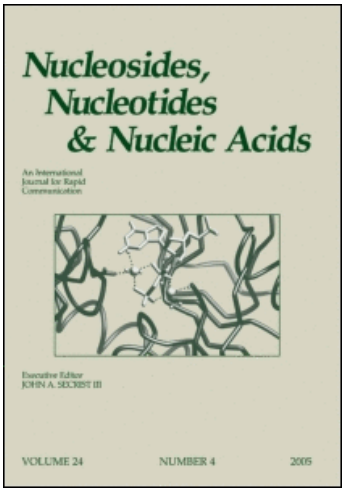

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Glycosylation of Mono- and Bicyclic Dicarbonic Acid Imides

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GLYCOSYLATION OF MONO- AND BICYCLIC DICARBONIC ACID IMIDES

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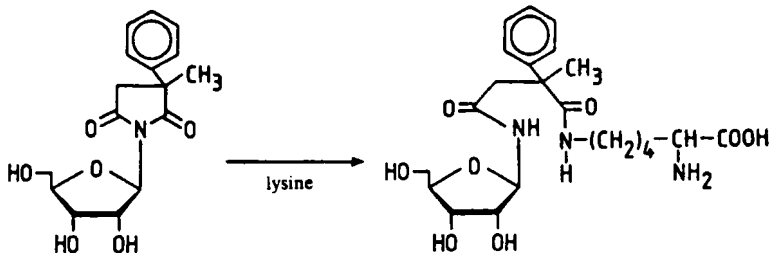
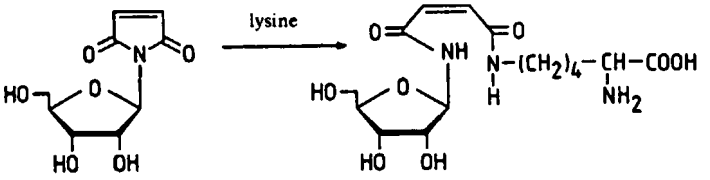
ABSTRACT. - Glycosylation of some mono- and bicyclic dicarbonic acid imides was performed via the Friedel-Crafts-catalyzed silyl Hilbert-Johnson reaction. The occurrence of β-N-ribosylation was established by ^{1}H and ^{13}C NMR spectroscopy. The electron distributions in the lactam region of the N-silylated cyclic imides strongly influence the glycosylation. The N-glycosylated cyclic imides are potential agents for glycoalkylation of lysine residues in proteins.

In addition to the well established specificity for thiol groups N-ethylmaleinimide is known to react with amino acid side chains [1-2]. Of interest in this context is the naturally occurring nucleoside showdomycin which contains maleinimide as an aglycon and acts as a suicide substrate [3]. Our efforts were therefore directed to the N-glycosylation of mono- and bicyclic dicarbonic acid imides which are potential agents for glycoalkylation of e.g. lysine. This has been ascertained by ring opening reactions



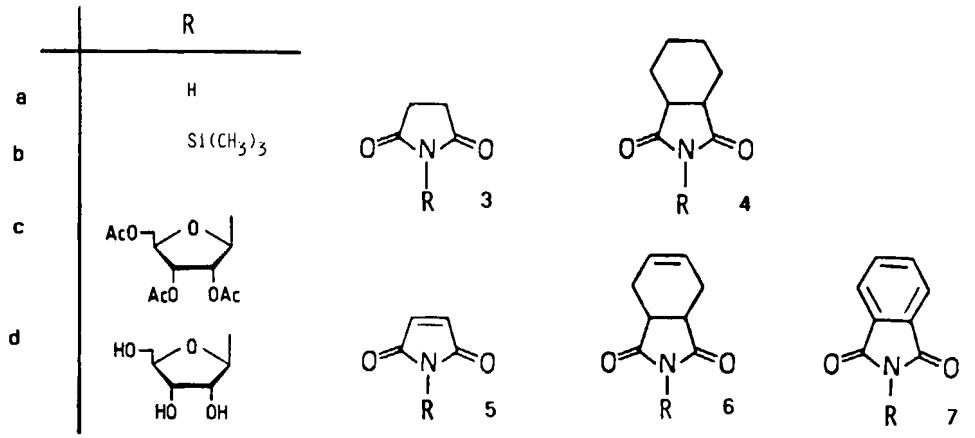
1 2

of 3-methyl-3-phenyl-1-β-D-ribofuranosylpyrrolidin-2,5-dione (1) [4] and of isoshowdomycin (5d) with lysine leading to 2 and 8, respectively [5].



5d 8

Glycosylation of the mono- and bicyclic imides 3a-7a was performed via the Friedel-Crafts-catalyzed silyl Hilbert-Johnson reaction [6-9]. The silylation of the imides was carried out with either hexamethyldisilazan or N,O-bis-(trimethylsilyl)trifluoracetamide [5, 10]. The ^{29}Si-signal around 13 ppm indicated that all the trimethylsilyl compounds 3b-7b prepared were N-silylated. The proton signals of the cyclic imides between 10.8-11.33 ppm indicated a similar basicity in all cases so that only N-silylated products were obtained.



Among the N-silylated imides the compounds 3b, 4b and 6b could be converted to the appropriate nucleosides 3d, 4d and 6d. The ribosylation was performed by reaction of 3b, 4b and 6b with peracylated ribose in acetonitrile in the presence of tin tetrachloride as the catalyst to give the electrophilic sugar cation. The other N-silyl imides 5b and

compd.	^{29}Si-NMR* ppm	^{13}C-NMR** (C=O) ppm	ribosylation yield in %
3b	13.70	182.09	86
4b	13.45	184.32	16
5b	12.82	176.00	0***
6b	13.92	184.95	37
7b	12.87	172.51	0 (trace)

(*) and (**) carried out in $CDCl_3$; (***) 5d was synthesized according to [12].

7b did not yield the desired sugar derivatives. Due to the above mentioned nucleophilic ring opening reactions with amino compounds such as lysine or ammonia, the deprotection of the acylated products 3c, 4c and 6c was carried out with HCl in methanol giving 3d, 4d and 6d in good yield. The occurrence of β-N-glycosylation was established by ^{1}H and ^{13}C NMR spectroscopy; the symmetry of each aglycon was proved by the identical ^{13}C NMR singlet of the imide carbonyls. The N-ribosylated compounds 3c, 4c and 6c were generated very probably from the primarily formed O-ribosides by transribosylation which, according to [11], is possible in the presence of excess peracylated sugar. The formation of the O-glycosides requires an intermediate lactimisation of the N-silyl compounds which depends on the electron distribution of the lactam system. In the case of 3b, 4b and 6b the ^{13}C NMR signal of the carbonyl atoms is centered around 184 ppm whereas it is shifted upfield in the silylated components 5b and 7b (Table). That means, in contrast to the compounds 3b, 4b and 6b the electron distributions in the lactam region of 5b and 7b apparently do not allow intermediate lactimisation.

In summary , N-glycosylated maleinimides possess two bioreactive sites, namely, the double bond for the addition of thiols and the lactam bond for the nucleophilic ring opening reaction. The corresponding succinimide derivatives are distinguished by one bioreactive site only. Thus they have potential as specific agents for site-directed glycosuccinylation of lysine residues in proteins.

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