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THE ARNDT-EISTERT REACTION OF δ-OXO-(13-17)-PENTANORALABDAN-12, 19-DIOIC ACID-19-METHYL ESTER

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The keto acid (III) has been synthesized from podocarpic acid. Ozonolysis of methyl podocarpate and subsequent catalytic hydrogenation of resulting product provided the keto-acid (II). The Arndt-Eistert reaction was successfully used to extend the side chain by one carbon atom to obtain the keto acid (III).

Key words: Arndt-Eistert reaction, δ-oxo-(13-17) pentanorlabdan-12.

INTRODUCTION

The synthesis of various diterpenoids is of special importance because of their complex structures and pharmaceutical properties. Two of the diterpene intermediates, I and III are exceptionally important for the synthesis of a variety of diterpenes. While the keto acid, I, has been synthesized [1] and also obtained as a degradation product of neoabietic acid [2] or polyalthic acid [3] the isomeric keto acid III [4,5] was not yet readily available from a cheap natural source. The purpose of this investigation was to synthesize III from podocarpic acid, a readily available resin acid.

The goal was accomplished by the controlled ozonolysis of methyl podocarpate [6] to get a hydroperoxy lactone which on catalytic hydrogenation affords the keto acid II [6]. The Arndt-Eistert reaction was successfully used to extend the side chain by one carbon atom to get the desired keto acid (III).

EXPERIMENTAL

8β-Hydroperoxy-8α-hydroxy-(13-17)-pentanorlabd-9 (II)-en-12, 19-dioic acid 19 methyl ester 8α-12 lactone (IV). Methyl podocarpate, 450 mg, dissolved in 5 ml of methanol and 5 ml of methylene chloride was ozonized at -78° for 6 hr. The rate of flow of ozone through the solution was adjusted to 0.4 mg of ozons/minute. The flow rate provides the desired amount of ozone (2 moles, 10 % excess) in 6 hr. The amount of ozone passing through the solution in a given period of time was determined by passing the gas through a 2 % solution of potassium iodide and titating against standard sodium thiosulfate. The solution was transferred to a flask and solvent removed *in vacuo* (aspirator) at 35° to give the crude hydropenoxide (320 mg) as a white solid. The latter was dissolved in chloroform, washed with water, brine, filtered through anhydrous sodium sulfate and solvent was evaporated *in vacuo* to give 290 mg (62 %) of the hydroperoxide as a colourless solid. It was crystallized from 1:2 chloroform-hexane, m.p. 183°, ν_{max}. 3280 (OOH), 1758 (lactone), 1725 (COOMe), 1638 (C=C) and 870 cm^{-1} (O–O); δ 1.135 (s, 3H, C-20 methyl), 1.22 (s, 3H, C-18 methyl), 3.72 (s, 3H, C-19 $COOCH_3$), 5.79 (s, 1H vinylic) and 9.08 (s, 1H, OOH).

