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Steroidal Cyclobutanones

Short Communication

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Cycloaddition of dichloroketene and 3-, 7-, 17-, and 20-methylene steroids affords the corresponding cyclobutanones in yields reflecting the steric crowding around the reacting olefinic double bond.

(Keywords: Steroidal cyclobutanones; [2 + 2] Cycloaddition of dichloroketene and methylene steroids)

Steroid-Cyclobutanone (Kurze Mitteilung)

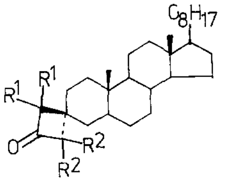
Cycloaddition von Dichlorketen an 3-, 7-, 17- und 20-Methylen-Steroide ergab die jeweiligen Cyclobutanonderivate in Ausbeuten, die den sterischen Gegebenheiten rund um die reagierenden olefinischen Doppelbindungen entsprechen.

An efficient synthetic method for preparing cyclobutanones, versatile intermediates in organic synthesis [1, 2], is the reaction of reactive ketenes, for example dichloroketene (*DCK*), with olefins [1, 3, 4]. Steroidal cyclobutanones were obtained in reactions of *DCK* with ring A unsaturated cholestanes [5, 6]. Cycloaddition of methylene steroids and ketenes seems a potentially useful reaction leading to diverse spirosteroids *via* spiro-cyclobutanones. Cycloaddition of this type has not been described and reactions of alicyclic methylene compounds with haloketenes are scarce [7–9]. Steroidal spiro compounds are of importance due to the biological activity of some of their representatives [10]. We wish to report preliminary results of our studies on the synthesis of steroidal cyclobutanones which are mostly spiranes. As the model olefins 3-, 6-, 7-, 17-, and 20-methylene steroids have been chosen.

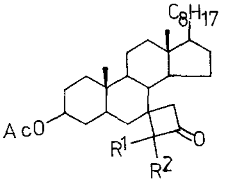
The reaction of 3-methylene-5α-cholestane with *DCK* generated from trichloroacetyl chloride and zinc [5] gave a mixture of epimeric dichlorocyclobutanones **1** and **2** in the ratio 3.7:1. These cycloadducts were unstable and partially decomposed on SiO_2 column allowing the isolation of **1** and **2** in 64 and 17% yield, respectively, by combination of crystallization and chromatography. When the crude cycloaddition product was dehalogenated with zinc in *Ac*OH the spiro-cyclobutanone **3** was obtained in 94% yield.

The stereochemistry of cyclobutanones **1** and **2** follows from the generally accepted mechanism of these cycloadditions which proceeds with orthogonal approach of the ketene to an alkene according to a ($\pi 2s + \pi 2a$) mechanism [11]. The axial approach of *DCK* to the exomethylene double bond resulting from a less steric interaction with 1α and 5α axial hydrogens favours the formation of **1** as the major, more polar product. This stereochemistry was confirmed by ^{13}C nmr spectra in which a downfield shift of the equatorial 4′-methylene carbon in **1** and of dichloromethylene carbon in **2** of the cyclobutanone ring was observed [9], when compared with signals of the axial carbons of the same type.

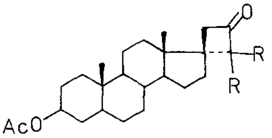
Cycloaddition of *DCK* to the more hindered double bond in 3β-acetoxy-7-methylene-5α-cholestane afforded two epimeric spirocyclobutanones **4** in the ratio 3:1 (total yield 36%). The major product was that resulting from "axial attack" of the ketene on the *exo* double bond. The dichlorocyclobutanone **4** was unstable and could not be isolated pure. The reaction of crude **4** with zinc in *Ac*OH at room temperature gave an



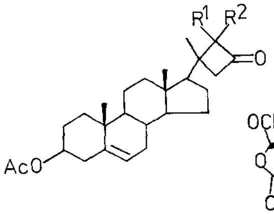
1 $R^1=H$ $R^2=Cl$
2 $R^1=Cl$ $R^2=H$
3 $R^1=R^2=H$



