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SYNTHESIS OF QUINAZOLINE DERIVATIVES CONTAINING VERATROLE AND BENZO-15-CROWN-5 MOIETIES

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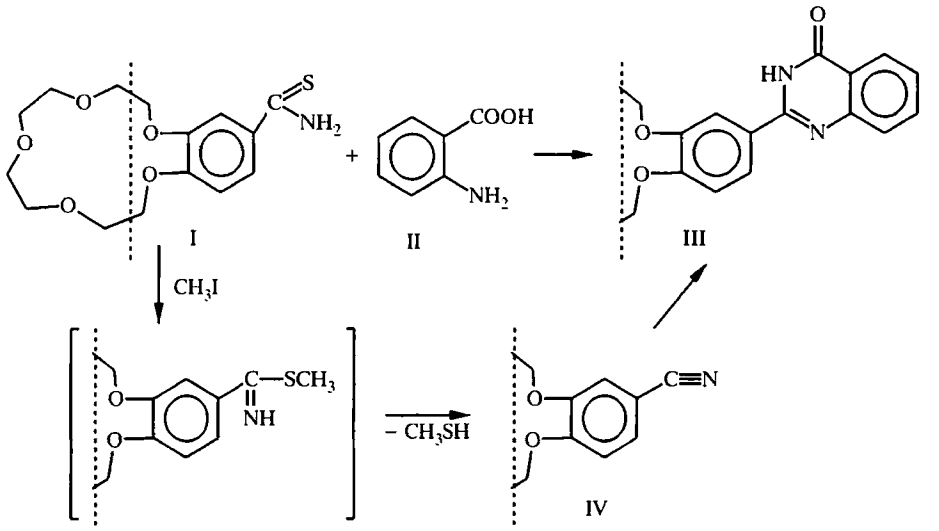
The condensation of (benzo-15-crown-5)-4'-thiocarboxamide with anthranilic acid is studied for the first time. Novel representative of crown ethers incorporating the quinazoline moiety is synthesized. Methylation of (benzo-15-crown-5)-4'-thiocarboxamide proceeds anomalously giving (benzo-15-crown-5)-4'-carbonitrile. (Benzo-15-crown-5)-4'-thiocarboxamide is reacted with thioveratramide in order to compare the reaction paths.

Derivatives of quinazol-4-one exhibit a wide range of biological activity [1]. Addition of a substituent in the 2- or 3-position can greatly enhance that activity [2].

Crown ethers have recently attracted much attention. Complex formation ability and membrane activity can impart new properties to the molecules or intensify their activity. It seemed interesting to introduce a crown ether fragment in the 2-position of quinazol-4-one. Therefore, we synthesized benzo-15-crown-5 (B15C5) containing quinazolone moiety.

One of the methods for preparing quinazol-4-ones is to condense thioamides with anthranilic acid. We previously have defined the conditions for preparing (benzo-15-crown-5)-4'-thiocarboxamide (I) [3].

Scheme 1



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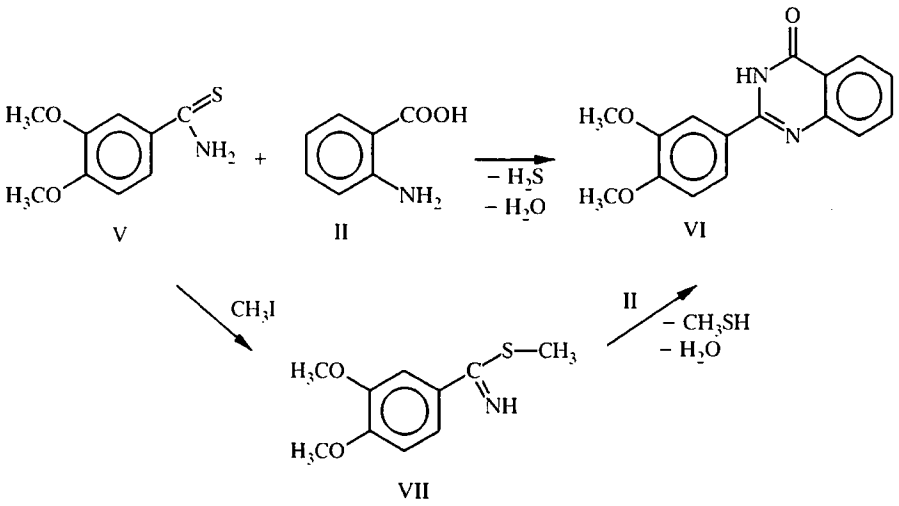
In the present work, thioamide I was condensed with anthranilic acid (II) to produce quinazol-4-one with a crown ether moiety in the 2-position (Scheme 1).

