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.

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1. Introduction

Hexamethylenetetramine** (1; C₈H₂N₄; M.W. 140.19; m.p. 285–295°, sublimation), is formed in nearly quantitative yield from the condensation of ammonia and formaldehyde¹⁻³.⁴

$$\text{6 H}_2\text{CO} + 4 \text{NH}_3 \xrightarrow{\mu^+} 1$$

Large scale preparations and properties of hexamethylenetetramine have been reviewed². 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 methods⁵,⁶.

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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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. 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; 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 (I) H₂SO₄·6 H₂O and (II) H₂SO₄·8 H₂O which are stable up to 180°. With salicyclic acid 1 forms a 1:1 molecular complex. These complex salts as well as those of 1 with urea have found applications in human and veterinary therapy.

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).

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.

2.2. Quaternary Salts of Hexamethylenetetramine

Alkyl halides react with hexamethylenetetramine in chloroform to give the quaternary salts 3 which undergo hydrolysis in aqueous solution to generate formaldehyde. The stability of the salts 3a–c in air increases in the order 3a < 3b < 3c and all are sensitive to heat.

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 or haloacetonitriles in tetrachloromethane solution.

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12 M. D. Maskovskij, Lekarstvennaya sredstva, Medicina, Moskva, 1972, Chapter 1, p. 68, Chapter 2, p. 431.
16 H. Böhme, M. Haake, Arch. Pharm. 300, 682 (1967).
Similarly quaternary salts, prepared in 80–90% yield in chloroform from I and haloalkyl nitrites have bactericidal and fungicidal activity. The reaction of hexamethylenetetramine (I) with 2-bromo-N-methyl-phenylacetamide (5) to give the salt 6 in 90% yield has been studied by N.M.R.-spectrometry.

![Chemical structure](image)

**3. Introduction of Amino Groups via Hexamminium Salts**

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

**Scheme A**

In strongly acidic media (usually ethanol/concentrated hydrochloric acid) primary amines 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 \( \alpha \)-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).

**Table 1. Selected Examples of the Delépine Reaction**

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( X )</th>
<th>Yield [%]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Br</td>
<td>100</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Cl</td>
<td>74</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Br</td>
<td>74</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Cl</td>
<td>93</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>COOH</td>
<td>94</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Br</td>
<td>58–93</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>( \text{H}_2\text{C}-\text{N}^{+}\text{H}_2\text{H}_2 )</td>
<td>COOH</td>
<td>87</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>( \text{H}_2\text{C}-\text{CH}-\text{CH}_2 )</td>
<td>( \text{H}_2\text{C}-\text{CH}-\text{CH}_2 )</td>
<td>85</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>90</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>100</td>
<td>30, 31</td>
<td></td>
</tr>
<tr>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>( \text{H}_2\text{C}-\text{NH}^{-}\text{CH}_2 )</td>
<td>50–71</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

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23 B. Reichert, W. Dornis, Arch. Pharm. 282, 100 (1944).
1-(2-Aminoacetyl)-3-hydroxy-4-methoxybenzene Hydrochloride (8): 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 hexaminiun salts in formic acid leads to the formation of methylamines. 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 hexaminiun salt supplying both amine and formaldehyde.

Reaction of hexamethylene tetramine with substituted oxiranes is also a modification of the Delépine reaction. With hexamethylenetetramine (I) 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 z,β-amino alcohols have exhibited interesting pharmacological properties.

Scheme B

<table>
<thead>
<tr>
<th>Oxirane 9</th>
<th>Amino alcohol 10</th>
<th>m.p.</th>
<th>Yield Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-C-H₂-C-H₂-NH₂</td>
<td>75–76°</td>
<td>79</td>
<td>33</td>
</tr>
<tr>
<td>H₂C</td>
<td>73–74°</td>
<td>98</td>
<td>33, 34</td>
</tr>
<tr>
<td>HO</td>
<td>181–183°</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>C₆H₄-O-C-H₂-OH</td>
<td>275–278°</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>C₆H₄(O)-O-C-H₂-OH</td>
<td>136°</td>
<td>65</td>
<td>33</td>
</tr>
</tbody>
</table>

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

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

Hexamethylenetetramine (1) can be used as a catalyst in the preparation of urea from ammonia and carbon dioxide. The reagent serves to increase both the yield of urea and the degree of utilization 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 Hexaminiun Salts

As shown in Scheme A, aldehydes can be obtained from the reaction of hexaminiun salts 2 derived from alkyl and aralkyl (mostly arylethyl) halides. This process, known as the Sommelet reaction, was reviewed in 1954. The Sommelet reaction proceeds in three steps: (1) formation of the hexaminiun 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).

