HETEROCYCLIC AMIDINES : I. A ONE-STEP SYNTHESIS OF NEW α-SUBSTITUTED IMIDAZOLYLPHENYLACETIC ACIDS

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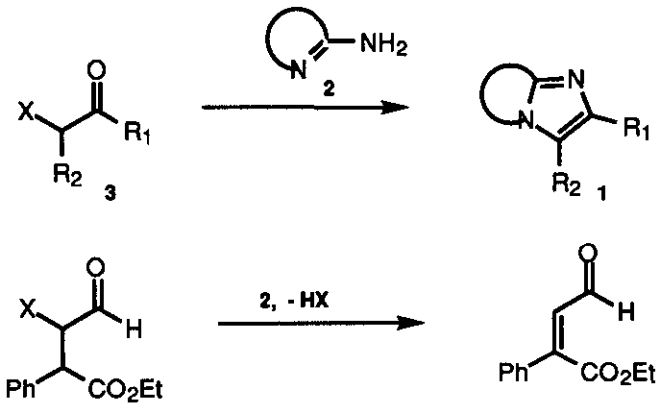
Abstract - The reaction of α-phenyl-ß-formylacrylic derivatives with various amidines (benzamidine, acetamidine) and heterocyclic amidines (2-aminopyridines, 3-aminopyridazines), yields α-substituted imidazolylphenylacetic acids and imidazo[1,2-*x*]azines bearing a phenylacetic acid residue in position 3. Some mechanistic aspects of the cyclocondensation reaction will be discussed.

Within the scope of our current research on original benzodiazepine receptor ligands,[1-3] we considered of special interest the synthesis of a series of 3-(α-phenyl ethoxycarbonylmethyl)-imidazo[1,2-*b*]pyridazines (**14-18**). The usual route for the preparation of 1,2-disubstituted imidazo[1,2-*x*]azines (**1**) involves the cyclocondensation of an heterocyclic amidine (**2**) with substituted halomethyl ketones (**3**) (R_1 and $R_2 \neq H$),[4,5] as shown in Scheme 1. For the synthesis of 3-monosubstituted imidazole derivatives (**1**) ($R_1 = H$, $R_2 \neq H$), a corresponding substituted α-haloacetaldehyde would be needed in the same reaction pathway. Such compounds are generally unstable and, to our knowledge, only phenylbromoacetaldehyde has been used for building 3-phenylimidazo[1,2-*x*]azines (**1**) ($R_1 = H$, $R_2 = Ph$)[6].

In addition, for the specific α-haloacetaldehyde (**3a**) ($R_1 = H$, $R_2 = CH(Ph)CO_2Et$), an amidine facilitated dehydrohalogenation leading to ethyl α-phenyl-ß-formylacrylate (**4a**) was observed. However the ß-formylacrylate (**4a**) is a polyelectrophilic reagent, and may itself

react readily with heterocyclic amidines. The present paper describes the reaction of benzamidine, acetamidine, and several heterocyclic amidines with the ethyl ester (**4a**), or with the corresponding sodium salt (**4b**).

