SYNTHESIS OF NEW STEROIDAL PYRIMIDOBENZIMIDAZOLE DERIVATIVES

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Synthesis of benzimidazo[1,2-a]pyrimidines has gained considerable interest because of the pronounced biological activity of these compounds. They were reported to have antibacterial, anticaner, sedative, and antiarrhythmic. Some of them (fasiplon, taniplon, divaplon) have found application as anxiolytic drugs. However only a few steroid fused pyrimido[1,2-a]benzimidazoles have been described so far. Since nowadays there is a tendency to combine two pharmacophores in one hybrid molecules, which potentially is more effective than its individual components, we attempted to connect steroid skeleton with benzimidazo[1,2-a]pyrimidine.

To synthesize the steroidal pyrimidobenzimidazole derivative we have carried out the condensation of 16-dehydropregnenolone acetate with 2-aminobenzimidazole under various reaction conditions (Fig. 1). As 2-aminobenzimidazole possesses two nucleophilic nitrogen atoms (NH2 and N3) the condensation may lead to two isomeric pyrimidines. However, the aromatic product was formed regioselectively, by conjugated addition of N3 of benzimidazole to C16 of steroid, followed by cyclization, autoxidation, and aromatization. Unexpectedly, the major product was accompanied by the D-homo ketone produced by competitive α-ketol type rearrangement of the hydroperoxide intermediate. The tentative mechanism is postulated. The elucidation of the product structures was carried out by NMR, IR, MS and X-ray methods as well as chemical evidences.

Fig. 1. The reaction between 16-dehydropregnenolone acetate and 2-aminobenzimidazole.

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