TERPENOIDS-LXXX

SYNTHESIS OF ISOBICYCLOEKASANTALIC ACID AND RELATED PRODUCTS*

P. RANI BAI, B. B. GHATGE and S. C. BHATTACHARYYA National Chemical Laboratory, Poona, India

(Received 27 September 1965)

Abstract—The crystalline lactone obtained by hydration of tricyclo and/or bicycloekasantalic acid is shown to be a mixture of two components. LAH reduction of the lactone gave a mixture of two crystalline diols which were separated by crystallization and reconverted to the corresponding lactones by oxidation with alkaline potassium permagnanate. These diols on dehydration followed by oxidation gave isobicycloekasantalic acids, (+), (-), and (\pm) forms of which have been synthesized from the respective comphenes by following a three stage reaction sequence.

IN AN earlier communication¹ dealing with transformations in the santalene-longifolene series, the lactone (I) was discussed. It was shown that Semmler's bicycloekasantalic acid is a mixture of true bicycloekasantalic acid (III) and isobicycloekasantalic acid (IV), the latter being formed via methyl migration. A synthesis of the isobicyclo acid (IV) from the lactone (I) was also described. However, it has been mentioned that the lactone (I), the alcohol (VI) and the isobicyclo-acid (IV) show low optical rotations. This could be either due to the low inherent optical activity of these compounds or due to their extensive racemization-epimerization during formation. This prompted an investigation into the homogenity of the lactone (I) which, is a beautifully crystalline solid, showing a sharp m.p. at 103°. Elaborate chromatography of the lactone on alumina failed to give any higher melting material. Products obtained from the various fractions showed the same m.ps as mentioned before. On the other hand, GLC analysis of the lactone on a polyester column gave indication of the presence of two compounds, one of which appeared as a shoulder. TLC also gave two closely overlapping spots suggesting the presence of at least two compounds which we were unable to separate. The lactone mixture was therefore reduced with LAH to give the crystalline diol² (V, m.p. 83–103°) with low optical rotation ($\sim +5^{\circ}$). This on repeated crystallization from benzene gave two pure (GLC/TLC) constant melting diols-A and -B. The diol-A, m.p. 133°, showed good optical rotation (+29°). The diol-B melted at 110° and had a low optical rotation $(+3^\circ)$. Another diol, m.p. 76° of negligible optical rotation (-1.17°) was also obtained in small quantities in the mother liquors. Diol-A on oxidation with alkaline potassium permanganate and further processing gave via the hydroxy acid, the corresponding lactone, m.p. 121-122° and rotation +43°. The diol-B on similar treatment gave a lactone, m.p. 104-105°, and rotation $+3^{\circ}$. It is thus clear that the lactone initially obtained by hydration of

Communication No. 835 from the National Chemical Laboratory, Poona-8.

¹ P. Rani Bai, S. Y. Kamat, B. B. Ghatge, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* 21, 629 (1965).

³ Suryakumari Ramaswamy, S. K. Ramaswamy and S. C. Bhattacharyya, J. Org. Chem. 27, 2791 (1962).

bicycloekasantalic acid and/or tricycloekasantalic acid is a mixture of at least two lactones, one of which has low optical rotation and the other having much higher rotation.

Dehydration with acetic anhydride of diol-A gave homogeneous (GLC/TLC) isobicycloekasantalol (VI) with high levorotation (-120°). However, similar dehydration of diol-B afforded homogeneous (GLC/TLC) isobicycloekasantalol with a low optical rotation (-6°). If the two diols-A and -B are epimers at the C₅ asymmetric



carbon atom, then with the destruction of this active centre by dehydration, both the diols should afford the same isobicycloekasantalol (VI) with comparable optical rotations. This, however, was found not to be the case. Furthermore, oxidation of the highly levorotatory isobicycloekasantalol (VI) mentioned above to the corresponding crystalline, strongly levorotatory acid (IV), lactonization of this acid, reduction of the resulting lactone and dehydration of the diol thus obtained afforded only the inactive form of the alcohol and not the highly levorotatory form. Hydration of tricycloekasantalic acid by sulphuric acid to the lactone seems also to affect the other asymmetric centres. The hydration reaction thus appears to be a deep seated one.