Condensation of compounds I and II produces 2-(B15C5-4^1-yl)quinazol-4-one (III) in 50% yield. Addition of anthranilic acid in portions increases the yield and shortens the reaction time.

In contrast with amide and thioamides, imino esters and imino thioesters react readily with *o*-amino acids [1]. Therefore, we methylated I with methyl iodide in order to prepare the corresponding imino thioester. However, B15C5-4^1-carbonitrile (IV) was unexpectedly obtained in high yield. Apparently I is initially alkylated at the sulfur atom, methyl mercaptan is lost, and the intermediate imino thioester transforms into a nitrile. Such a transformation, caused by the presence of the macrocycle, is not observed for thioveratramide (see below). Nitrile IV condenses with difficulty with anthranilic acid and gives quinazolone III only in very low yield.

The condensation of thioveratramide (V) with anthranilic acid II was studied for comparison. The product was 2-(3^1,4^1-dimethoxyphenyl)quinazol-4-one (VI) in 35% yield. Alkylation of thioamide V with methyl iodide proceeds normally to give the methyl iminothioveratrate (VII) in high yield. The reaction of VII with II gives the quinazolone VI (Scheme 2).

Scheme 2

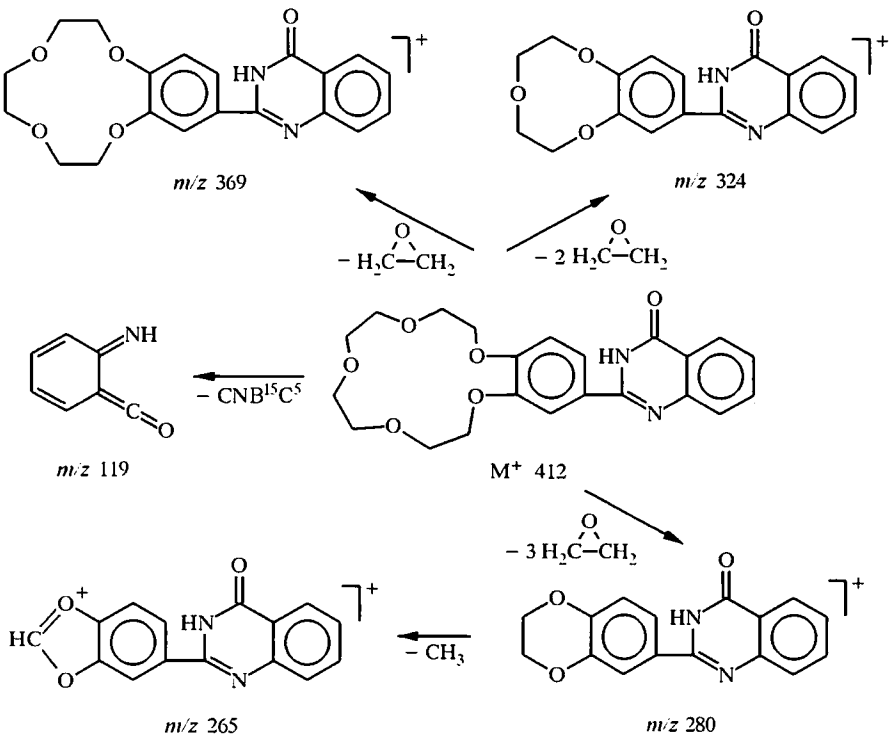


The structures of the prepared compounds were confirmed by spectral methods. The PMR spectrum of quinazolone VI contains a signal of the NH proton at 10.75 ppm. Protons of the benzene ring of the veratroyl moiety appear as a doublet at 8.25 ppm (6^1-H), a singlet at 7.75 ppm (2^1-H), and a doublet at 6.92 ppm (5^1-H). The aromatic protons of the quinazolone ring appear as a doublet at 7.78 ppm with spin–spin coupling constant (SSCC) of 2.5 Hz (8-H), a doublet at 7.62 ppm (5-H), and a multiplet at 7.25-7.50 ppm (6-H and 7-H). Protons of the methoxyl groups give two singlets at 4.0 and 3.95 ppm. The IR spectrum contains absorption bands of the NH moiety at 3445 and 3250-3065 cm^{-1}. The C=O moiety gives an intense band at 1669 cm^{-1}; the C=N group at 1605 cm^{-1}. The mass spectrum of the obtained compound also confirms the formation of 2-(3^1,4^1-dimethoxyphenyl)quinazol-4-one with M^+ 282.

