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INTRAMOLECULAR BASE-CATALYZED REACTIONS INVOLVING INTERACTION BETWEEN BENZENE NITRO GROUPS AND *ortho* CARBON CHAINS

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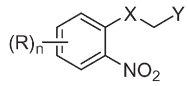
Dedicated to Dr. Alfred Bader on the occasion of his 85th birthday in recognition of his outstanding contribution to the science of chemistry.

The review is focused on the understanding of processes involving chemical interaction between benzene nitro group and *ortho* carbon chain containing heteroatom (N, O, S) adjacent to the ring. In most cases these compounds undergo base-catalyzed cyclization to give heteroaromatic *N*-oxides that can be subsequently transformed to related heterocycles under the same conditions. However, in some cases, depending on substitution of the benzene ring, side chain or the base used, the formation of other compounds – both heterocyclic and non-heterocyclic such as nitroso and azoxy compounds, spiro Meisenheimer adducts – is observed. Review with 31 references.

Keywords: Cyclization involving nitro group; *o*-Nitroanilines; *o*-Nitrophenyl sulfides; *o*-Nitrophenyl ethers; Benzimidazole *N*-oxides; Benzothiazole *N*-oxides; Benzimidazol-2(3*H*)-ones; 1-Hydroxyquinoxaline-2,3(1*H*,4*H*)-diones; Azoxy compounds.

1. INTRODUCTION

This review is focused on the understanding of processes involving chemical interaction between benzene nitro group and *ortho* carbon chain containing heteroatom adjacent to the benzene ring (Chart 1).

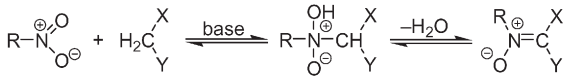


X = O, S, NH, NR
Y = COOR, CN, COR, Ar, R
n = 0-2

CHART 1

The synthetic value of such reactions has been extensively reviewed[1] previously but the last review on this topic by Preston and Tennant is more than 35 years old. Therefore we have attempted to revisit this subject and, together with some of our own papers in the field, to contribute to understanding of the processes involved. The types of reaction to be discussed include redox processes, formation of Meisenheimer adducts and, in particular, base-catalyzed cyclizations involving intramolecular condensations of the aldol type for which the nitro group provides the electrophilic center. Such reactions lead often, but not always, to benzoazaheterocycles and in many cases afford otherwise inaccessible products (e.g., heteroaromatic *N*-oxides of unequivocal structure and nitroso arenes). The reactions in which the nitro group is modified prior to interaction (e.g., cyclizations involving reduction of the nitro group by an external reagent) are excluded from the scope of the review.

The nitro group can provide the electrophilic centre for base-catalyzed addition reactions of the type exemplified by the aldol condensation (Scheme 1).



SCHEME 1

However, for the nitro group it must be expected that resonance (of the lone-pair of negatively charged oxygen and nitrogen) will significantly lower reactivity of the "nitrosyl" component. The lowering of nitro group reactivity is apparently severe for intermolecular reactions. To the best of our knowledge, there exists no intermolecular reactions involving interaction between a resonance-stabilized carbanion and nitro group. On the other hand, there exist a lot of examples[1] where intramolecular attack of a resonance-stabilized carbanion on the nitro group proceeds smoothly to

give five- or six-membered heterocyclic rings. In those cases the lower nucleophilicity (or reactivity in terms of rate constant *k*) of a resonance-stabilized carbanions is compensated by its high effective molarity[2a,2b] and by other factors such as ring strain[2c,2d] of the ring formed, entropy term[2c], steric and conformational demands[2e], medium, etc. Only strong carbon nucleophiles such as organometallic compounds[3] react with both unsaturated aliphatic and aromatic nitro compounds to give various products (secondary amines, hydroxylamines, azo compounds, nitroxides, etc.) depending on the conditions, structure and molar ratio of starting materials. It is also well known that activated aromatic nitro groups undergo replacement by various nucleophiles[4]. The intramolecular version of this reaction, where the nucleophilic group is incorporated in the formed ring, is called aromatic nucleophilic denitrocyclization[5].

Therefore, it is sometimes hard to predict whether the starting compound with general formula in Chart 1 will undergo cyclization involving the nitro group, some kind of redox process, simple formation of Meisenheimer adducts or substitution of the nitro group. The following examples should help to answer this question.

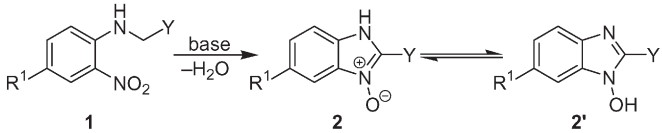
2. *o*-NITROANILINE DERIVATIVES

The cyclization of substituted *o*-nitroanilines[1e] (X = NH, NR; Chart 1), involving a condensation reaction of the nitro group and a nucleophilic center in the *o*-substituent, is recognized as a standard method for the preparation of benzimidazole *N*-oxides. It is convenient to consider these compounds under two headings, namely, those involving monosubstituted *o*-nitroanilines (X = NH; Chart 1) and those involving disubstituted *o*-nitroanilines (X = NR; R = alkyl, acyl, tosyl, alkoxycarbonyl, etc.; Chart 1).

2.1. Monosubstituted o-Nitroanilines

As early as 1963, Loudon and Tennant have reported[6a] the hydroxide anion-catalyzed cyclization of 2-(4-methyl-2-nitroanilino)-1-phenylethan-1-one (**1a**) giving 2-benzoyl-5-methylbenzimidazole-3-oxide (**2a**), which is in tautomeric equilibrium with 2-benzoyl-1-hydroxy-6-methylbenzimidazole (**2a′**) (Scheme 2). However, when the same reaction was carried out in sodium methoxide or ethoxide solutions[6b], the main reaction product was 4-methyl-2-nitroaniline (42 and 45%, respectively) and only traces of **2a** were isolated. The mechanism of this cleavage is far from clear: the only other product isolated was the corresponding alkyl benzoate. The expected

cyclizations giving benzimidazole *N*-oxides also proceeded when Y was an aryl group, e.g., phenyl[6c,6d], substituted phenyl[6e,6f] and thiazolyl[6g]. Both acyl and aryl groups behave as weak electron acceptors and a strong base (sodium hydroxide, sodium methoxide, sodium hydride) generating carbanion is required for successful cyclization.

