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Bromination of Methyl 3-Oxo-5β-cholanate at C-2

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Molecular bromine is usually used to prepare α-bromo ketones and α-bromo aldehydes. On the other hand, iodine monobromide has been used for this purpose only in a few cases.[1,2]

In the present study **1** was subjected to the action of 2 equiv of iodine monobromide. Two definite stages could be distinguished (Scheme I) by using the nmr technique.

The compound obtained in the first stage, which terminated after about 2 hr, was characterized by its singlet at δ 1.09 and somewhat broad doublet centered at δ 4.98. From the melting point and other physical data this compound proved to be identical with 4β-bromo ketone[3] obtained by the usual bromination of **1** with 1 equiv of bromine.

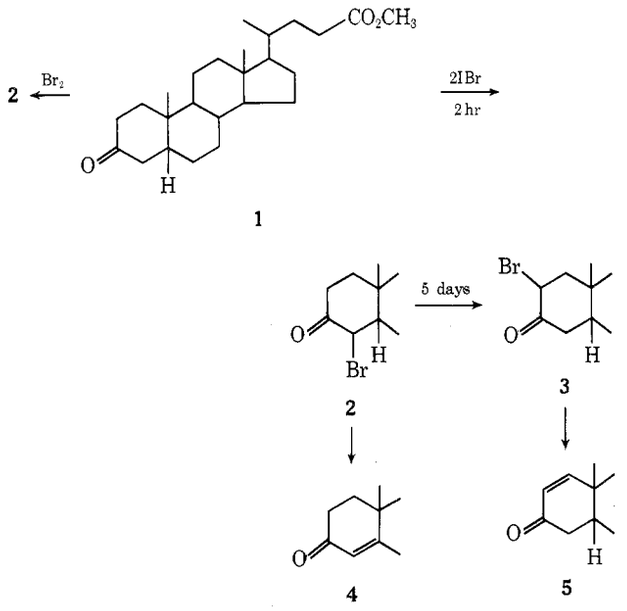
The second stage extended over a longer period of time (5 days), during which a singlet at δ 1.07 and a quartet centered at δ 4.73 gradually developed at the expense of the previous signals, which eventually completely disappeared (see Experimental Section). The characteristic quartet of the final product **3** unequivocally establishes the location and orientation of the bromine atom in this compound to be 2β (equatorial).[4] The configuration of the hitherto unknown compound **3** was also confirmed by other spectroscopic data.

The carbonyl frequency in the ir spectrum of **3** is higher than that of the parent ketone **1**. The observed shifts of 24 and 17 cm^{-1} for **3** and **2**, respectively, are to be expected for equatorial bromine substituents.[5] Additional evidence for the proposed orientation of the bromine substituent in both **2** and **3** was obtained from the location of the carbonyl absorption in the uv spectrum; the values of their λ_{max} are very close to that of the parent compound **1** (see Experimental Section).

Surprisingly, despite the distinct differences in the other physical constants, the mass spectra of the two bromo compounds **2** and **3** have much in common, indicating possible rearrangement during the fragmentation process.

Chemical evidence for the above assigned structure was provided by the conversion of **3** to the known α,β-unsaturated ketone **5**[3] (~50% yield) by the action of Li_2CO_3 in DMF.[6] The parallel reaction carried out on the isomeric 4β-bromo ketone **2** (Scheme I) proceeded smoothly to give methyl 3-oxo-4-cholenate (**4**)[3] as the major product, but the 2β-bromo isomer **3** reacted much more slowly. The elimination process involved, as expected,[7,8] a partial rearrangement yielding a mixture of methyl 3-oxo-5β-chol-1-enoate (**5**) and methyl 3-oxo-4-cholenate (**4**) in approximately 1:1 ratio. The location of the double bond in **5** was disclosed in the nmr spectrum; the two doublets centered at δ 6.8 and 5.84 are attributable to C-1 and C-2 vinylic protons, respectively. In contrast the single vinylic proton in compound **4** resonates at δ 5.71.

Scheme I



Preliminary experiments showed that complete monobromination could not be achieved with less than 2 equiv of IBr. It was assumed, therefore, that the reaction might be represented stoichiometrically as follows: 1 + 2IBr → 2 + I_2 + HBr. Accordingly, complete rearrangement of the 4β-bromo ketone **2** to 2β-bromo ketone **3** was effected by subjecting the former to the action of 1 equiv of I_2 and a catalytic amount of HBr in acetic acid. Thus, it is evident that the iodine formed during the first stage of the bromination was responsible for the rearrangement in the second stage of the reaction.

