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SYNTHESIS AND SOME CONVERSIONS OF N-SUBSTITUTED BENZIMIDAZOLE-2-SULFONIC ACIDS

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A series of N-substituted benzimidazole-2-sulfonic acids was synthesized in good yield by the N-alkylation of benzimidazole-2-sulfonic acids by alkylation with simple and functionalized alkylating agents under mild conditions. The corresponding N-substituted benzimidazolones and also primary, secondary, and tertiary amines were obtained by the action on the obtained compounds of alkali, ammonia, ammonium acetate, and amines.

Keywords: 2-aminobenzimidazoles, benzimidazolones, benzimidazole-2-sulfonic acids, N-alkylation, nucleophilic substitution.

The sulfonyl group in benzimidazole-2-sulfonic acids is a good nucleophile, consequently these compounds provoke considerable interest as intermediates in the synthesis of various, including practically significant, derivatives of benzimidazole, in particular 2-amino and 2-alkoxy benzimidazoles, and benzimidazolones [1-5]. Until now, however, only certain representatives of N-substituted benzimidazole-2-sulfonic acids have been described. They were synthesized in two stages from 1-alkyl or 1-benzyl benzimidazoles. On thiolating these compounds under forcing conditions (220-250°C) 1-substituted 1,3-dihydro-2H-benzimidazole-2-thiones are formed, which are then oxidized to the corresponding sulfonic acids with $KMnO_4$, H_2O_2, or sodium percarbonate [1, 2, 6-8]. It is evident that in one of these stages, when labile N-substituents are present in the molecule, their thermal or oxidative destruction is possible.

To overcome the limitations mentioned we have developed a method of alkylating N-unsubstituted benzimidazole-2-sulfonic acids **1a,k** with simple or functionalized alkylating reagents. This process takes place under mild conditions (50-70°C), in good yield in water, alcohol, or aqueous-alcoholic medium in the presence of 2 equiv. alkali. Somewhat unexpectedly the sulfonic acids are alkylated approximately as readily as the benzimidazole itself [9], although the electron-withdrawing sulfonyl group must significantly reduce the electron density on the nitrogen atom and thereby aid a reduction of its reactivity. This is probably connected with the fact that under the reaction conditions the sulfonyl group is in the less electron-withdrawing anionic form. The synthetic usefulness of N-substituted sulfonic acids **2a-k** was demonstrated by us in the example of their reactions with alkali, ammonia, and amines, which lead to the corresponding 1-substituted benzimidazolones **3c,d,i,k** and 2-aminobenzimidazoles of types **4-6**, including those with ω-dialkylaminoalkyl or β-aryloxyethyl groups.

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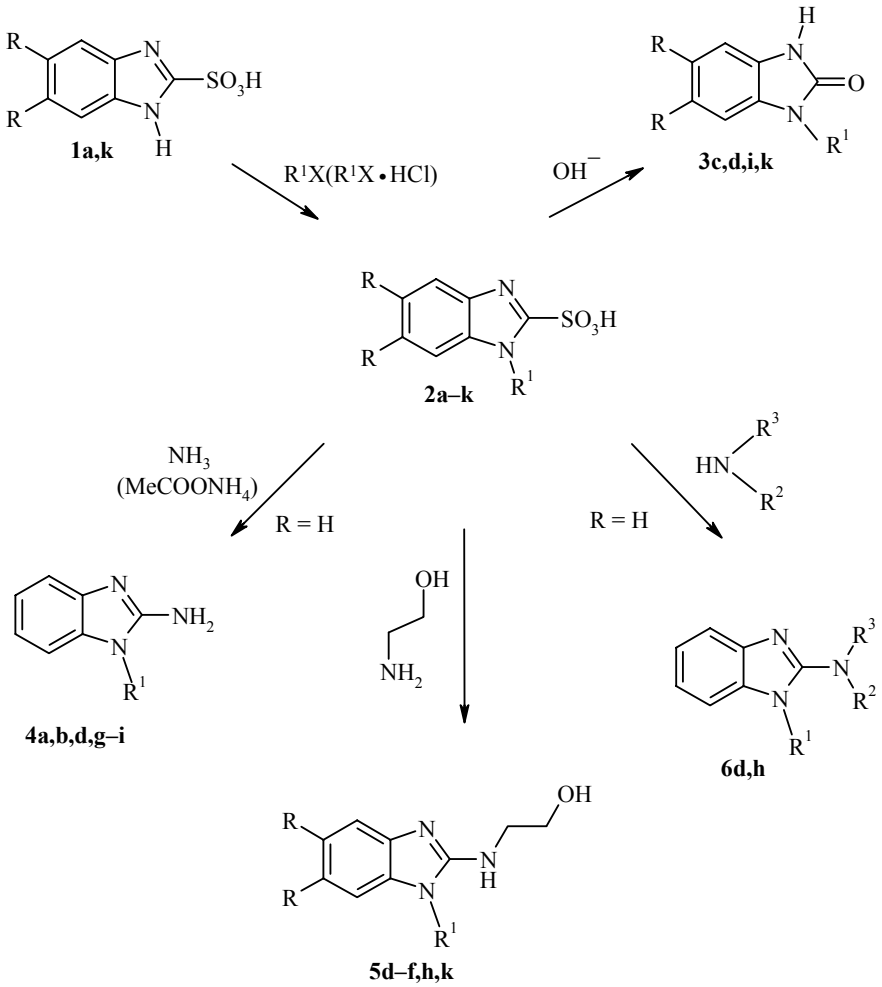