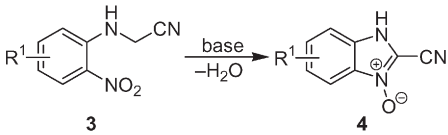


	R^1	Y	Base	Yield (%)	Ref.
a	CH_3	C_6H_5CO	NaOH/H_2O	not given	6a
			MeONa/MeOH	2	6b
			EtONa/EtOH	3	6b
b	H	C_6H_5	NaOH/MeOH	79	6c
			NaH/DMSO	75	6d
c	H	4-$O_2NC_6H_4$	MeONa/MeOH	37	6e
d	H	4-ClC_6H_4	NaOH/MeOH	51	6f
e	H	4-$MeOC_6H_4$	NaOH/MeOH	not given	6f
f	NO_2	C_6H_5	NaOH/MeOH	not given	6f
g	Cl	C_6H_5	NaOH/MeOH	not given	6f
h	H	thiazol-2-yl	KOH/EtOH	not given	6g
i	H	thiazol-4-yl	NaOH/EtOH	not given	6g

SCHEME 2

The situation is more complex for *o*-substituted nitroanilines carrying a stronger electron acceptor group Y, e.g., carboxy, ester, amide or nitrile group. The structure of the products formed strongly depends on further substitution of the benzene ring and also on the reaction medium used.

Substituted 2-(2-nitroanilino)acetonitriles **3** underwent[7a–7e] cyclization under extremely mild conditions (sodium/potassium carbonate or piperidine in ethanol) to give corresponding 2-cyanobenzimidazole *N*-oxides **4** (Scheme 3) which can be easily transformed[7c] into 2-unsubstituted benzimidazole *N*-oxides. The reaction fails for the 2,4-dinitrophenyl derivative[7c] **3h**, where only dark red resinous material was obtained, and for the 2,6-dinitrophenyl derivative[7e] **3m**, where 1-hydroxy-4-nitrobenzimidazol-2(3*H*)-one was the only isolated product. This compound is probably formed[7a,7e] by nucleophilic substitution of the cyano group with the hydroxide anion in 2-cyano-7-nitrobenzimidazole 3-oxide.



3 4

	R^1	Base	Yield (%)	Ref.
3a	H	Na_2CO_3/EtOH/H_2O	77	7a,b
		K_2CO_3/EtOH	54	7c
3b	4-Me	K_2CO_3/EtOH	53	7c
3c	4-OMe	K_2CO_3/EtOH	51	7c
3d	4-Cl	K_2CO_3/EtOH	58[a]	7c
3e	4-F	K_2CO_3/EtOH	71	7c
		piperidine/EtOH	46	7c
3f	5-F	K_2CO_3/EtOH	70	7c
3g	3-NO_2	K_2CO_3/EtOH	34	7c
3h	4-NO_2	K_2CO_3/EtOH	0	7c
3i	4-NHAc	K_2CO_3/EtOH	71	7d
3j	4-$MeSO_2NH$	K_2CO_3/EtOH	92	7d
3k	4-COOEt	K_2CO_3/EtOH	84	7d
3l	6-Me	K_2CO_3/EtOH	63[b]	7e
3m	6-NO_2	K_2CO_3/EtOH	0[c]	7e

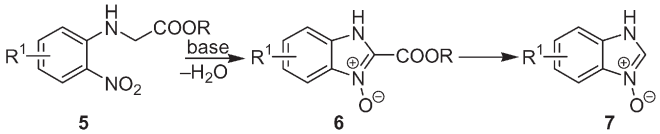
[a]Another isolated product was 2-(4-chloro-2-nitroanilino)acetamide (23%).
[b]Another isolated product was 1-hydroxy-4-methylbenzimidazol-2(3*H*)-one (6%).
[c]The only isolated product was 1-hydroxy-4-nitrobenzimidazol-2(3*H*)-one (39%).

SCHEME 3

Ester function (Y) is also very effective in stabilizing the adjacent negative charge which appears to be necessary for successful cyclization. Indeed, many substituted *N*-(2-nitrophenyl)glycine esters[7c–7f,8a] were cyclized to 2-(alkoxycarbonyl)benzimidazole *N*-oxides (Scheme 4) but certain[7d] substituents (5-NH_2, 5-Me_2N, 5-$EtOCOCH_2NH$) completely inhibited this reaction or another products[7e,8b,8c] were formed.

The failure of glycine esters **5e** and **5i**–**5k** to undergo cyclization is evidently due to the positive mesomeric effect of the alkyl-substituted or unsubstituted 5-amino group. Direct conjugation of 5-amino (σ_p^+ = –1.30)[9], 5-(dimethylamino) (σ_p^+ = –1.70)[9] and 5-[(ethoxycarbonyl)methylamino] group with the nitro group in *ortho*-position reduces the electrophilicity of the nitro group to such an extent that it is unreactive towards attack by the adjacent nucleophile. 4-Acetylamino (σ_m = +0.21)[9] and 5-acetylamino (σ_p^+ = –0.60)[9] groups behave as a relatively weaker electron acceptor and donor, respectively, and cyclization proceeds smoothly. On the other hand,

derivative **5s** reacts with sodium methoxide in methanol[8b] to give unexpected product – 5-nitrobenzimidazol-2(3*H*)-one. The mechanism of this reaction probably involves expected cyclization to **6s** and methoxide-catalyzed cleavage of the ester group (in the form of dimethyl carbonate) to give **7s** (Scheme 4). Addition of the hydroxide anion (present as impurity) to position 2 of **7s** followed by the base-catalyzed expulsion[1c] of another hydroxide anion from nitrogen leads to 2-hydroxy-5-nitrobenzimidazole which tautomerizes to give the final product. However, a kinetic study[8b]

