3-Bromomethylcholest-2-ene and its Reactions

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Received 2 May 2000

2α-Bromocholestan-3-one treated with Grignard reagent prepared from dibromomethane afforded 3-bromomethylcholest-2-ene. Its reactions with chromium(III) salts, sodium, and *N*-bromosuccinimide—2,2′-azobis(2-methylpropionitrile), respectively are described.

A family of dimeric steroid pyrazines *I* (cephalostatins, ritterazines, Scheme 1) has been recently discovered [1, 2]. Many of its representatives show an extraordinary cytostatic activity. Mode of action of these compounds is still unknown and there is a question about the significance of a central pyrazine ring [3, 4]. If it is only a spacer a homoaromatic (benzene) ring could replace it.

This paper presents an attempt of synthesis of such steroid dimers *II* (Scheme 1) in a cholestane system.

In the first experiment 2α-bromocholestan-3-one (*III*) was subjected to Grignard reagent prepared from dibromomethane [5]. The primary product of the reaction was presumably 2α-bromo-3-methylenecholestane. The intermediate underwent allylic rearrangement with the assistance of $MgBr_2$ present in the system giving the product, 3-bromomethylcholest-2-ene (*IV*). An alternative mechanism of compound *IV* formation may also be considered provided that the major component of the reagent was bromomethylmagnesium bromide [5]. However, the latter mechanism is rather unlikely since the reagent was prepared using an excess of magnesium amalgam.

No coupling reactions under these conditions were observed. Coupling of compound *IV* was attempted in several experiments. One of them was dehalogenative dimerization with $CrCl_3$—$LiAlH_4$ [6, 7]. However, the coupling products were not found and the only reaction product appeared to be 3-methylenecholestane (*V*) [8]. The next attempt was the Wurtz type reaction [9] of the bromo compound *IV* but instead of coupling, its reduction to the known 3-methylcholest-2-ene (*VI*) [8] was observed. There was no radical reaction of *IV* induced with 2,2′-azobis(2-methylpropionitrile) (AIBN), while radical bromination with stoichiometric amount of *N*-bromosuccinimide (NBS) in the presence of AIBN took place simultaneously at both allylic positions 1α and 4α. No monobrominated products were detected and equimolar mixture of the starting material *IV* and the dibromo product *VII* was obtained. Bromine attacked steroid molecule from its less hindered lower side. In the product *VII* thus formed bromine atoms occupy a pseudo-axial 1α-position and a pseudo-equatorial 4α-position. This is proved by the corresponding coupling constants. From the constant $J_{1\beta,2} = 6.4$ Hz follows the torsion angle H-1β—C-1—C-2—H-2 smaller than 40°, while the constant $J_{4\beta,5\alpha} = 9.7$ Hz is typical for the axial-axial couplings [10].

Further studies on the synthesis of steroid dimers with a central benzene ring are in progress.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus of the Boetius type. NMR spectra were taken with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with TMS as the internal standard. Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FTIR spectrometer as chloroform solutions unless otherwise stated. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on "70-230 mesh" silica gel (Merck).

3-Bromomethylcholest-2-ene (*IV*)

Magnesium amalgam was prepared from magnesium turnings (1.5 g; 0.06 mol) and mercury (4 cm^3) by stirring and heating at 80—100°C. After cooling, anhydrous ether (20 cm^3) was added followed by dropwise addition of dibromomethane (2 cm^3; 0.028 mol). The reaction mixture was heated for 2 h and the grey suspension thus obtained was transferred to the flask containing 2-bromocholestan-3-one (466 mg; 1 mmol). The reaction mixture was stirred overnight, quenched with dilute HCl and extracted with chloroform. The dried extract was evaporated *in vacuo* and an oily residue was chromatographed on silica gel column.

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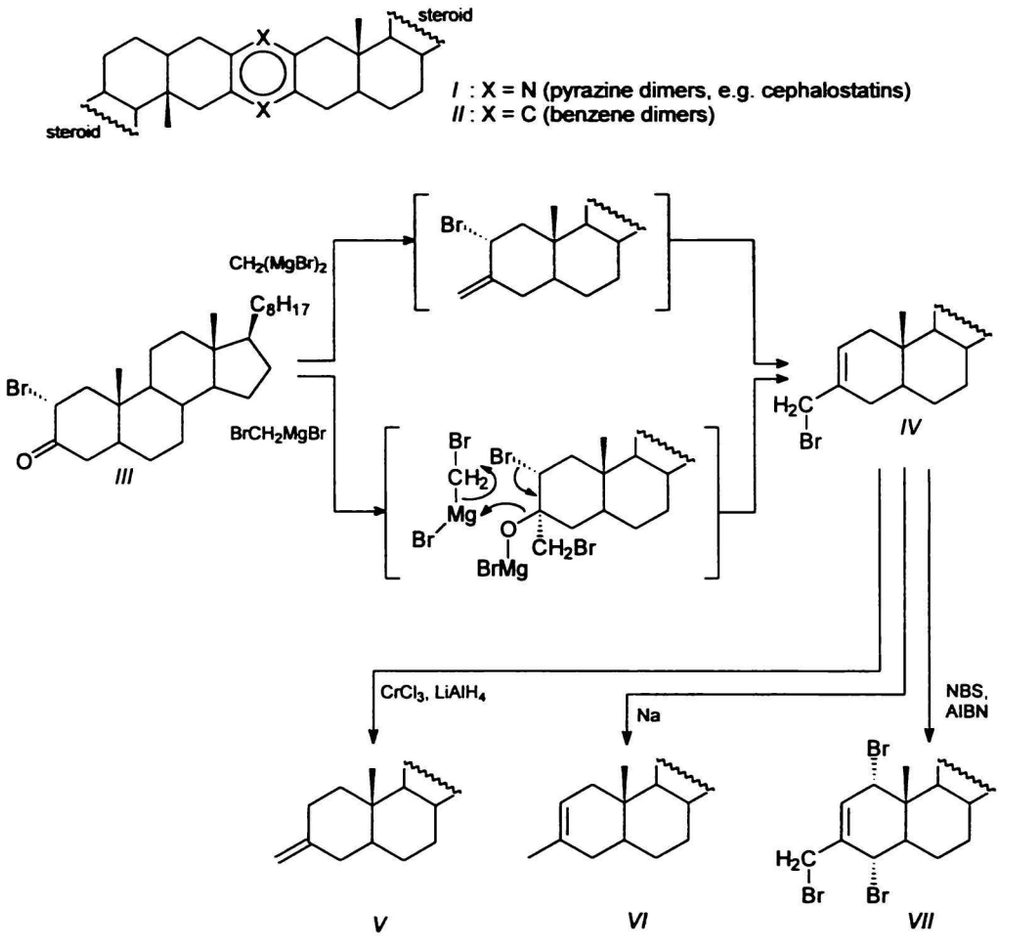