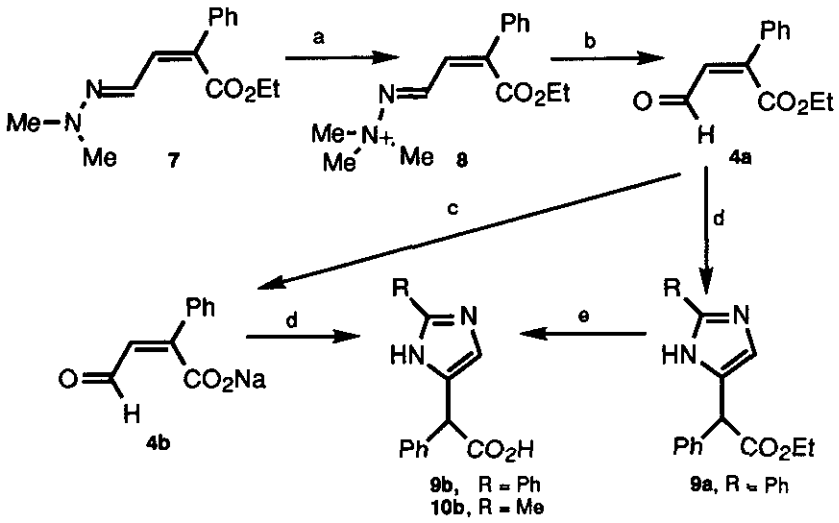


Scheme 1

RESULTS AND DISCUSSION

The compound (**4a**) was conveniently prepared by acid hydrolysis of the corresponding ethyl α-phenyl-ß-formylacrylate dimethylhydrazone methiodide (**8**), which was quantitatively obtained by quaternization of the corresponding *N,N*-dimethylhydrazono ester (**7**) with methyl iodide[7] (Scheme 2). The latter ester (**7**) was prepared by aldol condensation of ethyl phenylacetate with glyoxal *N,N*-dimethylhydrazone in presence of sodium hydride as a base.[8] Benzamidine, the first compound examined, reacted with the Michael acceptor (**4a**) to yield 2-phenyl-5-(α-phenylethoxycarbonylmethyl)imidazole (**9a**) with a satisfactory yield.

Acid hydrolysis of imidazo ester (**9a**) led to the corresponding acid (**9b**), which was recovered as its unionized form, as shown by the presence of the characteristic CO_2H band at 1725 cm^{-1} in its ir spectrum. The same acid derivative (**9b**) could be directly obtained by cyclocondensation of benzamidine with the sodium salt (**4b**) of α-phenyl-ß-formylacrylic acid. The main physical data related to α-imidazolylphenylacetic acid derivatives are listed in Tables 1 and 2. Nmr spectra of fused bicyclic derivatives show a characteristic methine proton signal around 5.4 ppm, while the imidazolic proton appears at 7.6 ppm.

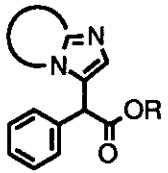


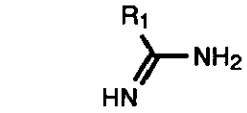
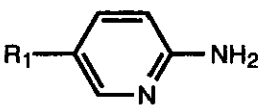
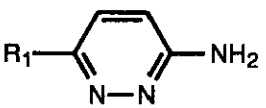
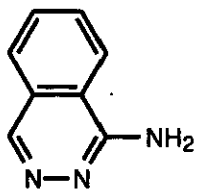
Scheme 2

The hygroscopic properties of the starting acetamidine hydrochloride combined with the catalytic effect of the imidazole ring in water hydrolyzing processes[9] may account for the exclusive recovery of the acid derivative (**10b**), when starting from the ester (**4a**).

When the reaction was carried out with 2-aminopyridines, two different compounds were obtained depending upon the nature of the substituents of the pyridine nucleus. Reacting 2-amino-5-methylpyridine with **4a** afforded the 3-substituted imidazo[1,2-*a*]pyridine (**11a**), while its 5-chloro analogue took place in a different way yielding a yellow compound, for which nmr, combined with elemental analysis, allowed us to assign the structure (**12**) for this new compound. Thus, the replacement of the 5-methyl group by a 5-chloro substituent dramatically modifies both the reactivity and the nucleophilic character of the amidine function toward the ß-formylacrylate (**4a**). When the 2-aminopyridines were replaced by various 3-aminopyridazines as well as by 3-aminophthalazine, the reaction gave exclusively the corresponding imidazo[1,2-*b*]pyridazines (**14-18**). Except for 2-amino-5-chloropyridine, all the considered heterocyclic amidines yielded the sole regioisomer (**1**) [R_1=H, R_2= CH(Ph)CO_2Et].

Table 1. Physical data of α-substituted imidazolyl phenyl acetic acids and esters