The migration of the bromine atom from C-4 to the less hindered C-2 position[9–12] was effected by iodine and hydrogen bromide taken together; in the presence of iodine alone the rearrangement was slower; hydrogen bromide in the absence of iodine proved to be entirely ineffective.

In our opinion the driving force for the migration is the ability of the iodine molecule to form a charge-transfer complex with the carbonyl group of the substrate.[13] The coordinated iodine molecule adjusts itself to the steric and stereoelectronic requirements of the rearrangement reaction. The debromination at C-4 and rebromination at C-2

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relieves the strain at the C-4 position[10-12] imposed by the bromine atom.

The tendency of the molecule to part from the bromine atom at C-4 is also reflected by the facile dehydrobromination of 4β-bromo ketone **2** as compared to 2β-bromo isomer **3**.

Another noteworthy observation is that the bromination of **1** to produce 4β-bromo ketone **2** is much slower with IBr (2 hr) than with Br_2 (5 min). Moreover, the slow rate of the monobromination with IBr did not change appreciably when 1, or even 2, equiv of Br_2 was added to the reaction mixture, implying that in the presence of IBr enolization is depressed. This peculiar behavior could be a result of molecular compound formation between the 3-keto substrate and iodine monobromide.[14-18] The coordinated IBr molecule would then interfere in the process of enolization initiated by the protonation at the oxygen carbonyl group.

The introduction of bromine at C-2 in methyl 3-oxo-5β-cholanate (**1**) is significant, since it is the first reported case in which heterolytic bromination of **1** takes place exclusively at a site unfavorable for enolization.

Experimental Section

Ultraviolet spectra were determined with a Unicam ultraviolet spectrophotometer (Model Sp 300A). Infrared spectra were measured in potassium bromide disks using a Perkin-Elmer spectrophotometer (Model 337). Nmr spectra were recorded on a Jeol C-60-H high-resolution nmr spectrometer with tetramethylsilane as internal standard. CD spectra were obtained using a Cary 60 recording spectropolarimeter. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a CH5 Varian MAT mass spectrometer. IBr was prepared by dissolving 1 g of iodine and 0.614 g of bromine in 50 ml of glacial acetic acid (1 mmol of IBr per 6.35 ml). Column chromatography and tlc were carried out on silica gel (Hopkins and Williams) and Kieselgel GF 254 from Stahl Merck, respectively.

Methyl 3-Oxo-5β-cholanate (1) was prepared according to the procedure of Fieser and Ettorre:[19] mp 119° (lit.[19] mp 119–120°); ir 1706 cm^{-1} (C=O); uv (ethanol) 285 nm (ε 19); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 3.68 (s, 3, 24-OCH_3); CD (ethanol) $[\theta]_{262}$ 0, $[\theta]_{285}$ −1600, $[\theta]_{318}$ 0; mass spectrum *m/e* (rel intensity) 388 (base peak, M^+), 537 (52, M − 31), 275 (93).

Bromination of 1 with IBr for 2 Hr. To a solution of **1** (388 mg) in acetic acid (10 ml) 2 equiv of IBr (12.7 ml) was added. After standing for 2 hr at room temperature the reaction mixture was diluted with water (100 ml) and sufficient sodium bisulfite was added. The precipitate was filtered, washed with water, and dissolved in chloroform. The solvent was removed and the solid residue was crystallized from methanol to yield pure 4β-bromo ketone **2**: mp 100–100.5° (lit.[3] mp 96–101°); $[\alpha]_D$ ($CHCl_3$) +51.0°; ir 1725 (C=O), 710–700 cm^{-1} (C–Br); uv (ethanol) 280 nm (ε 25); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.09 (s, 3, 19-CH_3), 3.67 (s, 3, 24-OCH_3), 4.90 and 5.07 (d, 1, H–C–Br); CD (ethanol) $[\theta]_{250}$ 0, $[\theta]_{282}$ −660, $[\theta]_{300}$ 0, $[\theta]_{310}$ +240, $[\theta]_{330}$ 0; mass spectrum *m/e* (rel intensity) 468, 466 (0, M^+), 355 [base peak, M − (HBr + 31)], 419, 417 (9, M − 49), 387 (60, M − Br), 369 [33, M − (HBr + H_2O)], 337 (33), 55 (66, CH_2=CHC≡O^+).

