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Mannich Reaction as a Convenient Route to New Macrocyclic Compounds Containing an Uracil Fragment

S. G. Fattakhov, S. E. Solov'eva, Yu. Ya. Efremov, I. Kh. Rizvanov, and V. S. Reznik

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, Kazan, Tatarstan, Russia

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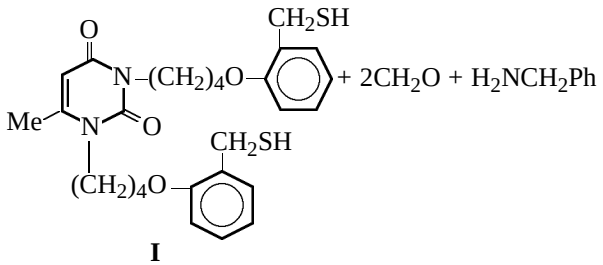
Abstract — Mannich reaction of 1,3-bis[4-(2-mercaptomethylphenoxy)butyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione, formaldehyde, and *N*-benzylamine afforded a 24-membered macrocyclic compound containing an uracil fragment, 1,3-(11-benzyl-6,7 : 15,16-dibenzo-5,17-dioxa-9,13-dithia-11-aza-6,15-heneicosadiene-1,21-diyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione.

Macrocyclic compounds with fragments structurally similar to biologically important molecules (e.g., nucleic acids) are of great interest as potential physiologically active substances and complexing agents. It is known that Mannich reactions of thiols with primary amines lead to formation of S-aminomethylation products [1, 2]. It is also known that the Mannich reaction with 1,2-ethanedithiol, acetophenone, and formaldehyde gives rise to 6-benzoyl-1,4-dithiacyclopentane [3] and that 4-amino-3-aryl-5-mercaptotriazoles react with aldehydes to afford cyclic intramolecular Mannich reaction products [4].

In the present study we used aminomethylation of dithiols to synthesize new macrocyclic structures containing an uracil fragment and sulfur, oxygen, and nitrogen atoms in the macroring. By reaction of 1,3-bis[4-(2-mercaptomethylphenoxy)butyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**I**) [5] with formaldehyde and benzylamine we obtained a 24-membered macrocyclic compound, 1,3-(11-benzyl-6,7 : 15,16-dibenzo-5,17-dioxa-9,13-dithia-11-aza-6,15-heneicosadiene-1,21-diyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**II**) in 33% yield.



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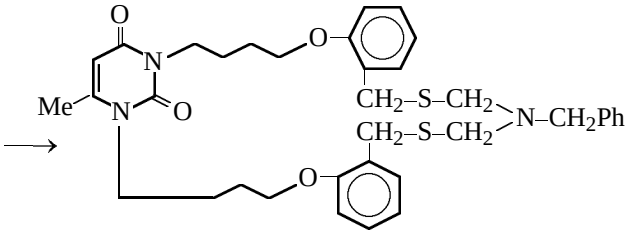

II

The structure of **II** was proved by the ^1H and ^{13}C NMR, IR, and high-resolution mass spectra. In the mass spectrum we observed the molecular ion peak corresponding to the proposed structure. The IR spectrum of **II** contained absorption bands at 1615, 1650, 1695, and 760 cm^{-1}, which are typical of uracil derivatives [6]; a set of bands was assigned to the benzene ring vibrations; and no S–H (2560 cm^{-1}) or N–H absorption (3250–3300 cm^{-1}) was present. The ^1H and ^{13}C NMR parameters of product **II** were consistent with its structure (see Experimental).

Presumably, the proposed procedure is of general character, and it can be extended to various dithiols and primary amines. As a result, macrorings with various structures and sizes could be synthesized, depending on the length and structure of the fragment between the thiol groups.

EXPERIMENTAL

The IR spectrum of the compound **II** dispersed in mineral oil was recorded on a Specord IR-75 spectrometer (4000–400 cm^{-1}). The molecular weight was determined from the high-resolution mass spectrum which was obtained on an MH-1310 instrument (60 eV; direct sample admission into the ion source; peak superposition technique). The NMR spectra were recorded in $CDCl_3$ using a Varian Gemini spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C); TMS was used as internal reference. The progress of the

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reaction was monitored by TLC on Silufol UV-254 plates (development with iodine vapor). Column chromatography was performed on silica gel L 40/100 μm (Chemapol).

1,3-(11-Benzyl-6,7 : 15,16-dibenzo-5,17-dioxa-9,13-dithia-11-aza-6,15-heneicosadiene-1,21-diyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (II). To a solution of 1 g of 1,3-bis[4-(2-mercaptomethylphenoxy)butyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**I**) in 40 ml of ethyl acetate and 15 ml of dioxane we added with stirring a solution of 0.2 g of benzylamine and 0.3 ml of a 40% formaldehyde solution. The mixture was stirred for 8 h at 45°C. When the reaction was complete (TLC), the solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel with successive elution with hexane, diethyl ether, and diethyl ether–ethyl acetate (2 : 1). Product **II** was isolated as a colorless amorphous powder. Yield 0.4 g (33%), R_f 0.25 (diethyl ether), mp 47–48°C. ^{1}H NMR spectrum, δ, ppm: 1.87 br.s (8H, β,β′-CH_2, γ,γ'-CH_2), 2.20 s (3H, Me), 3.65–4.16 m (18H, α,α'-CH_2N_{ur}, δ,δ'-CH_2O, CH_2SCH_2, NCH_2), 5.55 s (1H, 5-H), 6.75–7.40 m (13H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 19.77 (Me); 24.89, 26.49, 26.73, 26.96 (β,β',γ,γ'-CH_2); 30.54, 30.84 ($ArCH_2S$); 41.00 (N^1CH_2); 45.00 (N^3CH_2); 55.88, 56.41, 56.90 (SCH_2N, NCH_2Ph); 67.43, 67.67 (CH_2O); 101.76 (C^5); 111.50, 120.28, 120.64, 127.31, 128.23, 128.49, 129.36, 130.11, 130.39, 139.50 (C_{arom}); 151.50 (C^6); 156.30 (C^2=O), 162.00 (C^4=O). The indices α, α', β, β', etc. refer to the methylene groups with respect to the uracil N^1 and N^3 atoms. Found: *M* 645.269. $C_{36}H_{43}N_3O_4S_2$. Calculated: *M* 645.2695.

In addition, we isolated 0.16 g of a fraction eluted first (diethyl ether–hexane, 1 : 1) and 0.6 g of a fraction eluted last (benzene–methanol, 1 : 1). These fractions contained mixtures of products which we failed to separate.

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