Trace	2·5	0·0	
(V)	1676	4·5	34·6	1·8	4·7	0·0	m.s., i.r., n.m.r., u.v.
(VI)	1760	0·8	18·0	0·9	1·6	0·0	r.i., m.s., i.r., n.m.r., u.v.
(VII)	1789	2·8 [l]	29·3	1·4 [l]	3·2 [l]	0·0	m.s., i.r., u.v.
(IV)	1796		7·9			84·0	r.i., m.s., i.r., n.m.r., u.v.
(VIII)	1901	74·5	5·8	64·7	72·4	16·0	r.i., m.s., i.r., n.m.r., u.v.
(IX)	1906	13·9	1·0	24·5	11·9	0·0	r.i., m.s., i.r., n.m.r., u.v.
(III)	1972	3·3	3·3	6·5	3·7	0·0	r.i., m.s., i.r., n.m.r., u.v.

[a] All yields were reproducible to ±2%. [b] Measured at 210° on a 15% Apiezon on Chromosorb P column. [c] $LiAlH_4$: $AlCl_3$: ketone 1·0 : 1·8 : 0·8. [d] $LiAlH_4$: $AlCl_3$: ketone 1·0 : 0·8 : 0·8. [e] $LiAlH_4$: $AlCl_3$: ketone 1·0 : 2·0 : 0·5. [f] The ketone and $AlCl_3$ (0·8 : 0·8) were added to premixed $LiAlH_4$ and $AlCl_3$ (1·0 : 1·0). [g] Simultaneous addition of $LiAlH_4$ and $AlCl_3$ to ketone. [h] Addition of ketone to $LiAlH_4$ with subsequent addition of $AlCl_3$. [i] Basic work-up conditions. [j] Acidic work-up conditions. [k] r.i. is Kovats' retention index identical with that of authentic sample. Full spectral data are available on request. [l] Accurate measurements of relative areas of the two peaks could not be made at low concentrations.



SCHEME 1



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[11] R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, 1958, **80**, 2896.
[12] J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1960, 1406.
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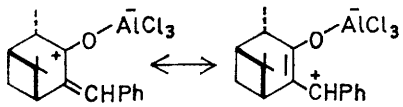
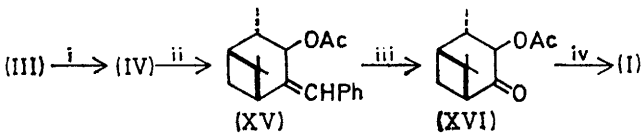
[14] E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, 1966, **88**, 729.

Jones and his co-workers [8] that the sequence used for the ketone *trans*-position of the steroidal 17-ketones [4] is not applicable to the conversion of cyclohexanone derivatives.



(XIV)

Huang-Minlon reduction of 4-benzylidene-2β*H*-pinan-3-one (III) gave only 4-benzyl-2β*H*-pinane (94%) with 4-benzyl-2β*H*-pin-3-ene (V) (6%) and the recently described ketone transposition sequence involving decomposition of α-acetoxy oxime-*O*-acetates with chromous acetate [9] could not be applied to the 2β*H*-pinan-3-one system as the initial nitrosation of the ketone gave intractable tars. The successful conversion of 2β*H*-pinan-3-one into 2β*H*-pinan-4-one (I) was eventually accomplished by the modified procedure described by Jones and his co-workers (Scheme 2) and involved reductive cleavage of 3-acetoxy-2β*H*-pinan-4-one (XVI), which was readily obtained by the ozonolysis of the 3-acetoxy-4-benzylidene derivative (XV).