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32 Ref. 21, p. 204 and references cited therein.
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: 48.3–50.7 g (77–80%) based on hexaminium bromide, 64% based on 2-methyl-naphthalene; m.p. 58.5–59.5°.

A generally accepted mechanism for the Sommelet reaction was proposed later and is illustrated by the example in Scheme D.

Scheme D

The hexaminium salt A, derived from halide 16 and I, 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, 2-ethylphenylamine on reaction with formaldehyde, followed by hexamine, gives acetonaphone. Following this

2-Formylnaphthalene 43:

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 1.5 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 hexamethylene-tetramine (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 x 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,
route benzophenone, fluorenone, and some unsaturated alicyclic ketones were prepared. 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, allows the preparation of ortho-hydroxy aromatic aldehydes. The procedure consists in treatment of phenols with hexamine in glycerol or glyceric acid (HBO₂ in dry glycerol) or glacial acetic acid. The reaction 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-methyphenol (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.

Table 4. Selected Examples of the Duff Reaction

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent/Other</th>
<th>Aldehyde</th>
<th>Yield [%]</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₃C₆H₄N⁺</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>19</td>
<td>49</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>75</td>
<td>52</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>HBO₂ / glycerol</td>
<td>H₂C₆H₅OH</td>
<td>55</td>
<td>53</td>
</tr>
</tbody>
</table>

Table 5. Formylation of Aromes 24 with Hexamethylenetetramine (1) in Trifluoroacetic Acid

<table>
<thead>
<tr>
<th>Arom 24</th>
<th>Ratio of 1: TFA</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-C₆H₄OH</td>
<td>1:1</td>
<td>t-C₆H₄OH</td>
<td>75</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>1:1</td>
<td>H₂C₆H₄OH</td>
<td>50</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>1:1</td>
<td>H₂C₆H₄OH</td>
<td>11</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>1:4</td>
<td>H₂C₆H₄OH</td>
<td>32</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>2:1</td>
<td>H₂C₆H₄OH</td>
<td>74</td>
</tr>
<tr>
<td>H₂C₆H₄OH</td>
<td>1:1</td>
<td>H₂C₆H₄OH</td>
<td>37</td>
</tr>
</tbody>
</table>

The first step is probably the formation of methylamine 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—CH₂—N═CH₂, 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-xylene, hexamine (I), 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.

Intermediate formation of salt 26 clearly shows that this process is related to the Sommellier and Delépine reactions. Some heterocycles, such as indoles and azaindoles, can be readily formulated with hexamine (see Table 6).

Table 5. (continued)

<table>
<thead>
<tr>
<th>Arene</th>
<th>Ratio of</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>2:1</td>
<td>-O-CHO</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ O-H</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>t-C₆H₅</td>
<td>t-C₆H₅</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>t-C₆H₅</td>
<td>HO-CHO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H₃C</td>
<td>H₃C</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>H₃C</td>
<td>H₃C</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield [%]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHO</td>
<td>25</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>CHO</td>
<td>74</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>CHO</td>
<td>50</td>
<td>58</td>
</tr>
</tbody>
</table>

7-Azaindole-3-carboxaldehyde (3-Formyl-1H-pyrrolo[2,3-β]pyridine): A solution of 7-azaindole (23.6 g, 0.20 mmol) and hexamine (420 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 crystallize overnight. Recrystallization 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. 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. 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%.

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.

59 T. Urbanski, Chemistry and Technology of Explosives 3, 87 (1967).
Scheme F

Other authors\(^{34}\) 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.\(^{6,5,64}\)

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).


Degradative nitrosation of hexamine in aqueous solution was carried out by simultaneous addition of hydrochloric or acetic acid\textsuperscript{71,72} and a solution of sodium nitrite. The main factor determining the nature of the products is the pH of the solution.

Scheme G

Thus, in hydrochloric acid at pH 1 the trinitroso compound \(42\) (50 \% yield; m.p. 104.5–106\(^\circ\)) is formed exclusively, at pH 2 a mixture of \(42\) and \(43\) (m.p. 196–200\(^\circ\)) is obtained, between pH 3 and 6 only \(43\) (72–76 \% yield; m.p. 203.5–207\(^\circ\)) is formed\textsuperscript{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\(^\circ\)) of \(42\) and \(43\) (1:3:3), or pure \(43\) (1:6:6)\textsuperscript{11}.

