Asymmetric Monobromination of Steroidal Aldehydes. Iodine Bromide, a New Monobrominating Agent for Aldehydes

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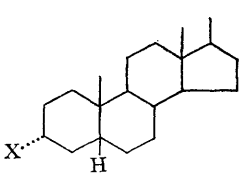
WE report the preparation and properties of 23-bromocholanal (II) and of some 22-bromonorcholanals (V and VI), by use of iodine bromide, a selective brominating agent for steroidal aldehydes. Although iodine bromide has been used for bromination of cholestanone,[1] no record of its use in bromoaldehyde synthesis was hitherto known.

Iodine bromide effects monobromination of cholanal (Ia), norcholanal (Ib), and 3α-acetoxynorcholanal (Ic) in high yields:

$$\underset{\underset{\text{R}}{|}}{\text{MeCH}\cdot[\text{CH}_2]_n\cdot\text{CH}_2\cdot\text{CHO}}\ (\text{I}) + 2\text{IBr} \xrightarrow[\text{AcOH, } 30^\circ]{\text{HBr}} \underset{\underset{\text{R}}{|}}{\text{MeCH}\cdot[\text{CH}_2]_n\cdot\text{CHBr}\cdot\text{CHO}}\ (\text{II—IV}) + \text{I}_2 + \text{HBr}$$



		X	*n*
=R	(Ia, II)	H	1
	(Ib, III)	H	0
	(Ic, IV)	OAc	0
	(Id)	OH	0

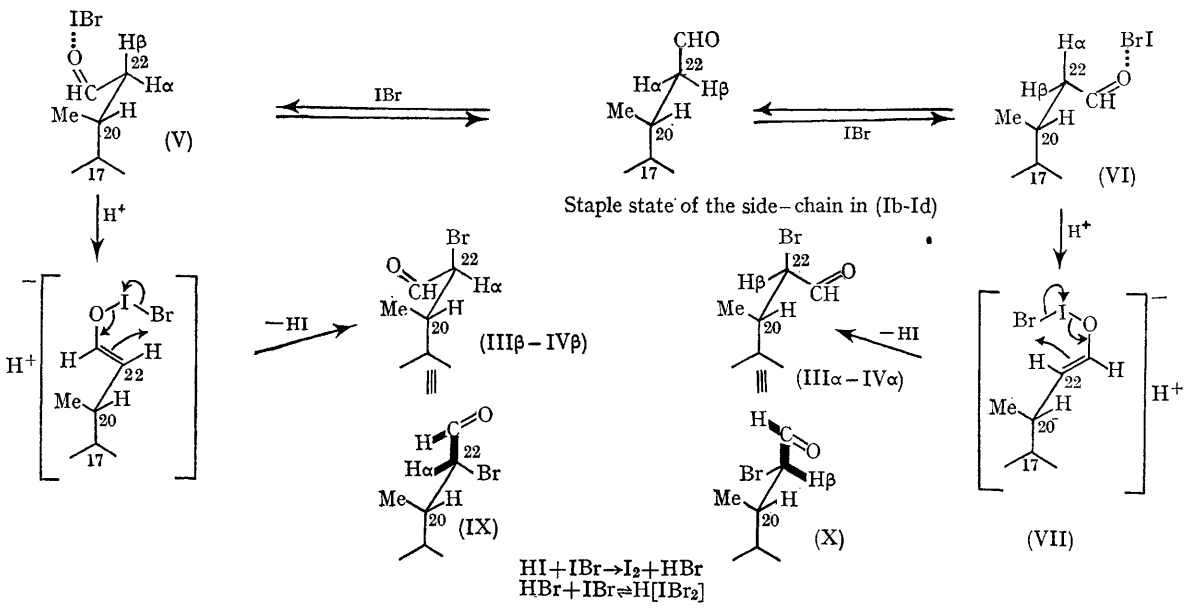
The monobromo-aldehydes (II, III, and IV) are diastereoisomeric mixtures of the 23α- and 23β-configuration in (II) and of 22α-, 22β-configuration in (III) and (IV), in the sense of the Plattner convention.[2]

The reaction gives preference to the diastereoisomeric product in which the entering bromine substituent acquires the β-orientation. The stereoisomeric distribution in products varies from 71 : 29% in (II) to 83 : 17% in (III) and (IV), displaying an increase of asymmetric induction as the reaction site becomes closer to the asymmetric centre at C-20.[3]

To a solution of (Ib)[4] (1 mmole) in glacial acetic acid (20 ml.) was added a solution of iodine bromide[5] (3 mmole) in AcOH (15 ml.) and 1 ml. of 2% HBr in AcOH. The reaction mixture was kept overnight at 30° and then extracted with benzene. Removal of solvent provided an almost quantitative yield of the monobromo-aldehyde (III), m.p. 134—138°, $[\alpha]_D^{27}$ + 59°, ν_{KBr} 1730, 2690 cm.$^{-1}$.

