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CoTPP-CATALYZED REACTION OF SATURATED BICYCLIC ENDOPEROXIDES[1]

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Summary: Saturated bicyclic endoperoxides were exposed to CoTPP (Cobalt-meso-tetraphenylporphyrine) in chloroform, the peroxide bond was cleaved and a mixture of products arising from fragmentation and reduction obtained.

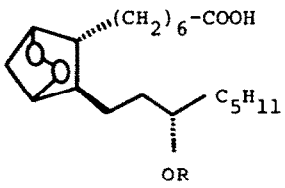
Unsaturated bicyclic endoperoxides have become increasingly significant in a variety of chemical[2] and biochemical transformations.[3]

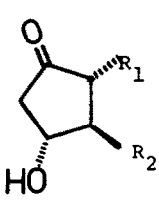
One of the common reactions of unsaturated [n.2.2] bicyclic endoperoxides is the cleavage of the oxygen-oxygen bond followed by addition of the oxygen radicals to the adjacent double bond to give bisepoxides with syn-configuration.[2]

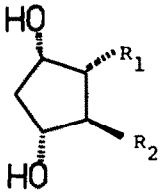
However, in strained molecules and in systems containing the perturbed diene moiety, thermolysis is always accompanied by side reactions. One of these side reactions is the formation of epoxy-ketones.[2] Recently, we have applied cobalt-meso-tetraphenylporphyrine (CoTPP)-catalyzed rearrangement[4] to the unsaturated bicyclic endoperoxides which give epoxy-ketones as major products upon thermolysis. The application of CoTPP suppressed the side reactions completely and increased the yield for the formation of bisepoxides up to 100 %.[5] In the case of the 6,7-dioxabicyclo [3.2.2]nona-2,8-diene we have also established the decomposition mechanism.[6]

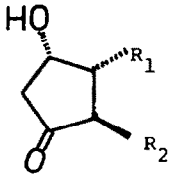
The chemistry of the unsaturated bicyclic endoperoxides has been studied in detail. However, it appears that the chemistry of saturated bicyclic endoperoxides has been confined to their thermolysis, photolysis and catalytic reduction. Recently, Bloodworth et al.[7] submitted saturated bicyclic endoperoxides to flash vacuum pyrolysis and isolated keto-aldehydes, epoxy-aldehydes, cycloalkane-1,4-diones and dialdehydes as fragmentation products. Reaction mechanism was interpreted in terms of oxygen radicals. An extensive study of the catalytic decomposition of saturated bicyclic endoperoxides has been done with Pd(0)[8] and Ru(II).[9] Similar decomposition products have been observed.

As a logical extension of our work, we have studied CoTPP-catalyzed reaction of the saturated bicyclic endoperoxides.









3 4 5

1 R: H

2 R: OH

R_1: $-CH_2-CH=CH-(CH_2)_3-COOH$

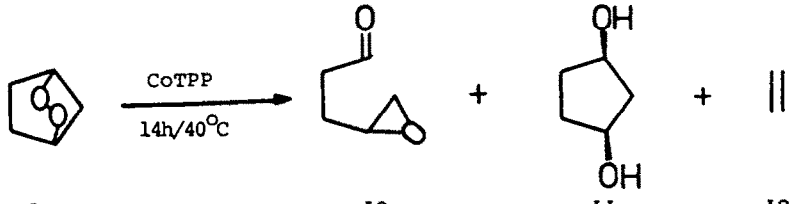
R_2: $-CH=CH-CH(OH)-C_5H_{11}$

Prostaglandin endoperoxides (1) and (2) are the immediate biological precursors of prostaglandins such as prostaglandin E_2 (3), prostaglandin $F_{2\alpha}$ (4) and prostaglandin D_2 (5).[10] The isolation of the two prostaglandin bicyclic endoperoxides PGG (1) and PGH (2) has initiated considerable synthetic interest in the 2,3-dioxabicyclo [2.2.1] heptane structure (6).

