Tetrahedron. Vol. 25, pp. 3801 to 3805. Pergamon Press 1969. Printed in Great Britain

THE PREPARATION AND STEREOCHEMISTRY OF THE VERBANOLS AND VERBANONES

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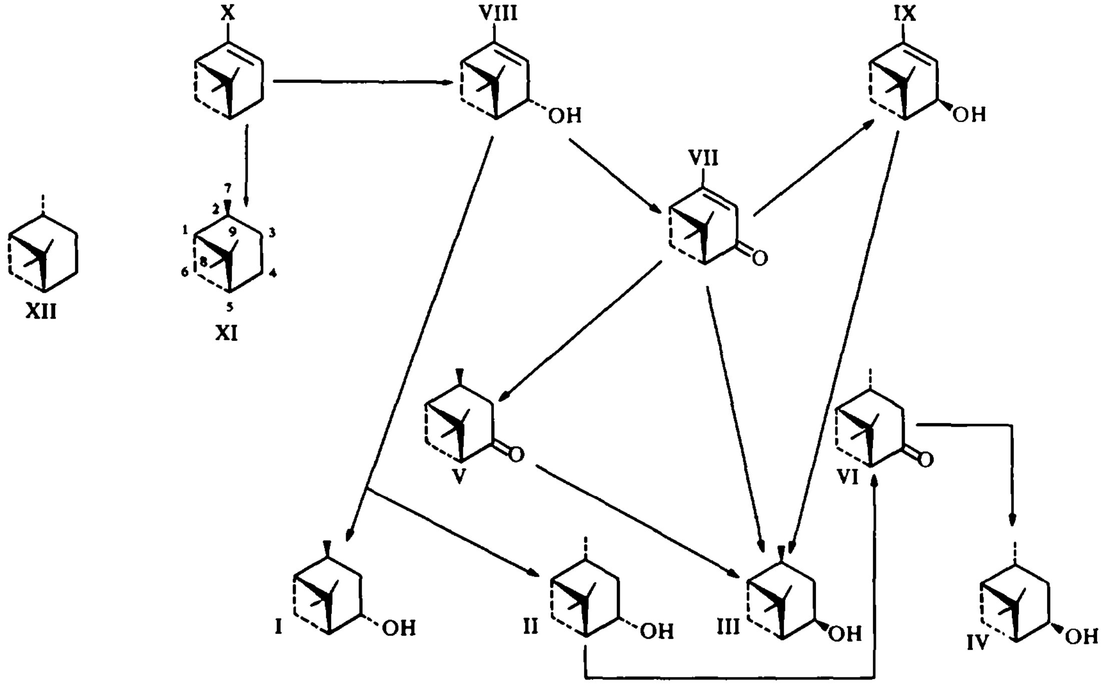
(*Received in the UK* 28 *February* 1969; *Accepted for publication* 10 *April* 1969)

Abstract—The four verbanols and the two verbanones have been prepared and their stereochemistry characterized for the first time. It is shown that the literature dealing with these compounds contains several errors in identification.

THE literature dealing with compounds of the pinane group is extensive but the stereochemistry of the four pinan-4-ols (verbanols), and the two pinan-4-ones (verbanones) has not been fully investigated. Much of the previous work on these compounds was done without the aid of modern instrumental methods of analysis and this has led to serious errors in identification. Only two of the four verbanols and one of the two verbanones have been prepared previously and what was thought to be a third verbanol isomer was in fact one of the two already known. This paper describes the preparation of all four verbanols and both verbanones but first briefly reviews the previous work on the subject.

