NEW METHOD OF SYNTHESIS OF THE 1,3,2-DIOXAZOLIDINE RING*

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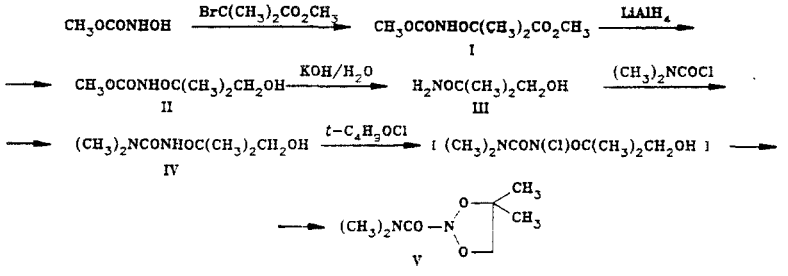
A new method of synthesis of the 1,3,2-dioxazolidine ring is developed based on the synthesis of 2-dimethylcarbamoyl-4,4-dimethyl-1,3,2-dioxazolidine by intramolecular cyclization of 1,1-dimethyl-3-(1,1-dimethyl-2-oxyethoxy)-3-chlorourea.

Optically active compounds with an asymmetrically substituted nitrogen atom at present are known only for 1-alkyldiaziridines [2]. The NH pyramid which is stable under usual conditions is also observed in 2H-oxaziridines [3] and only in two heterocycles of large size, the five- and six-membered rings with the ONHO fragment [4, 5], in which, in agreement with the value of [5], the inversion barrier of the nitrogen atom in 1,3,2-dioxazolidine is the same as in diaziridines (~28 kcal/mole). The combination of high configurational stability of the nitrogen atom and the substantial hindrance to HN exchange make these compounds convenient objects for stereochemical studies [5] and create the circumstances for separation of chiral 2H-1,3,2-dioxazolidines into antipodes, however, only 1,3,2-dioxazolidine has been described [4]. Thus, in this work an attempt at the synthesis of chiral 4,4-dimethyl-1,3,2-dioxazolidine is made.

The single known method of synthesis of 2H-1,3,2-dioxazolidines is the base hydrolysis of their 2-dimethylcarbamoyl derivatives [4], therefore, the synthesis of 2-dimethylcarbamoyl-4,4-dimethyl-1,3,2-dioxazolidine (V) was planned for solving the problem at hand. Unsubstituted 2-dimethylcarbamoyl-1,3,2-dioxazolidine was synthesized earlier by two methods, acid catalyzed reaction of 1,1-dimethyl-3,3-dimethoxyurea with ethyleneglycol or intramolecular cyclization of 1,1-dimethyl-3-methoxy-3-(2-oxyethoxy)urea [4]. For synthesis of V, the first method apparently is not suitable since it requires carrying out the cyclization with a sterically hindered glycol. We modified and simplified the second intramolecular synthetic variant based on reaction of 3-alkoxy-1,1-dimethyl-3-chlorourea with alcohols, in which nucleophilic displacement of the chlorine atom with formation of 3,3-dialkoxy-1,1-dimethyl urea occurs [6].



The starting alkoxyamine III was obtained by the synthetic method for 2-oxyethoxyamine [7]. Further, it underwent N-dimethylcarbamoylation, N-chlorination (without separation), and cyclization with base.

Thus, a new method of synthesis of the 1,3,2-dioxazolidine ring was developed. Earlier, bi- and tricyclic 1,3,2-dioxazolidines were synthesized by thermal [8] and photochemical

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[9, 10] 1,3-cycloaddition of nitro compounds to olefins, and N-t-alkyl-1,3,2-dioxazolidines by acid catalyzed intra- or intermolecular cyclizations of N-t-alkyl-N,N-dialkoxyamines [11].

Unfortunately, attempted base hydrolysis of V for synthesis of 4,4-dimethyl-1,3,2-dioxazolidine was unsuccessful, apparently because of its thermal instability. The latter is characteristic of V which is decomposed upon distillation in vacuum (80°C, 1 mm Hg std.), and also upon chromatographing on a column (Al_2O_3, neutral to Brockman, ether eluent).

EXPERIMENTAL

PMR spectra were taken on Jeol JNM-C-60 HL, Bruker WP-80SY, and Bruker WM-400 NMR spectrometers with internal standard TMS. Elemental analyses for C, H, and N corresponded to those calculated.

α-[N-(Methoxycarbonyl)aminooxy]isobutyric Acid Methyl Ester (I, $C_7H_{13}NO_5$). To a solution of 0.23 mole of sodium methylate in 120 ml absolute methanol were added 21 g (0.23 mole) N-oxyurethylane and 41.8 g (0.23 mole) α-bromoisobutyric acid methyl ester. The mixture was held for one day at 20°C, then refluxed for 14 h. The solvent was removed in vacuum, the residue was extracted with ether, the extract was evaporated in vacuum, and the residue was distilled. Yield 36.4 g (83%) I, bp 96°C (1 mm Hg std.). PMR spectrum (60 MHz, CCl_4): 1.61 (6H, s, CH_3C), 3.82 (6H, s, CH_3O), 7.81 ppm (1H, s, NH).