1-5 a-i R = H, **k** R = Me; **2-6 a** R^1 = Me, **b** R^1 = Et, **c** R^1 = Bn, **d**, **k** $R^1 = PhO(CH_2)_2$, **e** $R^1 = p\text{-}ClC_6H_4O(CH_2)_2$, **f** $R^1 = p\text{-}MeC_6H_4O(CH_2)_2$, **g** $R^1 = Et_2N(CH_2)_2$, **h** R^1 = β-piperidinoethyl, **i** R^1 = β-morpholinoethyl, **j** $R^1 = Me_2N(CH_2)_2$, **6 d** $R^2,R^3 = (CH_2)_2O(CH_2)_2$, **h** $R^2,R^3 = (CH_2)_4$

Reaction with ammonia and low-boiling amines is usually carried out in an autoclave [3]. We found however that to obtain primary 2-aminobenzimidazoles it was far more convenient to use ammonium acetate as the reactant. This enables nucleophilic substitution of an amino group to be carried out with practically the same yield but at atmospheric pressure. In the same manner 2-amino-1-(β-phenoxyethyl)benzimidazole (**4d**) in particular was obtained, the synthesis of which by amination of 1-(β-phenoxyethyl)-2-benzimidazole with sodium amide according to Chichibabin was previously unsuccessfully effected due to destruction of the N-substituent [13].

It is interesting to note that benzimidazole-2-sulfonic acid interacts with ammonium formate in a completely different way. In this case in place of the formation of amino derivatives reduction of the sulfonic acid group is observed combined with desulfurization [15].