Compd No	Starting amidine	R1	R	Reaction[a] Time	Yield %	mp(b)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
9a		Ph	OEt	3	66	98	$C_{19}H_{18}N_2O_2$	74.48	5.92	9.14	74.55	6.02	9.15
9b		Ph	OH	3	77	196-99	$C_{17}H_{14}N_2O_2$	73.36	5.07	10.07	73.70	5.21	9.84
10b		Me	OH	6	70	293	$C_{12}H_{12}N_2O_2$	66.64	5.59	12.95	66.21	5.04	12.71
11a		Me	OEt	48	70	120	$C_{18}H_{18}N_2O_2$	73.44	6.16	9.51	73.61	6.30	9.52
11b		Me	OH	5	72	283	$C_{16}H_{14}N_2O_2$	72.16	5.29	10.52	72.10	5.27	10.51
14a		Ph	OEt	8	55	70	$C_{22}H_{19}N_3O_2$	73.93	5.35	11.75	73.90	5.32	11.66
15a		p-$MeOC_6H_4$	OEt	24	53	75	$C_{23}H_{21}N_3O_3$	71.30	5.46	10.84	71.89	5.35	10.70
15b		p-$MeOC_6H_4$	OH	20	70	177	$C_{21}H_{17}N_3O_3$	70.18	4.76	11.69	70.20	4.70	11.70
16a		OMe	OEt	6	60	77	$C_{17}H_{17}N_3O_3$	63.58	5.50	13.49	65.40	5.45	13.70
16b		OMe	OH	2	95	136	$C_{15}H_{13}N_3O_3$	62.59	4.62	14.83	63.17	4.57	14.68
17a		Cl	OEt	30	69	69	$C_{16}H_{14}N_3O_2Cl$	60.86	4.46	13.30	60.90	4.40	13.30
17b		Cl	OH	3	90	180	$C_{14}H_{10}N_3O_2Cl$	58.44	3.50	14.60	58.39	3.50	14.58
18a			OEt	12	50	73	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.39	5.16	12.51
18b			OH	12	60	179	$C_{18}H_{13}N_3O_2$	71.27	4.35	13.85	71.40	4.32	13.52

a) Reaction times and yields for the acids preparation are relevant to the acid hydrolysis step starting from the corresponding imidazo esters
(see Experimental Part).
b) The esters were recrystallized from hexane except for **9a, 11a**, and **16a** (isopropyl ether).

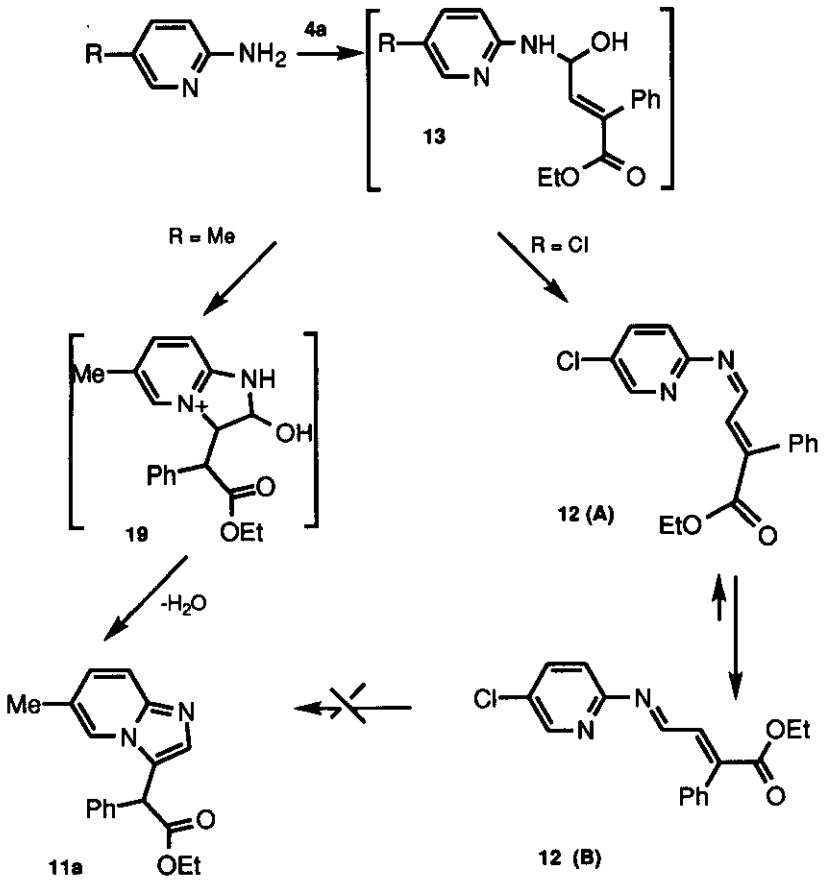
Table 2. Typical ^{1}H-nmr data of imidazolic derivatives

