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# SYNTHESIS OF 13,15-ISOXAZOLINO-15-HETEROARYL-PROSTANOIDS

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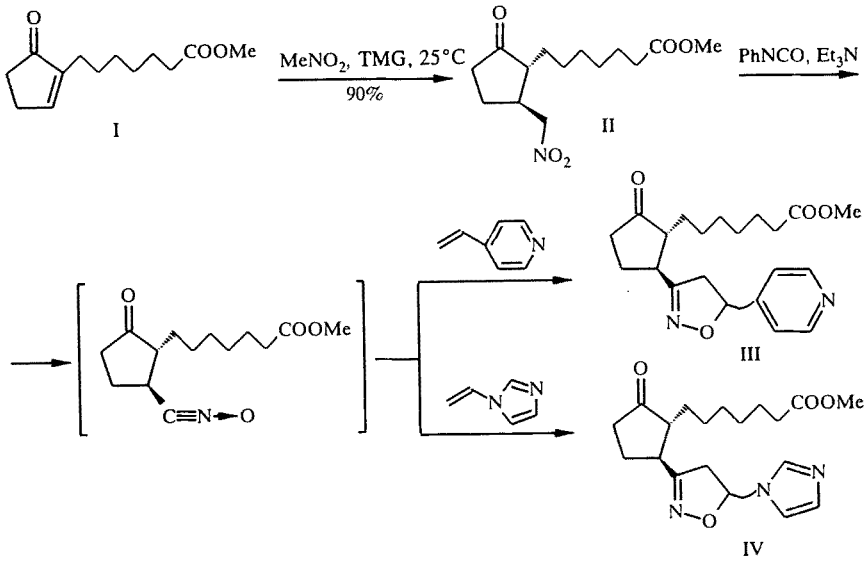
*The synthesis of new intermediates for 15-heteroarylprostanoids has been effected by the isoxazole method.*

Among prostanoids modified with heteroatoms at various positions in the prostane skeleton, many compounds have been found with actions more specific and prolonged than the natural compounds [1, 2], which is one of the chief problems in the synthesis of prostaglandin analogs. The synthesis is described in the present study of new heteroprostanoids with an ω chain modified with several heteroatoms, forming two different heterocycles, using the nitrile oxide (isoxazole) approach for forming the structure of the prostanoid side chains [3, 4]. For this purpose, the conjugate addition product of nitromethane to 2-methoxycarbonylcyclopent-2-en-1-one (I), viz. ester (II), was treated with phenyl isocyanate to give the corresponding nitrile oxide, which reacted *in situ* with 4-vinylpyridine or 1-vinylimidazole forming the adducts (III) and (IV), respectively. The latter represent a new group of modified prostanoids.




The structures of adducts (III) and (IV) were established on the basis of spectral data. In the IR spectra of the products of 1,3-dipolar cycloaddition there were no bands for the stretching vibrations of the nitro group but a characteristic absorption band for the stretching vibrations of the C=N bond was observed at 1595-1615 $cm^{-1}$. Peaks were observed in the mass spectra corresponding to the molecular ions of the adducts. There were characteristic multiplet signals in the PMR spectra for the 4-H and 5-H protons of the isoxazoline ring and also signals for the pyridine ring at 7.2-8.0 ppm for compound (III) and for the imidazole ring at 7.0-8.5 ppm for compound (IV), together with signals for the cyclic protons of the carbocycle, the alkyl protons of the α chain and of the ester group. The multiplicity of the signals for the protons in positions 4 and 5 of the isoxazoline ring indicates the formation of two isomeric cycloadducts. On the basis of their PMR spectra such pairs of products,

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indistinguishable in chromatographic mobility, must be assigned to stereoisomerism at $C_{(5)}$ of the isoxazoline formed by nonstereoselective addition of the nitrile oxide. If these adducts were regioisomers then their PMR spectra would differ significantly. The relatively low yield of the product (IV) is evidently linked with the effect of the heteroatom of the imidazole ring on the electron density distribution in 1-vinylimidazole. However the formation of a regioisomeric adduct which might have been expected under electronic control of the reaction was not observed in this case.

