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SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND DIURETIC ACTIVITY OF 8-AMINO-SUBSTITUTED 7-ETHYLTHEOPHYLLINES

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A method was developed for preparing previously unreported 8-amino-substituted 7-ethyltheophyllines, potential biologically active compounds. Their physicochemical properties and diuretic activity were studied.

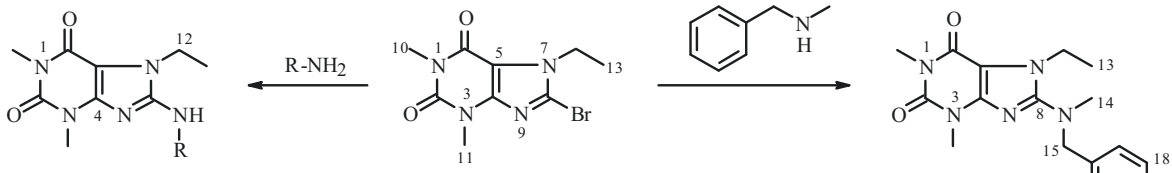
Keywords: synthesis, theophylline derivatives, diuretic activity.

Theophylline, a purine-type alkaloid, is used in medical practice as a bronchodilator, CNS stimulant, vasodilator, and diuretic agent [1–3]. Structural modification of theophylline created a series of analogs (dyphylline, xanthinol nicotinate, tophylline, etc.) that possessed the above activities and are widely used in practical healthcare [2, 3].

Research on the discovery of bioactive compounds among theophylline derivatives is currently being conducted in various countries [4–9].

In continuation of our own research on the chemical and biological properties of xanthines [10–14], we developed simple synthetic methods for new 7,8-disubstituted theophyllines and studied their effects on diuresis in white rats.

The starting synthon was 8-bromo-7-ethyltheohylline (**1**) [15]. The presence of the Br atom in **1** made it a versatile starting compound for producing various 8 *C*-, *N*-, *S*-, and *O*-substituted 7-ethyltheophyllines, i.e., potentially bioactive compounds. Scheme 1 shows that heating **1** with an excess of primary or secondary amine in aqueous MeOH at 150°C led to the corresponding 8-amino-substituted 7-ethyltheophyllines (**2**–**10**). Synthesized aminotheophyllines **2**–**10** were white crystalline compounds that were insoluble in H_2O and soluble in alcohols, dioxane, DMF, and DMSO.



2 - 9 **1** **10**

R = *n*-C_3H_7 (**2**); *n*-C_4H_9 (**3**); *i*-C_4H_9 (**4**); *sec*-C_4H_9 (**5**); *i*-C_5H_{11} (**6**), $CH_2CH(OH)CH_3$ (**7**), furyl-2-methyl (**8**); pyridyl-3-methyl (**9**)

Scheme 1

PMR spectra proved unambiguously the structures of the synthesized compounds. Thus, the presence of the *n*-propylamino group in 8-*n*-propylamino-7-ethyltheophylline (**2**) was confirmed by a 1H triplet at 6.58 ppm (NH), a quartet at 3.30 (2H, H-14), a multiplet at 1.61 (2H, H-15), and a triplet at 0.95 (3H, H-16) in its PMR spectrum. The N^1- and N^3-methyl protons resonated as strong 3H singlets at 3.40 and 3.21 ppm, respectively. The methylene and methyl protons of the 7-ethyl substituent appeared as a classical quartet and triplet at 4.08 and 1.23 ppm, respectively. Spectra of the other 8-amino-substituted theophyllines (**3**–**10**) contained all resonances of substituent protons at the appropriate field in the particular form and intensity.

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TABLE 1. Diuretic Activity of Synthesized **2**–**10**, %

Compound	Activity	Compound	Activity
2	158.0	**7**	210.0
3	170.4	**8**	268.0
4	175.8	**9**	189.5
5	165.8	**10**	185.6
6	160.7	Hypothiazide	178.1

