REVIEWS

Hexamethylenetetramine, A Versatile Reagent in Organic Synthesis

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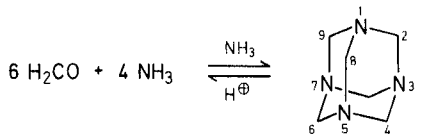
Hexamethylenetetramine, readily obtainable from ammonia and formaldehyde, is a rather stable reagent with an adamantane-like structure. In acidic media the reagent can be cleaved to give C—N-subunits or ammonia + formaldehyde. These fragmentation products can then undergo synthetically useful reactions with appropriate substrates. The present article gives a summary of the formation of hexaminium salts and their use for the introduction of amino and formyl groups. There follows a discussion of the use of hexamethylenetetramine for the synthesis of some triaza- and tetraaza systems and for ring-closure reactions to form five-, six-, or seven-membered ring systems.

Hexamethylentetramin, ein stabiles Reagenz mit Adamantan-Struktur, wird in saurem Medium unter Bildung von Bruchstücken mit C—N-Bindungen sowie Ammoniak und Formaldehyd gespalten. Diese Bruchstücke können synthetisch wertvolle Reaktionen eingehen. Der vorliegende Artikel gibt eine Zusammenfassung über die Bildung von Hexaminium-Salzen und deren Verwendung zur Einführung von Amino- und Formyl-Gruppen. Weiterhin wird über die Verwendung von Hexamethylentetramin zur Synthese einiger Triaza- und Tetraaza-Ringsysteme sowie für Ringschluß-Reaktionen unter Bildung von 5-, 6- und 7-gliedrigen Ring-Systemen berichtet.

1. Introduction

Hexamethylenetetramine** (**1**; $C_6H_{12}N_4$; M.W. 140.19; m.p. 285–295°, sublimation), is formed in nearly quantitative yield from the condensation of ammonia and formaldehyde[1, 2, 3].



1

Large scale preparations and properties of hexamethylenetetramine have been reviewed[4]. The compound is soluble in water, chloroform, ethanol, and some other organic solvents. In neutral, aqueous solution **1** remains stable even at elevated temperatures; thermal decomposition becomes significant only at 270°.

Hexamethylenetetramine has a symmetrical adamantane-like structure and is rather stable although dihetero-substituted methylene groups are known to be highly reactive. The chemical and steric equivalence of the four nitrogen atoms has been demonstrated by various physico-chemical methods[5, 6].

On protonation of one nitrogen atom, the hexamethylenetetramine molecule looses its symmetry and various acid-catalysed fragmentation processes may thus occur. Depending on the conditions, two, three, or more carbon-nitrogen subunits can be formed, or the reagent can serve as a source of formaldehyde and ammonia. Thus, the reagent can be used in the synthesis of alicyclic or heterocyclic structures or it can be employed to introduce functional groups into suitable molecules.

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** Other names used are hexamine, hexamethyleneamine, formamin, aminoform, urotropine, 1,3,5,7-tetraazaadamantane, 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane, methanamine.

[1] F. Meissner, *British Patent* 722434 (1955); *C. A.* **50**, 5019 (1956).
[2] F. Meissner, E. Schweidessen, *U. S. Patent* 2762800 (1956); *C. A.* **50**, 15602 (1956).
[3] F. Meissner, E. Schweidessen, *U. A. Patent* 2762799 (1956); *C. A.* **51**, 2848 (1957).

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Furthermore, hexamethylenetetramine forms complex salts with metal ions and organic and inorganic acids and molecular complexes with alkyl or aryl halides, phenols, and naphthols. These complexes can undergo decomposition under various conditions to give amines, aldehydes, or heterocyclic products.

2. Hexaminium Salts

2.1. Salts with Acids

Interactions of hexamethylenetetramine (**1**) with dilute organic and inorganic acids have been investigated[7]. Less than four molecules of acid form donor-acceptor bonds with **1** even in the presence of a large excess of acid. The number of acid molecules bound to **1** decreases with increasing acidity of the acid (with formic, acetic, and chloroacetic acid 3 molecules of acid are bonded to **1**, with nitric acid 2, and with hydrochloric acid 1. With hydrofluoric acid, complexes containing 1–4 molecules of HF per molecule of **1** are formed[8]; the structures of these salts have been determined by X-ray diffraction analysis.

On heating at 20° hexamethylenetetramine (**1**) and sulphuric acid form two salts, 2 (**1**)·H_2SO_4·6 H_2O and (**1**)·H_2SO_4·8 H_2O which are stable up to 180°. With salicylic acid **1** forms a 1:1 molecular complex[10]. These complex salts as well as those of **1** with urea have found applications in human and veterinary therapy[11,12].

Hexamethylenetetramine (**1**) forms hydrogen-bonded 1:1 complexes with 1,3-dihydroxybenzene (88% yield) and 1,3-dihydroxy-5-methylbenzene (80% yield) and a 1:2 complex with 1,3-dihydroxy-2,5-dimethylbenzene (73% yield)[13].

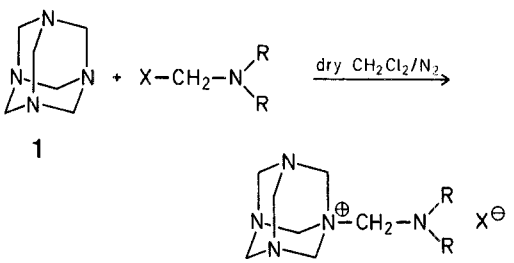
The formation of iron(III) complexes in *p*-xylene with various ligands has been investigated; of the nitrogen-containing ligands such as urea, 1,6-diaminohexane, hexamethylenetetramine (**1**), and phosphorus-oxygen ligands such as triethyl phosphate, **1** was found to be one of the most powerful complexing agents[14].

2.2. Quaternary Salts of Hexamethylenetetramine

Alkyl halides react with hexamethylenetetramine in chloroform to give the quaternary salts **2**[15]. The starting materials are soluble whereas the products crystallise out, further purification of **2** is usually not possible.

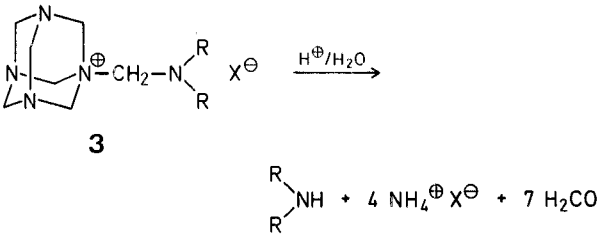
1 **2**

α-Halogenated tertiary amines react with **1** to give the quaternary salts **3a–c** which undergo hydrolysis in aqueous solution to generate formaldehyde[16]. The stability of the salts **3a–c** in air increases in the order **3a** < **3b** < **3c** and all are sensitive to heat.



3a R = CH_3, X = Cl
b R R = $-(CH_2)_5-$, X = Cl; 86% yield
c R R = $-(CH_2)_2-O-(CH_2)_2-$, X = Br; 63% yield

In dilute aqueous acid the quaternary salts **3** decompose to give the secondary amine, formaldehyde, and the ammonium salt of the acid.



3

In dilute aqueous acid the quaternary salts **3** decompose to give the secondary amine, formaldehyde, and the ammonium salt of the acid.

Various biologically active quaternary salts of the type **4** have been prepared from reactions of **1** with haloacetates[17] or haloacetonitriles[18] in tetrachlormethane solution.

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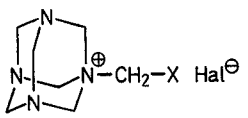
[4] *Ullmanns Encyklopädie der technischen Chemie*, 3. Band; Urban & Schwarzenberg, München–Berlin, 1953, p. 164.
[5] A. F. Andersen, *Acta Crystallogr.* **10**, 107 (1957).
[6] L. N. Becka, D. W. J. Cruickshank, *Acta Crystallogr.* **14**, 1092 (1961).
[7] D. I. Belkin, I. V. Belkina, M. J. Rozkin, *Zh. Org. Khim.* **41**, 655 (1970).
[8] A. A. Ennan, O. M. Brazovskaya, A. N. Chotobarev, *Zh. Obshch. Khim.* **45**, 706 (1975).
[9] A. A. Ennan, O. M. Brazovskaya, V. A. Lapshin, L. P. Berezina, *Zh. Obshch. Khim.* **46**, 716 (1976).
[10] A. Akbaev, *Zh. Prikl. Khim.* **48**, 1638 (1975).
[11] I. E. Mozgov, *Farmakologija*, Ed. Kolos, Moskva 1969, p. 341.
[12] M. D. Maskovskij, *Lekarstvennie sredstva*, Medicina, Moskva, 1972, Chapter 1, p. 68, Chapter 2, p. 431.
[13] T. S. Kabina, E. E. Potapov, A. Ratsep, I. A. Tutorskii, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.* **17**, 1185 (1974); *C.A.* **82**, 16449 (1975).
[14] V. R. Rozenberg, G. V. Motsarev, A. A. Ushakov, B. A. Suvorov, *Neftekhimija* **14**, 885 (1974); *C. A.* **82**, 170238 (1975).
[15] W. A. Jacobs, M. Heidelberger, *J. Biol. Chem.* **20**, 659 (1915).
[16] H. Böhme, M. Haake, *Arch. Pharm.* **300**, 682 (1967).
[17] C. E. Pawlovski, *U. S. Patent* 3624253 (1971); *C. A.* **76**, 59666 (1972).
[18] C. E. Pawlovski, *U. S. Patent* 3624254 (1971); *C. A.* **76**, 59667 (1972).



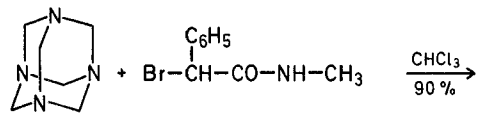
X = $COOCH_3$, $COOC_2H_5$, $COOCH_2-C\equiv CH$, $CH_2-CBr=CH_2$, $CH_2-CH=CH_2$, $CH_2-CCl=CH_2$, CN

Hal = Cl, Br, J

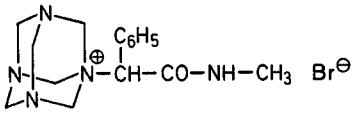
4

Similarly quaternary salts, prepared in 80–90 % yield in chloroform from **1** and haloalkylnitriles have bactericidal and fungicidal activity[19].

The reaction of hexamethylenetetramine (**1**) with α-bromo-*N*-methyl-phenylacetamide (**5**) to give the salt **6** in 90 % yield has been studied by N.M.R.-spectrometry[20].



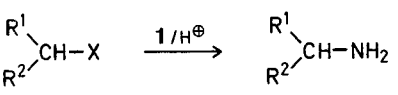
1 5



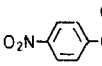
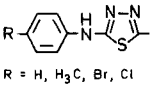
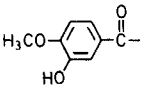
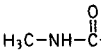
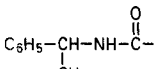
6

α-Hexaminium-*N*-methyl-phenylacetamide Bromide (6)[20]: α-Bromo-*N*-methyl-phenylacetamide (**5**; 0.60 g, 2.62 mmol) and hexamethylenetetramine (**1**; 0.37 g, 2.63 mmol) are dissolved in chloroform (4 ml) and stirred at room temperature for 6 h. The solid hexamethylenetetramine hydrobromide formed (40 mg; m.p. 202–204°) is filtered off. Petroleum ether (10 ml; b.p. 40–60°) is added with stirring to the filtrate whereupon an amorphous product separates immediately. This solid is filtered off and dried under vacuum (0.02 torr) over phosphorus pentoxide to give the product; yield: 870 mg (90 %; m.p. 125–130° (dec.).

