SYNTHESIS OF 13,15-PYRAZOLOPROSTANOIDS

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The synthesis of novel prostanoids with a pyrazole fragment in the \alpha-chain is reported starting from isoxazole derivatives.

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We have previously carried out the synthesis of 13,15-isoxazoloprostanoids 1-3 [1, 2] which have a fully formed prostaglandin (PG) structure (functionalized carbocycle, \alpha- and \omega- chains) and can be considered as a group of biologically active analogs of 11-desoxyprostaglandins [3]. These compounds are convenient precursors of prostanoids with an open chain in which the C13-C15 fragment of the \omega-chain corresponds to one of the possible variants realized by the latent bifunctionality of the isoxazole (isoxazoline) ring. We have reported the fission of the heterocycle of the 13,15-isoxazoloprostanoids 1-3 leading to the corresponding 13-amino-13-en-15-oxoprostanoids 4-6 [2].

As an extension of our work on the use of this isoxazole strategy for forming the modified \omega-chain of the prostanoids [1, 2, 4] we describe in this paper the reactions of the enamino ketones 4-6 with hydrazines as a method for preparing novel modified PG's with a pyrazole fragment in the \omega-chain. The starting compounds 1, 2, 4, and 6 in these reactions are a mixture of isomers at the C9 atom and 3 and 5 are the pure 9\alpha-epimers.

Reaction of phenylhydrazine hydrochloride with compounds 4 and 5 and potassium acetate in aqueous methanol [5] at room temperature for 48 h gives the N-phenyl substituted pyrazoles 7 and 8 respectively and their structures were confirmed by physicochemical methods of analysis (Table 1). Hence, in the IR spectra of the pyrazoles 7 and 8, in place of the absorption bands for the stretching vibrations of the C=O and C=C bonds (1610, 1530 cm\(^{-1}\)) characteristically seen in the spectra of the starting enamino ketones, there is observed a band for the stretching vibration of the C=N group in the pyrazole ring (1550 cm\(^{-1}\)) together with the absence of absorptions for the amino group (3200, 3400 cm\(^{-1}\)). In their \(^1\)H NMR spectra, the signal for the heteroaromatic proton at C14 is shifted to lower field (6.02-6.06 ppm) when compared with the signal for the vinyl proton in the starting compounds 4, 5 (5.05-5.08 ppm). A similar shift is experience by the signal for the methine proton at C15 (2.3-2.5 to 2.76-3.06 ppm), in addition to the appearance of the multiplet signal for the phenyl substituent at 7.4 ppm. The broadened singlet signals of the amino group in the starting enamines are not observed.

Reaction of the enamino ketones 4, 6 with hydrazine hydrate in methanol at room temperature gives the corresponding pyrazoles 9, 10 in 70-80% yield. Their IR spectra (as the spectra of the phenylpyrazoles 7, 8) show a C=N absorption band at 1560 cm\(^{-1}\) and, in contrast to the starting enamino ketones, the absence of absorption bands for the conjugated C=O and C=C bonds as well as the amino group.

The \(^1\)H NMR spectra of compounds 9, 10 (as the spectra of 7, 8) show a characteristic downfield shift for the signals of the protons at the C14 atom (in the region of 5.8 and 6.4 ppm respectively) when compared with the signals for the starting enamino ketones 4 and 6 at 5.05 and 5.8 ppm respectively as do the signals of the protons at C12 (2.3-2.5 to 2.76-3.06 ppm). The spectra of the pyrazoles 9, 10 also show broadened singlet signals for the NH group in the region 3.8-5.2 ppm (9b at 7.8 ppm).
The preferred formation of the regioisomers 7-10, with the substituents $R^1$ and $R^2$, bound to the neighbouring C and N atoms, can be explained on the basis of the mechanism of the reaction of hydrazines with enamino ketones [6], according to which the first stage of the synthesis occurs via "reenamination" of the starting enamino ketone and formation of a hydrazon with a subsequent cyclization to the pyrazole. This is confirmed by comparison of the $^1H$ NMR spectra of the obtained products with the spectra of the materials related to the structure of the pyrazoles [7]. The chemical shifts of the allyl protons in the pyrazole derivatives are characteristic for the regioisomers and this is due to their different shielding by the C=N and C=C bonds of the heterocycle. From the increased chemical shifts of the 12-H and 16-H protons, the pyrazoles obtained were assigned the regioisomer structures 7-10. The existence of an overall correlation of the $^1H$ NMR spectra of the pyrazoles 7-10 with those of the corresponding isoxazoles 1-3 should also be noted. Hence, in the spectra of the latter, the 12-H proton is found in the region 2.9-3.1 ppm (2.8-3.1 for the pyrazoles) and the triplet for the methylene protons of the C$_{10}$H$_2$ fragment at 2.7 ppm (2.6 for compounds 7, 9, 10) and this can serve as indirect confirmation of the structure of the obtained pyrazoles as the regioisomers 7-10. Moreover, the stereochemistry of the 8-H, 9-H, and 12-H chiral centers in the prostanooid molecule is retained in the reaction process as confirmed by the corresponding $^1$H NMR spectroscopic parameters [8].

In the synthesis of compounds 9 and 10 there are also formed ~5% of regioisomeric pyrazoles 11, 12, as judged by the $^1$H NMR spectra of the reaction mixtures. The signals for the 12-H protons in the regioisomeric products 11, 12 are displaced to downfield when compared with the analogous protons of the pyrazoles 9, 10. Lowering of the regioselectivity of the reaction may be explained by the fact that the hydrazine molecule is less polar and more compact when compared with the phenylhydrazine molecule.