1-(ω-Dialkylaminoalkyl)benzimidazole-2-sulfonic acids **2g-k**, in difference to the other 1-substituted sulfonic acids synthesized by us, dissolve readily in water. Consequently their preparation and subsequent replacement of the sulfonic acid group was carried out as a one-pot process. The exception was 1-(β-piperidinoethyl)benzimidazole-2-sulfonic acid (**2h**) which precipitated from the reaction mixture as the poorly soluble potassium salt.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %*[2]
		C	H	N		
2b	$C_9H_{10}N_2O_3S$	47.32 / 47.78	4.21 / 4.46	12.07 / 12.38	315-316	87
2c	$C_{14}H_{12}N_2O_3S$	58.01 / 58.32	3.98 / 4.20	9.51 / 9.72	263-265	80
2d	$C_{15}H_{14}N_2O_4S$	56.37 / 56.59	4.41 / 4.43	9.15 / 8.80	281-284	59
2e	$C_{15}H_{13}ClN_2O_4S$	51.34 / 51.07	4.24 / 3.71	8.31 / 7.94	270-273	81
2f	$C_{16}H_{16}N_2O_4S$	57.73 / 57.82	4.58 / 4.85	8.57 / 8.43	238-241	59
2k	$C_{17}H_{18}N_2O_4S$	58.64 / 58.94	4.93 / 5.24	7.87 / 8.09	258-261	80
3c	$C_{14}H_{12}N_2O$	75.21 / 74.98	5.43 / 5.39	12.51 / 12.49	194-196 [10]	60
3d	$C_{15}H_{14}N_2O_2$	70.62 / 70.85	5.94 / 5.55	11.17 / 11.02	132-134	72
3i	$C_{13}H_{17}N_3O_2$	63.64 / 63.14	6.78 / 6.93	17.33 / 16.99	126-127	34
3k	$C_{17}H_{18}N_2O_2$	72.37 / 72.32	6.65 / 6.43	10.13 / 9.92	196-197	72
4d	$C_{15}H_{15}N_3O$	71.12 / 71.13	6.35 / 5.97	16.38 / 16.59	167-168	83
4j	$C_{12}H_{18}N_4$	66.13 / 66.02	8.27 / 8.31	25.96 / 25.66	150 [13]	50
5d	$C_{17}H_{19}N_3O$	68.04 / 68.67	6.45 / 6.44	14.67 / 14.13	198-199	86
5e	$C_{17}H_{18}ClN_3O_2$	61.67 / 61.54	5.57 / 5.47	13.00 / 12.66	194-195	75
5f	$C_{18}H_{21}N_3O_2$	69.03 / 69.43	6.86 / 6.80	13.77 / 13.49	225-226	63
5h	$C_{16}H_{24}N_4O \cdot 2HCl$	52.77 / 53.19	7.03 / 7.25	15.07 / 15.51	195-197	65
5k	$C_{19}H_{23}N_3O_2$	69.88 / 70.13	7.01 / 7.12	13.01 / 12.91	182-183	72
6d	$C_{19}H_{21}N_3O_2$	70.55 / 70.57	6.77 / 6.55	13.17 / 12.99	119-120	69
6h	$C_{18}H_{26}N_4 \cdot 2HCl$	58.56 / 58.22	7.87 / 7.60	15.44 / 15.09	254-255	67

* Compounds **2b**, **4b** were recrystallized from water, **2c** from aqueous alcohol, **2d,e,f,k**, **3c,k**, **4j**, **5d,f,l**, **6d,h** from ethanol, **3d** from *iso*-octane, **3i** from CCl_4, **4d**, **5e** from 2-propanol, and **5h** from MeCN.