An analysis of the test results for the effects of aminotheophyllines **2**–**10** on diuresis in white rats showed that all tested compounds possessed pronounced diuretic effects that were comparable or superior to that of hypothiazide (Table 1). Hydroxypropylaminotheophylline **7** and furylmethylaminotheophylline **8** turned out to be stronger diuretics than furosemide, one of the most potent diuretics used in modern medical practice. The experimental database will have to be significantly expanded to assess the effect of the 8-substituent on the diuretic effect of the 7-ethyltheophyllines. However, preliminary conclusions can already be drawn. Butylaminotheophyllines **3**–**5** were the most active, with the activity practically independent of the butyl structure, in the series of 8-alkylamino-substituted **2**–**6**. Propyl- (**2**) and *i*-amylaminotheophylline (**6**) had less pronounced effects (158.0 and 160.7%, respectively). It could be assumed that the diuretic activity in this series of compounds would not be substantially altered if the carbon chain in the 8-position was lengthened further. Additional structural modification of existing substituents such as introduction of heterocycles and amino-, hydroxy-, and SO_3H-groups seemed advantageous for increasing the strength and duration of the diuretic effect. Research in this direction is continuing, especially since 7-ethyl-8-(furyl-2)methylaminotheophylline (**8**) may be used in medicine as a diuretic agent after in-depth studies.

EXPERIMENTAL

Melting points were determined in open capillaries on a PTP apparatus (M). Elemental analyses were performed on an Elementar Vario L cube. IR spectra were taken on a Bruker Alpha spectrometer in the range 4000–400 cm^{-1} using an ATR accessory (direct sample introduction). NMR spectra were recorded in DMSO-d_6 with TMS internal standard on a Bruker SF-400 spectrometer (operating frequency 400 MHz). Elemental analyses of all compounds agreed with those calculated.

General Method for Synthesizing 8-Amino-7-ethyltheophyllines (2–10). A mixture of 8-bromotheophylline (**1**, 2.87 g, 0.01 mol) [15] and the appropriate amine (0.04 mol) in H_2O (20 mL) and MeOH (30 mL) was heated in a sealed ampul for 3 h at 150°C and cooled. The contents were diluted with H_2O. The resulting precipitate was filtered off, rinsed with H_2O, and crystallized from aqueous *i*-PrOH.

8-*n*-Propylamino-7-ethyltheophylline (2). $C_{12}H_{19}N_5O_2$, mp 215–216°C, yield 89.5%. IR spectrum (ν, cm^{-1}): 3361 (NH), 2950, 2920, 2860 (CH), 1692, 1635 (C=O), 1580 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.58 (1H, t, J = 7.4, NH), 4.08 (2H, q, J = 14.8, H-12), 3.40 (3H, s, H-10), 3.21 (3H, s, H-11), 3.30 (2H, q, J = 15.6, H-14), 1.61 (2H, m, H-15), 1.23 (3H, t, J = 5.9, H-13), 0.95 (3H, t, J = 6.3, H-16).

8-*n*-Butylamino-7-ethyltheophylline (3). $C_{13}H_{21}N_5O_2$, mp 177–178°C, yield 66.2 %. IR spectrum (ν, cm^{-1}): 3340 (NH), 2941, 2905, 2871 (CH), 1692, 1642 (C=O), 1610 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.77 (1H, t, J = 7.1, NH), 4.05 (2H, q, J = 12.9, H-12), 3.38 (3H, s, H-10), 3.30 (2H, q, J = 14.4, H-14), 3.18 (3H, s, H-11), 1.56 (2H, m, H-15), 1.35 (2H, m, H-16), 1.21 (3H, t, J = 6.7, H-13), 0.94 (3H, t, J = 7.2, H-17).

8-*iso*-Butylamino-7-ethyltheophylline (4). $C_{13}H_{21}N_5O_2$, mp 186–187°C, yield 80.0%. IR spectrum (ν, cm^{-1}): 3351 (NH), 2956, 2903, 2890 (CH), 1689, 1645 (C=O), 1571 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.84 (1H, t, J = 6.3, NH), 4.07 (2H, q, J = 14.0, H-12), 3.37 (3H, s, H-10), 3.18 (3H, s, H-11), 3.12 (2H, t, J = 6.8, H-14), 1.92 (1H, m, H-15), 1.21 (3H, t, J = 7.1, H-13), 0.91 (6H, d, J = 5.7, H-16,17).

8-*sec*-Butylamino-7-ethyltheophylline (5). $C_{13}H_{21}N_5O_2$, mp 223–224°C, yield 48.8%. IR spectrum (ν, cm^{-1}): 3329 (NH), 2945, 2908, 2895 (CH), 1683, 1647 (C=O), 1581 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.48 (1H, t, J = 7.7, NH), 4.09 (2H, q, J = 15.6, H-12), 3.82 (1H, m, H-14), 3.37 (3H, s, H-10), 3.16 (3H, s, H-11), 1.56 (2H, m, H-16), 1.20 (6H, m, H-13, 15), 0.91 (3H, d, J = 5.9, H-17).