Table 1. Selected Examples of the Delépine Reaction

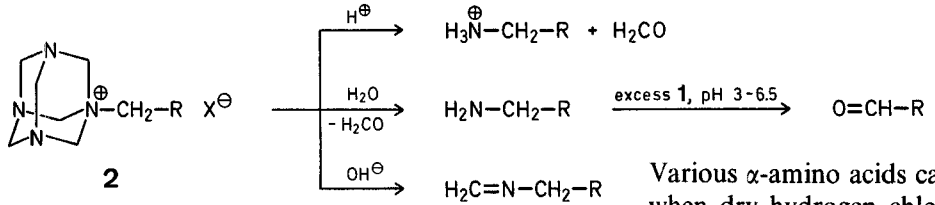


7 8

R^1	R^2	X	Yield [%]	Reference
	H	Br	100	23
	H	Cl	74	24
	H	Br	74	25
 R = H, H_3C, Br, Cl	H	Cl	—	26
	H	Cl	93	27
H	COOH	Cl	94	28
H_3C, n-C_4H_9, $(H_3C)_2CH-CH_2$, $C_6H_5-CH_2$	COOH	Br	58-93	28
	C_6H_5	Br	87	29
	C_6H_5	Br	100	29
n-$C_4H_9-C\equiv C-C\equiv C-$	H	Cl	66	30, 31
$Cl-(CH_2)_n-C\equiv C-$ n = 2-5	H	Cl	50-71	31

3. Introduction of Amino Groups via Hexaminium Salts

Hexaminium salts **2** can be isolated when the preparation is carried out in polar, aprotic solvents. In protic media the hexaminium salts decompose to give various products depending on the pH value of the solution (see Scheme **A**)[21].



2

Scheme **A**

In strongly acidic media (usually ethanol/concentrated hydrochloric acid) primary amines[22] are formed with the formaldehyde being removed as volatile formaldehyde diethylacetal. This reaction, known as the Delépine reaction, is useful for the conversion of alkyl halides to primary amines without concomitant formation of secondary amines and has the advantages of (1) cheap reagent, (2) simple reaction conditions and apparatus, and (3) short reaction time.

Various α-amino acids can be prepared in this way, when dry hydrogen chloride gas in dry ethanol is used, hydrochlorides of the corresponding esters are obtained (see Table 1 for some examples).

[19] S. J. Kuhn, *U. S. Patent* 3524854 (1970); *C. A.* **73**, 87943 (1970).

[20] V. Šunjić, F. Kajfež, M. Štromar, N. Blažević, M. Oklobdžija, *Bull. Sci. Sect. A Yougosl.* **18**, 226 (1973); *C. A.* **80**, 82346 (1974).

[21] S. J. Angyal, *Org. React.* **8**, 197 (1954).

[22] M. Delépine, *Bull. Soc. Chim. Fr.* **13**, 358 (1895).

[23] B. Reichert, W. Dornis, *Arch. Pharm.* **282**, 100 (1944).

[24] J. Graymore, D. R. Davies, *J. Chem. Soc.* **1945**, 293.

[25] G. M. Long, D. H. Troutman, *J. Am. Chem. Soc.* **71**, 2469, 2473 (1949).

[26] I. Simiti, L. Proinov, *Arch. Pharm.* **303**, 134 (1970).

[27] A. E. Nodiff, J. M. Hulsizer, K. Tanabe, *Chem. Ind. (London)* **1974**, 962.

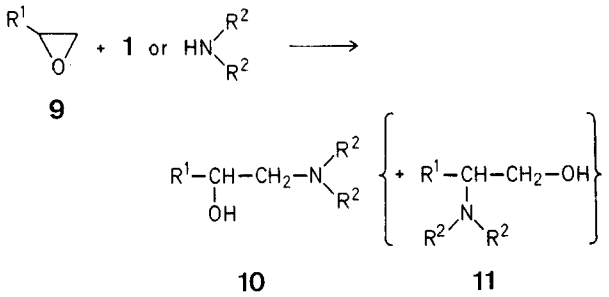
[28] G. Hillman, A. Hillman, *Z. Physiol. Chem.* **283**, 71 (1948).

1-(α-Aminoacetyl)-3-hydroxy-4-methoxybenzene Hydrochloride (8)[27]:

A mixture of 1-chloroacetyl-3-hydroxy-4-methoxybenzene (**7**; 7.0 g, 0.035 mol), hexamethylenetetramine (**1**; 4.9 g, 0.035 mol), sodium iodide (5.3 g, 0.035 mol), and ethanol (400 ml) is stirred at room temperature for 24 h. The resultant, off-white crystals are filtered, washed with cold ethanol, and heated under reflux in ethanol (300 ml)/concentrated hydrochloric acid (20 ml) for 2 h. On cooling of the mixture, the product separates as white crystals; yield: 7.0 g (93 %); m.p. 250–252° (decomp.) with darkening at 230°.

Heating of hexaminium salts in formic acid leads to the formation of methylamines[32]. The first stage of this process is the Delépine reaction and the second stage may be considered as a special example of the Eschweiler-Clarke methylation; the hexaminium salt supplying both amine and formaldehyde.

Reaction of hexamethylenetetramine with substituted oxiranes is also a modification of the Delépine reaction. With hexamethylenetetramine (**1**) 1-amino-2-hydroxy alcohols **10** (R = H) only are obtained whereas reactions of **9** with primary, secondary, and tertiary amines gives rise to a mixture of **10** and the isomeric 2-amino-1-hydroxy alcohol **11** (see Scheme **B** and Table 2). Several such α,β-amino alcohols have exhibited interesting pharmacological properties.



9 **10** **11**

Scheme **B**

Table 2. Selected Reactions of Oxiranes **9** with Hexamethylenetetramine (**1**) in Chloroform

Oxirane **9**	Amino alcohol **10**	m.p.	Yield [%]	Ref.
	$HO-CH_2-CH_2-NH_2$	75–76°	79	33
	$H_3C-CH(OH)-CH_2-NH_2$	73–74°	99	33, 34
	$ClCH_2-CH(OH)-CH_2-NH_2$	181–183°	45	33
	$C_6H_5-CH(OH)-CH_2-NH_2$	275–278°	100	33
	$C_6H_5O-CH_2-CH(OH)-CH_2-NH_2$	136°	46	33

[29] F. Kajfež, T. Kovač, M. Mihalić, B. Belin, V. Šunjić, *J. Heterocycl. Chem.* **13**, 561 (1976).

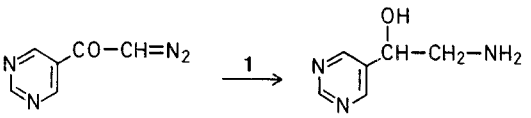
[30] Y. Besace, I. Marszak, *C. R. Acad. Sci. Paris, C* **270**, 1605 (1970).

1-Amino-2-propanol Hydrochloride (10; $R^1 = CH_3$, $R^2 = H$)[33, 34]:

Methyloxirane (7.0 g, 0.07 mol) is added to a solution of hexamethylenetetramine (8.0 g, 0.06 mol) in chloroform (100 ml) and the mixture is warmed at 50° for 4 h. *α-Hydroxypropylhexaminium chloride* is thus obtained by filtration; yield: 7.9 g (56 %).

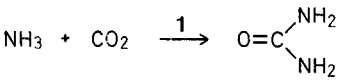
α-Hydroxypropylhexaminium chloride (1.0 g, 4.3 mmol) is dissolved in ethanol (15 ml), treated with concentrated hydrochloric acid (2 ml) and heated on a water bath for 10 min to give, after filtration, 1-amino-2-propanol hydrochloride free of the corresponding bis- and tris[hydroxyalkyl]amines; yield: 0.47 g (99 %); m.p. 73–74°.

Some other applications of hexamethylenetetramine for the introduction of amino groups cannot be classified as Delépine-type reactions[35]. Thus, diazomethyl 5-pyrimidinyl ketone (**12**) can be converted to 5-(2-amino-1-hydroxyethyl)-pyrimidine (**13**) on treatment with hexamethylenetetramine.



12 **13**

Hexamethylenetetramine (**1**) can be used as a catalyst in the preparation of urea from ammonia and carbon dioxide[36]. The reagent serves to increase both the yield of urea and the degree of utilisation of ammonia, e.g. a 6 : 6 : 1 molar mixture of ammonia/carbon dioxide/hexamethylenetetramine gives rise to an 80 % yield (based on ammonia) of urea.



4. Introduction of Formyl Groups via Hexaminium Salts

As shown in Scheme **A**, aldehydes can be obtained from the reaction of hexaminium salts **2** derived from alkyl and aralkyl (mostly arylmethyl) halides. This process, known as the Sommelet reaction[37, 38] was reviewed in 1954[21]. The Sommelet reaction proceeds in three steps: (1) formation of the hexaminium salt **2**, (2) hydrolysis of **2** at pH 7 to give an amine **14**, and (3) reaction of this amine with excess **1** to give the aldehyde **15** (Scheme **C**).

[31] Y. Besace, A. Marszak-Fleury, I. Marszak, *Bull. Soc. Chim. Fr.* **4**, 1468 (1971).

[32] Ref. [21], p. 204 and references cited therein.

[33] H. J. Roth, A. Brandau, *Arch. Pharm.* **292**, 761 (1959).

[34] H. J. Roth, *Arch. Pharm.* **292**, 76 (1959).

[35] E. Reimann, *Justus Liebigs Ann. Chem.* **1975** (7–8) 1252.

[36] A. N. Sarbaev, V. I. Kucheryavyi, L. M. Kozenko, *Zh. Prikl. Khim.* **42**, 2528 (1969).

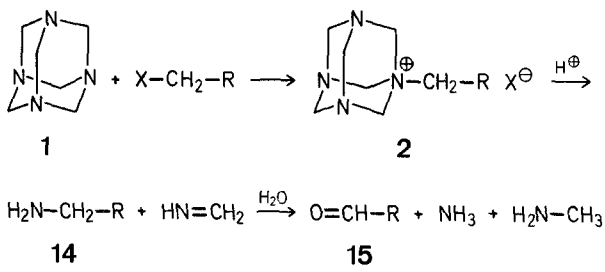
[37] M. Sommelet, *C. R. Acad. Sci. Paris* **157**, 852 (1913).

[38] M. Sommelet, *Bull. Soc. Chim. Fr.* **13**, 1085 (1913).

[39] S. J. Angyal, R. C. Rassack, *Nature* **161**, 723 (1948).

[40] S. J. Angyal, D. R. Penman, G. P. Warwick, *J. Chem. Soc.* **1953**, 1742.

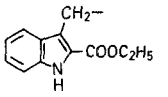
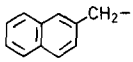
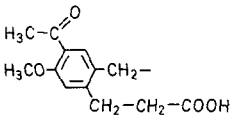
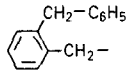
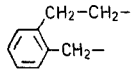
[41] H. R. Snyder, S. Swaminathan, H. J. Sims, *J. Am. Chem. Soc.* **74**, 5110 (1952).



Scheme C

Studies have suggested that the Sommelet reaction involves an oxidation-reduction process as shown in the last reaction in Scheme C[24,39]. Essentially, the amine **14** is oxidised by methylimine (a sub-unit of hexamethylenetetramine) to the aldehyde and ammonia. Later[40], it was suggested that the reaction includes a hydride transfer step.

