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# DICHLOROBIS(BENZONITRILE)PALLADIUM(II). A NEW STEREOSPECIFIC CHLORINATING AGENT OF STEROLS

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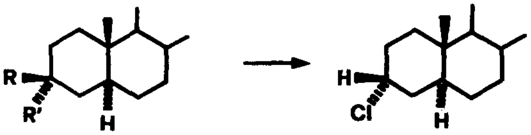
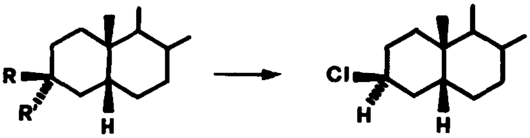
In connection with our current work on the development of new synthetic methods in the steroid field through organometallic and coordination compounds, we have found that dichlorobis-(benzonitrile)palladium(II) exhibits the features of a stereospecific chlorinating agent of sterols. $Pd(PhCN)_2Cl_2$[1] reacts stereospecifically with 5α- or 5β-cholestan-3-ols to give the 3-chloro derivatives in high yields. The reactions are performed with equimolar amounts of the reagents in benzene solution at 60° for two hours.



I R=OH R'=H
II R=H R'=OH

III



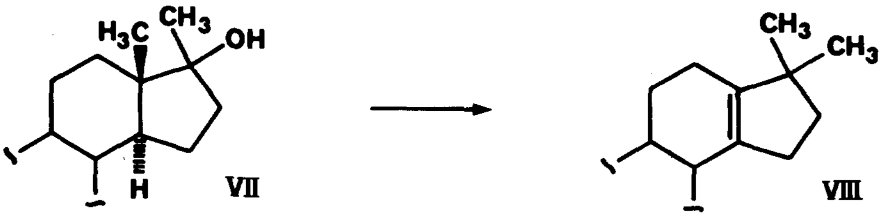
IV R=OH R'=H
V R=H R'=OH

VI

Both cholestanol (I) and epicholestanol (II) give 3α-chloro-5α-cholestane (III) (80%) and $\Delta^2$--cholestene (20%). Coprostanol (IV) and epicoprostanol (V) afford 3β-chlorocoprostane (V) (85%). The reaction products were identified by NMR spectroscopy, specific optical rotatory power, and melting points.[2] No reaction occurs by treatment of the sterols with HCl, while the epimerization of the sterols in the reaction has been excluded by thin-layer chromatography. The palladium salt may be recovered almost quantitatively after the hydrolysis of the reaction mixture and converted to $PdCl_2$.

It must be emphasized that the stereochemical course of the chlorinating mode of $Pd(PhCN)_2Cl_2$ is markedly at variance with that of the commonly used reagents such as $SOCl_2$ (retention)[3] and $PCl_5$ (inversion).[4] In fact, we observe a configuration inversion when the OH group is equatorially oriented as in I and V, and a substitution with retention when the OH group is axially oriented as in II and IV, the substitution stereoselectivity being closely connected to the environment of the alcoholic group. The reaction of cholesterol with the complex gives cholesteryl chloride (80%; mp 96°, lit[5] 96°), as both thionyl chloride[6] and phosphorous pentachloride.[7] The retention of configuration is in agreement with the behaviour usually observed in the replacement reactions at C-3 in the 3β-substituted $\Delta^5$-steroids, which is ascribed to the operation of an unimolecular mechanism with the formation of a homoallylic carbocation.[8,9]

An example which proves the formation of an intermediate carbocation assisted by the angular methyl is given by the reaction of 17β-methyl-17α,3β-diol-androst-5-en-3-acetate (VII), which affords 17-methyl-3β-ol-androsta-5,13-dien-3-acetate (VIII) (mp 88°, lit[10] 88°), through a Wagner-Meerwein rearrangement.



The influence of the steric environment on the reactivity of the coordination compound is evidenced by hindered sterols as 11α- and 12α-hydroxyandrostane, 2α-methyl-cholestan-3β-ol, and 2,2-dimethyl-cholestan-3β-ol, 4,4-dimethyl-cholestan-3β-ol forming the corresponding chloro derivative in low yields (20%). This regioselective action of Pd(PhCN)$_2$Cl$_2$ has been tested on the methyl ester of the 3α,12α-dihydroxycholanic acid; the expected 3β-chloro-12α-hydroxy derivative was obtained (85%, mp 134°, lit[11] 135°).

Kinetic studies are in progress to clarify the operating mechanism. The preliminary step must involve the coordination of the alcoholic group to the metal. Accordingly, (i) the esterification of the -OH group as benzoate or tosylate inhibits the reactions; (ii) in the spectrum of Pd(PhCN)$_2$Cl$_2$ the absorption maximum at 370 nm immediately shifts to 440 nm by the addition of sterols and simple alcohols, in agreement with the replacement of a nitrogen-bonded ligand in higher position in the spectrochemical series.[12]

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