8-*iso*-Amylamino-7-ethyltheophylline (6). $C_{14}H_{23}N_5O_2$, mp 169–170°C, yield 81.3%. IR spectrum (ν, cm^{-1}): 3353 (NH), 2940, 2910, 2890 (CH), 1692, 1642 (C=O), 1575 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.73 (1H, t, J = 6.1, NH), 4.06 (2H, q, J = 12.9, H-12), 3.38 (3H, s, H-10), 3.33 (2H, q, J = 14.3, H-14), 1.64 (1H, m, H-16), 1.45 (2H, q, J = 13.5, H-15), 1.20 (3H, t, J = 12.7, H-13), 0.93 (6H, d, J = 5.3, H-17, 18).

8-(2-Hydroxypropylamino)-7-ethyltheophylline (7). $C_{12}H_{19}N_5O_3$, mp 226–227°C, yield 59.4%. IR spectrum (ν, cm^{-1}): 3380 (NH), 3250 (OH), 3005, 2980, 2906 (CH), 1690, 1651 (C=O), 1592 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.95 (1H, t, J = 6.2, NH), 4.70 (1H, d, J = 5.4, OH), 4.04 (2H, q, J = 12.0, H-12), 3.80 (1H, m, H-15), 3.32 (3H, s, H-10), 3.20 (2H, t, J = 6.2, H-14), 3.12 (3H, s, H-11), 1.64 (1H, m, H-16), 1.14 (3H, t, J = 7.4, H-13), 1.05 (3H, d, J = 6.6, H-16).

8-(Furyl-2-methylamino)-7-ethyltheophylline (8). $C_{14}H_{17}N_5O_3$, mp 210–211°C, yield 62.7%. IR spectrum (ν, cm^{-1}): 3341 (NH), 2945, 2903, 2881 (CH), 1691, 1645 (C=O), 1582 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.43 (1H, d, J = 5.7, H-18), 7.41 (1H, t, J = 6.6, NH), 6.31 (1H, t, J = 5.4, H-17), 6.22 (1H, d, J = 5.4, H-16), 4.51 (2H, d, J = 6.8, H-14), 4.08 (2H, q, J = 15.0, H-12), 3.39 (3H, s, H-10), 3.19 (3H, s, H-11), 1.21 (3H, t, J = 7.0, H-13).

8-(Pyridyl-3-methylamino)-7-ethyltheophylline (9). $C_{15}H_{18}N_6O_2$, mp 177–178°C, yield 82.8%. IR spectrum (ν, cm^{-1}): 3372 (NH), 3060, 3026, 2915 (CH), 1693, 1637 (C=O), 1611, 1575 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.58 (1H, s, H-15), 8.43 (1H, d, J = 3.5, H-19), 7.74 (1H, d, J = 7.8, H-17), 7.60 (1H, t, J = 5.7, NH), 7.30 (1H, q, J = 8.5, H-18), 4.50 (2H, d, J = 5.3, H-14), 4.04 (2H, q, J = 15.9, H-12), 3.33 (3H, s, H-10), 3.13 (3H, s, H-11), 1.18 (3H, t, J = 7.1, H-13).

8-*N*-Methylbenzylamino-7-ethyltheophylline (10). $C_{17}H_{21}N_5O_2$, mp 81–82°C, yield 79.5%. IR spectrum (ν, cm^{-1}): 3041, 3007, 2980 (CH), 1692, 1645 (C=O), 1608 (C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.30 (5H, m, H-17–21), 4.43 (2H, s, H-15), 4.17 (2H, q, J = 15.5, H-12), 3.42 (3H, s, H-10), 3.23 (3H, s, H-11), 2.88 (3H, s, H-15), 1.35 (3H, t, J = 6.2, H-13).

Diuretic activity of the synthesized compounds (**2**–**10**) was studied by the method of Berkhin [16] in tests on Wistar white rats (150–180 g). The tested compounds and reference standard (hypothiazide) were injected i.p. as thin aqueous suspensions stabilized with Tween-80 at a dose of 1/20 of the mol. mass with 5% aqueous load. Table 1 presents the test results for diuretic activity.

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