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NEW REACTION OF BENZOCROWN DERIVATIVES OF 5-AMINO-4-IMIDAZOLECARBOXAMIDES LEADING TO CONDENSED TETRACYCLIC SYSTEMS

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A new cyclization reaction has been described for 5-amino-4-imidazolecarboxamides containing a benzocrown ether fragment at $N_{(1)}$ by the action of nitrous acid, which proceeds at the amino group of the imidazole ring and benzene ring of the macroheterocyclic fragment instead of the expected closure of the triazine ring to give a 2-azapurine analog, namely, 1-R-imidazo[4,5-d]triazin-4-one, where R is the benzo-12-crown-4 or benzo-15-crown-5 residue.

The heterocyclic system combining a purine system with a macrocyclic crown ether fragment holds interest not only relative to molecular design since it combines a natural product and purely synthetic fragment linked into a single molecule [1], but also as a compound with potential physiological activity and complexation properties [2].

5-Amino-4-iminocarbonylimidazoles such as Ia react with formamide to give hypoxanthine derivatives [3]. These derivatives react with HNO_2 to give the corresponding imidazo[4,5-*d*]-1,2,3-triazines (II), which are purine azaanalogs [4].

PMR spectroscopy and mass spectrometry were used to show that the reaction of carboxamides (Ib) and (Ic) containing a benzocrown ether fragment at $N_{(1)}$ in the imidazole system with formamide leads to the expected purines (IIIb) and (IIIc), but the "normal" course of the reaction with nitrous acid is radically altered: imidazo[5,1-*c*]-1,2,4-triazino[5,6-*d*]benzocrown ethers (IVb) and (IVc) were obtained in good yield instead of the expected imdiazo[4,5-*d*]-1,2,3-triazines (IIb) and (IIc). The formation of (IVb) and (IVc) may be attributed to the enhanced sensitivity of the phenylene rings in aminobenzocrown ethers to electrophilic attack [5].

There are two possible pathways for the formation of IVa and IVc: initial diazotization and formation of diazonium salts (Vb) and (Vc) with subsequent azo coupling at the phenylene ring (pathway A) or initial nitrosation of the phenylene ring with formation of nitroso derivatives (VIb) and (VIc) and subsequent intramolecular condensation to give the final products (pathway B). The authors prefer pathway A since even the nitration of aminobenzocrown ethers requires more vigorous conditions, while NO_2^+ is a stronger electrophile in aromatic substitution reactions than NO^+ [6, 8]. Evidence for this is found in the relatively facile nitration and difficult, complex nitrosation of *p*-substituted anilines and alkoxybenzenes [6].

The synthesis of IVb and IVc proceeds smoothly under mild conditions featuring the action of HNO_2 at 0°C and subsequent warming to room temperature over 1.5 h; the yields are almost quantitative.

The PMR spectra completely confirm the structures of IVb and IVc. The signals of the protons of the tetracyclic condensed systems in 4-aminocarbonylimidazo[5,1-*c*]-1,2,4-triazino[5,6-*d*]benzo-12-crown-4 and 4-aminocarbonylimidazo[5,1-*c*]-1,2,4-triazino[5,6-*d*]benzo-15-crown-5 are shifted downfield relative to the signals of the imidazole proton and protons of the benzene ring of the bicyclic purine system in IIIb and IIIc. For example, the signals for IIIb in DMSO-d_6 are: 8.12 (1H, s, 8-H), 7.25-7.50 (3H, m, H_{Ph}). The signals for IVb are: 9.25 (1H, s, 8-H), 8.22 (1H, s, H_{Ph}), and 8.30 (1H, s, H_{Ph}). The aromatic proton multiplet for the purine crown derivative IIIb is replaced in IVb by singlets for the two protons in the *para* position of the benzene ring. The signals for the amide protons are broad singlets at 7.80-7.92 ppm.

The IR spectra of IVb and IVc retain the NH group stretching bands at 3400 cm^{-1} and amide I (1680 cm^{-1}) and amide II bands (1530 cm^{-1}) of the starting benzocrown imidazoles Ib and Ic. The physicochemical indices of the compounds synthesized and the product yields are given in Table 1.