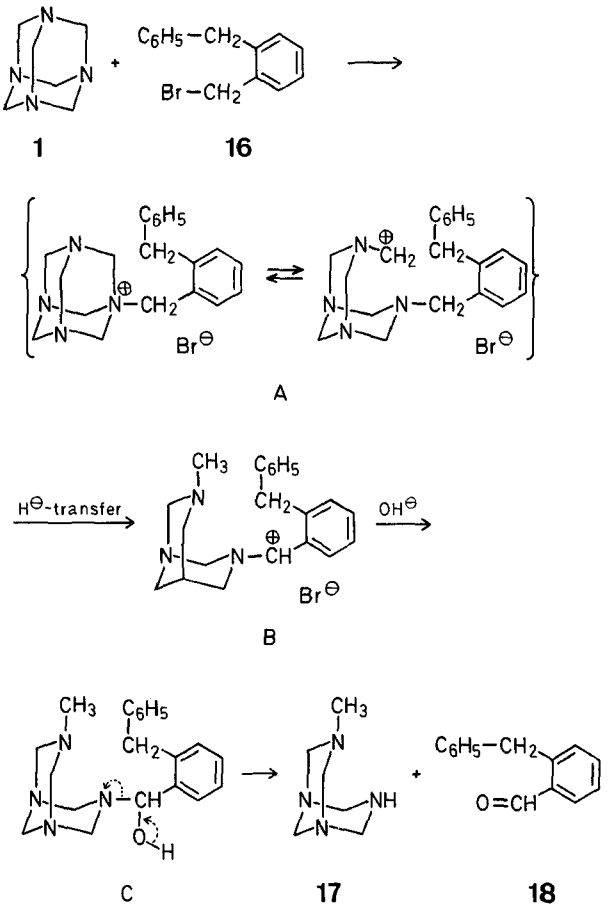
Table 3. Selected Examples of the Sommelet Aldehyde Synthesis

R—CH_2—	X	Solvent	Yield [%]	Ref.
	$N(CH_3)_2$	HOAc	68–72	41
	Br	$CHCl_3$/HOAc	77–80	42
	Cl	HOAc	70	43
	Br	$CHCl_3$	46	44
	Br	$CHCl_3$	42	44

2-Formylnaphthalene[42]**:**
To a solution of technical grade 2-methylnaphthalene (71.0 g, 0.5 mol) in tetrachloromethane (450 g, analytical grade) in a 1-l two-necked flask fitted with a mechanical stirrer and a reflux condenser *N*-bromosuccinimide (89.0 g, 0.5 mol) is added and the resultant mixture is heated with stirring under reflux for 16 h. The precipitated succinimide is filtered off and the solvent removed from the filtrate under reduced pressure. The resultant brown oil is dissolved in pure chloroform (300 ml) and this solution is rapidly added to a stirred solution of preformed hexamethylenetetramine (84.0 g, 0.5 mol) in pure chloroform (150 ml) in a 2-l three-necked flask fitted with an addition funnel, reflux condenser, and a mechanical stirrer. The addition rate is regulated to maintain a vigorous reflux, subsequently the mixture is heated under reflux for 0.5 h, cooled, and filtered. The powder-like solid which separates almost immediately on commencing the addition is filtered, washed with cold petroleum ether (2 × 100 ml, b.p. 40–60°), and dried to give the *hexaminium bromide*; yield: 146.5 g (79%); m.p. 174–176°.

This product is heated in 50% acetic acid (750 ml) under reflux for 2 h, then concentrated hydrochloric acid (150 ml) is added and refluxing is continued for 5 min. The mixture is cooled, extracted with ether, the solvent removed from the extract, and the residue crystallised from the minimum amount of *n*-hexane to give white, crystalline *2-formylnaphthalene*; yield: 48.8–50.7 g (77–80% based on hexaminium bromide, 64% based on 2-methylnaphthalene); m.p. 58.5–59.5°.

A generally accepted mechanism for the Sommelet reaction was proposed later[45,46] and is illustrated by the example[47] in Scheme D.



Scheme D

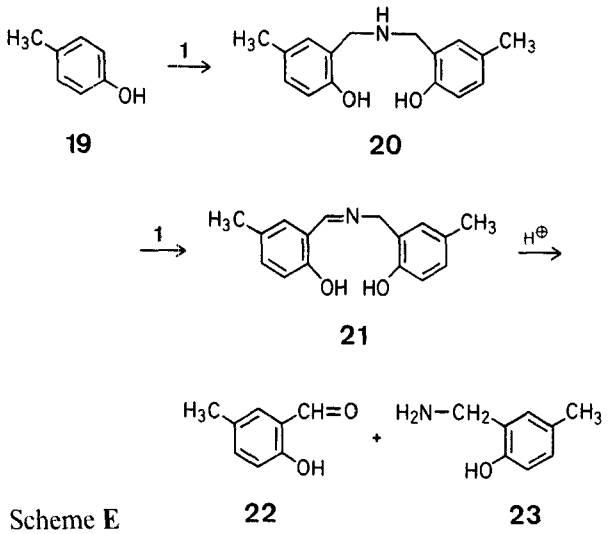
The hexaminium salt A, derived from halide **16** and **1**, undergoes hydride transfer to form the carbenium salt B which reacts with the nucleophilic hydroxy ion present to yield C which, in turn, undergoes cleavage to give the aldehyde **18** and the amine **17**.

Under similar conditions, secondary halides, or the amines formed as intermediates, undergo Sommelet-type reactions yielding ketones. Thus, α-ethylphenylamine on reaction with formaldehyde, followed by hexamine, gives acetophenone[24]. Following this

[42] H. M. Doukas, *J. Chem. Educ.* **31**, 21 (1954).
[43] R. Durand-Dran, M. Lecocq, R. Quelet, *C. R. Acad. Sci. Paris* **250**, 2727 (1960).
[44] J. Schnekenburger, R. Kaufmann, *Arch. Pharm.* **304**, 254 (1971).
[45] P. Le Henaff, *C. R. Acad. Sci. Paris* **253**, 2706 (1961).
[46] P. Le Henaff, *Ann. Chim.* **7**, 367 (1962).
[47] J. Schnekenburger, R. Kaufmann, *Arch. Pharm.* **304**, 259 (1971).

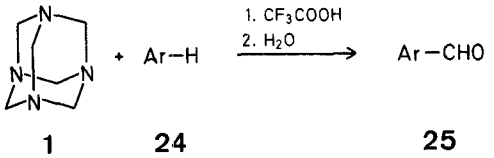
route benzophenone, fluorenone, and some unsaturated alicyclic ketones were prepared[21]. Usually the yields were low and this type of Sommelet reaction was not studied extensively.

Using hexamine as a reagent, it is possible to introduce a formyl group into various aromatic or heteroaromatic compounds. These reactions cannot be regarded as purely Sommelet reactions, although the conditions applied are very similar. One type, termed the Duff reaction[48], allows the preparation of *ortho*-hydroxy aromatic aldehydes. The procedure consists in treatment of phenols with hexamine in glyceroboric acid (HBO_2 in dry glycerol) or glacial acetic acid. The reaction[49] seems to involve an aminomethylation, forming the secondary amine, which undergoes the Sommelet reaction to yield an aldehyde as shown in Scheme E for *p*-methylphenol (**19**), for further examples see Table 4.



Scheme E

A modification of this reaction uses trifluoroacetic acid as solvent and a variety of aromatic compounds **24**, including simple hydrocarbons, can thus be converted into aldehydes **25**[54].



Reaction conditions are milder and yields are higher than in the Duff procedure[48, 55, 56]. A high *para*-regioselectivity is observed when the formylation is conducted under these conditions. Some recent examples are summarised in Table 5.

Table 4. Selected Examples of the Duff Reaction

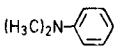
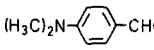
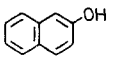
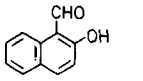
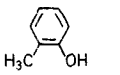
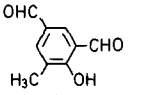
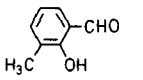
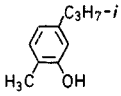
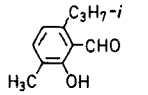
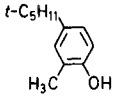
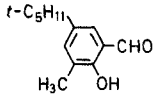
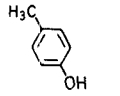
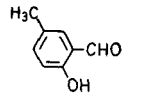
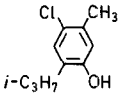
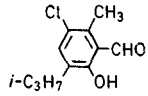
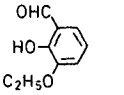
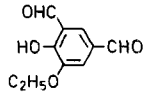
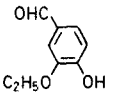
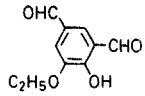
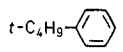
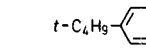
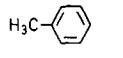
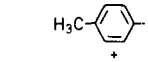
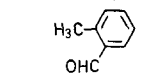
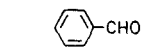
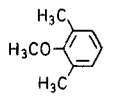
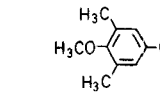
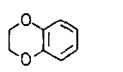
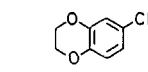
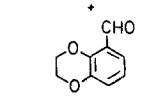
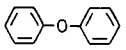
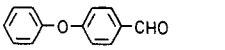
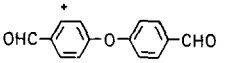
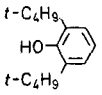
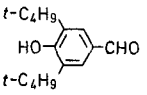
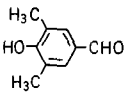
Substrate	Solvent	Aldehyde	Yield [%]	References
	R–OH		38	50
	HBO_2/ glycerol		27	48
	HBO_2/ glycerol		4	48
			14	48
	HBO_2/ glycerol		25	48
	HBO_2/ glycerol		19	51
	HBO_2/ glycerol		19	49
	HOAc		75	52
	HOAc/HCl		67	53
	HOAc/HCl		55	53

Table 5. Formylation of Arenes **24** with Hexamethylenetetramine (**1**) in Trifluoroacetic Acid[54]

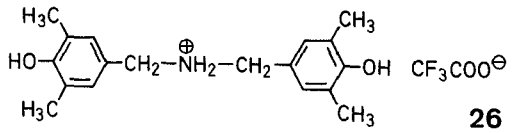
Arene **24**	Ratio of **1**: TFA	Product **25**	Yield [%]
	1 : 1		75
	1 : 1		50
			11
	1 : 4		32
	2 : 1		74
	1 : 1		37
			2

[48] J. C. Duff, *J. Chem. Soc.* **1941**, 547.
[49] J. C. Duff, V. J. Furness, *J. Chem. Soc.* **1951**, 1512.
[50] J. C. Duff, *J. Chem. Soc.* **1945**, 276.
[51] L. M. Liggett, H. Diehl, *Proc. Iowa Acad. Sci.* **52**, 191 (1945); *C. A.* **41**, 110 (1947).
[52] G. Zigeuner, K. Jellinek, *Monatsh. Chem.* **90**, 297 (1959).
[53] E. Profft, W. Krause, *Arch. Pharm.* **298**, 148 (1965).

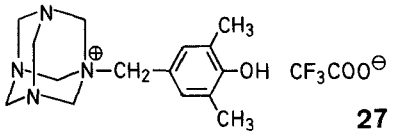
Table 5. (continued)

Arene **24**	Ratio of **1**: TFA	Product **25**	Yield [%]
	2 : 1		29
			25
	1 : 1		60
	1 : 1		95

The first step is probably the formation of methylimine or methylenimine derivatives, which are precursors of the aldehydes. Imines were isolated in some instances, e.g., when the reaction products from toluene were subjected to rapid hydrolytic work-up. In this case the *para*- and *ortho*-toluimines were obtained predominantly. Whether such products are formed by rearrangement of the methylenimine Ar—CH_2—N=CH_2, or arise through exchange reactions involving methylamine, is not yet clarified. Other kinds of intermediates could be isolated under non-hydrolytic conditions at room temperature. Thus, a mixture of 2,6-xylenol, hexamine (**1**), and trifluoroacetic acid kept below 30° for 3 h gave a complex mixture of products, from which the dibenzylammonium salt **26** (41%) and the hexaminium salt **27** (15%) were isolated.



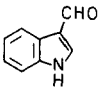
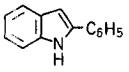
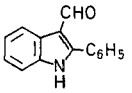
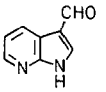
26



27

Intermediate formation of salt **26** clearly shows that this process is related to the Sommelet[21] and Delépine[22] reactions. Some heterocycles, such as indoles[57] and azaindoles[58], can be readily formylated with hexamine (see Table **6**).

Table 6. Formylation of Indoles and 7-Azaindole (1*H*-Pyrrolo[2,3-*b*]pyridine in Acetic Acid

Substrate	Product	Yield [%]	Reference
		25	57
		74	57
		50	58

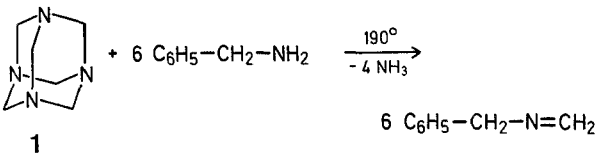
7-Azaindole-3-carboxaldehyde (3-Formyl-1*H*-pyrrolo[2,3-*b*]pyridine)[58]:

A solution of 7-azaindole (23.6 g, 0.20 mmol) and hexamine (42.0 g, 0.30 mmol) is heated under reflux with stirring for 6 h in 33% acetic acid (250 ml). The resultant solution is diluted with water (500 ml), and the product allowed to crystallise overnight. Recrystallisation of the crude product from water gives long white needles; yield: 14.9 g (50%); m.p. 216–218°.

5. Formation of Triaza- and Tetraaza-Heterocyclic Derivatives

Using various agents, it is possible to decompose hexamine into diverse mono- or bicyclic derivatives which are sometimes stable enough to be isolated and studied[59, 60, 61]. The reagents used are various bases, acids, as well as several phosphorus or sulfur containing agents.