The strongly levorotatory (-120°) , isobicycloekasantalol (VI) on oxidation with chromic acid gave a crystalline strongly levorotatory (-112°) , isobicycloekasantalic acid (IV), m.p. 98°. This optically active form of the acid can be synthesized from levorotatory (-68°) camphene. Camphene (VIIb) was converted by the Prins reaction to the active (-95°) 8-camphenyl carbinol (VIII). Conversion of the alcohol to the

optically active (-55°) bromide (IX) by PBr₃-pyridine, followed by cynation and hydrolysis afforded the active form of the acid (IV), m.p. 96–98°, $(\alpha)_D - 68^{\circ}$. Similar series of reactions carried out with (+) camphene (+86.6°) gave (+) isobicycloekasantalic acid (+87°), m.p. 98–102°. In a similar manner, synthesis of the nearly (±) form of the acid was also carried out using camphene of low optical rotation (+18°).

Since the stereochemistry of (+) and (-) camphene is known,³ the corresponding acids (IV) derived from these will be necessarily represented by the stereoformulae Xa and Xb. At present we do not have enough information regarding the complete steric structure of the lactone (I) and diol (V). But, since the diol-A, m.p. 133°, and the lactone derived from it by oxidation can be converted to the crystalline acid (Xb) the partial stereoformulae for these two should be XI and XII.

The lactone prepared by Bhati,⁴ m.p. 103–104°, has a specific optical rotation of -5.6° , and has been assigned the stereoformula XIII. Synthesis of optically pure lactones via pure (+) or (-) camphenilone is now receiving attention.

EXPERIMENTAL

M.ps and b.ps are uncorrected. Rotations were taken in CHCl₂ solution. IR spectra were determined on a Perkin-Elmer Infracord spectrophotometer by H. Gopinath and K. G. Deshpande. Microanalyses were carried out by Pansare and colleagues and GCl by Bapat and Sankpal.

Prins reaction on camphene. A mixture of camphene, m.p. 49° , $(\alpha)_D + 18.9^{\circ}$ (22 g), glacial acetic acid (150 ml) and paraformaldehyde (4.8 g) were refluxed in an oil bath for 16 hr. The reaction mixture was cooled, diluted with water, and extracted with ether. The ether extracts were washed with 5% Na₂CO₃aq, water, dried and the solvent removed. The resulting ester (25 g) was hydrolysed by refluxing with alcoholic KOH (250 ml; 0.6N) for 2 hr. The reaction mixture was poured into water, extracted with ether, washed with water, dried and the solvent removed. the resulting alcohol (20 g) was chromatographed on neutral alumina grade II (600 g) and eluted with pet. ether, pet. etherbenzene, benzene and ether. The ether fraction (8.8 g) was distilled to obtain the pure (GLC/TLC) alcohol, b.p. 110–140° (bath)/10 mm., α_D (neat), 21.5°; n_B^{ss} 1.5010. (Found: C, 79.03; H, 10.64. C₁₁H₁₈O requires: C, 79.46; H, 10.92%.) Typical IR bands at: 3400, 1031 (--CH₃OH); 840, 820 (>C=-CH-) cm⁻¹.

Conversion of the alcohol to the bromide (IX). To a mixture of the alcohol (8.05 g), dry pyridine (10 ml) and dry pet. ether (40-60°, 100 ml) in a 3-necked flask cooled in ice was added dropwise during the course of 45 min, a mixture of freshly distilled PBr₃ (8 ml) in dry pet. ether (50 ml). The stirring was continued for 1 hr at ice bath temp and then for 2 hr at the room temp and allowed to stand overnight. The reaction mixture was refluxed on a water bath for $2\frac{1}{2}$ hr, cooled, mixed with water, extracted with ether, washed with 5% Na₂CO₃, aq followed by 2% HCl, water, dried and the solvent removed. The residue was distilled to obtain the bromide, b.p. 117-124° (bath)/2.5 mm, (α)_p +14.12° (c, 5.66), n_{D}^{33} , 1.5231. (Found: Br, 33.44; C₁₁H₁₇Br requires: Br, 34.86%.)