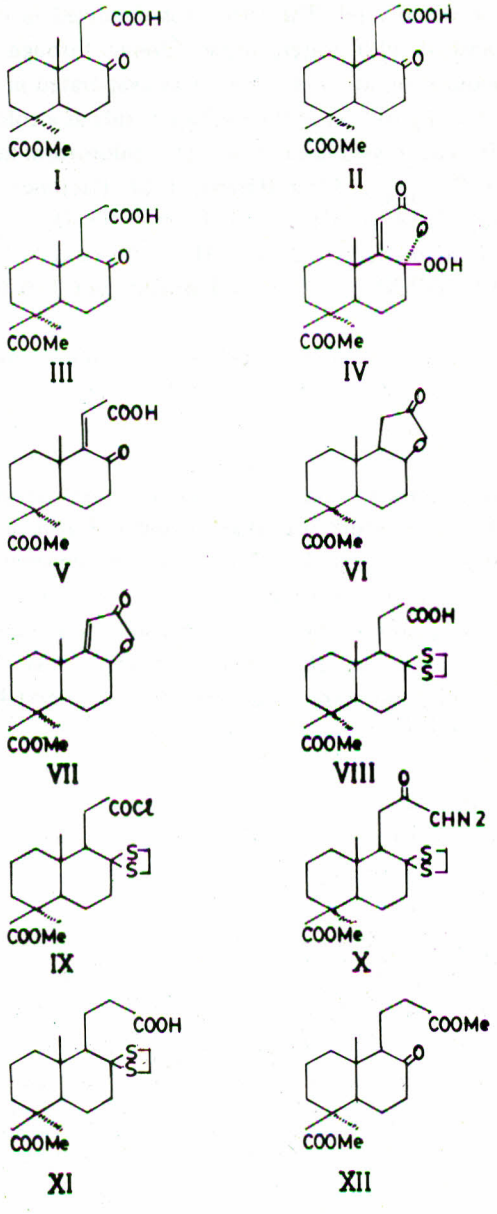
8-Oxo-(13-17)-pentanorlabdan-12, 19-dioic Acid-19-methyl ester. (II). The crude hydroperoxide, 510 mg, dissolved in 5 ml of 95 % ethanol was added to a pressure bottle containing a suspension of 50 mg of 5 % palladium-charcoal catalyst in 5 ml of 15 minutes prehydrogenated ethanol. The mixture was shaken under 3 atm, pressure of hydrogen overnight. The TLC of the mixture showed the presence of some unsaturated keto acids hence fresh catalyst was added and hydrogenation continued for another 12 hours. The reaction mixture was filtered through celite and evaporated under vaccum to give 420 mg of the keto acid, II, as a colourless solid.

Recrystallization from 1:2 ethyl acetate-hexane gave II as colourless needles, 402 mg (79 %), m.p. 170°; νmax 3500 and 1730 cm^{-1}; δ 0.57 (s, 3H C-20 methyl), 1.30 (s, 3H, C-18 methyl), 3.66 (s, 3H, C-19 ester) and 9.4 (s, 1H, COOH).

Conversion of the keto acid, II, to the lactone (VI). A solution of 296 mg of the keto acid II in 0.5 ml of benzene was added in portions to an ice cold, well-stirred solution of 0.25 ml of oxalyl chloride in 0.5 ml of benzene. The reaction mixture was stirred at room temperature for two hours. A TLC of the reaction mixture showed that the reactants formed one major product. The solvent was removed under vacuum to get a white crystalline solid

which was recrystallized from 1:3 ethyl acetate-hexane to give 230 mg (83 %) of the desired lactone, m.p. 115°; r.f. 0.45 (silica gel G; 25 % ethyl acetate-hexane); ν_{max} 1730 (COOMe) and 1800 cm^{-1} (lactone); δ 0.88 (s, 3H, C-20 methyl), 1.26 (s, 3H, C-18 methyl), 3.08 (s, 2H, C-11 protons) and 6.37 (s, 3H, ester).

8 α-hydroxy-(13-17)-pentanorlabd-9 (II)-en-12, 19-dioic acid 19-methyl ester 8 α-12-lactone (VII). The keto acid, II, (100 mg) was added in portions to a well stirred solution of 50 mg of thionyl chloride in 1 ml of hexane. The mixture was stirred at 0° for one hr and then at 50° for 8 hours. The solvent was removed under vacuum. A yellow residue was formed which on crystallization from 1:3 ethyl acetatehexane gave pure lactone V; 51 mg (55 %),



as a white crystalline solid, m.p. 144°; r.f. 0.19 (silica gel G; 1:3 ethyl acetatehexane); ν_{max} 1725 (ester), 1760 (lactone) and 1640 cm^{-1} (C=C); δ 0.99 (s, 3H, C-20 methyl), 1.22 (s, 3H, C-18 methyl), 3.66 (s, 1H, vinylic).