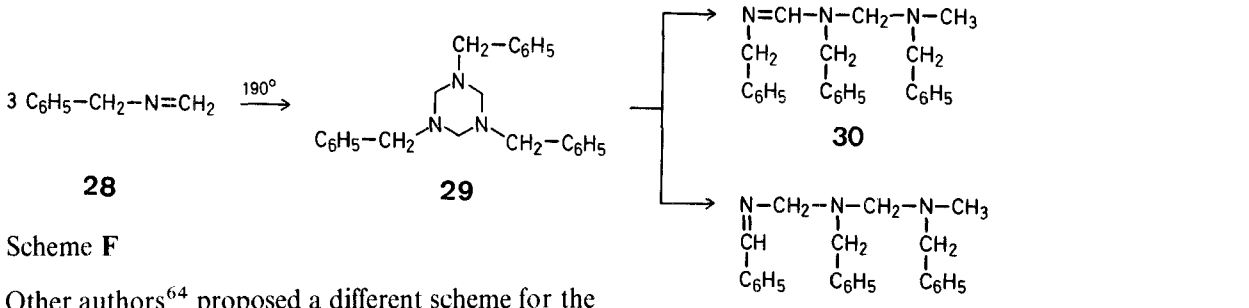
The condensation product of benzylamine and hexamine, **28**, polymerizes when heated for an extended period[62, 63]. Depending on both temperature and time, different mixtures of products result, e.g. on increasing the heating time from 75 to 150 min the average molecular weight of the condensation products decreases from 314 to 218 and the yield from 99.2 to 98.5%[62].



1 **28**

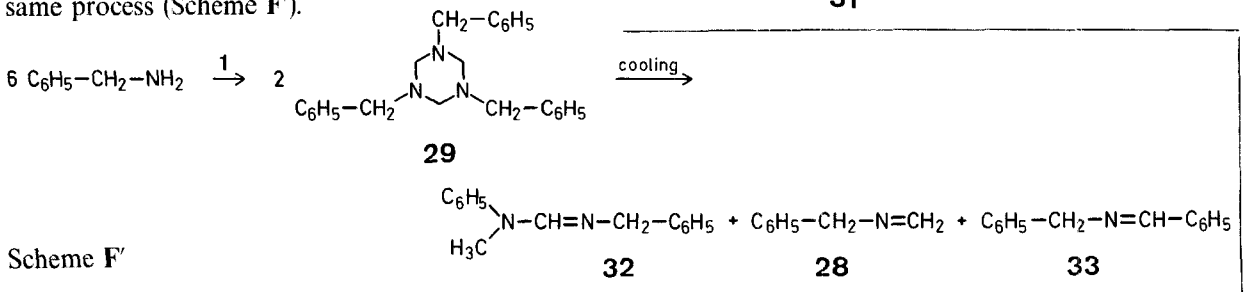
In the mixture of products resulting from the condensation of **1** and benzylamine, **29** was identified and converted into the open-chain isomeric products **30** and **31** according to Scheme **F**[63].

[54] W. E. Smith, *J. Org. Chem.* **37**, 3972 (1972).
[55] L. N. Ferguson, *Chem. Rev.* **38**, 230 (1946).
[56] C. F. H. Allen, G. W. Leubner, *Organic Syntheses, Coll. Vol.* IV, 1963, p. 866.
[57] A. Chatterjee, K. M. Biswas, *J. Org. Chem.* **38**, 4002 (1973).
[58] A. J. Verbiscar, *J. Med. Chem.* **15**, 149 (1972).
[59] T. Urbanski, *Chemistry and Technology of Explosives* **3**, 87 (1967).
[60] L. Stefaniak, T. Urbanski, M. Witanowski, H. Januszewski, *Rocz. Chem.* **43**, 1687 (1969).
[61] J. McKenna, J. M. McKenna, B. A. Wesby, *J. Chem. Soc. D* **1970**, 867.
[62] E. V. Zakharov, S. A. Balezin, O. P. Murashova, E. S. Ivanov, N. J. Podobaev, N. V. Lardash, *Zh. Prikl. Khim.* **47**, 2351 (1974).
[63] G. Olkoks, *Geterocikličeskie Soedinenija i Polimeri na jih osnove*, Mir, Moskva, 1970, p. 136.
[64] O. P. Murashova, L. I. Virin, V. R. Rozenberg, G. V. Motsarev, V. J. Kolbasov, Yu. A. Safin, R. V. Dzhagatspanyan, *Zh. Prikl. Khim.* **48**, 1802 (1975).



Scheme F

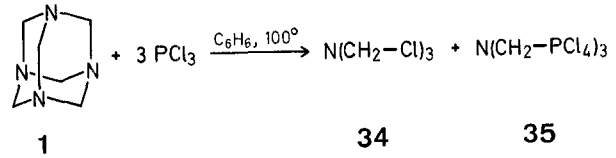
Other authors[64] proposed a different scheme for the same process (Scheme F').



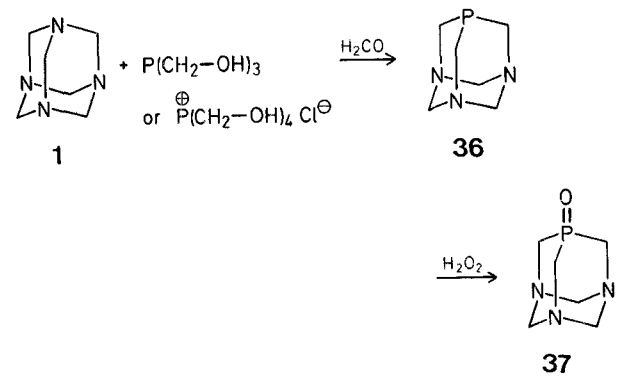
Scheme F'

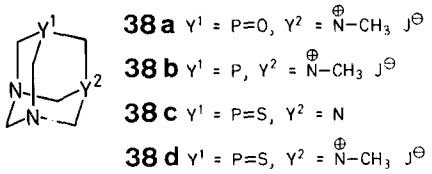
The first step yielded 75 % of compound **29** on heating the reactants for 0.5 h at 190°, or for 2 h at 170°. The unseparated mixture of products obtained when the above reaction is carried out at 180–200° is usually designated BA-6. This mixture was shown to protect metals against corrosion under acidic conditions[65,69].

By treating hexamine with phosphorus pentachloride in a 1 : 3 molar ratio, Fluck and Meiser[66] prepared tris[chloromethyl]amine (**34**) in almost quantitative yield. They assumed that compound **35** might have been formed as a second product.



Daigle et al.[67,68,69] prepared a monophosphorus analog of hexamine, **36** (40% yield) from hexamine and tris[hydroxymethyl]phosphine or tetrakis[hydroxymethyl]phosphonium chloride. Oxidation of **36** with hydrogen peroxide at room temperature gave phosphoadamantane-7-oxide (**37**).





38a Y^1 = P=O, Y^2 = $\overset{\oplus}{N}$–CH_3 $J^{\ominus}$

38b Y^1 = P, Y^2 = $\overset{\oplus}{N}$–CH_3 $J^{\ominus}$

38c Y^1 = P=S, Y^2 = N

38d Y^1 = P=S, Y^2 = $\overset{\oplus}{N}$–CH_3 $J^{\ominus}$

Compound **37** was quaternised by refluxing with iodomethane in methanol/ethanol, to give the azonium oxide **38a**. Compound **36** on refluxing with iodomethane in acetone gave the simple azonium compound **38b**. Addition of sulphur to **36** gave compound **38c**, which, after refluxing with iodomethane, gave **38d**.

1,3,5-Triaza-7-phosphaadamantane (36):
A solution of tetrakis[hydroxymethyl]phosphonium chloride (23 g, 0.947 mol), previously made neutral by the addition of 50 % aqueous sodium hydroxide (63.85 g, 0.798 mol), is mixed with 37 % aqueous formaldehyde (400 g, 5 mol). Hexamine (140 g, 1 mol) is added and the resultant solution is left at room temperature overnight. After partial (~ 80 %) evaporation of water, followed by filtration, and washing with cold ethanol (200 ml) the product **36** is obtained; yield: 106.9 g (72 %).

Daigle et al.[70] prepared a sulphur and phosphorus-containing derivative of hexamine, 2-thia-1,3,5-triaza-7-phosphaadamantane-2,2-dioxide (**39**) from tris[hydroxymethyl]phosphine, sulphamide, and hexamine in excess formaldehyde (Scheme G) and converted it to **40** and **41** as before.

[65] G. L. Nemchanimova, K. E. Peredelskiy, *Zh. Prikl. Khim.* **47**, 1879 (1974).

[66] E. Fluck, P. Meiser, *Angew. Chem.* **83**, 721 (1971); *Angew. Chem. Int. Ed. Engl.* **10**, 653 (1971); *Chem. Ber.* **106**, 69 (1973).

[67] D. J. Daigle, A. B. Pepperman Jr., S. L. Vail, *J. Heterocycl. Chem.* **11**, 407 (1974).

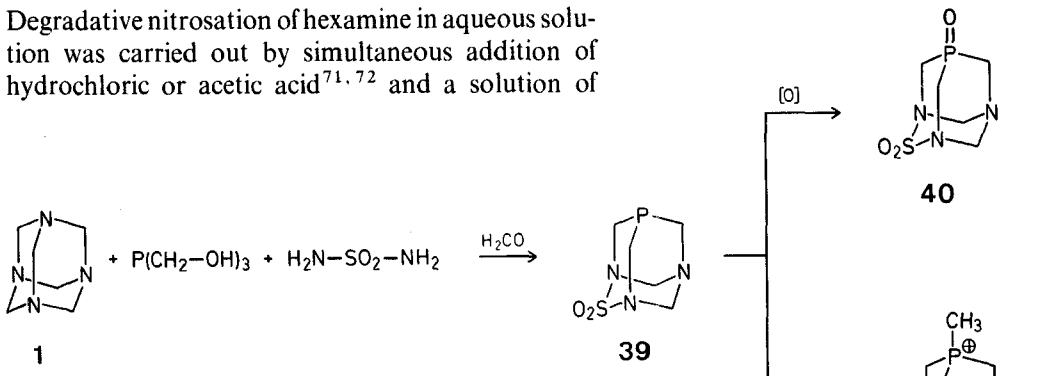
[68] D. J. Daigle, A. B. Pepperman Jr., *U. S. Patent* 391 189 (1973); *C. A.* **81**, 120788 (1974).

[69] D. J. Daigle, A. B. Pepperman Jr., *J. Heterocycl. Chem.* **12**, 579 (1975).

[70] D. J. Daigle, A. B. Pepperman Jr., G. Bondreaux, *J. Heterocycl. Chem.* **11**, 1085 (1974).

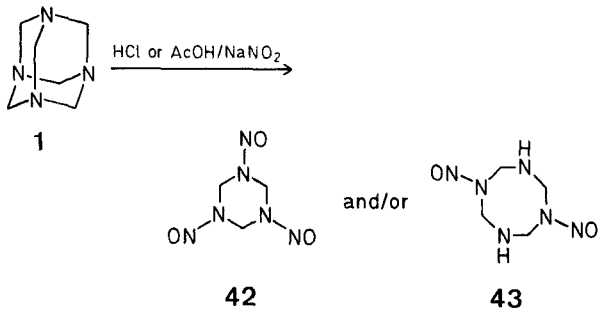
[71] W. E. Bachmann, N. C. Deno, *J. Am. Chem. Soc.* **73**, 2777 (1951).

Degradative nitrosation of hexamine in aqueous solution was carried out by simultaneous addition of hydrochloric or acetic acid[71,72] and a solution of



Scheme G

sodium nitrite. The main factor determining the nature of the products is the pH of the solution.



