

Nitroimidazoles: Part VI—N-(1-Alkyl-5-nitroimidazol-2-yl)-heteroarenes†‡

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Condensation of 1-methyl-2-methylsulphonyl-5-nitroimidazole (2) with imidazole affords the corresponding 2-(N-imidazolyl) derivative (7a) with good antiprotozoal activity. Analogous imidazoles (7b-k), pyrrole (5), indole (6), benzimidazole (10), its tetrahydro derivative (11), pyrazoles (12a-d), indazoles (17a and b), triazole (19), benzotriazole (21a and b) and tetrazole (22) are prepared similarly. Condensation of 2 with 2, 5-dimethyl-4-nitropyrazole affords the expected 12f, which partly undergoes reaction with another molecule of 2 to yield 14. Sulphone (2) and 3-methyl-5-pyrazolinone combine to form the O-alkyl derivative (16a), characterised further as the acetyl derivative (16b). ¹³C as well as ¹H NMR spectra and solvent-induced shifts are used to assign unique structures, when two or more alternatives are possible, e.g. 7g, 7h, 12d, 16a and 19. The synthesis of 1-n-butyl-(9a); and 1-(2-methoxyethyl)-(9b) analogues of 7a is also described. 25 and 26 are respectively thiazolyl and pyridyl analogues of 7a, while 23a, 23b and 24 are homologues.

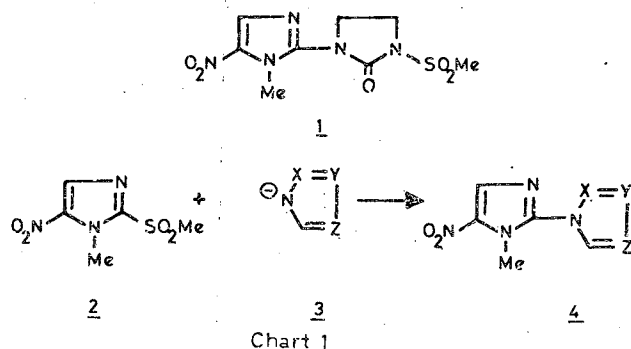
The outstanding antiprotozoal activity of 1-methylsulphonyl-3-(1-methyl-5-nitroimidazolyl)-2-imidazolidinone (1)** reported in an earlier paper¹ of this series and interesting chemistry associated with 1 and analogous oxazolidinones² inspired the synthesis of nitroimidazoles in combination with other five-membered rings. One of the several possibilities was 5-ring heteroaromatics, among which the earliest tried was imidazole itself which afforded 7a with pronounced antiamoebic and antitrichomonal activities. An expanded study was thus justified and the results are reported in this paper.

The synthetic sequence (Chart 1) employed involved, as in earlier work^{1,2}, the condensation of the sulphone (2) with the sodium salt of the heteroaromatic 3, affording 4 in moderate to very good yields. Some benzologues of 3 were also utilised.

Condensation of 2 with pyrrole, indole, imidazole and 2-substituted imidazoles proceeded uneventfully

to provide 5, 6, 7a and 7b-e respectively. The yield of 5 was moderate (26%); with indole the yield rose to 45% while 7a was formed in 60% yield, demonstrating the better nucleophilicity of imidazolyl versus indolyl and pyrrolyl anion. Sulphone (7f) arose from 7e by peroxide oxidation. 4-Nitroimidazole and 2-methyl-4-nitroimidazole can lead to either 4- or 5-nitro-derivative. The single product isolated in the two instances were formulated as 7g and 7h respectively rather than as 8a and 8b for the following reasons: (i) alkylation of 4-nitroimidazoles under basic conditions is known to yield 4-nitro-derivatives as the sole or main product³; (ii) 7g and 7h incorporate nitroimidazole rings with protons at C-4 and C-5' respectively, while the alternatives 8a and 8b would have protons at C-4 and C-4'. It is known that protons at C-5 in 1-substituted imidazoles undergo a considerable shift ($\Delta\delta$) in their PMR spectra in switching from CDCl₃ to DMSO-*d*₆ as solvent, while $\Delta\delta$ for C-4 protons is much less^{4,5}. The $\Delta\delta$ observed for 7g was: C-4H 0.20; C-2'H, 0.53; and C-5'H, 0.80; and for 7h: C-4H 0.34; and C-5'H 0.65. (iii) δ C-4 for 5-nitroimidazoles is around 132 and for C-5 in 4-nitroimidazoles 121 ppm. The ¹³C NMR spectrum of 7h displayed signals of C-4 at 130.2 and C-5' at 121.0 ppm. The products from 2, 4-dimethyl-, 2-ethyl-4-methyl- and 4-phenyl-imidazoles are formulated respectively as 7i; 7j and 7k for similar reasons.