The prostanoids thus obtained with heterocyclic fragments in the chain are in turn convenient intermediates for 15-heteryl substituted prostaglandin analogs, conversion to which is effected by selective fission of the isoxazoline ring after preliminary modification by the scheme described by us for analogous intermediates [5].

## EXPERIMENTAL

The IR spectra were taken in films on a UR-20 spectrometer, and the PMR spectra on a Bruker WP-200 (200 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained on a Varian MAT-311 instrument with an ionizing energy of 70 eV. Column chromatography was carried out on 40/100 $\mu$ silica gel (Czechoslovakia). Silufol UV-254 (Serva) and Kieselgel 60 $F_{254}$ (Merck) plates were used for TLC in the system chloroform–methanol, 85:15, visualizing with anisaldehyde. Preparative TLC was carried out on glass plates with Kieselgel L 5/40 $\mu$, the eluent being 5% methanol in chloroform.

**2$\alpha$-(6-Methoxycarbonylhexyl)-3$\beta$-{3-[5-(4-pyridyl)4,5-dihydroisoxazolyl]}cyclopentan-1-one (III), $C_{21}H_{28}N_2O_4$ and 3$\beta$-{3-[5-(1-Imidazolyl)-4,5-dihydroisoxazolyl]}-2$\alpha$-(6-methoxycarbonylhexyl)cyclopentan-1-one (IV), $C_{19}H_{27}N_3O_4$.** Phenyl isocyanate (3 mmoles) and triethylamine (0.1 ml) were added in turn to 2-(methoxycarbonylhexyl)-3-nitromethylcyclopentan-1-one (II) (1 mmole) and the vinylhetarene (5-7 mmoles) dissolved in dry benzene (15 ml) in an atmosphere of argon. The mixture was carefully heated to 30-35°C with stirring (until turbidity), maintained at the same temperature for 4 h, and then at room temperature for 36 h. The solid was filtered off, the filtrate passed onto a column of aluminum oxide, and the column washed with a mixture of ether and hexane. The product was washed from the column with 20% methanol in ether, and when necessary purified further by column chromatography on silica gel using gradient elution with ether–methanol, or by preparative TLC. Compound (III) was obtained from the nitromethylcyclopentanone (II) and 4-vinylpyridine as a 1:1 mixture of stereoisomers. IR spectrum: 1740, 1605, 1565, 1440, 1412, 820 $cm^{-1}$. PMR spectrum: 1.25-2.60 (17H, m, $CH_2$, CH chain and carbocycle); 2.92 (1H, q, J = 18.0 and 7.0 Hz, 4-$H_{isoxazole}$); 2.98 (1H, m, 3-$H_{carbocycle}$); 3.50 (1H, J = 18.0 and 10.0 Hz, 4-$H_{isoxazole}$); 3.68 (3H, s, OMe); 5.65 (1H, m, 5-$H_{isoxazole}$); 7.23 and 8.60 ppm (4H, m, $H_{pyridine}$). $M^+$ 372. Yield 85%.

Compound (IV) was obtained from the nitromethylcyclopentanone (II) and 1-Vinylimidazole in 55% yield as a 1:1 mixture of stereoisomers. IR spectrum: 1740, 1605, 1550, 1500, 1440, 760 $cm^{-1}$. PMR spectrum: 1.25-2.55 (17H, m, $CH_2$, CH chain and carbocycle); 3.05 (1H, q.q, $J_{2,3}$ = 11.0 Hz, 3-$H_{carbocycle}$); 3.15 and 3.24 (1H, d t, $J_{gem}$ = 18, $J_{4,5}$ = 3.5 Hz, 4-$H_{isoxazole}$); 3.54 (1H, q.q, J = 18.0 and 9.0 Hz, 4-$H_{isoxazole}$); 3.66 (3H, s, OMe); 6.44 (1H, d.d, J = 9.0 and 3.5 Hz, 5-$H_{isoxazole}$); 6.90, 7.12, 7.68 ppm (3H, s.s.s, $H_{imidazole}$). $M^+$ 361.

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