Conversion of the keto acid II to its thioketal (VIII). The keto acid, [11] (50 mg) was dissolved in 25 drops of ethanedithiol, cooled to 0°, and 12 drops of $BF_3.O(C_2H_5)_2$ was added to the solution, and was left at room temperature for ten hr. Aqueous methanol (1:4 methanol-water), 10 ml, was added to the solution and extracted with ethyl acetate (3 x 10 ml). The combined extracts were washed with brine (3 x 10 ml), filtered through anhydrous sodium sulfate and evaporated under vacuum at 40° to give the desired thioketal as a yellow-white solid. Recrystallization from 1:3 ethyl acetatehexane gave the pure thioketal, 58 mg (94 %), as a white crystalline solid, m.p. 230-32°; r.f. 0.5 (silica gel G, 25 % ethyl acetate-hexane);- ν_{max} 3500, 1715 and 1600 cm^{-1} δ 0.8 (s, 3H C-20 methyl), 1.16 (s, 3H, C-18 methyl), 3.40 (m, 4H, thioketal) and 3.70 (s, 3H, ester).

Conversion of thioketal X to acid chloride (IX). The well-dried thioketal 372 mg was taken in a three neck round bottom flask. Oxalyl chloride (1.0 gm) was added dropwise and with stirring. The solid immediately turned into an orange solution with evolution of gases. The mixture was stirred at room temperature for two hr. Dry nitrogen gas was passed through the solution for 10 minutes. The excess oxalyl chloride was removed under vacuum to give a thick red oil. The acid chloride thus obtained is unstable and decomposes-polymerises after a few hours. The product showed absorption in the infrared at 1730, 1780 cm^{-1}

Conversion of the acid chloride XI to diazoketone (X). A cold solution of 200 mg of acid chloride XI in 5 ml of absolute ether was added dropwise to an excess of an ice cold solution of diazomethane in absolute ether. Brisk evolution of HCl gas was observed. The reaction mixture was left at room temperature for four hr. The excess of ether was removed under vacuum. The crude diazoketone as a dark red oil was obtained. A TLC of the crude mixture showed the presence of a few minor impurities having higher r.fs than the diazoketone. The reaction mixture was chromatographed by a silica gel column. The impurities were washed with 5 % ethyl acetate-hexane, while the pure diazoketone remained in the column. Elution with ethyl acetate gave pure diazoketone, 90 mg (45 %), as a viscous oil, ν_{max} 2100, 1710 and 1620 cm^{-1}; δ 0.59 (s, 3H, C-20 methyl), 1.21 (s, 3H, C-18 methyl), 2.14 (s, diazoproton), 3.36 (m, 4H thioketal) and 3.62 (s, 3H, ester).

Conversion of the diazoketone to the keto acid (III). A solution of 396 mg of diazoketone, XII, in 1 ml of dioxane was added dropwise with stirring to a mixture of 0.2 gm of silver oxide, 0.1 gm of anhydrous sodium carbonate and 0.1 gm of sodium thiosulfate, in 5.0 ml of water at 60°. A brisk evolution of nitrogen was observed. Stirring was continued for one hr, after addition the temperature of the mixture was raised to 90°. The solution was cooled and the black silver residue was removed by filtration. The clear, almost colorless filtrate was acidified with dil. HNO_3 and the extracted with ethyl acetate (3 x 10 ml).

The combined extracts were washed with water, and brine, dried over sodium sulfate and solvent evaporated under vacuum to get a mixture of keto acid, III, and the thioketal XIV. Refluxing the mixture with 5 % methanolic KOH for 15 minutes, followed by acidification with dil. HCl gave the keto acid III, 195 mg (63 %); max 3500 and 1725 cm^{-1}.

Esterification of the keto acid III with diazomethane to give (XII). To an ice cold solution of 155 mg of keto acid III in 3 ml of ether, an excess of diazomethane in ether was added. Brisks evolution of nitrogen gas was observed. The solution was allowed to stand at 0° for one hr. Removal of solvent under vacuum gave the pure keto ester XV, 160 mg (99 %), ν_{max} 1705 and 1730 cm^{-1}; δ 0.56 (s, 3H C-20 methyl), 1.24 (s, 3H, C-18 methyl), 3.64 (S, 3H, ester) and 3.70 (s, 3H, ester).