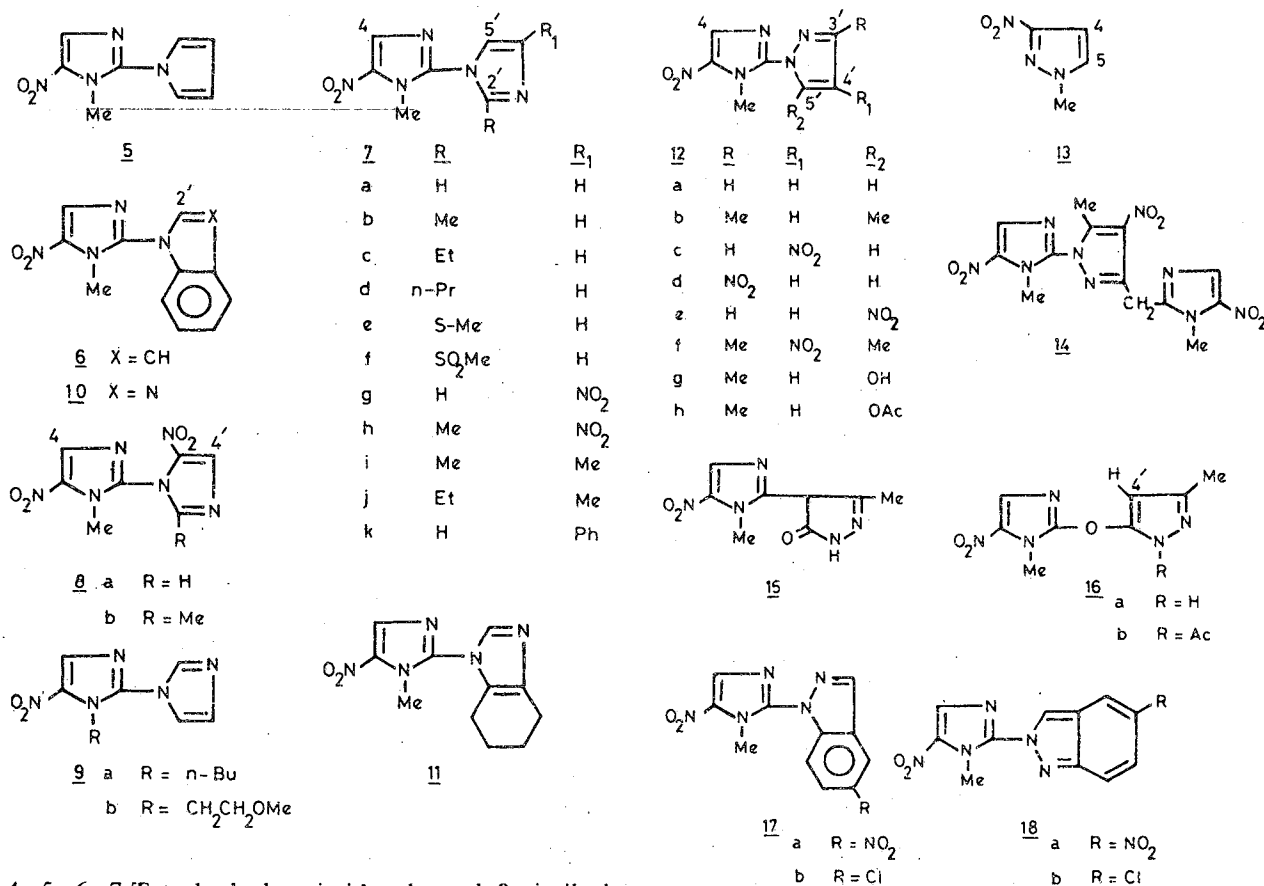
Two analogues of 7a were also synthesised for structure-activity relationship wherein the methyl group was replaced by *n*-butyl (9a) and methoxyethyl (9b) groups using the appropriate analogues of 2¹. The benzimidazole derivative (10) was also synthesised for a similar reason. The structure of 10 rested especially on PMR data (DMSO-*d*₆) [C-4H 8.20(s), C-2' 8.60(s)].



