

## SYNTHESIS OF ANAGADIOL\*

K. WAISSER, J. URBAN and A. VYSTRČIL

Department of Organic Chemistry,  
Charles University, 128 40 Prague 2

Received June 10th, 1974

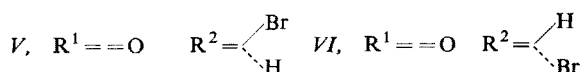
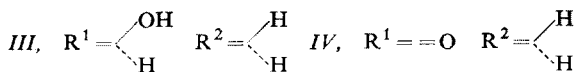
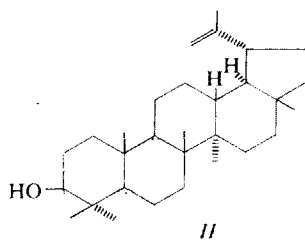
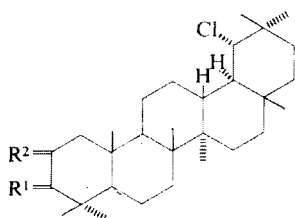
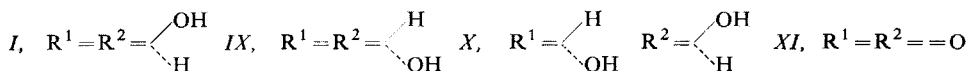
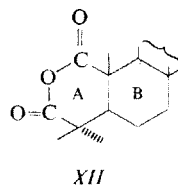
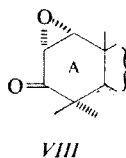
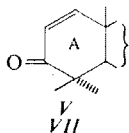
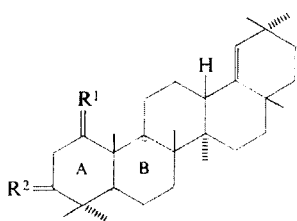
A synthesis of anagadiol (*I*) from lupeol (*II*) was worked out, representing a confirmation of the structure of anagadiol (*I*) proposed by González.

Anagadiol (*I*) was found<sup>1</sup> in *Salvia Broussonetii* BENTH. and its structure was proposed in the same paper. As we observed that the optical rotation value of one of the degradation products did not agree with the expected value calculated from the molecular rotation difference we decided to synthesize anagadiol from lupeol (*II*). Lupeol (*II*) was recently obtained by total synthesis by Stork and coworkers<sup>2</sup>, and therefore the synthesis of anagadiol (*I*) from lupeol (*II*) may also be considered a total synthesis. The procedure worked out by us may be divided into three parts: *a*) preparation of 1,8-oleanadien-3-one (*VII*), *i.e.* the formation of the 18-oleanene skeleton, *b*) the preparation of 1,3-diols isomeric with anagadiol, *c*) the conversion of the hydroxyl groups in the positions 1 and 3 to 1 $\beta$ , 3 $\beta$ , *i.e.* the configuration corresponding to anagadiol (*I*).

Under the effect of hydrogen chloride lupeol (*II*) undergoes relatively easily the Wagner–Meerwein rearrangement under formation of 19 $\alpha$ -chloro-18 $\alpha$ -oleanan-3 $\beta$ -ol<sup>3</sup> (*III*) which is then further oxidized with chromium trioxide in dimethylformamide. The product *IV* obtained displayed in its IR spectrum characteristic absorption at 1705 cm<sup>-1</sup> due to a carbonyl group. We reacted compound *IV* with an equivalent amount of bromine. According to an analogy<sup>4</sup> the formation of a mixture of two bromo derivatives, *V* and *VI*, could be expected. This mixture was submitted without further separation to dehydrohalogenation by heating with lithium chloride in dimethylformamide. We supposed that the reaction would lead not only to dehydrobromination under formation of a double bond in the position 1,2 (as may be expected from analogous reactions<sup>4,5</sup>), but also to the splitting off of hydrogen chloride under formation of the 18, 19 double bond. The mentioned supposition was confirmed, *i.e.* the product *VII* contained in its infrared spectrum an absorption maximum at 1670 cm<sup>-1</sup> due to the stretching vibration of the carbonyl group

\* Part XL in the series Triterpenes; Part XXXIX: This Journal 39, 3741 (1974).