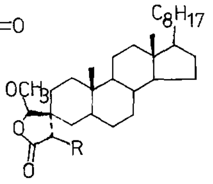
4 $R^1=R^2=Cl$
5 $R^1=H$ $R^2=Cl$
6 $R^1=R^2=H$



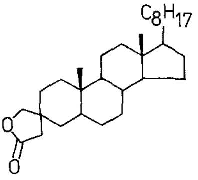
7 $R=Cl$
8 $R=H$



9 $R^1=R^2=Cl$
10 $R^1=H$ $R^2=Cl$
11 $R^1=R^2=H$



12 $R=Cl$
13 $R=H$



14 3β —CH_2CO—
15 3α —CH_2CO—

unseparable mixture of two monochloro compounds **5** isolated in 23% yield. The same reaction at reflux gave **6** (16%).

When 6-methylene-5α-cholestane reacted with *DCK* the expected cycloadduct has not been obtained.

The reaction of 3β-acetoxy-17-methylene-5α-androstane with *DCK* gave one compound (65% yield) as a result of the "axial attack" of the ketene approaching from the "α" side of the steroid. The cycloaddition product (65% yield estimated on the basis of the IR spectrum) was an unstable compound and again could not be isolated pure (the crude reaction product had a spectral characteristic in accordance with the presence of **7**). Reduction of crude **7** with zinc in refluxing *Ac*OH gave **8** (41% total yield) [12].

3β-acetoxy-20-methylene-5-pregnene, surprisingly, gave also one isomer of the cycloadduct **9** (83%). The trisubstituted 5,6-double bond was found inert toward *DCK*, presumably due to steric crowding in the transition state leading to the fused cyclobutanone system. Selective dehalogenation (Zn, *Ac*OH, room temp.) of **9** afforded chlorocyclobutanone **10** (85%). The same reaction carried out at reflux gave cyclobutanone **11** (98%).

Bayer-Villiger oxidation of **2** with *MCPBA* failed, while oxidation in basic solution (H_2O_2—NaOH, *Me*OH—*THF*) gave a mixture of two isomeric methoxy-chlorolactones **12**.

Isomer A (42% isolated yield) had ν_{max} 1 785 cm^{-1} and δ (H) 4.86 (1 H, s), 4.17 (1 H, d, J = 3.5 Hz), 3.46 (3 H, s); isomer B (13%) had ν_{max} 1 790 cm^{-1} and δ (H) 5.06 (1 H, s), 4.33 (1 H, d), and 3.57 (3 H, s); both compounds gave intense molecular ions at m/z 506 and isotope ions at 508. Reduction of **12** (Zn, *Ac*OH) afforded the methoxylactone **13** [ν_{max} 1 780 cm^{-1}; δ (H) 4.85 (1 H), 3.47 (3 H), and 2.45 (2 H); δ (C) 175.8, 111.8; m/z 472 (M^+)].

The isomeric spirolactones **14** and **15** were obtained in the ratio 45:55 (99% yield) when **3** was oxidized with H_2O_2—NaOH in *Me*OH—*THF* mixture. Compounds **14** and **15** were of similar polarity and could be partly separated by chromatography in 23 and 50% yield, respectively.

Characteristic Spectral Data of Steroidal Cyclobutanones and Lactones

All compounds gave satisfactory elemental analyses and mass spectral fragmentations in accord with the assigned structures.

1: Mp. 164–166 °C; ν_{max}: 1 775 cm^{-1}; δ (H): 2.91 (2 H, brs); δ (C): 194.0, 91.9, 55.0; $\Delta\varepsilon$ −0.49 (317 nm).
2: Mp. 181–183 °C; ν_{max}: 1 810 cm^{-1}; δ (H): 3.00 (2 H, s); δ (C): 193.3, 93.1, 52.8; $\Delta\varepsilon$ −0.25 (314 nm).
3: Mp. 187–190 °C; ν_{max}: 1 775 cm^{-1}; δ (H): 2.70 (4 H, s); δ (C): 208.1, 58.4, 56.6; $\Delta\varepsilon$ −0.15 (301 nm).