Compd No	Solvent[a]	^{1}H-nmr
9a	**C**	7.90-7.50 (m, 2H), 7.50-7.00 (m, 8H), 6.90 (s, 1H), 5.05 (s, 1H).
9b	**M**	7.80 (m, 2H), 7.50-7.20 (m, 8H), 6.85 (s, 1H), 5.00 (s, 1H).
10b	**T**	7.70-7.40 (m, 5H), 7.18 (s, 1H), 5.25 (s, 1H), 2.27 (s, 3H).
11a	**C**	7.58 (s, 2H), 7.50-7.20 (m, 5H), 7.25 (AB, J_{ab} = 10, $\Delta\delta$ = 0.55, 2H), 5.21 (s, 1H), 2.26, (s, 3H).
11b	**M**	7.85 (s, 1H), 7.45-7.10 (m, 7H), 7.40 (s, 1H), 5.09 (s, 1H), 2.29 (s, 3H).
14a	**C**	7.60-7.30 (m, 8H), 7.70 (s, 1H), 8.05-7.95 (m, 2H), 7.25 (AB, Jab = 10, $\Delta\delta$ = 0.88, 2H), 5.51 (s, 1H).
15a	**C**	8.05 (AB, Jab = 9, $\Delta\delta$ = 0.60, 2H), 7.60 (AB, Jab = 9, $\Delta\delta$ = 0.93, 4H) 7.60-7.20 (m, 5H), 7.47 (s, 1H), 5.69 (s, 1H), 3.82 (s, 3H)
15b	**D**	7.93 (AB, Jab = 8, $\Delta\delta$ = 0.57, 2H), 7.65 (AB, Jab = 7.9, $\Delta\delta$ = 0.95, 4H), 7.70-7.30 (m, 5H), 7.56 (s, 1H), 5.57 (s, 1H), 3.93 (s, 3H).
16a	**C**	7.55-7.12 (m, 5H), 7.52 (s, 1H), 7.25 (AB, Jab = 10, $\Delta\delta$ = 1.14, 2H), 5.38 (s, 1H), 3.90 (s, 3H).
16b	**M**	7.60-7.20 (m, 6H), 7.38 (AB, Jab = 10, $\Delta\delta$ = 1.0, 2H), 5.40 (s, 1H), 4.00 (s, 3H).
17a	**C**	7.50-7.27 (m, 5H), 7.67 (s, 1H), 7.44 (AB, Jab = 9.4, $\Delta\delta$ = 0.86, 2H), 5.40 (s, 1H).
17b	**M**	7.60-7.40 (m, 5H), 7.92 (s, 1H), 8.09 (AB, Jab = 10, $\Delta\delta$ = 0.58, 2H), 5.55 (s, 1H).
18a	**C**	8.60 (s, 1H), 8.42 (d, 1H), 7.90-7.80 (m, 2H), 7.70-7.60 (m, 1H), 7.50-7.20 (m, 5H), 7.47 (s, 1H), 5.54 (s, 1H).
18b	**D**	9.15 (s, 1H), 8.55-8.40 (m, 1H), 8.40-8.20 (m, 1H), 8.15-8.00 (m, 1H), 8.00-7.80 (m, 1H), 7.70-7.30 (m, 5H), 7.35 (s, 1H), 5.56 (s, 1H).

a) Nmr spectra carried out in $CDCl_3$ (C) ; TFA (T) ; CD_3OD (M), or $(CD_3)_2SO$ (D).

These results can be interpreted by taking into account the relative nucleophilicities of both the exo- and the endocyclic nitrogen of the different heterocyclic amidines toward a given electrophilic system. Thus, as supported by experimental data from the literature,[10,11] it has been observed that acylation, carbamoylation, and more generally reactions with carbonyl compounds, occur always on the exocyclic amino group of heterocyclic amidines whereas the

most basic endocyclic nitrogen is more easily substituted by an alkyl halide,[12,13] or by a typical Michael acceptor, such as reactive acrylic derivatives,[14] or ethyl propriolate.[15]