RESULTS AND DISCUSSION

Commercial podocarpic acid was selected as the starting material for the synthesis of the keto acid III. Bell and Gravestock [6] reported a two-step synthesis of the keto acid II. This involved controlled ozonolysis of ring C of methyl podocarpate to afford hydro peroxy lactone IV which, on subsequent hydrogenation, on palladium at atmospheric pressure gave the keto acid II [6]. Since the rate of hydrogenolysis of the hydroperoxy bond is faster than the addition of hydrogen to the double bond, the unsaturated keto acid, IV can be obtained as the major product, if the hydrogenation is carried out for a short time or if a relatively inactive catalyst is used. For better yield the hydroperoxy lactone must be purified with 1:1 ethylacetate-hexane before hydrogenation. The crude product if hydrogenated, a mixture of saturated and unsaturated acids V is obtained, due to the poisoning of the catalyst which results in an incomplete hydrogenation.

The synthesis of III from II involves the elongation of the side chain by one carbon atom. The Arndt-Eistert reaction seems to be the best possible way to accomplish the desired goal, since the other methods involve many more steps and use drastic reducing conditions which might reduce other sensitive ester and keto groups present in the molecule.

The acid chloride used in the first step of the Arndt-Eistert reaction may be prepared by any of the usual methods. For mild conditions oxalyl chloride is used. A solution of the keto acid II, in benzene, on treatment with oxalyl chloride, however, did not gave the corresponding acid chloride. The reaction product was identified by spectral data to be the enol-lactone VI. The infrared spectrum of this lactone showed absorption at 1800 cm^{-1} for the lactone without any absorption in the vicinity of 1600 cm^{-1} for the double bond, as expected for a tetra substituted double bond. The n.m.r. spectrum of the lactone also does not show any olefinic proton.

The solution of the keto acid II in benzene on treatment with thionyl chloride affords the more stable lactone VII. Honce is evident that the keto group at C-8 is protected before the formation of the acid chloride. As a keto group can be best protected by forming an enol acetate, ketal or thioketal. Ketals are usually easier to hydrolyse the ketones than thioketals.

Acetic anhydride or isopropenyl acetate are commonly used for preparing enol acetates. Treatment of keto acid II with acetic anhydride and sodium acetate do not result in enol acetate formation but instead gave a mixture of lactones VI and VII.

The keto acid, II, on treatment with isopropenyl acetate in the absence of catalyst, gave no reaction. However, when the keto acid was heated under reflux with isopropenyl acetate and a trace of p-toluenesulfonic acid, the reaction completed in 10 minutes and the product identified as lactone VI.

Lactone VI, on standing at room temperature for some time, isomerises to a more stable conjugated form. The process is gradual and can be followed by TLC or infrared spectrum. The non-conjugated lactone, VI, r.f. 0.45 (silica gel G; ethyl acetate-hexane in 1:3 ratio); i.r. 1800 cm^{-1} begins to isomerize within 24 hr. to the conjugated form, r.f. 0.19; i.r. 1640, 1770 cm^{-1} and completes in 6 days and accelerate when refluxed in hexane or benzene.

Various attempts to prepare the ketal of the keto acid, II, using different catalysts like BF_3. $O(C_2H_5)_2$, *p*-toluenesulfonic acid etc., were unsuccessful. The reaction could do not occur even by refluxing for 7 days using a Dean Stark water separator. While the keto acid II did not react with ethylene glycol, it did so quite readily on treatment with ethane dithiol, using $BF_3.O(C_2H_5)_2$ as the catalyst. The reaction was complete in a moderate span of

time and yields of thioketal (VIII) were excellent.

After protecting the keto group, attempts were made to prepare the corresponding acid chloride. A solution of the thioketal in henzene, on treatment with freshly distilled thionyl chloride, resulted in the complete polymerization of the reaction mixture. A solution of the thioketal in benzene did not react with oxalyl chloride, even after refluxing the solution for considerable period of time.