conjugated with a double bond. The absorption maximum at  $830\text{ cm}^{-1}$  was assigned to the out-of-plane bending vibration of the isolated hydrogen atom on the double bond. The absorption in the  $885\text{--}895\text{ cm}^{-1}$  region, characteristic of the out-of-plane vibrations of the double bond hydrogen atoms of the isopropenyl group was not evident in the infrared spectrum. In the PMR spectrum the signals of 3 protons bound to double bonds were clearly visible. We assigned the broad singlet at 4.88 p.p.m. to the proton bound in the position 19, the doublet at 7.16 p.p.m. ( $J_{1,2} = 10\text{ Mz}$ ) to the proton in the position 1, and the doublet at 5.81 p.p.m. to the proton in the position 2. Hence, we assigned the product the structure of 1,18-oleanadien-3-one (VII). Ketone VII was further transformed to an epoxide under the effect of hydrogen peroxide in alkaline medium. According to analogies<sup>5,6</sup> we expected the formation of 1 $\alpha$ ,2 $\alpha$ -epoxy-18-oleanen-3-one (VIII). In the infrared spectrum of the product we assigned the absorption maximum at  $1703\text{ cm}^{-1}$  to the  $\nu(\text{C}=\text{O})$  vibration, and the maximum at  $875\text{ cm}^{-1}$  to the skeletal vibration of the epoxide cycle. Keto epoxide VIII was reduced with lithium aluminum hydride. Two diols IX and X were isolated



from the reaction mixture which was chromatographed on a thin layer. The first of them, with lower adsorptivity, displayed in the infrared region absorption at  $3637\text{ cm}^{-1}$  and  $3525\text{ cm}^{-1}$ , indicating the presence of an intramolecular hydrogen bond, and we therefore assigned it the structure of 18-oleanen-1 $\alpha$ ,3 $\alpha$ -diol (*IX*). However, as their preparative separation on alumina or silica gel columns was rather difficult, and not indispensable for further work, we omitted it in further, repeated, experiments.

The conversion of the hydroxyl groups to the configuration 1 $\beta$ ,3 $\beta$  was carried out in the conventional manner<sup>7,8</sup>. A mixture of diols *IX* and *X* was oxidized with Jones reagent to dione *XI*. However, the oxidation should be carried out carefully because an excess of the reagent led to the formation of anhydride *XII*. 18-Oleanene-1,3-dione (*XI*) when reduced with sodium in 1-propanol gave the thermodynamically most stable 1 $\beta$ ,3 $\beta$ -diol *I* as the main product. In this product both hydroxyl groups are equatorial. Reduction of 1,3-diones with sodium in 1-propanol was already described for other series of pentacyclic triterpenes<sup>7,8</sup>. The physical constants of the 18-oleanen-1 $\beta$ ,3 $\beta$ -diol (*I*) obtained were in agreement with those described for anagadiol<sup>1</sup> (*I*) isolated from natural material. Hence, it may be stated that González and coworkers<sup>1</sup> determined the structure of anagadiol correctly, but that the optical rotation value of 1,8-oleanadien-3-one (*VII*) prepared on degradation of the natural product is incorrect.

## EXPERIMENTAL

The melting points were measured on a Kofler block and they are uncorrected. Optical rotations were measured in chloroform with a  $\pm 2^\circ$  accuracy on a polarimeter ETL-NPL, Bendix-Ericsson, with objective indication. For the identification of the substances infrared spectra were measured in 5–8% chloroform solutions on a UR-20 spectrophotometer. For the infrared study of hydrogen bonds the spectra were measured on a Unicam SP 700 instrument at  $25^\circ\text{C}$  in tetrachloromethane (conc.  $1-4 \cdot 10^{-3}\text{M}$ ). The UV spectra were measured with a Unicam SP 700 apparatus in cyclohexane. The PMR spectra were taken with a Varian HA 100 (100 MHz) apparatus in deuteriochloroform with tetramethylsilane as internal reference. The chemical shift values are given in  $\delta$ -scale in p.p.m. Samples for analysis were dried at  $100^\circ\text{C}$  and 0.1 Torr pressure over phosphorus pentoxide for 16–24 hours. For chromatography and filtration neutral alumina (Reanal) of activity II according to Brockmann was used. For thin layer chromatography Kieselguhr G with gypsum according to Stahl was employed. The substances were detected under the UV light after spraying with a morine solution in methanol (0.02%). For the washing of ethereal extracts 5% hydrochloric acid, 5% sodium carbonate, and 5% sodium hydrogen carbonate were used.

### 19 $\alpha$ -Chloro-18 $\alpha$ -oleanen-3-one (*IV*)

Chromium trioxide (6 g) and 2 ml of conc. sulfuric acid were added in small portions at room temperature to a solution of 2.85 g of 19 $\alpha$ -chloro-18 $\alpha$ -oleanan-3 $\beta$ -ol<sup>3</sup> (*III*) in 400 ml of dimethylformamide. The mixture was allowed to stand for 24 hours, then poured into water, extracted with ether and the extract washed and filtered through a small layer of alumina. The filtrate was evaporated and the residue crystallized twice from chloroform-methanol. Yield 2.04 g of product *IV*, m.p.  $216-218^\circ\text{C}$ ,  $[\alpha]_{\text{D}} -7^\circ$  (*c* 0.60). For  $\text{C}_{30}\text{H}_{49}\text{ClO}$  (461.2) calculated: 78.12% C, 10.71% H, 7.69% Cl; found: 78.45% C, 10.55% H, 7.93% Cl. IR spectrum:  $1705\text{ cm}^{-1}$  (C=O).