Scheme 1

Elution with hexane yielded *IV* (98 mg; 21 %), m.p. = 103—106 °C (hexane). IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 2933 ν(C—H), 1662 ν(C=C), 1467 δ(C—H), 1382 δ-(C—H), 606 ν(C—Br). ^1H NMR spectrum ($CDCl_3$), δ: 5.80 (m, 1H, H-2), 3.95 (s, 2H, CH_2—Br), 0.89 (m, 9H, CH_3-20, CH_3-26, CH_3-27), 0.73 (s, 3H, H-19), 0.66 (s, 3H, H-18); ^{13}C NMR spectrum ($CDCl_3$), δ: 133.3 (C), 127.2 (CH), 56.4 (CH), 56.3 (CH), 53.8 (CH), 42.5 (C), 41.4 (CH), 40.1 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 39.4 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.6 (CH), 34.4 (C), 31.7 (CH_2), 31.3 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.2 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.1 (CH_2), 18.7 (CH_3), 12.0 (CH_3), 11.8 (CH_3). Mass spectrum, m/z (I_r/%): 464 and 462 (13, M^+), 447 (7), 449 (8), 383 (100), 316 (73).

3-Methylenecholestane (*V*)

To the suspension of anhydrous chromium(III) chloride in THF (0.2 cm^3) lithium aluminium hydride (3 mg; 0.08 mmol) was portionwise added and the mixture was magnetically stirred at room temperature for 15 min. Anhydrous DMF (0.2 cm^3) and *IV* (14 mg; 0.03 mmol) were then added and stirring was continued for 4 h. The reaction mixture was quenched with water, extracted with hexane, and the crude product obtained by evaporation of the extract *in vacuo* was purified on a silica gel column. Hexane eluted consecutively *V* (6 mg; 52 %), m.p. = 64—65 °C; Ref. [8] gives m.p. = 65—66 °C, and the starting material (5 mg; 36 %).

3-Methylcholest-2-ene (*VI*)

To the solution of *IV* (20 mg; 0.043 mmol) in anhydrous 1,2-dimethoxyethane (0.5 cm^3) sodium (3 mg; 0.13 mmol) was added. The reaction mixture was stirred overnight in an oil bath at 90—92 °C and the product was purified by a silica gel column chromatography with hexane. Yield 12 mg (72 %), m.p. = 79—82 °C, Ref. [8] gives m.p. = 82—83 °C, the product being identical in all respects with the compound described in the literature.

3-Bromomethyl-1α,4α-dibromocholest-2-ene (*VII*)

A solution of *IV* (30 mg; 0.065 mmol), AIBN (12

mg; 0.065 mmol), and NBS (11 mg; 0.065 mmol) in anhydrous tetrachloromethane (1 cm^3) was heated under reflux for 1 h. After removal of the solvent the residue was chromatographed on a silica gel column. Hexane eluted 5 mg (17 %) of the unreacted starting material, further elution with hexane—benzene mixture (φ_r = 85:15) afforded the product (5.5 mg; 14 %), m.p. = 68—70 °C (hexane). IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 2935 ν(C—H), 1467 δ(C—H), 1382 δ(C—H), 555 ν(C—Br). ^1H NMR sectrum ($CDCl_3$), δ: 6.25 (d, 1H, J = 6.4 Hz, H-2), 4.71 (d, 1H, J = 9.7 Hz, H-4β), 4.56 (d, 1H, J = 10.1 Hz, CH_2—Br), 4.44 (d, 1H, J = 6.4 Hz, H-1β), 3.98 (d, 1H, J = 10.1 Hz, CH_2—Br), 0.90 (m, 12H, CH_3-19, CH_3-20, CH_3-26, CH_3-27), 0.67 (s, 3H, H-18); ^{13}C NMR ($CDCl_3$); δ: 135.3 (C), 130.8 (CH), 57.4 (CH), 56.0 (CH), 55.9 (CH), 54.9 (CH), 49.6 (CH), 45.4 (CH), 42.4 (C), 41.2 (C), 39.5 (CH_2), 39.3 (CH_2), 36.7 (CH_2), 36.1 (CH_2), 35.7 (CH), 35.3 (CH), 30.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 26.6 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 19.7 (CH_2), 18.7 (CH_3), 12.3 (CH_3), 12.0 (CH_3). Mass spectrum, m/z (I_r/%): 624, 622, 620, 618 (all < 1, M^+), 543 (16), 541 (31), 539 (16), 462 (16), 461 (32), 460 (18), 459 (32), 381 (100).

Acknowledgements. Financial support from the University of Bialystok (Grant No. BW-177/99) is gratefully acknowledged.

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