2-Methyl-2-[N-(methoxycarbonyl)aminooxy]propanol (II, $C_6H_{13}NO_4$). To a suspension of 8.1 g (0.21 mole) lithium aluminum hydride in 250 ml absolute ether were added dropwise with mixing at 0°C 21.1 g (0.11 mole) I in 50 ml absolute ether. The mixture was stirred for 5 h at 0°C, the excess aluminum hydride was destroyed by adding successively 8 ml H_2O, 8 ml 25% aqueous KOH, and 24 ml H_2O. The precipitate was separated and washed with ether. The ether extracts were combined and evaporated in vacuum, the residue was distilled, and the distillate was crystallized from a mixture of ether with pentane. Yield 12.4 g (69%) II, bp 109°C (1 mm Hg std.), mp 91-92°C. PMR spectrum (80 MHz, acetone-D_6): 1.13 (6H, s, CH_3C), 3.29 (2H, d, J_{CHOH} = 7.9 Hz, CH_2), 3.68 (3H, s, CH_3O), 4.10 (1H, t, OH), 8.99 ppm (1H, s, NH).

2-(Aminooxy)-2-methylpropanol (III, $C_4H_{11}NO_2$). A solution of 8.45 g (0.15 mole) KOH and 12.3 g (75 mmole) II in 50 ml H_2O was held for 5 days at 80°C, then extracted with ether (3 × 80 ml). The extract was dried over Na_2SO_4 and evaporated in vacuum, the residue was distilled. Yield 2.55 g (31%) III, bp 65°C (1 mm Hg std.). PMR spectrum (400 MHz, $CDCl_3$): 1.14 (6H, s, CH_3C), 3.50 (1H, t, OH), 3.58 (2H, d, J_{CHOH} = 5.2 Hz, CH_2), 5.08 ppm (2H, s, NH_2).

3-(1,1-Dimethyl-2-oxyethoxy)-1,1-dimethylurea (IV, $C_7H_{16}N_2O_3$). A solution of 2.55 g (28 mmole) III, 2.9 g (28 mmole) triethylamine, and 3.08 g (28 mmole) dimethylcarbamoylchloride in 50 ml absolute benzene was held for 7 days at 20°C, then was refluxed for 5 h. The precipitate was separated, the solvent was removed from the filtrate in vacuum, and the residue was crystallized from benzene. Yield 3.49 g (69%) IV, mp 163-164°C. PMR spectrum (60 MHz, $CDCl_3$): 1.26 (6H, s, CH_3C), 3.00 (6H, s, CH_3N), 3.43 (2H, d, J_{CHOH} = 6.8 Hz, CH_2), 5.28 (1H, t, OH), 7.28 ppm (1H, s, NH).

2-Dimethylcarbamoyl-4,4-dimethyl-1,3,2-dioxazolidine (V). To a suspension of 2.43 g (13.8 mmole) IV in 20 ml CH_2Cl_2 were added at −78°C 1.68 g (15.5 mmole) t-butylhypochlorite, then a solution of 1.68 g (13.8 mmole) 2,4,6-trimethylpyridine in 20 ml CH_2Cl_2. The mixture was held at 20°C for 30 min, diluted with 50 ml CCl_4, the precipitate separated, and the filtrate evaporated in vacuum. The residue was extracted with ether, the extract was evaporated in vacuum. Yield 1.64 g (68%) V. PMR spectrum (60 MHz, CCl_4): 1.33 (6H, s, CH_3C), 2.90 and 3.03 (6H, d, CH_3N), 4.98 ppm (2H, s, CH_2).

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NEW METHOD FOR PREDICTING THE ANTIBACTERIAL PROPERTIES OF SEMISYNTHETIC PENICILLINS.

1. LOGICAL STRUCTURAL ANALYSIS

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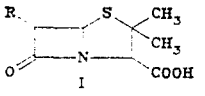
A new method for predicting the antibacterial properties of semisynthetic penicillins based on statistical evaluation of the merit of including functional groups, heteroatoms, and cyclic systems in fixed positions on the side chain of antibiotics is proposed.

The necessity of finding new medicinal semisynthetic penicillins is explained by the ability of pathogenic microorganisms to develop resistance to regularly used antibiotics. The methodology of identifying new effective compounds in a series of structural analogs of penicillin by antibacterial screening in vitro has remained unchanged for almost 30 years and is based mostly on the identification of empirical relations between the structure of the R group which is varied and the antimicrobial properties of the antibiotic I.



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A characteristic feature of such an approach is the absence of any limitation on structural modification of the side chain. It is not surprising that the quantity of semisynthetic penicillins, I, synthesized in the 1960-1980 period is estimated at not less than 20 thousand and the structure of the R substituent in them is characterized by unusual variety.

However, recently the intensity of screening new compounds has markedly decreased, aided somewhat by an impasse in planning the synthesis of structural analogs of antibiotics. This important stage of the study until now was primarily based on intuitive evaluation of the usefulness of including in the side chain of I aliphatic, aromatic, and heterocyclic systems which have not been used or modification of those already used in practice (ampicillin, amoxycillin, etc.). Such a method of identifying promising substances is accompanied by the synthesis of an unjustifiably large quantity of their weakly active derivatives.

The main reason for the low productivity of this approach is the absence of an effective predictive method which allows a quantitative evaluation of the promise of including

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