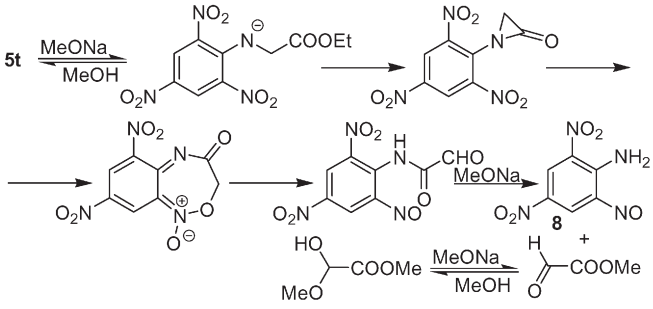


	R^1	R	Base	Yield (6; %)	Ref.
5a	H	Et	EtONa/EtOH	31	7c
5b	4-Me	Et	EtONa/EtOH+DMF	46	7c
5c	4-OMe	Et	EtONa/EtOH	68	7c
5d	4-NO_2	Et	piperidine/EtOH	56	7c
5e	5-NH_2	Et	Na_2CO_3/EtOH	0[a]	7d
5f	4-NHAc	Et	K_2CO_3/EtOH	61	7d
5g	5-NHAc	Et	K_2CO_3/EtOH	67	7d
5h	6-NHAc	Et	K_2CO_3/EtOH	43	7f
5i	4-NO_2-5-NH_2	Et	EtONa/EtOH+DMF	0[a]	7d
5j	4-NO_2-5-Me_2N	Et	EtONa/EtOH+DMF	0[a]	7d
5k	4-NO_2-5-$EtOCOCH_2NH$	Et	EtONa/EtOH+DMF	0[a]	7d
5l	6-Me	Et	K_2CO_3/EtOH	55	7e
5m	6-NO_2	Et	K_2CO_3/EtOH+DMF	0[b]	7e
5n	4-CF_3-6-NO_2	Me	Et_3N/EtOH	0[b]	7e
5o	4-CF_3	Me	K_2CO_3/MeOH	not given[c]	7e
5p	4-F	Me	K_2CO_3/MeOH	*72*[c]	7e
5q	4-CF_3-6-Cl	Me	Et_3N/toluene	*31*[c]	7e
5r	4,6-$(F)_2$	Me	K_2CO_3/MeOH	*85*[c]	7e
5s	4-NO_2	Me	Na_2CO_3/MeOH	63	8a
		Me	MeONa/MeOH	0[d]	8b
5t	4,6-$(NO_2)_2$	Et	MeONa/MeOH	0[e]	8c

[a]The only isolated product was free acid or starting material.
[b]Main isolated products were corresponding substituted 1-hydroxyquinoxaline-2,3-(1*H*,4*H*)-diones (see Fig. 2).
[c]The yield quoted for compound **7**.
[d]The only isolated product was 5-nitrobenzimidazol-2(3*H*)-one (71%).
[e]The only isolated product was 2,4-dinitro-6-nitrosoaniline (75%).

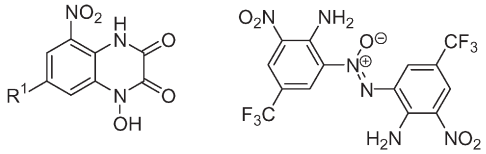
SCHEME 4

carried out under pseudo-first-order conditions has shown that a mixture of substances, whose electronic spectra did not resemble those of 5-nitrobenzimidazol-2(3*H*)-one, was formed. 2,4,6-Trinitrophenyl derivative **5t** underwent oxidative cleavage of the carbon side chain to give 2,4-dinitro-6-nitrosoaniline (**8**) and methyl glyoxylate hemiacetal under the same reaction conditions. The suggested mechanism[8c] involves intramolecular attack of negatively charged nitrogen on the carbonyl group giving a reactive aziridinone intermediate which decomposes to products (Scheme 5). A complex mixture[7e] of products containing traces of 2-nitro-6-nitroso-4-(trifluoromethyl)aniline was obtained when 2,6-dinitro-4-(trifluoromethyl) derivative **5n** was treated with sodium hydrogencarbonate in methanol.



SCHEME 5

Also base-catalyzed cyclizations of glycine esters **5m** and **5n** bearing an additional nitro group in the other *ortho*-position were anomalous. The main components of the formed complex mixtures were always the corresponding 1-hydroxyquinoxaline-2,3(1*H*,4*H*)-diones and azoxy compounds (Chart 2).

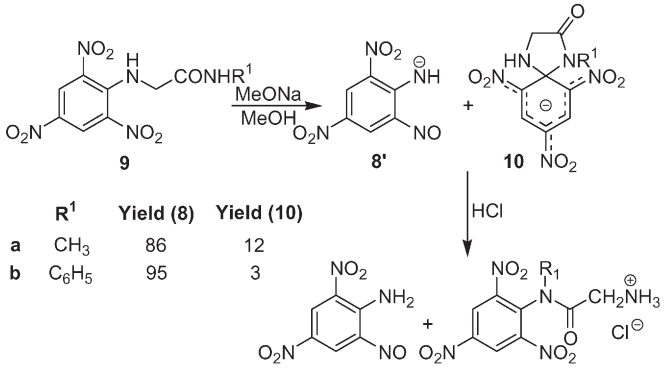


	Yield (%)		Yield (%)
R^1 = H	37	R^1 = H	trace
CF_3	39	CF_3	15

CHART 2

The four instances[7e] where compounds **7o**–**7r** instead of **6o**–**6r** were obtained possibly represent an isolation problem rather than that of the absence of **6o**–**6r**. Final treatment of the crude product with 5 M HCl solution probably caused a rapid ester hydrolysis and its decarboxylation.

Much less attention has been devoted to the cyclization of the parent carboxylic acids (Y = COOH). The only two published articles have dealt with cyclizations of *N*-(2,4-dinitrophenyl)glycine in 0.2 M phosphate buffer[10a] at pH 8.5 or in 0.2 M sodium hydroxide[10b] which gave 6-nitrobenzimidazole 1-oxide (i.e., the product of decarboxylation) in almost 73% yield. For analogous 2,6-dinitrophenyl and 2,4,6-trinitrophenyl derivatives, similar hydroxide-catalyzed cyclization and decarboxylation in aqueous dioxane were also studied[10b]. The same authors[10a] also reported cyclization of 2-[2-(2,4-dinitroanilino)acetamido]acetic acid (DNP-Gly-Gly) in a buffered medium giving 2-[*N*-(carboxymethyl)carbamoyl]-5-nitrobenzimidazole 3-oxide. In this case, the secondary amide group (–CONH–CH_2COOH) served as an activating group for cyclization. The reactivity[8c,11] of N^2-(2,4,6-trinitrophenyl)glycinamides **9** was also studied in methanolic sodium methoxide solutions. The reaction of *N*-methyl-N^2-(2,4,6-trinitrophenyl)glycinamide (**9a**)[8c] and *N*-phenylamide (**9b**)[11] with methanolic sodium methoxide gave the anion of 2,4-dinitro-6-nitrosoaniline as the main reaction product together with 3′-methyl-2,4,6-trinitro-4′-oxospiro-[benzene-1,2′-imidazolidin]ide (**10a**) or 2,4,6-trinitro-4′-oxo-3′-phenyl[benzene-1,2′-imidazolidin]ide (**10b**) instead of desired 2-carbamoyl-5,7-dinitrobenzimidazole 3-oxides. Acidification of the reaction mixture with aqueous hydrochloric acid causes ring opening (Smiles rearrangement) of spiro adducts **10** and formation of compounds **11** (Scheme 6). The pro-