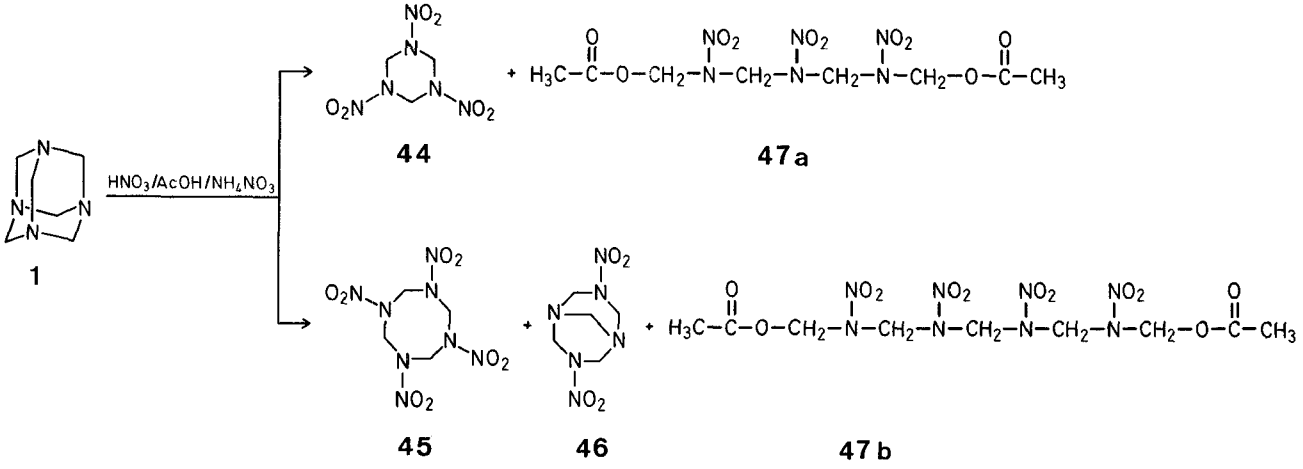
Thus, in hydrochloric acid at pH 1 the trinitroso compound **42** (50 % yield; m.p. 104.5–106°) is formed exclusively, at pH 2 a mixture of **42** and **43** (m.p. 196–200°) is obtained, between pH 3 and 6 only **43** (72–76 % yield; m.p. 203.5–207°) is formed[71].

Variation of the molar ratio of hexamine:hydrochloric acid:sodium nitrite results in formation of pure **42** (1:6:1–3), a mixture (m.p. 155–204°) of **42** and **43** (1:3:3), or pure **43** (1:6:6)[71].

When acetic acid was employed, however, the only product obtained over a wide range of conditions was the dinitroso compound **43**[71].

1,3,5-Trinitrosohexahydro-*s*-triazine (42; trinitrosotrimethylenetriamine) and 1,5-Dinitrosooctahydro-1,3,5,7-tetrazocine (43): Hexamine (7 g, 0.05 mol) is dissolved in ice/water (200 ml), after which a solution of sodium nitrite (15 g, 0.22 mol) in water (50 ml) and 6 normal hydrochloric acid are added simultaneously. Hydrochloric acid is added at the rate necessary to maintain the desired pH. The mixture is kept at 0° for pH 1, 30 min; pH 2, 45 min; pH 3, 60 min; pH 4, 5 days. The products are then collected by filtration; yield at pH 1; 50 % of **42**; m.p. 104.5–106°; at pH 4: 72 % of **43**; m.p. 207°.

Hexamine reacts with nitric acid in the presence of acetic acid and ammonium nitrate to give highly explosive cyclotrimethylene-trinitramine (**44**), also called RDX, in 82 % yield[74,75]. The reaction was studied in detail: two main types of cleavage of hexamine were observed and products **44–47** were identified.



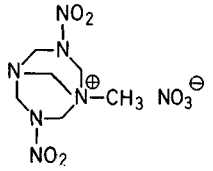
The study of this reaction suggested that one type of cleavage might produce compounds containing three amino nitrogen atoms, such as RDX **44** and the linear trinitramine (1,7-diacetoxy-2,4,6-trinitro-2,4,6-triazaheptane **47a**). Another type of cleavage might lead to compounds with four amino nitrogen atoms such as DTP **45**, HMX **46**, and the linear

[72] H. Krzikalla, H. Pohlemann, T. Toepel, *German Patent* 1004618 (1957); *C. A.* **53**, 18075 (1959).
[73] *Belgium Patent* 613501 (1962); *C. A.* **58**, 1618 (1963).
[74] W. E. Bachmann, W. J. Horton, E. L. Jenner, N. W. Mac Naughton, L. B. Scott, *J. Am. Chem. Soc.* **73**, 2769 (1951).
[75] W. E. Bachmann, E. L. Jenner, *J. Am. Chem. Soc.* **73**, 2773 (1951).
[76] L. Stefaniak, T. Urbanski, M. Witanowski, A. R. Farminer, G. A. Webb, *Tetrahedron* **30**, 3775 (1974).

tetranitramine (1,9-diacetoxy-2,4,6,8-tetranitro-2,4,6,8-tetraazanonane **47b**).

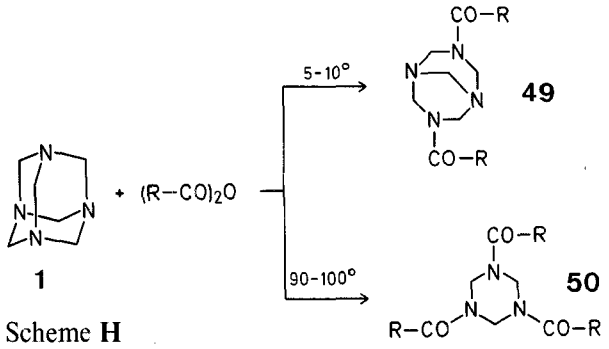
The first type of cleavage is favoured at high concentrations of nitric acid and acetic anhydride in the reaction mixture. The second type of cleavage occurs at lower acidity. These results are similar to those obtained in the reaction of hexamine with nitrous acid in aqueous solution. Under highly acidic conditions, trinitrosotrimethylenetriamine (**42**) is the main product, whereas, at lower acidities **43** is formed[71].

Stefaniak and coworkers[76] also prepared some of the 1,3,5,7-tetraazabicyclo-3,3,1-nonane derivatives **46** and **48** for structural studies.



48

The reaction of hexamine with acetic anhydride has been studied recently by several authors[77,78-81] and can be formulated as in Scheme **H**.



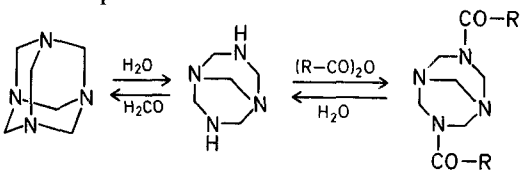
Scheme **H**

The yields of **49** never exceeded 45%. Siele et al.[79] reported a simple procedure for the preparation of **50a** (Table 7) in >90% yield. This procedure was also applied for the preparation of the analogues **49b–e**.

Table 7. Products of Acylation of Hexamine (**1**)

Product	R	Acylating agent	Temperature	Yield [%]	Ref.
49a	CH_3	$(CH_3CO)_2O$/NaOH	10°	98	79
49a	CH_3	$(CH_3CO)_2O$/NH_4OAc	5–10°	100	79
49a	CH_3	ketene/NaOAc	15–20°	65	79
49b	H	$(HCO)_2O$/NaOAc	0–10°	22	79
49c	C_2H_5	$(C_2H_5CO)_2O$/NaOAc	0–10°	52	79
49d	*n*-C_3H_7	(*n*-$C_3H_7CO)_2O$/NaOAc	0–10°	52	79
49e	C_6H_5	$(C_6H_5CO)_2O$/NaOAc	55°	13	79
50a	CH_3	$(CH_3CO)_2O$	90–100°	—	78
50b	C_2H_5	$(C_2H_5CO)_2O$	90–100°	—	78
50c	*n*-C_3H_7	(*n*-$C_3H_7CO)_2O$	90–100°	—	78

Using acetic anhydride, water, and hexamine, at 5–10°, **49a** is obtained in 65–73% yield (based on hexamine). The yield of **49a** rises to 80%, when the reaction is conducted in the presence of an inorganic base, in an amount equivalent to the acetic acid formed. The effectiveness of water in promoting the formation of **49** presumably results from the equilibrium shift shown in Scheme **I**[80]. Compound **51** is probably the species undergoing acylation when water is present.



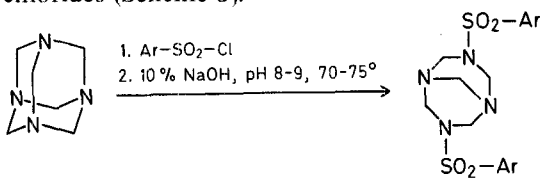
1 **51** **49**

Scheme **I**

It was found that ketene could be substituted for acetic anhydride in the preparation of **49a**; yields as high as 65% were obtained.

3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (49a)[79]: Acetic anhydride (30.6 g, 0.3 mol) is added dropwise over 60 min with stirring and cooling at 5–10° to a slurry prepared from hexamine (14 g, 0.1 mol), ammonium acetate (6.2 g, 0.08 mol), and water (7 ml). The solution finally resulting from this procedure is stirred at 10° for 30 min and evaporated to dryness to give crude **49a**; yield: 25.2 g. Recrystallisation from acetone gives pure **49a**; yield: 21.2 g (100%); m.p. 192°.

Yoshida et al.[81] have studied the selective ring opening of 1,7-bis[sulphonamido]tetraazabicyclo-[3.3.1]nonanes **52** using the electrophilic species $NO^{\oplus}$ and $NO_2^{\oplus}$. In these experiments the authors obtained 1,3,5,7-tetraazacyclooctanes as products. The starting compounds, namely the various bis[sulphonamido]tetraazabicyclo[3.3.1]nonanes, were obtained by reacting hexamine with arenesulphonyl chlorides (Scheme **J**).



1 **52**

Scheme **J**

Table 8. Sulphonamide Derivatives of 1,3,5,7-Tetraazabicyclo-[3.3.1]nonanes[81]

Product	Ar	Yield [%]
52a	4-H_3C—C_6H_4	46
52b	C_6H_5	56
52c	3-Cl—C_6H_4	38
52d	4-Br—C_6H_4	8
52e	3-O_2N—C_6H_4	11

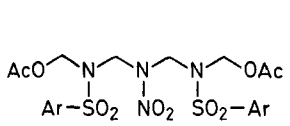
[77] E. B. Hodge, *J. Org. Chem.* **37**, 320 (1972).

[78] M. Warman, V. I. Siele, E. E. Gilbert, *J. Heterocycl. Chem.* **10**, 97 (1973).

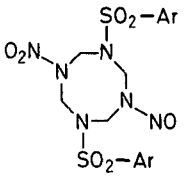
[79] V. I. Siele, M. Warman, E. E. Gilbert, *J. Heterocycl. Chem.* **11**, 237 (1974) and references cited therein.

[80] Y. Ogata, A. Kawasaki, *The Chemistry of the Carbonyl Group*, Vol. 2, J. Zabicky, Ed., Interscience, New York 1970, p. 51.

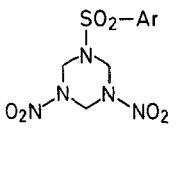
Treatment of compounds **52a** and **52c** with 70% nitric acid and acetic anhydride at −10° gave considerable amounts of resinous products; compound **53** was the major product, with the admixture of a small amount of **55**.



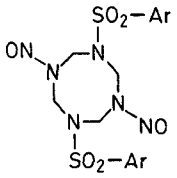
53



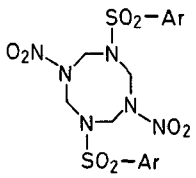
54 a-e



55 a-e



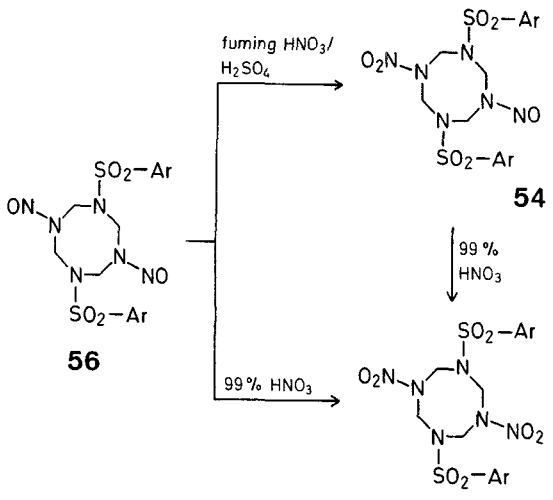
56 a-e



57 a-e

Liquid dinitrogen tetroxide, on reaction with compounds **52a–e**, gave the tetrazocine derivatives **54a–e** in 45 to 85% yields. The same reagent in combination with sulphuric acid on reaction with **52a–e** led to the formation of triazacyclohexanes **55a–e** and tetrazocine derivatives **56a–e**. Compounds **56a–e** could be easily transformed to dinitro derivatives **57a–e** with excess 99% nitric acid.

