SYNTHESIS AND CRYSTAL STRUCTURE OF 29,30-DIBROMOALLOBETULIN

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The bromination of betulin with bromine was descibed. The reaction in chloroform proceeded smoothly to form 29,30-dibromoallobetulin in 80% yield.

Key words: betulin, allobetulin, bromination, XSA, NMR spectroscopy.

Stereospecific synthetic transformations of the available lupane-type triterpene betulin (**1**) are of interest for the preparation of pharmacologically valuable compounds. Derivatives of 20(29)-lupene that contain oxygenated C-28 atoms are known to isomerize when treated with acidic agents into oleanane-type compounds [1]. We found that bromination of **1** with bromine in $CHCl_3$ proceeded smoothly to give 29,30-dibromoallobetulin (**2**).

The product yield was highest for bromination in light at room temperature for 2 h using equimolar amounts of reagents. The yield of **2** reached 80%. Using 1.5 equivalents of brominating agent lowered the yield and formed side products. Performing the reaction in the dark also lowered the yield of **2** to 6%. The structure of **2** was established using spectral data and was confirmed by an x-ray structure analysis (XSA) (Fig. 1). The PMR spectrum contained five singlets for methyls (δ 0.74, 0.82, 0.91, 0.95, and 0.96 ppm), two AB-X systems for CH_2 groups (δ 3.34-3.64 ppm, J = 10.7; 3.57-3.69 ppm, J = 10.0 Hz), and two doublets for C-28 methylene protons (δ 3.46 and 3.81 ppm, J = 8.1 Hz). The H-19 proton was a broad singlet at 3.96 ppm (J_{hw} = 2.5 Hz). The H-3 proton gave a doublet of doublets centered at 3.18 ppm (J = 11.5 and 4.9 Hz).

All six-membered rings in crystalline **2** are *trans*-fused and adopt the chair conformation. The ring with the oxygen bridge is a slightly distorted chair. The C17C28O1C19 torsion angle is 3.5(2)°. The geometry of **2** was not analyzed because of large mean-square uncertainties in the bond lengths and angles. However, bond lengths averaged over the two independent molecules are close to those in allobetulone [2] and 2β-bromo-19β,28-epoxy-18α-oleanan-3-one [3].

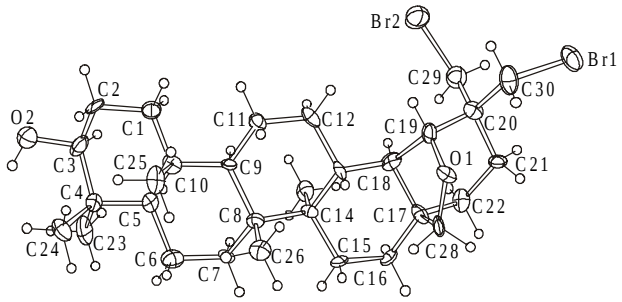

Fig. 1. The crystal structure of **2**.