Blumann and Zeitschel[1] reduced verbenone (VII) with sodium and moist ether and produced a white crystalline verbanol but they did not attempt to assign the stereochemistry of this compound. Bose[2] in a review of the work on the verbanols and verbanones cited the fact that the reduction of various monocyclic αβ unsaturated ketones with sodium and ethanol gives predominantly the most thermodynamically stable isomer and related this to the reduction of verbenone (VII) stating that Blumann and Zeitschel's compound must be verbanol (II) with the C-7 Me group and the OH group *trans* to the bridgehead Me groups. This conclusion did not take into account the fact that verbenone (VII) is bicyclic and the β side of the molecule, that is the side bearing the two geminal Me groups, is severely hindered. Since reduction of bicyclic ketones generally occurs from the less hindered side of the molecule, the major product of the reduction of verbenone (VII) with sodium and ethanol or moist ether should be neo-isoverbanol (III) and not verbanol (II). This is confirmed by the present work.

Wienhaus and Schumm[3] reduced verbenone (VII) in the presence of Pd-C but did not attempt to elucidate the stereochemistry of the verbanone produced. The product of the Wolff-Kishner reduction of this verbanone was a pinane whose physical characteristics were recorded. Bose[2] states that these physical constants are similar to those recorded for *trans*-pinane (XII) and therefore Wienhaus and Schumm's verbanone must be the *trans*-isomer (VI). The purities of the comparison compounds were unknown and it is doubtful that the compounds were pure enough for an



examination of their refractive indices and densities to be of assistance to the assignment of their structures.

Cocker *et al*[4] hydrogenated α-pinene (X) using a variety of catalysts and solvents at different pressures and temperatures and showed that the major product is always *cis*-pinane (XI). The reason for this is similar to that advanced above for the reduction of verbenone (VII) with sodium and ethanol. α-pinene (X) and verbenone (VII) approached the surface of the catalyst from the less hindered side of the molecule and the resulting reduction product should therefore have the C-7 Me group *cis* to the bridgehead Me groups. The present work shows that the surface catalysed reduction product of verbenone (VII) is *cis*-verbanone (V).

The work of Blumann and Zeitschel on the reduction of verbenone has been repeated and shown to give a mixture of isomers which could not be separated by recrystallization. The m.p. of this mixture was identical to that recorded by Blumann and Zeitschel for their "verbanol". The composition of the mixture was shown by gas chromatography to be neo-isoverbanol (III) 65%, isoverbanol (I) 20% and verbanol (II) 15%. The gas chromatographic relative retentions of the isomers present in the mixture were too close to permit separation by preparative gas chromatography and the sodium and ethanol reduction of verbenone was not used as a source of pure neo-isoverbanol (III).

Catalytic hydrogenation of verbenone (VII) yielded exclusively *cis*-verbanone (V). Platinum oxide and Pd-C in neutral and acid solution all gave *cis*-verbanone, further catalytic reduction of which gave neo-isoverbanol (III) exclusively. The *cis* orientation of the OH group relative to the bridgehead Me groups in neo-isoverbanol was confirmed when the same isomer was produced by the hydrogenation of *cis*-verbenol (IX). The neo-isoverbanol (III) was identical to the major component produced by the reduction of verbenone (VII) with sodium and ethanol.

Isoverbanol (I) was prepared by the hydrogenation of *trans*-verbenol (VIII) with platinum oxide catalyst in cyclohexane solution. The white crystalline isoverbanol was recrystallized to a constant m.p. of 75° but by gas chromatography it was found to contain only 90% isoverbanol. The pure compound when isolated had a m.p. of 87°. The m.p. of 75° of the impure isoverbanol is similar to that recorded in the literature.[2, 5, 6]

As above, the hydrogenation of *trans*-verbenol (VIII) with platinum oxide catalyst in cyclohexane gave chiefly isoverbanol (I), but when 5% Pd-C in ethanol was used a mixture of isoverbanol (I) 55% and verbanol (II) 45% resulted. The verbanol was separated by preparative gas chromatography. The explanation for the formation of verbanol (II) under the reaction conditions described may be that the *trans* orientation of the OH group in *trans*-verbenol (VIII) makes the α side of the molecule sterically nearly equal to the hindered β side. The use of 5% Pd-C, which is less catalytically active than platinum oxide, allows the β side of the molecule to approach the catalyst with the subsequent formation of verbanol (II). An additional interesting possibility is that in using ethanol as solvent the OH group in *trans*-verbenol may form H-bonds with the ethanol resulting in greater steric hindrance to the α side of the molecule again allowing the formation of verbanol. This theory was tested by substituting cyclohexane for ethanol in a further hydrogenation of *trans*-verbenol with 5% Pd-C. The ratio of isoverbanol (I) to verbanol (II) was 67 :33 which lends some support to the theory.