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4, 5, 6, 7-Tetrahydrobenzimidazole and 2 similarly afforded 11.

Reaction of 2 with the sodium salt of pyrazole afforded 12a in 34% yield, but with 3, 5-dimethylpyrazole, the yield of 12b dropped to 20%, perhaps due to crowding at the anionic centre. 4-Nitropyrazolyl ion proved to be a better nucleophile affording 12c in 54% yield. 3-Nitropyrazole and 2 can lead to either 12d or 12e; structure (12d) was preferred for the following reasons: (i) 3-Nitropyrazole leads to 1-methyl-3-nitro derivative (13) under alkaline conditions; and (ii) ¹³C NMR data for the proton bearing aromatic carbon atoms in 12d (δ C-4 130.0, C-4' 104.6 and C-5'] 134.5 ppm). The last two shifts are very close to those observed for the analogue 13 (δ C-4 103.1 and δ C-5 133.3 ppm). We felt that solvent-induced shift of the pyrazole protons could also be used to differentiate between 12d and 12e. Hence a limited study was carried out on these pyrazole derivatives, the results of which are reported in Table 1. $\Delta\delta = (\delta_{\text{DMSO-d}_6} - \delta_{\text{CDCl}_3})$ for C-5'H in 13 was of the order observed for 4-nitroimidazole derivatives^{4,5} (0.53), but only 0.14 as expected for C-4'H.

However for the other pyrazoles, $\Delta\delta$ observed had the following values: C-5'H, 0.07-0.30; C-4'H 0.03-0.18; C-3'H 0.05-0.44. Extension of the experience with 4-nitroimidazoles would have predicted a much larger $\Delta\delta$ values for C-5'H. However, while the assignment of

Table 1—PMR Data for Some Pyrazoles

Compd	δ H (ppm) (CDCl ₃)				δ H (ppm) (DMSO-d ₆)			
	C-4	C-3'	C-4'	C-5'	C-4	C-3'	C-4'	C-5'
12a	7.96	8.20	6.52	7.83	8.10	8.25	6.55	7.90
12b	7.90	—	6.03	—	8.17	—	6.21	—
12c	7.98	8.91	—	8.35	8.05	9.35	—	8.65
12d	7.98	—	7.16	8.32	8.20	—	7.33	8.60
12f	8.01	—	—	—	—	—	—	—
13	—	—	6.88	7.45	—	—	7.02	7.98
16a	7.75	—	5.95	—	—	—	—	—
16b	7.75	—	6.28	—	7.95	—	6.45	—

PMR signals in 12d is clear, there is some ambiguity in the case of 12a and 12c where C-3' and C-5'H signal assignments are not as rigorous.

Condensation of the sulphone (2) with the sodium salt of 3, 5-dimethyl-4-nitropyrazole gave an apparently homogenous product which was considered to be the desired derivative 12f on the basis of analytical and mass spectral data (80% yield as 12f), but the PMR spectrum had far more signals in the aromatic and methyl regions than expected. Careful chromatography on silica gel resolved the problem by providing two pure compounds 12f and 14 in the ratio of about 3:1 (PMR). The structural assignments were

