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21-FLUORO-CARDENOLIDES

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For estimation of the influence of fluorination at C21 of the lactone ring of cardenolides on their cardiac activity we have synthesized 21$_\alpha$ - and 21ß-fluoro-cardenolides by treatment of 21ß-bromo-cardenolides with AgF. Prior to allylic bromination of cardenolides their OH- groups are protected by CCl_3CH_2OCO- groups and deprotected after fluorine introduction. Alternative use of CH_3CO- or CCl_3CO- groups leads to lactone ring opening or 21-F/21-OMe exchange during deprotection beside formation of Δ^{16} derivatives. As NMR shows, the energy minimum for rotation of the lactone ring relative to the steroid skeleton around the bond C17-C20 is shifted by 21-F substitution by about 180° to C22 near C14. Furthermore, rotational mobility of the lactone ring is more strongly reduced by 21-F than by 21-CH_3, -Cl, -Br, -CN, possibly by stronger dipole orientation. The influence of 21-F substitution in cardenolides on their cardiac activity (measured as inhibitory strength on Na,K-ATPase of guinea pig cardiac muscle or human brain) depends on the structure of parent compounds: Strong reduction of activity ($\sim$ 1/30) in 16ß-O-acetyl cardenolides, no or slight reduction (1/1 - 1/5, 21ß-epimer more active than 21 α) in 16ß-OH cardenolides, and strong increase of activity ($\sim$ 40 times) in Δ^{16} cardenolides. The known fluorination at C22 leads to increased activity and C21 near C14 conformation. This favours the conclusion that C22 near C14 conformation is less favourable for the interaction with the ATPase. The activity enhancement by 21-F in the Δ^{16} series must be related to its altered lactone ring conformation (s-trans).