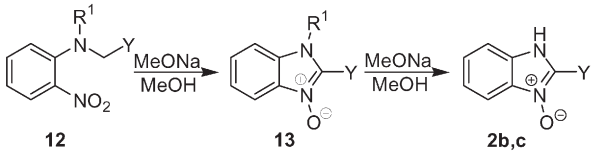
	R^1	Yield (8)	Yield (10)
a	CH_3	86	12
b	C_6H_5	95	3

SCHEME 6

posed mechanism of formation of nitroso compound **8** is the same as in the case of ester **5t** (Scheme 5). Amides **9a** and **9b** react more slowly[11] than similar ester **5t** by two orders of magnitude, which means that the rate-limiting step involves departure of methylamine or aniline. Replacement of the methyl group in **9a** by the phenyl group lowers the content of **10b** because the aniline anion is a better leaving group than the anion of methylamine. The reaction giving reactive aziridinone in the first step (cf. Scheme 5) is 2.5 times faster[11] for amide **9b** compared with **9a**.

2.2. Disubstituted o-Nitroanilines

Surprisingly, corresponding *N*,*N*-disubstituted *o*-nitroanilines with unsubstituted benzyl group on nitrogen (Y = C_6H_5), i.e., *N*-benzyl-*N*-tosyl-2-nitroaniline (**12f**)[12] *N*-benzyl-*N*-mesyl-2-nitroaniline (**12g**)[6e] and *N*-benzyl-*N*-methyl-2-nitroaniline (**12j**)[6d] do not undergo cyclization under a variety of basic conditions (Scheme 7). *N*-Acyl-*N*-benzyl derivatives **12h** and **12i** are cyclized because they undergo prior deacylation[6e] to give **1b**. On the other hand[6e], 4-nitrobenzyl derivatives (**12a**–**12e**; Y = 4-$O_2NC_6H_4$), whose methylene group is about two orders of magnitude more acidic, are cyclized in boiling sodium methoxide solutions to give 1-substituted benzimidazole 3-oxides (**13a**–**13e**) which subsequently undergo methanolysis to **2c** and



12 **13** **2b,c**

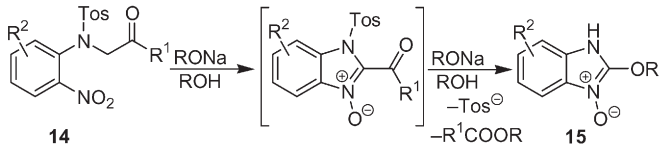
	R^1	Y	Yield 2b,c (%)	Ref.
a	4-$CH_3C_6H_4SO_2$	4-$O_2NC_6H_4$	38*	12
b	4-CH_3SO_2	4-$O_2NC_6H_4$	50	6e
c	C_6H_5CO	4-$O_2NC_6H_4$	42	6e
d	CH_3CO	4-$O_2NC_6H_4$	56	6e
e	COOEt	4-$O_2NC_6H_4$	71	6e
f	4-$CH_3C_6H_4SO_2$	C_6H_5	0	12
g	4-CH_3SO_2	C_6H_5	0	6e
h	C_6H_5CO	C_6H_5	21	6e
i	CH_3CO	C_6H_5	17	6e
j	CH_3	C_6H_5	0	6d

*Another isolated product was 1-methoxy-2-(4-nitrophenyl)benzimidazole (10%).

SCHEME 7

corresponding methyl ester (Scheme 7). In the case of cyclization of **12a**, the by-product formed (methyl tosylate) behaves as a methylating agent, which converts **2c** to 1-methoxy-2-(4-nitrophenyl)benzimidazole.

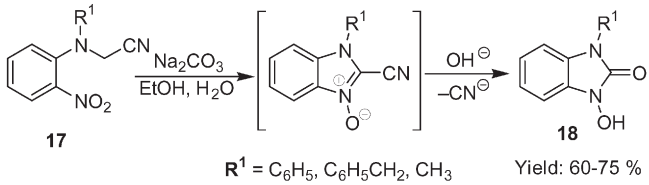
An unexpected product of cyclization[6b] was found when the activating 4-nitrophenyl group in **12a** was replaced by benzoyl or acetyl group (Scheme 8). In this case both acyl groups are cleaved off and the final product is the corresponding 2-alkoxybenzimidazole 3-oxide **15**. The yields of this reaction vary from zero to 80% depending on the substituent in the benzene ring and the catalyzing alkoxide used. The best results were obtained with sodium ethoxide. In sodium propoxide, isopropoxide and in particular *tert*-butoxide, the cyclization is accompanied by cleavage to give a primary aniline. The same anilines or *N*-tosylanilides are exclusively formed in alkoxide solutions from similar compounds whose activating acyl group is replaced[6b] by the ethoxycarbonyl or cyano group.



	R^1	R^2	Yield 15 (%) R = Me	R = Et
a	C_6H_5	H	0	80
b	C_6H_5	4-Me	47	62
c	C_6H_5	4-Cl	28	68
d	C_6H_5	4-OMe	34	68
e	C_6H_5	5-Me	45	41
f	CH_3	H	0	40
g	CH_3	4-Me	47	82
h	CH_3	4-OMe	15	53

SCHEME 8

An interesting anomaly[6b] is provided by the cyclization of the 6-methyl-2-nitroaniline derivatives (**14i**, $R^1 = C_6H_5$, R^2 = 6-CH_3; **14j**, $R^1 = CH_3$, R^2 = 6-CH_3; Scheme 8) giving 1-hydroxy-4-methylbenzimidazol-2-one (**16**). Similar derivatives **18** carrying methyl, benzyl or phenyl group in position 1 were prepared[7a,7e] by cyclization of corresponding *N*-substituted (2-nitroanilino)acetonitrile (**17**) in aqueous ethanolic sodium carbonate (Scheme 9).