1,18-Oleanadien-3-one (*VII*)

A solution of 0.8 g of bromine in 4 ml of acetic acid was added to a solution of 2 g of chloroketone *IV* in 27 ml of chloroform and 27 ml of acetic acid over 15 minutes under stirring. The mixture was stirred for 15 minutes, then allowed to stand for one hour, and poured into a 5% sodium carbonate solution, extracted with ether, and the extract washed with sodium carbonate, water and filtered through a small layer of alumina. The solvents were distilled off and the residue crystallized from chloroform-methanol. Yield 1.12 g of product, m.p. 221–227°C,  $[\alpha]_D -37^\circ$  (*c* 0.67). We believe on the basis of an analogy<sup>4</sup> that it is a mixture of bromo ketones *V* and *VI*. The crude mixture of bromo ketones (1.12 g) was refluxed with 2 g anhydrous lithium chloride in 50 ml of dimethylformamide for 7 hours, then diluted with water and extracted with ether. The ethereal extract was washed with water, filtered through a small layer of alumina and the filtrate evaporated. The residue was chromatographed on 100 g of alumina. Benzene (350 ml) eluted the less polar impurities and a further 200 ml of benzene eluted ketone *VII*. After repeated crystallization from chloroform-methanol the yield was 870 mg of ketone *VII*, m.p. 130–132°C,  $[\alpha]_D +53^\circ$  (*c* 0.60). For  $C_{30}H_{46}O$  (422.7) calculated: 85.24% C, 10.97% H; found: 85.56% C, 11.03% H. IR spectrum  $1670\text{ cm}^{-1}$  (C=O),  $830\text{ cm}^{-1}$  (CH=). PMR spectrum: 0.76 s (CH<sub>3</sub>); 0.95 s (2 · CH<sub>3</sub>); 1.16 s (CH<sub>3</sub>); 4.88 s (C<sub>(19)</sub>-H); 5.81 d (C<sub>(2)</sub>-H); 7.16 d (C<sub>(1)</sub>-),  $J_{1,2} \approx 10\text{ Hz}$ . UV spectrum: 224 nm ( $\epsilon$  11 110).

1 $\alpha$ ,2 $\alpha$ -Epoxy-18-oleanen-3-one (*VIII*)

Solutions of sodium hydroxide in ethanol 10% (10 ml) and 30% hydrogen peroxide (25 ml) were added dropwise simultaneously over 20 minutes to a stirred and water cooled solution of 520 mg of ketone *VII* in 65 ml of dioxan and 15 ml of ethanol. The mixture was stirred for 8 hours, allowed to stand for 12 hours at room temperature, diluted with water and extracted with ether. The ethereal layer was washed with dilute hydrochloric acid, water, and filtered over a small layer of alumina. The residue after evaporation of the solvents was crystallized twice from chloroform-methanol. Yield 410 mg of product *VIII*, m.p. 180–183°C,  $[\alpha]_D +86^\circ$  (*c* 0.69). For  $C_{30}H_{46}O_2$  (438.7) calculated: 82.13% C, 10.57% H; found: 82.47% C, 10.93% H. IR spectrum:  $1703\text{ cm}^{-1}$  (C=O),  $875\text{ cm}^{-1}$  (epoxide).

18-Oleanene-1 $\alpha$ ,3 $\alpha$ -diol (*IX*) and 18-oleanene-1 $\alpha$ ,3 $\beta$ -diol (*X*)

An ethereal solution (75 ml) of ketone *VIII* (360 mg) and lithium aluminum hydride (250 g) was refluxed for 6 hours and the mixture was poured into 75 ml of ethyl acetate, washed with dilute hydrochloric acid, sodium hydrogen carbonate, and water, and filtered through a small layer of alumina. The filtrate was evaporated and the residue (350 mg) separated by thin-layer chromatography in benzene-ether 3 : 1. After crystallization (chloroform, light petroleum) of the less polar fraction 70 mg of diol *IX* were obtained, m.p. 200–203°C,  $[\alpha]_D +7^\circ$  (*c* 0.37). For  $C_{30}H_{50}O_2$  (442.7) calculated: 81.39% C, 11.38% H; found: 81.48% C, 10.93% H; IR spectrum:  $3637\text{ cm}^{-1}$  (OH) and  $3525\text{ cm}^{-1}$  (H...OH). The more polar fraction gave after crystallization 190 mg of diol *X*, m.p. 193–195°C (chloroform-light petroleum),  $[\alpha]_D +17^\circ$  (*c* 0.73). For  $C_{30}H_{50}O_2$  (442.7) calculated: 81.39% C, 11.38% H; found: 81.30% C, 11.17% H. IR spectrum (in CHCl<sub>3</sub>):  $993\text{ cm}^{-1}$ ,  $1037\text{ cm}^{-1}$ ,  $1055\text{ cm}^{-1}$ ,  $3633\text{ cm}^{-1}$ .