When acetic acid was employed, however, the only product obtained over a wide range of conditions was the dinitroso compound \(43\)\textsuperscript{71}.

1,3,5-Trinitrosohexahydro-s-triazine (42); trinitrosotrimethylene-triazine and 1,5-Dinitrosooctahydro-1,3,5,7-tetrazocine (43): Hexamine (7 g, 0.05 mol) is dissolved in ice-water (300 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\(^\circ\) 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\(^\circ\); at pH 4: 72 \% of \(43\); m.p. 207\(^\circ\).

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\textsuperscript{74,75}. The reaction was studied in detail: two main types of cleavage of hexamine were observed and products 44–47 were identified.

\textsuperscript{71} H. Krzikalla, H. Pohlemann, T. Toepel, German Patent 1004618 (1957); C. A. 53, 18075 (1959).
\textsuperscript{72} Belgium Patent 613501 (1962); C. A. 58, 1618 (1963).
\textsuperscript{73} E. W. Bachmann, W. J. Horton, E. L. Jenner, N. W. Mac Naughton, L. B. Scott, J. Am. Chem. Soc. 73, 2769 (1951).
\textsuperscript{74} E. W. Bachmann, E. L. Jenner, J. Am. Chem. Soc. 73, 2773 (1951).
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, trinitrosotrimethylenetetramine (42) is the main product, whereas, at lower acidities 43 is formed.11

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

The reaction of hexamine with acetic anhydride has been studied recently by several authors and can be formulated as in Scheme H.

Scheme H

The yields of 49 never exceeded 45%. Siele et al. 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.

Using acetic anhydride, water, and hexamine, at 5–10°C, 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 I80. Compound 51 is probably the species undergoing acylation when water is present.

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)81

Acetic anhydride (30.6 g, 0.3 mol) is added dropwise over 60 min with stirring and cooling at 5–10°C 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°C for 30 min and evaporated to dryness to give crude 49a; yield: 25.2 g. Recrystallization from acetone gives pure 49a; yield: 21.2 g (100%); m.p. 192°C.

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 NO2 or NO2-. 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).

Scheme J

Table 7. Products of Acylation of Hexamine (1)

<table>
<thead>
<tr>
<th>Product</th>
<th>Acylating agent</th>
<th>Temperature</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>(CH3)2CO2O/NaOH</td>
<td>10°C</td>
<td>98%</td>
</tr>
<tr>
<td>49b</td>
<td>(CH3)2CO2O</td>
<td>5–10°C</td>
<td>100%</td>
</tr>
<tr>
<td>49c</td>
<td>HN3</td>
<td>15–20°C</td>
<td>65%</td>
</tr>
<tr>
<td>49d</td>
<td>(CH3)2CO2O</td>
<td>0–12°C</td>
<td>22%</td>
</tr>
<tr>
<td>49e</td>
<td>(CH3)2CO2O</td>
<td>0–10°C</td>
<td>52%</td>
</tr>
<tr>
<td>49f</td>
<td>(CH3)2CO2O</td>
<td>0–10°C</td>
<td>52%</td>
</tr>
<tr>
<td>49g</td>
<td>(CH3)2CO2O</td>
<td>0–10°C</td>
<td>52%</td>
</tr>
<tr>
<td>50a</td>
<td>(CH3)2CO2O</td>
<td>55°C</td>
<td>13%</td>
</tr>
<tr>
<td>50b</td>
<td>(CH3)2CO2O</td>
<td>90–100°C</td>
<td>78%</td>
</tr>
<tr>
<td>50c</td>
<td>(CH3)2CO2O</td>
<td>90–100°C</td>
<td>78%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>52a</td>
<td>4-HC≡C—C6H4</td>
<td>46</td>
</tr>
<tr>
<td>52b</td>
<td>C6H5</td>
<td>56</td>
</tr>
<tr>
<td>52c</td>
<td>3-Cl—C6H4</td>
<td>38</td>
</tr>
<tr>
<td>52d</td>
<td>4-Br—C6H4</td>
<td>8</td>
</tr>
<tr>
<td>52e</td>
<td>3-O2N—C6H4</td>
<td>11</td>
</tr>
</tbody>
</table>
Treatment of compounds 52a and 52c with 70% nitric acid and acetic anhydride at −10°C gave considerable amounts of resinous products; compound 53 was the major product, with the admixture of a small amount of 55.

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).

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.