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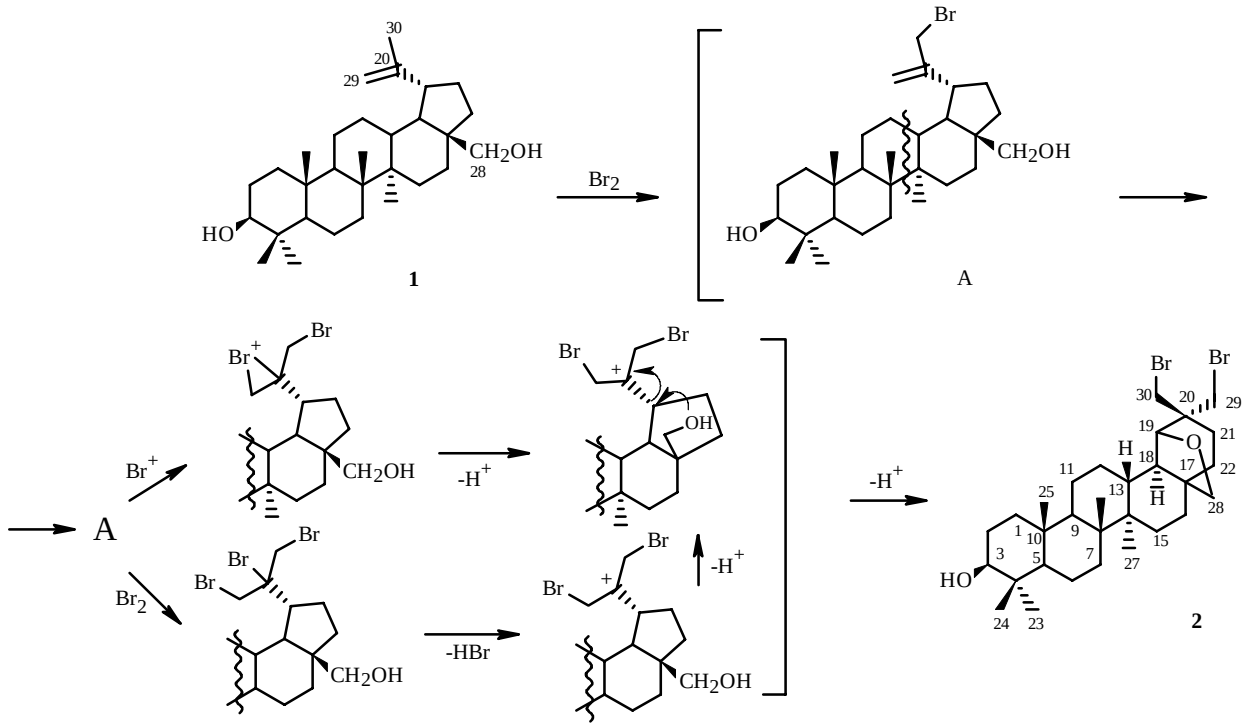
Thus, bromination of betulin with bromine in $CHCl_3$ induces "betulin-allobetulone" rearrangement [4]. It can be assumed that the reaction included a sequence of electrophilic addition steps of bromine to the isopropenyl group of the lupane skeleton and dehydrohalogenation with conversion into the product of allylic bromination A. Because the only reaction product is an oleanane-type dibromo derivative, it can be assumed that the product of allylic bromination A is converted further by attack of a bromonium ion on the isopropyl group to form a three-member bromonium ion that decomposes with loss of the C-29 proton. By another pathway, the isopropyl group of the C-30 allylic bromination product either gives the C-20 cation or undergoes simultaneous opening of the ring and addition-loss of bromine to form **2**.



We note that allylic bromination also occurs using NBS in DMSO and the acetate of betulonic acid methyl ester [5] and lupenylacetate [6]. In both instances, products of allobetulonic rearrangement were isolated as reaction products together with the 30-bromo derivatives of betulin.

Thus, bromination of betulin with bromine in $CHCl_3$ is a convenient method for preparing 29,30-dibromoallobetulin.

EXPERIMENTAL

Solvents were purified by standard methods. The course of the reaction was monitored by TLC on Silufol UV-254 plates (eluent $CHCl_3$:C_6H_6:$C_2H_5O_2CCH_3$, 4:8:1). IR spectra were recorded on a Vector-22 instrument for samples in KBr disks. PMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 instrument [working frequency 500.13 MHz (^1H) and 125.76 MHz (^{13}C)] in $CDCl_3$ solutions. Signals in NMR spectra were assigned using ^1H—^1H (COSY) and ^1H—^{13}C (COSY, COLOC) two-dimensional correlation experiments.

The XSA was performed on a Bruker P4 diffractometer (Mo Kα-radiation, graphite monochromator, 2θ/θ-scanning at 2θ < 50°). A crystal of the acetone solvate of **2** of dimensions 0.98 × 0.12 × 0.05 mm was grown by successive crystallization from acetone:hexane. The crystals were monoclinic, a = 7.486(2), b = 29.895(6), c = 14.042(3) Å, β = 100.72(1)°, V = 3087.7(11) Å^3, space group $P2_1$, Z = 4. The occupancy of atoms in the structure led to the composition $2C_{30}H_{48}O_2Br_2 + C_3H_6O$, d_{calc} = 1.354 g/cm^3, μ = 2.653 mm^{-1}. Intensities of 5534 independent reflections were measured. Absorption corrections were not applied. The structure was solved by direct methods using the SHELXS-97 program. Structure factors were refined by full-matrix anisotropic least-squares methods using the SHELXL-97 program. Parameters of H atoms were calculated in each refinement cycle using coordinates of the associated C atoms. The acetone solvate was disordered over several positions. The final refinement over all F^2 gave wR_2 = 0.2038 and S = 1.038 with 613 parameters refined (R = 0.08630 for 2643