Anal. Calcd: C, 64.24; H, 8.35; Br, 17.13. Found: C, 64.10; H, 8.25; Br, 17.16.

Bromination of 1 with Br_2 in the Presence of IBr. To a solution of **1** (388 mg) in acetic acid (10 ml), 1 equiv of IBr (6.4 ml) and 1 equiv of Br_2 were added. The product which was isolated after 2 hr by the above procedure proved to be identical in all respects with 4β-bromo ketone **2**. The same result was also obtained when **1** was subjected to the action of 2 equiv of Br_2 in the presence of 1 equiv of IBr under the same conditions.

Methyl 2β-Bromo-3-oxocholanate (3). To a solution of methyl 3-oxo-5β-cholanate (**1**, 500 mg) in acetic acid (10 ml), 2 equiv of IBr solution (16.4 ml) and 2 drops of 10% HBr in acetic acid were added and the reaction mixture was kept for 5 days at 30°. The brown residue which was obtained after the usual work-up was chromatographed and purified by plc (8% acetic acid in benzene). Recrystallization from methanol yielded 300 mg of pure methyl 2β-bromo-3-oxocholanate (**3**): mp 85°; $[\alpha]_D$ ($CHCl_3$) +2.4°; ir 1730 (C=O), 702 cm^{-1} (C–Br); uv (ethanol) 280 nm (ε 25); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.07 (s, 3, 19-CH_3), 3.7 (s, 3, 24-OCH_3), 4.57, 4.66, 4.80, and 4.88 (q, 1, H–C–Br); CD (ethanol) $[\theta]_{258}$ 0, $[\theta]_{287}$ −1600, $[\theta]_{332}$ 0; mass spectrum *m/e* (rel intensity) 468, 466 (0, M^+), 355 (base peak), 419, 417 (13), 387 (85), 369 (47), 337 (53), 55 (91).

Anal. Calcd: C, 64.24; H, 8.35; Br, 17.13. Found: C, 64.04; H, 8.17; Br, 17.37.

Table I
Formation of 2β-Bromo Ketone 3

Time, hr	Height of peak at δ 1.07/ height of peak at δ 1.09
12	~0.1
36	~1.2
60	~20
84	~30
120	No peaks at δ 1.09 and 5.07

Bromination of 1 with IBr at Different Intervals of Time. To a solution of **1** (388 mg) in acetic acid (10 ml) 2 equiv of IBr (12.7 ml) and 2 drops of 10% HBr were added and the reaction mixture was kept at 30°. Aliquots of 4 ml were taken after 12, 36, 60, 84, and 120 hr and analyzed by nmr after the usual work-up. The formation of 2β-bromo ketone **3** was followed by the appearance of the peaks at δ 1.07, 4.57, 4.66, 4.80, and 4.88. The results are summarized in Table I.

Rearrangement of 2 to 3. To a solution of 4β-bromo ketone **2** (467 mg) and I_2 (254 mg) in acetic acid (10 ml), 2 drops of 10% HBr in acetic acid was added. The reaction mixture was kept at 30°. Aliquots of 2 ml were taken after 12, 36, 60, 84, and 120 hr and analyzed by nmr. The results were similar to those represented in Table I for the formation of 2β-bromo ketone **3** by the action of iodine monobromide on **1**.

The rearrangement with I_2 was not complete after 5 days in the absence of HBr. HBr alone was found to be ineffective.

Registry No.—**1**, 1173-32-6; **2**, 52032-49-2; **3**, 52032-50-5; IBr, 7789-33-5.

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Synthesis of Methyloxocyclopentaneacetic Acids

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In studying the synthesis of a carbocyclic analog of muscarone,[1] 4-methyl-3-oxo-1-cyclopentaneacetic acid was required. An attempt was made to synthesize it by a Wittig reaction between 4-methyl-4-cyclopentene-1,3-dione[2] and triphenylcarbethoxymethylenephosphorane[3] using benzoic acid as catalyst.[4] Contrary to reports[5,6] on similar experiments, the reaction took place under mild conditions, yielding ethyl 3-methyl-4-oxo-2-cyclopenten-1-ylideneace-