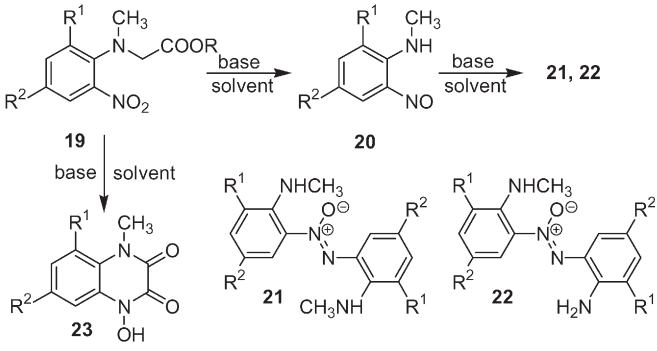


SCHEME 9

The formation of the imidazolone ring takes place in two steps. The first step produces expected 1-substituted-2-cyanobenzimidazole 3-oxide whose cyano group is subsequently[7a,7e,13] substituted by the OH group and the intermediate formed tautomerizes to **18**. In the case of formation of **16**, an alkoxy group has to be replaced by the hydroxide anion which is also present after cyclization step in alkoxide solution as a by-product.

The reaction of substituted methyl *N*-(2,4-dinitrophenyl)sarcosinate[8b,14a] **19a** with sodium methoxide in methanol and that of ethyl ester[14b] **19b** with various bases in ethanol/DMF mixture was independently studied by Macháček's and Smith's group (Scheme 10). Their results were partly different. Macháček et al. reported that the reaction of methyl ester **19a** with sodium methoxide proceeds in two steps, the second one being substantially slower. The first step produced *N*-methyl-4-nitro-2-nitrosoaniline (**20a**) in a very good yield (77% for the reaction of ethyl ester with sodium methoxide in a methanol/DMSO mixture) which subsequently underwent the reaction with sodium methoxide to give a mixture of two azoxy compounds (**21** and **22**). The same azoxy compounds **22** together with 1-hydroxy-4-methyl-7-nitroquinoxaline-2,3(1*H*,4*H*)-dione (**23**) were found by Smith et al.[14b] to be the main products formed from ethyl ester **19b** and sodium ethoxide or potassium carbonate in ethanol/DMF. Methyl *N*-(2,4,6-trinitrophenyl)-sarcosinate[14c] also gives *N*-methyl-2,4-dinitro-6-nitrosoaniline (**20c**) as the main reaction product together with traces of azoxy compound **22c**. Other substituents in *para*-position ($R^2 \neq NO_2$) suppress[14a] the formation of azoxy compounds **21** and **22** and the main reaction product is corresponding 1-hydroxy-4-methylquinoxaline-2,3(1*H*,4*H*)-dione (**23d**, **23e**). The mechanism of formation of substituted quinoxaline-2,3(1*H*,4*H*)-diones was proposed[14a,14b] (Scheme 11) although its second step involving attack of carbanion on oxygen atom of the nitro group is rather questionable.

N-(2,4,6-Trinitrophenyl)sarcosine (**24a**) itself undergoes[15a] a base-catalyzed intramolecular nucleophilic addition of terminal carboxylate anion to give the Meisenheimer adduct, 3′-methyl-2,4,6-trinitro-5′-oxospiro[benzene-1,2′-oxazolidin]ide (**25**) (Scheme 12). Similar behavior was also observed for



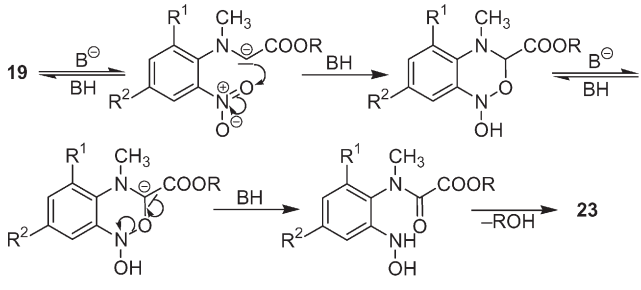
					Yield (%)				
	R^1	R^2	R	Base/Solvent	20	21	22	23	Ref.
a	H	NO_2	Me	MeONa/MeOH+DMSO	77	2	21	0	8b
				MeONa/MeOH+DMF	0	0	19	21	14a
b	H	NO_2	Et	EtONa/EtOH+DMF	0	0	32	19	14b
				K_2CO_3/EtOH+DMF	0	0	4	35	14b
				Et_3N/EtOH	0	16	0	0	14b
				DBU/DMSO	0	0	trace	33	14a
c	NO_2	NO_2	Me	MeONa/MeOH	57	0	–[a]	0	14c
d	NO_2	H	Et	K_2CO_3/EtOH	0	0	0	19[b]	14a
e	H	H	Et	EtONa/EtOH	0	0	0	44	14a
f	H	CF_3	Et	K_2CO_3/EtOH	–[c]	0	0	31	14a

[a]Product **22** is formed after acidification of the reaction mixture.

[b]Hydrochloride; other isolated products were 1-methyl-7-nitrobenzimidazol-2(3*H*)-one and 8-nitroquinoxalin-2(1*H*)-one.

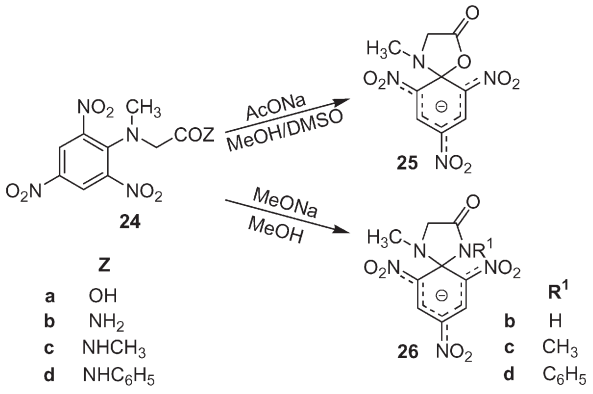
[c]Other isolated products were 5-(trifluoromethyl)benzimidazole 3-oxide and 1-methyl-6- (or 7)-(trifluoromethyl)quinoxalin-2(1*H*)-one.