18-Oleanene-1,3-dione (*XI*)

Jones reagent (1.5 ml; 400 mg of CrO<sub>3</sub>) was added to 350 mg of a mixture of diols *IX* and *X* in 170 ml of acetone over 1 minute under stirring. After two additional minutes the mixture was

poured into 20 ml of a saturated aqueous oxalic acid solution, diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate and water and filtered through a small layer of alumina, and the filtrate evaporated. The residue was purified by thin layer chromatography in benzene-ether 5 : 1. After crystallization the yield was 150 mg of diketone XI, m.p. 110–112°C (chloroform-light petroleum)  $[\alpha]_D + 66^\circ$  (c 0.39). Literature<sup>1</sup> gives m.p. 112–114°C,  $[\alpha]_D + 61^\circ$ . IR spectrum: 1710  $\text{cm}^{-1}$ , 1730  $\text{cm}^{-1}$  (C=O).

#### 18-Oleanene-1 $\beta$ ,3 $\beta$ -diol (I)

Sodium (2.3 g) was added in small portions over 30 minutes to a boiling solution of dione XI (150 mg) in 45 ml of 1-propanol. The mixture was refluxed for 45 minutes, then poured into water and extracted with ether. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, filtered through a small layer of alumina and the filtrate evaporated. The residue was chromatographed on a thin-layer in benzene-ether 1 : 3. After crystallization from chloroform-light petroleum 50 mg of diol were obtained, m.p. 213–215°C,  $[\alpha]_D + 3^\circ$  (c 0.31). For  $\text{C}_{30}\text{H}_{50}\text{O}_2$  (442.7) calculated: 81.39% C, 11.38% H; found: 81.40% C, 11.20% H. Literature gives m.p. 212–214°C,  $[\alpha]_D + 5^\circ$ . IR spectrum (in chloroform): 996  $\text{cm}^{-1}$ , 1045  $\text{cm}^{-1}$ , 1246  $\text{cm}^{-1}$ , 3620  $\text{cm}^{-1}$ . PMR spectrum: 0.75 s (2 .  $\text{CH}_3$ ); 0.94 s (2 .  $\text{CH}_3$ ); 0.95 s (2 .  $\text{CH}_3$ ); 1.02 s ( $\text{CH}_3$ ); 1.10 s ( $\text{CH}_3$ ); 3.26 dd ( $\text{C}_{(1)}\text{—H}$  or  $\text{C}_{(3)}\text{—H}$ ),  $J_{\text{vic}} \approx 17$  Hz; 3.47 dd ( $\text{C}_{(3)}\text{—H}$  or  $\text{C}_{(1)}\text{—H}$ ),  $J_{\text{vic}} = 16$  Hz; 4.88 s ( $\text{C}_{(19)}\text{—H}$ ).

*We thank Dr J. Pecka and Dr S. Hilgard, Department of Organic Chemistry, Charles University, for the measurement of the infrared spectra. Our thanks are also due to Dr S. Hilgard for the measurement of the UV spectra. For analyses we thank the members of the Analytical Laboratory of the same Department and for the measurement of the PMR spectra Dr M. Buděšínský of the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague.*

#### REFERENCES

1. Gonzáles A. G., Bretón J. L., Fraga B. M.: *Chem. Commun.* 1971, 567.
2. Stork G., Ueyo S., Wakamatsu Z., Grieco P., Labovitz J.: *J. Am. Chem. Soc.* 93, 4945 (1971).
3. Halsall T. G., Jones E. H. R., Meakins G. D.: *J. Chem. Soc.* 1952, 2862.
4. Klinot J., Vystrčil A.: *This Journal* 31, 1079 (1966).
5. McGinnis E. L., Meakins G. D., Price J. E., Styles M. C.: *J. Chem. Soc.* 1965, 4379.
6. Waisser K., Vystrčil A.: *This Journal* 31, 3182 (1966).
7. Ganguly A. K., Govindachari T. R., Mohamed P. A., Rahimtulla A. D., Viswanathan N.: *Tetrahedron* 22, 1513 (1966).
8. Waisser K., Hilgard S., Zelenka A., Vystrčil A.: *This Journal* 38, 3521 (1973).

Translated by Ž. Procházka.