(XV) (XVI)

SCHEME 2

i, $NaBH_4$; ii, Ac_2O–pyridine; iii, O_3; iv, Zn–AcOH

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 237 spectrometer for pure liquids between sodium chloride plates and u.v. spectra were measured for *ca.* 10^{-5} M-solutions in ethanol on a Unicam SP 700 spectrometer. N.m.r. spectra were determined for *ca.* 40% solutions in CCl_4 at 60 MHz on a Perkin-Elmer R12 spectrometer with Me_4Si as an internal standard. Product analysis was carried out by g.l.c. on a Perkin-Elmer 452 gas chromatograph at 210° with a 2 m × ⅛ in column containing Apiezon L on Chromosorb P (15 : 85 w/w) and a N_2 inlet pressure of 15 lb in^{-2}. Kovats' retention indices were estimated by the usual method.[15] The mass spectra and molecular weights of the reaction products were obtained using a Perkin-Elmer Hitachi RMU-6E mass spectrometer by direct insertion of the sample trapped from the g.l.c. effluent or by direct 'on-line' technique using a Perkin-Elmer F11 gas chromatograph operated under the conditions described above.

*4-Benzylidene-2*βH*-pinan-3-one* (III).—2β*H*-Pinan-3-one (20 g), benzaldehyde (20 g), and sodium hydroxide (8·8 g) in aqueous ethanol (30%, 130 ml) were stirred under reflux for 24 h. The mixture was cooled to room temperature and extracted with ether (4 × 50 ml). The extracts were dried ($MgSO_4$) and evaporated to give the *benzylidene derivative* (19·6 g, 63%), b.p. 130—131° at 0·5 mmHg (Found: C, 85·2; H, 8·5. $C_{17}H_{20}O$ requires C, 84·95; H, 8·4%).

*Lithium Aluminium Hydride Reduction of 4-Benzylidene-*2βH*-pinan-3-one.—Method* 1. Lithium aluminium hydride (0·38 g, 0·01 mol) and aluminium chloride (1·3 g, 0·01 mol) were stirred in ether (10 ml) for 5 min before the benzylidene ketone (1·9 g, 0·008 mol), together with a further quantity of aluminium chloride (1 g, 0·008 mol), in ether (15 ml) was added. The mixture was stirred under reflux for 2 h, cooled to room temperature, and diluted with water (3 ml). After the addition of aqueous sodium hydroxide (20%, 3 ml) and water (9 ml) the precipitate was removed and washed with ether (10 ml). The organic layer and the ethereal extracts were combined, dried ($MgSO_4$), and evaporated to give an oil which was analysed by g.l.c.

Method 2. The benzylidene ketone (2·4 g, 0·01 mol) in ether (10 ml) was added to lithium aluminium hydride (0·5 g, 0·013 mol) in ether (15 ml) and the solution was set aside at room temperature for 30 min. Aluminium chloride (1·3 g, 0·01 mol) was then added to it and the mixture was set aside at room temperature for a further 1 hr. The work-up procedure was as described in Method 1.

Method 3. Aluminium chloride (4·6 g, 0·035 mol) in ether (20 ml) was added to lithium aluminium hydride (0·7 g, 0·018 mol) in ether (20 ml) at room temperature. The solution was set aside for 5 min at room temperature, after which the benzylidene ketone (2·4 g, 0·01 mol) was added, and the mixture was stirred under reflux for 2 h. The work-up procedure was as described in Method 1.

Method 4. The benzylidene ketone (1·9 g, 0·008 mol) in ether (130 ml) was added slowly to a suspension of aluminium chloride (3·5 g., 0·03 mol) and lithium aluminium hydride (0·6 g, 0·015 mol) in ether (80 ml.). The mixture was heated under reflux for 2·5 h and then slowly poured onto ice (700 g) and hydrochloric acid (2N; 30 ml) and extracted with ether (3 × 100 ml). The extracts were dried ($MgSO_4$) and evaporated to give an oil which was analysed by g.l.c.

Method 5. The benzylidene ketone (2·4 g, 0·01 mol) in ether (10 ml) was added to lithium aluminium hydride (0·5 g, 0·013 mol) in ether (15 ml) and the solution was set aside for 30 min at room temperature. The work-up procedure was as described in Method 1.

*4-Benzyl-*2βH*-pinan-3-one* (VIII).—Catalytic hydrogenation of 4-benzylidene-2β*H*-pinan-3-one (2·5 g) in methanol (60 ml) over 5% palladized carbon (0·8 g) during 6 h gave *4-benzyl-*2βH*-pinan-3-one* (2·2 g, 86%), b.p. 132° at 0·5 mmHg (Found: C, 84·4; H, 9·2. $C_{17}H_{22}O$ requires 84·2; H, 9·15%).