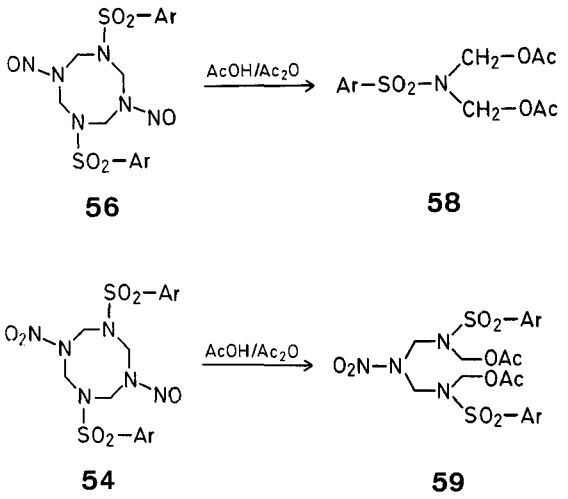
The tetrazocine derivatives, **54** and **56**, may be subjected to the following transformations to **57**, which show the interrelationships among the three groups of products (Scheme **K**).



56 **54** **57**

Scheme **K**

According to Scheme **L**, the tetrazocine derivatives **56** were cleaved by acetic anhydride/acetic acid, to give compound **58**; similar treatment of **54** gave **59** in 59% yield.



56 **58**

54 **59**

Scheme **L**

Compound **57**, apparently, did not react with acetic anhydride and acetic acid. These results show that the cleavage of compounds **54** and **56** occurs at the carbon-nitrogen bonds adjacent to the N—NO function, but not at those adjacent to $N—NO_2$, which confirms the great stability of the $O_2N—N—CH_2—N—NO_2$ grouping.

6. Ring Closure Reactions using Hexamethylenetetramine

Hexamine can be used in making different ring systems containing five, six, or seven ring members. Thus imidazolo, isoindolo, quinazoline, quinoline, and benzodiazepine derivatives were obtained by hexamine-induced ring closure. Generally, the precursors for such compounds should have two reactive functionalities, which may react with hexamine in one or more steps, yielding various heterocyclic compounds. Usual starting compounds are *o*-quinone, halo ketones, or amino ketones. During these reactions hexamine decomposes, giving fragments of different size, down to a —CH=N— group.

6.1. Formation of Five-Membered Rings

Several chloro-, bromo-, and nitro-1*H*-phenanthro[9,10-*d*]imidazoles **61a–f** were synthesised from phenanthroquinones **60**, ammonium acetate, and hexamine (Scheme **M**)[82].

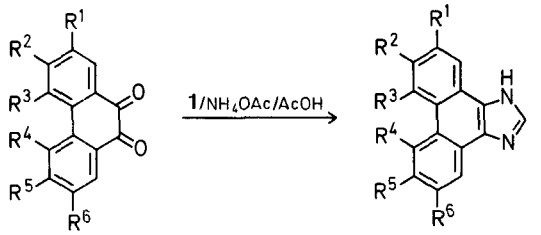
1*H*-Phenanthro[9,10-*d*]imidazoles 61a–f; General Procedure[82]: To a stirred solution of phenanthroquinone (2 mmol) in boiling glacial acetic acid (25 ml), ammonium acetate (3.8 g, 49 mmol) is added, followed by hexamine (0.392 g, 2.8 mmol) dissolved in glacial acetic acid (5 ml). The resultant solution is heated for 1 h, the solvent evaporated in vacuo, and the crude product crystallised from ligroin or glacial acetic acid; yields: 61–80%. Pure products are obtained by recrystallisation from methanol.

Starting from 2-chloroacetamido-5-chlorobenzophenone, the hexaminium salt **63a** was synthesised[83], which decomposed in alcoholic solution giving bis-

[81] H. Yoshida, G. Sen, B. S. Thyagarajan, *J. Heterocycl. Chem.* **10**, 279 (1973).

[82] E. Kessler, *Monatsh. Chem.* **98**, 1512 (1967).

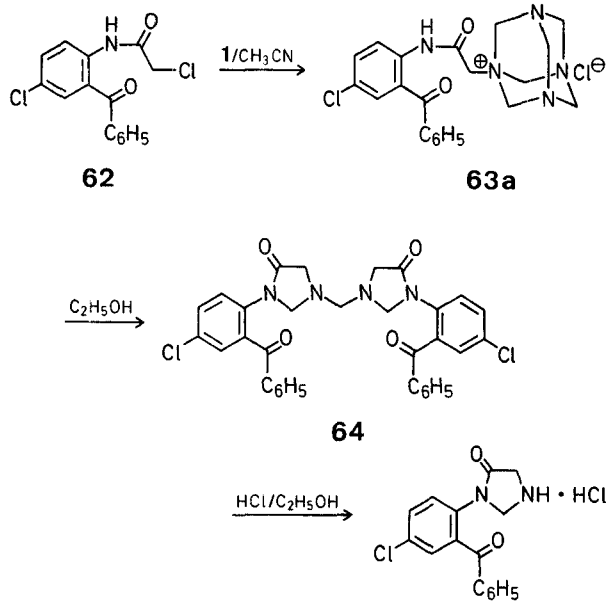
and mono-imidazolidin-4-one derivatives **64** and **65** as shown in Scheme **N**.



60 a-f **61 a-f**

61	R^1	R^2	R^3	R^4	R^5	R^6
a	H	Cl	H	H	H	H
b	H	Br	H	H	Br	H
c	NO_2	H	H	H	Br	H
d	NO_2	H	H	H	H	H
e	H	H	NO_2	H	H	H
f	NO_2	H	H	H	H	NO_2

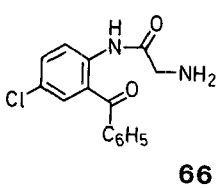
Scheme **M**



62 **63a** **64** **65**

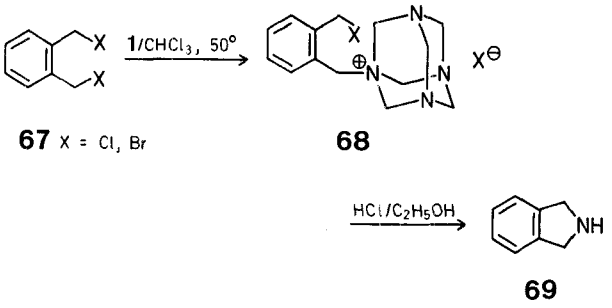
Scheme **N**

The unstable compounds **64** and **65** yielded 1,4-benzodiazepine when boiled in alcohol[83]. To prove that the intermediates immediately preceding the closure of the seven-membered ring do indeed possess structures **64** and **65**, authentic samples of these compounds were synthesised by another procedure[84] from 2-glycinamido-5-chlorobenzophenone (**66**) and compared with the original products.



66

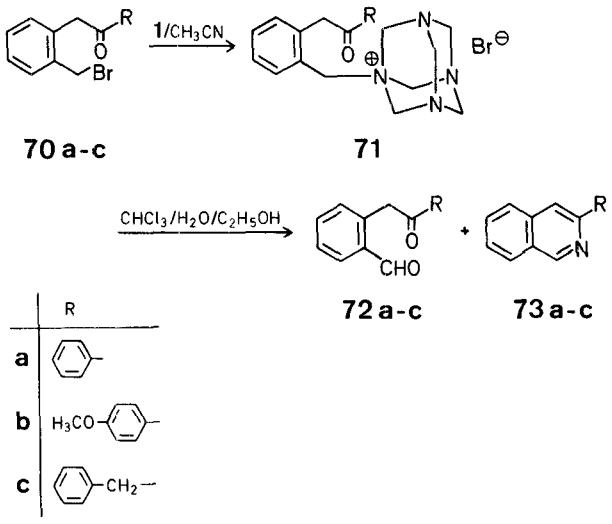
Dauth and Becker[85] developed a method for the preparation of 1,3-dihydroisoindole (**69**) via a hexaminium salt **68**.



67 X = Cl, Br **68** **69**

6.2. Formation of Six-Membered Rings

Syntheses of six-membered nitrogen heterocycles by incorporation of one or two nitrogen atoms from hexamine, are scarcely mentioned in the literature[44,86]. Thus, 2-substituted benzyl bromides **70** form stable quaternary compounds **71**[44] with hexamine in acetonitrile. In chloroform solution containing small amounts of water or ethanol, however, decomposition takes place, yielding the aldehyde **72**. When compound **70** contained a carbonyl group in 2'-position of the side chain, the main products formed were isoquinolines **73**, accompanied by minor amounts of aldehydes **72** (Scheme **O**).



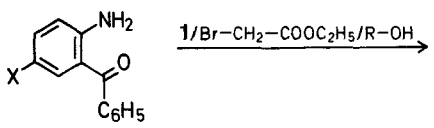
70 a-c **71** **72 a-c** **73 a-c**

	R
a	
b	
c	

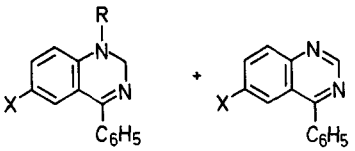
Scheme **O**

Recently the formation of several quinazolines following the same reaction pattern was described[87]. 2-Amino-5-substituted benzophenones **74a–c** reacted with hexamine, in the presence of ethyl bromoacetate to give quinazoline derivatives **75a–c** and **76a, b** according to Scheme **P**.

[83] N. Blažević, V. Šunjić, I. Crvelin, D. Kolbah, F. Kajfež, *J. Heterocycl. Chem.* **9**, 531 (1972).
[84] *Swiss Patent* 465621; *C. A.* **71**, 61382g (1969).
[85] C. Dauth, H. G. O. Becker, *J. Prakt. Chem.* **312**, 440 (1970).
[86] H. Möhrle, B. Gusowski, *Chem. Ber.* **106**, 2485 (1973).
[87] N. Blažević, M. Oklobdžija, V. Šunjić, F. Kajfež, D. Kolbah, *Acta Pharm. Jugosl.* **25**, 223 (1975).



74 a-c



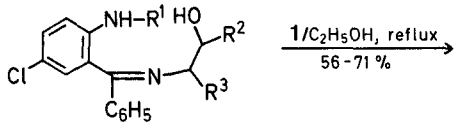
75 a-c 76 a,b

74	X	75	X	R	76	X
a	NO_2	a	NO_2	CH_2OCH_3	a	Cl
b	Cl	b	NO_2	$CH_2OC_2H_5$	b	CH_3
c	CH_3	c	NO_2	H		

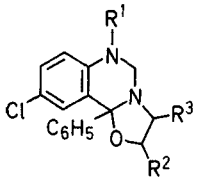
Scheme P

It was found that benzophenones with electron-accepting substituents (**74a**, $X = NO_2$) gave a mixture of dihydroquinazoline derivatives **75a–c**. In contrast, benzophenones with electron-donating substituents ($X = Cl$, CH_3, **74b–c**) gave only quinazolines **76a, b**.

When benzophenone-imine derivatives **77a–e** were reacted with hexamine in boiling ethanol, similar cyclisations occurred, which led to heterocycles with three condensed rings, i.e. 9-chloro-10b-phenyl-2,3,5,6-tetrahydrooxazolo[2,3-*d*]quinazolines **78a–e**[87].



77 a-e



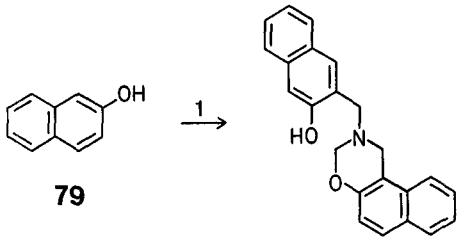
78 a-e

78	R^1	R^2	R^3	Yield [%]
a	H	H	H	60
b	CH_3	H	H	71
c	CH_3	CH_3	H	57
d	CH_2CH_2OH	H	H	58
e	CH_3	H	C_2H_5	56

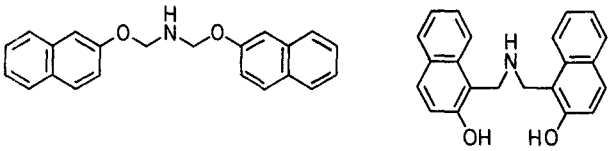
9-Chloro-10b-phenyl-2,3,5,6-tetrahydrooxazolo[2,3-*d*]quinazolines 78a–e[87]:

Compound **77** (34.7 mmol) and hexamine (140 mmol) are dissolved in 96 % ethanol (80 ml) and heated under reflux for 48 h. Thereafter the ethanol is completely evaporated in vacuo. The dry residue is dissolved in water (200 ml) and the solution extracted with benzene (150 ml). The aqueous layer is reextracted with another portion of benzene (150 ml), and the second extract added to the first. The combined extracts are washed with water (3 × 100 ml), dried with sodium sulphate, freed from solvent by evaporation, and the residue is crystallised from a suitable solvent.