T.l.c. shows that (III) comprises a diastereoisomeric mixture, where the predominant component has the lower R_f value. In the n.m.r. spectrum (III) displays two singlets attributable to C-18 protons at 39·6 and 43·2 c./sec.[6] in a ratio of 17 : 83. Also, in the aldehydic proton region two doublets with a similar ratio are noted, centred at 562 c./sec. with *J* 4·2 c./sec. and 570 c./sec. with *J* 1·5 c./sec., respectively.

The separation of the diastereoisomers of (III) was achieved by column chromatography (silica



gel) with light petroleum as eluant. The pure (III-β) had m.p. 142—143°, $[\alpha]_D^{27}$ +41·5° ($CHCl_3$, 1%). The minor component (III-α), was obtained in about 90% purity (based on n.m.r. analysis) and its estimated optical rotation was $[\alpha]_D^{27}$ +148° ($CHCl_3$, 1%).

The mono-bromoaldehyde (II) from the (Ia) → (II) reaction had m.p. 95—97°, $[\alpha]_D^{27}$ +60 ($CHCl_3$, 1%), ν_{KBr}, 1720, 2700 cm.$^{-1}$. Compound (IV) had m.p. 169—170°, $[\alpha]_D^{27}$ +65° ($CHCl_3$, 1%), ν_{KBr} 1725, 1730, 2700 cm.$^{-1}$.

The reaction is acid-catalysed, involving three moles of iodine bromide with liberation of one mole of elemental iodine.

If iodine bromide is added to (Id), a 1 : 1-complex is obtained which analyses as [Id][IBr], and which, when fresh, gives (Id) and IBr dissolution in polar solvents. On standing, it changes slowly into (IV)† with evolution of hydrogen iodide. This suggests that in the course of the reaction iodine is being reduced from the oxidation state +1 to −1. In solution, the hydrogen iodide is being oxidized by the IBr present as soon as it is formed. Models show that at the complex stage, formation of (V) is less hindered than formation of (VI) from (Ib—Id), giving preference to the (V) → (VII) → (III-β—IV-β) sequence over that of (VI) → (VIII) → (III-α)—(IV-α).

Mechanistic study has shown that under proper conditions the bromination of (Id) by means of bromine in acetic acid similarly proceed *via* fast formation of a 1 : 1-complex $[Br_2][Id]$, followed by elimination of HBr and formation of an identical (IV-α : IV-β) mixture.

The data now at hand suggest that in (III-β—IV-β) the C-22 proton and the aldehydic proton are approximately at right angles (IX), whereas in (III-α—IV-α) the aldehydic proton and the C-22 proton acquire *anti*-relationship (X). These representations are consistent with the coupling-constant data assembled in the Table.

That the spatial arrangement in β-oriented

TABLE

Chemical shifts and coupling constants of C-18 *methyl and aldehydic protons in diastereoisomeric pairs of monobromo-aldehydes (c./sec.)*

Isomeric form	(II-β)	(III-β)	(IV-β)	(II-α)	(III-α)	(IV-α)
δ (C-18 H)	42·0	43·2	43·8	38·4	39·6	40·8
Aldehydic proton:						
Chemical shifts (δ)	561	570	572	552	562	566
Coupling constant (J)	3·0	1·5	1·5	4·0	4·2	4·2

† In case of (Id), iodine bromide was found also to catalyse effectively acetylation of the 3α-hydroxy-group, and the resulting product was (IV).

bromo-aldehydes is less strained than in the α-oriented products is inferred from the slow change of (III-β) into (III-α) when treated with sodium bromide in refluxing acetone. This allows the conclusion that the reaction is kinetically controlled.

Although the configurational assignments at C-23 (II-β and II-α) and at C-22 (III-a—IV-α and III-β—IV-β) are consistent with the data presented here and with the prevailing views concerning asymmetric induction,‡ they should be regarded as tentative until more conclusive data are available.

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‡ The asymmetric induction rules set by W. G. Dauben, D. F. Dickel, O. Jeger, and V. Prelog (*Helv. Chim. Acta*, 1953, **36**, 308, 320, 325) have recently been extended to asymmetric oxymercuration of alkenes (J. Oda, J. Nakagawa, and Y. Inonye, *Bull. Chem. Soc. Japan*, 1967, **40**, 373; M. Kawana and S. Emoto, *Bull. Chem. Soc. Japan*, 1967, **40**, 618). Our work suggests that it can also be extended to certain electrophilic substitutions of the type described here.

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