A sample of the mixture of isoverbanol (I) and verbanol (II) was oxidized with sodium dichromate in acetic acid to a mixture of *cis*-verbanone (V) 55% and *trans*-verbanone (VI) 45%. The *trans*-verbanone was isolated by preparative gas chromatography.

Some of the pure *trans*-verbanone (VI) was reduced with sodium dihydro bis-(2-methoxyethoxy) aluminate* to neo-verbanol (IV). The reduction of the ketone again occurred from the α side of the molecule to produce the hydroxyl group *cis* to the bridgehead Me groups.

The four isomeric verbanols and both verbanones had now been prepared and their conformations determined by NMR spectroscopy which agree with the chemical evidence for their structures. The orientations of the OH group in all four verbanols were known by their relation to the corresponding verbenols. Neo-isoverbanol (III) was prepared from *cis*-verbenol (IX). Hydrogenation of *trans*-verbenol (VIII) produced isoverbanol (I) and verbanol (II). The OH group in the remaining isomer, neo-verbanol (IV) must therefore be *cis* to the bridgehead Me groups. This isomer resulted from the reduction of *trans*-verbanone (VI) and taking into consideration that reduction in the pinane system occurs preferentially from the α side of the molecule the expected orientation of the OH group in neo-verbanol (IV) produced would be *cis*. The four verbanols can be related to the two verbanones and the structure

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* Sodium dihydro bis-(2-methoxyethoxy) aluminate is a new reducing agent supplied by CHEMAPOL Foreign Trade Corporation of Czechoslovakia. It has reducing properties similar to LAH but has much less affinity for water and is therefore easier to use.

of each of these was determined from a comparison of their NMR spectra with those of *cis*- and *trans*-pinane[4] and *cis*- and *trans*-pinan-3-one.[9] The resonances for the C-7 and C-9 Me groups in *cis*-verbanone are at a lower magnetic field than the corresponding resonances for *trans*-verbanone owing to the proximity of the Me groups and the van der Waal forces[10] in the *cis* isomer.

From this information the orientation of the C-7 Me group in each of the four verbanols was determined.

The original α-pinene that was used to produce the *trans*-verbenol for this work was not optically pure. The m.p. of each isomer was recorded but this is not necessarily the same as the m.p. of the optically pure isomer. Sufficient quantities of the pure isomers were not available to measure their optical rotations accurately.

EXPERIMENTAL

Analytical gas chromatography and relative retentions expressed as Kovats Indices[7] (K.I.) were measured on a W. G. Pye Panchromatograph using 16 ft by $\frac{1}{8}$ inch internal diam columns packed with 20% Carbowax 20M on 60–80 mesh acid washed celite at 140°.

Preparative gas chromatography was performed on a F & M 775 chromatograph using 20 ft by $\frac{3}{4}$ inch internal diam columns packed with 20% Carbowax 20M on 30–60 mesh Chromosorb P at 140°.

IR spectra were recorded on a Unicam S.P.200 spectrophotometer calibrated with indene. The spectra of the verbanols were recorded as solns in CS_2 from 650 cm^{-1} to 1300 cm^{-1} and in CCl_4 from 1300 cm^{-1} to 5000 cm^{-1}. The spectra of the verbanones were recorded as neat liquids.

NMR spectra were recorded as 20% solns in CCl_4 on a Perkin Elmer R10 spectrophotometer. Chemical shifts are expressed in delta units.