The product from 2-naphthol (**79**) and hexamine, described by Galimberti and Erba[88], was incorrectly formulated as bis[2-naphthyloxymethyl]amine (**81**). Burke et al.[89] described this product as an *o*-substituted derivative of 2-naphthol, **82**. Later, Möhrle et al.[86] defined the same product as a Mannich base **80**, i.e. a compound with one additional ring of the dihydro-1,3-oxazine type.



79 80



81 82

6.3. Formation of Seven-Membered Rings

Hexamine was widely used for cyclisation of 1,4-benzodiazepines, compounds belonging to one of the most important group of agents with central nervous activity[90]. No mention was found in the literature of the use of hexamine in formation of other 7-membered nitrogen heterocycles.

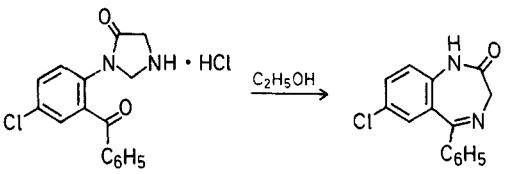
The broad spectrum of medical applications of 1,4-benzodiazepines triggered the development of a variety of methods for the synthesis of these compounds[91–95]. The crucial step in various syntheses of 1,4-benzodiazepine is the introduction of the future N-4 nitrogen atom, linked to closure of the seven-

[88] P. Galimberti, C. Erba, *Gazz. Chim. Ital.* **77**, 375 (1947).
[89] W. J. Burke, M. J. Kolbezen, R. J. Reynolds, G. A. Short, *J. Am. Chem. Soc.* **78**, 805 (1956).
[90] O. Randall, W. Schallek, L. H. Sternbach, R. Y. Ning in M. Gordon, Ed., *Medicinal Chemistry 4/III Psychopharmacological Agents*, Academic Press, 1974, p. 175–281.
[91] L. H. Sternbach, E. Reeder, *J. Org. Chem.* **26**, 1111 (1961).
[92] L. H. Sternbach, R. J. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, A. Stempel, *J. Org. Chem.* **27**, 3788 (1962).
[93] G. N. Walker, *J. Org. Chem.* **27**, 1929 (1962).
[94] S. C. Bell, T. S. Sulkovski, C. Gochman, S. J. Childress, *J. Org. Chem.* **27**, 562 (1962).
[95] G. A. Archer, L. H. Sternbach, *Chem. Rev.* **68**, 747 (1968).

membered diazepine ring. The reagent most frequently used in this step is ammonia, but syntheses using ammonia often result in low yields and impure products.

The final step in the synthesis of 1,4-benzodiazepines is very similar to one of the procedures used in the syntheses of an α-amino acid in which hexamine was reported to be a suitable reagent[28]. It was, therefore, assumed that hexamine might also serve well in the synthesis of 1,4-benzodiazepin-2-ones[83,96,97] **83** and 1,4-benzodiazepines[98,99] **86** and **87**. The method, as finally adopted for the benzodiazepinone synthesis, proceeded in two steps: the first step was the formation of a hexaminium salt (see Scheme **N**), which, in the second step, underwent alcoholysis to give the desired 1,4-benzodiazepine-2-one derivative. The study of the reaction pathway shows, that ring closure of 1,4-benzodiazepines using hexamine is mechanistically different from that using ammonia.

Large rate differences were observed in the solvolysis of hexaminium salts, depending on the substituent on the amino group in the starting 2-aminobenzophenones. *N*-Unsubstituted 2-aminobenzophenones undergo decomposition giving products of the imidazolidin-4-one type (see Scheme **N**). The imidazolidinone ring, then, recyclised into 1,4-benzodiazepin-2-one, as shown in Scheme **Q**.

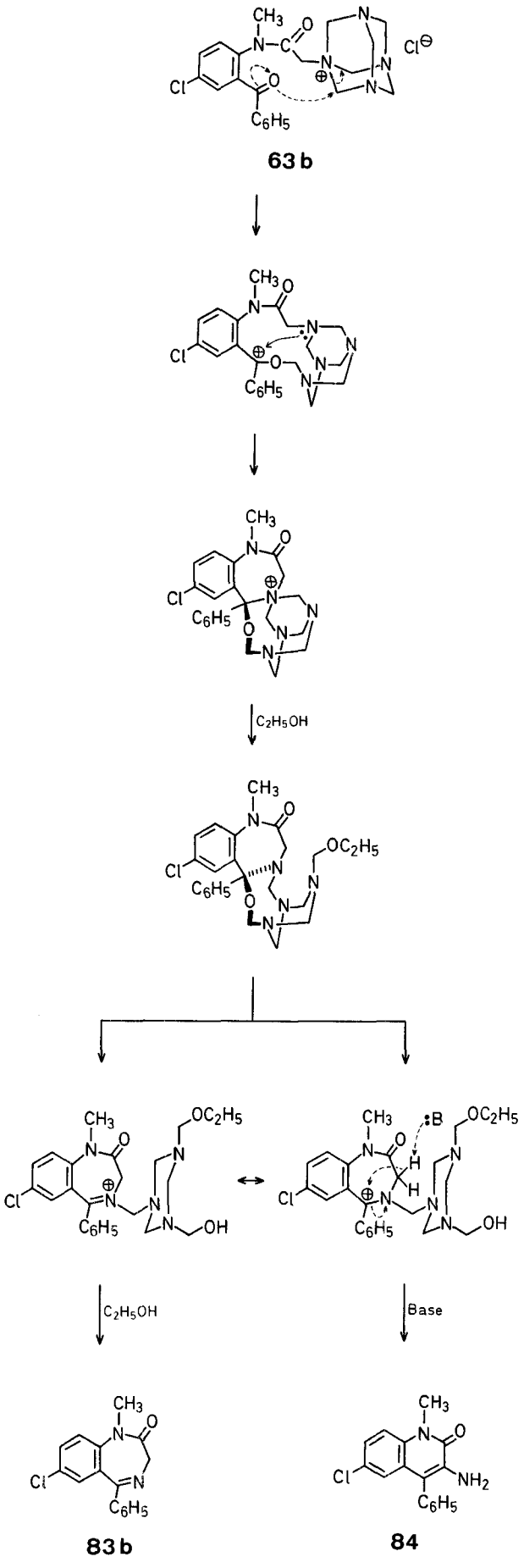


65 **83 a**

Scheme **Q**

On the other hand, *N*-1 substituted compounds[83] gave high yields of 1,4-benzodiazepin-2-ones in very pure form (Scheme **R**).

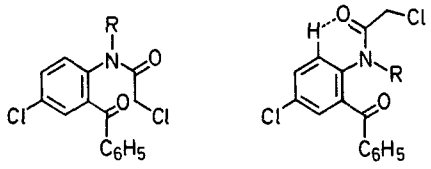
No intermediate or side product formation was observed in these instances. Only when the amount of alcohol used in solvolysis was insufficient, was it possible to identify compound **84** as a side product. This compound was described earlier[100,101] as being a by-product in the cyclisation of 2-haloacetamido-5-chlorobenzophenone into 1,4-benzodiazepin-2-one using ammonia. In addition, a base-catalysed recyclisation of *N*-4-acetyl-1,4-benzodiazepin-2-one into the *N*-acetyl derivative of **84** has also been described[101]. We suggest that the base-catalysed conversion of **63** into **83** produces an intermediate with a positively charged nitrogen atom, as indicated in Scheme **R**.



63 b **83 b** **84**

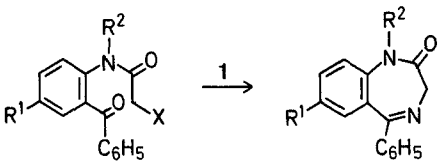
Scheme **R**

Heating hexamine with **83** under the same conditions as used with **63** gave no **84**, which excludes the recyclisation **83**→**84**. Various fragments formed by hexamine decomposition might be imagined as base catalysts, acting via ammonia or methylenimine, but an intramolecular C-3 deprotonation of **63b** by secondary amino groups from partially decomposed hexamine residues is also a possible pathway. It seems, that differences in conformation between the isomeric structures A and B resulting in H-bond formation are of prime importance.



A B

Space-filling models suggest that conformation B cannot be achieved when R = CH_3, but is possible when R = H. Table 9 presents the yields in 1,4-benzodiazepine-2-ones, diversely substituted, to illustrate the efficiency of the "hexamine-method" for 1,4-benzodiazepine-2-ring closures.



62 **83**

Table 9. 1,4-Benzodiazepin-4-one Ring Closures with Hexamine

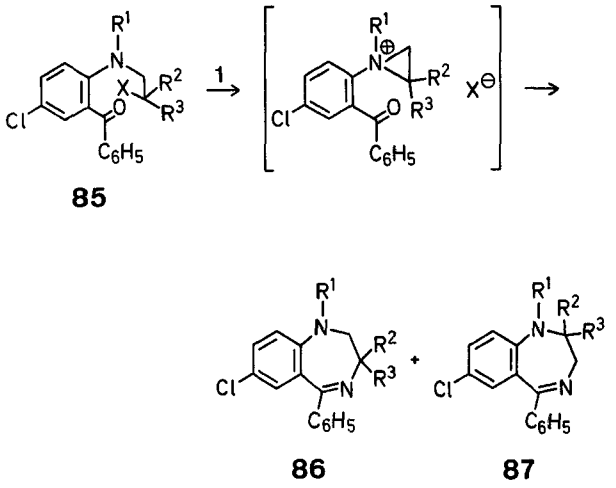
Starting compound	X	R^1	R^2	Product	Yield [%]	Ref.
62a	Cl	Cl	H	**83a**	70–80	96
62b	Br	Cl	H	**83a**	70–80	96
62c	Cl	Cl	CH_3	**83b**	80	96,97
62d	Br	Cl	CH_3	**83b**	85–90	96
62e	Br	NO_2	H	**83c**	70–80	96
62f	Cl	NO_2	H	**83c**	70–80	96

7-Chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine-2-one (83b)[96]:

A mixture of 2-(2-chloro-*N*-methyl-acetamido)-5-chlorobenzophenone (1.0 g, 3.1 mmol), and hexamine (1.0 g, 7.0 mmol) in absolute ethanol (15 ml) is heated under reflux for 10 h. The resultant solution is evaporated to dryness under reduced pressure, the residue is dissolved in water (10 ml), and the solution shaken with benzene (10 ml). The benzene layer is separated and the aqueous layer extracted with two additional 10-ml portions of benzene. The benzene layers are combined, washed, and dried with sodium sulphate. After evaporation to dryness in vacuo, the residue is dissolved in ether. Chilling induces crystallisation, and the crystals are collected and washed with ether: yield: 0.79 g (80 %); m.p. 128–130°.

[96] N. Blažević, F. Kajfež, *J. Heterocycl. Chem.* **7**, 1173 (1970).
[97] A. R. N. Shenoy, P. R. Shankaran, S. B. Rao, *Indian J. Pharm.* **34**, 48 (1972).

Treatment of the 2-(*N*-β-haloalkyl)-amino-5-chlorobenzophenone **85** with hexamine in ethanol resulted in ring closure to give a mixture of 2-deoxy-1,4-benzodiazepines **86** and **87**[98,99].