*[2] Yield of compound **2g** was 67% and **2j** 50% (according to the yield of amino derivative in the reaction with ammonia) and of compounds **2h** 78 and **2i** 70% (according to the yield of the potassium salt of the sulfonic acid).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian XL 300 (300 MHz) instrument in a mode internally stabilized by the polar resonance of the ^{2}H line of the deuterated solvent. The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)*
1	2
2d	4.51 (2H, t, *J* = 4.9, CH_2); 5.12 (2H, t, *J* = 4.9, CH_2); 6.78 (2H, d, *J* = 8.3, *o*-H_{Ph}); 6.85 (1H, t, *J* = 7.4, *p*-H_{Ph}); 7.18 (2H, t, *J* = 7.8, *m*-H_{Ph}); 7.60 (2H, m, H-5,6); 7.75 (1H, d, *J* = 8.0, H-4 or H-7); 8.05 (1H, d, *J* = 7.7, H-7 or H-4)
2e	4.51 (2H, t, *J* = 5.0, CH_2); 5.12 (2H, t, *J* = 5.0, CH_2); 6.81 (2H, d, *J* = 8.9, *o*-H_{Ph}); 7.16 (2H, d, *J* = 8.5, *m*-H_{Ar}); 7.54-7.67 (2H, m, H-5,6); 7.75 (1H, d, *J* = 7.20, H-7 or H-4); 8.04 (1H, d, *J* = 7.7, H-4 or H-7)
2k	2.42 (3H, s, CH_3); 2.45 (3H, s, CH_3); 4.50 (2H, t, *J* = 4.9, CH_2); 5.04 (2H, t, *J* = 4.9, CH_2); 6.79 (2H, d, *J* = 8.3, *o*-H_{Ph}); 6.87 (1H, t, *J* = 7.5, *p*-H_{Ph}); 7.20 (2H, t, *J* = 7.9, *m*-H_{Ph}); 7.47 (1H, s, H-4); 7.73 (1H, s, H-7 or H-4)
3d	4.30 (4H, s, CH_2CH_2); 6.86 (2H, d, *J* = 8.0, *o*-H_{Ph}); 6.93 (1H, t, *J* = 7.5, *p*-H_{Ph}); 7.05-7.17 (3H, m, $H_{Ar.}$); 7.20-7.29 (3H, m, $H_{Ar.}$); 9.06 (1H, br. s, NH)
3i	2.54 (4H, t, *J* = 4.9, NCH_2); 2.64 (2H, t, *J* = 7.5, NCH_2); 3.63 (4H, t, *J* = 5.3, $2OCH_2$); 3.99 (2H, t, *J* = 7.5, NCH_2); 6.99-7.11 (4H, m, H_{Ar}); 8.91 (1H, s, NH) [14]
3k	2.27 (3H, s, CH_3); 2.31 (3H, s, CH_3); 4.26 (4H, s, CH_2CH_2); 6.8-7.1 (5H, m, H_{Ar}); 7.23-7.28 (2H, m, H_{Ar}); 8.83 (1H, s, NH)
4d	4.30 (2H, t, *J* = 4.8, CH_2); 4.37 (2H, t, *J* = 4.8, CH_2); 5.05 (2H, br. s, NH_2); 6.84 (2H, d, *J* = 8.4, *o*-H_{Ph}); 6.97 (1H, t, *J* = 7.9, *p*-H_{Ph}); 7.05-7.30 (5H, m, H_{Ar}); 7.44 (1H, d, *J* = 7.5, H-4 or H-7)
5d	3.47 (2H, q, $J_{CH2–NH} = J_{CH2–CH2}$ = 5.4, $\underline{CH_2}NH$); 3.66 (2H, t, $J_{CH2–NH}$ = 5.5, $\underline{CH_2}OH$); 4.20 (2H, t, *J* = 5.2, CH_2); 4.37 (2H, t, *J* = 5.2, CH_2); 4.90 (1H, br. s, NH); 6.57 (1H, t, *J* = 6.0, *p*-H_{Ph}); 6.83-6.96 (5H, m, H_{Ar}); 7.12-7.25 (4H, m, H_{Ar})
5e	3.45 (2H, q, $J_{CH2–NH} = J_{CH2–CH2}$ = 5.3, $\underline{CH_2}NH$); 3.64 (2H, t, $J_{CH2–NH}$ = 5.3, $\underline{CH_2}OH$); 4.19 (2H, t, *J* = 5.4, CH_2); 4.35 (2H, t, *J* = 5.4, CH_2); 4.88 (1H, br. s, OH); 6.55 (1H, t, *J* = 5.4, NH); 6.81-6.94 (4H, m, H_{Ph} + H-5,6); 7.10-7.21 (4H, m, H_{Ph} + H-4,7)
5f	2.23 (3H, s, CH_3); 3.46 (2H, q, $J_{CH2–NH} = J_{CH2–CH2}$ = 5.3, $\underline{CH_2}NH$); 3.64 (2H, t, $J_{CH2–NH}$ = 5.3, $\underline{CH_2}OH$); 4.15 (2H, t, *J* = 5.5, CH_2); 4.34 (2H, t, *J* = 5.5, CH_2); 4.90 (1H, br. s, OH); 6.55 (1H, t, *J* = 5.3, NH); 6.74 (2H, d, *J* = 8.6, *o*-H_{Ar}); 6.8-6.9 (2H, m, H-5,6); 6.99 (2H, d, *J* = 8.2, *m*-H_{Ar}); 7.10-7.17 (2H, m, H-4,7)
5h*[2]	1.40-2.15 (6H, m, 3-,4-,5-CH_2, piperidyl); 3.20 (2H, br. m, CH_2); 3.44 (2H, br. t, *J* ~ 7.0, CH_2); 3.52 (1H, br. s, NH); 3.58 (2H, br. q, *J* ~ 5.0, $NH\underline{CH_2}$); 3.73 (2H, t, *J* = 5.0, $\underline{CH_2}OH$); 4.89 (2H, t, *J* = 8.0, $N_{(1)}CH_2$); 7.19-7.35 (2H, m, H-5,6); 7.41 (2H, d, *J* = 7.3, H-4 or H-7); 7.96 (1H, d, *J* = 7.2, H-7 or H-4); 9.94 (1H, br. t, *J* ~ 5.0, NH); 11.77 (1H, br. s, NH); 13.44 (1H, br. s, NH)
5k	2.25 (3H, s) and 2.27 (3H, s) – 5-CH_3 and 6-CH_3, 3.44 (2H, q, J_1 = 5.1; J_2 = 5.1, $NH\underline{CH_2}$); 3.64 (2H, t, *J* = 5.1, $\underline{CH_2}OH$); 4.18 (2H, t, *J* = 5.4, CH_2); 4.30 (2H, t, *J* = 5.4, CH_2); 5.06 (1H, br. s, NH); 6.44 (1H, t, *J* = 5.7, *p*-H_{Ph}); 6.87 (2H, d, *J* = 8.0, *o*-H_{Ph}); 6.90 (1H, s) and 6.93 (1H, s) – H-4,7); 7.22 (2H, t, *J* = 8.0, *m*-H_{Ph})
6d	3.36 (4H, t, *J* = 4.7, CH_2NCH_2); 3.87 (4H, t, *J* = 4.7, CH_2OCH_2); 4.37 (2H, t, *J* = 5.5, CH_2); 4.46 (2H, t, *J* = 5.5, CH_2); 6.83 (2H, d. t, J_1 = 7.8; J_2 = 1.0, *o*-H_{Ph}); 6.97 (1H, tt, *J* = 7.4, *J* = 0.8, *p*-H_{Ph}); 7.15-7.32 (4H, m, H-5,6 + *m*-H_{Ph}); 7.32-7.41 (1H, m, H-4 or H-7); 7.61-7.69 (1H, m, H-7 or H-4)
6h*[2]	1.42-2.23 (6H, m, $3CH_2$); 2.11 (4H, br. t, *J* ~ 6.5, $NCH_2\underline{CH_2}\underline{CH_2}$, pyrrolidyl); 3.05 (2H, br. m, CH_2); 3.44 (2H, br. m, CH_2); 3.52-3.69 (2H, br. m, CH_2); 3.94 (4H, br. t, *J* ~ 6.5, CH_2NCH_2, pyrrolidyl); 4.93 (2H, br. t, *J* ~ 6, CH_2); 7.22-7.34 (2H, m, H_{Ar}); 7.50-7.59 (1H, m, H_{Ar}); 7.81-7.91 (1H, m, H_{Ar})