Scheme 3

The α-phenyl-ß-formylacrylate (**4a**) presents mainly two electrophilic centers, the ß-carbon bearing the formyl group, and the latter moiety which is highly reactive, as additive carboxylate and phenyl electron-widthdrawing effects are transmitted through the double bond. In addition, the presence of an amino group in position 2 of the endocyclic nitrogen of heterocyclic amidines sterically hinders nucleophilic attack onto the endocyclic nitrogen, and thus favors the involvement of the exocyclic nitrogen, when reacting with hindered electrophiles.[12] These steric effects,[16] combined with electronic properties[13] dealing with the hard-soft acid-base (HSAB) theory[17,11] are predominant in the control of the reaction of

different heterocyclic amidines with various electrophiles.

According to these considerations, and taking into account the formation of the Schiff base (**12**), when starting from 2-amino-5-chloropyridine, the hydroxyaminal (**13**) would be expected as the first intermediate. It results from the attack of the sp^3 exocyclic nitrogen of heterocyclic amidines, which behaves as the hard center of the amidine, onto a carbonyl group which resembles a carbonium (hard center following the HSAB theory).

The intermediate (**13**) may either undergo water elimination and afford the Schiff base (**12**), or cyclocondense to the dihydroimidazole (**19**), which led readily to the corresponding imidazole (**11a**).

The competition between the two different pathways leading either to the Schiff base (**12**) or the imidazoheterocycle (**11a**) is strongly dependent upon the physical properties of the considered heterocyclic amidine. The 2-amino-5-methylpyridine is about three hundred times more basic than its 5-chloro analogue[18,19] (pKa = 7.2 and 4.7 respectively). Thus the relatively less basic 5-chloro intermediate (**13**) (R = Cl) probably is not nucleophilic enough to be readily cyclized *via* intramolecular Michael addition of the endocyclic nitrogen onto the side chain bearing an acrylate moiety. Thus it favors a relatively easy water elimination in intermediate (**13**) leading to a stable Schiff base.[20] However, the latter compound (**12**) can no longer be converted into the corresponding derivative (**11a**) (Scheme 3). The complete loss of sp^3 character of the exocyclic nitrogen in **12** may lead to a dramatic decrease of the intrinsic nucleophilicity of the endocyclic nitrogen of such compounds.[21] However it is noteworthy that other Schiff bases deriving from 2-aminopyridines have been alkylated by methyl iodide.[22] Thus a more favourable full-trans conformation (B) for the azadiene (**12**) may strongly account for its inactivity in internal and reversible cyclization processes.

This reaction constitutes a versatile method for the preparation of new ring-condensed imidazolyl phenylacetic acids, and can be extended to various 3-functionalized imidazo[1,2-*x*] heterocycles.

EXPERIMENTAL

Melting points were recorded on a Gallenkamp melting point apparatus and were

uncorrected. Nmr spectra were recorded on Bruker WP80 (80 MHz) and WP 200SY (200 MHz) instruments, and chemical shifts are reported in parts per million (δ) relative to Me_4Si. Ir spectra were taken with a Pye Unicam SP300 spectrophotometer using KBr disks. Thin layer chromatography (tlc) on precoated silica gel plates (Kieselgel OF_{254} "230-400 Mesh", Merck) were used for monitoring the course of the reactions. Acetamidine and benzamidine salts, 2-amino-5-chloropyridine, and 2-amino-5-methylpyridine were respectively purchased from Aldrich (France) and Fluka (Germany). 3-Aminophthalazine[23] and 2-amino-5-phenyl-1,3,4-thiadiazole[24,25] were prepared following literature procedures. The preparation of 6-substituted 3-aminopyridazines has been described elsewhere.[26-28]

Ethyl 2-phenyl-4-oxobutenoate (4a) and its sodium salt (4b)