SCHEME 10



SCHEME 11

sarcosinamides[11,15b,15c] **24b**–**24d** in sodium methoxide solutions where 3′-substituted-1′-methyl-2,4,6-trinitro-4′-oxospiro[benzene-1,2′-imidazolidin]ides (**26b**–**26d**) were formed exclusively (Scheme 12). There are two main reasons for a big difference in reactivity of glycinamides **9a**, **9b** producing 2,4-dinitro-6-nitrosoaniline (**8**) as the main product (cf. Scheme 6) and sarcosinamides **24b**–**24d**. First, the methyl group cannot be cleaved from the aniline nitrogen to give a reactive anion which is important (but not essential) for further reaction (see Scheme 6). Second, the methyl group decreases[2e,16] the population of rotamers, favoring the terminal amide anion orientation that is effective for intramolecular attack. As a result, as the amide nitrogen and carbon C-1 are brought into close proximity, the value of the cyclization rate constant increases by more than four orders of magnitude. In the case[15d] of *N*-(2,4-dinitrophenyl)-*N*-methylsarcosineamide (**24e**), carbon C-1 is less electron-deficient because of the absence of one *ortho*-nitro group which also increases the population of rotamers. Both these factors slow down the cyclization giving corresponding spiro adduct and the parallel reaction[15d] leading to *N*-methyl-4-nitro-2-nitrosoaniline (**20a**) occurs again.

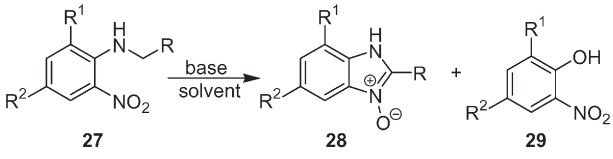


SCHEME 12

2.3. o-Nitroanilines Without Activating Y Group

In all cases presented above, the activating group Y (Chart 1) played an important role in interaction between side chain and *ortho*-nitro group. Its electron withdrawing ability that stabilizes adjacent carbanion is an essential property for cyclization reactions. It is therefore quite surprising that *N*-butyl-2,6-dinitroaniline (**27a**) also undergoes cyclization[17a] to 7-nitro-

2-propylbenzimidazole 3-oxide (**28a**) under base catalysis (Scheme 13). The reaction yields and product composition are strongly dependent[17a,17b] on the concentration of sodium hydroxide and also on the water/dioxane ratio. In 10% aqueous dioxane two products are formed, i.e., 7-nitro-2-propylbenzimidazole 3-oxide (**28a**) and 2,6-dinitrophenol (**29a**). The kinetics[17b] of the formation of phenol **29a** is of the second order in hydroxide concentration while that of benzimidazole *N*-oxide **28a** is of the first order. Therefore, the **29a**/**28a** ratio increases with increasing hydroxide concentration from 1:10 in 0.08 M NaOH to 1:1 in 1 M NaOH. In 60% aqueous dioxane solution[17a] of 0.2 M sodium hydroxide the only product is **28a**. The cyclization leading to benzimidazole *N*-oxides was also successful[10b,17a–17d] for other 6-substituted-2-nitroanilines. The presence of the second electron-withdrawing *ortho*-group has an important but not yet clear role in the formation of *N*-oxide (cf. behavior of **27a**, **27b**, **27e**–**27i** and **27c**, **27d**, **27j**).



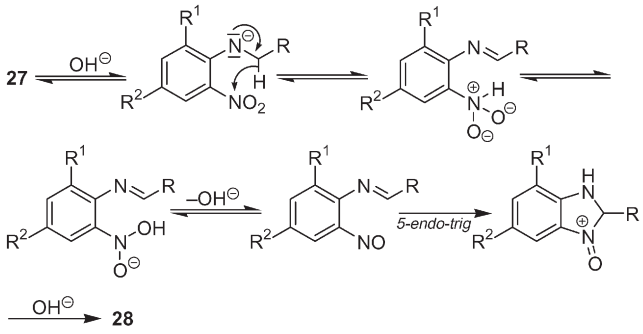
27 **28** **29**

	R^1	R^2	R	Base/Solvent	Yield (%) 28	29	Ref.
a	NO_2	H	Pr	0.2 M NaOH/60% aq. dioxane	96	0	17a
b	NO_2	NO_2	Pr	0.01 M NaOH/60% aq. dioxane	46	10	17a
				0.2 M NaOH/60% aq. dioxane	0	100	17a
c	H	NO_2	Pr	0.01 M NaOH/60% aq. dioxane	0	100	17a
d	H	H	Pr	0.2 M NaOH/60% aq. dioxane	0	100	17a
e	CF_3	NO_2	Pr[a]	K_2CO_3/EtOH	*ca* 80	0	17c,d
f	NO_2	CF_3	Pr[b]	0.1 M NaOH/60% aq. dioxane	75	–[c]	17d
g	NO_2	NO_2	Me	K_2CO_3/EtOH	*ca* 80	0	17c
h	NO_2	H	Et	0.2 M NaOH/60% aq. dioxane	76	0	17d
i	NO_2	H	$(CH_2)_2COOH$	dtto	83	7	10b
j	H	NO_2	CH_2COOH	dtto	0	94	10b

[a]The same results were achieved with R = H, CH_3, CH_2OH, CH_2CH_2COOH.
[b]The same yield was obtained with R = Et.
[c]Phenol was formed but could not be isolated.

SCHEME 13

This observation casts doubt on the simple aldol-type condensation mechanism for the cyclization of these compounds. It appears that the (acidic) hydrogen of the amino group plays a role in this cyclization because *N*-butyl-*N*-methyl-2,6-dinitroaniline gave[17b] only 2,6-dinitrophenol (**29b**). The suggested mechanism[17b,17e] involves pre-equilibrium producing aniline anion which then undergoes the hydride shift from carbon side chain to the nitro group and elimination of the hydroxide anion to give an *o*-nitroso intermediate. This intermediate can undergo intramolecular cyclization to give benzimidazole *N*-oxide (Scheme 14). However, the literature[18a] indicates that such 5-*endo-trig* process is a disfavored mode of ring closure. On the other hand it was found that similar cyclization of *N*-ethylidene-4-nitro-2-nitrosoaniline formed in situ from 4-nitro-2-nitrosoaniline and acetaldehyde proceeds in 50% acetic acid[18b].