6 7 8 9

Therefore, in this work we have studied four saturated bicyclic endoperoxides (6) (7), (8), and (9). Especially, we were interested in the endoperoxides (6) and (7) since they contain the dioxacyclopentane unit as in the prostaglandin endoperoxides.

2,3-Dioxabicyclo[2.2.1]heptane[11] (6) was synthesized by photooxygenation of cyclopentadiene and subsequent diimide reduction as described in the literature.



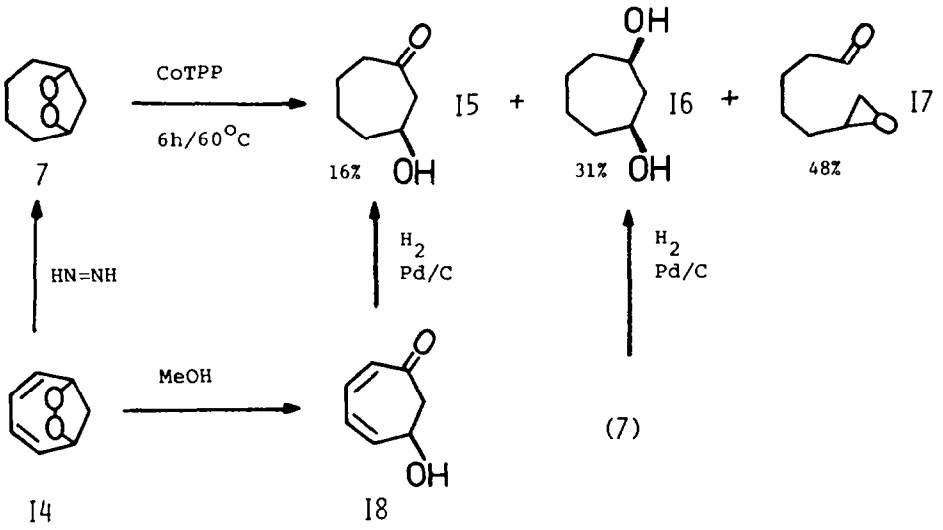
6 10 11 12

37 % 41 % 10 %

SCHEME 1

2,3-Dioxabicyclo[2.2.1]heptane (6) was exposed to CoTPP in chloroform for 14 h, the peroxide bond was cleaved and a mixture of products was obtained arising from fragmentation and reduction.[12] Decomposition of (6) was monitored by ^{1}H-NMR. Products (10)[13] and (11)[14] were identified by spectral comparison with authentic samples prepared by reported procedures. As a major product 4,5-epoxypentanal (10) was formed with cyclopentane-1,3-diol (Scheme 1). We were not able to detect any traces of hydroxy ketone.

As a second system we have studied 7,8-dioxabicyclo[4.2.1]nonane (7). In connection with our studies on photooxygenation we have isolated (14) formed by [2+6]cycloaddition of singlet oxygen to cycloheptatriene. Repeated reduction of (14) with diimide provided (7) in high yield.[15]