To 15.0 g (60.9 mmol) of ethyl 4-dimethylhydrazino-2-phenylcrotonic acid ethyl ester (**7**)[8] in 40 ml of DMF was added MeI (43.22 g, 0.305 mol) under stirring and left at room temperature for 3 days. The medium was poured into ether (250 ml) and the resulting solid was collected, dissolved in a minimum of MeOH and precipitated again with ether yielding a solid (21.75 g, 92%), which was used in the next step without any purification. mp 105-108°C. The iodide salt (7.5 g, 19.32 mmol) was taken up into a mixture of 400 ml of water and 500 ml of toluene in presence of 3 ml of concentrated HCl and refluxed for 5 h. The organic layer was separated, dried over Na_2SO_4, and evaporated under vacuum to give a crude yellow oil. After chromatography over silica gel using a mixture of ethyl acetate-hexane (1:5) as eluent, 3.24 g (82 %) of pure ethyl 2-phenyl-4-oxobutenoate, (**4a**) were obtained. ^{1}H-Nmr ($CDCl_3$) δ : 1.30 (t, J = 7 Hz, 3H), 4.30 (q, J = 7 Hz, 2H), 6.95 (d, J = 7 Hz, 1H), 7.30-7.60 (m, 5H), 9.70 (d, J = 7 Hz, 1H). The corresponding sodium salt (**4b**) was prepared quantitatively by treatment of 4-phenyl-5-hydroxy-2-(5*H*)-furanone[29] in EtOH with one equivalent of 1N NaOH solution, removal of solvents and trituration of the salt with a mixture of EtOH-Et_2O. After filtration the solid was dried and used without further purification.

General method for the preparation of 3-(ethyl α-phenylacetate)imidazo[1,2-x]azines (11a, 14a-18a)

A mixture of 0.61 g (3 mmol) of **4a** and 3 mmol of the suitable amidine was refluxed in 30 ml

of THF (or in absolute EtOH for benzamidine) for a 36-48 h period (see Table 1), and the course of the reaction was monitored by tlc analysis. The cold solution was evaporated under vacuum, taken up in water, extracted with ether and dried over Na_2SO_4. After evaporation of the solvent, the crude material was purified by recrystallization from hexane (or diisopropyl oxide for **9a**, **11a** and **16a**),or chromatographied over silica gel using a mixture of ethyl acetate-hexane (4:1) as eluant.

Ethyl 4-(5-chloropyridin-2-yl)imino-2-phenyl-2-butenoate (12)

A solution of 2-amino-5-chloropyridine (0.25 g, 2 mmol) and **4a** (0.408 g, 2 mmol) in 30 ml of absolute ethanol was refluxed for 12 h. After removal of the solvent, the residue was taken in H_2O and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness. Recrystallization from diisopropyl ether yielded **12** as light yellow crystals (0.50 g, 81 %). mp 127-130°C. Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.49 ; H, 4.80 ; N, 8.90. Found : 64.42 ; H, 4.54 ; N, 9.13. ^{1}H-Nmr ($CDCl_3$) δ : 1.35 (t, J = 7 Hz, 3H), 4.30 (q, J = 7 Hz, 2H), 7.20 (d, J = 9 Hz, 1H), 7.40 (s, 5H), 7.60 (d, J = 9 Hz, 1H), 7.65 (dd, J = 3 and 9 Hz, 1H), 8.30 (d, J = 3 Hz, 1H), 8.80 (d, J = 9 Hz, 1H).

Preparation of imidazo acids (9b, 11b, 15b-18b)

a) Acid hydrolysis of imidazo esters **(9a, 11a, 15a-18a)**

The title imidazo ester (3 g in 50 ml of 10 % HCl solution) was gently refluxed until the disappearance of starting material (monitored by tlc in AcOEt). The acidic medium was partially neutralized to pH 4.5 with a saturated solution of $NaHCO_3$. After removal of the solvent, the residue was triturated with hexane, the resulting solid was filtered off and rinsed with cold EtOH. After filtration of the solid, the ethanolic phase was evaporated under vacuum and yielded nearly quantitatively the imidazo acid, which was further recrystallized from EtOH.

b) Preparation starting from **4b**. Typical procedure

A solution of 0.145 g (1.16 mmol) of 6-methoxy-3-aminopyridazine and 0.23 g (1.16 mmol) of **4b** in 30 ml of EtOH was gently refluxed for 24 h. After removing of the solvent, the crude residue was triturated with AcOEt, decanted, dissolved in water, and carefully acidifed with

dilute HCl solution until the precipitation of the product, which was collected by filtration under vacuum. The crude material was heated in MeOH in presence of charcoal, recovered and recrystallized from EtOH yielding pure imidazo acid (**16b**).

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