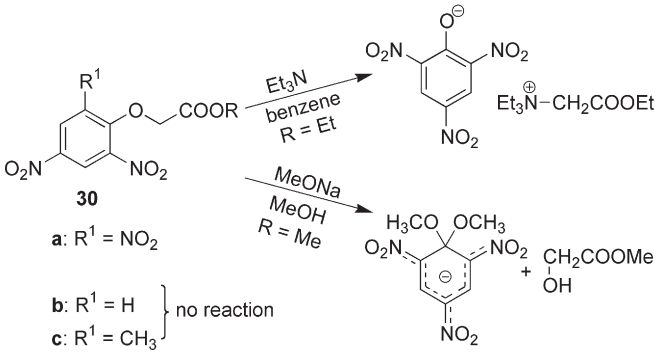


SCHEME 14

3. *o*-NITROPHENYL ETHER DERIVATIVES

The reaction of substituted *o*-nitrophenyl ethers (X = O; Chart 1), containing activated methylene group has been studied much less extensively. Thermally[19] induced intramolecular reaction of the nitro group and carbon side chain gave benzoxazoles in very poor yields (typically 3–12%). A further studied example was the reaction of (2,4,6-trinitrophenoxy)acetic acid esters (**30a**) with triethylamine[20a] or sodium methoxide[20b]. Both these reagents behave as nucleophiles and the only products are [(ethoxycarbonyl)-methyl]triethylammonium 2,4,6-trinitrophenoxide (SN2) or 1,1-dimethoxy-2,4,6-trinitrobenzenide (SNAr-AE) (Scheme 15). The corresponding 2,4-dinitro and 6-methyl-2,4-dinitro derivatives (**30b**, **30c**) do not react with triethylamine[20a] even in boiling benzene. This behavior can be as-

cribed to the lower nucleofugality of 2,4-dinitrophenoxide or 6-methyl-2,4-dinitrophenoxide compared with 2,4,6-trinitrophenoxide. On the other hand, methyl glycolate is also a good leaving group in SNAr reactions and base-catalyzed cleavage of the C–O bond is faster than cyclization to benzoxazole *N*-oxides.

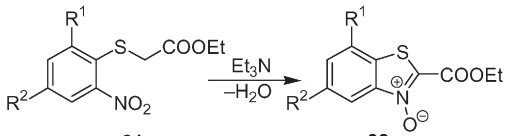


SCHEME 15

4. *o*-NITROPHENYL SULFIDE DERIVATIVES

The negative charge on a carbanion (necessary for cyclization) is effectively stabilized[21] by neighboring electron-withdrawing groups (Y; Chart 1) such as carbonyl, cyano, and aryl. In 2-nitrophenyl sulfides the sulfur itself (X = S; Chart 1) can act as a stabilizing group. The ability of sulfur atoms to stabilize adjacent carbanions has been well known for a long time. This is in part due to resonance stabilization through the participation of *d*-orbitals of sulfur, although theoretical work has challenged the importance of this interaction, suggesting that the stabilization is mainly due to polarizability[22] of sulfur. The properties of the sulfur center result in enhanced acidity, kinetic as well as thermodynamic, of hydrogen atoms in appositions to the sulfur. Therefore it is not surprising that the behavior of *o*-nitrophenyl sulfide derivatives is similar to that of 2-nitroanilines.

As early as 1959 Morgan[23a] reported the base-catalyzed cyclization of a 2-nitrophenacyl sulfide to give a complex mixture containing at least twelve compounds, three of which were characterized as benzothiazole derivatives. The mechanism of benzothiazole formation is unclear particularly in relation to the nature and timing of the reduction process which must be involved.



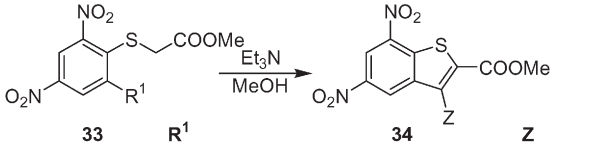
31 **32**

	R^1	R^2	Yield
a	NO_2	H	72
b	NO_2	Me	85
c	NO_2	Cl	80
d	NO_2	NO_2	76
e	NO_2	CF_3	80
f	NO_2	CN	80
g	NO_2	COOEt	83
h	NO_2	COOH	83

	R^1	R^2	Yield (%)
i	NO_2	$CONH_2$	88
j	NO_2	C_6H_5CO	67
k	NO_2	H	67
l	CH_3	NO_2	86
m	CF_3	NO_2	82
n	CF_3	CF_3	22
o	SO_2NH_2	NO_2	72
p	$NaSO_3$	NO_2	73

SCHEME 16

Expected benzothiazole *N*-oxides **32** were obtained[23b] when *in situ* generated [(2-nitrophenyl)sulfanyl]acetates **31** reacted with triethylamine in methanol, ethanol or benzene (Scheme 16). This reaction proceeded smoothly[23b–23d] for a variety of 6-substituted [(2-nitrophenyl)sulfanyl]-acetates (prepared by independent synthesis) with the exception of 6-(methoxycarbonyl)[23c,23d] and 6-cyano[23e] derivative **33**. In those particular cases the internal nucleophile (carbanion) exclusively attacked the ester and cyano function instead of the nitro group and resulting products were substituted thiophenes **34** (Scheme 17). Similar cyclization was also described for other [2-(methoxycarbonyl)-[24a] and [2-(cyanophenyl)sulfanyl]-acetates[24b].



33 **34**

	R^1
a	COOMe
b	CN

	Z
a	OH (71 %)
b	NH_2 (58 %)

SCHEME 17

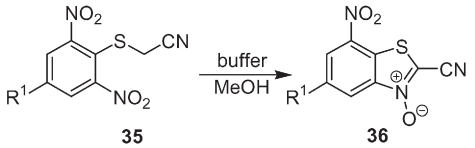
A comparison of reactivity of ester and nitro functions[3c] towards nucleophilic attack by external carbon nucleophile (Grignard reagent) gave the opposite result, i.e., the nitro group was attacked preferentially.

The presence of the second substituent in *ortho*-position has a crucial role in the formation of *N*-oxide because ethyl [(2,4-dinitrophenyl)sulfanyl]-acetate[23b], ethyl [(3,5-dinitropyridin-2-yl)sulfanyl]acetate[20a] and ethyl

[(2,4-dinitronaphthalen-1-yl)sulfanyl]acetate[20a] do not undergo cyclization reaction. The difference in behavior of these derivatives is obviously due to steric effects. The substituents in 2- and 6-positions sterically enforce such a conformation of the side chain that approaches the arrangement of the transition state of the cyclization step.