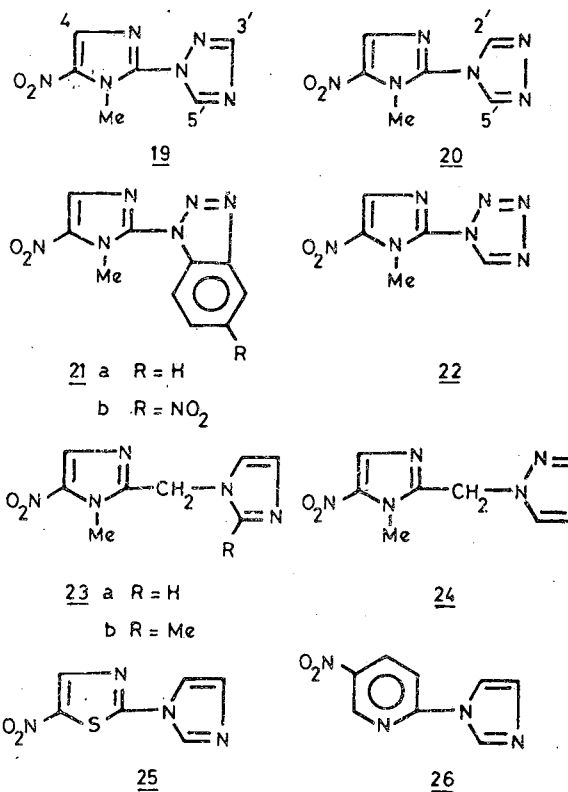
especially supported by PMR data: **12f** C-4H, 8.01 (s), N-Me, 3.98 (s), 2C-Me, 2.74 (s), 2.00 (s); **14** 2C-4H, 7.88 (s), 7.68 (s); $-\text{CH}_2$, 4.83 (s); 2N-Me, 4.04 (s), 4.01 (s), one C-Me, 2.66 (s). Obviously the initially formed **12f** had given rise to a carbanion which became involved with **2** in a substitution reaction. We expect the methyl group at C-3' in **12f** to be more activated than the one at C-5' and formulate the product accordingly as **14**.

The reaction of 3-methylpyrazolin-5-one with **2** can give rise to a product by heteroarylation on nitrogen, oxygen or carbon atom. The first can again exist in the enol **12g** or its keto form. C-Alkylation would lead to **15** which can also go over to an enol. O-Alkylation should afford **16a**. The presence in the PMR spectrum (CDCl_3) of the product of a singlet at 5.95 (C-4'H) and a broad singlet at 11.1 which disappeared with D_2O ruled out **15**, leaving **12g** and **16a** for consideration. A study of the acetyl derivative allowed us to differentiate between the two and settle in favour of **16a**. The PMR spectrum (CDCl_3) of the acetyl derivative had signals at 6.28 (C-4'H, s), 3.95 (N-Me, s) and 2.63 (C-3' Me, OCOMe, s). More importantly its IR spectrum exhibited a band at 1740 cm^{-1} resembling those of N-acetylpyrazole ($\nu\text{C}=\text{O}$ at 1730 cm^{-1}) and 1,4-diacetyl-5-methylpyrazole ($\nu\text{C}=\text{O}$ at 1730 cm^{-1}). Thus the acetyl derivative is formulated as **16b** and the precursor as **16a**. The O-acetyl derivative **12h**, being an enol acetate, would be expected to show a band at 1780 cm^{-1} in the IR spectrum.

5-Nitro- and 5-chloroindazoles upon reaction with the sulphone (**2**) gave high yields of products formulated as **17a** and **17b** respectively. Structures **18a** and **18h** although not completely ruled out are considered unlikely since these are partially deprived of aromaticity.

Condensation of *s*-triazole with **2** afforded a product in 42% yield which could be **19** or **20**. The PMR spectrum of the product exhibiting three singlets one-proton each in the aromatic region at 8.0 (C-4H), 8.25 (C-3'H) and 9.0 (C-5'H) decidedly favoured **19** over **20**; the latter having a symmetrically substituted triazole ring would show one singlet for both C-2'H and C-5'H. Products were also obtained from benzotriazole (53%) and 5-nitrobenzotriazole (80%) which are somewhat arbitrarily formulated as **21a** and **21b** respectively. The product obtained in 9% yield from tetrazole can be formulated in two ways, **22** being one of them.

Homologues **23a** and **23b** of the active preparation **7a** were obtained by the condensation of 1-methyl-2-chloromethyl-5-nitroimidazole with the sodium salts of imidazole and its 2-methyl derivative respectively, while with pyrazole, **24** was obtained. Similar condensation of appropriate halides with imidazole led to the thiazole **25** and pyridine **26**.



The physical data of the compounds synthesised are listed in Table 2.

Experimental Procedure

Syntheses of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**2**) and its 1-(*n*-butyl) and 1-(2-methoxyethyl) analogues are described in our earlier paper¹.