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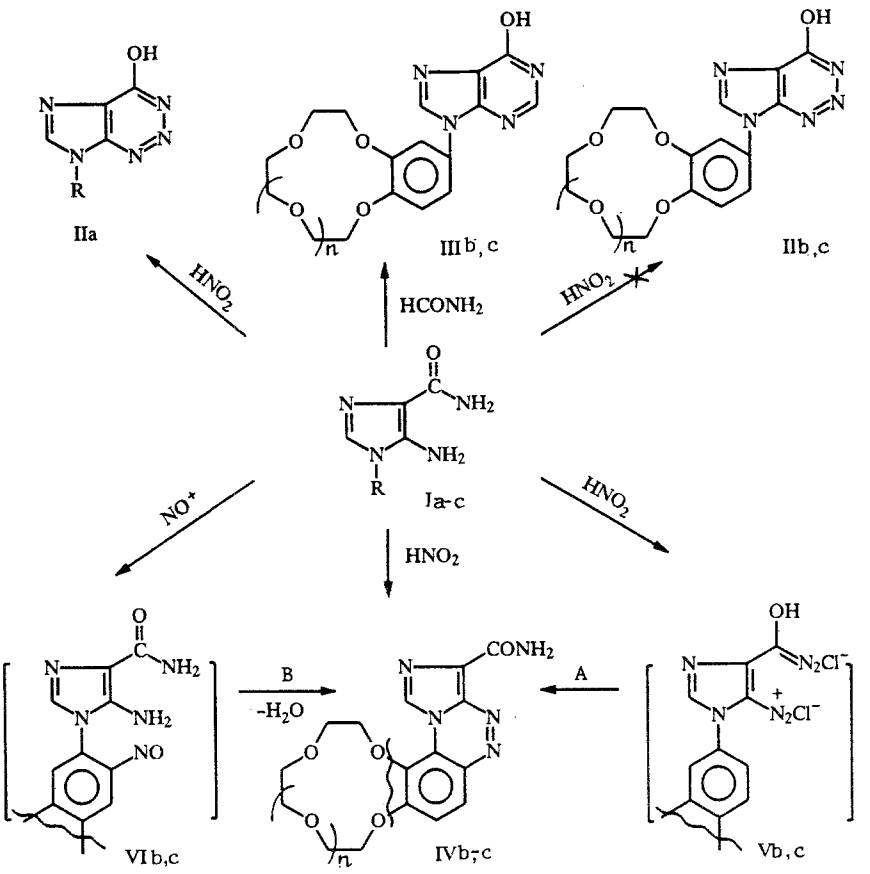
ribofuranosyl; b R = benzo-12-crown-4-yl; c R = benzo-15-crown-5-yl



I—VI a R = H, CH_3,

EXPERIMENTAL

The IR spectra were obtained for vaseline mulls on a Specord IR-75 spectrometer. The mass spectra were taken on a Varian MAT-2 spectrometer at 70 eV and a temperature exceeding the melting point of the samples studied. The molecular masses were established mass spectrometrically and correspond to the calculated values. The PMR spectra were taken on a Bruker AM-250 spectrometer at 250 MHz in DMSO-d_6 with TMS as the internal standard.

The purity of Ib, Ic, IIIb, IIIc, IVb, and IVc and the reaction course were checked by thin-layer chromatography on Silufol UV-254 plates using 8:1 and 5:1 chloroform—methanol as the eluent. Products IVb and IVc have bright yellow fluorescence when irradiated with UV light.

The results of the elemental analysis for the compounds synthesized for C, H, and N corresponded to the calculated values.

1-(4-Benzo-15-crown-5)yl-5-amino-4-aminocarbonylimidazole Ic and 9-(4-benzo-15-crown-5)yl-6-hydroxypurine IIIc have been described in our previous work [9].

1-(4-Benzo-12-crown-4)yl-5-amino-4-aminocarbonylimidazole (Ib). The reaction mixture obtained according to Sen and Ray [7] over 7 h was treated as follows After cooling and standing for 15 h, the precipitate of Ib was filtered off. The filtrate was evaporated to dryness at reduced pressure and the residue was dissolved in water. The precipitate of Ib was combined with the first portion, washed with water and acetonitrile, and recrystallized from ethanol.