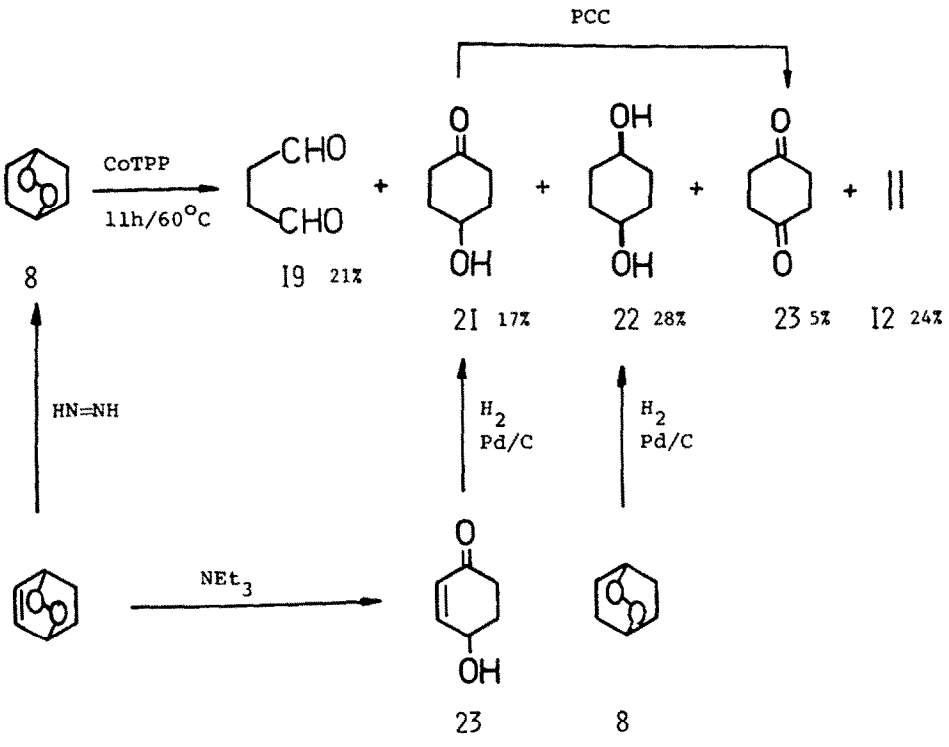


SCHEME 2

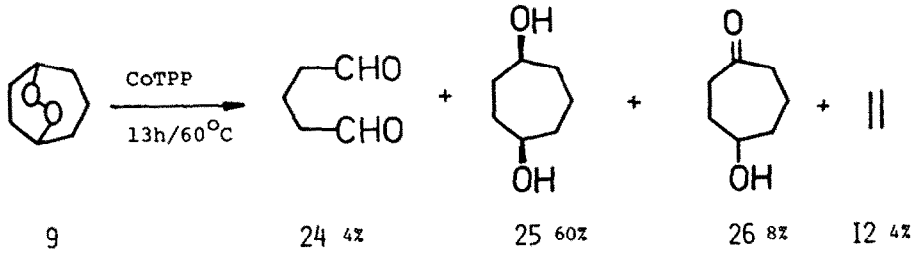
Similar decomposition modes were observed when 7,8-dioxabicyclo[4.2.1]nonane (7) was submitted to the same reaction conditions. The results are illustrated in scheme 2. The hydroxy-ketone (15) and 1,3-diol[15] (16) were characterized again by comparison with authentic samples prepared as shown in scheme 2. 6,7-Epoxyheptanal was formed as the major product.[7c] The structure of this compound was determined on the basis of spectral data. The ^{1}H-NMR spectrum of (17) is highly characteristic. Thus, all three epoxide protons show a multiplet at 2.50-2.95 ppm while the aldehyde proton constitutes a triplet at 9.65 ppm. Methylenic protons near to carbonyl group give rise to a multiplet at 2.10-2.50 ppm while the other methylenic protons are located at 1.10-1.80 ppm. IR-spectrum also supports this proposed structure.

In order to study the effect of the ring size on the decomposition mode we have prepared (8)[11,16] and (9)[11,17] according to the literature procedures. These two endoperoxides are differing from (6) and (7) since they contain dioxacyclohexane units.

In the cases of 2,3-dioxabicyclo[2.2.2]octane[11] (8) and 6,7-dioxabicyclo[3.2.2]-nonane[11,15] (9) were no trace of epoxy-aldehydes detected. 1,4-Diols were formed as major products besides hydroxy-ketones, glutaric dialdehyde and succinic dialdehyde. The structures of the formed products were determined by comparison with authentic samples (Scheme 3 and 4).



