SYNTHESIS OF BICYCLIC ANALOGUES OF DEOXYVASICINONE

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6-Methyl-2,3-tri-, -tetra-, and -pentamethylene-3,4-dihydropyrimidin-4-ones and 6-phenyl-2,3-tri-3,4-dihydropyrimidin-4-one (bicyclic analogues of deoxyvasicinone) have been synthesized by the condensation of ethyl esters of β-aminocrotonic and β-aminocinnamic acids with lactams. It has been shown that the occurrence of the reaction and yields of the products of the condensation of ethyl β-aminocrotonate with lactams depend both on the number of methylene groups in the lactams and also on the reaction conditions. With an increase in the number of methylene groups of the lactams the yields of condensation products decrease.

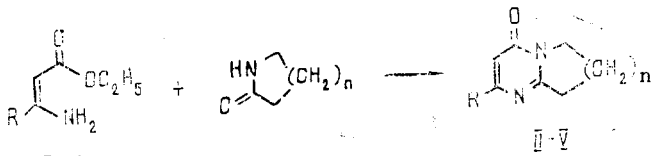
Deoxyvasicinone derivatives possess various biological activities [1]. It therefore appeared of interest to synthesize 2,3-polymethylene-3,4-dihydropyrimidin-4-ones – analogues and homologues of deoxyvasicinone having no condensed benzene ring. Up to the present there have been no reports of the synthesis and chemical transformations of these compounds.

To synthesize the 2,3-polymethylene-3,4-dihydropyrimidinones we performed the condensation of the ethyl esters of β-aminocrotonic and β-aminocinnamic acids (Ia and b) with lactams.

Ethyl β-aminocrotonate reacts with γ-butyrolactam in the presence of such condensing agents as phosphorus pentachloride and phosphorus oxychloride with the formation of 6-methyl-2,3-trimethylene-3,4-dihydropyrimidin-4-one (II).

In the presence of phosphorus pentachloride, the yield of (II) was only 28%. The most suitable condensing agent proved to be phosphorus oxychloride (yield 70%). The yield of (II) also depended on the temperature of the reaction mixture: at 20°C in 2 h 32% of product was formed, while on heating in the boiling water bath the yield was 70%. The ratio of the initial reactants also played no small role. At a ratio of ethyl β-aminocrotonate to γ-butyrolactam of 1:1, compound (II) was formed with a yield of about 40%, while at a ratio of 1:1.5 the yield was 70%. A further increase in the amount of lactam, and also a prolongation of heating did not lead to an increase in the reaction yield.

In order to synthesize six- and seven-membered analogues of these compounds we studied the reaction of ethyl β-aminocrotonate with δ-valero- and ε-caprolactams under analogous conditions, which led to 6-methyl-2,3-tetra- and -pentamethylene-3,4-dihydropyrimidin-4-ones (III and IV) with yields of 57 and 48%, respectively.



Ia,b

II-V

II. R = CH_3, n=1
III. R = CH_3, n=2
IV. R = CH_3, n=3
V. R = C_6H_5 n=1

On the basis of the facts given above, it may be concluded that the best conditions for the reaction of ethyl β-aminocrotonate with lactams are a ratio of the reactants of 1:1.5, the presence of phosphorus oxychloride as condensing agent, and a reaction of temperature

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of 90-95°C. With an increase in the number of methylene groups in the lactams their reactivities decrease.

6-Phenyl-2,3-trimethylene-3,4-dihydropyrimidin-4-one (V) – an analogue of 2,3-trimethylene-3,4-dihydroquinazolin-4-one having an uncondensed benzene ring in the pyrimidine nucleus was obtained from ethyl β-aminocinnamate and γ-butyrolactam under analogous conditions with a yield of 56%.

The IR spectra of compounds (II-V) contained absorption bands in the 1530-1625 cm^{-1} region characteristic for the combination of double bonds (N=C and C=C) of the pyrimidine ring, while the amide carbonyls in the 2,3-polymethylene-3,4-dihydropyrimidin-4-ones absorbed in the 1630-1690 cm^{-1} region.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer, mass spectra on a MKh-1303 instrument, and PMR spectra on a JNM-48-100 instrument (with HMDS as internal standard).

The ethyl esters of β-aminocrotonic and β-aminocinnamic acids were obtained from acetoacetic and benzoylacetic esters by known methods [3]. δ-Valerolactam was synthesized as described in [2].

6-Methyl-2,3-trimethylene-3,4-dihydropyrimidin-4-one (II). With stirring and water cooling, 65 ml of phosphorus oxychloride was added in portions to a mixture of 25.8 g (0.2 mole) of ethyl β-aminocrotonate and 25.5 g (0.3 mole) of γ-butyrolactam, and the mixture was heated on the boiling water bath for 2 h. Then it was cooled with ice water and made alkaline to pH 9. The resulting solution was extracted with chloroform, and the organic layer was dried with anhydrous sodium sulfate. After the chloroform had been evaporated off, the residue was distilled in vacuum. bp 180-185°C (0.76 kgf/cm^2). Yield 20 g (70%), R_f 0.58 (Al_2O_3: chloroform–hexane (2:1)). Mass spectrum, m/z (%): 150 M^+ (45), 149(20), 121(60), 109(40), 90(80), 80(40), 66(100), 54(80). PMR spectrum (δ scale, ppm): 2.1 s (3 H, CH_3); 2.32 m (2 H, 8-CH_2); 3.43 t (2 H, 7-CH_2); 4.23 t (2 H, 9-CH_2).

When the reaction was performed at 20°C, the yield of desired product was 32%. 6-Methyl-2,3-tetra- and -pentamethylene-3,4-dihydropyrimidin-4-ones and 6-phenyl-2,3-trimethylene-3,4-dihydropyrimidin-4-ones were synthesized similarly.

6-Methyl-2,3-tetramethylene-3,4-dihydropyrimidin-4-one (III). In a similar way to that described above, 12.8 g (0.1 mole) of ethyl β-aminocrotonate, 14.5 g (0.14 mole) of δ-valerolactam, and 20 ml of phosphorus oxychloride yielded 9.3 g (57%) of 6-methyl-2,3-tetramethylene-3,4-dihydropyrimidin-4-one. bp 160-165°C (0.66 kgf/cm^2). Mol. mass 164 (mass spectroscopically). R_f 0.30 (Al_2O_3; chloroform–hexane (1:1)).

6-Methyl-2,3-pentamethylene-3,4-dihydropyrimidin-4-one (IV). In a similar way to that described above, 25.8 g (0.2 mole) of ethyl β-aminocrotonate, 34 g (0.3 mole) of ε-caprolactam, and 65 ml of phosphorus oxychloride yielded 17 g (48%) of 6-methyl-2,3-pentamethylene-3,4-dihydropyrimidin-4-one. bp 168-170°C (0.71 kgf/cm^2). R_f 0.79 (Al_2O_3: chloroform–hexane (1:1)).

6-Phenyl-2,3-trimethylene-3,4-dihydropyrimidin-4-one (V). In a similar way to that described above, 13 g (0.07 mole) of ethyl β-aminocinnamate, 9 g (0.11 mole) of γ-butyrolactam, and 20 ml of phosphorus oxychloride yielded 8 g (56%) of 6-phenyl-3,3-trimethylene-3,4-dihydropyrimidin-4-one with bp 130-135°C (0.7 kgf/cm^2). Mol. mass 212 (mass-spectrometrically)

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