4-Aminocarbonylimidazo[5,1-*c*]-1,2,4-triazino[5,6-*d*]benzo-12-crown-4 (IVb). A solution of 0.1 g (0.0014 mole) $NaNO_2$ in 10 ml water was added in one portion to a solution of 0.2 g (0.00057 mole) Ib in 1.7 ml 6 N hydrochloric acid at 0°C. The reaction mixture was maintained at 0°C for 10 min, brought to room temperature, and stirred for an additional 1 h. The precipitate formed was filtered off, washed with water, dried in a rotary evaporator, and recrystallized from ethanol.

TABLE 1. Physicochemical Indices for Compounds Synthesized

Compound	Chemical formula	M^+	T_{mp}, °C	Reaction time, h	PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}	Yield, %
Ib	$C_{16}H_{20}N_4O_5$	348	165	22	8,06 (1H, s, =CH im.); 6,99...7,20 (3H, m, H_{Ph}); 6,90 (1H, br.s, $CONH_2$); 6,82 (1H, br.s, $CONH_2$); 5,76 (2H, br.s NH_2)	3410, 3310 (NH); 2990 (CHar.); 2880 (OCH); 2840 (CH_2); 1700 (C=O am. I); 1630 (CO II); 1580 (NH); 1450 (C=Car.); 1220 (NH); 1150 (C-O)	72
IIIb	$C_{17}H_{18}N_4O_5$	358	261	8,5	12,50 (1H, s, OH); 8,46 (1H, e, -CH pyr.); 8,12 (1H, s, CH im.); 6,5...7,25 (3H, m H_{Ph})	3050 (CHar.); 2900 (CH_2); 1660 (C=Car.); 1590 (C=Car.); 1500 (C=Car.); 1110 (C—O)	80
IVb	$C_{16}H_{17}N_5O_5$	359	312	1,5	9,25 (1H, s, =CH im.); 8,30 (1H, s, H_{Ph}); 8,22 (1H, , H); 7,93 (1H, br.s -CONH2); 7,71 (1H, br.s, -CONH2); 3,24...4,50 (12H, m, CH_2O)	3360 (NH); 3080 (CHar.); 2900 (OCH); 2870 (CH); 1680 (CO am. I); 1630 (C=O am. II); 1600 (NH); 1530 (C=Car.); 1430 (CH_2); 1250 (NH); 1150 (C—O); 900 (C=Car.)	92
IVb	$C_{18}H_{21}N_5O_6$	403	308	1,5	9,27 (1H, s, =CH im.); 8,09 (1H, s, H_{Ph}); 8,07 (1H, s, H_{Ph}); 7,93 (1H, br.s NH_2); 7,69 (1H, br.s, NH_2); 2,63...4,37 (16H, m, CH_2O)	3400 (NH); 3110 (CHar.); 1680 (C=O am. I); 1600 (C=O am. II); 1530 (C=Car.); 1430 (CH_2); 1260 (NH); 1130 (C—O); 800 (C=Car.)	90

An analytical sample was obtained by chromatography on an alumina column with chloroform as the eluent. For complete extraction of the product from the reaction mixture, the mother liquor was evaporated on a rotary evaporator and the residue after washing with water was also purified by column chromatography.

4-Aminocarbonylimidazo[5,1-*c*]-1,2,4-triazino[5,6-*d*]benzo-15-crown-5 (IVc) was obtained analogously to IVb.

9-(4-Benzo-12-crown-4)yl-6-hydroxypurine (IIIb). A sample of 0.4 g (0.004 mole) Ia in excess (6 ml) freshly distilled formamide was heated at reflux on an oil bath maintained at 185°C over 5 h. Formamide was distilled off at reduced pressure and the reaction mixture was poured onto ice. Product IIIb was filtered off and purified by heating in methanol at reflux with activated charcoal. An analytical sample of IIIb was recrystallized from ethanol.

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