SCHEME III



SCHEME IV

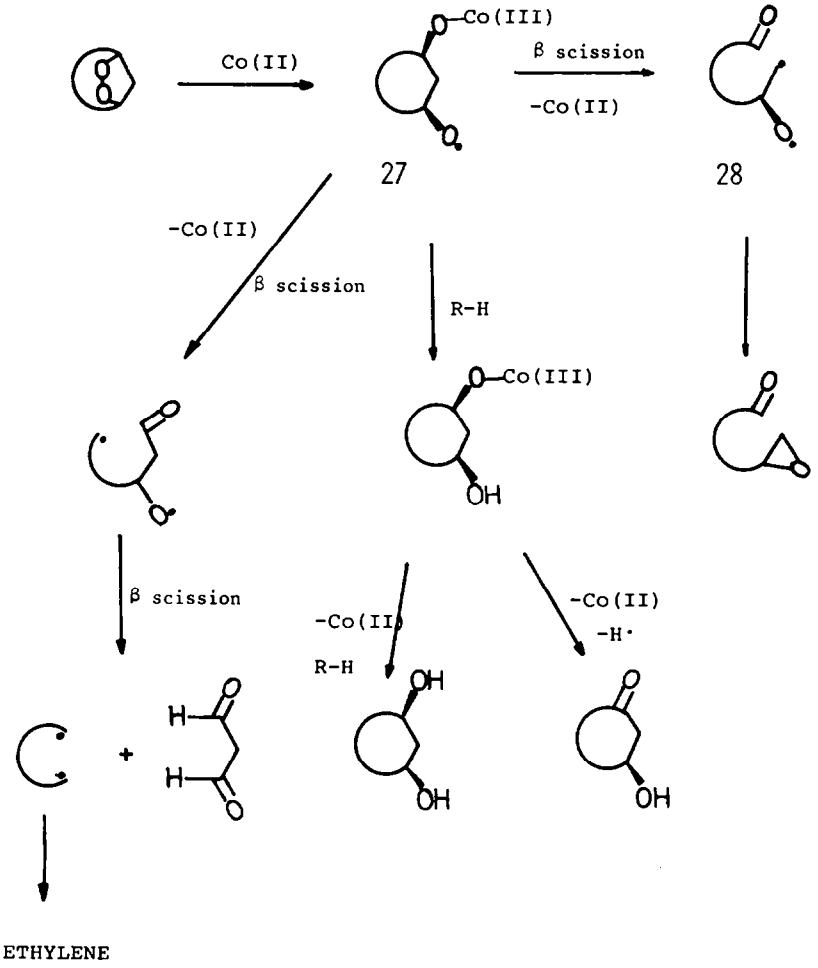
DISCUSSION

Clearly, differing behaviour has resulted from our work. Thus, [2.2.1] and [4.2.1] peroxides (6 and 7) underwent rearrangement and fragmentation giving epoxy-aldehydes and 1,3-diols as major products. This can be attributed to the similar structural units of these endoperoxides. Namely both endoperoxides contain one carbon-bridge, it is broken with formation of carbonyl group and epoxide. The bicyclic endoperoxides (8 and 9) did not provide any traces of epoxy-aldehydes. In the cases of (8 and 9) which contain a two carbon-bridge, fragmentation occurs with the elimination of ethylene. The proportion of the fragmentation products like ethylene and dialdehydes de-

creases upon releasing the strain in the molecule. This tendency can be nicely seen by going from (8) to (9).

Obviously, such reactions, CoTPP-catalyzed decomposition of endoperoxides involve radical pathways. The formation of the products is reasonably understood in terms of the mechanism outlined in scheme 5. The radical depicted as (27) resulting from electron transfer reaction between Co(II) species and endoperoxides serves as a key intermediate. This radical undergoes various transformations. Formation of (27) followed or accompanied by β-scission of a carbon-carbon bond might generate diradical (28). Cyclization of (28) could produce epoxy-aldehydes. Double β-scission of carbon-carbon bonds occurs in the cases of (6), (8) and (9) to form ethylene and dialdehydes as fragmentation products. Otherwise, the radical (27) can abstract hydrogen atoms from the donors to afford 1.4-diols or lose a hydrogen to form hydroxy-ketone.