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

1H-Phenanthro[9,10-d]imidazoles 61a–f; General Procedure82:

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-chloracetamido-5-chlorobenzophenone, the hexaminium salt 63a was synthesised83, which decomposed in alcoholic solution giving bis-
and mono-imidazolidin-4-one derivatives 64 and 65 as shown in Scheme N.

Dauth and Becker developed a method for the preparation of 1,3-dihydrosoindole (69) via a hexaminium salt 68.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>Br</td>
</tr>
<tr>
<td>c</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>d</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>H</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>f</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NO₂</td>
</tr>
</tbody>
</table>

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. Thus, 2-substituted benzyl bromides 70 form stable quaternary compounds 71 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 isooquinolines 73, accompanied by minor amounts of aldehydes 72 (Scheme O).

The unstable compounds 64 and 65 yielded 1,4-benzodiazepine when boiled in alcohol. 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 from 2-glycinamido-5-chlorobenzophenone (66) and compared with the original products.

Recently the formation of several quinazolines following the same reaction pattern was described. 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.

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Hexamethylenetetramine, A Versatile Reagent in Organic Synthesis

Scheme P

It was found that benzenophenes with electron-accepting substituents (74a, X = NO₂) gave a mixture of dihydroquinazoline derivatives 75a–c. In contrast, benzenophenes with electron-donating substituents (X = Cl, CH₃, 74b–c) gave only quinazolines 76a, b.

When benzenophene-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-tetrahydroxazolo[2,3-d]quinazolines 78a–e.

6.3. Formation of Seven-Membered Rings

Hexamine was widely used for cyclisation of 1,4-benzodiazipines, compounds belonging to one of the most important group of agents with central nervous activity. 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-benzodiazipines triggered the development of a variety of methods for the synthesis of these compounds. The crucial step in various syntheses of 1,4-benzodiazipine is the introduction of the future N-4 nitrogen atom, linked to closure of the seven-

---

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 a-amino acid in which hexamine was reported to be a suitable reagent. It was, therefore, assumed that hexamine might also serve well in the synthesis of 1,4-benzodiazepin-2-ones and 1,4-benzodiazepines. The method, as finally adopted for the benzodiazepinine synthesis, proceeded in two steps: the first step was the formation of a hexamium 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 hexamium 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, recycelys into 1,4-benzodiazepin-2-one, as shown in Scheme Q.

![Scheme Q](image)

On the other hand, N-1 substituted compounds 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 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 recylisation of N-4-acetyl-1,4-benzodiazepin-2-one into the N-acetyl derivative of 84 has also been described. 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.

![Scheme R](image)
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 methyleneimine, 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.

![Chemical structures](Image)

Space-filling models suggest that conformation B cannot be achieved when R = CH₃, 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.

![Chemical structures](Image)

<table>
<thead>
<tr>
<th>Starting compound</th>
<th>X</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>62a</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>83a</td>
<td>70–80</td>
<td>96</td>
</tr>
<tr>
<td>62b</td>
<td>Br</td>
<td>Cl</td>
<td>H</td>
<td>83a</td>
<td>70–80</td>
<td>96</td>
</tr>
<tr>
<td>62c</td>
<td>Cl</td>
<td>Cl</td>
<td>CH₃</td>
<td>83b</td>
<td>80</td>
<td>96,97</td>
</tr>
<tr>
<td>62d</td>
<td>Br</td>
<td>Cl</td>
<td>CH₃</td>
<td>83b</td>
<td>85–90</td>
<td>96</td>
</tr>
<tr>
<td>62e</td>
<td>Br</td>
<td>NO₂</td>
<td>H</td>
<td>83c</td>
<td>70–80</td>
<td>96</td>
</tr>
<tr>
<td>62f</td>
<td>Cl</td>
<td>NO₂</td>
<td>H</td>
<td>83c</td>
<td>70–80</td>
<td>96</td>
</tr>
</tbody>
</table>

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

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 87⁹⁸,⁹⁹.

![Chemical structures](Image)

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, R² or R³ ≠ 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.