*4-Benzylidene-3-hydroxy-*2βH*-pinane* (IV).—4-Benzylidene-2β*H*-pinan-3-one (10 g) and sodium borohydride (1·25 g) in tetrahydrofuran (400 ml) and methanol. (75 ml) were stirred at room temperature for 3 h and then poured into ice–water (200 ml). Extraction of the aqueous solution with ether (5 × 60 ml) and evaporation of the dried extracts gave the *hydroxy-compound* (9·3 g, 92%), b.p. 124—126° at 0·2 mmHg (Found: C, 84·3; H, 8·8. $C_{17}H_{22}O$ requires C, 84·2; H, 9·15%).

*4-Benzyl-3-hydroxy-*2βH*-pinane* (IX).—Catalytic hydrogenation of 4-benzylidene-3-hydroxy-2β*H*-pinane (3·5 g) in methanol (60 ml) over 5% palladized carbon (1·0 g) during 15 h gave *4-benzyl-3-hydroxy-*2βH*-pinane* (3·0 g, 85%), b.p. 138° at 0·5 mmHg (Found: C, 83·3; H, 9·7. $C_{17}H_{24}O$ requires C, 83·55; H, 9·9%).

4-Benzylidenepin-2-ene (VI).—4-Benzylidene-3-hydroxy-2β*H*-pinane (4·0 g) was stirred with fused potassium

[15] R. A. Jones, 'An Introduction to Gas-Liquid Chromatography,' Academic Press, London, 1970, p. 93.

hydrogen sulphate (2·5 g) at 80° for 1 h. The mixture was cooled, water (50 ml) was added, and the aqueous solution was extracted with ether (3 × 30 ml). The combined extracts were washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to give *4-benzylidenepin-2-ene* (3·0 g, 80%), b.p. 126—129° at 0·5 mmHg (Found: C, 91·0; H, 9·2. $C_{17}H_{20}$ requires C, 91·0; H, 9·0%).

4-Benzyl-2βH-pin-3-ene (V).—This compound (Found: C, 89·8; H, 9·5. $C_{17}H_{22}$ requires C, 90·2; H, 9·8%) was isolated by preparative g.l.c. from the products of the reduction method 2 (see above) using a Perkin-Elmer F21 chromatograph with a 1 m × $\frac{3}{8}$ in column containing Silicone Fluid MS200 on Chromosorb A (10 : 90 w/w) and operated with a temperature programme of 3° min^{-1} over the temperature range 150—180°, and with nitrogen as carrier gas at an inlet pressure of 30 lb in^{-2}.

2βH-Pinan-4-one (I).—4-Benzylidene-3-hydroxy-2β*H*-pinane (7 g) was converted by the standard procedure with acetic anhydride (42 ml) and pyridine (50 ml) into its *acetoxy-derivative* (6·5 g, 80%), b.p. 140° at 0·8 mm (Found: C, 80·3; H, 8·3. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

The acetate (3 g) in methanol (220 ml) and ethyl acetate (100 ml) was ozonized at −70° until a faint blue colour persisted. Nitrogen was then passed through the solution for 10 min and acetic acid (60 ml) was added. The solution was warmed to 30° and zinc dust (70 g) was added at such a rate that the temperature did not exceed 35°. The mixture was filtered and the filtrate was concentrated under reduced pressure to *ca.* 75 ml. Water (100 ml) was added and the aqueous solution was extracted with ether (4 × 50 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 25 ml.) and water (2 × 25 ml), dried ($MgSO_4$), and evaporated to give *3-acetoxy-2βH-pinan-4-one* (2·0 g, 90%), b.p. 76—78° at 0·2 mmHg (Found: C, 68·5; H, 8·7. $C_{12}H_{18}O_3$ requires C, 68·5; H, 8·6%).

Reductive cleavage of the acetoxy-compound (1 g) with activated zinc dust (80 g) in acetic acid (60 ml) [8] gave 2β*H*-pinan-4-one (0·5 g, 69%), b.p. 90—91° at 7 mmHg (Found: C, 79·0; H, 10·5. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%).

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