The structure of 2-(B15C5-4^1-yl)quinazol-4-one (III) was established by IR and mass spectrometry. Poor solubility prevented the PMR spectrum from being recorded. The molecular ion of the compound III loses one, two, and three units of ethylene oxide to give daughters with *m/z* = 369, 324, and 280. The last ion loses CH_3 group to give a fragment with *m/z* = 265. Such loss of CH_3 is characteristic of crown ethers [4-7] (Scheme 3).

The IR spectrum contains absorption bands confirming the structure of the compound under study. The NH bands appear at 3441 and 3184-3085 cm^{-1}. The C=O moiety gives an intense band at 1668 cm^{-1}; C=N group at 1601 cm^{-1}.

Scheme 3



EXPERIMENTAL

IR spectra were obtained on a Perkin–Elmer 2000 Fourier spectrometer in KBr pellets. Mass spectra were recorded on an MX-1303 instrument. PMR spectra were obtained on a Tesla BS-567/100 MHz instrument in $CDCl_3$ and $(CD_3)_2O$ with HMDS as internal standard.

Condensation Procedure. A previously ground mixture of thioamide I or V (0.5 mmol) and anthranilic acid II (0.5 mmol) is fused during 2 h at 140-150°C. Anthranilic acid (1.5 mmol) is added in portions during the heating. The course of the reaction is followed by TLC on aluminum oxide or Silufol. The resulting mixture is decomposed with $NaHCO_3$ solution after the reaction is complete. The resulting oil is washed with $NaHCO_3$ solution to remove the excess of the acid II. The residue is washed with water, dried, and recrystallized.

2-(3^1,4^1-Dimethoxyphenyl)quinazol-4-one (VI). Yield 35% (based on thioveratramide V) and 65% (based on iminoester VII); mp 237-238°C (benzene–acetone). TLC was performed using benzene–acetone (3:1) as eluent. PMR spectrum: 10.75 (1H, s, NH); 8.25 (1H, d, 6^1-H); 7.75 (1H, s, 2^1-H); 6.92 (1H, d, 5^1-H); 7.78 (1H, d, 8-H); 7.62 (1H, d, 5-H); 7.25-7.50 (2H, m, 6- and 7-H); 4.00 (3H, s, OCH_3); 3.95 ppm (3H, s, OCH_3). IR spectrum: 3445, 3250-3065 (NH), 1669 (C=O), 1605 cm^{-1} (C=N). Found: M^+ 282.163438. $C_{16}H_{14}N_2O_3$. Calculated: M 282.100437.

2-(Benzo-15-crown-5-4^1-yl)quinazol-4-one (III). Yield 50% (based on B15C5-4^1-thiocarboxamide) and 1% (based on B15C5-4^1-carbonitrile); mp 223-225°C (acetone–hexane). TLC eluent chloroform–acetone–hexane–alcohol (2:2:2:0.1). IR spectrum: 3441, 3184, 3085 (NH), 1668 (C=O), 1601 cm^{-1} (C=N). Found: M^+ 412.163438. $C_{22}H_{24}N_2O_6$. Calculated: M 412.163428.

Methyl Iminothioveratrate (VII). Solution of thioveratramide (2.5 mmol) in dioxane (5 ml) is treated under stirring with methyl iodide (10 mmol) and KOH (10 mmol) dissolved in water (1 ml). The reaction is performed at 25°C for 4.5 h. The course of the reaction is followed by TLC on aluminum oxide using benzene–acetone (3:1) as eluent. Dioxane is removed after the reaction stops. The oil is recrystallized from benzene. Yield 65%; mp 175-179°C. PMR spectrum: 7.77 (1H, d, 6-H); 7.70 (1H, s, 2-H); 7.13 (1H, d, 5-H); 3.93 (6H, d, OCH_3); 3.0 ppm (3H, s, SCH_3). Found: M^+ 212.074527. $C_{10}H_{14}NO_2S$. Calculated: M 212.074522.

Benzo-15-crown-5-4^1-carbonitrile (IV). The reaction is performed for 30 min by the method described above and is monitored on Silufol using chloroform–acetone (3:1) as eluent. The product is isolated by recrystallization from acetone with subsequent precipitation by hexane. Yield 87%; mp 86-87°C. PMR spectrum: 7.2 (1H, dd, J = 2.5, J = 7.5 Hz, 5^1-H); 7.0 (1H, d, J = 2.5 Hz, 3^1-H); 6.8 (1H, d, 6^1-H); 3.6-4.17 ppm (16H, m, OCH_2). IR spectrum: 3750, 2230 (CN); 2880-2930, 1120 (COC); 1600, 1520 (=CH); 880, 860, 820 cm^{-1} (1,2,4-substituted benzene). Found, M^+ 293.126324. $C_{15}H_{19}NO_5$. Calculated: 293.111061.

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