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SHORT COMMUNICATIONS

Synthesis of Pyrrolyl-Substituted Steroids through Dihydroisoxazole Derivatives

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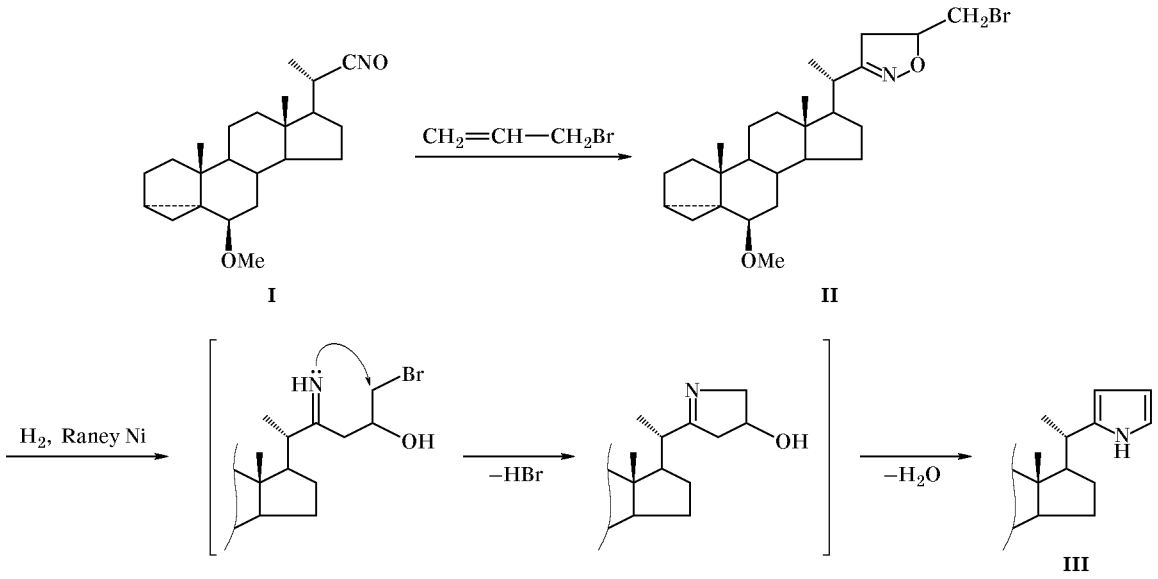
The nitrile oxide technique based on 1,3-dipolar cycloaddition of nitrile oxides to olefins or acetylenes with subsequent transformations of the adducts is an important method for preparation of complex organic compounds [1], including heterocyclic derivatives [2]. We previously demonstrated the efficiency of this procedure in building up steroid side chains, specifically in the synthesis of insect hormones and brassinosteroids [3–11]. While studying new applications of the nitrile oxide technique, involving bromo derivatives of isoxazolyl steroids, we have discovered an interesting transformation of dihydroisoxazole ring under conditions of reductive cleavage, which leads to formation of a pyrrole ring.

By 1,3-dipolar cycloaddition of nitrile oxide **I** [5] to allyl bromide we obtained bromo derivative **II** [12] whose hydrogenation in the presence of boric acid gave compound **III**. The spectral parameters of the latter indicated the presence of a new heteroring in the steroid side chain. The IR spectrum of **III** contained no carbonyl absorption, and in the ^{1}H NMR spectrum three one-proton quartets were observed at δ 5.86, 6.12, and 6.62 ppm. These signals were assigned to pyrrole ring protons.

Examples of formation of substituted pyrroles by recyclization of isoxazoles and 4,5-dihydroisoxazoles with an appropriate carbonyl-containing substituent are known from the literature [2]. In these cases the pyrrole heteroring is formed via intramolecular addition of amino group to the carbonyl carbon atom, and the subsequent dehydration yields an aromatic system. The formation of product **III** in the hydrogenation of **II** over Raney nickel is likely to result from intramolecular nucleophilic substitution involving the



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bromomethyl group. The imino group formed by hydrogenation of the N–O bond acts as nucleophile which replaces the bromine atom at C^{25}, leading to closure of dihydropyrrole ring. Protonation of the hydroxy group and elimination of water give aromatic pyrrole system.

(20*S*)-6β-Methoxy-20-(2-pyrrolyl)-3α,5-cyclo-5α-pregnane (III). Compound **II** [12], 380 mg, was dissolved in a mixture of 25 ml of ethyl acetate and 25 ml of ethanol. Boric acid, 185 mg, was added to the solution, and hydrogenation over Raney nickel was carried out for 3 h. The mixture was filtered, the catalyst was washed with boiling ethanol, the filtrate was evaporated, and the residue was subjected to column chromatography on silica gel using cyclohexane–ethyl acetate mixtures (60 : 1, 40 : 1, and 20 : 1) as eluent. Yield 136 mg (47%). ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.28 d (3H, 21-Me, J = 7 Hz), 2.78 m (1H, 6-H), 3.32 s (3H, OMe), 5.86 q (1H, H_{arom}), 6.12 q (1H, H_{arom}), 6.62 q (1H, H_{arom}). IR spectrum, ν, cm^{-1}: 3030–2810, 1710, 1570, 1460, 1380, 1330, 1300, 1285, 1205, 1100, 1025, 980.

The ^{1}H NMR spectrum was recorded from a solution of **III** in $CDCl_3$ on a Bruker AC-200 spectrometer (200 MHz) using TMS as internal reference. The IR spectrum (700–3600 cm^{-1}, KBr) was measured on a UR-20 instrument. The progress of the reaction was checked by TLC on Kieselgel 60 F_{254} plates (Merck).

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