* The ^{1}H NMR spectra of compounds **2d,e,k**, **5d-f,h,k**, and **6h** were taken in DMSO-d_6, and of the remainder in deuterochloroform.
*[2] Dihydrochloride.

1-Methyl- and 1-Ethylbenzimidazole-2-sulfonic Acids 2a,b. The appropriate dialkyl sulfate (13 mmol) was added with stirring to a solution of sulfonic acid **1a** (1.98 g, 10 mmol) and KOH (1.34 g, 20 mmol) in water (15 ml), and the mixture stirred for 4 h at 50°C. After cooling, the reaction mixture was acidified with conc. HCl to pH 4-5. The solid N-substituted sulfonic acid which separated was filtered off, washed with water and with acetone, and dried.

Compound **2a** had mp 329-331°C (recrystallized from water) [2], yield 98%.

1-Benzylbenzimidazole-2-sulfonic Acid (2c) was obtained analogously from sulfonic acid **1a** and benzyl chloride in aqueous alcohol (2:1) at 60-70°C during 5-6 h.

1-(β-Aryloxyethyl)benzimidazole-2-sulfonic Acids 2d-f,k were synthesized from sulfonic acids **1a,k** and the appropriate β-aryloxyethyl bromides in alcohol at 70°C during 3 h. The reaction products were isolated as for sulfonic acids **2a,b**.