We also observed the formation of 1.4-cycloalkane-diols when the reaction was carried out in CCl_4 which can not transfer any hydrogen atom to molecules. Therefore, we came to the conclusion that the some part of starting material and or formed products have to be the source of hydrogen for the formation of 1,4-cycloalkane-diols.



SCHEME V

The radical (27) behave differently from free radicals formed by thermolysis and photolysis of bicyclic endoperoxides. Under flash vacuum pyrolysis[7a,b], dioxabicyclo-[n.2.2]alkanes fragment to give, by loss of hydrogen and ethylene, mixtures of cycloalkane-1,4-diones and dialdehydes. Under direct photolysis[7c], these endoperoxides mainly undergo dehydrogenation to cycloalkane-1,4-diones and rearranged products. In the case of CoTPP-catalyzed reaction, the most significant product is 1,4-cycloalkane-diols which are not observed by thermolysis and photolysis.

EXPERIMENTAL SECTION

Solvent and starting material were purified according to standard literature procedures. Thin-layer chromatography was performed on Merck $60F_{254}$ sheets. Silica gel were employed for column chromatography. A Perkin-Elmer Model 337 spectrophotometer was used to record the IR spectra. ^{1}H-NMR spectra were recorded on a Varian EM-360 spectrometer.

Reaction of 2,3-dioxabicyclo [2.2.1] heptan (6) with CoTPP[18]

To a stirred solution of the 170 mg (1.7 mmole) 2,3-dioxabicyclo [2.2.1] heptane (6) in 5 ml of dry $CHCl_3$ was added a solution of 8.5 mg CoTPP (0.011 mmole) in 2 ml of $CHCl_3$. The resulting mixture was stirred at 40° for 14 h. Rotoevaporation of the solvent gave an oily residue which was chromatographed over 20 g silicagel (0.01-0.2 mm), eluiting with $CHCl_3$/petroleum ether (1:1). As first eluate TPP was collected. As a second fraction 63 mg of the 4.5-epoxy-pentanal (10) was isolated. Eluiting with $CHCl_3$/MeOH (19:1) gave 71 mg of 1,3-diol (11). For further purification of (11) TLC was used.

The same reaction was done in a sealed NMR-tube in small scale. Ethylene concentration was determined by integration of ethylene and aldehyde peaks.

4,5-Epoxy-pentanal (10) was characterized by comparison of the physical data with those reported in the literature.[13]

Authentic sample of cis-1,3-cyclopentane diol (11) was prepared by catalytic hydrogenation of (6) in ethanol (Pd/C) according to the procedure reported by Salomon.[14]

Reaction of 7,8-dioxabicyclo [4.2.1] nonane (7) with CoTPP

128 mg (1.0 mmole) of 7,8-dioxabicyclo [4.2.1] nonane (7) was dissolved in 5 ml of $CHCl_3$. To this solution was added a solution of 12 mg (0.015 mmole) CoTPP in 2 ml of $CHCl_3$ and the resulting mixture was stirred at 60°C for 6 h. The reaction was monitored by TLC and ^{1}H-NMR. The solvent was evaporated and the oily residue was chromatographed on 20 g silica gel column eluiting with $CHCl_3$/petroleum ether (1:1). After separation of TPP, 61 mg (48 %) of 6,7-epoxy-heptanal (17) as colourless oil was collected. ^{1}H-NMR (CCl_4); δ: 9.64 t, aldehyde proton, 2.95-2.50 m, epoxide protons (3H), 2.50-2.10 m, methylenic protons (2H), 1.80-1.10 m, methylenic protons (6H). IR (CCl_4) ; 3040, 2915, 2850, 2705, 1722, 1458, 1410, 1210 cm^{-1}. Satisfactory elemental analysis based on $C_7H_{10}O_2$. Eluiting with $CHCl_3$ gave 21 mg (16 %) of hydroxy-ketone (15) and eluting with $CHCl_3$ with $CHCl_3$/MeOH (19:1) provided 40 mg (31 %) of 1.3-diol (16).

