The Bromination of saturated 3-Ketosteroids with N-Bromo-Imides

In recent issues of this journal, reports have appeared on the reaction of unsaturated ketones with N-bromosuccinimide. BUU-HOÏ[1] reported that in aliphatic ketones (*mesityl oxide type*), the bromine entered the α-position, whereas MEYSTRE and WETTSTEIN[2] found that in Δ^4-3-ketosteroids (e. g. testosterone or progesterone) bromination occurred preferentially in the allyl position. As far as we are aware, only two publications have appeared on the bromination of saturated ketones with N-bromo-imides. WOHL[3] brominated acetoacetic ester and SCHMID and KARRER[4] reported the successful bromination of cyclohexanone and of a ketopelargonic acid derivative.

We were interested in studying the bromination of saturated 3-ketosteroids with these reagents because (a) if successful, it would afford a means of brominating without the simultaneous liberation of hydrogen bromide which may cause subsequent rearrangements, and (b) to determine whether the conventional rules[5] set forward for the reaction with bromine (substitution at C_2 in members of the *allo* and at C_4 in those of the *normal* series) would hold also for this type of reagent.

It was found that by refluxing equimolar quantities of steroid ketone and N-bromosuccinimide or N-bromophthalimide in carbon tetrachloride solution in strong light[6], reaction was complete after one to two minutes as evidenced by sudden decolorization and quantitative recovery of the halogen-free imide. Evaporation of the filtrate to dryness *in vacuo* and recrystallization from a suitable solvent yielded the corresponding monobrominated steroid ketone, which in each case was found to be identical with the corresponding sample prepared by the conventional bromine-acetic acid method. The yields obtained by either method are comparable. In the absence of light, the reflux time had to be extended to about one-half hour to obtain similar results. Cholestanone-3, dihydrotestosterone hexahydrobenzoate, and methyl 3-ketoalloetiocholanate gave the corresponding 2-bromo derivatives whereas coprostanone-3 and methyl 3-keto-12-hydroxycholanate led to the respective 4-bromo compounds[7]. The above results indicate that bromination of saturated 3-ketosteroids by this method is feasible and that the substitution takes place at the same carbon atom and in the same stereochemical position as found for brominations in acetic acid[5].

Furthermore, it was of interest to us to determine whether additional bromination of the bromoketones could be accomplished with these reagents. Refluxing of 2-bromocholestanone with a slight excess over the equimolar amount of N-bromosuccinimide in carbon tetrachloride solution on exposure to strong light for one minute gave 51% of crude 2,2-dibromocholestanone. The purified product gave no depression in m.p. on admixture with an authentic sample[1]. It is interesting to note that only starting material could be recovered when the same reaction was carried out in the absence of strong light, notwithstanding the fact that the reaction time was prolonged to one and one-half hours. This is in contrast to the above-mentioned monobromination of cholestanone, which was essentially complete after one-half hour in the dark.

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Zusammenfassung

Die Bromierung von gesättigten 3-Keto-steroiden mit N-Brom-succinimid oder N-Brom-phthalimid liefert die 2-Brom-3-keto-steroide bei Verbindungen, die der *allo*-Reihe angehören, und die 4-Brom-3-keto-steroide bei Vertretern der *normal*-Reihe. Die weitere Bromierung eines 2-Brom-3-ketons zum 2,2-Dibrom-3-keton ist möglich.

[1] BUU-HOÏ, Exper. *2*, 310 (1946).

[2] MEYSTRE and WETTSTEIN, Exper. *2*, 408 (1946).

[3] WOHL, Ber. *52*, 51 (1919). - WOHL and JASCHINOWSKI, *ib. 54*, 476 (1921).

[4] SCHMID and KARRER, Helv. chim. acta *29*, 573 (1946).

[5] Cf.: BUTENANDT and WOLFF, Ber. *68*, 2091 (1935).

[6] Cf.: MIESCHER and co-workers, Helv. chim. acta *28*, 1252, 1497 (1945); *ib. 29*, 33, 627 (1946).

[7] In the latter case the crude bromination product, which was difficult to purify, was dehydrobrominated with pyridine to give methyl Δ^4-3-keto-12-hydroxycholenate, m. p. 145–147,5° C, $[\alpha]_D^{23} = +80{\cdot}3^0$ (acetone), max. at 242 mμ ($\log \Sigma = 4{\cdot}28$ in ethanol), in ca. 30% overall yield. RIEGEL and MCINTOSH, J. amer. chem. Soc. *66*, 1099 (1944) obtained this compound in 35% yield, m. p. 144–145° C by the conventional bromination method followed by treatment with pyridine. BURCKHARD and REICHSTEIN, Helv. chim. acta *25*, 821 (1942) reported m. p. 150–152° C, $[\alpha]_D^{17} = +80{\cdot}9^0$ (acetone).

[1] 2,2-Dibromocholestanone-3, m. p. 145–147° C, $[\alpha]_D^{22} = +104^0$ (chloroform) was obtained by the recently described method (WILDS and DJERASSI, J. amer. chem. Soc. *68*, 2125, footnote 22a (1946). Its structure has been proven by conversion to Δ^1-2-bromocholestenone-3, m. p. 91·5–92·5° C, $[\alpha]_D^{24} = +37{\cdot}4^0$ (chloroform), max. at 255·5 mμ ($\log \Sigma = 3{\cdot}93$ in ethanol). The details will appear in a subsequent publication from this laboratory.

Action de l'eau oxygénée sur un anaérobie strict

Au cours de leurs travaux sur l'action toxique de l'oxygène, ELLIOT et LIBET[1], STADIE[2], DICKENS[3], MANN et QUASTEL[4] ont montré que cette action s'expliquait par l'empoisonnement de certaines diastases. Nous avons de notre côté constaté que:

1° Lorsque l'on ajoute de faibles quantités d'eau oxygénée à une suspension de *Cl. saccharobutyricum* dans un tampon de phosphate renfermant du glucose, en atmosphère d'azote, on constate un arrêt de la production d'H_2 qui reprend, après un temps de latence, avec une vitesse égale à celle du témoin.

2° Pour des quantités plus fortes d'eau oxygénée, le temps de latence augmente et la reprise de la production d'H_2 se fait à une vitesse plus faible que celle du témoin.

3° Enfin à partir d'une certaine concentration en eau oxygénée, l'arrêt de la production d'H_2 est définitif.

4° On a donc une concentration provoquant un arrêt réversible et une concentration provoquant un arrêt irréversible. Ceci est à rapprocher des ancienes constatations de QUASTEL et STEPHENSON[5] sur l'action de l'eau oxygénée dans la croissance de *Cl. sporogenes*.

5° Les quantités d'eau oxygénée nécessaires pour produire le phénomène sont fonction du poids des bac-

[1] ELLIOT et LIBET, J. biol. Chem. *143*, 227 (1942).

[2] STADIE, RIGGS et HANGAARD, Amer. J. med. Sci. *207*, 84 (1944).

[3] DICKENS, Bioch. J. *40*, 145 et 171 (1946).

[4] MANN et QUASTEL, Bioch. J. *40*, 139 (1946).

[5] QUASTEL et STEPHENSON, Bioch. J. *20*, 1125 (1926).