1-(ω-Dialkylaminoalkyl)benzimidazole-2-sulfonic Acids 2g-j. A solution of sulfonic acid **1a** (1.98 g, 10 mmol), KOH (2.1 g, 32 mmol), and the appropriate ω-aminoalkyl chloride hydrochloride (12 mmol) in water (10 ml) was stirred for 4 h at 60-70°C. In the case of sulfonic acids **2g,i,j** the reaction mixture was cooled, washed with benzene (10 ml) to remove the excess of alkylating agent, acidified to pH 4-5 with conc. HCl, and used in this form for subsequent conversions.

In the case of 1-(β-piperidinoethyl)-substituted sulfonic acid **2h** the poorly soluble potassium salt was precipitated from the reaction mixture on cooling, and was filtered off, washed with acetone, and dried.

1-Substituted Benzimidazolones 3c,d,i,k. A solution of the appropriate 1-substituted sulfonic acid (10 mmol) and KOH (4 g, 60 mmol) in water (10 ml) was boiled for 4-5 h, cooled, and acidified with acetic acid to pH 6. After 10 h the solid benzimidazolone was filtered off, washed with a small volume of cold water, and dried. In the case of compounds **3d,k** the reaction products were dissolved in chloroform, and chromatographed on a column of Al_2O_3 (20 x 70 mm) in chloroform, before recrystallization.

1-Alkyl(β-phenoxyethyl)-2-aminobenzimidazoles 4a,b,d. A mixture of the appropriate sulfonic acid (10 mmol) and ammonium acetate (3.9 g, 50 mmol) in water (2 ml) was boiled for 3 h. On cooling the mixture was made alkaline with 20% NaOH solution, the precipitated solid amine was filtered off, and washed with water. Compound **4a** had mp 201-202°C [9], 64% yield; **4b** mp 155-156°C [11], 98% yield.

2-Amino-1-(ω-dialkylaminoalkyl)benzimidazoles 4g-j. An aqueous solution of 1-(ω-dialkylamino-alkyl)benzimidazole-2-sulfonic acid **2g,i,j**, obtained from unsubstituted acid **1a** (20 mmol), or a solution obtained by acidifying with HCl a suspension of sulfonic acid **2h** potassium salt (20 mmol) in water (25 ml), was saturated with ammonia, and then heated in an autoclave for 2 h at 140-160°C. After cooling, the solid amine **4h,i** was filtered off, and washed with water.

In the case of amine **4g** a viscous oil was isolated from the reaction mixture and crystallized by treatment with hot octane (10 ml). Compound **4g** had mp 134-135°C (recrystallized from octane) [9], yield was 61%, **4h** mp 176°C [12], yield 61%, **4i** mp 190-191°C [12], yield 70%. Mixing tests of compounds **4g-i** with known samples melted with no depression of melting point.

Amine **4j** was extracted from the reaction mixture with chloroform (3 × 15 ml) and was then isolated in the usual way.

2-(β-Hydroxyethylamino)benzimidazoles 5d-f,h,k. A mixture of the 1-substituted sulfonic acid (5 mmol) and monoethanolamine (3 g, 50 mmol) was heated for 1 h at 150-160°C. After cooling, the mixture was treated with water (5 ml) and the separated solid amine was filtered off.

In the case of amino alcohol **5h** the sulfonic acid **2h** was previously obtained from its potassium salt by treatment with conc. HCl to pH 1, and evaporated to dryness on a water bath. After carrying out the reaction aminoalcohol **5h** was extracted with chloroform (2 x 20 ml), and purified by chromatography on a column of Al_2O_3 (20 × 40 mm), eluting with chloroform. The compound was identified as the dihydrochloride, which was obtained by treatment of an acetone solution of the base with gaseous HCl.

Tertiary Amines 6d,h. A solution of benzimidazole-2-sulfonic acid **2d** (5 mmol) in morpholine (5 ml) was boiled for 3 h, cooled, water (10 ml) was added, and the solid amine **6d** was filtered off. With pyrrolidine the reaction was carried out at 150-160°C in a sealed ampul. After cooling, and treating with water, compound **6h** was extracted with chloroform, the solvent was distilled, and the oily amine was converted into the dihydrochloride by the method described above

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