Catalytic hydrogenation[15] of the endoperoxide (7) over Pd/C in ethylacetate afforded the known cis-1,3-cycloheptane-diol (16)[17] and 3-hydroxycyclohetanone (15)[19] in 55 and

38 % yield, after column chromatography on silica gel eluiting with $CHCl_3$/MeOH (19:1) and MeOH.

The methanolysis[20] of the endoperoxide (14) at 30°C afforded (18) in 57 % yield. Catalytic reduction of (18) over Pd/C in MeOH gave also the known 3-hydroxy-cycloheptanone (15).

Reaction of 2,3-dioxabicyclo [2.2.2] octane (8) with CoTPP

228 mg (2 mmole) of (8) and 17 mg (0.02 mmole) of CoTPP was dissolved in 12 ml of $CHCl_3$. The solution was kept at 60°C for 11 h. After rotoevaporation of the solvent the residue was chromatographed on silica gel.

1. fraction, eluiting with $CHCl_3$/petroleum ether (1:1) : 36 mg (21 %) glutaric dialdehyd
2. fraction, eluiting with $CHCl_3$/petroleum ether (1:1) : 11.5 g (4 %) 1,4-cyclohexanedione
3. fraction, eluiting with $CHCl_3$: 38 mg (17 %) hydroxy-ketone (21)
4. fraction, eluiting with $CHCl_3$/MeOH (19:1) 65 mg (28 %) 1,4-cyclohexanediol (22).

Synthesis of 4-hydroxycyclohexanone (21)

To a magnetically stirred solution of 224 mg (2 mmole) of 3,4-dioxabicyclo [2.2.2]-oct-2-ene in 10 ml of CH_2Cl_2 was added a solution of 303 mg (3 mmole) of NEt_3 in 10 ml of CH_2Cl_2 at 0°C. After complete addition the mixture was stirred for 8 h at room-temperature. The reaction was monitored by TLC. The solvent was evaporated and the residue purified by column chromatography on 10 g of silica gel, eluiting with $CHCl_3$/ petroleum ether (3:2), affording the pure (23) in high yield of 75 %.

Catalytic hydrogenation of 4-hydroxycyclohex-2-enone in methanol over Pd/C gave the authentic sample, the 4-hydroxycyclohexanone.[21]

Synthesis of 1,4-Cyclohexandione

In a typical small scale experiment, pyridinium chlorochromate (PCC) (1 mmole) was suspended in methylene chloride (ca. 5 ml) and the 4-hydroxycyclohexanone (0.5 mmole) in 5 ml of methylene chloride was rapidly added at room temperature. After 2 h oxidatio the black reaction mixture was diluted with 5 volumes ether, the solvent was decanted, and the black solid was washed twice with ether. Product was isolated simply by filtration of the organic extracts through silica gel (5 g). Yield was 87 %.

1,4-Cyclohexanediol[22] was synthesized by catalytic reduction of (8).

Reaction of 6,7-dioxabicyclo [3.2.2] nonane (9) with CoTPP

Same procedure was applied to (9). Eluiting with $CHCl_3$/petroleum ether (1:1), $CHCl_3$ and $CHCl_3$/MeOH (1:1) gave dialdehyde (24), hydroxy-ketone (26) and 1,4-diol (25).

Glutaric dialdehyde is a commercialy available compound. 4-Hydroxycycloheptanon[14,2] and 1,4-cycloheptanediol[18] were synthesized by catalytic reduction of the 5,6-dioxabicyclo [3.2.2] nonadi-2,8-ene according to the procedure reported by Adam and Balci.[18]

ACKNOWLEDGEMENT

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