1-Methylimidazol-2-yl-5-nitroimidazole (7a)—To a solution of imidazole (1.7 g) in dimethylformamide (20 ml) was added 50% NaH (1.2 g) under stirring at $5-10^\circ$. The reaction mixture was stirred at $10-15^\circ$ for 30 min more after which a solution of **2** (5.1 g) in dimethylformamide (20 ml) was added dropwise keeping the temperature of the reaction mixture between 15 and 20° . The reaction mixture was stirred at room temperature for 4 hr more, the solvent removed under reduced pressure, the residue dissolved in chloroform and filtered. The filtrate was evaporated *in vacuo* and the gummy residue obtained converted into nitrate salt.

Other compounds prepared by similar method are listed in table 1.

In the reaction of **2** with the sodium salt of 3, 5-dimethyl-4-nitropyrazole a mixture of **12f** and **14** was obtained. These were separated by chromatography on silica gel using CHCl_3 -MeOH (99:1) as the eluent.

Acetylation of 16a—A mixture of **12g** (0.3 g) and acetic anhydride (1.5 ml) was heated under reflux for 30 min. The residue was cooled, ice added and left at

Table 2 — Nitroimidazolylazoles

Compd	Yield %	Crystallised from	m.p. (°C)	Mol. formula	M ⁺ m/z	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
5	26	CH ₂ Cl ₂ + MeOH - hexane	94	C ₈ H ₈ N ₄ O ₂	192	49.99	4.20	29.16	50.36	4.47	29.40
6	45	CH ₂ Cl ₂ -hexane	179	C ₁₂ H ₁₀ N ₄ O ₂	242	59.50	4.16	23.13	59.38	4.38	23.40
7a	66	CH ₂ Cl ₂ -hexane	99-100	C ₇ H ₇ N ₅ O ₂	—	43.52	3.65	36.26	43.74	3.90	36.53
7a*		MeOH	155-6(d)	C ₇ H ₇ N ₅ O ₂ .HNO ₃	—	32.82	3.15	32.81	33.08	3.32	33.09
7a†		—	1550-55	C ₇ H ₇ N ₅ O ₂	—	56.69	3.96	18.37	56.88	4.19	18.33
7b*	55	MeOH-EtOAc	200	C ₉ H ₉ N ₅ O ₂ .HNO ₃	—	35.56	3.73	31.10	35.84	4.00	31.45
7c*	35	MeOH-EtOAc	180	C ₉ H ₁₁ N ₅ O ₂ .HNO ₃	—	38.03	4.26	29.57	38.14	4.41	29.47
7d*	40	MeOH-EtOAc	149-50	C ₁₀ H ₁₃ N ₅ O ₂ .HNO ₃	—	40.27	4.73	28.18	40.53	4.98	28.48
7e*	49	EtOH	144-5	C ₈ H ₉ N ₅ O ₂ .S.HNO ₃	—	31.79	3.34	27.81	31.89	3.59	28.13
7f	72	Benzene	146-7	C ₈ H ₉ N ₅ O ₄ S	—	35.43	3.35	25.83	35.76	3.44	25.95
7g	42	DMF	225-6	C ₇ H ₆ N ₆ O ₄	238	35.30	2.54	35.29	35.60	2.80	35.67
7h	35	CH ₂ Cl ₂ + MeOH - Hexane	188-90	C ₈ H ₈ N ₆ O ₄	252	38.10	3.20	33.33	38.43	3.59	33.49
7i*	46	CH ₃ OH-EtOAc	159-60	C ₉ H ₁₁ N ₅ O ₂ .HNO ₃	—	38.03	4.26	29.57	37.54	4.50	29.42