Conversion of the bromide to the acid (IV). To a solution of the bromide (1.5 g) in alcohol (18 ml) was added an aqueous solution of KCN (2.4 g in 4 ml water) and the mixture refluxed for 15 hr. To this mixture was added 20% alcoholic KOH (10 ml) and the refluxing continued for 10 hr. The reaction mixture was poured into water, extracted repeatedly with ether. The alkaline aqueous portion was filtered and acidified in the cold. The resulting free acid was extracted with ether, washed with water till neutral, dried and the solvent removed to yield the acid (0.3 g) which was crystallized from pet. ether, m.p. 104° , (α)_p + 15.32° (c. 2.90). (Found: C, 74.64; H, 9.51. C₁₂H₁₈O₃ requires: C, 74.19; H, 9.34%.) Typical IR bands at 816 (>C=CH=); doublet at 1399, 1377 (>C< CH_3) cm⁻¹.

Prins reaction on (+) camphene and its subsequent conversion to (+) isobicycloekasantalic acid. Prins reaction was carried out as in the previous case. (+) Camphene, $(\alpha)_D + 86^\circ$ (9.97 g) gave 5 g of Prins alcohol, having the same b.p. as reported earlier, and $(\alpha)_D + 103^\circ$ (c, 4.96). It showed correct

⁸ G. Ourisson, Bull. Soc. Chim. Fr. 895 (1955).

⁴ A. Bhati, J. Org. Chem. 27, 2135 (1962).

elemental analysis. It was converted into the bromide (α)_D + 79.7° (c, 3.7) in the same fashion. Cynation of this bromide and its subsequent hydrolysis gave (+) isobicycloekasantalic acid, (α)_D + 87° (c, 2.13), m.p. 98.5° to 102°. (Found: C, 74.10; H, 8.89. C₁₈H₁₈O₂ requires: C, 74.19; H, 9.34%.)

Prins reaction on (-) camphene and its subsequent conversion to (-) isobicycloekasantalic acid. (-) Camphene, $(\alpha)_D - 68^\circ (9.7 \text{ g})$ was subjected in exactly the same manner to Prins reaction to yield the Prins alcohol, $(\alpha)_D - 95^\circ (c, 2.26)$. It showed correct elemental analysis. Conversion of this alcohol gave the bromide having $(\alpha)_D - 55^\circ (c, 0.49)$. Cynation of the bromide and subsequent hydrolysis yielded (-) isobicycloekasantalic acid, $(\alpha)_D - 68^\circ (c, 1.00)$, m.p. 96-98°. (Found: C, 73.10; H, 8.65. C₁₃H₁₈O₈ requires: C, 74.19; H, 9.34%.) Though the sample was slightly impure, because of paucity of material further purification was not attempted.

Conversion of tricycloekasantalic acid to the lactone (I). It was carried out according to the procedure described earlier.^{3,5}

Conversion of the lactone (I) to the diols-A and -B. The lactone, m.p. 103° , $(\alpha)_{\rm D} + 7^{\circ}$ (13 g), dissolved in dry ether (200 ml) was added dropwise to a stirred slurry of LAH (4.09 g) in dry ether (200 ml) in a 3-necked flask cooled in ice. The reaction mixture was stirred for 1 hr at 0° and refluxed for 5 hr. The excess of LAH was decomposed by careful addition of moist ether followed by water. The reaction mixture was filtered, the filtrate washed with water, dried and the solvent removed. The crude diol (12 g), m.p. 80–92°, $(\alpha)_{\rm D} + 4.2^{\circ}$ was repeatedly (6 times) crystallized from benzene to yield diol-A (2 g), m.p. 133°, $(\alpha)_{\rm D} + 29^{\circ}$ (c, 2.27). (Found: C, 72.46; H, 10.66. C₁₃H₃₃O₃ requires: C, 72.68; H, 11.18%.) Typical IR bands at: 3400, 1114, 1071, 1039 (-OH); doublet at: 1372 and 1354 (>C< CH₃/CH₃)cm⁻¹. The mother liquors of these crystallizations afforded the constant melting diol-B, m.p. 110°, $(\alpha)_{\rm D} + 3^{\circ}$ (c, 3.3). (Found: C, 73.03; H, 10.85. C₁₃H₃₂O₃ requires: C, 72.68; H, 11.18%.) It gave the same typical IR bands. Once again, the mother liquors of these crystallizations yielded in small amounts a diol of m.p. 76°, $(\alpha)_{\rm D} - 1.17^{\circ}$.