F > 4σ). The rather high R factor is explained most likely by the highly disordered acetone. The absolute configuration of **2** was determined from the Flack parameter x = 0.009 (0.024). The molecules of **2** in the crystal form a complicated three-dimensional supramolecular motif through two O–H...O H-bonds [H(2C)...O(2′) 2.18(5) Å, O(2)...O(2′) 2.91(2) Å; O(2)–H(2C)...O(2′) 149(4)° and H(2′C)...O(1) 2.14(5) Å, O(2′)...O(1) 2.96(2) Å; O(2′)–H(2′C)...O(1) 173(4)°] and an intermolecular Br...H contact (3.02 Å) that is slightly shortened compared with the sum of the van der Waal radii (3.15 Å).

29,30-Dibromoallobetulin (2). A solution of betulin (1.0 g, 2.26 mmol) in $CHCl_3$ (50 mL) was treated dropwise with cooling (10-15°C) with a solution of bromine (0.1 mL, 2.26 mmol) in $CHCl_3$ (5 mL), stirred for 2 h at room temperature (TLC monitoring), treated with water (25 mL), and stirred vigorously. The organic phase was removed. The aqueous phase was extracted with ether (3 × 35 mL). The combined extracts were washed successively with saturated solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. The solvent was removed. The resulting yellow oily compound (1.55 g) was ground with aqueous ethanol (1:1 ethanol:water volume ratio). The resulting solid was chromatographed over an Al_2O_3 column (hexane eluent). Recrystallization from acetone and then hexane afforded **2** (1.1 g, 80%) as white needle-like crystals, R_f 0.76, mp 281-282°C, $C_{30}H_{47}O_2Br_2$. IR spectrum (ν, cm^{-1}): 3390, 1374, 1360, 1250, 1035, 879, 679. PMR spectrum (δ, ppm, J/Hz): 0.69 (1H, dt, J = 10.4, 2.6, H-5), 0.74 (3H, s, H_3-26), 0.82 (3H, s, H_3-24), 0.91 (3H, s, H_3-27), 0.95 (3H, s, H_3-23), 0.96 (3H, s, H_3-25), 0.9-1.7 (m, 23H, H_2-1, H_2-2, H_2-6, H_2-7, H-9, H_2-11, H_2-12, H-13, H_2-15, H_2-16, H-18, H_2-21, H_2-22), 3.18 (1H, dd, J = 11.5, 4.9, H-3), 3.34 (1H, dd, J = 10.6, 1.7, H-29), 3.46 (1H, d, J = 8.1, H-28), 3.57 (1H, dd, J = 10.0, 1.7, H-30), 3.64 (1H, d, J = 10.7, H-29), 3.69 (1H, d, J = 10.0, H-30), 3.81 (1H, dd, J = 8.1, 1.3, H-28), 3.96 (1H, br.s, $w_{1/2}$ = 2.5, H-19), 7.15 (1H, br.s, OH).

^{13}C NMR spectrum (δ, ppm): 13.4 (C-27), 15.3 (C-26), 15.6 (C-25), 16.4 (C-24), 18.1 (C-6), 20.8 (C-11), 25.6 (C-2), 26.1 (C-12), 26.7 (C-15), 27.2 (C-21), 27.8 (C-23), 28.0 (C-16), 33.8 (C-7), 34.3 (C-13), 37.1** (C-20), 37.0** (C-10), 36.0 (C-22), 38.7 (C-1), 40.5* (C-4), 40.7* (C-8), 41.4 (C-14), 41.6 (C-29), 41.6 (C-30), 43.6 (C-17), 47.2 (C-18), 50.8 (C-9), 55.3 (C-5), 71.6 (C-28), 77.8 (C-3), 82.7 (C-19). *An alternate assignment is possible.

The XSA data were deposited in the Cambridge Crystallographic Data Centre (CCDC 297414).

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