5: (A mixture of two isomers); $\nu_{\max}$: 1 792, 1 723 cm^{-1}; δ (H): 4.65 (1 H, m), 4.56 (1 H, dd, $J = 2.9$, $J = 3.2$), 3.25 (1 H, dd, $J = 18.3$, $J = 3.2$), 2.55 (1 H, dd, $J = 18.3$, $J = 2.9$), 4.69 (1 H, m), 3.39–2.29 (4 H, m); δ (C): 201.6, 70.3 (7*R*,2′*S* isomer, 25%), 69.3 (7*S*,2*R* isomer, 75%); $\Delta\varepsilon$ -0.80 (304 nm).

6: Mp. 107–111 °C; $\nu_{\max}$: 1 770, 1 725, 1 255 cm^{-1}; δ (H): 4.69 (1 H, m), 3.34–2.29 (4 H, m); δ (C): 209.1, 59.0, 51.3; $\Delta\varepsilon$ $+0.13$ (303 nm).

7: (As a mixture with the substrate); $\nu_{\max}$: 1 805, 1 725, 1 255 cm^{-1}; δ (H): 3.45 (1 H, d, $J = 17$), 2.66 (1 H, d, $J = 17$); δ (C): 192.3, 90.9.

8: Mp. 202–206 °C; $\nu_{\max}$: 1 773, 1 723, 1 255 cm^{-1}; δ (H): 4.68 (1 H, m), 3.21–2.35 (4 H, m); δ (C): 207.8, 54.2, 51.3; $\Delta\varepsilon$ -0.43 (295 nm).

9: Mp. 212–213 °C; $\nu_{\max}$: 1 810, 1 725, 1 255 cm^{-1}; δ (H): 5.39 (1 H, m), 4.59 (1 H, m), 3.42 (1 H, d, $J = 16.2$), 2.70 (1 H, d, $J = 16.2$); δ (C): 192.9, 94.8, 53.9; $\Delta\varepsilon$ -0.90 (309 nm).

10: Mp. 195–198 °C; $\nu_{\max}$: 1 788, 1 723, 1 255 cm^{-1}; δ (H): 5.39 (1 H, m), 4.86 (1 H, dd, $J = 2.2$, $J = 1.9$), 4.60 (1 H, m), 3.08 (1 H, dd, $J = 16.2$, $J = 2.2$), 2.58 (1 H, dd, $J = 16.2$, $J = 1.9$), 2.03 (3 H, s); δ (C): 199.6, 68.1, 54.7; cd $+1.81$ (298 nm).

11: Mp. 208–210 °C; $\nu_{\max}$: 1 770, 1 721, 1 252 cm^{-1}; δ (H): 5.39 (1 H, m), 4.60 (1 H, m), 3.35–2.31 (4 H, m), 2.03 (3 H, s); δ (C): 2.08, 59.3, 55.7; $\Delta\varepsilon$ -0.25 (304 nm).

12: Isomer A (42% isolated yield) had $\nu_{\max}$: 1 785 cm^{-1} and δ (H): 4.86 (1 H, s), 4.17 (1 H, d, $J = 3.5$), 3.46 (3 H, s); isomer B (13%) had $\nu_{\max}$: 1 790 cm^{-1}; δ (H): 5.26 (1 H, s), 4.33 (1 H, d), 3.57 (3 H, s). Both compounds gave intense molecular ions at m/z 506 and isotope ions at 508.

13: Oil; $\nu_{\max}$: 1 780 cm^{-1}; δ (H): 4.81 (1 H), 3.44 (3 H) and 2.41 (2 H); δ (C): 175.8, 111.8; m/z 472 (M^+).

14: Mp. 191–193 °C; $\nu_{\max}$: 1 775 cm^{-1}; δ (H): 4.11 (2 H, s), 2.25 (2 H, s); δ (C): 176.8, 76.6, 43.3, and 40.3; m/z 442 (M^+, 88%).

15: Mp. 170–172 °C; $\nu_{\max}$: 1 775 cm^{-1}; δ (H): 3.93 (2 H, s), 2.39 (2 H, s); δ (C): 176.8, 80.0, 40.9, and 39.7; m/z 442 (M^+, 81%).

Acknowledgement

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