Since the products of the reaction include CO and CO_2 gases, therefore, it is expected that the rate of the forward reaction should increase by increasing the concentration of the starting materials. The rate of reaction should therefore increase if use of solvent is avoided and this was found to be the case. Addition of oxalyl chloride to thioketal resulted in formation of acid chloride (IX), in 20 minutes. The acid chloride, a pale yellow oil, is an unstable compound and tends to polymerize on keeping overnight. The acid chloride thus obtained is reasonably pure and satisfactory for further treatment. Purification by vacuum distillation is not advisable since it is substantial of decomposed and polymerized.

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazoketones [7]. The preparation of the diazoketone from acid chloride is easily carried out by addition of diazomethane; a relatively simple procedure. The purification of the diazoketone can be best accomplished by passing the crude reaction mixture through a column of silica gel and removing the impurities by washing with a 5 % solution of ethyl acetate-hexane. The diazoketone being highly polar stays near the origin in this relatively non-polar system. After removing the impurities, elution of the column with ethyl acetate affords the diazoketone. Attempts to crystallize the diazoketone from various solvents were not successful.

The diazoketone (X) shows characteristic infrared and n.m.r. spectra. A very strong absorption at 2100 cm^{-1} (diazo group), even stronger than the carbonyl absorption, is observed in the infrared. The n.m.r. spectrum shows an absorption at δ=2.14 p.p.m. due to the CHN_2 functionality.

The Wolff rearrangement of the diazoketone can be accomplished by the use of various reaction conditions likes heating in benzyl alcohol, silver oxide or silver benzoate have been reported. Wilds and Meader [8] have reported that in many cases better yields of the rearranged products are obtained if benzyl alcohol is used instead of silver oxide. Newman and Beal [9] have reported a "modified Arndt-Eistert" reaction, by using silver benzoate [9] in triethylamine for the Wolff rearrangement.

The diazoketone (X), on treatment with benzyl alcohol at 180° for 30 minutes, gave the corresponding benzyl ester. The removal of benzyl alcohol from the product was relatively difficult. Vacuum distillation of the alcohol is not satisfactory. Column chromatography (silica gel, ethyl acetate-hexane) of the reaction mixture gives better results. The first few fractions contain benzyl alcohol while the latter fractions contain the benzyl ester along with some other impurities. The process was thus not very satisfactory in our case.

Not having much success with benzyl alcohol, we decided to use silver oxide as a catalyst. A solution of the diazoketone in dioxane was added dropwise with stirring to a mixture of silver oxide, anhydrous sodium carbonate and sodium thiosulfate dissolved in water at 60° with brisk evolution of nitrogen. The reaction completed in one hour. A T.L.C. of the product showed two major spots which were identified as the keto acid III and the thioketal (XI) by spectral evidence. The thioketal, on treatment with a dilute aqueous solution of sodium hydroxide and subsequent acidification, gave the corresponding keto acid (III).

The treatment of keto acid III with diazomethane gives the corresponding ester XII. While satisfactory yields of keto acid III were obtained, we wanted to explore whether the use of Newman and Beal's modified Arndt-Eistert method (silver benzoate in triethylamine) would improve the yields. The reaction was not successful, in our case and no significant improvement in the yield was observed.

REFERENCES

1. A Ogiso and S.W. Pelletier, Chem. Commun., **2**, 94 (1967).
2. E. Wenkert, R.W.J. Carrey and C. Kaneko, J. Amer. Chem. Soc., **83**, 4440 (1961).
3. K.W. Gopinath, T.R. Govindachari, P.C. Parthasarathy and N. Viswanathan, Helv. Chim. Acta., **44**, 1040 (1961).
4. W.G. Dauben and V.F. German, Tetrahedron, **22**, 679 (1966).
5. G. Hauser, R. Lombard and G. Ourisson, Tetrahedron, **12**, 205 (1961).
6. R.A. Bell and M.B. Gravestock, Can. J. Chem., **48**, 1105 (1970).
7. For a review, W.E. Bachmann and W.S. Struve, Org. Reactions **1**, 38 (1942).
8. A.L. Wilds and A. L. Meader, J. Org. Chem., **13**, 763 (1948).
9. M.S. Newman and P.S. Beal, J. Amer. Chem. Soc., **71**, 1506 (1949).