Dehydration of the diol-A to the unsaturated ester. A mixture of the diol-A (0.96 g), anhydrous sodium acetate (1·1 g) and acetic anhydride (6 ml), were refluxed in an oil bath for 5 hr. The reaction mixture was cooled, and the excess of acetic anhydride was decomposed by adding water and warming on a water bath (15 min). It was cooled, mixed with water, extracted with ether, and the ether extracts washed with water, 5% Na_aCO_aaq, water, dried and the solvent removed. The ester (1·1 g) was chromatographed on neutral alumina grade II (25 g) and eluted with pet. ether (40-60°), and finally ether. The pet. ether fraction was distilled to yield the pure (GLC/TLC) unsaturated ester, b.p. 100-110° (bath)/0·4 mm, (α)_D -130° (c, 2·5). (Found: C, 75·91; H, 9·99. C₁₄H₃₃O₃ requires: C, 75·63; H, 9·97%.) Typical IR peaks at 1730, 1235 (acetate), doublet at 1383, 1361 (>C< CH₃/CH₃); 829, 848,

891 (>C==CH--) cm⁻¹.

Saponification of the unsaturated ester to isobicycloekasantalol (VI). A mixture of the ester (0.8 g) and alcoholic KOH (10 ml; 2N) was refluxed for $3\frac{1}{2}$ hr. The reaction mixture was cooled, diluted with water, extracted with ether, the ether extracts washed with water, dried and the solvent removed. The product (0.6 g) obtained was distilled to yield the pure (GLC/TLC) unsaturated alcohol, b.p. 110-120° (bath)/2.5 mm, (α)_D -120° (c, 2.06). (Found: C, 79.14; H, 11.04. C₁₃H₂₀O requires: C, 79.56; H, 11.20%.) Typical IR bands at : 3450, 1053 (-CH₂OH); doublet at 1387, 1364 (>C< $\frac{CH_8}{CH_4}$); 1678, 848, 825 (>C=CH-) cm⁻¹.

Oxidation of isobicycloekasantalol to isobicycloeka santalic acid (IV). To the alcohol (0.4 g) dissolved in acetone (15 ml), Jones reagent⁶ (1 ml; 8N chromic acid in H₈SO₄) was gradually added with ice-cooling and occasional shaking during 3 min. After keeping in the ice bath for further 5 min, the product was decomposed with MeOH (2 ml) in the usual way, and extracted with ether, washed thoroughly with 5% Na₂CO₃aq, and then separated into neutral and acidic portions. The former on spectral evidence was found to consist of aldehyde and alcohol. The acidic portion (0.156 g) was crystallized from pet. ether (40-60°) to yield the acid, m.p. 98°, (α)_D -112° (c, 0.79). (Found: C, 74.84; H, 9.71. C₁₃H₁₈O₂ requires: C, 74.19; H, 9.34%.) Characteristic IR peaks at 816 (>C=CH=); doublet at 1395, 1374 (>C<CH₈/CH₈) cm⁻¹.

^b F. W. Semmler and K. Bode, Ber. Dtsch. Chem. Ges. 40, 1124 (1907).

K. Bowden, J. M. Heilborn, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc. 39 (1946).

Permanganate oxidation of the diol A (V) to the lactone (XII). The diol (0.4 g) in water (40 ml) containing KOH (0.10 g) was oxidized by gradual addition of powdered KMnO₄ (1.2 g) during 4 hr under stirring and at water bath temp. The reaction mixture was filtered and the filtrate was extracted with ether to remove neutral material if any. The alkaline aqueous layer was acidified in the cold, extracted with ether, and the ether extracts washed with KOHaq, water, dried and the solvent removed to yield the lactone (0.28 g). This was crystallized from pet. ether (60–80°), m.p. 121–122°, (α)_D +43° (c, 2.84). (Found: C, 74.46; H, 9.55. C₁₉H₁₈O₈ requires: C, 74.19; H, 9.35%.) Typical IR bands at: 1770 (γ -lactone); doublet at 1378, 1390 ($>C< CH_8 \ CH_8$) cm⁻¹.