7j*	45	MeOH-EtOAc	178-80	C ₁₀ H ₁₃ N ₅ O ₂ .HNO ₃	—	40.27	4.73	28.18	40.37	4.96	28.38
7k*	67	CH ₂ Cl ₂ -MeOH -Hexane	170	C ₁₃ H ₁₁ N ₅ O ₂	269	57.98	4.12	26.01	57.80	4.38	26.27
9a*	20	MeOH-EtOAc	82-3	C ₁₀ H ₁₃ N ₅ O ₂ .HNO ₃	—	40.27	4.73	26.82	40.55	4.51	26.71
9b*	40	MeOH-Et ₂ O	152-3	C ₉ H ₁₁ N ₅ O ₃ .HNO ₃	—	36.00	4.03	27.99	35.94	4.28	28.36
10	80	CH ₂ Cl ₂ + MeOH - Et ₂ O	190	C ₁₁ H ₉ N ₅ O ₂	243	54.32	3.73	28.80	54.57	4.00	29.09
11	36	H ₂ O	122-4	C ₁₁ H ₁₃ N ₅ O ₂	—	53.43	5.30	28.33	53.70	5.61	28.56
12a	34	CH ₂ Cl ₂ -Hexane	139	C ₇ H ₇ N ₅ O ₂	193	43.52	3.65	36.26	43.50	3.90	36.42
12b	20	CH ₂ Cl ₂ -Et ₂ O	138-40	C ₆ H ₁₁ N ₅ O ₂	—	48.86	5.01	31.66	48.98	5.31	31.50
12c	54	CHCl ₃ - Pet. ether	131-2	C ₇ H ₆ N ₆ O ₄	—	35.30	2.54	35.29	35.39	2.80	35.08
12d	48	CHCl ₃ -Et ₂ O	120-21	C ₇ H ₆ N ₆ O ₄	—	35.30	2.54	35.29	35.51	2.70	35.60
12f	60	CH ₂ Cl ₂ -Hexane	132-36	C ₉ H ₁₀ N ₆ O ₄	266	40.60	3.79	31.57	40.81	3.83	31.31
14	20	CH ₂ Cl ₂ -Et ₂ O	190-93	C ₁₃ H ₁₃ N ₉ O ₆	391	39.90	3.35	32.22	39.98	3.69	32.24
16a	24	CH ₂ Cl ₂ -Et ₂ O	143-4	C ₈ H ₉ N ₅ O ₃	223	43.05	4.06	31.38	43.07	4.40	31.59
16b	40	CH ₂ Cl ₂ -Et ₂ O	110-11	C ₁₀ H ₁₁ N ₅ O ₄	—	45.28	4.18	26.41	45.45	4.40	26.09
17a	69	DMF-Et ₂ O	205-6	C ₁₁ H ₈ N ₆ O ₄	—	45.84	2.80	29.16	46.20	3.08	28.78
17b	65	DMF	196-7	C ₁₁ H ₈ ClN ₅ O ₂	—	47.58	2.90	25.22	47.90	3.14	24.95
19	48	CH ₂ Cl ₂ -Et ₂ O	149-50	C ₆ H ₆ N ₆ O ₂	194	37.11	3.11	43.29	37.12	3.35	43.61
21a	53	CH ₂ Cl ₂ -hexane	122	C ₈ H ₈ N ₆ O ₂	244	49.18	3.30	34.42	48.98	3.57	34.14
21b	80	MeOH	148-9	C ₁₀ H ₇ N ₇ O ₄	289	41.53	2.44	33.90	41.64	2.76	33.42
22	9	CH ₂ Cl ₂ -Et ₂ O	80-81	C ₅ H ₅ N ₇ O ₂	—	30.77	2.58	50.25	30.42	2.61	49.82
23a	28	MeOH	183	C ₈ H ₉ N ₅ O ₂ .HNO ₃	—	35.56	3.73	31.10	35.81	3.97	31.16
23b	55	EtOAc	210	C ₉ H ₁₁ N ₅ O ₂	221	48.86	5.01	31.66	48.96	5.29	31.99
24	26	CH ₂ Cl ₂ -Hexane	83	C ₈ H ₉ N ₅ O ₂	207	46.37	4.38	33.80	46.63	4.70	33.84
25	12	MeOH	139-40	C ₈ H ₄ N ₄ O ₂ S	196	36.74	2.06	28.57	36.52	2.42	28.15
26	70	Dioxane	225-7	C ₈ H ₆ N ₄ O ₂	—	50.53	3.18	29.47	50.93	3.50	29.33

*As salts of HNO₃.

†As 2-hydroxy-3-naphthoate.

room temperature for 30 min. The solid obtained was filtered off, washed with water and recrystallized from methylene chloride-ether to afford **16b** (150 mg), m.p. 110-111°.

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