Trans-*Verbenol* (VIII). α-Pinene was oxidized by air blowing through at 80° for 36 hr.[8] The hydroperoxides formed were reduced with alkaline Na_2SO_3 and the resulting mixture was fractionally distilled to produce pure *trans*-verbenol, K.I. 1712.

Verbenone (VII). *trans*-Verbenol (500 g) was oxidized with sodium dichromate (400 g) in AcOH (2 ltrs). The product was washed, dried and distilled to produce pure verbenone (435 g), K.I. 1752.

cis-*Verbanone* (V). Verbenone (48 g) was hydrogenated at 22° in the presence of PtO_2 (0·12 g) in cyclohexane (50 ml) at atm press. When the intake of H_2 had slowed considerably the soln was filtered and the cyclohexane removed under vacuum. The composition of the resulting oil (47 g) was *cis*-verbanone 87% and neo-isoverbanol 13%. The *cis*-verbanone was purified by preparative gas chromatography, K.I. 1693, NMR C-7 Me 1·18 (doub. $J = 7$ Hz), C-8 Me 1·35, C-9 Me 0·99; IR 748, 791, 846, 868, 889, 917, 931, 945, 953, 984, 1009, 1031, 1043, 1104, 1147, 1167, 1185, 1201, 1235, 1249, 1283, 1305, 1333, 1346, 1372, 1378, 1386, 1413, 1705 cm^{-1}.

Neo-isoverbanol (III). Verbenone was hydrogenated under the same conditions described for *cis*-verbanone. This time the reaction was allowed to continue until no further H_2 was taken in. The oil was filtered and the cyclohexane removed under vacuum. The white crystalline product was pure neo-isoverbanol, K.I. 1752, m.p. 69·5°, NMR C-7 Me 1·07 (d, $J = 7$ Hz) C-8 Me 1·22, C-9 Me 1·16, C–4 H 4·22 (m); IR 799, 854, 901, 913, 931, 942, 983, 1003, 1025, 1108, 1131, 1168, 1188, 1251, 1289, 1318, 1334, 1360, 1367, 1375, 1386 cm^{-1}.

cis-*Verbenol* (IX). To verbenone (10 g) in refluxing benzene (50 ml) were slowly added 20 ml of a 70% soln of sodium dihydro bis-(2-methoxyethoxy) aluminate* in benzene. After 1 hr the excess reagent was destroyed by adding an excess of 15% HCl aq. The benzene layer was washed, dried and distilled. After removal of the benzene a fraction (6·5 g) with the composition *cis*-verbenol 82% and *trans*-verbenol 18% was obtained.

A portion (1 g) of this fraction was hydrogenated with $Pt\text{-}O_2$ (0·015 g) as catalyst in cyclohexane (5 ml). When the reduction was complete the soln was filtered and the cyclohexane removed under vacuum leaving a white crystalline solid with the composition neo-isoverbanol 81% and isoverbanol 19%.

Isoverbanol (I). *trans*-Verbenol (10 g) was hydrogenated in the presence of PtO_2 (0·2 g) in cyclohexane (20 ml). On completion of the reduction the soln was filtered and the cyclohexane removed under vacuum. The white crystalline product had the composition isoverbanol 91% and verbanol 9%. Pure isoverbanol was

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* See footnote p. 5.

obtained by preparative gas chromatography, K.I. 1775, m.p. 87°, NMR C-7 Me 1·01 (d, $J = 7$ Hz), C-8 Me 1·22, C-9 Me 0·97, C-4 H 4·18 (m); IR 763, 810, 853, 883, 918, 935, 951, 984, 1000, 1036, 1047, 1087, 1111, 1131, 1152, 1173; 1211, 1257, 1297, 1345, 1358, 1368, 1377, 1387 cm^{-1}.

