SYNTHESIS OF PRECURSORS
OF HETEROCYCLIC cis-β-AMINO
ALCOHOLS BY INTRAMOLECULAR
AMIDOALKYLATION OF
4-HYDROXYOXAZOLIDIN-2-ONES*

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The reaction of intramolecular amidokylation of 4-hydroxyoxazolidin-2-ones leads to formation of novel and rare heterocyclic systems: substituted 1,5,6,10-tetrahydro[1,3]oxazolo[4,3-a]isoquinolin-3-ones, 3a,4,5,10b-tetrahydro[1,3]dioxolo[4',5':6,7]naphtho[1,2-d][1,3]oxazol-2(1H)-ones, and 5,6,10a-tetrahydro-1H-d[1,3]oxazolo[3,4-d:4,3-g][1,4]-diazepine-3,8-diones. Mild reaction conditions and the simplicity of isolation of the compounds formed make it possible to obtain the indicated heterocycles in high yields.

Keywords: cis-β-amino alcohols, 4-hydroxyazolidin-2-ones, di[1,3]oxazolo[3,4-d:4,3-g]diazepine-3,8-diones, [1,3]dioxolo[4',5':6,7]naphtho[1,2-d][1,3]oxazol-2(1H)-ones, [1,3]oxazolo[4,3-a]isoquinolin-3-ones, calycotomine, intramolecular amidokylation.

We earlier studied in details the reaction of dioxolanones 1 with amines, leading to oxazolidinones 2 [1]. Under intramolecular amidokylation conditions, such oxazolidinones are sources of acyliminium ions which can react with various π- and n-nucleophiles. If a π-electron donor functional group is present in the chain of one of the oxazolidinone substituents, then the acyliminium ion reacts with it. In particular, it has been shown that the presence of a 4-methyl-3-pentenyl residue in the position 5 of the oxazolidinone ring makes it possible to obtain derivatives of 1-oxa-3-azapentalen-2-one, which can be considered as precursors of cyclopentane cis-β-amino alcohols [2].

An activated benzene ring also can act as such a π-electron donor substituent. To study the behavior of the activated benzene ring under intramolecular amidokylation conditions, we synthesized the starting oxazolidinones 2a-d from dioxolanones 1a-d and 2-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine).

In the 1H NMR spectra of oxazolidinones 2a-d (Table 1), we see characteristic signals from the hydroxyl and methyl groups in the 4 position; for the benzene ring, there are three proton signals. In the IR spectrum (Table 2), we detect vibrations of the C=O and OH groups; in the mass spectrum (Table 2), there is a signal for the molecular ion peak.

* Dedicated to the memory of A. N. Kost in celebration of the 85th anniversary of his birth.
From oxazolidinones 2a-d, we obtained derivatives of the alkaloid calycotominine.

We used standard conditions described in [3]. In the opinion of the authors of that review, HCOOH is simultaneously the best acid agent and solvent. In our experiments, the results of cyclization were identical in HCOOH and CF₃COOH: tetrahydroisoquinolines 4a-d were formed in high yields. The starting oxazolidinones 2a-d were reacted without preliminary purification; they may contain the dehydration product (the corresponding 4-methyleneoxazolidin-2-one) as an impurity. But just as for oxazolidinone 2, in acid medium it is converted to the same acylinium species A through which the amidoalkylation process also occurs. In the ¹H NMR spectra of tetrahydroisoquinolines 4, we see two singlets from the aromatic protons in the 7 and 10 positions (6.45-6.63 ppm) with intensities ¹H (sometimes, just one singlet with intensity 2H), which indicates the site of attack by the acylinium ion on the benzene ring. Furthermore, we see signals from the methyl group at the 10b position (1.49-1.53 ppm, 3H), the protons on the CH₂CH₂ moiety of the piperidine ring (2.6-4.13 ppm, three or four series of multiplets with total intensity 4H), the OMe group on the benzene ring (3.82-3.84 ppm, one singlet (6H) or two singlets (3H each)). There is an absorption band for the C=O group in the IR spectra. In the mass spectra of tetrahydroisoquinolines 4, there is a signal for the molecular ion.

According to our preliminary investigations, base hydrolysis of tetrahydroisoquinoline 4a leads to formation of the corresponding trimethyl-substituted calycotominine; future publications will focus on the hydrolysis results.

In [4], the tetrahydroisoquinoline E is described, which is related to our tetrahydroisoquinoline 4a but has an n-butyl group in the 10b position rather than a methyl group. It was synthesized in HCOOH from the corresponding oxazolidinone C. The starting oxazolidinone C was prepared from oxazolidin-2,4-dione B by reaction with butyllithium; in this case, the reaction was complicated by formation of the by-product D.