85 **86** **87**

Scheme S

We assume that β-participation of the vinylogous-amide-nitrogen took place during ammonolysis of the 2-(β-haloethyl) derivatives **85**. However, an intermediate formation of aziridinium derivatives cannot be conveniently demonstrated when 2,3-unsubstituted benzodiazepines are the expected products of reaction, since the same product would be formed by both direct ring closure, or β-participation of the *N*-2 atom. In the preparation of chiral derivatives (N.B., when one of the substituents on the β-*C*-atom in **85**, R^2 or $R^3 \neq H$, this atom is chiral), however, different structural and stereoisomers should arise, according to the mechanism shown in Scheme S. The starting compounds, products, yields, and regioselectivities in these reactions are given in Table 10.

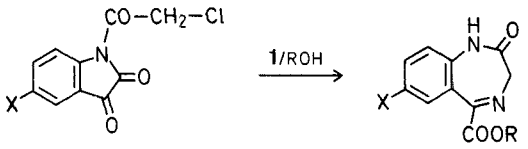
Table 10. 1,4-Benzodiazepine Ring Closure with Hexamine

Starting compound	X	R^1	R^2	R^3	Product	Yield [%]	Regio-selectivity[a]	Ref.
85a	Br	CH_3	H	H	**86a**	88	—	98
85b	Cl	H	H	H	**86b**	75	—	98
85c	Br	CH_3	D	D	**86c**	70	45/55	99
85d	Br	CH_3	H	CH_3	**86d**	72	57/43	99

[a] Ratio of 2- vs. 3-substituted 1,4-benzodiazepines. Individual values have been obtained by G.L.C.

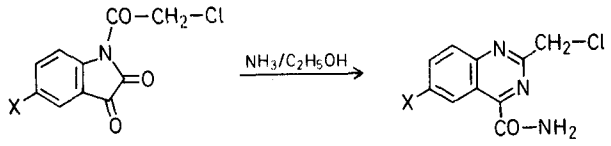
[98] N. Blažević, F. Kajfež, *J. Heterocycl. Chem.* **8**, 845 (1971).
[99] M. Mihalić, V. Šunjić, P. Mildner, F. Kajfež, *Croat. Chem. Acta* **48**, 125 (1976).
[100] R. I. Fryer, B. Proust, L. H. Sternbach, *J. Chem. Soc.* **1964**, 3097.
[101] R. I. Fryer, L. H. Sternbach, *J. Org. Chem.* **30**, 524 (1965).
[102] M. Ogata, H. Matsumoto, *Chem. Ind. (London)* **1976**, 1067.

Ogata and Matsumoto[102] developed another method for the synthesis of 1,4-benzodiazepin-2-ones by ring expansion with hexamine. Starting from suitably substituted derivatives of isatin **88**, they obtained substituted benzodiazepines **89**.



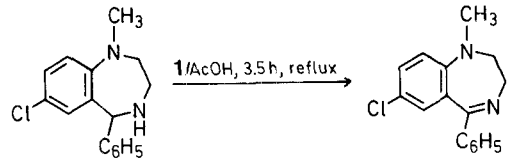
88 **89**

Interestingly, recyclisation after isatin ring opening with hexamine gives rise to derivatives of the seven-membered 1,4-benzodiazepine, while ammonia, in a similar reaction, causes recyclisation to six-membered quinazolines **90**.



88 **90**

Finally, hexamine can be used to oxidise a preformed tetrahydro seven-membered ring, as in the synthesis[103,104] of 2,3-dihydro-1,4-benzodiazepines **92** starting from 1,2,3,4-tetrahydro derivatives **91**.



91 **92**

7. Conclusions

This article shows that hexamine can be used in many different ways in organic synthesis. As a reagent, hexamine decomposes under the influence of various agents, into fragments that can react further to give compounds of the tetraaza- and triaza-type. Another group of reactions encompasses the well known Delépine reaction for the synthesis of amines, and the equally well-known Sommelet and Duff reactions for the synthesis of aldehydes. In the Delépine reaction hexamine contributes one of its nitrogens to build the amine function, and in the Duff reaction it contributes the —CH= function. We may assume, that hexamine reacts as an amine in one instance, and as an aldehyde in another. However, in the Sommelet reaction hexamine behaves as an oxidising agent which oxidises the $—CH_2Cl$ group into a —CHO group.

Recently, hexamine was used in syntheses of five-, six-, and seven-membered heterocycles. In these cyclisation processes, hexamine supplies one or two nitrogen atoms, or a —CH=N— function, to the newly formed heterocycles. These reactions are very complex, and their mechanisms can be only guessed. The starting compounds should have two functionalities between which the hexamine fragments are built to form a heterocycle.

Only a few references dealing with different molecular complexes of hexamine have been included. Such complexes find application as explosives, anticorrosive agents, and drugs.

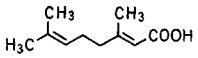
Received: April 28, 1978

[103] K. Ishizumi, K. Mori, Y. Komeno, J. Katsube, H. Yamamoto, *Japanese Patent* 7739690; *C. A.* **87**, 152287 (1977).

[104] K. Ishizumi, Y. Komeno, K. Mori, J. Katsube, *Japanese Patent* 7765287; *C. A.* **87**, 172889 (1977).

Errata and Addenda 1979

M. Contento, D. Savoia, C. Trombini, A. Umani-Ronchi, *Synthesis* **1979** (1), 30–32;
The structure for compound **3c** (p. 31, Table 1) should be:

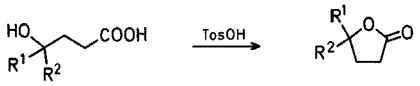


A. Mignot, H. Moskowitz, M. Miocque, *Synthesis* **1979** (1), 52–53;
The correct name for Tetramisole® should be 6-phenyl-2,3,5,6-tetrahydroimidazolo[2,1-*b*]thiazole.

A. N. Pudovik, I. N. Konovalova, *Synthesis* **1979** (2), 81–96;
The first sentence of the experimental procedure on p. 96 should read as follows:
Dialkyl phosphite or phosphorothioate (0.01 mol) is added to the azo compound (0.01 mol) in ether (10 ml).

In Table 13 (p. 96) the entries R^2 for compounds **63b** and **63c** should be 4-H_3C—C_6H_4 and 4-O_2N—C_6H_4, respectively.

Abstract 5422, *Synthesis* **1979** (2), 160;
The formula scheme for the conversion **3**→**4** should be:



3 **4**

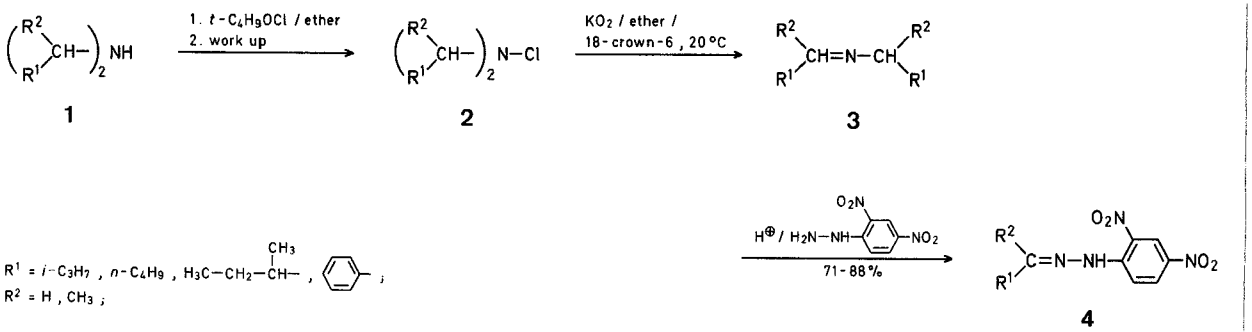
N. Blažević, D. Kolbah, B. Belin, V. Šunjić, F. Kajfež, *Synthesis* **1979** (3), 161–176;
Compounds **78a–e** (p. 173) should be named:
9-chloro-10b-phenyl-2,3,5,6-tetrahydro-10b*H*-[1,3]oxazolo[3,2-*c*]-quinazolines.

K. Herrmann, G. Simchen, *Synthesis* **1979** (3), 204–205
The lines 10 to 17 of the text (p. 204) should read as follows:

sche Acrylcyanide zugänglich[1,5,6]. Aliphatische Carbonsäure-halogenide hingegen setzen sich mit Tetraethylammoniumcyanid zu Acyloxymalodinitrilen („dimere Acrylcyanide") um, wofür auch die hohe Cyanidionen-Konzentration verantwortlich ist[1]. Die Reaktion aliphatischer Säurechloride **(2)** mit Cyanotrimethylsilan **(1)**[7–10] sollte deshalb eine geeignete Synthesenmethode für 2-Oxo-alkannitrile (aliphatische Acrylcyanide, **3**) darstellen. Bisher konnte allerdings nur

L. Caglioti, F. Gasparrini, D. Misiti, G. Palmieri, *Synthesis* **1979** (3), 207–208;
The italic sub-headings in the Table (p. 208) should be *From tosylhydrazones, From* N-*methyl*-N-*tosylhydrazones,* and *From 2,4-dinitrophenylhydrazones.*

Abstract 5440, *Synthesis* **1979** (3), 238;
The formula scheme for the conversion **1**→**4** should be as follows:

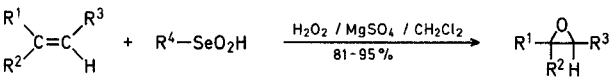


R^1 = *i*-C_3H_7, *n*-C_4H_9, H_3C—CH_2—$CH(CH_3)$—, C_6H_5—;
R^2 = H, CH_3;

C. Venturello, R. D'Aloisio, *Synthesis* **1979** (4), 283–287;
Entries 3 and 4 of the Mass spectrum column of Table 1 (p. 284) should be 284 (^{35}Cl) and 318 (^{35}Cl), respectively.

J. S. Davidson, *Synthesis* **1979** (5); 359–361;
Compounds **6** (p. 360) should be named:
3,4-diaryl-5-oxo-3,4-dihydro-1*H*-1,2,4-triazoles.

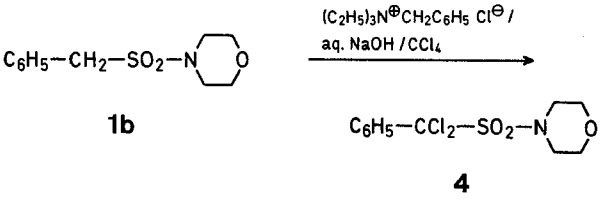
Abstracts 5494, *Synthesis* **1979** (5), 399;
The formula scheme for the conversion **1**→**3** should be as follows:



1 **2** **3**

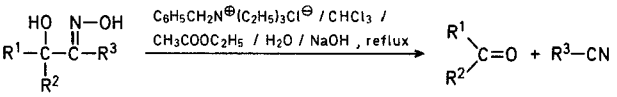
C. Skötsch, I. Kohlmeyer, E. Breitmaier, *Synthesis* **1979** (6), 449–452;
The name for compound **10a** should be:
3-Methyl-5,6,7,8-tetrahydroisoxazolo[5,4-*b*]chinolin.

J. Goliński, A. Jończyk, M. Mąkosza, *Synthesis* **1979** (6), 461–463;
The formula scheme for the conversion **1b**→**4** (p. 462) should be as follows:



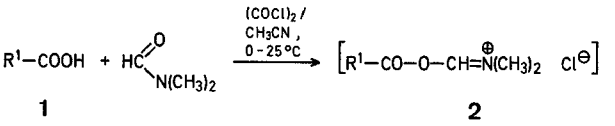
1b **4**

Abstract 5520, *Synthesis* **1979** (6), 479;
The formula scheme should be as follows:



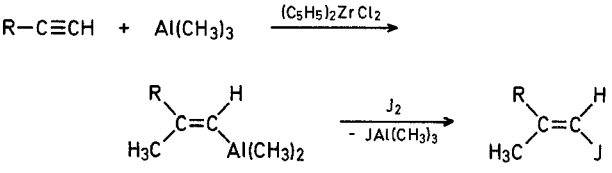
1 **2** **3**

Abstract 5521, *Synthesis* **1979** (6), 479;
The formula scheme for the conversion **1**→**2** should be as follows:



1 **2**

E. Negishi, D. E. Van Horn, A. O. King, N. Okukado, *Synthesis* **1979** (7), 501–502;
For clarity, the following formula scheme should be added:



A. McKillop, D. W. Young, *Synthesis* **1979** (7), 481–500;
The heading for Table 24 (p. 496) should be:

Table 24. Oxidation of Alcohols to Aldehydes and Ketones using Potassium Permanganate/Molecular Sieves[172].