![Chemical structures](Image)

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

Starting compound X R¹ R² R³ Product Yield Regioselectivity * [%] Ref. | 85a | Br | CH₃ | H | 86a | 88 | — | 98 |
| 85b | Cl | H  | H | 86b | 75 | — | 98 |
| 85c | Br | CH₃| D | 86c | 70 | 45/55 | 99 |
| 85d | Br | CH₃| H | CH₃| 86d | 72 | 57/43 | 99 |

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

---

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

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

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

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 \(-\text{CH}==\text{N}\) 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 \(-\text{CH}_2\text{Cl}\) group into a \(-\text{CHO}\) 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 \(-\text{CH}==\text{N}\) 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


Errata and Addenda 1979

The structure for compound 3e (p. 31, Table 1) should be:

\[
\begin{align*}
\text{H}_2\text{C} & \text{H} \text{H} \\
\text{C} & \text{H} \\
\text{COON} & \text{H} \\
\end{align*}
\]

A. Mignot, H. Moskowitz, M. Miosque, Synthesis 1979 (1), 52-53;
The correct name for Tetramisole® should be 6-phenyl-2,3,5,6-tetrahydroimidazol-2(1H)-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 phosphate 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 R² for compounds 63b and 63c should be 4-H₂C—C—H₂ and 4-O₆N—C—H₆, respectively.

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

\[
\begin{align*}
\text{HO} & \text{R}^2 \text{COOH} \\
\text{NaOH} & \text{R}^2 \text{COOR} \\
\end{align*}
\]

Compounds 78a-e (p. 173) should be named:
9-chloro-10b-phenyl-2,3,5,6-tetrahydro-10bH-(1,3)oxazole[3,2-ε]-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 15,16. Aliphatische Carbonsäure-halo-
genide hingegen setzen sich mit Tetraethylammoniumcyanid zu
Acylxamalodinitrilren ("dimer acrylcyanide") um, wofür auch
die hohe Cyanidion-Konzentration verantwortlich ist 17. Die
Reaktion aliphatischer Säurechloride (2) mit Cyanotrimethylsilyl-
(1) 18 sollte deshalb eine geeignete Synthesenmethode für 2-Oxo-
alkanitrile (aliphatische Acrylcyanide, 3) darstellen. Bisher konnte
allerdings nur

The italic sub-headings in the Table (p. 208) should be From tosyl-
hydrzones, From N-methyl-N-tosylhydrzones, and From 2,4-di-
nitrophenyhydrzones.

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

\[
\begin{align*}
\text{R}^2 & \text{C} = \text{CH} \\
\text{NH} & \text{R}^2 \text{C} = \text{C} \text{H} \\
\end{align*}
\]

C. Venturinello, R. D'Aloisio, Synthesis 1979 (4), 283-287;
Entries 3 and 4 of the Mass spectrum column of Table 1 (p. 284) should be 286 (M⁺) and 318 (M⁺), respectively.

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

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

\[
\begin{align*}
\text{R}^1 & \text{C} = \text{C} \text{H} \\
\text{R}^2 & \text{C} = \text{C} \text{H} \\
\text{H}_2\text{H}_2 & \text{O} \\
\text{O} & \text{H}_2\text{O} / \text{MgSO}_4 / \text{CH}_2\text{Cl}_2 \\
\text{R}^1 & \text{C} = \text{C} \text{H} \\
\end{align*}
\]

C. Skötsch, I. Kohn, S. Purina, Synthesis 1979 (6), 449-452;
The name for compound 10a should be:
3-Methyl-5,6,7,8-tetrahydroidoxazolino[5,4-b]chinolin.

J. Golinski, A. Joncezy, M. Matkova, Synthesis 1979 (6), 461-463;
The formula scheme for the conversion 1b→4 (p. 462) should be as follows:

\[
\begin{align*}
\text{CH}_2\text{H}_5 & \text{CH} = \text{S} \text{O}_2 \text{N} \\
\text{Cl}_2 & \text{CH}_2\text{H}_5 \text{C} = \text{O} \\
\text{NaOH} / \text{CCl}_4 & \\
\end{align*}
\]

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

\[
\begin{align*}
\text{HO} & \text{C} = \text{O} \\
\text{OH} & \text{C} = \text{O} \\
\text{CH}_2\text{COOH} & \text{C} = \text{O} \\
\text{CH}_2\text{COOH} & \text{C} = \text{O} \\
\text{H}_2\text{O} / \text{NaOH} + \text{reflux} & \\
\end{align*}
\]

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

\[
\begin{align*}
\text{COOH} & \text{H(NCH}_3)_2 \\
\text{ICOOCH} & \text{H(NCH}_3)_2 \\
\text{H}_2\text{O} / \text{CH}_2\text{N} \text{H}_2 \\
\end{align*}
\]

For clarity, the following formula scheme should be added:

\[
\begin{align*}
\text{R} & \text{C} = \text{H} \\
\text{Al(CH}_3)_3 & \\
\text{IC}_{\text{H}}\text{H}_2\text{ZrCl}_2 & \\
\text{J}_2 & \text{J}_2 \\
\end{align*}
\]

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.