The detailed mechanism of the cyclization of methyl ester analogues of **31a**[25a], **31d**[25b], and **31g**[25c] was studied in methanolic buffer solutions by kinetic methods. It was found that the reaction was always subject to general base catalysis with the rate-limiting step involving either cleavage of proton from the starting material or the diffusion separation of the ion pair C^-BH^+ into free carbanion and protonated base.

Recently we have published the synthesis[26a] of 2-cyano-7-nitrobenzothiazole 3-oxide (**36a**) and 2-cyano-5,7-dinitrobenzothiazole 3-oxide (**36b**) and kinetic study[26b] of their formation (Scheme 18).



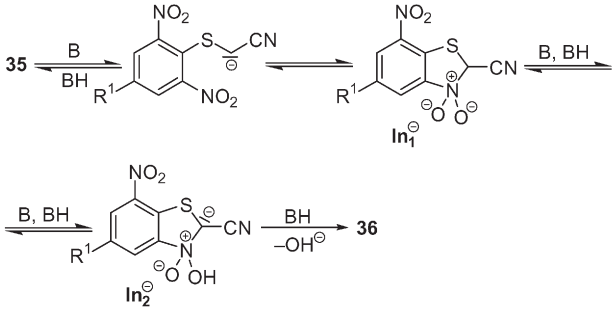
35 **36**

	R^1	Yield (%)
a	H	57
b	NO_2	56

SCHEME 18

It was found that the reaction involves both general acid and general base catalyses whose manifestation depends on the pK_a of the acid-buffer component and the ratio of both buffer components. In weakly basic buffers the rate-limiting step is C–H bond breaking in the cyclic intermediate $\mathbf{In_1}^-$, while in strongly basic buffers the rate-limiting step is the general-acid-catalyzed elimination of hydroxy group from the intermediate $\mathbf{In_2}^-$ (Scheme 19). The reason for the change in mechanism (cf. esters **31**) is that the nitrile group adjacent to carbanionic center considerably differs from that of the ester group bound in the same way. In the case of esters, their conjugated base is stabilized by both the negative inductive effect of the ester group and partial delocalization of the electron pair being released over the carbonyl group[27]. This delocalization is not synchronous with the C–H bond breaking (the principle of nonperfect synchronization[28]). The interaction between a carbanion center and an α-cyano group is largely[21a] inductive; stabilization of cyanocarbanions by transfer of the negative charge onto the α-cyano group is relatively unimportant in comparison

with their stabilization by the polar effect of the cyano group. The density of negative charge at the carbon atom of the CH group in the carbanion is substantially higher in a nitrile than in an ester. The proton transfer in both directions is substantially faster than that in the case of esters of comparable acidity[29].



SCHEME 19

5. CONCLUSIONS

A base-catalyzed transformation of substituted *o*-nitroanilines, *o*-nitrophenyl ethers and *o*-nitrophenyl sulfides represents quite complicated and often unpredictable class of reactions. Various authors have studied those reactions under very different conditions (various solvents and their mixtures, bases, temperature, etc.); therefore their results are sometimes difficult to compare. In many cases the only reaction product (often regarded as the main product) was identified although it was isolated only in a low yield.

The intuitively assumed benzimidazole and benzothiazole *N*-oxides are formed in most cases but several prerequisites must be fulfilled. This means that the nitro group can act as an electrophilic centre for the *ortho* carbon chain containing an active methylene group (–N–CH_2–Y and –S–CH_2–Y) only in those cases when Y (Chart 1) is a good electron-withdrawing group (such as aryl, carbonyl, cyano and ester) and the reactivity of nitro group is not lowered by direct conjugation with the other electron-donating substituent in the benzene ring. Sometimes, depending on conditions and further substitution, the stabilizing group Y can be splitt off from the final benzimidazole *N*-oxide skeleton and the unsubstituted derivative undergoes consecutive reactions with nucleophiles (especially with hydroxide anion) to give another benzimidazole derivative.

On the other hand, the presence of two (exceptionally one) strong electron-withdrawing groups bound in the benzene ring, such as nitro and trifluoromethyl, completely change reactivity of the starting *o*-nitroaniline derivative. Simple cyclization leading to benzimidazole *N*-oxides is suppressed and new reaction pathways involving either side chain cleavage, some kind of redox process or formation of Meisenheimer adducts occur. 2-Nitrosoanilines and their coupling products (azoxy compounds) together with 1-hydroxyquinoxaline-2,3(1*H*,4*H*)-diones were isolated in proportions depending on reaction conditions. All of these products must have the same precursors, a nitroso compound and a hydroxylamine compound. Moreover, *N*-(2,4,6-trinitrophenyl)sarcosine and its *N*-methyl- or *N*-phenylamide undergo parallel cyclization (*ipso* attack) to give fairly stable spirocyclic Meisenheimer adducts that can be re-opened in acid medium (Smiles rearrangement).

The observation that *o*-nitroanilines without activating group Y also undergo cyclization to give benzimidazole *N*-oxide casts doubt on the simple aldol-type condensation mechanism and an alternative mechanism must be taken into account. The suggested mechanism involves the hydride shift from the carbon side chain to the nitro group and elimination of the hydroxide anion giving *o*-nitroso intermediate which cyclizes to benzimidazole *N*-oxide.

Replacement of the nitrogen bridge between the benzene ring and methylene group by oxygen (X = O; Chart 1) leads to a dramatic change in reactivity. *o*-Nitrophenyl ethers do not undergo base-catalyzed cyclization at all and the only reaction observed was nucleophilic displacement of the carbon side chain. On the other hand, in corresponding *o*-nitrophenyl sulfides the sulfur atom (X = S; Chart 1) participates in stabilization of negative charge on the methylene group and all 6-substituted *o*-nitrophenyl sulfides smoothly undergo base-catalyzed cyclization to give corresponding benzothiazole *N*-oxides.

At the end of this review, it must be stated that the reactions involving interaction between a nitro group and the adjacent *ortho* carbon chain are not limited only to *o*-substituted nitrobenzene derivatives. When the benzene ring is replaced by similar heterocycle like pyridine[7c,30] or pyrimidine[31] ring then similar results are often obtained.

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