Verbanol (II). *trans*-Verbenol (10 g) was hydrogenated in the presence of 5% Pd-C (0·35 g) in EtOH (20 ml)' On completion of the reduction the soln was filtered and the EtOH removed under vacuum. The white crystalline product had the composition isoverbanol 55% and verbanol 45%. Pure verbanol was isolated by preparative gas chromatography, K.I. 1759, m.p. 62·5°; NMR C-7 Me 0·94 (d, $J = 7$ Hz), C-8 Me 1·22, C-9 Me 0·78, C-4 H 4·00 (m); IR 778, 822, 877, 889, 922, 938, 990, 1019, 1055, 1085, 1126, 1142, 1170, 1213, 1226, 1258, 1299, 1327, 1368, 1374, 1385 cm^{-1}.

trans-*Verbanone* (VI). *trans*-Verbenol (50 g) was hydrogenated under the conditions described above for the preparation of verbanol. Without separation the mixture of isoverbanol 55% and verbanol 45% (39 g) was oxidized with sodium dichromate (40 g) in AcOH (200 ml). When the reaction was complete water (200 ml) was added and the oil layer separated. This was washed, dried and distilled to give a mixture (39 g) of *cis*-verbanone 55% and *trans*-verbanone 45%. Pure *trans*-verbanone was isolated by preparative gas chromatography, K.I. 1667; NMR C-7 Me 1·06 (d, $J = 7$ Hz), C-8 Me 1·34, C-9 Me 0·82; IR 755, 808, 882, 892, 907, 923, 948, 993, 1005, 1043, 1076, 1096, 1125, 1163, 1201, 1231, 1250, 1268, 1282, 1299, 1326, 1345, 1372, 1377, 1388, 1413, 1707 cm^{-1}.

Neoverbanol (IV). To *trans*-verbanone (5 g) in refluxing benzene (25 ml) were slowly added 10 ml of a 70% soln of sodium dihydro bis-(2-methoxyethoxy) aluminate in benzene. After 1 hr the excess reagent was destroyed with an excess of 15% HClaq. The benzene layer was washed, dried and distilled. After removal of the benzene a fraction (4 g) with the composition neo-verbanol 94% and verbanol 6% was obtained. Pure neoverbanol was isolated by preparative gas chromatography, K.I. 1734, m.p. 40·5°, NMR C-7 Me 0·88 (d, $J = 7$ Hz), C-8 Me 1·20, C-9 Me 1·05, C-4 H 4·15 (m); IR 770, 811, 845, 871, 891, 930, 943, 950, 987, 1002, 1013, 1045, 1057, 1087, 1111, 1167, 1207, 1261, 1291, 1303, 1328, 1347, 1360, 1371, 1390 cm^{-1}.

Reduction of verbenone. Na (50 g) was added in portions to a stirred soln of verbenone (30 g) in EtOH (500 ml). After 2 hr excess water was added and the solid filtered off. Three recrystallizations from pet ether (40–60) grade gave a white solid, m.p. 58° with the composition neo-isoverbanol 65%, isoverbanol 20% and verbanol 15%.

REFERENCES

[1] A. Blumann and O. Zeitschel, *Ber. Dtsch. Chem. Ges.* **46**, 1191 (1913).

[2] A. K. Bose, *J. Org. Chem.* **20**, 1010 (1955).

[3] H. Wienhaus and P. Schumm, *Liebigs. Ann.* **20**, 429 (1924).

[4] W. Cocker, P. V. R. Shannon and P. A. Staniland, *J. Chem. Soc.* (C), 41 (1966).

[5] D. V. Banthorpe and D. Whittaker, *Chem. Revs.* 651 (1966).

[6] S. S. Poddubnaya, V. G. Cherkaev and T. A. Rudolfi, *Chem. Abstr.* **62**, 11855h (1965).

[7] L. S. Ettre, *Anal. Chem.* **36**, 8 31A (1964).

[8] Brit. Pat. 761,686.

[9] P. Teisseire, A. Galfre, M. Plattier and B. Corbier, *Recherches* No. 15, 64 (1966).

[10] N. Nakagawa and S. Saito, *Tetrahedron Letters* 11, 1003 (1967).